

Abstract

Dendritic cells (DCs) are the sentinels of the immune system, and thus specialized in transporting foreign antigen to T cells and initiating activation of innate and adaptive immune responses. In this work, we first explore how DCs sense viral pathogens and stimulate antigen-specific T cell responses. In particular, we find the DC-targeting HIV-1 derived lentiviral vector (LV) is a potent T cell vaccine in vivo. However, the exact mechanism behind such efficient immunization is not clear. Interestingly, we find that DC activation is triggered by cellular DNA packaged in LVs and at least partially dependent on the STING protein. Innate immune activation is independent of MyD88, TRIF and IPS-1, ruling out an involvement of Toll-like receptors or RIG-I-like receptor signaling. Further, we find that antigenic protein delivered in viral particles via pseudotransduction is sufficient to stimulate an antigen-specific immune response. Delivery of the viral genome encoding the antigen increases the magnitude of this response in vivo, but is irrelevant in vitro. Thus, pseudotransduction, genomic transduction, and STING-mediated activation thus collaborate to make the DC-targeted LV a uniquely powerful immunogen. In addition, we explore how DCs mediate HIV-1 infection of T cells via cell-to-cell infection. In particular, we assess how DC-to-T cell transmission of HIV-1 allows for a concentrated amount of virus to be directed to an uninfected T cell. We report that DCs amplify the efficiency of T cell infection, resulting in anti-retroviral drug insensitivity compared to T cell infection in the absence of DCs. The DC-mediated amplification and drug-insensitivity of T cell infection are both entirely dependent on physical cellular interactions. Further, we find that the input of a virus is important to the drug insensitivity of DC-to-T cell infection, but not DC-free T cell infection. Thus, we have studied two separate roles of DCs: initiating immune responses to LVs and mediating transmission of infectious HIV-1. The study of these roles is important to discovering novel immune adjuvants and identifying targeted therapeutics to inhibit viral dissemination.