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COMMENTARY

Bio-inspired virus-like nanovesicle for effective vaccination

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ABSTRACT

Developing effective vaccines is of vital importance for protecting public health by preventing potential pandemics or by controlling ongoing ones. However, there is a threshold of rapidly design and develop effective vaccines to prevent virus infection. Inspired by the natural budding processes associated with cell membrane scission when enveloped viruses invade host cells and replicate themselves, a similar strategy was applied to achieve virus-mimetic nanovesicles (VMVs). This strategy loaded genetically engineered viral antigens onto mammalian cell membranes to produce antigen-loaded vesicles, and then used surfactants to optimize their size and stability. The VMVs resemble natural viruses in size, shape and specific immune function and have protein antigens in the correct conformation on their exterior to elicit robust immunogenicity. This was confirmed in animal models against influenza A (H1N1) virus, demonstrating that VMVs could be a versatile platform for vaccine development.

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Vaccines are a great triumph to combat pathogen-initiatedpandemics, which are a significant threat to public health by causing wide infection and severe mortality each year.[1] Traditional vaccines approved for human use mainly consist of killed or inactivated version of an organism that elicit specific immunogenicity against infections and reduce potential morbidity and mortality. However, many conventional vaccines encounter the problem of safety considerations due to the presence of viral genetic substrates. Alternative safer approaches were applied to design and manufacture vaccines. Subunit protein antigens have attracted much attention for widespread immunization due to their safety and purity, yet their primary obstacle is provoking sufficient immune response when administrated alone.[2] For an even greater improvement of their immunogenicity, the protein antigens are generally administrated with adjuvant or other delivery systems,[3,4] such as proteins, liposomes or lipid vehicles etc., to further promote the host immune response against the delivered antigens.[5] Yet, protein antigens encounter the barriers of being difficult to produce the native conformational epitopes of the viral proteins as well as maintaining the conformation in antigen-carriers, which are both important for simulating the immune response. Therefore, the key factor in the success of desirable vaccines critically relays on preciously reproducing them with similar characteristics as natural viruses.[6]

Bio-inspired nanocarriers, such as virus-like particles,[7] membrane vesicles[8,9] and exosomes[10] etc., offer versatile platforms for delivering bioactive compounds, including vaccines, to specific targets with significantly improved diagnosticor therapeutic effects.[11,12] Inspired by the natural processes of viruses invade a host cell and release the replicated ones in membrane vesicles through a budding process,[9] a similar strategy was applied to generate virus-mimetic vesicles (VMVs) that harbor genetically engineered viral antigens onto cell membranes.[13] Thereafter, the antigen-loaded VMVs were made to be nanoscale uniform vesicles by adding surfactants to optimize their stability and size to resemble natural viruses of equal geometrical parameters and display "native" conformation of epitopes in antigens.

As a proof of concept, HEK 293T and Hela cell lines were genetically modified to stably express cell membrane vesicles with sig-16L2-eGFP recombinant protein that included an epitope sequence from the L2 protein of human papillomavirus 16 (HPV16) on the surface. This protein could be used to trace protein sorting and vesicle transport to demonstrate that the sig-16L2-eGFP proteins were localized to the Golgi body via a signal peptide sorting route and then anchored to the plasma membrane by transport vesicles. Nanocale VMVs (50-150 nm) with similar morphology of virus were obtained after treating the cell membrane vesicles described above with surfactants, while a high yield of VMVs (64 ± 27 μg) loading the sig-16L2 epitope on the exterior could be harvested from 10^6 cells. The L2 antigen-loaded VMVs were capable of inducing a much higher level of antibody titers in response to the L2 polypeptide after intramuscular (i.m.) or intravenous (i.v.) administration, with or without Alum adjuvant to prohibit the infection by HPV16 as tested in animal models, compared to that of free L2 peptide group with Alum adjuvant. The VMVs could promote the delivery of antigens to immune system due to their large molecular weight and exogenous properties.[14]

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After showing that the VMVs could be designed to induce an antibody response against HPV16, the VMVs were then designed in a similar manner to carry the integral hemagglutinin (HA) glycoprotein (VMV-HA) from influenza A (H1N1) virus. The VMVs were obtained with HEK 293 cells and surfactants were again utilized so the VMVs resemble the influenza virus morphology. Influenza is the most widely spread pandemics and outbreaks occur yearly with renewed virus variation[15] that requires a fast design and production of vaccines to match the newly viruses as well to assolve the tenuous nature of vaccine supply.[1,16] The VMV-HA nanoparticles display the correct epitope conformation of HA glycoprotein to induce high levels of specific neutralizing antibody titers as inactivated influenza viruses, while efficiently agglutinating red blood cells (RBC) as an active influenza virus. The VMV-HA induced an efficient humoral immune response when tested in mice after i.m. administration. It was found to elicit high levels of serum IgG titers with or without Alum adjuvant, comparable to levels induced by standard HA glycoproteins, and also induced neutralization activities and HA inhibition response (HAI) of antibodiesagainst live H1N1 influenza viruses similar to that induced by purified HA subunit vaccines. Importantly, all of the mice that were intramuscularly vaccinated by VMV-HA with Alum adjuvant were able to survive and recover their bodyweight after being intranasal exposed to 50 times the lethal dose of mouse-adapted H1N1 virus, compared to the 100% lethality of the mice that received blank VMV. Thus, the protective efficacy of VMV-HA is comparable to both inactive virus and HA protein with Alum adjuvant, demonstrating high performance for inducing immunogenicity.

In summary, a versatile platform of VMV has been developed in a bioinspired manner that could successfully deliver antigens on their exterior for vaccines by maintaining the natural conformation of epitopes in antigens, and by inducing robust, straightforward and tunable immune responses to prohibit infection from viruses. It is an effective and safe immune engineering strategy for vaccine innovation, which also could be applied to develop vaccines or drugs against a wide range of immune-compromised diseases, inflammation and other infectious diseases. It could be further engineered to deliver bioactive compounds with specific ligands on the surface for targeted drug delivery and therapy.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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