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Mini Review

Influenza Virus Lung Infection

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Introduction

Influenza viral lung infection is a common acute respiratory infection. Influenza A and B viruses cause human influenza. All age people can be affected. Most people is mild and recover within a week, but a few of influenza is severe and even death. Influenza related severe complication include Influenza pneumonia, secondary bacterial pneumonia, ARDS, and extra pulmonary complication [1,2]. Individuals infected influenza at greater risk of severe disease or complications are pregnant women, children, the elderly, individuals with chronic disease (such as chronic cardiac, pulmonary, renal, metabolic, neurodevelopmental, liver or hematologic diseases) and individuals with immunosuppressive conditions (such as HIV/AIDS, receiving chemotherapy or steroids, or malignancy) [3].

Human Airway and Lung Innate Defense and Immunity to Influenza Virus

The respiratory system consists of the upper respiratory tract (the nasal cavity, pharynx and larynx) and the lower respiratory tract (trachea, bronchi) and alveoli. The different cell composition of airway and lung may have different defense and immunity to microbial invasion.

We breathe every minute. Some of the inhaled air containing dust, microbes and environmental particle can cause respiratory disease. Normally, human respiratory tract innate defense maintain a pathogen-free environment in a healthy lung. Cells that participate in innate immunity include ciliated epithelial cells, goblet cells, dendritic cells, airway macrophages, alveolar macrophages, neutrophils, and pneumocystises.

Secreted products that contribute to innate immunity include antimicrobial peptides, inflammatory mediators, mucin, and secretory IgA [4,5]. The conducting airway epithelial cells provide both mechanical (ie ciliated epithelial movement and mucus production) and biochemical barriers (ie antimicrobial enzymes/peptides) that inhibit colonization of lungs by most microorganisms [6]. Antimicrobial enzymes/peptides include defensins, cathelicidin, antiproteases, lysozyme, lactoferrin, chemokines, collectins [7]. There are Type 1, type 2 and type 3 immunity response to different pathogen, such as virus, bacteria, and fungi. Type 1 immunity is main immunity response to virus [8,9]. Innate immunity induce and regulate adaptive immunity in infection.

The defence mechanisms of the innate immune system are a formidable barrier to influenza virus. Type I IFNs produced by macrophages, pneumocytes, DCs and plasmacytoid DCs (pDCs) induce an antiviral state. There are a variety of IAV inhibitors in respiratory lining fluid, including SP-D, SP-A, MBL, H-ficolin, LL-37, and other anti-microbial peptides. AMPs are antimicrobial peptides that not only play important roles as host defense against pathogens but also modulate inflammatory responses, and thus they are potential candidates for IAV treatment [10,11].

Influenza Virus Lung Infection

Influenza viruses resident in upper respiratory tract-the nasal cavity, pharynx and larynx and oral. Upper respiratory tract influenza infection is mild, while lung infection with influenza virus infection may have severe symptoms (cough, sputum, short of breath, dyspnea, cyanosis, trachypnea, fever). The primary mechanism of influenza virus lung infection pathophysiology is lung inflammation and compromise caused by direct viral infection of the respiratory epithelium [3].When alveolar epithelium cell is infected by influenza virus, alveolar cell may swell, injury or necrosis. Lung inflammation of influenza virus infection result in macrophage, lymphocyte, monocyte, dendrite cell recruitment, infiltration and release cytokines, chemokines such as IL-1,TNF-alpha, IL-6, IL-8, IFN and so on. Injury of small airway and alveolar epithelium cell lead to pulmonary function (ventilation function or gas exchange function) reduction.

Viral infection of the lung occur in 3 stages. First is the initiation phase. Second is resolution phase. Third is the restoration phase [6]. Restoration of the respiratory epithelial barrier after injury (chemical or viral) can be divided into 3 stages: (1) coverage

by neighboring epithelial cells of the denuded area through local spreading and migration, (2) migration and proliferation of progenitor cells to reconstitute the epithelium, and (3) differentiation of epithelial cells/progenitors into defined cell types to restore barrier and respiratory function [6,12]. The self-renewal and differentiation of various lung epithelial cells are modulated by neighboring epithelial cells, mesenchymal cells, airway smooth muscle, neurons and neuroendocrine cells, endothelium, and various leukocyte populations [13]. AT1 cells and AT2 cells are able to proliferate, or alveolar epithelial progenitors (AEPs), preferentially re-enter the cell cycle after injury, self-renew, and regenerate mature AT1 and AT2 cells [14,15].

Lung respiratory function can start to be restored within days after viral clearance, depending on the severity of the infection and the extent of lung involvement. The lung's ability to regenerate the epithelium damaged will also determine whether normal pulmonary function is regained or complications occur.

There are different prognosis after influenza virus lung infection. (1) Influenza virus lung infection is completely cleared, lung inflammation is resoluted, and the lung will recovery normally. (2) Influenza virus lung infection persist, or lung regeneration compromise, lung function worsen and secondary complication (hypoxygen, acute lung injury, ARDS, secondary bacterial infection, even death) may occur (3). Influenza virus in lung infection entering into blood or other organ such as heart, brain, or hypoxia may lead to inflammation and injury, severe influenza extrapulmonary complications may occur, such as myocardiolitis, encephalitis (4). Influenza virus lung infection result in exacebation of underline illness or chronic disease.

Co-Pathogenesis of Influenza Viruses with Bacteria in the Lung

Co-pathogenesis of influenza viruses with bacteria in the lung is common [16]. Bacterial coinfections are the primary cause of mortality in influenza- infected patients. Viruses are frequently identified in the respiratory tract of patients with pneumonia requiring ICU admission, with a strong predominance of influenza and rhinovirus [17]. There may be influenza viruse in exacerbations of COPD or asthma besides bacteria [18].

Legionella pneumophila, Streptococcus pyogenes, Neisseria meningitidis, Moraxella catarrhalis, S. pneumoniae, H. influenzae, S. aureus, Pseudomonas aeruginosa as well as a number of other Streptococcus and Staphylococcus spp. have all been associated with co-infection of influenza. However, S. pneumoniae, H. influenzae, and S. aureus are the most commonly reported bacteria associated with co/secondary infections during influenza pandemics [19,20]. Bacterial respiratory infection during influenza virus infection can be divided into combined viral/bacterial pneumonia or secondary bacterial infection following influenza [21].

The probable mechanism of co-pathogenesis of influenza viruses with bacteria in the lung is complicated. There are influenza virus, bacteria and host interact [16].The summary of the probable mechanism of co-pathogenesis of influenza viruses with bacteria: 1. epithelial damage enhancing bacterial adherence 2. Alteration of epithelium through sialidase activity.3.Upregulation of receptors for bacterial adherence. 4.Mechanical alterations to airway or Eustachian tube function.5.Changes in tropism of virus (ability to access the lower lung,6.Increased inflammation through expression of PB1-F2 .7.Anergy of pattern recognition receptors to bacteria during resolution of inflammation .8.Alteration of bacterial clearance by viral effects on specific immune cells (macrophages, neutrophils, NK cells).9.Dysregulation of protective immune pathways (RIG-I, PKR, 2′-5′ OAS, PI3K) by NS-1 .10.Cleavage of influenza virus hemagglutinin by bacterial proteases.11.Synergistic effects on inflammation and cell death of bacterial cytotoxins with the viral cytotoxin PB1-F2 [22]. These mechanisms result in dysfunction of lung physiology.

Diagnosis, Treatment and Prevention

Patients with influenza virus lung infection should be treated with antivirals in addition to symptomatic treatment as soon as possible. Neuraminidase inhibitors (i.e. oseltamivir, zanamivir) should be prescribed as soon as possible for a minimum of 5 days and can be extended to satisfactory clinical improvement. There are some new antiviral drugs, Such as baloxavir marboxil (baloxavir) [23,24]. Patient with influenza co-pathogenesis lung infection, appropriate treatment is required.

Prevention is very important for reducing incidence, mainly vaccination and personal protective measures. The effective way to prevent the disease is vaccination by injected inactivated influenza. WHO recommends annual vaccination for: pregnant women at any stage of pregnancy; children aged between 6 months to 5 years; elderly individuals (aged more than 65 years); individuals with chronic medical conditions; health-care workers.

Personal protective measures include in details: regular hand washing; Good respiratory hygiene. Early self-isolation of those having influenza symptoms; Avoiding close contact with sick people. Room ventilation; Stop smoke and alcohol intake; Well nutrition; Proper sport.

If there are contact closely with patient with influenza virus lung infection, you may choose to take antivirals to protect or prevent influenza virus infection as prophylaxis [25].

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