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Commentary

Mucosal immunity to SARS-CoV-2: a clinically relevant key to deciphering natural and vaccine-induced defences

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The unusually rapid development of large-scale vaccines against coronavirus disease 2019 (COVID-19) was a historical moment for clinical healthcare. However, it took precedence over the fundamental immunological work needed for a fuller understanding of the critical components of immunity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Consequently, almost all studies of the immune response in COVID-19 have focused exclusively on serum antibodies and systemic cell-mediated immunity including innate responses [1]. It is true that, just like the 'far, dark side of the Moon', which is invisible from the earth, the mucosal response to pathogens is a far, dark side of immunity that is poorly or not visible from the peripheral blood and more complicated to probe than systemic immunity.

This commentary aims to explain why in-depth studies of mucosal immunity would significantly optimize our understanding, both pathophysiologically and clinically, of natural and vaccine-induced immune defences against SARS-CoV-2, a key issue in the current pandemic.

The rationale for the early mucosal immune responses against SARS-CoV-2 starts with its entry and early replication in upper airway mucosal surfaces, especially the nasopharynx. Upper airway antigenic priming gives rise to a dynamic, compartmentalized regional immune network, based on an interactive specific mucosal immune (innate and adaptive) response in nasopharyngeal-associated lymphoid tissue (NALT) inductive site, and subsequently in remote effector sites. These include the tracheobronchial epithelium, regional lymph nodes and nearby secretory glands (i.e., salivary, lacrimal or lactating mammary glands). NALT is itself a compartment of organized mucosa-associated lymphoid tissue (MALT), which is by far the largest component of the entire immune system.

Studying mucosal immunity to SARS-CoV-2 is at best accomplished by pairing the collection of blood and mucosal tissue samples or fluids, e.g. non-invasive nasal washes/swabs or salivary samples, or bronchoalveolar lavage (BAL) fluid from intubated patients.

Critical components of the airway mucosal immunity network which play a key role in fighting SARS-CoV-2 include mucosal immunoglobulins (Igs) - especially secretory IgA (S-IgA) - and tissue-resident memory (T_{RM}) T and B cells as components of local adaptive immunity, and mucosa-associated invariant T (MAIT) cells, mucosal complement activation and mucosal interferons (IFNs), as components of local innate immunity. These components are discussed below.

Natural SARS-CoV-2 infection does induce mucosal (e.g., in saliva, nasal swab/wash or BAL fluid) S-IgA as well as systemic IgG antibody responses [2]. Mucosal IgA dominates, together with systemic IgA and a peripheral expansion of IgA plasmablasts with mucosal homing potential, the early neutralizing antibody response to SARS-CoV-2 [3]. SARS-CoV-2 neutralizing activity of IgA polymers, the primary antibody form (dimers and tetramers) in the nasopharynx, proved on average 15-fold and approximately sevenfold more potent than that of IgA monomers and plasma IgG, respectively [4]. Finally, mucosal (salivary) antibody response was suggested to serve as a surrogate measure of systemic immunity to SARS-CoV-2. A critical, recent clinical observation is that COVID-19 patients with gastrointestinal (GI) symptoms display a better clinical outcome with a significantly lower death rate than patients without GI symptoms [5]. SARS-CoV-2 particles and mRNA can be found in duodenal and ileal biopsies of patients even 3 months after onset of COVID-19 despite absent SARS-CoV-2 mRNA in nasopharyngeal swabs at the time of intestinal biopsy. Thus, intestinal viral pools of SARS-CoV-2 may stimulate a sustained production of mucosal neutralizing S-IgA antibodies within MALT compartments including the airways, especially through a two-way gut–lung axis immune interconnectedness.

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Antigen-specific T_{RM} T cells induce rapid in situ protection upon viral antigen re-challenge at mucosal sites of entry (e.g., NALT) for respiratory pathogens including SARS-CoV-2. These cells reflect a tissue compartmentalization of the human immune system. Paired studies of respiratory wash and blood samples in severe COVID-19 showed activated T_{RM} T cells in the airways that do not correlate with systemic blood T cell responses, clearly suggesting that tissues, rather than blood, are where anti-SARS-CoV-2 lasting immune cells act [6]. Likewise, specific lung-resident memory B cells are formed early at the portals of pathogen entry following mucosal infection, and provide better protection than circulating memory cells.

MAIT cells are major actors of the epithelial barrier protection and favour the maintenance of both tissue-resident and central memory T cells. MAIT altered functions in lung and blood are associated with clinical parameters and outcome, and may be a new target for interventional therapeutic approaches in severe SARS-CoV-2 infection [7].

Excessive complement activation in COVID-19 patients contributes to a cytokine storm that may come with the disease. Conversely, complement deficiencies appear to be protective. The reason why the protective complement system is converted into a harmful one may be primarily rooted in the overwhelming mucosally produced complement, since direct signatures of complement activation were demonstrated within cells of the BAL fluid (where serum-derived complement was absent) of COVID-19 patients [8].

Mucosally administered recombinant type I IFN-β-1a, whose activity is impaired at the systemic and mucosal levels in COVID-19, safely induced greater odds of clinical improvement and rapid recovery, in non-ventilated hospitalized COVID-19 patients, compared with the placebo group [9]. Conversely, parenterally administered IFN-β-1a showed no meaningful clinical efficacy according to interim results of the WHO Solidarity randomized trial in more than 2000 patients [10].

While currently licensed intramuscular SARS-CoV-2 vaccines provide highly effective protection again both asymptomatic and symptomatic COVID-19, whether the induction of mucosal immunity by systemic immunization is phantom or reality remains debated [11]. According to a classic dogma, parenterally administered vaccines against mucosal pathogens induce primarily serum antibodies, but are poorly capable of generating protective mucosal immunity, at the pathogen entry site [2]. This dogma should be nuanced. Mucosal surfaces such as the lower airways are permeable to transudation of serum IgG antibodies, and intramuscular COVID-19 vaccination of breastfeeding women induces robust secretion of SARS-CoV-2-specific IgA and IgG antibodies in breast milk [12].

Those nuances notwithstanding, systemic vaccination alone does not induce the whole variety of compartmentalized local immune responses observed after mucosal vaccination with the same antigen. As a respiratory virus, SARS-CoV-2 may require higher levels of mucosal immunity to truly slow or block transmission [2]. Indeed, the most direct pathway to sterilizing and population immunity may be especially boosted through mucosal vaccine delivery to promote anti-SARS-CoV-2 S-IgA and T_{RM} cells at the nasopharyngeal site of virus entry and replication. Experimentally, a single intranasal dose of adenovirus-vectored vaccine protects against SARS-CoV-2 infection in the upper and lower respiratory tract in rhesus macaques [13]. Moreover, mucosal vaccines for establishing T_{RM} cells could be particularly beneficial for pathogens that undergo rapid mutation, like SARS-CoV-2, and therefore evade antibody-mediated protection [14].

Comparing natural immunity to SARS-CoV-2 infection with that induced by current parenteral vaccines is of special interest. Systemic vaccination and natural infection are likely to elicit different responses at mucosal sites. Re-infection rates after a first SARS-CoV-2 infection may help quantify the immunizing effect of potential mucosal vaccines which partially mimic natural infection. Higher antibody levels are obtained after a single mRNA vaccine (BNT162b2) dose in persons with a previous natural SARS-CoV-2 infection than after two vaccine doses in previously uninfected subjects [15]. Intranasal vaccines might marshal early protective immune responses in the upper respiratory tract before SARS-CoV-2 gains a foothold in the lower respiratory tract. They may offer broader and more effective local tissue-resident protection (S-IgA, airway T_{RM} cells) and might control infectiousness, contagiousness, viral spread and onward transmission more closely than does parenteral vaccination alone [16].

Finally, in addition to the careful selection of vaccine antigens and platforms, the route of vaccination may be an integral consideration of vaccine strategies, especially for mucosal pathogens such as SARS-CoV-2. While they may require the use of adjuvants and repeated delivery, mucosal (e.g., nasal, oral) vaccines are advantageous both in evoking strong local and systemic immune response and offering lower cost - e.g. for mass immunization in resource-limited, population-dense settings - and needle-free administration. Worldwide, the combination of mucosal and parenteral vaccines has proven useful against pathogens with mucosal entry such as poliovirus, influenza viruses or rotavirus [2,16–18]. Mucosal vaccination may speed up the achievement of herd immunity, particularly through its ease of delivery to underprivileged people of low- and middle-income countries [2,16]. A mucosal SARS-CoV-2 vaccine, e.g. targeting nasal mucosa, could be optimal were it also proven to be safe, but there are also critical regulatory concerns about stability and efficiency. Whether intranasal delivery of SARS-CoV-2 mRNA vaccines could promote T_{RM} T cells and T_{RM} B cells and protection in the lungs is of particularly interest [19]. In conclusion, strong current data emphasize the need to understand local immune responses to SARS-CoV-2, and indicate that research on mucosal, natural and vaccine-mediated, immunity to SARS-CoV-2 is of great translational and clinical relevance.

Transparency declaration

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