2017년 대한면역학회 춘계학술대회

2017년 대한면역학회
춘 계 학 술 대 회

- 일자 : 2017년 4월 13일(목) ~ 14일(금)
- 장소 : 가톨릭대학교 성의회관 마리아홀

- 주관 : 대한면역학회

Immunovation

The Korean Association of Immunologists

2017년 대한면역학회 춘계학술대회
대한면역학회

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- 일시: 2017년 4월 13일 (목) 12:30 – 19:30
  2017년 4월 14일 (금) 08:50 – 18:10

- 장소: 가톨릭대학교 성의회관 마리아홀

주관: 대한면역학회

인 사 말 씀

새봄을 맞아 2017년 대한면역학회 춘계학술대회에 여러분을 초대합니다.

대한면역학회는 다가오는 4월 13일과 14일 가톨릭대학교 성의회관 마리아홀에서 춘계학술대회를 개최합니다. 첫날에는 최근 생명과학 전분야에 걸쳐 큰 관심이 집중되고 있는 유전체빅데이터 분석과 gene editing 및 마이크로바이옴에 대한 이해가 면역학연구에 어떻게 활용될 수 있는지를 심도 깊게 다루는 교육세션을 준비하였습니다. 둘째 날에는 면역조절 기전에 대한 새로운 연구동향과 함께 면역질환 치료의 최신지견을 소개하고자 관련분야의 저명한 기초, 임상연구자들을 모셨습니다.

특히 올해에는 대한류마티스학회와 함께 공동 심포지엄을 새롭게 구성하여 기초면역학자와 임상의사간의 상호이해의 폭을 넓히는 시간을 마련하였습니다. 이와 함께 Young Investigator Session과 Poster/Oral Presentation을 진행하여 젊은 연구자 및 차세대 면역학도들과 함께 교류하는 자리도 준비하였습니다.

2017년 대한면역학회 춘계학술대회를 통하여 회원들 간 활발한 학문교류 및 친목도모의 뜻 깊은 시간을 가지시길 바랍니다.

2017년 4월

대한면역학회 회장 **박 정 규**

2017년 대한면역학회 춘계학술대회

목 차

2017년 대한면역학회 춘계학술대회
일 정 표

일시 : 2017년 4월 13일 (목) 12:30~19:30
2017년 4월 14일 (금) 08:50~18:10
장소 : 가톨릭대학교 성의회관 마리아홀

Day 1. 2017년 4월 13일 목요일 — **Education Program**

12:30～13:30	**Registration**	
13:30～13:40	**Introduction**	**김완욱** 학술위원장
13:40～14:50	**Lecture I. Precise Medicine: Genomic Big Data Analysis in Immune System**	**좌장: 박영민**(건국대)
13:40～14:15	1. Applying Genomics to Immuno-Compromised rare Disease Patients for Precision Medicine	**최무림**(서울의대)
14:15～14:50	2. Genomic Big Data Analysis of Immune Diseases: HLA Fine-Mapping and Subgroup Identification	**한 범**(울산의대 아산병원)
14:50～15:10	*Coffee break*	
15:10～16:20	**Lecture II. Microbiota in Immune Homeostasis and Diseases**	**좌장: 이명식**(연세의대)
15:10～15:45	1. Host, Microbiome, and Health	**고광표**(서울대)
15:45～16:20	2. Impact of Drugs on host Health Via Gut Bacterial and Viral Community Change	**배진우**(경희대)
16:20～16:40	*Coffee break*	
16:40～17:50	**Lecture III. Gene Editing: Recent Advance and its Clinical Applications**	**좌장: 강창율**(서울약대)
16:40～17:15	1. Genome Editing in Human Stem Cells and Animals	**김진수**(서울대)
17:15～17:50	2. Clinical Application of Gene Editing in Immunologic Diseases	**주지현**(가톨릭의대)
17:50～19:30	**Reception**	

Day 2. 2017년 4월 14일 금요일		Symposium Program
08:50～09:00	**Opening address**	**박정규** 회장
09:00～10:15	**Block Symposium I. Signal Regulation of Immune Response and Tolerance**	**좌장: 이왕재**(서울의대)
09:00～09:25	BSI-1. Novel Host Regulators in Innate Immune Responses against Virus Infection	**이종수**(충남대)
09:25～09:50	BSI-2. Lymphocyte Microvilli are Specialized for Intra- and Intercellular Communication	**전창덕**(GIST)
09:50～10:15	BSI-3. Mesenchymal Stem/Stromal Cell-Mediated Immune Tolerance	**오주연**(서울대병원)
10:15～10:50	*Coffee break*	
10:50～12:30	**Young Investigator**	**좌장: 김평현**(강원대)
10:50～11:10	YI-1. Functional Energetics of Neutrophils and Macrophages	**전현식**(고려대)
11:10～11:30	YI-2. Autophagy Primes Neutrophils for Neutrophil Extracellular Trap Formation During Sepsis	**홍장원**(경북대)
11:30～11:50	YI-3. IL-4 Homeostasis is Regulated by Innate T Cells	**이유정**(포항공대)
11:50～12:10	YI-4. IL-22, a Double Edged Sword in Skin Immune System	**윤주한**(C&C신약연구소)
12:10～12:30	YI-5. Versatile Strategy for Controlling the Specificity and Activity of Engineered T Cells	**김찬혁**(KAIST)
12:30～13:30	*Lunch*	
13:30～14:30	**Poster Presentation**	
14:30～15:30	**Oral Presentation**	**좌장: 이종길**(충북약대)
15:30～16:00	*Coffee break*	
16:00～17:40	**Block Symposium II. Clinical and Experimental Immunology: Immuno-Pathogenesis of Human Diseases**	**좌장: 최인홍**(연세의대)
16:00～16:25	BSII-1. Innate Cytokines in Nasal Allergic Diseases	**김대우**(서울의대)
16:25～16:50	BSII-2. Severe Asthma ; Unmet Need in Chronic Airway Allergic Inflammatory Diseases	**조유숙**(울산의대 아산병원)
16:50～17:15	BSII-3. Pathogenesis of Inflammatory Bowel Diseases: An Aberrant Interplay Between Host and Microbes	**천재희**(연세의대)
17:15～17:40	BSII-4. Current Issues in Lymphoma and its Evolving Therapeutic Strategies	**조석구**(가톨릭의대)
17:40～18:10	**시상 및 폐회**	

Block Symposium I

Signal Regulation of Immune Response and Tolerance

Chair: 이왕재(서울의대)

09 : 00 ~ 09 : 25 Novel Host Regulators in Innate Immune Responses against Virus Infection
이종수(충남대)

09 : 25 ~ 09 : 50 Lymphocyte Microvilli are Specialized for Intra- and Intercellular Communication
전창덕(GIST)

09 : 50 ~ 10 : 15 Mesenchymal Stem/Stromal Cell-Mediated Immune Tolerance
오주연(서울대병원)

[BSI-1]

Novel Host Regulators in Innate Immune Responses Against Virus Infection

Jong-Soo Lee

College of Veterinary Medicine, Chungnam National University, Daejeon, Republic of Korea

Early recognition of invading viruses by host cells is critical to antiviral innate immunity. Invading viruses trigger type I interferon-mediated antiviral responses and induce production of effector proteins that inhibit completion of the virus cycle and virus dissemination in vivo. Germline-encoded pattern recognition receptors (PRRs) within the innate immune system sense signature molecules expressed by pathogens, known as pathogen-associated molecular patterns (PAMPs). To date, PRRs are classified into three families: retinoic acid inducible gene (RIG)-I-like receptors (RLRs), Toll-like receptors (TLR), and the nucleotide oligomerization domain (NOD) and leucine-rich repeat and pyrin domain-containing (NLRP) proteins.

Especially, RLRs such as RIG-I and melanoma differentiation-associated gene-5 (MDA-5) are important molecules that detect viral RNA in the cytosol. Upon recognition of viruses, particularly RNA viruses, RIG-I is activated and interact with the downstream adapter molecule, mitochondrial antiviral signaling protein (MAVS; IPS-1, VISA, Cardif). Then it activates type I interferon responses via downstream signaling molecules TBK1/IKKi and IRF3, and NF-κB activation via IKK, to elicit inflammatory responses.

Interferon- or NF-κB-mediated immune responses need to be tightly regulated to maintain host innate immune responses against virus infection. Hence, molecules involved in regulating interferon-mediated innate immune response are the subject of much research.

Here, we will discuss about novel host regulators, FAS-associated factor-1 (FAF1), Glutamyl-prolyl-tRNA synthetase (EPRS) and Histone deacetylase 6 (HDAC6), as positive regulators for innate immune responses against RNA virus infection.

[BSI-2]

Lymphocyte Microvilli are Specialized for Intra- and Intercellular Communication

Chang-Duk Jun

School of Life Sciences, Gwangju Institute of Science and Technology (GIST), Korea

A few decades ago, scientists discovered some surprising situations, in which proteins specific for one cell type were found in small quantities on the surface of other cell types[1]. Now, it is clear that this process is important in the regulation of immune responses[2–5]. This process has been referred to as 'trogocytosis' (from the Greek word *trogo*, meaning 'gnaw' or 'nibble')[3], because it is believed that the conjugated cells extract or 'tear off' the membrane patches of donor cells as cells part. To our surprise, however, the molecular mechanism of trogocytosis is unclear. In addition, nothing is evidenced whether the surface proteins are the only targets of trogocytosis. Lymphocytes are rarely smooth, but contain a variety of finger-like protrusions called microvilli[6,7]. Interestingly, we found that one T cell makes multiple contacts with antigen-presenting cells (APCs) through microvillar extensions, and then it leaves microvilli-originated membrane vesicles (MMVs), but not membrane patches, on the surface of APCs. Using GFP-tagged V-set and transmembrane domain containing 5 (VSTM5) as a specific probe for microvilli, we were able to trace the movement of microvilli in live T cells. Indeed, microvilli were observed at all stages of the T-cell activation, and were separated from the T-cell body during and after immune synapse formation. The MMVs contained crucial T-cell proteins such as TCR complex proteins, Zap70, LCK, CXCR4, and CD40L and also activated dendritic cells regardless of TCR-engagement. Collectively, these are decisive demonstration that T-cell microvilli are "immunological synaptosome" that carries T-cell messages to APCs, thereby implying that MMVs could be a vector specialized for intercellular communications.

References

1. Hudson, L., Sprent, J., Miller, J. F. & Playfair, J. H. B cell-derived immunoglobulin on activated mouse T lymphocytes. *Nature* **251,** 60−2 (1974).
2. Davis DM. Intercellular transfer of cell-surface proteins is common and can affect many stages of an immune response. 238−243 (2007).
3. Joly, E. & Hudrisier, D. What is trogocytosis and what is its purpose? *Nat. Immunol.* **4,** 815 (2003).
4. Ahmed, K. A. & Xiang, J. Mechanisms of cellular communication through intercellular protein transfer. *J. Cell. Mol. Med.* **15,** 1458−1473 (2011).
5. Gutie, C. et al. Transfer of extracellular vesicles during immune cell-cell interactions. *Immunol. Rev.* **251,** 125−142 (2013).
6. Berlin, C. et al. alpha 4 integrins mediate lymphocyte attachment and rolling under physiologic flow. *Cell* **80,** 413−22 (1995).
7. von Andrian, U. H., Hasslen, S. R., Nelson, R. D., Erlandsen, S. L. & Butcher, E. C. A central role for microvillous receptor presentation in leukocyte adhesion under flow. *Cell* **82,** 989−99 (1995).

[BSI-3]

Mesenchymal Stem/Stromal Cell-Mediated Immune Tolerance

Joo Youn Oh

Department of Ophthalmology, Seoul National University Hospital, Seoul, Korea

Mesenchymal stem/stromal cells (MSCs) are the focus of intensive efforts directed at developing cell-based therapies in immunologic disorders. However, one of the paradoxical observations made so far is that MSCs have a short window of therapeutic activity in mice but suppress immune responses that can take weeks to develop. My team has been focusing our efforts to elucidate the action and mechanisms of MSCs using models for auto- and allo-immune ocular disorders under the hypothesis that MSCs primarily affect the innate immune system that controls development of acquired immunity. Specifically, I will here present the data on how MSCs induce the immune tolerance through myeloid cell modulation.

Young Investigator

Chair: **김평현**(강원대)

10：50～11：10 Functional Energetics of Neutrophils and Macrophages
전현식(고려대)

11：10～11：30 Autophagy Primes Neutrophils for Neutrophil Extracellular Trap Formation During Sepsis
홍장원(경북대)

11：30～11：50 IL-4 Homeostasis is Regulated by Innate T Cells
이유정(포항공대)

11：50～12：10 IL-22, a Double Edged Sword in Skin Immune System
윤주한(C&C신약연구소)

12：10～12：30 Versatile Strategy for Controlling the Specificity and Activity of Engineered T Cells
김찬혁(KAIST)

[YI-1]

Functional Energetics of Neutrophils and Macrophages

Hyun Sik Jun

Laboratory of Immune Regulation, Department of Biotechnology and Bioinformatics, Korea University

Neutrophils are the most abundant key circulating leukocyte in humans and play a fundamental role in the innate immune response. Upon most inflammatory responses, neutrophils are not only the first immune cells that kill invading bacteria and fungi, but they also shape the overall immune response by signaling to dendritic cells, monocytes, and T cells. This is best exemplified by patients with neutropenia or neutrophil dysfunction, who are susceptible to bacterial and fungal infection and patients with viral infection. These diverse functions are bioenergetically expensive, requiring precise control of cellular metabolic pathways. Given that neutrophils lack significant stores of nutrients like other immune cells, their functions can only be exerted if they can uptake glucose, amino acids, and fatty acids from their microenvironment.

Inherited autosomal recessive metabolic disorders, glycogen storage disease type Ib (GSD-Ib) and severe congenital neutropenia syndrome 4 (SCN4), are caused by deficiencies of glucose-6-phosphate transporter (G6PT) and glucose-6-phosphatse-β (G6Pase-β), respectively. They manifest both neutropenia and neutrophil dysfunction of which causes include decreased glucose uptake, G6P, lactate, ATP, and NADPH, consequently resulting in impaired metabolism in neutrophils. Recently, HIF-1α and PPAR-γ, important transcriptional regulators of glucose uptake and glycolysis, have been aberrantly upregulated in neutrophils of GSD-Ib patients and treatment with a PPAR-γ antagonist was shown to be effective in recovery of neutrophil functions. Given the current paucity of effective therapeutic strategies for targeting neutrophilic inflammation and the profound consequences of impaired metabolism for key neutrophil functions, investigating the metabolic flux is of fundamental importance in neutrophils.

Our research focuses are to i) identify key metabolic factors in innate immune cells including neutrophils, macrophages, and dendritic cells in terms of their essential functions, ii) dissect interactions among innate immune cells, adaptive immune cells, and nonimmune cells, and iii) develop effective therapies for patients manifesting neutropenia and neutrophil dysfunction.

[YI-2]

Autophagy Primes Neutrophils for Neutrophil Extracellular Trap Formation During Sepsis

Chang-Won Hong

Department of Physiology School of Medicine Kyungpook National University

Neutrophils are key effectors in the host's immune response to sepsis. Excessive stimulation or dysregulated neutrophil functions are thought to be responsible for sepsis pathogenesis. However, the mechanisms regulating functional plasticity of neutrophils during sepsis have not been fully determined. We investigated the role of autophagy in neutrophil functions during sepsis in patients with community-acquired pneumonia. Neutrophils were isolated from septic patients, and stimulated with phorbol 12-myristate 13-acetate (PMA). The levels of reactive oxygen species (ROS) generation, neutrophil extracellular trap (NET) formation, and granule release, and the autophagic status were evaluated. The effect of neutrophil autophagy augmentation was further evaluated in a mouse model of sepsis. Neutrophils isolated from patients who survived sepsis showed an increase in autophagy induction, and were primed for NET formation in response to subsequent PMA stimulation. In contrast, neutrophils isolated from patients who did not survive sepsis showed dysregulated autophagy and a decreased response to PMA stimulation. The induction of autophagy primed healthy neutrophils for NETs formation and vice versa. In a mouse model of sepsis, the augmentation of autophagy improved survival via a NET-dependent mechanism. These results indicate that neutrophil autophagy primes neutrophils for increased NET formation, which is important for proper neutrophil effector functions during sepsis. Our study provides important insights into the role of autophagy in neutrophils during sepsis.

Keywords: Neutrophil, Autophagy, Sepsis, Neutrophil extracellular trap

[YI-3]

IL4 Homeostasis Is Regulated by Innate T Cells

You Jeong Lee

Division of Integrative Bioscience and Biotechnology Pohang University of Science and Technology

Helper T cell balance is important in shaping a proper immune repertoire against intracellular or extracellular antigens. B6 and BALB/c mice are representative Th1 and Th2-dominant strains, and they are very distinct in their immunological nature. Compared to B6 mice, BALB/c mice have more than a 100-fold higher serum IgE levels but are less efficient in developing Th1 responses. As a Th2 response requires IL4 for its initiation, we tracked the cells providing IL4 at the steady state and identified iNKT cells as a source of IL4 in BALB/c mice. Through intracellular staining for transcription factors, we have defined three subsets of iNKT cells (NKT1, NKT2 and NKT17) that produced IFN γ , IL4 and IL17 respectively. NKT2 cells were particularly enriched in BALB/c mice and were localized thymic medulla and T cell zone of spleen and lymph node. Comprehensive genetic analysis revealed NKT subsets share more genetic signatures with those of $\gamma\delta$ T and innate lymphoid cells (ILCs) rather than conventional helper T cells. Collectively these results suggest innate lineage T cell, including iNKT and $\gamma\delta$ T cells do pivotal roles regulating IL4 homeostasis.

[YI-4]

IL-22, a Double Edged Sword in Skin Immune System

Juhan Yoon*, Juan Manuel Leyva-Castillo, Nidhi Malhotra, Raif Geha

*Division of Immunology, Children's Hospital and Department of Pediatrics, Harvard Medical School, Boston, MA 02115. *C&C Research Laboratories, DRC, SKKU, Gyeonggi-do, Korea*

IL-22 is a member of the IL-10 family of cytokines produced by several type of immune cells, including Th17, Th22, γδ T cells and type 3 innate lymphoid cells. It signals through the IL-22 receptor, which is highly expressed on epithelial cells, including keratinocytes, suggesting an important role for IL-22 signaling in promoting healthy skin barrier. Additionally, *Il22* mRNA expression, and T cells that produce IL-22, but not IL-17, are significantly increased in the skin lesions of patients with AD. Furthermore, serum IL-22 levels are elevated in AD patients. It suggests that IL-22 may be involved in the pathogenesis of AD. However, the exact role of IL-22 in the skin is not well understood. We here provide a protective role of IL-22 in limiting the growth of S aureus in mechanically injured skin of mice. Mechanical injury induces IL-22 expression in the skin. This is dependent on IL-23 and γδ T cells. IL-22 is important for the expression of AMPs and neutrophil-attracting chemokines, neutrophil recruitment, and containment of S aureus infection in mechanically injured skin. On the other hand, we also demonstrated that antigen application to mouse skin subjected to tape stripping, a surrogate for skin scratching, induces an IL-22 response that is essential for skin inflammation including epidermal thickening and keratinocyte proliferation in the allergen sensitized skin, as both were absent in Il22−/− mice. Furthermore, we describe for the first time a novel pathway in which endogenous TLR4 ligands released upon mechanical skin injury trigger keratinocyte production of IL-23, which targets the IL-23R expressing subpopulation of skin DCs to up-regulate their endogenous IL-23 production and drive IL-22 production by naive CD4+ T cells. Similarly, IL-23 was released in human skin upon scratching and polarized human skin DCs to drive IL-22 production by T cells. Our findings suggest the utility of the ongoing trials of IL-23 and IL-22 blockade in AD. Altogether, our results indicate that IL-22 has both beneficial and detrimental effects on the limiting of bacterial infection and inflammation in the skin, respectively.

[YI-5]

Versatile Strategy for Controlling the Specificity and Activity of Engineered T Cells

Chan Hyuk Kim

Department of Biological Sciences, KAIST, Daejeon, Korea

Cancer immunotherapy has been drawing growing attention as a novel promising therapeutic modality for cancer. Unlike conventional chemo- or radiotherapy, immunotherapy treats cancer by unleashing the suppressed activity of the patient's own immune system and harnessing its power to fight cancer, to achieve robust anti-tumor responses while minimizing collateral damages to normal tissues. Among several immunotherapeutic approaches, second generation CD19-targeting chimeric antigen receptor (CAR) T cells engineered with costimulatory signaling domains have generated unprecedented anti-leukemic responses in patients with refractory B-cell leukemia. In light of their clinical promise, there has been an explosion of interest in CAR-T cells for cancer immunotherapy, especially for the treatment of relapsed, refractory malignancies. However, the inability to control the activity of this potent "live" drug has resulted in severe treatment related toxicities and the constraint in targeting more than one antigen have limited its general application. In this talk, I will discuss our recent research efforts focusing on addressing these limitations of current CAR-T therapy.

Block Symposium II

Clinical and Experimental Immunology: Immuno-Pathogenesis of Human Diseases

Chair: **최인홍**(연세의대)

16：00～16：25	Innate Cytokines in Nasal Allergic Diseases **김대우**(서울의대)
16：25～16：50	Severe Asthma ; Unmet Need in Chronic Airway Allergic Inflammatory Diseases **조유숙**(울산의대 아산병원)
16：50～17：15	Pathogenesis of Inflammatory Bowel Diseases: An Aberrant Interplay Between Host and Microbes **천재희**(연세의대)
17：15～17：40	Current Issues in Lymphoma and its Evolving Therapeutic Strategies **조석구**(가톨릭의대)

[BSII-1]

Innate Cytokines in Nasal Allergic Diseases

Dae Woo Kim

Boramae Medical Center, Seoul National University

Nasal allergic diseases such as allergic rhinitis and chronic rhinosinusitis can be understood as a dysfunctional host-environment interaction at the nasal and sinus mucosa. Bacterial and viral infections, fungal extracts, and protease allergens have potential roles in upper airway inflammation as external stimuli. The epithelial barrier is the first line of defense; its breakdown can play a significant role in allowing external stimuli to enter nasal tissue and provoke immune responses. Functional and mechanical defects have been reported in upper airway inflammation. Protease activated receptor (PAR) contributes to the production of cytokines and chemokines from the epithelium in response to external stimuli such as bacteria, fungi, and allergens. Epithelial barrier destroyed by protease activities enables allergens to pass physical epithelial barriers, culminating in allergen sensitization. It also signals epithelial cells to secrete innate cytokines, then, facilitates the inducing of eosinophilic inflammation. Epithelial-derived innate cytokines such as IL-25, IL-33, and TSLP may also participate in the evolution of chronic rhinosinusitis with nasal polyps (NP) as well as allergic rhinitis. IL-33 is secreted by immune cells such as macrophages and dendritic cells as well as epithelial cells. Full-length IL-33 is extracellularly released when epithelial cells undergo necrosis and necroptosis via tissue damage caused by external stimuli. Biologically active full-length IL-33 plays a role in mucosal inflammation recruiting neutrophils via chemokines including CXCL-1 and CXCL-2. Of interest, another research suggested a potential role of IL-33 in eosinophilic inflammation by demonstrating a splice variant of IL-33 missing exons 3 and 4, which localizes to the cytoplasm of epithelial cells, is actively released and strongly related to Th2 inflammation whereas full length is not. Several studies sought to investigate the expression and role of IL-33 in chronic rhinosinusitis (CRS). There have been conflicting results on the expression of IL-33 in CRS. Authors recently demonstrated IL-33 was upregulated in other CRS tissues and correlated with Th1/Th17 cytokines. IL-33 may contribute to inducing different types of inflammation under various microenvironments. IL-17E, also known as IL-25 is released by Th2 cells, mast cells, eosinophils as well as epithelial cells. It is produced and stored in the cytoplasm of the epithelial cells as results of external stimuli including allergen proteases. IL-25 transcript levels are reported to increase in CRS tissues including NP and correlated with disease severity and blood eosinophilia, whereas one earlier study reported that IL-25 and GATA-3 transcripts were decreased in NP versus control tissues. Additionally, IL-17RB(+) polyp-derived Th2 cells were identified in NP, which co-expressed ST-2 and enhanced IL-5 and IL-13 production in response to IL-25 and IL-33. Protein levels of IL-25 were up-regulated in non-eosinophilic NP as well as eosinophilic NP. Of note, the fact that IL-25, known as a cytokine involved in diverse Th2-mediated diseases, is also correlated with inflammatory mediators involved in Th1 and Th17 responses in Asian subjects suggests that it may play diverse roles in polypogenesis besides promoting Th2 inflammation. Blockade of IL-25 reduced the burden of NP in a mouse model of NP and represented a potential novel therapeutic target. TSLP is well known to be induced in airway epithelial cells by viruses, TLR3 agonists, protease, and pro-inflammatory cytokines. IL-1 β and TNF-α regulate TSLP transcript expression in an NF-κB-dependent manner. Several researchers demonstrated that TSLP mRNA was overexpressed in eosinophilic NP and associated with Th2 inflammation. TSLP induces the differentiation of naïve T cells into effector Th2 cells via enhancement of

OX40L-OX40 axis on the interaction between dendritic cells and CD4 T cells. TSLP protein is post-translationally modified by endogenous protease. The cleaved TSLP shows higher activity, producing IL-5 when stimulated with IL-1 β, than the full-length form. Of interest, authors recently demonstrated that TSLP production was induced by periostin in epithelial cells under Th2 high inflammatory condition like eosinophilic NP. Until now, TSLP has been consistently reported to have a pathological role in eosinophilic NP unlike IL-25 and IL-33.

Epithelial-derived cytokines such as IL-25, IL-33, and TSLP exert effects on type 2 innate lymphoid cells (ILC2s). Innate lymphoid cells (ILCs) are lymphocyte-like cells but lack markers of mature lymphocytes and do not express allergen-specific T cell receptors. ILC2s are regarded as innate counterparts of Th2 cells because both share the same functional module on the basis of their mutual production of signature cytokines such as IL-5 and IL-13. Interestingly, IL-33- and IL-25-activated ILC2s can induce eosinophilic airway inflammation accompanied by airway hyper-responsiveness even in recombination-activating gene (Rag) knockout mice, which means ILC2s function independent of acquired immunity. ILC2s are abundant and also have a close relationship with higher tissue and blood eosinophilia in NP, clinically related to worsening nasal symptom scores and asthma comorbidity. A recent study reported that there was spatial co-localization between ILC2s and eosinophils in NP. A co-culture of eosinophils and ILC2s augmented the activation of eosinophils and prolonged their survival, and in return, pre-activated eosinophils enhanced IL-5 production of ILC2s in an IL-4 dependent manner. Of note, ILC2s have a functional plasticity responsive to environmental cues including viral infection. Mouse ILC2s in the lung undergo T-bet-mediated plasticity in response to infection including influenza virus, respiratory syncytial virus, *Haemophilus influenza*, and *Staphylococcal aureus*. Human ILC2s can be converted into ILC1s by IL-12 and reversed by IL-4, or into IFN-γ / IL-13 dual-producing ILC1s in response to both IL-1β and IL-12. T cells that are able to produce both IFN-γ and IL-13 induce enhanced airway hyper-responsiveness compared to conventional Th2 cells. Thus, ILC2 plasticity may contribute to disease heterogeneity which might lead to recalcitrancy and exacerbations of inflammatory diseases.

Epithelial cell-derived innate cytokines including TSLP exert major effects on Th2 inflammation. However, there has been no study regarding its effect on nasal allergic diseases, although one previous study investigated the inhibitory effects of anti-TSLP on allergen-induce asthmatic response. The therapeutic roles of anti-IL-25 and anti-IL-33 remain unclear and need further investigation. Therefore targeting epithelial derived innate cytokines can be promising because it may control upstream mediators that T cell subsets don't act on.

[BSII-2]

Severe Asthma; Unmet Need in Chronic Airway Inflammatory Diseases

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Asthma is an airway allergic inflammatory disease that typically shows eosinophilic airway inflammation. The development of asthmatic airway inflammation is critically linked to various cytokines such as IL-4, IL-5, IL-9, and IL-13 mainly secreted from Th2 cells and ILC2. IL-33, IL-25, and TSLP from bronchial epithelial cells are also closely associated with the asthmatic airway inflammation. Although asthma is a heterogeneous clinical syndrome and the exact pathogenesis has not been clearly defined, in general, eosinophilic inflammation itself can be controlled by corticosteroid. In fact, 90-95% of the asthmatics have been effectively treated by using inhaled corticosteroid (ICS) in clinical practice.

However, 5-10% of asthmatic patients, who cannot be controlled by using ICS and other currently available anti-asthmatic medications, are considered severe asthma and those severe asthmatics become a big burden. The severe asthma patients are suffering from not only uncontrolled asthma symptoms but also serious adverse reactions from long-term use of systemic corticosteroids. Therefore, severe asthma is an important medical unmet need among chronic airway inflammatory diseases and new therapeutic strategies are urgently needed. There is also a heterogeneity in severe refractory asthma. In terms of features of airway inflammation, both eosinophilic inflammation and neutrophilic inflammation exist. Although vigorous researches have been carried out so far, the precise causes of severe refractory asthma have not been clearly elucidated. Interestingly, the reason why the eosinophilic inflammation in the airways of severe asthmatic patients is steroid insensitive or resistant is unclear. Furthermore, neutrophilic inflammation in severe asthma has not even clearly characterized.

Several novel biologics targeting eosinophilic airway inflammation by blocking various Th2 cytokines are just about to be launched in clinical practice. It is expected that corticosteroid insensitive eosinophilic inflammation may be controlled from those novel biologics. However, at this moment, there is no new drug available for neutrophilic inflammation of severe asthma.

In conclusion, severe asthma is serious medical unmet need and the studies to investigate underlying mechanism of development of steroid resistant eosiophilic inflammation and the neutrophilic inflammation are definitely needed.

Keywords: Severe asthma, Steroid resistance, Eosinophil, Neutrophil, Allergic inflammation

[BSII-3]

Pathogenesis of Inflammatory Bowel Diseases: an Aberrant Interplay Between Host and Microbes

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Ulcerative colitis (UC) and Crohn's disease (CD) are the two major clinical phenotypes of inflammatory bowel diseases (IBDs), which are chronic relapsing inflammatory disorders of the gastrointestinal tract. Though the exact pathogenesis remains unknown, IBD is thought to arise from a dysregulated mucosal immune response to enteric microflora or environmental factors in genetically susceptible individuals. Clinical characteristics, epidemiologic and genetic evidence have implied that IBD is a related polygenic disease. The gastrointestinal tract in which this disease occurs is central to the immune system, and the innate and the adaptive immune systems are balanced in complex interactions with intestinal microbes under homeostatic conditions. However, in IBD, this homeostasis is disrupted and uncontrolled intestinal inflammation is perpetuated. The disturbance of the immune system and/or imbalanced interactions with microbes leads to development of chronic intestinal inflammation when certain environmental factors trigger genetically susceptible hosts. Recently, the pathogenesis of IBD has become better understood owing to advances in genetic and immunologic technology. Traditionally, Th1 cells have been thought to play an important role in pathogenesis related to the chronicity of intestinal inflammation, especially in CD, whereas Th2 cells have been thought to play an important role in UC. Recently, however, activation of Th17 cells and imbalance of Th17/regulatory T (Treg) cells are recognized to be an important component in the development of intestinal inflammation. Moreover, new therapeutic strategies are now being implemented that accurately target the pathogenesis of IBD. Future novel biologics should overcome the limitations of current therapies and ensure that individual patients can be treated with optimal drugs that are safe and precisely target IBD.

[BSII-4]

Current Issues in Lymphoma and its Evolving Therapeutic Strategies

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Based on 2010 report of Korea Central Cancer Registry, 4,183 people in the Korea were newly diagnosed as Hodgkin's or non-Hodgkin's lymphoma, and 1,505 deaths from the disease and 22,447 as having lymphoma were reported. The treatment of patients with non-Hodgkin lymphoma has essentially remained the same for more than three decades, with the exception of the inclusion of monoclonal anti-CD20 agents in combination strategies. Front-line regimens continue to be predominantly based on cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), or on variations of this regimen. Salvage regimens are predominantly platinum-based regimens, such as DHAP (dexamethasone, high-dose cytarabine, and cisplatin) or ICE (ifosfamide, carboplatin, and etoposide). Similarly, the treatment of Hodgkin lymphoma continues to be based on ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine), a regimen that was introduced in the 1970s. Over the several decades, the pathological classification of lymphoma has substantially improved. The WHO currently classifies lymphoma into about 40-50 distinctive subtypes. While this classification improved the accuracy and consistency of the histological diagnosis of lymphoma, it had little impact on advancing new drug development or improving the cure rate of this disease. However, modern advances in lymphoma biology and genomics have revealed these histopathological subtypes to be heterogeneous and produced a large amount of knowledge regarding the molecular pathogenesis of lymphoma. New target agents include several categories such as 1) targeted monoclonal antibodies with unconjugated antibodies for B- and T/NK-lineage antigens, 2) TNF receptor superfamily members, 3) antibody–drug conjugates, 4) molecules targeting oncogenic pathways of PI3K/Akt/mTOR pathway, 5) proteasome inhibition, 6) histone deacetylases, 7) Immunomodulatory drugs, 8) targeting BCR signaling, 9) targeting apoptosis machinery, and 10) JAK and STAT pathway. Several drugs have showed excellent clinical outcomes in phase I/II/III studies for patients with relapsed or refractory lymphoma and been continued to randomized clinical trials. However, some drugs showed lack efficacy or unacceptable toxic effects because the poor clinical outcomes and variability observed in clinical responses likely result from underlying molecular heterogeneity. In the era of personalized medicine, the challenge for the treatment of patients with lymphoma will involve correctly matching a molecularly targeted therapy to the unique genetic and molecular composition of each individual lymphoma. In the future, emerging biomarkers will be able to guide treatment decisions for patients with lymphoma, and explore the potential challenges and strategies for making biomarker-driven personalized medicine a reality in the cure and management of this disease.

Oral Presentation

Chair: **이종길**(충북약대)

Functional Restoration of HCV-Specific T Cells after Antiviral Treatment in Patients with Chronic Hepatitis C
한지원(카이스트)

Mesenchymal Stem Cell-Derived Exosomes Induce T Cell-Cycle Arrest and Inhibit Th17 Differentiation by Destabilizing ROR γ t via Inhibition of Ubiquitin Ligase Activity of CBP/p300 by Eid3
이선호(서울대)

Platelet-Activating Factor Mediates Endotoxin Tolerance by Regulating Indoleamine 2,3-dioxygenase-dependent Expression of the Suppressor of Cytokine Signaling 3
노경태(국군의학연구소)

Protein Tyrosine Phosphatase Conjugated with a Novel Transdermal Delivery Peptide, AP-rPTP Alleviates Both Atopic Dermatitis- and Psoriasis-Like Inflammatory Skin Disease
김원주(한양대)

A Selective Jak1 Inhibitor, Filgotinib (GLPG0634) Suppresses Lymphocytic Infiltration in the Salivary Gland of Non Obese Diabetic Mice via Suppression of BAFF and IP10 Production of Salivary Gland Epithelial Cells
이재선(가톨릭대)

[OP 1]

P-047 Functional Restoration of HCV-Specific T Cells after Antiviral Treatment in Patients with Chronic Hepatitis C

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With the recent introduction of direct acting antivirals (DAAs), which inhibit viral replication and infection through blocking nonstructural proteins, more than 90% of patients with chronic HCV infection were able to achieve SVR with less adverse events than interferon-based regimens; Nevertheless, there is a possibility that small amount of HCV RNA in the liver and circulation, risk of relapse, and risk of reinfection still remain in patients with SVR after DAA treatment; However, it remains unclear whether functionally exhausted HCV-specific T cells can be restored after complete viral clearance and its association with clinical outcomes. In this study, we try to identify the functional restoration of HCV-specific CD8+ T cells, which directly kills HCV-infected cells after DAA treatment with time. By using ELISpot with overlapping peptides corresponding non-structural proteins of HCV, which are relatively well conserved than other HCV proteins, we found that early, transient restoration of CD8+ dominant, HCV-specific IFN-γ responses. Restored CD8+ T cells also showed polyfunctionality, which expressed TNF-α and CD107a simultaneously after HCV-peptide stimulation. In addition, in line with previous study, proliferative capacity of HCV-specific CD8+ T cells also tended to be improved after DAA treatment, especially at 12 weeks of treatment. HCV-specific T cell exhaustion, represented by PD-1 expression, had a tendency to be improved and maintained after DAA treatment also at the early timepoint, but terminally differentiated phenotype of HCV-specific T cells was maintained constantly. Thus, it is necessary to find out a particular mechanism to explain the transient restoration of HCV-specific CD8+ T cell responses although T cell exhaustion seems to be improved.

Keywords: Chronic hepatitis C, Direct acting antiviral, HCV-specific T cell, T cell restoration

[OP 2]

P-031 Mesenchymal Stem Cell-Derived Exosomes Induce T Cell-Cycle Arrest and Inhibit Th17 Differentiation by Destabilizing RORγt via Inhibition of Ubiquitin Ligase Activity of CBP/p300 by Eid3

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Mesenchymal stem cells (MSCs) have been shown to alleviate inflammation and autoimmune diseases. However, the underlying mechanisms are not yet fully understood. In this study, MSC-derived exosomes (MSC-exo) were tested for their immunosuppressive effects. The MSC- exo exhibited potent suppressive effects on T cell proliferation and differentiation. MSC-exo induce T cell cycle arrest and reduced the level of ROR γ t in Th17 differentiation condition. To further examine the effect of MSC-exo *in vivo*, experimental autoimmune encephalomyelitis (EAE) was induced in mice, and each group was given with MSC-exo or exosome-depleted culture supernatant. The development of EAE was alleviated and the expression of ROR γ t and IL-17A were notably suppressed by MSC-exo. Furthermore, Eid3 was founded in MSC-exo which have known as inhibitor of CBP/p300 ubiquitin ligase. MSC-exo indeed destabilized ROR γ t by suppressing CBP/P300 mediated K63-linked polyubiquitination of ROR γ t. Thus, we propose Immunomodulatory mechanism of MSC-exo, specifically inducing cell-cycle arrest and abrogating stability of ROR γ t.

Keywords: Mesenchymal stem cell, Exosome, Th17 cell, EAE, Immunomodulation

[OP 3]

P-059 Platelet-Activating Factor Mediates Endotoxin Tolerance by Regulating Indoleamine 2,3-dioxygenase-dependent Expression of the Suppressor of Cytokine Signaling 3

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Indoleamine 2,3-dioxygenase (IDO) mediates immune tolerance, and suppressor of cytokine signaling 3 (SOCS3) negatively regulates the JAK/STAT signal transduction pathway. We determined previously that platelet-activating factor (PAF) protects mice against LPS-induced endotoxic shock, but its detailed mechanism of action was unknown. We performed survival experiments in $IDO^{+/+}$ and $IDO^{-/-}$ mice using an LPS- induced endotoxemia model and rated organ injury (neutrophil infiltration and liver function). Using ELISA and Western blotting, we also investigated the mechanism of PAF-mediated endotoxin tolerance during endotoxemia. PAF-mediated endotoxin tolerance was dependent on IDO *in vivo* and *in vitro* and was not observed in $IDO^{-/-}$ mice. JAK/STAT signaling, crucial for SOCS3 expression, was also impaired in the absence of IDO. In an IDO- and STAT-dependent manner, PAF mediated a decrease in IL-12 and a dramatic increase in IL-10 and reduced mouse mortality. In addition, PAF attenuated LPS-mediated neutrophil infiltration into the lungs and interactions between neutrophil-like (THP-1) and endothelial cells (human umbilical vein endothelial cells). These results indicate that PAF-mediated endotoxin tolerance is initiated via IDO- and JAK/STAT- dependent expression of SOCS3. Our study has revealed a novel tolerogenic mechanism of IDO action and an important association between IDO and SOCS3 with respect to endotoxin tolerance.

Keywords: Platelet-activating factor, Endotoxin tolerance, Indoleamine 2, 3-dioxygenase, Suppressor of cytokine signaling 3, Endotoxemia

[OP 4]

P-007 Protein Tyrosine Phosphatase Conjugated with a Novel Transdermal Delivery Peptide, AP-rPTP Alleviates Both Atopic Dermatitis- and Psoriasis-Like Inflammatory Skin Disease

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Atopic dermatitis (AD) and psoriasis are the two most common chronic inflammatory skin diseases. There is an unmet medical need to overcome limitations for transcutaneous drug development posed by the skin barrier. We aimed to identify a novel transdermal delivery peptide and to develop a transcutaneously applicable immunomodulatory protein for treating AD and psoriasis. We identified and generated reporter proteins conjugated to AP, a novel transdermal delivery peptide of human origin, and analyzed the intracellular delivery efficiency of these proteins in mouse and human skin cells and tissues using multi-photon confocal microscopy. We also generated a recombinant therapeutic protein, AP-rPTP, consisting of the phosphatase domain of T cell protein tyrosine phosphatase (TC-PTP) conjugated to AP. The immunomodulatory function of AP-rPTP was confirmed in splenocytes upon cytokine stimulation and TcR stimulation. Finally, we confirmed the *in vivo* efficacy of AP-rPTP transdermal delivery in OXA-induced contact hypersensitivity, OVA-induced atopic dermatitis-like, and imiquimod-induced psoriasis-like skin inflammation models. AP-conjugated reporter proteins exhibited significant intracellular transduction efficacy in keratinocytes, fibroblasts, and immune cells. In addition, transcutaneous administration of AP-dTomato resulted in showed significant localization into the dermis and epidermis in both mouse and human skin. AP-rPTP inhibited pSTAT1, pSTAT3, and pSTAT6 in splenocytes and regulated T cell activation and proliferation. Transcutaneous administration of AP-rPTP significantly ameliorated skin tissue thickening, inflammation, and cytokine expression in both atopic dermatitis- and psoriasis-like dermatitis models. We identified a 9-amino acid-long novel transdermal delivery peptide, AP, and demonstrated its feasibility for transcutaneous biologic drug development. Moreover, AP-rPTP is a novel immunomodulatory drug candidate for human dermatitis.

Keywords: Atopic dermatitis, Psoriasis, Transdermal delivery peptide, Protein tyrosine phosphatase, TC-PTP

[OP 5]

P-001 A Selective Jak1 Inhibitor, Filgotinib (GLPG0634) Suppresses Lymphocytic Infiltration in the Salivary Gland of Non Obese Diabetic Mice via Suppression of BAFF and IP10 Production of Salivary Gland Epithelial Cells

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Background: Interferon (IFN) signatures are upregulated in patients with primary Sjögren's syndrome(SS) and IFNs are considered to play a pathogenic role in pSS. Therefore, Janus kinase (Jak) which mediates interferon signaling pathway may be a good therapeutic target. We set out to investigate whether a selective Jak1 inhibitor, filgotinib would ameliorate disease-related parameters in non-obese diabetic (NOD) mice, an SS animal model.

Results: Five differential expressed genes(DEGs) were analysed by microarray with Illumina H-12 expression between peripheral mononuclear cells(PBMCs) from healthy controls and pSS patients enrolled Korean Initiative Sjogren's Syndrome (KISS) cohort. Of note, salivary flowrate of filgotinib-treated mice were greater than those of controls. Histologic evaluation of salivary gland revealed that the lymphocytic infiltration was markedly reduced in the mice treated with filgotinib, especially IFN-gamma producing cells and B220+ cells. Also, BAFF and IP10 were decreased in the gland from filgotinib administered mice. We identified salivary-specific functional molecule such as aquaporin-5, cytokeratin-19 and alpha amylase in 3 dimensional culture by matrigel, where showed SGEP cells induced by IFNa with filgotinib down-regulated Tfh cell differentiation by IFNa-treated SGEP cells. Filgotinib suppressed downstream pathway of IFN receptor independently of PIAS1/3 or SOCS1/3. Finally, Jak1 inhibition suppressed not only expression of aicda and xbp1 but also the production of IgG in CD19+ B cells.

Conclusion: Filgotinib suppresses SFR decrease and lymphocytic infiltration of salivary gland of NOD mice by suppressing BAFF and IP10 expression of SGEP cells. Jak1 inhibition may be a novel therapeutic approach for SS.

Keywords: Sjogren's syndrome, Type I Interferon, Jak1 inhibitor, BAFF, IP10

올해 우수 논문 초록
(2016년 1월 1일 이후 발표)

[The Journal of Clinical Investigation]

Transcription Factor NFAT5 Promotes Macrophage Survival in Rheumatoid Arthritis

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Apoptotic death of activated macrophages is important for controlling chronic inflammation and its defect in these cells has been implicated in the pathogenesis of rheumatoid arthritis (RA). However, the molecular signatures defining apoptotic resistance of RA macrophages have not been fully understood. Here, global transcriptome profiling of RA macrophages revealed that nuclear factor of activated T-cells 5 (NFAT5), an osmoprotective transcription factor, is one of the critical regulators for a wide range of pathologic processes of synovial macrophages, including cell cycle, apoptosis, and proliferation. Analysis of transcriptomes in NFAT5-deficient macrophages demonstrated the molecular networks defining cell survival and proliferation. Proinflammatory M1 polarizing stimuli and hypoxic conditions were responsible for enhanced NFAT5 expression in RA macrophages. An *in vitro* functional study demonstrated that NFAT5-deficient macrophages were more susceptible to apoptotic death. Specifically, chemokine ligand 2 (CCL2) was secreted in an NFAT5-dependent fashion and it bestowed RA macrophages apoptotic resistance *in vitro*. When recombinant CCL2 was administered into one of the affected joints of NFAT5 (+/−) mice, joint destruction as well as macrophage infiltration was significantly increased, demonstrating the essential role of NFAT5-CCL2 axis in arthritis progression *in vivo*. Moreover, NFAT5-deficient macrophages were more susceptible to apoptosis and were less efficient in promoting joint destruction than NFAT5-sufficient macrophages when injected intra-articularly. Conclusively, NFAT5 regulates macrophage survival by inducing CCL2 secretion. Our results provide the first evidence that NFAT5 expression in macrophages enhances chronic arthritis by conferring apoptotic resistance to activated macrophages.

Keywords: Nuclear Factor of Activated T-cells 5, Transcriptome, Macrophage Survival, Chemokine Ligand 2, Rheumatoid Arthritis

[Immunity]

Reconstruction of LPS Transfer Cascade Reveals Structural Determinants within LBP, CD14, and TLR4-MD2 for Efficient LPS Recognition and Transfer

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Lipopolysaccharide (LPS), the major component of the outer membrane of Gram-negative bacteria, binds Toll-like receptor 4 (TLR4)-MD2 complex and activates innate immune responses. LPS transfer to TLR4-MD2 is catalyzed by both LPS binding protein (LBP) and CD14. To define the sequential molecular interactions underlying this transfer, we reconstituted in vitro the entire LPS transfer process from LPS micelles to TLR4-MD2. Using electron microscopy and single-molecule approaches, we characterized the dynamic intermediate complexes for LPS transfer: LBP-LPS micelles, CD14-LBP-LPS micelle, and CD14-LPS-TLR4-MD2 complex. A single LBP molecule bound longitudinally to LPS micelles catalyzed multi-rounds of LPS transfer to CD14s that rapidly dissociated from LBP-LPS complex upon LPS transfer via electrostatic interactions. Subsequently, the single LPS molecule bound to CD14 was transferred to TLR4-MD2 in a TLR4-dependent manner. The definition of the structural determinants of the LPS transfer cascade to TLR4 may enable the development of targeted therapeutics for intervention in LPS-induced sepsis.

[Proc Natl Acad Sci U S A.]

A Mechanism for the Induction of Type 2 Immune Responses by a Protease Allergen in the Genital Tract

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The genital mucosa is a barrier that is constantly exposed to a variety of pathogens, allergens, and external stimuli. Although both allergen exposure and parasite infections frequently occur in the genital area, the mechanism by which immune responses – particularly type 2 immunity – are induced has rarely been studied in the genital mucosa. Here, we demonstrate the induction of T helper type 2 (Th2) immunity in the genital mucosa in response to a model allergen, the protease papain. Intravaginal papain immunization induced type 2 immunity in a manner that was dependent on protease activity and the estrous phase of the mice. In addition, IL-33 was released from the vaginal epithelia after intravaginal papain immunization, leading to the activation of type 2 innate lymphoid cells (ILC2s). Moreover, the IL-33-MyD88 signalling pathway was critical for the induction of type 2 immunity. We also found that Th2 differentiation in response to intravaginal papain treatment requires a specific DC subset that is controlled by IRF4. These findings suggest that type 2 immunity is induced by a unique mechanism in the genital tract, which is an important, but often overlooked, barrier surface.

[Nature Communications]

25-hydroxycholesterol Contributes to Cerebral Inflammation of X-linked Adrenoleukodystrophy (X-ALD) through Activation of the NLRP3 Inflammasome

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X-linked adrenoleukodystrophy (X-ALD), caused by an *ABCD1* mutation, is a progressive neurodegenerative disorder associated with the accumulation of very long-chain fatty acids (VLCFA). Cerebral inflammatory demyelination is the major feature of childhood cerebral ALD (CCALD), the most severe form of ALD, but its underlying mechanism remains poorly understood. Here, we identify the aberrant production of cholesterol 25-hydroxylase (*CH25H*) and 25-hydroxycholesterol (25-HC) in the cellular context of CCALD based on the analysis of ALD patient-derived induced pluripotent stem cells and *ex vivo* fibroblasts. Intriguingly, 25-HC, but not VLCFA, promotes robust NLRP3 inflammasome assembly and activation via potassium efflux-, mitochondrial ROS- and liver X receptor-mediated pathways. Furthermore, stereotaxic injection of 25-HC into the corpus callosum of mouse brains induces microglial recruitment, interleukin-1β production, and oligodendrocyte cell death in an NLRP3 inflammasome-dependent manner. Collectively, our results indicate that 25-HC mediates the neuroinflammation of X-ALD via activation of the NLRP3 inflammasome.

[J Allergy Clin Immunol]

Programmed Cell Death-ligand 1 Alleviates Psoriatic Inflammation by Suppressing IL-17A Production from Programmed Cell Death 1-high T Cells

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Background: Psoriasis is one of the most common chronic inflammatory diseases in the skin. Recently, IL-17-producing T cells have been shown to play a critical role in psoriatic inflammation. Programmed cell death-1 (PD-1) is a co-inhibitory receptor expressed on T cells in various chronic inflammatory diseases; however, the expression and function of PD-1 during psoriatic inflammation have not previously been characterized.

Objective: We examined PD-1 expression on IL-17A-producing T cells from Imiquimod (IMQ)-treated mice and psoriasis patients. Additionally, we investigated the therapeutic effect of recombinant programmed cell death ligand-1 (PD-L1) protein on IMQ-induced psoriatic inflammation.

Methods: PD-1 expression on IL-17A-producing $\gamma\delta$ T cells from IMQ-treated mice was examined using multi-color flow cytometric analysis. In the psoriatic skin of patients, PD-1 and IL-17A expression was analyzed using immunofluorescence. The therapeutic effect of PD-L1-Fc fusion protein (PD-L1-Fc) was assessed in IMQ-treated mice *ex vivo* and *in vivo*.

Results: During IMQ-induced psoriatic inflammation, PD-1 is overexpressed on $CD27^{-}V\gamma1^{-}$ $\gamma\delta$ T cells. Further, PD-1 expression on $IL\text{-}17A^{+}$ T cells was confirmed in psoriatic skin tissues from patients and IMQ-treated mice. In the $CD27^{-}V\gamma1^{-}$ $\gamma\delta$ T cell population, $V\gamma4^{-}$ $\gamma\delta$ T cells with $V\gamma6$ mRNA expression showed a high level of PD-1 expression. Further, these $PD\text{-}1^{hi}V\gamma4^{-}$ ($V\gamma6^{+}$) $\gamma\delta$ T cells were specialized for anti-CD3-induced IL-17A production, which was inhibited by PD-L1-Fc protein treatment. In IMQ-treated mice, PD-L1-Fc protein reduced psoriatic inflammation when given alone and enhanced the therapeutic effect of anti-p40 when given in combination.

Conclusion: PD-1 is overexpressed in IL-17A-producing T cells in both IMQ-treated mice and psoriasis patients. Moreover, recombinant PD-L1-Fc protein alleviates psoriatic inflammation in IMQ-treated mice.

[Molecular Cell]

Binding of Membrane Lipids by the SH2 Domains of ZAP70 and Lck is Essential for T Cell Receptor Signaling

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T cells are activated by antigen recognition of T cell receptors (TCRs). The TCR signaling pathway involves several cytosolic tyrosine kinases, phosphatases and adaptor molecules, many of which have Src-homology 2 (SH2) domains. SH2 domain is a prototypic protein-interaction domain that reads phosphotyrosine (pY) signals to link various tyrosine kinase substrates to downstream signaling molecules. Using biophysical approaches, we found that the majority of human SH2 domains effectively binds the plasma membrane-mimetic vesicles with submicromolar affinities. The SH2 domains have alternate cationic patches for lipid binding separate from the pY-binding pockets and simultaneously interact with pY-peptides and membrane lipids independently of each other. Among the proteins expressed in T cells, we found that the SH2 domain of Lck and C-terminal SH2 domain (cSH2) of ZAP70 strongly bind membrane lipids. Especially, ZAP70-cSH2 domain showed specificity for PI(3,4,5)P3. To investigate the physiological significance of lipid binding activities of SH2 domains of the proteins, we mutated specific residues involved in the lipid binding and reconstituted T cell lines lacking the endogenous proteins with the mutants. We found that many aspects of the TCR signaling were significantly down-regulated in the cells expressing lipid binding-defective proteins. Our data demonstrate that the direct lipid binding by SH2 domains confers exquisite modulation of ZAP70 and Lck functions and TCR signaling.

[Nature Communications]

Stepwise Phosphorylation of p65 Promotes NF-κB Activation and NK Cell Responses During Target Cell Recognition

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NF-κB is a key transcription factor that dictates the outcome of diverse immune responses. How NF-κB is regulated by multiple activating receptors that are engaged during natural killer (NK)-target cell contact remains undefined. Here we show that sole engagement of NKG2D, 2B4 or DNAM-1 is insufficient for NF-κB activation. Rather, cooperation between these receptors is required at the level of Vav1 for synergistic NF-κB activation. Vav1-dependent synergistic signalling requires a separate PI3K-Akt signal, primarily mediated by NKG2D or DNAM-1, for optimal p65 phosphorylation and NF-κB activation. Vav1 controls downstream p65 phosphorylation and NF-κB activation. Synergistic signalling is defective in X-linked lymphoproliferative disease (XLP1) NK cells entailing 2B4 dysfunction and required for p65 phosphorylation by PI3K-Akt signal, suggesting stepwise signalling checkpoint for NF-κB activation. Thus, our study provides a framework explaining how signals from different activating receptors are coordinated to determine specificity and magnitude of NF-κB activation and NK cell responses.

[Nature Communications]

YY1 Inhibits Differentiation and Function of Treg Cells by Blocking Foxp3 Expression and Activity

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Regulatory T (Treg) cells are essential for maintenance of immune homeostasis. Foxp3 is the key transcription factor for Treg-cell differentiation and function; however, molecular mechanisms for its negative regulation are poorly understood. Here we show that YY1 expression is lower in Treg cells than Tconv cells, and its overexpression causes a marked reduction of Foxp3 expression and abrogation of suppressive function of Treg cells. YY1 inhibits Smad3/4 binding to and chromatin remodeling of the Foxp3 locus. In addition, YY1 interrupts Foxp3-dependent target gene expression by physically interacting with Foxp3 and by directly binding to the Foxp3 target genes. Thus, YY1 inhibits differentiation and function of Treg cells by blocking Foxp3.

Keywords: Treg, Foxp3, YY1

Poster Presentation

P-001 A Selective Jak1 Inhibitor, Filgotinib (GLPG0634) Suppresses Lymphocytic Infiltration in the Salivary Gland of Non Obese Diabetic Mice via Suppression of BAFF and IP10 Production of Salivary Gland Epithelial Cells

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Background: Interferon (IFN) signatures are upregulated in patients with primary Sjögren's syndrome(SS) and IFNs are considered to play a pathogenic role in pSS. Therefore, Janus kinase (Jak) which mediates interferon signaling pathway may be a good therapeutic target. We set out to investigate whether a selective Jak1 inhibitor, filgotinib would ameliorate disease-related parameters in non-obese diabetic (NOD) mice, an SS animal model.
Results: Five differential expressed genes(DEGs) were analysed by microarray with Illumina H-12 expression between peripheral mononuclear cells(PBMCs) from healthy controls and pSS patients enrolled Korean Initiative Sjogren's Syndrome (KISS) cohort. Of note, salivary flowrate of filgotinib-treated mice were greater than those of controls. Histologic evaluation of salivary gland revealed that the lymphocytic infiltration was markedly reduced in the mice treated with filgotinib, especially IFN-gamma producing cells and B220+ cells. Also, BAFF and IP10 were decreased in the gland from filgotinib administered mice. We identified salivary-specific functional molecule such as aquaporin-5, cytokeratin-19 and alpha amylase in 3 dimensional culture by matrigel, where showed SGEP cells induced by IFNa with filgotinib down-regulated Tfh cell differentiation by IFNa-treated SGEP cells. Filgotinib suppressed downstream pathway of IFN receptor independently of PIAS1/3 or SOCS1/3. Finally, Jak1 inhibition suppressed not only expression of aicda and xbp1 but also the production of IgG in CD19+ B cells.
Conclusion: Filgotinib suppresses SFR decrease and lymphocytic infiltration of salivary gland of NOD mice by suppressing BAFF and IP10 expression of SGEP cells. Jak1 inhibition may be a novel therapeutic approach for SS.

Keywords: Sjogren's syndrome, Type I Interferon, Jak1 inhibitor, BAFF, IP10

P-002 Aberrant Expression of Interleukin-10 and Activation-induced Cytidine Deaminase in B Cells from Patients within Behçet's Disease

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Despite extensive studies, the pathogenesis of Behçet's disease (BD) is still not clear. In particular, B cells in patients with BD have not been elucidated. Activation-induced cytidine deaminase (AID) is a critical enzyme for immunoglobulin (Ig) heavy chain class switching and somatic hypermutation in B cells, and abnormal expression of AID in various immune conditions has been intensively studied. B10 cells, an interleukin (IL)-10-secreting subset of regulatory B cells, function to downregulate inflammation and autoimmunity. Thus, in this study, we investigated the relevance of B cells in patients with BD. We measured the plasma levels of IL-10 and IgA and the proportion of $CD43^+$ B cells, excluding naïve B cells, in patients with BD and healthy controls (HCs). *IL-10* and *AID* mRNA levels were assessed in B cells from fresh peripheral blood of 16 patients with BD and 16 age- and sex-matched HCs. Plasma levels of IL-10 in patients with BD did not differ from those in HCs. Similarly, there were no significant differences in plasma levels of IgA, although a slight increase was observed in patients with BD compared with that in HCs. There were no differences in $CD43^+CD19^+$ B cell numbers between patients with BD and HCs. However, *IL-10* mRNA levels were significantly reduced, whereas *AID* mRNA levels were dramatically increased in B cells from patients with BD compared with HCs. Collectively, our results provide insights into the role of B cells in patients with BD.

Keywords: Behçet's disease, B cells, Activation-induced cytidine deaminase, Interleukin-10, CD43

P-003 Amelioration of Allergic Airway Inflammation by Fatty Acids of Sea Cucumber

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Fatty acids are common components in nature and its various biological effects such as regulation of intracellular pathway, transcriptional factor activity and gene expression are already known. Sea cucumber, known as "sea ginseng", contains more than 50 kinds of nutrients including amino acids, essential or polyunsaturated fatty acids, vitamins and trace elements etc., and active substances. In previous study, we determined anti-asthmatic effects of sea cucumber total extracts via increase of regulatory T cells. In this study, we separated sea cucumber total extracts to 4 phases and confirmed high levels of IL-10 in splenocyte treated with n-hexane phase, which contains a lot of fatty acids. To evaluate their anti-asthma effects, we induced allergic airway inflammation in mice after 7 oral administrations of n-hexane phase. The hyper-responsiveness value in mice with ovalbumin (OVA)-alum-induced asthma after oral injection of n-hexane phase group was significantly lower than that in the OVA-alum-induced asthma group. In addition, the number of eosinophils in the lungs of asthma-induced mice pre-treated with n-hexane phase significantly decreased compared to that in PBS pre-treated mice. Also, inflammation scores and percentage of PAS-positive cells of n-hexane phase administrated group were significantly decreased compared to PBS administrated group. These results suggest that two facts. First, sea cucumber extract can ameliorate allergic airway inflammation. And second, fatty acids are major components in this anti-asthmatic response raised by sea cucumber extracts.

Keywords: Fatty acids, Sea cucumber, Asthma, Anti-asthma, Allergic airway inflammation

P-004 Effect on Protease Allergen Induced Ocular Allergic Reaction in vitro of Three New Antihistamine Agents

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Recently, ocular allergy patient by fine dust are increasing and because of this reason, many new antihistamine agents are introduced. The cornea of a person wearing contact lenses can be induced ocular irritation and can be obtained foreign body sensation. To evaluate the effects of new introduced four antihistamine agents (Alcaftadine, Bepotastine-besilate and Olopatadine), we checked biological effects of the antihistamine agents to human corneal epithelial cell (HCEC) and conjunctival epithelial cells (HConEC) *in vitro*. After induction of allergic inflammation using *Aspergillus* protease, known as common allergen from various substances, on human corneal epithelial cells and human conjunctival epithelial cells, 3 antihistamine agents were treated. After treatment, the cells were evaluated cytotoxicity, cell migration, micro-morphological changing with scanning electron microscopy (SEM) and transmission electron microscopy (TEM). The cytokines and chemokines levels (IL-5, IL-25, Eotaxin, TARC and TSLP) were measured by qPCR (quantitative PCR). As a results, the cytotoxicity was found less in alcaftadine than in bepotastine-besilate and olopatadine. Olopatadine and Bepotastine-besilate treated cells could be found more vacuoles, plasma membrane damage, cytoplasmic and nuclear degeneration than those of alcaftadine. Cell migration were significantly exhibited by alcaftadine than those of bepotastine-besilate and olopatadine in HCEC after 18hrs administration. The all cytokines and chemokines levels was lower in alcaftadine administration group after allergy-induced HConEC than those of other group. These results suggested that alcaftadine might be the most appropriated antihistamine agent.

Keywords: Antihistamine agent, Corneal cytotoxicity, Conjunctival allergy

P-005 Extracellular Vesicles in Adipose Stem Cells Alter Gene Expression in a Murine Model of Allergic Airway Inflammation

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In a previous study, we demonstrated that intravenous administration of extracellular vesicles (EV) in adipose stem cells could significantly reduce allergic symptoms and suppress eosinophilic inflammation. In an ovalbumin-induced mouse model, we applied microarray gene expression analysis after extracellular vesicles in adipose tissue stem cells intravenous administration. The Affymetrix Whole transcript Expression array process was executed. In total, 868 genes were differentially expressed by more than a 1.5-fold change in EV-administrated groups compared with the ovalbumin-induced mouse model. Gene-Enrichment and Functional Annotation analysis for significant probe list was performed using Gene Ontology (GO). GO categories enrichment analysis of 868 differentially expressed genes in accordance with biological process; molecular function; and cellular component. GO analysis showed that these differential genes were mostly involved in immune system process, regulation of immune system process, antigen binding and catalytic activity. Our observations suggest that an altered gene expression might be involved in the amelioration of allergic airway inflammation.

Keywords: Extracellular Vesicles, Adipose Stem Cells, Allergic Airway Inflammation

P-006 Identification of Functional Epitopes for Anti-Aquaporin 5 Autoantibodies in Control Individuals and Patients with Sjogren's Syndrome

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Recently, we reported the presence of anti-aquaporin 5 (AQP5) IgG in patients with primary Sjogren's syndrome (SS) with a sensitivity of 0.73 and specificity of 0.68. The aim of this study was to identify functional epitopes for the anti-AQP5 autoantibodies detected in control subjects and SS patients. Recognition of epitopes by anti-AQP5 autoantibodies was evaluated by indirect immunofluorescence (IIF) assay performed in the presence or absence of peptides corresponding to the second transmembrane helix and extracellular loops A, C and E of AQP5. Functional epitopes were determined by measuring the effects of purified IgG and neutralizing peptides on the transepithelial osmotic permeability (P_f[1]) of MDCK cells expressing AQP5. In the IIF assay, 26 out of 27 SS samples were inhibited by at least one peptide, while only 7 out of 14 control samples were inhibited by any peptide. Overall, SS samples were inhibited by peptides corresponding to A, C, and E by approximately 40 to 50%, whereas control samples were inhibited only by peptides corresponding to E by less than 20%. A cyclized peptide mimicking E (E1) was most frequently recognized and best differentiated between SS and control samples. Incubation of MDCK-AQP5 cells with SS-, but not with control-IgG, significantly decreased P_f[1], which was reversed by the neutralization of IgG binding to any of the extracellular loops. The prevalent recognition of functional epitopes by anti-AQP5 autoantibodies from SS patients suggests that anti-AQP5 autoantibodies act as mediators of glandular hypofunction and a potential therapeutic target in SS.

Keywords: Sjogren's syndrome, AQP5, Autoantibodies, Indirect immunofluorescence, MDCK cells

P-007 Protein Tyrosine Phosphatase Conjugated with a Novel Transdermal Delivery Peptide, AP-rPTP Alleviates Both Atopic Dermatitis- and Psoriasis-like Inflammatory Skin Disease

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Atopic dermatitis (AD) and psoriasis are the two most common chronic inflammatory skin diseases. There is an unmet medical need to overcome limitations for transcutaneous drug development posed by the skin barrier. We aimed to identify a novel transdermal delivery peptide and to develop a transcutaneously applicable immunomodulatory protein for treating AD and psoriasis. We identified and generated reporter proteins conjugated to AP, a novel transdermal delivery peptide of human origin, and analyzed the intracellular delivery efficiency of these proteins in mouse and human skin cells and tissues using multi-photon confocal microscopy. We also generated a recombinant therapeutic protein, AP-rPTP, consisting of the phosphatase domain of T cell protein tyrosine phosphatase (TC-PTP) conjugated to AP. The immunomodulatory function of AP-rPTP was confirmed in splenocytes upon cytokine stimulation and TcR stimulation. Finally, we confirmed the *in vivo* efficacy of AP-rPTP transdermal delivery in OXA-induced contact hypersensitivity, OVA-induced atopic dermatitis-like, and imiquimod-induced psoriasis-like skin inflammation models. AP-conjugated reporter proteins exhibited significant intracellular transduction efficacy in keratinocytes, fibroblasts, and immune cells. In addition, transcutaneous administration of AP-dTomato resulted in showed significant localization into the dermis and epidermis in both mouse and human skin. AP-rPTP inhibited pSTAT1, pSTAT3, and pSTAT6 in splenocytes and regulated T cell activation and proliferation. Transcutaneous administration of AP-rPTP significantly ameliorated skin tissue thickening, inflammation, and cytokine expression in both atopic dermatitis- and psoriasis-like dermatitis models. We identified a 9-amino acid-long novel transdermal delivery peptide, AP, and demonstrated its feasibility for transcutaneous biologic drug development. Moreover, AP-rPTP is a novel immunomodulatory drug candidate for human dermatitis.

Keywords: Atopic dermatitis, Psoriasis, Transdermal delivery peptide, Protein tyrosine phosphatase, TC-PTP

P-008 Strong Association of Two Amino Acids in Both HLA-DPB1*0202 and DPB1*0501 with Autoimmune Thyroid Disease in Korean Children

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The autoimmune thyroid diseases (AITD) are complex diseases whose underlying pathoetiology stems from a genetic-environmental interaction, between susceptibility genes and environmental triggers that orchestrates the initiation of an autoimmune response to thyroid antigens, leading to the onset of disease. Several AITD susceptibility genes have been identified, with HLA appearing particularly to be of major importance. Human leukocyte antigen (HLA) is highly polymorphic and associated with autoimmune thyroid disease (AITD) as well as with other autoimmune diseases. In this study, we further defined the association of HLA class II with early-onset AITD, which have shown stronger genetic susceptibility compared with late-onset AITD. The genotypes of HLA-DRB1, DQB1, and DPB1 on AITD were analyzed in 66 Korean children with AITDs (Graves' disease (GD) = 35, Hashimoto's disease (HD) = 31) and 142 healthy control using sequence-based typing. Although it is an analysis of a small number of patients, HLA-DPB1*0501 (RR=4.8, Pc=0.035) and DPB1*0202 (RR=6.9, Pc=0.001) were significantly associated with GD and HD, respectively. Furthermore, HLA-DPB1*0501 showed a significant difference between GD and HD (Pc=0.028). HLA-DRB1*0803-DQB1*0601-DPB1*0202 (RR=35.3, P=0.00005) was found as a strongly associated haplotype in GD. For analysis of single nucleotide polymorphism of HLA-DPB1, 190 C (Leu) (RR=18.0, P=0.00003) and 252 G (Glu) (RR=18.0, P=0.00003) present in DPB1*0202 and DPB1*0501 showed higher relative risks value compared those analyzed by genotype. Our results suggest that common molecular structure in both HLA-DPB1*0202 and DPB1*0501 may affect the pathogenesis of early-onset AITD.

Keywords: Autoimmune thyroid disease, Graves' disease, Hashimoto's disease, Human leukocyte antigen class II, Korean children

P-009 Superoxide Dismutase 3 Attenuates Experimental Th2-driven Allergic Conjunctivitis

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Allergic conjunctivitis is an inflammatory eye disease mediated by Th2 type immune response. The role of extracellular superoxide dismutase 3 (SOD3) in immune response and allergic conjunctival inflammation was examined in a murine model for experimental allergic conjunctivitis (EAC). Allergic conjunctivitis was induced in mice by allergen challenge with ovalbumin in alum via the conjunctival sac. SOD3 was topically applied and allergy indicators were compared. Clinical signs associated with conjunctivitis, such as OVA-specific IgE production, IgG1/G2a ratio and eosinophil infiltration, were drastically reduced in mice treated with SOD3. They also had less dendritic cells and CD4+ T cells in conjunctiva than controls. Attenuated allergic inflammation was accredited to reduced Th2 type cytokine responses and increased Treg cytokine in draining lymph node. The characteristics of EAC were attributed to the absence of SOD3. Our findings suggest that SOD3 might be considered as a potential target for Th2-driven allergic conjunctival inflammation.

Keywords: Allergic conjunctivitis, SOD3, Eosinophil, IgE, Th2 type immune response

P-010 Fabrication of Antigen-Encapsulated Biodegradable PLGA Nanoparticles for Efficient MHC Class II-Restricted Presentation

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The use of biodegradable poly(lactic-co-glycolic acid) (PLGA) nanoparticles with encapsulated antigens represents an exciting approach for efficient induction of the antigen-specific immune responses via selective targeting of the antigen to APCs. In the present study, we prepared PLGA nanoparticles containing bovine serum albumin or ovalbumin, using a $W_1/O/W_2$ double emulsion solvent evaporation method. Dichloromethane or ethyl acetate was used as an organic phase (O) and polyvinyl alcohol as a secondary aqueous phase (W_2) stabilizer. The size of the nanoparticles and encapsulation efficiency of the antigen were critically dependent on the formulation and process parameters. A large particle size with high encapsulation efficiency of the antigen was obtained when high W_2/O phase ratio (v/v) was used. Nanoparticles fabricated in a phase ratio of 4 (v/v) were larger in particle size and higher in encapsulation efficiency, but were less efficient in MHC class Ⅱ-restricted antigen presentation by dendritic cells (DCs), compared to those fabricated in a phase ratio of 2.75 (v/v). Nanoparticles inducing the most efficient MHC class II-restricted antigen presentation were fabricated when W_2/O phase ratio was 2.75 (v/v). The present study shows that the DC antigen presentation can be affected by particle size than antigen encapsulation efficiency.

Keywords: PLGA nanoparticle, Dendritic cell, MHC class II-restricted presentation

P-011 Proliferation-Inducing Activity of Minocycline on Bone Marrow-Derived Dendritic Cells

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Minocycline was recently shown to increase the generation of bone-marrow-derived dendritic cells (BM-DCs) when used together with mGM-CSF and mIL-4. In the present study, we investigated the growth promoting activity of minocycline on various cell lines and normal T cells. In addition, we identified genes involved in minocycline-induced growth promotion. BM-DCs generated in the presence of minocycline was increased by more than 50% in cell number compared to untreated control BM-DCs. Minocycline also increased the proliferation of a dendritic cell line DC2.4, a fibroblast cell line NIH3T3, and a T cell hybridoma B3Z cell lines, anti-CD3 and anti-CD28 mAb-primed splenic T cells, but with much weaker potency compared to that on BM-DCs. To identify the genes that are induced by minocycline, we performed microarray analysis and q(RT)-PCR analysis for the BM-DCs treated with or without minocycline. We found that the expression of Id3 gene was the most highly induced by minocycline treatment. Other genes that were induced by minocycline include Wnt2 and Ttll7. The present study shows that minocycline exerts potent growth-promoting activity on especially on BM-DCs when used together with mGM-CSF and mIL-4, most probably by inducing the expression of Id3 gene.

Keywords: Minocycline, Dendritic cell, Growth promotion, Id3

P-012 Casein Kinase 2 Regulates Balance of Th17 Versus Treg Cell Differentiation

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Th17 cells promote, whereas regulatory T (Treg) cells inhibit, inflammatory reactions. Thus, the Th17/Treg cell balance is critically important in inflammatory diseases. However, the molecular mechanisms underlying this balance are unclear. Here, we demonstrate that casein kinase 2 (CK2) is a critical determinant of the Th17/Treg cell balance. Both inhibition of CK2 with a specific pharmacological inhibitor, CX-4945, and shRNA-mediated knockdown suppressed Th17 cell differentiation but reciprocally induced Treg cell differentiation in vitro. Moreover, CX-4945 ameliorated symptoms of experimental autoimmune encephalomyelitis and reduced Th17 cell infiltration into the central nervous system. Mechanistically, CX-4945 inhibited the IL-6/STAT3 and Akt/mTOR signaling pathways. Thus, CK2 plays a crucial role in regulating the Th17/Treg balance.

Keywords: Casein Kinase 2, CX-4945, Th17, Treg, EAE

P-013 Comparison of Myeloid-derived Suppressor Cells Population in Different Lung Diseases

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Myeloid-derived suppressor cells (MDSCs) are consisted of heterogeneous population including myeloid progenitor cells and immature myeloid cells and play an important role in suppression of host immune responses. Although initial observations and the most of MDSCs research focus on immune regulation in the tumor environment, accumulating evidence has shown that MDSCs also regulate immune responses during bacterial and parasitic infections, acute and chronic inflammation, traumatic stress, sepsis and transplantation. Although Tuberculosis, pneumonia, and lung cancer are the most common in the lung diseases, it is still difficult to make a precise and quick diagnosis of these disease. Because initial presenting symptoms such as fever, cough, expectoration, hemoptysis, weight loss and anorexia of lung disease are similar. Therefore a prompt differential diagnosis of lung disease are required for preventing exposure to inappropriate medication. The aim of this study was to explore the diagnostic value of MDSCs in different lung diseases. We analyzed $CD14^-CD11b^+CD33^+$ MDSC and their $CD15^+$ granulocytic proportion in peripheral blood of bacterial pneumonia, pulmonary tuberculosis, lung cancer patient and normal control group. We observed that the MDSCs accumulate in large numbers in the lung diseases compared with healthy controls. In the lung cancer patients, MDSCs levels were correlated with cancer stage. MDSCs population of bacterial pneumonia patients was significantly higher than that in pulmonary tuberculosis patients. Therefore, MDSCs can be potential immune parameter to distinguish lung diseases especially bacterial pneumonia and pulmonary tuberculosis.

Keywords: Myeloid-derived suppressor cells, Bacterial pneumonia, Pulmonary tuberculosis, Lung cancer

P-014 Efforts to Identify the Dendritic Cell-specific Antigen Recognized by the Monoclonal Antibody 2A1 Reveal Candidate Genes

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The monoclonal antibody (mAb) named 2A1 detects dendritic cells (DCs) in mouse samples of vitro cultures and in situ tissues. mAb 2A1 has been known to recognize the intracellular granules in mature DCs and thus distinguish DCs from other immune cells such as macrophages, B cells, T cells, and NK cells. Moreover, we uncovered that mAb 2A1 labeled a novel population of DC subsets in the culture of bone marrow (BM) with FMS-like tyrosine kinase 3 ligand (Flt3L). Thus far, the function as well as the identity of the antigen recognized by mAb 2A1 (2A1 antigen) have never been explored. To identify the 2A1 antigen, we produced DCs from the culture of BM with granulocyte-macrophage colony stimulating factor (GM-CSF) and prepared lysates therefrom. In the meantime, we purified and conjugated mAb 2A1 to carbohydrate coupling resin. Then, the cell lysates were subjected to affinity chromatography using 2A1 and control mAb-conjugated resins. The eluents were concentrated by drying and analyzed further on SDS-PAGE followed by Coomassie Blue staining. Two unique bands were located and excised from the Coomassie Blue stain for the peptide identification by IM/MS. The analysis of IM/MS data unveiled 19 candidate genes for 2A1 antigen. Based on the results of RT-qPCR between DCs and non-DCs on respective 19 candidate genes, the final candidate gene(s) will be selected, cloned into a mammalian expression vector, and expressed into protein for the confirmation of reactivity to mAb 2A1.

Keywords: Affinity chromatography, Antigen identification, Dendritic cells, Lineage marker

P-015 IFN-γ-induced MHCII+ Inflammatory Monocytes Play a Role for Regulating CD8 T Cell Responses in Acute LCMV Infection

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During viral infection, monocytes play a protective role for clearance of pathogens. However, little is known about the role of recruited monocytes after effector phase, especially as regard to their effects to T cells. Here, we have investigated the phenotypes, the origin and inducing factor, and the effects to CD8 T cells of inflammatory monocytes in virus-infected mice. During Lymphocytic choriomeningitis virus (LCMV)-Arm infection, $CCR2^+$ inflammatory monocytes were accumulated in lymphoid organs and reached their peak at day 8 post infections. Inflammatory monocytes of infected mice expressed high levels of MHCII and low levels of CD11c, which overlap with phenotypes of DC and those of macrophage, respectively. We found that IFN-gamma (IFN-γ) is a factor that differentiates $MHCII^+$ monocytes from BM progenitor cells. Among the BM progenitor cells, common monocyte progenitors (cMoPs) were rapidly converted to $MHCII^+$ inflammatory monocytes in response to GM-CSF and IFN-γ *in vitro*. In addition, cMoPs that were adoptively transferred to infected recipients were differentiated to $MHCII^+$ inflammatory monocytes. $MHCII^+$ monocytes-primed CD8 T cells had comparable proliferative capacity to conventional DCs (cDCs)-primed CD8 T cells. However, $MHCII^+$ monocytes-primed CD8 T cells more efficiently produce IL-2 while they produce less IFN-γ and granzyme B, compared to cDCs-primed CD8 T cells. Our data suggest that IFN-γ-induced $MHCII^+$ inflammatory monocytes and cDCs would play different roles for regulating CD8 T cell responses during acute LCMV infection.

Keywords: Inflammatory monocytes, Dendritic cells, LCMV, Interferon-gamma, CD8 T cells

P-016 Myeloid-Derived Suppressor Cells Are Controlled by Regulatory T Cells via TGF-b During Murine Colitis

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Myeloid-derived suppressor cells (MDSCs) are well known regulators of regulatory T cells (Treg cells); however, the direct regulation of MDSCs by Treg cells has not been well characterized. We find that colitis caused by functional deficiency of Treg cells leads to altered expansion and reduced function of MDSCs. During differentiation of MDSCs in vitro from bone marrow cells, Treg cells enhanced MDSC function and controlled their differentiation through a mechanism involving transforming growth factor-b (TGF-b). TGF-b-deficient Treg cells were not able to regulate MDSC function in an experimentally induced model of colitis. Finally, we evaluated the therapeutic effect of TGF-b-mediated in-vitro-differentiated MDSCs on colitis. Adoptive transfer of MDSCs that differentiated with TGF-b led to better colitis prevention than the transfer of MDSCs that differentiated without TGF-b. Our results demonstrate an interaction between Treg cells and MDSCs that contributes to the regulation of MDSC proliferation and the acquisition of immunosuppressive functions.

Keywords: MDSCs, Inflammation, Colitis, TGF-β

P-017 Placenta Growth Factor Regulates Th17 Cell Generation: A Novel Link between Angiogenesis and Autoimmunity

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Placenta growth factor (PlGF), a known angiogenic factor, has been implicated in inflammation and cancer, but its role in T helper (Th) cell generation is largely unknown. Here, we identified that PlGF was secreted by $CD4^+$ T cells, specifically Th17 cells. T cell-produced PlGF was functionally active for angiogenesis. Interestingly, PlGF deficiency reduced IL-17 production by $CD4^+$ T cells, whereas PlGF excess promoted it *in vitro*. Specifically, PlGF regulated Th17 cell differentiation and plasticity, replacing IL-6 activity. PlGF promotion of Th17 cell generation was mediated through activation of STAT3. Moreover, genetic ablation of *PlGF* reduced the severity of delayed type hypersensitivity and experimental autoimmune encephalomyelitis, a Th17 disease model, and IL-17 production in mice, which were restored by the adoptive transfer of *PlGF*-overexpressed $CD4^+$ T cells. Overall, our data demonstrate that Th17 cell-produced PlGF directly controls the commitment to the Th17 response, linking angiogenesis to Th17 cell polarization and autoimmunity.

Keywords: Placenta Growth Factor, Th17 cells, STAT3, Autoimmune Diseases

P-018 Primary Lymphocyte Infection Models of KSHV

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Kaposi's sarcoma-associated herpesvirus belongs to human herpesvirus family and induces at least 3 malignancies, including Kaposi's sarcoma (KS) and two B cell lymphomas. As it causes B cell malignancies, it seems clear that KSHV infects B cells in vivo. In fact, one in 10^4-10^5 B cells in the blood of KS patients harbors the KSHV genome. However, in vitro B cells, both primary and established, have been refractory to KSHV infection. We employed tonsillar human lymphocyte aggregate culture (HLAC) and demonstrated that both B and T cells are susceptible to KSHV infection. T cells supported KSHV entry much better than B cells, but viral gene expression was not evident, indicating an abortive nature. Interestingly, established B cells remained resistant to cell-free virus stocks. When co-cultured with a virus-producing cell line, established B cell lines were rendered susceptible to KSHV infection suggesting that cell-mediated transmission was much more efficient. Now infection models for B cells, both primary and established, are available, thus unprecedented opportunities are ahead for the analysis of mechanisms of tumorigenesis in B cells.

Keywords: Kaposi's sarcoma-associated herpesvirus, Infection model, Cell-mediated transmission

P-019 Protective effects of *Cinnamomum cassia* (Lamaceae) Against Gout and Septic Responses via Attenuation of Inflammasome Activation in Experimental Models

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Cinnamomum cassia (family, Lauraceae) is considered one of the 50 fundamental herbs in traditional Chinese medicine. it is commonly used for treating dyspepsia, gastritis, blood circulation, and inflammatory diseases. The anti-inflammatory action of an ethanol extract of *C. cassia* (CA), and its underlying mechanisms were explored in both *in vitro* cellular and *in vivo* murine models. Bone marrow-derived macrophages (BMDMs) were used to study the regulatory effect of CA on inflammasome activation. A lipopolysaccharide (LPS)-induced sepsis mouse model and a monosodium urate (MSU)-induced gout model were employed to study the effect of CA on *in vivo* efficacy. CA improved the survival rate in the LPS-induced septic shock mouse model and inhibited inflammasome activation including NLRP3, NLRC4, and AIM2, leading to suppression of interleukin-1 β secretion. Further, ASC oligomerization and its speck formation in cytosol were attenuated by CA treatment. Furthermore, CA improved both survival rate of LPS-induced septic shock and gout murine model.CA treatment significantly attenuated danger signals-induced inflammatory responses via regulation of inflammasome activation, substantiating the traditional claims of its use in the treatment of inflammation-related disorders.

Keywords: *Cinnamomum cassia*, Inflammasome, ASC, Sepsis, Gout

P-020 T Cell-derived Factors Are Involved in Modulation of KSHV Replication

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Kaposi's sarcoma-associated herpesvirus (KSHV) is a lymphotropic human herpesvirus, mainly infecting B cells as well as endothelial cells. Recently, it has been shown that KSHV infects T cells at even higher frequency compared to that of B cells although the viral infection was abortive in nature. T cells have been shown to infiltrate into tumor lesions, but it seems that they remain uninfected. Their roles in viral replication and/or tumorigenesis remain elusive. We set out to test whether T cell-derived soluble factors are involved in the modulation of KSHV replication. Human tonsillar T cells were either co-cultured with B cells or cultured in pure culture in the presence/absence of polyclonal T cell activator (concanavalin A). At ays post-culture, culture supernatants were collected and subjected to 64-PLEX ELISA. Cytokines and chemokines were assessed for their relative abundance and their putative roles in viral replication were tested on a KSHV-producing cell line.

Keywords: Kaposi's sarcoma-associated herepesvirus, Co-culture, Soluble factor

P-021 Deficiency of IL-1Ra Promote Th17 Cell Activation and Dermal Fibrosis in Scleroderma

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Systemic sclerorsis (SS) is an autoimmune connective tissue disease inducing chronic inflammatory response. The feature of scleroderma is hardening skin changes that become stiff and thickened part or systemic of the skin due to excessive accumulation collagen within the dermis and abnormality of blood vessel system. Since the pathogenesis of scleroderma is an unknown, therapeutic agents of this disease is absent yet. This study is aim to determine whether pathogenic mechanism to inflammation in accordance with the interleukin (IL)-1 signaling activation and excessive differentiation of T helper (Th)17 cells in bleomycin induced scleroderma. We found that IL-1 receptor antagonist (IL-1Ra) knockout mice developed severe experimental bleomycin-induced scleroderma. However, bleomycin-induced dermal fibrosis in IL-1Ra and IL-17 double knockout (DK) mice decreased than those in IL-1Ra knockout mice. In murine sclerodermatous cGVHD model, IL-Ra and IL-17 DK mice also displayed less fibrosis and inflammation in the target tissue compared with IL-1Ra KO mice. Administration of anakinra, a recombinant human IL-1 receptor antagonist, attenuated the development of severe scleroderma and fibrosis. These results indicate the pivotal contribution of IL-1 and IL-17 to the pathologic tissue fibrosis of SSc murine models. Our results indicate the critical role of IL-1 signaling in the development of tissue fibrosis, suggesting that biomolecular IL-1/IL-17 targeting might be a potential therapeutic approach to SSc.

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Keyword: IL-1 Ra, Th17 cell, Systemic sclerorsis

P-022 G Protein-coupled Receptor Kinase (GRK)2 is a Key Negative Regulator of itch: L-glutamine Attenuates itch via a Rapid Induction of GRK2

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Most itch mediators or pruritogen activate G-protein coupled receptor (GPCR), and trigger itch via activation of the GPCR-mediated signaling pathways. GPCR is desensitized by G protein-coupled receptor kinases (GRKs) via its phosphorylation. However, it is unknown whether GRK affects itch. In this study, we demonstrate that GRK negatively regulates various pruritogen-mediated itch in mice. In addition we confirm that glutamine (Gln), an anti-itch amino acid demonstrated previously, suppresses itch by increasing GRK protein levels. GRK2 siRNA enhanced itch responses evoked by histamine, chloroquine (CQ), and DNCB-induced contact dermatitis (CD), whereas GRK2 overexpression using adenovirus expressing GRK2 (Ad-GRK2) reduced the itch responses. Gln reduced all itch evoked by histamine, CQ, and DNCB-induced CD. The Gln's anti-itch activities were all reversed by pretreatment of GRK2 siRNA. Gln application resulted in a rapid and strong expression GRK2 in not only DNCB-induced CD (within 10 min), but also cultured rat dorsal root ganglion cells, F11 (within 1 min). Our data indicate that GRK2 is a therapeutic target for the treatment of itch.

Keywords: itch, GRK2, Glutamine, Histamine, Chloroquine, Contact dermatitis

P-023 Inhibitory Effects of *Aralia continentalis* Ethanol Extract and Its Active Component Continentalic Acid on Inflammatory Mediator Production in IL-1β-stimulated Human Osteoarthritis Chondrocyte

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Aralia continentalis from Imsil (ICF-2), widely used in some countries of East Asia as an medicinal herb possesses diverse remedial values including anti-inflammatory, anti-febrile, analgesic and anti-spasmodic effects. The aim of this study was to investigate the anti-inflammatory and anti-arthritic effect of 50% ethanol extract of ICF-2 in the interleukin (IL)-1β-stimulated human chondrocyte, an in vitro model of osteoarthritis (OA). Human OA chondrocytes were treated with ICF-2 extracts of 50, 80 or 100 μg/ml, and subsequently with 10 ng/ml IL-1β, and further incubated for another 24 hrs. Ethanol extract of ICF-2 significantly inhibited IL-1β-induced expression of IL-6, IL-8, MMP-1, MMP-13 and COX-2, and PGE2 production, but not MMP-3 expression in the chondrocytes. ICF-2 extract also modulated the IL-1β-induced translocation of nuclear factor (NF)-κB (p65) into the nucleus and phosphorylation ERK, JNK and p38 of MAPK pathways. As an index chemical of ICF-2, continentalic acid exhibited a significant inhibitory activity on IL-1β-induced expression of IL-6, IL-8 and MMP-13, of which activity was compatible with that of ICF-2 extract including an equivalent amount of continentalic acid. Kaurenoic acid, another representative chemical component, also inhibited the expression of those proteins at the concentration of 20 times higher than continentalic acid. These results suggested that the 50% ethanol extract of ICF-2 and its diterpene component, continetalic acid have a significant anti-inflammatory effect in the IL-1β-stimulated human OA chondrocytes. Thus, the ICF-2 extract can be a potential candidate for developing new medicines or dietary supplements for the treatment of osteoarthritis and continentalic acid might be the active ingredient. (This research was supported by the Ministry of Agriculture, Food and Rural Affairs (MAFRA), through the 2015 Healthy Local Food Branding Project of the Rural Resources Complex Industrialization Support Program)

Keywords: *Aralia continentalis*, Inflammation, Osteoarthritis, Chondrocyte, Continentalic acid

P-024 Interplay of KSHV and Jak-STAT Pathway

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Kaposi's sarcoma-associated herpesvirus belongs to gamma-herpesvirus subfamily and like its close cousin Epstein-Barr virus (EBV), it induces various tumors, including Kaposi's sarcoma (KS), multicentric Castleman's disease (MCD) and primary effusion lymphoma (PEL). It has long been established that KSHV infection activates signal transducer and activator of transcription 3 (STAT3) in response to interleukin-6 (IL-6) stimulation. Relative importance of IL-6 and STAT3 in the tumorigenesis has been speculated, however, its role in the viral replication is not known. We set out to test whether STAT3 activation is involved in the viral gene expression, genome replication, and viral exit. siRNA knockdown of STAT3 severely impaired viral progeny production as well as gene expression. On the other hand, when constitutively active STAT3 was stably expressed, viral replication was several fold increased. These data indicate that Jak-STAT3 pathway play an important role in KSHV replication.

Keywords: Kaposi's sarcoma-associated herpesvirus, Signal Transducer and Activator of Transcription 3

P-025 The Effect of the *Litsea japonica* Fruit Flesh n-hexane Extract (LJF-HE) in a MIA-induced OA Rat Model

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Osteoarthritis (OA) is a degenerative disease of joint that affects cartilage and is accompanied by secondary inflammation of synovial membranes. In this study, we examined the OA therapeutic effects of *Litsea japonica* (*L. japonica*), which grows in Jeju island of Korea. LJF-HE is prepared from fruit flesh of *L. japonica* by n-hexane. The therapeutic effects of LJF-HE were evaluated in lipopolysaccharide (LPS)-induced inflammatory response in macrophages and in rats of monoiodoacetate (MIA)-induced OA model. We showed that the LJF-HE inhibited productions of proinflammatory mediators such as nitric oxide (NO), prostaglandin E_2 (PGE_2), interleukin (IL)-6, and tumor necrosis factor (TNF)-α in activated macrophages. In addition, the phosphorylated levels of p38 MAPK and JNK were significantly inhibited by the extract. Oral administration of LJF-HE (25, 50, and 100 mg/kg, 21 days) dramatically decreased the serum levels of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α and pro-inflammatory mediators such as leukotreine B4 (LTB4) and deoxypyridinoline (DPD) in MIA-induced osteoarthritic rats. In accordance with serum levels of inflammatory metabolites, the enzymes involving in arachidonic acid metabolism such as cyclooxygenase (COX-2) and 5-lipoxygenase (LOX-5) were also inhibited by LJF-HE. Also, expressions of *IL-6*, *IL-1*β, *TNF-*α and *cox-2* mRNA were suppressed in joint of LJF-HE treatment group compared with that of control group. Our results suggest that LJF-HE has therapeutic effects for osteoarthritis by inhibiting inflammatory activity and OA related mediators.

Keywords: Osteoarthritis, *Litsea japonica*, Monoiodoacetate (MIA)-induced OA

P-026 C5a Receptor Signaling in Peyer's Patch $CD11b^{-}CD8^{-}$ Dendritic Cells Promotes Antigen-specific IFN-γ-producing T-cell Responses

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Complement 5a (C5a) receptor (C5aR) modulates adaptive immunity by enhancing Th1 polarization or by inducing $CD8^+$ T cell immunity either directly or via modulation of dendritic cells (DCs). C5aR is expressed in systemic myeloid cells and some epithelial cells, but little is known for its expression in Peyer's patch (PP) cells. Although we previously reported its expression by M cells in PP and its role as a receptor for M cell-targeting Co1 ligand, the effect of C5aR on other PP cells is not clearly understood. In this study, we found that $CD11c^+CD11b^-CD8^-$ PP DCs expressed C5aR, and its activation by the ligand for Ca5R in vitro induced IFN-γ-producing cells from naïve $CD4^+$ T cells. Additionally, application of the Co1 peptide to dengue virus antigen (Ag) induced Ag-specific IFN-γ-producing $CD8^+$ T cells. We conclude that C5aR plays a role as a mucosal immune modulator in PPs, and Co1 peptide-mediated C5aR activation contributes to the development of an effective $CD8^+$ T-cell immune response after mucosal immunization. (This study was supported by 2014K1B1A1073861 through the National Research Foundation (NRF) funded by the Korean Ministry of Science, ICT, & Future Planning and by HI15C3039 through the Korea Health Industry Development Institute (KHIDI) funded by the Korean Ministry of Health and Welfare.)

Keywords: C5a receptor, CD8+ T cell, IFN-γ, Ligand, Peyer's patch

P-027 Ginsenoside Rp1 Modulates Radiation Effects on the Lipopolysaccharide-Stimulated J774A.1 Murine Macrophage Cells while Suppressing the CT26 Colon Cancer Cell Phenotype Changes

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Background: The Present study was designed to evaluate the inhibitory effect of Ginsenoside-Rp1 (G-Rp1), a stable derivative of ginsenoside-Rg3, on ionizing radiation (IR)-enhanced lipopolysaccharide (LPS)-induced pro-inflammatory production.
Methods: Using ELISA, real time PCR analysis, western blotting, wound healing assay and migration assay, we investigated the inhibitory effect of G-Rp1 on IR-enhanced and LPS-mediated IL-1β productions in J774 murine macrophage cells.
Results: G-Rp1 induced strong down-regulation of IR-enhanced and LPS-induced IL-1β levels. G-Rp1 showed inhibitory effects on activation of IR-induced DNA damage-related signaling molecules such as histone H2AX, checkpoint kinase1 (chk1) and checkpoint kinase2 (chk2). Indeed, G-Rp1 down-regulated IR-mediated ERK and p38 MAPK activations.
Conclusion: Our result supports that G-Rp1 modulates radiation effects on macrophage cells.

Keywords: *Panax ginseng*, G-Rp1, Radiation, Macrophages, Cancer Stem Cells

P-028 Human Mesenchymal Stem Cells Induce the Expression of $CD4^+$ $CD25^+$ $FoxP3^+$ Programmed Cell Death-1^+ Regulatory T Cell

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Mesenchymal stem cells (MSCs) have profound immunomodulatory properties. Using their properties, MSCs-based therapies have been applied in several inflammatory diseases. The immune modulation of MSCs is related to inhibition of immune cell proliferation and activation. T cells are critical effector immune cells in affecting and regulating immune response and can differentiate into one of several subtypes, including T_H1, T_H2, T_H17 or regulatory T cells (Tregs). In this study, we investigated the immunomodulatory property of MSCs on T cells. We co-cultured human bone marrow-derived MSCs (BM-MSCs) and mouse $CD4^+$ T cells directly. The effect of BM-MSCs on T cell differentiation was assessed by T cell subtype markers by flow cytometry, and supernatants for induced production of cytokines. Gene and protein expressions were analyzed by qRT-PCR and western blot, respectively. In addition, immunohistochemistry and Tregs suppression assay were performed in inflammatory tissues in collagen induced arthritis (CIA) mice. The expressions of $CD4^+CD25^+FoxP3^+$ PD-1^+ Tregs were highly induced in co-culture condition. Human BM-MSCs significantly induced the Tregs by increasing programmed cell death-1 (PD-1) and Neuropilin-1 (Nrp-1) expressions in vitro. However, human BM-MSCs did not induce the $FoxP3^+$ Tregs in the splenic $CD4^+$ T cells from PD-$1^{-/-}$ mice. Moreover, immunohistochemical analysis of inflamed tissues in BM-MSC treated CIA mice showed significant immunopositive staining for PD-1 on T cells. Our data showed that human BM-MSCs induced the PD-1^+ Tregs in both *in vitro* and *in vivo*.

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Keywords: Mesenchymal stem cells, Regulatory T cells, Programmed cell death-1, Immune modulation

P-029 Kinetic Study on the Differentiation of Inducible Treg by TGF-β1 and Lactoferrin

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TGF-β1 is well known to stimulate naïve T cells to differentiate into regulatory T cells. We first found that lactoferrin (LF) also stimulate naïve $CD4^+$T cells to express Foxp3 similar to TGF-β1. LF increased Foxp3 expression in dose-dependent manner and further synergized with TGF-β1. Interestingly, TGF-β1 augmented shedding of CD62L while LF strongly inhibited its shedding, suggesting that LF-induced Treg cells is less differentiated into effector cells. Through the experiment on time-lapse reciprocal effect of two molecules, it was found that the synergistic effect on Foxp3 expression was the greatest when the two molecules were presented from the beginning together. In this, it was also found that both molecules could induce Foxp3 expression regardless of CD62L shedding.
We next examined the effect of TCR-stimulating intensity on Foxp3 expression by using different dose of coated anti-CD3 Ab. Its expression by TGF-β1 required much weaker TCR stimulation than LF. Nevertheless, combined effect of two molecules was evident at the strong TCR stimulation.
Taken together, the present kinetic study reveal that TGF-β1 and LF affect Treg differentiation distinctively although both molecules enable naïve T cells to express Foxp3 transcription factor.

Keywords: Treg, TGF-β1, Lactoferrin, Foxp3, CD62L

P-030 M2 Macrophages Induced by Mesenchymal Stem Cells Provide Anti-inflammatory Milieu for Inducing Regulatory T cells in Collagen Induced Arthritis Mice

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Objective: Mesenchymal stem cells (MSCs) have immunomodulatory properties. These unique functions led to the consideration of their use for inflammatory diseases such as rheumatoid arthritis. However, the comprehensive host immune response by MSCs are not fully understood. In this study, we investigated the immune modulatory property of human adipose-derived (hAD-) MSCs on macrophages in collagen induced arthritis (CIA) mice, and the mechanism that hAD-MSCs affected macrophages in vitro and in vivo.
Methods: CIA was induced in DBA/1J mice. hAD-MSCs were intraperitoneally injected into CIA mice, and the therapeutic efficacy of hAD-MSCs was evaluated. Peritoneal macrophages (PM) and splenic T cells were analyzed. In vitro experiment, macrophages were co-cultured with hAD-MSCs directly at 1:5 ratio for 24 hours. Macrophages phenotype polarization and cytokine expression levels were analyzed by FACS and ELISA. Protein and mRNA expressions were examined by Western blot and qPCR analysis.
Results: hAD-MSCs ameliorated the severity of CIA mice through inducing M2 macrophages in peritoneum. The emergence of M2 macrophages preceded to that of Tregs in CIA mice. hAD-MSCs enhanced IL-10 and TGF-β1 expressions of M2 macrophages, and hAD-MSCs reduced the RAGE, NF-κB expression and modulated STAT family of macrophages.
Conclusion: hAD-MSCs exerted the therapeutic effects through the induction of M2 macrophages in CIA mice. Induced M2 macrophages produced IL-10 and TGF-β1 which might result in anti-inflammatory milieu for inducing Treg.

Keywords: Mesenchymal stem cells, Immune modulation, M2 macrophage, Regulatory T cells

P-031 Mesenchymal Stem Cell-derived Exosomes Induce T Cell-cycle Arrest and Inhibit Th17 Differentiation by Destabilizing RORγt via Inhibition of Ubiquitin Ligase Activity of CBP/p300 by Eid3

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Mesenchymal stem cells (MSCs) have been shown to alleviate inflammation and autoimmune diseases. However, the underlying mechanisms are not yet fully understood. In this study, MSC-derived exosomes (MSC-exo) were tested for their immunosuppressive effects. The MSC-exo exhibited potent suppressive effects on T cell proliferation and differentiation. MSC-exo induce T cell cycle arrest and reduced the level of RORγt in Th17 differentiation condition. To further examine the effect of MSC-exo *in vivo*, experimental autoimmune encephalomyelitis (EAE) was induced in mice, and each group was given with MSC-exo or exosome-depleted culture supernatant. The development of EAE was alleviated and the expression of RORγt and IL-17A were notably suppressed by MSC-exo. Furthermore, Eid3 was founded in MSC-exo which have known as inhibitor of CBP/p300 ubiquitin ligase. MSC-exo indeed destabilized RORγt by suppressing CBP/P300 mediated K63-linked polyubiquitination of RORγt. Thus, we propose Immunomodulatory mechanism of MSC-exo, specifically inducing cell-cycle arrest and abrogating stability of RORγt.

Keywords: Mesenchymal stem cell, Exosome, Th17 cell, EAE, Immunomodulation

P-032 Poly-γ-glutamate Shows Protective Effect Against DSS-induced Colitis by Changing Gut Microbiota

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Poly-γ-glutamate(γ-PGA) is peptide polymer which is reported to regulate immune system. However, its effect on gut microbiota is still unknown. Here, we tried to prove that γ-PGA treatment regulates immune system by changing gut microbiota. We used dextran sodium sulfate (DSS) induced colitis which is widely used as disease model of human ulcerative colitis. First of all, we confirmed that C57/bl6 mice treated with 2,000kDa γ-PGA in drinking water showed alleviation in symptoms in comparison with control which only drank normal drinking water when colitis was induced by DSS. Second, we cohoused mouse in order to prove the effect of gut microbiota. We found out that PBS treated mouse co-housed with γ-PGA treated group showed delayed DSS induced colitis response in comparison with control group which was treated with PBS. To further strengthen our hypothesis, we analyzed gut bacteria composition by sequencing 16sRNA from stools. In phylum, mice that were treated with γ-PGA showed increment in proteobacteria and decrement in firmicutes in comparison with control group. Control group showed increment in verrucomicrobia. In family, control group showed increased in erysipleotrichaceae and akkermansiaceae which are known to promote inflammation in colon. γ-PGA treated group showed increase in bacteroidaceae which contains species that are known to suppress inflammation. In conclusion, our data shows that treatment of γ-PGA enhanced immune system by changing gut microbiota.

Keywords: Poly-γ-glutamate, DSS-induced Colitis, Gut Microbiota

P-033 Ssu72 attenuates autoimmune arthritis via targeting of STAT3 signaling and Th17 activation

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STAT3 orchestrates differentiation of several types of cells including those in IL-17-releasing Th17 cells. Dysregulation of Th17 cells results in chronic inflammatory response. Ssu72 is a phosphatase that is essential to the regulation of transcription. However, function of Ssu72 affecting the STAT3 activation and Th17 cells differentiation is uncertain. Here, we found that Ssu72 overexpression would suppress STAT3 activation and Th17 cells in vitro. Systemic infusion of Ssu72 attenuated experimental autoimmune arthritis by reducing STAT3 activity and the differentiation of Th17 cells. It also reduced joint destruction, serum immunoglobulin concentration and osteoclastogenesis, but increased the number of marginal zone B cells and B10 cells. These effects were associated with reduction of p-STAT3 and suppression of Th17 cell formation in vivo. These data suggest that Ssu72 is related with STAT3 activation and the immune-inflammatory response, and its overexpression on T-cell-mediated immunity has potential for the treatment of autoimmune arthritis.

Keywords: Ssu72, STAT3, Th17, Rheumatoid arthritis

P-034 Synergistic Effect effects of *Lactobacillus acidophilus* and Kartogenin in Monosodium Iodoacetate Induced Osteoarthritis Inflammation and Joint Pain

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Osteoarthritis (OA) is a degenerative joint disease characterized by articular cartilage degradation and pain. *Lactobacillus acidophilus* (*L. acidophilus*) has beneficial effects in experimental rheumatoid arthritis (RA) by suppressing inflammatory immune responses. Recently, a small drug-like molecule, Kartogenin (KGN) showed the upregulataion of chondrogenesis in marrow-derived mesenchymal stem cells (MSCs). This study aimed to identify whether *L. acidophilus* and KGN can improve pain severity and synergistic enhances cartilage repair in OA rat models. Experimental OA was induced by an intra-articular (IA) injection of monosodium iodoacetate (MIA) and injection with KGN in Wistar rats. *L. acidophilus* and Celecoxib was orally administered into OA rats. Celecoxib is a potent nonsteroidal anti-inflammatory drug in Osteoarthritis patients and positive control. Pain was assessed by measuring the paw withdrawal latency and threshold. Histological analysis and micro CT were used to analyze cartilage destruction. Gene expression was measured by real-time polymerase chain reaction. Oral administration of *L. acidophilus* and KGN IA injection more effectively reduced pain and cartilage destruction than Celecoxib. *L. acidophilus* treated interleukin-1 β-stimulated human OA chondrocytes decreased mRNA level of proinflammatory factors and matrix metalloproteinases (MMPs). The major purpose of this study was to evaluate synergistically therapeutic effects of *L. acidophilus* and KGN on pathological responses in experimental rat model of osteoarthritis (OA).

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Keywords: OA, *L. acidophilus*, Chondrocyte, KGN

P-035 TAGLN2 Inhibits Arp2/3 Complex-nucleated Actin Branching and Controls Microvillus Formation in Antigen-polarized T Cells

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One interesting feature of early T-cell antigen recognition is the extension of microvilli toward the cell being recognized. However, little is known about the factors that control microvillus formation or extension in early antigen-recognizing T cells. Here, we found that TAGLN2, a small actin-binding protein predominantly expressed in T cells, is specifically localized at the microvilli. Ectopic expression of TAGLN2 enhanced microvillus formation, and the opposite results were obtained by TAGLN2 depletion. Interestingly, TAGLN2 binds to actin at Arp2/3−actin binding sites, leading to the inhibition of actin branching. Consequently, Arp2/3 was excluded from the TAGLN2-enriched polarized area. Notably, T-cell −antigen-presenting cell (APC) conjugation and the resulting T-cell activation were correlated with the presence and length of microvilli. These results strongly suggest that TAGLN2 plays a key role in microvillus formation at the early stage of T-cell antigen recognition potentially via suppression of Arp2/3-nucleated actin branching

Keywords: TAGLN2, Microvillus, ARP2/3, Antigen-recognition

P-036 Targeting Redox-regulation of TCR Signal by Suppressors of Cytokine Signaling during T cell Activation and Differentiation

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Suppressors of cytokine signaling (SOCS) act as multi-functional regulators during T cell activation and differentiation. Since our recent studies indicated their role in anti-oxidant defense system in the immune-inflammatory condition, we have investigated redox-regulation of TCR signaling by SOCS. It was observed that TCR stimulation provoked early ROS generation and the subsequent induction of anti-oxidant factors (AOFs) including the Nrf2 and Trx system. The TCR downstream signals were blocked by pre-treatment of anti-oxidant agent NAC, suggesting the critical role of ROS signal during T cell activation. In fact direct exposure of T cells to low conc (1 uM) of hydrogen peroxide was sufficient to induce T cell activation signaling along with AOFs. While both SOCS1 and SOCS3 levels were substantially increased upon TCR and ROS stimulation, the over-expression of SOCS1 or SOCS3 each significantly down-regulated intracellular ROS through the activation of AOFs such as Nrf2, Trx, Trx reductase, and SOD. The anti-oxidant function of SOCS in T cell differentiation signaling was then investigated. Both SOCS1 and SOCS3 blocked the TCR/ROS-induced activation of Th2 transcription factors such as NFATC2, STAT6 and ATFII leading to the suppression of IL-4 production. In mouse splenocytes and T cell lines ROS signal induced Th17 and Treg transcription factors with different kinetics. Indeed, the use of SOCS1 or SOCS3 knock-down cells suggests that SOCS1 and SOCS3 may regulate Th17 vs Treg differentiation pathways by differentially affecting RORrt and FoxP3 induction and activation. < Supported by KRF grants # 2015003291 and # 2016911262>

Keywords: Suppressors of cytokine signaling, Redox regulation, TCR signal, T cell differentiation

P-037 The Anti-inflammatory Effect of Novel Fungus-derived Compounds

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The fungal extracts are extensively used as a sources of nutritional foods and drug precursors due to have an anti-biotic, anti-cancer, anti-inflammation and anti-cholesterol effects. However, it has been poorly reported for the anti-inflammatory effects of fungus-derived compounds against bacterial-induced toxicity. Here, we found novel fungus-derived compounds and investigated the anti-inflammatory effects in *in vitro*. To determine the concentration of fungus-derived compounds, we performed MTS assay in RAW264.7 cells. The cell toxicity of twenty fungus-derived compounds was not shown between 0.5 μl/ml and 40 μl/ml of concentration in RAW264.7 cells. To investigate the anti-inflammatory effects of fungus-derived compounds, we analyzed the production of reactive oxygen species (ROS) and nitric oxide (NO) and gene expression of proinflammatory cytokines. The production of ROS and NO was reduced by treatment of fungus-derived compounds in RAW264.7 cells after stimulation of lipopolysaccharide (LPS). Moreover, the gene expression of proinflammatory cytokines including IL-1β, IL-6 and TNF-α was also decreased by treatment of fungus-derived compounds in LPS-stimulated RAW264.7 cells. Therefore, these data suggest that the novel fungus-derived compounds have an anti-inflammatory effects, and which is increased the possibility of candidate for material of drugs.

Keywords: Fungus-derived compounds, ROS, NO, Pro-inflammatory cytokines

P-038 The Short-Chain Fatty Acid Sodium Butyrate Ameliorate Autoimmune Arthritis Via Regulation Of Th17/Treg Balance And Induction Of Breg

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Rheumatoid Arthritis (RA) is characterized by polyarthritis and is an autoimmune disease of unknown origin. The disease not only causes destruction and deformation of the joints but also affects the whole body such as anemia, vasculitis, and skin ulcers. There are no complete remedies for RA. Although prescription of anti-inflammatory drugs, anti-rheumatic drugs, steroids, and TNF blockers could improve symptoms, it also has side effects. Therefore, in order to decrease the side effects on the drug, the gut microbiome-derived metabolites known to regulate the immune system among the substances in the living body have been used. Gut microbiome is not only protects the intestinal surface from external harmful bacteria, but also deeply participates in the development of the immune system and secretes various metabolites. Particularly, *clostridia* is known to secrete SCFA (short chain fatty acid) as metabolite and induce Treg cells in naïve CD4 + T cells. Such as acetate, butyrate and propionate are secreted from *clostridia* as metabolite. Butyrate (one of the SCFA) has an anti-inflammation effect through GPCR (G-protein receptor) or HDACi (histone deacetylase inhibitor). To explore the impact of butyrate on regulation of Th17/Treg balance and differentiation and autoimmune arthritis animal model. We found that the arthritis score and incidence were kept low in the butyrate treated group compared to the control group. Butyrate administration further suppressed IL-17 levels and Th17 generation and induced Treg and Breg. Although further study about the exact mechanism is necessary, the possibility a new therapeutic target on RA treatment by bioactivity of butyrate has been confirmed. Our results suggest that butyrate plays a key role in regulating the Th17/Treg balance and ultimately protects the joint inflammation against the development of rheumatoid arthritis.

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Keywords: Sodium Butyrate, Short-Chain Fatty Acid, Rheumatoid Arthritis, Th17, Treg

P-039 AMPK Activation Alone is Insufficient for Inducing Antimicrobial Responses Against Mycobacteria in Macrophages

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Metformin is a widely used anti-diabetic drug targeting AMP-activated protein kinase (AMPK) pathway, and reported to activate anti-mycobacterial activities in human macrophages. However, little is known about its roles and mechanisms in macrophage antimicrobial functions against *Mycobacterium tuberculosis* (Mtb). First, we examined whether metformin was able to induce the phosphorylation of AMPK and its downstream target, acetyl-CoA carboxylase (ACC), in bone marrow-derived macrophages (BMDMs) under both uninfected and Mtb-infected conditions. Similar effects were seen for metformin and AICAR in terms of both AMPK and ACC phosphorylation in BMDMs, with both drugs inducing phosphorylation in dose- and time-dependent manners. We next examined the effect of each of these agents on intracellular mycobacterial survival in BMDMs. Treatment of Mtb-infected BMDMs with AICAR suppressed intracellular bacterial growth in a dose-dependent manner. In contrast, metformin treatment failed to inhibit the intracellular survival of Mtb in BMDMs. We next examined whether metformin treatment activates autophagy in Mtb-infected macrophages. Metformin treatment robustly up-regulated LC3-II fractions in BMDMs, as determined by immunoblotting, similarly to that seen in AICAR-treated cells. However, in contrast to AICAR, metformin treatment up-regulated the expression of autophagy substrate SQSTM1/p62 in uninfected and Mtb-infected BMDMs. Furthermore, metformin markedly suppressed the rate of proteolysis in long-lived proteins in both Mtb-infected and uninfected BMDMs, as compared with AICAR. These data suggest that metformin treatment is unable to induce a true autophagic flux. Taken together, these data indicate that AMPK activation alone is insufficient for inducing antimicrobial responses against Mtb in macrophages.

Keywords: Mycobacterium tuberculosis, Metformin, AMP-activated protein kinase, Macrophages

P-040 Autophagy Primes Neutrophils for Neutrophil Extracellular Trap Formation During Sepsis

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Excessive or dysregulated functions of neutrophils are considered responsible for the pathogenesis of sepsis. To understand the function of neutrophil during sepsis, we hypothesized that neutrophils from septic patients are either primed or easily stimulated, and autophagy is responsible for the activation of neutrophils. To investigate this, we isolated neutrophils from community acquired pneumonia-induced septic patients, and investigated the functions of neutrophils. Neutrophils were isolated from septic patients who have admitted to the intensive care units, and the morphology, the expression of surface phenotypic markers, the generation of reactive oxygen species (ROS), neutrophil extracellular traps (NETs) formation, granule release, and autophagy were examined. Neutrophils isolated from septic patients showed increased vacuolization with decreased mean lobe counts and showed several changes in phenotypic markers. Further, sepsis neutrophils have increased NETs formation and degranulation markers in response to stimulation. We also found that autophagy is responsible for the priming effect of sepsis neutrophils. Moreover, sepsis neutrophils from non-survivor showed impairment in autophagy with decreased NETs formation. In murine sepsis model, the enhancement of neutrophil autophagy improved survival via increased NETs formation. Together, our study suggests an important insights into role of autophagy in neutrophils during sepsis.

Keywords: Neutrophils, Autophagy, Sepsis, Neutrophil extracellular traps

P-041 BY55/CD160 Receptor is Essential to the Control of Legionella Infection

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The BY55/CD160 receptor is anchored onto cell membrane through glycosylphosphatidylinositol (GPI) and expressed mainly on cytolytic cells such as CD8+ T cells, natural killer (NK) T cells and NK cells as a member of immunoglobulin superfamily. In NK cells, BY55/CD160 receptor binds to MHC class I molecules on target cells with low affinity in humans, whereas BY55/CD160 receptor on T cells suppresses the T cell reactions through its interaction with herpesvirus entry mediator (HVEM) ligand on dendritic cells (DCs). In addition to BY55/CD160 receptor, HVEM also binds to other cell receptors such as gD, BTLA, LIGHT and LT α 1 β 1. One of in vivo characteristics of HVEM−MHC class I−BY55/CD160 interaction has recently been known as a major regulator of the induction and production of cytokines in NK cells, which is essential to early control of tumor development. Recent publications demonstrated that IFN-γ, a major cytokine produced in NK cells, was essential to the control of legionella in in vivo pulmonary and intravenous infections of mice. MyD88, an adaptor protein to various Toll-like receptors (TLRs), is essential to the production of IFN-γ in innate immune responses, indirectly implying the roles of TLRs in control of legionella infections. Now, we have found out that BY55/CD160 receptor has important roles in controlling legionella during pulmonary and intravenous infections, probably through production of IFN-γ in NK cells. Thus we'd like to suggest BY55/CD160 receptor as a novel therapeutic target in treatment of legionella infections and to do so, invent optimal agonists and antagonists, and investigate the relevant signaling mechanisms.

Keywords: BY55/CD160 receptor, Legionella, IFN-γ, NK cells, Therapeutic target

P-042 Different Functions of Neutrophil-derived Microvesicles and Trails

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Neutrophils release different types of extracellular vesicles with diverse biological activities. Neutrophil-derived microvesicles induces aggregation of bacteria and, hence, arrest the growth of bacteria. Neutrophils also deposit chemokine-containing extracellular vesicles known as trail, which can guide the migration of virus-specific CD8+ T cells. Although these neutrophil-derived extracellular vesicles have diverse functions ranging from the immune modulation to antimicrobial activity, their specific characterization has not been fully understood. Here, we studied the differences in compositions and functions between neutrophil-derived microvesicles and trails. We investigated the effects of different stimulants on microvesicles and trails formation. Chemoattractants, inflammatory cytokines, and bacteria induced the generation of microvesicles and trails from neutrophils. Microvesicles and trails showed similar patterns of surface marker expression including phosphatidylserine and MCP-1. Both mircovesicles and trails have direct bactericidal activity and induced chemotaxis of monocytes. However, microvesicle and trails have different effects on the phenotype polarization of macrophages. Additionally, neutrophil-derived extracellular vesicles were also detected in the serum of healthy donors, and their number was significantly increased in the serum of septic patients. Together, our study suggests the important insights into the understanding the neutrophil-derived microvesicles.

Keywords: Neutrophils, Neutrophil-derived extracellular vesicles, Microvesicles, Trails

P-043 Effect of Proton Beam Irradiation on Anti-inflammatory Activity of Quercetin

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Irradiation for food has the potential both of disinfecting dried food to reduce storage losses and disinfesting fruits and vegetables to meet quarantine requirements for export trade. But the ionizing radiation used for food processing is limited to gamma ray of cobalt ^{60}Co and cesium ^{137}Ce, electron beam of energy of 10 MeV or less, and X-ray of energy of 5 MeV or less. This experiment was carried out to prove the possibility of food irradiation by proton beam. Quercetin is a flavonoid found in many fruits, and grains. It is known that *in vitro* as well as in a few animal models to have several potential anti-inflammation and anti-cancer activities. In this study was compared the anti-inflammatory effect of Proton ray-irradiated quercetin and intact quercetin. First, proton ray-irradiated quercetin alleviated toxicity. Secondly, both of them inhibited the production of nitric oxid (NO) and pro-inflammatory cytokine level, such as TNF-α, IL-6, in LPS-induced macrophage. Also suppressed expression of NF-κB, and MAPKs in a dose-dependent manner. Additionally, quercetin inhibited IL-1β, where NLRP3 inflammasome is constitutively activated. Finally, treatment with quercetin partially protected against LPS-induced sepsis in C57BL/6 mice, and results were better in the experimental group with proton beam irradiation. Considering this point, proton beam irradiation not only lowers the toxicity but also increases the anti-inflammatory effect. So These experimental results suggest the possibility that proton rays can be used for food irradiation.

Keywords: Quercetin, Proton beam irradiation, Anti-inflammatory effect, NLRP3

P-044 ER Stress-mediated Mitochondrial Fragmentation in *Mycobacterium tuberculosis*-infected Macrophages

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Apoptosis is an important host defense mechanism against mycobacterial infection. However, the exact regulatory mechanisms are not well-known. Recent reports suggest that bacterial infection regulates mitochondrial fusion and fission in various ways to interfere with apoptosis. Here, we've *Mycobacterium tuberculosis* (Mtb) and examined mitochondrial network in murine macrophages. Mtb H37Rv increased mitochondrial fragmentation and mitofusion-2 (MFN2) degradation, leading to mitochondrial fission. Interestingly, Mtb H37Ra infection significantly induced mitochondrial fission than Mtb H37Rv. Mtb H37Ra infected macrophages reduced mitochondrial membrane potential (MMP) than Mtb H37Rv infected macrophages. We confirmed the increased levels of Parkin production during mycobacterial infection, contributed to the reduction of MFN2. The degradation of MFN2 was increased Mtb infected macrophage apoptosis. To determine the role of ER (endoplasmic reticulum) stress in production of Parkin for mitochondrial dynamics, we used 4-phenylbutyric acid (4-PBA) to reduce ER stress responses. As expected, 4-PBA pretreatment reduced Parkin production but the level of MFN2 production was recovered similar to that of an unstimulated control. Moreover, intracellular survival of mycobacteria was decreased in siMFN2-transfected macrophages. Therefore, we suggest that MFN2 production is important role for anti-mycobacterial host defense.

Keywords: *Mycobacterium tuberculosis*, Endoplasmic reticulum stress, Mitochondria

P-045 Establishment of a Mouse Model of Behavioral Disorder Caused by a Fragment of Ebola Virus Soluble Glycoprotein

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Ebola virus (EBOV), a member of the family *Filoviridae*, is a causative agent of a severe Ebola virus disease (EVD). EVD is highly lethal, with case fatality rate up to 90%. After incubation period as long as 21 days, most case of EVD begins with flu-like symptoms, which common signs are fever, sore throat, vomiting, and stomach pain. And EVD develops into serious disaster with diarrhea, disorientation, hypotension, and hemorrhage. Recently, a retrospective cohort study revealed that disorientation was a reliable predictor of death in human cases. In this study, we have established a murine model of behavioral disorder caused by an EBOV protein. C-terminal 70 amino acid region placed behind the editing site of GP/sGP gene is highly conserved among five Ebola species and has a possibility as an immune regulatory molecule. This region (sGPcd) was tested to investigate its role in mice. Recombinant EGFP protein containing sGPcd were expressed in E. coli and purified by Ni-NTA affinity chromatography. Moreover, Female BALB/c mice (12-week-old) were intravenously injected into their tail veins with recombinant protein containing sGPcd. After injection, behavioral changes were monitored, recorded, and analyzed. This research was supported by Basic Science Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Education(2015R1D1A3A01019005)

Keywords: Ebola virus disease, Ebola Virus, Soluble Glycoprotein, Inflammation, Behavior analysis

P-046 Estrogen-related Receptor-alpha Activates the Macrophage Expression of Autophagy-related Genes through Binding to the Specific ERRE Sites of Target Genes

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The orphan nuclear receptor estrogen-related receptor (ERR) α is a key regulator of energy homeostasis and mitochondrial function. Autophagy, an intracellular degradation process, is a critical innate effector against intracellular microbes. Here, we demonstrate that ERR α is required for the activation of autophagy to promote innate antimicrobial defense against mycobacterial infection. AMP-activated protein kinase pathway and sirtuin 1 activation led to induction of ERR α, which is essential for the autophagosome formation, in bone marrow-derived macrophages. ERR α enhanced the transcriptional activation of numerous autophagy-related genes (ATGs) containing ERR response elements in their promoter regions. We focused on the mechanistic role of ERR α in the transcriptional activation of *Atg5*, *Becn1*, and *Atg16l1*, which were the most differentially expressed transcripts between $Esrra^{+/+}$ and $Esrra^{-/-}$ BMDMs. We thus performed chromatin immunoprecipitation assays to assess the binding of ERR α to the promoters of these genes. ERR α is recruited to the promoter regions of *Atg5*, *Becn1*, and *Atg16l1* to promote transcriptional activation of these genes. Thus, we identify ERR α as a critical activator of autophagy via transcriptional control to promote antimicrobial host responses.

Keywords: ERR α, Autophagy, *Mycobacterium tuberculosis*

P-047 Functional Restoration of HCV-specific T cells after Antiviral Treatment in Patients with Chronic Hepatitis C

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With the recent introduction of direct acting antivirals (DAAs), which inhibit viral replication and infection through blocking nonstructural proteins, more than 90% of patients with chronic HCV infection were able to achieve SVR with less adverse events than interferon-based regimens; Nevertheless, there is a possibility that small amount of HCV RNA in the liver and circulation, risk of relapse, and risk of reinfection still remain in patients with SVR after DAA treatment; However, it remains unclear whether functionally exhausted HCV-specific T cells can be restored after complete viral clearance and its association with clinical outcomes. In this study, we try to identify the functional restoration of HCV-specific CD8+ T cells, which directly kills HCV-infected cells after DAA treatment with time. By using ELISpot with overlapping peptides corresponding non-structural proteins of HCV, which are relatively well conserved than other HCV proteins, we found that early, transient restoration of CD8+ dominant, HCV-specific IFN-γ responses. Restored CD8+ T cells also showed polyfunctionality, which expressed TNF-α and CD107a simultaneously after HCV-peptide stimulation. In addition, in line with previous study, proliferative capacity of HCV-specific CD8+ T cells also tended to be improved after DAA treatment, especially at 12 weeks of treatment. HCV-specific T cell exhaustion, represented by PD-1 expression, had a tendency to be improved and maintained after DAA treatment also at the early timepoint, but terminally differentiated phenotype of HCV-specific T cells was maintained constantly. Thus, it is necessary to find out a particular mechanism to explain the transient restoration of HCV-specific CD8+ T cell responses although T cell exhaustion seems to be improved.

Keywords: Chronic hepatitis C, Direct acting antiviral, HCV-specific T cell, T cell restoration

P-048 Gene and Protein Expression Analysis in a Collagen-Induced Animal Model

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Interest in rheumatoid arthritis is growing in aging societies. According to Korea Ministry of Health and Welfare, the number of people suffered from arthritis has been increased from 408 million to 449 million between 2011 and 2015. In addition, arthritis became second to none in terms of diagnosis of more than 60's people. Therefore, we have tried to find molecular and immunological mechanisms using collagen-induced arthritis (CIA) model. Male DBA/1J mice (6–8 weeks old) were inoculated bovine type II. Blood from control and CIA mice was collected in PAXgene RNA tube, and microarray analysis was performed with GeneChip® Mouse Gene 2.0 ST Array following the manufacturer's instructions. Data were analyzed using KEGG pathway. To investigate different protein expressions in CIA model, proteome array was performed using ProteomeProfiler™ Mouse Cytokine Array. Depends on KEGG pathway analysis, we found that genes involved in MAPK signaling pathway (*Dusp3*, *Rps6ka2*, *Fos*, *Flna*) were significantly increased while, Natural killer cell mediated cytotoxicity (*Klrd1*, *Lck*, *Ncr1*, *Lat*) and Jak-STAT signaling pathway (*Stat4*, *Ccnd2*, *Il7r*, *Il2rb*) were decreased. In proteome analysis, we observed that IP-10, MIG, BLC, and I-TAC proteins were increased more than twice. Results should be confirmed by different methods, however, our results might be useful to understand molecular and immunological mechanisms of arthritis.

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Keywords: Rheumatoid arthritis, Collagen-induced arthritis model, Microarray, Proteome analysis

P-049 Improved Production of Soluble Recombinant Thioredoxin Peroxidase of *C. sinensis* and Its Inhibitory Role in Apoptosis

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Clonorchis sinensis is a carcinogenic liver fluke distributed in East Asia including Korea, China, Vietnam, and parts of Russia. Adult worm of *C. sinensis* can dwell in bile duct for over 10 years and its chronic infection promotes persistent oxidative stress such as reactive oxygen species (ROS). To ensure parasite's long-term survival, anti-oxidant mechanism is important and Thioredoxin peroxidase (TPX) is one of the redox enzymes used by parasites. Main function of TPX is neutralizing H_2O_2 and it also has additional functions including regulating apoptosis. Here, we produced soluble recombinant TPX protein of *C. sinensis* (rCsTPX) in *Eschericia coli* system and investigated its modulation of apoptosis. Because of low solubility of rCsTPX, at first, most of the expressed protein was insoluble form. To improve its solubility, we changed the expression conditions such as isopropyl β-D-1-thiogalactopyranoside (IPTG) concentration, temperature, or duration of induction. Eventually we set the proper expression condition that we can get soluble form of rCsTPX at 20°C. With this soluble rCsTPX, its inhibitory effect of apoptosis was observed in macrophage cell line and T cell line. In conclusion, these results suggest the better method of producing soluble rCsTPX and further imply that rCsTPX has inhibitory function of apoptosis as a potential candidate for therapeutic application.

Keywords: *C. sinensis*, Thioredoxin peroxidase, Apoptosis, Anti-apoptotic effect

P-050 Interaction Between *Trichomonas vaginalis* and the Prostate Epithelium

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Most men infected with *T. vaginalis* are asymptomatic and can remain undiagnosed and untreated. This has been hypothesized to result in chronic persistent prostatic infection. Adhesion of the protozoan organisms to mucosal cells is considered a first and prerequisite step for *T. vaginalis* infection. Adhesion of *T. vaginalis* to prostate epithelial cells has not yet been observed; however, there are several reports about inflammation of prostate epithelial cells induced by *T. vaginalis*. The aim of this study was to investigate whether adhesion and cytotoxicity of *Trichomonas vaginalis* are involved in inflammation of prostate epithelial cells. When RWPE-1 cells were infected with *T. vaginalis* (1:0.4 or 1:4), adhesion of *T. vaginalis* continuously increased for 24 or 3 hr, respectively. The cytotoxicity of prostate epithelial cells infected with *T. vaginalis* (RWPE-1:*T. vaginalis* = 1:0.4) increased at 9 hr; at an infection ratio of 1:4, cytotoxicity increased after 3 hr. When the RWPE-1 to *T. vaginalis* ratio was 1:0.4 or 1:4, production of IL-1β, IL-6, CCL2, and CXCL8 also increased. Epithelial-mesenchymal transition (EMT) was verified by measuring decreased E-cadherin and increased vimentin expression at 24 and 48 hr. Taken together, the results indicate that *T. vaginalis* adhered to prostate epithelial cells, causing cytotoxicity, pro-inflammatory cytokine production, and EMT. Our findings suggest for the first time that *T. vaginalis* may induce inflammation via adhesion to normal prostate epithelial cells.

Keywords: *Trichomonas vaginalis*, Epithelial cells, Cell adhesion, Inflammation

P-051 Interleukin-15 Receptor Alpha Ameliorates the HSV-induced Behçet's Disease Symptoms in Mouse Model

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It has been suggested that IL-15 and IL-15 receptor alpha (IL-15Ra) can be innovative therapeutic targets for Behçet's disease (BD) through up-regulation of IL-15Ra. However, there were no evidence data for BD patients or mouse model until now. The expression of IL-15Ra was evaluated in BD patients and BD mice and pIL-15/15Ra complex expressing vector was applied to BD mice as a therapeutic supplement for the improvement of BD symptoms. The frequencies of IL-15Ra in peripheral blood mononuclear cells of BD patients and BD mice were analyzed by flow cytometry and the change of disease severity score was traced in BD mice. The frequencies of IL-15Ra+ cells and its combinations CD56+ IL-15Ra+, CD11b+IL-15Ra+ and CD11c+IL-15Ra+ cells were different between active BD patients and healthy controls. The BD symptoms of mice were improved after pIL-15/15Ra expressing vector injection. BD mice treated with pIL-15/15Ra vector increased the frequencies of IL-15Ra+ cells in peritoneal macrophages (p=0.02) and lymph nodes cells (p=0.05) compared with control vector pcDNA3.1 treated BD mice. pIL-15/15Ra vector to BD mice significantly decreased the disease severity compared to control treated BD mice (p=0.016). In IL-2/IL-2 antibody complex treated BD mice, IL-15Ra+ cells were higher than that in the IgG treated BD mice in spleen (17.69 ± 4.39% *vs*. 13.38 ± 7.64%, p=0.2) and PBMC (9.08 ± 4.06% *vs*. 8.60 ± 5.75%). In addition, BD mice treated with colchicine (p=0.0003) and pentoxifylline (p=0.0001) also increased IL-15Ra+ cells in lymph nodes compared with not treated BD mice. The obtained results showed correlation of IL-15Ra in mouse model of Behçet's disease.

Keywords: IL-15R alpha, HSV, Behcet's disease, Mouse model

P-052 Interleukin-33 Regulates Intestinal Inflammation by Modulating Macrophages in Inflammatory Bowel Disease

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IL-33 is a member of IL-1 cytokine superfamily that signals through ST2 receptor, and induces helper T cell type 2 immune response. Type 2 immune response by Th2/Treg may differentiate monocytes into M2 type macrophages. Type 2 cytokines induced by M2 type macrophages have anti-inflammatory and epithelial wound healing functions. However, the role and underlying mechanisms of IL-33 in inflammatory bowel disease (IBD) remain poorly understood. Accordingly, we sought to clarify the role and underlying mechanisms of IL-33 in IBD including UC, CD, and intestinal BD. The serum IL-33 levels in patients with IBD were lower than those in normal controls, whereas the sST2 levels in patients with IBD were higher than those in normal controls. Recombinant mouse IL-33 administration substantially ameliorated TNBS and DSS- mediated colonic tissue injury and clinical symptoms of colitis. Additionally, degree of wound healing was significantly faster in IL-33 treated PBMCs in both healthy controls and IBD patients. Moreover, when we co-cultured human monocytes and lymphocytes with the treatment of recombinant human IL-33 for 24 hours, we found more intensified CD206 fluorescence, an M2 macrophage surface marker, than untreated group. We demonstrated plasma levels of IL-33 were significantly decreased, but soluble ST2 levels were increased in patients with IBD compared to healthy individuals. Moreover, IL-33 restored goblet cell numbers and induced macrophage switching from the M1 to the M2 phenotype. These effects were sufficient to ameliorate colitis in DSS, TNBS, and peritoneal cavity cell transfer models. IL-33 facilitated goblet cell restoration via modulating macrophages toward the M2 phenotype. In addition, wound healing was significantly faster in IL-33-treated human monocyte-derived macrophages than in control cells, which could be attributed to increased polarization into M2 macrophages.

Keywords: Inflammatory bowel disease, Macrophage, Goblet cell, Interleukin-33

P-053 Metformin Ameliorates Sjögren's Syndrome-like Disease in the NOD/ShiLtJ Mouse by Regulating the Th17/Treg Cells Balance

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OBJECTIVE: Metformin is used to treat type 2 diabetes. We sought to determine whether metformin reduces inflammation, by regulating p-signal transducer and activator of transcription 3 (STAT3) expression and T-helper 17 (Th17) cell/regulatory T cell balance, in a mouse model of Sjögren's Syndrome.
METHODS: NOD/ShiLtJ mice were administered metformin for 9 weeks and their tissues were analyzed. The infiltration of lymphocytes in salivary and lacrimal glands were detected using H&E and immunohistochemistry. Proinflammatory cytokine and IgG was determined using enzyme-linked immunosorbent assay. Th17 and Treg cell population was determined using flow cytometry,
RESULTS: The saliva flow rate was lower in the mice administered with the metformin compared with those administered with the saline. Metformin decreased the infiltration of lymphocytes into both the salivary glands and lacrimal glands Also, metformin reduced immunoglobulin and the expression of proinflammatory cytokines including IL-6, TNF-α, IL-21. The numbers of $CD4^+IFN\text{-}\gamma^+$, $CD4^+IL\text{-}17^+$ cells in the metformin-treated group were significantly lower than in the control group. The number of $CD4^+CD25^+FOXP3^+$ cells were significantly higher in metformin-treated group. Metformin inhibited Th17 cell differentiation and reciprocally enhanced the Treg population via downregulation of STAT3. In addition, expression of inflammatory cytokines decreased in a dose-dependent manner in inflamed human salivary gland cells cultured with metformin at various concentrations.
CONCLUSIONS: Metformin attenuates sjögren's syndrome severity and recovers salivary flow rate. Also, metformin reduced inflammation through the regulation of Th17/Treg balance. Our results have increased our understanding of this chronic inflammatory disease, and support the strategy of using p-STAT3 inhibitors to treat sjögren's syndrome.

Keywords: Sjögren's Syndrome, STAT3, Th17/Treg, Metformin

P-054 *Mycobacterium tuberculosis* H37Ra Infection and Hypertension

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Patients with hypertension are increasing worldwide. It is involved in several serious diseases that threatens the patient's life such as arteriosclerosis, cerebral infarction, and myocardial infarction. The inflammatory response plays an important role in the pathogenesis of hypertension. To explore the role of hypertension in mycobacterial infection, we compared pathophysiological characterization between wild type mice (control group) and angiotensin II-induced hypertensive mice (hypertension group). Following Angiotensin II ($0.7mg/Kg/day^{-1}$) infusion in C57BL/6 mice, Mtb H37Ra was infected intra- tracheal with approximately $1x10^6$/CFU of bacilli. We found that ER stress responses were increased in hypertensive mice lung tissue. Severe inflammatory lesions and fibrosis were increased in hypertension group compared with controls. Mtb infection was severe in hypertensive mice lung comparing to the control. These results suggest that hypertension might be harmful for host protection from mycobacterial infection.

Keywords: *Mycobacterium tuberculosis*, Hypertension, ER stress

P-055 Neoagarooligosaccharides Prevent Septic Shock by Modulating A20- and Cyclooxygenase-2-mediated Interleukin-10 Secretion in a Septic-shock Mouse Model

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Analysis of the signaling mechanism triggered by endotoxin-mediated toll-like receptor-4 activation using immune cell systems or rodent models may help identify potential agents for the prevention of Gram-negative bacteria infection. β-agarase cleaves the β-1,4-linkages of agar to produce neoagarooligosaccharides (NAOs), which have various physiological functions. The aim of this study was to investigate the efficacy of NAOs in preventing experimental sepsis caused by the administration of endotoxin or Gram-negative bacteria. Organ damage and neutrophil infiltration in an endotoxemia and septic-shock mouse model were suppressed by NAOs. Pro-inflammatory cytokine level was decreased, but IL-10 level was increased by NAO-treatment. Further induction by NAOs in the presence of endotoxin was associated with a significant induction of A20 and cyclooxygenase (COX)-2 expressions. Our data suggest that NAOs have a beneficial preventive effect in septic shock correlated with the enhancement of IL-10 via the induction of A20 and COX-2.

Keywords: Neoagarooligosaccharides, Sepsis, Prevention, A20, COX-2, IL-10

P-056 p204 Is a Critical Modulator in Innate Immunity

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p204 is one of the murine p200 family members and has been regarded as a modulator in multiple biological functions. Interferon-inducible protein (IFI)-16, considered as a human counterpart of p204, was described as an intracellular direct sensor of viral DNAs, as a result, to induce interferon (IFN)-β production in macrophages. Although a number of emerging studies have investigated the function of p204 as a pathogen sensor akin to IFI16, its role *in vitro*, especially, *in vivo* remains unclear due to the lack of p204-deficient animal models. In this study, we first generated the $p204^{-/-}$ mice. p204 deficiency led to significant defect in inflammatory responses mediated by extracellular lipopolysaccharide (LPS) in macrophages, as demonstrated by dramatic reductions of LPS-mediated IFN-β and pro-inflammatory cytokines. The serum levels of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β were also significantly reduced in $p204^{-/-}$ mice with LPS challenge. Moreover, p204-/- mice were much more resistant to LPS shock than wild type mice. Mechanistic studies demonstrated that LPS-activated NF-κB and IRF-3 pathways were significantly suppressed in the p204-deficient macrophages. Taken together, these results strongly indicate that p204 is a critical modulator for the LPS signaling in macrophage-mediated innate immunity and also suggest that p204 could be a potential target to prevent and treat inflammatory and infectious diseases.

Keywords: p204, Inflammatory Responses, Macrophages, LPS, TLR4

P-057 p204 Is a Novel Regulator in Non-Canonical Inflammasome Activation

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Previous studies have demonstrated that p204, one of the p200 family members, plays an anti-pathogenic role in innate immunity, however, the underlying mechanism has been poorly understood. In this study, the novel role of p204 against intracellular lipopolysaccharide (LPS), a major pathogenic component in Gram-negative bacteria in a non-canonical inflammasome pathway was explored in macrophage-mediated innate immunity. p204-deficient (p204-def.) Raw264.7 cells were generated by CRISPR/Cas9 technology, and IL-1β secretion and cytotoxicity were significantly suppressed in the p204-def Raw264.7 cells transfected with LPS. LPS structure has been known as a critical determinant for inflammatory responses in macrophages. IL-1β secretion and cytotoxicity were induced in the Raw264.7 cells transfected with tetra- or hexa-acylated LPS, not with hepta-acylated LPS, and markedly decreased in the p204-def Raw264.7 cells. Interferon-inducible protein (IFI)-16 has been regarded as a human counterpart of p204, and IFI16-deficient (IFI16-def.) U937 cells were generated by CRISPR/Cas9 technology. IL-1β secretion and cytotoxicity were significantly suppressed in the IFI16-def U937 cells transfected with LPS. Taken together, these results suggest that p204 is a potentially critical regulator in a non-canonical inflammasome activation in macrophage-mediated innate immunity.

Keywords: p204, IFI16, Intracellular LPS, Non-canonical inflammasome, Macrophage

P-058 Parasite Infection Alters IL-4 Secreting T Cells

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The parasitic infection enhanced the level of some cytokines related to T helper 2 (Th2) responses. However, which types of cells produced mainly these kinds of cytokines are still unknown. Focusing on interleukine-4 (IL-4) cytokine, we used genetically controlled mice expressing GFP while cells activated to express IL-4. Two hundred fifty Trichinella spiralis muscle larva were administered orally and sacrificed at 4-weeks after infection. Splenocytes and lymphocytes isolated from peripheral lymph node and mesenteric lymph nodes were analyzed by Fluorescence activated cell sorter (FACS) analysis using several cell specific markers. The most noteworthy result is increasing of IL-4 secreting T cell in immune tissue after infection. Especially, It was increased IL-4 production in central memory T cells and effector memory T cells. Although IL-4 secreting natural killer cells were decreased, but IL-4 secreting natural killer T cells were increased.

Keywords: Parasite infection, Th2 responses, Immune system

P-059 Platelet-activating Factor Mediates Endotoxin Tolerance by Regulating Indoleamine 2,3-dioxygenase-dependent Expression of the Suppressor of Cytokine Signaling 3

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Indoleamine 2,3-dioxygenase (IDO) mediates immune tolerance, and suppressor of cytokine signaling 3 (SOCS3) negatively regulates the JAK/STAT signal transduction pathway. We determined previously that platelet-activating factor (PAF) protects mice against LPS-induced endotoxic shock, but its detailed mechanism of action was unknown. We performed survival experiments in $IDO^{+/+}$ and $IDO^{-/-}$ mice using an LPS-induced endotoxemia model and rated organ injury (neutrophil infiltration and liver function). Using ELISA and Western blotting, we also investigated the mechanism of PAF-mediated endotoxin tolerance during endotoxemia. PAF-mediated endotoxin tolerance was dependent on IDO *in vivo* and *in vitro* and was not observed in $IDO^{-/-}$ mice. JAK/STAT signaling, crucial for SOCS3 expression, was also impaired in the absence of IDO. In an IDO- and STAT-dependent manner, PAF mediated a decrease in IL-12 and a dramatic increase in IL-10 and reduced mouse mortality. In addition, PAF attenuated LPS-mediated neutrophil infiltration into the lungs and interactions between neutrophil-like (THP-1) and endothelial cells (human umbilical vein endothelial cells). These results indicate that PAF-mediated endotoxin tolerance is initiated via IDO- and JAK/STAT-dependent expression of SOCS3. Our study has revealed a novel tolerogenic mechanism of IDO action and an important association between IDO and SOCS3 with respect to endotoxin tolerance.

Keywords: Platelet-activating factor, Endotoxin tolerance, Indoleamine 2, 3-dioxygenase, Suppressor of cytokine signaling 3, Endotoxemia

P-060 Pravastatin and Sarpogrelate Synergistically Ameliorate Atherosclerosis in LDLr-Knockout Mice

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Pravastatin is a lipid-lowering agent that attenuates atherosclerosis. However, the multifactorial pathogenesis of atherosclerosis requires other drugs with different anti-atherogenic mechanisms. We chose sarpogrelate as an anti-platelet agent and a novel component of a complex drug with pravastatin due to its high potential but little information on its beneficial effects on atherosclerosis. Low-density lipoprotein receptor-knockout mice were fed a high fat, high-cholesterol diet and treated with pravastatin alone, sarpogrelate alone, or a combination of both drugs. Although sarpogrelate alone did not significantly reduce atherosclerotic plaque areas, co-treatment with pravastatin significantly decreased aortic lesions compared to those of the pravastatin alone treated group. The combined therapy was markedly more effective than that of the single therapies in terms of foam cell formation, smooth muscle cell proliferation, and inflammatory cytokine levels. These results suggest that pravastatin and sarpogrelate combined therapy may provide a new therapeutic strategy for treating atherosclerosis.

Keywords: Atherosclerosis, Diet, Statins, Lipoprotein receptors, Inflammatory cytokines

P-061 The Pathogenesis of Interleukin-22 and Its Receptor in UVB-induced Skin Inflammation

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Recent studies show that IL-22, a cytokine produced by activated CD4+ T cells and NK cells, plays a pathogenic role in acute and chronic skin diseases. Unlike IL-22 produced in immune cells, the expression IL-22R α, a functional subunit of IL-22R, is mostly restricted to non-hematopoietic cells in organs like skin and pancreas. Although it is well known that UVB induces skin inflammation, there have been no reports regarding the role of UVB in regulating the expression of IL-22R α receptor so far. This study aims to investigate the expression of IL-22 α in keratinocytes and it related mechanisms during a skin inflammatory response by UVB irradiation, as well as the effects of IL-22 on the proliferation and the pro-inflammatory cytokine production from UVB-irradiated keratinocytes. The expression of IL-22Ra on UVB-irradiated human and mouse skin were examined by immunohistochemistry. IL-22R α is increased in HaCaT and primary human keratinocytes after UVB irradiation through the translocation of IL-22R α from the cytosol to the membrane. We also found that increase in the expression of IL-22R α is mediated by the activation of the PI3K/Akt pathway. Moreover, the suppressed proliferation of keratinocytes caused by UVB irradiation can be recovered with an IL-22 treatment. At the same time, IL-22 increases the production of IL-1 α, -6 and -18 in UVB-irradiated HaCaT and primary human keratinocytes. The increased expression of IL-22R α is closely related with the proliferation of keratinocytes and the production of inflammatory cytokines (IL-1 α, -6 and -18), during UVB-induced skin inflammation. It suggests that UVB facilitates skin inflammation by increasing the expression of IL-22R α in keratinocytes. Therefore, our study provides a new insight into UVB-induced skin inflammation and the regulation of related inflammatory skin diseases.

Keywords: Interkeukin-22, Skin inflammation, UVB, HaCaT

P-062 TNF Superfamily Members Regulate Kaposi's Sarcoma-Associated Herpesvirus

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OX40 and 4-1BB belongs to tumor necrosis factor superfamily members which are involved in various cellular processes. OX40 and 4-1BB are known to modulate T cell activation and memory T cell generation. Recently, it has been shown that congenital loss of functional OX40 on T cells is responsible for aggressive childhood development of Kaposi's sarcoma. Therefore, it seems that OX40 co-stimulation is required for in the adequate generation of KSHV-specific T cell activation. Here, using specific antibodies, either activating or inhibiting to OX40 or 4-1BB, we provide a molecular basis of OX40-mediated KSHV regulation.

Keywords: Kaposi's sarcoma-associated herpesvirus, OX40, Viral replication

P-063 Transcription Factor EB Enhances Phagosomal Maturation and Antimicrobial Responses During Mycobacterial Infection

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Transcription factor EB (TFEB) transcriptionally regulates numerous genes involved in multiple steps of autophagy, including autophagosomal and lysosomal biogenesis and substrate targeting and degradation. However, the function of TFEB in mycobacterial infection has not been known. In this study, we investigated the role of TFEB in PPAR-α–mediated phagosomal maturation and antimicrobial responses in bone marrow-derived macrophages (BMDM) during mycobacterial infection. We found that PPAR-α agonists led to robust expression and rapid nuclear translocation of TFEB. PPAR-α stimulation significantly increased translocation of cytosolic TFEB to the nucleus in *Ppara*$^{+/+}$ BMDM, this was markedly decreased in *Ppara*$^{-/-}$ BMDM. We next examined the role of TFEB in PPAR-α–mediated induction of genes involved in autophagosomal formation and maturation into autolysosomes. Knocking-down of TFEB reduced phagosomal maturation and antimicrobial responses. Taken together, our data indicate that PPAR-α mediates antimicrobial responses to mycobacterial infection by inducing TFEB.

Keywords: Transcription factor EB, Mycobacterial infection, Autophagy

P-064 Type I Interferon Signaling Sustained During Chronic Viral Infection Directly Enhance NK Cell-mediated Immunosurveillance for Cancer

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The importance of natural killer cells (NK cells) in the early immune response to viruses or bacteria infection is well known. However, the physiological role of NK cell in a host infected with the chronic virus has not been extensively studied. To identify the role of NK cell at the late stage of chronic virus infection was studied in the mice persistently infected with lymphocytic choriomeningitis virus clone13 (CL13). In this study, we found that terminally differentiated CD27^{low}KLRG1^{+}CD11b^{high} NK cells were more abundant in the chronically infected mice than in naïve mice. Furthermore, the NK cells from CL13-infected mice showed less expression of inhibitory receptors, NKG2A and Ly49C/I than those from naïve mice. The low expression of inhibitory receptors enhanced the NK cell activity, which could be seen by increasing the expression of CD69 and granzyme B (Gzm B). At the functional level, NK cells in the CL13-infected mice displayed increased ex vivo IFN-γ production and *in vitro* cytotoxicity. We found that type I interferon (type I IFN) signaling is the key mechanism of increased NK cell activity. Indeed, the CL13-infected mice, but not naive mice, dramatically delayed tumor formation when various tumor cells such as B16F10 melanoma, EG7 thymoma, and TC-1 lung adenocarcinoma were inoculated. Suppression of tumor formation in CL13-infected mice was abrogated by either depletion of NK cells or blockade of type I IFN receptor, suggesting that NK cell-mediated cytolytic activity induced by type I IFN s plays an important role in the inhibiting tumor formation during chronic viral infection.

Keywords: Type I interferon, Natural kiiler cells, Tumor, Lymphocytic choriomeningitis virus

P-065 *Ureaplasma urealyticum* Increase Proinflammtory Mediator via TLR2 and NOD1 Signaling in Mouse Peritoneal Mesothelial Cells

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Problem: *Ureaplasma urealyticum* (*U. urealyticum*), an opportunistic pathogen of the human urogenital tract, has been implicated in contributing to pelvic inflammatory disease and chorioamnionitis. Mesothelial cells that line the serous cavities and outer surface of internal organs are involved in inflammatory responses induced by microbial stimuli and bacterial infection. Upon exposure to bacterial products, mesothelial cells secrete chemokines, but the signaling pathways of these cells involved in innate immune responses to *U. urealyticum* remain largely unknown. We investigated which Pattern Recognition Receptors (PRRs) is important for activation of innate immune response of mesothelial cells against *U. urealyticum*.
Method of study: Peritoneal mesothelial cells were isolated from Wild-Type, TLR2, TLR4, NOD1, and NOD1/TLR2 KO mice by trypsin digestion. The cells were treated with TLR and NOD ligands and infected *U. urealyticum* at the indicated multiplicity of infection (MOI). The responses were measured by ELISA and Immunoblotting.
Results: Production of IL-6, CXCL1, and CCL2 was increased in peritoneal mesothelial cells by *U. urealyticum*. *U. urealyticum* induced activation of MAPKs via TLR2 and NOD1.
Conclusion: This study suggests that *U. urealyticum* induces peritoneal inflammation via TLR2 and NOD1 signaling.

Keywords: *U. urealyticum*, Peritoneal mesothelial cells, TLR2, NOD1, Proinflammatory mediator

P-066 Alteration of Gut Microbiota by Statins Leverages Immune Responses Association with Regulation of Inflammatory Responses

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Gut microbiota plays important role in intestinal immune homeostasis, various dietary interventions are associated with the composition of gut microbiota. Recent studies reported that medication modulated the gut microbiota, which was revealed to be a contributing factor to metabolic improvements. In this study, the characteristics of gut microbiota by statins (Atorvastatin and Rosuvastatin) was investigated in aged obese mouse and described the association between gut microbiota and immune responses. As expected, statins significantly improved the metabolic profiles including body weight, serum glucose, and total cholesterol. Both Atorvastatin and Rosuvastatin significantly increased the abundance of genus *Bacteroides*, *Butyricimonas*, and *Mucispirillum*. Moreover, those abundances were correlated with the regulation of inflammatory responses. Our finding identified the modulation of gut microbiota by statins leverages immune responses association with inflammatory responses.

Keywords: Gut microbiota, Atorvastatin, Rosuvastatin, Immune responses

P-067 Formyl Peptide Receptor-2 Signaling in Peyer's Patch Follicular Dendritic Cells Contributes to Mucosal Homeostasis

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Peyer's patch (PP), a mucosal immune inductive site, is required for the induction of antigen-specific IgA immune response. Generation and maintenance of germinal center (GC) is necessary to produce high quality antibodies, but little is known for the regulatory mechanism of PP GC maintenance. Especially, information for the modulation of follicular dendritic cells (FDCs) is limited while FDCs play a critical role as an initiator for follicle formation during GC generation. In this study, we investigated the role of formyl peptide receptor (FPR)-mediated signaling in FDCs for the maintenance of PP GCs, because FPRs recognize microbiota and initiate an innate immune response by chemotaxis. We found that FDC, a key organizer of B cell follicles and GCs in mucosal immunity, expresses Fpr2. Additionally, Fpr2-mediated signaling in PP FDCs promoted the expression of Cxcl13 and B cell activating factor together with B cell proliferation and activation. Collectively, we suggest that Fpr2-mediated signaling in FDCs plays a key role in GC maintenance in PPs and results in an antigen-specific IgA response in the gut mucosal immune compartment. (This study was supported by the Basic Science Research Programs (2016R1A2B2010096 to Y.-S. Jang and 2014R1A1A 3051207 to S.-H. Kim) through the NRF funded by Korean Ministry of Science, ICT & Future Planning.)

Keywords: Follicular dendritic cells, Formyl peptide receptor-2, Germinal center, Peyer's patch

P-068 Receptor Tyrosine Kinase Expressed on Epithelial Cell Regulates the Migration of $\gamma\delta$ Intraepithelial Lymphocytes in Small Intestine

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Intraepithelial lymphocytes of the small intestine involve ~50-60% of $\gamma\delta$ TCR-expressing T cells ($\gamma\delta$ T cell). Although it has been known that $\gamma\delta$ T cells play a critical role for bacteria killing and regulation of inflammation in the small intestine, the regulation of $\gamma\delta$ T cells population remains to be unraveled. Furthermore, defined regulating mechanism underlying receptor tyrosine kinase expressed on epithelial cell (REE)-induced cytokines poorly understood yet. In this study, we observed that population of $\gamma\delta$ T cells were increased in REE knock out (KO) mice compared with wild type (WT) mice. The $\gamma\delta$ T cells of REE KO showed not significant difference in survival, proliferation and differentiation compared with WT mice. However, the infiltration efficiency of $\gamma\delta$ T cells was higher in REE KO than WT mice. The increased population of $\gamma\delta$ T cells in REE KO mice alleviated small intestine length, disease activity index (DAI) and inflammation on listeria infection. Taken together, these results suggested that deficiency of REE positively regulated the infiltration of $\gamma\delta$ T cells and result in increased resistance to bacterial infection. Therefore, REE may play a critical role in the regulation of $\gamma\delta$ T cells population and provide a useful strategy for prevention of small intestine inflammation.

Keywords: $\gamma\delta$ T cells, Small intestine, Inflammation

P-069 A Small Molecule Inhibitor, Inflachromene, Reduces the Early Loss of Islet Graft after Transplantation

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Pancreatic islet transplantation is one of the best cure for patients suffering from type 1 diabetes mellitus, especially the ones with hypoglycemia unawareness. Despite the apparent advances in allogeneic islet transplantation field, significant loss of implanted islet in the immediate post-transplantation period is still a big concern in the clinics. One of the factors determining the successful engraftment of the islets after the transplantation procedure is the danger-associated molecular patterns (DAMPs) secreted by pancreatic islets or the immune cells near the allograft. High-mobility group box 1 (HMGB1) protein is one of the best characterized DAMP molecules so far, and they have been known to cause damage against islet cells owing to its pro-inflammatory effect. HMGB1 can be passively released by transplanted murine islet cells after taking damage from cytokines, hypoxic state, reactive oxygen species (ROS), and other DAMPS. The released HMGB1 can harm other islet cells by interacting with receptors expressed on murine islets such as TLR2 and TLR4, thereby forming a vicious cycle. Here, we show *in vitro* that a small molecule inhibitor inflachromene (ICM), which was reported to be potent in blocking HMGB1 and HMGB2 secretion in microglial cells, was capable of blocking the secretion of HMGB1 from MIN6 cells, a murine pancreatic β cell line. Moreover, it was demonstrated *in vivo* that ICM treatment was highly effective for glycemic control after marginal-mass islet transplantation, which suggests that ICM could spare the transplanted islet mass.

Keywords: Pancreatic islet, HMGB1, Hypoxia, Cytokine damage, Inflammation

P-070 Cell-mediated Transmission of KSHV into Transformed B Cell Line

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Kaposi's sarcoma-associated herpesvirus is a lymphotropic gamma-herpesvirus and as such infects B cells in vivo, inducing two different B cell lymphoma: primary effusion lymphoma and multicentric Castleman's disease. However, paradoxically, B cell lines have been refractory to KSHV infection in vitro. Here, we provide strong evidence that transformed B cell lines can be rendered susceptible only when exposed to cell-associated viruses. Cell-free virus stocks were unable to infect BJAB and Ramos cell lines even at MOI 106, suggesting only cell associated viruses can enter B cell lines. There seem no post-entry blocks as infected BJAB cells were able to be induced when treated with histone deacetylase inhibitors. Detailed biochemical analysis of KSHV-mediated perturbation of B cell biology is now made available.

Keywords: Kaposi's sarcoma-associated herpesvirus, Cell-mediated transmission, B cell lymphoma

P-071 Ectopic Expression of the Membrane-Bound Form of IL-17A Promotes the Growth and Tumorigenicity of Cancer Cells

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Interleukin-17A is a member of the IL-17 family, and is known as CTLA8 in the mouse. It is produced by T lymphocytes and NK cells and has proinflammatory roles, inducing cytokine and chemokine production. However, its role in tumor biology remains controversial. We investigated the effects of locally produced IL-17A by transferring the gene encoding it into mouse tumor cells including B16 melanoma, and MethA fibrosarcoma, either in a secretory or in a membrane-bound form. Expression of the membrane-bound form on CT26 colon cancer cells dramatically enhanced their proliferation in vitro. The enhanced growth was shown to be due to an increased rate of cell cycle progression: after synchronizing cells by adding and withdrawing colcemid, the rate of cell cycle progression in the cells expressing the membrane-bound form of IL-17A was much faster than that of the control cells. Both secretory and membrane-bound IL-17A induced the expression of Sca-1 on the cancer cells, which is commonly associated with aggressive phenotype of cancer cells. When tumor clones were grafted into syngeneic BALB/c mice, the tumor clones expressing the membrane-bound form IL-17A grew rapidly; those expressing the secretory form also grew faster than the wild type CT26 cells, but slower than the clones expressing the membrane-bound form. These results indicate that IL-17A promotes tumorigenicity, in part, by enhancing cell cycle progression. This finding should be considered in treating tumors and immune-related diseases.

Keywords: Interleukin-17A, Membrane-bound form, Cell cycle, Tumorigenicity

P-072 Peripheral CD4/CD8 Double Positive T cells as a Specific Biomarker for Graft Rejection in Islet Transplantation

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Previous observation has shown that there were substantial number of CD4/CD8 double positive (DP) T cells in peripheral blood and secondary lymphoid organs in human and animals. DP T cells were functionally equivalent to conventional CD4 or CD8 T cells with respect to their helper or cytotoxic activity. DP T cells highly expressed CXCR5 and PD-1 levels, and showed equivalent capacity for secretion of IFN-γ, IL-4, and IL-21 as compared to that of CD4 T cells. They also have strong capacity for production of granzyme B and perforin as compared to that of CD8 T cells. In addition, these cells expressed eomesodermin and promyelocytic leukemia zinc finger protein (PLZF) in steady status. In islet transplantation model, it turned out that absolute number of DP T cells were positively correlated with graft rejection, whereas this was not the case in long-term survival group. Effector memory T cell (TEM) subpopulations of DP T cells were significantly increased only in graft rejection group, whereas this is not the case in TEM of CD8 T cells where there was no difference between rejection and survival group. Taken together, peripheral DP T cells have dual functions with respect to getting in both helper and cytotoxic immune responses. Based on all of this data, we suggest that DP T cells may play some role in the process of graft rejection during islet transplantation.

Keywords: DP T cells, Helper function, Cytotoxic activity, Transplantation, Rhesus monkey

P-073 An Experimental Verification of The Adjuvant Effect of M Cell-targeting Molecules Combined with MERS-CoV Antigen by Intranasal Immunization

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Middle East respiratory syndrome coronavirus (MERS-CoV) is a novel lineage C betacoronavirus that can cause an acute viral respiratory disease in humans with a mortality of nearly 44%. Human disease is zoonotic in origin and human-to-human transmission have been reported. Potential animal reservoirs and mechanisms of transmission of MERS-CoV to humans remain unclear. Unfortunately, a specific drug treatment for MERS-CoV is not available and thus the need for development of effective vaccination strategies to prevent MERS-CoV infection and further spread is urgent. Previously, we searched for an ideal adjuvant to improve antigen delivery and promote antigen-specific mucosal and systemic immune response via oral administration against MERS-CoV antigen. In this study, to identify an effective mucosal and systemic immune response via intranasal administration, we investigated the antigen delivery to nasopharynx-associated lymphoid tissues (NALT) and immunogenicity using three different RBD fragment fused with defined M cell-targeting molecules. The results showed that fusion proteins elicited higher antigen-specific mucosal IgA and systemic IgG antibody responses than original RBD fragments in immunized mice and also delivery of fusion proteins to nasal immune inductive site was quite effective. Additionally, the fusion proteins elicited substantially TH1-associated immune response and IL-17 cytokine when compared with control group. These results show that our M cell-targeting molecule effectively enhance both humoral and cellular immunity and could be a potential adjuvant for immunization against MERS-CoV infections. (This study was supported by HI15C3039 through the Korea Health Industry Development Institute (KHIDI) funded by the Korean Ministry of Health and Welfare.)

Keywords: Intranasal immunization, Ligand, M cell, MERS-CoV, Vaccine

P-074 Combination Therapy of Flagellin-adjuvanted Therapeautic Vaccine and Local Radiation(IR) Induces Long-term Antitumor Effect in a Mouse Cervical Cancer Model

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Accumulating evidence demonstrates that radiotherapy enhances anti-tumor immune responses induced by immunomodulatory therapeutic approaches. Radiotherapy (RT) is widely used cost-effective therapeutics for the various cancers having accompanying adverse effect. Recently it has been reported that flagellin derivatives significantly reduced the severity of radiation-induced side effect and accelerated tissue recovery. We previously demonstrated that flagellin potentiates tumor antigen-specific $CD8^+$ T cell immune responses through TLR5 signaling in a TC-1 cancer immunotherapy (IT) model. And intravaginal (IVAG) co-administration of E6/E7 peptides with flagellin resulted in tumor suppression indicating flagellin is a potent vaginal adjuvant for a therapeutic peptide cancer vaccine. In this regard, we examined whether flagellin can be used as an adjuvant performing dual role of radioprotection and immunomodulation in an RT/IT combinatorial cervical cancer therapeutic model. When the tumor-bearing mice (5 ~8 mm in mean diameter) were locally received 20 Gy single dose irradiation, tumor growth was significantly reduced. Additional administration of flagellin-adjuvanted peptide vaccine showed comparable inhibitory effect on tumor growth. Surprisingly the combination therapy of flagellin-adjuvanted cancer vaccine and radiotherapy induced eradication of tumor mass and long-term memory protection against the re-challenge of the same tumor. These results suggest that flagellin is a promising radioprotective adjuvant for RT/IT combination therapeutics modalities against intractable cancers.

Keywords: Flagellin, TLR5, Combination therapy, Immunotherapy, Radiotherapy

P-075 IL-21-mediated Reversal of NK Cell Exhaustion Facilitates Anti-tumour Immunity in MHC Class I-deficient Tumours

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During cancer immunoediting, loss of MHC class I (MHC-I) in neoplasm contributes to the evasion of tumours from host immune system. Recent studies have demonstrated that most NK-cells that are found in advanced cancers are defective, releasing the malignant MHC-I-deficient tumours from NK-cell dependent immune control. Here, we show that an NKT-cell-ligand-loaded tumour-antigen expressing APC-based vaccine effectively eradicates these advanced tumours. During this process, we find that the co-expression of Tim-3 and PD-1 marks functionally exhausted NK-cells in advanced tumours and that MHC-I downregulation in tumours is closely associated with the induction of NK-cell exhaustion in both tumour-bearing mice and cancer patients. Furthermore, the recovery of NK-cell function by IL-21 is critical for the anti-tumour effects of the vaccine against advanced tumours. These results reveal the process involved in the induction of NK-cell dysfunction in advanced cancers and provide a guidance for the development of new strategies for cancer immunotherapy.

Keywords: IL-21, NK cell, Exhaustion, Immunotherapy, Tumor vaccine

P-076 N-terminal Domain of Porcine Epidemic Diarrhea Virus Contains the Antigenicity Capable of Inducing Mucosal Immune Response

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Porcine epidemic diarrhea (PED), caused by PED virus (PEDV) infection in pigs, has been constantly occurring in many countries including Korea. Although attenuated PEDV vaccines based on PEDV CV777, DR13 and SM98 strains are currently available, the efficacy of the vaccines is limited because the currently prevalent PEDV strain in Korea does not perfectly match with the vaccine strains. Previous studies have suggested the C-terminal domain (CTD) of PEDV spike protein as a vaccine target because PEDV infection is initiated by the interaction between CTD of PEDV spike protein and aminopeptidase N of the gut epithelial cells. However, it was recently reported that CTD is relatively variable in field strains of PEDV and is not a decisive factor for PEDV infection. Therefore, development of a new effective mucosal vaccine against PEDV infection is essentially required. In this study, we selected the N-terminal domain (NTD) of PEDV as a new PEDV vaccine candidate antigen because NTD recognizes the N-acetylneuraminic acid, a co-receptor of PEDV, and is relatively conserved in filed strains. We generated the recombinant NTD protein using *E. coli* expression system and investigated its potential as a mucosal vaccine antigen by applying M cell-targeting strategy through assessing its mucin-binding activity via confocal laser scanning microscopy and ELISA. The immunogenicity was also investigated by measuring the level of NTD-specific IgG and IgA in serum and fecal extracts. Collectively, we suggest that recombinant NTD protein can be applied as a new mucosal vaccine candidate antigen against PEDV infection. (This work was supported by a grant from the Next-Generation BioGreen 21 Program, Project No. PJ011801, Rural Development Administration of Korea.)

Keywords: PEDV, N-terminal domain of PEDV, Mucosal vaccine

P-077 Cell Enrichment-free Massive Ex-vivo Expansion of Peripheral CD20$^+$ B Cells via CD40-CD40L Signals in Non-human Primates

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Non-human primates (NHPs) are valuable as preclinical resources that bridge the gap between basic science and clinical application. B cells from NHPs have been utilized for the development of B-cell targeted drugs and cell-based therapeutic modalities; however, few studies on the ex-vivo expansion of monkey B cells have been reported. In this study, we developed a highly efficient ex-vivo expansion protocol for monkey B cells resulting in 99% purity without the requirement for prior cell-enrichment procedures. To this end, monkey peripheral blood mononuclear cells (PBMCs) were stimulated for 12 days with cells constitutively expressing monkey CD40L in expansion medium optimized for specific and massive expansion of B cells. The B cells expansion rates obtained were 2-5 times higher than those previously reported in humans, with rates ranging from 7.9 to 16.6 fold increase. Moreover, expanded B cells sustained high expression of co-stimulatory molecules including CD83 and CD86 until day 12 of culture, and the simple application of a brief centrifugation resulted in a CD20(+) B cell purity rate of greater than 99%. Furthermore, small amounts of CD3(+)CD20(+)BT-like cells were generated and CD16 was expressed at moderate levels on expanded B cells. Thus, the establishment of this protocol provides a method to produce quantities of homogeneous, mature B cells in numbers sufficient for the in vitro study of B cell immunity as well as for the development of B cell-diagnostic tools and cell-based therapeutic modalities.

Keywords: B cell, Expanson, Non-human Primates

P-079 Multiple Biomarkers for Diagnosis and Detecting Method of Systemic Lupus Erythematosus (SLE)

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Systemic lupus erythematosus (SLE) is an autoimmune disease in which the immune dysregulation produces autoantibodies that cause inflammation and attack the body's own organ system. Thus, the pathogenesis of SLE closely related to the autoantibody production. Up to now, there is no complete cure for SLE, early diagnosis is critical to managing the symptoms and lessening the development of damage to organs. Since the last decade Omics-based biomarker screening have been extensively utilized for diagnosis of various diseases. We try to search for SLE-specific autoantibody to predict and monitor patients with SLE, performed biomarker validation studies. Human serum samples were collected healthy controls (HCs, n=5) and patients with SLE (n=10), and were subjected to 22K protein microarrays. Analysis of 22K protein microarray data identifies significantly different Sixty-five proteins between SLE and HCs. Interestingly, Lupus Marker (LM)A was simultaneously expressed with LMB and LMC in 4 of 10 patients with SLE. In addition, more SLE patients serum samples were tested by dot-blotting assay also showed that Lupus Marker(LM)A was simultaneously expressed with LMB and LMC in 51 of 100 patients with SLE, compared with HCs and rheumatoid arthritis (RAs) control. In this research, we validated protein isoforms of LMA, LMB, and LMC in serum samples with SLE patients and successfully distinguished between SLE and HCs using proteomic and molecular approaches. Thus, finding reliable multiple biomarkers for SLE will help to monitor SLE disease and facilitate early diagnosis and intervention to improve favorable outcomes.

Keywords: Systemic lupus erythematosus, Autoimmune disease, Autoantibody, Biomarker, Microarray

P-078 Metformin Induce Anti-Inflammatory Effet of Cartilage and Dorsal-Root Ganglia against Monosodium Iodoacetate-Induced Osteoarthritis in Rats

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Osteoarthritis (OA) is the most widespread joint disease, but the mechanism is not clearly known. Oxidative stress and inflammation are thought to be associated with the development of osteoarthritis. Metformin is a genarally used drug for treatment of type 2 diabetes. Moreover, it is known to AMP-activated protein kinase (AMPK) activator. AMPK is a major cellular regulator of lipid and glucose metabolism. In addition, AMPK activates autophagy. Recently, OA treatment studies through AMPK activation are progressing in various group. In our study, Metformin has an inhibitory effect on Monosodium Iodoacetate (MIA) induced osteoarthritis rat model. Pain was assessed by measuring the paw withdrawal latency and threshold. Cartilage destruction was analyzed Micro-CT and histopathology. Metformin reduced the expression of interleukin-1β (IL-1β), IL-6, inducible nitric oxide synthase (iNOS) in articular cartilage. The effects of Metformin on mRNA expression were examined in human OA chondrocytes. mRNA levels of catabolic factors were reduced in IL-1β-stimulated human OA chondrocytes. On the other hand, AMPK was increased by Metformin. Futhermore, clinical results show that osteoarthritis and type 2 diabetes patients who had a follow-up 3 years after the evaluation are slowly progressing after taking the Metformin. our data suggest that the acceleration of AMPK by Metformin reduces catabolic cartilage damage in human OA

Keywords: Osteoarthritis, Metformin, AMPK

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References 1. Keystone EC et al. J Rheumatol. 2013;40(9):1487-1497 2. Keystone EC et al. J Rheumatol. 2014;41(1):5-14

[제품명] 휴미라주 40mg/0.8ml프리필드주입기 **[효능·효과]** 성인 1. 류마티스 관절염: 메토트렉세이트를 포함한 DMARDs(disease-modifying anti-rheumatic drugs)에 대한 반응이 적절하지 않은 성인의 중등도에서 중증의 활동성 류마티스 관절염의 치료, 이전에 메토트렉세이트로 치료받지 않은 성인의 중증의 활동성 및 진행성 류마티스 관절염의 치료, 이 약은 단독투여 또는 메토트렉세이트나 다른 DMARDs와 병용투여할 수 있다. 메토트렉세이트에 내약성이 없거나 지속적인 병용투여가 부적절한 경우에는 단독투여한다. 이 약과 메토트렉세이트와의 병용투여는 관절손상 진행속도를 감소시키고(X-선측정 결과) 신체활동기능을 향상시킨다. 2. 건선성 관절염: 이전에 DMARDs(disease-modifying anti-rheumatic drugs)에 대한 반응이 적절하지 않은 성인의 활동성 및 진행성 건선성 관절염의 치료. 이 약은 다발성 대칭성 이환을 지닌 환자의 말초 관절손상 진행속도를 감소시키고(X-선측정 결과), 신체활동기능을 향상시킨다. 3. 축성 척추관절염: (1) 강직성 척추염 기존 치료에 대한 반응이 적절하지 않은 성인의 중증의 강직성 척추염의 치료 (2) 방사선학적으로 강직성 척추염이 확인되지 않는 중증 축성 척추관절염: 방사선학적 검사에서 강직성 척추염이 확인되지 않으나, 성상된 CRP 수치 및/또는 MRI상 객관적인 염증의 징후를 보이는 중증 축성 척추관절염의 치료. 이 약은 비스테로이드성항염제(NSAIDs) 약물에 대한 반응이 적절하지 않은 경우 또는 이러한 치료방법이 금기인 성인의 중등도에서 중증의 활성 궤양성 대장염의 치료 7. 베체트 질환: 스테로이드 또는 면역억제제 등의 통상적인 치료에도 적절한 반응이 나타나지 않는 베체트 질환의 치료 8. 화농성 한선염: 기존의 전신 요법에 적절한 반응을 나타내지 않는 중등도에서 중증의 활성 화농성 한선염의 치료 ≥0.1 소아 크론병은 — 17세 일치 영양요법, 코르티코스테로이드, 면역조절제 등의 치료에 적절한 반응을 나타내지 않거나, 내약성이 없는 경우 또는 이러한 치료방법이 금기인 소아 환자는 — 17세에서 중증의 활성 크론병의 치료 2. 소아 특발성 관절염: (1) 다관절형 소아 특발성 관절염 하나 이상의 DMARDs(disease-modifying anti-rheumatic drugs)에 대해 부적절한 반응을 보인 2세 이상의 소아 및 청소년에서 활성 다관절형 소아 특발성 관절염의 치료 (2) 골부착부위염 관련 관절염: 기존 치료에 적절한 반응을 나타내지 않거나 내약성이 없는 6세 이상 어린이 및 청소년의 활성 골부착부위염 관련 관절염의 치료 3. 소아 판상 건선: 국소 치료 및 광선요법에 적절한 반응을 나타내지 않거나, 해당 치료가 부적절한 4세 이상의 어린이 및 청소년의 중증 만성 판상 건선의 치료 **[용법·용량]** 환자가 지가 주사하는 것이 적절하며 필요시 치료 추적이 가능하다고 의사가 판단하는 경우. 환자는 주사방법에 대한 교육을 받은 후 이 약을 자가 주사할 수 있다. 성인 1. 류마티스 관절염: 성인 류마티스 관절염 환자에 대한 이 약의 권장 용량은 아달리무맙 40 mg을 2주에 1회 피하주사한다. 이 약을 투여하는 동안 메토트렉세이트의 병용투여를 유지한다. 글루코코르티코이드, 살리실산염, 비스테로이드성항염증제(NSAIDs), 진통제, 다른 DMARDs의 병용투여를 유지할 수 있다. 단독요법의 경우 이 약에 대한 반응이 감소한 환자는 40 mg 1주 1회로 증량하면 유용한 효과를 얻을 수 있다. 2. 건선성 관절염, 강직성 척추염 및 방사선학적으로 강직성 척추염이 확인되지 않는 중증 축성 척추관절염: 건선성 관절염, 강직성 척추염 및 방사선학적으로 강직성 척추염이 확인되지 않는 중증 축성 척추관절염 환자에 대한 이 약의 권장 용량은 아달리무맙 40 mg을 2주에 1회 피하주사한다. 상기 효능·효과에 대해 임상적인 반응은 보통 치료 12주 이내에 나타나며, 이 기간 내에 반응을 나타내지 않는 환자의 경우에는 투여 지속여부를 신중히 재고한다. 3. 성인 크론병: 성인 중등도에서 중증 크론병에 대한 이 약의 권장 용량은 첫 주에 아달리무맙 80 mg을 투여하고 첫 투여 후 2주 후에 40 mg을 투여한다. 빠른 효과를 얻어야 할 필요가 있는 경우에는, 유도 요법동안 이상반응에 대한 위험성이 증가한다는 것을 알리고, 첫 주에 160 mg을 투여하고하루에 4번 주사하거나, 이틀에 걸쳐 2번씩 주사할 수 있다) 첫 투여 후 2주 후에 80 mg을 투여할 수 있다. 유도 요법의 경우 이 약은 코르티코스테로이드제와 병용투여한다. 코르티코스테로이드제의 내약성이 없거나, 지속적인 병용투여가 부적절한 경우 단독투여할 수 있다. 유도 요법 후, 아달리무맙 40 mg을 2주에 1회 피하주사한다. 단약 투여를 중지하고 재발의 증상과 징후가 나타나면 이 약을 재투여 할 수 있다. 8주 이상의 투여 중지 후 재투여에 대한 경험은 거의 없다. 장기 요법 동안 임상 지침에 따라 코르티코스테로이드제의 투여를 서서히 줄일 수 있다. 이 약에 대한 반응이 감소한 환자는 40 mg 1주 1회로 증량하면 유용한 효과를 얻을 수 있다. 4주까지 반응을 보이지 않는 환자의 경우는 투여 지속여부를 신중히 재고한다. 4. 건선 성인에 대한 이 약의 권장 용량은 첫 회에 아달리무맙 80 mg을 피하로 투여하고, 이어서 첫 투여 후 1주일 후에 40 mg을 격주로 투여한다. 16주 이내에 반응을 나타내지 않는 환자의 경우에는 투여 지속여부를 신중히 재고한다. 5. 화농성 대장염: 성인 중등도에서 중증의 궤양성 대장염에 대한 이 약의 권장 용량은 아달리무맙 160 mg을 투여하고하루에 4번 주사하거나, 이틀에 걸쳐서 2번씩 주사할 수 있다) 첫 투여 2주 후에 80 mg을 투여한다. 2주 이내에 반응을 나타내지 않는 환자의 경우에는 투여 지속 여부를 신중히 재고한다. 6. 베체트 질환: 성인에 대한 이 약의 권장 용량은 첫 회에 160 mg을 피하로 투여하고 이어서 첫 투여 2주 후에 80 mg을 투여한다. 첫 투여 4주 후부터는 40 mg을 격주로 투여한다. 12주 이내에 반응을 나타내지 않는 환자의 경우에는 투여 지속 여부를 신중히 재고한다. 7. 화농성 한선염: 이 약의 권장용량은 첫 회에 160 mg을 피하로 투여하고 (하루에 4번 주사하거나, 이틀에 걸쳐 2번씩 주사할 수 있다) 이어서 첫 투여 2주 후에 80 mg을 투여한다(하루에 2번 주사한다). 첫 투여 4 주 후부터는 40 mg을 매 주 투여한다. 필요 시, 이 약의 치료 기간 동안 항생제를 계속 투여할 수 있다. 12주 이내에 반응을 나타내지 않는 환자의 경우에는 투여 지속 여부를 신중히 재고한다. 치료를 중단해야 하는 경우, 40mg 매주 투여로 재투여할 수 있다. 소아 1. 소아 크론병 체중이 < 40 kg인 소아 크론병 환자 소아 중증 크론병에 대한 이 약의 권장 용량은 첫 주에 아달리무맙 40 mg을 투여하고 첫 투여 후 2주 후에 20 mg을 투여한다. 빠른 효과를 얻어야 할 필요가 있는 경우에는, 유도 요법동안 이상반응에 대한 위험성이 증가한다는 것을 알리고, 첫 주에 80 mg을 투여하고하루에 2번 주사할 수 있다) 첫 투여 후 2주 후에 40 mg을 투여할 수 있다. 유도 요법 후, 이 약 20 mg을 2주에 1회 피하 주사한다. 충분한 반응이 나타나지 않는 일부 환자의 경우 매주 이 약 20 mg 투여로 빈도를 높이는 것이 유익할 수 있다. 체중이 ≥ 40 kg인 소아 크론병 환자 소아 중증 크론병에 대한 이 약의 권장 용량은 첫 주에 80 mg을 투여하고 첫 투여 후 2주 후에 40 mg을 투여한다. 빠른 효과를 얻어야 할 필요가 있는 경우에는, 유도 요법동안 이상반응에 대한 위험성이 증가한다는 것을 알리고, 첫 주에 160 mg을 투여하고하루에 2번 주사할 수 있다) 첫 투여 후 2주 후에 80 mg을 투여할 수 있다. 유도 요법 후, 이 약 40 mg을 2주에 1회 피하주사한다. 충분한 반응이 나타나지 않는 일부 환자의 경우 매주 이 약 40 mg 투여로 빈도를 높이는 것이 유익할 수 있다. 12주까지 반응을 나타내지 않는 환자의 경우에는 투여 지속 여부를 신중히 재고한다. 2. 소아 특발성 관절염 (1 다관절형 소아 특발성 관절염 이 약은 2세 이상 소아를 대상으로 연구된 바 없다. 체중 15 kg 미만 소아 환자 대상 치료에 대한 가능한 데이터는 제한적이다. 이 약은 메토트렉세이트와 병용하여 투여한다. 메토트렉세이트에 내약성이 없거나 메토트렉세이트와 함께 지속적으로 투여하는 것이 부적절할 경우에는 이 약을 단독요법으로 투여할 수 있다. 2— 2세 이상의 다관절형 소아 특발성 관절염 환자에 대한 이 약의 권장 용량은: 24 mg/m² BSA(body surface area)에서 최대 아달리무맙 40 mg까 — 단독 또는 20 mg/2 — 4세 미만을 대상 피하주사를 통해 격주 투여한다. 주사 용량은 환자의 신장 및 체중에 따라 선택한다. 1)4세 이상의 다관절형 소아 특발성 관절염 환자 대상 임상 시험에서 사용된 용량은 24 mg/m² body surface area에서 최대 아달리무맙 40 mg을 단회 피하주사를 통해 격주 투여한다. 주사 용량은 환자의 신장 및 체중에 따라 선택한다. 이 약은 6세 미만의 골부착부위염 관련 관절염 환자를 대상으로 연구된 바 없다. 3. 소아 판상 건선: 소아 판상 건선에 대한 이 약의 권장용량은, 0.8mg/kg (1회 최대 용량 40 mg)를 처음 2회는 매주 피하주사하고, 이후에는 격주로 투여한다. 16주 이후에도 반응을 나타내지 않는 환자의 경우에는 투여 지속여부를 신중히 재고한다. 만약 이 약으로 다시 치료할 경우, 위에서 제시한 용량과 치료기간을 따라야 한다. 소아 판상 건선으로 4세 미만의 어린이에게 이 약을 사용한 적은 없다. 주사 용량은 환자의 체중에 따라 선택한다. **[주요 사용상의 주의사항]** 1. 경고 1) 감염 이 약의 투여 전, 투여 동안 및 투여 후 결핵을 포함한 감염에 대해 면밀히 모니터링해야 한다. ① 심각한 감염 ② 결핵 ③ 기타 기회감염 ④ 악성종양과 림프종증상 질환 ⑤ B형 간염 재활성화 ⑥ 신경학적 반응 2. 다음 환자에는 투여하지 말 것 1) 이 약 또는 이 약의 성분에 과민증인 환자 2) 활동성 결핵 또는 패혈증, 기회감염과 같은 다른 중증 감염이 있는 환자 3) 중등도 내지 중증의 심부전(NYHA class III/IV) 환자 ※ 자세한 제품정보는 제품설명서를 참조해 주십시오. **[제조원]** 제조의뢰자: AbbVie Ltd, Maidenhead, SL6 4XE, U.K. 제조자원액: AbbVie Bioresearch Center, Inc. 100 Research Drive Worcester, MA01605, USA. 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