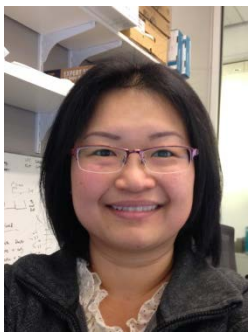
SIgN Immunology Seminar



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RIG-ging the host innate immune response for antiviral therapy

Host
Dr Katja Fink
Singapore Immunology Network, A*Star

Date
Tuesday
22 December 2015

Time
11am – 12pm

Venue
SIgN Seminar Room
Immunos Building
Level 4
Biopolis

Retinoic acid inducible gene I (RIG-I) is an intracellular pathogen recognition receptor that senses viral nucleic acids from RNA viruses and is essential for directing and priming the host immune response to limit virus infections. RIG-I signaling initiates antiviral programs that restrict virus infection and activate many cell types, including dendritic cells and macrophages for antigen presentation and cytokine production. A diverse small molecule library was used in a cell-based screening approach to identify drug-like compounds that target the RIG-I signaling pathway. We identified small molecule compounds that activate IRF3, a key transcription factor to differentially induce discrete subsets of innate immune and antiviral genes. We hypothesize that these compounds will induce tissue-wide innate antiviral immunity that can be effectively used in therapeutic approaches to control RNA virus infections. We tested a class of hydroxyquinoline compounds for the ability to suppress infection by a broad range of RNA viruses. Compound administration significantly decreased the viral RNA load and infectious virus production in cultured cells that were infected with viruses of the families *Flaviviridae*, *Filoviridae*, *Orthomyxoviridae*, *Arenaviridae* and *Paramyxoviridae*. We show that compounds from a second class of benzothiazole compounds directly engage RIG-I to promote its association with known signaling partners. Compound treatment resulted in the activation of IRF3 and NF-kB transcriptional programs that feature the expression of many innate immune genes, chemokines and cytokines and additionally promoted the maturation of dendritic cells to enhance antigen driven activation of CD8+ T cells in cell culture models. Importantly, when administered to mice in combination with either an experimental influenza A virus or West Nile virus vaccine, the benzothiazole compounds enhanced protection of mice and improved clinical scores over vaccine alone in response to subsequent virus challenge. Thus, we have identified novel small molecule RIG-I agonists that activate the innate immune response. Our studies reveal the strong potential of developing small molecule RIG-I agonists as broad-spectrum antiviral agents to control RNA virus infection or as adjuvants to potentiate vaccine immunity.