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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Abstract

Background

BST2 (also known as Tetherin) has three known functions:
- It restricts the release of HIV-1 by cross-linking virions to infected cell surface GPI-anchored proteins (GPIs) on the cell surface.
- It acts as a sensor of virus assembly and triggers signaling through NF-kB in infected T cells.
- It inhibits TNF-mediated type I IFN production in pDCs by engaging the A17 pDC-inhibitor receptor.

Experimental Design

GFP-expressing NL4-3 WT/ILT7+ (donor) HIV.

Results

Role of Vpu during innate sensing

During HIV-1 infection, Vpu is capable of controlling IFN-I production by pDCs.

‘Free’ BST2 is found on the surface of WT HIV-1-infected T cells

In the presence of Vpu, the long BST2 isoform is degraded, while both isoforms are displaced from viral assembly sites.

In summary

- Innate sensing of HIV-1-infected MT4 and primary CD4+ T cells by pDCs was found to be significantly suppressed in the presence of Vpu.
- Depletion of BST2 or ILT7 on donor cells or pDCs, respectively, as well as blocking of BST with anti-BST antibodies or a soluble form of ILT7 abrogated Vpu-mediated downregulation of innate sensing, suggesting that Vpu exploits the cross-talk between BST2 and ILT7 to suppress anti-HIV responses by pDCs.
- In the presence of Vpu, residual BST2 molecules, consisting mostly of short isoforms, are detected outside of viral assembly sites where they are free to interact with ILT7.
- In the absence of Vpu, entrainment of progeny virions by BST2 inhibits the interaction between BST2 and ILT7.
- Vpu-mediated suppression of IFN-I production requires engagement and activation of the ILT7 pDC inhibitory receptor by BST2.

Through a highly sophisticated targeted regulation of BST2 isoforms, Vpu promotes HIV-1 release and interferes with pDC antiviral responses.

Model

In DU HIV-1-infected cells:

Vpu partially downmodulates surface BST2 and relocalizes remaining molecules outside viral assembly sites where they are free to interact with ILT7.

In WT HIV-1 infected cells:

Vpu partially downmodulates surface BST2 and relocalizes remaining molecules outside viral assembly sites where they are free to interact with ILT7.

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The datasets presented in this study can be found in online repositories. The names of the repository/repositories and access number(s) are listed in the results section of the manuscript.

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Data availability

The datasets generated for this study are available on request to the corresponding author.