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THE HONG KONG UNIVERSITY OF SCIENCE & TECHNOLOGY

Division of Life Science

Seminar Notice

"Cytokines and Cerebral Malaria"

by **Prof. F.Y. Eddy Liew FRS**

University of Glasgow, UK

Abstract:

Cytokines are hormones of the immune system. Cytokine-targeting represents a major triumph in immunology scientifically, clinically and commercially. There is therefore considerable interest in discovering novel cytokines. I will illustrate the pleiotropic role of cytokines by focusing on interleukin (IL)-33. IL-33 is a member of the IL-1 family. It is the ligand of ST2, which is expressed mainly on Th2 cells, epithelial cells, neuronal cells and mast cells. IL-33 can skew a predominantly Th1 cell population to Th2 cells phenotype in vivo. Furthermore, IL-33 potently induces Type 2 innate lymphocyte (ILC2) and alternatively activated macrophages (M2), leading to the differentiation of regulatory T cells (Tregs). This pleiotropic nature is demonstrated in the role of IL-33 in tissue and metabolic homeostasis, infection, inflammation, cancer and diseases of the central nervous system.

Of all the organs in human and mice, brain and the spinal cord express the highest level of IL-33. IL-33 might thus play an important role in diseases of the central nervous system, such as cerebral malaria (CM).

CM is a complex parasitic disease caused by Plasmodium sp. CM is a fatal disease especially in children. Currently there is no effective treatment. Failure to establish an appropriate balance between pro- and anti-inflammatory immune responses contributes to the development of cerebral pathology. Using the blood-stage PbA (Plasmodium berghei ANKA) model of infection, administration of IL-33 prevented the development of experimental cerebral malaria (ECM) in mice and reduced the production of inflammatory mediators. IL-33 drives the expansion of ILC2 that produce Type-2 cytokines (IL-4, IL-5 and IL-13), leading to the polarization of the anti-inflammatory M2 macrophages, which in turn expand Foxp3+ Tregs. However, IL-33 failed to prevent the multiplication of the parasites and the mice eventually succumbed to the infection. Thus a combination of IL-33 and anti-malaria drugs may overcome this problem.

Non-biased whole brain transcriptomic analysis of anti-malarial drug chemotherapy (artesunate + chloroquine, AC) of ECM and bioinformatics revealed IL33 as a critical regulator of neuro-inflammation and cerebral pathology that was down regulated in the brain during fatal ECM and in the acute period following AC treatment of ECM. Consistent with this, administration of IL33 alongside AC significantly improved the treatment success of established ECM. Mechanistically, IL33 treatment reduced inflammasome activation and IL1β production in microglia and intra-cerebral monocytes in the acute recovery period following treatment of ECM. Moreover, treatment with the NLRP3-inflammasome inhibitor MCC950 alongside AC phenol-copied the protective effect of IL33 therapy in improving the recovery from established ECM. Furthermore, production of IL1β by macrophages, stimulated by AC, was inhibited by MCC950. This series of study therefore demonstrates that manipulation of the IL33-NLRP3 axis may be an effective therapy to suppress neuro-inflammation and improve the efficacy of anti-malarial drug treatment of clinical cerebral malaria, which afflicts over half a million children annually worldwide.

Date : 27 February 2018 (Tuesday)

Time : 3:00 p.m.

Venue : Room 4582 (Lifts 27-28)
The Hong Kong University of Science & Technology
Clear Water Bay, Kowloon

(Host faculty: Prof. Karl Herrup)

ALL ARE WELCOME!!