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The Role of Mucosal Immunity in the Control of Respiratory Infectious Diseases

Yue Zhang

Columbian College of Arts & Sciences, The George Washington University, Washington D.C., The United States
Corresponding author: yzhang57@gwu.edu

Abstract:

Respiratory infectious pathogens such as influenza, respiratory syncytial virus (RSV), and SARS-CoV-2 persist as significant threats to global health. Most of the pathogens come in through the respiratory mucosa, with the local immune mechanisms as the first line of defense. Here, we explore the role of mucosal immunity, such as secretory immunoglobulin A (sIgA), tissue-resident memory T cells (TRM), and inducible bronchus-associated lymphoid tissue (iBALT), in the management of respiratory infections in this research. The mechanistic part illustrates how mucosal vaccination achieves these reactions by protecting within the zone of pathogen entry. There is now experimental data on live attenuated influenza vaccination (LAIV), studies on preclinical SARS-CoV-2 mucosal vaccine, and early human trials that demonstrate the possible role of mucosal vaccination in limiting viral replication and transmission. But the translational challenge is still with various aspects, such as uniform mucosal immune correlates, heterogeneity in formulation and delivery, and regulatory obstacles. Mucosal vaccines provide a compelling complement to systemic immunization but remain challenging to implement. By acting via both systemic and local immunity, these vaccines are likely to play a role in comprehensive respiratory disease control as well as preparing populations for pandemics. These results highlight the necessity for mucosal immunity to be considered as a pillar of future vaccine development and public health policy framework.

Keywords: Mucosal immunity; respiratory infectious diseases; secretory IgA.

1. Introduction

Respiratory infectious diseases, such as influenza, respiratory syncytial virus (RSV), and SARS-CoV-2, are common infectious diseases that represent a global health threat in the host, during which the presence of pathogens of respiratory pathogens is mainly acquired via the respiratory mucosa. The mucosal

surface of the respiratory tract is the primary mechanism of exposure of pathogens to the immune system. Mucosal immune mechanisms (e.g., sIgA, tissue-resident memory T cells (TRM), and inducible bronchus-associated lymphoid tissue (iBALT)) are the first line of defense in resisting respiratory pathogens; they act at the entry site and so represent a major advantage over systemic immunity that acts after the introduction of the pathogen into the host [1]. Despite considerable progress in vaccine development, existing intramuscular vaccines—the most prominent systemic vaccine approach—have shown substantial difficulties in eliciting mucosal immunity [2]. Although these vaccines can obtain substantial levels of serum IgG antibodies to prevent severe disease (e.g., hospitalization and death), they frequently do not form strong local immune responses at the surfaces of the respiratory mucosa where pathogens (e.g. influenza viruses and SARS-CoV-2) initially infect, and this protective gap explains why vaccinated individuals are able to continue to contract and transmit respiratory pathogens, thus pointing to the immense need for mucosal immunity-targeted vaccine strategies [3,4].

The formulation of mucosal vaccines, in particular into intranasal or inhaled formulations, represents a very encouraging method for correcting for such limitations. The LAIV and related vaccines, among which the live attenuated influenza vaccine (LAIV) has become the only licensed mucosal vaccine for the treatment of respiratory diseases to date, show that intranasal vaccination can stimulate systemic (serum IgG) as well as local (nasal sIgA, respiratory TRM) immune responses [5]. These mucosal responses have been found to be associated with attenuation of viral shedding and limited transmission. A generation of mucosal vaccine platforms is now emerging for SARS-CoV-2 and other respiratory pathogens, extending and continuing the precedent set by this pioneering approach [6].

This paper investigates the mechanism, experimental and clinical evidence, and translational potential of mucosal immunity in the control of respiratory infectious diseases to establish a conceptual framework. Through analysing the different immunological pathways activated by mucosal vaccination, we hope this article may help explain how these approaches can integrate into existing immunisation strategies. Moreover, the study will explore existing difficulties in translating mucosal vaccines from preclinical methods to clinical usage, and what they mean for wider public health policy (and therefore pandemic preparedness) [7].

2. The Empirical Evidence Transformation Challenge and Public Health Significance of the Mechanism of Action of Respiratory Mucosal Vaccines

2.1 Mechanistic Basis

2.1.1 Secretory IgA and epithelial transport

Mucosal immunity builds respiratory defense barriers through multidimensional synergistic action; the key elements of mucosal immunity consist of three fundamental interlocking factors that work synergistically to develop a cumulative, holistic defense network. Polymeric IgA secreted into the respiratory mucosa by plasma cells is pivotal in mucosal defense against respiratory pathogens. This antibody is transported across epithelial cells via the polymeric immunoglobulin receptor (pIgR), which cleaves during transcytosis, producing secretory IgA (sIgA). The secretory component protects IgA against enzymatic degradation and anchors it in the mucus layer, enabling it to neutralize viruses and toxins without causing inflammation [1]. In the context of influenza and coronavirus infections, sIgA has been shown to prevent viral adherence to epithelial cells, serving as the first line of defense against viral entry [2]. The ability of mucosal vaccines to promote this pathway gives a strong mechanistic basis for their advancement [3].

2.1.2 Tissue-resident memory T-cells (TRM)

There are also significant tissue-resident memory T cells (TRM) present in the airway that provide mucosal defense. In contrast to circulating T cells, TRM are confined to sites of the mucosa following antigen exposure, where they can react quickly to reinfection. These cells possess retention markers such as CD69 and CD103, allowing for long-term persistence within the epithelium and lung parenchyma. TRM upon re-contact with the pathogen mount accelerated interferon-γ responses and cytotoxic activity, often containing infection before systemic immunity is mobilized [3]. We also note their utility by means of animal models as well: local priming through the mucosal vaccination has been found to produce more efficient TRM populations than intramuscular vaccination [4]. This rapid, close-to-home defensive localisation emphasizes the additional advantage of mucosal approaches for the control of respiratory infections.

2.1.3 Inducible bronchus-associated lymphoid tissue (iBALT)

Apart from antibody- and T-cell responses, mucosal vaccination can also take advantage of the formation of

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inducible bronchus-associated lymphoid tissue (iBALT). iBALT develops after infection or inflammation and resembles the appearance of secondary lymphoid organs and consists of organized B-cell follicles and T-cell zones. It is a site where adaptive immune responses can initiate in the lung directly, in which IgA-secreting plasma cells and effector T cells are rapidly produced [4]. Studies in mice have demonstrated that vaccines capable of inducing iBALT can provide long-lasting protection against respiratory viruses by accelerating local immune responses [1]. Mucosal immunization produces these tertiary lymphoid structures, resulting in an added layer of immunity in the respiratory mucosa and hence, protective immunity is not only systemic but also locally maintained in the respiratory tract.

2.1.4 Integrated protective network

These mechanisms demonstrate a multi-layered defense system unique to mucosal immunity. Secretory IgA neutralizes pathogens at the surface before they establish infection [1]. TRM cells stand ready to deliver rapid cytotoxic responses upon reinfection [3]. iBALT provides a structural basis for sustaining adaptive immune activity within the lung [4]. This combination of humoral (sIgA-mediated neutralization), cellular (TRM-mediated rapid cytotoxicity), and organizational (iBALT-mediated immune persistence) components explains why mucosal vaccination can achieve outcomes—such as reducing initial infection (by blocking pathogen adherence) and viral shedding (by limiting local replication)—that are difficult to replicate with intramuscular vaccines alone. These insights form the immunological foundation for designing respiratory vaccines that aim not only to prevent severe disease but also to interrupt transmission chains [3].

2.2 Experimental and Clinical Evidence

Given the mucosal immune response established above, numerous experiments, including clinical studies, have confirmed the potential of mucosal vaccines for the prevention and control of respiratory diseases. Of the above, the live attenuated influenza vaccine (LAIV) is the first example to achieve clinical transformation, and novel coronavirus (SARS-CoV-2) mucosal vaccine research further expands its application boundary, pushing the clinical boundaries of development further.

2.2.1 Live attenuated influenza vaccine (LAIV) as a proof-of-concept

The well-recognized mucosal vaccine against respiratory pathogens includes the intranasally administered LAIV. Unlike inactivated influenza vaccines administered intramuscularly, LAIV replicates in the cooler environment of the nasal mucosa, thus fostering systemic and local immune responses. LAIV has been demonstrated to potentiate nasal IgA and induce tissue-resident T cells in the respiratory tract as per clinical studies [5]. These mucosal responses are directly tied to less viral shedding, reducing the chances of secondary transmission [6]. The mucosal vaccine showed significant protective efficacy (through large-scale programs in children and healthy adults) and supports the hypothesis that it is effective in real-world immunization [7].

2.2.2 Immune profiling of LAIV

Outside of clinical implications, mechanistic studies have also identified how LAIV stimulates compartmentalized immunity. Specifically, the nasal wash evidence demonstrated a strong IgA induction that persisted throughout influenza seasons. These findings are distinct from systemic antibody titers, indicating the potential error in serum levels, which may be a contributing factor in underestimating mucosal protection. Moreover, T cell responses during LAIV are spatially distributed in the upper airways and facilitate rapid recall at the point of pathogen entry [5]. These results highlight that mucosal endpoints rather than systemic indicators are critical for assessing vaccine effectiveness.

2.2.3 Preclinical evidence from SARS-CoV-2 mucosal vaccines

The newest generation of mucosal vaccine platforms has been tested in animal models during the COVID-19 pandemic. Intranasal spike-based vaccines in mice were effective in eliciting potent IgA and increasing tissue-resident memory T cells in the lung, resulting in a decrease in viral titers in both the upper and lower respiratory tract [8]. Ferret tests supported this, which revealed reduced nasal viral shedding upon mucosal immunization [9]. Inhaled vaccines in non-human primates provided not only protection against severe disease but also against onward transmission and pointed to their great potential as community-level interventions [9]. Thus, these preclinical data together extend the LAIV example to new pathogens and demonstrate that using mucosal vaccines can alter the structure and dynamics of infectious disease in ways intramuscular vaccines cannot.

2.2.4 Emerging human clinical trial data

The translation of these results to humans has begun with Phase I and II studies. A single available open-label trial of an inhaled aerosol COVID-19 vaccine showed significant induction of mucosal IgA in the respiratory tract in addition to systemic IgG, with a favorable safety profile [10]. Systematic review of clinical data showed that mucosal vaccines on multiple platforms are predominantly

immunogenic and well-tolerated, although efficacy endpoints are still underpowered because of small sample sizes [11]. These results show that mucosal delivery is possible in humans and may facilitate activation of the targeted immune systems, albeit more major trials are needed to confirm protective effects.

2.2.5 Comparison with intramuscular vaccination

The different value of the mucosal vaccines is presented when compared to their intramuscular counterparts. Intramuscular vaccines consistently induce serum IgG and lessen severe adverse events, but they do not frequently produce enough nasal IgA or establish TRM in the respiratory tract [12]. This gap can account for why, in vaccinated individuals, the respiratory pathogens can still be contracted and transmitted. Mucosal vaccination, on the other hand, aims to fill this gap, thus strengthening local immunity at the site of the initial access of pathogens. Reviews of SARS-CoV-2 vaccine development have emphasized that the combination of systemic-based and mucosal strategies may yield maximal protection through a reduction in disease severity and transmission [13]. This implies that different heterologous prime-boost regimens could represent a more effective approach in future immunization programs.

2.2.6 Integrated interpretation of evidence

In conclusion, given clinical trial results and early clinical performance with SARS-CoV-2 mucosal vaccine, it can be concluded that the primary benefit of mucosal vaccine rests on two major components: local immune induction and transmission control—these two points are the shortcomings of current intramuscular injection vaccines. Evidence from LAIV, early clinical trials, preclinical SARS-CoV-2 studies, and early clinical trials supports that the mucosal vaccines have benefits over and above systemic vaccines. The effect of LAIV in an ad-hoc treatment of seasonal influenza has been confirmed in the wild [5]. Animal models emphasize the mechanistic ability of mucosal delivery to decrease replication and shedding [8]. Human treatment has verified feasibility and immunogenicity; however, large-scale effectiveness is still to be demonstrated [11]. Together, these results suggest that mucosal vaccines may add an important layer in respiratory disease management and serve as adjunctive rather than supplementary systemic measures to the current strategies.

2.3 Challenges in Translational Science

Although the mechanism and evidence of mucosal vaccines are validated, translation from laboratory to clinical use remains a multidimensional challenge - not only scientific and technological bottlenecks, but also the adjustment of the regulatory system to public health practices. It is very difficult to translate the results into the clinical use of mucosal vaccines; the single biggest bottleneck is the absence of standardized correlates of protection to mucosal immunity. While systemic vaccines employ standardized evaluation criteria (serum IgG titers ≥1:40 for influenza and neutralizing antibody titers ≥1:20 for SARS-CoV-2) [12,13], mucosal immunity evaluation relies on complex indicators—such as nasal IgA titers, sIgA affinity for pathogen antigens, and TRM prevalence in respiratory tissues—that lack unified detection standards and threshold definitions. Nevertheless, the detection techniques and critical values for this study show considerable variance in the identified data [12]. Some, for instance, have the advantage of employing nasal IgA as protective alternative indicators, whereas others focus on TRM phenotype analysis [11]. This heterogeneity challenges the efforts of regulatory agencies to create a standard endpoint for review, which complicates vaccine approval and the standardization of clinical trial design.

The differences in the drug formulation and in the delivery of antigen introduce another major obstacle: nasal vaccines need to overcome a variety of individual differences in terms of mucociliary clearance, enzymatic degradation and antigen airway deposition among users. Small droplet sizes or delivery systems are just a few nuclei of these that can matter — and they can make a huge effect on immune response, even if it's one or two centimeters in size. The nasal lipid nanoparticle mRNA vaccine in some animals has potential in several studies, although various human subjects achieve it with very different efficacy as well [9]. In addition, various methods of delivery, including nasal spray, dry powder, and inhaled aerosol, have distinct merits and drawbacks regarding their stability, simplicity and local immune activation capacity that complicate dose control and mass production [10]. At the same time, safety and regulatory issues are not to be ignored: though nasal vaccines generally lead to mild adverse effects like nasal congestion and a runny nose, serious adverse incidents associated with nasal adjuvants have, in history, caused regulatory agencies to broaden safety monitoring [12]. The long-term safety of repeated mucosal booster vaccination (particularly in children having immature nasal mucosa and immune systems) has not been established [12]. This conservative attitude has prolonged the period of trials, increased research and development costs, and reduced the readiness of the industry to invest.

In addition, integrating mucosal vaccines into the existing vaccine system—predominantly based on intramuscular injection—is hard: the current supply chain, medical management training and cold chain logistics have all been optimized for injectable vaccines, and introducing nasal

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or inhalation vaccines involves developing new devices, developing regulations, and education and promotion. But policymakers, without clear evidence of advantages, may take a wait-and-see attitude. There's also confusion in how the public feels about it: there are those who want the vaccine to be needle-free, others who have worries about inhaled or nasal products. Such logistical and socio-technical challenges result in, if scientific and technological barriers are overcome, widespread usage of mucosal vaccines is likely to be slow and difficult. In short, challenges in achieving transformation from mucosal vaccines fall into four essential categories of interest: science, technology, regulation and public health [13]. Only by overcoming these barriers systematically can their potential for respiratory disease prevention and management actually be realized.

2.4 Broader Implications

Assuming the above transformation barriers can be overcome, mucosal vaccines will shift the paradigm of respiratory disease prevention and control. Their central value is not only for increasing individual protections but also for group-level prevention and control as "blocking transmission," which is important to guiding public health practice.

2.4.1 Reducing transmission at the community level

And perhaps the single most noticeable benefit of these mucosal vaccines is their anti-virulence effect. In addition to suppressing viral shedding, mucosal immunity and mucosal vaccines can block viral shedding and continued viral transmission. Such vaccines can also prevent replication, as the latter involves immune mechanisms that are dependent on secretory IgA and local T-cell responses in the upper respiratory tract to block pathogens from spreading. This contradicts intramuscular vaccines, which aim to protect against a serious disease and do not, more often than not, prevent asymptomatic infection [3]. Research from LAIV programs indicates that, once mucosal immunity is developed, not only are vaccinated individuals shielded, but also chains of transmission in schools and homes are disturbed [5]. When new disease agents emerge, such as SARS-CoV-2, even a slight effect toward reduction in transmission will also be of great public health benefit, specifically for groups of people who engage frequently in close contact, such as children and healthcare workers [13].

2.4.2 Complementarity with systemic vaccines

Mucosal vaccines should be considered as one layer of defense, rather than a replacement for intramuscular immunization. Systemic vaccines produce a well-established level of circulating IgG that acts against infection and death, and mucosal platforms provide another layer of entry resistance. A heterologous prime-boost strategy, where an intramuscular priming dose and a mucosal boost are administered sequentially, could leverage these advantages [12]. Preclinical and early clinical trials have already shown that these regimens expand the repertoire of immune protection and extend the persistence of protection [10]. This dual strategy corresponds to the notion of "sterilizing immunity," the concurrent systemic and mucosal responses that work to not only eliminate disease but also to block infection and spread [11].

2.4.3 Policy and long-term perspective

If validated through large-scale trials, mucosal vaccines could reshape vaccination policy by adding a transmission-blocking component to existing immunization programs. This shift would have an especially huge impact on pandemic preparedness, where preventing early community transmission is as relevant as preventing serious outcomes. For now, to tap this potential, policymakers have to reconcile scientific promise with logistical realities and integrate it into existing infrastructures [12]. Finally, the broader purpose is that mucosal immunity provides a model for designing more broad-based vaccines that are sensitive to both individual and population levels and so advance the aims of public health beyond individual-level disease prevention [13].

3. Conclusion

Mucosal immunity provides the body's most immediate and adaptive defense against respiratory pathogens. Acting at the point of pathogen entry, it provides advantages that systemic immunity does not achieve on its own. In this article, we have described the mechanism by which mucosal immune responses (secretory IgA, tissue-resident memory T cells, and inducible bronchus-associated lymphoid tissue) modulate infection, limiting viral replication and transmission. Experimental and clinical data repeatedly support the ability of mucosal vaccination to enhance these local responses, creating a new layer of immunostability that augments conventional intramuscular immunomodulation. The results indicate that mucosal vaccines are not just a substitute for but a tactical upgrade to current immunization mechanisms. They are particularly beneficial for the reduction of community transmission, a concern when controlling both seasonal and pandemic outbreaks. Because mucosal vaccination activates both local and systemic immune pathways, it may deliver a broader form of protection—reducing disease severity as well as interrupting transmission chains. This holistic strategy

represents a departure from previous vaccine development strategies that favored individual immunity at the expense of population-level disease control. However, it is not easy to achieve this potential. Standardized markers with which to measure mucosal protection should be developed in scientific and regulatory systems. Just as much will be needed to deliver consistent efficacy and to garner public acceptance, progress in formulation, delivery technology, and safety assessment is necessary. Furthermore, successful implementation will rely on collaboration among scientists, medical practitioners, policymakers, and the public health community. Mucosal immunity, therefore, represents a template for vaccine innovation in the future – at the nexus of immunology and translational science and a pathway towards the development of better, more adaptable immune strategies to respiratory disease. Mucosal vaccines are likely to redefine preventive medicine by changing the manner in which societies think about respiratory health, from a focus on the treatment process to proactive care of the body at a population level.

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