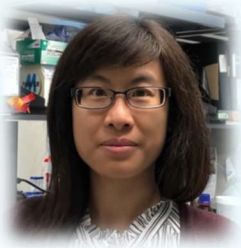
感染病態学セミナー

Neuroimmunology of Cryptococcal Meningitis: Exploring the Roles of CNS-localized Myeloid Cells in T-cell Responses

The recruitment and activation of CD4 T-cells within the CNS during infection is only partially understood. We have used a model of cryptococcal meningitis, a lethal fungal neurological infection that is dependent on CD4 T-cells for protection, to delineate the cell populations and events regulating entry of CD4 T-cells to the fungal-infected brain. We developed a novel TCR transgenic mouse model (CnTII-Tocky) to analyze anti-fungal CD4 T-cell responses and the role of myeloid cells in these responses. This model reports Nr4a3-dependent TCR signaling activity and cytokine production of *Cryptococcus*-specific CD4 T-cells during *in vivo* infection, enabling us to correlate T-cell numbers, proliferation, fungal burden, TCR signaling and cytokine production in the same animal. Using these mice, we show that fungal-specific CD4 T-cells only migrate into the CNS during acute meningitis but not chronic infection. Infiltrating CD4 T-cells had undergone rounds of division, produced IFNγ and did not engage their TCR as they expressed low TCRβ and reduced Nr4a3-dependent TCR signaling. Acute meningitis induced high numbers of inflammatory CXCL10+ macrophages. Single-cell RNA-seq analysis of macrophages revealed significant heterogeneity however antigen presentation and T-cell engagement pathways were largely localized to one population that shared characteristics with border macrophages. In contrast, CNS-resident microglia did not significantly upregulate genes involved with T-cell activation and appeared relatively unchanged in both acute and chronic CNS infection models. Taken together, our results show that monocyte-derived macrophages infiltrate the CNS during acute fungal infection and produce CXCL10 to recruit IFNγ-producing T-cells, which have limited TCR-dependent interactions with CNS-resident myeloid cells. In contrast, chronic infection suppresses the development of the macrophage population for CNS recruitment of T-cells. Taken together, we have delineated a complex series of events that regulate CD4 T-cells entry to the CNS during cryptococcal meningitis, revealing several novel targets for immune-based therapies for this life-threatening infection.



Dr. Man Shun Fu, Research Fellow,
Institute of Immunology & Immunotherapy,
College of Medical and Dental Sciences,
University of Birmingham, Birmingham, UK

2023.08.02(Wed) 17:30~18:30

【6号館1F 講堂/ Auditorium, School of Medicine Building 6 (B08) 1F】

＊この講義は、医学履修課程「国際交流セミナー(アドバンスド講義科目)」を兼ねています。
This special lecture is transferable with “Advanced Lecture course: International Interchange Seminar” for Medical Science Doctoral Course.

お問い合わせ
感染病態学分野/Department of Clinical Microbiology and Infection
☎ 022-717-8681（内線:8681）
✉ ko-sato@med.tohoku.ac.jp