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The lymphatic system and COVID-19 vaccines

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Understanding the precise mechanism of vaccine-induced protection and the immune correlates of protection against coronavirus disease 2019 (COVID-19) is crucially important for developing next-generation vaccines that confer durable and protective immunity against COVID-19. Similar factors are also important for other infectious diseases. Here, I briefly summarize the mechanism of action of the currently used COVID-19 mRNA vaccines from the viewpoint of the function of the lymphatic system.

KEYWORDS

COVID-19, lymphatics, lymph node, mRNA vaccines, SARS-CoV-2

COVID-19 and its vaccines

Coronavirus disease 2019 (COVID-19) emerged suddenly in December 2019 in Wuhan, China. It is caused by a novel single-stranded RNA virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1, 2). To date, this virus has infected almost 600 million people, which has resulted in more than 6 million deaths globally, as of the end of August 2022 (3).

COVID-19 spreads from person to person mainly *via* the respiratory route, specifically through airborne macro- and micro-droplets (or aerosols) emitted by virus carriers. Two types of cell surface proteins are involved in the SARS-CoV-2 infection of human cells. One is angiotensin-converting enzyme (ACE2), to which the viral spike (S) protein of SARS-CoV-2 binds. It is expressed in varying degrees by a wide range of tissue types (4). The other cell surface protein is transmembrane serine protease 2 (TMPRSS2), which proteolytically cleaves the viral S protein, allowing the virus to enter and infect human cells (5). TMPRSS2 is also expressed by a number of cell types. Owing to the wide expression of both ACE2 and TMPRSS2, SARS-CoV-2 targets not only respiratory epithelial cells but also a variety of other cell types, including intestinal epithelial cells, blood vascular endothelial cells, adipocytes, cardiomyocytes, and neuronal cells, which enables this virus to enter and damage numerous tissues in the body. Such behavior is in marked contrast with that of other respiratory viruses, such as influenza virus, which target mainly the cells of the respiratory tract.

At present, the most effective prevention measure against COVID-19 is vaccination (6). Two different mRNA vaccines, namely the Pfizer (BNT162b2) vaccine and the Moderna (mRNA-1273) vaccine, are being widely used. A two-dose series of either of these mRNA vaccines has been shown to markedly reduce the risk of not only symptomatic infection but also hospitalization and mortality from COVID-19 (7, 8). Booster immunizations can further enhance the protection from the primary series vaccination that otherwise wanes over time (9–11).

These mRNA vaccines aim to induce immunity against the S protein of SARS-CoV-2. This protein consists of an apical S1 subunit, which contains an N-terminal domain (NTD) and a receptor-binding domain (RBD), and a membrane-proximal S2 subunit; the S1 subunit binds to the ACE2 on human cells, whereas the S2 subunit is responsible for the fusion of viral and cellular membranes (12). These subunits are functionally indispensable for viral binding to and entry into human cells, and correspondingly, antibodies and T cells generated against this protein have been shown to have the capacity to inhibit SARS-CoV-2 infection of human cells (13).

Several strategies have been adopted to increase the immunogenicity of the COVID-19 mRNA vaccines (14–16). First, all uridine residues in the S protein mRNA have been replaced with N1-methyl pseudouridine residues; this strategy helps the exogenous RNA to evade recognition by innate immunity receptors such as Toll-like receptors (TLRs) (17). Second, a 5'-cap structure, a polyadenosine (poly-A) tail, and untranslated regions (UTRs) have all been included in the vaccine mRNA because these components facilitate the translation of viral proteins and provide protection from the ubiquitous exonucleases in the body. Third, to reduce mRNA degradation after vaccine administration and to promote mRNA delivery into cells, the mRNA has been encapsulated in biodegradable lipid nanoparticles consisting of cationic lipids, phospholipids, cholesterol, and polyethylene glycol-containing lipids. These lipid nanoparticles also act as an adjuvant component of the mRNA vaccines, inducing interleukin (IL)-6 cytokine production, which leads to the strong induction of T follicular helper T cells, germinal center B cells, and memory B-cell responses in the draining lymph nodes (LNs) of vaccine recipients (18). Fourth, to make the S protein more immunogenic, the furin cleavage site between S1 and S2 has been removed, and two amino acid residues in S2 have been substituted with proline (K986P/V987P), which together allow the formation of a relatively stable S protein trimer when the mRNA is incorporated and translated into proteins in target cells (16).

Because of these modifications, the COVID-19 mRNA vaccines are highly immunogenic, inducing strong serum neutralizing antibody responses in most individuals, whereas infection with SARS-CoV-2 produces more variable neutralizing antibody responses (19, 20); in both cases,

epitopes that overlap the ACE2-binding site in the RBD are targeted strongly by the generated antibodies. While neutralizing antibodies are a principal host defense mechanism against viral invasion, the mRNA COVID-19 vaccines also activate T cells, which play an important role in limiting disease severity and duration, as described below.

COVID-19 mRNA vaccines are delivered to the draining LNs via the lymphatics to induce immune priming

Another remarkable feature of the COVID-19 mRNA vaccines is that they can be readily incorporated into the lymphatic system. This is mainly because these vaccines are encapsulated in lipid nanoparticles approximately 100 nm in diameter. Lipids are known to be preferentially transported to the lymphatic system (21), and particles with a size range of 10 to 100 nm readily enter into the lymphatics (22).

The COVID-19 mRNA vaccines are administered intramuscularly (into the deltoid muscle in most cases), and muscles are rich in both blood vessels and lymphatics. Because these vaccines are preferentially transported into the lymphatics as described above, following their intramuscular injection, they are swiftly delivered to the lymph nodes that drain the muscle. Studies with experimental animals revealed that vaccine transport after intramuscular injection is restricted mainly to the local LNs that drain the injection site and that the vaccine is not readily disseminated systemically (23–25), unless non-physiologically large doses are injected. Indeed, a PET CT (positron emission tomography and computed tomography) study using [¹⁸F] FDG in human volunteers confirmed that prominent vaccine-associated LN swelling occurs selectively in the axillary and supraclavicular LNs of the ipsilateral side in relation to the vaccine injection site (26). Another study found that the LN swelling often persisted for more than 12 weeks (27). These LNs are the sites where the cells of the innate and adaptive immune systems interact.

In the draining LNs, although most phagocytic cells can internalize the mRNA vaccine, macrophages within the subcapsular sinus and dendritic cells (DCs) within the interfollicular area are the main groups that abundantly take up specific antigens. However, it is mainly DCs that exhibit high levels of translation of the vaccine mRNA and the upregulation of key co-stimulatory molecules (CD80 and CD86) essential for efficient antigen presentation to naïve T cells (24). These DCs subsequently display an upregulation of type I interferon (IFN)-inducible genes, leading to the production of a number of cytokines/chemokines required for antigen-specific stimulation of naïve T and B lymphocytes.

Within DCs, the majority of the S protein *in situ* generated from the vaccine mRNA is degraded in endosome-derived proteasomes, and some of the generated peptides are transported to the endoplasmic reticulum, where they are loaded onto class I major histocompatibility complexes (MHCs). Additionally, part of the S protein is produced and secreted as an exogenous protein by the cells that took up the mRNA. It is then taken up by professional antigen-presenting cells, such as DCs, in which the protein is processed and presented in class II MHCs. Peptide presentation by class II MHCs also occurs on the surface of DCs after their uptake of cell debris containing the vaccine-encoded protein. These peptide-loaded MHC class I and class II molecules on the surface of DCs subsequently present their antigens to antigen-specific CD4⁺ and CD8⁺ T cells, respectively (28, 29).

Detectable protein production can be found for up to ten days at the site of injection after the intramuscular injection of a COVID-19 mRNA vaccine (30). While some muscle cells endocytose the vaccine components, they are unable to effectively present the encoded antigen to the lymphoid system because they lack expression of the key co-stimulatory molecules (CD80 and CD86) essential for efficient antigen presentation to antigen-inexperienced naïve lymphocytes (31). Therefore, mRNA translation in muscle cells does not seem to play a major role in the induction of protective immune responses against SARS-CoV-2.

The innate immune activation by mRNA vaccines sometimes occurs in excess, resulting in adverse reactions, which can include pain, swelling, and redness at the local injection site (32, 33). Systemic side effects, such as allergy, chills, fever, and headache, are also often observed in recipients of COVID-19 mRNA vaccines. The occurrence of side effects from vaccination with a COVID-19 mRNA vaccine is likely a consequence of the intrinsic adjuvant activity of the current lipid nanoparticle formulation, which induces the robust production of inflammatory cytokines, such as IL-6, by the innate immune system (18); such a response tends to be more prominent in young people. Nevertheless, it should be noted that lipid nanoparticle-mediated IL-6 production is critical for the induction of follicular helper T cells in response to mRNA vaccination and that the protective vaccine effect is low in the absence of follicular helper T-cell proliferation (18).

COVID-19 mRNA vaccines activate adaptive immunity in the draining LNs

The transport of vaccine antigen to the draining LNs is crucial for the initiation of systemic immune responses against the relevant pathogen by T and B cells (23). Previous studies

have indicated that protective immunity against COVID-19 is mediated by both key arms of the adaptive immune system, i.e., humoral immunity and cellular immunity (34–37), and that antibody and T-cell responses tend to work in a compensatory manner to provide protection (38). Humoral immunity generates antibodies and memory B cells, while cellular immunity leads to the activation of antigen-specific helper CD4⁺ T cells and cytotoxic CD8⁺ T cells (13), which both occur in the draining LNs (39, 40).

Antibodies are particularly important in early protection against viral infection because they block infection by binding the virus and preventing viral entry into host cells. Additionally, memory B cells can produce high-affinity neutralizing antibodies upon re-encounter with the same virus. T cells, in contrast, are unable to block the initial infection process. Instead, they become activated upon antigen presentation by DCs, after which they proliferate to limit viral replication and spread. The CD4⁺-dependent cytotoxic CD8⁺ T-cell response is particularly important, and when the population of these cells expands within 7 days of symptoms and peaks at 14 days, viruses are cleared effectively (41), leading to mild rather than severe disease (42). Consistently, most individuals with resolved infections show robust and broad enhanced T-cell responses against multiple regions of SARS-CoV-2 (43, 44). Vaccine-induced T-cell responses have good cross-reactivity to the many variants of SARS-CoV-2 that have emerged recently (45, 46).

Turner et al. (40) examined antigen-specific B-cell responses in the peripheral blood and draining LNs of Pfizer mRNA vaccine recipients. They found that the populations of circulating immunoglobulin (Ig)G- and IgA-secreting plasmablasts that target the SARS-CoV-2 S protein peaked 1 week after the second immunization, declining thereafter, and that plasma neutralizing IgG antibody titers also showed similar kinetics. These researchers also conducted a needle biopsy of the draining LNs and examined cellular responses *in situ*. They found that S-binding germinal centers increased in frequency after the second immunization and that these germinal centers persisted at high frequency for 15 weeks. S-binding plasmablasts were also abundant in the draining LNs and persisted there even after they became undetectable in the peripheral blood. The majority of monoclonal antibodies generated from the germinal center-derived B cells strongly reacted with the S protein RBD as expected, while some reacted with the S proteins of the human betacoronaviruses OC43 and HKU1. These results indicate that the S-binding germinal centers recruited not only naïve B cells targeting unique epitopes within the SARS-CoV-2 S protein but also pre-existing memory B cells directed against epitopes conserved among human betacoronaviruses.

Nevertheless, patients with X-linked agammaglobulinemia have been reported to recover from COVID-19 (47), indicating

that antibody-independent mechanism(s) also plays an important role in virus clearance.

COVID-19 mRNA vaccines induce memory responses

Upon immunization with multiple doses of COVID-19 mRNA vaccine, SARS-CoV-2-reactive memory B cells appear systemically and persist for more than 6 months (48), subsequent to the appearance of the S protein-binding germinal centers in the draining LNs (40). Booster vaccinations increase the frequency of these memory B cells, inducing them to produce antibodies with significantly higher potency and breadth compared with the antibodies obtained after the second COVID-19 vaccine dose (49). Additionally, these antibodies are capable of neutralizing SARS-CoV-2 variants of multiple lineages (50), reducing the escape by mutant virus strains relative to ancestral virus (50, 51).

What should be improved with mRNA vaccines?

For non-COVID-19 respiratory virus infections, pre-existing immunity induced by natural infection or vaccination has been reported to induce antibody-dependent enhancement (ADE) of disease in some instances (52). Indeed, infectivity-enhancing antibodies have been found in a proportion of COVID-19 patients, and these antibodies tend to bind to a specific site of the SARS-CoV-2 S protein (53, 54). Nevertheless, the production of such antibodies was associated with the production of neutralizing antibodies, and enhancing antibodies did not induce ADE when neutralizing antibodies were present at high levels *in vitro* (53). Because of these observations, ADE continues to be a substantial concern in the development of COVID-19 vaccines. To the best of my knowledge, however, there is currently no evidence of vaccine-associated enhanced respiratory disease occurring following immunization with the COVID-19 mRNA vaccines currently in use, although this issue warrants further investigation because a new generation of mRNA vaccines is now becoming available.

In addition to the potential ADE issue, one major problem with the current COVID-19 mRNA vaccines, although they are highly effective at reducing the incidence and severity of SARS-CoV-2 infection, is the waning of their efficacy with increasing time since the second dose (11, 55). However, this issue seems to be more related to the pathogen than it is to the specific vaccines. A longitudinal study on SARS-CoV-2 reinfection indicates that, with natural infection, the mean time by which there is a 5% cumulative risk of reinfection was only approximately 140 days

post-symptom onset, which is less than half of the mean time to a cumulative 5% risk of breakthrough infection following vaccination with Pfizer or Moderna mRNA vaccine (both required approximately 350 days post-vaccination to reach this point) (20). These results indicate that the immunity induced by SARS-CoV-2 natural infection begins to wane after several months post-infection and that the immunity from natural infection lasts for a much shorter length of time compared with the duration of vaccine-mediated immunity.

While inducing durable immunity against SARS-CoV-2 does not appear to be an easy task, there may be at least a couple of ways of making the COVID-19 vaccine response more durable. One is to enhance the innate immune mechanism through which mRNA vaccines stimulate protective antibody responses. The other is to enhance the adaptive immune mechanism, particularly to enhance T-cell memory cell responses. Regarding the former, using other types of lipid particles or adding an appropriate adjuvant to the mRNA vaccines is a possibility, but this approach carries the possibility of increasing the incidence of adverse reactions as well. Regarding the latter, attempting to stimulate T cells with not only the S protein but also the matrix (M) protein and nucleocapsid (N) protein is also a possibility (56). The inclusion of other viral structural protein epitopes may strengthen T-cell responses, thereby amplifying and diversifying the induced antibody response against SARS-CoV-2.

While the current COVID-19 mRNA vaccines are highly protective against the development of severe disease, they elicit limited immune responses in the respiratory tract (57). Vaccines targeting the respiratory mucosa are now under development with the hope of inducing robust and durable immunity specifically in the respiratory tract. In particular, a mucosal booster vaccine may be an effective strategy to achieve more robust and long-lasting immunity against SARS-CoV-2.

Conclusion

COVID-19 vaccine development is moving forward at unprecedented speed, but several challenges remain. For example, the current COVID-19 mRNA vaccines are less effective at blocking infection by the newly arising SARS-CoV-2 variants, although protection against severe disease remains well preserved. Additionally, only relatively weak immune responses are induced in the mucosa of many vaccine recipients, and even when such responses are successfully induced, they tend to wane rapidly. Furthermore, the virus continues evolving ways to evade our immune response. Thus, there is an urgent need to develop pan-coronavirus vaccines that can target not only the current SARS-CoV-2 variants but also future variants. The development of mucosal vaccines that are

delivered across mucosal barriers may also present a promising strategy to promote durable protection against SARS-CoV-2 at the mucosal level.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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References

- Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A review. *JAMA* (2020) 344:782–93. doi: 10.1001/jama.2020.12839
- Hu B, Guo H, Zhou P, Shi Z-L. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol* (2021) 19:141. doi: 10.1038/s41579-020-00459-7
- Available at: <https://www.worldometers.info/coronavirus/>.
- Kuba K, Yamaguchi T, Penninger JM. Angiotensin-converting enzyme 2 (ACE2) in the pathogenesis of ARDS in COVID-19. *Front Immunol* (2021) 12:732690. doi: 10.3389/fimmu.2021.732690
- Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* (2020) 181:271–280.e8. doi: 10.1016/j.cell.2020.02.052
- Barouch DH. Covid-19 vaccines — immunity, variants, boosters. *New Engl J Med* (2022) 387:1–3. doi: 10.1056/NEJMra2206573
- Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *New Engl J Med* (2020) 387:2603–15. doi: 10.1056/NEJMoa2034577
- Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *New Engl J Med* (2021) 384:403–16. doi: 10.1056/NEJMoa2035389
- Tregoning JS, Flight KE, Higham SL, Wang Z, Pierce BF. Progress of the COVID-19 vaccine effort: Viruses, vaccines and variants versus efficacy, effectiveness and escape. *Nat Rev Immunol* (2020) 21:626. doi: 10.1038/s41577-021-00592-1
- Chaudhary N, Weissman D, Whitehead KA. mRNA vaccines for infectious diseases: Principles, delivery and clinical translation. *Nat Rev Drug Discovery* (2021) . 20:817–38. doi: 10.1038/s41573-021-00283-5
- Feikin DR, Higdon MM, Abu-Raddad LJ, Andrews N, Araos R, Goldberg Y, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: Results of a systematic review and meta-regression. *Lancet* (2022) 399:924–44. doi: 10.1016/S0140-6736(22)00152-0
- Harvey WT, Carabelli AM, Jackson B, Gupta RK, Thomson EC, Harrison EM, et al. SARS-CoV-2 variants, spike mutations and immune escape. *Nat Rev Microbiol* (2021) 19:409–24. doi: 10.1038/s41579-021-00573-0
- Wherry EJ, Barouch DH T. Cell immunity to COVID-19 vaccines. *Science* (2022) . 377:821–2. doi: 10.1126/science.add2897
- Bettini E, Locci M. SARS-CoV-2 mRNA vaccines: Immunological mechanism and beyond. *Vaccines* (2021) 9:147–65. doi: 10.3390/vaccines9020147
- Hogan MJ, Norbert P. mRNA vaccines in the COVID-19 pandemic and beyond. *Ann Rev Med* (2022) . 73:17–39. doi: 10.1146/annurev-med-042420-112725
- Gohda E. Effectiveness of and immune responses to SARS-CoV-2 mRNA vaccines and their mechanisms. *J Disast Res* (2022) 17:7–20. doi: 10.20965/jdr.2022.p0007
- Karikó K, Buckstein M, Ni H, Weissman D. Suppression of RNA recognition by toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA. *Immunity* (2005) 23:165–75. doi: 10.1016/j.immuni.2005.06.008
- Alameh MG, Tombácz I, Bettini E, Lederer K, Sittplangkoon C, Wilmore JR. Lipid nanoparticles enhance the efficacy of mRNA and protein subunit vaccines by inducing robust T follicular helper cell and humoral responses. *Immunity* (2021) . 54:2877–2892.e7. doi: 10.1016/j.immuni.2021.11.001
- Hall V, Foulkes S, Insalata F, Kirwan P, Saei A, Atti A. Protection against SARS-CoV-2 after covid-19 vaccination and previous infection. *New Engl J Med* (2022) 386:1207–20. doi: 10.1056/NEJMoa2118691
- Townsend JP, Hassler HB, Sah P, Galvani AP, Dornburg A. The durability of natural infection and vaccine-induced immunity against future infection by SARS-CoV-2. *Proc Natl Acad Sci USA* (2022) 119:e2204336119. doi: 10.1073/pnas.2204336119
- Dixon JB. Mechanisms of chylomicron uptake into lacteals. *Ann NY Acad Sci* (2010) . 1207 Suppl:E52–7. doi: 10.1111/j.1749-6632.2010.05716.x
- Lee J, Kim D, Byun J, Wu Y, Park J, Oh YK. *In vivo* fate and intracellular trafficking of vaccine delivery systems. *Adv Drug Delivery Res* (2022) 186:114325. doi: 10.1016/j.addr.2022.114325
- Liang F, Lindgren G, Sandgren KJ, Thompson EA, Francica JR, Seubert A. Vaccine priming is restricted to draining lymph nodes and controlled by adjuvant-mediated antigen uptake. *Sci Transl Med* (2017) 9:eal2094. doi: 10.1126/scitranslmed.aal2094
- Liang F, Lindgren G, Lin A, Thompson EA, Ols S, Röhss J, et al. Efficient targeting and activation of antigen-presenting cells *In vitro* and *In vivo* after modified mRNA vaccine administration in rhesus macaques. *Mol Ther* (2017) . 25:2635–47. doi: 10.1016/j.ymthe.2017.08.006
- Lindsay KE, Bhosle SM, Zurla C, Beyersdorf J, Rogers KA, Vanover D, et al. Visualization of early events in mRNA vaccine delivery in non-human primates via PET-CT and near-infrared imaging. *Nat BioMed Engin* (2019) . 3:371–80. doi: 10.1038/s41551-019-0378-3
- Cohen D, Krauthammer SH, Wolf I, Even-Sapir E. Hypermetabolic lymphadenopathy following administration of BNT162b2 mRNA covid-19 vaccine: Incidence assessed by [18F]FDG PET-CT and relevance to study interpretation. *Eur J Nucl Med Mol Imaging* (2021) . 48:1854–63. doi: 10.1007/s00259-021-05314-2
- Ha SM, Chu AJ, Lee J, Kim S-Y, Lee SH, Yoen H. US Evaluation of axillary lymphadenopathy following COVID-19 vaccination: A prospective longitudinal study. *Radiol* (2022) 305:46. doi: 10.1148/radiol.220543
- Rijkers GT, Weterings N, Obregon-Henao A, Lepolder M, Dutt TS, van Overveld FJ, et al. Antigen presentation of mRNA-based and virus-vectored SARS-CoV-2 vaccines. *Vaccines* (2021) . 9:848–65. doi: 10.3390/vaccines9080848
- Heinz FX, Stiasny K. Distinguishing features of current COVID-19 vaccines: Knowns and unknowns of antigen presentation and modes of action. *NPJ Vaccines* (2021) . 6:104. doi: 10.1038/s41541-021-00369-6

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30. Cagigi A, Loré K. Immune responses induced by mRNA vaccination in mice, monkeys and humans. *Vaccines* (2021) . 9:61–75. doi: 10.3390/vaccines9010061
31. Behrens L, Kerschensteiner M, Misgeld T, Goebels N, Wekerle H, Hohlfeld R. Human muscle cells express a functional costimulatory molecule distinct from B7.1 (CD80) and B7.2 (CD86) *in vitro* and in inflammatory lesions. *J Immunol* (1998) 161:5943–51.
32. Awaysa T, Moroi M, Enomoto Y, Kunimasa T, Nakamura M. What should we do after the COVID-19 vaccination? vaccine-associated diseases and precautionary measures against adverse reactions. *Vaccines* (2022) . 10:866–79. doi: 10.3390/vaccines10060866
33. Rosa Duque JS, Wang X, Leung D, Cheng SMS, Cohen CA, Mu X, et al. Immunogenicity and reactogenicity of SARS-CoV-2 vaccines BNT162b2 and CoronaVac in healthy adolescents. *Nat Comm* (2022) . 13:3700. doi: 10.1038/s41467-022-31485-z
34. Ni L, Ye F, Cheng M-L, Feng Y, Deng Y-Q, Zhao H, et al. Detection of SARS-CoV-2-specific humoral and cellular immunity in COVID-19 convalescent individuals. *Immunity* (2020) . 52:971–7. doi: 10.1016/j.immuni.2020.04.023
35. Li K, Huang B, Wu M, Zhong A, Li L, Cai Y, et al. Dynamic changes in anti-SARS-CoV-2 antibodies during SARS-CoV-2 infection and recovery from COVID-19. *Nat Comm* (2020) 11:6044. doi: 10.1038/s41467-020-19943-y
36. Chia WN, Zhu F, Ong SWX, Young BE, Fong S-W, Le Bert N, et al. Dynamics of SARS-CoV-2 neutralising antibody responses and duration of immunity: A longitudinal study. *Lancet Microbe* (2021) . 2:e240–9. doi: 10.1016/S2666-5247(21)00025-2
37. Miyasaka M. COVID-19 and immunity: Quo vadis? *Int Immunol* (2021) . 33:507–13. doi: 10.1093/intimm/dxab008
38. Menges D, Zens KD, Ballouz T, Caduff N, Llanas-Cornejo D, Aschmann HE, et al. Heterogenous humoral and cellular immune responses with distinct trajectories post-SARS-CoV-2 infection in a population-based cohort. *Nat Comm* (2022) . 13:4855. doi: 10.1038/s41467-022-32573-w
39. Mudd PA, Minerina AA, Pogorelyy MV, Turner JS, Kim W, Kalaidina E, et al. SARS-CoV-2 mRNA vaccination elicits a robust and persistent T follicular helper cell response in humans. *Cell* (2022) . 185:603–615.e15. doi: 10.1016/j.cell.2021.12.026
40. Turner JS, O'Halloran JA, Kalaidina E, Kim W, Schmitz AJ, JQ Z, et al. SARS-CoV-2 mRNA vaccines induce persistent human germinal centre responses. *Nature* (2021) . 596:109–13. doi: 10.1038/s41586-021-03738-2
41. Notarbartolo S, Ranzani V, Bandera A, Gruarin P, Bevilacqua V, Putignano AR. Integrated longitudinal immunophenotypic, transcriptional and repertoire analyses delineate immune responses in COVID-19 patients. *Sci Immunol* (2021) 6: eabg5021. doi: 10.1126/sciimmunol.abg5021
42. Bergamaschi L, Mescia F, Turner L, Hanson AL, Kotagiri P, Dunmore BJ, et al. Longitudinal analysis reveals that delayed bystander CD8⁺ T cell activation and early immune pathology distinguish severe COVID-19 from mild disease. *Immunity* (2021) . 54:1257–75. doi: 10.1016/j.immuni.2021.05.010
43. Sekine T, Perez-Potti A, Rivera-Ballesteros O, Strålin K, Gorin JB, Olsson A, et al. Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. *Cell* (2020) . 183:158–168.e14. doi: 10.1016/j.cell.2020.08.017
44. Peng Y, Mentzer AJ, Liu G, Yao X, Yin Z, Dong D, et al. Broad and strong memory CD4⁺ and CD8⁺ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19. *Nat Immunol* (2020) . 21:1336–45. doi: 10.1038/s41590-020-0782-6
45. Goel RR, Apostolidis SA, Painter MM, Mathew D, Pattekar A, Kuthuru O, et al. Distinct antibody and memory b cell responses in SARS-CoV-2 naïve and recovered individuals following mRNA vaccination. *Sci Immunol* (2021) 6: eabi6950. doi: 10.1126/sciimmunol.abi6950
46. Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. *Science* (2021) 371:eabf4063. doi: 10.1126/science.abf4063
47. Soresina A, Moratto D, Chiarini M, Paolillo C, Baresi G, Focà E, et al. Two X-linked agammaglobulinemia patients develop pneumonia as COVID-19 manifestation but recover. *Pediatr Allergy Immunol* (2020) 31:565–9. doi: 10.1111/pai.13263
48. Gaebler C, Wang Z, Lorenzi JCC, Muecksch F, Finkin S, Tokuyama M, et al. Evolution of antibody immunity to SARS-CoV-2. *Nature* (2021) 591:639–44. doi: 10.1038/s41586-021-03207-w
49. Muecksch F, Wang Z, Cho A, Gaebler C, Ben Tanfous T, DaSilva J, et al. Increased memory b cell potency and breadth after a SARS-CoV-2 mRNA boost. *Nature* (2022) . 607:128–34. doi: 10.1038/s41586-022-04778-y
50. Hachmann NP, Miller J, Collier A-Y, Ventura JD, Yu J, Rowe M, et al. Neutralization escape by SARS-CoV-2 omicron subvariants BA.2.12.1, BA.4, and BA.5. *Pro Nat Acad Sci USA* (2022) . 387:86–8. doi: 10.1056/NEJMc2206576
51. Garcia-Beltran WF, Lam EC, St. Denis K, Nitido AD, Garcia ZH, Hauser BM, et al. Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity. *Cell* (2021) . 184:2372–83. doi: 10.1016/j.cell.2021.03.013
52. Takada A, Kawaoka Y. Antibody-dependent enhancement of viral infection: Molecular mechanisms and *In vivo* implications. *Rev Med Biol* (2003) . 13:387–98. doi: 10.1002/rmv.405
53. Liu Y, Soh WT, Kishikawa JI, Hirose M, Nakayama EE, Li S, et al. An infectivity-enhancing site on the SARS-CoV-2 spike protein targeted by antibodies. *Cell* (2021) . 184:3452–3466.e18. doi: 10.1016/j.cell.2021.05.032
54. Liu Y, Nakazaki Y, Arase H. Infectivity-enhancing antibodies against SARS-CoV-2. *Translat Regul Sci* (2022) . 4:1–4. doi: 10.33611/trs.2021-021
55. Naaber P, Tserel L, Kangro K, Sepp E, Jürjenson V, Adamson A, et al. Dynamics of antibody response to BNT162b2 vaccine after six months: A longitudinal prospective study. *Lancet Region Health Europe* (2021) 10:100208. doi: 10.1016/j.lanepe.2021.100208
56. Vallejo A, Martín-Hondarza A, Gómez S, Velasco H, Vizcarra P, Haemmerle J, et al. Cellular responses to membrane and nucleocapsid viral proteins are also boosted after SARS-CoV-2 spike mRNA vaccination in individuals with either past infection or cross-reactivity. *Front Microbiol* (2021) . 12:812729. doi: 10.3389/fmicb.2021.812729
57. Tang J, Zeng C, Cox TM, Li C, Son YM, Cheon IS, et al. Respiratory mucosal immunity against SARS-CoV-2 following mRNA vaccination. *Sci Immunol* (2022) eadd4853. doi: 10.1126/sciimmunol.add4853