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NK-dependent survival of HIV-1 infected DCs. Pivotal role of HMGB1

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Background

Dendritic cells (DCs) are professional antigen-presenting cells that form cellular networks surveying for pathogens and providing the first immunological barrier to the external environment. The fate of DCs is dependent on a cross-talk with NK cells that may lead to DC's killing (editing) which is believed to keep in check their quality and quantity. Considering that HIV-1-infected DCs may become persistent viral reservoirs, we addressed the question of NK's role in infected DC's elimination as well as the mechanisms involved.

Methods

Immature DCs (iDCs) were derived from CD14+ monocytes cultured for 6 days in the presence of IL-4 and GM-CSF. iDCs were infected with R5-HIV-1BAL (DC_{HIV}). 24 h cocultures with autologous purified activated NK cells (aNK) were performed and DC's apoptosis was analyzed by multiparametric flow cytometry, combining 7-AAD staining with the detection of death/survival molecules. Gene array analyses were performed to detect variations in gene expression between different coculture conditions. siRNA magnetofection was performed to silence c-FLIP and c-IAP2 anti-apoptotic genes' expression in DCs. Live video microscopy was used to dissect apoptotic events during aNK-iDC contact.

Results

We show that, while iDCs were susceptible to NK editing, involving TRAIL/DR4 and not the perforin-pathway, DCHIV were resistant to NK-dependent cytotoxicity. We report that NK cells induce in DC_{HIV} a dramatic increase in the expression of two anti-apoptotic molecules, c-FLIP and c-IAP2, responsible for the resistance of DCHIV to TRAIL-induced apoptosis. Moreover, we found that HMGB1, a key mediator of NK-DC crosstalk, is responsible for the upregulation of these two inhibitors. The consequence of the escape of DC_{HIV} from NK cytotoxicity is an HMGB1-dependent increase in HIV replication in DCs, which is mediated by HMGB1.

Discussion

These observations show that under physiological conditions, the editing process of iDCs by NK cells occurs through rapid induction of TRAIL apoptosis in iDCs. Following HIV infection of DCs, NK cells increase DCs' survival through an HMGB1-dependant mechanism inducing c-IAP2 and c-FLIP upregulation. This study provides new insights into how HIV hijacks DCs and uses the NK-DC crosstalk to maintain viability of long-term reservoirs, and it identifies potential therapeutic targets to eliminate infected DCs.

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