Article @ Virology

Study on the Microorganism Infection and Pathogenic Mechanisms in Humans

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ABSTRACT

As we all know, humans are currently living in an era of a global village, and infectious diseases remain a major cause of morbidity and mortality worldwide. Viral and bacterial infections will increase with the continuous growth of the global population. To better prevent and control infectious diseases, a comprehensive understanding of their pathogenic mechanisms is required.The scientific community has not yet fully elucidated many aspects of the pathogenic mechanisms of microorganisms. This article aims to clarify a series of activities and processes that occur after pathogenic microorganisms enter the human body, providing a theoretical basis for the further development of targeted new drugs against microorganisms. Given the variety of viruses and bacteria, specific discussions will be made using *Rabies virus*, *Streptococcus pneumoniae*, and *Mycobacterium tuberculosis* as representative examples.

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Abbreviations: RABV, Rabies Virus; CNS, Central Nervous System; RNP, Ribonucleoprotein complex; nAchR, nicotinic Acetylcholine Receptors; MT, Microtubule; CbpA, Choline-binding protein A; TB, Tuberculosis.

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Introduction

As is well known, despite the widespread use of antibiotics and vaccines, infectious diseases remain a primary cause of morbidity and mortality worldwide. Recent epidemiological studies predict that viral and bacterial infections will increase concomitantly with the sustained growth of the global population. Consequently, there is an urgent need to develop a new generation of anti-infective drugs to address these diseases. However, the development of such drugs necessitates a comprehensive under--standing of the pathogenic mechanisms.

Therefore, this paper aims to elucidate a series of activities and processes that occur when pathogenic microorganisms enter the human body, providing a theoretical foundation for the improved development of novel drugs targeting microorganisms. Given the multitude of viral and bacterial species, specific elaboration will be conducted using rabies virus, *Streptococcus pneumoniae* and *Mycobacterium tuberculosis* as exemplary cases.

Human Rabies

Rabies is a zoonotic disease caused by rabies virus infection. Once the disease occurs, it is 100% fatal. Rabies virus (RABV) is a typical neurotropic virus belonging to the genus Lyssavirus of the family Rhabdoviridae. It has a bullet-shaped appearance, a helical symmetric nucleocapsid, an envelope on the surface, and contains single-stranded RNA. According to official estimates, more than 55,000 people die from the disease each year, but this figure may be significant underestimated [1,2]. Although rabies has been studied for hundreds of years and the development of RABV vaccines has made great contributions to preventing its spread, as a highly contagious disease, it can only be prevented and controlled but still cannot be treated after the disease occurs. Therefore, by focusing on the rabies virus replication cycle and its interaction with host cells, in-depth research can be carried out to understand the rabies virus life cycle and provide assistance for the pathogenesis and treatment of rabies.

Human infection with rabies mainly comes from the bite of rabid dogs, and the rabies virus cannot penetrate intact skin. However, contact of infected saliva with wounds, mucous membranes or skin abrasions may lead to infection, and aerosol and organ transplant transmission have also been reported [3-5]. There are two types of rabies encephalitis/furious and paralytic. The encephalitis type is more common, with initial symptoms of fever, paresthesia at the bite site and pharyngitis, followed by typical rabies and hydrophobia, paralysis, coma, and ultimately death. The paralytic type presents with ascending paralysis and no typical symptoms, which often makes diagnosis difficult [6].

Humans are infected with rabies virus, which mainly enters the body through bites

and other routes. Initially, it replicates and proliferates in small amounts in muscle tissue and infects the motor neurons that control the muscles. The virus then spreads centripetally to the central nervous system (CNS) through axonal transport, with the virus spreading at a rate of 12 to 24 mm per day. After entering the CNS, the virus preferentially tends to invade neurons and glial cells in the gray matter. Subsequently, the virus spreads rapidly within the CNS, causing progressive encephalitis[7,8]. The virus life cycle model is shown in Figure 1.

RABV enters cells via receptor-mediated endocytosis, releasing ribonucleoprotein complex (RNP) into the cytoplasm. The RNP undergoes transcription, forming Negri bodies, where RABV assembles and releases complete viral particles from the host cell[9].

Studies have shown that rabies virus enters cells mainly by binding to nicotinic

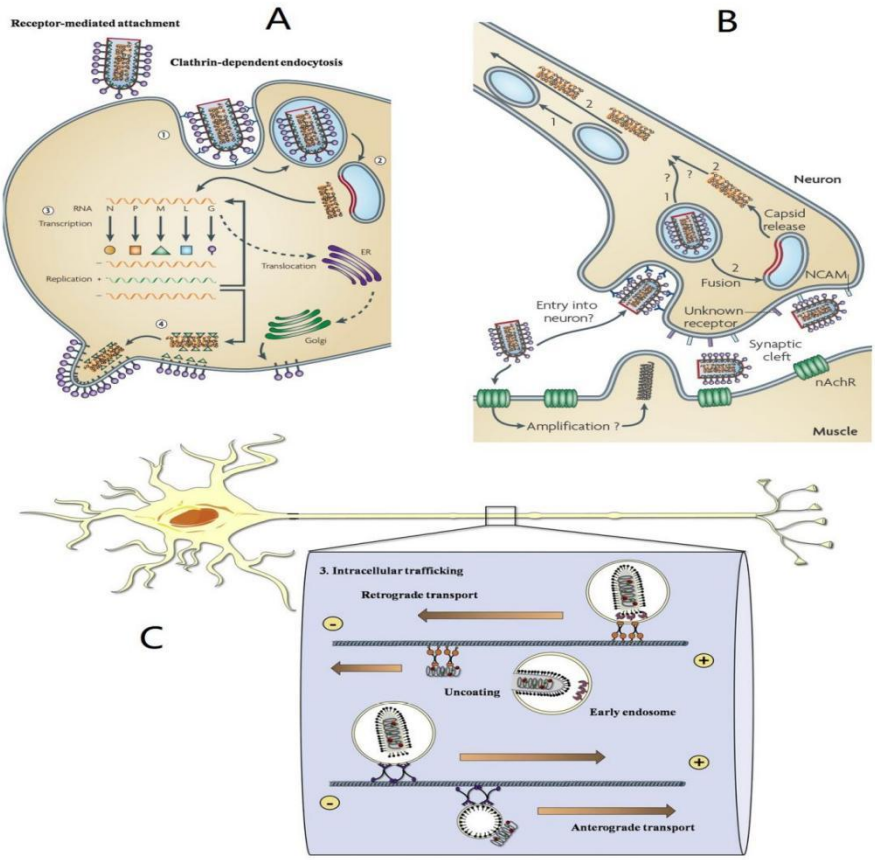

Fig. 1: The life cycle of rabies virus and the pathogenesis of rabies[9,10]

A: Mechanism of RABV infection in host cells.

B: Rabies virus entry into neurons from muscle cell.

acetylcholine receptors (nAchR) on the cell surface and endocytosis with the help of cell membrane proteins. For mammalian host infection, nAchR are located in the postsynaptic sarcolemma. Studies have shown that the initial rabies virus replication is carried out in muscle cells, that is, nAchR may be used to infect muscle cells,and enriches rabies virus at the neuromuscular junction or synaptic cleft, making the connected motor neurons more effectively infected [9].

Rabies virus enters neurons through neural cell adhesion molecule (NCAM) or another unknown receptors.The intracellular traffick--ing process is inevitably dependent on the cellular microtubule (MT) network and MT motors. There coexists bi-directional intraneuronal transport on MTs. Two plausible different mechanisms were proposed in either direction, wherein dynein or kinesin motors. Overall, the precise mechanisms of RABV intracellular trafficking remain elusive, and the ways in which these factors cooperate requires further elucidation[10].

Overall, an in-depth understanding of the biological mechanism of the virus will help unravel the mystery of RABV neuro--pathogenesis and lead to improved antiviral therapeutics.

Streptococcus pneumoniae

Streptococcus pneumoniae, commonly referred to as pneumococcus, is a Gram--positive bacterium that is a major human pathogen responsible for a range of infections[11,12]. It can cause various infections, such as pneumonia, meningitis, sepsis, and sinusitis. Pneumococcal disease is contagious and can spread through respiratory droplets when someone coughs or sneezes[12]. In 2017, the WHO included *S. pneumoniae* as one of 12 priority pathogens. The continued high burden of disease and rising rates of resistance to penicillin and other antibiotics have renewed interest in prevention. Understanding the mechanisms by which *S. pneumoniae* infects and causes disease is crucial for developing effective prevention and treatment strategies. The infection process involves several key steps[13] (see Fig.2).

Transmission: Spread of *S. pneumoniae* occurs through close contact with carriers, especially young children. Up to 27-65% of children and less than 10% of adults are carriers of *S. pneumoniae*[14]. It is more frequent during drier, colder months when airway secretions are more copious. Viral infections of the upper respiratory tract can also increase the likelihood of transmission.

Colonization: *S. pneumoniae* must come into contact with mucosal surfaces of the human upper respiratory tract, particularly the nasopharynx[12], for the source and first step of transmission to occur[13]. The bacteria require multiple bacterial agents to colonize and persist on mucosal surfaces at a density and duration sufficient for transmission to occur. Carriage involves a symbiotic relationship between bacteria and host.

Adherence and Invasion: *S. pneumoniae* produces various surface proteins and

adhesins that facilitate adherence to host cells. Adherence is followed by invasion, during which the bacteria penetrate the epithelial barriers of the respiratory tract. Pneumococci are equipped with enzymes like neuraminidases and hyaluronidases that aid in tissue penetration. In the case of meningitis, the bacterium must breach the blood-brain barrier(see Fig.3).

S. *pneumoniae* possesses various virulence factors that contribute to its ability to cause disease[12]. These include the capsule, as well as surface proteins like pneumococcal surface protein A (PspA), choline-binding protein A (CbpA), and the ancillary pilus subunit RrgA. These proteins interact with host receptors on respiratory epithelial cells, vascular endothelial cells, and brain microvascular endothelium, facilitating invasion and tissue penetration.

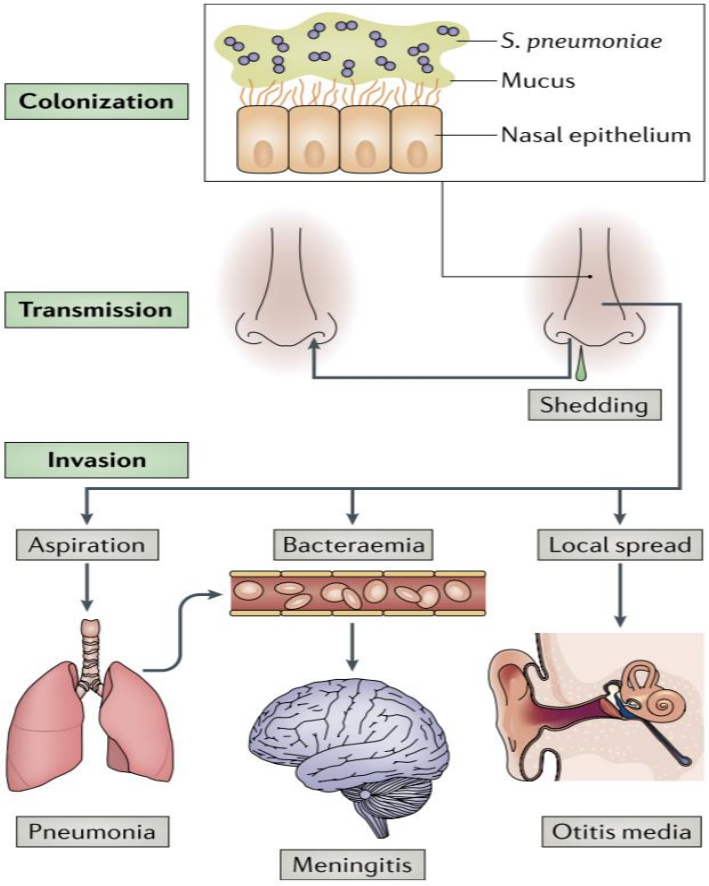

Fig. 2 The life cycle of *Streptococcus pneumoniae* and the pathogenesis of pneumococcal disease.

Immune response: The host immune response plays a crucial role in controlling S. pneumoniae infection. Once inside the host, The bacterium faces challenges from the host immune system. Neutrophils and other immune cells are recruited to the site of infection to eliminate the bacteria. However, *S. pneumoniae* has mechanisms to evade immune clearance, such as CbpE, CPS, CbpA, PspA, etc.

In general, the main steps for S. pneumoniae to invade the host are these steps. After infection, *S. pneumoniae* can cause different illnesses depending on the depending on the site of infection.

For example, in the lungs it can cause community-acquired pneumonia, and in the middle ear it can cause otitissite of infection. media. Invasive diseases such as sepsis and meningitis can occur when bacteria enter the bloodstream or breach the blood-brain barrier.

S.pneumoniae has proved to be a truly resilient foe. It has overcome selective pressure from multiple classes of antibiotics and now seems to be adapting to the immune pressure of widespread immunization[12,15]. These developments demonstrate that we cannot be complacent, and further insights are needed to combat pneumococcal disease.

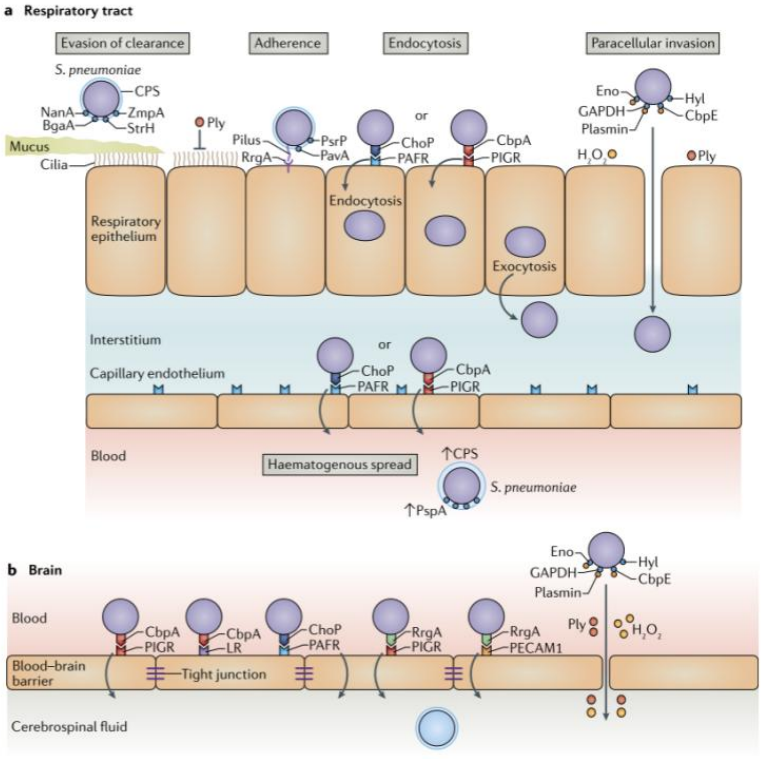

Fig. 3 Stages in pneumococcal adherence and invasion.

Mycobacterium tuberculosis

Tuberculosis (TB) is a contagious disease caused by infection with Mycobacterium tuberculosis (Mtb) bacteria[16,17]. It is spread through the air when a person with TB disease of the lungs or throat coughs, speaks or sings, and people nearby breathe in these bacteria and become infected[18,19]. The infection process involves several key steps[20] (see Fig.4).

Transmission: M. tuberculosis primarily infect the respiratory tract when a person inhales droplets containing the bacteria that are released into the air when an infected individual coughs or sneezes.

Alveolar Macrophage Phagocytosis: Once inhaled, the bacteria reach the alveolar space in the lungs and encounter alveolar macrophages, which are the primary cells that M. tuberculosis infects[16,19]. The bacteria are internalized by the alveolar macrophages through receptor-mediated phagocytosis. Once inside the macrophages, M. tuberculosis actively blocks the fusion of the phagosome (the compartment containing the bacteria) with the lysosome (the compartment containing enzymes that can kill the bacteria). This allows the bacteria to survive and replicate within the macrophages.

Granuloma Formation: M. tuberculosis can also disrupt the phagosomal membrane and release bacterial products, including bacterial DNA, into the cytosol of the macrophages[17]. This can activate the immune response and lead to the recruitment of immune cells, such as T cells and B cells, to the site of infection. These immune cells form a structure called a granuloma, which is a characteristic feature of TB infection.

Latent Infection or Active Disease: If the immune response is successful in containing the infection, the bacteria can enter a quiescent or latent state within the granuloma[16]. In this state, the individual may not show any symptoms of TB and is not contagious[17]. However, if the immune response fails to control the infection, the bacteria can continue to replicate within the granuloma, leading to the development of active TB disease[21]. Active TB disease is characterized by symptoms such as cough, fever, night sweats, weight loss, and fatigue. In advanced stages of the disease, individuals may also experience persistent coughing up of blood. Active TB disease can be contagious, especially in cases of active pulmonary TB where the bacteria are present in the respiratory secretions and can be transmitted to others through coughing or sneezing[21].

In general, active TB disease is characterized by symptoms such as persistent cough, hemoptysis (coughing up blood), chest pain, weight loss, fatigue, and night sweats. The severity and manifestations of TB can vary widely among individuals[21].

Overall, TB can cause disease throughout the body, although it primarily affects the

lungs. The progression from latent infection to active disease depends on the interaction between the bacteria and the host immune response.

Conclusion

In summary, while the mechanisms through which various pathogenic microorganisms induce disease in the human body exhibit nuanced distinctions, they generally encompass the sequential processes of transmission, colonization, invasion, replication, and release. However, the specific anatomical sites of infection and the diversity of virulence factors among different viral and bacterial species dictate the wide spectrum of resulting symptoms.

Furthermore, numerous aspects in the realm of microorganism pathogenesis remain inadequately elucidated by the scientific community. Consequently, researchers to dedicate additional time and efforts towards a more profound exploration, considering the intricate variations in microorganism behavior and the expansive domains yet to be comprehensively understood.

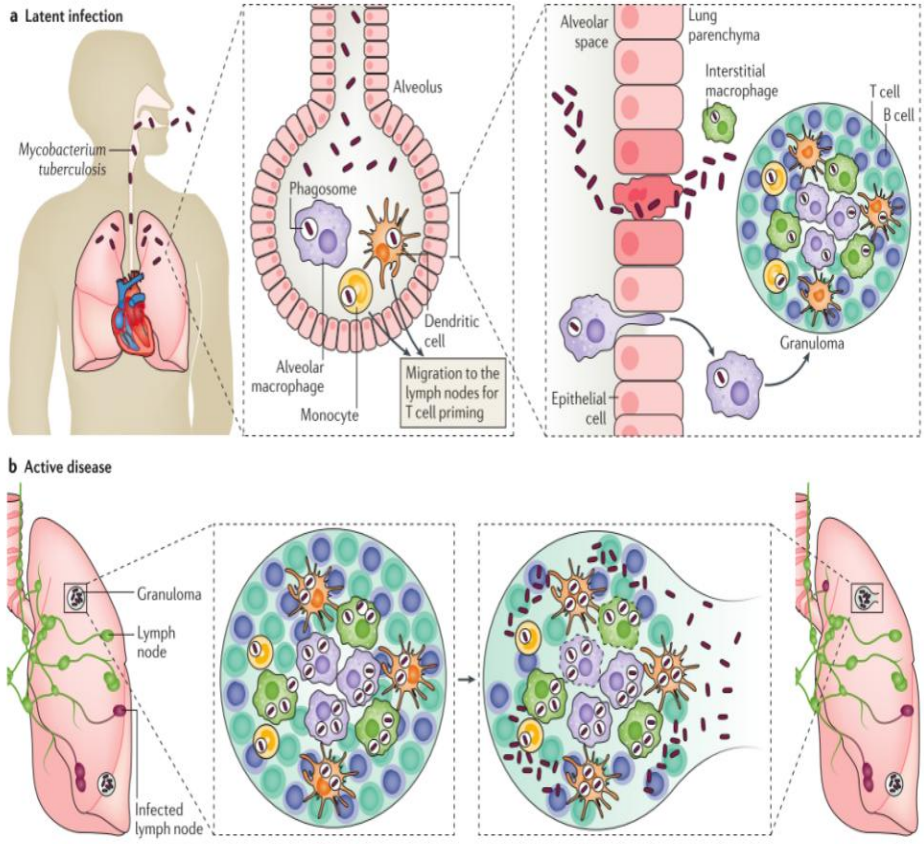

Fig. 4 Stages in pneumococcal adherence and invasion.

Competing interests

The authors declare all financial and non-financial competing interests.

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