

LTRC Concept Sheet # 05-03-0001

CD8 Tc1 Cells and Macrophages in COPD Pathogenesis

Abstract: COPD is a progressive disease that inexplicably develops in only a minority of chronic smokers. In histopathologic terms, COPD results from inflammatory, fibrotic, and destructive changes of the airways and alveoli. CD8 T cells and macrophages (M ϕ) are increased in the airways and alveoli in COPD, and the prevalence of these two cell types correlates in a complex fashion with the severity of airflow obstruction and emphysema. How CD8 T cells and M ϕ might induce the histopathology of COPD remains incompletely understood. Lung CD8 T cells are believed to produce IFN- γ , which in turn induces macrophages to secrete matrix metalloproteinase 12 (MMP-12), a protease essential for the development of emphysema in a murine model. Analysis of human lung tissue is essential to increase understanding of the interactions of CD8 T cells and lung M ϕ . This project tests whether inflammation and lung destruction develops in some smokers due to bi-directional positive feedback between CD8 Tc1 cells and M ϕ via exaggerated cytokine production, namely IL-15, and contact-dependent interactions. IL-15 can be produced by M ϕ and lung parenchymal cells and enhances the survival of CD8 T cells in an IL-2-independent fashion. Production of MMPs by M ϕ , including lung M ϕ , can be stimulated not only by soluble T cell products such as IFN- γ but also by direct contact with activated T cells. The mechanisms responsible for this stimulation are incompletely defined, but plausibly include CD40/CD154 interactions, through which T cells can stimulate production of MMP-1, -2, -3, and -9 by endothelial cells.