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Study of the Role of IL-1 and IL-18 in Triggering IFNgamma Production and their Association with Exacerbation of Chronic Obstructive Pulmonary disease

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Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) are frequently associated with respiratory infections. Pathogen- triggered inflammasome activation is expected to lead to IL-1 and IL-18 release, pro-inflammatory cytokines important for host defence and also implicated as key drivers of chronic inflammation in COPD. We previously reported the release of IL-1alpha, IL-1beta and IL-18 by Human Rhinovirus (HRV)-infected bronchial epithelial cells (1). Whilst we showed the important autocrine or paracrine effect of IL-1 on epithelial cells, amplifying the inflammatory response, there was no such role for IL-18. To study its possible contribution during lung infection, we focused on how it might impact NK and T cell responses, in particular IFNgamma production which is known to be downstream of IL-18 in certain settings.

First, immunohistochemical methods were used to study the potential sources of IL-18 in the lung tissue of 31 COPD patients (of varying clinical severities) and 15 control subjects. In addition to the weak IL-18 staining of the airway epithelium, we found a strong IL-18 immunoreactivity associated with antigen presenting cells within lymphoid aggregates, notably CD68+CD163+ and CD68+CD163- macrophages as well as CD68-CD163-CD11c+ myeloid DCs. The total number of IL-18+ cells was increased in the more advanced stages of COPD as lymphoid aggregates number and size increased. In an attempt to model in vivo mechanisms during infection, we investigated the effect of epithelial or myeloid-derived IL-18 on IFNgamma-producing cells. Surprisingly, when the supernatant of HRV-infected normal bronchial epithelial cells or LPS-stimulated monocytes was used to activate NK cells, IFNgamma induction was fully blocked by an IL-1 receptor antagonist (97.73% [range 0.17, N=2] and 88.02% inhibition [N=1] respectively) but not by an IL-18 antagonist (31.76% [range 9.08, N=2] and 16.41% inhibition [N=1] respectively). In addition, we showed in a co-culture/transwell system of LPS/IL-12-stimulated monocytes and NK cells that IL-18 requires the close proximity of the producing and responding cells as indicated by the fact that a 57.40% inhibition of IFNgamma (range 6.71, N=2) was achieved by IL-18BPa in a co-culture system whilst the inhibition was 9.92% (range 21.79, N=2) in a transwell system.. Linking our observations with what might occur in the lung of COPD patients during infection, we studied the association of IFNgamma with IL-1 and IL-18 in 35 sputum samples obtained from patients experiencing an exacerbation of COPD. Spearman correlation showed a significant relationship between IFNgamma and IL-1alpha (R=0.66, p=1.56E-14), IL-1beta (R=0.56, p=6.57E-10) and IL-18 (R=0.55 p=1.23E-09). Among 175 analytes measured (Human Map V1.6, Myriad RBM Inc.), these three cytokines were in the top 10 analytes most significantly associated with IFNgamma.

Taken together, these results identify epithelial cells, macrophage and dendritic cells as potential sources of IL-18 in the lung. During a COPD exacerbation, IL-18 may act in concert with IL-1 to enhance IFNgamma production by NK cells and T cells. The differential spacio-temporal release of IL-1 and IL-18 may impact their respective downstream effect, with IL-18 acting locally whilst IL-1 having a longer range of action.

(1) Piper SC et al, PLoS One 28;8(5):e63365, 2013