Angiopoietin-like 4 Increases Pulmonary Tissue Leakiness and Damage during Influenza Pneumonia

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Background/Objective
Excessive host inflammatory responses negatively impact disease outcomes in respiratory infection. Host-pathogen interactions during the infective phase of influenza are well studied, however little is known about the host' s response during the repair stage. Designing effective vaccines and treatment options has proven challenging in view of the rapid evolution of the virus. A better understanding of the host response during the pulmonary repair phase may facilitate innovative treatment strategies. To our knowledge, angiopoietin-like 4 (ANGPTL4) has not been studied in detail in influenza pneumonia, and study on this host response factor may open door to new intervention strategies.

Method
By injection of ANGPTL4 antibody or using transgenic mouse models, effect of ANGPTL4 was studied in mouse models infected with different strains of influenza virus. Mechanism of ANGPTL4 regulation and downstream effects in disease outcomes were analyzed. Screening of patient lung biopsies with pneumonia was also conducted for ANGPTL4 levels.

Result
Here we show that influenza infection stimulated the expression of angiopoietin-like 4 (ANGPTL4) via a direct IL6-STAT3-mediated mechanism. ANGPTL4 enhanced pulmonary tissue leakiness and exacerbated inflammation-induced lung damage. The treatment of infected mice with neutralising anti-ANGPTL4 antibodies significantly accelerated lung recovery and improved lung tissue integrity. ANGPTL4-deficient mice also showed reduced lung damage and recovered faster from influenza infection when compared to their wild type counterparts. Retrospective examination of human lung biopsies from infection-induced pneumonia with tissue damage showed elevated expression of ANGPTL4 when compared to normal lung samples.

Conclusion
These observations underscore the important role that ANGPTL4 plays in lung infection and damage, and may facilitate new therapeutic strategies for the treatment of influenza pneumonia.