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CHAPTER TWO

Immunology of SARS-CoV-2 infections and vaccines

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections trigger viral RNA sensors such as TLR7 and RIG-I, thereby leading to production of type I interferon (IFN) and other inflammatory mediators. Expression of viral proteins in the context of this inflammation leads to stereotypical antigen-specific antibody and T cell responses that clear the virus. Immunity is then maintained through long-lived antibody-secreting plasma cells and by memory B and T cells that can initiate anamnestic responses. Each of these steps is consistent with prior knowledge of acute RNA virus infections. Yet there are certain concepts, while not entirely new, that have been resurrected by the biology of severe SARS-CoV-2 infections and deserve further attention. These include

Advances in Immunology, Volume 151
ISSN 0065-2776
https://doi.org/10.1016/bs.ai.2021.08.002

production of anti-IFN autoantibodies, early inflammatory processes that slow adaptive humoral immunity, immunodominance of antibody responses, and original antigenic sin. Moreover, multiple different vaccine platforms allow for comparisons of pathways that promote robust and durable adaptive immunity.

1. SARS-CoV-2 background and history

In late 2019, a pneumonia outbreak occurred in the city of Wuhan. Metagenomic sequencing of patient samples revealed a novel coronavirus with high sequence similarity to severe acute respiratory coronavirus (SARS-CoV) (Wu, Zhao, et al., 2020; Zhou, Yang, et al., 2020), which had caused a limited epidemic in the early 2000s (Drosten et al., 2003). Due to the similarities in sequence and disease manifestations, this novel coronavirus was called SARS-CoV-2. The disease caused by SARS-CoV-2 is called coronavirus disease 2019 (COVID-19). As of this writing, there have been nearly 200 million COVID-19 cases reported worldwide and 4 million deaths (WHO, n.d.). Both numbers almost certainly underestimate the true toll of the pandemic, which may cause 10 million deaths before widespread vaccination and low endemicity is reached. Though the fatality rate in those who are infected is lower than that of the first SARS-CoV (Levin et al., 2020), the pandemic has proven difficult to contain through nonpharmaceutical interventions. Viral loads and transmissibility often peak prior to symptom onset (Arons et al., 2020; Cevik et al., 2021; Jones et al., 2021; Marks et al., 2021), rendering ineffective countermeasures such as quarantine following illness. The basis for this long presymptomatic phase and transmission has not been adequately explained, but likely lies in the substantial innate immune evasion properties of the virus.

2. Viral entry, innate recognition, and immune evasion

2.1 Coronavirus lineages and entry receptors

Coronaviruses are enveloped positive-sense RNA viruses categorized into α, β, γ, and δ lineages (Peck, Burch, Heise, & Baric, 2015). SARS-CoV-2 and its pathogenic cousins SARS-CoV and Middle Eastern Respiratory Syndrome (MERS) viruses are members of the β lineage, as are the less pathogenic strains OC43 and HKU1 that cause cold-like symptoms. NL63 and 229E are endemic α-coronaviruses that also usually cause mild upper respiratory tract infections. The seroprevalence is over 90% for

exposures to OC43, HKU1, NL63, and 229E (Gorse, Patel, Vitale, & O'Connor, 2010). How these prior mild infections might shape responses to SARS-CoV-2 will be discussed below. Together, these strains are the major coronaviruses that cause human disease.

All coronaviruses use the viral Spike protein to mediate cellular entry, though the host receptor varies with the strain. For SARS-CoV and SARS-CoV-2, the entry receptor is Angiotensin-converting enzyme 2 (ACE2) (Li et al., 2003; Wrapp et al., 2020). For MERS virus, the entry receptor is CD26 (Lu et al., 2013). This difference in tropism can be explained in part by a unique disulfide bond in the MERS virus Spike that dramatically kinks the external surface of the receptor binding domain (Lu et al., 2013). In other cases, such as for the α-coronavirus NL63, the host cellular entry receptor is still ACE2 despite little sequence similarity with SARS-CoV-2 Spike (Hofmann et al., 2005). The ability of coronavirus Spike proteins to tolerate mutations is arguably the biggest challenge for the humoral immune system to keep up with viral evolution and immune escape variants, as discussed below.

For some RNA viruses, such as Hepatitis C and Zika, species and cellular tropism is governed by multiple pathways aside from just entry receptor binding (Ding, von Schaewen, & Ploss, 2014). For example, Zika virus antagonizes human STAT2, but not mouse STAT2 (Gorman et al., 2018). Therefore, mice are not susceptible to Zika infections. Yet for coronaviruses found in bats, binding to the ACE2 receptor seems to be the major, and perhaps only, limiting factor to infectivity and potentially transmissibility (Menachery et al., 2015). Problematically, the affinity of SARS-CoV-2 Spike for ACE2 is ~15 nM, which is over 20 times tighter than that of SARS-CoV Spike (Wrapp et al., 2020). Further, there appears to be additional biophysical room for improved binding, demonstrated by the affinity-enhancing N501Y mutation observed in several highly transmissible viral variants (Starr et al., 2020). The extent to which these Spike protein affinity-enhancing mutations are responsible for increased transmissibility is unknown. It also remains unknown whether there is an upper limit of Spike-ACE2 affinity above which SARS-CoV-2 would take a fitness cost, as has been observed in influenza (Hensley et al., 2009). Regardless, given that entry receptor interactions are the primary and sometimes the only barrier to infectivity and species tropism, zoonotic reservoirs in bats and other species render the *Coronaviridae* family an ever-present pandemic threat.

Capitalizing on this property, transgenic mouse models have been created that express human ACE2 under the control of the Keratin

18 promoter, which drives expression in airway epithelia (Chow et al., 1997; McCray et al., 2007). These animals had been used as models for SARS-CoV infections and captured some essential aspects of human disease, including myeloid and lymphoid infiltrates into the lungs, cytokine storms, and eventual lethality (McCray et al., 2007). Yet there are some limitations to this model, as ACE2 expression levels and cell type specificity are not fully physiological. For these reasons, alternative models have been developed in which human ACE2-encoding adeno-associated virus is delivered to the airway prior to SARS-CoV-2 infection (Israelow et al., 2020). In other model systems, SARS-CoV-2 has been adapted for mouse tropism (Leist et al., 2020). Each of these model systems has its own advantages, but also drawbacks in that cell type-specific ACE2 expression levels and/or Spike protein affinity are not well-matched to what is observed in humans.

2.2 Innate immune activation

Attachment and internalization of SARS-CoV-2 into endosomal compartments is promoted by Spike protein, which is cleaved into S1 and S2 subunits by furin during virus production (Johnson et al., 2021) (Fig. 1). Subsequent membrane fusion of internalized virions to access the cytoplasm is then promoted by the host serine protease TMPRSS2 (Hoffmann et al., 2020). Upon uncoating and release of the viral RNA into the cytoplasm, SARS-CoV-2 initially transcribes the open-reading frames (ORF) 1a and 1b that encode two polypeptide chains. These are further cleaved into functional nonstructural proteins (nsps) necessary for the subsequent transcription and replication of the viral genome. Replication of the viral RNA genome and transcription of subgenomic RNAs encoding additional ORFs occurs in specialized ER-associated double-membrane vesicles (DMVs). These DMVs are induced by the viral proteins nsp3 and nsp4 (Knoops et al., 2008; Oudshorn et al., 2017; Snijder et al., 2020; Stertz et al., 2007; Ulasli, Verheije, de Haan, & Reggiori, 2010). Aside from RNA synthesis, DMVs shield newly formed RNA adducts from innate sensors before the viral RNAs are released into the cytosol for translation and viral assembly at the ER-Golgi intermediate compartment (Klein et al., 2020; Wolff, Zheng, Koster, Snijder, & Bárcena, 2020).

Based on the entry mechanisms and localization patterns of the viral RNAs, one can thus predict the innate sensors and their effector mechanisms that become activated to dictate the ensuing course of the disease. In principle, the primary cellular innate sensors capable of directly detecting RNA

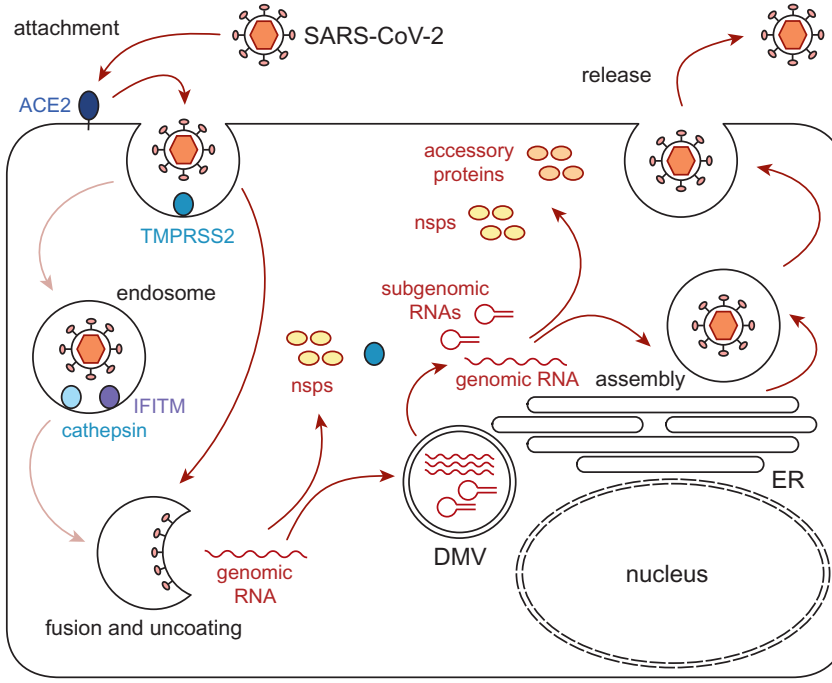

Fig. 1 Cellular entry of SARS-CoV-2. Upon docking to the attachment receptor ACE2, SARS-CoV-2 requires additional proteolytic steps of its Spike (S) protein to facilitate membrane fusion. Prior furin-mediated cleavage into to the S1 and S2 subunits enables further cleavage of S2 by the cellular protease TMPRSS2 and subsequent membrane-fusion at or near the plasma membrane. It is thought that in the absence of a furin cleavage site or in cells lacking TMRPRSS2, SARS-CoV-2 is forced to enter the cytoplasm following the cleavage of S by cathepsin found in endosomes. However, endosomes also harbor the interferon-induced transmembrane (IFITM) proteins that interfere with viral membrane fusion, thereby restricting entry of SARS-CoV-2 to the endosomal pathway. Most primary human cells exert selection pressure for SARS-CoV-2 variants containing furin cleavage sites. Following membrane fusion, the genomic RNA supports initially the translation of the SARS-CoV-2 open reading frame 1 to generate multiple nonstructural proteins (nsps). Nsp3 and nsp4 are required to establish a specialized cellular compartment consisting of ER-derived double-membrane vesicles (DMV) that function as major sites for the replication of the genomic RNA and the transcription of subgenomic RNA that encode both structural and accessory proteins. It is thought that DMVs are also important to shield newly formed RNA intermediates from the cytosolic detection by the innate immune system. Assembly of the genomic RNAs and structural proteins, consisting of nucleocapsid (N), membrane (M), envelope (E), and spike (S) proteins, occurs in the ER-Golgi intermediate compartment (ERGIC, not shown) before the virions are released from the cell.

viruses comprise the type I IFN-inducing sensors that include TLR3 (which detects endosomal dsRNA (Alexopoulou, Holt, Medzhitov, & Flavell, 2001)), TLR7 (which detects endosomal ssRNA (Diebold, Kaisho, Hemmi, Akira, & Reis e Sousa, 2004)), RIG-I (which detects cytosolic RNA with 5′ triphosphates or Cap0 structures (Devarkar et al., 2016; Hornung et al., 2006; Pichlmair et al., 2006)), and MDA-5 (which detects long cytosolic dsRNA (Yoneyama et al., 2005)). In addition, viral activity can be detected by NLRP3 and other inflammasome-forming NLRs (Allen et al., 2009; Ichinohe, Lee, Ogura, Flavell, & Iwasaki, 2009; Rajan, Warren, Miao, & Aderem, 2010; Thomas et al., 2009; Wang et al., 2014). The cytosolic DNA-sensing cGAS/STING pathway may also indirectly promote antiviral immunity (Schoggins et al., 2014; Sun et al., 2012), perhaps by sensing mitochondrial damage or transposon-derived DNA species (Sun et al., 2017). Collectively, detection of viral infections by these innate sensors leads to the transcriptional induction of type I and type III interferons (IFNs), IFN-sensitive genes (ISGs), proinflammatory cytokines, and posttranslational processing of IL-1 family members.

The relative importance of individual innate sensors and their downstream signaling and effector molecules in SARS-CoV-2 recognition and pathogenesis remains unresolved, in part due to the deficiencies in mouse models of infection as described above. Nonetheless, key features of the mechanisms that instruct innate sensing of SARS-Cov-2 have begun to emerge. In Calu-3 cells, a human airway epithelial line, MDA-5 is required to induce type I IFN, whereas RIG-I is dispensable (Yamada et al., 2021; Yin et al., 2021). Yet compared to infections by other RNA virus such as Sendai, type I IFN production is substantially delayed, likely due to immune evasion mechanisms discussed further below. In other human lung cell lines and primary cells, MDA-5 is dispensable for suppressing viral replication under conditions with high RIG-I expression. Instead, RIG-I suppresses viral replication through an IFN-independent mechanism that involves the direct interference of RIG-I with the initial phase of viral replication (Yamada et al., 2021). In these *in vitro* studies, TLR3 played a minimal role in type I IFN production and suppression of viral replication. Although *in vitro* experiments to test the functional importance of TLR3 and TLR7 have been inconsistent, human genetic studies demonstrate an unequivocally important role for these sensors in countering SARS-CoV-2. In a cohort of over 600 patients with severe COVID-19, 3.5% had inborn mutations in genes involved in type I IFN production, such as *Tlr3* and *Irf7* (Zhang et al., 2020). This frequency is far greater than that

observed in the general population and in those with mild or asymptomatic SARS-CoV-2 infections. Moreover, young men with loss-of-function mutations in X-linked *Tlr7* were far more likely to develop severe COVID-19 than would be expected by chance (van der Made et al., 2020), demonstrating the importance of these TLRs and type I IFN in the control of SARS-CoV-2.

2.3 Regulation of type I and type III IFN responses in SARS-CoV-2 infection

Compared to other respiratory viruses such as influenza A and RSV, SARS-CoV-2 infections induce an unusual transcriptional profile characterized by attenuated type I and type III IFN responses alongside robust expression of proinflammatory cytokines and chemokines (Blanco-Melo et al., 2020; Hoagland et al., 2021). Consistent with these findings, sera from COVID-19 patients revealed suppressed type I and type III IFN responses compared to influenza A infections (Galani et al., 2021). More prominent late-stage IFN responses become apparent only in a subset of patients with more severe disease (Galani et al., 2021). Some patients with severe disease may also exhibit slightly delayed but prolonged type I and type III IFN responses alongside cytokines typically associated with type 2 immunity such as IL-5 and IL-13 (Lucas et al., 2020). In contrast, three studies of sera or PBMCs from COVID-19 patients suggested that suppressed type I and type III IFN responses are a particular hallmark of patients with severe disease (Combes et al., 2021; Hadjadj et al., 2020; Harb et al., 2021). It is possible that differences in patient population characteristics explain some of these discrepant findings, underscoring a key point to be learned here, namely the extreme variability in outcomes and immune responses after infection. Regardless, these studies all support the notion of dysregulated type I and III IFN and cytokine responses that dictate disease outcome.

SARS-CoV-2 shares this pattern of a dysregulated innate immune response with its relatives SARS-CoV and MERS-CoV (Cheung et al., 2005; Lau et al., 2013; Menachery et al., 2014; Spiegel et al., 2005; Zhou et al., 2014; Ziegler et al., 2005). Following infections of mice with SARS-CoV, delayed type I IFN responses lead to a recruitment of pathogenic lung monocytes that mediate inflammation, vascular leakage, and reduced T cell immunity (Channappanavar et al., 2016). The timing of the type I IFN signals in this model system matters, as both the genetic inactivation of type I IFN signaling and the early provision of exogenous type I IFN reduce lung pathology (Channappanavar et al., 2016).

Similar observations have been made in MERS-CoV infections (Channappanavar et al., 2019). Thus, attenuated and delayed IFN responses are likely to have serious long-term consequences for the regulation of the innate immune response, in addition to their failure to control early viral replication.

Type I IFN responses are attenuated by both viral virulence factors and, in some patients, aspects of the host response. SARS-CoV-2 encodes antagonists that interfere with the IFN response at several stages, including proximal innate sensing, downstream cell signaling, and, following the production of type I IFN, IFN signaling itself (Lei et al., 2020; Xia et al., 2020) (Fig. 2). SARS-CoV-2 shares this feature with SARS-CoV and MERS-CoV, although the latter two viruses may be less efficient in suppressing the IFN response (Xia et al., 2020). Detection of viral RNAs by Rig-I or MDA5 is antagonized in several ways. The viral proteins nsp14 and nsp16 both disguise viral RNA from detection by Rig-I or MDA5 by capping the 5′ end through their guanine-N7-methyltransferase and 2′-O-methyl-transferase activities, respectively (Daffis, Samuel, Suthar, Gale, & Diamond, 2008). In addition, overexpression of nucleocapsid protein (N) and nsp5 suppresses Rig-I by interfering with TRIM25-mediated ubiquitination (Chen et al., 2020; Hu et al., 2017; Li et al., 2020; Oh & Shin, 2021; Wu, Ma, et al., 2020; Zhao et al., 2021). Downstream signaling molecules required for the induction of IFN (and cytokine) responses are targets of multiple viral proteins as well. For example, both the N and membrane proteins (M) can interfere with the formation of macromolecular aggregates of MAVS, the essential signaling adaptor for RIG-I-like receptors, thus disrupting this activating signaling platform (Fu et al., 2021; Wang, Dai, et al., 2021). Likewise, ORF9b may interfere with MAVS function through its association with TOM70, an important cofactor for signaling (Jiang et al., 2020; Shi et al., 2014; Thorne et al., 2021). Further downstream, ORF9b prevents type I IFN induction by preventing the ubiquitination of IKKγ, whereas nsp6 and nsp13 bind to TBK1 to prevent the phosphorylation of IRF3 (Guo et al., 2021, p. 13; Wu, Shi, et al., 2021; Xia et al., 2020). Ultimately, the translocation of the essential transcription factors into the nucleus is blocked as well. As with SARS-CoV, ORF3b of SARS-CoV-2 inhibits type I IFN production by blocking IRF3 nuclear localization (Miorin et al., 2020; Xia et al., 2020). Yet, the potency of SARS-CoV-2 Orf3b is greatly increased relative to that of SARS-CoV by the absence of a nuclear localization signal sequence, demonstrating that the inhibition of IRF3 occurs in the cytoplasm (Konno et al., 2020).

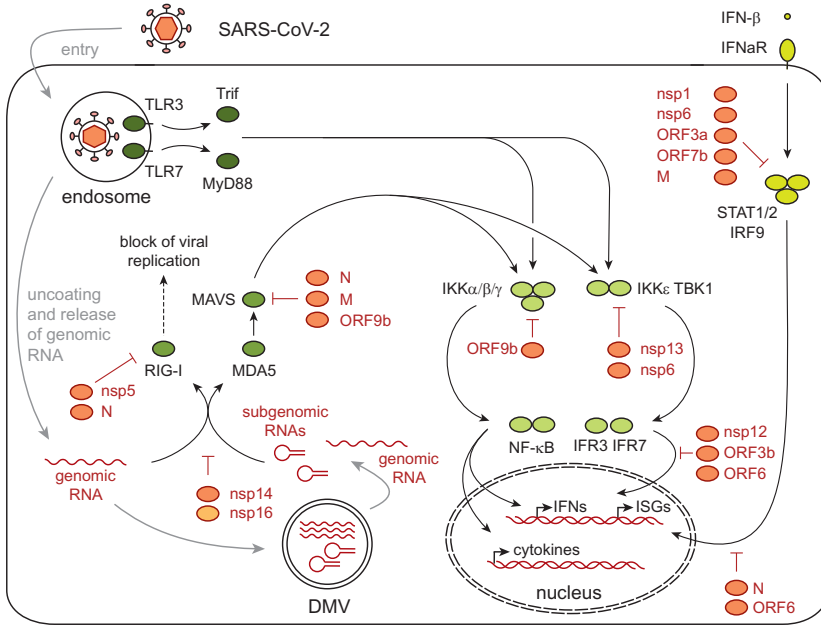

Fig. 2 Innate sensing and viral antagonism in SARS-CoV-2 infections. Following cell entry, SARS-CoV-2 can be detected in endosomes by the double-stranded RNA-sensing TLR3 and the single-stranded RNA-sensing TLR7. These receptors transmit their signals via the essential signaling adaptors TRIF and MyD88, respectively, to ultimately induce type I and type III IFNs, IFN-sensitive genes (ISGs), and proinflammatory cytokines. Upon viral uncoating and release of genomic RNA into the cytosol, the viral RNA itself can be sensed by RIG-I. It is thought that RIG-I interferes directly with the initial stage of genomic RNA replication without the typical activation of the signaling adaptor MAVS and the downstream IFN and cytokine responses. Instead, the induction of the latter signals occurs through the detection of viral RNAs by MDA5 predominantly at later stages in the viral life cycle. In addition to the direct induction of IFNs and ISGs, autocrine or paracrine signaling of type I IFNs can induce the subsequent production of IFNs and ISGs as well. Multiple SARS-CoV-2 proteins serve as virulence factors that interfere with the IFN and cytokine responses at multiple levels. Host proteins are shown in green and viral proteins are shown in orange. Dark orange indicates a confirmed function for SARS-CoV-2, whereas light orange indicates a postulated function for SARS-CoV-2 based on known functions in SARS-CoV or MERS-CoV. Not shown is the detection of viral activity of SARS-CoV-2 by the NLRP3 inflammasome.

Similarly, nsp12 and ORF6 have also been implicated in interfering with nuclear translocation of IRF3 (Wang, Zhou, et al., 2021; Xia et al., 2020). As secreted type I IFN functions in both autocrine and paracrine manner to induce ISGs, it is not surprising that the IFN signaling cascade itself is also antagonized by SARS-CoV-2. Cell signaling is antagonized

by nsp1 and nsp6 and others, which prevent phosphorylation of STAT1 or STAT2 downstream of the IFN alpha/beta receptor (IFNaR) and prevent their association with IRF9 (Xia et al., 2020). In both SARS-CoV and SARS-
CoV-2, ORF6 also sequesters the STAT1-STAT2-IRF9 complex from the nucleus, thereby limiting type I IFN-induced signaling and transcription (Frieman et al., 2007; Miorin et al., 2020, p. 6; Xia et al., 2020).

The multitude and polyfunctionality of SARS-CoV-2 virulence factors raise the possibility that mutations in highly transmissible SARS-CoV-2 variants evade the innate immune response to different degrees. For example, the alpha variant expresses much higher levels of ORF6, ORF9b, and N, along with a reduced activity of IRF3 and STAT1 and STAT2 when compared to two early SARS-CoV-2 lineage B isolates, possibly due to mutations in a transcriptional element found in the N open reading frame (Thorne et al., 2021). This finding therefore suggests that differences in the transmissibility and disease severity between individual SARS-CoV-2 variants may be also caused, in addition to mutations found in the S protein (see further below), by their differential ability to manipulate the innate immune response.

Aside from viral interference with type I IFN responses, the host immune response itself may also counter effective IFN responses, thus promoting more severe disease. Immune-modulating autoreactive antibodies that antagonize IFN had been seen in other infections before, but the prevalence of such responses had not been fully appreciated. Thus, it was quite remarkable to find antitype I IFN neutralizing antibodies in 10% of patients with severe COVID-19 (Bastard et al., 2020). In addition, severe COVID-19 has also been associated with autoantibodies with unknown specificities that nonetheless inhibit type I IFN signaling in part through FcγRIIb engagement (Combes et al., 2021). A large number of autoantibodies specific to other cytokines in addition to type I IFNs have also been documented, suggesting that the generation of immune-modulating autoantibodies is a common feature of COVID-19 (Wang, Mao, et al., 2021). Interestingly, the same study also identified tissue-specific autoantibodies, thus raising the possibility that the autoreactive antibodies not only interfere with the control of the virus but also contribute to the pathology of COVID-19. Anti-type I IFN antibodies can also correlate with higher viral loads and suppressed ISG responses in myeloid cells of severe COVID-19 patients (van der Wijst et al., 2021; Wang, Mao, et al., 2021). These studies

all identify autoantibodies as important contributors to the pathology in a subset of patients with severe disease. The ontogeny of these antibodies is not entirely clear, but they can be detected in the early stages of infection, suggesting that they may arise from a preexisting pool of autoreactive B cells. Importantly, while they are typically absent in the general uninfected population, a small number of individuals can carry antitype I IFN antibodies prior to SARS-CoV-2 infection (van der Wijst et al., 2021). It is therefore possible that preexisting autoantibodies can identify individuals with an increased risk for severe COVID-19.

Given the importance of type I IFN responses in influencing disease outcome of COVID-19, type I IFN administration has been considered as a potential clinical treatment option. This approach has been already tested in SARS and MERS infections. In these infections, type I IFN treatment is clearly beneficial in both mice and nonhuman primates (Chan et al., 2015; Channappanavar et al., 2016, 2019; Falzarano et al., 2013; Haagmans et al., 2004). However, human SARS and MERS studies came to mixed conclusions, suggesting that type I IFN treatment is at best moderately successful in these infections (Arabi et al., 2020; Loutfy et al., 2003; Omrani et al., 2014; Stockman, Bellamy, & Garner, 2006; Zhao, 2003). The reasons for the relative ineffectiveness of type I IFN treatment in SARS and MERS are not entirely clear. However, type I IFNs may be more promising for the treatment of SARS-CoV-2 and early results from clinical trials suggest that the administration of type I IFN may indeed lead to clinical improvement of patients with severe COVID-19 (Alavi Darazam et al., 2021; Li et al., 2021; Lokugamage et al., 2020; Monk et al., 2021).

Together, these data demonstrate that type I IFN is an essential protective cytokine if induced early after infection. Mouse models of SARS-CoV and prior general knowledge on the antiviral functions of type I IFN would have predicted this, but important questions remain about the function of type I and type III IFNs in SARS-CoV-2 infections. For example, the innate sensing mechanisms and their viral antagonisms are incompletely understood but clearer insights are needed to identify the causes for severe COVID-19 disease and facilitate more targeted IFN-based therapies. Moreover, the frequency of antibody-mediated antagonism among severe COVID-19 patients was surprisingly high. The events that lead to this antagonism need further investigation. Do many severe infections induce such a response? If so, why? Does a lifetime of such experiences lead to memory B cells that mount anamnestic anti-IFN responses? Does

this help explain why older adults are so much more susceptible to severe COVID-19? The pandemic has certainly highlighted the need to answer such questions, specifically to enable more targeted therapeutic interventions.

2.4 Inflammatory cytokine production in severe COVID-19

In concert with an absence of type I IFN signaling, severe COVID-19 is associated with a broad and uncoordinated cytokine storm (Hadjadj et al., 2020). Early in the response, type 1 cytokines predominate, as would be expected and desired based on knowledge gained from SARS-CoV infections (Li et al., 2008). Yet as the response progresses, an unusual signature of type 2 and 3 cytokines emerges (Lucas et al., 2020). These are accompanied by proinflammatory cytokines such as IL-6 and IL-12 as well as members of the IL-1 family of cytokines that lie downstream of inflammasome activation such as IL-1 or, especially, IL-18 (Laing et al., 2020; Lucas et al., 2020; Mathew et al., 2020; Rodrigues et al., 2021). The primary cell types responsible for lung inflammation during severe COVID-19 are likely myeloid cells such as monocytes and macrophages (Szabo et al., 2021). In support of this, inflammatory monocytes and macrophages that were recruited by a delayed type I IFN response (see above) were also a major the source of these cytokines in a mouse model of SARS-CoV (Channappanavar et al., 2016, 2019). Importantly, ablation of these cells improved disease in mice, suggesting that the neutralization of specific effector cytokines secreted by these cells may be a promising therapeutic approach for patients with COVID-19. Consistent with such findings, the administration of dexamethasone, a broadly acting corticosteroid, improves the outcome of severe COVID-19 (Cain & Cidlowski, 2017; RECOVERY Collaborative Group et al., 2021). However, efforts to neutralize specific cytokines have had mixed success. For example, IL-6 was a promising target, as antibodies blocking IL-6 signaling have had success in diseases such as rheumatoid arthritis. However, antibodies that block IL-6 signing have provided minimal clinical benefit in hospitalized COVID-19 patients (Lescure et al., 2021; Soin et al., 2021; Stone et al., 2020; The REMAP-CAP Investigators, 2021). In contrast, interference with IL-1 signaling is showing more promise in small initial clinical studies (Cavalli et al., 2020; Huet et al., 2020; Ucciferri et al., 2020). At first glance, these data may suggest that severe COVID-19 and its associated immunopathology might be caused by the breadth of the cytokine storm instead of any single inflammatory factor, thus limiting the therapeutic potential of neutralizing antibodies to

individual cytokines. However, given that pleiotropic cytokines like IL-1 and IL-6 are also essential regulators of both the innate and adaptive immune response, the clinical outcome of cytokine signaling blockade is the net result of both their positive and negative effects on COVID-19 pathology. It is possible that more targeted approaches that interfere with specific aspects of cytokine signaling may improve the clinical outcome of severe COVID-19.

3. T cell responses to SARS-CoV-2

3.1 T cell priming

As dendritic cells express minimal levels of ACE2, direct infection by SARS-CoV-2 of antigen-presenting cells is unlikely (Zhang et al., 2005). Thus, the initial T cell activation in SARS-CoV-2 infections likely occurs through indirect priming by dendritic cells. In this setting, infected and dying cells such as airway epithelia are engulfed and, in conjunction with activation by pathogen-associated molecular patterns, dendritic cells present SARS-CoV-2 peptides to T cells. The precise subsets of antigen-presenting cells that prime $CD4^+$ and $CD8^+$ T cells *in vivo* are not known. Yet by analogy to many prior mouse and human studies, $CD8^+$ T cells are presumably primed by conventional type 1 (cDC1) cells in lymph nodes, whereas $CD4^+$ T cells are first activated by cDC2 cells (Hildner et al., 2008; Schlitzer et al., 2013; Williams et al., 2013). The frequencies of cDCs in the peripheral blood are modestly reduced during acute COVID-19, and this is correlated with small reductions in T cell numbers and activation (Zhou, To, et al., 2020). The significance of these findings remains to be determined, as there is a redistribution of T cells to the lungs during the acute phase of infections, which may underlie the apparent transient T cell lymphopenia in circulation (Laing et al., 2020; Mathew et al., 2020). Indeed, T cells sampled from the respiratory tract displayed tissue-resident transcriptional programs and produced protective cytokines such as IFN-γ (Szabo et al., 2021). Accordingly, the numbers of such T cells correlated well with disease outcomes (Szabo et al., 2021).

3.2 T cell specificities

T cell reactivity to SARS-CoV-2 is broad and encompasses all known viral proteins. In ~70% of COVID-19 patients, circulating virus-specific $CD8^+$ T cells were detected (Grifoni et al., 2020; Sekine et al., 2020). These $CD8^+$ T cells recognized peptide:MHCI from the viral Spike, M, and ORF proteins, and were marked by expression of IFN-γ and Granzyme B

(Grifoni et al., 2020; Sekine et al., 2020). In nonhuman primate models, $CD8^+$ T cells mediate protection against SARS-CoV-2, especially when only low levels of neutralizing antibodies are present (McMahan et al., 2021).

$CD4^+$ T cells were even more robust and polarized to Th1 fates. In mild disease, IL-4 or IL-17 production by SARS-CoV-2-specific $CD4^+$ T cells was not detected (Grifoni et al., 2020; Rodda et al., 2021), though this may well be different in severe disease. Based on earlier findings of a pathogenic role of Th2 cytokines in SARS-CoV and other respiratory infections and the presence of such cytokines in cases of SARS-CoV-2 infection, one would expect such aberrant $CD4^+$ T cell responses in patients with severe COVID-19, especially by lymphocytes in the lung (Castilow, Olson, & Varga, 2007; Deming et al., 2006; Li et al., 2008; Lucas et al., 2020). In addition, emerging evidence points toward a correlation between dysregulated Treg responses and disease severity of COVID-19 patients, though the data do not fully agree. Based on the analysis of *in vitro*-activated PBMCs from COVID-19 patients, severe disease is characterized by a suppressed frequency of Tregs (Meckiff et al., 2020). Yet studies that measured the abundance of Tregs directly in PBMCs from COVID-19 patients showed an increased frequency of Tregs in cases with severe disease (Galván-Peña et al., 2020; Vick et al., 2021). Interestingly, Tregs in these patients expressed gene signatures that resembled those found in tumor-infiltrating Tregs with immune-suppressive properties (Galván-Peña et al., 2020). Consistent with such observations, increased levels of $Notch4^+$ Tregs have also been found to positively correlate with disease severity (Harb et al., 2021). Importantly, mouse models of viral RNA-induced airway inflammation or influenza infection showed that the Treg-specific expression of Notch4 can interfere with the IL-18-mediated induction of amphiregulin, which is important for tissue repair (Harb et al., 2021). Abrogation of Notch4 signaling or administration of amphiregulin promoted tissue repair and limited inflammation in the lungs of these mice (Harb et al., 2021). Thus, $Notch4^+$ Tregs may actively promote lung pathology of COVID-19 patients with severe disease (Harb et al., 2021).

The numbers of virus-specific $CD4^+$ T cells correlate well with the magnitude of the antibody response (Rydyznski Moderbacher et al., 2020). These robust $CD4^+$ T cell responses are driven in part by cross-reactive memory lymphocytes generated by prior common coronavirus infections (Grifoni et al., 2020; Le Bert et al., 2020; Mateus et al., 2020). Such memory T cells were detected in a large fraction of SARS-CoV-2 unexposed individuals (Braun et al., 2020; Le Bert et al., 2020; Mateus et al., 2020; Sekine et al., 2020). These preexisting memory $CD4^+$ T cells

are unlikely to prevent infections or transmission, but might reduce COVID-19 severity (Lipsitch, Grad, Sette, & Crotty, 2020). Similar to total SARS-CoV-2 $CD4^+$ T cell responses, the frequencies of circulating T follicular helper (cTfh cells), whose measurements serve as surrogates for bona fide Tfh cells found in the germinal centers, are also positively correlated with the magnitude of antibody responses to SARS-CoV-2 in COVID-19 patients (Boppana et al., 2021; Juno et al., 2020; Meckiff et al., 2020; Zhang et al., 2021). However, this correlation may not hold for patients who suffer from severe disease and death. For such individuals, high and persistent viral loads are associated with a general lymphopenia including a decrease of cTfh cells and a corresponding reduction of anti-SARS-CoV-2 antibodies (Silva et al., 2021). Severe disease is also associated with an unusual Tfh subset that expresses genes typical for cytotoxic responses. Such cytotoxic Tfh cells have been previously suggested to promote the killing of B cells and may explain the loss of germinal center B cells seen in deceased COVID-19 patients, although, as explained further below, this may be a transient phenomenon for most recovering individuals (Dan et al., 2019; Kaneko et al., 2020).

At the conclusion of the response, stable pools of memory $CD4^+$ and $CD8^+$ T cells are maintained (Dan et al., 2021; Rodda et al., 2021). Encouragingly, T cell reactivity is maintained despite the emergence of several problematic antibody escape variants of SARS-CoV-2 (Geers et al., 2021; Tarke, Sidney, Methot, Zhang, et al., 2021), though hints of $CD8^+$ T cell escape are beginning to emerge (Agerer et al., 2021). By analogy to preexisting common coronavirus-specific memory T cells, these variant cross-reactive T lymphocytes are likely to blunt disease severity following subsequent heterologous SARS-CoV-2 exposures even in the absence of sterilizing antibody responses (Sekine et al., 2020).

4. Antibody responses to SARS-CoV-2

4.1 Initial antibody responses to SARS-CoV-2

SARS-CoV-2-specific antibodies first become detectable 1–2 weeks postsymptom onset, which in turn lags the actual exposure by 1–2 weeks (Long, Liu, et al., 2020). Oddly, the isotype distribution of the early serum antibody response is highly variable (Long, Liu, et al., 2020). As IgM is the initial isotype expressed by naïve B cells, one would have expected IgM antibodies to precede IgG and IgA (Baumgarth, Nikolich-Žugich, Lee, & Bhattacharya, 2020). Yet this is not consistently the case (Long, Liu, et al., 2020). There are several possible explanations for how

virus-specific serum IgG is sometimes seen before IgM. First, class switch recombination often occurs very early during a primary antibody response, usually preceding germinal center reactions (Roco et al., 2019). Given the intrinsically different signaling properties between IgM and IgG isotypes (Engels et al., 2009), it is possible that class-switched B cells preferentially differentiate into antibody-secreting extrafollicular plasma cells. Second, IgG production could originate from preexisting class-switched memory B cells formed in response to prior common β-coronavirus infections. Neutralizing epitopes are not well-conserved between SARS-CoV-2 and the common OC43 or HKU1 viruses, but several other antigens on Spike protein are similar. Most of these common non-neutralizing epitopes fall within the S2 region and are presumably not under selective immune pressure to change (Anderson et al., 2021; Song et al., 2021). Longitudinal tracking of responses in mild and severe COVID-19 revealed these types of "original antigenic sin" types of responses (Sokal et al., 2021). In these findings, cross-reactive B cells were somatically mutated, indicative of prior memory, and produced a large portion of early antibodies (Anderson et al., 2021; Sokal et al., 2021). Yet these cross-reactive nonneutralizing antibodies and cells were progressively replaced by primary responses to unique portions of SARS-CoV-2 Spike protein (Sokal et al., 2021).

In the early stages of all primary T cell-dependent antibody responses, short-lived extrafollicular plasma cells are formed that secrete large quantities of mostly low-affinity antibodies (Sze, Toellner, de Vinuesa, Taylor, & MacLennan, 2000). As these cells die within a few weeks into the response, serum antibodies also decline. During the initial months of the pandemic, several studies raised concerns that the duration of protective antibody production and immunity after SARS-CoV-2 infections was unusually short-lived, potentially lasting only several months (Ibarrondo et al., 2020; Seow et al., 2020; Tillett et al., 2021). Yet for most infections, this decay is not linear. Short-lived plasma cells are typically replaced by a smaller number of germinal center-derived affinity-matured antibody-secreting long-lived plasma cells, mostly localized in the bone marrow (Amanna, Carlson, & Slifka, 2007; Benner, Hijmans, & Haaijman, 1981; Manz, Thiel, & Radbruch, 1997; Slifka, Antia, Whitmire, & Ahmed, 1998). Due to their high affinities, relatively few antibodies derived from long-lived plasma cells are required to confer protection so long as they target the key virus-neutralizing epitopes (Purtha, Tedder, Johnson, Bhattacharya, & Diamond, 2011). Because human long-lived plasma cells persist on average for over 20 years (Halliley et al., 2015; Landsverk et al., 2017), a stable nadir of protective antibodies is maintained durably in a typical antiviral immune response.

4.2 Durability of antibody responses to SARS-CoV-2

Multiple studies have confirmed a wide degree of variability in antibody levels that generally correlate with disease severity (Long, Tang, et al., 2020; Ripperger et al., 2020). Given this enormous variability in responses, it is entirely possible that protective immunity does not persist in a small subset of convalescent individuals. Yet the worries that immunity was inherently short-lived after COVID-19 and SARS-CoV-2 reinfections were common, seem premature in retrospect. Some studies of autopsy samples from patients who succumbed to COVID-19 revealed an absence of germinal centers (Duan et al., 2020; Kaneko et al., 2020), as has been observed in mouse models of highly inflammatory bacterial and parasitic infections (Di Niro et al., 2015; Popescu, Cabrera-Martinez, & Winslow, 2019; Vijay et al., 2020). The absence of germinal centers could in turn impact both affinity maturation and the duration of immunity (Linterman et al., 2010; Weisel, Zuccarino-Catania, Chikina, & Shlomchik, 2016; Zotos et al., 2010). However, this disruption of germinal centers in severe COVID-19 patients appears transient, as affinity maturation proceeds normally over time following recovery from severe COVID-19 (Sokal et al., 2021). Moreover, several studies which longitudinally followed antibodies for several months demonstrated a conventional humoral response to SARS-CoV-2, in which neutralizing titers were stably maintained after an initial decline (Dan et al., 2021; Gudbjartsson et al., 2020; Isho et al., 2020; Iyer et al., 2020; Ripperger et al., 2020; Wajnberg et al., 2020). Accordingly, bone marrow plasma cells can be detected long into convalescence (Turner, Kim, et al., 2021). Subsequent prospective and observational studies demonstrated very low rates of SARS-CoV-2 reinfections in recovered individuals (Abu-Raddad, Chemaitelly, Coyle, et al., 2021; Abu-Raddad et al., 2020; Lumley et al., 2021). These data are consistent with observations in SARS-CoV convalescent individuals, in whom neutralizing antibodies were still detected 17 years after infection (Tan et al., 2020). Thus, the preponderance of evidence suggests that immunity to SARS-CoV-2 infections is durable following acute infections.

Some of the assumptions regarding transient humoral immunity arose from prior studies on common coronavirus infections. Using anamnestic antibody responses to the conserved nucleocapsid protein as markers of reinfections, a recent study estimated that humoral immunity to OC43, HKU1, NL63, and 229E lasts for only several months (Edridge et al., 2020). However, there are alternative interpretations for these data.

First, antibody levels in this study never declined to background levels (Edridge et al., 2020), arguing against transience of plasma cells. Second, human challenge studies with 229E revealed resistance to homologous reinfections for at least a year after the primary infection (Reed, 1984). Symptomatic disease was not observed, and antibody levels were maintained well above background throughout the course of the study (Callow, Parry, Sergeant, & Tyrrell, 1990). Conversely, intentional secondary challenges with related but heterologous α-coronaviruses did cause productive infections and cold-like symptoms in trial volunteers (Reed, 1984). These data argue that "reinfections" may be caused by the underappreciated genetic diversity of and immune escape by common coronaviruses (Lau et al., 2011; Pyrc et al., 2006; Woo et al., 2006), rather than a waning of immunity. Consistent with this interpretation, serum samples from the 1980s were fully capable of neutralizing common coronaviruses that were circulating at the time, but not those that emerged later (Eguia et al., 2021). In contrast, sera from later years neutralized coronaviruses from earlier times (Eguia et al., 2021). Thus, the dogma that antibody production is inherently short-lived after coronavirus infections is not well-supported.

4.3 Protection by antibodies against COVID-19

Patients with severe disease consistently show robust spike protein-specific and neutralizing antibodies that exceed the levels seen in mild or asymptomatic infections (Long, Tang, et al., 2020; Ripperger et al., 2020). Such findings raised the possibility that antibodies are not protective against SARS-CoV-2. This seems unlikely for several reasons. First, passive transfer of neutralizing polyclonal or monoclonal antibodies protects against infection and severe disease, both in patients and macaques (McMahan et al., 2021; Weinreich et al., 2021). Second, vaccine efficacy correlates well with neutralizing antibody levels (Khoury et al., 2021). Moreover, among patients with severe COVID-19, the timing of antibody production correlates with outcomes. Those that mount early antibody responses tend to recover more often than those with delayed responses (Lucas et al., 2021). Together, these data emphasize that neutralizing antibodies are protective against infections, just as with nearly every other acute virus infection (Zinkernagel & Hengartner, 2006).

There are several possible explanations as to why elevated virus-specific antibodies correlate with severe disease. First, the antibodies are likely to be a marker rather than a cause of unchecked viral replication and

immunopathology. As discussed above, in severe COVID-19, neutralizing antibodies are often accompanied by pathogenic anti-IFN autoantibodies. Indeed, in the early stages of severe disease, an unusual memory B cell subset typically associated with autoimmunity is observed (Jenks et al., 2018; Woodruff et al., 2020). Second, virus-specific antibodies in severe COVID-19 tend to be afucosylated (Chakraborty et al., 2021). This under-glycosylation increases the affinity to the activating FcγRIIIa and promotes myeloid cell activation and inflammation (Chakraborty et al., 2021; Wang et al., 2017). Together, these data demonstrate that while SARS-CoV-2 is susceptible to antibody-mediated neutralization, accompanying changes in antibody glycosylation and specificities are pathogenic. Given these issues, the use of convalescent plasma to treat COVID-19 is not justified and may be dangerous. Instead, defined neutralizing monoclonal antibody cocktails are a far safer and more effective route to temporary immunity (Weinreich et al., 2021).

All SARS-CoV-2-neutralizing monoclonal antibodies that have been described to date bind to Spike protein. Of these, almost all recognize either the receptor binding domain or the N-terminal domain of the S1 subunit (Barnes, Jette, et al., 2020; Barnes, West, et al., 2020; Cerutti et al., 2021; Liu et al., 2020; McCallum et al., 2021; Pinto et al., 2020; Zost et al., 2020). Rare, coronavirus-cross-reactive, and weakly neutralizing epitopes within S2 also exist (Ng et al., 2020; Song et al., 2021), though these are not consistently elicited during infections (Anderson et al., 2021). Within the receptor binding domain, at least three different classes of non-overlapping neutralizing antibodies exist. These either directly and competitively inhibit Spike-ACE2 interactions, or prevent conformational changes in RBD that are necessary for ACE2 attachment (Barnes, Jette, et al., 2020). Other neutralizing monoclonal antibodies recognize a common "supersite" in the Spike N-terminal domain (Cerutti et al., 2021; McCallum et al., 2021). These antibodies may inhibit the switch from the prefusion to post-fusion confirmation of Spike protein (Chi et al., 2020)—a topic that is of high relevance for vaccines and discussed further below.

4.4 Viral evolution and escape from antibodies

The prescient prior studies on common coronaviruses as discussed above should have led to an early focus on SARS-CoV-2 viral evolution rather than on waning of immunity. Yet large-scale sequencing of viral genomes from patient samples began only toward the end of 2020, and even then,

only in certain countries. The lack of widespread sequencing even today leaves an incomplete picture of viral evolution and the emergence of problematic variants. As of this writing, over 90% of COVID-19 cases worldwide are estimated to be driven by highly transmissible SARS-CoV-2 variants of concern. Several of these highly transmissible variants contain mutations in key antibody epitopes and, as a result, are partially resistant to neutralization by convalescent serum from ancestral lineage infections (Edara et al., 2021), and fully resistant to some monoclonal antibodies (Starr et al., 2021). These immune escape mutations, the most substantial of which are seen in the beta/B.1.351 variant (Garcia-Beltran et al., 2021; Zhou et al., 2021), were unexpected. At the time of their discoveries, herd immunity had not yet been reached in any country and there seemed to be no obvious transmission advantage to the variants to acquire such changes. Moreover, these variants contain far more Spike mutations than would be expected by molecular clock analysis at this point in the pandemic (Davies et al., 2021). Though speculative, some of these variants may have arisen following prolonged within-host evolution in immunocompromised individuals who were unable to clear the infection. In some of these patients, partial immune selective pressure was applied through administration of convalescent plasma, allowing for the emergence of transmissible and immune escape variants (Avanzato et al., 2020; Aydillo et al., 2020; Choi et al., 2020; Kemp et al., 2021; McCarthy et al., 2021).

Unlike influenza viruses, SARS-CoV-2 does not have a segmented genome. Thus, it cannot undergo dramatic antigenic shifts in cells coinfected by heterologous viruses to escape immunity, though rare recombination events are possible (Goldstein, Brown, Pedersen, Quinlan, & Elde, 2021). Rather, point mutations and deletions sequentially accumulate during SARS-CoV-2 replication. At least 4–5 distinct neutralizing epitopes exist on SARS-CoV-2 Spike protein (Barnes, Jette, et al., 2020; Cerutti et al., 2021; McCallum et al., 2021; Song et al., 2021). Thus, one would not expect the emergence of escape variants under selection by polyclonal neutralizing antibodies in convalescent plasma. Yet neutralizing antibodies are not evenly distributed across these epitopes. A single E484K point mutation in Spike leads to a large loss in overall antibody binding and neutralization by convalescent sera from ancestral lineage infections (Greaney et al., 2020; Starr et al., 2021). Conversely, supersite mutations in the Spike N-terminal domain have a more modest impact on neutralization by convalescent sera (Planas et al., 2021). While there is substantial variation across individuals, these data highlight the concept of immunodominance in

antibody responses and the opportunities it creates for viral evolution. Immunodominance or lack thereof may explain why, despite comparable mutation rates, measles and polio have been driven to very low endemicity through vaccination and natural infection, whereas influenza and coronaviruses have not (Greaney, Welsh, & Bloom, 2021). The factors that drive antibody immunodominance in SARS-CoV-2 infections remain to be studied. By analogy to HIV studies, precursor frequency, avidity, and self-reactivity are plausible candidates to explain why certain B cell clones and antibody specificities predominate in SARS-CoV-2 infections (Abbott et al., 2018; Doyle-Cooper et al., 2013).

5. Vaccines against SARS-CoV-2

In what will undoubtedly be recognized as one of the most remarkable feats in biomedical history, highly effective vaccines against SARS-CoV-2 were developed and deployed in less than a year after the public reporting of its nucleotide sequence. There are currently six vaccines that are WHO-approved, and several others are likely forthcoming in the next few months. The vaccines encompass several different platforms, using both new and traditional technologies. Here, we will focus predominantly on mRNA, adenovirus, and protein nanoparticle technologies (Fig. 3).

5.1 mRNA vaccines

The first vaccines to receive authorization from regulatory agencies in the United Kingdom and North America were from Pfizer/BioNTech and Moderna. Remarkably, in independent US Food and Drug Administration (FDA) phase 3 trials, the Pfizer/BioNTech and Moderna vaccines demonstrated efficacies of 95% and 94%, respectively. These vaccines remain the gold standard for efficacy against ancestral strains and new variants of concern, with good safety profiles. By no means were these results guaranteed, as this was the first instance of mRNA-based vaccines that were widely deployed, and some other mRNA-based vaccine candidates failed. Although the funding initiative that led to their development in the United States was called Operation Warp Speed, this seems a misnomer given the decades of basic research that enabled the remarkable success of these vaccines.

mRNA transfection as a gene-delivery platform had been studied for decades, primarily through the work of Kariko and Weissman at the University of Pennsylvania. The theoretical advantages of an mRNA-based

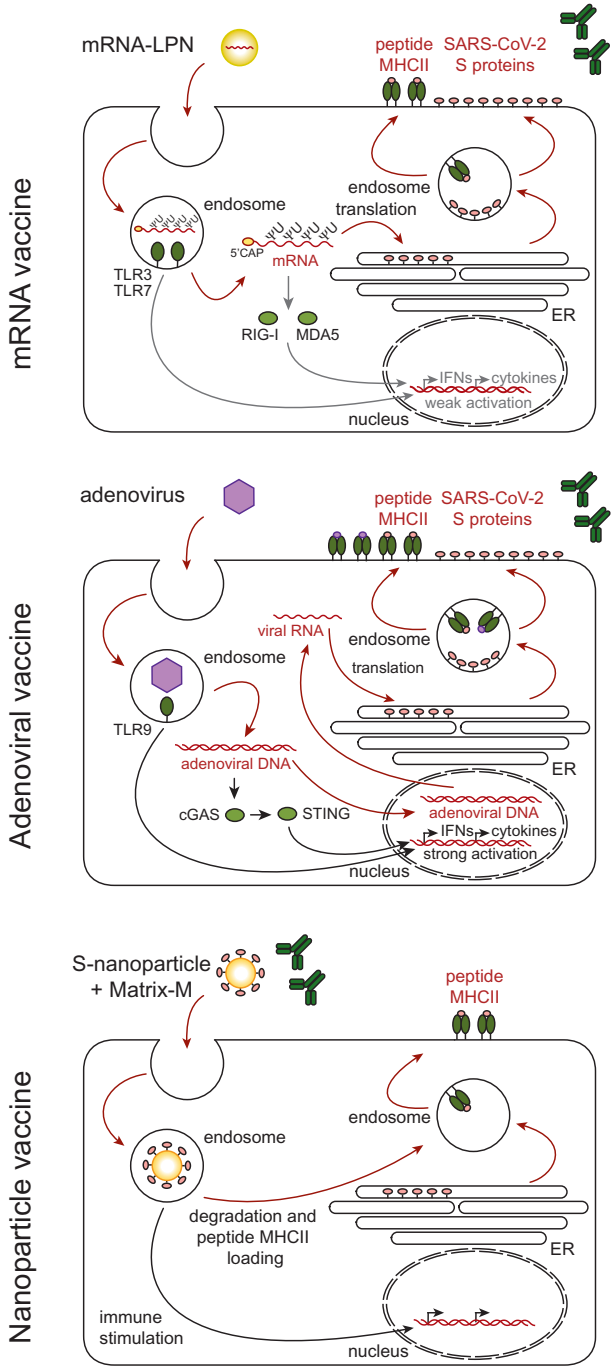

Fig. 3 See figure legend on opposite page.

approach are lack of integration into host genomes and titratability of downstream protein expression. Yet, the same cellular sensors such as TLR7 and RIG-I that detect viral RNA also recognize synthetic mRNA. Because synthetic mRNA lacks virally-encoded antagonists of type I IFN, early attempts to perform mRNA transfections ended with massive IFN responses, very little protein expression, and rapid cell death (Karikó, Ni, Capodici, Lamphier, & Weissman, 2004). To circumvent these problems, uridines were replaced by isomeric pseudouridines, which are abundant in ribosomal RNA but largely absent in mRNA. This replacement led to a near complete evasion of recognition by TLR3, 7, and 8 and robust protein expression (Karikó, Buckstein, Ni, & Weissman, 2005; Karikó et al., 2008). Additional steps, such as inclusion of methylcytidines, the addition and modification of the 5′ CAP structure, or the elimination and purification of double-stranded RNA adducts during the production process further reduced IFN responses and cellular cytotoxicity (Nelson et al., 2020; Warren et al., 2010). Together, these modifications allowed candidate vaccines against other pathogens, such as Zika virus, to

Fig. 3 Principles of current COVID-19 vaccines. *mRNA vaccines* encode the S protein in a lipid-nanoparticle (LNP)-encapsulated mRNA. The mRNA-LNP is taken up via pinocytosis by dendritic cells and other cells. Unmodified mRNA leads to the innate immune activation by Toll-like receptors and Rig-I-like receptors that induce an antiviral state and promote the inhibition of protein translation. mRNAs used in many vaccine approaches contain pseudo-uracils (ψU) as well as 5′-CAP structures and 2′-O-methylations to avoid the activation of these innate immune pathways. The efficient production of S protein and its transport to the cellular surface as peptide-MHCII complexes and as native protein enable the activation of cognate $CD4^+$ T cells and B cells (here symbolized by antibodies), respectively. Of note, the mRNA-LNPs retain some residual immune stimulatory activity that leads to the (presumably weak) production of innate cytokines necessary to induce the adaptive immune response. In the absence of such signals, the mRNA-LNPs induce a tolerizing adaptive immune response. *Adenoviral vaccines* also deliver genetic information necessary for the production of S protein. However, this occurs in form of DNA provided by an adenovirus of uncommon serotype. Accordingly, these vaccines trigger different innate sensors. Adenoviral vaccines also generate T and B cell responses that target the adenovirus itself and may interfere with subsequent vaccinations if given too early. *Nanoparticle vaccines* resemble most closely traditional subunit vaccines. However, the S proteins are arranged as multimers in complex with the nanoparticle and activate B cells directly. The multivalent arrangement of the S proteins is thought to mimic more closely the structure of real viruses and induce superior B cell responses. Because the nanoparticles themselves do not possess immune-stimulatory properties, they are administered together with an adjuvant such as the saponin-based Matrix-M. Most but not all COVID-19 vaccines use a modified form of S protein that contains two proline residues to stabilize a prefusion conformation that is targeted by most neutralizing antibodies.

show preclinical success in animal models (Richner et al., 2017). A key remaining issue is the nature of the inflammatory adjuvanting factors in these vaccines. It is possible that residual engagement of TLRs or RIG-I by the mRNA itself or RNA impurities drives enough inflammation for a productive immune response. In addition, the lipid nanoparticle delivery vehicles in which the mRNA resides can themselves be adjuvanting, for example by the net charge-mediated targeting of dendritic cells or the immune-modulatory properties of some of the components (Kranz et al., 2016; Pardi, Hogan, Porter, & Weissman, 2018; Pardi, Hogan, & Weissman, 2020; Verbeke, Lentacker, Smedt, & Dewitte, 2019). Conversely, modifications to the lipid nanoparticles can also render such pseudouridine-containing mRNA-lipid nanoparticles immunologically silent, thus allowing for the expression of tolerizing antigens to treat autoimmunity (Krienke et al., 2021).

A second key basic science innovation came from structural studies of respiratory syncytial virus (RSV). The most potent neutralizing antibodies against RSV bind to a metastable prefusion conformation of the viral type 1 fusion glycoprotein F (Magro et al., 2012; McLellan, Chen, Leung, et al., 2013). Presumably because of this instability, such antibodies are poorly elicited by natural infections. A combination of structure-guided point mutations led to a stable form of F protein locked as a trimer in the prefusion conformation (McLellan, Chen, Joyce, et al., 2013). When used as an immunogen, this prefusion trimer yielded markedly improved neutralizing antibody responses over unmodified F protein (McLellan, Chen, Joyce, et al., 2013). These same lessons were then applied to the coronavirus Spike proteins, which are also type 1 fusion glycoproteins, of HKU1 (Kirchdoerfer et al., 2016), MERS (Pallesen et al., 2017), and SARS-CoV (Kirchdoerfer et al., 2018) to elicit neutralizing antibodies that recognize the prefusion conformation. Two prolines introduced in the S2 region of Spike were the key changes that allowed for a stabilization of this prefusion conformation (Kirchdoerfer et al., 2016, 2018; Pallesen et al., 2017). When the nucleotide sequence of SARS-CoV-2 was published, the prototype was already in place of how to generate a prefusion-stabilized conformation of this novel coronavirus. Indeed, prefusion-stabilized and transmembrane-anchored Spike protein enhanced neutralizing antibody responses over unmodified Spike when delivered as an mRNA vaccine in animal models (Corbett et al., 2020). This early basic work paved the way for the success of mRNA vaccines, without which the pandemic outlook would be grim.

A two-shot course, spaced apart by 3–4 weeks, was designed for clinical trials. Phase 1 trials for both the Moderna and Pfizer/BioNTech vaccines

demonstrated highly robust overall and neutralizing antibodies that exceeded the mean values observed in convalescent plasma after infection (Anderson et al., 2020; Mulligan et al., 2020; Sahin et al., 2020). These antibodies were maintained at high levels for at least 6–7 months, the longest timepoint that could be measured given the recency of immunizations, and were remarkably unaffected by age (Widge et al., 2020). Persistent germinal center reactions were observed that lasted for months (Turner, O'Halloran, et al., 2021), more reminiscent of influenza infections in mice than of short-lived responses after hapten immunizations (Bannard et al., 2013). Both Spike-specific $CD4^+$ and $CD8^+$ T cells were also generated after the second immunization (Anderson et al., 2020; Geers et al., 2021; Sahin et al., 2020; Tarke, Sidney, Methot, Yu, et al., 2021).

These outstanding immunogenicity profiles gave rise to phase 3 efficacies of 94% and 95% for Moderna and Pfizer/BioNTech for reducing the chances of symptomatic COVID-19 (Baden et al., 2021; Polack et al., 2020). These efficacies are on par with the best vaccines ever made. Initially, some concerns remained that antibodies elicited by these intramuscular vaccines would not reach upper respiratory mucosal surfaces, and thus might not prevent infections and transmission (Hassan et al., 2020; Jeyanathan et al., 2020). Rather, because antibodies more easily reach the lower respiratory tract where the most severe COVID-19 symptoms occur (Jones & Ada, 1987), the vaccines might prevent only the symptoms of infections. Fortunately, these concerns have thus far turned out to be unwarranted, though the delta variant may upend these considerations. Like highly effective intramuscular vaccinations against other viruses such as measles and smallpox that are transmitted through the respiratory tract, mucosal IgG against Spike can be detected postimmunization (Mades et al., 2021). Accordingly, both the Moderna and Pfizer/BioNTech vaccines have been very effective at preventing overall infections, symptomatic or not, with strong effects seen after just the first immunization (Thompson et al., 2021). Moreover, consistent with a robust and multilayered immune response, breakthrough infections are associated with reduced viral loads relative to those who are unvaccinated (Levine-Tiefenbrun et al., 2021). As a result, community transmission has fallen precipitously in countries with high vaccination rates (Milman et al., 2021).

Encouragingly, the efficacy of these mRNA vaccines has largely held in the face of multiple viral variants of concern. Despite a substantial drop in neutralizing antibody titers against the beta (B.1.351), gamma (P.1), and delta (B.1.617) variants, the real-world effectiveness of the Pfizer vaccine

against symptomatic COVID-19 remains high (Abu-Raddad, Chemaitelly, & Butt, 2021; Bernal et al., 2021). These findings strongly indicate that neutralizing antibodies in conjunction with T cells mediate protection from disease, given the retained reactivity by T cells to these variants of concern (Geers et al., 2021; Tarke, Sidney, Methot, Yu, et al., 2021). This conclusion is further supported by nonhuman primate studies, in which the importance of $CD8^+$ T cells was shown when limiting quantities of immune serum were passively transferred (McMahan et al., 2021). Nonetheless, booster shots against the beta variant sharply increase neutralizing antibody titers in individuals who had previously received both mRNA doses against the ancestral strain (Wu, Choi, et al., 2021). More analysis of the epitope specificity of these responses is clearly needed, but these data assuage some concerns that original antigenic sin will limit the effectiveness of subsequent variant-based booster immunizations (Worobey, Plotkin, & Hensley, 2020).

5.2 Adenovirus-based vaccines

A second vaccine platform that has seen success is based on adenoviruses, nonenveloped double-stranded DNA viruses that offer the practical advantage of high stability with normal refrigeration. The AstraZeneca/Oxford and Janssen vaccines use replication-incompetent adenoviruses to deliver genes encoding Spike protein to cells. The Russian Sputnik V vaccine also uses adenoviruses (Jones & Roy, 2021), yet there is less published data on this vaccine and it will not be discussed further here. Because the seroprevalence against common adenovirus serotypes is quite high, preexisting immunity can limit the effectiveness of such vaccines, as was seen in earlier failed HIV vaccine trials (Ledford, 2007). To circumvent this problem, unusual adenovirus serotypes were chosen to which humans are not exposed. Though not studied in detail for these vaccines specifically, innate sensing of these adenoviral vectors was presumably mediated by the endosomal and cytosolic DNA sensing pathways of TLR9 and cGAS/STING, which instruct subsequent adaptive B and T cell responses (Lam, Stein, & Falck-Pedersen, 2014; Zhu, Huang, & Yang, 2007). A concern for adenovirus-based vaccines is thus that subsequent immunizations may be impeded by preexisting vector immunity.

AstraZeneca/Oxford used a chimpanzee adenovirus serotype to evade preexisting immunity. Perhaps of importance, this vaccine did not use the prefusion-stabilized Spike protein, unlike the other vaccines discussed in this chapter. The AstraZeneca/Oxford vaccine showed robust antibody

production in nonhuman primates and protection against severe disease, though not against overall infections when very high challenge doses of SARS-CoV-2 were used (van Doremalen et al., 2020). Phase 1 human data were somewhat more mixed, with antibody levels near or below the median values observed in convalescent plasma (Folegatti et al., 2020). T cell responses were near the lower limit of detection after one dose (Ewer et al., 2021), though these presumably improve after the second immunization. In phase 3 trials to test efficacy, across multiple doses, the AstraZeneca vaccine showed an overall efficacy of 70% against symptomatic COVID-19 (Voysey et al., 2021). It is possible that this high, but reduced efficacy relative to the mRNA vaccines is due in part to lower antibody titers, which in turn is influenced by the decision not to use prefusion-stabilized Spike protein. The efficacy of the AstraZeneca vaccine drops precipitously against the beta variant (Madhi et al., 2021), though in all likelihood there is still some protection against severe disease against this and other variants such as delta (Public Library—PHE National—Knowledge Hub, n.d.).

Janssen used the rare Ad26 serotype to circumvent preexisting immunity. In contrast to AstraZeneca, the prefusion conformation of Spike was used. A single dose of the Janssen vaccine led to neutralizing antibody levels that exceeded the median titers in convalescent plasma in younger adults, though levels seen in older adults over 65 was less impressive (Sadoff, Le Gars, et al., 2021). Both Spike-specific $CD4^+$ and $CD8^+$ T cell responses were detectable well above background levels (Sadoff, Le Gars, et al., 2021). In phase 3 trials, the overall efficacy of the Janssen vaccine in preventing COVID-19 was only 66%, though this was much higher for preventing severe disease (Sadoff, Gray, et al., 2021). Intriguingly, though, both neutralizing antibody levels and overall efficacy appeared to improve over time (Sadoff, Gray, et al., 2021; Sadoff, Le Gars, et al., 2021), in parallels to the persistent germinal center reactions observed after mRNA vaccination (Turner, O'Halloran, et al., 2021). Moreover, unlike the AstraZeneca vaccine, efficacy was maintained against variants of concern circulating in Brazil and South Africa (Sadoff, Gray, et al., 2021). These data imply different correlates of protection for the Janssen vaccine relative to AstraZeneca that perhaps depends more heavily on variant-agnostic T cells.

5.3 Protein nanoparticle-based vaccines

A third platform for SARS-CoV-2 vaccines is protein-based. Disappointingly, traditional subunit-based Spike protein vaccines tested by Sanofi and

GlaxoSmithKline were discontinued due to poor immunogenicity results in older adults. Yet fortunately, protein-based vaccines by Novavax have progressed and shown outstanding immunogenicity and efficacy. A likely key to this success is adoption of the principles of multimerization and B cell precursor avidity.

Vaccines that elicit durable antibody production and humoral immunity typically have high antigen valency (Slifka & Amanna, 2019). Moreover, the magnitude of antibody responses is improved dramatically by multimerization of immunogens that self-assemble into nanoparticles (Abbott et al., 2018; He et al., 2016; Jardine et al., 2015; Kanekiyo et al., 2013; Marcandalli et al., 2019; McGuire et al., 2016; Sliepen et al., 2015; Yassine et al., 2015). This is likely due to antigenic thresholds that restrict B cell clones from participating in the response unless a certain avidity is reached (Biram et al., 2019; Schwickert et al., 2011; Taylor, Pape, Steach, & Jenkins, 2015; Zaretsky et al., 2017). The high B cell precursor avidity afforded by highly multimerized antigens allows these cells to contribute to and persist in germinal center reactions and generate long-lived plasma cells (Abbott et al., 2018; Shih, Meffre, Roederer, & Nussenzweig, 2002; Wong et al., 2020). The Novavax vaccine employs these principles through the generation of prefusion-stabilized Spike protein nanoparticles produced in insect cells (Tian et al., 2021). Alongside the saponin-based adjuvant Matrix-M (Magnusson et al., 2018), these nanoparticles elicited strong neutralizing antibody responses in animals, leading to sterilizing immunity against subsequent SARS-CoV-2 challenges (Guebre-Xabier et al., 2020; Tian et al., 2021). In human phase 1 data, the Novavax vaccine induced very high neutralizing antibody titers, far exceeding those observed in convalescent plasma. CD4 T cell responses were also detectable, though CD8 T cells were not tested (Keech et al., 2020). Phase 3 data demonstrated an exceptionally high efficacy of 96% against symptomatic disease caused by ancestral strains of SARS-CoV-2, and overall efficacy of 90% including variants of concern circulating in the United States (Heath et al., 2021). Adverse events were less frequent than observed with mRNA vaccines (Baden et al., 2021; Heath et al., 2021; Polack et al., 2020).

Somewhat unexpectedly, the Novavax vaccine efficacy was more substantially reduced against the SARS-CoV-2 beta variant than were the mRNA vaccines (Abu-Raddad, Chemaitelly, & Butt, 2021; Shinde et al., 2021). With the caveat that the confidence intervals were quite wide, the observed efficacy was only 60% for HIV participants (Shinde et al., 2021). If these efficacy numbers hold, there are several potential

immunological explanations. One possibility is that the breadth and immunodominance of antibodies following Novavax vaccination is different and/or narrower than that induced by mRNA vaccines. This could render Novavax vaccines more susceptible to antibody escape mutations. Yet there did not seem to be any obvious evidence of this in side-by-side comparisons of Novavax and Moderna vaccine responses (Shen et al., 2021). Alternatively, $CD8^+$ T cell frequencies are expected to be lower for Novavax than for mRNA vaccines. Protein nanoparticles would presumably need to be endocytosed by cDC1 cells and cross-presented to prime $CD8^+$ T cells (Theisen et al., 2018), whereas mRNA vaccines could potentially directly transduce cDC1 cells and lead to cytosolic expression and generation of peptides for MHCI. Given the likely importance of Spike-specific $CD8^+$ T cells in cross-protection against variants when antibody titers are diminished (Geers et al., 2021; McMahan et al., 2021; Tarke, Sidney, Methot, Yu, et al., 2021), low frequencies of these cells could explain drops in efficacy against the beta variant.

6. Conclusions

The underlying immunology of SARS-CoV-2 infections and COVID-19 has largely conformed to our prior understanding of basic immunology. This prior knowledge is directly responsible for the success of vaccines against SARS-CoV-2. Nonetheless, certain understudied concepts have come to the forefront that require more attention. The sheer magnitude of the pandemic affords the field of immunology the opportunity to better define the connections between innate immune evasion, disease severity, and adaptive immunity in the face of viral evolution. Such basic understanding will help prepare for and prevent future pandemics.

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