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Extracellular ATP induces the rapid release of HIV-1 from virus containing compartments of human macrophages

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Background: The human immunodeficiency virus type-1 (HIV-1) infects CD4+ T lymphocytes and myeloid cells, in particular tissue macrophages. In comparison to T cells, infected macrophages differ both in terms of decreased to absent cytopathicity and for actively accumulating new progeny HIV-1 virions in Virus Containing Compartments (VCC). For these reasons, infected macrophages are believed to act as “Trojan horses” carrying infectious particles to be released upon cell death or functional stimulation.

Methods: The U937-derived chronically HIV-1 infected promonocytic cell line UI was differentiated into macrophage-like cells (D-UI cells) by PMA in the presence of urokinase-type plasminogen activator to favor virion retention in intracellular vacuoles and then shortly exposed to extracellular (e) ATP to induce their release. Primary human monocyte-derived macrophages (MDM) of HIV-1 seronegative donors were infected either with an R5 HIV-1 strain or with a VSVg-pseudotyped vector expressing eGFP. Both D-UI cells and MDM were stimulated with eATP to induce the release of virions from VCC. Live imaging analysis was used to study the morphological effects of eATP on HIV-1 infected macrophages.

Results: Short term (5-30 min) eATP stimulation induced massive membrane blebbing and a rapid release of mature HIV-1 infectious virions from primary human MDM infected in vitro in the absence of cell death. The same phenomenon was reproduced in chronically infected D-UI cells. Virion release was associated with a depletion of intracellular virions, as measured by intracellular p24 Gag staining and by visual imaging. Pharmacological inhibition of the microvesicle release pathway and of the ATP receptor (R) P2X7 prevented eATP-induced virion release from both acutely infected MDM and D-UI cells.

Conclusions: Short (min) eATP stimulation induces the release of HIV-1 virions in both primary MDM and in D-UI cells, via interaction with P2X7R and in the absence of significant cytopathicity. Pharmacologic interference with the microvesicle release pathway and with the P2X7R prevented this effect suggesting that they could represent novel exploitable targets for interfering with the reservoir of HIV-1 virions of infected tissue macrophages.