IL-36γ Promotes Alveolar Macrophage Survival During Influenza Infection, Limiting Morbidity and Mortality

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Influenza viral illness has been a high priority research topic in public health and immune pathogenesis, but the roles of individual cytokines in controlling the infection remains unclear. The IL-36 family of proteins is made up of novel IL-1 family members that have shown key roles in lung immunity to bacterial infections, but the role of IL-36γ in influenza infection is unknown. We investigated the function of IL-36γ during infection with low and high pathogenesis strains of influenza. IL36g mRNA is upregulated in the lung following influenza infection with both H1N1 and H3N2 influenza. Genetic deletion of Il36g results in greatly increased morbidity, mortality, and viral titers compared to mice replete for the gene. This difference correlates with increased pro-inflammatory cytokines in the airways of mice early during infection. Flow cytometric analysis of the immune compartment revealed a dramatic loss of alveolar macrophages by three days post-infection. Previous studies have shown that alveolar macrophages have a key role in limiting early viral replication and preventing death during lethal influenza infection. We observed that the alveolar macrophages in Il36g−/− mice have an M2-like phenotype at baseline, possibly contributing to their rapid depletion. Transfer of WT alveolar macrophages to Il36g−/− mice prior to influenza infection leads to increased survival compared to mock-transferred Il36g−/− mice. These data indicate that IL-36γ is a key protein in driving alveolar macrophage survival during influenza infection and protecting against severe disease.

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