Vaccine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

The key role of rubella virus glycoproteins in the formation of immune response, and perspectives on their use in the development of new recombinant vaccines

Ekaterina K. Petrova*, Anastasia A. Dmitrieva, Ekaterina A. Trifonova, Nikolai A. Nikitin, Olga V. Karpova

Faculty of Biology, Department of Virology, Lomonosov Moscow State University, 1/12 Leninskie Gory, Moscow 119234, Russia

ARTICLE INFO

Article history:
Received 3 August 2015
Received in revised form
29 December 2015
Accepted 5 January 2016
Available online xxx

Keywords:
Rubella virus
Glycoproteins E1 and E2
Epitopes
Development of recombinant vaccines

ABSTRACT

Rubella is a highly contagious viral disease which is mostly threatens to women of reproductive age. Existent live attenuated vaccines are effective enough, but have some drawbacks and are unusable for a certain group of people, including pregnant women and people with AIDS and other immunodeficiency. Thereby the development of alternative non-replicating, recombinant vaccines undoubtedly is needed. This review discusses the protein E1 and E2 role in formation of immune response and perspectives in development of new generation recombinant vaccines using them.

1. Introduction

Rubella is a highly contagious viral disease. The most significant consequence of rubella infection is the transfer of rubella virus to an unborn fetus, where significant birth defects often result. The death of the fetus or congenital malformations, which are known as congenital rubella syndrome (CRS), can occur in 80–85% of cases of rubella virus infection during the first trimester of pregnancy. Worldwide, it is estimated that more than 100,000 children in developing countries are born with CRS each year [1].

In recent times, due to the development and application of highly effective vaccines, there has been a major reduction in the risk of rubella virus infection. However, the rubella vaccine used nowadays consists of an attenuated strain of rubella virus that cannot be recommended during pregnancy, despite the absence of adverse effects in babies born to mothers who were inadvertently vaccinated with the live-attenuated vaccine [2–4]. We have to take into account that live attenuated vaccines containing replicating virus have the risk of reverting back to their virulent form and cause the disease [5]. Vaccination of adult women has been associated with chronic arthritis which is thought to be due to persistence of the vaccine virus [4,6]. The rate of vaccine-associated chronic arthritis appears to be extremely low [7–9], however chronic arthritis following rubella vaccination is included in the National Vaccine Injury Compensation Program [10]. Furthermore another complications of vaccination may occur such as post-infections encephalopathy, Guillain–Barré syndrome, haematological complications: transient thrombocytopenia, purpuric rash, haemolytic anemia [4,11–13]. Additionally, AIDS children and children with other immunodeficiencies also cannot be vaccinated with the current attenuated rubella virus vaccine, and can suffer severely from rubella infection [14]. The availability of a nonreplicating vaccine would offer an alternative that potentially should not be associated with different complications and limitations including the drawbacks of human cell line-derived vaccines such as adverse and allergic reactions and also strict storage conditions. Therefore, the development of a new generation of safe vaccines is needed.

During viral infection, antibodies specific to three structural proteins of the rubella virus (capsid protein (C protein), and glycoproteins E1 and E2) develop. Capsid protein is an internal protein not normally exposed to the immune system in its native form. In the natural infection the protective immune response is predominantly directed toward the glycoproteins [15], mainly against the glycoprotein E1. However, antibodies to glycoprotein E1 persist within the infected person for decades, and progressively increase their affinity [16]. For a period of a month, antibodies to

* Corresponding author. Tel.: +7 495 939 53 67; fax: +7 495 938 06 01.
E-mail address: petrova@mail.bio.msu.ru (E.K. Petrova).

http://dx.doi.org/10.1016/j.vaccine.2016.01.010
0264-410X/

Fig. 1. *The structure of rubella virus genome.* Modified from ViralZone (http://viralzone.expasy.org/all_by_species/626.html).

glycoprotein E2 disappear, and do not undergo further maturation stages. Specific E2 antibodies are also able to neutralize viral infection in vitro [17], although the contribution of this mechanism to the formation of the immune response requires further investigation. Currently, in order to develop new recombinant vaccines to proteins E1 and E2, antigenic properties are being studied.

This paper discusses the role of the proteins E1 and E2 in the formation of immune response, and perspectives on the development of a new generation vaccines that might use them.

2. Rubella virus

The rubella virus is a member of the Togaviridae family and is the sole member of the genus Rubivirus. Rubella virus virions are round and are covered with a lipid envelope. The diameter of virus particles varies from about 57 nm to 86 nm [18]. The rubella virus has two envelope glycoproteins: E1 and E2. Nucleocapsid contains a single-stranded, positive-sense RNA of 9762 nucleotides [19]. The genome structure of rubella virus is showed in Fig. 1. The capsid of rubella virus virions is formed by C protein that is able to block infected cells' proteins' functions, and provides immune response and programmed cell death [20]. Rubella virus structural proteins are translated as the precursor of polyprotein (pl 10) with the order of translation NH2-C-E2–E1-COOH on 24S subgenomic mRNA. Then, synthesized polyprotein is cleaved with the formation of membrane proteins E1 and E2, and a capsid protein [21]. E1 and E2 exist as heterodimers [22].

The tomographic data showed rows of density, formed by glycoprotein E1 and E2 spikes, which extend up to 8 nm from the membrane of the rubella virion surface, and are formed into parallel rows [18]. It was established that rubella virus glycoprotein E1 is more accessible for glycosidases, trypsine and monoclonal antibodies than E2 [23–25]. According to the present data the model of organization rubella virus glycoproteins spikes was drawn (Fig. 2). E2 might form connections between alternating pairs of rows, where it would be somewhat covered by the E1 spikes [18].

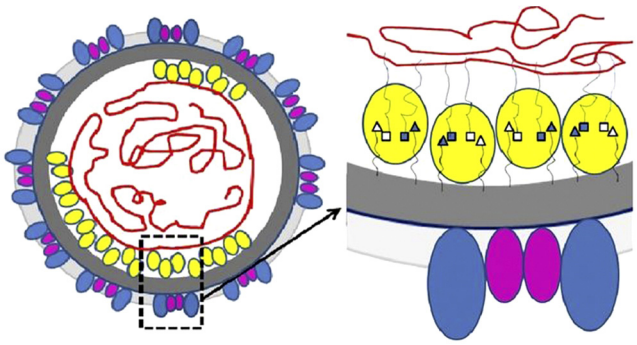

Fig. 2. *Diagram of a rubella virus virion cross-section showing the ectodomains of E1 (blue) and E2 (magenta) glycoproteins, the capsid protein dimer (yellow), and genomic RNA (red).* The gray region denotes the membrane layer (dark gray) plus the glycoproteins. In the magnified section, the polypeptide connections (thin lines) of the N termini (□) and C termini (Δ) of the capsid protein to the RNA and membrane, respectively, are shown. The filled and open shapes denote the termini pointing toward and away from the plane of the paper [92]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Glycoprotein E1 epitopes.

Amino acid residues	Epitope properties	Reference
193–269	Hemagglutinating activity for 214–240 aa.; Neutralizing activity for 214–233 aa.	Chaye et al. [43]
202–283	Neutralizing activity	Wolinsky et al. [44]
208–239	Neutralizing activity	Cordoba et al. [42,45]
213–239	Neutralizing activity	Mitchell et al. [31]; Li et al. [41]
221–239	Neutralizing activity	Wolinsky et al. [40]
243–286	–	Lozzi et al. [39]
245–285	Hemagglutinating activity	Ho-Terry et al. [37]; Terry et al. [38]
234–252	Neutralizing activity	Mitchell et al. [31]
254–285	Neutralizing activity	Mitchell et al. [31]
272–285	Neutralizing activity	Mitchell et al. [31]

3. Glycoprotein E1

Glycoprotein E1 (481 aa.) is a protein with a molecular weight of 58 kDa and is a rubella virus structural surface protein [24,26]. Glycoprotein E1 contains a fusion peptide ($E1_{181}$–$E1_{109}$ aa.), which provides virus entry into the cell [27,28]. What is more, this region of E1 is important for interaction with E2 [29]. It has been shown that rubella virus glycoprotein E1 has main antigenic determinants, and is responsible for both cellular and humoral immune response [15,30,31]. E1 epitopes are associated with hemagglutinating [17,22], as well as neutralizing, activities [32]. Most frequently, at least three main glycoprotein E1 epitopes are mentioned (see Table 1, Fig. 3) [17,22,23]. At the same time, the combination of hemagglutinating and neutralizing properties differs, according to various papers (see Table 1, Fig. 3) [24,33–36]. Green and Dorsett [17] established that all three epitopes are functionally distinguishable: the first epitope has only hemagglutination activity, the second one has only neutralizing activity, while the third one has both activities. According to other research, two of the epitopes have both hemagglutinating and neutralizing activity, and the third has neutralizing activity only [35,37].

According to a number of reports, glycoprotein E1 epitopes are localized from 245 to 285 [37,38], from 243 to 286 [39], from 221 to 239 [40,41], from 208 to 239 [42], from 193 to 269 [43], and from 202 to 283 amino acid residues [44]. Hemagglutinating activity has been shown for the E1 region from 214 to 240 aa. [43], and from 245 to 285 aa. [38], while neutralizing activity has been shown for the E1 region from 202 to 283 [44], from 208 to 239 [45], from 214 to 233 [43], from 213 to 239 [41], from 221 to 239 [40], from 213 to 239, 234–252, 254–285 and 272–285 amino acid residues [31]. Some other researchers have reported five [36] or six epitopes [46].

According to Li and colleagues [41], R237H and H238R changes in neutralizing the epitope of E1 lead to antibody attachment loss, while Q236D change considerably reduces attachment affinity. This epitope is completely buried at the centre of the E1 trimer. The structure therefore predicts that antibodies bound to this site would block E1 trimerization for entry [26].

Lozzi and coauthors [39] found out that regions of glycoprotein E1 from 250 to 252, from 260 to 263, from 273 to 275 and from 278 to 285 amino acid residues were absolutely needed for interactions with antibodies. Each of these regions is important for obtaining optimal antigenic activity. When nearby amino acid residues were added to these epitopes, the ability of antibodies to bind with them increased. Such activity increase may be connected with the fact that amino acid residues are involved in the construction and stabilization of protein E1's conformational structure [47].

The glycoprotein E1 epitope (208–239 aa.) is conservative for all rubella virus strains, and is responsible for rubella virus

Please cite this article in press as: Petrova EK, et al. The key role of rubella virus glycoproteins in the formation of immune response, and perspectives on their use in the development of new recombinant vaccines. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2016.01.010