Medical & healthcare, Drug development

Low-inflammatory lipid nanoparticle-based mRNA vaccine elicits protective immunity against H5N1 high-pathogenicity avian influenza virus with reduced adverse reactions

Vaccine Creation Group, BIKEN Innovative Vaccine Research Alliance Laboratories, Research Institute for Microbial Diseases

Specially Appointed Professor Yasuo Yoshioka

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

Abstract

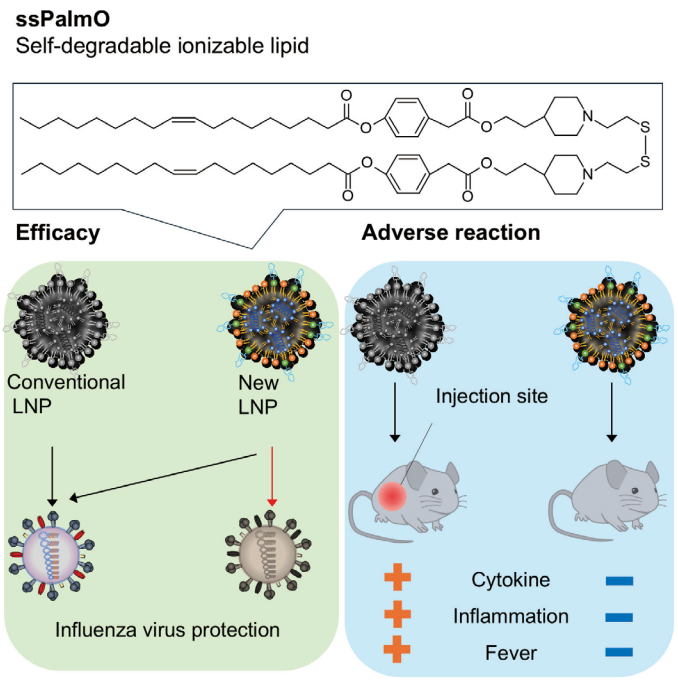
Messenger RNA vaccines based on lipid nanoparticles (mRNA-LNPs) are promising vaccine modalities. However, mRNA-LNP vaccines frequently cause adverse reactions such as swelling and fever in humans, partly due to the inflammatory nature of LNP. Modification of the ionizable lipids used in LNP is one approach to avoid these adverse reactions. Herein, we report the development of mRNA-LNP vaccines with better protective immunity and reduced adverse reactions using LNP, which contains a disulfide (SS)-cleavable bond and pH-activated lipid-like materials with oleic acid (ssPalmO) as an ionizable lipid ($LNP_{ssPalmO}$). We used mRNA expressing H5N1 subtype high-pathogenicity avian influenza virus-derived hemagglutinin or neuraminidase to generate mRNA-LNP vaccines against H5N1 influenza. Compared with conventional LNP, mRNA-$LNP_{ssPalmO}$ induced comparable antigen-specific antibodies and better interferon-gamma (IFN-()(producing T-helper type-1 (Th1) responses in mice. Both mRNA-$LNP_{ssPalmO}$ and conventional mRNA-LNP conferred strong protection against homologous H5N1 virus challenge. In addition, mRNA-$LNP_{ssPalmO}$ showed better cross-protection against heterologous H5N1 virus challenge compared with conventional mRNA-LNPs. Furthermore, we observed that mRNA-$LNP_{ssPalmO}$ induced less inflammatory responses (e.g., inflammatory cytokine production and vascular hyperpermeability) and fewer adverse reactions (e.g., weight loss and fever) compared with conventional mRNA-LNP. These results suggest that mRNA-$LNP_{ssPalmO}$ would be a safe alternative to conventional vaccines to overcome mRNA-LNP vaccine hesitancy.

Background & Results

In recent years, H5N1 subtype high-pathogenicity avian influenza virus has infected wild bird and poultry populations across the globe. Although H5N1 influenza viruses are unlikely to infect humans, several human infections have been confirmed due to the global spread of this virus in various animals. Therefore, the development of vaccines against H5N1 is a public health priority. Messenger RNA vaccines based on lipid nanoparticles (mRNA-LNPs) are promising vaccine modalities against H5N1 influenza viruses. However, mRNA-LNP vaccines cause adverse reactions in humans, partly due to the inflammatory nature of LNPs. The ionizable lipids used in LNPs primarily contribute to the inflammatory nature of LNPs, which suggests that modifying the ionizable lipids may help prevent these adverse reactions. Here, mRNA-LNP vaccines with superior protective immunity and reduced adverse reactions against H5N1 influenza virus were developed using a biodegradable “SS-cleavable and pH-activated lipid-like material with oleic acid (ssPalmO)” as the ionizable lipid. We compared the vaccine functions and adverse reactions of mRNA-$LNP_{ssPalmO}$ and mRNA-LNP with conventional ionizable lipid (mRNA-LNP_{conv}). mRNA-$LNP_{ssPalmO}$ induced antigen-specific IgG levels comparable to those of mRNA-LNP_{conv}. $LNP_{ssPalmO}$ induced more IFN-γ-producing T cells than mRNA-LNP_{conv}. Both mRNA-$LNP_{ssPalmO}$ and mRNA-LNP_{conv} conferred strong protection against homologous H5N1 viral challenge. In addition, mRNA-$LNP_{ssPalmO}$ showed superior cross-protection against heterologous H5N1 virus challenge than mRNA-LNP_{conv}. Furthermore, mRNA-$LNP_{ssPalmO}$ reduced inflammatory cytokine secretion and adverse reactions compared to mRNA-LNP_{conv}.

Significance of the research and Future perspective

Collectively, these results indicate that mRNA-$LNP_{ssPalmO}$ is an alternative mRNA-LNP vaccine platform that overcomes the limitations associated with mRNA-LNP vaccines.



In this study, we demonstrate the potential of an mRNA-$LNP_{ssPalmO}$ vaccine to provide comparable protective immunity against H5N1 influenza viruses and fewer adverse reactions associated with reduced inflammatory responses compared with conventional mRNA-LNP vaccines. Our findings suggest that mRNA-$LNP_{ssPalmO}$ is a safe alternative to conventional vaccines for overcoming mRNA-LNP vaccine hesitancy.

Patent

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