How HIV-1 uses a non-canonical autophagic pathway to overcome BST2 restriction factor

Clarisse Berlioz-Torrent, Institut Cochin, Paris.
clarisse.berlioz@inserm.fr

HIV-1 (Human immunodeficiency virus type 1) remains a major global public health issue, with over 650,000 deaths attributed to its infections in 2021. In the battle against the spread of HIV-1 but also other viruses, the host immune system has developed an arsenal of defenses, including intrinsic cellular mechanisms that involve complex interactions between viral and cellular proteins. Host restriction factors are an important facet of these innate defences against the virus. Amongst them, BST2 / Tetherin exerts its antiviral activity on numerous enveloped viruses by physically retaining newly formed viral particles at the surface of infected cells, efficiently blocking their dissemination. Additionally, BST2 acts as a sensor for infection, triggering an antiviral state within the infected cells.
Lentiviruses, including HIV-1, have undergone evolutionary adaptations and developed diverse strategies to overcome cellular barriers. Through protein-protein interactions involving viral accessory proteins, lentiviruses often target restriction factors to degradation. The Vpu accessory protein of HIV-1 is one of the strategies developed by the virus to counteract BST2. Vpu reduces the presence of BST2 at the viral budding sites by modifying BST2 intracellular trafficking and degradation. In our team, we revealed that Vpu *via* its interaction with the autophagy-related protein LC3C subverts a cellular degradation mechanism, resembling LC3-associated pathways, to counteract BST2 antiviral activities. The LC3-associated pathway is a non-canonical autophagy process controlled by a subset of ATG proteins, linking activation of a surface receptor with phagocytosis or endocytosis. This pathway has a prominent anti-inflammatory function and represents a key cell intrinsic restriction mechanism against infections. We recently conducted a detailed examination of the initial events that lead to the targeting of BST2 into an LC3C-associated pathway subverted by Vpu and highlighted that HIV-1 uses this pathway to attenuate the inflammatory responses triggered by BST2-mediated sensing of viruses

The autophagy-related protein ATG5 is a central mediator of a non-canonical autophagy pathway hijacked by HIV-1 to weaken the host's response to infection. Judith D, Berlioz-Torrent C. Autophagy. 2023 Jul 9:1-3.

ATG5 selectively engages virus-tethered BST2/tetherin in an LC3C-associated pathway. Judith D, Versapuech M, Bejjani F, Palaric M, Verlhac P, Kuster A, Lepont L, Gallois-Montbrun S, Janvier K, Berlioz-Torrent C. Proc Natl Acad Sci U S A. 2023 May 16;120(20):e2217451120.

LC3C Contributes to Vpu-Mediated Antagonism of BST2/Tetherin Restriction on HIV-1 Release through a Non-canonical Autophagy Pathway. Madjo U, Leymarie O, Frémont S, Kuster A, Nehlich M, Gallois-Montbrun S, Janvier K, Berlioz-Torrent C. Cell Rep. 2016 Nov 22;17(9):2221-2233.