The Kinetics of Type I Interferons During Influenza A Virus Infection

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Abstract

Influenza A virus (IAV) infections pose a considerable public health threat and are a leading cause of death. The host immune response works to limit virus growth and quickly resolve the infection. Type I interferons (IFN-α, β) play a role in this by inhibiting the infection of epithelial cells and by stimulating and regulating the activity of immune cells. To investigate the role of type I IFNs during IAV infection, we infected groups of mice with influenza A/Puerto Rico/8/34 (PR8) and measured their viral load, IFN-α and IFN-β concentration. The data indicated a two-phase decline in viral loads and a double peak in IFN-α and IFN-β. However, the dynamics of IFN-α and IFN-β differ considerably. Because published kinetic models of type I IFN dynamics fail to reproduce these data, we developed a new model that describes type I IFN production from different sources and then fit the model to the data. The results suggested that the first waves of IFN-α, β are produced by infected epithelial cells while the second waves are produced by immune cells (e.g., macrophages and/or dendritic cells). In addition, the model reveals that effector $CD8^+$ T cell-mediated damage may activate IFN-α^+ immune cells, a finding suggestive of IFN-α's role in wound healing. We further used the model to assess the contribution of each source in limiting viral spread and found a role for epithelial-derived, but not immune-derived, type I IFN. Taken together, these results provide a well characterized model for type I IFN dynamics during IAV infection that give insight into the mechanisms of viral control and the regulation of host immune responses.