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Biomimetic nanoparticles as universal influenza vaccine

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A B S T R A C T

Pandemic virus infections pose a major public health threat globally. Much efforts have been devoted to suppress the virus, including vaccine prevention, autoimmunity enhancement, and anti-virus drugs treatment. Among these strategies, development of novel and improved vaccine technologies attracts broad attention as they can nip the virus outbreak in the bud and avoid the appearance of public health emergency. However, current influenza vaccines only provide protection against homologous viruses. Therefore, chemical technologies are being employed for the development of new and improved vaccine, such as chitosan, plant polysaccharides and virus-like particles. In addition, recently, Wang et al. offered a promising means to develop universal viral vaccine through biomimetic nanoparticles and heterosubtypic protection could be achieved. These strategies with multidisciplinary collaboration are promising to make conceptual and technological advances of modern vaccinology to address pandemic virus infections.

Pandemic virus infections, such as seasonal influenza, severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus, pose a major public health threat globally [1,2]. Much effort has been devoted to suppress the virus, including vaccine prevention, autoimmunity enhancement, and anti-virus drugs treatment. Among these strategies, development of novel and improved vaccine technologies attracts broad attention as they can nip the virus outbreak in the bud and avoid the appearance of public health emergency. Therefore, Wang et al. [1] recently offer a promising means: they develop universal viral vaccine through biomimetic nanoparticles.

The conventional vaccines function by inducing primarily neutralizing antibody responses against viral hemagglutinin and neuraminidase [3]. Whereas, these surface proteins undergo continuous antigenic drift, leading to reduced coverage and limited efficacy of these vaccines, especially against novel pandemic viruses. In contrast to B cells-produced antibody responses, lung CD8\(^+\) resident memory T cells (T\(_{RM}\) cells) induced after natural viral infection can provide heterosubtypic protection against a variety of virus subtypes [4]. Similarly, replicating vaccines, such as live vector-engineered influenza vaccines, can induce CD8\(^+\) T\(_{RM}\) cells. However, efficacy of these vaccines is limited because a balance must be maintained between immunogenicity and safety, and they are suitable in only some populations due to compromise with preexisting immunity. Moreover, nonreplicating viral vaccines are alternative strategies, but poor T cell immunity response can be induced by them. Hence, some researchers have turned to materials science for inspiration in overcoming these shortcomings.

Many materials have been synthesized and employed for the development of improved vaccine. A typical example is chitosan, a functional polysaccharide obtained from the alkaline deacetylation of chitin composed of glucosamine and N-acetylgalactosamine. It is both relatively safe penetration enhancer and potent immunostimulant. Some plant polysaccharides may also be promising candidates for immune stimulating complexes. In addition, biomimetic concepts have been proposed. Virus-like particles are developed to mimic the live virus and deliver antigen at the mucosal surfaces. They are composed of viral structural proteins, and can be easily recognized by the immune system, inducing cellular and humoral immune responses.

Inspired by natural pulmonary surfactant (PS) layer, Wang et al. created 2',3'-cyclic guanosine monophosphate–adenosine monophosphate (cGAMP) encapsulated PS-biomimetic nanoparticles to potentiate heterosubtypic immunity (Fig. 1). The cGAMP is a secondary messenger in immune response to viral infections, and can agitate the stimulator of interferon genes (STING), which stimulated the expression of type I interferons (IFN-Is) and then induced immunity mediated by CD8\(^+\) T cells [5]. Hence, Wang et al. employed the cGAMP as an adjuvant to extend the coverage of nonreplicating influenza vaccines. PS layer, a mixture of proteins and lipids produced by alveolar epithelial cells (AECs), forms a strong barrier which prevented cGAMP from accessing...
AECs. As PS can be recognized by lung alveolar macrophages (AMs), the authors synthesized nanoparticles whose lipid composition and charge resembled PS for cGAMP encapsulation. Disguised as "self", the intra-nasally administered PS-GAMP nanoparticles escaped immune surveillance and readily entered AMs through surfactant protein-A (SP-A) and SP-D as they were PS-biomimetics. The cGAMP was released in the cytosol of AMs, and then transferred from AMs to AECs through gap junctions. STING pathway was subsequently activated both in AMs and AECs without breaching PS barriers.

Intranasal application of inactivated H1N1 vaccine and PS-GAMP nanoparticles adjuvant conferred robust heterosubtypic protection against both H1N1, H3N2, H5N1 and H7N9. Wang et al. found that during this cross-protection process, the PS-GAMP-adjuvanted influenza vaccine stimulated rapid recruitment and differentiation of antiviral natural killer cells, as well as pulmonary CD11b+ dendritic cells (DCs) which presented antigen to T cells to bridge innate and adaptive immunity. Afterwards, these CD11b+ DCs efficiently cross-primed and induced robust proliferation of typical T<sub>RM</sub> phenotypic CD8+ T cells in the respiratory system to provide long-term protection. Further experiments demonstrated that cGAMP-STING-activated AECs played a critical role in orchestrating DCs recruitment and subsequent CD8+ T cells accumulation to generate broad cross-protection against various influenza viruses.

Universality and instantaneity are important in vaccine development. PS-GAMP is designed as an independent mucosal adjuvant. Apart from inactivated influenza viral vaccines, it’s suitable for vaccines comprising cocktails of influenza vaccine subunits or multiple B and T epitopes. The capability of PS-GAMP to potentiate heterosubtypic influenza immunity makes it promising for universal influenza vaccine development. In addition, the PS-GAMP can induce robust cross-protection within 2 days after vaccination, while the current influenza vaccines require at least 10–14 days. Early protection is crucial in protecting first responders and high-risk individuals, and most effective in controlling the spread of virus, which can accelerate exponentially in an epidemic phase, and avoid pandemics.
Although promising advance has been made toward universal influenza vaccines through PS-biomimetic nanoparticles combined with inactivated influenza virus to elicit T cell-mediated heterosubtypic immunity, this strategy is still mainly biological vaccine and far away from pure chemical vaccine. For future development, two main aspects are still desired: first, new advances in virology should be made to realize rapid identification of novel virus and analysis of antigen to provide effective templates for real pure chemical vaccines fabrication; second, more materials and chemical synthesis methods, such as nanotechnology, microfluidic technology and microfabrication technology etc., should be developed or employed to bring improved chemical vaccines into reality and simplify the vaccine process. We believe that the multidisciplinary collaboration is promising to realize these challenges and make conceptual and technological advances of modern vaccinology.

Declaration of competing interest

The authors declare that they have no conflict of interest.

CRediT authorship contribution statement

Fengyuan Wang: Writing - original draft. Guopu Chen: Visualization. Yuanjin Zhao: Writing - review & editing.

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