Probing contrasting functions of viral proteins: as assemblies for drug delivery and stimulators for host protein aggregation

Abstract

Historically, viruses have been significant contributors to morbidity and mortality in humans, which is recently exemplified by the global impact of the COVID-19 pandemic. Unraveling the virus lifecycle and developing effective therapeutics constitute critical research endeavors. Viruses hijack host cellular machinery for replication and assembly, with sustained viral infections posing a threat by compromising the host immune system, leading to potentially fatal outcomes. Recent studies indicate that viruses may facilitate the development of neurodegenerative disorders in humans. Examples include Herpes Simplex Virus-1 (HSV-1), which has been linked to Alzheimer's, Multiple Sclerosis (MS), and Parkinson's disease; Human T-cell Leukemia Virus type-1 (HTLV-1) which has been associated with tropical spastic paraparesis; and HIV, linked to the HIV-associated neurodegenerative disorder (HAND's). Thus, developing treatment strategies to prevent or slow down neurotropic virus-induced neurodegenerative disorders is a priority, which requires a deeper understanding of virus-host interaction pathways. Studying conserved sequences in viruses may be an essential tool for generating basic knowledge of such pathways. Such conserved sequences encode structural and non-structural viral proteins critical for various infection cycle stages. These sequences aid in identifying specific viruses and provide insights into conserved host-pathogen interaction techniques and can even serve as epitopes for vaccine development. In the first part of the thesis work, we sought to elucidate the functional significance of the conserved pentapeptide sequence (VGGVV) identified in Aβ and analogous aggregation-prone viral proteins, such as the Virion Infectivity Factor (Vif-1) of Human Immunodeficiency Virus 1 (HIV-1). HIV plaques, detected in the cerebral tissue of the afflicted individuals, have been found to harbor beta-amyloid protein responsible for debilitating neurodegenerative Alzheimer's disease. A meticulous examination of Vif-1 was conducted to discern its propensity for inducing aggregation in Aβ peptides. The study provided insights into the molecular mechanisms underpinning the correlation between viral infection and protein amyloid aggregation. In the second part of the thesis, we explored the possibility of utilizing virus-like particles of Chikungunya Virus (CHIKV) as protein nanocontainers for delivery of foreign material to specific cell types. CHIKV VLPs were chemically modified to allow the conjugation of small, targeting peptides on the surface. The particles were subjected to a limited denaturation strategy to allow incorporation of fluorescent dye. The engineering strategies employed here resulted in the targeting of CHIKV VLPs to bone cells and breast carcinoma cells, as well as the deposition of the packaged cargo in target cells, indicating the potential of CHIKV nanocontainers for therapeutic delivery.

Thus, this study delves into both the disease-causing aspects of viruses and the therapeutic potential of virus nanocontainers. The findings of this work may contribute to advancing our understanding of virus-host interaction and pave the way for innovative therapeutic strategies involving virus-like particles.