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Review

Vaccines based on virus-like nano-particles for use against Middle East Respiratory Syndrome (MERS) coronavirus

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ABSTRACT

Recent advances in virus-like nanoparticles against Middle East respiratory syndrome-related coronavirus (MERS-CoV) can initiate vaccine production faster for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), while ensuring the safety, easy administration, and long-term effects. Patients with this viral pathogen suffer from excess mortality. MERS-CoV can spread through bioaerosol transmission from animal or human sources. The appearance of an outbreak in South Korea sparked off a strong urge to design strategies for developing an effective vaccine since the emergence of MERS-CoV in 2012. Well unfortunately, this is an important fact in virus risk management. The studies showed that virus-like nanoparticles (VLPs) could be effective in its goal of stopping the symptoms of MERS-CoV infection. Besides, due to the genetic similarities in the DNA sequencing of SARS-CoV-2 with MERS-CoV and the first identified severe acute respiratory syndrome (SARS-CoV) in China since 2002/2003, strategic approaches could be used to manage SARS-CoV 2. Gathering the vital piece of information obtained so far could lead to a breakthrough in the development of an effective vaccine against SARS-CoV-2, which is prioritized and focussed by the World Health Organization (WHO). This review focuses on the virus-like nanoparticle that got successful results in animal models of MERS-CoV.

Contents

1. Introduction

The Middle East respiratory syndrome (MERS) is a highly infectious viral disease that first appeared in 2012 at Saudi Arabia, originally crossing the species barrier from camels to humans, and an outbreak caused many deaths in South Korea [1–4]. The high mortality of MERS-related coronavirus (MERS-CoV) was ≈35%, led the World Health Organization to the conclusion that employing effective countermeasures like vaccination were needed to reduce MERS-CoV epidemic impact [5,6]. In vaccine production, a major limiting factor in designing comprehensive delivery systems for aerosol transmissible diseases is the enhancement of efficacy and easy vaccine administration [1,7]. Extensive information on transmission, pathogenesis, and epidemiology of MERS-CoV is needed in

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both humans and animals to facilitate the development of a new vaccine [8]. Recently, the focus is concentrated on MERS-CoV spike (S) protein, a viral surface glycoprotein, providing the basis for the synthesis of virus-like particles (VLPs) [8]. Vaccines based on antibodies, DNA [9], adenoviruses, vectors [10,11], antigen and adjuvant delivery have shown potentially promising results and may support future developments based on virus-mimicking behavior. Synthetic vaccines for MERS-CoV utilizing potent antigens in combination of proper adjuvant could increase the potency of the prepared vaccine [12]. In this manner, the nanoscale morphology that is very similar to that of a native MERS-CoV virus [13] with consideration of sequenced delivery of antigen and adjuvant [14] could enhance the immunogenicity and promote danger signals that mimic the authentic MERS-CoV virus.

The S protein of MERS-CoV is an essential component of the immunogenic vaccines of the future with the advantage of facilitating virus attachment step via Human Dipeptidyl Peptidase 4 (hDPP4) [15–18]. In the current outbreak, severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) uses its S proteins to bound to the angiotensin-converting enzyme 2 and enter the cells with affinities of at least 10 time more severe than acute respiratory syndrome (SARS) [19]. Novavax (USA) designed a virus-like particle (VLP) from MERS-CoV S protein that induced neutralizing antibodies and enhanced the immune response after one injection in a mice model [20,21]. The synthesis of VLPs in vaccine technology is a novel strategic approach to developing new and more effective vaccines [22]. Using appropriate design of VLPs by S protein of SARS-CoV-2 and proper adjuvants can also stimulate the immune system of the body to produce countermeasures that are more effective. The present review further explores the concept of virus mimicking nanoparticles and the development of nanoparticle vaccines against MERS-CoV. The genetic sequence of SARS-COV 2 is closely related to the MERS-CoV and SARS-CoV [23], hence, the information obtained from their vaccine advancement efforts could help to progress the development cycle of SARS-CoV-2 vaccine. Herein, this review focuses on the virus-based nanoformulations that have successful results in animal models of MERS-CoV in the hope finding a more effective approach to manage these epidemic diseases.

2. Advantages of nanoparticle-based vaccine

Nanoparticles designed to mimic viruses with engineered nanoscale morphology [13], multivalent antigens [24], and colonizing antigens/adjuvants (danger signals); using a single nanoparticle may promote immune responses via antigen processing and immune system engagement [14]. Nanoscale VLPs with viral characteristics are transported better through the lymphatics and capillaries in comparison with smaller subunit vaccines [13,25–27]. This improves cellular uptake and reduces the systemic inflammatory response [26]. Besides, the ability to deliver multiple antigens promotes antigen-presenting cell or accessory cells to function more effectively, hence, T cell receptors can recognize the synthesized complexes that increase immunogenicity and potency of the vaccine, which could protect the safety and welfare of the patients [25]. Innate immune system activation and better cellular uptake of VLPs, consisting of recombinant viral antigens and adjuvants, can enhance the effects of the complement cascade to attack pathogens and the presentation to follicular dendritic cells, which lead to B cell activation and potentiation of the immune system by inducing proactive immune responses against viral infections [13,28]. In fact, synthetic nano VLPs elicit virus-like characteristics and evoke immune responses against viral infections, which is an essential aspect of vaccine design, development, and future disease management [29–34]. Another advantage is the formation of protein corona around the synthetic nanoparticles via surface passivation that, at first glance, prevents agglomeration and increases the size especially in inorganic nanostructures, but promotes the innovative design of complex vaccines using nanocarriers and proteins via Van der Waals and covalent interactions [35–40]. For instance, VLPs based on inorganic gold nanoparticles have higher surface energy than their organic counterparts, which interact strongly with biomolecules, antigens, and adjuvants, through weak electric forces such as Van der Waals force and dipole–dipole interaction, or covalent bond [38,41].

3. Spike protein of MERS-CoV

The immunogenic MERS-CoV proteins include Spike (S), membrane (M) and envelope (E). Among them, the S protein mediates viral entry into the host cells [42]; accordingly, the S protein can be used as the principal targeting agent against MERS-CoV, because of having the ability to build the developing strategies for new generation of virus-mimicking vaccines. [20,43,44]. The S protein could self-assemble into a crown-like nanoparticle with about 25 nm in diameter, in which the size was reduced to about one-quarter of MERS-CoV, and could trigger cell attachment, including fusion and cellular binding [45,46]. In an animal model, the potential of S proteins to stimulate immune responses is confirmed in the presence of alum induced neutralizing antibodies [20]. The S glycoprotein has two subunits, S1 and S2. The S1 subunit binds to the hDPP4 receptor, and the S2 subunit is involved in membrane fusion (virus-cell fusion) [47]. Some neutralizing antibodies deactivate the S1 subunit, receptor-binding domain (RBD), by blocking the interaction with hDPP4, and this could be a principal target in the vaccine development of MERS-CoV [48–55]. Recently, Th1 mediated immunity was seen after induction of virus-neutralizing antibodies after immunization of macaca mulatta by an S protein based VLP against MERS-CoV [42]. VLPs based on S protein also showed a Th1 and Th2 mediated immunity in mice primed with rAd5-vector [56].

4. Vaccines based on Virus-like Particles (VLPs)

High levels of an immunogenically active drug may lead to inflammatory and excessive immunological responses. Therefore, safety precautions and new formulations may be needed to reduce the side effects [31,57,58]. Nanoscale vaccines based on calcium phosphate nanobioceramics [59], liposomes [30,60], polymer-based microparticles [61,62], cationic polymers [63,64], virus-like nanoparticles (VLPs) [65], nanoparticle assemblies from multimeric peptides [66,67] and gold nanoparticles [41,68] could target the lymphatic system and would improve safety and efficacy. In addition, the mentioned structures are amenable for modifications that may increase the biocompatibility, lead to size control, stability, and controlled antigen/adjuvant loading and release.

VLPs are widely used in vaccines as carriers and are comparable to subunit vaccines, in which a viral protein is generated [69–72]. VLPs are recombinant forms of viral proteins and adjuvants with the potential for developing a self-assembled structure. They can act as an adjuvant due to their small size and give rise to the potential immunogenic epitopes that produce higher immunogenicity. Other adjuvants could also be used to cause greater immune responses in comparison with the virus [42,73,74]. The designed vaccines have used recombinant forms or viral proteins including S, S1, or RBD, and vector or DNA based adjuvants against MERS-CoV infection (Table 1). Animals vaccinated with VLPs were shown to effectively overcome the virus due to an increased immune response [20,49,75].

Table 1
Designed VLPs against MERS-CoV.

Treatment	Responses	Animal model	Ref.
rAd5-S protein and alum-adjuvanted recombinant S protein	Mixed Th1/Th2 immune responses, heterologous prime–boost	SPF BALB/c mice	[56]
S protein VLP in the presence of alum	Induction of neutralizing antibody	BALB/c mice	[20]
A recombinant form of MERS-CoV S protein with Matrix-M1adjuvant	Stimulation of neutralizing antibody	BALB/c mice	[76]
poly(c-di-GMP inside lactic-co-glycolicacid) with MERS-CoV RBD antigens	elicitation of neutralization antibody, antigen-specific T cell responses, an inducer of type I interferons	C57/BL6 mice (DPP4-transgenic)	[5]
cVLP of CPV VP2 structural protein with the MERS-CoV RBD in presence of Alum and poly(I:C) adjuvants	Mixed Th1/Th2 immunity, elicited neutralizing antibody, induction of B- and T-cell, IFN-γ induction	BALB/c mice	[77]
cVLP of CPV VP2 structural protein with the MERS-CoV RBD	B- and T-cell induction, mixed Th1 and Th2 responses, expression of IFN-α/β	rhesus macaques	[78]
VLP obtained from a polyclonal immunoglobulin G (IgG) antibody and a clade B S protein	High neutralizing antibody titers, passive immunotherapy, robust immune response	BALB/c mice (Ad5-hDPP4–transduced)	[79]
VLP obtained from MERS-CoV RBD protein and bacterioferritin	interfere with the binding to the hDPP4 receptor and immune responses by the assembly of antigens	BALB/c mice	[80]

Recently, silkworm larvae have been used to generate the S protein of MERS-CoV, which was then used to prepare nanovesicles [42] by surfactant treatment [81] and mechanical extrusion [82,83]. Recombinant proteins of S, E and M were used to synthesize MERS-CoV VLPs, tested in an animal model and were associated with greater immunogenicity [42]. Nanoparticles derived from rAd5-S protein with alum mediated neutralizing antibodies showed a successful immune response against MERS-CoV, tested in vivo using specific pathogen-free BALB/c mice, which increased Th1 and Th2 immunogenicity [56]. In another study, nanoparticle was fromed a recombinant of SAB-301, a polyclonal immunoglobulin G (IgG) antibody, and a clade B S protein that lowered the MERS-CoV infection below the in vivo detection limits [79]. The VLP vaccine platform engineered by employing the recombinant E protein of another virus could produce a chimeric VLP (cVLP), in which different epitopes trigger the cell attachment to different antibodies [84]. For instance, the structural protein of canine parvovirus (CPV), VP2, was fused with the MERS-COV RBD, generating a cVLP that could increase the immune responses in mice [77]. The recombinant form of S protein of MERS-CoV and influenza A virus M1 protein also showed greater immunogenicity in a mouse model [85]. Nanoparticles from the recombinant form MERS-CoV S protein and M1 protein prevented the virus replication in the lungs of the vaccinated mice [48,86–88]. Aggregations of viral antigens due to protein misfolding may lead to the lower solubility of VLPs. RNA as a molecular chaperone was used as a folding agent and subsequently, it was fused with the RBD of MERS-CoV. The sera that was separated after immunization of the mouse with the synthetic VLP, showed the blockage of the binding site to hDPP4 of MERS-CoV RBD [1].

Enzymes such as viral proteases encoded by DNA or RNA of the virus or signaling proteins like interferons could be implemented to increase the immunogenicity of the prepared vaccines. Reports showed MERS-CoV uses the protein-coding genes of the host cell, including TMPRSS2 (Transmembrane Serine Protease 2), FURIN (paired basic amino acid cleaving enzyme) and cathepsins, to facilitate virus-cell fusion [89-91]. The presence of a subgroup of interferons, Human type I interferons (IFNs) as an important mediator of the innate immune system could also effective against MERS-CoV. It seems that viral replication and transmission of MERS-CoV was prevented by controlling the previously mentioned cell proteases and the presence of cytokines of the innate immune system [89-94]. IFN signaling is effective after antigen presentation; otherwise, it suppresses the innate immune system [30,62,95]. Therefore, the sequencing of the release mechanism and timing affect the results. The optimal arrangement of the antigen and adjuvant should be taken into consideration in the engineered nanoparticle vaccines [96-98]. The stimulator of interferon genes (STING) agonists combined with antigen presentation could also activate adaptive immunity [99–101]. The synthetic hollow VLPs (hVLPs) have the advantage of encapsulating cargoes that are tailored to meet the timing and dosing requirements using recombinant viral antigens [5]. The mouse immunized with a hollow VLP, composed of a polymeric hollow nanoparticle, RBD antigen and STING agonist, was capable of promoting long-lasting T cells and Th1/Th2 immune responses. The mechanism of action was similar to other STING mediated stimulations and led to generation protective neutralizing antibodies against MERS-CoV [5,99,102].

5. Conclusion

Advances in virus-like nanoparticles against MERS-CoV could help to adopt some basic information against SARS-CoV 2. VLPs are flexible and can be designed for specific aims, for example, to increase vaccine safety and efficacy. Wise recombinant of a subunit antigen and an adjuvant can heighten the innate and adaptive immune responses. It seems timing in adjuvant and antigen release could greatly influence the effectiveness. As this review represents, the nano-engineering of viral proteins could open a new horizon for the preparation of an effective MERS-CoV vaccine.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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