Vaccine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Development and clinical applications of novel antibodies for prevention and treatment of respiratory syncytial virus infection

Asuncion Mejias MD, PhD, MSc [a,*], Cristina Garcia-Maurino MD [a], Rosa Rodriguez-Fernandez MD, PhD [a,b], Mark E. Peeples PhD [a], Octavio Ramilo MD [a,*]

[a] Center for Vaccines and Immunity, The Research Institute at Nationwide Children's Hospital, Department of Pediatrics, The Ohio State University College of Medicine, Columbus, OH, USA

[b] Department of Pediatrics, Hospital Infantil Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain

ARTICLE INFO

Article history:
Available online xxxx

Keywords:
RSV
Monoclonal antibodies
Nanobodies

ABSTRACT

Respiratory syncytial virus (RSV) remains a significant cause of morbidity and mortality in infants and young children, immunocompromised patients and the elderly. Despite the high disease burden, an effective and safe vaccine is lacking, although several candidates are currently in development. Current treatment for RSV infection remains largely supportive and RSV-specific options for prophylaxis are limited to palivizumab. In the past few years, novel therapeutic options including nanobodies, polyclonal and monoclonal antibodies have emerged and there are several products in preclinical and Phase-I, -II or -III clinical trials. The major target for antiviral drug development is the surface fusion (F) glycoprotein, which is crucial for the infectivity and pathogenesis of the virus. Solving the structures of the two conformations of the RSV F protein, the prefusion and postfusion forms, has revolutionized RSV research. It is now known that prefusion F is highly superior in inducing neutralizing antibodies. In this section we will review the stages of development and availability of different antibodies directed against RSV for the prevention and also for treatment of acute RSV infections. Some of these newer anti-RSV agents have shown enhanced potency, are being explored through alternative routes of administration, have improved pharmacokinetic profiles with an extended half-life, and may reduce design and manufacturing costs. Management strategies will require targeting not only high-risk populations (including adults or immunocompromised patients), but also previously healthy children who, in fact, represent the majority of children hospitalized with RSV infection. Following treated patients longitudinally is essential for determining the impact of these strategies on the acute disease as well as their possible long-term benefits on lung morbidity.

1. Introduction

Respiratory syncytial virus (RSV) is the main cause of bronchiolitis and pneumonia, in infants and toddlers, accounting for ~60% of all lower respiratory tract infections (LRTI) in preschool-aged children worldwide. Globally, it is estimated that RSV causes about 34 million episodes of acute LRTIs in children under five years of age, resulting in ~3.4 million hospitalizations per year [1,2]. In the developing world, RSV is associated with significant morbidity and represents the second most common cause of infant mortality [3]. In addition, RSV also causes significant disease in immunocompromised hosts and in the elderly [4,5].

By their first birthday nearly 70% of infants have been infected with RSV at least once. Seropositivity is ~100% by 2 years of age. Despite the high disease burden, an effective vaccine or specific therapy is lacking, although there are several products at different stages of development [6]. Epidemiologic studies have identified specific groups of infants at high-risk for severe disease and mortality including premature birth, compromised cardiopulmonary function (chronic lung disease or congenital heart disease), Down syndrome, and immunodeficiencies. However, the majority of infants requiring hospitalization for RSV LRTI do not have any risk factors and are previously healthy [7,8]. Of those, up to 20% will be treated in the pediatric intensive care unit (PICU) [9,10].

RSV has also been associated with the development of persistent wheezing and asthma inception [11–13]. Thus, it is possible

* Corresponding authors at: Division of Pediatric Infectious Diseases and Center for Vaccines and Immunity, The Research Institute at Nationwide Children's Hospital and The Ohio State University College of Medicine, Columbus, OH 43205, USA.

E-mail addresses: asuncion.mejias@nationwidechildrens.org (A. Mejias), octavio.ramilo@nationwidechildrens.org (O. Ramilo).

http://dx.doi.org/10.1016/j.vaccine.2016.09.026
0264-410X/

that interventions aimed at reducing the acute burden of RSV disease may also have an impact on the development of long-term pulmonary sequela [14].

2. Viral structure and targets for monoclonal antibodies

RSV is an enveloped, negative sense, single strand RNA virus that belongs to the family *Paramyxoviridae*, subfamily *Pneumovirinae*. Human RSV includes two antigenic subgroups, A and B, which can co-circulate during the same season and exhibit genome-wide sequence divergence. The RSV genome contains 15,222 nucleotides that encode eleven proteins (Fig. 1). The RSV envelope contains three viral transmembrane surface glycoproteins: the attachment (G) protein, the fusion (F) protein, and the small hydrophobic (SH) protein. Of these proteins, SH is not required for initiating virus infection. On the other hand, the F and G proteins are crucial for the infectivity and pathogenesis of the virus, and carry the antigenic determinants that elicit the production of neutralizing antibodies by the host [15]. The F protein performs a dramatic structural rearrangement to cause membrane fusion, and is more highly conserved among RSV strains than the G protein (Fig. 2). For these reasons, the F protein represents the major target for antiviral drug development, both small molecules and neutralizing antibodies [6,16].

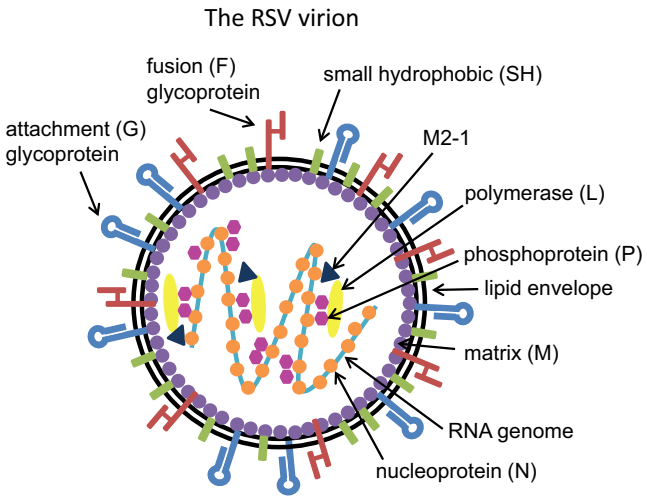

Fig. 1. Anatomy of RSV. RSV is an enveloped, negative sense, single strand RNA virus whose genome contains 10 genes (15,222 nucleotides) encoding eleven proteins. Of the three transmembrane surface glycoproteins, the attachment (G) and fusion (F) proteins, are crucial for the infectivity and pathogenesis of the virus, and are the targets for neutralizing antibodies. Modified from Johnson S.M thesis dissertation.

The G protein initiates infection by targeting the apical surface of the ciliated cells of the airways and mediates adherence of the virus to these host cells [17]. Heparan sulfate, surfactant protein A, annexin II and CX3CR1 have all been shown to bind the G protein and proposed as cellular receptors for RSV [18–21]. Recently, CX3CR1 was identified on the cilia of well differentiated human ciliated airway cells, acting as a cellular receptor for the G protein [22–24]. The F protein is essential for viral entry and initiates viral penetration by fusing the viral and cellular membranes [16]. In non-polarized laboratory cells, the F protein also promotes cell-to-cell fusion producing the characteristic syncytia. However, in polarized well differentiated human airway cells, the F protein does not cause cell-cell fusion probably because the F protein is limited to the apical domain [17,25]. RSV lacking its G gene is infectious, though poorly, suggesting that the F protein may also have attachment activity [26]. Heparan sulfate, ICAM-1, TLR-4 and nucleolin have been proposed as cellular receptors for the F protein [26–30].

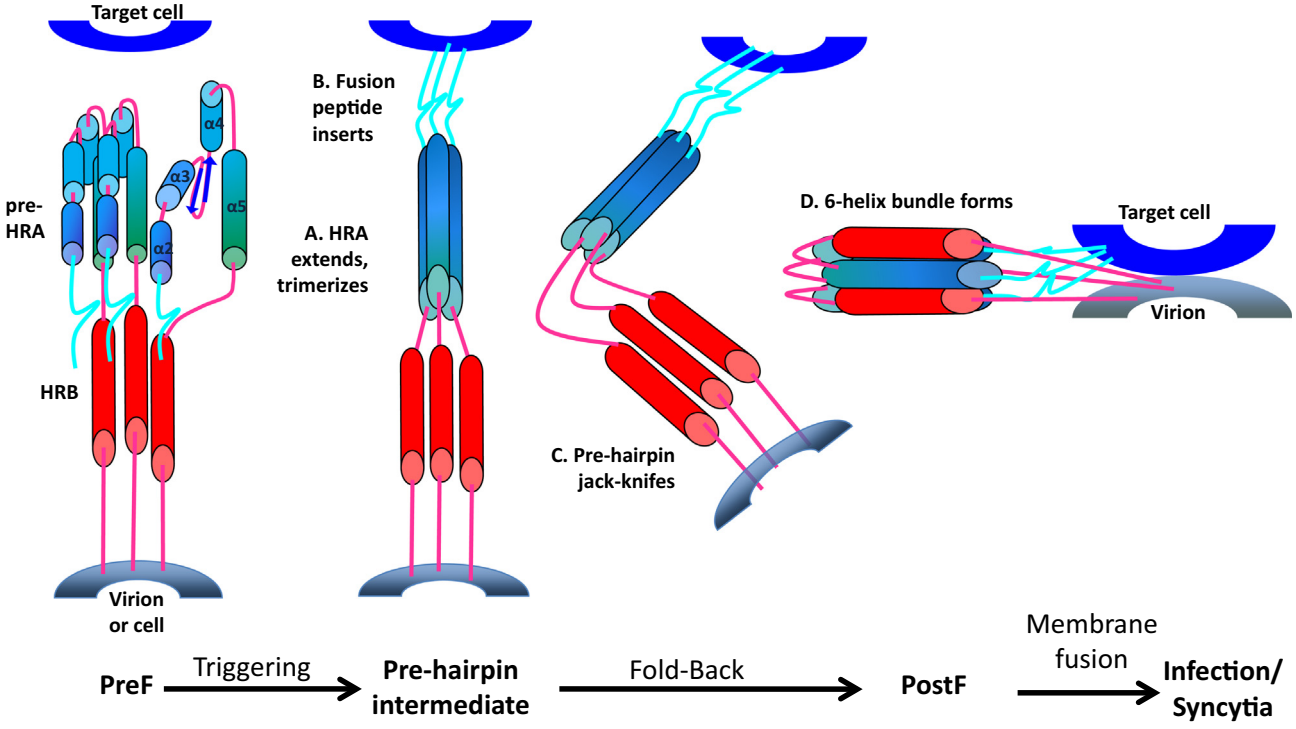

Fig. 2. Refolding of the RSV F protein. The F glycoprotein is present in two forms, a metastable prefusion F (preF), the active form on the virion membrane, and the postfusion F (postF) after triggering, refolding and bringing the virus and target cell membrane together to initiate fusion and infection. It is not clear what causes the F protein to trigger. Modified from Costello H.M et al. [69].

Please cite this article in press as: Mejias A et al. Development and clinical applications of novel antibodies for prevention and treatment of respiratory syncytial virus infection. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2016.09.026