5th CSI/JSI/KAI Joint Symposium on Immunology
"Frontier in Immunology Research in the Aftermath of the Pandemic"

Venue

Conference and Accommodation

X Wave Makuhari (クロスウェーブ幕張)

https://x-wave.orix.co.jp/makuhari/

1-3 Nakase, Mihama-ku, Chiba, Chiba 261-8501, Japan

〒261-8501 千葉県千葉市美浜区中瀬１丁目３

Get together party

Hotel The Manhattan (Makuhari)

https://www.the-manhattan.co.jp/lang/en/

2-10-1, Hibino, Mihama-ku, Chiba, Chiba 261-0021, Japan

〒261-0021 千葉県千葉市美浜区ひび野２丁目１０−１

January 13th (Sat)

Arrival, Reception (X Wave Makuhari)

19:00-21:00 Welcome Dinner (at X Wave Makuhari)

January 14th (Sun) (at X Wave Makuhari)

8:30-9:00 **Opening Remarks**

Tomohiro KUROSAKI (President of JSI)

Chang-Duk JUN (President of KAI)

Bo HUANG (CSI)

Session 1 Control of Immune microenvironment

Co-chair: Dr. Kiyoshi TAKEDA and Dr. Shicheng SU

9:00-9:20 Kiyoshi TAKEDA (Osaka University, Japan):
Regulation of intestinal homeostasis

9:20-9:40 Sang-il LEE (Gyeongsang National University, Korea):
Interaction between stromal cells and immune cells in rheumatoid arthritis

9:40-10:00 Shicheng SU (Sun Yat-sen University, China):
Different routes, same destination, not same destiny-
High endothelial venules mold immunogenicity of passing tumor cells

10:00-10:20 Koji HASE (Keio University, Japan):
The pathological link between the intestinal immune system and autoimmune disorders

10:20-10:40 **Coffee Break**

Session 2 Innate Lymphoid Cells

Co-chair: Dr. Tae-Gyun KIM and Dr. Kazuyo MORO

10:40-11:00 Hye Young KIM (Seoul National University, Korea):
The Protective Role of Integrin α4β7 and Amphiregulin-Expressing Innate Lymphoid Cells in Lupus Nephritis

11:00-11:20 Kazuyo MORO (Osaka University, Japan):
Activation of ILC2s through constitutive IFNγ signaling reduction leads to spontaneous pulmonary fibrosis

11:20-11:40 Hui PENG (University of Science and Technology of China, China):
Development and function of liver-resident NK cells/ILC1s: from fetal to adult life

11:40-12:00 Tae-Gyun KIM (Yonsei University, Korea):
Skin microbe-dependent early postnatal TSLP-ILC2 priming axis is co-opted in adulthood

12:00-13:00 **Lunch**

Session 3 Innate immunity and hematopoiesis

Co-chair: Dr. Yuting MA and Dr. You-me KIM

13:00-13:20 Yuting MA (Chinese Academy of Medical Sciences, China):
Stress reshapes the immune microenvironment and macroenvironment

13:20-13:40 You-me KIM (KAIST, Korea):
Prostaglandin E2 signaling in dendritic cells and the intestinal homeostasis

13:40-14:00 Hongyan WANG (Chinese Academy of Sciences, China):
Macrophage, Metabolism and Inflammation

14:00-14:20 Lanfen CHEN (Xiamen University, China):
Functions of Hippo kinases Mst1/2 in the immune system

14:20-14:40 **Coffee Break**

Session 4 Gene regulation in the control of immunity

Co-chair: Dr. Osamu TAKEUCHI and Dr. Huabing LI

14:40-15:00 Osamu TAKEUCHI (Kyoto University, Japan):
Post-transcriptional regulation of immunity by Regnase-1-like endoribonucleases

15:00-15:20 Xiaoyu HU (Tsinghua University, China):
Therapeutically targeting human cytokine release syndrome

15:20-15:40 Huabing LI (Shanghai Jiao Tong University, China):
RNA Modification in Immunity

15:40-16:00 Minako ITO (Kyushu University, Japan):
Significance of regulatory T cells in the central nervous system

16:20-18:00 **Poster Session** (at X Wave Makuhari)

19:00 **Get together party** (at Hotel The Manhattan)

January 15th (Mon) (at X Wave Makuhari)

Session 5 Control of Acquired Immune cells

Co-chair: Dr. Sayuri YAMAZAKI and Dr. HoKeun KWON

8:30-8:50 Sayuri YAMAZAKI (Nagoya City University, Japan):
Immune regulation mediated by crosstalk between dendritic cells and regulatory T cells

8:50-9:10 Chang-Duk JUN (Gwangju Institute of Science and Technology, Korea):
T-cell immunological synaptosomes: Physiology and Application

9:10-9:30 HoKeun KWON (Yonsei University College of Medicine, Korea):
FoxP3-expressing T cells ensure proper neurodevelopment in fetuses.

9:30-9:50 Kiyoshi HIRAHARA (Chiba University, Japan):
Pathological tissue inflammatory memories

9:50-10:10 **Coffee Break**

Session 6 Anti-tumor immunity

Co-chair: Dr. Seung-Woo LEE and Dr. Bo HUANG

10:10-10:30 Doo Hyun CHUNG（Seoul National University, Korea):
CRIF1 deficiency-mediated glutaminolysis induces Foxp3low inflammatory non-suppressive regulatory T cells, thereby promoting anti-tumor immunity

10:30-10:50 Xindong LIU (The Third Military Medical University, China):
Neutralizing IL-8 potentiates immune checkpoint blockade efficacy for glioma

10:50-11:10 Hideki UENO (Kyoto University, Japan):
B Cells in the Tumor Microenvironment

11:10-11:30 Seung-Woo LEE (POSTECH, Korea):
IL-7-primed bystander CD8 tumor-infiltrating lymphocytes optimize the antitumor efficacy of T cell engager immunotherapy in solid tumors

11:30-11:50 Bo HUANG (Chinese Academy of Medical Sciences, China):
Drug tumor microparticles: novel immunotherapy for malignant effusion and ascites

12:15-13:30 **Lunch**

Session 7 Immune responses against microbial infection

Co-chair: Dr. Ji Yun NOH and Dr. Sho Yamasaki

13:00-13:20 Ji Yun NOH (Korea University, Korea):
Immune response to SARS-CoV-2 vaccination: insights into clinical research on influenza

13:20-13:40 Sho YAMASAKI (Osaka University, Japan):
Human T cell responses against infection

13:40-14:00 Eui-Cheol SHIN (KAIST, Korea):
IL-15-induced bystander T cell activation in human viral disease

14:00-14:20 Yunlong CAO (Peking University, China):
Evolution of SARS-CoV-2 antibody responses and immune evasion hotspots ECM1

14:20-14:40 Cevayir COBAN (The University of Tokyo, Japan):
Immune memory during malaria and vaccination

14:40-14:50 **Closing remarks**

18:00 **Dinner** (at X Wave Makuhari)

Speakers

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Education and Appointments

1992	M. D. Osaka University, Medical School
1998	Ph. D. Osaka University, Graduate School of Medicine
1998-1999	Research Associate, Hyogo College of Medicine
1999-2003	Research Associate, Research Institute for Microbial Diseases, Osaka University
2003-2007	Professor, Medical Institute of Bioregulation, Kyushu University
2007-Present	Professor, Immunology Frontier Research Center, Graduate School of Medicine, Osaka University
2019-Present	Director, Immunology Frontier Research Center, Osaka University

Speciality & Research Field of Interest

Mucosal Immunology, Inflammation, Microbiota, Epithelia

Selected Publications

1. Yokoi T, Murakami M, Kihara T, Seno S, Arase M, Wing JB, Søndergaard JN, Kuwahara R, Minagawa T, Oguro-Igashira E, Motooka D, Okuzaki D, Mori R, Ikeda A, Sekido Y, Amano T, Iijima H, Ozono K, Mizushima T, Hirota S, Ikeuchi H, Takeda K: **Identification of a unique subset of tissue resident memory CD4$^+$ T cells in Crohn's disease.** ***Proc. Natl. Acad. Sci. USA*** 120, e2204269120 (2023).
2. Morita N, Umemoto E, Fujita S, Hayashi A, Kikuta J, Kimura I, Haneda T, Imai T, Inoue A, Mimuro H, Maeda Y, Kayama H, Okumura R, Aoki J, Okada N, Kida T, Ishii M, Nabeshima R, Takeda K: GPR31-dependent dendrite protrusion of intestinal CX_3CR1^+ cells by bacterial metabolites. ***Nature*** 566,110-114 (2019).
3. Okumura R, Kurakawa T, Nakano T, Kayama H, Kinoshita M, Motoka D, Gotoh K, Kimura T, Kamiyama N, Kusu T, Ueda Y, Wu H, Iijima H, Barman S, Osawwa H, Matsuno H, Nishimura J, Ohba Y, Nakamura S, Iida T, Yamamoto M, Umemoto E, Sano K, Takeda K: Lypd8 promotes the segregation of flagellated microbiota and colonic epithelia. ***Nature*** 532, 117-121 (2016)
4. Tsai SH, Kinoshita M, Kusu T, Kayama H, Okumura R, Ikeda K, Shimada Y, Takeda A, Yoshikawa S, Kurashima Y, Sato S, Umemoto E, Kiyono H, Karasuyama H, Takeda K: Ectoenzyme E-NPP3 (CD203c) negatively regulates ATP-dependent chronic allergic responses by basophils and mast cells. ***Immunity*** 42, 279-293 (2015).
5. Atarashi K, Nishimura J, Shima T, Umesaki Y, Yamamoto M, Onoue M, Yagita H, Ishii N, Evans R, Honda K, Takeda K: ATP drives lamina propria TH17 cell differentiation. ***Nature*** 455, 808-812 (2008).

Regulation of intestinal homeostasis

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[2] Department of Microbiology and Immunology, Graduate School of Medicine, Osaka University

Keywords: microbiota, metabolites, intestine

The intestine is a unique tissue where microbiota exists. In a healthy condition, the activity of intestinal immunity is finely regulated to prevent inflammatory responses to the microbiota. Dysregulated interaction of intestinal microbiota and intestinal immunity causes the development of inflammatory bowel disease (IBD) represented by Crohn's disease and ulcerative colitis.

We analyze the mechanisms by which gut homeostasis is regulated by focusing on the barrier function of colonic epithelial cells that are responsible for the segregation of intestinal microbiota and immunity. Indeed, the presence of bacteria on the epithelial surface of the large intestine was reported in several mouse models of intestinal inflammation. We found that Lypd8, which is selectively expressed on colonic epithelial cells, blocks the direct interaction of intestinal microbiota with the host cells, thereby regulating intestinal homeostasis.

We also analyze how intestinal microbiota, which does not directly contact the intestinal epithelia, act on the host. We identified bacterial metabolites that initiate immune responses by acting on intestinal myeloid cells. Intestinal CX3CR1+ myeloid cells extend their dendrites into the lumen to uptake luminal antigens and induce adaptive immune responses. We purified luminal contents that induce dendrite extension of CX3CR1+ myeloid cells. It was found that lactate and pyruvate, which were produced in the intestinal lumen by bacteria, induce dendrite extension through Gpr31 and enhance immune responses against intestinal pathogenic bacteria. Thus, bacterial metabolites are responsible for the host and microbiota interaction for the maintenance of intestinal homeostasis. We then analyzed whether bacterial metabolites are implicated in the pathogenesis of IBD. Lysophosphatidylserine, which was increased in the intestinal lumen of Crohn's disease patients, who had an increased number of bacteria possessing the phospholipase A gene, was found to mediate exacerbation of intestinal inflammation. Thus, bacterial metabolites mediating the host and microbiota interaction are implicated in intestinal homeostasis and intestinal inflammation.

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Education and Appointments

1987 - 1995	Chonbuk National University Medical School (M.D.)
2008 - 2010	Postgraduate School, Chonnam National University Medical School (Ph.D.)
2006 - 2011	Assistant Professor, Internal Medicine, Gyeongsang National University Medical School
2010 - 2012	Visiting Scholar of Rheumatology, UCSD, CA, USA
2012 - 2015	Associate Professor, Gyeongsang National University Medical School
2016 - present	Professor, Gyeongsang National University Medical School
2023	Vice President, The Korean association of immunologists
2024	President, The Korean association of immunologists

Speciality & Research Field of Interest

Autoimmune diseases, Interactions of stromal cells and immune cells

Selected Publications

1. Kim MG, Choe YH, Lee SI. Lessons from the Success and Failure of Targeted Drugs for Rheumatoid Arthritis: Perspectives for Effective Basic and Translational Research. **Immune Netw** 2022 Feb 22
2. Kim DE, Kim MG, Kim TW, Choe YH, Noh HS, Jeon HM, Kim SH, Lee YE, Hur GY, Lee GM, Shin KH, Lee SI, Lee SH. Lymph node-fibroblastic reticular cells regulate differentiation and function of CD4 T cells via CD25. **J Exp Med** 2022 2;219(5)
3. Lee HJ, Lee WJ, Hwang SC, Choe YH, Kim SB, Bok EY, Lee SY, Kim SJ, Kim HO, Ock SA, Noh HS, Rho GJ, Lee SI, Lee SL. Chronic inflammation-induced senescence impairs immunomodulatory properties of synovial fluid mesenchymal stem cells in rheumatoid arthritis. **Stem Cell Res Ther** 2021 14;12(1):502
4. Kim MG, Choe YH, Lee HW, Jeon MG, Park JH, Noh HS, Cheon YH, Park HJ, Shin SJ, Lee KL, Lee SI. Blockade of translationally controlled tumor protein attenuated the aggressiveness of fibroblast-like synoviocytes. **Exp Mol Med** 2021 Jan;53(1):67-80.
5. Woo SJ, Noh HS, Lee NY, Cheon YH, Yi SM, Jeon HM, Bae EJ, Lee SI, Park BH. Myeloid sirtuin 6 deficiency accelerates experimental and human rheumatoid arthritis by enhancing macrophage activation and infiltration into synovium. **EBioMedicine**. 2018 Dec;38:228-237.
6. Cheon YH, Lee SG, Kim M, Kim HO, Sun Suh Y, Park KS, Kim RB, Yang HS, Kim JM, Son CN, Kyoung Park E, Kim SH, Lee SI. The association of disease activity, pro-inflammatory cytokines, and neurotrophic factors with depression in patients with rheumatoid arthritis. **Brain Behav Immun**. 2018 Oct;73:274-281

Interaction between stromal cells and immune cells in rheumatoid arthritis

Sang-Il LEE

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Autoimmune diseases involve intricate interactions between immune cells and stromal cells, which can contribute to the pathophysiology of conditions like rheumatoid arthritis (RA). In addition to immune cells, certain stromal cells like fibroblast-like synoviocytes (FLS), lymph node fibro-reticular cells (LN-FRC), and mesenchymal stem/stromal cells (MSC) have been implicated in the development and progression of RA. Unfortunately, these stromal cells can take on dysfunctional or aggressive properties in the context of autoimmune disease, which can impact infiltrating immune and tissue resident cells. Recently, we reported three important perturbations of stromal cells that contribute to the immuno-pathogenesis of RA, which could inform future therapies for the condition. Firstly, T cell zone FRCs of LNs (LN-TRCs) expressing CD25 can promote T helper 17 (Th17) cell differentiation and Th17 response-related gene expression in Th17-dependent autoimmune diseases. Secondly, the downregulation of negative regulators like Raf kinase inhibitory protein (RKIP) or phospholipase C-eta2 (PLCH2) in upstream cellular signaling pathways can lead to the aggressiveness of RA-FLS, promoting arthritic inflammation and joint destruction. Lastly, cellular senescence resulting from chronic inflammation can reduce the immunomodulatory properties of synovial fluid-derived MSCs in long-term RA. My presentation will cover recent progress on the molecular signature and functions of stromal cells, with particular emphasis on their interaction with immune cells in the pathophysiology of autoimmune diseases.

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Education and Appointments

2003-2010	Sun Yat-sen University (M.D. in General Surgery)
2013-2015	Sun Yat-sen University (Ph.D. in General Surgery)
2010-2013	Resident Doctor in General Surgery, Sun Yat-sen Memorial Hospital
2014-2018	Attending Doctor in Breast Surgery, Sun Yat-sen Memorial Hospital
2016 -2019	Associate Investigator of Tumor Immunology, Sun Yat-sen Memorial Hospital
2019-2022	Associate Chief Physician of Breast Surgery, Sun Yat-sen Memorial Hospital
2020-present	Investigator of Tumor Immunology, Sun Yat-sen Memorial Hospital
2022-present	Chief Physician of Breast Surgery, Sun Yat-sen Memorial Hospital
2023-present	Professor of Breast Surgery, Sun Yat-sen Memorial Hospital

Speciality & Research Field of Interest

Inflammatory microenvironment, Clinical applications of immunotherapy, Endoscopic Breast Surgery

Selected Publications

1. XW Liu[#], YW Lu[#], JY Huang[#], Y Xing[#], HQ Dai, LL Zhu, SR Li, JW Feng, BX Zhou, JQ Li, QD Xia, J Li, M Huang, YT Gu, SC Su*. $CD16^{+}$ fibroblasts foster a trastuzumab-refractory microenvironment that is reversed by VAV2 inhibition. ***Cancer Cell*** 2022, 40(11):1341-1357.e13.
2. J Li[#], YY Ye[#], ZH Liu[#], GY Zhang[#], HQ Dai, JQ Li, BX Zhou, YH Li, QY Zhao, JY Huang, JW Feng, S Liu, PG Ruan, JJ Wang, J Liu, M Huang, XW Liu, SB Yu, ZY Liang, LP Ma, XX Gou, GL Zhang, N Chen, YW Lu, C Di, QD Xia, JY Pan, R Feng, QQ Cai, SC Su*. Macrophage mitochondrial fission improves cancer cell phagocytosis induced by therapeutic antibodies and is impaired by glutamine competition. ***Nature Cancer*** 2022 , 3(4): 453-470.
3. QY Zhao[#], JY Liu[#], H Deng[#], RY Ma[#], JY Liao, HX Liang, JX Hu, JQ Li, ZY Guo, JC Cai, XD Xu*, ZL Gao*, SC Su*. Targeting Mitochondria-Located circRNA SCAR Alleviates NASH via Reducing mROS Output. ***Cell*** 2020, Oct 1;183(1):76-93.e22.
4. LB Yang, Q Liu, XQ Zhang, XW Liu, BX Zhou, JN Chen, D Huang, JQ Li, HL Li, F Chen, J Liu, Y Xing, XM Chen, SC Su*, EW Song*. DNA of Neutrophil Extracellular Traps Promotes Cancer Metastasis via CCDC25. ***Nature*** 2020, 583(7814): 133-138.
5. YW Lu[#], QY Zhao[#], JY Liao[#], EW Song, QD Xia, JY Pan, YH Li, JQn Li, BX Zhou, YY Ye, C Di, SB Yu, YJ Zeng, SC Su*. Complement Signals Determine Opposite Effects of B Cells in Chemotherapy-Induced Immunity. ***Cell*** 2020, March 19;180(6):1081-1097.e24.

Different routes, same destination, not same destiny-
High endothelial venules mold immunogenicity of passing tumor cells

Qidong XIA, Shicheng SU

Breast Tumor Center, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, China

By depicting immune cell atlases during neoadjuvant chemotherapy, we have identified an $ICOSL^+$ B cell subset that merges in tertiary lymphoid structures (TLSs) after chemotherapy. ICOSL in B cells boosts anti-tumor T cell immune response. The signature of $ICOSL^+$ B cells is imprinted by complement signaling, which is triggered by immunogenic cell death in TLSs (Lu, et al Cell 2020). The importance of $ICOSL^+$ B cells in TLSs in T cell-mediated immunity after neoadjuvant chemotherapy has been confirmed in other types of malignancies (Lv J, et al Nat Med. 2023). High endothelial venules (HEVs) are also a special lymphoid structure. Recent studies show that HEVs offer another portal for tumor metastasis. Leaving the immunosuppressive primary tumor microenvironment, most of circulating tumor cells are annihilated by host factors, such as immune cells in circulation and distant organs. By deep learning algorithm analysis of sentinel lymph nodes, multi-omics profiling and injecting photoconvertible cells into HEV-conditional knockout mice, our unpublished data suggest a fundamental difference between HEVs and non-HEV blood vessels in shaping immunogenicity and future fates of passing tumor cells.

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Education and Appointments

1993-1995	Toyama Medical and Pharmaceutical University, Graduate School of Pharmaceutical Science (M.S.)
1995-2000	Research Scientist, Yamanouchi Pharmaceutical Co. Ltd.
2000-2002	Postdoctral Fellow, Department of Medicine, University of California at San Diego
2002-2004	Assistant Professor, Cancer Research Institute, Kanazawa University
2004-2012	Research scientist, Research Center for Allergy and Immunology, RIKEN
2012-Present	Project Professor (*Currently, Visiting Professor)*, International Research and Developmental Center for Mucosal Vaccines Institute of Medical Science (IMSUT), The University of Tokyo
2014-Present	Professor, Division of Biochemistry, Faculty of Pharmacy, Keio University
2022-Present	Project Professor, The Institute of Fermentation Sciences (IFeS), Faculty of Food and Agricultural Sciences, Fukushima University.

Speciality & Research Field of Interest

Mucosal immunity, Intestinal microbiota, M cells

Selected Publications

1. Michelson DA, Hase K, Mathis D et al., Thymic epithelial cells co-opt lineage-defining transcription factors to eliminate autoreactive T cells. **Cell**. 185:2542-2558.e18 (2022)
2. Nakamura A, Hase K et al., Symbiotic polyamine metabolism regulates epithelial proliferation and macrophage differentiation in the colon. **Nat Commun.** 12:2105 (2021).
3. Kimura I, Hase K et al., Maternal gut microbiota in pregnancy influences offspring metabolic phenotype. **Science**, 367: eaaw8429 (2020).
4. Nagai M, Hase K et al., Fasting-refeeding impacts immune cell dynamics and mucosal immune responses. **Cell** 178: 1072-1087 (2019).
5. Furusawa Y, Hase K et al., Commensal microbe-derived butyrate induces colonic regulatory T cells. **Nature** 504: 446-450 **(**2013).

The pathological link between the intestinal immune system and autoimmune disorders

Seiga KOMIYAMA[1], Daisuke TAKAHASHI[1], Koji HASE[1,2]

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[2] IFeS, Faculty of Food and Agricultural Sciences, Fukushima University, Fukushima 960-1296, Japan

Commensal microbiota in the gut plays a significant role in the development of various immune cell subsets including Treg and Th17 cells in the intestine. Compelling evidence has demonstrated that abnormalities in the gut microbiota (dysbiosis) significantly contribute to the development systemic autoimmune diseases such as rheumatoid arthritis and multiple sclerosis. However, the underlying pathological mechanisms are not yet fully understood. We recently found that the M-cell-dependent uptake of commensal bacteria into Peyer's patches plays an essential role in the development of experimental autoimmune encephalomyelitis (EAE). In M cell-deficient mice, EAE symptoms are alleviated, whereas in M cell-hyperplasia mice, the symptoms were exacerbated. Interestingly, Peyer's patches harbour a substantial number of IL-17A-producing γδT (γδT17) cells, which are activated in response to certain bacterial species. Furthermore, the transfer of PP γδT cells from wild-type to γδT-deficient mice exacerbated the disease severity of EAE. Thus, γδT17 cells acquire the encephalitogenic phenotype in PPs in the presence of commensal bacteria and thus contribute to the pathogenesis of EAE.

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Education and Appointments

1997- 2001	Ewha Womans University, B.S. in Biology
2001- 2003	Seoul National University, M.S in Genetics
2003 - 2006	Seoul National University College of Medicine, Ph.D. in Immunology
2006 -2011	Harvard Medical School/BCH, Research fellow
2011- 2013	Harvard Medical School/BCH, Research associate
2014 - 2020	Seoul National University College of Medicine, Associate Professor
2021- present	Seoul National University College of Medicine, Professor

Speciality & Research Field of Interest

Innate immunity, mucosal immunity,

Selected Publications

1. Ham JH, Kim JH, Shon KH, Park IW, Choi BW, Chung DH, Cho SH, Kang HR, Jung JW*, **Kim HY***. Cigarette smoke aggravates asthma by inducing memory-like type 3 innate lymphoid cells (Nat Commun. 2022 Jul 4;13(1):3852. doi: 10.1038/s41467-022-31491-1)
2. Ryu SW, Shin JW, Kwon S, Lee J, Kim YC, Bae YS, Bas YS, Kim DK, Kim YS, Yang SH, **Kim HY***. Siglec-F-expressing neutrophils are essential for creating a 3 pro-fibrotic microenvironment in the renal fibrosis (J Clin Invest. 2022. https://doi.org/10.1172/JCI156876)
3. Ko YG, Kim, MH, Park JY, Gil CH, Kim TS, Choi JY, Chung DH, Kim HK, Kim DY*, **Kim HY***. Chronic rhinosinusitis endotypes associate with distinct local cytokine milieus that shape the distribution of innate lymphoid cells. (Allergy. 2022 Mar 31. doi: 10.1111/all.15300)
4. Shin JW, Kim, JH, Ham S, Choi, SM, Lee CH, Lee JC, Kim JH, Cho SH, Kang HR, Kim YM, Chung DH, Chung Y, Bae YS, Bae YS, Roh TY, Kim T, **Kim HY***. A unique population of neutrophils generated by air pollutant-induced lung damage exacerbates airway inflammation (J Allergy Clin Immunol 2021 Oct 12;S0091-6749(21)01520-7).
5. Kim JH, Shin JW, Lee HJ, Kim JH, Choi SM, Lee CH, Kang HR, Park SH, Bae YS, Chung DH, **Kim HY***. Serum amyloid A promotes emphysema by triggering the reciprocal activation of neutrophils and ILC3s. (Clin Transl Med. 2021 Dec;11(12):e637. doi: 10.1002/ctm2.637)
6. Kim JH, Chang Y, Bae B, Sohn KH, Cho SH, Chung DH, Kang HR*, **Kim HY*** Innate immune crosstalk in asthmatic airways: innate lymphoid cells coordinate the polarization of lung macrophage. (J Allergy Clin Immunol. 2019 May;143(5):1769-1782.e11. doi: 10.1016/j.jaci.2018)

The Protective Role of Integrin α4β7 and Amphiregulin-Expressing Innate Lymphoid Cells in Lupus Nephritis

Hye Young KIM

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Type-2 innate lymphoid cells (ILC2s) have emerged as key immune-response regulators in renal-inflammatory diseases such as lupus nephritis. However, the mechanisms underlying ILC2 adhesion and migration in kidneys remain poorly understood. Here, we elucidated the critical role of integrin α4β7 in mediating renal ILC2 adhesion and function. We found that integrin α4β7 enables the retention of ILC2s in the kidney by binding to VCAM-1, E-cadherin, or fibronectin on structural cells. Moreover, integrin α4β7 knockdown resulted in reduced production of the reparative cytokine Amphiregulin (Areg) by ILC2s. In lupus nephritis, TLR7/9 signaling within the kidney microenvironment downregulated integrin α4β7 expression, leading to decreased Areg production and promoting the egress of ILC2s. Notably, IL-33 treatment upregulated ILC2 integrin α4β7 and Areg expression, thereby enhancing survival and mitigating inflammation in lupus nephritis. These findings highlight the potential of targeting ILC2 adhesion as a therapeutic strategy for autoimmune kidney diseases.

Keywords: innate lymphoid cells, tissue residency, adhesion molecules, lupus nephritis, amphiregulin

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Education and Appointments

2003	D.D.S., Nihon University School of Dentistry
2007 - 2011	Postdoctoral fellow, Keio University School of Medicine
2010	Ph.D., Keio University School of Medicine
2011 - 2016	Investigator, PRESTO, JST
2012 - 2015	Senior research scientist, RCAI-IMS, RIKEN
2015 -	Team leader, IMS, RIKEN (present)
2019 -	Professor, Osaka University (present)
2019 -	Concurrent professor, IFReC, Osaka University (present)
2019 -	Concurrent professor, Graduate School of Frontier Biosciences, Osaka University (present)

Speciality & Research Field of Interest

Innate lymphoid cells, Type 2 diseases

Selected Publications

1. Otaki N, Motomura Y, Terooatea T, Kelly T, Mochizuki M, Takeno N, Koyasu S, Tamamitsu M, Sugihara F, Kikuta J, Kitamura H, Shiraishi Y, Miyanohara J, Nagano Y, Saita Y, Ogura T, Asano K, Minoda S, Moro K. Activation of ILC2s through constitutive IFNγ signaling reduction leads to spontaneous pulmonary fibrosis. **Nature communications** (In press).
2. Hikichi Y, Motomura Y, Takeuchi O, Moro K. Posttranscriptional regulation of ILC2 homeostatic function via tristetraprolin. **JEM** 218 (2021)
3. Koga S, Hozumi K, Hirano KI, Yazawa M, Terooatea T, Minoda A, Nagasawa T, Koyasu S, Moro K. Peripheral PDGFRα+gp38+ mesenchymal cells support the differentiation of fetal liver-derived ILC2. **JEM** 215, 1609-1626 (2018)
4. Moro K, Kabata H, Tanabe M, Koga S, Takeno N, Mochizuki M, Fukunaga K, Asano K, Betsuyaku T, Koyasu S. Interferon and IL-27 antagonize the function of group 2 innate lymphoid cells and type 2 innate immune responses. **Nature immunology** 17, 76-86 (2016)
5. Kabata H, Moro K (equal contribution), Fukunaga K, Suzuki Y, Miyata J, Masaki K, Betsuyaku T, Koyasu S, Asano K. Thymic stromal lymphopoietin induces corticosteroid resistance in natural helper cells during airway inflammation. **Nature communications** 4, 2675 (2013)
6. Moro K, Yamada T, Tanabe M, Takeuchi T, Ikawa T, Kawamoto H, Furusawa J, Ohtani M, Fujii H, Koyasu S. Innate production of T(H)2 cytokines by adipose tissue-associated c-Kit+Sca-1+ lymphoid cells. **Nature** 463, 540-544 (2010)

Activation of ILC2s through constitutive IFNγ signaling reduction leads to spontaneous pulmonary fibrosis

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Pulmonary fibrosis (PF), a condition characterized by inflammation and collagen deposition in the alveolar interstitium, causes dyspnea and fatal outcomes. The bleomycin-induced pulmonary fibrosis mouse model has advanced our understanding of fibrosis caused by DNA damage to epithelial cells. However, the detailed mechanisms underlying fibrosis induced by endogenous factors such as aging remain unclear.
We discovered that *Ifngr1*$^{-/-}$*Rag2*$^{-/-}$ mice, lacking the critical suppression factor for group 2 innate lymphoid cells (ILC2s), spontaneously develop PF. In the onset phase of fibrosis, ILC2 subpopulations expressing high levels of *Il1rl1* (IL-33 receptor) were observed, and fibrosis disappeared in ILC-deficient or IL-33-deficient mice. Although ILC2s are typically localized near bronchioles and blood vessels, an increase in ILC2s was noted in fibrotic areas alongside IL-33-positive fibroblasts during fibrosis. Co-culture analysis revealed that activated ILC2s directly induce collagen production from fibroblasts. Furthermore, increased *IL1RL1* and decreased *IFNGR1* expressions were confirmed in ILC2s from individuals with idiopathic PF, emphasizing the relevance of *Ifngr1*$^{-/-}$*Rag2*$^{-/-}$ mice as a novel mouse model for fibrosis research.

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Education and Appointments

2002 - 2006	University of Science and Technology of China (B.S.)
2006 - 2012	University of Science and Technology of China (Ph.D.)
2012 - 2014	Postdoc, University of Science and Technology of China
2014 - 2019	Associate Professor, University of Science and Technology of China
2019 - present	Professor, University of Science and Technology of China

Speciality & Research Field of Interest

NK cells and innate lymphoid cells

Selected Publications

1. Bai L#, Vienne M#, Tang L#, Kerdiles Y#, Etiennot M, Escaliere B, Galluso J, Wei H, Sun R*, Vivier E*, Peng H*, Tian Z*. Liver type 1 innate lymphoid cells develop locally via an interferon-γ-dependent loop. **Science**. 2021; 371(6536):eaba4177.
2. Song J#, Song H#, Wei H, Sun R*, Tian Z*, Peng H*. Requirement of RORα for maintenance and antitumor immunity of liver-resident natural killer cells/ILC1s. **Hepatology**. 2022; 75(5):1181-1193.
3. Tang F#, Li J#, Qi L, Liu D, Bo Y, Qin S, Miao Y, Yu K, Hou W, Li J, Peng J, Tian Z, Zhu L*, Peng H*, Wang D*, Zhang Z*. A pan-cancer single-cell panorama of human natural killer cells. **Cell**. 2023; 186(19):4235-4251.
4. Zhou J, Peng H*, Li K, Qu K, Wang B, Wu Y, Ye L, Dong Z, Wei H, Sun R, Tian Z*. Liver-resident NK cells control antiviral activity of hepatic T cells via PD-1/PD-L1 axis. **Immunity**. 2019; 50(2):403-417.
5. Chen Y#, Wang X#, Hao X, Li B, Tao W, Zhu S, Qu K, Wei H, Sun R*, Peng H*, Tian Z*. Ly49E separates liver ILC1s into embryo-derived and postnatal subsets with different functions. **J Exp Med**. 2022; 219(5):e20211805.

Development and function of liver-resident NK cells/ILC1s: from fetal to adult life

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NK cells are critical innate immune effectors and abundantly present in the liver. We and other groups have previously found that the liver contains a unique NK cell subset, which is termed the liver-resident NK cell and currently categorized as a member of the innate lymphoid cell (ILC) family, namely type 1 ILCs (ILC1s). Compared to circulating NK cells that have been extensively studied for decades, research on liver ILC1s remains in its infancy. Our recent study shows that hematopoietic progenitors with ILC1 development potential are present in the fetal and adult liver, and other groups find that common progenitors to all known ILC subsets also exist in the adult bone marrow. To assess the contribution of different hematopoietic waves to liver ILC1s in detail, we used genetically inducible fate mapping models combined with scRNA-seq, and found that liver ILC1s were heterogeneously composed of subsets with different hematopoietic origins and functions. In particular, a small population with highly cytotoxic potential was generated during embryonic period and self-maintained into adulthood. In contrast, the rest ILC1s were generated postnatally, and their frequency increased with age. Unlike embryonic-derived liver ILC1s that exert host protection against viral infections in newborn mice, adult ILC1s could promote viral escape via inhibiting antiviral T cell responses. Therefore, these findings highlight heterogeneous composition of liver ILC1s with hematopoietic and functional distinct subsets that dynamically change with age.

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Education and Appointments

2001-2007 Yonsei University College of Medicine (M.D.)
2008-2012 Resident, Department of Dermatology, Severance Hospital
2012-2017 Medical Scientist Training Program, Yonsei University College of Medicine (Ph.D.)
2015-2016 Visiting Fellow, Department of Dermatology, Brigham & Women's Hospital, Harvard Medical School
2017-2019 Clinical Fellow, Clinical Research Assistant Professor, Department of Dermatology, Yonsei University College of Medicine
2019-2021 Translational Research Assistant Professor, Department of Microbiology and Immunology, Yonsei University College of Medicine
2021-present Assistant Professor, Yonsei University College of Medicine

Specialty & Research Field of Interest

Psoriasis and autoimmune connective tissue diseases
Ontogeny and function of skin-resident immune and non-immune cells in health and disease

Selected Publications (*equal contribution)

1. Kim SH, Oh J, Roh WS, Park J, Chung KB, Lee GH, Lee YS, Kim JH, Lee HK, Lee H, Park CO, Kim DY, Lee MG*, Kim TG*. Pellino-1 Promotes Intrinsic Activation of Skin-Resident IL-17A-Producing T Cells in Psoriasis. **J Allergy Clin Immunol**. 2023;151(5):1317-1328.
2. Chung KB, Oh J, Roh WS, Kim TG*, Kim DY*. Core Gene Signatures of Atopic Dermatitis Using Public RNA-Sequencing Resources: Comparison of Bulk Approach with Single-Cell Approach. **J Invest Dermatol**. 2022;142(3 Pt A):717-21.e5.
3. Lee HJ*, Kim TG*, Kim SH, Park JY, Lee M, Lee JW, Lee SH, Lee MG. Epidermal Barrier Function Is Impaired in Langerhans Cell-Depleted Mice. **J Invest Dermatol**. 2019;139(5):1182-1185.
4. Kim TG, Kim SH, Park J, Choi W, Sohn M, Na HY, Lee M, Lee JW, Kim SM, Kim DY, Kim HP, Choi JH, Park CG, Lee MG. Skin-Specific CD301b+ Dermal Dendritic Cells Drive IL-17-Mediated Psoriasis-Like Immune Response in Mice. **J Invest Dermatol**. 2018;138(4):844-53.
5. Kim TG, Kim M, Lee JJ, Kim SH, Je JH, Lee Y, Song MJ, Choi Y, Chung YW, Park CG, Cho JW, Lee MG, Lee YS, Kim HP. CCCTC-binding factor controls the homeostatic maintenance and migration of Langerhans cells. **J Allergy Clin Immunol**. 2015;136(3):713-24.

Skin microbe-dependent early postnatal TSLP-ILC2 priming axis is co-opted in adulthood

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Although early life colonization of commensal microbes contributes to long-lasting immune imprinting in host tissues, little is known regarding the pathophysiological consequences of postnatal microbial tuning of cutaneous immunity. Here, we show that postnatal exposure to specific skin commensal *Staphylococcus* species promotes the extent of atopic dermatitis (AD)-like inflammation in adults through priming of group 2 innate lymphoid cells (ILC2s). Early postnatal skin was dynamically populated by discrete subset of primed ILC2s driven by microbiota-dependent induction of thymic stromal lymphopoietin (TSLP) in keratinocytes. Specifically, indole-3-aldehyde-producing tryptophan metabolic pathway, shared across *Staphylococcus* species, was involved in TSLP-mediated ILC2 priming. Furthermore, we demonstrate a critical contribution of the early postnatal *Staphylococcus*-TSLP-ILC2 priming axis in facilitating AD-like inflammation in adulthood that was not replicated by later microbial exposure. Thus, our findings highlight the fundamental role of time-dependent neonatal microbial-skin crosstalk in shaping the threshold of innate type 2 immunity in later life.

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Education and Appointments

2008 - 2011	L'École Doctorale de Cancérologie, Université Paris-Sud 11 (Ph.D.)
2011 - 2013	Postdoctoral fellow, Institut de Cancérologie Gustave Roussy
2013 - 2015	Postdoctoral fellow, Université Paris Descartes
2015 - present	Principal investigator, Institute of Systems Medicine, Chinese Academy of Medical Sciences
2016 - present	Doctoral supervisor, Peking Union Medical College
2021 - present	Associate Dean, Institute of Systems Medicine, Chinese Academy of Medical Sciences
2023 - present	Associate Director, National Key Laboratory of Immunity and Inflammation

Speciality & Research Field of Interest

Cancer Immunology, Stress response, Cell death, Neuroendocrine-immune crosstalk

Selected Publications

1. Stress-glucocorticoid-TSC22D3 axis compromises therapy-induced antitumor immunity. ***Nat Med***. 2019 Sep;25(9):1428-1441.
2. Chemotherapy-induced antitumor immunity requires formyl peptide receptor 1. ***Science*** 2015 Nov 20;350(6263):972-8.
3. Anticancer chemotherapy-induced intratumoral recruitment and differentiation of antigen-presenting cells. ***Immunity*** 2013 Apr 18;38(4):729-41.
4. Arsenic trioxide elicits prophylactic and therapeutic immune responses against solid tumors by inducing necroptosis and ferroptosis. ***Cell Mol Immunol***. 2023 Jan;20(1):51-64.
5. The cancer-immune dialogue in the context of stress. ***Nat Rev Immunol*** 2023 Oct 13. doi: 10.1038/s41577-023-00949-8

Stress reshapes the immune microenvironment and macroenvironment

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The widespread nervous system and immune system throughout the body can perceive and respond to internal and external stimuli. The "neuro-immune" interaction is crucial for regulating various physiological and pathological processes. Unexpectedly, we found that stress can disrupt the neuro-immune homeostasis, suppress bone marrow hematopoiesis, and significantly enhance extramedullary hematopoiesis in the spleen, leading to an increase in red cell precursors and platelets, as well as anemia. Stress also significantly increases the proportion of myeloid cells. Depletion of myeloid cells or blocking their migration results in acute death of stressed mice. Stress significantly impairs anti-tumor and antiviral immune responses. We elucidate the key mechanisms by which stress inhibits bone marrow hematopoiesis and promotes extramedullary hematopoiesis in the spleen, with a focus on the macroenvironment of the organism, the microenvironment of the bone marrow and spleen, and the regulatory role of CD11b+ myeloid cells. We also clarify the crucial regulatory role of myeloid cells in stress-induced anemia and acute death. Furthermore, we try to determine whether stress-induced extramedullary hematopoiesis is reversible and explore the key regulatory mechanisms to restore hematopoietic homeostasis. Additionally, we investigate whether the abnormal expansion of myeloid cells, red cell precursors, and platelets after stress is associated with stress-induced metabolic disorder and whether they participate in regulating anti-tumor and antiviral immune responses, along with the underlying key mechanisms.

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2008 - 2009	Research Investigator, Novartis Institutes for Biomedical Research
2009 - 2018	Assistant/Associate Professor, POSTECH
2018 - present	Associate Professor, KIAST

Specialty & Research Field of Interest

Innate immunity, Microbiota-host interaction, Immune cell signaling

Selected Publications

1. Song HS, Park S, Huh JW, Lee YR, Jung DJ, Yang C, Kim SH, Kim HM, Kim YM (2022) N-glycosylation of UNC93B1 at a specific asparagine residue is required for TLR9 signaling. **Front Immunol** 13:875083
2. Kang W, Park A, Huh JW, You G, Jung DJ, Song M, Lee HK, Kim YM (2020) Flagellin-stimulated production of interferon- β promotes anti-flagellin IgG2c and IgA responses. **Mol Cells** 43:251-63
3. Hong CP, Park A, Yang BG, Yun CH, Kwak MJ, Lee GW, Kim JH, Jang MS, Lee EJ, Jeun EJ, You G, Kim KS, Choi Y, Park JH, Hwang D, Im SH, Kim JF, Kim YK, Seoh JY, Surh CD, Kim YM, Jang MH (2017) Gut-specific delivery of Th17 cells reduces obesity and insulin resistance in mice. **Gastroenterology** 152:1998-2010
4. Park MJ, Sheng R, Silkov A, Jung DJ, Wang ZG, Xin Y, Kim H, Thiagarajan-Rosenkranz P, Song S, Yoon Y, Nam W, Kim I, Kim E, Lee DG, Chen Y, Singaram I, Jang MH, Hwang CS, Honig B, Ryu S, Lorieau J, Kim YM, and Cho W (2016) SH domains serve as lipid binding modules for pTyr-signaling proteins. **Mol Cell** 62:7-20
5. Huh JW, Shibata T, Hwang M, Kwon EH, Jang MS, Fukui R, Kanno A, Jung DJ, Jang MH, Miyake K, Kim YM (2014) UNC93B1 is essential for the plasma membrane localization and signaling of Toll-like receptor 5. **Proc Natl Acad Sci USA** 111:7072-7
6. Kim J, Huh J, Hwang M, Kwon EH, Jung DJ, Brinkmann MM, Jang MH, Ploegh HL, Kim YM (2013) Acidic amino acid residues in the juxta-membrane region of the nucleotide-sensing toll-like receptors are important for UNC93B1 binding and signaling. **J Immunol** 190:5287-95

Prostaglandin E_2 signaling in dendritic cells and the intestinal homeostasis

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The intestine maintains immune homeostasis even though it is constantly exposed to dietary antigens, commensal microbiota, and opportunistic pathogens. At steady state, the intestine harbors the highest proportion of Th17 cells compared to other organs and those Th17 cells play a critical role in maintaining epithelial barrier function and preventing microbial dysbiosis. A unique ability of intestinal lamina propria dendritic cells (LP-DCs) to produce a high amount of IL-6 is critical for the intestinal Th17 differentiation and the gut homeostasis. However, the specific regulatory mechanisms determining the distinct characteristics of LP-DCs are not well understood.

In this study, we found that prostaglandin E_2 (PGE_2) signaling regulates IL-6 production by LP-DCs and controls the intestinal immune responses. Prostaglandin E_2 (PGE_2) is present more abundantly in the gastrointestinal tract than in any other organs, and DCs differentiated from pre-cDCs in vitro in the presence of PGE_2 upregulate expression of the signature genes of LP-DCs. Additionally, PGE_2 enhances IL-6 production in DCs via EP4, one of the four PGE_2 receptors (EP1-4), and promotes the differentiation of Th17 cells. DC-specific EP4 deficient mice ($EP4^{\Delta DC}$) have fewer intestinal Th17 cells compared to control mice and show symptoms of gut barrier leakage even at steady state, such as neutrophil infiltration into the intestine, mesenteric lymphadenitis, and an increase in microbiota-specific serum IgA titers. $EP4^{\Delta DC}$ mice are also more susceptible to DSS-induced colitis and oral bacterial infection. Together, our results demonstrate that cell-intrinsic PGE_2-EP4 signaling endows LP-DCs with distinct characteristics that set them apart from DCs in other organs and critically contributes to intestinal homeostasis.

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Education and Appointments

2010 - Professor & Academic committee member, SIBCB, CAS, Shanghai, China

2006 - 2010 Research Fellow, Dept of Pathology, University of Cambridge, UK

2001 - 2006 PhD student & Research Associate, Imperial College London, UK

1993 - 1998 - 2001 BSc,& MSc, Anhui Medical University, China

Specialty & Research Field of Interest

Macrophage in Infection and Tumor, Inflammation, Cholesterol metabolism

Selected Publications

1. Xiaojing Li*, Linlin Qi*, Dan Yang, ShuJie Hao, Fang Zhang, Xingguo Zhu, Yue Sun, Chen Chen, Jing Ye, Jing Yang, Ling Zhao, Daniel Altmann, Shengbo Cao, **Hongyan Wang#**, Bin Wei#. Meningeal lymphatic vessels mediate the drainage of virus from the central nervous system and protect against neurotropic virus infection. **Nature Neuroscience**, 2022 May;25(5):577-587. **(Nat Rew Neurol 2022, Research Highlight)**
2. J Xiao*, WY Li*, X Zheng, L Qi, H Wang, C Zhang, XP Wan, YX Zheng, RY Zhong, X Zhou, Y Lu, ZQ Li, Y Qiu, C Liu, F Zhang, YB Zhang, XY Xu, ZZ Yang, HL Chen, QW Zhai, B Wei#, **H Wang#**, Targeting 7-Dehydrocholesterol Reductase Integrates Cholesterol Metabolism and IRF3 Activation to Eliminate Infection. **Immunity,** 2020, 52: 1-14 **(Immunity, Previews)**
3. Y Lu*, Y Qiu*, P Chen, H Chang, L Guo, F Zhang, L Ma, C Zhang, X Zheng, J Xiao, R Zhong, L Han, X Xu, Y Zhang, D Li, G Zhong, R Boyton, Y Huang, Y He, R Hu#, B Wei#, **H Wang#** The ER-localised Hrd1 ubiquitinates and inactivates Usp15 to promote TLR4-induced inflammation during bacterial infection. **Nature Microbiology**, 2019,4:2331-46
4. WY Li*, J Xiao*, X Zhou, M Xu, C Hu, X Xu, Y Lu, CLiu, S Xue, LNie, H Zhang, ZLi, Y Zhang, F Ji, L Hui, W Tao, B Wei# and **H Wang#**, STK4 regulates TLR pathways and protects against chronic inflammation–related hepatocellular carcinoma. **J Clin Invest**, 2015; 125(11):4239-54
5. Zhang Y*, Lu Y*, Ma L, Jiao S, Chen J, Gao Y, Liu C, Duan Z, Li D, He Y, Wei B#, **Wang H#** Activation of vascular endothelial growth factor receptor-3 in macrophages restrains TLR-NF-κB signaling and protects from endotoxin shock. **Immunity**, 2014, 40: 501-514 **(Cover Story)**

Macrophage, Metabolism and Inflammation

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Macrophages mediate inflammatory responses and multiple inflammatory diseases, including infection, autoimmune disease, and cancer. Cholesterol metabolism is vital to manipulate macrophage function. We are interested to identify which key enzymes in lipid/ cholesterol metabolism could affect macrophage polarization, inflammation and immune surveillance. In this talk, I will introduce how the metabolites 7DHC and LPA-1 affect IFN-I and ISG production in macrophages to control virus infection. We also screened the levels of cholesterol metabolites in plasma of SLE patients to identify 7a-25OH as the key metabolite that modulates macrophage-mediated inflammation and the development of SLE. Recently, we used three types of immunosuppressive macrophages to identify which oxysterol and the related cholesterol enzyme as a metabolic checkpoint to control the development of solid tumors.

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Education and Appointments

1993 - 1997 Xiamen University (BS)
1997 - 2000 Xiamen University (MS)
2001 - 2006 Albert Einstein College of Medicine (Ph.D)
2006 - 2012 Research fellow, Harvard Medical School
2012 - 2013 Associate Professor, School of Life Sciences, Xiamen University
2013 - present Professor, School of Life Sciences, Xiamen University

Speciality & Research Field of Interest

Hippo signaling, Innate immunity, Immune homeostasis,

Selected Publications

1. Liu Q, Li J, Zhang W, Xiao C, Zhang S, Nian C, Li J, Su D, Chen L, Zhao Q, Shao H, Zhao H, Chen Q, Li Y, Geng J, Hong L, Lin S, Wu Q, Deng X, Ke R, Ding J, Johnson RL, Liu X, Chen L*, Zhou D*. Glycogen accumulation and phase separation drives liver tumor initiation. **Cell**. 2021 Oct 28; 184(22):5559-5576.e19.
2. Geng J, Shi Y, Zhang J, Yang B, Wang P, Yuan W, Zhao H, Li J, Qin F, Hong L, Xie C, Deng X, Sun Y, Wu C, Chen L*, Zhou D*. TLR4 signalling via Piezo1 engages and enhances the macrophage mediated host response during bacterial infection. **Nat Commun**. 2021 Jun 10; 12(1):3519.
3. 7Wang P, Geng J, Gao J, Zhao H, Li J, Shi Y, Yang B, Xiao C, Linghu Y, Sun X, Chen X, Hong L, Qin F, Li X, Yu JS, You H, Yuan Z, Zhou D, Johnson RL, Chen L*. Macrophage achieves self-protection against oxidative stress-induced ageing through the Mst-Nrf2 axis. **Nat Commun.** 2019; 10(1):755.
4. Geng J, Yu S, Zhao H, Su X, Li X, Wang P, Xiong X, Hong L, Xie C, Gao J, shi Y, Peng J, Johnson RL, Xiao N, Lu L, Han J, Zhou D*and Chen L*. The transcriptional coactivator TAZ regulates reciprocal differentiation of Th17 cells and Treg cells. **Nat Immunol.** 2017, Jul; 18(7):800-812.
5. Geng J, Sun X, Wang P, Zhang S, Wang X, Wu H, Hong L, Xie C, Li X, Zhao H, Liu Q, Jiang M, Chen Q, Zhang J, Li Y, Song S, Wang HR, Zhou R, Johnson RL, Chien KY, Lin SC, Han J, Avruch J, Chen L*, Zhou D*. Kinases Mst1 and Mst2 positively regulate phagocytic induction of reactive oxygen species and bactericidal activity. **Nat Immunol.** 2015 Nov; 16(11):1142-52.

Functions of Hippo kinases Mst1/2 in the immune system

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The Hippo pathway has been originally identified as a key regulator of tissue homeostasis and organ size control in multiple organisms. Recent studies have shown that the non-canonical Hippo signaling pathway, centered on the core Hippo signaling kinases Mst1/2, regulates immune responses and functions through synergistic interaction with other signaling pathways in immune cells, and plays an important role in maintaining the homeostasis of the immune system. Our group's research focuses on the Hippo signaling pathway regulating innate immune cells host defense, redox homeostasis, response to microenvironment stiffness, as well as T cells differentiation and activation. Recently, we reported that TLR4 signaling interacts with the mechanosensor Piezo1 to activate Mst1/2 kinases, which enhances phagocytosis and efficiently scavenges of bacteria in phagocytes by regulating reactive oxygen species (ROS) production. These results suggested that TLR4 drives the Mst1/2 kinases-mediated innate immune response via Piezo1 providing critical insight for understanding macrophage mechanophysiology and the host response.

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Education and Appointments

1989 - 1995	Osaka University Medical School (M.D.)
1997 - 2001	Graduate School of Medicine, Osaka University (Ph.D.)
2002 - 2004	Postdoctoral fellow, Harvard Medical School
2004 - 2007	Assistant Professor, RIMD, Osaka University
2007 - 2012	Associate Professor, RIMD, Osaka University
2012 - 2018	Professor, Institute for Virus Research, Kyoto University
2018 - present	Professor, Graduate School of Medicine, Kyoto University

Speciality & Research Field of Interest

Innate immunity, Post-transcriptional regulation

Selected Publications

1. Uehata T, Yamada S, Ori D, Vandenbon A, Giladi A, Jelinski A, Murakawa Y, Watanabe H, Takeuchi K, Toratani K, Mino T, Kiryu H, Standley DM, Tsujimura T, Ikawa T, Kondoh G, Landthaler M, Kawamoto H, Rodewald HR, Amit I, Yamamoto R, Miyazaki M, Takeuchi O. Regulation of lymphoid-myeloid lineage bias through Regnase-1/3-mediated control of Nfkbiz. **Blood**. 2023 Nov 3:blood.2023020903.
2. Yaku A, Inagaki T, Asano R, Okazawa M, Mori H, Sato A, Hia F, Masaki T, Manabe Y, Ishibashi T, Vandenbon A, Nakatsuka Y, Akaki K, Yoshinaga M, Uehata T, Mino T, Morita S, Ishibashi-Ueda H, Morinobu A, Tsujimura T, Ogo T, Nakaoka Y, Takeuchi O. Regnase-1 Prevents Pulmonary Arterial Hypertension Through mRNA Degradation of Interleukin-6 and Platelet-Derived Growth Factor in Alveolar Macrophages. **Circulation.** 2022 146:1006-1022.
3. Tse KM, Vandenbon A, Cui X, Mino T, Uehata T, Yasuda K, Sato A, Tsujimura T, Hia F, Yoshinaga M, Kinoshita M, Okuno T, Takeuchi O. Enhancement of Regnase-1 expression with stem-loop-targeting antisense oligonucleotides alleviates inflammatory diseases. **Sci Transl Med.** 2022 14:eabo2137.
4. Yamasoba D, Sato K, Ichinose T, Imamura T, Koepke L, Joas S, Reith E, Hotter D, Misawa N, Akaki K, Uehata T, Mino T, Miyamoto S, Noda T, Yamashita A, Standley DM, Kirchhoff F, Sauter D, Koyanagi Y, Takeuchi O. N4BP1 restricts HIV-1 and its inactivation by MALT1 promotes viral reactivation. **Nat Microbiol.** 2019 Sep;4(9):1532-1544.
5. Mino T, Murakawa Y, Fukao A, Vandenbon A, Wessels HH, Ori D, Uehata T, Tartey S, Akira S, Suzuki Y, Vinuesa CG, Ohler U, Standley DM, Landthaler M, Fujiwara T, Takeuchi O. Regnase-1 and Roquin Regulate a Common Element in Inflammatory mRNAs by Spatiotemporally Distinct Mechanisms. **Cell.** 2015 May 21;161(5):1058-1073.

Post-transcriptional regulation of the immune system by Regnase-1-like endoribonucleases

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Post-transcriptional regulation by RNA-binding proteins (RBPs) is critical for the control of immune cell activation. Regnase-1, an RBP, acts as an endoribonuclease that degrades inflammatory mRNAs by recognizing stem-loop (SL) structures in the 3' untranslated regions (3'UTRs). Dysregulated expression of Regnase-1 is associated with the pathogenesis of inflammatory and autoimmune diseases in mice and human. Regnase-1 is involved in a variety of inflammatory diseases including ulcerative colitis, pulmonary fibrosis, multiple sclerosis and pulmonary hypertension. The expression of Regnase-1 is maintained by self-regulation degrading its own mRNA. We developed a therapeutic strategy to suppress inflammatory responses by blocking Regnase-1 self-regulation, which was mediated by the simultaneous use of two antisense-oligonucleotides (ASOs) to alter the binding of Regnase-1 toward the SL structures in its 3' UTR. Regnase-1-targeting ASOs not only enhanced Regnase-1 expression but also effectively reduced the expression of multiple proinflammatory transcripts in macrophages. Administration of Regnase-1-targeting ASOs ameliorated acute respiratory distress syndrome, lung fibrosis and encephalitis mouse models through suppression of inflammatory cascades. Collectively, MO-mediated disruption of the Regnase-1 self-regulation pathway is a potential therapeutic strategy to enhance Regnase-1 abundance, which, in turn, provides therapeutic benefits for treating inflammatory diseases by suppressing inflammation. Recently, we found that the ASOs targeting SL structures are more widely applicable to immune regulation. Regnase-3, a Regnase-1-related protein, and Regnase-1 are found to function in hematopoietic stem and progenitor cells (HSPCs) for the determination of myeloid and lymphoid lineages by degrading *Nfkbiz* mRNA. An ASO designed to inhibit SL structures in *Nfkbiz* 3' UTR successfully augmented Nfkbiz expression and facilitated myelopoiesis. These results suggest that ASO-mediated inhibition of mRNA degradation via Regnase-1-related endoribonucleases is a prominent strategy to control immune responses.

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Education and Appointments

1997 Beijing Medical University (currently Peking University Health Science Center), (B.M.)
2004 Cornell University Weill Graduate School of Medical Sciences, New York, NY, (Ph.D.)
2004 - 2005 Postdoctoral Fellow, Research Division, Hospital for Special Surgery, New York, NY
2005 - 2008 Instructor, Research Division, Hospital for Special Surgery, New York, NY
2008 - 2014 Assistant Scientist, Research Division, Hospital for Special Surgery, New York, NY
2010 - 2014 Assistant Professor of Immunology, Department of Medicine, Weill Cornell Medicine, New York, NY
2014 - present Principal Investigator, Institute for Immunology at Tsinghua University
2014 - 2017 Associate Professor, Tsinghua University School of Medicine
2016 - present Vice Chair, Department of Basic Medical Sciences, Tsinghua University School of Medicine
2017 - 2020 Associate Professor, Tsinghua University School of Medicine
2020 - present Professor of Immunology, Tsinghua University School of Medicine
2022 - present Director, Institute for Immunology at Tsinghua University

Speciality & Research Field of Interest

Innate immune effector functions and implications in human diseases

Selected Publications

1. Shang Y, Coppo M, He T, Ning F, Yu L, Kang L, Zhang B, Ju C, Qiao Y, Zhao B, Gessler M, Rogatsky I, Hu X. The transcriptional repressor Hes1 attenuates inflammation by regulating transcription elongation. Nature Immunology 2016; 17:930-937
2. Liang S, Guo XK, Ou J, Huang R, Xue Q, Zhang B, Chung Y, Wu W, Dong C, Yang X, Hu X. Nutrient sensing by the intestinal epithelium orchestrates mucosal antimicrobial defense via translational control of Hes1. Cell Host & Microbe 2019; 25:706-718
3. Ji L, Zhao X, Zhang B, Kang L, Song W, Zhao B, Xie W, Chen L*, Hu X* (*co-corresponding author). Slc6A8-mediated creatine uptake and accumulation reprogram macrophage polarization via regulating cytokine responses. Immunity 2019; 51:272-284
4. Zhang B, Zhang Y, Xiong L, Li Y, Zhang Y, Zhao J, Jiang H, Li C, Liu Y, Liu X, Liu H, Ping YF, Zhang QC, Zhang Z, Bian XW*, Zhao Y* and Hu X* (*co-corresponding authors). CD127 imprints functional heterogeneity to diversify monocyte responses in human inflammatory diseases. Journal of Experimental Medicine. 2022; 219(2):e20211191
5. Yang Y#, Zhang Y#, Xing X, Xu G, Lin X, Wang Y, Chen M, Wang C, Zhang B, Han W, Hu X*(*co-corresponding authors). IL-6 translation is a therapeutic target of human cytokine release syndrome. Journal of Experimental Medicine. 2023; 220(11):e20230577.

Therapeutically targeting human cytokine release syndrome

Xiaoyu HU

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Chimeric antigen receptor (CAR) T therapies have achieved remarkable successes for treating hematologic malignancies yet are often accompanied by severe cytokine release syndrome (CRS). Here, an accidental clinical observation raised the possibility that metoprolol, an FDA-approved adrenergic receptor blocker widely used for cardiovascular conditions, may alleviate CAR T-induced CRS. Metoprolol effectively blocked IL-6 production in human monocytes through unexpected mechanisms of action of targeting IL-6 protein translation but not IL6 mRNA expression. Mechanistically, metoprolol diminished IL-6 protein synthesis via attenuating eEF2K-eEF2 axis-regulated translation elongation. Furthermore, an investigator-initiated phase I/II clinical trial demonstrated favorable safety profile of metoprolol in CRS management and showed that metoprolol significantly alleviated CAR T-induced CRS without compromising CAR T efficacy. These results repurposed metoprolol, a WHO essential drug, as a potential therapeutic for CRS and implicated IL-6 translation as a mechanistic target of metoprolol, opening venues for protein translation-oriented drug developments for human inflammatory diseases.

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Education and Appointment

1999-2002 B.S., Nankai University
2002-2005 M.S., Nankai University
2005-2011 Ph.D., Rutgers, the State University of New Jersey
2012-2017 Postdoc Fellow, Yale University
2017-present Principal Investigator, Professor, Shanghai Institute of Immunology, Shanghai Jiao Tong University School of Medicine

Speciality & Research Field of Interest

T cells, Macrophages, Cancer Immunology, RNA modification, post-transcriptional regulation

Selected Publications

1. Ding C#, Yu Z#, Sefik E#, Zhou J#, Kaffe E, Li B, Wang L, Flavell RA, Hu W, Ye Y, **Li HB***. A Treg specific long non-coding RNA maintains immune-metabolic homeostasis in ageing liver. ***Nature Aging***, 2023; 3(7):813-828.
2. Liu Y#, Zhou J#, Li X#, Zhang X#, Shi J#, Wang X, Li H, Miao S, Chen H, He X, Dong L, Lee GR, Zhen J, Liu RJ, Su B, Ye Y, Flavell RA*, Yi C*, Wu Y*, **Li HB***. tRNA-m1A modification promotes T cell expansion via efficient MYC protein synthesis. ***Nature Immunology***, 2022; 23(10):1433-1444.
3. Ding C#, Xu H#, Yu Z#, Roulis M, Qu R, Zhou J, Oh J, Craford J, Gao Y, Jackson R, Sefik E, Li S, Wei Z, Skadow M, Yin Z, Ouyang X, Wang L, Zou Q, Su B, Hu W*, Flavell RA*, **Li HB***. RNA m6A demethylase ALKBH5 regulates the development of γδ T cells. ***Proc Natl Acad Sci U S A***. 2022;119(33):e2203318119.
4. Chen B#, Hu J#, Hu X#, Chen H, Bao R, Zhou Y, Ye Y, Zhan M*, Cai W*, Li H*, **Li HB***. DENR controls JAK2 translation to induce PD-L1 expression for tumor immune evasion. ***Nature Communications***, 2022; 13(1):2059.
5. Zhang T#, Ding C#*, Chen H# Zhao J, Chen J, Chen B, Mao K, Hao Y, Roulis M, Xu H, Kluger Y, Zou Q, Ye Y, Zhan M*, Flavell RA*, **Li HB***. m6A mRNA modification maintains colonic epithelial cell homeostasis via NF-κb-mediated anti-apoptotic pathway. ***Science Advances***, 2022; 8(12):eabl5723.

RNA Modification in Immunity

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To date, more than 100 chemical modifications have been identified in RNA, however most of their functions are still unknown. The four major RNA modifications, i.e., m6A, m1A, alternative polyadenylation (APA), and adenosine-to-inosine RNA editing (A-I editing), modulated by 'writers', 'erasers' and 'readers' of those marks, constitute critical mechanisms of epigenetic regulation in immune response and tumorigenesis. The post-transcriptional epigenetic regulation over RNAs is characteristic of fast turnover of RNAs and could regulate immune cells to quickly respond to stimuli and adapt to the microenvironment. We systematically investigate the m6A function in T cells, Macrophages and Intestinal epithelial cells, whose malfunctions will lead to inflammatory bowel disease (IBD). We published a serial of 5 papers to reveal the m6A targeting specificity in fast responding immune cells, and we propose a new m6A working model in which m6A acts as a "gas pedal" specifically targeting immediate-early response genes, such as Socs in T cells, *Irakm* in macrophages and *Nfkbia* in colonic epithelial cells, to trigger their rapid degradation and to ensure that the immune cells can quickly respond to the external stimuli and adapt to the environment.

While we are working on m6A, we are also very interested in how m6A coordinates with other major RNA modifications to regulate immune cell functions during inflammation and cancer. By analyzing TCGA databases, we constructed a RNA modification 'writer' score composed of m6A, m1A, APA and A-I editing writer genes, and found that crosstalk among those writer genes could defines colorectal cancer microenvironments. Thus, our group further explored the function of m1A in immune cells. we found that upon exit from quiescence, T cells upregulate tRNA-m1A58 "writer" proteins TRMT61A and TRMT6 which confer m1A58 RNA modification to a specific subset of early expressed tRNAs. Those m1A modified early tRNAs enhance translation efficiency, enable rapid and necessary synthesis of MYC and other key functional proteins. The MYC proteins then guides the exit of naïve T cells from quiescence state into a proliferative state, and promotes rapid T cell expansion after activation. Conditional deletion of Trmt61a gene in mouse CD4+ T cells causes MYC protein deficiency and cell cycle arrest, disrupts T cell expansion upon cognate antigen stimulation, and alleviates colitis in a mouse adoptive transfer colitis disease model. Our study elucidates for the first time, to our knowledge, the in vivo physiological roles of dynamic tRNA-m1A58 modification in T-cell-mediated pathogenesis, and reveals a novel mechanism of tRNA-m1A58 controlled T cell homeostasis and signal-dependent translational control of early key proteins.

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Education and Appointments

2007-2011	Dep of Biomedical Science, Kyushu University School of Medicine.
2011-2013	Graduate School of Medical Science, Kyushu University.
2013-2016	Department of Microbiology and Immunology, Keio University School of Medicine. (Ph.D.)
2016-2020	Postdoctoral fellow, Keio University School of Medicine.
2016-2020	Assistant Professor, Keio University School of Medicine.
2020-present	Associate Professor, MIB, Kyushu University

Speciality & Research Field of Interest

Neuroimmunology

Selected Publications

Ito M. et al. Brain regulatory T cells suppress astrogliosis and potentiate neurological recovery. Nature. 2019; 565(7738): 246-250

Significance of regulatory T cells in the central nervous system

Minako ITO

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Kyushu University

In recent years, the interaction between the nervous system and the immune system has emerged as a focal point of research, spanning various medical disciplines.

Using a mouse model of cerebral infarction called the middle cerebral artery occlusion model, we are studying the significance of immune responses during the acute and chronic phases after cerebral infarction. We have found that innate immune-related inflammation, mainly by macrophages and γδ T cells, plays a major role in the acute phase of cerebral inflammation, while a large amount of T cells infiltrate the brain in the chronic phase, which is a very unique aspect of cerebral inflammation. In particular, we have shown that regulatory T cells (Treg) acquire brain-specific properties and contribute to the recovery of neurological symptoms by regulating excessive activation of microglia and astrocytes.

During the chronic phase of cerebral infarction, Tregs were also increased in the peripheral blood, with enhanced suppressive capacity and characteristics similar to tissue Tregs. At the time of recurrent cerebral infarction, Treg increase and suppression of inflammation, resulting in reduced cerebral infarction. Tregs with the same T-cell receptor were more likely to infiltrate during initial and recurrent infarction, suggesting that once Tregs recognize the antigen, they may reactivate and respond quickly. We also identified oxytocin as another inhibitory factor that is elevated in the brain and peripheral blood during the chronic phase of cerebral infarction. Oxytocin reduced cerebral infarction, and oxytocin receptor antagonists delayed recovery of neurological symptoms during the chronic phase of cerebral infarction. These results suggested that oxytocin and Treg may be important in the suppression of inflammation and tissue repair during stroke.

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Education and Appointments

1985-1991 School of Medicine, Tokyo Medical and Dental University (M.D.)
1991-1995 Graduate School of Medicine, Tokyo Medical and Dental University (Ph.D.)
1995-1998 Dermatologist, affiliated hospitals of Tokyo Medical and Dental University
1999-2001 Research Fellow for Young Scientists, Japan Society for the Promotion of Science, Shimon Sakaguchi lab, Kyoto University
2001-2009 Research Associate, Research Assistant Professor, Ralph Steinman lab, The Rockefeller University, New York, USA.
2009- 2011 Specifically Appointed Associate Professor, Department of Microbiology and Immunology, Graduate School of Medicine, Hokkaido University
2011-2012 Lecturer, Department of Dermatology, Dokkyo Medical Univ. Koshigaya
2012-2014 Associate Professor, Department of Dermatology, Nagoya City University, Graduate School of Medicine, Nagoya, Japan.
2014.12- Current position

Speciality & Research Field of Interest

Immunoregulation by regulatory T cells and dendritic cells

Selected Publications

*Corresponding author

1. Minohara K, Imai M, Matoba T, Wing JB, Shime H, Odanaka M, Uraki R, Kawakita D, Toyama T, Takahashi S, Morita A, Murakami S, Ohkura N, Sakaguchi S, Iwasaki S, Yamazaki S *. Mature dendritic cells enriched in regulatory molecules may control regulatory T cells and the prognosis of head and neck cancer. ***Cancer Science***. 2023 114(4):1256-1269.
2. Uraki R, Imai M, Ito M, Shime H, Odanaka M, Okuda M, Kawaoka Y, Yamazaki S*. Foxp3^{+} CD4^{+} regulatory T cells control dendritic cells in inducing antigen-specific immunity to emerging SARS-CoV-2 antigens. ***PLoS Pathogens*** 2021 17:e1010085 (1-24).
3. Shime H, Odanaka M, Tsuiji M, Matoba T, Imai M, Yasumizu Y, Uraki R, Minohara K, Watanabe M, Bonito AJ, Fukuyama H, Ohkura N, Sakaguchi S, Morita A, Yamazaki S*. Proenkephalin^{+} regulatory T cells expanded by ultraviolet B exposure maintain skin homeostasis with a healing function. ***Proc. Nat. Acad. Sci. U.S.A.*** 2020 117:20696-20705.
4. Matoba T, Imai M, Ohkura N, Kawakita D, Ijichi K, Toyama T, Morita A, Murakami, S, Sakaguchi S, Yamazaki S*. Regulatory T cells expressing abundant CTLA-4 on the cell surface with a proliferative gene profile are key features of human head and neck cancer. ***Int J Cancer*** 2019 144: 2811-2822.
5. Yamazaki S*, Odanaka M, Nishioka A, Kasuya S, Shime H, Hemmi H, Imai M, Riethmacher D, Kaisho T, Ohkura N, Sakaguchi S, Morita A. Ultraviolet B induced maturation of CD11b-type Langerin^{-} dendritic cells controls the expansion of Foxp3^{+} regulatory T cells in the skin. ***J Immunol.*** 2018 200:119-129.

Immune regulation mediated by crosstalk between dendritic cells and regulatory T cells

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$CD25^+CD4^+$ regulatory T(Treg) cells, expressing Foxp3 transcription factor, constitute about 5-10% of peripheral $CD4^+$ T cells and maintain immunological self-tolerance. Professor Shimon Sakaguchi discovered $CD25^+CD4^+$ Treg cells in 1995. When I joined to his lab, I was lucky to participate in the discovery that Treg cells not only suppress autoimmunity but also tumor immunity (Shimizu, Yamazaki, Sakaguchi. *J Immumol* 1999). Now it is well-established that Treg cells suppress various important immune responses such as autoimmunity, tumor immunity, transplant rejection, allergy, inflammation and responses to infectious agents. Therefore, controlling antigen-specificity of Treg cells should be an ideal strategy to inhibit only unwanted immune responses. Together with Professor Ralph M. Steinman, the Nobel Laureate in 2012, I also discovered that antigen-specific Treg cells were expanded by professional antigen-presenting cells, dendritic cells (DCs) (Yamazaki, Steinman et al, *J Exp Med*, 2003). Since then, my research has been focusing on the crosstalk between Treg cells and DCs. Here in Nagoya City University, we showed that some crosstalk between Treg cells and DCs is regulating immune homeostasis. First, Treg cells were expanded in the ultraviolet B (UVB)-exposed skin with interacting with a special subset of DCs. The UVB-expanded skin Treg cells had a unique gene expression pattern and a healing function. Second, there was a special subset of DCs associated with Treg cells in human head and neck cancer. Third, by manipulating Treg-DC crosstalk, adaptive immune responses against SARS-CoV2 antigens were induced effectively without adjuvants. Therefore, targeting Treg-DC crosstalk could be innovative strategies to control immunity against diverse diseases. We hope that our research will contribute to the benefits of humanity in the future.

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Education and Appointments

2023-Present	President, Korean Association of Immunologists (KAI)
2015-Present	Director, Immune Synapse and Cell Therapy Research Center (Creative Research Initiative Program - NRF)
2006-Present	Professor, School of Life Science, GIST
2005-2006	Associate Professor, Department of Physiology, School of Medicine, Kyungpook National University
1998-2001	Post-Doc fellow, Harvard Medical School
1993-1996	Kyungpook National University, Immunology (PhD)

Speciality & Research Field of Interest

T-cell immunological synaptosomes, Cell adhesion and migration in immunity, Lymphocytes development

Selected Publications

1. Park JS, Kim JH, Soh WC, Kim NY, Lee KS, Kim CH, Chung IJ, Lee S, Kim HR, Jun CD. Trogocytic molting of T cell microvilli upregulates T cell receptor surface expression and promotes clonal expansion. ***Nat Commun.*** 2023 May 24;14(1):2980. doi: 10.1038/s41467-023-38707-y.
2. Kim HR, Park JS, Kim NY, Jun CD. T Cell Immunological Synaptosomes: Definition and Isolation. ***Methods Mol Biol.*** 2023:2654:201-215. doi: 10.1007/978-1-0716-3135-5_13. (Book).
3. Kim CH, Park SM, Lee SJ, Kim YD, Jang SH, Woo SM, Kwon TK, Park ZY, Chung IJ, Kim HR, Jun CD. NSrp70 is a lymphocyte-essential splicing factor that controls thymocyte development. ***Nucleic Acids Res.*** 2021 Jun 4;49(10):5760-5778. doi: 10.1093/nar/gkab389.
4. Kim HR, Park JS, Park JH, Fatima Y, Kim CH, Oh SK, Chung IJ, Jun CD. Cell-permeable transgelin-2 as a potent therapeutic for dendritic cell-based cancer immunotherapy. ***J Hematol Oncol.*** 2021 Mar 17;14(1):43. doi: 10.1186/s13045-021-01058-6.
5. Kim HR, Mun Y, Lee KS, Park YJ, Park JS, Park JH, Jeon BN, Kim CH, Jun Y, Hyun YM, Kim M, Lee SM, Park CS, Im SH, Jun CD. T cell microvilli constitute immunological synaptosomes that carry messages to antigen-presenting cells. ***Nat Commun.*** 2018 Sep 7;9(1):3630. doi: 10.1038/s41467-018-06090-8.

T-cell immunological synaptosomes: Physiology and Application

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Microvilli are outer membrane organelles that contain cross-linked filamentous actin. Unlike well-characterized epithelial microvilli, T-cell microvilli are dynamic similar to those of filopodia, which grow and shrink intermittently via the alternate actin-assembly and -disassembly. T-cell microvilli are specialized for sensing antigens on the surface of antigen-presenting cells (APCs). Thus, these finger-shaped microprotrusions contain many signaling-related proteins and can serve as a signaling platforms that induce intracellular signals. However, they are not limited to sensing external information but can provide sites for parts of the cell-body to tear away from the cell. Cells are known to produce many types of extracellular vesicles (EVs), such as exosomes, microvesicles, and membrane particles. T cells also produce EVs, but little is known about under what conditions T cells generate EVs and which types of EVs are released. We discovered that T cells produce few exosomes but release large amounsts of microvilli-derived particles during physical interaction with APCs. Although much is unanswered as to why T cells use the same organelles to sense antigens or to produce EVs, these events can significantly affect T cell fate, including clonal expansion and death. Since TCRs are localized at microvilli tips, this membrane event also raises a new question regarding long-standing paradigm in T cell biology; i.e., surface TCR downmodulation following T cell activation. Since T-cell microvilli particles carry T-cell message to their cognate partner, these particles are termed T-cell immunological synaptosomes (TISs). We discuss the potential physiological role of TISs and their application to immunotherapies.

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Education and Appointments

1998-2005	Konkuk University (B.Sc.)
2005-2011	Gwangju Institute of Science and Technology (GIST), Ph.D.
2011-2017	Postdoctoral fellow, Harvard Medical School
2017-2019	Research Associate, Harvard Medical School
2019-present	Assistant Professor, Yonsei University College of Medicine

Speciality & Research Field of Interest

T cell immunity, Immune-Gut-Brain axis

Selected Publications

1. Exploring probiotic effector molecules and their mode of action in gut–immune interactions. Choong-Gu Lee, Kwang Hyun Cha, Gi-Cheon Kim, Sin-Hyeog Im*, Ho-Keun Kwon*, **FEMS Microbiol Rev.** 2023 Jul 5;47(4):fuad046..
2. A Moonlighting Protein Secreted by a Nasal Microbiome Fortifies the Innate Host Defense Against Bacterial and Viral Infections. Gwanghee Kim, Yoojin Lee, Jin Sun You, Wontae Hwang, Jeewon Hwang, Hwa Young Kim, Jieun Kim, Ara Jo, In ho Park, Mohammed Ali, Jongsun Kim, Jeon-Soo Shin, Ho-Keun Kwon*, Hyun Jik Kim*, Sang Sun Yoon*, **Immune Netw.** 2023 Aug;23(4):e31.
3. WNK3 inhibition elicits anti-tumor immunity by suppressing PD-L1 expression on tumor cells and activating T cell function. Hyun Ju Yoon1*, Gi-Cheon Kim*, Sejin Oh, Yunji Lee, Min Seo Kim, Yong Keun Kim, Gino Kwon, Ho-Keun Kwon# &, Hyun Seok Kim#. WNK3 inhibition elicits anti-tumor immunity by suppressing PD-L1 expression on tumor cells and activating T cell function. **Experimental & Molecular Medicine.** 2022 Nov;54(11):1913-1926.
4. Maternal inflammation and its ramifications on fetal neurodevelopment. Ho-Keun Kwon*, Gloria B Choi, Jun R Huh*. **Trends in Immunology**. 2022, Mar;43(3):230-244.
5. Probiotics-derived metabolite ameliorates skin allergy by promoting differentiation of FOXP3 + regulatory T cells. Hye-Ji Kang*, Gi-Cheon Kim*, Choong-Gu Lee*, Sunhee Park, Garima Sharma, Ravi Verma, Sin-Hyeog Im#, Ho-Keun Kwon#. **J Allergy Clin Immunol**. 2021, Apr Apr;147(4):1517-1521

FoxP3-expressing T cells ensure proper neurodevelopment in fetuses.

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Maintenance of immunological tolerance at the maternal-fetal boundary is required for fetal development and produces long-lasting effects on offspring's health. Exposure to infection or other inflammatory stimuli during pregnancy, coined Maternal Immune Activation (MIA), leads to brain pathologies and abnormal behavioral phenotypes in the affected offspring. We and others previously showed that T cells (Th17) expressing interleukin-17a (IL-17a) in pregnant mothers promote the development of MIA-associated phenotypes in their offspring. However, it is not known how these pathogenic immune cell activities are controlled during normal pregnancy. Here we report in pregnant mothers that FoxP3 expressing regulatory T cells (Tregs) and human commensal bacteria enhancing their differentiation play pivotal roles in suppressing MIA-associated phenotypes in their offspring. Compared to those in non-pregnant females, Tregs in pregnant mice expresses higher levels of the Th17 cell-defining transcription factor RORγt (retinoid-related orphan receptor γt). Furthermore, either a partial depletion of Tregs or removal of RORγt expression in the Treg compartment of pregnant mice renders their offspring to exhibit certain MIA-associated behavioral abnormalities. Lastly, Tregs can be harnessed to prevent the development of MIA-associated phenotypes in offspring, born to mothers infected with influenza virus H1N1. In sum, our findings suggest that enhancing Treg function in human pregnant mothers, who are exposed to infection or under other inflammatory conditions, may reduce a likelihood of bearing children with inflammation-induced neurodevelopmental disorders.

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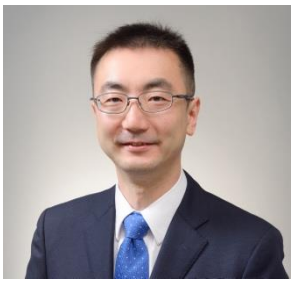

Education and Appointments

1995-2001	School of Medicine, Niigata University (M.D.)
2004-2008	Graduate School of Medical and Dental Sciences, Niigata University (Ph.D.)
2009-2013	Postdoctoral visiting fellow, National Institutes of Health, U.S.A.
2013-2016	Associate Professor, Department of Advanced Allergology of the Airway, Graduate School of Medicine, Chiba University
2016-2022	Associate Professor, Graduate School of Medicine, Chiba University
2022-present	Professor, Graduate School of Medicine, Chiba University

Speciality & Research Field of Interest

Chronic Inflammation, Immunological Memory, Lung Immunology

Selected Publications

1. Kumagai, J., Kiuchi, M., Kokubo, K., Yagyu, H., Nemoto, M., Tsuji, K., Nagahata, K., Sasaki, A., Hishiya, T., Onoue, M., Shinmi, R., Sonobe, Y., Iinuma, T., Yonekura, S., Shinga, J., Hanazawa, T., Koseki, H., Nakayama, T., Yokote, K., **Hirahara, K.** The USP7-STAT3-granzyme-Par-1 axis regulates allergic inflammation by promoting differentiation of IL-5 producing Th2 cells. ***Proc. Natl. Acad. Sci. USA*** in press.
2. Sato, Y., Silina, K., van den Broek, M., **Hirahara, K.**, and Yanagita, M.: The roles of tertiary lymphoid structures in chronic diseases. ***Nat. Rev. Nephrol.*** 19:525-537 (2023).
3. Okano, M., **Hirahara, K.**, Kiuchi, M., Onoue, M., Iwamura, C., Kokubo, K., Hishiya, T., Morimoto, Y., Ikehara, Y., Murakami, A., Ebihara, N., and Nakayama, T.: Interleukin-33-activated neuropeptide CGRP-producing memory Th2 cells cooperate with somatosensory neurons to induce conjunctival itch. ***Immunity*** 55(12):2352-2368.e7 (2022).
4. Ichikawa, T., **Hirahara, K.**, Kokubo, K., Kiuchi, M., Aoki, A., Morimoto, Y., Kumagai, J., Onodera, A., Mato, N., Tumes, D. J., Goto, Y., Hagiwara, K., Inagaki, Y., Sparwasser, T., Tobe, K., and Nakayama, T.: $CD103^{hi}$ T_{reg} cells constrain lung fibrosis induced by $CD103^{lo}$ tissue-resident pathogenic CD4 T cells. ***Nat. Immunol.*** 20(11):1469-1480 (2019).
5. Morimoto, Y., **Hirahara, K.,** Kiuchi, M., Wada, T., Ichikawa, T., Kanno, T., Okano, M., Kokubo, K., Onodera, A., Sakurai, D., Okamoto, Y., and Nakayama, T.: Amphiregulin-producing pathogenic memory T helper-2 cells instruct eosinophils to secrete osteopontin and facilitate airway fibrosis. ***Immunity*** 49(1):134-150.e6 (2018).

Pathological tissue inflammatory memories

Kiyoshi HIRAHARA

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Type 2 inflammation causes tissue damage during chronic allergic inflammation. Ex-inflamed tissues often store “tissue inflammatory memories”, which include tissue resident memory T (T_{RM}) cells and ectopic lymphoid tissues such as inducible bronchus associated lymphoid tissue (iBALT) in the lung. Diverse types of cells including stromal cells, epithelial cells and immune cells, work each other and play key roles in shaping the tissue inflammatory memories. Furthermore, the interconnection of different biological systems, such as the immune and nervous systems, hampers the elucidation of tissue inflammatory memories. Importantly, the pathological tissue inflammatory memories are involved in induction of chronic inflammation. In this talk, I will focus on the tissue inflammatory memory-dependent peripheral nerve elongation, which causes the severe itch in inflamed tissues. Understanding of the mechanisms underlying the induction of tissue inflammatory memories is essential for the establishment of next-generation therapies for intractable allergic diseases.

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Education and Appointments

1982-1988	Seoul National University College of Medicine (M.D.)
1989-1996	Seoul National University College of Medicine (Ph.D.)
1988-1992	Seoul National University Hospital, (Intern and Resident for Pathology)
1996-2000	Postdoctoral fellow, National Institute of Health, USA
2000-2001	Assistant Professor, BK21, Seoul National University College of Medicine
2001-present	Professor, Department of Pathology, Seoul National University College of Medicine

Speciality & Research Field of Interest

Immune regulation, Metabolism, Gender-specific immunity

Selected Publications

1. Jaemoon Koh et al., De novo fatty-acid synthesis protects invariant NKT cells from cell death, thereby promoting their homeostasis and pathogenic roles in airway hyperresponsiveness. **eLife**, in press
2. Jae Sung Ko et al., Ssu72 phosphatase directly binds to ZAP-70, thereby providing fine-tuning TCR signaling and preventing spontaneous inflammation. **Proc Natle Acad Sci USA** Aug 31;118(35), 2021
3. Dongjin Jeong et al., Soluble Fas ligand drives autoantibody-induced arthritis by binding to DR5/TRAIL-R2, **eLife**, Jul 5;10, 2021.
4. Yeon Duk Woo, et al., Ssu72 phosphatase is critical for alveolar macrophage development and allergic asthma by fine tuning of GM-CSF receptor signaling, **J Allergy Clin Immunol**, Sep 8;S0091, 2020.
5. Jaemoon.Koh et al., IL-23-producing human lung cancer cells promote tumor growth via conversion of ILC1 into ILC3, **Clin Cancer Res**, 2019
6. Yeon Duk Woo et al., Invariant NKT cell-mediated XCL1-XCR1 axis promotes airway hyperresponsiveness by recruiting CD103+ dendritic cells. **J Allergy Clin Immunol**. S0091-6749(18) 30283, 2018
7. Donghyun et al., Cytosolic Pellino-1-mediated K63 ubiqutination of IRF5 in M1 macrophages regulates glucose intolerance in obesity. **Cell Reports**, 25;20(4), 832, 2017

CRIF1 deficiency-mediated glutaminolysis induces Foxp3^{low} inflammatory non-suppressive regulatory T cells, thereby promoting anti-tumor immunity

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Human FOXP3^{low}CD45RA^{-} inflammatory non-suppressive (INS) cells were identified recently. Unlike conventional regulatory T cells (Tregs), they produce proinflammatory-cytokines, exhibit reduced suppressiveness, and promote rather than impair anti-tumor immunity. In spite of their implication in tumors, the mechanism for generation of FOXP3^{low}CD45RA^{-} INS cells *in vivo* is unclear. We showed that the FOXP3^{low}CD45RA^{-} cells in human tumors demonstrate attenuated expression of CRIF1, a vital mitochondrial regulator. Mice with CRIF1 deficiency in Tregs bore Foxp3^{low} INS-Tregs with mitochondrial dysfunction and metabolic reprograming. The enhanced glutaminolysis activated α-ketoglutarate-mTORC1 axis, which promoted proinflammatory-cytokine expression by inducing EOMES and SATB1 expression. Moreover, chromatin openness of the regulatory regions of the *Ifng* and *Il4* genes was increased, which facilitated EOMES/SATB1 binding. The increased α-ketoglutarate-derived 2-hydroxyglutarate downregulated Foxp3 expression by methylating the *Foxp3*-gene regulatory regions. Furthermore, CRIF1-deficiency-induced Foxp3^{low} INS-Tregs suppressed tumor growth in an IFN-γ dependent manner. Thus, CRIF1-mediated mitochondrial and metabolic homeostasis is critical for inducing Foxp3^{low} INS-Tregs including FOXP3^{low}CD45RA^{-} cells that promote anti-tumor immunity.

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Education and Appointments

1994-1998	Lanzhou University, Lanzhou, China ,Bachelor's degree
2001-2004	East China Normal University, Shanghai, China,Master
2004-2009	Ph.D,University of Maryland, College Park, MD, USA,
1998-2001	Research Staff,Shanghai Transgenic Research Center, Shanghai, China.
2009-2014	Postdoctoral fellow,MD Anderson Cancer Center, Houston, TX, USA.
2014-present	Professor ,South West Hospital, South West Cancer Center, Chongqing, China.
2022-present	PI, Jinfeng Laboratory, Chongqing, China.

Speciality & Research Field of Interest

tumor immunity

Selected Publications

1. Haofei Liu, Qiwen Zhao, Leyong Tan, Xin Wu, Rui Huang,Yonglin Zuo,Longjuan Chen, Jigui Yang,Zuo-Xin Zhang,Wenchen Ruan,Jiayang Wu,Fei He, Yiliang Fang, Fangyuan Mao, Peipei Zhang,Xiaoning Zhang,Peidi Yin,Zexuan Yan,Wenwen Xu,Huimin Lu,Qingrui Li,Mei Liang,Yanjun Jia,Cong Chen,Senlin Xu,Yu Shi,Yi-Fang Ping,Guang-Jie Duan,Xiao-Hong Yao,Zhijian Han, Tao Pang,Youhong Cui,Xia Zhang,Bo Zhu,Chunjian Qi, Yan Wang,* Sheng-Qing Lv,* Xiu-Wu Bian,* and **Xindong Liu***.Neutralizing IL-8 potentiates immune checkpoint blockade efficacy for glioma. ***Cancer Cell*** 41, 693–710, April 10, 2023
2. Xin Wu, Yun Wang, Rui Huang, Qujing Gai, Haofei Liu, Meimei Shi, Xiang Zhang, Yonglin Zuo,Longjuan Chen, Qiwen Zhao, Yu Shi, Fengchao Wang, Xiaowei Yan, Huiping Lu, Senlin Xu,Xiaohong Yao, Lin Chen, Xia Zhang, Qiang Tian, Ziyan Yang, Bo Zhong, Chen Dong, Yan Wang*,Xiu-wu Bian*, and **Xindong Liu***, Sostdc1-producing follicular helper T cells promote regulatory follicular T cell differentiation, ***Science***. 2020 Aug 21;369(6506):984-988.
3. Xiao-Hong Yao, Zhi-Cheng He, Ting-Yuan Li, Hua-Rong Zhang, Yan Wang, Huaming Mou,Qiaonan Guo, Shi-Cang Yu, Yanqing Ding, **Xindong Liu***, Yi-Fang Ping*, and Xiu-Wu Bian*,Pathological evidence for residual SARS-CoV-2 in pulmonary tissues of a ready-for-discharge patient, ***Cell Research***. 2020 Jun;30(6):541-543
4. **Xindong Liu***, et al.. Large-scale single-cell analysis reveals critical immune 2 characteristics of COVID-19 patients.***Cell***, 2021 April, Pages 1895-1913.e19
5. **Liu X**, et al. Genome-wide Analysis Identifies Bcl6-Controlled Regulatory Networks during T Follicular Helper Cell Differentiation. ***Cell reports*** 2016 14(7), 1735-1747.
6. **Liu X*** et al., Transcriptional factor Achaete-Scute homologue 2 initiates T follicular Helper cell development. ***Nature***, 2014, 507, 513-518.

Neutralizing IL-8 potentiates immune checkpoint blockade efficacy for glioma

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Malignant gliomas are largely refractory to immune checkpoint blockade (ICB) therapy. To explore the underlying immune regulators, we examine the microenvironment in glioma and find that tumor-infiltrating T cells are mainly confined to the perivascular cuffs and express high levels of CCR5, CXCR3, and programmed cell death protein 1 (PD-1). Combined analysis of T cell clustering with T cell receptor (TCR) clone expansion shows that potential tumor-killing T cells are mainly categorized into pre-exhausted/exhausted and effector CD8+ T subsets, as well as cytotoxic CD4+ T subsets. Notably, a distinct subpopulation of CD4+ T cells exhibits innate-like features with preferential interleukin-8 (IL-8) expression. With IL-8-humanizedmouse strain,we demonstrate that IL-8-producing CD4+ T, myeloid, and tumor cells orchestrate myeloid-derived suppressor cell infiltration and angiogenesis, which results in enhanced tumor growth but reduced ICB efficacy. Antibody-mediated IL-8 blockade or the inhibition of its receptor, CXCR1/2, unleashes anti-PD-1-mediated antitumor immunity. Our findings thus highlight IL-8 as a combinational immunotherapy target for glioma.

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Education and Appointments

1992 M.D.	Graduate from Faculty of Medicine, Kyoto University, Kyoto, Japan.
2001 Ph.D.	Post-Graduate School of Medicine. Kyoto University. Kyoto, Japan.
2001	Post-Doctoral Fellow. Baylor Institute for Immunology Research (BIIR), Dallas, TX, USA.
2004	Assistant Investigator. BIIR
2009	Associate Investigator. BIIR
2011-2016	Investigator. BIIR
2016.4	Professor, Global Health and Emerging Pathogens Institute; Professor, Department of Microbiology. Icahn School of Medicine at Mount Sinai, New York, NY, USA
2019.7	Professor, Department of Immunology, Graduate School of Medicine, Kyoto University. Kyoto, Japan (Cross-appointment with Mount Sinai until 2021.3)
2021.4	Full-time Professor, Department of Immunology, Graduate School of Medicine, Kyoto University. Kyoto, Japan

Speciality & Research Field of Interest

Human Immunology, Adaptive Immunity, Human T cell subsets

Selected Publications

1. Horiuchi S, Wu H,,,,, UENO H. Tox2 is required for the maintenance of GC TFH cells and the generation of memory TFH cells. ***Science Advances***. 2021;7(41):eabj1249.
2. H, Witzl A, UENO H. Assessment of TCR signal strength of antigen-specific memory CD8(+) T cells in human blood. ***Blood Advances***. 2019;3(14):2153-63.
3. UENO H*, Banchereau J*, Vinuesa CG*. Pathophysiology of T follicular helper cells in humans and mice. ***Nature Immunology***. 2015;16(2):142-52.
4. Jacquemin C, Schmitt N,,,, UENO H*, Blanco P*. OX40 Ligand Contributes to Human Lupus Pathogenesis by Promoting T Follicular Helper Response. ***Immunity.*** 2015;42(6):1159-70.
5. Schmitt N, Liu Y,,,,, UENO H. The cytokine TGF-beta co-opts signaling via STAT3-STAT4 to promote the differentiation of human TFH cells. ***Nature Immunology.*** 2014;15(9):856-65.
6. Bentebibel SE, Lopez S,,,, UENO H. Induction of ICOS+CXCR3+CXCR5+ TH cells correlates with antibody responses to influenza vaccination. ***Science Translational Medicine.*** 2013;5(176):176ra32.

B Cells in the Tumor Microenvironment

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Immune cells play a crucial role in the tumor microenvironment (TME), and differences in their quality and quantity significantly impact the cancer outcome. While research on macrophages and CD8+ cytotoxic T cells in the TME has advanced, the role of B cells in the TME remains largely unclear.

B cells, in addition to differentiating into antibody-producing cells, have functions as antigen-presenting cells for T cells and as cytokine-producing cells. Studies using mouse models have demonstrated that B cells in the TME are diverse, and their phenotype, gene expression patterns, and cytokine production can contribute to both anti-cancer and pro-cancer effects. However, in the human TME, it is still unclear which B cells are involved in anti-cancer effects and which ones may induce cancer proliferation. Furthermore, it is unclear whether B cells directly exert anti-cancer effects or are indirectly important for building anti-cancer immune responses in the TME.

Using single-cell RNA sequencing (scRNAseq) and single-cell B cell receptor sequencing (scBCRseq), we analyzed B cells in the tumor microenvironment of endometrial cancer at the single-cell level and evaluated their diversity and correlation with prognosis. In several cases, we found clonally expanded phenotypic cells that had undergone class switching to IgG. Additionally, pathological histological analysis revealed that cases with a high IgG/IgA ratio in B cells, rather than the frequency of B cells in the TME, had a favorable prognosis. Therefore, the selective expansion of IgG-expressing B cell clones in the TME is considered crucial for effective anti-cancer effects.

Then, how do these IgG-expressing B cells undergo differentiation induction and clonal expansion in the TME? How do precursor cells of IgG-expressing B cells differ from IgA-expressing B cells? What does the IgG produced by IgG-expressing B cells recognize? In my talk, we aim to discuss the anti-cancer effects of B cells in the human TME.

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Education and Appointments

1994-2000	Department of Life Sciences, POSTECH (Ph.D.)
2004-2008	Postdoctoral fellow, La Jolla Institute for Allergy and Immunology
2009-2011	Instructor, La Jolla Institute for Allergy and Immunology
2012-2015	Assistant Professor, Department of Life Sciences, POSTECH
2016-2022	Associate Professor, Department of Life Sciences, POSTECH
2023-present	Professor, Department of Life Sciences, POSTECH

Specialty & Research Field of Interest

Immunotherapy, Epithelial-Immune interaction

Selected Publications

1. Sora Kim, Young-Min Kim, Hyekang Kim, Yeon-Woo Kang, Subin Park, Sang-In Yang, Donghoon Choi, Young Chul Sung, Seung-Woo Lee**.** 2021. Fc-fused IL-7 mobilizes long-term HSCs in a pro-B cell-dependent manner and synergizes with G-CSF and AMD3100**.** *Leukemia*. 35(10) 3030-3034.
2. Sookjin Moon, Yunji Park, Sumin Hyeon, Young-Min Kim, Ji-Hae Kim, Hyekang Kim, Subin Park, Kun-Joo Lee, Bon-Kyoung Koo, Sang-Jun Ha, Seung-Woo Lee. 2021. Niche-specific MHC II and PD-L1 regulate $CD4^{+}CD8\alpha\alpha^{+}$ intraepithelial lymphocyte differentiation. *J Exp Med*. 218(4): e20201665.
3. Gihoon You, Yangsoon Lee, Yeon-Woo Kang, Han Wook Park, Kyeongsu Park, Hyekang Kim, Young-Min Kim, Sora Kim, Ji-ae Kim, Dain Moon, Hyejin Chung, Wonjun Son, Ui-Jung Jung, Eunyoung Park, Shinai Lee, Yong-Gyu Son, Jaehyun Eom, Jonghwa Won, Yunji Park, Jaeho Jung, Seung-Woo Lee. 2021. B7-H3×4-1BB bispecific antibody augments antitumor immunity by enhancing terminally differentiated $CD8^{+}$ tumor-infiltrating lymphocytes. *Sci Adv*. 7(3): eaax3160.
4. Young-Min Kim, Hyekang Kim, Seungwon Lee, Sora Kim, Jong-Uk Lee, Youngwoo Choi, Han Wook Park, Gihoon You, Hansol Kang, Seyoung Lee, Jong-Sook Park, Yunji Park, Hae-Sim Park, Choon-Sik Park, Seung-Woo Lee. 2020. Airway G-CSF identifies neutrophilic inflammation and contributes to asthma progression. *Eur Respir J*. 55(2): 1900827-1900912.
5. Seungwon Lee, Hyekang Kim, Gihoon You, Young-Min Kim, Seunghun Lee, Viet-Hoan Le, Ohseop Kwon, Sin-Hyeog Im, You-Me Kim, Kwang Soon Kim, Young Chul Sung, Ki Hean Kim, Charles D. Surh, Yunji Park, Seung-Woo Lee. 2019. Bone marrow CX3CR1+ mononuclear cells relay systemic microbiota signal to control hematopoietic progenitors in mice. *Blood*. 134(16): 1312-1322 (Cover article)

IL-7-primed bystander CD8 tumor-infiltrating lymphocytes optimize the antitumor efficacy of T cell engager immunotherapy in solid tumors

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Bispecific T cell engagers (TCEs) show promising clinical efficacy in blood tumors, but their application to solid tumors with immunosuppressive environments remains challenging. Here, we show that Fc-fused IL-7 (rhIL-7-hyFc) changes the intratumoral CD8 T cell landscape, allowing TCE-immunotherapy to function effectively in solid tumors. rhIL-7-hyFc monotherapy induced a dramatic increase in CD8 tumor-infiltrating lymphocytes (TILs) in various solid tumors in mice and humans, but the majority of these cells were PD-1-negative tumor non-responsive bystander T cells. However, they were non-exhausted and central memory-phenotype CD8 T cells with high TCR-recall capacity that can be triggered by tumor antigen-specific TCEs to acquire tumoricidal activity. Single-cell transcriptome analysis revealed that rhIL-7-hyFc-induced bystander CD8 TILs transformed into a cycling subset of transitional T cells by TCE-redirection with decreased memory markers and increased cytotoxic molecules. Notably, TCE treatment had no major effect on tumor-reactive exhausted CD8 TILs. Our results suggest that TCE-immunotherapy primarily targets bystander rather than tumor-reactive CD8 TILs and that rhIL-7-hyFc treatment promotes the antitumor efficacy of TCE-immunotherapy by increasing TCE-sensitive bystander CD8 TILs in solid tumors.

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Education and Appointment

1988-1993	M.D. Hubei Medical University, Wuhan
1996-2002	Ph.D of Biochemistry & Molecular Biology, Tongji Medical College, Huazhong University of Science & Technology, Wuhan
2002-2006	Postdoc, Karolinska Iinstitutet (Sweden), University of Calgary (Canada), and Mount Sinai School of Medicine (USA)
2006-2012	Associate Professor & Professor, Department of Biochemistry and Molecular Biology, Tongji Medical College, Wuhan
2012.3-	Professor & vice Chairman of Department of Immunology, Chinese Academy of Medical Sciences, Beijing

Specialty and Research Field of Interest

Tumor immunology and immunotherapy, metabolism, mechano-oncology, and microparticles

Selected Publications

1. Zhou L, Wu D, Zhou Y, Wang D, Fu H, Huang Q, Qin G, Chen J, Lv J, Lai S, Zhang Y, Zhang X, Huang B. Tumor cell-released kynurenine biases MEP differentiation into megakaryocytes in cancer patients by activating AhR-RUNX1. ***Nat Immunol.*** 2023; online
2. Lv J, Zhou Y, Zhou N, Wang Z, Chen J, Chen H, Wang D, Ma J, Liu Y, Wan Y, Zhang Y, Zhang H, Huang B. Epigenetic modification of CSDE1 locus dictates immune recognition of nascent tumorigenic cells. ***Sci Transl Med.*** 2023;15:eabq6024.
3. Tang K, Zhang H, Deng J, Wang D, Liu S, Lu S, Li Y, Chen J, Lv J, Ma J, Huang B. Ammonia detoxification promotes CD8+ T cell memory development by urea and citrulline cycles. ***Nat Immunol.*** 2023;24:162-173.
4. Zhang H, Liu J, Yang Z, Wei K, Zhu L, Tang L, Wang D, Zhou Y, Lv J, Zhou N, Tang K, Ma J, Huang B. TCR activation directly stimulates PYGB-dependent glycogenolysis to fuel the early recall response in CD8+ memory T cells. ***Mol Cell.*** 2022;82:3077-3088.e6.
5. Lv J, Liu Y, Mo S, Zhou Y, Chen F, Cheng F, Li C, Tang K, Ma J, Wang Z, Zhu Q, Tong WM, Huang B. Gasdermin E mediates resistance of pancreatic adenocarcinoma to enzymatic digestion through a YBX1-mucin pathway. ***Nat Cell Biol.*** 2022;24:364-372.

Drug tumor microparticles: novel immunotherapy for malignant effusion and ascites

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Naïve T cells encounter antigens in draining lymph nodes, where they are primed by dendritic cells and differentiate into effector T (Teff) cells. Following antigen clearance, effector cells enter a contraction phase and die, while a minority of Teff cells survive and acquire a memory phenotype, conferring the host with the ability to defend against pathogen re-infection or tumorigenesis. This process is involved in memory formation and maintenance, a key issue of immunology. The nature of memory lies in the long-time survival of T cells. Cells use the molecule ATP for energy. During the process of ATP production, reactive oxygen species (ROS) and ammonia (NH3) byproducts are produced, both of which can be cytotoxic and limit cellular longevity. Therefore, memory T cells need to develop machinery to clear both ROS and ammonia. We found that CD8+ memory T cells use the ketogenesis, gluconeogenic pathway, glycogenesis, glycogenolysis and pentose phosphate pathway to generate NADPH for ROS clearance, and employ both the urea and citrulline cycles to clear ammonia, thus enabling memory formation and maintenance.

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Education and Appointments

1999-2005	Korea University College of Medicine (M.D.)
2007-2009	Korea University Graduate School (M.S.)
2009-2013	Korea University Graduate School (Ph.D.)
2013	Honorary research associate, The University of Hong Kong
2013-2019	Assistant professor, Division of Infectious Diseases, Department of Internal Medicine, Korea University College of Medicine
2021-2022	Visiting professor, KAIST Graduate School of Medical Science and Engineering
2019-present	Associate professor, Division of Infectious Diseases, Department of Internal Medicine, Korea University College of Medicine

Speciality & Research Field of Interest

Clinical immunology for influenza, respiratory viruses infection, and herpes zoster, Vaccine clinical researches

Selected Publications

1. Enhanced antibody responses in fully vaccinated individuals against pan-SARS-CoV-2 variants following Omicron breakthrough infection. Cell Rep Med. 2022 Oct 18;3(10):100764.
2. Robust neutralizing antibody responses after single-dose BNT162b2 vaccination at long intervals from prior SARS-CoV-2 infection and ceiling effect with repeated vaccination. J Infect. 2022 Nov;85(5):573-607.
3. The generation of stem cell-like memory cells early after BNT162b2 vaccination is associated with durability of memory CD8+ T cell responses. Cell Rep. 2022 Jul 26;40(4):111138.
4. BNT162b2-induced memory T cells respond to the Omicron variant with preserved polyfunctionality. Nat Microbiol. 2022 Jun;7(6):909-917.
5. T cell-oriented strategies for controlling the COVID-19 pandemic. Nat Rev Immunol. 2021 Nov;21(11):687-688.

Immune response to SARS-CoV-2 vaccination: insights into clinical research on influenza

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The coronavirus disease 2019 (COVID-19) pandemic results in devastating impact on the economy, society, and public health. SARS-CoV-2 vaccination induces virus-specific immunity protecting hosts from infection and severe diseases. Neutralizing antibodies (nAbs) that interfere with the entry of SARS-CoV-2 into host cells are considered to be a key for host protection. However, due to the declining titers over time and/or the emergence of viral escape variants, strategies that only focus on neutralizing antibodies may be insufficient. Compared with nAbs, SARS-CoV-2-specific memory T cells are maintained for a relatively long time and there is increasing evidence that SARS-CoV-2 variants rarely escape memory T cell responses elicited by SARS-CoV-2 vaccination. We therefore need to continue work on such vaccines that induce durable and broad protective T cell-mediated immunity against COVID-19. Extent and duration of influenza epidemic vary from year to year. Multiple factors such as characteristics of circulating influenza viruses, immunity of the population, and transmissibility of viruses could affect the impact of influenza epidemic. Most seasonal influenza are mild and self-limiting. However, complications and hospitalizations are more frequent among older adults, children aged < 2 years, and those with underlying medical conditions that confer higher risk for influenza-related complications. I describe the characteristics of immune response by SARS-CoV-2 vaccination and discuss clinical research on influenza.

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Education and Appointments

1993	Kyoto University, Agriculture (M.S.)
1993 - 1999	Research Scientist, Mitsubishi Chemical Corporation
1999 - 2004	Assistant Professor, Chiba University Graduate School of Medicine
2004 - 2009	Senior Scientist, RCAI, RIKEN
2009 - 2017	Professor, Medical Institute of Bioregulation, Kyushu University
2017 - present	Professor, RIMD/IFReC, Osaka University

Specialty & Research Field of Interest

C-type lectin receptors, T cell receptors

Selected Publications

1. Ishizuka S, van Dijk JHM, Kawakita T, Miyamoto Y, Maeda Y, Goto M, Le Calvez G, Groot LM, Witte MD, Minnaard AJ, van der Marel GA, Ato M, Nagae M, Codée JDC, Yamasaki S. PGL-III, a Rare Intermediate of *Mycobacterium leprae* Phenolic Glycolipid Biosynthesis, Is a Potent Mincle Ligand. ***ACS Cent. Sci.*** 2023 9(7):1388-1399.
2. Watanabe M, Motooka D, Yamasaki S. The kinetics of signaling through the common FcRγ chain determine cytokine profiles in dendritic cells. ***Sci. Signal.*** 2023 16(775):eabn9909.
3. Shimizu T, Schutt CR, Izumi Y, Tomiyasu N, Omahdi Z, Kano K, Takamatsu H, Aoki J, Bamba T, Kumanogoh A, Takao M, Yamasaki S. Direct activation of microglia by β-glucosylceramide causes phagocytosis of neurons that exacerbates Gaucher disease. ***Immunity*** 2023 56(2):307-319.e8.
4. Haji S, Ito T, Guenther C, Nakano M, Shimizu T, Mori D, Chiba Y, Tanaka M, Mishra SK, Willment JA, Brown GD, Nagae M, Yamasaki S. Human Dectin-1 is *O*-glycosylated and serves as a ligand for C-type lectin receptor CLEC-2. ***eLife*** 2022 Dec 8;11:e83037.
5. Shibata K, Motozono C, Nagae M, Shimizu T, Ishikawa E, Motooka D, Okuzaki D, Izumi Y, Takahashi M, Fujimori N, Wing JB, Hayano T, Asai Y, Bamba T, Ogawa Y, Furutani-Seiki M, Shirai M, Yamasaki S. Symbiotic bacteria-dependent expansion of MR1-reactive T cells causes autoimmunity in the absence of Bcl11b. ***Nat. Commun.*** 2022 13(1):6948.
6. Lu X, Hosono Y, Nagae M, Ishizuka S, Ishikawa E, Motooka D, Ozaki Y, Sax N, Maeda Y, Kato Y, Morita T, Shinnakasu R, Inoue T, Onodera T, Matsumura T, Shinkai M, Sato T, Nakamura S, Mori S, Kanda T, Nakayama EE, Shioda T, Kurosaki T, Takeda K, Kumanogoh A, Arase H, Nakagami H, Yamashita K, Takahashi Y, Yamasaki S. Identification of conserved SARS-CoV-2 spike epitopes that expand public cTfh clonotypes in mild COVID-19 patients. ***J. Exp. Med.*** 2021 218(12):e20211327.

Human T cell responses against infection

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Cellular and humoral responses constitute fundamental elements of adaptive immunity to achieve successful protection against infection. In contrast to antibody-mediated immunity, T cell-mediated immune responses have not been fully characterized on a clonotype resolution. Using PBMCs from infected and vaccinated donors, we identified dominant clonotypes and epitopes of virus-reactive T cells which were associated with symptoms and immunological memory. We also observed unusual clonal T cell responses and unique viral adaptation during infection in immunodeficient patients lacking humoral immunity. In this symposium, we would like to share and discuss our insights obtained from chronological × clonological analysis of human T cell responses during infection.

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Education and Appointments

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2002-2007	Research Fellow, NIDDK, NIH, Bethesda, MD, USA
2007-present	Assistant Professor, Associate Professor, and Professor, KAIST Graduate School of Medical Science and Engineering, Daejeon, Korea
2021-present	Director, The Center for Viral Immunology, Korea Virus Research Institute, Institute for Basic Science, Daejeon, Korea

Speciality & Research Field of Interest

Viral immunology, Immune aging, Tumor immunology, and Human immune monitoring

Selected Publications

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IL-15-induced bystander T cell activation in human viral disease

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During viral infection, pre-existing memory $CD8^+$ T cells that are not specific for the infecting virus can be activated by cytokines without cognate antigens, termed bystander activation. Recent studies have demonstrated that bystander-activated $CD8^+$ T cells exert either protective or detrimental effects on the host depending on the infection model or disease. In this lecture, I will present our recent data showing the mechanisms and immunopathological roles of IL-15-induced bystander $CD8^+$ T cell activation in acute viral infection. In addition, I will discuss molecular regulations of bystander activation-related genes and clinical significance of bystander activation.

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Speciality & Research Field of Interest

B-cell adaptive immune response, antibody drugs and vaccine design

Selected Publications

1. **Y. Cao***#, F. Jian#, J. Wang#, Y. Yu#, W. Song#, A. Yisimayi, J. Wang, R. An, X.Chen, N. Zhang, Y. Wang, P. Wang, L. Zhao, H. Sun, L. Yu, S. Yang, X. Niu, T. Xiao, Q. Gu, F. Shao, X. Xiao, Y. Xu, R. Jin, Z. Shen, Y. Wang* & X. S. Xie*, *Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution.* ***Nature*** 614: 21-529. (2023).
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5. **Y. Cao**#, B. Su#, X. Guo#, W. Sun#, Y. Deng#, L. Bao#, Q. Zhu, X. Zhang, Y. Zheng, C. Geng, X. Chai, R. He, X. Li, Q. Lv, H. Zhu, W. Deng, Y. Xu, Y. Wang, L. Qiao, Y. Tan, L. Song, G. Wang, X. Du, N. Gao, J. Liu, J. Xiao, X. Su, Z. Du, Y. Feng, C. Qin*, C. Qin*, R. Jin*, X. S. Xie*, *Potent Neutralizing Antibodies against SARS-CoV-2 Identified by High-Throughput Single-Cell Sequencing of Convalescent Patients' B Cells*. ***Cell***. 182, 73-84.e16 (2020).

Evolution of SARS-CoV-2 antibody responses and immune evasion hotspots

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Constant evolution of SARS-CoV-2 gives rise to highly immune-evasive variants, posing a critical challenge to the efficacy of vaccines and neutralizing antibody (NAb) drugs. If we could predict the evolution of the virus, we can prepare broad-spectrum neutralizing antibodies and vaccines in advance. By integrating high-throughput deep mutational scanning (DMS) with single-cell VDJ sequencing, we can profile the escape mutations of a large collection of monoclonal antibodies isolated from current immune background. Based on these DMS profiles, we built a prediction model to identify mutation hotspots of the virus by considering the impact on immune evasion and ACE2-binding. Using this model, we were able to accurately predict the evolution trend of BA.5 as well as the prevalence of multiple later variants, including BQ.1.1 and XBB lineages. Also, our prediction model allows us to prospectively identify broad-spectrum neutralizing antibody drugs, including a featured broad-spectrum NAb, named SA55, isolated from SARS-CoV-2-vaccinated SARS convalescents. SA55 targets an extremely rare epitope and mutations that can escape it are less likely to appear, making it an advantageous drug candidate to afford long-lasting protection against current and future mutants.

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Education and Appointments

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2006 - 2010	Assistant Professor, Osaka University
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Specialty & Research Field of Interest

Plasmodium parasites-host interactions, Immunopathology, Vaccine

Selected Publications

1. Lee MSJ, Inoue T, Ise W, Matsuo-Dapaah J, Wing JB, Temizoz B, Kobiyama K, Hayashi T, Patil A, Sakaguchi S, Simon AK, Bezbradica JS, Nagatoishi S, Tsumoto K, Inoue JI, Akira S, Kurosaki T, Ishii KJ, **Coban C.** B cell intrinsic TBK1 is essential for germinal center formation during infection and vaccination in mice. **Journal of Experimental Medicine, 2022,** Feb 7;219(2):e20211336.
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Immune memory during malaria and vaccination

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The development of sterile immunity which would produce highly potent and life-lasting neutralizing antibodies is a prerequisite to any natural infection or vaccination. However, anti-disease immunity is not easy to develop against many infections, including malaria. The reasons for the lack of sterile immunity against malaria are largely unknown.

The germinal center (GC) is a site where somatic hypermutation and clonal selection are coupled for antibody affinity maturation against infections. However, how GCs are formed and regulated is incompletely understood. We recently identified an unexpected role of Tank-binding kinase-1 (TBK1) as a crucial B cell-intrinsic factor for GC formation (*Lee et al., J Exp. Medicine, 2022*). We found that TBK1 phosphorylation elevated in B cells during GC differentiation and regulated the IRF4/BCL6 expression balance by limiting CD40 and BCR activation through noncanonical NF-κB and AKT^{T308} signaling. In the absence of TBK1, CD40 and BCR signaling synergistically enhanced IRF4 expression in Pre-GC, leading to BCL6 suppression, and therefore failed to form GCs. As a result, during mouse malaria infection with PyNL, TBK1-deficient B cells failed to form GC despite normal Tfh cell differentiation. Moreover, memory B cells generated from TBK1-deficient B cells fail to confer sterile immunity upon reinfection, suggesting that TBK1 determines B cell fate to promote long-lasting humoral immunity during malaria.

The next question would be how to control re-infection? In my presentation, I will overview our recent findings and summarize our observations on how understanding host immunity can eliminate Plasmodium parasites.

Poster Presentations

Poster No. 1

Activation of retinoid X receptor facilitates differentiation of monocytes into CX_3CR1^{hi} macrophages via mitochondrial metabolism

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The mammalian intestine harbors a myriad of commensal microorganisms. Nevertheless, excessive immune response to the commensal microorganisms is prevented by anti-inflammatory machinery represented by the accumulation of regulatory T cells. Furthermore, a gut-resident macrophage subset that highly expresses CX_3CR1^{hi} also possesses anti-inflammatory properties such as IL-10 production. CX_3CR1^{hi} macrophages settle in the gut during the developmental stage and undergo self-renewing, although this population gradually decreases after weaning and monocytes differentiate into CX_3CR1^{hi} macrophages in the intestine. The underlying mechanism of monocyte-derived CX_3CR1^{hi} macrophage differentiation remains largely unknown. We recently found that monocytes and CX_3CR1^{hi} macrophages highly express retinoid X receptor (RXR), a nuclear receptor that heterodimerizes with other nuclear receptors, such as LXR and PPAR, to regulate multiple biological processes. CX_3CR1^{hi} macrophages decrease during colitis development; however, administration of an RXR agonist restored CX_3CR1^{hi} macrophages and decreased monocytes with inflammatory properties. Eventually, the RXR agonist ameliorated colitic symptoms. Likewise, treating bone marrow cells with an RXR agonist markedly enhanced the differentiation of CX_3CR1^{hi} macrophages.

Further, transcriptome and cell biological analyses demonstrated that RXR activation facilitated mitochondrial ATP production via oxidative phosphorylation at the stage of immature macrophages. Inhibition of mitochondrial ATP production canceled the effect of RXR activation on CX_3CR1^{hi} macrophage differentiation. In conclusion, RXR activation facilitates the differentiation of monocytes into CX_3CR1^{hi} macrophages through augmentation of mitochondrial metabolism and significantly contributes to immune homeostasis in the intestinal mucosa.

Poster No. 2

OTUD3 prevents ulcerative colitis by modulating STING activation in fibroblasts

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Ulcerative colitis (UC) develops through complicated interaction between the host and microbiot. In addition to immune cells and epithelial cells, intestinal fibroblasts are suggested to play crucial roles in the maintenance of the gut homeostasis and the pathogenesis of UC. However, influences of the host-microbiota interaction on physiology and pathophysiology of intestinal fibroblasts remain poorly understood. Here, we reveal that OTUD3 suppresses pathologic activation of fibroblasts exposed to microbial cyclic GMP-AMP (3'3'-cGAMP) by deubiquitinating stimulator of interferon genes (STING) in the colon. OTUD3 was specifically expressed in fibroblasts in human and murine colon. OTUD3 hydrolyzed K27-linked polyubiquitin chains on STING in colonic fibroblasts that incorporated 3'3'-cGAMP. The introduction of a *Sting* deficiency ameliorated DSS-induced colitis in *Otud3*$^{-/-}$ mice. Some intestinal bacteria species harboring oligo-nucleotide cyclase genes were increased together with their phages in UC patients. Mice harboring an UC risk missense variant in the *Otud3* gene showed pathological features of UC in the colon after transplantation of a fecal microbiota with the potential to produce excessive cGAMP from UC patients. Collectively, these results highlight a mechanism of the interaction between the host (OTUD3 in fibroblasts) and microbiota (STING agonist) in UC development.

Poster No. 3

Regulatory T Cells act as the guardians of mucosal immune homeostasis in chronic rhinosinusitis

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Chronic rhinosinusitis (CRS) is a complex inflammatory disease characterized by two distinct endotypes with diverse immune signatures, namely type 2 and non-type 2 inflammation. Regulatory T cells (Tregs) play a crucial role in maintaining immune homeostasis within mucosal tissues. However, the precise regulatory mechanisms of Tregs in CRS remain poorly understood. In this study, we employed an aspergillus protease and ovalbumin-induced chronic inflammation model to investigate the impact of Treg cells on CRS. During inflammation, the proportion of Treg cells within the $CD4^+$ T cell population was found to diminish, and a characteristic reprogramming was observed, characterized by increased expression of ST2 and decreased Rorγt. Depletion of endogenous Tregs led to exacerbated inflammation, highlighting the importance of Tregs in curbing effector functions. Utilizing flow cytometry and transcriptional profiling, we further characterized Tregs as an efficient subset capable of suppressing neutrophilic inflammation by restraining the pathogenicity induced by IFNγ and TNFα. These findings shed light on the therapeutic potential of harnessing Treg properties to target chronic inflammation and epithelial hyperplasia in CRS. Understanding the role of Tregs in CRS pathogenesis could pave the way for novel immunomodulatory approaches to alleviate disease burden and improve patient outcomes.

Poster No. 4

Innate Lymphoid Cells Contribute to Tissue Regeneration after Cardiotoxin-induced Muscle Injury

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Innate lymphoid cells (ILCs) are tissue-resident lymphocytes predominantly found in mucosal tissues of respiratory and digestive tracts. Known for their roles in early pathogen defense and tissue homeostasis, ILCs can be classified into three subsets based on their cytokine production and transcription factor expression: ILC1s, ILC2s and ILC3s. While extensive research has explored the diverse functions of ILCs in mucosal tissues, their presence and contributions in non-mucosal tissues, such as skeletal muscle, remain relatively unexplored.

To elucidate the role of ILCs in muscle tissue, we first validate the functionality of muscle resident ILCs in homeostasis. Subsequently, we generate a cardiotoxin (CTX)-induced muscle injury model to investigate the contribution of ILCs under disease condition. Following regenerative muscle injuries, we observed a notable increase in the number of ILCs during the acute inflammation phase. Additionally, we noticed putative interactions of ILCs with other immune cells. Further research will clarify the roles of ILCs in muscle regeneration and their complex interrelations within the tissue environment. Our findings open new avenues for understanding the dynamic involvement of ILCs in muscle regeneration and their potential as therapeutic targets in musculoskeletal conditions.

Poster No. 5

Maternal asthma alters the phenotype of group 2 innate lymphoid cells in the fetal lung and contributes to asthma exacerbation in offspring

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Background: Asthma is a chronic inflammatory lung disease characterized by symptoms like wheezing and coughing due to narrowed airways. Group 2 innate lymphoid cells (ILC2s) play important roles in its development. Asthma has part of its origin early in life, and maternal asthma attacks during pregnancy can increase the risk of asthma in offspring. However, the underlying mechanisms of asthma susceptibility transmission to offspring remains largely unknown. We used a pregnant asthmatic mouse model to analyze in detail the lung changes in their offspring during fetal and adult life.
Methods: Female mice were either sham sensitized or sensitized to ovalbumin (OVA) before mating. Allergic lung inflammation was induced in pregnant mice through intranasal allergen challenge using either phosphate-buffered saline (PBS) or OVA. Offspring were exposed to either PBS or house dust mite (HDM) during adulthood. Lung tissue from offspring was collected during fetal and adult stages and analyzed for immune cells and epithelial cells using flow cytometry, snRNA-seq, and scATAC-seq. Corticosterone in serum and amniotic fluid was analyzed by ELISA.
Results: In the lungs of prenatal offspring of asthmatic mothers, there were higher counts of eosinophils and ILC2s. When the offspring of OVA-exposed mothers were challenged with HDM, they had more severe asthma in adulthood than the offspring of non-asthmatic mothers. Detailed snRNA-seq analysis and scATAC-seq analysis of immune cells and epithelial cells in the lungs of the offspring during the embryonic period revealed that maternal asthma altered gene expression and chromatin accessibility in ILC2s. Eliminating ILC2s in the lungs of the offspring before and after birth with anti-IL7RA antibodies improved asthma exacerbation in the offspring. The stress hormone corticosterone was elevated in the amniotic fluid of asthmatic mothers. Hence, administering dexamethasone, a synthetic glucocorticoid, to pregnant mice altered the phenotype of ILC2s in the offspring's lungs, exhibiting a resemblance to the asthmatic model. These findings suggest that maternal asthma alters the phenotype of the fetal lung ILC2s, thereby increasing asthma susceptibility in the offspring. These insights into asthma transmission mechanisms carry significant implications for developing interventions to reduce the risk of asthma onset in offspring of asthmatic mothers.

Poster No. 6

Unveiling the crucial role of tuft cells in the amelioration of UC through appendectomy

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Ulcerative colitis (UC) is an inflammatory bowel disease characterized by chronic erosion and ulcers in the colon, which necessitates new therapeutic approaches. Cohort studies have shown that appendectomy (APX) reduces the risk of UC development, though the underlying mechanism remains elusive. In this study, we found that APX mice exhibit tuft cell hyperplasia as well as increased IL-25 production in the colon. IL-25 was found to alleviate colitis by markedly increasing group 2 innate lymphoid cells (ILC2) and inducing mucus production from goblet cells (GC) in an IL-13-dependent manner. Both IL-25-deficient and ILC2-deficient mice displayed reduced GC hyperplasia and APX-dependent colitis alleviation, suggesting that APX suppresses the development of colitis by strengthening the mucosal barrier through the tuft cell-IL-25-ILC2 axis. Notably, co-housing of mice with or without APX resulted in the loss of APX effects, suggesting that APX-induced changes in the gut microbiota are essential for tuft cell hyperplasia. Therefore, to identify the trigger that initiates tuft cell mediated ILC2 responses, we performed a comprehensive metabolic analysis and discovered that metabolite X (Patent pending) is markedly increased by APX. Administration of the metabolite X clearly induced tuft cell/ILC2 activation in the colon, resulting in the amelioration of colitis. Collectively, our findings demonstrate that APX initiates tuft cell mediated ILC2 activation and alleviates colitis by enhancing mucosal barriers. We believe that targeting tuft cells could offer a promising therapeutic strategy for UC patients.

Poster No. 7

The Actin-binding protein Transgelin-2: A Critical Regulator of Immune Cell Function

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Transgelin-2, a small actin-binding protein, is the only transgelin family member expressed in immune cells. We have investigated the roles of Transgelin-2 in diverse immune cells over an extended period. Transgelin-2 contributes to T cell activation by strengthening the actin cytoskeleton at the immunological synapse and stabilizing connections between T cells and B cells. Furthermore, transgelin-2 in cytotoxic T cells enhances adhesion to target cells by boosting the "inside-out" activation of leukocyte function-associated antigen 1 suggesting its potential role in anti-tumor efficacy of cytotoxic T cells by compensating for the lack of costimulation in the tumor microenvironment. In macrophages, while transgelin-2 expression in inactive conditions is very low, its expression is highly upregulated by bacterial endotoxins to enhance cytokine production and phagocytosis. We have recently reported that Transgelin-2 is dramatically upregulated in dendritic cells during maturation and lipopolysaccharide activation like macrophages. We showed that deletion of transgelin-2 in dendritic cells leads to significant defects in their abilities to home to draining LNs and to form optimal contacts with cognate $CD4^+$ T cells to prime T cells, and these changes were associated with a failure to suppress tumor growth and metastasis of B16F10 melanoma cells in mice. Finally, we provide promising evidence for the implication of recombinant transgelin-2 protein, engineered for cell-penetration and de-ubiquitination, potentiated DC functions to suppress tumor growth and metastasis, demonstrating that this small-actin binding protein represents a promising therapeutic approach for DC-based cancer immunotherapy.

Poster No. 8

Regulation of antibody responses by transcription factor EB

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Uncontrolled B cell responses are closely associated with development of several autoimmune diseases and can result in tissue damage and kidney failure. In an effort to identify a novel factor that regulates B cell response, we found that transcriptional factor EB (TFEB) is highly expressed in naïve B cells and its expression levels dynamically change during the process of plasma cell differentiation. In cell types other than B cells, TFEB is known to respond to various environmental cues by altering its phosphorylation status and nuclear localization. Activated TFEB promotes expression of genes associated with diverse biological pathways such as autophagy, lysosomal biogenesis, cellular metabolism, and immune responses. However, the role of TFEB in B cells is not much studied.

In order to elucidate the role of TFEB in B cells, we generated mice in which *TFEB* is specifically deleted in B cells. B cell-specific TFEB-deficient mice showed significantly higher serum antibody titers and increased numbers of bone marrow-resident antibody secreting cells compared to control mice both at steady state and after OVA immunization. In addition, increased fecal antibody titers were detected along with elevated germinal center responses in Peyer's patches in B cell-specific TFEB-deficient mice, indicating that TFEB negatively regulates B cell responses in vivo. Furthermore, we found that TFEB-deficient B cells undergo more efficient in vitro plasma cell differentiation than control B cells. Combined, these data demonstrate that TFEB is a novel B cell-intrinsic factor that negatively regulates plasma cell differentiation and prevents excess antibody production.

Poster No. 9

Regnase-1/3 controls hematopoietic lineage bias through degradation of *Nfkbiz* mRNA

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Hematopoietic stem and progenitor cells (HSPCs) are the source of daily hematopoiesis and give rise to all blood cell types. Recent work has revealed that the majority of HSPCs exhibit some degree of bias towards certain lineage outputs. However, cell-intrinsic regulatory mechanisms controlling HSPC lineage biases remain largely unclear.

Regnase-1 (Reg1) is an RNA decay enzyme that degrades mRNAs related to inflammatory responses. Reg1 recognizes stem loop (SL) structures containing pyrimidine-purine-pyrimidine loop in 3' untranslated region (3'UTR).

Here we show that Reg1 and its family member, Reg3, are critical in shaping HSPC lineage bias through degradation of *Nfkbiz* mRNA. *Reg1/Reg3*-double deficient (DKO) mice exhibited a significant reduction in T/B-lymphocytes and a concurrent increase in myeloid cells cell-intrinsically. In contrast, the single deficiency of *Reg1* or *Reg3* did not affect hematopoiesis in the BM. ScRNA-seq analysis of $Lin^{-}Sca\text{-}1^{+}Kit^{+}$ (LSK) cells revealed that DKO cells displayed an altered transcriptional profiling, favoring differentiation towards myeloid and megakaryo-erythroid lineages, while lymphoid signature genes were underrepresented. Among the upregulated genes in DKO cells, Nfkbiz and Ehd3 were identified as target genes of Reg1/3. Subsequently, Nfkbiz was found to exert a strong inhibitory influence on B cell differentiation. Notably, the genetic deletion of *Nfkbiz* led to a significant improvement in the hematopoietic changes observed in DKO mice. Given Nfkbiz's role as a transcription regulator that induces chromatin remodeling, we investigated the epigenetic landscape of $Flt3^{-}CD48^{-}$LSK cells using scATAC-seq, revealing increased accessibility of myeloid-related genes in DKO cells. Further deletion of *Nfkbiz* restored these changes in chromatin accessibility. Mechanistically, Reg1/3 recognize shared UAU-loop SL structures present in 3'UTR of *Nfkbiz*. Finally, by employing *Nfkbiz*-targeting antisense oligonucleotides against the SLs recognized by Reg1/3, we found that Nfkbiz can prime HSCs towards myeloid lineages, accelerating myeloid differentiation in response to IL-1β and TNF.

In conclusion, we demonstrate that the Reg1/Reg3-*Nfkbiz* axis regulates HSC lineage priming through chromatin remodeling.

Poster No. 10

Thioredoxin-interacting protein is essential for memory T cell formation via the regulation of the redox metabolism

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$CD4^+$ memory T cells are central to long-term immune protection and influence the progression of chronic inflammation. While metabolic reprogramming is critical for the generation of memory T cells, the mechanisms controlling the redox metabolism in memory T cell formation remain unclear. We found that reactive oxygen species (ROS) metabolism changed dramatically in T helper-2 (Th2) cells during the contraction phase in the process of memory T cell formation. Thioredoxin-interacting protein (Txnip), a regulator of oxidoreductase, regulated apoptosis by scavenging ROS via the nuclear factor erythroid 2-related factor 2 (Nrf2)-biliverdin reductase B (Blvrb) pathway. Txnip regulated the pathology of chronic airway inflammation in the lung by controlling the generation of allergen-specific pathogenic memory Th2 cells in vivo. Thus, the Txnip-Nrf2-Blvrb axis directs ROS metabolic reprogramming in Th2 cells and is a potential therapeutic target for intractable chronic inflammatory diseases. In addition, the expression of Txnip is regulated by various environmental factors, including glucose concentration. Therefore, Txnip is predicted to regulate memory T cell formation in response to environmental factors.

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Poster No. 11

Epigenetic scars in regulatory T cells are retained after successful treatment of chronic hepatitis C

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Background & Aims:
Chronic hepatitis C virus (HCV) infection results in abnormal immunological alterations, which are not fully normalized after viral elimination by direct-acting antiviral (DAA) treatment. Here we longitudinally examined phenotypic, transcriptomic, and epigenetic alterations in peripheral blood regulatory T (T_{REG}) cells from patients with chronic HCV infection according to DAA treatment.
Methods:
Patients with chronic genotype 1b HCV infection who achieved sustained virologic response (SVR) by DAA treatment and healthy donors were recruited. Phenotypic characteristics of T_{REG} cells were investigated through flow cytometry analysis. Moreover, transcriptomic and epigenetic landscape of T_{REG} cells were analyzed using RNA-seq and ATAC-seq analysis.
Results:
The T_{REG} cell population—especially the activated T_{REG} cell subpopulation—was expanded in peripheral blood during chronic HCV infection, and this expansion was sustained even after viral clearance. RNA-seq analysis revealed that viral clearance did not abrogate the inflammatory features, such as T_{REG} activation and TNF signal, of T_{REG} cells from patients. Moreover, ATAC-seq analysis showed inflammatory imprinting in the epigenetic landscape of T_{REG} cells from patients, which remained after treatment. Intracellular cytokine staining demonstrated that T_{REG} cells from patients with chronic HCV infection exhibited inflammatory features and TNF production that were maintained after viral clearance.
Conclusions:
Overall, our results showed that during chronic HCV infection, the expanded T_{REG} cell population acquired inflammatory features at phenotypic, transcriptomic, and epigenetic levels, which were maintained even after successful viral elimination by DAA treatment. Further studies are warranted to examine the clinical significance of sustained inflammatory features in the T_{REG} cell population after recovery from chronic HCV infection.

Poster No. 12

Metformin reduces the risk of developing atherosclerotic plaques associated with influenza A virus infection

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Cardiovascular disease is a leading cause of death worldwide. Influenza A virus infection can increase the risk of death from cardiovascular disease, and vaccination can reduce the risk of death from cardiovascular disease. In mouse study, we showed that the increased influx of immune cells into the lungs due to influenza A virus infection can cause worsening of arteriosclerosis. In addition, monocytes exposed to influenza A virus accumulated in atherosclerotic plaques, causing instability of atherosclerotic plaques due to increased expression of matrix metalloproteinase-13. Interestingly, the expression of matrix metalloproteinase-13 was found to be suppressed in the serum of patients diagnosed with influenza A virus who took metformin, the first line treatment of type 2 diabetes. Therefore, we investigated whether the worsening of arteriosclerosis caused by influenza A virus infection is suppressed by metformin treatment. *In vitro* and *in vivo* studies showed that viral replication and influenza A virus-induced cytokine expression were inhibited by metformin. In particular, MCP-1 and IP-10, cytokines related to cell infiltration, and cardiovascular disease development were significantly reduced by metformin under influenza A virus infection condition. As a result, the acute exacerbation of atherosclerosis caused by influenza A virus in mouse aorta was inhibited by metformin. In addition, we found that the regulation of AKT/MAPK signaling plays an important role in the mechanism of metformin. In conclusion, this suggests that taking metformin can control the worsening of atherosclerosis caused by influenza by maintaining homeostasis of the influx of immune cells.

Poster No. 13

Deciphering SARS-CoV-2-specific T cell responses to a clonotype resolution

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Human T cell receptors develop to form an extremely diverse repertoire to recognize a large variety of antigens. Upon exposure to the SARS-CoV-2 antigen, a few naïve T cells react and expand, resolve the infection, and finally constitute the antigen-specific memory T cell pool. In the homeostatic condition, the pathogen-specific T cells have high diversity and low frequency, which restrict the exploration of these cells. Single-cell–based TCR- and RNA-sequencing (scTCR/RNA-seq) analysis enable us to acquire TCR alpha-beta clonotype sequences, together with the gene expression signature of these individual T cells. However, the throughput of single-cell analysis is limited, and it is difficult to determine features such as antigen specificity and restricting-HLAs of a TCR pair after the cell was used for sequencing. Thus, selecting the antigen-specific T cells for single-cell analysis, and exploring the characteristics of a T cell using the information from single-cell data, are crucial for the investigation of T-cell responses against the pathogen. To identify clonotypes associated with SARS-CoV-2 defense, we stimulated the T cells with antigens for a short period or a long period, sorted the responded T cells based on activation marker expression or proliferation, and analyzed the T cells with scTCR/RNA-seq. To determine the epitopes and restricting HLAs of target TCRs, we reconstituted the paired TCR sequences in a reporter cell line. Using this methodology, we characterized dominant T cell clonotypes against SARS-CoV-2, as well as their epitopes that may indicate the critical antigenic regions. This information could contribute to the vaccine design in the future.

Poster No. 14

Kinetics and quality of mRNA vaccine-induced immune response against SARS-CoV-2

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Coronavirus disease 2019 (COVID-19), caused by infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to impact human lives globally. It is relatively established that the first dose of the mRNA vaccine could generate a robust $CD4^+$ T cell response against SARS-CoV-2 in unexposed individuals. The $CD8^+$ T cell response, however, occurred slowly and the magnitude varied largely between individuals. Meanwhile, several different studies have highlighted the existence of pre-existing T-cell immunity against SARS-CoV-2 as a result of past common cold infections with human endemic coronavirus. However, the functional implication of these pre-existing cross-reactive T cells remains a constant debate. Our study aimed to understand the kinetics and quality of the immune response induced by mRNA vaccines in two groups: healthy young medical workers and elderly patients with lung diseases. We stimulated T cells with the whole spike protein of SARS-CoV-2 and adopted a TCR strength marker, IRF4, to perform the activation-induced marker (AIM) assay. The results suggested that mRNA vaccines could robustly induce SARS-CoV-2 specific $CD4^+$ T cells and its high-affinity subset in both groups. Interestingly, there was no significant difference in the magnitude between the two groups shortly after vaccinations. We then combined the two groups and re-classified them into good, medium, and bad responders based on their induction of high-affinity SARS-CoV-2 specific $CD4^+$ T cells. We discovered that good responders generated higher levels of cytotoxic CD4+ T cells and neutralizing antibodies compared to bad responders, despite their similar frequencies of SARS-CoV-2 specific $CD4^+$ T cells. Surprisingly, no significant age differences were observed between good and bad responders, suggesting that age is not the primary factor determining a vaccine response. In addition, we observed a negative correlation between pre-existing cross-reactive $CD4^+$ T cells and the level of high-affinity and cytotoxic $CD4^+$ T cells respectively after vaccinations, suggesting a negative effect of pre-existing cross-reactive T cells. In conclusion, our findings suggested that high levels of pre-existing cross-reactive $CD4^+$ T cells may predict a weaker vaccine response, regardless of age. This study provides insights into the functional implications of pre-existing cross-reactive T cells and a perspective on redefining immunological age.

Poster No. 15

Recombinant IL-7 administration protects host from a wide range of acute respiratory virus infection through IL-17A-producing innate-like T cells

Subin Park
POSTECH

Repeated pandemics and epidemics caused by influenza virus and SARS-CoV have resulted in drastic effects on global public health. Although some vaccines and antiviral drugs achieved successes to control disease spread and morbidity, their limited application to new variants emphasize the requirements for broad-spectrum therapeutics. One strategy to achieve the goal is utilizing host immune system. Upon respiratory virus infection, various tissue resident immune cells mediate antiviral response. Both innate and adaptive T cells are one of major population that participate in the antiviral response through IFN-γ and IL-17A. Generation and maintenance of T cells often requires IL-7, a T cell homeostatic cytokine. Administration of recombinant IL-7 rapidly amplify T cells and has been an attempting strategy to boost T cell response in various disease. Especially, several studies have suggested potential of IL-7 administration in protection against respiratory infection.

To investigate the potential of recombinant IL-7 in protection against respiratory virus infection, we infected female C57BL/6 mice with various virus as influenza A virus, influenza B virus, SARS-CoV-2, and RSV. Surprisingly, administration of recombinant IL-7 induces protective effects against broad spectrum of viruses. To further investigate the mechanisms of IL-7-mediated antiviral effects, we used single cell RNA-sequencing paired with V(D)J sequencing and flow cytometric approaches on IAV infected mice. The mice administered with IL-7 displayed expansion of IFN-γ-producing conventional T cells and IL-17A-producing innate-like T cells. The administration of IL-7 also upregulated the expression of antiviral gene in both conventional and innate-like T cells. Cytokine depletion studies suggested that IL-17A-producing innate-like T cells, rather than IFN-γ-producing conventional T cells, are major population for the IL-7-mediated protective effects upon infection. In conclusion, we suggest the administration of recombinant IL-7 could be a potential broad-spectrum therapeutic by regulating early immune responses with IL-17A-producing innate-like T cells.

Poster No. 16

Evidence of a SARS-CoV-2 superantigen inducing broad T cell activation in multisystem inflammatory syndrome in children

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Background
Most cases of pediatric COVID-19 are asymptomatic or result in mild disease. However, a small number of children have been found to experience severe multisystem inflammatory syndrome (MIS-C) within a few weeks after SARS-CoV-2 infection. While causes for MIS-C remain unknown, studies have reported a skewing of the T cell receptor (TCR) repertoire in MIS-C patients, suggesting the potential relevance of a SARS-CoV-2 superantigen. However, evidence for the existence of a SARS-CoV-2 superantigen and its impact to MIS-C remain insufficient. Here, we aim to characterize the T cell landscape of MIS-C patients and investigate the potential presence and impact of a SARS-CoV-2 superantigen in MIS-C.

Methods
A cohort of four MIS-C patients treated with intravenous immunoglobulins and steroids were recruited, and peripheral blood samples were collected serially at the following timepoints: before, 1-2 days and 4-10 days after treatment. $CD4^+$ and $CD8^+$ T cells were sorted from isolated peripheral blood mononuclear cells through fluorescence-activated cell sorting and subjected to multiplex sequencing for single-cell analysis of gene, protein and TCR expressions.

Results
MIS-C patients exhibited elevated frequencies of effector $CD8^+$ and cycling T cells compared to healthy children, and the effector $CD8^+$ and cycling T cells of MIS-C patients also showed greater expression of cytotoxicity-related genes within each of their respective clusters relative to their healthy counterparts. Importantly, the TCRβ repertoire of certain MIS-C patients were found to be restricted and heavily skewed towards polyclonal TRBV11-2*01 cells. These cells localized mainly to effector $CD8^+$ and cycling T cell clusters and highly upregulated expression of effector and cytotoxicity genes. Furthermore, TRBV11-2*01 cells also showed enrichment of gene sets related TCR-mediated signaling.

Conclusion
Our findings indicate that MIS-C patients have a skewed TCR repertoire towards TRBV11-2*01 cells that are primarily comprised of effector and cycling $CD8^+$ T cells and are activated in a TCR-dependent manner, suggesting the potential existence and role of a SARS-CoV-2 superantigen in MIS-C.

Poster No. 17

De novo fatty-acid synthesis protects invariant NKT cells from cell death, thereby promoting their homeostasis and pathogenic roles in airway hyperresponsiveness

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Invariant natural-killer T (*i*NKT) cells play pathogenic roles in allergic asthma in murine models and possibly also humans. While many studies show that the development and functions of innate and adaptive immune cells depend on their metabolic state, the evidence for this in *i*NKT cells is very limited. It is also not clear whether such metabolic regulation of *i*NKT cells could participate in their pathogenic activities in asthma. Here, we showed that acetyl-coA-carboxylase 1 (ACC1)-mediated *de novo* fatty-acid synthesis is required for the survival of *i*NKT cells and their deleterious functions in allergic asthma. ACC1, which is a key fatty-acid synthesis enzyme, was highly expressed by lung *i*NKT cells from WT mice that were developing asthma. *Cd4*-Cre*Acc1*$^{fl/fl}$ mice failed to develop OVA-induced and HDM-induced asthma. Moreover, *i*NKT cell-deficient mice that were reconstituted with ACC1-deficient *i*NKT cells failed to develop asthma, unlike when WT *i*NKT cells were transferred. ACC1 deficiency in *i*NKT cells associated with reduced expression of fatty acid-binding proteins (FABPs) and peroxisome proliferator-activated receptor (PPAR)γ, but increased glycolytic capacity that promoted *i*NKT-cell death. Furthermore, circulating *i*NKT cells from allergic-asthma patients expressed higher *ACC1* and *PPARG* levels than the corresponding cells from non-allergic-asthma patients and healthy individuals. Thus, *de novo* fatty-acid synthesis prevents *i*NKT-cell death *via* an ACC1-FABP-PPARγ axis, which contributes to their homeostasis and their pathogenic roles in allergic asthma.

Poster No. 18

Regnase-1 haploinsufficiency in mice enhanced immunological responses against SARS-CoV-2 pneumonia, leading to better eradication of virus from lung.

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Regnase-1 (Reg1) suppresses excessive inflammation by degrading mRNAs encoding inflammatory mediators through the recognition of stem-loop structures. Reg1 deficiency in mice resulted in the development of severe inflammatory diseases, and its haploinsufficiency exacerbated experimental autoimmune encephalitis in mice. However, the function of Reg1 in SARS-CoV-2 infection is unknown. We found that overexpression of Reg1 inhibited SARS-CoV-2 replication in vitro via its RNase activity. However, experiments in mice suggested opposite functions. In response to infection with a mouse-adapted SARS-CoV-2 strain (MA10), *Reg1* heterozygous (+/–) mice showed less weight loss and were more protective against mild ($0.3MLD_{50}$) and severe ($3MLD_{50}$) doses of SARS-CoV-2 infection than wild-type controls. Lung histopathology analysis revealed that the development of pneumonia was ameliorated in $Reg1^{+/-}$ mice. Furthermore, analysis of lung immune cells showed that $Reg1^{+/-}$ mice had increased neutrophil infiltration, accompanied by an increase in serum G-CSF levels, following mild SARS-CoV-2 infection. Although serum cytokine levels and lung cytokine transcript expression were not altered, expression of CD11b and Siglec F on lung infiltrating neutrophils was decreased in $Reg1^{+/-}$ mice, suggesting that neutrophil function is altered by Reg1 haploinsufficiency. Our results suggest that Reg1 blockade may ameliorate SARS-CoV-2 infection by altering neutrophil-mediated immune defense mechanisms.