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Influenza vaccines: 'tailor-made' or 'one fits all'

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Currently used inactivated influenza vaccines aim at the induction of virus-neutralizing antibodies directed to the variable head domain of the viral hemagglutinin. Although these vaccines are effective against antigenically matching virus strains, they offer little protection against antigenically distinct drift variants or potentially pandemic viruses of alternative subtypes. In the last decades, the threat of novel influenza pandemics has sparked research efforts to develop vaccines that induce more broadly protective immunity. Here, we discuss the immune responses induced by conventional 'tailor-made' inactivated and live influenza vaccines and novel 'one fits all' candidate vaccines able to induce cross-reactive virus-specific antibody and T cell responses and to afford protection to a wider range of influenza viruses.

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Introduction

Influenza viruses are a leading cause of respiratory tract infections and worldwide between 290 000 and 650 000 patients die of influenza every year during seasonal epidemics (WHO; URL: http://www.who.int/mediacentre/factsheets/fs211/en/). The successful perpetuation of influenza viruses in the human population can at least in part be explained by their capacity to evade recognition by virus neutralizing antibodies that have been induced by previous infections or vaccinations. This antigenic drift is facilitated by accumulation of mutations in the proximity of the receptor-binding site (RBS) located in the variable head domain of the viral hemagglutinin (HA) [1,2]. The variable nature of seasonal influenza viruses complicates production of effective vaccines and requires annual updates of the vaccine composition to match the vaccine strains with the epidemic strains. Furthermore, the ever looming predominantly avian and swine influenza viruses that are antigenically distinct and able to infect humans regularly are of great concern and pose a pandemic threat. In the case of a pandemic outbreak with one of these viruses, the timely production of sufficient doses of a 'tailor-made' vaccine is a challenge as became clear during the pandemic of 2009, when in many countries vaccines became available after the peak of the pandemic. Although 'tailor-made' vaccines afford robust protection by the induction of strain-specific virus neutralizing antibodies, there is a clear need for 'one fits all' influenza vaccines (Table 1). Here we discuss immune responses induced by current and candidate future vaccines with emphasis on their breadth and capacity to react with various influenza viruses and their protective potential.

Humoral immune responses induced by licensed influenza vaccines

Protective immunity provided by currently licenced influenza vaccines is based on the induction of antibodies primarily targeting the surface protein hemagglutinin. Inactivated (split or subunit) vaccines produced in eggs or MDCK cells, and the recombinant baculovirus-expressed HA-based vaccine administered intramuscularly or intradermally induce HA-specific virus-neutralizing (VN) serum antibodies, which afford protection as was demonstrated in animal models and humans [3–5]. Strain-specific serum antibodies interfering with the binding of the viral particle to the target cells are typically measured by using the hemagglutination inhibition (HI) test. HI titer, which is a good proxy for VN antibodies, represents the best available correlate of protection for vaccine-induced humoral responses and was one of the primary criteria for vaccine licensure [5,6].

The HA comprises two regions: the immunodominant highly variable globular head that is located in the HA1 subunit and contains the RBS, and a relatively conserved subdominant stalk region responsible for fusion of viral and host cell endosomal membranes and subsequent viral entry [7–9]. The majority of antibodies induced by seasonal vaccines recognize epitopes located in (or adjacent to) the RBS and block viral attachment to sialic acids expressed on the surface of host respiratory epithelial cells [1,2,9,10]. However, these narrow strain-specific VN antibodies are only effective when the circulating influenza strains antigenically match the vaccine strains [11,12]. Because seasonal influenza viruses undergo antigenic drift, which allow them to evade recognition by VN antibodies induced by infection or vaccination, the vaccine composition has to be updated almost annually

Table 1

Comparison of 'tailor-made' and 'one fits all' influenza vaccines

Vaccine category	Correlate of protection	Target	Mode of action
Tailor-made	Antibodies	RBS in head domain of HA	Virus neutralization
One fits all		Stalk region of HA	ADCC, ADPC, VN Inhibition of fusion/entry, egress, HA maturation?
	Antibodies	M2e NP NA?	ADCC, ADPC
	CD4+ T cells	All proteins	Lytic activity, T cell help
	CD8+ T cells	Predominantly NP, M1, polymerases	Recognition and elimination of infected cells

[13,14]. Seven amino acid residues located close to the RBS have been identified as the main molecular determinants responsible for antigenic changes during the evolution of A/H3N2 viruses [1]. Of note, substitution of a single amino acid leads to new genetic variants that can escape the host immune responses [15]. Importantly, adaptation to replicate in embryonated chicken eggs can result in antigenic changes and consequently reduce vaccine efficacy [16–18].

The live-attenuated influenza vaccines (LAIVs), administered by the nasal route, induce serum antibody responses relatively poorly but efficiently induce protective mucosal IgA (SIgA) antibodies in the upper respiratory tract [19–23]. SIgA can neutralize the virus at the portal of entry, limiting viral spread in the respiratory tract. The LAIVs elicit multifaceted immune responses, similar to a natural infection. LAIV-induced mucosal antibodies and virus-specific T cell responses are likely to play a role in protective immunity.

Targets for cross-reactive antibody responses

Induction of 'tailor-made' strain-specific neutralizing antibodies targeting the highly variable globular head of HA is a major limitation of current inactivated vaccines because protection against drifted as well as shifted virus strains is limited. Vaccines able to elicit broad and long lasting humoral immune responses, ideally against influenza viruses of various subtypes, are currently under investigation.

In the context of 'one-fits all' vaccine development, the stalk domain of HA has attracted considerable interest as potential candidate in recent years [24–26]. This domain is functionally important and, in contrast to the globular head, more conserved across different viruses. Anti-stalk monoclonal antibodies isolated from human B lymphocytes have been shown to be broadly reactive with multiple strains of influenza A virus and displayed protective capacity against homologous and heterologous viruses [27–30,31•]. The anti-stalk antibodies may provide protective immunity by inhibiting the fusion process, virus egress from infected cells or proteolytic cleavage of the HA by host proteases [32,33,34•,35,36]. Furthermore, alternative mechanisms underlying the protective effect of those antibodies have been described, which include engagement of the Fc portion of the stalk-reactive antibodies with components of the complement system or Fcγ receptors (FcγRs) expressed on innate immune cells, leading to complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC), respectively. Both mechanisms lead to killing of influenza virus infected cells [37–40]. Furthermore, binding of Fc to FcγRs can induce antibody-dependent cellular phagocytoses (ADCP) and alveolar macrophages may play a role in the clearance of virus [35,41•,42•,43,44•]. Head-specific antibodies seem to mediate ADCC activity inefficiently and it has been proposed that for the optimal activation of effector cells two points of contact are required to narrow the immunological synapse. In addition to Fc/FcγR interaction, binding of HA to sialic acids on NK cells could facilitate this [39,45••]. Head-specific antibodies would prevent this.

Approaches that aim at the induction of broadly reactive HA-stalk specific antibodies are under development and include the use of headless HA by either deleting this region or increasing its glycosylation in order to mask the globular immunodominant domain [24,46]. An interesting approach is based on sequential immunization using chimeric HA constructs containing a conserved stalk region and a globular head from antigenically distinct HA strains (e.g. avian virus strains), to which humans are immunologically naïve [47–49]. This vaccination strategy should promote the recall responses of HA stalk-specific memory B cells with a modest globular head-specific antibody response.

Besides the stalk region of HA, other relatively conserved antigens such as neuraminidase (NA), matrix protein 2 (M2) and nucleoprotein (NP) are also of interest for inducing broad protective humoral immune responses.

The NA is the second surface glycoprotein and inhibition of its enzymatic activity by antibodies may reduce viral shedding and severity of the disease, as demonstrated in animals and humans [50]. However, other mechanisms involving the Fc-mediated effector functions might also