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INVITED REVIEW

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Tissue immunity to SARS-CoV-2: Role in protection and immunopathology*

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Summary

The SARS-CoV-2 pandemic has demonstrated the importance of studying antiviral immunity within sites of infection to gain insights into mechanisms for immune protection and disease pathology. As SARS-CoV-2 is tropic to the respiratory tract, many studies of airway washes, lymph node aspirates, and postmortem lung tissue have revealed site-specific immune dynamics that are associated with the protection or immunopathology but are not readily observed in circulation. This review summarizes the growing body of work identifying immune processes in tissues and their interplay with immune responses in circulation during acute SARS-CoV-2 infection, severe disease, and memory persistence. Establishment of tissue resident immunity also may have implications for vaccination and the durability of immune memory and protection.

KEYWORDS
lung immunity, lymph nodes, mucosal immunity, tissue resident memory cells

1 | INTRODUCTION

The global pandemic caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has now persisted for two years and impacted nearly everyone on the planet; resulting in nearly half a billion people infected, close to 6 million deaths worldwide, and immeasurable effects on overall health and well-being of the population. In contrast to other ubiquitous respiratory viruses, SARS-CoV-2 infection is unique in its wide range of clinical manifestations that comprise COVID-19, from minimal symptoms and mild disease to severe lung damage, acute respiratory distress syndrome (ARDS), multi-organ failure, and death. COVID-19 can also vary in durations from several days, to weeks, to persistence for months in the form of long COVID. In addition, the high transmissibility of SARS-CoV-2, along with the increasing mutation burden in emerging variant strains, has led to infectious spread even among individuals who have developed immunity through previous infection or vaccination.[1-3] In order to develop improved treatments for those at risk for severe COVID-19 and establish protective immunity to SARS-CoV-2 strains that continue to mutate and disseminate infections globally, new insights into the immune mechanisms that control infection severity and establish long-term protection are needed.

The disease outcome to SARS-CoV-2 infection depends on the immune response, which occurs at the site of infection in the lung and respiratory tract. In many individuals, virus is cleared from the lung with minimal damage, while in others, the immune response becomes dysregulated, resulting in extensive inflammation, severe lung damage, organ failure, and/or long-term effects even in those who recover. Characterizing the immune response to SARS-CoV-2 both in circulation and in the tissue sites of infection is necessary to gain new insights and develop strategies for protecting the population from current and future pandemic strains.

Coordinated processes between the innate and adaptive immune systems are essential to neutralize infections with minimal

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damage to the host. These responses are also spatially regulated; initial inflammatory processes, clearance mechanisms, and memory generation occur primarily at the site of infection and in nearby draining lymphoid organs. For respiratory viruses, infection induces early innate responses including the production of type I interferon (IFN) and proinflammatory cytokines by the infected cells themselves and by tissue-resident lung macrophages.[4,5] Dendritic cells in the lung become infected or take up free antigen and migrate to the lung-draining or mediastinal lymph nodes where they present viral antigens to T-cells. This results in activation and differentiation to various types of effectors $CD4^+$ and $CD8^+$ T-cells, some which migrate to the lung to coordinate viral clearance through effector cytokine production and direct lysis of infected cells, respectively. Another effector cell type, $CD4^+$ follicular helper T-cells (T_{FH}), promote B-cell differentiation in the LN to antibody-secreting plasma cells. In this way, the innate and antigen-specific adaptive immune response promote viral clearance through local processes in the infection site and systemically, through induction of humoral immunity.

After immune-mediated viral clearance, a subset of virus-specific T and B lymphocytes can persist as memory cells—some with the capacity to circulate through blood and tissues, and others which establish long-term residency in tissues to mediate localized protection at the infection site. For T-cells, the generation of tissue-resident memory $CD4^+$ and $CD8^+$ T-cells (T_{RM}) in the lung and respiratory tract can mediate efficacious protection to multiple respiratory viruses in mouse infection models, including influenza, respiratory syncytial virus (RSV), SARS-CoV-1 through effector function, cellular recruitment, and direct helper function in situ.[6-12] More recently, it was shown that tissue-resident memory B-cells (B_{RM}) along with T_{FH} cells are generated in the lung following influenza infection in mice and contribute to in situ protective responses.[7,13] B_{RM} in the lungs can rapidly differentiate in situ into antibody-secreting cells upon secondary infection and may complement T-cell effector function.[13] Together these, mouse studies reveal the importance of tissue localization for adaptive immunity.

In humans, the majority of $CD4^+$ and $CD8^+$ memory T-cells in the lung and other mucosal sites are T_{RM}, exhibiting phenotypes and transcriptional profiles similar to mouse T_{RM}.[14,15] B_{RM} have also been identified in human lymphoid and mucosal sites.[16] The generation and protective capacity of tissue-resident memory lymphocytes to virus infection including to SARS-CoV-2 in humans are challenging to characterize. Earlier results using organ donor samples and tissue explants indicate that respiratory viruses such as influenza can generate lung T_{RM}.[17,18]

For studying the diversity of immune responses and outcomes to SARS-CoV-2 in during this global pandemic, we remain limited largely to the sampling of human peripheral blood. However, where the opportunity presents and samples of the respiratory tract, lung, and other tissues are available, studying immune parameters in tissues can be highly informative for a more comprehensive profile of immune-mediated protection against SARS-CoV-2. In this review, we will discuss the current understanding of how immune responses to SARS-CoV-2 are mediated at the infection site, in lymphoid organs and circulation, how systemic and site-specific immune processes are associated with different infection outcomes, and the extent to which immune memory is established in circulation and tissues sites across the body. We further discuss the potential importance of localized immune responses in conferring long-term protection against SARS-CoV-2 and its emerging variants, as well as considerations for vaccine design and monitoring.

2 | TISSUE-SPECIFIC CLINICAL MANIFESTATIONS OF SARS-COV-2 INFECTION

In acute infection, the most common clinical manifestations of SARS-CoV-2 infection are in the respiratory tract, with severe disease characterized by pneumonia, respiratory failure, and lung damage.[19] Viral entry of SARS-CoV-2 is mediated through the direct binding of its surface glycoprotein, Spike (S), to angiotensin converting enzyme 2 (ACE2) receptors on target cells.[20-22] ACE2 is expressed in the respiratory tract and lung in addition to the gastrointestinal tract, kidneys, heart, and other sites, though its high level of expression in nasopharyngeal tissue which is the entry point for infection, makes it the prime site for initial infection.[20,23] In humans, viral RNA and proteins were detected primarily in the lung but also in visceral organs including the gastrointestinal tract, liver, kidney, heart, and brain.[24-26] While live virus can be isolated from the lungs, it is not readily isolated from other sites, such as intestines although viral RNA can be detected.[27] The presence of viral RNA or antigens across tissues could represent infection and perhaps explain the broad tissue dysfunction seen in COVID-19, it could also reflect trafficking of cells throughout the body.

Only certain cell types are fully permissive to SARS-CoV-2 viral replication and formation of infectious particles. Most consistently, studies have demonstrated the presence of viral RNA inside epithelial cells in the upper airways and lung, and macrophages in BAL and lung tissue.[23,25,28,29] The identification of virus in other cell types could be a result of phagocytosis, abortive infections, or even viral antigens bound to receptors on the cell surface.[30] Based on the cell tropism of SARS-CoV-2, it is more likely that the virus does not in fact cause de novo infection of many different tissues. Rather it seeds the distal tissues through migration of antigen presenting cells such as macrophages and dendritic cells that deposit in tissues. The virus begins its infection within the respiratory tract, after which the host must begin to mount a significant immune response originating at the infection site.

2.1 | Lung tissue damage and repair

Respiratory viruses, including SARS-CoV-2, are known to cause both lung damage through the lysis of virally infected cells, as well as immunopathology resulting from antiviral immune responses which are cytolytic for infected cells.[31,32] Acute infection with

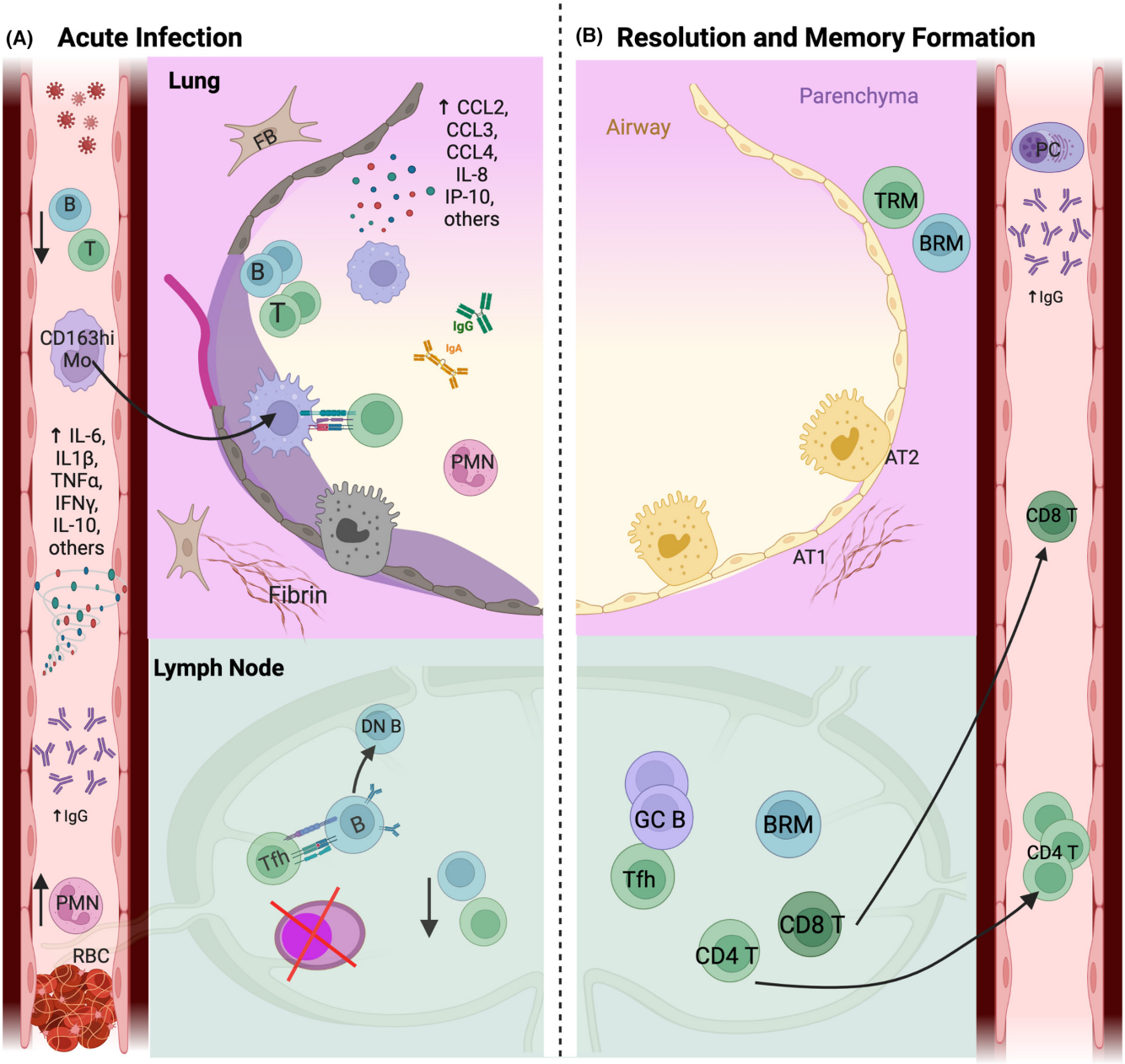

FIGURE 1 Immune responses in tissues and circulation during acute infection and after resolution. A, Interplay of tissue and circulating responses during acute infection. In circulation, (left) infected individuals exhibit lymphopenia and neutrophilia; red blood cells (RBC) form microvascular clots. There is induction of virus-specific antibodies, rapid production of inflammatory cytokines sometimes leading to cytokine storm, and enhanced levels of $CD163^+$ monocytes (Mo) that are recruited to the lung. Lung tissue (top, left) demonstrates diffuse alveolar damage including areas of edema, hyaline membranes, and pneumocyte necrosis. The alveolar sac becomes filled with lymphocytes (T cells [T], B cells [B]), macrophages that interact with T cells and produce inflammatory cytokines, and neutrophils (PMN) that create neutrophil extracellular traps. Pathological fibroblasts (FB) appear to begin the tissue repair process. In lymph nodes (bottom, left) there is destruction of germinal centers and decreased lymphocytes; extra-follicular T- and B-cell interactions lead to the development of double negative (DN) B cells. B, Maintenance of immune memory in circulation and tissues. Following viral clearance and tissue repair, virus-specific memory is maintained in the circulation and tissue sites including antibodies, $CD4^+$ T cells, $CD8^+$ T cells, and memory B cells. The alveolar sac in the lung (top, right) is cleared of immune cells, the alveolar cells (AT1/AT2) reform the epithelial barrier, and the lung parenchyma maintains tissue-resident memory T and B cells (T_{RM}/B_{RM}). The lymph node (bottom, right) is also a major reservoir for virus-specific memory, including persistent follicular responses with follicular helper T cells (T_{FH}) and germinal center B cells (GC B). Long lived plasma cells (PC) in circulation (also found in bone marrow) can maintain antibody titers

SARS-CoV-2 results in unique patterns of tissue damage and immune cell recruitment (Figure 1A). Clinically, patients infected with SARS-CoV-2 can develop acute respiratory distress syndrome (ARDS) with bilateral patchy infiltrates observed on computed tomography scans or chest radiographs. Upon autopsy, gross lung tissue is found to have patchy areas of inflammation and edema.[25]

Histopathological analysis most commonly shows some form of diffuse alveolar damage, in addition to the presence of hyaline membranes, pneumocyte necrosis, and capillary congestion[25,33] (Figure 1A). As the alveolar epithelial barrier breaks down and the alveolar sac becomes filled with lymphocytes and macrophages, pneumocyte progenitors fail to regenerate quickly enough to reform the barrier.[24]

The extent of tissue damage correlates both with time post-infection and the immune response.[33,34] Early in the disease course, when the lung has significant levels of viral RNA and high interferon expression, the tissue exhibits less damage. The extensive production of pro-inflammatory cytokines such as TNFα and IL-6, activate the complement system and downregulate cell junctions.[24,33] Pulmonary alveolar cells line the surface of the alveoli; alveolar type 1 (AT1) cells participate in gas exchange, while alveolar type 2 (AT2) cells produce surfactant and act as progenitors for AT1 cells. In COVID-19, there is a loss of the lung epithelia with a significant decrease in both AT1 and AT2 cells as well as ciliated cells, likely due to apoptosis following viral infection and impaired regeneration of AT1 cells.[24,34,35] These changes are particularly accentuated in severe disease; the number of epithelial cells in bulk lung tissue is positively correlated to number of days until death.[24]

Following viral clearance, inflammation and interferon expression abates and the process of tissue repair begins. This repair process is associated with increased expression of cycling markers, Ki67 and p53, in airway epithelial cells and a shift toward fibrosis with the appearance of pathological fibroblasts and enhanced expression of collagen and other markers of fibrosis[25,33,34] (Figure 1A). Although evidence points to these repair processes being self-limited in mild disease, more is known about them in severe disease, due to the study of postmortem lungs, which show extensive fibroblasts, endothelial cells, and collagen deposition.[24,34,36] The induction of fibrotic pathways in the later phases of the disease has implications for those who do in fact recover—already a significant number of lung transplants have been performed for patients who suffered from severe COVID-19.[37] Therefore, the disease process can be exacerbated by tissue immune responses during the acute response and recovery.

2.2 | Non-respiratory tissue manifestations of COVID-19

While the primary pathology of SARS-CoV-2 is in the lung, adult patients can also develop thrombotic, renal, cardiovascular, gastrointestinal, neurologic, dermatologic, endocrine, and hepatic complications.[38] Cardiac manifestations include myocarditis, arrythmias, and cardiomyopathy, while gastrointestinal damage caused by mesenteric ischemia has been manifests as ileocolitis with inflammatory cell infiltration and microvascular thrombi.[38,39] Common neurologic symptoms of COVID-19 including mild manifestations such as headache and confusion,[38] and other changes of short- or long-term duration such as loss of taste and smell, depression, and fatigue.[40] Dermatological manifestations indicative of inflammatory skin lesions were also observed in COVID-19.[41] The full spectrum of tissue pathologies caused by SARS-CoV-2 infection is continuing to be elucidated, and it will be important in future studies to determine whether they derive from direct infection at the site, immune-based damage or a combination of both.

Similar visceral pathology is also seen in children who are typically spared from respiratory disease, but in rare cases develop a life-threatening complication following infection: multisystem inflammatory syndrome (MIS-C). In MIS-C, there pathology is identified in multiple tissues including the heart, intestine, kidneys, and brain.[42,43] Severe cardiac dysfunction manifests in children with MIS-C resulting from myocarditis, pericarditis, and endocarditis.[44] In MIS-C patients, reactive microglia have been identified in the brain, which likely lead to their more severe neurologic complications such as encephalopathy and status epilepticus.[42,43] MIS-C is readily treated with steroids and remains extremely rare among pediatric infections—and may be even rarer among more recent variants such as Omicron. Nonetheless, SARS-CoV-2 as a respiratory virus is unique in its ability to cause severe damage across many tissue sites in individuals of all ages.

3 | SITE-SPECIFIC AND SYSTEMIC IMMUNE RESPONSES DURING ACUTE INFECTION

While the majority of studies analyzing innate and adaptive immune processes during acute infection, in mild and severe disease sample blood, understanding the immune processes that control infection and lead to pathology require sampling of the infection site. A number of studies have analyzed immune cells, gene expression, and functional mediators in the respiratory tract through sampling of airway washes from endotracheal tubes, bronchial alveolar lavage (BAL), or nasal swabs.[29,45-50] We and others have also implemented paired sampling of airway and blood samples from the same patient collected either singly or longitudinally over a symptomatic period to assess the connection between circulating and local immune responses in disease severity and outcome.[45,46,50,51] In addition, analysis of immune cells within lung autopsies[24,25,34,35] are also informative to dissect the immune reactions in situ, though these represent end-stage immune processes in individuals who succumbed to infection. As described below, these studies of immunity at the infection site compared with blood have revealed insights into how site-specific and systemic immune processes mediate protection and/or immunopathology during the acute response, and associations with disease severity and outcome.

3.1 | Innate immunity to SARS-CoV-2 infection: Site-specific and systemic responses

Upon infection of respiratory epithelial cells, SARS-CoV-2 induces multiple components of the innate immune response, detectable in the airways, lungs, and in blood. Importantly, these site-specific and systemic innate immune responses have been associated with clinical severity.

SARS-CoV-2 infection activates the type I IFN response, which acts intracellularly to inhibit viral replication, and stimulate the

production of cytokines and factors that mediate local and systemic immune cell recruitment and crosstalk. Within lung tissue, there was upregulation of both IFNα and IFNγ and elevated expression of many interferon stimulated genes (ISGs) including IRF1 and ADAR.[24,34] Within BAL, there is both upregulation of ISGs with direct antiviral activity as well as JAK, STAT1, STAT2, and IRF7, which could potentiate the interferon response.[52] However, this local interferon signaling may not be well reflected in blood, with some studies having found severe COVID-19 to be associated with a diminished type I IFN response.[53]

In addition to Type I interferons, other types of inflammatory cytokines and chemokines such as IL-8, IP-10, IL-6, IL-1β, CCL2, and CCL3 were shown to be highly elevated in BAL, respiratory, or nasal washes in a number of studies and quantitatively elevated compared with plasma[46-48,50] (Figure 1A). These pro-inflammatory cytokines play an important role in the anti-viral immune response by recruiting immune cells such as neutrophils and NK cells and leading to the priming and activation of T cells.[54,55] Interestingly, the increase in IL-6, IL-8 (CXCL8), IP-10 and CCL2 in the respiratory tract correlated with severe over mild disease in respiratory washes, suggesting a pathological role for these cytokines.[45,50] Moreover, excessively elevated levels of CCL2, CCL3, and CCL4 were found in respiratory washes obtained from intubated patients with severe COVID-19 that were not prevalent in circulation, while elevated levels of IL-6 and IL-8 were observed in both plasma and respiratory tract.[46] These results suggest that many inflammatory mediators originate in the respiratory tract, but some like IL-6 build up to systemic levels during prolonged infection. This prolonged synthesis of IL-6 and other cytokines in severe disease may result in excessive inflammation and tissue damage.

These respiratory cytokines and chemokines recruit and activated other innate immune cells. For example, IL-8 recruits neutrophils to the lungs (Figure 1A), and alterations in neutrophil counts and phenotypes in the blood are associated with severe disease. There is a significant increase in neutrophils and neutrophil precursors in the blood of individuals with severe COVID-19 along with increased eosinophils[56-58] (Figure 1A). In BAL, a portion of patients exhibited neutrophilia; the movement of neutrophils to the lung depletes the supply in the blood, inducing granulocyte differentiation with emergence of immature neutrophils from the bone marrow.[28,29,49] Neutrophils in tissues can form neutrophil extracellular traps (NETs) which participate in tissue damage; NETs have been found to persist in the lungs of patients who succumbed to severe COVID-19.[59,60] However, the majority of the elevated cytokines in the respiratory tract recruit and/or are produced by monocytes and macrophages, suggesting that myeloid-lineage cells are playing important roles in lung-specific pathology.

3.1.1 | Dysregulated myeloid activation and recruitment in severe COVID-19

Results from single cell profiling of the upper and lower respiratory tract, along with paired analysis of blood monocytes provide compelling evidence for a major role in macrophage-mediated inflammation and recruitment in lung damage during acute infection. Macrophages in the airways exhibit an activated profile, an interferon response signature, and upregulate transcripts encoding multiple leukocyte chemo-attractants such as CCL2, CCL3, CCL4, CCL20, inflammatory cytokines such as TNF and IL-1β, and inflammatory markers including complement and matrix metalloproteinases.[46,48,52,61] By contrast, myeloid cells (mostly monocytes) in paired blood samples form COVID-19 do not exhibit these inflammatory signatures, nor do macrophages in healthy airways.[46] These inflamed macrophage-like populations in the respiratory tract of severe COVID-19 likely consist of both resident macrophages and newly recruited monocytes from circulation, as suggested in paired airway and blood analysis.[46]

Monocytes in the peripheral blood of COVID-19 patients are phenotypically different from those in healthy individuals. Specifically, there is a significant reduction in $CD14^{+}CD16^{+}HLA\text{-}DR^{hi}$ classical monocytes and a shift to $CD14^{+}$ non-classical or intermediate monocytes which are also $HLA\text{-}DR^{lo}$.[46,57,58] This aberrant monocyte population resembles immature monocytes,[58] and also exhibits features of myeloid derived suppressor cells.[62] In respiratory washes and BAL, myeloid cells including monocytes, monocyte-derived macrophages, and resident alveolar macrophages were significantly increased in numbers and frequency compared to BAL of healthy controls.[29,34,46,49] Moreover, myeloid populations in the airways of severe COVID-19 patients also contained these aberrant monocyte populations found in blood, suggesting recruitment of peripheral monocytes to the site of infection.[46] The expression of CCR2, the receptor for CCL2, by blood monocytes coupled with the high-level expression of CCL2 in COVID-19 airways, provide evidence for monocyte recruitment from the blood to the lung through a CCR2-CCL2 axis.[46] A role for a CCL2-producing inflammatory macrophage in COVID disease severity is further supported by integrated analysis of scRNAseq data from multiple cohorts.[28,63] In nasopharyngeal samples, there were more recruited monocytes ($CD163^{+}$) than tissue-resident macrophages ($CD163^{+}CD206^{+}$) and these non-resident T-cells demonstrated a highly inflammatory profile.[48,62] Together, these results indicate that SARS-CoV-2 infection in the respiratory tract activates macrophages which recruit monocytes from the blood; this process can become dysregulated and perpetuate prolonged inflammation in the respiratory tract in severe disease.

3.2 | Adaptive immune responses in tissues in acute SARS-CoV-2 infection

Following the induction of an innate immune response at the site of infection, antigen presenting cells (e.g., dendritic cells) that have sampled infected tissue in the lung migrate into lung-associated lymph nodes present viral antigen as a means to activate lymphocytes. Activated T- and B-cells not only play crucial roles in the initial antiviral immune response during acute infection, but also serve as the main source of antigen-specific immune memory. During

SARS-CoV-2 infection, adaptive immune responses to acute infection can be detected across the spectrum of acute disease (asymptomatic, mild, and severe), and throughout convalescence. While virus-specific adaptive responses are typically measured in blood, means of sampling tissue-specific lymphocyte populations have provided valuable insight into immune response mechanisms. Analysis of antibody, B-cell, and T-cell responses in airway washes, nasal swabs, and aspirates of draining lymph nodes and bone marrow have revealed a diversely organized lymphocyte response to SARS-CoV-2 infection. These studies have revealed an interplay between tissue and circulating immune processes, and interactions between immune cells in tissues (Figure 1A).

3.2.1 | B-cell immunity to acute infection

The most readily and extensively measured indicator of antigen-specific adaptive immune responses during acute SARS-CoV-2 infection is the appearance of virus-specific antibodies in circulation. In symptomatic infection, seroconversion of individuals infected with SARS-CoV-2 occurs within the first 14 days postsymptom onset (PSO) and consist of antibodies specific for S and nucleocapsid (N).[64-67] Neutralizing activity of anti-S antibodies is associated with reactivity to the receptor-binding domain (RBD) and is measured in live virus or pseudovirus neutralization assays.[68] Antibody titers have been observed to peak around 3-4 weeks PSO followed by a steady decline coincident with viral clearance, as is typical for an acute viral infection.[69] The duration and magnitude of this antibody titer peak have been consistently found to be associated with disease severity; individuals with severe COVID-19 generally exhibit higher SARS-CoV-2-specific IgM, IgG, and IgA titers and neutralizing activity compared with those who experienced mild infection.[70,71] Certain studies have also reported a more skewed response toward N rather than S in severe disease, consistent with a more disseminated infection.[70] Further, the kinetics of antibody generation following infection can be differentially associated with disease severity though variable results were obtained in different studies,[70,72,73] showing the limitation of using serology to predict disease outcome.

Antibodies can also be detected in secretions and respiratory samples. Analysis of anti-SARS-CoV-2 antibodies in BAL and saliva revealed higher IgA compared with blood and significant neutralization activity,[74] suggesting B-cell responses mobilized at these different sites. In paired sampling of nasopharyngeal (NP) samples and plasma, anti-S and RBD antibody levels in NP samples correlated with levels in plasma, were mostly IgA, and were increased in severe compared with mild-or-moderate COVID-19.[75] Antibodies in the respiratory tract further correlated with the presence of virus-specific B-cells and lower viral load,[75,76] indicating potential protective capacity of these locally produced antibodies through direct neutralization or targeting the virus for clearance by innate cells.

During acute infection, activated plasmablasts can be detected in the blood during active disease along with other virus-specific B-cells.[77] Detection of virus-specific B-cells by direct antigen binding has revealed S, N, and RBD-specific B-cells in blood.[78,79] However, memory B-cells in human peripheral blood are in relatively low frequency, with most circulating B-cells being naïve[16]; memory or activated plasmablasts are largely confined to the spleen and other lymphoid sites.[16] Lymphoid sites provide the necessary anatomical structures and immune signaling required for B-cell activation. Interactions between B-cells and follicular helper T-cells (T_{FH}) cells, which promote B-cell differentiation and immunoglobulin class switching, occur primarily in lymphoid follicles in specialized structures called germinal centers (GCs).[80] Evidence for GC formation during acute infection can be derived from the observed maturation of the SARS-CoV-2 antibody response, involving progressive affinity maturation over time identified by several groups.[77,81] In severe COVID-19, evidence from post-mortem spleen and lung-associated lymph nodes reveals disrupted follicles and GC formation[82,83]; though these are late-stage manifestations and GC responses may have occurred earlier in the infection course.

Similar findings were observed in a more recent study comparing GC responses in the peribronchial lymph nodes of COVID-19 patients.[84] Additionally, comparison of the SARS-CoV-2-specific B-cell repertoires by examination of the single-cell BCR sequencing did reveal fewer mutated plasmablast and memory B-cell clones in patients with severe COVID-19 compared to those with mild disease.[85] The mechanisms by which severe COVID-19 may inhibit or disrupt the GC responses in lymphoid sites are unknown but may relate to elevated inflammatory processes observed in severe disease.

3.2.2 | T-cell responses to acute infection

Virus-specific T-cell responses are historically challenging to identify in humans, with direct binding assays using MHC-peptide complexes requiring identification of HLA type and immunodominant epitopes, and assessments using functional readouts reveal low frequencies and high variability. An elegant assay relying on activation-induced markers (AIMs) developed by Crotty and Sette,[86] has enabled ready detection and quantitation of antigen-specific human T-cells across HLA type. In this assay, peripheral blood mononuclear cells (PBMCs) are cultured with peptide pools containing epitopes of the major SARS-CoV-2 proteins, with responding T-cells subsequently identified by their expression of multiple activation markers by flow cytometry.[87] Studies in acute infection show the emergence of SARS-CoV-2-specific $CD4^+$ T-cells as early as 4 days PSO and identified in a higher proportion of patients in acute phases of disease than $CD8^+$ T-cells.[87-89] These virus-specific $CD4^+$ T-cells produce T_H1 cytokines including IFN-γ, TNF-α, and IL-2 that are more commonly associated with an antiviral response, with a minority of T-cells also producing IL-17A.[88-90] SARS-CoV-2-specific $CD8^+$ T-cells are also generated and produce effector cytokines such as IFN-γ and TNF-α, and cytolytic mediators such as Granzyme B, but are consistently found in lower frequencies compared to virus-specific $CD4^+$ T-cells in acute SARS-CoV-2 infection.[87-89] SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T-cells exhibit broad recognition of multiple

epitopes within S, Envelope (E), N, and Membrane (M) proteins, with $CD8^+$ T-cells additionally recognizing epitopes of internal viral proteins.[91,92] Therefore, like T-cells specific to other viruses, SARS-CoV-2-specific T-cells exhibit a broad reactivity to both structural and non-structural viral proteins.

Similar to analysis of innate responses, examination of T-cell responses outside of circulation and in tissue sites of infection is mostly limited to respiratory samples from patients with severe disease, and examination of post-mortem lungs of individuals who succumbed to COVID-19. Activated T_{RM} producing IFN-γ can be detected in the airways of SARS-CoV-2-infected patients,[46,49] with these reactive T_{RM} populations absent in uninfected airways.[46] Importantly, in our studies of paired, longitudinal sampling of blood and BAL of COVID-19 patients, increased $CD4^+$ T-cell frequencies in the airways of infected individuals correlated with survival from severe disease and younger age, while no similar correlations were observed for circulating T-cells[46]; suggesting a protective role of airway T-cells in SARS-CoV-2 infection. This role in protection from severe COVID-19 is further supported by analysis of scRNAseq datasets from respiratory washes and BAL, which show association of CXCR6 expression (a core marker for human T_{RM}[15]) with improved disease outcome.[28,93] Other studies of T-cells in respiratory samples and lung autopsies propose that activated T_{RM} in the respiratory tract may interact with infected tissue-resident macrophages, producing IFN-γ or IL-17, therefore propagating a persistent inflammatory state.[29,51] However, these studies compared immune responses in severe COVID-19 to mild or healthy controls and did not stratify the severe disease cohort by outcome. The ability to obtain rich transcriptome information from immune cells present in more accessible samples such as nasal swabs will enable a more fine-tuned assessment of the role of T-cell responses in situ in the early phases of disease.

What is becoming most apparent in acute SARS-CoV-2 infection is that coordinated responses between lymphocyte populations as measured in circulation, as well as robust (but not overexuberant) innate responses in the airway, often correlate with improved disease outcome.[88,94] Together, studies of severe COVID-19 have shown the importance of cooperative immune responses in the acute phase of SARS-CoV-2 infection, with the quality of these reactions dictating the generation subsequent maintenance of memory populations following infection resolution. Most importantly, it is important to critically assess the utility and accuracy of circulating markers as surrogates for tissue-specific responses, as there is mounting evidence of their discordance in predicting and assessing SARS-CoV-2 infection outcomes.

4 | ESTABLISHING AND MAINTAINING IMMUNE MEMORY TO SARS-COV-2 INFECTION

The widespread illness, morbidity, and mortality caused by SARS-CoV-2 infection has demonstrated the vulnerability of our population to viruses for which we lack pre-existing immunological memory. The coordinated primary exposure of the global population to SARS-CoV-2 provides an unprecedented opportunity to investigate the generation and maintenance of immune memory to respiratory viral infection, to define immune correlates of protection, and understand population-based heterogeneity. Similar to studies on acute responses, the majority of studies on SARS-CoV-2-specific B- and T-cell memory sample blood, though the cellular stores of immune memory largely reside within tissues. While analysis of tissue-specific adaptive immune responses in recovered individuals remains challenging, studies in lymph node aspirates and samples from organ donors are beginning to provide a more comprehensive assessment of the diversity and localization of SARS-CoV-2-specific memory (Figure 1B). Here, we discuss the growing body of work quantifying and characterizing the persistence of B- and T-cell memory against SARS-CoV-2, and how studies sampling lymphoid sites and other tissues may be informative for assessing its protective capacity and durability.

4.1 | Virus-specific memory in circulation

A multitude of studies have established that virus-specific antibodies, B-, and T-cells can be detected many months following resolution of SARS-CoV-2 infection. Earlier findings reported significant SARS-CoV-2-specific T- and B-cell responses up to a year post-infection.[79,95-98] SARS-CoV-2-specific antibodies can retain high neutralization titers months after infection, followed by a biphasic decay in magnitude.[69,95,98-100] Over time, the quality of the humoral response continues to evolve. The frequency of SARS-CoV-2 memory B-cells in blood progressively increases for longer than 150 days, reaching stable levels 6-12 months after infection.[101,102] Moreover, antibodies present at 6 months post-infection exhibit increased somatic hypermutation, increased neutralization potency, and greater breadth, leading to greater protection against viral escape mutants.[81] For T-cells, the magnitude of virus-specific $CD4^+$ and $CD8^+$ T-cells declines over time, with virus-specific $CD8^+$ T-cells also exhibiting a faster decline in the months following convalescence,[79] while both remain detectable for over a year post-infection.[103,104] Overall, these studies of circulating SARS-CoV-2-specific lymphocytes indicate robust generation of immune memory to infection; however, the role of circulating T cells in protection is not clear. Understanding how circulating responses reflect the long-term storage niches in tissues will be important to establish, as well as whether circulating virus-specific T cells migrate to the lung during secondary responses.

4.2 | SARS-CoV-2-specific immune memory in tissues

Different types of memory T-cells, memory B-cells, and long-lived antibody-secreting plasma cells are all maintained in tissues. A

comprehensive assessment of the generation and durability of immune memory requires sampling of multiple sites, but this is not generally feasible in individuals who recovered from mild disease. We have set up a human tissue resource in which we obtain blood and multiple lymphoid and mucosal tissues from brain-dead human organ donors, enabling study of immune cell composition, distribution, and properties within and across tissues, between individuals, and over age (for reviews, see Refs. 105-107). Our many studies on innate and adaptive immune cells in organ donor tissues have established that the tissue site is the major determining factor for immune cell composition, with this being highly consistent between individuals through decades of adult life.[108-112] Using these tissues, we have identified T_{RM} and B_{RM} in mucosal and lymphoid sites and their tissue-specific properties.[15,16,111] We have also investigated how T-cell memory to respiratory and systemic viruses is differentially maintained as resident and circulating populations.[17,113] Our regular access to organ donor samples during this pandemic has enabled study of immune memory to SARS-CoV-2 infection.

In a recent study, we investigated SARS-CoV-2-specific T- and B-cell memory in lymph nodes, bone marrow, lungs, spleen, and blood or previously infected organ donors; samples were collected just prior to mass vaccination in late 2020.[114] In tissues, SARS-CoV-2-specific $CD4^+$ T-cells exhibit significantly increased frequencies compared to $CD8^+$ T-cells, and with most responses targeted against the Spike protein, similar to the pattern observed in blood. Frequencies of SARS-CoV-2-specific $CD4^+$ T and $CD8^+$ T-cells predominated in the lung and lung-draining lymph nodes of convalescent donors but were not detected in tissues of pre-pandemic control donors. Further, antigen-specific T-cells were also detected in the bone marrow, spleen, and gut-draining lymph nodes.[114] Importantly, in the lungs, SARS-CoV-2-specific T-cells expressing CD103 were found, and to a lesser extent in lung-associated LN,[114] indicating formation of lung T_{RM} after SARS-CoV-2 infection. Moreover, there were differences in the functional profile of SARS-CoV-2 peptide stimulated tissue sites; there was increased production of proinflammatory cytokines such as TNF-α, IL-6, IL-12 in the lung, while a broader array of inflammatory and T_H2-like cytokines was produced in lymph nodes.[114] In other tissue-focused studies, SARS-CoV-2-specific $CD8^+$ T_{RM} has been identified in nasopharyngeal tissue as well as lung tissue explants.[62,115] The presence of lung TRM and the biased production of pro-inflammatory cytokines could direct rapid in situ responses upon viral challenge for long-term protection against recurrent severe disease.

Similar to analyses of SARS-CoV-2-specific T-cells, we also detected B-cells specific for S/RBD in multiple sites, including the lung and lung-associated LN, bone marrow, spleen, and gut-associated LN of previously infected organ donors.[114] SARS-CoV-2-specific memory B-cells were predominantly of IgG isotype in all sites, with IgA^+ B-cells also in the lung and spleen. Notably, the majority of SARS-CoV-2-specific B-cells expressed CD69 (a marker of B_{RM}) in the lung and lymph nodes, indicating that viral infection can lead to the establishment tissue localized immunity for B-cells.

Another vital form of B-cell memory comes in the form of long-lived plasma cells, which predominantly reside in the bone marrow where they contribute to the maintenance of circulating antibody titers for years following infection or vaccination.[116] Studies of bone marrow aspirates 7-11 months post-infection revealed persistence of SARS-CoV-2 S-specific bone marrow plasma cells, with their frequency correlating to circulating antibody titers.[117] Collectively, this data provides insight that SARS-CoV-2-specific humoral immunity present in circulation is associated with persistence of resident memory cells and antibody secreting cells in tissues (Figure 1B).

4.2.1 | Persistence of follicular responses after SARS-CoV-2 infection

Follicular responses following SARS-CoV-2 infection are important for optimal humoral immunity generation and maintenance. In non-human primate models of SARS-CoV-2 infection, robust T_{FH}-led GC reactions were generated in the mediastinal lymph nodes and led to the production of N- and Spike-specific B-cells.[118] In our study, an increased frequency of SARS-CoV-2-specific T_{FH} cells in lung-draining lymph nodes correlated with increased infiltration of antigen-specific B-cells into the lung.[114] We further identified the presence of GC B-cells in the lung-associated lymph nodes up to 6 months post infection, providing the first evidence of persistent antigen-specific germinal center responses in human tissues months following infection resolution.[114] These dynamically maintained GC responses may likely contribute to the observed maturation and increase in neutralization capacity of SARS-CoV-2-specific antibodies in circulation.[81] Together, these findings provide evidence that durable follicular responses can be generated following SARS-CoV-2 infection for long-lasting protection.

5 | IMMUNE CORRELATES OF PROTECTION GENERATED BY SARS-COV-2 INFECTION

The persistence of immune memory specific for SARS-CoV-2 is crucial for protective immunity. However, the high transmissibility of SARS-CoV-2 and the continuous emergence of new variants presents challenges for achieving complete immune-mediated protection. Animal models and multiple correlative studies in humans provide strong evidence that neutralizing antibodies specific for Spike RBD generated from primary infection play a key role in immune protection.[119-122] The magnitude of the circulating antibody titer that is required for immune protection is not known and will be important to define in the context of changes in antibody levels with time. In addition, circulating antibody titers may not be reflective of resident humoral immunity provided by tissue-resident memory B-cells or plasma cells. Memory B-cells residing in lymph nodes may be sufficient for rapid mobilization of humoral immunity, even if the levels of antibody maintained in circulation decline. For local

antibody-mediated protection, there is evidence for maintenance of IgA antibodies in the nasal passages,[74] though the longevity of mucosal IgA is variable[75] and their ability to block local infection is not known.

While humoral immunity plays a significant role in protection to SARS-CoV-2 infection by preventing viral entry into host cells, the ability of SARS-CoV-2 to be widely transmitted and to develop variants can evade pre-existing humoral responses. Variant strains with significant alterations in the S protein can evade neutralization as observed with Delta and Omicron strains,[123] providing the possibility of local respiratory infection from highly transmissible strains to bypass antibody-mediated protection and enable repeat infections. However, while virus neutralization with pre-existing SARS-CoV-2 Spike antibodies is reduced against some variants of concern (VOCs), the persisting immune response is sufficient to prevent severe disease in the face of reinfection.[124,125] Looking ahead, it will be important to consider how best to consistently elicit neutralizing humoral responses that can be more broadly conserved across VOCs.

By contrast to antibodies which largely target external viral proteins, cellular immunity provided by T-cells can establish a memory pool specific for wider breadth of antigenic epitopes representing internal proteins of the virus (such as those involved in viral replication) that are more broadly conserved between variant strains. For example, it was recently shown that $CD8^+$ T-cells specific for S protein retained up to 80% of their protective capacity against the most divergent of SARS-CoV-2 variants.[126] In non-human primates, depletion of $CD8^+$ T-cells resulted in increased breakthrough infections upon re-challenge.[127] Although T_{RM} can be generated to SARS-COV-2 infection in the human lung,[114] the protective efficacy of lung T_{RM} and localized T-cell responses in the associated LN remains to be assessed. Earlier evidence from mouse models of SARS-CoV-1, showed that memory CD4 T cells in the airways were protective against viral challenge,[12] suggesting that TRM in the respiratory tract are likely important for protection in situ.

Ultimately, as seen in acute infection, clearance and long-term protection against SARS-CoV-2 infection requires a coordinated response between lymphocyte populations, and a synergistic interaction of circulating and tissue-resident immunity. In this way, the decline in antibody responses in circulation and the loss of reactivity to viral variants can be bolstered by more durable tissue resident cellular immunity with broad specificity for invariant viral components.

6 | VACCINES AND CONSIDERATIONS FOR LONG-TERM SARS-COV-2 IMMUNE PROTECTION

The rapid development of efficacious vaccines for SARS-CoV-2, less than one year into the pandemic was an unprecedented achievement in biomedicine and immunology. In the United States, two mRNA vaccines—Moderna mRNA-1273 and Pfizer-BioNTech BNT162b2 have been the predominant vaccines administered to the population at-large. In clinical trials of these vaccines, 90-95% of individuals were protected against COVID-19.[128,129] However, at the time of the clinical trials, it was unclear which specific immune components were conferring this clinical efficacy.

As we are now one year past the beginning of mass vaccination with mRNA vaccines in the US, studies examining immune responses to the different vaccines, their longevity, and specificity are now emerging. A detailed discussion of the nature and durability of vaccine-generated immunity is beyond the scope of this review; however, it will be important to assess tissue memory cells to understand the basis of immunity and its durability. Studies in the blood of vaccinated individuals reveal robust anti-S and anti-RBD antibody responses that subsequently wane months following vaccination[130,131] but can be increased with additional vaccine boosters.[123] S-specific $CD4^+$ T cells are also generated from vaccines, and to a lesser extent, $CD8^+$ T cells and both are detectable months post-vaccination[131] and can cross react to variant strains.[126] Lymph node aspirate studies show evidence of germinal center formation and Tfh cells in the lymph nodes draining the site of vaccination,[132,133] indicating a role for T and B-cell collaboration for vaccine-elicited immunity. Interestingly, the frequency of circulating subsets, such as T_{FH}, RBD-specific memory B-cells, and plasmablasts did not correlate with their counterparts in the lymph nodes.[132] It will be important in future studies to closely monitor circulating T_{FH} responses, which for influenza vaccination correlate to vaccine responses.[134] The development of tissue-localized memory induced by the current mRNA vaccines is currently being evaluated in ongoing studies by our group.

An effective vaccine should generate a diverse memory response and targeting the generation of tissue-localized immunity should be considered for long-term strategies for broad-based protection to multiple strain of respiratory viruses (Figure 2). Promoting durable tissue immunity will depend on both the formulation and route of administration of the vaccine. Depending on the virus, different vaccine formulations (inactivated, live-attenuated, vectored, subunit etc.) will be more successful at inducing broad and tissue-localized immune responses.[135,136] Further, the route of administration (intramuscular, oral, intranasal) will work in concert with the vaccine formulation to dictate immune responses. In the case of respiratory viruses, we have previously showed in mouse studies of influenza vaccination that while inactivated vaccine formulations induced neutralizing antibodies, only the intranasally administered, live attenuated vaccine induced T_{RM} in the lung, which are required for cross-strain protection.[137] Similarly, for SARS-CoV-2 vaccination in mice, a single dose intranasal vaccine generated T_{RM} for protection against SARS-CoV-2 infectious challenge,[138] and in non-human primates, intravenous administration can also promote lung T_{RM}, as previously demonstrated in non-human primate studies where i.v. administration of BCG vaccine led to improved protection and generation of lung $CD4^+$ TRM, compared to intradermal BCG.[139] For SARS-CoV-2 vaccines, both IV and intranasal administrations of AstraZeneca vaccine ChAdOx1 nCoV-19/AZD1222 in non-human primates protected against disease and the i.n. vaccine

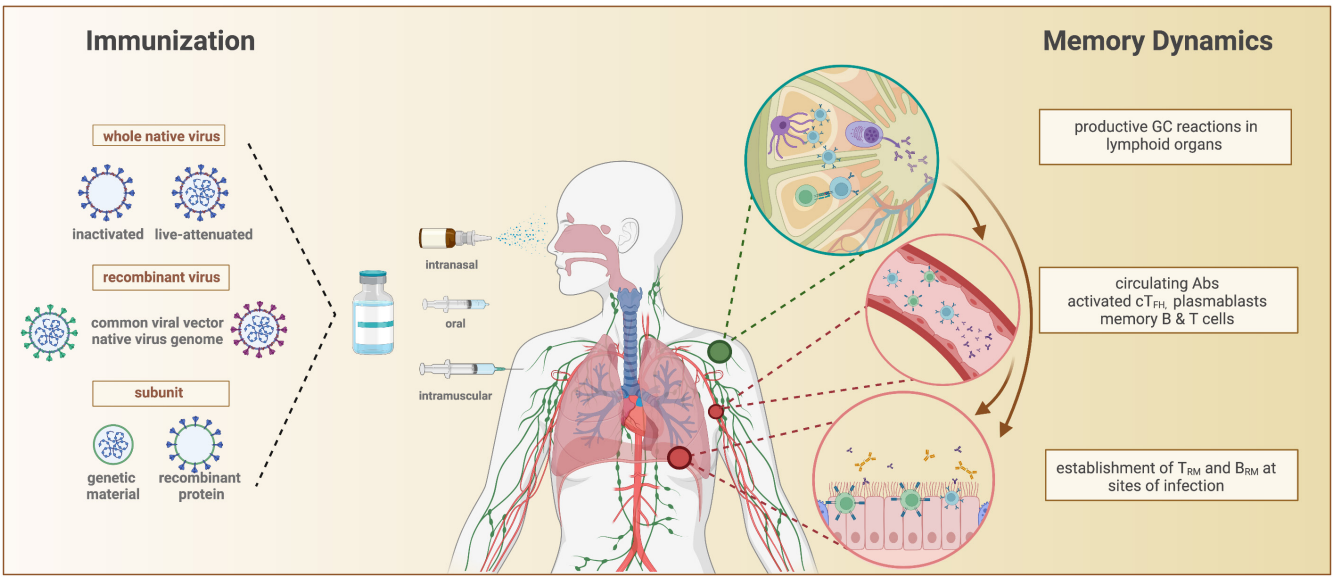

FIGURE 2 Considerations for inducing long-term antiviral immune protection in circulation and tissues through immunization. Many different factors will affect the durability and localization of immune responses following vaccination, including vaccine formulation, method of administration, and a range of host factors such as age, will all collectively determine the immunogenicity of a vaccine response and its potential for generating long term protective immunity. While memory responses are most accessible to quantify in circulation, establishing productive follicular responses and robust tissue-specific memory populations are critical in order to mitigate severe infection upon exposure to viral antigen following vaccination

further reduced viral replication in the respiratory tract.[140] Thus, other vaccine strategies that take into consideration both inducing a broad and tissue-resident response, such as a shift live or live-attenuated vaccines and change in administration route, should be considered in order to induce protection against ever-evolving strains.

Ultimately, given the rapid evolution of SARS-CoV-2 and its propensity to cause breakthrough infection in vaccinated individuals, durable immune memory may only be achieved through multiple exposures via sequential vaccination, natural infections, or a combination of both. A single vaccine dose induced significantly increased antibody, memory B-, and T-cell levels in hybrid-immune individuals, patients who were infected and subsequently vaccinated.[141,142] However, in most of these cases, an additional dose did not result in a significant increase in circulating SARS-CoV-2 specific antibodies and B cells. By contrast, naïve individuals who were not previously infected experienced boosts in antibody titers following their second dose, and in many cases reaching comparable levels to that of recovered individuals.[131,142] The form of lymphocyte memory that is initially induced and subsequently maintained in both previously infected and naïve individuals differ as well; recovered individuals generate substantial circulating SARS-CoV-2-specific memory B cells following vaccination, as well as antibodies with greater neutralization capacity than those of naïve individuals at the investigated timepoints.[142] Notably, in many early studies, antibody levels and neutralization capacities of recovered individuals are high prior to vaccination and persist, while those of naïve individuals increase with subsequent vaccine doses. Antigen-specific T-cell memory generation and maintenance seems to follow a similar trend, with increased frequencies in recovered individuals following vaccination in comparison to naïve patients.[142,143]

The immune responses generated during infection vs vaccination are important to define as the efficacy of existing vaccines continues to wane against newer variants. While early VOC reports showed cross-neutralization in naïve individuals,[144] the emergence of Omicron and with extensive mutations in the Spike protein has resulted in an increased number of breakthrough infections in vaccinated individuals.[145] Importantly, both the time since antigen exposure (infection or vaccination) as well as its antigenic form (variant) are major determinants of protection from subsequent variants which largely correlates with antibody responses.[146-148] However, SARS-CoV-2-specific T-cell responses in vaccinated and recovered individuals have proved to be more conserved in their ability to respond to emerging variants including Omicron based on in vitro assays.[149-151] Whether these conserved reactions as measured in culture reflect protection in vivo is unclear.

Understanding how immunity persists and responds at the tissue level is essential for developing improved strategies to provide durable and broad-based protection for future encounters with SARS-CoV-2. Within the lymph node, GC B-cells, GC T_{FH}, memory B cells, and plasmablasts increased upon subsequent vaccine doses.[132,152] Germinal center reactions in SARS-CoV-2-infection exhibit disrupted structure and function, while those following vaccination remain robust.[83,84] The intricacies of these responses in hybrid-immune individuals has not yet been explored. Characterizing hybrid immunity may be beneficial to determine if this diversity of immune responses is attributable to broader

tissue distribution or the generation of more tissue-resident cells for long-lasting protection (Figure 2).

7 | CONCLUDING REMARKS

The global pandemic of SARS-CoV-2 has enabled unprecedented investigations of the role of innate and adaptive immunity in protection, mitigation or perpetuation of disease pathology, and long-term memory responses. It has also become increasingly apparent how, despite its accessibility, circulating immune populations and analytes cannot always serve as reliable biomarkers for what is happening at the site of infection; the same holds true when studying immune memory as well. Studies of immune protection, especially at the site of infection and in lymphoid organs where immune responses are initiated and maintained are important to develop evidenced-based vaccine strategies to control the ongoing pandemic and future infectious threats. In this way, studies on immunity to SARS-CoV-2 can lead to new paradigms in understanding and monitoring human immune responses.

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CONFLICT OF INTEREST

There are no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

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