

STRONG CHILDREN'S RESEARCH CENTER

Summer 2016 Research Scholar

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ABSTRACT

Title:

Inhibitory Receptor Ligands on Alveolar Epithelial Cells as potential therapeutic targets for Pulmonary Inflammation and Lung Injury in *Pneumocystis* Pneumonia (PcP)

Background:

Pneumocystis (PC) is an opportunistic fungus that causes a limited asymptomatic infection in immunocompetent individuals but results in *Pneumocystis* Pneumonia (PCP) in subjects with impaired CD4⁺ T cell immunity. While detectable anti-PC antibody is commonly found in most humans by 2 years of age, approximately 400,000 cases of PCP occur yearly worldwide. PCP is the most frequent HIV-associated opportunistic infection, showing a 10-20% mortality rate for those with HIV/AIDS and a 30-50% mortality rate for those with cancer or other immune deficiencies. The mortality rate for those placed on a ventilator due to the side effects of PCP is 50% or even higher. The absence of CD4⁺ T cells during PCP is accompanied by the recruitment of CD8⁺ T cells to the lung, which are ineffective for host defense against *Pneumocystis* and cause inflammatory lung injury. Our laboratory recently determined that a high proportion of CD8⁺ T cells in the lungs during PCP express the inhibitory receptors PD-1 (programmed cell death protein 1) and Lag-3 (lymphocyte-activation gene 3). These receptors suppress CD8⁺ T cell effector function and may impair CD8 antifungal activity and/or limit immunopathogenesis during PCP.

Objective:

Because the tight attachment of *Pneumocystis* to alveolar epithelial cells has been shown to activate the NF- κ B pathway, we hypothesized that alveolar epithelial cells produce inhibitory ligands that contribute to the suppression of CD8⁺ T cells during PCP. To test our hypothesis, type II alveolar epithelial cell lines were stimulated in vitro with *Pneumocystis*, and PD-L1, PD-L2, and galectin-3 production was measured at the mRNA and protein level.

Results:

Our study suggests that alveolar epithelial cells secrete PD-L1, PD-L2, and Gal-3, suggesting that alveolar epithelial cells may contribute to CD8⁺ T cell suppression during PCP by stimulating the inhibitory receptors PD-1 and Lag-3.

Conclusion:

Modulating inhibitory receptor pathways may represent a potential adjunctive therapy to reduce lung injury and enhance fungal clearance in PCP patients.