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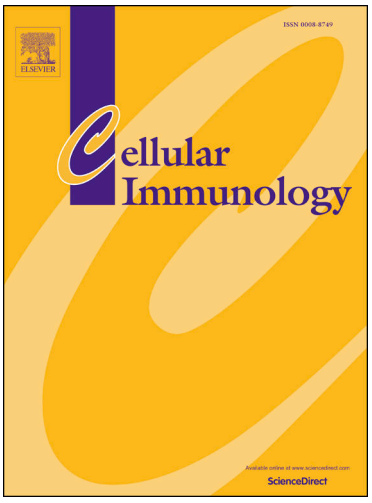

Protective immunity after COVID-19 has been questioned: what can we do without SARS-CoV-2-IgG detection?

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Title Page

Title: Protective immunity after COVID-19 has been questioned: what can we do without SARS-CoV-2-IgG detection?

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Severe acute respiratory syndrome corona virus 2 (~~The~~ SARS-CoV-2) induces a severe acute respiratory syndrome that is called ~~named as~~ COVID~~ovid~~-19. Clinical manifestations of COVID~~ovid~~-19 include diarrhea, pneumonia, lymphopenia, exhausted lymphocytes, and pro-inflammatory cytokine production. Immunology is part of the process of clinical evolution, but there are some questions around immunity-based~~ity~~ protection: (1) why ~~How~~ some infected people have only mild symptoms of the disease or are asymptomatic;~~?~~ (2) w~~W~~hy delayed and weak antibody responses are associated with severe outcomes;~~?~~ and (3) w~~W~~hy ~~the~~ positivity i~~o~~n molecular tests does not represent protective antibody~~ies~~ IgG.~~?~~ ~~-~~Perhaps T cell responses may be the~~a~~ key to solving~~e~~ those questions. ~~The~~ SARS-CoV-2-specific memory T cells persist ~~emerging~~ in peripheral blood and may be capable of~~it is able to~~ providing~~e~~ effective information about protective immunity. The T cells studies can be helpful int~~o~~ elucidating~~e~~ the pathways for development of vaccines, therapies, and diagnostics for COVID~~ovid~~-19 and for filling these immunology knowledge gaps.

Revised Manuscript – Correspondence – with track changes

Currently, the world is experiencing ~~experiencing~~ a~~the~~ novel and highly transmissible coronavirus (SARS-CoV-2) outbreak, which also ~~with high transmissibility and~~ causes high mortality [1,2]. ~~The~~ SARS-CoV-2 induces a severe acute respiratory syndrome, termed ~~named as~~ COVID~~ovid~~-19, in which immunology is part of the process of clinical evolution consisting of ~~with~~ lung tissue damage induced by an inflammatory response, such as a cytokine storm and~~,~~ macrophage~~s~~ and neutrophil~~s~~ activation [1,2]. ~~During infection,~~ A few studies have presented~~showed~~ ~~some~~ information about the immune response during this infection ~~attempting to control the infection~~, which involves ~~is driven to the~~ antibody~~ies~~ production and lymphocyte~~s~~ T cell activation, but the information is restricted to those ~~hospitalized~~ patients who were hospitalized because they had the virus and were symptomatic. ~~.~~ Over~~In~~ the ~~natural~~ course of the disease in ~~history with thos~~the~~e~~ hospitalized patient~~s~~ who recovered, ~~s,~~ antibody~~ies~~ production was shown to increase ~~is increasing~~ after the first week~~s~~ of symptom~~s~~ onset, which is ~~in recovery patients with hospitalization history, with a~~ suggestive positive correlation with disease severity [3,4]~~,~~ while T cells were also ~~are~~ activated; it ~~and~~ seems that memory phenotype also showed an increase ~~has also risen~~ after 14 days of hospitalization [5,6]. However, there are some questions around ~~-~~immunity-based~~ity~~ protection with respect to who does and does not need hospitalization.~~,~~ ~~and~~ T~~t~~he non-hospitalized~~is~~ population is considered a~~s~~ viral host by~~,~~ carrying the virus around~~,~~ and contributing ~~collaborating~~ to the spread of the virus ~~virus spread~~. Also, the other barrier in this outbreak is related to asymptomatic cases, mainly i~~o~~n health care professionals in the hospital, which could contribute to ~~increase~~ the increase in the number of ~~the~~ cases. The solution to stopping the viral spread appears to ~~has been~~ be ~~direct to~~ social distancing and massive testing, mainly for antibody~~ies~~ detection. Surprisingly, some ~~a part of~~ people who ~~are~~ presented ~~ing~~ positivity i~~o~~n results from the

furthermore,~~even more,~~ neutralizing antibodies were ~~are~~ low~~er~~ or not at all present~~,~~ even ~~though~~ in hospitalized patients [3,4]. This situation raise~~sd~~ questions about protective immunity and about the time need~~ed~~ for quarantine. Given that, a few studies have already show~~ned~~ that T cells might be the key to solv~~inge~~ this ~~dilemmaissue~~. Despite the finding that the virus can induce lymphopenia and cause a ~~the~~ delay in T cell~~s~~ pathway activation during~~on~~ the first days of infection, after two weeks of symptoms, SARS-CoV-2-specific memory T cell~~s~~ phenotypes (central memory for CD4 and effector memory for CD8 lymphocytes) start to emerg~~eing~~ in the peripheral blood. This process is capable ~~d and it is able~~ of ~~to~~ provid~~inge~~ useful ~~effective~~ information about protective immunity [6]. The data that are needed to describe ~~about~~ how the memory phenotypes of T cells can differentiate ~~on a~~ has~~follow-up study is~~ not been elucidated yet. ~~, and~~ The minimal amount of ~~few~~ information ~~available~~ is restricted to preprint~~ed~~ manuscripts, but it is enough to start a ~~have some~~ discussion about how the immune response should be evaluated. Nowadays, we have some vaccines targeting only T cell activation, thus providing robust memory T cell response, but the~~se~~ studies are still i~~o~~n the preclinical phase. Actually, we have seen a change in the protective immunity status o~~fn~~ viral diseases during vaccination~~,~~ in which ~~where~~ no ~~n~~ antibod~~yies~~ detection does not relate to ~~with~~ protective status because memory T cells can be activated and protect people from~~to~~ subsequent~~ly~~ reinfection [7,8]. Regarding respiratory infections, it also should be noted that viruses are ~~on~~ constantly changing~~e~~ via the~~,~~ induction of~~ing~~ viral mutations that can contribute to the viral escape of the host immune system. One of our hypotheses concerning ~~around~~ the novel coronavirus suggest it has the~~is about its~~ power to reduce B cell activity. ~~and~~ T~~t~~his pathway should be further explored. There is urgent need for solutions addressing ~~around~~ the time needed for quarantine in order to prevent shutting the economy down. There ~~to do not shut down the economy~~ may be ~~have~~ an answer to this problem in cellular response assays, in which the cost is similar compared to neutralizing antibodies tests. Once we can evaluate a small

cells after disease, ~~("in vitro" assays),~~ this will be enough to guarantee the immunity protection. Lymphocyte~~s~~ T cell assays ~~, have as Elispot tests (e.g.), has high~~s specificity and sensitivity. ~~and T~~there is a lot of information about how to assay ~~set up the~~ T cell immunity after infection, such as proliferation assays using viral particles as stimulators [9,10] and ~~,~~ also by optimizing the assays in B~~b~~iosafety L~~l~~evel 2 labs. The T cell assays could help ~~to~~ estimate the population's (hospitalized or not) immunity~~, hospitalized or not,~~ and will be feasible for ~~developing~~ countries with specialized immunology laboratories. Adding to that, the cellular assays will provide information that is useful ~~for~~ vaccine development to prevent and control this viral disease.

References

[1] C. Qin, L. Zhou, Z. Hu, S. Zhang, S. Yang, Y. Tao, C. Xie, K. Ma, K. Shang, W. Wang, D.-S. Tian, Dysregulation of immune response in patients with COVID-19 in Wuhan, China, Clin. Infect. Dis. (2020). https://doi.org/10.1093/cid/ciaa248.

[2] Y. Shi, Y. Wang, C. Shao, J. Huang, J. Gan, X. Huang, E. Bucci, M. Piacentini, G. Ippolito, G. Melino, COVID-19 infection: the perspectives on immune responses, Cell Death Differ. (2020) s41418-020-0530–3. https://doi.org/10.1038/s41418-020-0530-3.

[3] A.T. Huang, B. Garcia-Carreras, M.D.T. Hitchings, B. Yang, L. Katzelnick, S.M. Rattigan, B. Borgert, C. Moreno, B.D. Solomon, I. Rodriguez-Barraquer, J. Lessler, H. Salje, D.S. Burke, A. Wesolowski, D.A.T. Cummings, A systematic review of antibody mediated immunity to coronaviruses: antibody kinetics, correlates of protection, and association of antibody responses with severity of disease, Infectious Diseases (except HIV/AIDS), 2020. https://doi.org/10.1101/2020.04.14.20065771.

[4] F. Wu, A. Wang, M. Liu, Q. Wang, J. Chen, S. Xia, Y. Ling, Y. Zhang, J. Xun, L. Lu, S. Jiang, H. Lu, Y. Wen, J. Huang, Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications, Infectious Diseases (except HIV/AIDS), 2020. https://doi.org/10.1101/2020.03.30.20047365.

[5] I. Thevarajan, T.H. Nguyen, M. Koutsakos, J. Druce, L. Caly, C.E. van de Sandt, X. Jia, S. Nicholson, M. Catton, B. Cowie, S. Tong, S. Lewin, K. Kedzierska, Breadth of concomitant immune responses underpinning viral clearance and patient recovery in a non-severe case of COVID-19, Infectious Diseases (except HIV/AIDS), 2020. https://doi.org/10.1101/2020.02.20.20025841.

[6] D. Weiskopf, K.S. Schmitz, M.P. Raadsen, A. Grifoni, N.M.A. Okba, H. Endeman, J.P.C. van den Akker, R. Molenkamp, M.P.G. Koopmans, E.C.M. van Gorp, B.L. Haagmans, R.L. de Swart, A. Sette, R.D. de Vries, Phenotype of SARS-CoV-2-specific T-cells in COVID-19 patients with acute respiratory distress syndrome, Infectious Diseases (except HIV/AIDS), 2020. https://doi.org/10.1101/2020.04.11.20062349.

individuals who had lost protective antibodies after hepatitis B vaccination, Vaccine. 24 (2006) 572–577. https://doi.org/10.1016/j.vaccine.2005.08.058.

[8] J.G. Melgaço, L.N. Morgado, M.A. Santiago, J.M. de Oliveira, L.L. Lewis-Ximenez, B. Hasselmann, O.G. Cruz, M.A. Pinto, C.L. Vitral, A single dose of inactivated hepatitis A vaccine promotes HAV-specific memory cellular response similar to that induced by a natural infection, Vaccine. 33 (2015) 3813–3820. https://doi.org/10.1016/j.vaccine.2015.06.099.

[9] E.J. Grant, S.M. Quiñones-Parra, E.B. Clemens, K. Kedzierska, Corrigendum to "Human influenza viruses and CD8+ T cell responses" [Curr. Opin. Virol. 16 (2016) 132-142], Curr Opin Virol. 19 (2016) 99. https://doi.org/10.1016/j.coviro.2016.08.015.

[10] A. Pizzolla, L.M. Wakim, Memory T Cell Dynamics in the Lung during Influenza Virus Infection, J. Immunol. 202 (2019) 374–381. https://doi.org/10.4049/jimmunol.1800979.