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The road to a more effective influenza vaccine: Up to date studies and future prospects

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ABSTRACT

Influenza virus causes an acute respiratory infection in humans. Frequent point mutations in the influenza genome and occasional exchange of genetic segments between virus strains help the virus evade the pre-existing immunity, resulting in epidemics and pandemics. Although vaccination is the most effective intervention, mismatches between circulating viruses and vaccine strains reduce vaccine efficacy. Furthermore, current injectable vaccines induce IgG antibodies in serum (which limit progression of influenza symptoms) but not secretory IgA antibodies in the respiratory mucosa (which prevent virus infection efficiently). Therefore, numerous studies have attempted to improve influenza vaccines. The discovery of broadly neutralizing antibodies has progressed research into antigen design. Studies designed to improve vaccine efficacy by changing the vaccine administration route have also been conducted. A thorough understanding of the mechanisms underlying the action of various vaccines is essential if we are to develop a universal influenza vaccine. Therefore, evaluating the quality and quantity of antibodies induced by vaccines, which determine vaccine efficacy, is critical. However, at present vaccine evaluation relies on hemagglutination inhibition tests, which only measure the quantity of antibody produced. Antibody repertoires comprise a set of antibodies with specific genetic or molecular features that correspond to their functions. Genetically and functionally similar antibodies may be produced by multiple individuals exposed to an identical stimulus. Therefore, it may be possible to evaluate and compare multiple vaccine strategies in terms of the quality and quantity of an antibody response induced by a vaccine by examining antibody repertoires. Recent studies have used single cell expression and high-throughput immunoglobulin sequencing to provide a detailed picture of antibody responses. These novel methods may be critical for detailed characterization of antibody repertoires induced by various vaccination strategies.

Contents

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1. Introduction

Influenza is a highly contagious acute respiratory disease that causes mild to severe respiratory symptoms in humans. The etiological agent of this disease is influenza virus, which belongs to the family *Orthomyxoviridae* [1]. Influenza virus contains a segmented negative-strand RNA genome, which is subject to frequent mutation, particularly point mutations within the antigenicity-determining regions (i.e., antigenic drift) [2]. These mutations enable the virus to evade pre-existing immunity induced by past vaccination and infection, leading to large, local epidemics [3]. In addition, occasional exchange of genetic segments between genetically distinct virus strains (i.e., antigenic shift) gives rise to an unprecedented virus type [4].

Influenza virus targets epithelial cells lining the respiratory tract and causes local inflammation upon human infection [5]. The human immune system defeats viral infection chiefly via humoral immune responses; the main effectors are secretory IgA (S-IgA), which is localized at the surface of the respiratory epithelium, and IgG antibodies in the serum [6]. Thus, vaccination is currently the most effective intervention to mitigate the harm caused by this virus at both the individual and societal level.

The majority of current vaccines are of the injectable inactivated type, particularly detergent-disrupted split virus vaccines. Hemagglutinin (HA) is one of the major protective antigens expressed by the influenza virus and is a potential target for anti-influenza humoral immune responses. HA is integrated into the envelope of the virus particle and plays a role in viral attachment and entry into target cells [7]. HA expressed by influenza A viruses is classified into 18 antigenically distinct subtypes (H1–H18), whereas that expressed by influenza B viruses is classified as two separate lineages (Yamagata and Victoria) [8]. Currently, human influenza vaccines contain three or four formulation strains (A/H1N1, A/H3N2, and either or both of the two influenza B lineages) that circulate among human populations. Since virus antigenicity differs greatly according to the virus strain (regardless of HA subtype), vaccine compositions are updated annually in accordance with surveillance data reported by the World Health Organization [9]. Nevertheless, antigenic mismatches between circulating and vaccine virus strains can greatly reduce vaccine efficacy [10]. In addition, current inactivated vaccines are administered via either intramuscular or subcutaneous injection. These administration routes induce virus-specific IgG antibodies in the serum; however, it is secretory (s)IgA at the site of infection (i.e., the respiratory mucosal surface) that plays the major role in preventing infection. In other words, current vaccines, which only induce serum IgG antibodies, limit the severity of symptoms after influenza virus infection but do not prevent virus infection at the primary target site [6,11]. Therefore, more effective vaccines are needed, and numerous studies have attempted to develop a novel influenza vaccine. Here, we review current progress toward a more effective influenza vaccine, along with the research methods used. We will also provide some insight into future influenza vaccine research.

2. Characteristics of human antibodies specific for influenza viruses

Antibodies specific for the HA protein, induced by viral infection or vaccination, play a critical role in preventing/inhibiting viral replication, thereby limiting the severity of symptoms. HA comprises two domains: the membrane-distal globular head domain and the membrane-proximal stalk domain. Most HA-specific antibodies target the head domain [12,13]. Therefore, the head domain is constantly subject to strong evolutionary pressure, leading to frequent point mutations that result in antigenic drift, a process that enables the virus to evade anti-viral immune responses [2]. By contrast, the stalk domain of HA is relatively well-conserved among multiple virus subtypes [14]. This fact led to the idea that an antibody clone that binds to the stalk domain of HA might be capable of neutralizing multiple strains of influenza virus; such an antibody clone would be classed as a broadly neutralizing antibody (bnAb). Indeed, in 1993 Okuno et al. succeeded in identifying C179, a murine bnAb clone that recognizes the HA stalk domain and neutralizes both the H1 and H2 subtypes [15]. In 2008, another study identified a human-derived bnAb (A06) in an H5N1 avian influenza virus infection survivor; this antibody neutralized both the H1 and H5 subtypes [16,17]. Subsequent studies have identified other bnAbs in healthy humans [18–23], seasonal influenza convalescents [24,25]/vaccinees [13,24,26–38], pandemic influenza survivors [39,40]/vaccinees [41], and H5N1 avian influenza virus infection survivors [16,17]/vaccinees [42] (Table 1.). Some exhibited surprising breadth in terms of their neutralizing potency. For example, F16v3 neutralizes virus strains belonging to antigenically distinct groups 1 (H1 and H5) and 2 (H3 and H7) [24].

The discovery of bnAbs provided a substantial amount of valuable information. Structural analysis of complexes formed between bnAbs and HA revealed conformational epitopes on the HA surface that are highly conserved among various strains and subtypes of HA. The hydrophobic groove within the HA stalk domain is an example of such a highly conserved conformational epitope. Antibodies specific for these epitopes disrupt the low pH-induced conformational rearrangement of HA, which is an essential step required for fusion of the virus with the host cell membrane [18,30,37]. Epitopes recognized by bnAbs are also present in the head domain, in particular, the receptor-binding site (RBS). Antibodies that target the RBS inhibit the binding of HA to cellular receptors, although the neutralizing breadth of these antibodies is relatively limited compared with that of stalk-targeting bnAbs [21,25,31,34]. Identification of epitopes targeted by bnAbs has led to development of vaccine antigens that induce antibodies directed to these sites: these will be discussed later. In addition, the structural and genetic characteristics of bnAbs have been studied intensively. Diversity of the heavy and light chain genes within the variable region, which binds to an epitope, is due to V(D)J recombination and somatic hypermutation (SHM). The sites within the variable region that come into direct contact with their epitopes are called complementary determining regions (CDRs). HCDR3, which is encoded by the junction site of heavy chain V, D, and J segments, is the most variable whole antibody gene in terms of genetic sequence and length [43]. Therefore, it is the main region that defines antigen binding and antibody specificity [44,45]. B cells in the germinal centers of secondary lymphoid tissues undergo SHM, and B cells harboring mutations that increase antibody affinity for specific antigens are selected and expanded. This event increases the sequence diversity of the variable region [46]. Until recently, it was believed that these events occur randomly in individuals, and that established antibody repertoires comprise antibody clones that are unique to each individual. However, bnAbs share common characteristics, such as V(D)J gene usage, HCDR3 length, and SHM rate. In addition, studies reveal preservation of genetic signatures among bnAbs that have similar functional characteristics. For example, many bnAbs identified in various individuals make use of the same VH1-69 germline heavy chain. Most heavy chains derived from the VH1-69 germline harbor exposed hydrophobic residues at the tip of the HCDR2 loop, which stabilizes binding to the highly conserved hydrophobic groove in the HA stalk domain [16,18,26,34]. Several other bnAbs utilize the VH3-30 gene; these bnAbs are characterized by a long HCDR3 loop containing hydrophobic residues that contact the hydrophobic groove [23,24,35]. Further studies may enable us to

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