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Poster presentation

Mechanistic study of BST-2 down-modulation by HIV-1 Vpu

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Background

Mammals encode proteins that inhibit viral replication at the cellular level. In turn, certain viruses have evolved genes that can counteract these intrinsic restrictions. Human BST-2 (bone marrow stromal cell antigen 2, also named CD317/HM1.24/tetherin) is recently identified an IFN-induced antiviral protein that blocks release of human immunodeficiency virus type 1 (HIV-1) from the cell surface. This antiviral activity of BST-2 is counteracted by HIV-1 Vpu. Our group as well as the others have generated data showing that Vpu antagonizes human BST-2 (hBST2) but not BST-2 from African green monkeys (agm BST-2).

Methods and Results

Through mutagenesis study, we have mapped the determinants of sensitivity to Vpu to several sites within the transmembrane domain of agmBST-2, with deletion of the 22-LL-23 residues conferring the highest degree of resistance to Vpu. This resistance activity is further shown as a result of a weak association of agmBST-2 or the hΔLL22/23 mutant with Vpu and a refraction of these BST-2 proteins to down-modulation by Vpu. With the aim of assessing the involvement of the proteasome and the lysosome degradation pathways in Vpu-mediated down-modulation of hBST-2, specific proteasome inhibitors and lysosome inhibitors were tested for their ability of rescuing hBST-2 expression in the presence of Vpu. The results show that the proteasome inhibitors ALLN and MG132 restore hBST-2 expression to the control level, whereas, lysosome inhibitors chloroquine (CQ) or bafilomycin A1 (BafA1) partially blocks down-modulation of hBST2 by Vpu. To determine whether ubiquitination serves as the signal that triggers hBST-2 down-modulation, we first co-transfected the HA-ubiquitin DNA together with hBST-2 DNA in the presence or absence of Vpu. A specific HA-ubiquitin signal was not observed for hBST-2 with Vpu expression. Moreover, when the only two lysine residues (K18 and K21) within the cytoplasmic domain of hBST-2 were mutated, the K(18,21)R mutant is still sensitive to Vpu-induced down-modulation and is unable to restrict production of wild type HIV-1.

Conclusion

Taken together, our results suggest that Vpu triggers hBST-2 down-modulation mainly through the proteasome pathway. The down-modulation event may be triggered by signals other than direct ubiquitination of hBST-2.