https://doi.org/10.31005/iajmh.v4i.185

INTERAMERICAN JOURNAL OF MEDICINE AND HEALTH

The importance of the cellular immune response in Covid-19

Marcelo Henrique Napimoga[1], Antônio José de Pinho Jr[1]

Vaccines have transformed public health, particularly since the national immunization programs that were established and started in the 1970's in Brazil. In the past few weeks, we have seen the emergence of variants of SARS-CoV-2 (Severe Acute Respiratory Syndrome CoronaVirus 2), and the implications for public health are not yet known [1].

In vitro studies have highlighted the decrease in the neutralization of new viral variants by antibodies produced after vaccine stimulation, however, it is also important to highlight cell-mediated immunity (T lymphocytes) [2]. In fact, the mutations that are being described for SARS-CoV-2, raises concerns and questions about immunity acquired naturally (after remission of the disease) or through one of the vaccines that are being used around of the world. Data from the onset of the disease suggested that it could be compared to serious historical epidemics, such as the 1918 influenza epidemic [3], which over time has proved to be true.

Currently, doubts are being raised about the effectiveness of vaccines in these new described variants. However, due to the development in record time of vaccines, it has not yet been possible to establish all the data on the immune response so that in addition to highlighting the role of the humoral response (mediated by antibodies), it is also important that mediated by cells (T lymphocytes). From studies of individuals with acquired immunodeficiency, it is clear that while people with deficiency in the production of antibodies increases the susceptibility to the acquisition of infection, those who have T cell deficiency result in failure to control the pathogen after infection. For example, individuals with T cell deficiency infected by the varicella zoster virus are not able to control infection, becoming fatal, while individuals with antibody deficiency readily develops infection, but recover in the same way as immunocompetent individuals. Although the evidence for T cell involvement in vaccine-induced protection is limited, this is likely due, in part, to difficulties in accessing T cells to study once many T cells reside in tissues, as lymph nodes [4].

One of the main characteristics associated with an effective vaccine against SARS-CoV-2 is to develop neutralizing antibodies directed towards the spike protein. Antibodies to the SARS-CoV-2 receptor-binding domain (RBD) are critical to preventing virus entry into cells. Recent studies have shown that antibodies that bind to the RBD domain receptor are critical for long-term protective immunity to COVID-19 infection and are associated with better patient survival [5]. In a recent article it was demonstrated that the durability and robustness of the anti-SARS-CoV-2 antibody directed against RBD in 34 patients suspected or infected with SARS-CoV-2 showed a rapid decline in IgG antibodies directed to the SARS-CoV-2 RBD. Because of this decline, in his opinion, "they raise concerns that humoral immunity against SARS-CoV-2 may not be long-lasting in people with mild illness, which make up the majority of people with COVID-19 [6].

It is important to highlight that the initial responses mediated by IgG antibodies emanate from the germinal centers after the follicular T cells activate the virgin B cells to mature into activated B cells that progress to memory B cells and IgG-producing plasma cells. Plasma cells are short-lived and with dissipation, the initial IgG responses are eliminated. However, it should be understood that

Reprint requests and correspondence to:
Marcelo H. Napimoga, DDS, PhD (http://orcid.org/0000-0003-4472-365X)
Laboratory of Neuroimmune Interface of Pain Research, Faculdade São Leopoldo Mandic
R. José Rocha Junqueira, 13 Campinas/SP, 13045-755, Brazil
Telephone/fax: +55 19 3211 3600
E-mail: marcelo.napimoga@gmail.com or marcelo.napimoga@slmandic.edu.br

this does not mean that immunity has decreased, since the persistence of memory B cells and long-lived plasma cells residing in the bone marrow can reactivate specific antigen responses to the SARS-CoV-2 RBD domain. If an individual is exposed again, therefore, the classic secondary response that starts more quickly than the primary, has no IgM production, produces usually higher levels of IgG and finally with more specific antibodies and with greater binding capacity. In addition, the importance of T cell memory for the SARS-CoV-2 antigen must be taken into account, which can result in direct immunity of cytotoxic T cells and help with B cell responses [7].

In a previous study, CD4+ T cell responses against glycoprotein spike in the peripheral blood of patients with positive SARS-CoV-2 were examined, as well as in healthy controls. Spike reactive CD4+ T cells were detected in 83% of infected individuals. However, there was also the detection of reactive CD4+ T cells against spike protein in the peripheral blood of 35% of healthy donors [8]. CD4+ T cells against spike in healthy donors were targeted against the C-terminal epitopes of the spike protein and these epitopes were identified in endemic coronavirus spike proteins that are responsible for seasonal infections of the upper respiratory tract. In contrast to SARS-CoV-2, reactive CD4+ T cells from healthy donors also responded against the endemic human coronavirus spike protein 229E and OC43. This data raises important considerations since these CD4+ T cells can exert cross-immune responses to SARS-CoV-2 infection, including against the various genotypes of COVID-19 [9].

Another study used blood samples collected before the discovery of SARS-CoV-2 (2015-2018) and demonstrated the presence of memory CD4+ T cells against 142 SARS-CoV2 genome epitopes with similar affinity to those identified in patients recovering from infection by SARS-CoV-2, demonstrating the importance of CD4+ T cells in creating durable and cross-reacting immune responses to human coronaviruses, including SARS-CoV-2 [10].

In terms of understanding the duration and effectiveness of T cell responses to SARS-CoV-2, it is too early to determine this, as long-term studies will be needed in large populations. However, data presented previously are encouraging, since T cells reacted with multiple epitopes on SARS-CoV-2 [11]. At this point, little information is available on the presence or duration of B cells of SARS-CoV-2 reactive memory. However, it is important to note that the SARS-CoV-1 specific memory T cell can be detected 17 years after infection begins [12]. In a preprint published on February 9, the researchers found that most T-cell responses to vaccination against coronavirus or previous infection do not target regions that have been mutated into two recently discovered variants, including 501Y.V2 [13].

The ChAdOx1 nCoV-19 vaccine (AZD1222) consists of the replication-deficient simian adenovirus vector ChAdOx1, containing the structural full-length SARS-CoV-2 glycoprotein spike (GenBank MN908947). The humoral response to the SARS-CoV-2 spike protein peaked after 28 days of inoculation, and the cellular immune response was induced in all participants after 14 days of inoculation. Neutralizing antibodies were induced in all participants after a second dose of vaccine. Therefore, after two doses, a potent cellular and humoral response was present in all study participants [14]. The presence of cellular immunity seems to be fundamental for the persistence of a robust response to the virus in case of new exposure, especially in relation to these new variants, since complete loss of cross-immunity is unlikely when a T-dependent response has been established. Even the collaboration between T and B lymphocytes can be essential for persistent immunity as demonstrated in other immunization models [15]. This information is not available for the other vaccine that is being used in our country, since in the published study of Coronavac cell immunity was not evaluated [16]. However, vaccines with inactive viruses, without the presence of conjugate, are not good T-response activators and may need more frequent vaccine booster. Extrapolating this need to individuals recovered from illness, even in the asymptomatic form, seems an exaggeration since we never had any data to prove this hypothesis.

In the case of the current SARS-CoV-2 virus pandemic, there is an expectation that vaccines already approved will prevent the worsening and hospitalization caused by Covid-19 and could have a substantial impact on the public health of this disease around the world. At this point, we need to understand the entire context of the immune response to approved vaccines, and whether the new variants will have any impact on vaccine strategy.

Acknowledgements

This work was supported in part by the Brazilian funding agency São Paulo Research Foundation (FAPESP) (#2017/22334-9); Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) - Research Productivity

Fellowship to MHN and MCTIC (Ministério da Ciência, Tecnologia, Inovação e Comunicação)/CNPq.

REFERÊNCIAS

1. Freitas ARR, Giovanetti M, Alcantara LC. Variantes emergentes do SARS-CoV-2 e suas implicações na saúde coletiva. InterAm J Med Health 2021; 4:1-8.

2. Graham C, Seow J, Huettner I, et al. Impact of the B.1.1.7 variant on neutralizing monoclonal antibodies recognizing diverse epitopes on SARS-CoV-2 Spike. bioRxiv [Preprint]. 2021 Feb 3:2021.02.03.429355. doi: 10.1101/2021.02.03.429355. PMID: 33564766; PMCID: PMC7872354.

3. Freitas ARR, Napimoga M, Donalisio MR. Assessing the severity of COVID-19. Epidemiol Serv Saude. 2020;29(2):e2020119. doi: 10.5123/S1679-49742020000200008.

4. Pollard AJ, Bijker EM. A guide to vaccinology: from basic principles to new developments. Nat Rev Immunol. 2021 Feb;21(2):83-100. doi: 10.1038/s41577-020-00479-7.

5. Barnes CO, Jette CA, Abernathy ME, et al. SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies. Nature. 2020 Oct 12; 588: 682-687.

6. Ibarrondo FJ, Fulcher JA, Goodman-Meza D, et al. Rapid Decay of Anti-SARS-CoV-2 Antibodies in Persons with Mild Covid-19. N Engl J Med. 2020 Sep 10;383(11):1085-1087.Jordan SC. Innate and Adaptive Immune Responses to SARS-CoV-2 in Humans: Relevance to Acquired Immunity and Vaccine Responses. Clin Exp Immunol. 2021 Feb 3. doi: 10.1111/cei.13582. Online ahead of print.

7. Dan J, Mateus J, Yu K, et al. Immunological memory to SARS-CoV-2 assessed for greater than six months after infection. bioRxiv preprint doi: https://doi.org/10.1101/2020.11.15.383323.

8. Braun J, Loyal L, Frentsch M, et al. SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. Nature. 2020; 587: 270-274

9. Jordan SC. Innate and Adaptive Immune Responses to SARS-CoV-2 in Humans: Relevance to Acquired Immunity and Vaccine Responses. Clin Exp Immunol. 2021 Feb 3. doi: 10.1111/cei.13582.

10. Mateus J, Grifoni A, Tarke A. et al Selective and cross-reactive SARS-CoV-2 T-Cell epitopes in unexposed humans. Science. 2020; 370:89-94.

11. Peng Y, Mentzer A, Liu G, et al. Broad and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19. Nature Immunology. 2020; 21: 1336-1345.

12. Le Bert N, Tan A, Kunasegaran K, et al. SARS-CoV-2 specific Tcell immunity in cases of COVID-19 and SARS, and uninfected controls. Nature. 2020; 584: 457-462.Mateus J, Grifoni A, Tarke A. et al Selective and cross-reactive SARS-CoV-2 T-Cell epitopes in unexposed humans. Science. 2020; 370:89-94.

13. Skelly DT, Harding AC, Gilbert-Jaramillo J, et al. Preprint at https://www.researchsquare.com/article/rs-226857/v1. 2021.

14. Folegatti PM, Ewer KJ, Aley PK, et al. Oxford COVID Vaccine Trial Group. 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 Aug 15;396(10249):467-478. doi: 10.1016/S0140-6736(20)31604-4.

15. Malley R, Trzcinski K, Srivastava A, Thompson CM, Anderson PW, Lipsitch M. CD4+ T cells mediate antibody-independent acquired immunity to pneumococcal colonization. Proc Natl Acad Sci U S A. 2005 Mar 29;102(13):4848-53. doi: 10.1073/pnas.0501254102.

16. Wu Z, Hu Y, Xu M, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. 2021 Feb 3:S1473-3099(20)30987-7. doi: 10.1016/S1473-3099(20)30987-7.