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Study of the cross talk between dendritic cells and natural killer cells in the presence of a vaccine agent against cervical cancer

Cervical cancer is the third most frequent gynaecological malignancy in the world, which is caused by infection with high-risk human papillomaviruses (HPV). HPV16 is detected in more than 50% of these tumours. At the moment there are two prophylactic HPV-L1 virus like particle (VLP) vaccines on the market. These vaccines are highly efficient to protect against HPV16 infections, but not against established infections. The induction mechanism of an immune response against HPV is still not well known. Previous studies have shown that HPV-VLP are able to activate dendritic cells (DC), demonstrated by a partially maturated phenotype and cytokine production. Our lab recently showed that the entry of HPV-VLP L1 into natural killer (NK) cells requires CD16 expression and triggers cytotoxic activity and cytokine secretion. In the literature it is also shown that there is a bidirectional cross talk between DC and NK cells. In this context, we study the effect of HPV-VLP L1 on the cross talk between DC and NK cells.

In our project we differentiate $CD14^+$ cells into DC by culturing them 6 days in the presence of IL-4 and GM-CSF. With the ImmunoTools antibodies we could check the quality of the DC collected at day 6 ($CD14^-$ $CD1a^+$) and look if they are not yet activated (CD80, CD86 and HLA-DR). We could also check the quality of the isolated NK cells ($CD3^-CD56^+$ $CD16^+$). After co-culturing DC and NK cells we could check if there is an activation of DC (CD80,CD86 and HLA-DR) and NK cells (CD69 and HLA-DR).

We confirmed DC maturation by HPV-VLP and found that VLP L1 could also induce TNF-a and IFN- γ secretion. When we co-cultured DC and NK cells in the presence of VLP L1, we observed an up-regulation of CD69 and HLA-DR cell surface expression on NK cells. This up-regulation was mediated via cell-cell contact and soluble factors. Regarding HLA-DR, we observed different mechanisms in the NK cell subsets. Soluble factors play an important role for the $CD56^{bright}$ cells whereas soluble factors and cell-cell contact are both important for the $CD56^{dim}$ cells. We also observed an increased IFN-γ production and cytotoxic activity of NK cells in the presence of DC activated by VLP L1. Interestingly, NK cells seemed to further activate DC in the presence of VLP L1 as shown by an up-regulation of HLA-DR and CD86

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on DC. This up-regulation was mediated differently for both cell surface markers. For HLA-DR, it is mediated via cell-cell contact and soluble factors and for CD86, it is only cytokine dependent. Moreover, DC in the presence of VLP L1 and NK cells increased the production of IL12p70, but not the immunosuppressive cytokine IL10.

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