International Vaccine Design Center

Division of Infection Immunology (Human Immune-Profiling Team)

ヒト免疫プロファイリング系・感染免疫学分野

Professor	Cevayir COBAN, M.D., Ph.D. (Clinical Microbiology)	教　授	博士(医学)(臨床微生物学位)	チョバン　ジェヴァイア
Visiting Professor	Anavaj SAKUNTABHAI, M.D., Ph.D.	客員教授	博士(医学)	サクンタバイ　アナヴァジ
Project Assistant Professor	Michelle S.J. LEE, Ph.D.	特任助教	博士(医学)	リー　ミシェル

As a member of the International Vaccine Design Center of IMSUT, we focus on elucidating host-pathogen interactions in the context of emerging infectious diseases such as dengue and Covid19 and the neglected tropical diseases (i.e. malaria, leishmaniasis), to understand the virulence factors of these pathogens and ultimately to design successful vaccines against them.

1. Adjuvant discovery and development platform

Adjuvants are considered essential vaccine components for enhancing vaccine responses. As a member of IMSUT International Vaccine Design Center (https://vdesc.ims.u-tokyo.ac.jp/en/), we have systematically screened innate and adaptive immune signaling molecules involved in the mode of action (MOA) of adjuvants and vaccines. Recently, we have been involved in the discovery of novel adjuvants as part of the AMED SCARDA project. Our recent projects have focused on investigating B cell development and the pathways involved in germinal center (GC) formation for the generation of potent antibody responses against infections and during vaccination. We found that TBK1, the well-known innate immune signaling kinase that controls antiviral immune responses and nucleic acid-mediated type I interferon responses, is very important for the generation of GCs that confer sterile immunity to reinfection (*Lee et al., J Exp Medicine, 2022*).

2. Elucidation of host-pathogen interactions

Our laboratory has investigated several aspects of immunopathology caused by *Plasmodium* parasites. We have recently studied the immunopathology of cerebral malaria, the deadliest complication of human malaria infection, in the brain using the CUBIC clearance technique (*Matsuo-Dapaah et al., Int Immunology, 2021*). The 3D reconstruction of malaria-infected brain showed that olfactory bulb is disrupted during experimental cerebral malaria. We have recently made significant progress in understanding new cell types that accumulate/reside in the olfactory bulb and interact with *Plasmodium* parasites. Chronic bone loss is an unforeseen complication of malaria which is mediated via MyD88 adaptor protein (*Lee et al,. Science Immunology, 2017*). We have been studying to address the crucial cell types important for MyD88-mediated bone loss. We also investigate bone marrow niches responsible for malaria-induced loss of memory.

3. Infection and cancer

Previously, we investigated the role of Lipocalin 2 (LCN2, also known as siderocalin or neutrophil ge-

latinase-associated lipocalin (NGAL)) in malaria infection that bolsters innate and adaptive immune responses to malaria infection through modulation of iron metabolism (*Zhao et al., Cell Host Microbe, 2012*). LCN2 expression is also increased in cancer. In carcinogenesis stroma-associated immunity is an important regulator of tumor growth. Tumor cells create a microenvironment by releasing various mediators to maintain their presence and spread. Due to the infiltration of monocytes and leukocytes in tumor microenvironment, it is hypothesized that the iron balance is disrupted by excessive iron consumption, possibly leading to increased expression of LCN2 as an intracellular iron transporter. We recently investigated the expressions of programmed cell death ligand-1 (PD-L1) and LCN2 in breast cancers with various molecular subtypes, along with their correlations with other prognostic indicators, including Ki-67, lymph node metastasis, histological grade, tumor-infiltrating lymphocyte (TILs) accumulation, and necrosis. We found that there is an association of LCN2 with known prognostic factors and molecular subtypes. Moreover, significant elevations of LCN2 and PD-L1 expressions were observed in triple-negative and HER2-positive breast cancers. The findings from this research may contribute to the immunotherapeutic application of LCN2 and its prognostic significance in breast cancer management (*Ekemen et al., Breast Cancer: Targets and Therapy, in press*).

4. Infection and host genetics

The genetics of an individual contributes to the susceptibility and response to viral infections. International groups including Prof. Sakuntabhai's group formed a global network of researchers to investigate the role of human genetics in SARS-CoV-2 infection and COVID-19 severity (*COVID-19 Host Genetics Initiative. Mapping the human genetic architecture of COVID-19. Nature 600, 472–477, 2021*). Investigating the role of host genetic factors in COVID-19 severity and susceptibility can inform our understanding of the underlying biological mechanisms that influence adverse outcomes and drug development. Recently, they published a second update on mapping the human genetic architecture of COVID-19 (*The COVID-19 Host Genetics Initiative. A second update on mapping the human genetic architecture of COVID-19. Nature 621, E7–E26, 2023*). They performed a meta-analysis of up to 219,692 cases and over 3 million controls. They expanded the current knowledge of host genetics for COVID-19 susceptibility and severity by further doubling the case numbers from the previous data release and identifying 28 additional loci. Notably, they observed severity loci mapped to type I interferon pathway, while susceptibility loci mapped to viral entry and airway defense pathways, with notable exceptions for severity-classified TMPRSS2 and MUC5B loci.

Publications

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