Retrovirology

Poster presentation

Autophagy plays an essential role in HIV-1 infection

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HIV-1 can infect and replicate in both CD4 T cells and macrophages, and direct cell-to-cell spread is an important route of HIV-1 propagation. It requires interaction between HIV-1 envelope glycoproteins (Env, composed of gp120 and gp41), expressed at the surface of infected cells, and HIV-1 receptors, CD4 and a coreceptor, on the target cells. The gp120 interacts first with CD4, which triggers conformational changes leading to increased exposure of gp120 regions (including the V3 loop) able to bind to the coreceptor, mainly CCR5 or CXCR4. This interaction induces a structural rearrangement in gp41, insertion of its N terminus fusion peptide into the target membrane, and fusion. R5 and X4 HIV-1 strains use CCR5 and CXCR4, respectively, for entry. We have previously demonstrated that, independently of HIV-1 replication, X4 HIV-infected cells trigger autophagy in the uninfected CD4 T lymphocytes. Env-mediated autophagy is dependent on the gp41 fusogenic activity but is independent of a direct CD4- and CXCR4-mediated signaling pathway. Furthermore, this autophagy process is required to trigger CD4 T cell apoptosis since blockade of autophagy at different steps, by either drugs or short interfering RNAs specific for autophagy genes, totally inhibits Env-mediated apoptosis. Our last results show that autophagy and cell death are also induced in the uninfected CD4 T cells by HIV-1 R5 Env, while autophagy is inhibited in productively X4 or R5-infected CD4 T cells. In contrast, uninfected macrophages, a preserved cell population during HIV-1 infection, do not undergo X4 or R5 Env-mediated autophagy. Autophagosomes, however, are present in macrophages exposed to infectious HIV-1 particles, independently of coreceptor use. Interestingly, two populations of autophagic macrophages can be observed during their coculture with HIV-1-infected cells: one highly autophagic and the other weakly autophagic. Surprisingly, viruses could be detected in the weakly autophagic cells but not in the highly autophagic cells. In addition, we show that the triggering of autophagy in macrophages is necessary for viral replication but addition of Bafilomycin A1, which blocks the final stages of autophagy, strongly increases productive infection. Taken together, our data suggest that autophagy plays a complex, but essential, role in HIV pathology by regulating both viral replication and the fate of the target cells.

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