OA1-1

Viral protein U (Vpu) reduces innate sensing of human immunodeficiency virus type 1 (HIV-1)- infected T cells by plasmacytoid dendritic cells (pDCs) via a BST2- dependent process

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Background: BST2 is an interferon (IFN)-induced transmembrane protein that strongly restricts the release of HIV-1 by cross-linking nascent virions on infected cell surface. HIV-1 antagonizes BST2 restriction through Vpu, an accessory protein that downregulates BST2 at the cell surface. Apart from its function as an intrinsic antiviral factor, BST2 has been shown to inhibit TLR7/9-mediated type 1 IFN production in pDCs by engaging ILT7, an inhibitory receptor selectively expressed in these cells. Given that pDC's anti-HIV-1 responses are essentially resulting from TLR7-mediated sensing of infected cells, we examined whether Vpu could modulate detection of HIV-1 infection by pDCs.

Methods: PBMCs or isolated pDCs were co-cultured with T cells infected with wild type (WT) or Vpu-defective (ΔVpu) HIV-1 and innate sensing was evaluated by assessing the levels of IFN released in supernatants 22h later.

Results: Innate sensing of HIV-1-infected MT4 and primary CD4+ T cells by PBMCs was found to be significantly reduced in a Vpu-dependent manner. This effect of Vpu was linked to partial reduction of surface BST2 levels and absence of restricted virions on infected cell surface. Furthermore, downregulation of innate sensing by Vpu was shown to be independent of co-receptor usage, as both R5 and X4 HIV-1-infected cells were sensed with similar reduced efficiency as compared to their ΔVpu counterparts. As previously reported, most of the sensing of HIV-1-infected T cells relied on the presence of pDCs. Interestingly, shRNA-directed depletion of BST2 in HIV-1-infected T cells abrogated the Vpu-mediated downregulation of innate sensing and as such allowed pDCs to sense equally well WT or ΔVpu HIV-1-infected cells. Thus, reduction of innate sensing by Vpu relies on a process that is critically dependent on BST2, excluding the possibility that restricted virion clusters at the surface of ΔVpu HIV-1-infected cells might be sensed more efficiently by pDCs. **Conclusions:** Overall, these findings indicate that Vpu-mediated BST2 antagonism allows HIV-1 to dampen-down pDC-mediated sensing and IFN production via a process that likely relies on BST2/ILT7 engagement. Thus, through a highly sophisticated regulation of surface BST2 levels, Vpu appears to promote HIV-1 release while at the same time interfering with pDC antiviral responses.