

Public Abstract

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Title:RESTRICTION OF HIV BY TIM-FAMILY PROTEINS AND ANTAGONISM BY NEF

T-cell immunoglobulin (Ig) and mucin domain (TIM) proteins play important roles in immune regulation and viral infections. Recent studies indicate that TIM-1 promotes the entry of a wide range of enveloped viruses, likely by interacting with virions-associated phosphatidylserine (PS). TIM-family proteins are known to be expressed on human primary CD4⁺ T cells, macrophages as well as dendritic cells, which are the major targets for HIV-1 replication. However, the functional roles of TIMs in HIV-1 infection are currently not known.

In this Ph.D. thesis work, I demonstrate that expression of TIM-family proteins, which include human TIM-1, TIM-3 and TIM-4, significantly restricts HIV-1 release from viral producer cells. Expression of TIM-1 leads to the accumulation of mature viral particles on the plasma membrane, therefore inhibiting HIV-1 production. Notably, TIM-1 mutants that are defective for PS binding fail to block HIV-1 release, indicating that the interaction of TIM-1 and PS is required for TIM's inhibitory effect. Similar to other well-documented host restriction factors such as tetherin, TIM-1 is incorporated into nascent HIV-1 virions. In addition to HIV-1, I also find that TIM-1 is able to inhibit the release of other viruses such as murine leukemia virus (MLV) and Ebola virus (EBOV). Importantly, knockdown of endogenous TIMs in human macrophages promotes HIV-1 production, suggesting that TIM-family proteins can function as general intrinsic inhibitors of viral release.

HIV-1 accessory proteins play a critical role in antagonizing host restriction factors. I show in my Ph.D. thesis work that compared to wildtype and other variants, Nef-deficient HIV-1 particles are much more potently inhibited by TIM-1 for release. Consistent with this finding, ectopic expression of Nef efficiently overcomes the TIM-1 restriction of HIV-1. HIV-1 Nef does not appear to significantly downregulate TIM-1 expression on the cell surface, nor does it disrupt TIM-1 incorporation into HIV-1 virions. Interestingly, coexpression of SERINC3 and SERINC5 potentiates the ability of TIM-1 to inhibit HIV-1 release, and depletion of SERINCs in viral producer cells relieves the TIM-1 restriction of HIV-1 release. In addition to HIV-1 Nef, I find that the Nef proteins of simian immunodeficiency virus (SIV) and HIV-2 also antagonize the antiviral activity of TIM-1, suggesting an evolutionarily conserved role of the lentiviral Nef in counteracting TIMs.

Taken together, my Ph.D. thesis work has revealed a novel function of TIM-family proteins during HIV-1 infection, which strongly restricts viral release from the plasma membrane. Additionally, I demonstrate that lentivirus Nef proteins have evolved an efficient strategy to overcome the inhibitory effect of TIMs. The data I described in my Ph.D. thesis provide new insights into HIV-host interactions, particularly the interplay between TIMs, SERINCs and HIV-1 Nef.