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

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ABSTRACT

T-cell immunoglobulin (Ig) and mucin domain (TIM) proteins play an important role in promoting the entry of a wide range of enveloped viruses by interacting with virions-associated phosphatidylserine (PS). However, the roles of TIMs in HIV-1 infection are poorly understood.

In this Ph.D. thesis work, I demonstrate that expression of TIM-family proteins restricts HIV-1 release in viral producer cells by retaining mature viral particles on the plasma membrane. 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-mediated restriction. Consistent with this finding, knockdown of endogenous TIMs in human macrophages promotes HIV-1 production, suggesting that TIM-family proteins function as intrinsic inhibitors of viral release.

HIV-1 accessory proteins play a critical role in antagonizing host restriction factors. I show in this work that expression of TIM-1 exhibits stronger inhibition of the release of Nef-deficient HIV-1 compared to wildtype. Consistently, ectopic expression of Nef overcomes the TIM-1 restriction. 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 TIM-1-mediated restriction. My Ph.D. thesis work has provided new insights into HIV-host interactions, particularly the interplay between TIMs, SERINCs and HIV-1 Nef.