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The immunology of influenza virus-associated bacterial pneumonia

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Infection with influenza virus has been a significant cause of morbidity and mortality for more than a hundred years. Severe disease and increased mortality often results from bacterial super-infection of patients with influenza virus infection. Preceding influenza infection alters the host's innate and adaptive immune responses, allowing increased susceptibility to secondary bacterial pneumonia. Recent advances in the field have helped to define how influenza alters the immune response to bacteria through the dysregulation of phagocytes, antimicrobial peptides, and lymphocytes. Viral-induced interferons play a key role in altering the phenotype of the immune response. Potential genetic modifiers of disease will help to define additional immunologic mechanisms that predispose to viral, bacterial super-infection with the overarching goal of developing effective therapeutic strategies to prevent and treat disease.

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Introduction

Infection with influenza virus is a significant cause of morbidity and mortality throughout the world. Severe disease and increased mortality can often result from bacterial super-infection primarily with the Gram-positive organisms, *Staphylococcus aureus* or *Streptococcus pneumoniae*. This review discusses the recent advances in our understanding of the immunological mechanisms by which influenza A virus infection increases the susceptibility to secondary bacterial pneumonia and how this might inform future strategies to prevent or treat this lethal combination.

Seasonal influenza infection occurs annually, and baseline immunity to seasonal influenza infections exists within communities due to prior exposure. Influenza pandemics occur when a new, highly pathogenic virus strain emerges for which there is no immunity within the human population. Pandemic viruses spread easily from person to person across a wide geographic area, affecting a large proportion of the population. During the 1918 pandemic of influenza A virus H1N1, more than 50 million people died from influenza and bacterial super-infection [1]. During the 2009 pandemic of influenza A virus H1N1, 25–50% of hospitalized virus-infected patients were super-infected with bacterial pneumonia [2–7], and super-infection was associated with higher morbidity and mortality [2,6,8–10]. Vulnerability to secondary bacterial infection peaks at approximately one week post-influenza infection (Figure 1). Influenza virus infection facilitates secondary bacterial infection through multiple immunological mechanisms. Preceding influenza virus infection leads to the dysregulation of both innate and adaptive immune responses, predisposing the host to secondary bacterial infection. Understanding the immune mechanisms that predispose patients with influenza virus infection to bacterial super-infection is paramount to preventing deaths in future influenza virus pandemics.

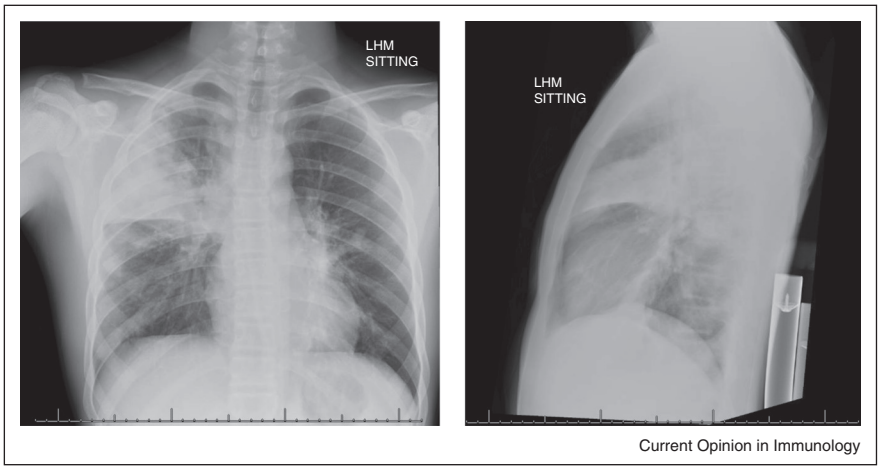
Influenza-induced defects in innate immunity against bacteria

Alveolar macrophages reside in the normal airway and are the first cells to defend against bacteria. Additionally, macrophages and neutrophils are recruited to the airways by cytokines and chemokines in order to ingest and kill bacteria. Preceding influenza infection causes dysregulation of both macrophages and neutrophils, limiting the ability to defend against subsequent bacterial infection (Figure 2).

Alterations in phagocyte quantity

Recent work has investigated how preceding influenza virus infection affects the number of macrophages and neutrophils available in the airway to fight bacterial infection. It has been shown that influenza virus infection resulted in the loss of 90% of mouse resident alveolar macrophages by one week post-infection, with the remaining 10% of macrophages displaying a necrotic phenotype [11••]. Cell death was thought to be related to a secondary necrotic process due to an increased

Figure 1

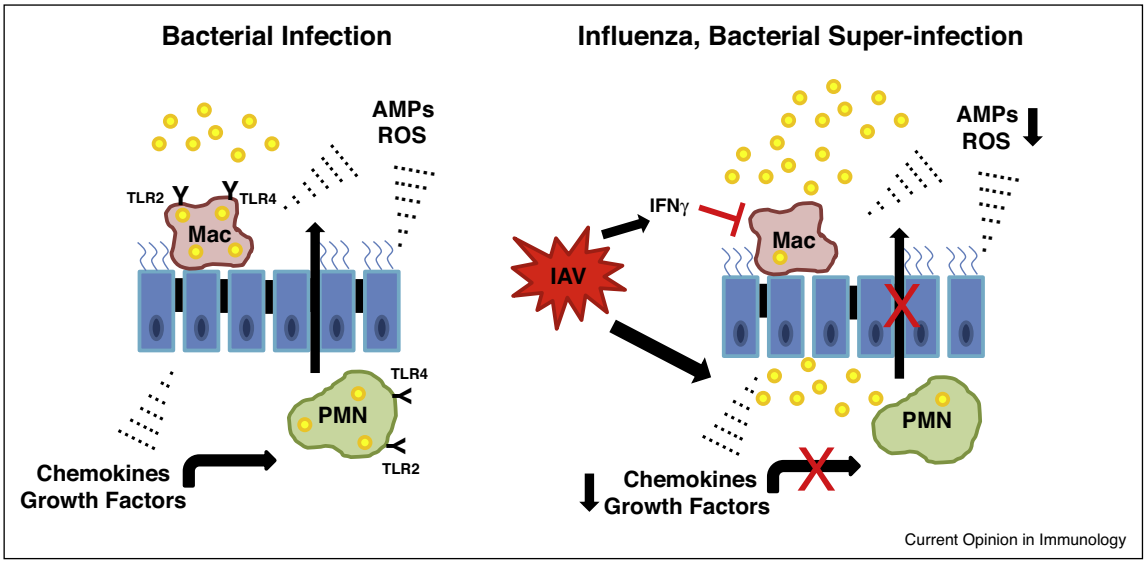


Chest radiographs of a child with influenza A H1N1 super-infected with methicillin-resistant *Staphylococcus aureus*. The window of vulnerability to secondary bacterial super-infection typically occurs typically one week post-influenza.

number of damaged macrophages (measured by distorted nuclei and an increase in the number of cytoplasmic vacuoles) in the airspace of influenza virus-infected mice compared with mock-infected mice. Recruited inflammatory monocytes replaced the resident cells during bacterial super-infection. This alteration of innate cells in the influenza virus-infected lung resulted in an early defect in *S. pneumoniae* uptake at three hours post-bacterial challenge. The alveolar macrophage population was fully replaced by two weeks post-viral infection and early innate host defense to *S. pneumonia* was restored.

Earlier work has demonstrated that influenza virus super-infection with *S. aureus* or *S. pneumoniae* resulted in enhanced neutrophilic inflammation in the lungs at time points mimicking human susceptibility to co-infection. More recent studies have confirmed these data. Mice infected with *S. aureus* six days after administration of

Figure 2



Preceding influenza attenuates innate host defense against secondary bacterial infection. In the context of bacterial infection alone, alveolar macrophages (Mac) recognize pathogens via pattern recognition receptors initiating an inflammatory cascade. Cytokines, antimicrobial peptides (AMPs), and reactive oxygen species (ROS) are generated by macrophages, recruited neutrophils, and the lung epithelium resulting in pathogen clearance. Preceding influenza (IAV) results in impaired macrophage and neutrophil killing of bacteria and decreased extracellular mediators (AMPs).