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Title: The critical role of interferon-gamma signaling in the respiratory immune response to influenza infection

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Body: We investigated the role of IFN-γ signaling on the resolution of lung inflammation and immune memory. IFN-γ-/- and IFN-gR-/- mice were infected with influenza H1N1(PR8). Bronchoalveolar lavage(BAL) was collected and eosinophils identified as SINGLEC-F+ve and CD11c-ve and neutrophils as Ly6G+ve and CD11c-ve. Influenza-specific CD8 T cells were identified with H2Db-NP366-374 tetramers. Cytokines were determined by ELISA, influenza-specific antibodies by red cell agglutination inhibition assay and mucus production by Periodic Acid Schiff staining. IFN-γ-/- mice produced a greater lung CD8 T cell response (WT 80,000, IFN-γ-/- 300,000 NP366-374 CD8 T cells p< 0.01). A higher percentage of NP366-374 CD8 T cells from IFN-γ deficient mice expressed a memory marker IL-7Ra (CD127) at day 8 (wild type, WT 5%, IFN-γ-/- 13% p<0.01) and increased amounts of BAL IL-5 (WT 80, IFN-γ-/- 280pg/ml p<0.001), Eotaxin (WT 100, IFN-γ-/- 220pg/ml p<0.01) and IL-10 (WT 20, IFN-γ-/- 320 pg/ml p<0.001). On day 11 there were increased numbers of eosinophils (WT 10,000, IFN-γ-/- 175,000 cells/lung p<0.001), macrophages (WT 25,000 IFN-γ-/- 140,000 cells/lung p<0.001) but not neutrophils (WT <500, IFN-γ-/- <500 cells/lung) and goblet cell hyperplasia. HK-x31 virus contains the H3N2 surface hemagglutinin and neuraminidase molecules and the internal (conserved) nuclear proteins of the PR8 virus. Reinfection of PR8 infected mice on day 120 days later demonstrated cross protection yet antibodies produced following infection with HK-x31 were only 10% cross reactive with PR8 although mice were completely protected from a lethal dose of virus. Thus IFN-γ signaling regulates lung pathology and the CD8 memory pool.