Singaporean Society for Immunology

Sponsored by: MERCK MILLIPORE

SgSI Seminar Series: Infectious Diseases

Date & Time: 21 November 2013 (Thursday), 4.30 - 5.30pm

*Venue: Seminar Room 6, Symbiosis Level 5, Fusionopolis

Host: Dr Katja Fink, SIgN

Seats are limited and registration is based on first-come first-served. Click here to register now!

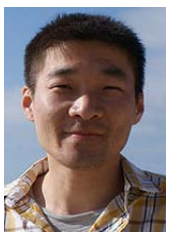
Dr. Ashley St. John

Assistant Prof

Duke-NUS

Mast Cells: Newly Described Players in Dengue Immunity and Immune Pathology

Dengue virus is a re-emergent tropical infectious disease that is endemic in Singapore and causes ~390 million infections per year, worldwide. Infected patients can experience a broad spectrum of disease, ranging from asymptomatic infections, to acute febrile infection, to hemorrhagic complications that can potentially lead to shock and/or death. Immune-mediated pathology is thought to underlie the vascular leakage that occurs during symptomatic dengue infection, but the precise mechanisms that govern the balance between immune protection and pathology remain unclear. We observe that mast cells, which are granulated immune cells that are distributed throughout connective tissues and lining blood vessels, are strongly activated by dengue virus in vivo. At sites of skin infection, mast cells release granules containing vasoactive mediators and produce chemokines that promote the recruitment of NK cells and NKT cells, leading to viral clearance from the skin and draining lymph nodes. Thus, mast cell activation contributes to immune defense during localized, cutaneous dengue infection. However, during systemic infection, we observe that mast cell-derived vasoactive products, including proteases and leukotrienes, become elevated in the serum of experimentally infected animals and that this promotes vascular leakage. Treatment of infected animals with mast cell-stabilizing drugs or a leukotriene receptor antagonist restores vascular integrity, supporting that excess mast cell products can mediate dengue immune pathology. Validation of these findings using human clinical samples revealed that the mast cell-specific product, chymase, is a predictive biomarker distinguishing the mild and severe forms of disease, with a direct correlation between levels of systemic mast cell activation and dengue severity. These findings open new avenues of research surrounding the topics of dengue immunity and pathogenesis and reveal potential cellular and molecular targets for developing dengue prognostic tools and for therapeutics to prevent dengue-induced vascular pathology.



Dr. Dahai Luo

Nanyang Assistant Prof

NTU

Dissecting the Molecular Details of Viral RNA Sensing and Response by the Innate Immune Receptor RIG-I

Retinoic acid inducible gene I (RIG-I) is a major cellular pathogen recognition receptor (PRR) that senses viral RNA pathogen associated molecular patterns (PAMPs) in the cytoplasm of infected cells. RIG-I recognizes a broad spectrum of viruses, including the negative-stranded vesicular stomatitis virus, influenza, and rabies viruses; and also positive-stranded viruses such as dengue and hepatitis C virus. Upon binding and activation by viral RNA, RIG-I recruits the adaptor protein IPS-1 (also known as MAVS, CARDIF or VISA). This leads to the activation of antiviral responses mediated by type I interferon (IFN) and inflammatory cytokines.

To understand the molecular basis of this process, I determined the first crystal structure of RIG-I in complex with double-stranded RNA. The dsRNA is sheathed within a network of protein domains that include a conserved "helicase" domain (HEL), a specialized insertion domain (HEL2i), and a C-terminal regulatory domain (CTD). A V-shaped pincer connects the HEL2 and CTD by gripping a α-helical shaft that extends from HEL1. More recently, I captured RIG-I in complex with a 5'-triphosphorylated RNA stem-loop similar to that of influenza and other viral RNAs. By comparing structures of RIG-I/RNA complexes that are bound to nucleotide analogs, and combining this information with biochemical data from analytical ultracentrifugation studies, we establish the structural basis for ATP- stimulated RIG-I activation. Extensive structural rearrangements upon RNA binding are likely to activate the N terminal caspase activation and recruitment domains (CARDs). It reveals a complex interplay between conserved motor domains, accessory mechanical domains and RNA, thereby expanding our understanding of the structural and functional diversity of molecular machines. My on-going effort is to define the very basic molecular activator of RIG-I by applying a combination of structural, biochemical, biophysical, and *in vivo* approaches. The findings can guide therapeutic development targeting RIG-I.

*Address: 3 Fusionopolis Way, Symbiosis, Singapore 138633
Nearest Bus Stop: Bus 91 (walk 1 min from bus stop B18051)
Nearest MRT Station: One-North CC23 (walk 1 min from Exit C)

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