DC infected by the ANRS MVA_{HIV} vaccine candidate primes 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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Background: 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 Ankara encoding an HIV polypeptide (MVA_{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_{HIV}-infected DC are able to induce anti-HIV specific NK cell activity remains undetermined.

Methods: DC were infected by MVA_{HIV}, or MVA_{WT} vector as control, and co-cultured with autologous NK cells for 4 days. Then, NK cells were transferred to a plate containing recently infected DC or CD4+ T cells, and p24 production was determined at days 7 and 10 post-infection by ELISA test and flow cytometry. The implication of NK cell receptors NKG2D and NKp46, and membrane-bound IL-15 (mbIL-15) on MVA-infected DC, during the priming of NK cells was determined by using blocking mAbs.

Results: We found that NK cells primed by MVA_{HIV}-infected DC are significantly better at controlling HIV-1 replication in autologous DC and CD4+ T cells as compared to those primed by MVA_{WT}-infected DC. The specificity of anti-HIV NK cell activity was determined by measuring the NK cell activity against CMV-infected DC and target cells. In depth analysis of the priming showed that blockade of NKG2D and NKp46 during the priming induced decreased and increased anti-HIV-1 NK cell activity, respectively. Blockade of NKG2D during priming of NK cells by MVA_{HIV}-infected DC endowed NK cells with a particular NK cell receptor repertoire, with a marked decreased expression of activating receptors, and resulted in lower expression of mbIL-15 on MVA-infected DC; whereas blockade of NKp46 resulted in increased expression of mbIL-15 on MVA-infected DC.

Conclusions: These data demonstrate that the MVA_{HIV} vaccine candidate is able to induce a specific anti-HIV-1 NK cell activity following their interaction with MVA_{HIV}-infected DC, and that the acquisition of such antiviral activity relies on a modulated crosstalk involving NKG2D and NKp46 on NK cells and the regulation of mbIL-15 on infected DC.