HIV's Ticket to Ride: Cytotoxic T-Lymphocyte-Activated Dendritic Cells Exploited for Virus Intercellular Transfer

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FIG. 1. Live-cell differential interference contrast image of eukaryotic green fluorescent protein (EGFP)-expressing HIV-1-like particles trafficking via dendritic cell (DC) membrane bridges.

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FOR HIV-1 TO EFFECTIVELY ESTABLISH infection and persistence, it must circumvent host immune detection. The capacity of HIV-1 to efficiently mutate and generate multi-variant strains in response to host immune selective pressure provides the virus with a particularly effective means of evading cytotoxic T-lymphocyte (CTL) recognition and elimination.¹ However, a novel concept has emerged suggesting that HIV-1 can actually benefit from the strategic “baiting” and partial activation of HIV-1-specific CTL responders.² Driven by immune pressure, CTL epitope divergence can result in the occurrence of surviving epitope variants capable of selectively activating the helper activity of preexisting cross-reactive CTL to create a safe haven for the virus within antigen-presenting dendritic cells (DC). Instead of dampening the immune response through CTL recognition and subsequent killing of these HIV-1 antigen-expressing DC targets, a dysfunctional CTL:DC cross-talk occurs. As a result, these DC become activated and programmed to differentiate into proinflammatory cells displaying unique features that contribute to viral dissemination and persistence.²

We have found that CTL-activated DC are capable of producing high levels of proinflammatory cytokines such as interleukin (IL)-12 and IL-6, but also simultaneously express some immunosuppressive factors such as IL-10 and PD-L1, which may contribute to their resistance to direct cellular attack. They are also programmed to produce a wide range of chemokines, including CCL4, CCL5, CXCL9, and CXCL10, that can preferentially attract activated CD4⁺ T helper (Th) cells, the main target of HIV-1 infection. Moreover, the production of CCL19 by these DC also promotes their interaction with CCR7⁺/CD45RA⁺ naive Th cells as well as CCR7⁺/CD45RO⁺ central memory Th cells, the major cellular reservoir of latent HIV-1.³ During this secondary interaction with Th cells, these CTL-programmed DC uniquely undergo fantastic morphological changes, characterized by their rapid development of numerous, far-reaching tunneling nanotube-like membrane protrusions. This intriguing phenomenon ultimately leads to the formation of complex nanotube networks, which facilitate the direct transfer of both cell surface and cytoplasmic components between interconnected neighboring and distant cells. Importantly, these membrane bridges can also serve as highways for HIV-1 to utilize for efficient cell-to-cell transfer (Fig. 1).

Our findings add a new dimension to the proposed concept of “original antigenic sin”⁴ in which the promiscuous nature of preexisting CTL can be exploited by an evolving virus to modulate the functional and physical characteristics of the DC, and to create an inflammatory environment suitable for viral spread and persistence within the host. These findings also highlight the need to consider the detrimental potential of selectively activating dysfunctional memory CTL responses when implementing anti-HIV-1 vaccine strategies.

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Author Disclosure Statement

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