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ABSTRACT

Statement of the Problem. The respiratory mucosal immune system must maintain a fine balance between protection from infectious pathogens and avoidance of collateral damage to lung tissue. Upset of this balance is associated with inflammation seen in disease states as varied as pneumonia, pulmonary sarcoidosis and asthma. Respiratory infections trigger the recruitment of various populations of immune cells into the lung, including T cells which are major mediators of viral and bacterial clearance. This often results in immune-mediated tissue damage and disrupted lung function. Targeting pathological/inflammatory T cells recruited to the lung during respiratory infections while maintaining protective/beneficial subsets is vital for the development of protective vaccines and for improving treatment of viral and bacterial pneumonias.

Aim 1: Define the subsets of tissue-resident T cells within the lung and decipher the mechanisms involved in tissue-retention and tissue-specific homing.

Aim 2: Determine the contribution of CD4 T cells recruited into the lung from lymphoid reservoirs and lymphoid organs to lung immunopathology.

Experimental Approach. To investigate the relative contributions of lung-resident and circulatory/systemic memory CD4 T cells to viral immunity and lung pathology, we will perform adoptive transfers of these populations and assess their ability to clear influenza from the respiratory tract, while maintaining the integrity and function of the lung parenchyma. In order to understand how various memory T cell subsets are recruited and maintained in different lung niches, we will use a novel in vivo labeling technique as well as confocal microscopy to analyze cell localization in the lung in response to influenza infection.

Significance of the results. This proposal aims to improve our understanding of lung resident T cell subsets and to evaluate the role memory cells from systemic lymphoid pools play in lung immunopathology. The findings of this study will potentially have major implications on public health; respiratory infections affect a wide segment of the population and immune-mediated respiratory damage is a major complication of numerous other diseases.

LAY SUMMARY

The respiratory immune system, which protects the body from inhaled pathogens, often causes deleterious effects on lung tissue. In many human diseases, the resulting immune-mediated damage disrupts normal lung function and accounts for much of the morbidity and mortality seen with viral and bacterial pneumonias. We found that T cells that permanently reside within the lung protect against infection without causing damage to lung tissue, while T cells recruited from lymphoid reservoirs fail to control infection and cause greater tissue damage. This study aims to better understanding the dichotomy between the two populations, with the intent to improve current treatment options for inflammatory lung disease. This study will provide tools to enhance immunity to respiratory pathogens and also ways to prevent immune cell-mediated lung damage.