Extracellular ATP Induces the Rapid Release of HIV-1 from Virus Containing Compartments of Human Macrophages

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A major obstacle to the eradication of HIV-1 by combination antiretroviral therapy (cART) is the formation of cellular reservoirs in CD4+ T lymphocytes and tissue macrophages. Infected macrophages assemble new virions in subcellular vacuoles known as virus containing compartments (VCC), hiding them from the immune system and, in part, from antiretroviral agents. We demonstrated that extracellular ATP is capable of inducing the rapid release of virions accumulated in VCC via interaction with the P2X7 receptor and without inducing cell death, whereas the antiprogptotic agent Imipramine blocks the release. Thus, our study identifies two "druggable" targets affecting the release of stored virions from infected human macrophages that could bear relevance for purging HIV-1 reservoirs in individuals receiving cART.

**Figure 1. Extracellular ATP Induces Release of HIV-1 Virions from Human Primary Monocyte-Derived Macrophages (MDM)**

**Figure 2. HIV-1 Virions Released from Infected MDM by ATP Stimulation Arc Infections**

**Figure 3. ATP Induces Release of Virions from MDM–Associated VCC**

**Figure 4. ATP-Dependent Virion Release from MDM Is Not Associated with Significant Cytotoxicity**

**Figure 5. ATP-Dependent Virion Release from MDM Is Controlled by P2X7R and by the Microvesicle/Ectosomal Release Pathway**

**CONCLUSIONS**

In this study, we have demonstrated that ATP is a potent inducer of virion release from VCC, a functional subcellular compartment uniquely observed in both infected and uninfected macrophages. The effect of ATP was not the result of either passive (necrosis) or active (apoptosis) cytotoxicity. The inductive effect of ATP in infected MDM is mediated, at least in part, by its binding to the parapcnic P2X7 receptor and it is prevented by Imipramine, an antidepressant agent that blocks the microvesicle release pathway. Thus, ATP represents a physiological stimulus with the capacity to induce a rapid release of performed, infectious HIV-1 virions accumulated in this VCC of macrophages. See F. Graziano et al., PNAS, June 8, 2015.