Review Article

Research progress on the mechanism of secondary bacterial infection of influenza virus

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ABSTRACT

A secondary bacterial infection of the influenza virus in the lungs is a key cause of exacerbation and death. The pathogenesis is characterized by complex interactions between co-infecting pathogens and the host, leading to the destruction of the physical barrier of the airways and the dysregulation of the immune response. This article will review the progress of the mechanism of secondary bacterial infection of influenza virus and provide strategies for preventing the co-infection of influenza virus and bacteria.

Key words: Bacteria, co-infection, influenza virus

INTRODUCTION

Influenza virus is one of the important causes of high morbidity and mortality in humans worldwide. The high mortality caused by severe influenza virus infection is often closely related to secondary bacterial infections during the influenza virus epidemic.[1] In 1918, the "Spanish flu" was the worst influenza pandemic ever, with 95% of the deaths attributed to the co-infection of influenza viruses and bacteria.[2] During the H1N1 influenza pandemic in 2009, 25% to 50% of hospitalized virally infected patients were infected with bacterial pneumonia, and the risk of death was significantly increased.[3-5] Of the more than ten species of bacteria that have been reported to be co-infected with influenza, *Streptococcus pneumoniae* is considered to be the most common cause, and *Staphylococcus aureus* is gradually becoming an important pathogen of influenza-related fulminant pneumonia in many countries and regions around the world.[6,7] Influenza viruses cause disorders in both innate and adaptive immune responses, making the host susceptible to secondary bacterial infections through a variety of immune mechanisms.[1] The study of the pathogenesis of susceptibility to bacterial infection in patients with influenza virus infection is an important frontier of current research work on influenza, and it is essential to prevent future influenza virus pandemics and avoid high mortality.[8] This review discusses recent advances in the immune mechanisms of secondary bacterial infections following influenza virus infection and provides strategies for preventing and treating co-infection with influenza viruses and bacteria.

INFLUENZA VIRUS AGGRAVATES PULMONARY FUNCTION

Multiple physiological changes such as lung airway epithelial damage, surface-active substance destruction, and inflammatory cell infiltration caused by influenza virus infection provide the conditions of secondary bacterial

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infections.[9] The release of cellulose and the secretion of mucin cause small airway obstructions, leading to increased dead space ventilation and a significant decrease in the ability to diffuse oxygen and carbon dioxide.[10] At the same time, the reduced frequency and incoordination of ciliary movements results in reduced oxygen exchange in the lungs, decreased airway hyperresponsiveness, and decreased bacterial clearance.[11] Therefore, the presence of influenza virus in the lung makes it easier for bacteria inhaled from the environment or bacteria from the upper respiratory/digestive tract to enter the lower respiratory tract and cause bacterial infection.[12] These respiratory dysfunctions are particularly pronounced in patients with underlying lung diseases, such as those with chronic obstructive pulmonary disease (COPD), who are more likely to develop acute COPD and bacterial pneumonia during influenza virus infection.[13]

INCREASED BACTERIAL ADHESION RECEPTORS

It is currently believed that secondary bacterial infections following viral infections are closely related to highly pathogenic influenza virus-associated respiratory epithelial damage, providing a favorable adhesion point for bacteria.[14,15] Human autopsy results revealed that during the pandemic of influenza virus, a large number of bacteria adhered to the damaged part of airway epithelium.[16] A series of virulence factors expressed by bacteria can adhere to the basement membrane or extracellular matrix, such as *S. pneumoniae* surface protein A and choline binding protein A, serine-rich repetitive proteins, microorganism surface components that recognize adhesion matrix molecules (MSCRAMM members) family, and non-MSCRAMM members (Sdr) of serine-aspartate dipeptide repeats in *S. aureus*.[17] Certain viruses, such as the mouse-adapted influenza virus strain PR8, cause significant apoptosis of epithelial cells in the body, exposing airway adhesion sites, and thus prone to bacterial infection.[18]

MULTIPLE RECEPTOR-MEDIATED MECHANISMS INVOLVING IN SECONDARY BACTERIAL INFECTIONS

The virulence of influenza viruses often manifests as polygenic traits. Any mutation that increases virus adaptability or cytotoxicity may cause epithelial damage and secondary bacterial infections. More serious ones such as viral cytotoxins PB1-F2 can cause cell death and cytokine storms.[19,20] Other receptor-mediated mechanisms can also lead to repeated bacterial infections following viral infections, but to a lesser extent in inflammation and clinical manifestations, which is why most of the seasonal influenza virus strains we have observed do not cause severe lung injury. These receptor-mediated mechanisms include: (1) influenza neuraminidase cleaves sialic acid in airway epithelial cells, destroys sialylated mucin, and exposes hidden receptors on host cells that can be adhered by *S. pneumoniae*, thereby inducing bacterial infection.[21]

Common lung-infecting bacteria, such as *S. pneumoniae*, typically produce neuraminidase, which acquires receptors and evades host defenses by cleaving epithelial cell sialic acid from protective mucins, thereby avoiding aggregation and clearance.[22] The host's inflammatory response to viral infections can change the regulatory status of a variety of proteins, including certain proteins that are conducive to the invasion of pneumococcal to the human body and cause infections, such as platelet-activating factor receptors.[23] After viral infection, airway changes may provide more sites for bacterial adhesion during the healing process of airway endothelial cell injury.[24] Damaged cells or cells in a state of intermediate differentiation can express apical receptors, including ethyleneated glycans (such as GalNacβ1-4Gal) or α5β1 integrin, making it easier for *S. aureus* or *Pseudomonas aeruginosa* to attach. Areas that are not fully healed expose basement membrane elements, such as laminin or type I and IV collagen, with fibrin and fibrinogen deposition, resulting in stronger and more stable adhesion of *S. pneumoniae*, *Haemophilus influenzae*, and *S. aureus*.[25] This is also one of the mechanisms by which patients often show signs of secondary bacterial infections during the recovery phase of influenza virus infection.

CHANGES IN VIRUS TROPISM

Whether in the upper or lower respiratory tract, virus polymorphisms can change the tropism of influenza viruses and promote co-infection with viruses and bacteria. The characteristics of influenza virus hemagglutinin determine the virus's tendency in the respiratory tract. First, the influenza virus can more efficiently bind to the sialic acid end via an α2,3 or α2,6 linkage.[26] Both types of sialic acid are present in the upper and lower airways, but α2,3 receptors are thought to have a greater role in promoting deep bacterial infections.[27] The second is the glycosylation status of hemagglutinin. The collagen agglutinin in the surfactant can bind to the highly glycosylated hemagglutinin protein so that the highly glycosylated virus is cleared from the airway by the cilia movement.[28] Poorly glycosylated viruses have a stronger ability to bind to the α2,3-linked sialic acid receptor. For example, the 1918 pandemic strain is an influenza virus that is very likely to cause secondary bacterial pneumonia.

CHANGES IN PATHOGEN RECOGNITION RECEPTOR PATHWAYS

When the host's immune system is normal, the immune response is mediated by recognizing the pattern recognition receptors on the surface of the pathogen. The toll-like receptor (TLRs) pathway is the host's common immune pathway for influenza and bacteria.[29] In *S. pneumoniae* pneumonia, bacteria can activate and regulate multiple

responses of the human immune system in the lungs, and are ultimately controlled by these response pathways, which can be manipulated by influenza viruses through multifunctional helper protein expression.[30] One reason is that influenza virus nonstructural protein 1 interferes with the lungs' immune response to bacterial attack. Taking Gram-positive cocci infection as an example, the host's early response to bacteria is affected by the previous induction of interferon.[31] This type of interferon is a type I interferon produced after TLR 104 recognizes the viral nucleic acid, and can inhibit the response of macrophages and neutrophils[31] which play an important role in removing bacteria from the lungs. By damaging the natural killer cell response and the direct effects of chemokines, it inhibits acute pro-inflammatory cytokines and reduces the normal phagocytic activity of macrophages and neutrophils. In addition, the influenza virus specifically depletes airway-resident macrophages, resulting in defects in early bacterial monitoring and phagocytosis. Studies have shown that influenza virus causes 90% of alveolar macrophages to disappear after 1 week of infection in mice, and the remaining 10% of macrophages show a necrotic phenotype.[32] The time it took for these alveolar macrophages to die during the initial stages of infection and be replaced by the proliferation and differentiation of macrophages from other categories within the next 2 weeks has exceeded the human body's window for immediate infection clearance. Some scholars compared human neutrophils after exposure to methicillin-resistant *S. aureus* (MRSA) and cases of MRSA pneumonia after infection with influenza virus, and found that in the latter cases, the neutrophil surface marker CD11b was upregulated and the neutrophil mortality was significantly increased.[33] Compared with mice infected with *S. pneumoniae* alone, the number of neutrophils in bronchoalveolar lavage fluid was significantly reduced 24 h after bacterial infection in mice with secondary *S. pneumoniae* infection after 2 and 6 weeks of influenza virus PR8 infection. The decrease in neutrophil aggregation is associated with the continued desensitization of macrophages to TLR ligands,[34] suggesting that influenza viruses induce the host to prolong the state of sustained suppression of the immune response, thereby increasing the risk of secondary bacterial infection.

In summary, the pathogenesis of co-infection with influenza viruses and bacteria has a multifactorial basis. A variety of innate immune mechanisms promote the inflammatory response of influenza viruses and bacteria, leading to the coordinated activation of immune responses and aggravating inflammation. At present, the pathogenesis of bacterial infection secondary to influenza virus infection is still mainly based on animal model data. The epidemiological analysis of influenza virus combined with bacterial infection lacks accurate assessment. The accuracy of rapid diagnosis of influenza virus and bacterial co-infection needs to be improved. How to transform the research results of the existing mechanisms into effective treatments that can improve clinically critical patients and ultimately reduce the mortality of influenza and bacterial co-infection is still a serious challenge facing for the timely and effective prevention and control of co-infection.

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Conflicts of interest

There are no conflicts of interest.

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