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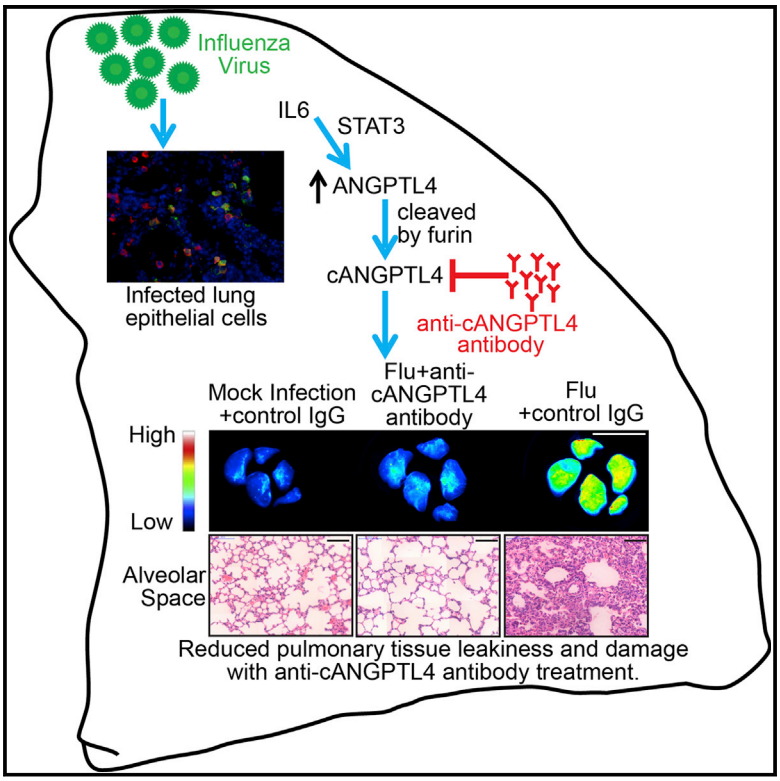
Report

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

Graphical Abstract



Highlights

- ANGPTL4 is upregulated by a STAT3-mediated mechanism during influenza pneumonia
- ANGPTL4-deficient mice show reduced lung damage and accelerated lung recovery
- Antibodies targeting ANGPTL4 reduce pulmonary tissue leakiness and damage
- ANGPTL4 is a potential biomarker for respiratory infection and pneumonia

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In Brief

Li et al. show that influenza infection stimulates the expression of ANGPTL4 through a STAT3-mediated mechanism. Host ANGPTL4 enhances pulmonary tissue leakiness and exacerbates inflammation-induced lung damage. ANGPTL4 deficiency improves pulmonary tissue integrity and accelerates lung tissue recovery.

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

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SUMMARY

Excessive host inflammatory responses negatively impact disease outcomes in respiratory infection. Host-pathogen interactions during the infective phase of influenza are well studied, but little is known about the host's response during the repair stage. 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. Treatment of infected mice with neutralizing 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 biopsy specimens from infection-induced pneumonia with tissue damage showed elevated expression of ANGPTL4 when compared to normal lung samples. These observations underscore the important role that ANGPTL4 plays in lung infection and damage and may facilitate future therapeutic strategies for the treatment of influenza pneumonia.

INTRODUCTION

The occurrence of annual epidemics and random global pandemics of influenza exerts a large public health burden worldwide (Mizgerd, 2006; Armstrong et al., 1999). However, designing effective vaccines and treatment options has proven challenging in view of the rapid evolution of the virus. While many aspects of host-pathogen interactions during the course of an influenza infection have been studied, there is less information on the host response during the repair stage of an infection (Mizgerd, 2008). A better understanding of the host response during the pulmonary repair phase may facilitate innovative treatment strategies. Host-specific biomarkers, indicative of the severity of lung tissue damage, could be exploited to delineate opportunities for therapeutic intervention.

Host immune responses are extremely important for containing influenza infections (Julkunen et al., 2000). Through the combined action of innate and adaptive immune responses, the infectious pathogen becomes inactivated and cleared from the body, repair processes start to resolve the tissue damage, and long-term immunity is ultimately established. However, excessive and prolonged inflammation may be detrimental to the host and contribute to the greater morbidity and mortality associated with influenza-induced inflammatory injury (Akaike et al., 1996; Monsalvo, 2010; Nicholls and Peiris, 2005; Buchweitz et al., 2007). Exaggerated inflammatory responses in the lung parenchyma can destroy alveoli, induce excessive edema, precipitate hypoxia, and cause pulmonary impairment (Narasaraju et al., 2011). Studies have documented that inflammatory injury to the lungs represents a major factor for the fatalities associated with pandemic H1N1-2009, highly pathogenic avian influenza viruses, and severe acute respiratory syndrome (SARS) coronavirus (Monsalvo, 2010; Nicholls and Peiris, 2005). Although inflammatory processes represent important therapeutic targets, anti-inflammatory therapies may also inhibit critical immune functions that mediate pathogen clearance, and they run the risk of enhancing pathogen replication and secondary infection (Uchide and Toyoda, 2011; Snelgrove et al., 2006; Aldridge et al., 2009; Ballinger and Standiford, 2010). An ideal treatment regimen should minimize the tissue damage caused by inflammation and facilitate recovery without interfering with the host's antiviral and antibacterial responses.

Angiopoietin-like 4 (ANGPTL4) belongs to a family of angiogenic-regulating, secreted proteins that bear a high similarity to members of the angiopoietin (ANG) family. However, ANGPTL4 does not bind to ANG receptor TIE1/2, indicating that ANGPTL4 exerts its distinct functions via a different mechanism from ANG proteins (Zhu et al., 2012; Grootaert et al., 2012).

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