SIgN Immunology Seminar

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Replicase proteins of chikungunya virus both generate and antagonize antiviral responses

Host
Dr Lisa Ng
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Date
Monday
16 March 2015

Time
11am – 12pm

Venue
SIgN Seminar Room
Immunos Building
Level 4
Biopolis

Alphaviruses are small positive strand RNA viruses from family Togaviridae. In nature they are transmitted by mosquitoes. Replication of alphaviruses in mosquitoes is largely non-pathogenic. In contrast, alphaviruses are pathogenic to their vertebrate hosts and several of alphaviruses, including Chikungunya virus (CHIKV), are important human pathogens.

CHIKV expresses virus-specific part of the replicase in form of polyprotein precursor. This precursor is subsequently cleaved by protease activity of nsP2 to form early and subsequently late replicase. Early replicase consists from uncleaved P123 polyprotein and nsP4 and responsible for synthesis of negative-strand RNA. Late replicase consists from mature nsP1-nsP4 proteins and synthesizes positive-strand RNAs: new genomes and subgenomic RNAs for structural proteins. Alphavirus ns-proteins are known to have multiple enzymatic and non-enzymatic functions which are crucial for virus replication. In cells the replication proteins interact with each other and with viral RNAs forming replicase complexes. Our studies have revealed that formation of functional replicase complexes is strictly dependent from expression and precise regulation of ns-polyprotein processing. Mutations inactivating crucial enzymatic activities of ns-proteins block or modulate activities of replicase complexes. Furthermore, mutations shown to reduce cytotoxicity of CHIKV infection compromise both enzymatic activities of CHIKV nsP2 and activities of replicase complexes.

In last few years we have described novel mechanism how related alphavirus, Semliki Forest virus (SFV) induces strongly enhanced interferon (IFN) synthesis. Surprisingly, it was found that native CHIKV replicase completely lacks such property. Using a panel of mutant CHIKV replicases it was found that the ability to induce IFN production via production of non-viral PAMP RNAs is property of early, but not late, replicase complex. Early replicase of CHIKV is less stable than that of SFV resulting in higher specificity of template selection. Comparison of replicases of two viruses allowed identification of molecular determinants, crucial for production of IFN-inducing molecules of non-viral origin. When introduced into CHIKV genome, such changes had minimal, if any, effect on virus replication but activated the alternative IFN-induction pathway; corresponding replicases and viruses are characterized by strongly elevated IFN induction.