Medical & healthcare, Drug development

Efficient adjuvant-free intranasal vaccine platform that harnesses previously induced immunity

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Researchmap https://researchmap.jp/read0076530?lang=en

Abstract

Intranasal vaccines are anticipated to be powerful tools for combating many infectious diseases, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), because they induce not only systemic immunity but also mucosal immunity at the site of initial infection. However, they are generally inefficient in inducing an antigen-specific immune response without adjuvants. Here, we developed an adjuvant-free intranasal vaccine platform, which utilizes the pre-existing immunity induced by previous infection or vaccination to enhance vaccine effectiveness. Here, we made RBD-HA, a fusion of the receptor binding domain (RBD) of the Spike protein derived from SARS-CoV-2 as a vaccine target with hemagglutinin (HA), to test whether HA-specific pre-existing immunity could be utilized. We showed that intranasal immunization with RBD-HA without an adjuvant in previously influenza virus-infected mice elicited a robust production of RBD-specific systemic IgG and mucosal IgA by utilizing not only HA-specific pre-existing IgG but also $CD4^+$ T cells. Furthermore, RBD-HA protected mice in both the upper and lower respiratory tracts against SARS-CoV-2 infection. In addition, pre-existing immunity induced by *Streptococcus pneumoniae* infection and an injectable mRNA vaccine can be utilized, suggesting high versatility of the vaccine system. Thus, we propose an adjuvant-free intranasal vaccine platform that could induce strong systemic and mucosal protective immunity.

Background & Results

Traditional parenteral vaccines do not completely prevent viral infection and transmission because of poor induction of respiratory mucosal immunity. Recent outbreaks of COVID-19 have increased the demands for development of intranasal vaccines because they induce not only systemic immunity but also mucosal immunity at the site of initial infection. As revealed by preclinical studies on COVID-19 and influenza, intranasal vaccination is also known to reduce viral shedding and transmission when compared to parenteral vaccines. Despite these studies, there are currently only a few approved intranasal vaccines. Most intranasal subunit vaccines are inefficient in inducing an antigen-specific immune response, hence require adjuvants to enhance immunogenicity. However, administration of adjuvants to the respiratory tract in humans raises concerns about adverse reactions.

In this study, we developed an effective adjuvant-free intranasal vaccine platform that utilizes pre-existing immunity induced by previous infection or vaccination. We made RBD-HA, a fusion of the receptor binding domain (RBD) of Spike protein derived from SARS-CoV-2 as a vaccine target with hemagglutinin (HA) derived from influenza viruses, which many of us have specific immunity to, as a carrier protein. We revealed intranasal immunization with RBD-HA without an adjuvant in previously influenza virus-infected mice, but not in naive mice, elicited robust production of RBD-specific systemic IgG and mucosal IgA, which protected mice efficiently from SARS-CoV-2 infection. Further, we showed pre-existing HA-specific IgG and $CD4^+$ T cells contribute to enhance RBD-specific immune responses by intranasal RBD-HA. Fusion with vaccine antigens derived from *Streptococcus pneumoniae* or respiratory syncytial virus induced vaccine antigen specific antibodies. In addition, pre-existing immunity induced by injectable mRNA vaccine can be utilized to enhance vaccine antigen-specific immune responses, suggesting high versatility of pre-existing host immunity for our vaccine system, emphasizing its potential clinical applications.

Significance of the research and Future perspective

The results of this study imply the promising potential of this intranasal vaccine platform to address problems associated with intranasal vaccines.

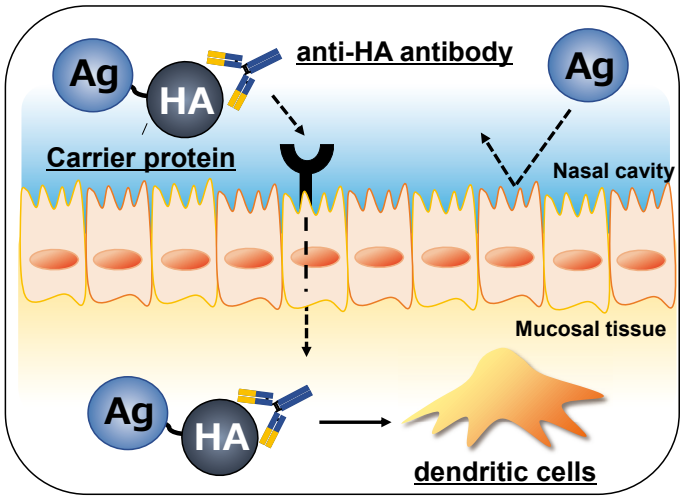

Figure: We propose an adjuvant-free intranasal vaccine platform that utilizes pre-existing antibodies to induce strong systemic and mucosal protective immunity. a vaccine antigen fused with a carrier protein that recognizes pre-existing antibodies can facilitate passage through the mucosal barrier and be simultaneously picked up by dendritic cells. We developed a vaccine antigen consisting of the RBD of the spike protein derived from SARS-CoV-2 fused with hemagglutinin (HA) derived from influenza viruses. This HA protein serves as a carrier protein, taking advantage of the pre-existing antibody that many individuals possess against HA.

Patent PCT/JP2021/038496, PCT/JP2023/013408

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