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Biomaterials for intranasal and inhaled vaccine delivery

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Delivery of vaccines by nasal sprays may enable more robust, protective mucosal immune responses against infectious diseases, such as COVID-19, compared with intramuscular injection. In this Comment, we highlight how biomaterials can be designed to allow intranasal and inhaled vaccination.

Mucosal vaccination technologies would allow the creation of accessible and effective vaccines[1]. Fear of needles or pain associated with intramuscular injections can make vaccination distressing, particularly for children. Alternatively, respiratory vaccines are less painful, and easily administered without medical training, which could benefit communities with inadequate access to professional medical care. Formulations for respiratory vaccines as dry powders that are stable in ambient temperatures may also improve the global distribution of vaccines in low-resources settings. In addition, administration of inhalable vaccines does not require trained personnel compared with intramuscular vaccines. Nasal spray vaccines localize mainly in the upper airway, and aerosolized vaccines inhaled through the nose or mouth can reach deep into the lungs. Respiratory vaccines can also provide both local and systemic immunity against a pathogen. The mucosal immune system creates a local immune memory of the pathogen-specific antigen, which is rapidly reactivated upon re-exposure to the same antigen. Importantly, local reactivation after mucosal vaccination occurs faster than reactivation of a systemic response. For example, combining an intramuscular COVID-19 vaccine with a local intranasal 'booster' dose of COVID-19 spike protein resulted in increased neutralizing mucosal antibody production against COVID-19 infection compared with intramuscular vaccination or booster alone[2]. Furthermore, mucosal vaccination can provide cross-protection, leading to the formation of neutralizing antibodies in multiple mucosal sites; for example, intranasal vaccination can provide intestinal immunity.

FluMist is a US Food and Drug Administration (FDA)-approved live-attenuated influenza virus mucosal vaccine in the form of a nasal spray, which is used as an alternative to the flu shot. However, the vaccine formulation may not provide a sufficient immune response and adequate protection in children, for whom intranasal administration would likely be preferred[1]. On the other hand, many intranasal vaccines, including COVID-19 intranasal vaccines currently in clinical trials (NCT04816019, NCT04839042, NCT04798001 and NCT04954287), are based on viral vectors, which are limited by the immunogenicity of the viral components. In comparison to these virus-based approaches, non-viral biomaterial formulations could provide a safer alternative.

Barriers to respiratory delivery

For many respiratory infectious diseases, including COVID-19, vaccines targeted to the upper airways may be preferable to prevent initial infections in the nose. To achieve this, aerosolized vaccines can be directed to specific airway regions by controlling droplet size in the micron range to target the nasal or tracheal region or sub-micron range to target the bronchial regions. Once administered, respiratory vaccine formulations need to overcome various airway barriers to achieve protection (Fig. 1). The mucus lining the airway acts as a semi-permeable barrier to inhaled materials, and foreign material is usually rapidly cleared by motile cilia on the epithelial surface of the respiratory tract. Depending on their size and surface chemistry, vaccine nanoformulations consisting of nucleic acids, lipids, polymers, proteins and/or entire viruses can be trapped within mucus following inhalation. For example, adenoviral vectors used in the development of vaccines against SARS-CoV-2, HIV and tuberculosis can adhere to mucus[3], limiting the ability of the virus to reach target cells (for example, pulmonary dendritic cells) to elicit robust mucosal immune responses. Non-viral vaccine platforms, such as lipid-based mRNA vaccines, can be designed to overcome the mucus barrier, and may thus allow respiratory vaccination. For example, an inhaled nanoparticle vaccine coated with polyethylene glycol (PEG) can rapidly penetrate the mucus barrier and enhance the proliferation of antigen-specific T cells in the lungs and lymph nodes, as compared with intramuscular delivery of a carrier free vaccine[4].

Biomaterials as vehicles and adjuvants

Lipid nanoparticles can be used to encapsulate nucleic acid or protein vaccines and protect their cargo from degradation by nucleases and proteases, for example, for mRNA vaccines against COVID-19. The remarkable efficacy of mRNA lipid nanoparticle vaccines is attributed to the intrinsic adjuvant functions of the nanoparticles, promoting helper T cell and B cell maturation and proliferation[5]. In addition to lipid-based formulations, vaccines can be made of cationic polymeric nanoparticles delivering nucleic acids. Of note, polyethyleneimine (PEI) has been explored for intranasal vaccine delivery, owing to its adjuvant properties. For example, mRNA can be encapsulated in PEI conjugated to cyclodextrin to design an intranasal vaccine for Zika virus infections, allowing more efficient lymph node targeting and low toxicity, compared to PEI alone[6]. Lung-derived exosomes that contain SARS-CoV-2 receptor-binding domains can be designed as inhalable vaccines, generating a robust immune response in the airways of mice[7]. Alternatively, self-assembling peptides, consisting of a $CD8^+$ T cell epitope fused to a β-sheet nanofiber assembly domain, have been used as inhaled vaccines where immunogenicity can be increased by tuning material properties, such as shape, size, charge and surface composition[8]. Peptide-based amphiphilic antigen immunoconjugates, termed immunogens, that self-assemble into nanoscale micelles have also proven useful for mucosal vaccination[9]. When delivered intranasally, these immunogen nanoparticles are efficiently trafficked to

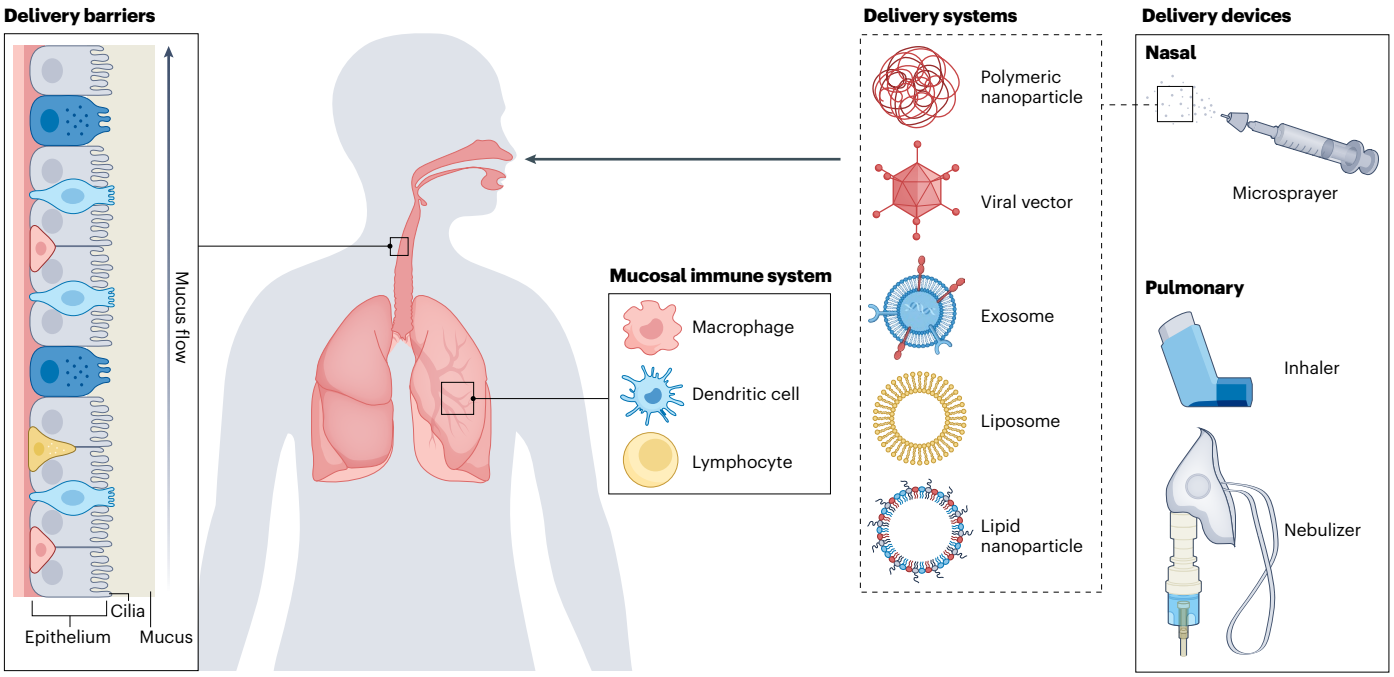

Fig. 1 | Intranasal and inhaled vaccine delivery. The delivery barriers, the immune system in the lung and airways, vaccine delivery nanosystems and delivery devices.

nasal-associated lymphoid tissue (NALT), leading to an IgG and IgA immune response, which persist in the nose and other mucosal tissues, such as the vaginal and gastrointestinal tracts.

Adjuvants tailored for respiratory and mucosal delivery should be carefully selected in vaccine development, based on the required immune responses. Effective vaccination at mucosal sites requires adjuvants capable of generating robust IgA antibody responses and inducing systemic immunity through the activation of B cells and dendritic cells. Aluminum salt, for example, is widely used as an adjuvant in parenteral vaccines, but does not induce IgA antibody secretion when used in mucosal vaccines. Adjuvants for mucosal administration are typically immunostimulatory molecules, such as cytokines, toll-like receptors (TLRs) or other pathogen- or danger-associated molecular patterns (PAMPs or DAMPs). In particular, TLR agonists, such as cytosine-phosphate-guanine (CpG, TLR9) and polyinosinic:polycytidylic acid (Poly:IC, TLR3) are well tolerated at low doses and produce strong B cell responses at mucosal sites. Other biomaterials, such as chitosan, can also act as adjuvants in intranasal subunit vaccines, producing strong mucosal immune responses[10].

Outlook

Intranasal vaccine platforms, such as FluMist, are often designed based on traditional vaccination technologies. However, intranasal vaccines should be designed to target specific cells in the NALT, such as M cells, which are responsible for antigen uptake and for the generation of specific immune responses in mucosal compartments. Nanoparticle-based delivery systems can also be used for the development of boosters, which can be repeatedly administered without inducing immunogenicity often associated with viral vectors. Several clinical trials are currently underway for intranasal and inhaled vaccines against COVID-19 (ref.[1]). Previous clinical trials for aerosolized tuberculosis and measles vaccines have shown that targeting the respiratory mucosa provides effective immunity. However, the lack of appropriate animal models for intranasal and pulmonary delivery methods hinders their clinical development. Therefore, developing new techniques and devices that closely mimic human respiration and mucosal barriers will be necessary to support vaccine translation. Additionally, advances in dry powder formulations may enable the development of inhaled vaccines with longer shelf-life, compared with liquid-based formulations, for easier global distribution to low-resource areas, without cold-chain facilities.

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Competing interests

All authors declare no competing interests.