Role of hypercytokinemia in the pathogenesis of H5N1 influenza virus infection in mice with altered NF-kappaB signalling pathway

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The infection with highly pathogenic H5N1 avian influenza viruses causes a disease with severe pathology in avian and mammalian species including humans. The fatal outcome of human H5N1 influenza virus infection is associated with lymphopenia and hypercytokinemia. Because proinflammatory cytokines are markedly elevated during H5N1 influenza virus infection, the role of the "cytokine storm" is controversial discussed. Most cytokines and chemokines involved in hypercytokinemia are regulated through the NF-kappaB pathway.

To investigate the role of the cytokinemia in the pathogenesis after H5N1 infection we used NF-kappaB p50 knockout mice. The p50 subunit together with p65 represent the classical NF-kappaB pathway that is involved in the induction of most proinflammatory cytokines. Thus we questioned whether hypercytokinemia was still present in p50 knockout mice and if absence of this cytokine storm would have any influence on the pathogenesis. Our results revealed no difference in mortality, viral tropism, onset of disease and viral titers in organs after infection of p50-/-, p50+/- and p50 +/+ control animals with H5N1 influneza virus. Interestingly, we found a strong reduction of hypercytokinemia in p50-/- mice. Here, only interferon induced protein 10 (IP10) was still present in the lungs of p50-/- mice after H5N1 infection. From this data one might conclude that either the cytokine storm is not involved in H5N1 pathogenesis or IP10 plays the dominant role in this process.

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