Interaction and modulation of the human complement system by chikungunya virus.

Complement system is one among the major effectors of the innate arm of the immune system. It acts as a canonical first line of defence against a multitude of pathogens and altered host cells. Both enveloped and non-enveloped viruses have been shown to activate complement resulting in virus neutralization. Facing constant selection pressure during co-evolution, viruses have acquired a range of countermeasures to circumvent the complement system. These include targeting key molecules and enzymatic complexes within the system, hijacking host complement-regulators, encoding functional homologs of complement proteins, encoding proteases that inactivate complement and the inhibition or the downregulation of the synthesis of complement proteins.

Chikungunya virus (CHIKV) belongs to the genus Alphavirus of the Togaviridae family. It is an emerging pathogen capable of causing explosive outbreaks. Complement activation, directly or indirectly plays an important role in limiting viral dissemination, thereby largely influencing the magnitude of pathogenesis and associated disease outcomes. Prior studies with related alphaviruses showed that exacerbation in arthritogenic alphavirus-induced pathogenesis is due to its interaction with multiple immune components, including the complement system. Viremia, concomitant to CHIKV infection makes the exposure of the virus to complement inevitable, yet very little is known about CHIKV-complement interactions. The overall goal of the project was to decipher the complex interaction between CHIKV and the complement system.

Chikungunya virus, like other viruses, was found to activate complement, but unlike many of them, it could effectively resist complement-mediated neutralization. Although gradient-purified virus could activate complement, CHIKV-infected cells failed to do so. While antibodies from seropositive individuals could effectively neutralize CHIKV, a synergistic enhancement in complement-dependent neutralization was not observed. Although complement activation by CHIKV resulted in the deposition of key complement components C3 and C4 on the surface of the virion, it did not support virus neutralization suggesting the existence of a complement modulatory mechanism associated with the virus. The investigation into the mechanism by which CHIKV resist complement revealed that, unlike other viruses CHIKV possessed a unique complement specific factor I-like protease activity previously reported only in the case of the Nipah virus. This activity associated with CHIKV could limit complement by inactivating C3b into inactive C3b (iC3b), the complement component known to significantly contribute to disease pathogenesis following alphavirus infections. The factor I-like activity was specific for C3b, but had negligible effect on C4b, yet another complement substrate. Inactivation of C3b by CHIKV was largely dependent on the virus concentration and the concentration of the cofactor factor H, a soluble complement regulator. The origin of factor I-like protease activity associated with CHIKV raised two possibilities, whether it is (a) virus-derived or (b) host-derived factor I. Functional cofactor activity assay with factor I function-blocking antibody revealed that the antibody could specifically block the function of host factor I, but had a negligible effect on the factor I-like activity associated with CHIKV. Furthermore, a cocktail of protease inhibitors could completely inhibit the CHIKV associated factor I-like activity but had minimal or no effect on host factor I. Taken together our findings suggest that complement modulatory action of CHIKV is attributed to the factor I-like activity of viral origin.

Our study not only addresses the complement-CHIKV interaction, it also sheds light on the evasion strategies adopted by CHIKV, which might further strengthen our understanding of alphavirus-induced pathogenesis.