Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Infectious Diseases Now xxx (xxxx) xxx

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Original article

What are the prospects for durable immune control?

J.D. Lelievre [a], J. Bauer [b,*]

[a] Immunologie clinique et maladies infectieuses, Hôpital Henri-Mondor, 94000 Créteil, France
[b] Service Universitaire des Maladies Infectieuses et du Voyageurs, CH Dron, 59200 Tourcoing, France

ARTICLE INFO

Article history:
Available online xxxx

Keywords:
SARS CoV-2
Neutralizing antibodies
Immune control
Vaccine immunogenicity
Immune memory

ABSTRACT

During the SARS CoV-2 primary infection, the neutralizing antibodies focused against the spike (S) glycoproteins are responsible for blockage of virus-host cell interaction. The cellular response mediated by CD4+ and CD8+ T-cells is responsible for control of viremia.

Immune memory against SARS-CoV-2 depends on virus type, replication kinetics and route of penetration. The formation and persistence of germinal centers are critical for the generation of affinity-matured plasma cells and memory B cells capable of mediating durable immunity. They can persist up to 30 weeks after vaccination and several months after infection. Heterogeneity in the longevity of the vaccination-induced GC response is significant.

1. Introduction

During primary infection, the main determinants of immune response are the neutralizing antibodies directed against the spike (S) glycoproteins and responsible for blockage of virus-host cell interaction. The cellular response mediated by CD4+ and CD8+ T-cells is responsible for control of viremia. Certain populations of CD8 T-cells are found in the mucous membranes. These tissue-resident-memory cells are difficult to study but seem to play a crucial role in immune response against COVID-19. The mucosal immune response varies from one individual to another, correlated or not with the systemic response or the severity of the symptoms, and it also depends on the local microbiome [1].

Immune memory against SARS-CoV-2 depends on several parameters: virus type, replication kinetics and the route of penetration. To be effective against a high-replicating kinetic virus such as SARS-CoV-2, neutralizing antibody titers need to be high.

Immune control durability against other coronaviruses responsible for mild upper respiratory tract infection has been studied. Eguia RT et al. found that as human coronavirus 229E evolves, its spike protein accumulates mutations (4 % divergence between the spikes and 17 % divergence in their RBDs) that escape neutralization by older human sera. The rate at which viral evolution degrades immunity varies among individuals, but in some cases less than a decade of evolution is sufficient to completely eliminate neutralization by human sera, which is potent against contemporaneous viruses [2]. The above-mentioned spikes and RDB mutations occur more rapidly in SARS-CoV-2 and explain the currently observed immune evasion to antibody neutralization. Callow KA et al. showed in a viral challenge study that significantly higher neutralizing antibody titers could protect individuals against reinfection [3].

Humoral responses against SARS-CoV-2 follow the classical adaptative immune response pathway, with establishment of a germinal center allowing the differentiation of short-lived plasma cells into long-lived plasma cells and memory B cells. The latter have receptors for immunoglobulins adapting over time under the influence of antigenic stimulation. Germinal center (GC) formation and persistence are critical in the generation of affinity-matured plasma cells and memory B cells capable of mediating durable immunity. They can persist up to 30 weeks after vaccination and for several months after infection [4]. Heterogeneity in the longevity of vaccination-induced GC response is significant.

Besides germinal centers, long-lived plasma cells represent a key cell population responsible for long-term antibody production and serological memory [5]. They are found in bone marrow, of which the fatty involution seen in elderly patients could explain the decreased immune response. One of the hypotheses explaining the low immunogenicity of COVID-19-vaccine is the low density of spike (S) glycoprotein and the consequently small number of antigens exposed to plasma cells and memory B cells.

The maturation of memory B-cells occurs over time (up to 6 months after SARS-CoV-2 infection), and it may provide long-term protection [6]. B-cell clones expressing broad and potent antibodies are selectively retained in the repertoire over time and markedly expand after infection and vaccination. Maturation of memory B-cells consequently counterbalances the decline of antibody titer (Table 1).

* Corresponding author.
E-mail address: bauerjules@gmail.com (J. Bauer).

https://doi.org/10.1016/j.idnow.2022.09.010

Please cite this article as: J.D. Lelievre and J. Bauer, What are the prospects for durable immune control?, Infectious Diseases Now, https://doi.org/10.1016/j.idnow.2022.09.010

Table 1
Memory B cell and antibody response according to Laidlaw BJ & Ellebedy AH [4].

Memory B cell response		over time →		
Memory B cell number		+	++	+++
Memory B cell-derived antibody	Neutralizing activity	+	++	+++
	Neutralizing breadth	+	++	+++
Overall antibody response		**over time →**		
Titers		+++	++	+
Neutralizing activity		+	++	+++
Neutralizing breadth		+	++	+++

Wang Z et al. suggested that immunity in convalescent individuals is very long-lasting and that convalescent individuals who receive available mRNA vaccines will produce antibodies and memory B cells likely to be protective against circulating SARS-CoV-2 variants [7]. However, maturation of memory B cells after two doses of vaccine is less pronounced than after infection and requires an additional dose for the cells to continue to mature [8]. Two shots of the mRNA vaccines induce peak antibody and memory B cell responses against SARS-CoV-2 in naïve patients, whereas only one shot induces peak responses in convalescent patients [9].

In Omicron infections, the plasma cell antibody production related to previous infection by non-Omicron variants or to a vaccine based on the Wuhan strain is insufficient [10]. A booster dose is needed to obtain significant maturation of memory B cells and to stimulate neutralization activity. Today's populations are heterogeneous with regard to humoral immunity. While convalescent serum infected by the Wuhan/D614G strain prior to vaccination has no neutralizing immunity against Omicron, a high level of neutralization has been observed in serum from vaccinated persons secondarily infected by the Delta variant [11].

After two doses, vaccine effectiveness wanes rapidly, with limited effects on infection and mild disease occurring as soon as 20 weeks later, whatever the vaccine [12]. On the other hand, effectiveness against severe disease and fatal outcome, which is driven by cellular immunity mediated by T cells, is usually preserved after infection or a two-dose regimen [13]. Vaccination (with mRNA vaccine) induces an anti-spike T-cell response quantitatively equivalent to infection but with a more pronounced CD8 response in the event of infection [14].

Contrary to B-cell epitopes, T-cell epitopes are antigens located outside spike (S) glycoproteins (M antigen, N antigen, Open Reading Frame) and have no role in viral fitness; as a result, they are not affected by mutations occurring during viral evolution. Jergovic M. et al. showed that T-cell responses against Omicron spike peptides are generally preserved and that IFN-γ producing T-cell responses remain equivalent to the response against the ancestral strain [15]. Although T cell response seems scarcely impacted by Omicron, we do not yet have data comparing the post-infectious T-cell responses with other strains.

Vaccine schedules seems to have a significant impact, insofar as extension of the dosing interval leads to an increase in peak neutralizing antibodies and B-cells that is consistent with plasma cell maturation. Whereas an extended regimen enriches virus-specific CD4+ T cells, an overly abbreviated regimen may decrease T-cell population [13].

In conclusion, the impact of variants on immune response has a predominant effect on humoral immunity. Similar findings could be of crucial importance in determination of the main orientations of vaccination policy: Should we continue vaccination with current vaccines so as to protect the most vulnerable individuals, or should we develop new vaccines that will impact cellular immunity and mucosal immunity? What is the optimal timing for a booster dose, taking into account a predictable decrease in neutralizing antibody titers and plasma cell maturation?

2. Disclosure of interest

The authors declare no conflict of interest.

3. Funding

The meeting in which this topic was presented was funded by the French Infectious Diseases Society (SPILF).

4. Authors' contributions

All authors contributed equally to this work.

References

[1] Smith N, Goncalves P, Charbit B, Grzelak L, Beretta M, Planchais C, et al. Distinct systemic and mucosal immune responses during acute SARS-CoV-2 infection. Nat Immunol 2021;22(11):1428–39.
[2] Eguia RT, Crawford KHD, Stevens-Ayers T, Kelnhofer-Millevolte L, Greninger AL, Englund JA, et al. A human coronavirus evolves antigenically to escape antibody immunity. PLOS Pathog 2021;17(4):e1009453.

[3] Callow KA, Parry HF, Sergeant M, Tyrrell D, a., J.. The time course of the immune response to experimental coronavirus infection of man. Epidemiol Infect 1990;105:435–46.
[4] Laidlaw BJ, Ellebedy AH. The germinal centre B cell response to SARS-CoV-2. Nat Rev Immunol 2022;22(1):7–18.
[5] Hammarlund E, Thomas A, Amanna IJ, Holden LA, Slayden OD, Park B, et al. Plasma cell survival in the absence of B cell memory. Nat Commun 2017;8(1).
[6] Sokal A, Chappert P, Barba-Spaeth G, Roeser A, Fourati S, Azzaoui I, et al. Maturation and persistence of the anti-SARS-CoV-2 memory B cell response. Cell 2021;184(5):1201–1213.e14.
[7] Wang Z, Muecksch F, Schaefer-Babajew D, Finkin S, Viant C, Gaebler C, et al. Naturally enhanced neutralizing breadth against SARS-CoV-2 one year after infection. Nature 2021;595(7867):426–31.
[8] Cho A, Muecksch F, Schaefer-Babajew D, Wang Z, Finkin S, Gaebler C, et al. Anti-SARS-CoV-2 receptor-binding domain antibody evolution after mRNA vaccination. Nature 2021;600(7889):517–22.
[9] 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 after mRNA vaccination. Sci Immunol 2021;6(58).
[10] Planas D, Saunders N, Maes P, Guivel-Benhassine F, Planchais C, Buchrieser J, et al. Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. Nature 2022;602(7898):671–5.
[11] Walls AC, Sprouse KR, Bowen JE, Joshi A, Franko N, Navarro MJ, et al. SARS-CoV-2 breakthrough infections elicit potent, broad, and durable neutralizing antibody responses. Cell 2022;185(5):872–880.e3.
[12] Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. N Engl J Med 2022;386(16):1532–46.
[13] Payne RP, Longet S, Austin JA, Skelly DT, Dejnirattisai W, Adele S, et al. Immunogenicity of standard and extended dosing intervals of BNT162b2 mRNA vaccine. Cell 2021;184(23):5699–5714.e11.
[14] Painter MM, Mathew D, Goel RR, Apostolidis SA, Pattekar A, Kuthuru O, et al. Rapid induction of antigen-specific CD4+ T cells guides coordinated humoral and cellular immune responses to SARS-CoV-2 mRNA vaccination. Immunity 2021;386(16):1532–46.
[15] Jergovic M, Coplen CP, Uhrlaub JL, Beitel SC, Burgess JL, Lutrick K, et al. Resilient T cell responses to B.1.1.529 (Omicron) SARS-CoV-2 variant. Infectious Diseases (except HIV/AIDS); 2022 janv [cité 29 mars 2022]. Disponible sur: http://medrxiv.org/lookup/doi/10.1101/2022.01.16.22269361.