REVIEW

Insights into the immune responses of SARS-CoV-2 in relation to COVID-19 vaccines

Heedo Park[†], Mee Sook Park[†], Jong Hyeon Seok, Jaehwan You, Jineui Kim, Jeonghun Kim, and Man-Seong Park[*]

Department of Microbiology, Institute for Viral Diseases, Chung Mong-Koo Vaccine Innovation Center, College of Medicine, Korea University, Seoul 02841, Republic of Korea

The three types of approved coronavirus disease 2019 (COVID-19) vaccines that have been emergency-use listed (EUL) by the World Health Organization are mRNA vaccines, adenovirus-vectored vaccines, and inactivated vaccines. Canonical vaccine developments usually take years or decades to be completed to commercialization; however, the EUL vaccines being used in the current situation comprise several COVID-19 vaccine candidates applied in studies and clinical settings across the world. The extraordinary circumstances of the COVID-19 pandemic have necessitated the emergency authorization of these EUL vaccines, which have been rapidly developed. Although the benefits of the EUL vaccines outweigh their adverse effects, there have been reports of rare but fatal cases directly associated with COVID-19 vaccinations. Thus, a reassessment of the immunological rationale underlying EUL vaccines in relation to COVID-19 caused by SARS-COV-2 virus infection is now required. In this review, we discuss the manifestations of COVID-19, immunologically projected effects of EUL vaccines, reported immune responses, informed issues related to COVID-19 vaccination, and the potential strategies for future vaccine use against antigenic variants.

Keywords: COVID-19, SARS-CoV-2, immune response, mRNA-1273, BNT162b2, ChAdOx1 nCoV-19, Ad26.COV2.S, vaccine

Introduction

Coronavirus disease 2019 (COVID-19) was first observed in Wuhan, China in December 2019 as "pneumonia of un-

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[†]These authors contributed equally to this work.
[*]For correspondence. E-mail: ms0392@korea.ac.kr

known cause" (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline#event-0; last accessed on November 9, 2021). Very quickly, a COVID-19 pandemic began that has so far claimed more than four million lives globally and included more than 200 million confirmed cases of infection (https://covid19.who.int/; last accessed on November 9, 2021). As the pandemic has progressed, COVID-19 has been shown to be a multifaceted disease involving more than "pneumonia." When the sequence of the virus causing COVID-19 became available, a race for vaccine development began. The speed and cooperative nature of the vaccine development process have been extraordinary; accordingly, the vaccine rollout began in December 2020 (Golob *et al.*, 2021). However, since vaccine development occurred very rapidly, the complete characteristics of SARS-CoV-2 infection and COVID-19 manifestations have not been reflected in the development process; moreover, the appearance of virus variants has not been considered. Indeed, the vaccines have been developed based on the reference sequence of the first isolate submitted directly to NCBI on January 5, 2020 (https://www.ncbi.nlm.nih.gov/nuccore/NC_045512; last accessed on November 9, 2021) and subsequently published with phylogenetic characterizations (Wu *et al.*, 2020); however, the virus infection characteristics have barely been revealed (Folegatti *et al.*, 2020; Mulligan *et al.*, 2020; Sadoff *et al.*, 2021). Given the enormous effort of the developers, the vaccines approved by the United States Food and Drug Administration or World Health Organization (WHO) as emergency-use listed (EUL) vaccines appear to reduce the rate of fatality in countries in which a large proportion of the population has been vaccinated (https://covid19.who.int/region/amro/country/us; last accessed on November 9, 2021). Although several virus variants have appeared since the Wuhan strain (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/; last accessed on November 9, 2021), few of the vaccines have lost their efficacy to the level of uselessness (Alrubayyi and Peppa, 2021; Tarke *et al.*, 2021). Notably, vaccine shortages and vaccine avoidance have occurred together because infrequent but fatal adverse effects of the vaccines have been reported (Cines and Bussel, 2021). Thus, mitigating vaccine avoidance by providing a better understanding of the vaccine mechanisms may be as critical as mitigating vaccine shortages by scaling-up production.

Both mRNA vaccines and adenovirus-vectored vaccines have been under development for decades but have never been approved for use before this pandemic (Heinz and Stiasny, 2021). However, the pandemic became a stage on which these ex-

perimental vaccine technologies could demonstrate their efficacy. In this review, we attempt to provide a better understanding of the workings of the EUL vaccines from an immunological perspective and we speculate on the causes of the manifested problems of these vaccines (Cines and Bussel, 2021; Kantarcioglu *et al.*, 2021; MacNeil *et al.*, 2021; Østergaard *et al.*, 2021; Pottegård *et al.*, 2021; Shay *et al.*, 2021). We achieve this by reviewing the current knowledge of COVID-19, SARS-CoV-2 infection characteristics, immune responses to the infection, and immune mechanisms of the EUL COVID-19 vaccines.

SARS-CoV-2 and COVID-19

The COVID-19 causative virus was initially named 2019-nCoV. Phylogenetically, the new coronavirus formed a clade within the subgenus *Sarbecovirus* of the genus *Betacoronavirus* from the subfamily *Orthocoronavirinae* of the family *Coronaviridae* (Lu *et al.*, 2020; Wu *et al.*, 2020; Zhu *et al.*, 2020). 2019-nCoV was recognized as forming a sister clade of SARS-CoV isolates in the phylogenetic relationship; thus, it was formally named SARS-CoV-2 by the Coronaviridae Study Group of the International Committee on Taxonomy of Viruses (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020).

Coronaviruses have a positive-sense RNA genome that is 26–32 kb in size. The coronavirus genome functions as an mRNA and has a standard eukaryotic 5′-cap structure and a 3′ polyadenylate tail. The translated genome produces an RNA-dependent RNA polymerase protein and other proteins involved in viral replication. During replication, full-length genomic transcripts and several nested subgenomic transcripts are generated in membranous compartments of double-membrane vesicles, i.e., away from the double-strand RNA detection conducted by the innate antiviral defense mechanism. Canonically, four major structural proteins of coronaviruses, namely the spike (S), membrane (M), and envelope (E) proteins in the viral membrane envelope and the nucleocapsid (N) protein in the ribonucleoprotein core, are translated from the individual subgenomic transcripts. The M protein is the most abundant structural protein in coronaviruses. The transmembrane proteins of the E, M, and S are initially inserted into the endoplasmic reticulum (ER) and then transit to the ER-Golgi intermediate compartment (ERGIC) for assembly. In the ERGIC, the progeny viral genomes in complex with the N proteins coalesce with the envelope components and bud. The progeny virions are released from the infected cells by exocytosis. Coexpression of the E and M proteins is essential for the virus-like particle formation that is necessary for virion assembly. The S protein is gathered into the virion but is not required for virion assembly; it is an entry attachment and membrane fusion protein, and the membrane fusion function is activated by S1-S2 cleavage in the protein. A fraction of S proteins not assembled into virions transit to the plasma membrane in some coronavirus infections, which results in syncytia formation around the infected cells. This overview is paraphrased excerpts from a virology textbook written by Masters and Perlman (2013).

Soon after the sequence of 2019-nCoV was released, comparative analyses of the structural data from the S protein of SARS-CoV and the S sequence of 2019-nCoV predicted the use of the host cell membrane protein, angiotensin converting enzyme 2 (ACE2), as an entry receptor, similar to that in SARS-CoV (Li *et al.*, 2003; Wan *et al.*, 2020a). It is well established that SARS-CoV-2 uses ACE2 as a receptor and that transmembrane protease serine subtype 2 (TMPRSS2) is the significant activating protease. It has a similar spectrum of cells as that of SARS-CoV (Hoffmann *et al.*, 2020). However, SARS-CoV-2 binds to ACE2 better than SARS-CoV can bind to this protein (Shang *et al.*, 2020), which explains why SARS-CoV-2 has become more widespread than SARS-CoV and suggests that the appearance of variants better adapted for transmission among humans through interaction with ACE2 is to be anticipated (Tegally *et al.*, 2021).

The type and location of ACE2- and TMPRSS2-expressing cells in the human body are critically associated with SARS-CoV-2 transmission and COVID-19 pathology. ACE2 and TMPRSS2 expression sites relevant to transmission and pneumonia are related to nasal epithelial cells and pneumocytes in the lungs, respectively (Sungnak *et al.*, 2020). However, ACE2 is abundantly expressed in endothelial cells and smooth muscle cells "in virtually all organs," although it is not expressed in immune cells (Hamming *et al.*, 2004). SARS-CoV-2 can also infect cells that do not express TMPRSS2, which occurs through the endosomal pathway. The endosomal cysteine proteases cathepsin B and L can cleave the S protein to S1 and S2 for the S protein activation required for fusion (Hoffmann *et al.*, 2020). Although conflicting reports exist on ACE2 expression in endothelial cells (Hamming *et al.*, 2004; Hoffmann *et al.*, 2020), SARS-CoV-2 infection in endothelial cells has been reported (Varga *et al.*, 2020; Wong *et al.*, 2021). Vascular endothelial cell infection with SARS-CoV-2 appears to be important for COVID-19 manifestation beyond respiratory symptoms and pneumonia.

Clinical phenotyping of COVID-19 into three stages has been proposed by (Siddiqi and Mehra, 2020). Stage 1 is graded as "mild" with symptoms early in infection often involving nonspecific malaise, fever, and a dry cough. Patients with a viral infection limited to Stage 1 would likely recover well. Stage 2 is graded as "moderate" with pulmonary involvement; it leads to viral pneumonia accompanied by a cough, fever, and possibly hypoxia. At Stage 2, pulmonary disease is established along with viral multiplication and localized inflammation in the lungs. Stage 3 is graded as "severe" with extrapulmonary systemic hyperinflammation in which inflammatory cytokines and biomarkers are elevated and shock, vasoplegia, respiratory failure, cardiopulmonary collapse, and myocarditis might manifest in Stage 3. Moreover, this stage can end in multiorgan dysfunction.

From postmortem cases of COVID-19, a few signs of extrapulmonary infection were reported with thrombotic features in at least one major organ in all complete autopsies (Hanley *et al.*, 2020). Plasma viremia of SARS-CoV-2 associated with severe disease represents a possible link to extrapulmonary multiorgan involvement (Li *et al.*, 2021b). In severe COVID-19, cardiovascular complications, microvascular and macrovascular thrombosis, thromboembolism, and severe endothelial injury have been observed (Ackermann *et al.*, 2020; Al-Samkari *et al.*, 2020; Oxley *et al.*, 2020; Varga

et al., 2020; Bellmunt-Montoya *et al.*, 2021). Vascular disease and thrombosis in COVID-19 have been shown to be re-capitulated in SARS-CoV-2 infected rhesus macaques (Aid *et al.*, 2020). COVID-19-associated endothelialitis resembles syndromes characterized by disruption of endothelial homeo-stasis and it results in dysregulation of coagulation, vascular tone, endothelial permeability, and vascular inflammation (Calabretta *et al.*, 2021). COVID-19-associated coagulopathy also appears as an endotheliopathy from endothelial cell in-fection of SARS-CoV-2 (Goshua *et al.*, 2020; O'Sullivan *et al.*, 2020; Leentjens *et al.*, 2021). The breadth and the extra-pulmonary manifestations of COVID-19 due to endothelial cell infection are implied by other endothelial cell-infecting viruses such as hantaviruses (Sahni, 2007; Noack *et al.*, 2020; Bae *et al.*, 2021). For instance, the thromboembolic compli-cations observed in COVID-19 patients have also been ob-served in hantavirus-infected cases (Connolly-Andersen *et al.*, 2015; Schmedes *et al.*, 2020). Although cases of blood donors later testing positive for COVID-19 have been re-ported, SARS-CoV-2 transmission from blood transfusion has not been reported (Leblanc *et al.*, 2020). This suggests that endothelial cell infection does not likely occur during the asymptomatic phase, which is consistent with coagulop-athy presumed to be due to endothelial cell infection asso-ciated with higher disease severity (Leentjens *et al.*, 2021).

Immune Responses against SARS-CoV-2

Although there is an ongoing battle against the causative disease of COVID-19, immune responses against SARS-CoV-2 have yet to be profiled sufficiently. In 2003, another type of coronavirus, namely SARS-CoV, emerged that infects the same types of cells as those infected by SARS-CoV-2. Thus, understanding SARS-CoV immunity could be an alterna-tive solution to understanding SARS-CoV-2 immunity. Studies performed using SARS-recovered individuals after 12–23 months (Yang *et al.*, 2007), at 6 years post-infection (Oh *et al.*, 2011), and at 9–11 years post-infection (Ng *et al.*, 2016) reported that SARS-CoV-specific memory CD4$^+$ and CD8$^+$ T cells persisted for up to 11 years post-infection, where CD4$^+$ T cells were prodominantly IFNγ-expressing T helper 1 (Th1) cells. To activate the most effective SARS-CoV-spe-cific CD8$^+$ T-cell response and memory, an association with the SARS-CoV CD4$^+$ T-cell response of Th1 activation in the first immune defense process would have been necessary (Medema *et al.*, 2001; Ronchese and Hermans, 2001). Inter-estingly, anti-SARS-CoV IgG antibody titers have been shown to decline over time to a baseline from before five years post-infection; indeed, the SARS-CoV-specific B-cell memory re-sponse was not detectable at six years post-infection (Tang *et al.*, 2011). It has also been shown that the T-cell responses of individuals who have recovered from SARS-CoV are highly cross-reactive to SARS-CoV-2 peptides and SARS-CoV-2 reactive T cells were found in people not exposed to SARS-CoV-2. This most likely arises due to previous infection with human "common cold" coronaviruses (Braun *et al.*, 2020; Le Bert *et al.*, 2020; Mateus *et al.*, 2020).

One study suggested that preexisting SARS-CoV-2 cross-reactive immunity from exposure to "common cold" corona-

viruses affects the course of COVID-19 (Lipsitch *et al.*, 2020). In another study, among the individuals who took PCR tests for endemic "common cold" coronaviruses (eCoV) within the past five years before the start of the COVID-19 pandemic, eCoV$^+$ (positive) individuals had milder COVID-19 symptoms than those of eCoV$^-$ (negative) patients in terms of ICU ad-mission, mechanical ventilation, and eventual death (eCoV$^+$ 4.8% versus eCoV$^-$ 17.7% of the hospitalized patients) under a similar level of preexisting morbidity (Sagar *et al.*, 2021). The preexisting cross-reactive immunity from eCoV infec-tion appears to be insufficient to block SARS-CoV-2 infection but nevertheless supports the fight against the disease.

Determining relationships between disease severity and im-mune responses allows us to understand which types of im-mune response could be protective and which are pathologic. Autopsies of fatal cases of COVID-19 have revealed deple-tion of CD8$^+$ T cells (Hanley *et al.*, 2020). Interestingly, spe-cific antibody responses in SARS-CoV-2 were shown to be more robust in patients with moderate/severe symptoms or those that were hospitalized compared with in patients ex-hibiting mild symptoms or those that were not hospitalized (Dan *et al.*, 2021; Tan *et al.*, 2021), and a higher level of nAb (neutralizing antibody) with higher disease severity was also observed with SARS-CoV infection (Li *et al.*, 2008). Contras-tingly, SARS-CoV-2-specific CD4$^+$ and CD8$^+$ T-cell memory responses tended to be lower in hospitalized patients com-pared with in unhospitalized individuals (Dan *et al.*, 2021). The presence of SARS-CoV-2-specific CD4$^+$ and CD8$^+$ T-cell responses in the acute phase has been significantly asso-ciated with mild disease, whereas the presence of nAb was not associated in this manner (Rydyznski Moderbacher *et al.*, 2020). SARS-CoV-2-specific CD4$^+$ T cells in the acute phase of COVID-19 primarily consist of follicular helper T cells and IFNγ-producing Th1 cells (O'Shea and Paul, 2010; Liao *et al.*, 2013; Li *et al.*, 2014); SARS-CoV-2-specific IFNγ$^+$ CD8$^+$ T cells have been detected as early as four days post-symptom onset (PSO) and are predominantly granzyme-ex-pressing cells (Rydyznski Moderbacher *et al.*, 2020). A higher frequency of IFNγ-secreting cells was present in both the early (days 1–15 PSO) and late (days 15–30 PSO) stages of mild COVID-19 cases but not in moderate/severe cases (Tan *et al.*, 2021). Notably, a fatal case was reported with nAb but without detectable SARS-CoV-2-specific CD4$^+$ and CD8$^+$ T-cell responses. In addition, a case was resolved without hospitalization and detectable nAb but with SARS-CoV-2-specific CD4$^+$ and CD8$^+$ T-cell responses (Rydyznski Moder-bacher *et al.*, 2020). All accounts suggest that the ability of T cell-mediated immunity to control infection in the acute phase is critically correlated with mild COVID-19 cases.

Serum antibody testing in patients that have fully recovered after a mild illness from SARS-CoV-2 infection have shown that most patients had confirmed COVID-19 seroconverted with IgG antibodies developing slowly over 7–50 days (median 24 days) PSO and 5–49 days (median 15 days) from symptom resolution; a positive antibody response to SARS-CoV-2 in-creased from 28% of patients within two weeks of symptom resolution to 94% within four weeks, and symptom duration was associated with higher antibody titers (Wajnberg *et al.*, 2020b). Although robust nAb responses to SARS-CoV-2 in-fection stable for at least five months have been reported

(Wajnberg *et al.*, 2020a), the role played by nAb in symptom resolution has yet to be confirmed. A clinical trial involving the nAb cocktail REGN-COV2, which included 1,000-fold titers relative to those achievable in convalescent plasma, showed a dramatic reduction in viral titers from baseline serum antibody-negative COVID-19 patients with a high baseline viral load at the beginning of the trial. However, the time required to alleviate symptoms was not strongly associated with treatment (Weinreich *et al.*, 2021). This finding is consistent with earlier observations of symptom resolution preceding antibody-positive responses in those patients that have recovered from mild illness (Wajnberg *et al.*, 2020b). Antibody-mediated pathogen clearance through the complement pathway could be a double-edged sword because of the accompanying adverse inflammatory cytokine responses. Therefore, determining whether there is a consistent association between high levels of nAb and severe COVID-19 in relation to the complement pathway might be therapeutically important (Santiesteban-Lores *et al.*, 2021).

Unlike with other viruses, such as the influenza virus that have infected humans for many years, the protective ability of nAb titers against SARS-CoV-2 has yet to be established (Krammer, 2020, 2021). However, it should not be considered possible for COVID-19 convalescents that possess nAb to become reinfected with the same strain of SARS-CoV-2 and develop COVID-19 again (Baumgarth *et al.*, 2020). However, those naturally infected with SARS-CoV-2 might become reinfected. Although reinfections appear mostly asymptomatic (Lumley *et al.*, 2021), more severe disease after reinfection cannot be ruled out. Drastic reduction of viral titer after nAb treatment as mentioned above suggests protective role of nAb, if present in enough concentration, against infection.

Immune Responses to COVID-19 Vaccines

The WHO EUL COVID-19 vaccines (https://extranet.who.int/pqweb/vaccines/covid-19-vaccines; last accessed on November 9, 2021) are classified into three types: mRNA, adenovirus-vectored, and inactivated-virus vaccines. In comparison to these vaccines, inactivated-virus vaccines (IVVs) use an established technology and have been used against many viruses including influenza viruses, hepatitis A virus, and poliovirus. Indeed, mRNA and adenovirus-vectored vaccines are newly approved technologies (Angeli *et al.*, 2021; Gebre *et al.*, 2021). Two EUL IVVs were derived from SARS-CoV-2 strains isolated in China (Wang *et al.*, 2020); these were developed by Sinopharm and Sinovac. Replication-incompetent adenovirus-vectored vaccines, ChAdOx1 nCoV-19 and Ad26.COV2.S, were developed by AstraZeneca and Janssen Pharmaceutical Company of Johnson & Johnson, respectively, and the BNT162b2 mRNA vaccine was developed by Pfizer/BioNTech using codon optimization of the full-length S amino acid sequence based on the genome sequence of the first isolate of the SARS-CoV-2 virus from Wuhan with two amino acids substitutions, K986P and V987P, in the S2 domain for stabilization of prefusion conformation (Folegatti *et al.*, 2020; Jackson *et al.*, 2020; Mulligan *et al.*, 2020; Walsh *et al.*, 2020; Wu *et al.*, 2020; Sadoff *et al.*, 2021). The mRNA-1273 vaccine by Moderna was also developed using a full-length SARS-CoV-2 sequence, most likely from the earliest isolates with two amino acids substitutions, as with the BNT162b2 mRNA vaccine. Except for the IVVs, all EUL vaccines express the full-length S protein of SARS-CoV-2 on the membrane of the cell that takes up the mRNA-lipid nanoparticle (mRNA-LNP) or is infected with the adenovirus vector. Phase I/II clinical trial assessments of the immune responses of the EUL vaccines are summarized in Table 1.

COVID-19 vaccine design was likely to have been based on

Table 1. Phase I/II clinical trial assessments of immune responses related to EUL vaccines

Vaccine (Reference)	Administration	Antibody response	T-cell response
mRNA-1273 of Moderna (Jackson *et al.,* 2020)	Membrane S protein-encoding mRNA-LNP, 100 µg/dose 2 doses 28 days apart	nAb after first dose: low response nAb after second dose: mean ID_{50} titer higher than that of HCS at 7 days post second dose	Strong Th1 skewed $CD4^+$ and low $CD8^+$ T-cell responses against S protein at 14 days post second dose
BNT162b2 of Pfizer/BioNTech (Walsh *et al.,* 2020)	Membrane S protein-encoding mRNA-LNP, 30 µg/dose 2 doses 21 days apart	nAb after first dose: low response nAb after second dose: IC_{50} GMT 1.5-3.6-fold of HCS at 7 days post second dose	Not measured
ChAdOx1 nCoV-19 of AstraZeneca (Folegatti *et al.*, 2020)	Membrane S protein-encoding ChAdOx1 vector, 5×10^{10} VP/dose 2 doses 28 days apart	nAb after first dose: 91% seroconversion ($PHE\ MNA_{80}$ median titer 51, 32-103) at day 28 nAb after second dose: 100% seroconversion ($PHE\ MNA_{80}$ median titer 136, 115-241) after second dose IC_{50} titers similar with HCS	IFNγ ELISpot response against S protein ($CD4^+$ or $CD8^+$ T cell not known) at day 7, peak at day 14 (median 1642, 1423-2009; baseline 108, 90-150); no change after second dose.
Ad26.COV2.S of Janssen (Sadoff *et al.,* 2021)	Membrane S protein-encoding Ad26 vector, > 8.92 log_{10} IU (5×10^{10} VP)/dose a single dose	nAb after first dose: 99% seroconversion (IC_{50} GMT 224, 168–298) at day 29. 100% (310, 228–422) at day 57. HCS GMT 522 nAb after second dose: no second dose	IFNγ expressing S peptide specific $CD4^+$ and $CD8^+$ T cells in 76% and 51%, respectively at day 15
CoronaVac of Sinovac (Zhang *et al.,* 2021)	Inactivated SARS-CoV-2 antigen, 600 SU (3 µg)/dose 2 doses 28 days apart.	nAb after first dose: 97% seroconversion at day 28 (no GMT data, no GMT basis) nAb after second dose: 97% seroconversion (GMT 44.1) at 28 days post second dose HCS GMT 163.7	T-cell responses measured using IFNγ ELISpot were low ($CD4^+$ or $CD8^+$ T cell not known)

studies of antigenicity in immune responses against SARS-CoV (Li *et al.*, 2008; Du *et al.*, 2009). A study by Li *et al.* (2008) in which the T-cell responses of SARS convalescents were analyzed for antigen specificity appears especially relevant. It showed that the S protein of SARS-CoV was significant for B- and T-cell antigens; CD4^{+} T-cell responses were mainly against the S protein, whereas CD8^{+} T-cell responses were across the SARS-CoV proteome, although the proportion of S proteins recognizing CD8^{+} T cells was still relatively high. This study suggests that the dominant antigen S protein alone could potentially produce nAb response, CD4^{+} and CD8^{+} T cell responses almost identical to the immune responses to SARS-CoV infection. In an animal experiment, it was shown that a DNA vaccine encoding the full-length S protein of SARS-CoV could induce both T-cell and nAb responses and thereby provide protective immunity (Du *et al.*, 2009). The mRNA and adenoviral-vectored vaccines encoding the full-length S protein of SARS-CoV-2 appear to have been designed for similar nAb and T-cell responses.

Cellular antigens directly presented on major histocompatibility complex (MHC) type I (MHC I) from *de novo* synthesis are cytosolic proteins as well as the signal peptides of the secreted and membrane proteins rather than the secreted proteins and membrane proteins themselves (Del Val *et al.*, 2020). Therefore, the membrane S protein of SARS-CoV must be cross-presented on MHC I of dendritic cells (DCs) by a phagosome and a toll-like receptor (TLR) signal-mediated pathway (Nair-Gupta *et al.*, 2014; Sengupta *et al.*, 2019; Colbert *et al.*, 2020). Antigen-presenting cells (APCs) do not express ACE2; moreover, SARS-CoV-2 infection to DCs using any other receptor than ACE2 has not been established (Campana *et al.*, 2020). Antibody-dependent enhancement (ADE) of the infection mechanism could be a substitute for the requirement of ACE2 in DC infection. There have been reports of no detection of ADE of SARS-CoV-2 infection (Kim *et al.*, 2021; Zheng *et al.*, 2021). On the other hand, detection of ADE of SARS-CoV-2 infection *in vitro* but no enhancement of disease *in vivo* has been reported (Li *et al.*, 2021a). Since the ADE of SARS-CoV and Middle East respiratory syndrome coronavirus infection and S protein-containing pseudovirus infections to Fc receptor (FcR)-expressing cells have been observed in terms of *de novo* viral protein synthesis (Jaume *et al.*, 2011; Wan *et al.*, 2020b), further studies on ADE of SARS-CoV-2 infection according to *de novo* viral protein synthesis rather than progeny virion production remain necessary.

Here, we consider whether the presence of S protein-responsive CD8^{+} T cells could be useful as cytotoxic T lymphocytes (CTLs) for clearing SARS-CoV- or SARS-CoV-2-infected cells. As discussed earlier, *de novo* synthesized S protein, which is a transmembrane protein, might not be presented on MHC I of the infected cell; thus, the infected cell might not be a target of S protein-specific CD8^{+} CTLs. It appears that CD8^{+} T-cell responses against cytosol-expressed proteins, such as the N protein and nonstructural proteins, could play a more critical role in clearing the infected cells. The presence of CD8^{+} T-cell responses against the whole proteome of SARS-CoV in SARS convalescents (Li *et al.*, 2008) appears to be a more logical outcome.

One question remains: where did the MHC I antigen come from in the SARS convalescent cases? Cross-presentation of
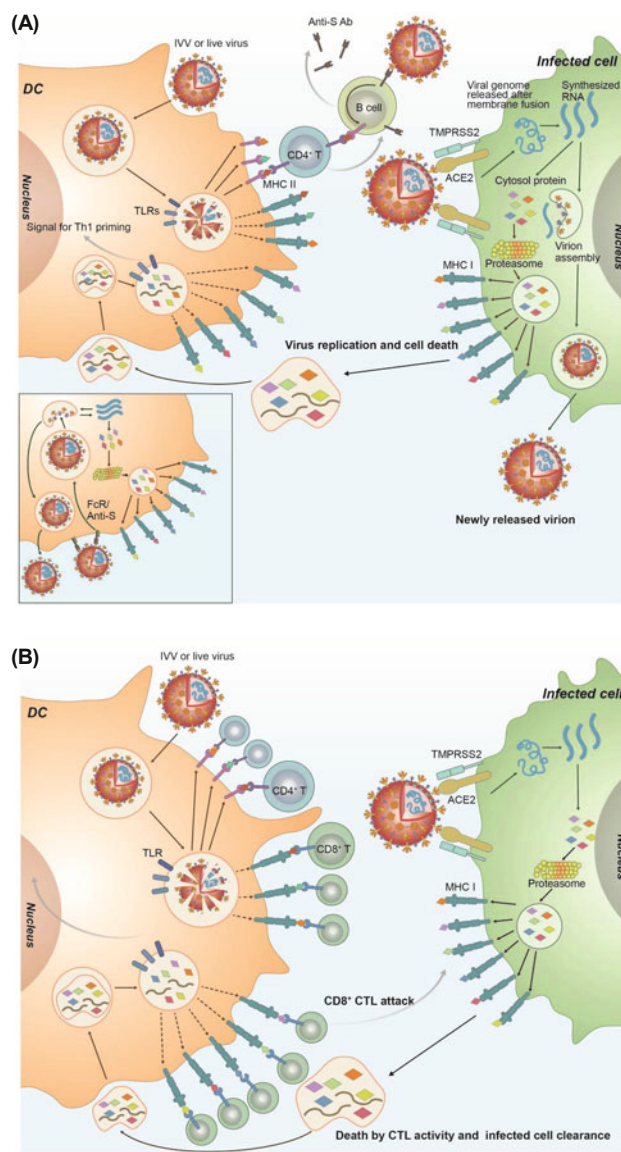

Fig. 1. Conceptualization of immune responses against SARS-CoV or SARS-CoV-2. (A) Acute phase of SARS-CoV or SARS-CoV-2 infection. Since SARS-CoV or SARS-CoV-2 does not infect antigen-presenting cells, the virion particles and dead cell fragments generated by the infected cells might be the source of antigens for presentation on major histocompatibility complex (MHC) II and cross-presentation on MHC I of dendritic cells (DCs). The virion particles may be taken up by the dominant antigen S protein-specific B cells and the structural proteins will be presented on MHC II of B cells, which will secure the help of structural protein-specific CD4^{+} T cells (only S protein-specific CD4^{+} T cell help is depicted for simplicity). Although the MHC I antigen source may be largely cross-presentation of the infected cell fragments, non-nAb capacity antibodies might be utilized for antibody-dependent enhancement of DC infection, providing MHC I with *de novo* synthesized cytosolic antigens (shown in boxed section). EUL inactivated-virus vaccines might be similar to the live virus for MHC II antigen presentation except for the limited duration of the antigens, but they are essentially different in relation to the MHC I antigen because of the lack of dead cell fragments. (B) Infection clearance of SARS-CoV or SARS-CoV-2 infection. CD8^{+} CTLs generated through the process depicted in (A) might clear the infected cells before releasing virion progeny from the infected cells. Pathways leading to the lysosome and antigen presentation on MHC I and MHC II are indicated by arrows. TLR signal-mediated antigen cross-presentation to MHC I is indicated by dotted arrows. Expression of antigens from dead infected cell fragments on MHC II of DC is omitted for simplicity. Molecules and cells are not drawn to scale.

the proteins from the uptaken virion would have activated CD8^{+} T cells specific to only the structural proteins, such as the S, M, and N proteins (not enough of the E protein is present), and only N protein-specific CD8^{+} CTLs would have been effective at clearing the infected cells by recognizing cytosol-expressed N proteins presented on MHC I of the infected cells. The diversity of CD8^{+} T-cell responses in the SARS convalescents most likely originated from the cross-presentation of dead infected and dead cell fragments containing diverse cytosol-expressed SARS-CoV antigens (Fig. 1A). Indeed, a high frequency of IFNγ-expressing T cells specific to *de novo* expressed viral proteins, such as ORF7 and ORF8 proteins of SARS-CoV-2 in the acute phase, was associated with mild COVID-19, whereas low T-cell responses with specificity predominantly related to the structural proteins was associated with severe COVID-19 (Tan *et al.*, 2021). Another plausible mechanism of cytosol-expressed SARS-CoV antigen presentation on MHC I of DC was ADE of DC infection by SARS-CoV, which could have occurred at a certain point over the course of infection when the S protein-specific antibody concentration was ideal for ADE of SARS-CoV infection (Fig. 1A). It is plausible that lower nAb titers consistently observed in unhospitalized mild COVID-19 patients relative to those observed in hospitalized patients might have been due to the antibody level being optimal for ADE of DCs and diverse cytosol-expressed SARS-CoV-2 protein-specific CD8^{+} CTL generation. Clearance of infected cells could eventually result in depletion of the antigen source, which would slow down further nAb responses. Although the CD8^{+} T cells responding against the membrane proteins, such as the S and M proteins, might not be effective for clearing infected cells, they would participate in skewing CD4^{+} T-cell responses to Th1 types by secreting IFNγ (Gajewski and Fitch, 1988) (Fig. 1B). Indeed, generation of SARS-CoV S protein-specific CD8^{+} T-cell memory alone was found to be primarily, although not completely, protective in SARS-CoV-challenged mice (Channappanavar *et al.*, 2014); however, this study did not show whether the viral titer reduction in the challenged mice at seven days post-infection was directly caused by S protein-specific CD8^{+} CTL activity.

Intramuscular-injected antigens are expected to be taken up mainly by APCs at the vaccine injection site (Fig. 2A). The inactivated whole-virion, mRNA-LNP, and the adenoviral-vectored vaccines might be the preferred size for macropinocytosis- or phagocytosis- mediated uptake by APCs such as DCs, monocytes, and macrophages (Frenz *et al.*, 2015). The difference between inactivated whole-virion particles and mRNA-LNP or adenoviral-vectored vaccines is that the S protein cannot be presented as an antigen on DCs directly when using mRNA-LNPs or adenovirus vectors through the lysosomal pathway. mRNA-LNPs are designed for endosomal fusion of the LNP and delivery of mRNA to the cytosol (Buschmann *et al.*, 2021) leading to S protein expression as an antigen. However, adenovirus particles that are macropinocytosed or phagocytosed by APCs without specific receptor-mediated uptake might be destroyed in the lysosome and would therefore be unable to deliver S protein-encoding DNA to the nucleus, which in turn would lead to the lack of S protein expression as an antigen. In contrast, adenoviral vector proteins processed in the lysosome might be pre-
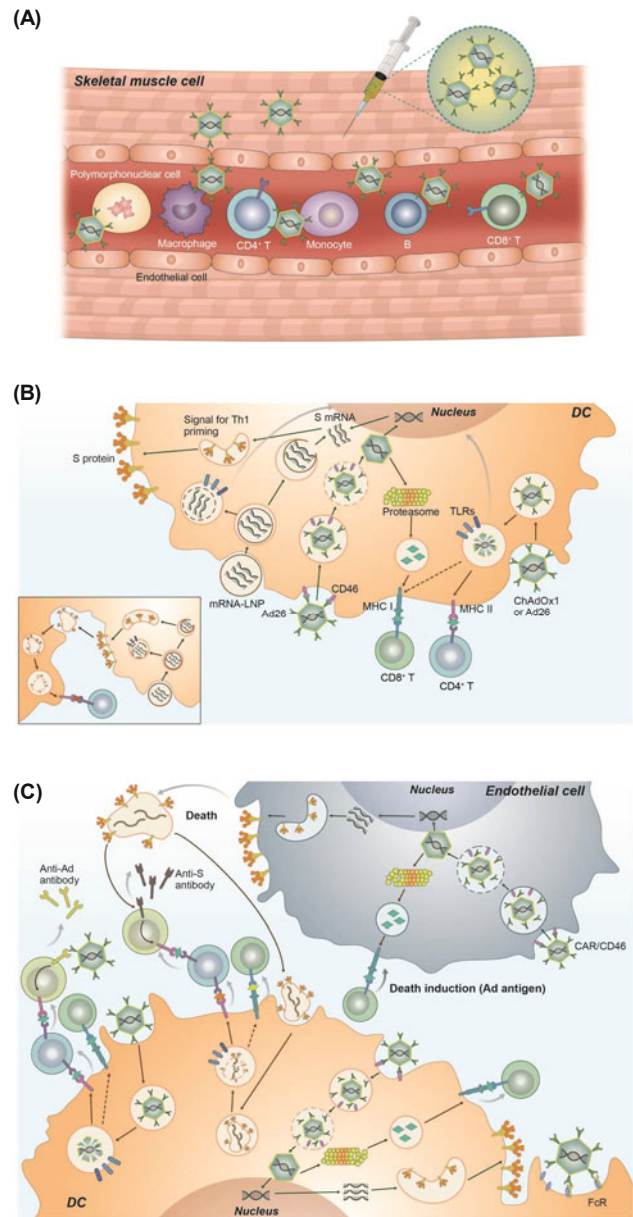

Fig. 2. **Conceptualization of antigen-presentation pathways in dendritic cells (DCs) via mRNA-LNP and adenovirus-vectored vaccines.** (A) An illustration of immune cells in the intramuscular injection site. Multinucleated skeletal muscle cells, DCs, and other innate and adaptive immune cells circulating in the muscle blood vessel lined with endothelial cells are depicted (Pillon *et al.*, 2013). Injury by injection recruit innate immune cells to the intramuscular site. (B) Antigen-presentation pathways to MHC I and MHC II in DCs and T-cell activation. Green arrows indicate signal pathways leading to the expression of the S protein on the cell membrane. Colored symbols, objects, and arrows are the same as those used in Fig. 1. The S protein expressed from mRNA-LNP or the adenovirus vector can be presented to MHC II only by uptake of membrane vesicles released by the DCs (shown in boxed section) or dead cell fragments. (C) Adenovirus-specific CD8^{+} CTLs activated as shown in (B) attack adenovirus vector-infected cells. The DCs can take up dead cell fragments for S protein antigen presentation on MHC II, S protein-specific CD4^{+} T-cell activation, subsequent S protein-specific B-cell activation, antibody production, and S protein antigen cross-presentation on MHC I. The ChAdOx1-vectored vaccine can mimic the Ad26-vectored vaccine after the second dose via the antibody-dependent enhancement of infection to DCs in the presence of anti-ChAdOx1 antibody (Valliyott *et al.*, 2020). Cells and molecules are not drawn to scale.

sented as antigens directly on APCs. Similar to IVVs, pathogen-induced innate immune signals used to prime APCs might come from the RNA and DNA of mRNA-LNPs and adenoviral particles that have failed to escape the endosome and have ended up in the late endosome/lysosome, respectively (Kawai and Akira, 2008; Farkas and Kemény, 2011; Leifer and Medvedev, 2016; Pardi *et al.*, 2018; Teijaro and Farber, 2021) (Fig. 2B).

Immune Responses to Inactivated SARS-CoV-2 Vaccine

Because SARS-CoV-2 does not infect DCs, inactivated SARS-CoV-2 vaccines can be considered similar to live SARS-CoV-2. However, SARS-CoV-2 IVVs and live SARS-CoV-2 are expected to induce different immune responses in terms of the magnitude of B- and CD4$^+$ T-cell activation and the diversity of CD8$^+$ T-cell responses. The source of SARS-CoV-2 antigens for presentation on MHC I and MHC II of DCs is direct virion particle uptake only with IVVs; however, dead infected cell fragments might also be available during natural infection (Fig. 1). Consistent with this notion, the nAb response against CoronaVac was much lower than that in human convalescent sera (Table 1). In terms of CD8$^+$ T-cell responses, only the structural S, M, and N proteins would be cross-presented on MHC I of DCs in IVV-vaccinated individuals, whereas diverse cytosol-expressed SARS-CoV-2 antigens from dead cell fragments might be cross-presented in those that were naturally infected (Fig. 1).

Furthermore, the presence and absence of persistent antigens in SARS-CoV-2 natural infection and IVV, respectively, would determine the degree of T-cell responses. The result of phase I/II clinical trials of CoronaVac have shown low IFNγ-expressing SARS-CoV-2-specific T-cell responses (Table 1) consistent with this notion. Such low IFNγ-expressing T-cell responses after vaccination with CoronaVac IVV suggest that a Th2-skewed T-cell response may have occurred. Higher Th2 responses were observed in fatal SARS and COVID-19 cases (Li *et al.*, 2008; Vaz de Paula *et al.*, 2020). A study using inactivated SARS-CoV vaccine showed the presence of Th2-type immunopathology after challenge with SARS-CoV in immunized mice (Tseng *et al.*, 2012). The possibility that a similar immunopathology would occur when an IVV-vaccinated individual becomes infected with SARS-CoV-2 is concerning.

Immune Responses to mRNA-LNP and Adenovirus-Vectored SARS-CoV-2 Vaccines

mRNA-LNPs do not require a receptor for internalization and delivery of mRNA to the cytosol (Hou *et al.*, 2021). However, the adenovirus that infects the target cell via a specific receptor can only deliver the antigen-encoding DNA to the nucleus. It is worthwhile to consider whether DCs express receptors for the adenovirus vectors. The adenovirus vectors of Janssen and AstraZeneca vaccines are human adenovirus serotype 26 (Ad26) and chimpanzee adenovirus-derived ChAdOx1, respectively (Folegatti *et al.*, 2020; Sadoff *et al.*,

2021). Ad26 utilizes CD46 as a primary receptor (Li *et al.*, 2012), whereas ChAdOx1, which is grouped similarly to human adenovirus serotype E (Morris *et al.*, 2016), uses the coxsackie adenovirus receptor (CAR) in the same manner as human adenovirus serotype E (Roelvink *et al.*, 1998). CD46 is expressed ubiquitously in human cells (Cardone *et al.*, 2011); in contrast, CAR is present in heart tissue, brain tissue, and epithelial and endothelial cells (Morris *et al.*, 2016), but it is not expressed sufficiently in DCs (Mizuguchi and Hayakawa, 2004). Mature skeletal muscle cells express CAR and CD46 at low levels and are poorly transduced by adenoviruses (Larochelle *et al.*, 2008). It is possible for Ad26 that utilizes CD46 to transduce DCs, endothelial cells, and many other types of cells. Given the universality of Ad26 receptor CD46 expression, the Ad26 target cell might be as universal as the mRNA-LNPs and furthermore take up Ad26 more readily than the mRNA-LNPs via receptor binding. However, endothelial cells are most likely cells to be transduced by ChAdOx1 that utilizes CAR at the site of the intramuscular injection or elsewhere.

Given the expression profile of the adenovirus receptor, the source of the S protein antigen generated by ChAdOx1 nCoV-19 vaccination appears to be dead cell fragments likely originating from infected endothelial cells (Fig. 2B and 2C). The sequence of events after the intramuscular injection of ChAdOx1 nCoV-19 is thought to be as follows: (i) an immune response to ChAdOx1, (ii) a ChAdOx1-specific CD8$^+$ CTL attack on ChAdOx1 nCoV-19-infected endothelial cells, (iii) uptake of the S protein-containing dead endothelial cell fragments and antigen presentation by APCs, and (iv) S protein-specific immune responses such as S protein-specific B-cell and CD4$^+$/CD8$^+$ T-cell responses. Although the early gene products of adenoviruses suppress MHC I antigen presentation in the infected cell resulting in CTL evasion (Wold and Ison, 2013), ChAdOx1 nCoV-19 is devoid of genes that express proteins with such functions (Almuqrin *et al.*, 2021). Therefore, exogenous adenovirus proteins might be presented on MHC I of the infected endothelial cells without suppression. The characterization of the adenovirus vector escaping the endosome through endosomal lysis (Masters and Perlman, 2013) provides processing of the adenoviral proteins that access the cytosol and proteasome for MHC I presentation during stage (ii) in the sequence described above. The sequence of events after the intramuscular injection of Ad26.COV2.S is likely to be similar to that for ChAdOx1 nCoV-19 in terms of CTL-mediated S protein cross-presentation on MHC I of DCs (Fig. 2C). The immune response to replication incompetent Ad26 has been shown to be Th1-skewed (Li *et al.*, 2012). Additionally, a clinical trial showed that vaccination with ChAdOx1 nCoV-19 induced a Th1-biased response (Folegatti *et al.*, 2020; Ewer *et al.*, 2021). The immune response to the ChAdOx1 vector itself would likely involve the Th1 type, as with Ad26. Overall, adenovirus-specific Th1 responses might help facilitate the generation of Th1-type T-cell responses against the S protein after ChAdOx1 nCoV-19 or Ad26.COV2.S vaccination (Folegatti *et al.*, 2020; Sadoff *et al.*, 2021).

mRNA-LNP and adenovirus-vectored vaccines are similar to live virus vaccines in terms of antigen persistence. Nonetheless, they are not specifically live virus vaccines without

direct presentation of the target antigen on MHC II of DCs. It is unclear how membrane-expressed S protein could be available as an antigen without CTL-involved dead cell fragment generation. DCs are known to release plasma membrane particles or vesicles (Théry *et al.*, 2009). An S protein-containing membrane vesicles (MVEs) released by S protein-expressing DCs is the most likely source of the S protein antigen presented on the MHC II of DCs (Fig. 2B). Immune responses from mRNA-LNP and Ad26- and ChAdOx1-vectored vaccines would depend on the abundance and duration of the S protein antigen source, which could include MVEs from DCs only, MVEs from DCs plus dead cell fragments, or dead cell fragments only (Fig. 2B and 2C).

Although the vaccines are expected to be largely taken up by APCs at the site of the injection, intramuscularly injected mRNA-LNP and adenovirus vector have been shown to spread systemically, with mRNA-LNP doing so to a greater degree than adenovirus vector, in mice (Pardi *et al.*, 2015; Liu *et al.*, 2017). For mRNA-LNPs, the expression of the encoded gene waned by day eight post-injection, with the most robust expression occurring during day 1 in the liver (Pardi *et al.*, 2015). In contrast, intramuscular injection of a replication-incompetent Ad5, which uses the same receptor as ChAdOx1, showed the highest expression of the encoded gene in mice at the injection site during day 1, and then several days of solid expression in the liver around days 6-9, followed by weak but persistent expression at the injection site even up to day 35 (Liu *et al.*, 2017). Intramuscularly injected ChAdOx1 and Ad26 might traffic in a similar manner and show similar encoded gene expression duration to that of Ad5. Prolonged expression of the encoded antigen in adenovirus-infected cells suggests that a potentially sustained release of the S protein-containing MVEs occurs from DCs infected with Ad26.COV2.S. Even in terms of the persistence of MVEs as the only source of the antigen, the immune response from Ad26.COV2.S vaccination is postulated to be stronger than that from mRNA-LNPs. For ChAdOx1 nCoV-19, despite the expression of the S protein in the infected cells potentially persisting, the availability of the S protein antigen as dead cell fragments is likely to be limited by the availability of ChAdOx1 antigen on MHC I of the infected cells as the specific CTL target (Fig. 2C).

Encoded S protein antigen presentation from mRNA-LNP vaccines involves two nonspecific steps: uptake of (a) the initial vaccine particle and (b) the membrane S protein containing fragment/vesicle. In contrast, step (b) is the only nonspecific step in the adenovirus-vectored vaccines. Consistently, the nAb responses of mRNA-LNPs after the first dose were relatively low compared to those of ChAdOx1 nCoV-19 after the first dose (Table 1). The "explosion" of nAb responses after the second dose of mRNA-LNPs might be due to enhanced uptake of the S protein-containing MVEs by the FcR-bearing DCs due to the assistance of low levels of S protein-specific antibodies generated from the first dose. The "explosion" of nAb responses in the heterologous vaccination of mRNA-LNPs after the first ChAdOx1 nCoV-19 dose compared with after two doses of the ChAdOx1 nCoV-19 vaccination (Schmidt *et al.*, 2021) might similarly be due to existing S protein-specific antibodies from the first dose of ChAdOx1 nCoV-19. The lack of such a dramatic enhancement of nAb response between first and second doses of ChAdOx1 nCoV-19 might

be due to high anti-vector antibody induced by the first dose (Stephenson *et al.*, 2021). Whether it occurs by vector antibody-FcR-mediated destruction of ChAdOx1 nCoV-19 particles or by ADE of DC infection (Fig. 2C), endothelial cell infection as the membrane S protein antigen source might be primarily averted with the second dose. Indeed, for Ad26.COV2.S vaccination, the second dose does not enhance the nAb response (Stephenson *et al.*, 2021).

Since MVEs from DCs are less likely to contain TLR ligands, the S protein in MVEs is not likely cross-presented efficiently on MHC I of DCs. After mRNA-1273 vaccination, the S protein-specific CD8$^+$ T-cell response has consistently been reported as low (Table 1). However, as discussed earlier, the S protein-specific CD8$^+$ CTL does not have an available target; thus, the effect of the inadequate CD8$^+$ T-cell response is likely to be relatively small. Indeed, robust IFNγ$^+$ Th1 CD4$^+$ T-cell responses would compensate, functionally, for low levels of CD8$^+$ T cells as the source of IFNγ, as was observed with mRNA-1273 vaccination (Table 1).

Rare Recapitulation of COVID-19 in COVID-19 Vaccine Recipients

Given the collected evidence, we can rationally deduce that a stronger S protein-specific nAb response from the first dose of ChAdOx1 nCoV-19 should originate from more endothelial cell infections as the source of the S protein antigen containing membrane fragments. If endothelial cell infection and endotheliopathy are vital factors in the COVID-19 vasculopathy (Goshua *et al.*, 2020; O'Sullivan *et al.*, 2020; Varga *et al.*, 2020), we speculate about the reason for adverse effects. Because of the replication incompetency of the adenovirus vectors, the number of virus particles per target cell will be limited. Therefore, assuming the same amount of infectious vaccine (Table 1), endothelial cell infection caused by ChAdOx1 is predicted to be greater than that caused by Ad26 since infection with the latter would include distribution to many cell types other than endothelial cells.

Although high titers of autoantibodies against platelet factor-4 have been shown to be present and widespread in vaccine-induced thrombotic thrombocytopenia (VITT) (Greinacher *et al.*, 2021; McGonagle *et al.*, 2021), the mechanism underlying the occurrence of VITT is unclear. In a few VITT cases, cerebral venous sinus thrombosis (CVST) in the portal, splanchnic or hepatic veins, deep venous thrombi, pulmonary emboli, and acute arterial thromboses were reported (Cines and Bussel, 2021). Interestingly, thromboses are relatively common among severe COVID-19 patients (Fraiman *et al.*, 2020; Favaloro *et al.*, 2021); thus, VITT could be considered a rare recapitulation of severe COVID-19.

The European Medicines Agency reported possible VITT cases, including at least 169 possible cases of CVST and 53 potential cases of splanchnic vein thrombosis, among 34 million recipients of the ChAdOx1 nCoV-19 vaccine. Additionally, 35 probable cases of central nervous system thrombosis were found among 54 million recipients of the Pfizer/BioNTech mRNA vaccine, 5 possible cases of CVST were reported among 4 million recipients of the Moderna mRNA vaccine, and 6 possible cases of CVST were recognized among more than

7 million recipients of the Ad26.COV2.S vaccine. The incidence of CVST in the general population is estimated at 0.22 to 1.57 cases per 100,000 people per year (Cines and Bussel, 2021). Thus, the number of cases of CVST among vaccinated individuals is not higher than the estimated incidences in the general population per year, with the possible exception of those vaccinated with ChAdOx1 nCoV-19 for which incidences are higher than the lower estimate and lower than the higher estimate of incidences in the general population per year. However, the number of individuals vaccinated with Ad26.COV2.S is low compared with those vaccinated with ChAdOx1 nCoV-19 and comparisons between these two vaccines must be made with caution. Nevertheless, it appears that the rate of CVST incidences among ChAdOx1 nCoV-19-vaccinated patients is comparatively higher than in those vaccinated with Ad26.COV2.S. This seems to be consistent with our reasoning based on the distribution of the vaccine infection target cells. However, 202 possible cases of VITT in 34 million recipients of the ChAdOx1 nCoV-19 vaccine (about 6 cases per million) is a very small number compared with more than 4 million deaths from 200 million confirmed cases of COVID-19 (> 20,000 deaths per million infected).

Strategy to Cope with Further SARS-CoV-2 Variants of Concern

Earlier, we discussed how nAb levels might not be robustly correlated with immune protection. Conversely, the protective efficacy against "variants of concern" (VOCs) may not be significantly affected by nAb titer reduction. The current EUL vaccines based on very early isolates of SARS-CoV-2 are known to lack efficacy against the highly transmissible β and δ VOCs in terms of nAb response (Garcia-Beltran *et al.*, 2021; Wall *et al.*, 2021a, 2021b). However, S protein-specific CD4+ and CD8+ T-cell responses induced by the mRNA vaccine are reduced minimally against the S proteins from these VOCs (Alrubayyi and Peppa, 2021; Tarke *et al.*, 2021). We also previously mentioned that the S protein-specific CD8+ T cells generated by S protein-targeting vaccines might not effectively clear the infected cells. Because of reduced nAb activity and ineffective S protein-specific CD8+ CTL activity, breakthrough infections of the currently dominant SARS-CoV-2 δ VOC as well as emerging VOCs are highly likely in those who are already vaccinated. However, it is also possible that the S protein-specific memory CD4+ and CD8+ T-cell responses, which are barely reduced against VOC S proteins, would be rapidly deployed for Th1-type immune responses and could help facilitate VOC S protein-specific B-cell responses. The antibodies from the vaccination might not be as effective in terms of neutralizing the VOCs but they may participate in the ADE of DC infection with the VOCs for the efficient generation of CD8+ CTL against diverse cytosol-expressed VOC SARS-CoV-2 proteins and thereby help clear the infected cells (Fig. 1). Indeed, anti-S protein seropositive reinfected cases confirmed by PCR tests appear to be asymptomatic (Lumley *et al.*, 2021). DCs infected with SARS-CoV-2 by ADE are presumably similar to FcR-bearing cells infected with SARS-CoV by ADE, which synthesize viral proteins without viral progeny production and therefore without the possibility of enhancing disease (Jaume *et al.*, 2011).

VOCs appear rapidly. Although some vaccines are still considered effective against such VOCs, these judgments have been based not on evidence from clinical trials but on laboratory data. Of course, conducting clinical trials to test for the efficacy of EUL vaccines against continuously appearing VOCs is impracticable. Under these circumstances, a full review on the effectiveness of emergency authorized vaccines and affirmation of the authorization of the effective vaccine platform followed by the encoded antigen replacement might be a more practical strategy. The example of the 2009 H1N1 influenza pandemic vaccine approval without clinical studies under the condition that the new monovalent vaccine follows the protocol previously established for seasonal vaccine production (https://www.fda.gov/vaccines-blood-biologics/vaccines/influenza-h1n1-2009-monovalent-vaccines-questions-and-answers; last accessed on November 9, 2021) might be applied for the modification of fully authorized vaccines to substitute only the S sequence for the variant S sequence.

Conclusion and Perspective

By conducting immunological analysis of the working mechanisms of EUL vaccines, we can determine the possible causes of issues related to the vaccinations and ascertain why the adenovirus-vectored vaccines are potentially more problematic than the mRNA-LNP vaccines (dependent on the administered dose). Clinical trials for optimally reducing the number of vaccine adenovirus particles in one dose would be beneficial, especially in relation to the ChAdOx1 nCoV-19 vaccine. It is also reasonable to suggest that, despite breakthrough infection of a VOC being possible after vaccination in terms of nAb response, the functioning T-cell responses would enable those infected to recover rapidly similar to in asymptomatic or mild cases of naïve infection. Because the T-cell responses appear to be more critical than the nAb responses against SARS-CoV-2, VOCs might result from the virus adapting to its human host and thereby producing enhanced replication and transmission competence with coincidental nAb evasion. It might still be possible to eradicate SARS-CoV-2 using global vaccination efforts and necessary social distancing; however, the question remains: can our vaccination drive be sufficiently rapid and globally conducted?

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Conflict of Interest

The authors declare no competing interests.

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