Mast Cells as Reservoirs for HIV Latency
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More than a decade ago, Bannert and colleagues first reported that human mast cell (MC) progenitors are susceptible to infection with HIV-1 [1]. This finding was confirmed and extended by other groups in the following years [2-5] providing in vivo evidence that tissue MCs, developing from infected human MC progenitors, remain productively infected in infected people [4]. Moreover, evidence was shown that Toll-like receptor (TLR) 2, TLR4, or TLR9 stimulation of latently infected mast cells induced re-initiation of HIV-1 replication [4].

Although this work introduced MCs as an important new reservoir for HIV-1 latency, few investigators have followed-up this important line of research. Recently CD34+ hematopoietic cell progenitors have been reported to contribute to viral persistence by serving as latent HIV-1 reservoirs in vitro and in vivo and it has been demonstrated that a switch to active infection is induced in these cells by the cytokines GM-CSF and TNF-a [6]. This report should reawaken interest in the potential role of MC progenitors in maintaining HIV-1 infection. At the same time, it raises a number of new questions, not only on the role which MCs play in HIV-1 infection but also on basic aspects of MC biology and differentiation.

Firstly, it remains to be clarified whether, in vivo, HIV-1 infects only MC progenitors or also fully differentiated MCs; secondly, whether HIV-1 shows differential tropism for MC progenitors versus mature MCs (CCR5 versus CXCR4-tropic HIV). One report indicates that HIV-1 does not infect primary human mature MCs derived from placental tissues [4]. Whether this finding is specific to placental-derived MCs or universal to all mature MC populations has still to be established.

Thirdly, which MC activation stimulus most effectively induces viral reactivation? Stimulation of the TLR-mediated signaling pathways in MC has been identified as one mode for HIV-1 reactivation in latently infected MCs [3]. What remains unclear is whether this effect can be extended to non-TLR and nonclassical agonists, and if it is relevant in vivo, e.g. during co-infection. It will be interesting to define to what extent allergens, hormones and neurotransmitters display a similar activating effect.

But fourthly, and most importantly, how critical the contribution of MC infection is to HIV infection, persistence and reactivation. Since mature MCs are very long-lived cells, in principle they offer a potentially dangerous viral reservoir making viral eradication difficult. Given the many other cell populations that are recognized as HIV-1 reservoirs (e.g., macrophages, dendritic cells, astrocytes, B cells, microglial cells, and of course CD4+ memory T cells) [7-12], how clinically relevant are MCs as an HIV reservoir?

As long-lived cells which populate virtually all tissues, are strategically positioned in close proximity to blood vessels and at epithelial interfaces exposed to environmental factors [13], MC are ideally suited to serve as viral latency reservoirs. Furthermore, whilst MC reside within defined tissue environments, under inflammatory conditions they have the ability to migrate to lymph nodes and central immune organs such as the spleen [14]. This potentially would allow contact with highly HIV-susceptible CD4+ T cells and thus sustained dissemination of the virus.

In summary, since latently infected MCs are protected from immune effector mechanisms or antiretroviral therapeutic agents it is important to experimentally better define the contribution of MCs to viral persistence.

References


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