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Influenza Virus: A Platform for Pathomechanism-Based Investigation of Drug and Vaccine Development

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Abstract. Influenza viruses belong to the family Orthomyxoviridae and represent a significant global public health concern due to their frequent epidemics and occasional pandemics. According to data from the World Health Organization (WHO), seasonal influenza A viruses (IAV) infect 3 to 5 million people globally each year, resulting in 290,000 to 650,000 deaths. Among all IAV proteins, the hemagglutinin (HA) and neuraminidase (NA) genes exhibit a high mutation rate, attributable to the lack of proofreading activity in the viral RNA-dependent RNA polymerase, leading to the emergence of new strains. Since mutated viruses can cause high infection rates in immunocompromised populations, continuous updates of antiviral drugs and vaccines are necessary, but this poses an economic burden. Current antiviral drugs and vaccines are insufficient to combat all influenza viruses, particularly mutated strains against which vaccines are largely ineffective. To alleviate the economic burden associated with developing new vaccines and drugs in response to viral mutations, the development of universal antiviral drugs and vaccines is imperative. This review will examine four key aspects: the pathogenesis of influenza, the development of anti-influenza drugs, the development of influenza vaccines, and the barriers to vaccine implementation. Through this analysis, the paper aims to provide support for the development of more effective antiviral agents and universal vaccines, as well as offer recommendations for improving the currently low rates of vaccine uptake.

Keywords: Epidemiology, Genomics, Influenza virus, Reassortment, Respiratory viruses

1. Introduction

The segmented nature of the influenza virus's negative-sense RNA genome, coupled with its reliance on viral RdRp for replication, underlies its capacity for antigenic drift and antigenic shift, driven by the specific functions of its constituent proteins. These processes enable the virus to evade the adaptive immune response developed by the host's immune system over time [1]. Nearly 10% of the global population is affected by influenza each year, resulting in approximately 500,000 deaths annually [2].

The influenza virus is the primary pathogen causing influenza. It invades host cells, hijacks the cell's biosynthetic machinery to replicate, and assembles new viral particles, which are then released to infect neighboring cells. A key feature of the influenza virus is its segmented negative-sense RNA genome, which relies on the virus's own RNA-dependent RNA polymerase for replication. The unique structure of the influenza virus genome and the functions of its viral proteins can undergo antigenic drift and antigenic shift. These processes allow the virus to evade the host immune system's specific responses over time [1].

The main reasons for the high mutation rate of the influenza virus are its segmented RNA genome and the rapid variation of key proteins. The genes encoding the viral surface glycoproteins hemagglutinin (HA) and neuraminidase (NA) are characterized by high mutability, which is a hallmark of their function/evolution. and changes in these proteins lead to continuous antigenic drift, causing seasonal epidemic strains to constantly evolve. More importantly, the segmented nature of the viral genome allows different strains to undergo genetic recombination when infecting the same host cell, producing offspring with entirely new antigen combinations—a process called antigenic shift, which is responsible for influenza pandemics.

HA mediates viral entry into host cells and facilitates the fusion of the host and viral membranes, while NA helps newly formed virus particles detach from the host cell surface. Frequent mutations in these two proteins not only reduce the effectiveness of existing vaccines but also create new challenges, such as resistance to antiviral drugs like neuraminidase inhibitors.

Therefore, a deeper understanding of the influenza virus's genome structure, mutation mechanisms (especially the evolutionary patterns of HA and NA), and their interactions with the host's immune system is crucial for developing more effective and broad-spectrum antiviral drugs and vaccines. In this article, This paper will focus on the characteristics of the influenza virus and provide theoretical support for its prevention and control based on its pathogenic mechanisms.

2. Pathogenic mechanisms of influenza virus-host interactions, viral mutation mechanisms, and the battle between the immune system and the virus

The influenza virus targets the sialic acid receptors on respiratory mucosal epithelial cells through its surface HA protein, while NA degrades sialic acid in the mucus layer, weakening its physical barrier and clearance functions. The virus then enters the cell via endocytosis.

Influenza virus-host interactions commence upon successful cellular invasion and subsequent appropriation of host biosynthetic machinery.This process involves sophisticated molecular mechanisms. A defining feature of influenza RdRP is its 'cap-snatching' capability – a conserved mechanism for viral transcription initiation. By cutting off the 5' cap structure of newly synthesized host mRNA, this enzyme employs the excised cap as a transcriptional primer to initiate viral mRNA transcription [3]. By stealing host mRNA caps, the virus ensures efficient expression of its own genes while disrupting the host cell's normal gene function—a critical step in viral infection. Understanding these mechanisms is essential for uncovering how the flu causes disease and identifying potential treatment targets.

Viral infection starts when HA binds to specific receptors on respiratory cells. The type of receptors HA prefers determines which species the virus can infect. HA activation through host proteases triggers membrane fusion events, through which the viral genome is released and transported to the nucleus for replication.

To evade the immune system, the virus continuously mutates its HA and NA proteins (antigenic drift) or undergoes gene reassortment (antigenic shift) to create new strains that escape antibody recognition. Meanwhile, the viral nonstructural protein NS1 blocks host signaling pathways, weakening early antiviral defenses. These interactions lead to the death and shedding of respiratory cells, excessive immune responses that damage lung tissue, and breakdown of the protective mucosal barrier—increasing the risk of secondary bacterial infections. Studying these mechanisms can help develop new strategies to block viral entry, stop replication, or regulate immune responses.

The nonspecific immune system includes physical and chemical barriers, which the virus can breach using its surface HA and NA proteins.

Cell-mediated and humoral immune responses are the body's defenses against viral invasion. After the virus enters the body, macrophages engulf it, and dendritic cells present the antigens to helper T cells in the lymph nodes, activating them. Helper T cells then trigger two immune responses: infected cells are killed by cytotoxic T cells releasing perforin, and the viruses inside are either destroyed or released into bodily fluids. Free viruses and those released from host cells are bound by Y-shaped proteins (antibodies) produced by plasma cells derived from B cells. This prevents the viruses from infecting other healthy cells and marks them for clearance by phagocytes.

Although both immune mechanisms generate long-lived memory B cells and memory T cells, ensuring rapid elimination of the same virus upon reinfection, mutated or reassorted viruses with altered surface antigens can evade recognition by these memory cells. antigens can evade recognition by these memory cells. As a result, the immune response fails to activate quickly, allowing the virus to continue infecting cells.

3. Vaccine development platform for influenza virus

Based on the above virus-host battle mechanisms, current prevention strategies focus on developing drugs and vaccines targeting conserved regions.

Compared to vaccines, small-molecule antiviral drugs can directly inhibit viral replication or block critical virus-host interactions. They are effective for early treatment, rapidly reducing viral load and alleviating symptoms, regardless of prior vaccination [4]. Due to the virus's high mutation rate, current antiviral drug research often targets conserved viral proteins like RdRp and 3CLpro to avoid resistance, cytotoxicity, and to achieve broad-spectrum effects. However, enthusiasm for antiviral drug research is currently low, with most drugs in clinical trials being immunostimulants or adjunct therapies [4].

Initially, influenza vaccines were produced using chicken eggs for large-scale manufacturing. Today, over 80% of market products are still egg-based. While this method is cost-effective and technically mature, it has several drawbacks. Cell-based vaccines are more effective than egg-based ones, and an increasing number of manufacturers are now adopting cell-based production [5].

Current seasonal flu vaccines only provide strain-specific protection due to the virus's rapid antigenic drift and shift, showing significantly reduced effectiveness against mismatched strains [6,7]. To overcome this limitation, new vaccine platforms focus on targeting conserved regions of the virus. Based on this strategy, there are two main approaches:1.Using structural biology to identify stable, less mutable conserved targets on viral surface glycoproteins and internal proteins, then designing matching antibodies to neutralize the virus. Examples include vaccines based on highly conserved epitopes in HA, NA, and M2, as well as those designed to induce T-cell immune responses targeting internal proteins like NP, PA, PB1, PB2, and M1 [8].

Employing advanced technologies to stimulate immune responses: mRNA vaccines can enhance both B-cell and T-cell responses, while adjuvant recombinant protein vaccines boost immune reactions to produce stronger antibodies. These methods, based on viral pathogenic mechanisms, lay the foundation for universal vaccine development. The success of COVID-19 mRNA vaccines not only demonstrated the feasibility of the mRNA platform with remarkable speed and efficacy but also expanded possibilities for treating various diseases [7].

4. Vaccine implementation barriers and solutions

Another reason for the ineffective prevention of influenza is low vaccination rates. The main causes of low influenza vaccination rates include: lack of awareness about disease severity, misconceptions about susceptibility, and accessibility issues. Factors such as rural residence, lack of vaccine knowledge, large families, low household income, and higher parental education levels also play a role [9]. A cross-sectional survey of residents in Shanghai's Pudong New Area showed that the primary reason adults refuse to vaccinate their children is concern about adverse reactions (21.49%), followed by the belief that their children are healthy and do not need vaccination (13.64%). Many caregivers underestimate the severity of influenza, confusing it with the common cold, and lack confidence in vaccine efficacy and importance, believing vaccines offer no protection against the ever-mutating virus. Healthcare workers play a crucial role in influencing parental vaccination decisions. parental vaccination decisions. An internet survey revealed that the top reason parents of children aged 6–59 months did not vaccinate their children was that healthcare workers did not recommend the influenza vaccine (21.1%), followed by lack of knowledge about the vaccine (19.2%). Additionally, most caregivers did not receive professional medical information, and insufficient communication between caregivers and healthcare workers further hindered their understanding of influenza risks and vaccine benefits [10].

Therefore, developing safer vaccines, improving their efficacy, and raising public awareness about vaccines can increase vaccination rates. Measures include optimizing vaccine funding mechanisms, expanding subsidy coverage, ensuring vaccination services, improving convenience, conducting public education campaigns on influenza risks and vaccine benefits, and enhancing awareness and acceptance, especially among high-risk groups [10]. Additionally, developing child-friendly vaccine formulations can boost vaccination rates among children.

5. Conclusion

The pathological interaction between the influenza virus and the host begins with the virus breaching the mucosal barrier and invading cells via its surface proteins HA and NA. Through strategies like "cap-snatching" (where RdRP hijacks host mRNA caps), the virus hijacks the host's synthetic machinery for efficient replication. The virus's dual mutation mechanisms (antigenic drift and reassortment-mediated antigenic shift) allow it to evade immune surveillance, while the NS1 protein suppresses interferon pathways, further weakening innate immunity. This leads to respiratory epithelial damage, inflammatory storms, and increased risk of secondary infections. The host counterattacks with a coordinated immune network: humoral immunity produces antibodies to neutralize extracellular viruses, while cellular immunity uses cytotoxic Tcells to eliminate infected cells. These responses, orchestrated by helper T cells, complement each other, with memory cells establishing long-term protection.

Current prevention strategies focus on two paths: antiviral drugs and vaccine development. Drug design targets conserved viral proteins (e.g., RdRp, 3CLpro) to avoid resistance, while vaccine development shifts from egg-based to cell-based production for better efficacy. Universal vaccines targeting conserved epitopes (e.g., HA/NA/M2) or internal proteins (e.g., NP/M1) aim to overcome strain-matching limitations. The mRNA platform, with its strong dual immune activation, is a promising direction. However, low vaccination rates remain a major challenge, requiring multi-dimensional interventions like optimized funding policies, improved doctor-patient communication, public education on influenza risks (especially in rural and low-awareness populations), and child-friendly formulations.

The development of flu vaccines has been ongoing for over 70 years. From single-strain to quadrivalent vaccines, from egg-based to mammalian cell culture production, and from inactivated to various new vaccine types - research has never stopped because flu viruses keep mutating.

Although quadrivalent flu vaccines offer more comprehensive protection, they haven't become the dominant type in the market due to economic and production limitations. Therefore, better vaccine production platforms that balance safety and cost-effectiveness are needed. Current research focuses on developing universal flu vaccines that can protect against all flu virus strains. This would solve the problems caused by antigenic drift, antigenic shift, or mixing of different virus strains. For example, to create vaccines that target stable parts of the virus that don't change much. Secondly, to develop mRNA and protein-based vaccines that can produce stronger immune responses in our bodies. These new vaccines could work against many different variants, which would save money on developing separate vaccines for each new strain. Another key objective is the establishment of reliable vaccine production systems to ensure rapid and sufficient vaccine supply during flu pandemics. Enhancing vaccine technology to improve efficacy can increase public trust and vaccination rates. Additionally, developing more user-friendly forms, such as nasal spray vaccines, would be particularly beneficial for children. These advancements would significantly strengthen global preparedness for future influenza outbreaks.

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