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Review

Functional and structural characteristics of secretory IgA antibodies elicited by mucosal vaccines against influenza virus

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ABSTRACT

Mucosal tissues are major targets for pathogens. The secretions covering mucosal surfaces contain several types of molecules that protect the host from infection. Among these, mucosal immunoglobulins, including secretory IgA (S-IgA) antibodies, are the major contributor to pathogen-specific immune responses. IgA is the primary antibody class found in many external secretions and has unique structural and functional features not observed in other antibody classes. Recently, extensive efforts have been made to develop novel vaccines that induce immunity via the mucosal route. S-IgA is a key molecule that underpins the mechanism of action of these mucosal vaccines. Thus, precise characterization of S-IgA induced by mucosal vaccines is important, if the latter are to be used successfully in a clinical setting. Intensive studies identified the fundamental characteristics of S-IgA, which was first discovered almost half a century ago. However, S-IgA itself has not gained much attention of late, despite its importance to mucosal immunity; therefore, some important questions remain. This review summarizes the current understanding of the molecular characteristics of S-IgA and its role in intranasal mucosal vaccines against influenza virus infection.

Contents

1. Introduction

Influenza virus is the etiological agent of influenza, which is characterized by sudden onset of high fever and respiratory symptoms that include cough and sore throat accompanied by systemic symptoms such as headache, muscle aches, and fatigue. Influenza viruses continually circulate in human populations worldwide. In temperate climates, influenza generally spreads throughout the population in a yearly outbreak (associated with the winter months); such outbreaks are known as seasonal influenza. Influenza shows less seasonality in regions closer to the equator, where the virus may circulate all year round and infections tend to occur either in two less pronounced peaks or at a constant rate throughout the year. Annually, influenza virus causes three to five million cases of severe illness and 250,000–500,000 deaths worldwide [1]. On rare occasions, a new strain is transmitted from animals to humans; because this virus is new to the human immune system, it spreads in a pandemic manner [2]. In the case of both seasonal and newly evolved virus stains, the most efficient countermeasure is prevention by means of vaccination. Infection with the influenza virus occurs via the respiratory system, usually the mucosal epithelium lining the upper respiratory tract. When humans

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become infected, an humoral immune response is triggered; this comprises mainly secretory IgA (S-IgA), which coats the mucosa of the respiratory system, and serum IgG antibodies [3]. Therefore, the humoral immune response tackles the infection in two ways: via secretion of S-IgA, which is the major contributor to humoral mucosal immunity and eliminates a pathogen before it passes the mucosal barrier, and by production of serum IgG, which passes from the serum to the mucus coatings via diffusion [3–5]. In addition to humoral responses, cell-mediated immune (CMI) responses are also activated by influenza virus infection. Although CMI responses are thought to play a significant role in preventing virus replication and improving clinical outcome, they do not confer sterilizing immunity (which is conferred by humoral immunity) [6]. Several clinical studies show that serum concentrations of antibodies against influenza virus correlate with the level of protection against influenza [7], indicating that humoral immunity plays a predominant role in protective immunity against the virus.

In general, influenza vaccinations are delivered via the subcutaneous or intramuscular routes. This results in an increase in serum antibody levels, but not in mucosal antibody levels (including S-IgA), thereby conferring protection from onset of disease but not preventing infection [8–11]. However, a growing body of evidence shows that mucosal antibodies and efficient protection from influenza virus infection can be elicited by intranasal vaccination, suggesting that this method (which induces mucosal antibodies such as S-IgA) may be more effective than parenteral alternatives [11–13]. Additionally, an intranasal influenza vaccine is attractive because it can raise dual systemic/mucosal responses, thereby providing increased protection; it is also expected to lead to increased influenza vaccination coverage because it is pain-free [14]. This review article focuses on the molecular characteristics of S-IgA in human external secretions and its role in protecting against influenza virus infection after intranasal vaccination.

2. Induction of mucosal immunity against influenza virus by mucosal influenza vaccines

Currently, intranasal mucosal vaccination against influenza using a live attenuated influenza vaccine (LAIV) is available in the United States and the European Union [15]. The main characteristic of an intranasal LAIV is that it mimics the natural route of infection and induces S-IgA production (in the upper respiratory tract) and serum IgG responses, in addition to CMI responses [12,16,17]. The LAIV first licensed as a trivalent formulation (LAIV3) in the US in 2003, is now available as a quadrivalent formulation (LAIV4). Several clinical studies compared the effectiveness of LAIV3 with that of an injectable trivalent inactivated influenza vaccine (IIV3). The results revealed that, although the efficacy of IIV3 was similar or slightly higher than that of LAIV3 in healthy adults aged 17–49 years old [8,18–21], the efficacy of LAIV3 was superior in children aged 6 months to 18 years [18,22–24]. However, the effectiveness of LAIV4 against A/H1N1pdm09 strains in children has fallen significantly [25–27]. This may be because the vaccine virus may not replicate well in the epithelial cells lining the human upper respiratory tract and so may not elicit an immune response strong enough to protect against influenza virus infection [28]. This raises a concern that the efficacy of intranasal LAIV relies on the processes of infection and replication in upper respiratory epithelial cells, both of which may be dependent on the particular LAIV strain(s) used.

Despite its limitations, LAIV is superior to conventional injected influenza vaccines in terms of inducing mucosal immunity [12,16,17]. The alternative strategy for inducing mucosal immunity is intranasal vaccination with an inactivated influenza virus vaccine. There have been numerous attempts to develop an inactivated influenza vaccine that can be administered via the mucosal route. Since the weak immunogenicity of an inactivated vaccine means that it cannot itself elicit a full immune response at the mucosal surface, an adjuvant is required to increase the immune response. Traditionally, bacterial toxins (cholera toxin and heat-labile enterotoxin [LT]) have been used to boost mucosal immune responses following intranasal vaccination. In the upper respiratory tract, these mucosal adjuvants induce S-IgA antibodies, which then provide effective cross-protection against different viruses of the same subtype [29,30]. However, studies report cases of Bell's palsy associated with administration of the first licensed inactivated virosomal-subunit influenza vaccine combined with LT (NasalFlu) [31,32]; therefore, the vaccine was withdrawn from clinical use. The following investigation revealed that Bell's palsy was caused (presumably) by the intrinsic characteristics of the LT, which targets neurons [33]. Many subsequent attempts have been made to identify an alternative to bacterial toxins for use as an adjuvant for intranasally administered inactivated vaccines. The candidates include synthetic dsRNAs [34–36], CpG [37], chitin, surf clam microparticles [38,39], α-galactosylceramide [40], poly (gamma-glutamic acid) nanoparticles [41], monophosphoryl lipid A [42], PolyI:PolyC12U [34,43], and the *S. cerevisiae* cell wall extract zymosan [44]. Numerous studies of innate immune systems indicate that pathogen-associated molecular patterns (PAMPs) and endogenous damage-associated molecular patterns (DAMPs) recognized by pattern-recognition receptors may also be candidate adjuvants [45]. Some of these stimulate the innate immune system. Administration of the candidate adjuvants along with inactivated influenza vaccine antigen to animal models, including mice and monkeys, elicits secretion of S-IgA antibodies onto the surface of the mucosal epithelium lining the upper respiratory tract; these antibodies provide protection against influenza virus infection [34–36,39,44]. However, unexpected adverse events (such as Bell's palsy) in the individuals receiving NasalFlu shows that the clinical utility/safety of intranasal inactivated influenza vaccines administered with candidate adjuvants requires further study in animal models prior to use in humans. In real terms, inactivated influenza vaccines combined with these novel adjuvants are at the middle stage of development; thus no mucosal adjuvant is authorized for practical use at the time of writing.

A whole inactivated virus vaccine (WIVV) is more immunogenic than a split-virus vaccine [46]. Also, intranasal administration of a WIVV, rather than a split-virus vaccine, induces a broad spectrum of heterosubtypic immunity against influenza virus infection [47]. Koyama et al. revealed that the higher immunogenicity of WIVV depends on intrinsic vRNAs, which are recognized by TLR7, and that this format of the vaccine is superior to a split-virus vaccine due to its priming effect in naïve subjects [48]. Taken together, these reports suggest that a WIVV could induce more effective immune responses than a split-virus vaccine after intranasal vaccination. Studies conducted in humans indicate that intranasal vaccination with WIVVs increases the production of both local influenza virus-specific IgA antibodies and serum hemagglutination-inhibiting (HI) antibodies [49,50]. Moreover, only two doses of an intranasal WIVV are needed to induce a >2.5-fold increase in the geometric mean titer (GMT) [11]; by contrast, intranasal administration of split-virus vaccines required four doses to induce a 2.5-fold increase in the GMT of serum neutralizing antibodies in humans [51], indicating that WIVV is more immunogenic than a split-virus vaccine when delivered via the intranasal route. Recent studies that analyzed nasal wash samples report that intranasal vaccination with WIVV induces HI and neutralizing antibody responses, which show a strong correlation with serum antibody responses, suggesting that effective local mucosal immune responses are evoked by intranasal administration of WIVV. Interestingly, serum neutralization titers correlated well

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