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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 stains 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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