SIgN Immunology Seminar

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Inflammasome activation in chronic inflammatory diseases

Host
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Date
Wednesday, 5 December 2012

Time
11am – 12pm

Venue
SIgN Seminar Room,
Immunos Building
Level 4
Biopolis

Innate immunity evolved to recognize microbial infection and to respond to danger signals that appear under disease conditions. The most recently described innate immune receptor family is the Nod-like receptor (NLR) family. The NLR member NLRP3 and the adapter protein ASC form a multi-molecular complex termed the NLRP3 inflammasome. Inflammasomes control the activity of caspase-1, which cleaves and activates the pro-form of the inflammatory cytokines IL-1b and IL-18. The NLRP3 inflammasome can be activated by various membrane active bacterial toxins or after phagocytosis of crystalline and aggregated materials. We demonstrated that crystals and aggregated peptides activate the NLRP3 inflammasome in macrophages and microglial cells and contribute to disease processes in murine models of atherosclerosis and Alzheimer's disease.

In addition, we have recently identified that inflammasome-independent, non-canonical IL-1b activation pathways exist. Fas, a tumor necrosis factor family receptor, is activated by the membrane protein Fas ligand (FasL) expressed on various immune cells. We have demonstrated that macrophages exposed to TLR ligands upregulate Fas, which renders them responsive to receptor engagement by Fas ligand. Fas signaling in macrophages and dendritic cells activates caspase-8, which matures IL-1β and IL-18 independently of inflammasomes or Rip3. Hence, Fas controls a novel non-canonical IL-1β activation pathway in myeloid cells, which could play an essential role in inflammatory processes, tumor surveillance and control of infectious diseases. Novel treatment approaches based on these data will be presented and discussed.