A Journey with Flaviviruses

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Abstract
Flaviviruses are small positive-strand RNA viruses with high medical importance. The main virus of concern in the tropical and sub-tropical region is dengue where infections are now detected in previously naïve regions. Another virus which holds threat is West Nile virus which recently gained endemicity in the Western hemisphere. Despite the prevalence of such infections, there is poor understanding of the mechanism of infection and replication of these viruses. A task was undertaken to study the flavivirus infection and replication in cells. The study on the early events of virus infection led to the discovery of αVβ3 integrin as the cellular receptor used by West Nile virus for entry. It was found that calpain affected actin filament reorganization which in turn promoted the critical alpha-beta heterodimer formation for integrin. This resulted in more efficient virus entry into host cells. Documentation of virus entry through clathrin-mediated endocytosis and transportation of the virus particles on the microtubule network to the perinuclear region for uncoating was achieved. Functional studies performed on the roles of the structural proteins during the virus assembly process found the capsid protein to have multiple non-structural roles in the virus replication process. This protein interacted with many host proteins in both the cell nucleus and cytoplasm paving the way for successful virus replication and assembly. Flaviviruses have also evolved strategies to evade and/or antagonize intrinsic cellular antiviral mechanisms. One of these antagonizing viral proteins is the endoplasmic reticulum (ER)-targeted NS1 (sNS1). The feasibility of anti-viral activity exerted through ectopic direct activation of the entire panel of IFN-stimulating genes (ISG) was examined. As a proof of concept, an engineered pharmacophore was shown to reduce West Nile virus titre by approximately 100-fold in wild-type virus challenge studies.

Selected Publications