

1st Pasteur-Asia Immunology Course

A seminar entitled

‘Innate Immune Recognition of Microbial Products by Toll-like receptors’

will be given by

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Date: Wednesday, 29 October 2008

Time: 09:00 am to 11:00 am

Venue: HKU-Pasteur Research Centre
1/F, Dexter HC Man Building
8 Sassoon Road, Pokfulam, Hong Kong

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Abstract:

A variety of microbial products including lipopolysaccharide (LPS) are known to stimulate the immune system. The Toll family of receptors has critical roles in microbial recognition and activation of defense responses. Cell surface TLR dimers consisting of TLR4/MD-2, TLR1/TLR2, or TLR2/TLR6 recognize microbial membrane components such as lipopolysaccharide (LPS) or lipopeptides, whereas nucleic acid sensing TLRs reside in intracellular organelle. Recently, the structure of the LPS sensor MD-2 and TLR4 was reported, revealing molecular basis for LPS recognition by immune cells. Specific interaction of a ligand with TLR is thought to trigger TLR dimerization and activate downstream signaling pathways mediated by a number of adaptor molecules like MyD88, TRIF/TICAM-1, TIRAP/Mal, and TRIF/TICAM-2. TLR signaling induces not only strong inflammation but also adaptive immune response.

Immune cells such as dendritic cells (DC) or macrophages express multiple TLRs, which are concomitantly activated in response to pathogens, since single microbes or viruses express a variety of TLR ligands. Although the ligand specificity and downstream signaling pathways of each TLR have been extensively studied, much less is known as to how TLR overall responsiveness in immune cells are regulated. In this regard, it is of note that CD14 and RP105 have been shown to regulate TLR2/4 responses, whereas UNC93B1 is required for nucleic acid-sensing TLR3/7/9. These molecules suggest a mechanism regulating responsiveness of multiple TLRs. We have recently cloned another molecule that regulates responsiveness of multiple TLRs. PRAT4A (A Protein associated with TLR4) was initially identified as a molecule associated with TLR4. PRAT4A consists of a signal peptide followed by about 240 amino acids. PRAT4A reside in the ER, where PRAT4A is associated with TLR4. Gene silencing of PRAT4A reduced cell surface expression of TLR4 and LPS responses. Further studies revealed that PRAT4A is also required for the proper subcellular distribution and responses of multiple TLRs other than TLR4. Expression of PRAT4A might regulate overall TLR responsiveness in immune cells, and could be a target for a therapy controlling TLR responsiveness.