Chronic SIV Infection Induces Differentiation and Accumulation of Cytotoxic CD16+ NK Cells in Lymph Nodes Followed by Transmigration to the Mucosae

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Chronic SIV infection induces differentiation and accumulation of cytotoxic CD16+ NK cells in lymph nodes followed by transmigration to the mucosae

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Background

Natural killer (NK) cells inhibit lentiviral replication both directly and indirectly, but substantial evidence also indicates HIV/SIV can induce NK cell dysfunction. NK cells can be subdivided based on expression of CD56 and CD16. In blood, cytotoxic CD16+ NK cells are the dominant subpopulation, while cytokine-secreting CD56+ and double-negative (DN) NK cells are the primary NK cells found in lymph nodes (LN). Furthermore, CD56+ and DN NK are thought to be precursor populations, whereas CD16+ NK cells are terminally differentiated. The effects of HIV/SIV infection on NK cell distribution, trafficking, and development are unclear.

Methods

Macaque NK cells were isolated from blood, LN, and mucosal tissues of naive and chronically SIV-infected animals and then analyzed phenotypically by surface and intracellular flow cytometry, evaluated functionally by ICS and in a direct killing assay against MHC-devoid 721.221 cells. In situ analyses were performed by immunohistochemistry.

Results

In peripheral blood of chronically infected animals, we found a specific expansion of CD16+ NK cells, coupled with high frequencies of cytotoxic perforin+ CD16+ NK cells in LN, where they are normally absent. Interestingly, classic LN-trafficking molecules, CD62L and CCR7, were downregulated to undetectable levels on blood and LN CD16+ NK cells, suggesting they did not migrate from extralymphoid tissues. Furthermore, the putative NK cell precursors, CD56+ and DN NK cells, exhibited increased proliferation and activation, providing a potential source of differentiated CD16+ NK cells. CD16+ NK cells in LN also upregulated the mucosa-trafficking marker, $\alpha 4\beta 7$, correlating with increased frequencies of cytotoxic CD16+ NK cells in colorectal and jejunum tissues of infected animals.

Conclusion

Our data suggest a novel mechanism whereby lentivirus infection induces differentiation of cytotoxic CD16+ NK cells, which are normally absent in LN, to differentiate in situ and then transmigrate to the gut mucosa, the primary site of virus replication.

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