A gammaherpesvirus affects type 2 innate lymphoid cells in the context of HDM-induced asthma

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The “Hygiene hypothesis” postulates that allergic diseases could be prevented by some infections in early childhood. Gammaherpesviruses (γ-HVs) are among the most prevalent human viruses and profoundly imprint on the immune system of their hosts. Using Murid gammaherpesvirus 4 (MuHV-4), a mouse model of human γ-HV infections, we recently showed that γ-HV infection inhibits the development of House Dust Mites (HDM)-induced airway allergy (Machiels et al., *Nature Immunology*, 18(12):1310-1320 (2017)). Group 2 innate lymphoid cells (ILC2s) play a major role in the initiation, maintenance and memory of type 2 immune responses. As activation of these cells can be modulated by viruses associated with asthma exacerbation, we investigated whether MuHV-4 infection affects the lung ILC2s compartment.

1. Gammaherpesvirus infection induces persisting changes in the alveolar niche that protect against airway allergy

MuHV-4 infection induces persisting changes in alveolar microenvironments (Alves) that protect against allergies. In the absence of a previous MuHV-4 infection, resident Alve cannot prevent dendritic cells (DCs) from inducing a strong TH2 response in HDM-induced asthma. MuHV-4 virus infects all cell types of Alves and a regulatory phenotype is in the infiltrating monocytes that are differentiating into Alves. Long-term persistence of spliced-variant 1A8 induces Alve in HDM-induced asthma by selectively interfering with the ability of DCs to trigger a TH2 response, without affecting T cells’ response. The aim of this work is to understand whether MuHV-4 infection alters the alveolar microenvironment-induced effect on lung ILC2s in the context of HDM-induced asthma.

2. MuHV-4 infection affects the function of lung ILC2s after HDM sensitization

We found that lung ILC2s from MuHV-4 infected mice are less responsive to HDM sensitization and production of type 2 cytokines IL-5 and IL-13 is reduced. The TH2-like phenotype in the infiltrating monocytes that are differentiating into Alves is modified by MuHV-4 infection, in line with previous studies showing that this virus can selectively inhibit the development of TH2 cells [Machiels et al., *Nature Immunology*, 18(12):1310-1320 (2017)].

3. MuHV-4 infection affects activation of ILC2s as revealed by lower expression of PD-1/KLRG1 after HDM sensitization

MuHV-4 infection inhibits the production of type 2 cytokines and reduces the number of ILC2s in the lung. These differences may have implications for the development of type 2 immunity and provide new insights into the role of MuHV-4 in asthma.

4. The reduced activation of lung ILC2s following MuHV-4 infection is not due to an intrinsic effect but is dependent on the microenvironment

Our results showed that MuHV-4 respiratory infection impairs the function of lung ILC2s following HDM treatment and reduces their capacity to produce type 2 cytokines IL-13 and IL-5. Micro-environment is needed to maintain this phenotype and IFN-γ plays a role in the decreased production of IL-5 cytokine. Single-cell RNA sequencing revealed shared general pattern upon HDM sensitization between mock and MuHV-4 infected groups and highlighted the presence of a sub-population of ILC2s expressing higher MHCIin in MuHV-4 HDM mice compared to their mock HDM counterparts. These differences may have a determining role in the subsequent development of immune responses against respiratory allergens.

5. IFN-γ production following MuHV-4 infection rapidly modifies ILC2s cytokines production

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6. MuHV-4 infection affects the transcriptional profiles of lung ILC2s clusters

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