DC infected by the ANRS MVA\textsubscript{HIV} vaccine candidate prime NK cells with anti-HIV specific activity through a mechanism involving NKG2D and NKP46 on NK cells and membrane-bound IL-15 on DC

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Introduction

Natural Killer (NK) cells are the major antiviral effector cell population of the innate immune system. It has been demonstrated that NK cell activity can be modulated by the interaction with dendritic cells (DC). The vaccine candidate Modified Vaccinia virus Ankara encoding an HIV polypeptide (MVA\textsubscript{HIV}) developed by the French National Agency for Research on AIDS (ANRS), has the ability to infect DC and to prime T cells. However, whether or not MVA\textsubscript{HIV}-infected DC are able to induce anti-HIV specific NK cell activity remains undetermined.

Objectifs

Analyze whether NK cells are able to acquire specific anti-HIV activity through the stimulation by MVA\textsubscript{HIV}-infected DC. And if so, investigate the implication of NK cell receptors as well as mblt-15 in the induction of the anti-HIV specific priming of NK cells.

Material and methods

DC were infected by MVA\textsubscript{HIV} or MVA\textsubscript{wt} vector as control and cocultured with autologous NK cells for 4 days. Then, NK cells were transferred to a culture of HIV-1-infected autologous DC or CD4+ T cells. The control of HIV-1 infection was assessed by intracellular staining of HIV-1 p24 at days 9 or 10 post-infection (p.i.) and analysis was done by flow cytometry. The implication of NKG2D and NKP46 on NK cells, and membrane-bound IL-15 (mblt-15) on DC, during the priming of NK cells was determined by using blocking mAbs.

Results

Control of HIV infection by NK cells is increased after MVA\textsubscript{HIV} Priming

MVA\textsubscript{HIV} Priming of NK cells seems to be anti-HIV specific

Increased early NK cell response against MVA\textsubscript{HIV} infected DC

Priming of NK cells by MVA\textsubscript{HIV} is modulated by NKG2D and NKP46

Conclusions

NK cells primed by MVA\textsubscript{HIV} have are better to control of HIV infection in autologous DC and CD4+ T cells. It is possible that NK cells select correctly HIV antigen loaded DC during the MVA\textsubscript{HIV} priming allowing for a specific stimulation. NKP46 blockade during MVA\textsubscript{HIV} priming increases NK cell control of HIV infection in DC, whereas blockade of NKG2D decreases NK cell control of HIV infection in DC and CD4+ T cells. NKG2D blockade decreases the expression of mblt-15, and as IL-15 is important only for MVA\textsubscript{HIV} priming, the decreased expression of mblt-15 after blockade of NKG2D might be responsible, at least in part, for the reduced HIV control.