Investigating the Role of Signal Transducer and Activator of Transcription 3 (STAT3) in Dengue Virus Propagation

Dengue fever is an arthropod-borne viral infection affecting millions of people annually during the breeding season of its vector mosquito. To date, no specific antiviral drug or vaccination is invented to fight against dengue virus. Since viruses depend on host factors for their propagation, recent approaches to developing antivirals include targeting host factors for inhibiting viral propagation. DENV has developed several co-existing strategies to avoid eradication by the host antiviral mechanism. DENV modulates host interferon response by attenuating its components, inhibiting their activation or promoting their degradation. This dissertation summarizes the studies we carried out to identify the role of a host transcription factor; STAT3 in dengue virus propagation to identify its potential as a suitable antiviral target. We first wanted to understand how DENV manipulates STAT3 induced interferon response to its benefit. By utilizing various cell culture techniques, we found that STAT3 is increased and activated in DV-2 infected A549 cells and knocking it out resulted in a substantial decrease in viral protein production and viral replication. Our results also demonstrated that DV-2 purposefully manipulates STAT3, which negatively regulates type I IFN signaling, to avoid host interferon response. These results thus established the role of STAT3 as a proviral factor. Moving ahead, we explored the potential of STAT3 inhibitor stattic as an antiviral agent. For this we performed a whole proteome analysis of infected cells by high throughput liquid chromatography mass spectrometry (LC-MS), wherein we observed that treatment with stattic induces multiple host defense mechanisms to counteract dengue infection. We also observed that treatment with stattic downregulates several pathways involved in viral transcription. Taken together these results suggest that inhibiting STAT3 by stattic or its derivatives may prove to be an effective strategy for the development of antiviral interventions.
Furthermore, to identify residues of STAT3 for the development of novel therapeutics we explored its interaction with some of the viral proteins translocating into the nucleus e.g., capsid and NS5 we identified some critical residues which mediate the interaction of STAT3 with viral NS5 protein. Since both STAT3 and NS5 are important antagonists of human innate immune response we propose that targeting the residues which mediate their interaction may aid in the screening of alternative antivirals against dengue. Overall, this study strongly indicates the regulatory role of a host transcription factor STAT3 in modulating viral propagation that may be targeted for the development of effective antiviral therapeutics.