

IFN γ and perforin synergistically control respiratory infection with murine gammaherpes virus 68

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We examined the role of IFN- γ and perforin during respiratory infection with murine gammaherpesvirus 68 (MHV68); a natural rodent pathogen closely related to the human Epstein-Barr virus and Kaposi's sarcoma virus.

Previous studies using gene deficient mice have shown that neither IFN γ nor perforin alone is pivotal for control of infectious virus. However, IFN γ ^{-/-} mice develop pulmonary and splenic fibrosis as well as splenic atrophy upon MHV68 infection. The entire pathology in these mice has been ascribed the activity of CD8 T cells, as depletion of this subset reverses the condition.

We report here that absence of the two main effector molecules of antiviral CD8 T cell, perforin and IFN γ , results in a fatal condition upon MHV68 infection with compromised virus control and severe pathology. MHV68-infected IFN γ and perforin double deficient mice (IFN γ , pfp^{-/-}) suffered from severe wasting disease and succumbed to infection within 2-4 month. The mice developed extreme splenomegaly with 4-6 times spleen enlargements observed already 20 days post infection and continuing throughout the 3-month period studied. Severe pathology was observed in spleen and lungs in terms of fibrosis, inflammation and – for the spleen -disruption of the normal architecture, and the mice failed to clear virus from the spleen and lungs. Neither pfp^{-/-}, IFN γ ^{-/-} or IFN γ R^{-/-} mice were compromised with respect to viral control. In general pfp^{-/-} mice had a mild infection course resembling that of infected wildtype mice, whereas IFN γ ^{-/-} and IFN γ R^{-/-} mice develop severe fibrosis and splenic atrophy as found previously by others. Thus, IFN γ and perforin work in concert to control viral replication and minimize pathology. In the absence of both effector molecules, the balancing race between the virus and the host is tipped in favour of the virus, and at the same time, excessive proliferation of splenocytes is triggered. This results in a fatal condition with virus-induced as well as immune-mediated pathology.