PROGRESS REPORT
Division of Molecular Pathology

Masato Kubo, D.M.S.

Members

Faculty members

Masato Kubo, D.M.S.
(Professor and Chairman)
Jumana Khalil (Assistant Professor)

Technical staff

Yasuyo Harada
Rieko Ohe
Ayako Sakurai
Tomoko Iwaoka

Guest researcher

Ryo Abe
Tatsuro Shimaoka
Takaya Nakamichi
Daisuke Hayashi
Hiroko Watanabe

Division of Molecular Pathology

Chairman: Masato Kubo, D.M.S.

This year, we are closing the doors of our laboratory at TSU. Since we launched this lab in 2009, we have been on the incredible journey we have shared over the past 15 years. Our long-term goal was to understand how type II cytokines (IL-4 and IL-13) and T cell-derived cytokines contribute to T and B cell immunity, significantly impacting several pathogenic situations. To reach this goal, we have pushed the boundaries of knowledge, tackled complex challenges, and accomplished numerous achievements. We extend our heartfelt gratitude to everyone who has been a part of our journey. Your dedication, passion, and hard work have been the cornerstone of our success. The friendships and professional relationships in RIBS of TUS forged here will undoubtedly continue to inspire and support us in our future endeavors. Thank you for the memories and the milestones. Here is to new beginnings and continued success in your future endeavors.

Masato Kubo, DMS

1) IL-13 signal in conventional dendritic cells controls allergic march initiated by cutaneous allergen sensitization.

Allergy is a complex array of diseases influenced by innate and adaptive immunity, genetic polymorphisms, and environmental triggers. Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by barrier defects and immune dysregulation. Skin barrier dysfunction in the setting of AD leads to cutaneous allergen sensitization (CAS), leading to the subsequent development of other allergic disorders such as asthma and food allergies because of the atopic march. However, the precise mechanisms by which CAS promotes IgE-mediated allergic responses remain unclear. Recently, we reported that IL-13 expression by type 2 T follicular helper T ($T_{FH}2$) has a critical role in generating high-affinity IgE antibodies. However, the mechanisms by which IL-13 leads to IgE-mediated allergic responses remain poorly defined.

We established a CAS model (MC903 induced skin inflammation model) that systemic secondary allergen priming gave rise to high-affinity IgE-mediated anaphylaxis and identified a unique role of the Interleukin (IL)-13 signal in dendritic cells (DCs). During atopic skin inflammation, Langerhans cells and DCs in the skin capture and deliver allergen information to local lymph nodes. DCs are essential immune sensors coordinating immune reactions by capturing and presenting antigens to T cells. In allergic responses, DCs play a crucial role in instructing two types of helper T cells — type 2 helper T (Th2) cells and T_{FH} cells — in allergic responses and IgE antibody responses. In skin sensitization, the differentiation and function of Th2 cells and T_{FH} cells are influenced by skin-derived factors, including epithelial cytokines, chemokines, and signaling pathways to modify the function of migratory DCs and conventional DCs.

Using the CAS mouse model, we identified the pivotal role of IL-13 signal in Type 2 conventional DCs (cDC2s) regulated recall activation of memory Th2 cells and the differentiation of allergen-specific T_{FH} cells. Deleting the IL-13 receptor (IL-13R) in DCs, but not in T and B cells, attenuated high-affinity IgE-

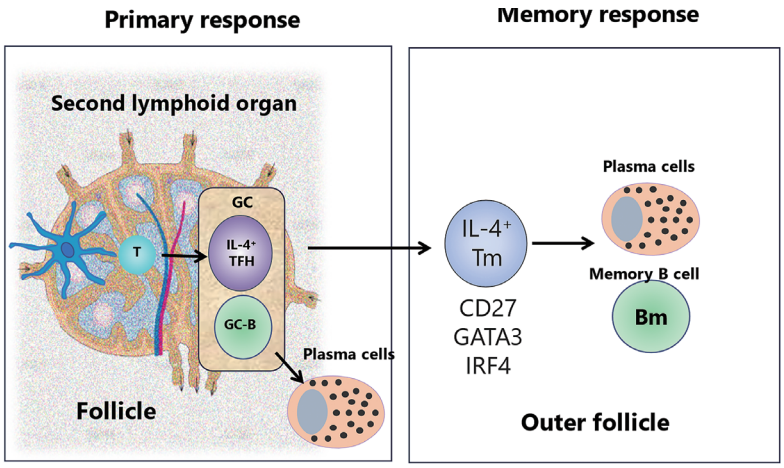
mediated anaphylaxis only when CAS first introduced the allergen. The IL-13 signal preferentially promoted the maturation of cDC2s by enhancing the expression of MHC class II and CD301b, which was critical for responsible for inducing Th2 and $T_{FH}2$ responses.

Collaborators:

Takahiro Matsuyama and Hiromasa Inoue (Kagoshima University), Takashi Watanabe (RIKEN IMS), Brian S. Kim (Washington University School of Medicine), Hideki Ueno (Kyoto University), Peter D. Burrows (University of Alabama at Birmingham)

2) Immune Responses Post-COVID-19 Vaccination: Coordination of Tfh and IL-4 Expressing Memory T Cells

Vaccines have proven most effective in eliciting an immune response capable of providing protective immunity in healthy individuals. However, the contribution of the Germinal Center (GC) and TFH responses to the primary and memory response to SARS-CoV-2 vaccination is poorly understood. In this study, we examined the antibody response to the recombinant spike protein derived from the Wuhan strain in mice, where the involvement of T_{FH} cells in the primary or memory response was eliminated. T_{FH}-mediated GC responses are essential for generating protective antibodies in the primary response against vaccinated antigens and for inducing memory T cell responses. In contrast, T_{FH}-mediated GC responses are dispensable for memory B cell responses. We found that the extrafollicular expansion of IL-4-expressing memory T cells (IL-4^{+}Tm), which express CD27, GATA3, and IRF4, but not CXCR5, correlated with the memory B cell responses, producing antibodies that effectively neutralize Omicron variants. Indeed, IL-4 signaling in B cells was critical for the memory response since the loss of IL-4 receptors in the memory phase attenuated the memory B cell response. These results indicate a crucial role of IL-4 in memory responses induced by SARS-CoV-2 boost immunization, highlighting the coordination of two arms of cellular immunity composed of follicular and extrafollicular T cells (T_{FH} and IL-4^{+}Tm) in assisting the expansion of antibody breadth and proliferation of B cells. These findings deepen our understanding of the role of T cell-derived signals in influencing the breadth of humoral responses to COVID-19 and



TFH cells and memory T cells in memory responses
TFH is induced by primary response, which mainly occurs in the germinal center, whereas memory response mainly occurs in outer follicle. In this case, IL-4-expressing memory T cells (IL-4^{+}Tm) play a role to control recall antibody responses.

could influence future vaccine strategies.

Collaborators:

Kosuke Miyauchi (National Institute of Infectious Diseases), Yuichiro Yamamoto and Kohji Noguchi (Tokyo University of Science), Rina Hashimoto and Kazuo Takayama (Kyoto University)

Publications

Masato Kubo, DMS

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