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Title: Targeting the IL-1β – IL-17A inflammatory axis for the treatment of viral-induced exacerbations of COPD

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Body: Chronic obstructive pulmonary disease (COPD) is one of the world's leading respiratory diseases, projected to be the 3rd leading cause of death by 2030. Acute worsening of the disease can be caused by bacterial and viral infections and is often associated with hospitalization. Although COPD exacerbations have been linked to enhanced recruitment of inflammatory cells, such as neutrophils, and to dysregulation of several inflammatory mediators, treatment predominantly relies on corticosteroid therapy with no therapeutic options available to stop disease progression. IL-1β levels are increased in COPD patients during acute exacerbation (Gessner, C. et al. Respir Med 2005; vol. 99 (10) pp. 1229-40); however, it remains to be determined if this is causative of lung dysfunction and exaggerated inflammation or simply associated with the disease. We found that the severity of COPD exacerbations, characterized by influx of neutrophils to the bronchoalveolar fluid (BALF) and by measurement of lung function, was reduced in mice lacking IL-1β. At early time points after infection this protective effect was mediated by decreased production of IL-17A by Th17 and γδ T cells. However, at the peak of viral infection, neutrophilic inflammation was independent of IL-17A but dependent on IL-1β signaling. Indeed, neutrophil recruitment at late time points during infection could be abrogated by treatment with the IL-1R antagonist Anakinra (Kineret). These data highlight IL-17A and IL-1β as targets for therapeutic intervention during viral-induced exacerbations of COPD.