

Intrinsic cellular defences and restriction factors

PE3

HIV-1 Vpu exploits the crosstalk between BST2 and the ILT7 receptor to inhibit innate sensing of infected T-cells by plasmacytoid dendritic cells

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Background: Plasmacytoid dendritic cells (pDCs) constitute a major source of type-I interferon (IFN-I) production during acute HIV infection. Their activation results primarily from TLR7-mediated sensing of HIV-infected cells. BST2/Tetherin is a restriction factor that suppresses HIV release by cross-linking virions at the cell-surface. HIV-1 overcomes BST2 antiviral activity through Vpu, which partially downregulates BST2 cell-surface expression. Apart from its direct antiviral activity, BST2 was shown to bind the ILT7 pDC-specific inhibitory receptor and repress IFN-I production by activated pDCs. Here, we examined whether Vpu-mediated BST2 antagonism could modulate innate sensing of HIV-infected cells by pDCs.

Methods: PBMCs or isolated pDCs were co-cultured with T cells infected with wild type or Vpu-defective HIV-1 and innate sensing was evaluated by monitoring IFN-I production. BST2-mediated activation of ILT7 signaling was analyzed using an ILT7-reporter cell system.

Results: We show that Vpu attenuates the production of IFN-I during sensing of HIV-1 infected cells by pDCs. This control of innate sensing by Vpu could be prevented by: 1) depletion of BST2 from infected donor cells; 2) depletion of ILT7 in pDCs; or 3) blocking BST2-ILT7 interaction using anti-BST2 antibodies or soluble ILT7. Using a BST2 mutant that cannot cross-link budding virions but yet retains the capacity to repress IFN-I production by pDCs, we show that virion trapping on infected donor cells prevents BST2 from eliciting an inhibition of IFN-I production by pDCs. Interestingly, confocal microscopy analysis of virus producing cells reveals that in presence of Vpu there is a residual pool of surface BST2, which is excluded from viral budding sites and thus potentially accessible for interaction with ILT7 on pDCs. Lastly, using an ILT7 reporter cell system, we provide evidence that Vpu-mediated BST2 antagonism modulates the levels of available surface BST2 capable of engaging and activating ILT7 upon cell-to-cell contact.

Conclusions: Overall, this study sheds light on a novel Vpu-BST2 interaction that allows HIV to control innate sensing of infected cells by pDCs via the negative signaling exerted by the ILT7-BST2 pair. This mechanism of innate immune evasion is likely to be critical for efficient viral dissemination and establishment of viral reservoirs during acute infection.