Persistent infection with oncogenic human papillomavirus (HPV) genotypes is a necessary cause of anogenital cancer and HPV infections account for more than 50% of infection-linked cancers in women worldwide. The immune system controls, at least partially, viral infection and subsequent tumor development. Around 90% of HPV-infected women will clear the virus within two years. However, it remains unclear which immune cells are implicated in host resistance to virus and tumor. Since HPV cannot grow in vitro, virus-like particles (VLP) composed of L1 or L1L2 capsid proteins, were used as a model for studying the NK cell response against the virus. Interestingly, a fast entry is observed into NK cells compared to DC (Fig 1). Furthermore, virus uptake by NK cells is mediated by macropinocytosis, whereas this entry is dependent of clathrin or caveolin endocytosis pathways in DC (Fig 1-2). We investigated whether the internalization of VLP is linked to NK cell activity and a higher cytotoxic activity and cytokine production (TNF-α and IFN-γ) is observed in the presence of HPV-VLP (Fig3). Using NK cell lines expressing or not CD16 (generous gift of B. Clémenceau, France) and blocking antibody, we demonstrated that CD16 is necessary for HPV-VLP internalization, but also for degranulation and cytokine production (Fig4).

1. Rapid HPV-VLP internalization in CD16+ NK cells

2. HPV-VLP uptake in NK cells is mediated by macropinocytosis

3. HPV-VLP induce cytotoxic activity and cytokine release by NK cells

4. CD16 is required for rapid HPV16-VLP uptake and NK cell activation

Conclusions
- NK cell infiltration in HPV-associated lesions (data not shown)
- HPV-VLP entry induces cytotoxic activity and cytokine secretion by CD16+ NK cells.
- CD16 is necessary for HPV-VLP entry by macropinocytosis and NK activation.

NK cells interact with HPV and could participate in the immune response against HPV-induced tumors.