中国科学: 生命科学 2023 年 第 53 卷 第 10 期: 1490 ~ 1498
SCIENTIA SINICA Vitae lifecn.scichina.com
《中国科学》杂志社 SCIENCE CHINA PRESS

评 述 南华大学衡阳医学院65周年庆专辑

新型冠状病毒中和抗体应答研究进展

滕石山, 瞿小旺*

南华大学衡阳医学院, 衡阳 421001
* 联系人, E-mail: quxiaowang@163.com

收稿日期: 2023-05-24; 接受日期: 2023-08-30; 网络版发表日期: 2023-09-26
国家自然科学基金(批准号: 92269115, 82061138020)资助

摘要 新型冠状病毒(severe acute respiratory syndrome coronavirus 2, SARS-CoV-2)是21世纪前20年第三种在人群中广泛传播的冠状病毒. 中和抗体作为特异性免疫应答的重要组成部分, 在新型冠状病毒感染预防、控制方面发挥了极其重要的作用. 持续、广谱的中和抗体应答, 对于新型冠状病毒突变体及未来潜在溢出的动物来源冠状病毒的预防具有极其重要的作用. 高亲和力中和抗体的生成与维持依赖于滤泡辅助性T(T follicular helper, T_{FH})细胞, 其与B细胞形成生发中心(germinal center, GC)促进B细胞成熟并分化为记忆B细胞和浆细胞同时产生抗体应答. 阐明新型冠状病毒感染和疫苗接种后中和抗体应答特点、广谱性、持续性及参与抗体应答的关键免疫细胞, 如T_{FH}细胞等, 对开发下一代广谱、长效冠状病毒疫苗具有重要的指导性作用. 本综述拟回顾总结新型冠状病毒自然感染与疫苗接种诱导的中和抗体应答研究进展, 旨在为新一代冠状病毒疫苗研发提供参考.

关键词 新型冠状病毒, 中和抗体, 滤泡辅助性T细胞

冠状病毒种类繁多, 宿主广泛存在并相互间紧密共存, 导致冠状病毒具有较高的跨种传播风险[1,2]. 21世纪前20年, 已有包括新型冠状病毒在内的三种动物来源的烈性冠状病毒(SARS-CoV-1, MERS-CoV, SARS-CoV-2)溢出并导致在人群中流行[3~8]. 未来不可测的冠状病毒外溢是不可避免的必然事件, 如何预防、阻断以及提前做好应对预案显得尤为迫切.

中和抗体作为宿主免疫应答的重要组成部分之一, 在新冠病毒感染早期控制病毒感染以及疫苗接种后预防病毒感染方面发挥了重要作用, 同时中和抗体或者康复血清治疗在一定程度上能降低疾病向重症化发展[9~12]. 当前预防性疫苗主要以诱导中和抗体应答来达到早期预防目的[13]. 新冠病毒自然感染和疫苗免疫诱导的中和抗体不仅可以通过阻断病毒膜蛋白与宿主受体结合抑制病毒感染, 同时还能通过Fc介导细胞发挥效应功能进一步协同控制感染[14,15].

然而, 相较于SARS-CoV-1, 新冠病毒棘突蛋白与人血管紧张素酶II受体(angiotensin-converting enzyme 2, ACE2)具有更高的亲和力, 且在选择压力下能快速进化为高传播力的突变体逃逸宿主免疫, 导致更广泛的感染[16~18]. 一方面, 新冠病毒自然感染和疫苗接种诱导的抗体水平随时间推移持续下降[19,20]; 另一方面,

引用格式: 滕石山, 瞿小旺. 新型冠状病毒中和抗体应答研究进展. 中国科学: 生命科学, 2023, 53: 1490–1498
Teng S S, Qu X W. Research progress on the neutralizing antibody response to SARS-CoV-2 (in Chinese). Sci Sin Vitae, 2023, 53: 1490–1498, doi: 10.1360/SSV-2023-0084

新冠病毒在选择压力下持续快速突变进化，逃逸宿主既有的免疫应答[18,21]. 因此，深入理解新冠病毒感染与疫苗接种后中和抗体应答特征与机制，开发能诱导广谱的、持续性抗体应答疫苗对新冠病毒的常态化防控以及应对未来可能出现的冠状病毒外溢具有重要意义.

1　新型冠状病毒自然感染与疫苗免疫的中和抗体应答特点

新冠病毒感染后，机体能在症状出现后的几天时间内迅速产生抗体，能同时或者先后发生IgM，IgG血清转换. 抗体滴度通常在血清转换后的1周左右达到平台期，约超过95%的新冠患者在急性感染期能产生抗体应答[22]. 目前的研究报道显示，超过90%的有症状感染康复患者中和抗体应答至少能持续16个月. 抗体应答水平除与年龄、性别等因素有关外，与症状严重程度呈正相关[23,24]. 但是，危重症患者存在感染早期抗体应答延滞，是造成疾病进展的重要原因之一. 感染早期快速的中和抗体应答与感染后良好预后有关，也可以作为疾病进展预测的标志物[9,10,25]. 这些结果显示，宿主中和抗体在急性感染早期的快速应答对病毒控制以及防止疾病进一步恶化至关重要. 此外，呼吸道黏膜免疫的建立对于预防呼吸道病毒再感染具有重要意义[26]. 新冠病毒自然感染不仅能诱导系统性的抗体应答，而且也能产生局部的黏膜免疫应答[27,28]. 急性感染期呼吸道分泌物IgA含量比IgG高，在感染早期发挥主要的中和作用，而且分泌型的IgA在康复后较长时间内仍能被检测到. 上呼吸道黏膜免疫的建立，能有效预防新冠病毒的再感染[26,27].

新冠病毒疫苗的接种是建立群体免疫的最有效手段，包括灭活疫苗、腺病毒载体疫苗、mRNA疫苗以及蛋白亚单位疫苗在内的多种疫苗快速投入使用，对预防新冠病毒感染以及减缓感染后疾病的进展有巨大的作用[29~32]. 各种疫苗的标准程序免疫接种后均能有效诱导保护性抗体应答，由于疫苗形式存在本质性差异以及接种剂量或程序的不同，各种疫苗诱导中和抗体的滴度存在较大差异[33,34]. 不同于自然感染，这些标准程序免疫接种所诱导的中和抗体应答，在6个月后其抗体应答几乎降低到基线[35~37]. 加强针免疫则能显著提升中和抗体应答水平，异源疫苗接种或序贯免疫显示出更好的提升效果[38~41]. 但是，短期内第四针免疫并不能进一步提升保护性抗体应答水平[42]. 不同于新冠病毒的自然感染，疫苗接种虽然能有效地诱导系统性的抗体应答，然而肌肉注射的疫苗通常不能诱导上呼吸道黏膜免疫应答，腺病毒载体疫苗的鼻腔免疫则能弥补这一缺陷，因此，肌肉注射与鼻腔免疫可诱导类似于自然感染过程中建立的局部与系统抗体免疫应答[43,44].

新冠病毒进入宿主细胞是由病毒棘突蛋白(spike, S)介导的，它是中和抗体唯一已知的靶点，包括两个功能性亚基，S1亚基和S2亚基. S1亚基负责与宿主细胞受体的结合，而S2亚基负责病毒膜与细胞膜的融合[45]. S蛋白上常见的抗体表位包括S1亚基的N端结构域(N-terminal domain, NTD)和受体结构域(receptor binding domain, RBD)以及S2亚基的茎螺旋(stem helix, SH)和融合肽(fusion peptide, FP)(图1C). 其中针对NTD和RBD的往往为强效中和抗体，但因其识别的序列突变频率较高，很容易导致病毒的免疫逃逸；而识别SH与FP的抗体，由于其识别的序列在冠状病毒中有较高的保守性，往往有极好的抗冠状病毒广谱性[46]. 因此，针对下一代抗冠状病毒广谱疫苗的设计，可以挑选S蛋白中保守的免疫表位设计疫苗，并且进行联合免疫，从而在免疫宿主体内诱导出高效、广谱的中和抗体.

中和抗体Fab段除能通过与S蛋白结合从而阻断其与ACE2结合来发挥中和作用外，也可以通过阻止S蛋白介导的病毒和细胞膜融合来抑制病毒的感染[47]. 其Fc段亦可通过招募Fc受体介导细胞效应功能[48,49]. 新冠病毒自然感染与疫苗免疫均能有效地诱导抗体Fc介导的细胞效应功能，这些细胞效应功能可协同中和抗体发挥保护性作用[14,15,49]. 有研究显示新冠病毒特异的单克隆中和抗体，其Fc介导的效应功能也是单克隆抗体发挥更佳中和能力所必需的[50]. 棘突蛋白RBD作为主要的免疫原，与抗体Fc融合进行免疫能显著增强其免疫后的抗体应答水平[51].

2　新型冠状病毒中和抗体广谱性应答与免疫逃逸

中和抗体的广谱性应答对于预防病毒突变体或进化保守的同类病毒具有重要意义. 早期的研究显示，急性感染期新冠病毒诱导的抗体能与SARS-CoV-1产生

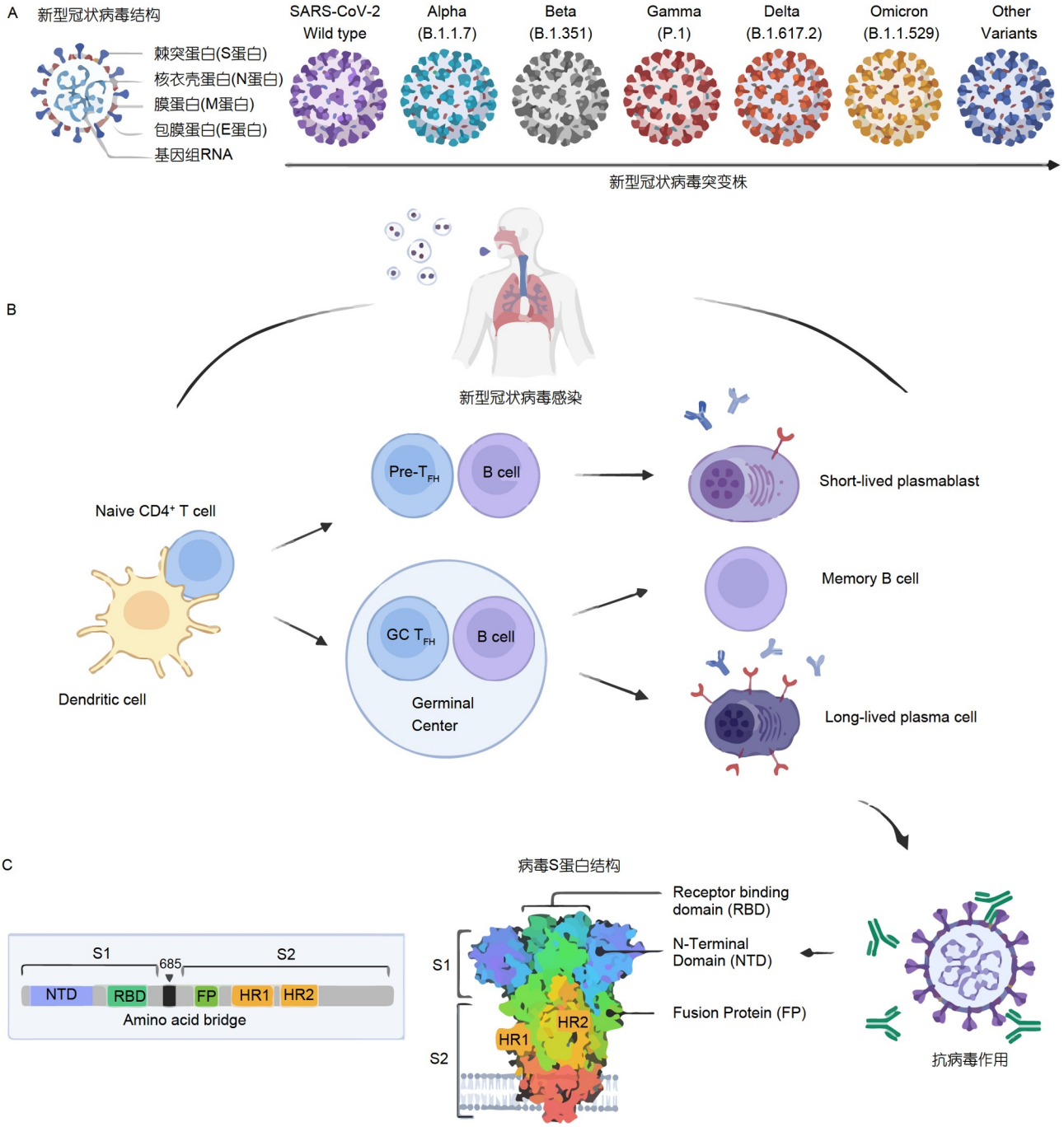

图 1 新型冠状病毒诱导的体液免疫应答. A: 新型冠状病毒结构及突变株; B: 新型冠状病毒急性感染期抗体应答及高亲和力中和抗体的生成路径; C: 中和抗体表位分布

Figure 1 Humoral immune response induced by SARS-CoV-2. A: Structure and variants of SARS-CoV-2; B: the pathway of SARS-CoV-2 acute infection phase and high-affinity neutralizing antibodies; C: distribution of neutralizing antibody epitopes

交叉应答, 但是很少能有交叉中和应答[52,53]. 新冠病毒感染同样能增强或诱导与MERS-CoV, 普通感冒冠状病毒HCoV-OC43, HCoV-HKU1, HCoV-229E, HCoV-NL63等棘突蛋白的交叉抗体应答, 由于这些病毒棘突蛋白S2的相对高度保守性, 这些交叉抗体主要作用于棘突蛋白的S2亚基[54,55]. 但是这些交叉抗体是否对新

冠病毒感染具有保护性, 存在一定的争议, 有待进一步研究证明[56,57]. 急性感染期诱导的抗体大多数为短效浆细胞分泌的低亲和力抗体, 在快速控制感染过程中发挥作用, 这些抗体在病毒得到清除后快速消退, 仅少数活化的B细胞被招募到生发中心, 在T细胞辅助下进一步成熟, 形成记忆性B细胞或长效浆细胞[58]. 因此, 新冠病毒康复期患者血清中和抗体显示更多的广谱交叉与中和活性. 已有报道(包括本团队前期研究)显示, 新冠康复患者血清部分能中和SARS-CoV-1, 以及来源于蝙蝠、穿山甲、果子狸等动物的Sarbecovirus[59]. 这些研究显示, 新冠病毒自然感染能诱导广谱交叉抗体应答, 并且能中和进化关系较近的动物来源的冠状病毒. 从康复患者外周血分离的多种单克隆抗体, 同样显示对这些病毒的广谱中和能力. 研究表明, 各种新冠疫苗接种亦能诱导不同来源的冠状病毒广谱交叉抗体应答, 且一些抗体具有广谱中和能力. 多项研究显示, 靶向SH的中和抗体可中和包括SARS-CoV-1, MERS-CoV以及SARS-CoV-2在内的多种人β冠状病毒[60,61]; 此外, Sun等人[47]发现的靶向FP中和抗体76E1对多种新冠突变株具有强效中和活性.

冠状病毒基因本身具有容易突变、重组的生物学特征. 在新冠病毒广泛传播, 疫苗大范围接种的前提下, 这种免疫压力加速了新冠病毒突变以适应宿主的进程[62,63]. 先后出现了在欧洲发现的D614G、在英国发现的Alpha(B.1.1.7)、在南非发现的Beta(B.1.351)、在巴西发现的Gamma(P.1)、在印度发现的Delta(B.1.617.2)及在南非发现的Omicron(B.1.1.529)等突变体(图1A), 由于棘突蛋白上突变的累积, 那些能显著增强与细胞受体ACE2亲和力且能逃逸宿主免疫压力的突变体获得了选择优势, 其结果就是病毒传播力变强、致病性降低、免疫抵抗增强[64]. 尽管新冠病毒疫苗同样能诱导包括SARS-CoV-1以及多种动物来源Sarbecovirus的交叉中和抗体应答[65], 但是Alpha, Beta, Gamma, Delta及Omicron等突变体对新冠病毒自然感染以及疫苗接种诱导的中和抗体免疫逃逸不断增强[64,66]. 自然感染以及疫苗接种诱导的中和抗体对早期出现的Omicron亚型BA.1(B.1.1.529.1)存在较好的交叉保护, 随着肆虐全球的Omicron进一步突变, 出现了越来越多的新突变体, 包括近期流行并占主导新突变体XBB.1.5和XBB.1.16, 它们显示出更强的免疫逃逸能力, 这是突破性感染发生的主要原因之一[67]. 新冠病毒感染后疫苗加强或疫苗标准程序接种后加强免疫, 均能显著提升中和抗体应答强度与广度, 增强对突变体的保护性应答[68,69].

3　新型冠状病毒中和抗体持续性应答及机制

尽管新冠病毒自然感染以及疫苗接种均能有效的诱导广谱性中和抗体应答, 但是中和抗体应答的持续性如何, 目前没有确切答案. 普通感冒冠状病毒感染诱导的抗体应答通常能持续一年左右, 而SARS-CoV-1和MERS-CoV感染康复后超半数患者中和抗体持续应答三年或更长时间, 尽管抗体滴度相较于高峰期低一个数量级以上[70~72]. 目前已有的跟踪调查研究显示, 新冠病毒初始感染康复后, 中和抗体滴度在康复早期阶段达到平台期后显著下降, 在后续阶段持续稳定在较低水平且持续至少16个月[73]. 新冠疫苗接种呈现与自然感染相似的动力学特征, 但中和抗体滴度消退更快, 加强接种能显著增强抗体的持续性应答[59,74].

抗体亲和力成熟是个持续的过程, 新冠病毒感染康复后几个月内抗体亲和力持续增强, 疫苗加强接种能进一步提升中和抗体的亲和力. 高亲和力抗体的生成与维持依赖于生发中心滤泡辅助性T(T follicular helper, T_{FH})细胞的辅助. T_{FH}细胞是新近确定的一类辅助性$CD4^+$ T细胞, 高表达趋化因子受体CXCR5(C-X-C chemokine receptor type 5)和PD-1(programmed cell death protein 1)[75]. Bcl-6(B-cell lymphoma 6 protein)为T_{FH}细胞的转录因子, T_{FH}细胞分泌IL-21(interleukin-21)在共刺激分子ICOS, CD40L, OX40等及TCR信号下与同源B细胞(cognate B cell)相互作用, 在二级淋巴器官滤泡(follicular)与B细胞相互作用形成生发中心[76,77]. 在生发中心抗原特异的T_{FH}细胞进一步筛选B细胞, 促进B细胞抗体基因重排、类别转换(class-switching)、体细胞突变(somatic hypermutation), 最终形成表达高亲和力抗体的记忆性B细胞和产生抗体的浆细胞[77,78](图1B). 这些长寿浆细胞大多数定居在骨髓中, 可分泌具有强效中和能力的抗体, 并维持在一定的水平, 协助机体有效控制病毒的感染; 同时, 记忆性B细胞与长寿浆细胞可共同建立体液免疫记忆, 从而有效预防病毒的再次感染[79].

大部分新冠康复患者产生了高亲和力抗体、较强的T_{FH}细胞应答与长效浆细胞[80]. 经过分析新冠康复感

染患者免疫应答, 发现新冠自然感染过程中主要诱导CCR6$^+$ T_{FH}细胞应答, 但是这些细胞和抗体应答无相关性[81~83]; 另一部分研究(包括本团队前期研究)表明, 新冠康复患者主要应答T_{FH}细胞为CXCR3$^+$ T_{FH}细胞, 且其与中和抗体应答相关[81,84,85]. 对于这些高亲和力抗体的生成与维持, T_{FH}细胞在这一过程中发挥了关键性作用. 在mRNA疫苗研究中, 发现免疫接种能有效地形成生发中心, 其维持时间可持续6个月以上. 在生发中心中, 抗原特异的GC T_{FH}细胞, GC B细胞相互作用, 形成记忆性B细胞和骨髓长效浆细胞[86,87]. 加强接种能显著促进预存的T_{FH}细胞应答, T_{FH}细胞可辅助记忆性B细胞分化为抗体分泌细胞, 显著提升抗体应答水平[88]. 本团队[65]的进一步研究发现, 新冠病毒自然感染和灭活疫苗接种后, CCR6$^+$ T_{FH}和CXCR3$^+$ T_{FH}(T_H1-like T_{FH})细胞显示出不同的应答特征, 然而CXCR3$^+$ T_{FH}相较于CCR6$^+$ T_{FH}细胞则表现出更强的抗原应答能力与更长的持续时间, 以及更强的辅助记忆性B细胞分化为抗原特异的抗体分泌细胞的能力. 这些结果证实了CXCR3$^+$ T_{FH}(或T_H1-like T_{FH})在新冠长效抗体应答中的核心作用[65]. 在其他病毒研究, 如流感疫苗免疫、HIV慢性感染、ZIKA病毒感染, 以及本团队早期在HCV慢性感染的研究中均发现, T_H1-like T_{FH}细胞的免疫应答与抗体生成或维持的数量与质量相关与新冠病毒感染类似[89~93]. 这些研究表明, 病毒感染和疫苗接种诱导的T_H1-like T_{FH}细胞是应答高亲和力抗体成熟与抗体水平维持的关键辅助性T细胞.

4 总结与展望

冠状病毒的跨种传播是个必然事件, 何时及以何种方式突破物种屏障, 催生下一次人类中的大流行是不可控的. 因此除了加强监测预警外, 开发冠状病毒通用抗病毒药物以及长效疫苗仍然是当前亟需解决的重要问题. 本文主要针对当前新冠疫苗所诱发的免疫应答缺陷, 结合新冠病毒自然感染的免疫应答特点, 探索了长效中和抗体应答的免疫学基础. 其中, 基于T_H1-like T_{FH}细胞在抗体亲和力成熟与抗体维持中的重要作用, 通过联合应用细胞因子或佐剂等靶向诱导抗原特异的T_H1-like T_{FH}分化, 对指导研发新一代长效冠状病毒疫苗具有重要指导价值.

参考文献

1 Ruiz-Aravena M, McKee C, Gamble A, et al. Ecology, evolution and spillover of coronaviruses from bats. Nat Rev Microbiol, 2022, 20: 299–314
2 Mallapaty S. Tens of thousands of people exposed to bat coronaviruses each year. Nature, 2022, 608: 457–458
3 Peiris J, Lai S T, Poon L, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet, 2003, 361: 1319–1325
4 Peiris J S M, Guan Y, Yuen K Y. Severe acute respiratory syndrome. Nat Med, 2004, 10: S88–S97
5 Zaki A M, van Boheemen S, Bestebroer T M, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med, 2012, 367: 1814–1820
6 Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature, 2020, 579: 265–269
7 Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med, 2020, 382: 727–733
8 Zhou P, Yang X L, Wang X G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature, 2020, 579: 270–273
9 Zhou Z H, Dharmarajan S, Lehtimaki M, et al. Early antibody responses associated with survival in COVID19 patients. PLoS Pathog, 2021, 17: e1009766
10 Lucas C, Klein J, Sundaram M E, et al. Delayed production of neutralizing antibodies correlates with fatal COVID-19. Nat Med, 2021, 27: 1178–1186
11 Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with COVID-19. N Engl J Med, 2021, 384: 229–237
12 Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci USA, 2020, 117: 9490–9496
13 Gilbert P B, Montefiori D C, McDermott A B, et al. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. Science, 2022, 375: 43–50
14 Selva K J, van de Sandt C E, Lemke M M, et al. Systems serology detects functionally distinct coronavirus antibody features in children and

elderly. Nat Commun, 2021, 12: 2037
15 Kaplonek P, Cizmeci D, Fischinger S, et al. mRNA-1273 and BNT162b2 COVID-19 vaccines elicit antibodies with differences in Fc-mediated effector functions. Sci Transl Med, 2022, 14: eabm2311
16 Xu Z, Kang X, Han P, et al. Binding and structural basis of equine ACE2 to RBDs from SARS-CoV, SARS-CoV-2 and related coronaviruses. Nat Commun, 2022, 13: 3547
17 Li L, Liao H, Meng Y, et al. Structural basis of human ACE2 higher binding affinity to currently circulating Omicron SARS-CoV-2 sub-variants BA.2 and BA.1.1. Cell, 2022, 185: 2952–2960.e10
18 Iketani S, Liu L, Guo Y, et al. Antibody evasion properties of SARS-CoV-2 Omicron sublineages. Nature, 2022, 604: 553–556
19 Ibarrondo F J, Fulcher J A, Goodman-Meza D, et al. Rapid decay of anti-SARS-CoV-2 antibodies in persons with mild COVID-19. N Engl J Med, 2020, 383: 1085–1087
20 Patalon T, Saciuk Y, Peretz A, et al. Waning effectiveness of the third dose of the BNT162b2 mRNA COVID-19 vaccine. Nat Commun, 2022, 13: 3203
21 Caniels T G, Bontjer I, van der Straten K, et al. Emerging SARS-CoV-2 variants of concern evade humoral immune responses from infection and vaccination. Sci Adv, 2021, 7: eabj5365
22 Long Q X, Liu B Z, Deng H J, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med, 2020, 26: 845–848
23 Chen X, Pan Z, Yue S, et al. Disease severity dictates SARS-CoV-2-specific neutralizing antibody responses in COVID-19. Sig Transduct Target Ther, 2020, 5: 180
24 Atyeo C, Fischinger S, Zohar T, et al. Distinct early serological signatures track with SARS-CoV-2 survival. Immunity, 2020, 53: 524–532.e4
25 Garcia-Beltran W F, Lam E C, Astudillo M G, et al. COVID-19-neutralizing antibodies predict disease severity and survival. Cell, 2021, 184: 476–488.e11
26 Mettelman R C, Allen E K, Thomas P G. Mucosal immune responses to infection and vaccination in the respiratory tract. Immunity, 2022, 55: 749–780
27 Sterlin D, Mathian A, Miyara M, et al. IgA dominates the early neutralizing antibody response to SARS-CoV-2. Sci Transl Med, 2021, 13: eabd2223
28 Butler S E, Crowley A R, Natarajan H, et al. Distinct features and functions of systemic and mucosal humoral immunity among SARS-CoV-2 convalescent individuals. Front Immunol, 2020, 11: 618685
29 Xia S, Zhang Y, Wang Y, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. Lancet Infect Dis, 2021, 21: 39–51
30 Folegatti P M, Ewer K J, Aley P K, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet, 2020, 396: 467–478
31 Polack F P, Thomas S J, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med, 2020, 383: 2603–2615
32 Yang S, Li Y, Dai L, et al. Safety and immunogenicity of a recombinant tandem-repeat dimeric RBD-based protein subunit vaccine (ZF2001) against COVID-19 in adults: two randomised, double-blind, placebo-controlled, phase 1 and 2 trials. Lancet Infect Dis, 2021, 21: 1107–1119
33 Naranbhai V, Garcia-Beltran W F, Chang C C, et al. Comparative immunogenicity and effectiveness of mRNA-1273, BNT162b2, and Ad26.COV2.S COVID-19 vaccines. J Infect Dis, 2022, 225: 1141–1150
34 Lim W W, Mak L, Leung G M, et al. Comparative immunogenicity of mRNA and inactivated vaccines against COVID-19. Lancet Microbe, 2021, 2: e423
35 Levin E G, Lustig Y, Cohen C, et al. Waning immune humoral response to BNT162b2 COVID-19 vaccine over 6 months. N Engl J Med, 2021, 385: e84
36 Goldberg Y, Mandel M, Bar-On Y M, et al. Waning immunity after the BNT162b2 vaccine in Israel. N Engl J Med, 2021, 385: e85
37 Atmar R L, Lyke K E, Deming M E, et al. Homologous and heterologous COVID-19 booster vaccinations. N Engl J Med, 2022, 386: 1046–1057
38 Zuo F, Abolhassani H, Du L, et al. Heterologous immunization with inactivated vaccine followed by mRNA-booster elicits strong immunity against SARS-CoV-2 Omicron variant. Nat Commun, 2022, 13: 2670
39 Yue L, Zhou J, Zhou Y, et al. Antibody response elicited by a third boost dose of inactivated SARS-CoV-2 vaccine can neutralize SARS-CoV-2 variants of concern. Emerg Microbes Infects, 2021, 10: 2125–2127
40 Zhang J, He Q, An C, et al. Boosting with heterologous vaccines effectively improves protective immune responses of the inactivated SARS-

CoV-2 vaccine. Emerg Microbes Infects, 2021, 10: 1598–1608
41 Krause P R, Fleming T R, Peto R, et al. Considerations in boosting COVID-19 vaccine immune responses. Lancet, 2021, 398: 1377–1380
42 Mallapaty S. Fourth dose of COVID vaccine offers only slight boost against Omicron infection. Nature, 2022, 10.1038/d41586-022-00486-9
43 Lapuente D, Fuchs J, Willar J, et al. Protective mucosal immunity against SARS-CoV-2 after heterologous systemic prime-mucosal boost immunization. Nat Commun, 2021, 12: 6871
44 Havervall S, Marking U, Svensson J, et al. Anti-spike mucosal IgA protection against SARS-CoV-2 Omicron infection. N Engl J Med, 2022, 387: 1333–1336
45 Walls A C, Park Y J, Tortorici M A, et al. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell, 2020, 181: 281–292.e6
46 Chen Y, Zhao X, Zhou H, et al. Broadly neutralizing antibodies to SARS-CoV-2 and other human coronaviruses. Nat Rev Immunol, 2023, 23: 189–199
47 Sun X, Yi C, Zhu Y, et al. Neutralization mechanism of a human antibody with pan-coronavirus reactivity including SARS-CoV-2. Nat Microbiol, 2022, 7: 1063–1074
48 Winkler E S, Gilchuk P, Yu J, et al. Human neutralizing antibodies against SARS-CoV-2 require intact Fc effector functions for optimal therapeutic protection. Cell, 2021, 184: 1804–1820.e16
49 Gorman M J, Patel N, Guebre-Xabier M, et al. Fab and Fc contribute to maximal protection against SARS-CoV-2 following NVX-CoV2373 subunit vaccine with Matrix-M vaccination. Cell Rep Med, 2021, 2: 100405
50 Yamin R, Jones A T, Hoffmann H H, et al. Fc-engineered antibody therapeutics with improved anti-SARS-CoV-2 efficacy. Nature, 2021, 599: 465–470
51 Liu Z, Xu W, Xia S, et al. RBD-Fc-based COVID-19 vaccine candidate induces highly potent SARS-CoV-2 neutralizing antibody response. Sig Transduct Target Ther, 2020, 5: 282
52 Lv H, Wu N C, Tsang O T Y, et al. Cross-reactive antibody response between SARS-CoV-2 and SARS-CoV infections. Cell Rep, 2020, 31: 107725
53 Yang R, Lan J, Huang B, et al. Lack of antibody-mediated cross-protection between SARS-CoV-2 and SARS-CoV infections. Ebiomedicine, 2020, 58: 102890
54 Grobben M, van der Straten K, Brouwer P J, et al. Cross-reactive antibodies after SARS-CoV-2 infection and vaccination. eLife, 2021, 10: e70330
55 Klompus S, Leviatan S, Vogl T, et al. Cross-reactive antibodies against human coronaviruses and the animal coronavirome suggest diagnostics for future zoonotic spillovers. Sci Immunol, 2021, 6: eabe9950
56 Greenbaum U, Klein K, Martinez F, et al. High levels of common cold coronavirus antibodies in convalescent plasma are associated with improved survival in COVID-19 patients. Front Immunol, 2021, 12: 675679
57 Anderson E M, Goodwin E C, Verma A, et al. Seasonal human coronavirus antibodies are boosted upon SARS-CoV-2 infection but not associated with protection. Cell, 2021, 184: 1858–1864.e10
58 Quast I, Tarlinton D. B cell memory: understanding COVID-19. Immunity, 2021, 54: 205–210
59 Jia J Z, Tan C W, Cheng S M S, et al. Priming conditions shape breadth of neutralizing antibody responses to sarbecoviruses. Nat Commun, 2022, 13: 6285
60 Wang C, van Haperen R, Gutiérrez-Álvarez J, et al. A conserved immunogenic and vulnerable site on the coronavirus spike protein delineated by cross-reactive monoclonal antibodies. Nat Commun, 2021, 12: 1715
61 Sauer M M, Tortorici M A, Park Y J, et al. Structural basis for broad coronavirus neutralization. Nat Struct Mol Biol, 2021, 28: 478–486
62 Cui J, Li F, Shi Z L. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol, 2019, 17: 181–192
63 Yewdell J W. Antigenic drift: understanding COVID-19. Immunity, 2021, 54: 2681–2687
64 Carabelli A M, Peacock T P, Thorne L G, et al. SARS-CoV-2 variant biology: immune escape, transmission and fitness. Nat Rev Microbiol, 2023, 21: 162–177
65 Zhang J, He R, Liu B, et al. Spike-specific CXCR3^{+} T_{FH} cells play a dominant functional role in supporting antibody responses in SARS-CoV-2 infection and vaccination. bioRxiv, 2022, 2022.08.09.503302
66 Qu P, Evans J P, Faraone J N, et al. Enhanced neutralization resistance of SARS-CoV-2 Omicron subvariants BQ.1, BQ.1.1, BA.4.6, BF.7, and

BA.2.75.2. Cell Host Microbe, 2023, 31: 9–17.e3
67 Yamasoba D, Uriu K, Plianchaisuk A, et al. Virological characteristics of the SARS-CoV-2 omicron XBB.1.16 variant. Lancet Infect Dis, 2023, 23: 655–656
68 Nemet I, Kliker L, Lustig Y, et al. Third BNT162b2 vaccination neutralization of SARS-CoV-2 Omicron infection. N Engl J Med, 2022, 386: 492–494
69 Wratil P R, Stern M, Priller A, et al. Three exposures to the spike protein of SARS-CoV-2 by either infection or vaccination elicit superior neutralizing immunity to all variants of concern. Nat Med, 2022, 28: 496–503
70 Edridge A W D, Kaczorowska J, Hoste A C R, et al. Seasonal coronavirus protective immunity is short-lasting. Nat Med, 2020, 26: 1691–1693
71 Cao W C, Liu W, Zhang P H, et al. Disappearance of antibodies to SARS-associated coronavirus after recovery. N Engl J Med, 2007, 357: 1162–1163
72 Kim Y S, Aigerim A, Park U, et al. Sustained responses of neutralizing antibodies against middle east respiratory syndrome coronavirus (MERS-CoV) in recovered patients and their therapeutic applicability. Clin Infect Dis, 2021, 73: e550–e558
73 Yang Y, Yang M, Peng Y, et al. Longitudinal analysis of antibody dynamics in COVID-19 convalescents reveals neutralizing responses up to 16 months after infection. Nat Microbiol, 2022, 7: 423–433
74 Zhong D, Xiao S, Debes A K, et al. Durability of antibody levels after vaccination with mRNA SARS-CoV-2 vaccine in individuals with or without prior infection. JAMA, 2021, 326: 2524–2526
75 Crotty S. T follicular helper cell biology: a decade of discovery and diseases. Immunity, 2019, 50: 1132–1148
76 Victora G D, Nussenzweig M C. Germinal centers. Annu Rev Immunol, 2022, 40: 413–442
77 Choi J, Crotty S. Bcl6-mediated transcriptional regulation of follicular helper T cells (TFH). Trends Immunol, 2021, 42: 336–349
78 Qi H. T follicular helper cells in space-time. Nat Rev Immunol, 2016, 16: 612–625
79 Qi H, Liu B, Wang X, et al. The humoral response and antibodies against SARS-CoV-2 infection. Nat Immunol, 2022, 23: 1008–1020
80 Wang Y, Tian Q, Ye L. The differentiation and maintenance of SARS-CoV-2-specific follicular helper T cells. Front Cell Infect Microbiol, 2022, 12: 953022
81 Juno J A, Tan H X, Lee W S, et al. Humoral and circulating follicular helper T cell responses in recovered patients with COVID-19. Nat Med, 2020, 26: 1428–1434
82 Dan J M, Mateus J, Kato Y, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science, 2021, 371: eabf4063
83 Rodda L B, Netland J, Shehata L, et al. Functional SARS-CoV-2-specific immune memory persists after mild COVID-19. Cell, 2021, 184: 169–183.e17
84 Gong F, Dai Y, Zheng T, et al. Peripheral CD4+ T cell subsets and antibody response in COVID-19 convalescent individuals. J Clin Invest, 2020, 130: 6588–6599
85 Zhang J, Wu Q, Liu Z, et al. Spike-specific circulating T follicular helper cell and cross-neutralizing antibody responses in COVID-19-convalescent individuals. Nat Microbiol, 2021, 6: 51–58
86 Turner J S, O'Halloran J A, Kalaidina E, et al. SARS-CoV-2 mRNA vaccines induce persistent human germinal centre responses. Nature, 2021, 596: 109–113
87 Turner J S, Kim W, Kalaidina E, et al. SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans. Nature, 2021, 595: 421–425
88 Liu Y, Zeng Q, Deng C, et al. Robust induction of B cell and T cell responses by a third dose of inactivated SARS-CoV-2 vaccine. Cell Discov, 2022, 8: 10
89 Bentebibel S E, Lopez S, Obermoser G, et al. Induction of $ICOS^{+}CXCR3^{+}CXCR5^{+}$ T_H cells correlates with antibody responses to influenza vaccination. Sci Transl Med, 2013, 5: 176ra132
90 Koutsakos M, Wheatley A K, Loh L, et al. Circulating T_{FH} cells, serological memory, and tissue compartmentalization shape human influenza-specific B cell immunity. Sci Transl Med, 2018, 10: eaan8405
91 Niessl J, Baxter A E, Morou A, et al. Persistent expansion and Th1-like skewing of HIV-specific circulating T follicular helper cells during antiretroviral therapy. Ebiomedicine, 2020, 54: 102727
92 Liang H, Tang J, Liu Z, et al. ZIKV infection induces robust Th1-like Tfh cell and long-term protective antibody responses in immunocompetent

mice. Nat Commun, 2019, 10: 3859

93 Zhang J, Liu W, Wen B, et al. Circulating CXCR3^{+} Tfh cells positively correlate with neutralizing antibody responses in HCV-infected patients. Sci Rep, 2019, 9: 10090

Research progress on the neutralizing antibody response to SARS-CoV-2

TENG ShiShan & QU XiaoWang

Hengyang Medical School, University of South China, Hengyang 421001, China

SARS-CoV-2, the third coronavirus outbreak in humans in the first two decades of 21st century, has caused widespread epidemics and transmission worldwide. As an important component of the specific immune response, neutralizing antibodies play a vital role in the prevention and control of novel coronavirus infections. A sustained, broad-spectrum neutralizing antibody response is essential for the prevention of SARS-CoV-2 variants and potential future outbreaks of animal-derived coronaviruses. High affinity neutralizing antibodies production and maintenance are dependent on follicular helper T cells, which are essential for germinal center formation and maintain and regulate the differentiation of germinal center B cells into memory B cells and plasma cells. Clarification of the characteristics, broad spectrum, and persistence of neutralizing antibody responses upon infection and vaccination with SARS-CoV-2 and the key immune cells involved in the antibody response, such as T_{FH} cells will be an important guide for the development of the next generation of broad-spectrum, long-lasting coronavirus vaccines. This review aims to summary the progress of research on the neutralizing antibody response induced by natural infection and vaccination of SARS-CoV-2 providing insights for the development of next-generation coronavirus vaccines.

SARS-CoV-2, neutralizing antibody, T follicular helper cell

doi: 10.1360/SSV-2023-0084