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Review

Universal anti-influenza vaccines based on viral HA2 and M2e antigens

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Summary. – Aquatic birds are the main reservoir of influenza A viruses (IAVs). These viruses can infect humans repeatedly and cause acute respiratory disease with potential of spread in the form of epidemics. In addition, avian influenza viruses that overcome the interspecies barrier and adapt to humans can cause a world-wide pandemic with severe consequences to human health. Therefore, scientists are focused on the development of a "universal" vaccine with a broad protective efficacy, i.e. against different subtypes of influenza A viruses and not only against the currently co-circulating human epidemic strains. Nowadays, several new vaccine design strategies have been described. Most of them utilize the conserved stem part of influenza surface glycoprotein hemagglutinin (HA) or the ectodomain of M2 (M2e) protein with proton-channel activity. A comparison of the efficacy of novel vaccines and their protective mechanisms against influenza infection is discussed in this review and should be considered for the construction of the most effective broadly protective vaccine with minimal side effects. This is the essential goal in influenza virus research today, especially when the infection with new human coronavirus SARS-CoV-2 can interfere with the course of influenza virus infection.

Keywords: influenza A virus; HA2 gp; M2 ectodomain; universal vaccine

Introduction

Influenza A viruses (IAVs) cause the acute respiratory disease in humans. Influenza epidemics are repeated yearly due to the high IAV variability. Sometimes a new IAV emerges in human population and spreads rapidly among humans causing pandemics because of the lack of herd immunity. The main reservoir of zoonotic IAVs is waterfowl. Avian influenza viruses can overcome interspecies barrier and, after accumulation of adaptive mutations required for virus propagation, they can be transmitted to new host. Avian IAV can be adapted to humans or to other mammals (Herfst *et al.*, 2014; Schrauwen and Fouchier, 2014; Saunders-Hastings and Krewski, 2016). The study of the amino acid markers specific for particular virus host is essential for the knowledge of possibilities and restrictions of inter-species transmission of zoonotic influenza viruses. Adaptive mutations leading to fixation of new host-specific markers were reported for human or equine IAVs (Miotto *et al.*, 2010; Mucha *et al.*, 2018).

Influenza infection of humans can have a spectrum of clinical symptoms from mild to severe, depending on the virus dose, the virulence of virus and the host immune

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Abbreviations: ADCC = antibody-dependent cellular cytotoxicity; ADP = antibody-dependent phagocytosis; HA = hemagglutinin; HA1 = heavy chain of HA; HA2 = light chain of HA; IAV(s) = influenza A virus(es); IgG = immunoglobulin G; KLH = Keyhole limpet hemocyanin; MAb(s) = monoclonal antibody(ies); M2 = matrix protein 2; M2e = ectodomain of M2; VLP = virus-like particle

system. During the usual epidemic season, characteristic manifestations of a relatively mild course of influenza infection include fever, myalgia, cough, weakness, but without health consequences. A severe course of illness appears especially in risk groups of patients – elderly people, immunocompromised persons, and patients suffering from chronic illness as are cardiovascular, respiratory (asthma), oncological diseases or metabolic disorders. In these cases, influenza infection may result in the viral pneumonia, sometimes even with fatal outcomes. Primary influenza infection is often associated with secondary bacterial respiratory infection that can have a dangerous progress (McCullers, 2014). Influenza can be treated with antivirotics - neuraminidase inhibitors, e.g. oseltamivir and zanamivir, or virus polymerase inhibitors, e.g. baloxavir and favipiravir (latter licensed in Japan only). However, all of the antivirotics mentioned above are effective when applied in the early phase of influenza infection (24–48 h after infection) and a later application would not be effective.

However, the most effective defense against influenza is the vaccination (Paules and Subbarao, 2017). Currently, two types of influenza vaccines containing IAV of H1 and H3 subtypes and one or two influenza B virus antigens are approved in human medicine. These are live attenuated vaccines, permitted only in USA and Russia, or inactivated vaccines (Nachbagauer *et al.*, 2018; Sunwoo *et al.*, 2018). The most commonly used inactivated vaccines are split virus vaccines and subunit vaccines containing purified surface glycoproteins of virus (Stropkovská *et al.*, 2010; Soema *et al.*, 2015). These influenza vaccines generally induce antibody response against the main immunogens of IAV, the surface glycoproteins hemagglutinin (HA) and neuraminidase (NA). Virus-neutralizing antibodies are targeted particularly against the globular part of HA, representing the highly variable region of HA. Because of the high variability of both, HA and NA, IAV can avoid the pre-existing immunity in human population and the effectivity of disease protection mediated by vaccination is lower (Gamblin and Skehel, 2010; van de Sandt *et al.*, 2012). Therefore, it is necessary to evaluate seasonal vaccine effectiveness yearly and to re-design vaccine composition for the subsequent season. Effectiveness of seasonal anti-influenza vaccines ranges usually between 30%–70% (Kissling *et al.*, 2014; Flannery *et al.*, 2017). Another disadvantage is that currently used seasonal inactivated vaccines do not induce efficient cellular immune responses and mucosal immunity (Chen *et al.*, 2001; Calzas and Chevalier, 2019; Mohn *et al.*, 2020).

To avoid the necessity of seasonal changes in vaccine production and to provide the protection against various IAV subtypes, an effort is focused on the development of IAV vaccines based on immune recognition of antigenically conserved IAV antigens (Gerhard *et al.*, 2006; Brandenburg *et al.*, 2013; Krammer, 2015; Krammer and Palese, 2015).

Such broadly cross-protective vaccines are targeted against the conserved parts of the surface IAV antigens HA, NA or matrix protein 2 (M2), eliciting mainly the antibody response (Gomez Lorenzo and Fenton, 2013). Another group of vaccines is targeted against internal proteins, matrix protein 1 (M1) or nucleoprotein (NP), inducing the cross-protection mediated by antigen-specific T-cells (Sridhar *et al.*, 2013; Epstein, 2018). In order to stimulate both virus-specific T-cell immunity and protective antibody response, some vaccines contain combination of internal proteins (NP, M1) with HA2 domain or M2 ectodomain (M2e), utilizing different ways of antigen presentation (Heinen *et al.*, 2002; Stepanova *et al.*, 2018; Tsybalova *et al.*, 2018; Sun *et al.*, 2019).

The majority of studies are focused on the HA2 and M2e, which are highly conserved even among different IAV subtypes. Though they are present on the surface of viral particle, their restricted accessibility is responsible for the low immunogenicity of these conserved antigens. Thus, the essential goal during the development of HA2- or M2e-based vaccines is to achieve the most effective increase of their immunogenicity (Kwong and Wilson, 2009) and many strategies were developed to enhance HA2 and M2e presentation to the immune system.

Strategies of the development of new HA2-based anti-influenza vaccines

HA is the main surface antigen of IAV. It is a glycoprotein composed of three identical monomers connected by intermolecular bonds. Each monomer consists of two subunits, HA1 and HA2 glycopolypeptides linked by disulphide bonds, which are products of post-translational proteolytic cleavage of HA precursor (HA0) (Skehel and Wiley, 2000; Sriwilaijaroen and Suzuki, 2012). HA has a dual role during the virus entry into the cell: i) the virus attachment to the cell via receptor binding site on HA1 globular part of HA trimer and ii) HA2 gp-mediated fusion of viral and endosomal membranes after internalization of virus into the endosome. The globular part of HA is immunodominant and induces virus-neutralizing antibodies that block the virus attachment to the cell surface by targeting the area near the HA receptor binding site. The stem of HA trimer is formed mainly by HA2 gp and only by small region of HA1. It is covered by globular part of HA, therefore, it is immunosubdominant (Fig. 1). The high genetic and structural plasticity of globular HA domain allows its high antigenic variability under the selection pressure of virus-neutralizing antibodies present in hu-

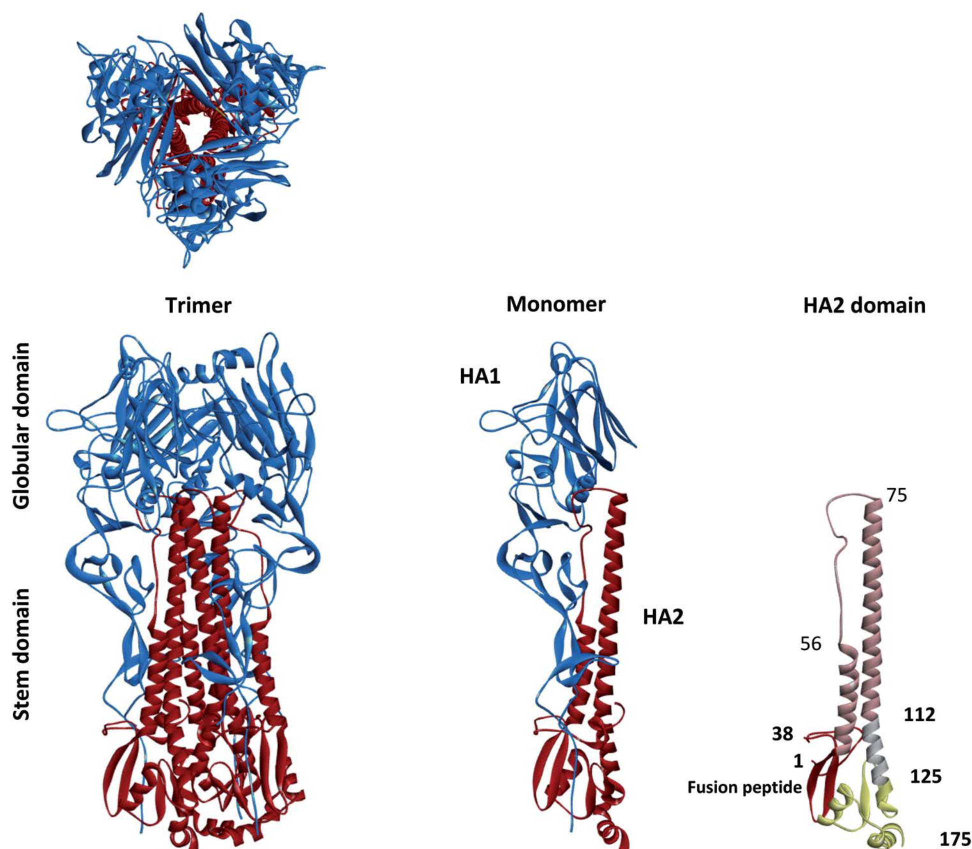

Fig. 1

The structure of hemagglutinin trimer, monomer and HA2 domain of influenza A H3 subtype

In the trimer and monomer molecule of HA, the immunodominant globular domain and immunosubdominant stem domain are colored blue and red, respectively. Despite the less accessible position of HA2 in the HA molecule, four antigenic regions were determined on HA2. Antigenic site I: red (aa1–38), two different antigenic sites II and IV in the same region: yellow (aa125–175) and site III: pink (aa38–112). The figure was created in Discovery Studio 4.1 visualizer. Source: PDB 4WE4.

mans who have overcome the infection or were vaccinated (Isin *et al.*, 2002; Vaccaro *et al.*, 2005). However, HA2 gp is a relatively conserved part due to its localization inside the HA trimer. The conservation of HA2 gp structure is essential for preservation of the function of the HA trimer in the fusion process (Godley *et al.*, 1992; Steinhauer, 1999; Cross *et al.*, 2009; Langley *et al.*, 2009; Hamilton *et al.*, 2012). HA2 gp attracted attention of researchers as a potential immunogen for the cross-protective vaccine preparation because of its position in HA molecule, sequence similarity between HA of different IAV strains and structural stability required for the fusion process.

The important property of anti-HA2 antibodies as a high cross-reactivity of HA2-specific monoclonal or polyclonal antibodies documented in many studies predetermined HA2 gp to be suitable immunogen inducing cross-protection (for review see Graves *et al.*, 1983; Becht *et al.*, 1984; Sanchez-Fauquier *et al.*, 1991; Okuno *et al.*, 1993; Varečková *et al.*, 2002, 2008; Ekiert *et al.*, 2009; Stropkovská *et al.*, 2009; Ekiert *et al.*, 2011; Tomčíková and Varečková, 2019).

Four antigenic sites on HA2 gp and their immunogenicity were described in our laboratory. It was shown that antibodies recognizing three of four antigenic sites inhibited the fusion activity of HA as well as the replication of different IAV subtypes and had protective potential *in vivo* (Varečková *et al.*, 2003a,b; Gocník *et al.*, 2007; Stropkovská *et al.*, 2009). These antigenic sites (Fig. 1) were defined using anti-HA2 monoclonal antibodies. Site I was localized at aa position 1–38 of the N-terminus of HA2, site II and IV were localized in the region of aa125–175 of HA2. Monoclonal antibodies against these sites inhibited the fusion activity of HA and protected mice against the lethal influenza infection. Antigenic site III was localized in the aa region 38–112 of HA2, but antibody targeted against this site (MAb CB8) did not inhibit fusion activity of HA and did not protect mice against the infection (Varečková *et al.*, 2003a,b, 2013; Gocník *et al.*, 2007). However, another

study revealed that repeated subclinical infection of mice with IAV results in the increased induction of HA2-specific antibodies (Kostolanský *et al.*, 2002). The levels of HA2-specific antibodies in convalescent human sera with confirmed influenza infection showed a raising trend with increasing age of patients (Staneková *et al.*, 2012). These studies also demonstrated differences in the immunogenicity of particular antigenic sites on HA2 gp. The most immunogenic was the region aa125–175 of HA2 N-terminus (Staneková *et al.*, 2012).

In parallel, other data about the ability of anti-HA2 antibodies to inhibit the virus replication or release have been published (Prabhu *et al.*, 2009; Krammer and Palese, 2013, 2015; Margine *et al.*, 2013a; Krammer, 2015; Nachbagauer *et al.*, 2016; Nachbagauer and Palese, 2018; Košík *et al.*, 2019), some of them were focused on the antibodies specific to the conformational epitope localized in the HA stem comprising HA1 and HA2 gps (Sui *et al.*, 2009).

The researchers put a great effort into solving the problem of low accessibility and low immunogenicity of HA2 gp with the goal to induce broadly specific protective anti-HA2 antibodies (Angeletti *et al.*, 2017). Various new strategies based on the more effective delivery or exposition of antigen to the immune system were developed (Staneková and Varečková, 2010; Wang *et al.*, 2010; Krammer and Palese, 2013; Margine *et al.*, 2013b; for review: Tomčíková and Varečková, 2019).

The first attempts to enhance the immunogenicity of HA2 gp utilized the carriers of different origins. As carries were frequently used Keyhole limpet hemocyanin (KLH) (Wang *et al.*, 2010; Staneková *et al.*, 2011; Janulíková *et al.*, 2012; Nachbagauer *et al.*, 2017), flagellin from the *Salmonella typhimurium* vaccine strain (Arnon, 2006; Ben-Yedida and Arnon, 2007; Stepanova *et al.*, 2018), nanoparticles (Kanekiyo *et al.*, 2013; Yassine *et al.*, 2015), or virus-like particles (VLP) (Kang *et al.*, 2012; Chen *et al.*, 2015). These vectors enable to present antigen in many copies, resulting in increased robustness of specific immune response. Other approach utilized non-infectious *Escherichia coli*-derived plasmids as DNA vaccines (Katz *et al.*, 2006). DNA vaccines induce T and B-cell immunity, similarly to virus vectors such as vaccinia virus (Gocník *et al.*, 2008), hepatitis B-virus or adenovirus (Nachbagauer and Krammer, 2017). Genetically detoxified bacterial adenylate cyclase toxin produced by gram-negative bacteria *Bordetella pertussis* (Staneková *et al.*, 2013) has also been successfully used as a non-replicating vector presenting ectodomain of HA2 gp (aa23–185 of N-terminus HA2). It turned out to be a good inductor of cross-protective antibody and T-cell immune response against lethal influenza infection because of the way of antigen presentation using this vector.

At the same time, many experiments redirecting the immune response to the conserved part of HA by modulation of the immunization protocols were described (Hai *et al.*, 2012; Krammer and Palese, 2014; Nachbagauer *et al.*, 2018; Sunwoo *et al.*, 2018). Multiple immunizations with chimeric molecules composed of the stem of one HA subtype and a globular part of different subtypes redirected the antibody response to the repeatedly presented conserved HA2-stem. These antibodies conferred anti-influenza protective immunity of broader efficacy (Margine *et al.* 2013a,b; Nachbagauer *et al.*, 2014; Klausberger *et al.*, 2016; Choi *et al.*, 2019). Vaccination strategy with chimeric HA is based on the immune memory, when the repeated immunization attracts the immune response to the conserved HA2 domain. Strategy utilizing the HA lacking the globular part of HA trimer was reported by many authors (Sagawa *et al.*, 1996; Bommakanti *et al.*, 2010; Steel *et al.*, 2010; Bommakanti *et al.*, 2012). It was also shown that the changes in the number of glycosylation sites on HA1 gp can refocus the immune response to the conserved HA2 gp (Vigerust *et al.*, 2007; Medina *et al.*, 2013; Eggink *et al.*, 2014; Tate *et al.*, 2014; Zhang *et al.*, 2015).

A new approach for preparation of vaccine antigen by the reverse genetic method (Fodor *et al.*, 1999; Neumann *et al.*, 1999; Hoffmann *et al.*, 2000; Kawaoka and Neumann, 2012) enabled the construction of attenuated or chimeric viruses that can consequently redirect the immune response to conserved immunosubdominant parts of viruses, such as the HA2 gp, M2e, or internal subdominant antigens (NP or M1 proteins), and simultaneously can stimulate the humoral as well as T-cell immune response (Klausberger *et al.*, 2016). In addition to the utilization of HA2 gp as an immunogen with cross-protective potential, the significant progress has been documented in studies focused on the M2e protein as an inductor of broadly-protective immunity.

Strategies of the development of M2e-based anti-influenza vaccines

M2 protein is 97 amino acid product of the second open reading frame of the IAV genome segment 7. A relatively small number of M2 proteins (approx. 23–60) are present in the viral envelope. However, M2 protein is abundantly expressed in the plasma membrane of IAV-infected cells – its C-terminal part is located in the cytoplasmic space, while N-terminus (23 aa-long ectodomain) is localized extracellularly (Fig. 2). Whole M2 molecule, including ectodomain, is highly conserved. The M2 protein is critical to the IAV life cycle since it forms a homotetramer that acts as a proton-selective transmembrane channel (Pinto *et al.*, 1992). The M2 channel allows pH regulation – acidification of the virion interior in endosome that triggers conformational changes in HA molecule leading to the fu-

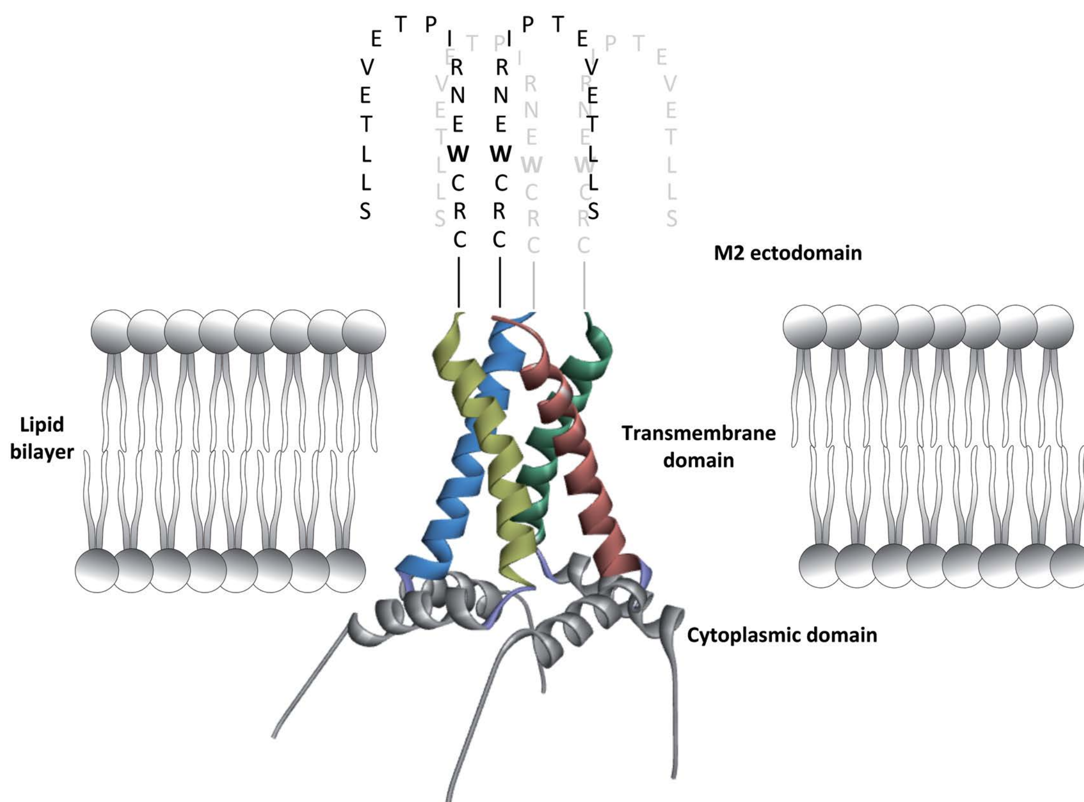

Fig. 2

Schematic illustration of matrix protein 2

M2 forms a proton-selective ion channel in viral or infected cell membranes. M2 assembles into tetramer and can be divided into three parts: extracellular domain, transmembrane domain, C-terminal (cytoplasmic) domain. Figure adapted according to Saelens (2019). (Source: PDB 2l0j; amino acid sequence (aa2–18) is derived from IAV A/Udorn/1972 H3N2, UniProtKB- Q20MD5).

sion of the viral and the endosomal membranes (Wharton *et al.*, 1994; Leiding *et al.*, 2010; Mezhenskaya *et al.*, 2019).

Vaccines based on the conserved sequence of M2 protein ectodomain (M2e) induce specific response that limits the replication and spread of the virus in the respiratory tract. This fact was first implied in a study showing that passive administration of M2-specific MAb 14C2 to mice was able to restrict virus multiplication and accelerate lung viral clearance following a sublethal IAV challenge. Moreover, localisation of virus protein M2 in the virion as well as in infected cells was unveiled by 14C2 (Zebedee and Lamb, 1988, 1989; Treanor *et al.*, 1990).

M2e contains several well-documented overlapping B-cell epitopes, MHC-I or MHC-II restricted epitopes, and also epitopes for some HLA molecules. The most important are B-cell epitopes and epitopes with MHC-II restriction for CD4+ T-cellular response (Mozdzanowska *et al.*, 2003; Zhang *et al.*, 2006; Grandea III *et al.*, 2010; Grant *et al.*, 2014; Eliasson *et al.*, 2017).

Anti-M2e antibodies do not neutralize the virus directly, but they have the ability to suppress the virus replication via involvement of antibody Fc-fragment into the immune response. M2e-specific antibodies act against IAV by the mechanism of antibody-dependent cellular cytotoxicity (ADCC) or antibody-dependent phagocytosis (ADP), resulting in the elimination of infected cells (Jegerlehner *et al.*, 2004; El Bakkouri *et al.*, 2011). Targeting vaccines to M2e makes it possible to achieve specific and long-term immune response mediated not only by antibodies, but also by effector and memory CD4+ T-cells (Staneková and Varečková, 2010; Schotsaert *et al.*, 2013; Eliasson *et al.*, 2017; Jageskanda *et al.*, 2017; Kolpe *et al.*, 2017).

The major challenge in the development of effective antiviral M2e-based vaccine is to overcome the weak immunogenicity of this molecule (Zhong *et al.*, 2014). Similarly as for the HA2-based vaccines, various approaches were used to enhance immunogenicity of M2e.

For more effective presentation of M2e to the immune cells and higher activation of humoral and T-cell immunity, viral vectors based on baculoviruses (Black *et al.*, 1993; Slepushkin *et al.*, 1995), papaya mosaic virus (PapMV) (Denis *et al.*, 2008), vaccinia viruses (Hessel *et al.*, 2014) and

adenoviruses (Coughlan *et al.*, 2015) have been utilized as antigen carriers. Promising method for elicitation of a robust immune response is also DNA vaccination with plasmid DNA that comprises genetic information for M2e (Yao *et al.*, 2019). Another option is represented by adjuvant substances applied together with the immunogen (Eliasson *et al.*, 2008) or carriers such as KLH (Fan *et al.*, 2004; De Filette *et al.*, 2011), nanoparticles, or VLP (Tao *et al.*, 2014, Kim *et al.*, 2013; Wang *et al.*, 2014; Deng *et al*, 2015).

Besides the way of immunogenicity improvement, an interesting question remains open: Which of the two influenza proteins - HA2 or M2e - provides more effective antiviral protection?

A simple comparison of *in vivo* immunization with KLH-conjugated HA2 fusion peptide 1-38 and M2e was performed (Staneková *et al.*, 2011). Repeatedly immunized mice were challenged with the lethal dose of homologous A/Mississippi/1/85(H3N2) or heterologous A/PR/8/34(H1N1) influenza A viruses. Immunization with the fusion peptide led to a 100% survival of mice infected with 1 LD_{50} of homologous as well as heterologous virus. However, survival rate decreased when the infectious dose was raised to 2 LD_{50}. The immunization with M2e induced effective cross-protection of mice infected even with 3 LD_{50} of both challenge viruses. Even though the protection induced by the HA2 fusion peptide was lower, it was still effective. Results of this study suggested that apart from the ectodomain of M2, HA2 fusion peptide could also be considered as a part of cross-protective influenza vaccine (Staneková *et al.*, 2011).

Another question of interest could be the quantification of the immunogen-specific antibodies necessary for protective effect against lethal dose of challenged mice. In passive transfer experiments, mice were immunized by intravenous route with different doses of anti-M2e polyclonal IgG in range from 40 to 320 µg and control mice were administered 320 µg of anti-KLH IgGs. The survival of these mice subsequently infected with 3 LD_{50} IAV was determined. An absolute protection (100% survival) was obtained with 320 µg of anti-eM2 IgGs, and a relatively strong protection (~80% survival, p = 0.024) with 160 µg. The amount 160 µg of IgGs represents approx. 100 µg IgGs per 1 ml of blood (Király *et al.*, 2011). These findings agree with the results obtained by Fu *et al.* (2009), who evaluated anti-M2e protective response, however, using of MAbs at doses of 0.2–2.0 mg per mouse. Another research group (Beerli *et al.*, 2009) found that the most effective anti-M2e MAb provided satisfactory protection against infection with 4 LD_{50} of virus even at dose of 20 µg per mouse. Such a high efficiency can be most probably ascribed to the high affinity (K_d = 4 nmol/l) of that particular MAb.

According to recently published experiments, there is a trend to use the combination of both M2e and HA2 immunogens in a single recombinant vaccine. One group of authors combined M2e and HA2 (aa76–130) inserted into the full-length flagellin from *Salmonella typhimurium* (Flg). Such vaccine administered subcutaneously to mice greatly increased antigen-specific T-cell response and provided full protection from lethal challenge with A/H3N2 and A/H7N9 (Stepanova *et al.*, 2018). Alternatively, these authors inserted HA2 polypeptide (aa76–130) into the recombinant Flg4M2e protein. Intranasal immunization of BALB/c mice with this protein considerably induced mucosal and systemic responses directed against both proteins with resulting antiviral effect and complete protection from lethal challenge with influenza viruses A/H3N2, A/H2N2, and A/H5N1 (Tsybalova *et al.*, 2018). Another research team developed an inactivated influenza virus with M2e epitope (aa2–16) inserted into the Ca2 antigenic site of A/PR8/34 (H1N1). Sequential immunization with these inactivated viruses substantially enhanced anti-M2e as well as anti-stalk region antibody responses providing superior protection of mice against a challenge with 5 LD_{50} of X-31 (H1N1) virus (Sun *et al.*, 2019).

Conclusion

Summarizing the situation in the research and development of new anti-influenza vaccines with broader efficacy, the conclusion can be made that a vaccine based on the combination of both HA2 and M2e proteins seems to be the most promising one. Current vaccines are targeted against the globular HA1 part of influenza hemagglutinin and antibodies against this domain inhibit attachment and entry of virus into the infected cells. These vaccines thus neutralize the infectivity of virus. However, HA1 gp is the most variable part of HA and antibodies are not always effective against new variants that usually cause the epidemic next season. Therefore, vaccines must be updated yearly. On the other hand, antibodies targeting conserved HA2 and M2e antigens do not neutralize virus. The HA2-specific antibodies mediate the protection against influenza infection in two ways: the direct effect of antibody that binds to the HA2 gp, resulting in the inhibition of the fusion process or blocking the HA conformational changes on endocytosed virus. As a consequence, the virus replication is restricted. Another way is the mechanism comprising the effector function of these antibodies (de Vries *et al.*, 2017; Tomčíková and Varečková, 2019). Anti-M2e antibodies, however, mediate the protection by their effector function only (Jegerlehner *et al.*, 2004; El Bakkouri *et al.*, 2011). Recently published data suggest that the development of universal anti-influenza vaccine may be achieved by combination of suitable vaccine candidates, such as conserved epitopes from IAV

proteins (HA, NP, M), and novel vaccination platforms (Nachbagauer and Palese, 2020; Vogel and Manicassamy, 2020). Further research is required to find an answer and for better understanding of these processes.

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