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Short Review

Exosomes-based particles as inhalable COVID-19 vaccines

Lu Fan [a,b], Li Wang [a,b], Xiaoju Wang [a], Hongbo Zhang [a,b,*]

[a] Pharmaceutical Sciences Laboratory, Åbo Akademi University, Turku, 20520, Finland
[b] Turku Bioscience Centre, University of Turku and Åbo Akademi University, Turku, 20520, Finland

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ABSTRACT

Coronavirus disease 2019 (COVID-19), a severely spreading pandemic, has dramatically brought physiological and economical burdens to people. Although the injectable vaccines have some achievements for coronavirus defense, they still generate accompanied pain, untoward reaction and cannot take part in mucosal immunity. Inhalable vaccines, as a safe, facile and efficient strategy, have been presented to protect body from virus by inducing robust mucosal immunity. Here, we give a perspective of an inhalable COVID-19 vaccine composed of lung-derived exosomes (a type of virus-like particle) conjugated with viral receptor-binding domain. The lung-derived exosomes act as carriers, such inhalable particles successfully reach at lung and reveal wider distribution and longer retention on respiratory mucosa. In addition, such vaccines induce the high production of specific antibodies and T cells in lung, significantly protecting host against coronavirus invasion. It is conceived that inhalable virus-like particles with long-term stability wound open a new avenue for vaccines delivery and further achieve vaccine popularization to against with COVID-19 pandemic.

Coronavirus disease 2019 (COVID-19), a globally spreading pandemic, is induced by acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) coronavirus [1,2], which has severely impacted the health care and economical systems worldwide [3–5]. Up to date, various kinds of COVID-19 vaccines have been developed and demonstrated effective to protect body from the SARS-CoV-2 virus. However, the most of current vaccines are intramuscular injection usually accompanied pain and untoward reaction [6,7], leading to low vaccination willingness of crowds [8]. In addition, injectable COVID-19 vaccines take effects by inducing antibodies in serum to fight against virus, while play little part in mucosal immunity. It is worth noting that the main spreading of SARS-CoV-2 virus between people is through small respiratory droplets and the respiratory mucosa is an initial path for virus invasion [9,10]. Thereby, the respiratory mucosal immunity performs vital functions in SARS-CoV-2 virus defense, which can provide a more effective and rapid local response to prevent virus from replicating in upper respiratory and to further block the transmission between people [11] (Fig. 1a).

In view of this, inhalable vaccine has been developed due to it's safe, noninvasive, convenient and highly absorptive features [12–15] (Fig. 1b). Nevertheless, the carriers of actives in atomized vaccine remain difficult with optimized physiochemical parameters [10,16]. Besides, several vaccines need to be stored in deep freezing condition to keep efficacy of bioactive, which has brought great cost and difficulties in long-term storage and transportation. Virus-like particles (VLPs), usually an artificial nanostructure, own similar morphology to natural virus yet fail to reproduce the virus and infect host [17–19], which could trigger robust cellular or humoral immunity reaction to against virus invasion [20,21]. Particularly, exosomes are a class of naturally-derived extracellular vesicles (approximately 100 nm in diameter) secreted from most cells, which have raised remarkable attention in drug delivery and immunization area [16] (Fig. 1c). Given that they contain and express parent cell-targeted protein on the membrane, cell-derived exosomes have a great capability to target and recognize the same receptor cells [22]. Additionally, exosomes could be engineered via modifying specific protein on the surface to endow them with unique properties [23–25]. Besides, such exosomes exhibit distinctively stable personality under extreme temperature, pH, or solvents [26]. Benefiting from these advantages, specific cell-derived exosomes are considered as ideal candidates for drug encapsulation and future vaccine development.

Recently, Ke Cheng and coworkers designed a novel inhalable COVID-19 vaccine based on exosomes, with effective mucosal immune stimulation and long-term stablity [10] (Fig. 2a). Such vaccine contained recombinant SARS-CoV-2 receptor-binding domain (RBD) conjugated onto the surface lung-derived exosome, creating the virus-like particles imitating the morphology of authentic virus. Previous researches have proved the effectiveness of SARS-CoV-RBD as a potential target for

* Corresponding author. Pharmaceutical Sciences Laboratory, Åbo Akademi University, Turku, 20520, Finland.
E-mail address: hongbo.zhang@abo.fi (H. Zhang).

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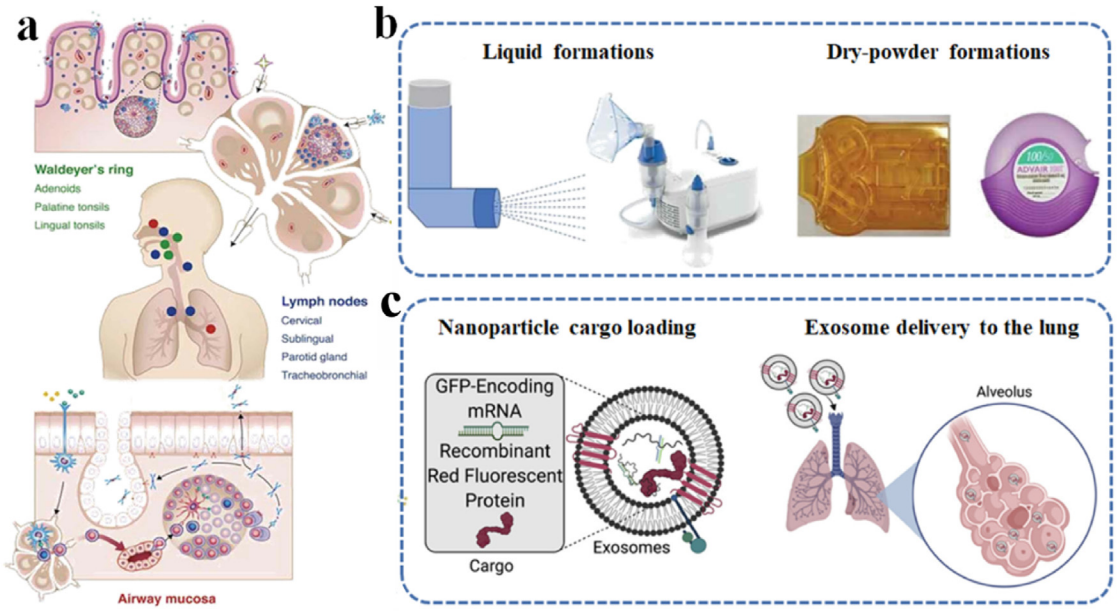

Fig. 1. (a) An overview of the respiratory tract's mucosal immune system. (b) Several inhalable devices for pulmonary vaccination [11]. (c) The nanostructure and application of exosome. Copyright 2022, ELSEVIER [16].

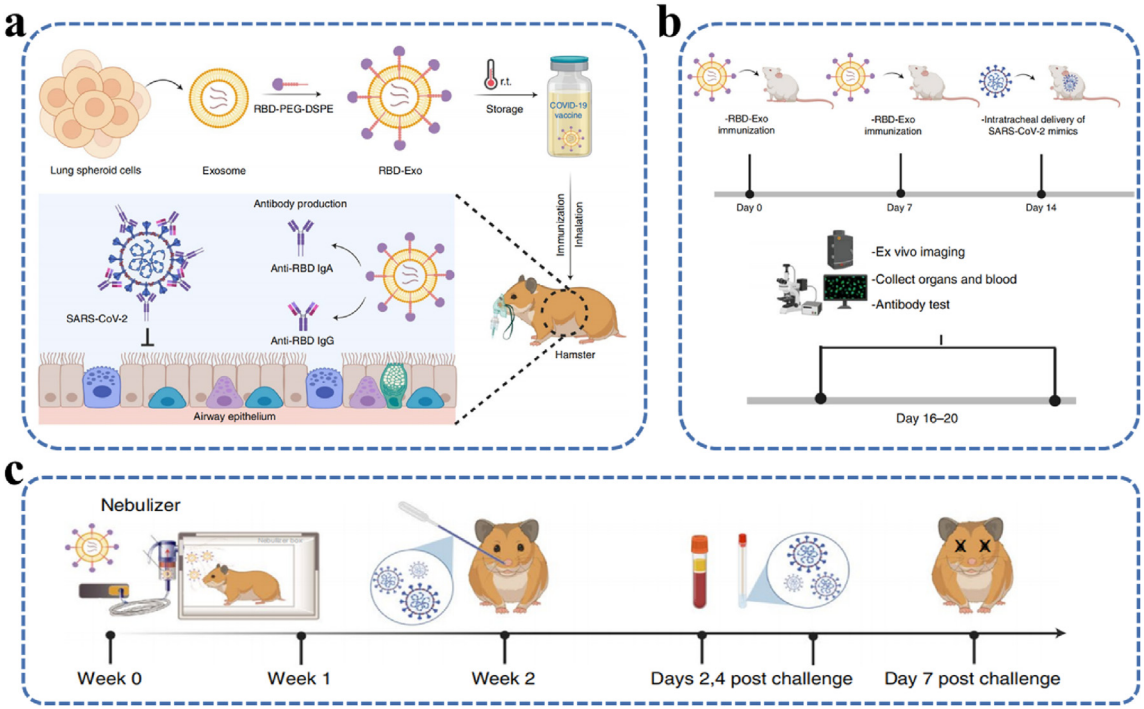

Fig. 2. (a) Schematic of the application of inhalated RBD-Exo VLP vaccine. (b) Inhalable VLPs vaccines on mice infected with SARS-CoV-2 mimics. (c) Inhalable VLPs vaccines on hamsters infected with high dose live SARS-CoV-2. Copyright 2022, Springer Nature [10].

antibody neutralization [27–29]. Additionally, owning to being secreted from the lung, the lung-derived exosomes exhibited a wider distribution and longer retention in lung than common liposome carriers, as well as enhanced internalization by antigen presenting cells (APCs). Based on above mentioned advantages, lung-derived exosomes was used as the backbone of virus-like particles (VLPs). By covalent modifications, it was successfully fabricated as the RBD-Exo VLPs. Furthermore, the obtained RBD-Exo VLPs owned excellent structural and biological stability at room temperature, revealing excellent manufacture in storage and transportation.

Specially, to evaluate the mucosal immune response induced by inhalable RBD-Exo VLPs, Ke Cheng and coworkers incubated mice with such inhaled VLPs, and then delivered SARS-CoV-2 into the mice trachea to simulate viral infection (Fig. 2b). After that, RBD-specific SIgA antibodies in serum and SARS-CoV-2-specific T-cell responses in pneumocytes of the mice were measured. It was worth noting that inhalable RBD-Exo VLPs provoked the highest level of SIgA antibodies, activated a robust immune response and also induced a high-level proliferation of T cells. Apart from that, nasopharyngeal associated lymphoid tissue participated in inhalable VLPs vaccine mediated immune response by

triggering a comparable SIgA antibody response. Collectively, the nebulization RBD-Exo VLPs vaccine had the ability to trigger mucosal immune response, which could further protect the organism against SARS-CoV replication.

Furthermore, researchers estimated the effect of inhalable RBD-Exo VLPs on preventing high dose live SARS-CoV-2 infection in the hamster model that could replicate serious diseases in clinic (Fig. 2c). Compared with others, RBD-Exo VLPs groups showed lower virus detection amount and the highest RBD specific serum antibody concentration in every tested time point. By multiple histological staining of lung tissue and in situ RNA hybridization assay, results proved that the inhaled RBD-Exo significantly reduced the virus level and alleviated inflammatory infiltration of lung. Apart from that, the clinical chemical and hematological parameters of hamsters incubated with the vaccine were within the normal level, which demonstrated inhalable VLPs' excellent performance preventing body from SARS-CoV-2 virus.

To sum up, this study pioneered a novel inhalable VLPs vaccine to against COVID-19 pandemic, based on the integration of SARS-CoV-2 RBD and lung-derived exosomes. Lung-derived exosomes acted as an excellent vehicle that effectively delivered vaccine to targeted site and had a longer retainment in lung for subsequent immunization. By triggering a robust mucosal and cellular immunity, such inhalable vaccine could effectively resist viral infection and reduce lung lesions and induce a robust T cell immune response. Compared with the currently marketed vaccine products, RBD-EXO stored stably at room temperature for 3 months, greatly reducing the cost of vaccination and exhibiting the considerable potential in application. Of all kinds of vaccine delivery strategies, inhalation vaccine was considered to be most promising. Benefiting from safe, painless and convenient advantages, it is expected to improve the people's willingness to vaccinate and further achieve global COVID-19 vaccine popularization. In future, efforts in designing virus-like particles are devoted to enhance the stability of the exosome carriers conjugated with specific protein domains, as well as improve production efficiency and expand the production scale of inhalable vaccines. Although with these challenges, room-temperature-stable inhaled vaccine such as RBD-Exo VLPs, could be an ideal vaccine candidate anticipated to forward researches and develops, which would greatly contribute to fight against the COVID-19 worldwide.

Author contributions

Hongbo Zhang conceived the idea. Lu Fan wrote the manuscript. Li Wang and Xiaoju Wang assisted the manuscript writing.

Declaration of competing interest

The authors declare no competing financial interests.

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