

REVIEW

Lymphopenia in COVID-19: Therapeutic opportunities

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is uncontrollably spread all over the world. The host immune responses strongly try to confront it with all the potential cells and cytokines. With chronically condition of SARS-CoV-2, natural killer cells and T cells become exhausted and decreasing their count leads to lymphopenia. Inability to eradicate the infected organ makes hyperinitiation of the immune system, which releases the excessive inflammatory cytokines to compensate the exhausted one as well as the low lymphocytes counts; it consequently leads to the cytokine storm syndrome. These mechanisms and the potential therapeutic targeting are discussed in this paper.

KEYWORDS

apoptosis, coronavirus, COVID-19, cytokine storm syndrome, inflammation, lymphopenia

1 | INTRODUCTION

Coronavirus belongs to a huge family of viruses, leading to heterogeneous group of disorders, from common cold to life-threatening diseases. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an underinvestigation strain of coronavirus that causes coronavirus disease 2019 (COVID-19), for which no effective treatment has been found until now. The outbreak of SARS-CoV-2 has rapidly spread throughout the world (Hanaei & Rezaei, 2020).

Recent studies have shown that lymphopenia with cytokine storm syndrome is found frequently among patients with COVID-19. These features could reveal that the adjusted immune system plays a key role in determining disease progress (Saghazadeh & Rezaei, 2020a). Thus, this paper aims to provide a review on mechanisms of lymphopenia and a perspective on the potential treatments.

2 | HOST IMMUNE RESPONSE

The efficient immune system is the basis of control and eradication of infections, but uncontrollable reactions likely lead to immunopathogenesis. The angiotensin-converting enzyme 2 of the host

cells membrane is the acceptor for S proteins of coronavirus. This binding causes a fusion between virus and the host cells releasing its RNA into the cells. Since coronavirus is an RNA virus, it is evident that these RNAs are identified by RNA sensors in cytosol such as RIG-I/MDA5 and receptors located endosomes, for example, Toll-like receptor 3 (TLR)-3 and TLR-7. Consequently, the downstream signaling cascade produces the proinflammatory cytokines and type I Interferons (IFN- α/β ; Kawai & Akira, 2010). IFN- α/β has an important role in early stages of viral infection by inhibiting the diffusion and replication of virus. The genomic similarity of SARS-CoV and SARS-CoV2 is roughly 88%. Continuous viral replication leads to the excessive release of type I IFN, and consequently, to the invasion of macrophages and neutrophils to various tissues and hyperproduction of proinflammatory cytokines. When COVID-19 breaks out, the total number of neutrophils and lymphocytes, which generate uncontrolled viral replication in early stages of infection, could be changed (M. Zheng et al., 2020).

In SARS-CoV, similar to other viruses, the adaptive immune response plays a critical role to restrict the viral infections. Natural killer (NK) cells and cytotoxic T cells (CTLs) have the ability to kill the viral infected cells, whereas the helper T lymphocytes adjust the total adaptive immune response. Antibodies have a protective role to limit

Abbreviations: CD, cluster of differentiation; COVID-19, corona virus disease 2019; CTL, cytotoxic T cells; GCSF, granulocyte-colony-stimulating factor; HCV, hepatitis C virus; IFN, interferon; NK cell, natural killer cell; NKG2A, natural killer group 2 member A; PD-1, programmed cell death protein 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Tim-3, T-cell immunoglobulin mucin-3; TLR, Toll-like receptor; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand.

the infection and prohibit the next reinfection. An activated circulating helper T lymphocyte and activated CD8⁺ T cells are gradually increasing in blood at the first week (Thevarajan et al., 2020). CD8⁺ T cells release the perforin and granzymes A and B that induce apoptosis in viral infected cells (Thevarajan et al., 2020).

3 | LYMPHOPENIA IN COVID-19

NK cells and CTLs are essential in control of the viral infection. In recent studies, it was shown that about 85% of the severely ill patients of COVID-19 are suffering the lymphopenia (Huang et al., 2020; Yang et al., 2020). Lymphopenia or lymphocytopenia is the condition with low counts of lymphocytes in the blood. Although T cells could be initially increased at the onset of COVID-19, these patients tended to have low lymphocyte count; the condition that is associated with increased COVID-19 severity. Therefore, individuals who died of COVID-19 are demonstrated to have had expressively lower lymphocyte level than survivors (Ruan, Yang, Wang, Jiang, & Song, 2020).

The study by M. Zheng et al. (2020) showed that the NK cells and CTLs were reduced significantly in patients with COVID-19. Notably, the number of NK and CTLs was remade after recuperation in these patients.

Moreover, another study showed that the total number of CD8⁺ and CD4⁺ T cells was adequately decreased in patients with SARS-CoV-2 infection, particularly in elderly patients more than 60 years old and patients needing intensive care unit (Diao et al., 2020).

4 | LYMPHOCYTES EXHAUSTION

Viral peptide antigens were presented to the naive CD4⁺ T cells by antigen-presenting cells, followed by their activation to produce tumor necrosis factor- α (TNF- α), interleukin (IL)-2, and IFN- γ . This process is promoted to differentiate CTLs, which are struggling to kill the infected cells by secreting granzyme and perforin (Bengsch, Martin, & Thimme, 2014). However, the chronic inflammatory situation and continuous stimulation of T cells result in a phenomenon, called T-cell exhaustion. Functions of the exhausted cells will be impaired; so, the inflammatory states will extend without effective limitation of infection (Bucks, Norton, Boesteanu, Mueller, & Katsikis, 2009). Previous studies showed a large amount of exhausted CD4⁺ and CD8⁺ T cells with high expression of inhibitory immune checkpoints in hepatitis C virus (HCV), human immunodeficiency virus, adenovirus, and hepatitis B virus infections (Okoye, Houghton, Tyrrell, Barakat, & Elahi, 2017). Exhausted T cells express the transcriptional regulators of forkhead box P3 and BLIMP-1, a set of inhibitory molecules (TRAIL, programmed cell death protein 1 [PD-1], cytotoxic T-lymphocyte-associated protein 4, T-cell immunoglobulin mucin-3 [Tim-3], 2B4, lymphocyte-activation gene 3, and B- and T-lymphocyte attenuator) as well as proinflammatory cytokines (TNF- α , IL-2, IL-10, and transforming growth factor- β ; Schietinger & Greenberg, 2014).

Furthermore, the upregulation of NKG2A expression leads to the functionally exhaustion of CD8⁺ and NK cells in patients with COVID-19. Notably, the decreased expression of NKG2A and number of CD8⁺ and NK cells were restored after therapies among the recuperated patients. Furthermore, PD-1, as the exhausted marker, has higher expression in T cells from patients with COVID-19 than health controls. Indeed hyperexpression of Tim-3 and PD-1 on T cells were observed during the progress of symptomatic stages, indicating T-cell exhaustion (Diao et al., 2020).

Hence, SARS-CoV-2 would deactivate the antiviral immunity at primary stage, but as more expression of NKG2A occurs, the exhausted CD8⁺ T and NK cells are created. Furthermore, the malfunctioned CD4⁺ T cells besides the improved expression of regulatory molecules such as TIGIT, Tim-3, and PD-1 in CD8⁺ T cells may play a role in making the disease gets worse (H.-Y. Zheng et al., 2020).

Furthermore, damage to function of CD4⁺ T cells also have made the patients with COVID-19 face to severe conditions (H.-Y. Zheng et al., 2020).

5 | POSSIBLE CAUSES OF LYMPHOPENIA

The main pathophysiology of SARS-CoV-2 infection in severe cases could be hypercytokinemia related to traumas. The presence of hypercytokinemia in patients with COVID-19 with lymphopenia can represent the uncontrolled progress of the pathogen that can be seen in severe patients. Interestingly, lymphopenia with hypercytokinemia was also apparent in severe patients with SARS-CoV (Cameron et al., 2007; Lee et al., 2003).

Recent evidence suggested that the main subgroup of patients with severe COVID-19 may suffer the cytokine storm syndrome. Secondary hemophagocytic lymphohistiocytosis (sHLH) is a hyperinflammatory syndrome that is usually activated by viral infections. The main symptoms of sHLH include cytopenia, continuous fever, and hyperferritinemia and almost 50% of patients have also affected by pulmonary involvement (Seguin, Galicier, Boutboul, Lemiale, & Azoulay, 2016). A cytokine profile, similar to sHLH, is related to the patients with severe COVID-19, as demonstrated by enhanced TNF- α , IL-7, IL-2, granulocyte-colony-stimulating factor (GCSF), monocyte chemoattractant protein 1, and macrophage inflammatory protein 1- α (Huang et al., 2020).

From the other point of view, the acute respiratory distress syndrome (ARDS) is the major cause of deaths by COVID-19. One of the main features of ARDS is cytokine storm, that is, lethal uncontrolled systemic inflammatory response, originating from the production of high levels of proinflammatory cytokines, including TNF- α , IL-6, IL-1 β , IFN- α , IFN- γ , IL-12, IL-18, IL-33, and so forth, by effector immune cells in SARS-CoV infections (Cameron, Bermejo-Martin, Danesh, Muller, & Kelvin, 2008; Huang et al., 2020). The cytokine storm may come with a terrible attack of the immune system to the body, leading to organ failure and ARDs, and subsequently, death in severe cases COVID-19.

Inefficiency to eliminate the infection and viral contaminated cells leads to out-of-control activation of the immune system with

excessive production of different cytokines. These hyperactivated cells may infiltrate various organs, creating extra cytokines, and clinical symptoms. The suppressive impact of TNF- α on hematopoiesis leads to cytopenia.

The possible mechanism of hypercytokinemia together with lymphopenia may adjust the lymphocytosis by proinflammatory cytokines. Moreover, to compensate for the exhausted lymphocytes malpractice, the proinflammatory cytokines are increasingly secreted by activated macrophages, neutrophils, and monocytes. Also, endothelial, epithelial, and dendritic cells help them to produce more proinflammatory cytokines.

Numerous studies confirmed that the increased proinflammatory cytokines play a critical role in the induction of lymphopenia. In addition to antiviral activity, IFN α/β can have antiproliferative, proapoptotic, and expression of cytokines and cytokine receptors, causing the immune modulation, particularly specific T CD8+ against viruses (Dierckx et al., 2017; Wandrer et al., 2016). In fact, the synergic action of most inflammatory cytokines such as IL-1, IFN- γ , and IL-6 was confirmed for inhibition of T-cell proliferation (Jeffery et al., 2009).

Moreover, most proinflammatory cytokines, like interferons, IL-27, IL-6, GCSF, IL-1, and macrophage colony-stimulating factor in infectious diseases, induce necessary myelopoiesis and granulopoiesis (Chiba et al., 2018).

Hyper-/proinflammatory cytokines provide an inverse correlation between the induction of granulopoiesis and lymphopoiesis in the bone marrow of patients with SARS-CoV infection. The increased number of monocytes and granulocytes produces more and more inflammatory cytokines and this detrimental positive feedback makes the patient's condition worse.

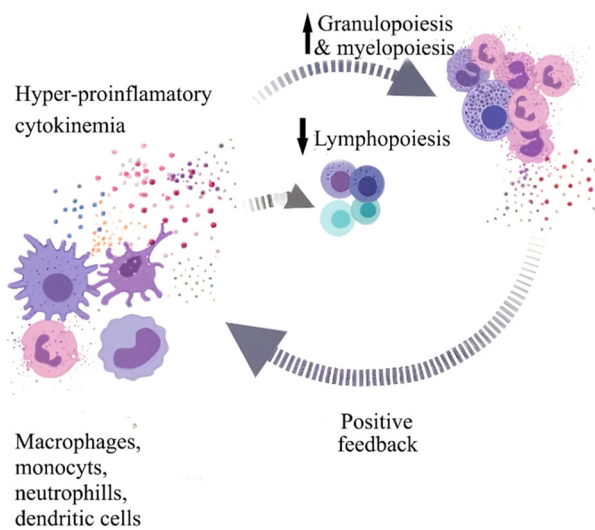


FIGURE 1 Hyperproinflammatory cytokines produce by activated macrophages, neutrophils and monocytes, dendritic cells, endothelial and epithelial by virus that induce granulopoiesis and reduce lymphopoiesis in the bone marrow. The increased number of monocytes and granulocytes produce more and more inflammatory cytokines and this detrimental positive feedback make intensify this condition (Created using BioRender: <https://biorender.com/>)

Accordingly, hypercytokinemia influences the lymphopenia and hence is incapable to defend against SARS-CoV-2 infection. The challenge gets worse when these low numbers of lymphocytes become exhausted. To compensate for the exhausted lymphocytes malpractice, the proinflammatory cytokines increasingly are secreted and these cytokines induce granulopoiesis versus lymphopoiesis (Figure 1).

It should be mentioned that cytokines might not the only cause of lymphopenia. Multiple mechanisms might work together to cause lymphopenia. SARS-CoV-2 might directly attack the lymphocytes or destroy lymphoid organs. Indeed as patients with severe phenotype of COVID-19 have elevated blood lactic acid levels, lymphopenia could be due to such metabolic molecules (Tan et al. 2020).

6 | APOPTOSIS IN T CELL AND NK CELL

Low count of lymphocytes may be derived from the excited lymphocytes cell death. Continuous viral permanence in SARS-CoV-2 infection may induce T-cell apoptosis cell death like HCV. Numerous proapoptotic molecules such as FasL, TNF- α , and TRAIL were upregulated in chronic HCV infection, propounding the immune cell death by the intrinsic and extrinsic pathways (Barathan et al., 2015). In the Middle East Respiratory Syndrome coronavirus infections, the cells underwent apoptosis (Mubarak, Alturaiki, & Hemida, 2019; Ying, Li, & Dimitrov, 2016). However, the exhaustion of NK and T cells is present in chronic infections and T-cell apoptosis; also occurs in the chronic condition of SARS-CoV infection (Barathan et al., 2018).

There is no study about the induction of the apoptosis of NK cells and T cells by SARS-CoV-2, but the stimulation of early apoptosis may be the cause of lymphopenia. As already mentioned, proinflammatory cytokines can stimulate apoptosis in T cells, especially in chronic virus infections. Subsequently, it might be important in the pathogenesis of SARS-CoV-2.

7 | POSSIBLE CONTRIBUTORY THERAPIES

It seems that SARS-CoV-2 may contain distinct immunopathology, compared to other coronaviruses. The disease development does not happen due to a single molecule; hence, there is an essential need to carry out more categorized analysis about various marker expressions. Identifying the potential factors in connection to the immune system may provide clues for finding a suitable treatment of COVID-19. Table 1 provides promising different therapies used for other viruses, which may be beneficial for COVID-19 treatment (Saghazadeh & Rezaei, 2020b). This information may provide a background in research perspectives for SARS-CoV-2 infection.

Intravenous immunoglobulin, plasma exchange, and IL-1 receptor antagonist are some of proposed therapies. IL-7 treatment reciprocates lymphopenia, which induced by IFN- α and incites specific CTLs responses in SARS-CoV-2 infection. Moreover, drugs targeting the proliferation of lymphocyte or inhibition of apoptosis (by

TABLE 1 Promising therapies that used for other viruses with distinctive pathobiology condition

	Drugs, biological, or chemical modifiers
Hypercytokinemia	NSAIDs (Bozza et al., 2008; Carter, 2007), Janus kinase inhibition, IL-1 and IL-6 receptor antagonist, SIP1R agonists (Oldstone & Rosen, 2014), p38 and MAPK inhibitors (Johnson et al., 2014), Zanamivir + COX-2 inhibitors (Walsh et al., 2011), IVIG
T-cell and NK cell lymphopenia	Cyclophosphamide followed by fludarabine (Cooley, June, Schoenberger, & Miller, 2007), IL-1 receptor antagonist, IL-7 agonists, HSCT
Exhausted lymphocytes	Histone deacetylase(iv) (Zhang et al., 2014), blockade PD-1 and or PD-L1 (Yi, Cox, & Zajac, 2010), TIM-3, CTLA-4, LAG-3, 2B4, BTLA, and TRAIL, blocking NKG2A or its ligand (HLA-E)
Apoptosis of T and NK cells	Resveratrol, coenzyme Q10, flavopiridol, roscovitine, simvastatin, flurbiprofen, rosiglitazone, minocycline (Sureda et al., 2011), PD1/PD-L1 inhibitors

Abbreviations: BTLA, B- and T-lymphocyte attenuator; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HSCT, hematopoietic stem cell transplantation; IL, interleukin; iv, in vitro study; IVIG, intravenous immunoglobulin; MAPK, mitogen-activated protein kinase; NK cell, natural killer cell; NKG2A, Natural killer group 2 member A; NSAID, nonsteroidal anti-inflammatory drug; PD-1, programmed cell death protein 1; SIP1R, sphingosine-1-phosphate receptor; Tim-3, T-cell immunoglobulin mucin-3; TRAIL, TNF-related apoptosis-inducing ligand.

suppression of PD1/PD-L1) could inhibit lymphopenia and also compensate the lymphocyte counts in severe patients of COVID-19.

Nevertheless, controlled immunosuppression is seen as a possibly useful option for hyperinflammation. A phase III randomized controlled trial among the patients with sepsis and hyperinflammation showed that anakinra (IL-1 blockade) leads to considerable survival without the occurrence of notable adverse events (Shindo, Unsinger, Burnham, Green, & Hotchkiss, 2015). A multicenter, randomized controlled trial among patients with COVID-19 pneumonia with cytokine storm syndrome has been licensed to use the tocilizumab (IL-6 receptor blockade) in China. Janus kinase, a factor in antiviral signaling pathway, inhibitors could also be beneficial for controlling the inflammation of SARS-CoV-2 (Richardson et al., 2020).

8 | CONCLUSION

What is certain is that any decrease in activity or the level of lymphocytes is as harmful as their overproduction or overactivation; but how to induce a well-adjusted immune response? Clarification of such issues would allow the additional description of the complicated SARS-CoV-2 pathogenesis, with fundamental implications for the development of more specific therapeutics.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

N. F. designed the study and provided initial draft of the manuscript. N. R. provided a critical review of the manuscript and performed last edited form of it.

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REFERENCES

- Barathan, M., Gopal, K., Mohamed, R., Ellegård, R., Saeidi, A., Vadivelu, J., ... Zandi, K. (2015). Chronic hepatitis C virus infection triggers spontaneous differential expression of biosignatures associated with T cell exhaustion and apoptosis signaling in peripheral blood mononucleocytes. *Apoptosis*, 20(4), 466–480. <https://doi.org/10.1007/s10495-014-1084-y>
- Barathan, M., Mohamed, R., Yong, Y. K., Kannan, M., Vadivelu, J., Saeidi, A., ... Esaki ShankarShankar, E. M. (2018). Viral persistence and chronicity in hepatitis C virus infection: role of T-cell apoptosis, senescence and exhaustion. *Cells*, 7(10), 165. <https://doi.org/10.3390/cells7100165>
- Bengsch, B., Martin, B., & Thimme, R. (2014). Restoration of HBV-specific CD8+ T cell function by PD-1 blockade in inactive carrier patients is linked to T cell differentiation. *Journal of Hepatology*, 61(6), 1212–1219. <https://doi.org/10.1016/j.jhep.2014.07.005>
- Bozza, F. A., Cruz, O. G., Zagne, S. M., Azeredo, E. L., Nogueira, R. M., Assis, E. F., ... Kubelka, C. F. (2008). Multiplex cytokine profile from dengue patients: MIP-1beta and IFN-gamma as predictive factors for severity. *BMC Infectious Diseases*, 8(1), 86. <https://doi.org/10.1186/1471-2334-8-86>
- Bucks, C. M., Norton, J. A., Boesteanu, A. C., Mueller, Y. M., & Katsikis, P. D. (2009). Chronic antigen stimulation alone is sufficient to drive CD8+ T cell exhaustion. *The Journal of Immunology*, 182(11), 6697–6708. <https://doi.org/10.4049/jimmunol.0800997>
- Cameron, M. J., Bermejo-Martin, J. F., Danesh, A., Muller, M. P., & Kelvin, D. J. (2008). Human immunopathogenesis of severe acute respiratory syndrome (SARS). *Virus Research*, 133(1), 13–19. <https://doi.org/10.1016/j.virusres.2007.02.014>
- Cameron, M. J., Ran, L., Xu, L., Danesh, A., Bermejo-Martin, J. F., Cameron, C. M., ... Poutanen, S. M. (2007). Interferon-mediated immunopathological events are associated with atypical innate and adaptive immune responses in patients with severe acute respiratory syndrome. *Journal of Virology*, 81(16), 8692–8706. <https://doi.org/10.1128/jvi.00527-07>
- Carter, M. J. (2007). A rationale for using steroids in the treatment of severe cases of H5N1 avian influenza. *Journal of Medical Microbiology*, 56(7), 875–883. <https://doi.org/10.1099/jmm.0.47124-0>
- Chiba, Y., Mizoguchi, I., Hasegawa, H., Ohashi, M., Orii, N., Nagai, T., ... Yoshimoto, T. (2018). Regulation of myelopoiesis by proinflammatory cytokines in infectious diseases. *Cellular and Molecular Life Sciences*, 75(8), 1363–1376. <https://doi.org/10.1007/s00018-017-2724-5>

- Cooley, S., June, C. H., Schoenberger, S. P., & Miller, J. S. (2007). Adoptive therapy with T cells/NK cells. *Biology of Blood and Marrow Transplantation*, 13, 33–42. <https://doi.org/10.1016/j.bbmt.2006.10.008>
- Diao, B., Wang, C., Tan, Y., Chen, X., Liu, Y., Ning, L., ... Chen, Y. (2020). Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019. *Frontiers in Immunology*, 11, 827.
- Dierckx, T., Khouri, R., Menezes, S., Decanine, D., Farre, L., Bittencourt, A., ... Weyenbergh, J. (2017). IFN- β induces greater antiproliferative and proapoptotic effects and increased p53 signaling compared with IFN- α in PBMCs of adult T-cell leukemia/lymphoma patients. *Blood Cancer Journal*, 7(1), e519. <https://doi.org/10.1038/bcj.2016.126>
- Hanaei, S., & Rezaei, N. (2020). COVID-19: Developing from an outbreak to a pandemic. *Archives of Medical Research*. Advance online publication. <https://doi.org/10.1016/j.arcmed.2020.04.021>
- Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., ... Gu, X. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, 395(10223), 497–506. [https://doi.org/10.1016/s0140-6736\(20\)30183-5](https://doi.org/10.1016/s0140-6736(20)30183-5)
- Jeffery, L. E., Burke, F., Mura, M., Zheng, Y., Qureshi, O. S., Hewison, M., ... Sansom, D. M. (2009). 1, 25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. *The Journal of Immunology*, 183(9), 5458–5467. <https://doi.org/10.4049/jimmunol.0803217>
- Johnson, J. C., Martinez, O., Honko, A. N., Hensley, L. E., Olinger, G. G., & Basler, C. F. (2014). Pyridinyl imidazole inhibitors of p38 MAP kinase impair viral entry and reduce cytokine induction by Zaire ebolavirus in human dendritic cells. *Antiviral Research*, 107, 102–109. <https://doi.org/10.1016/j.antiviral.2014.04.014>
- Kawai, T., & Akira, S. (2010). The role of pattern-recognition receptors in innate immunity: Update on Toll-like receptors. *Nature Immunology*, 11(5), 373–384. <https://doi.org/10.1038/ni.1863>
- Lee, N., Hui, D., Wu, A., Chan, P., Cameron, P., Joynt, G. M., ... Sung, J. (2003). A major outbreak of severe acute respiratory syndrome in Hong Kong. *New England Journal of Medicine*, 348(20), 1986–1994. <https://doi.org/10.1056/nejmoa030685>
- Mubarak, A., Alturaiki, W., & Hemida, M. G. (2019). Middle east respiratory syndrome coronavirus (MERS-CoV): Infection, immunological response, and vaccine development. *Journal of Immunology Research*, 2019, 1–11. <https://doi.org/10.1155/2019/6491738>
- Okoye, I. S., Houghton, M., Tyrrell, L., Barakat, K., & Elahi, S. (2017). Coinhibitory receptor expression and immune checkpoint blockade: Maintaining a balance in CD8+ T cell responses to chronic viral infections and cancer. *Frontiers in Immunology*, 8, 1215. <https://doi.org/10.3389/fimmu.2017.01215>
- Oldstone, M. B., & Rosen, H. (2014). Cytokine storm plays a direct role in the morbidity and mortality from influenza virus infection and is chemically treatable with a single sphingosine-1-phosphate agonist molecule. *Sphingosine-1-phosphate signaling in immunology and infectious diseases* (pp. 129–147). Cham, Switzerland: Springer. https://doi.org/10.1007/978-3-319-05879-5_6
- Richardson, P., Griffin, I., Tucker, C., Smith, D., Oechsle, O., Phelan, A., & Stebbing, J. (2020). Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *The Lancet*, 395(10223), e30–e31. [https://doi.org/10.1016/s0140-6736\(20\)30304-4](https://doi.org/10.1016/s0140-6736(20)30304-4)
- Ruan, Q., Yang, K., Wang, W., Jiang, L., & Song, J. (2020). Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Medicine*, 40(5), 846–848. <https://doi.org/10.1007/s00134-020-05991-x>
- Saghazadeh, A., & Rezaei, N. (2020a). Immune-epidemiological parameters of the novel coronavirus—A perspective. *Expert Review of Clinical Immunology*. Advance online publication. <https://doi.org/10.1080/1744666X.2020.1750954>
- Saghazadeh, A., & Rezaei, N. (2020b). Towards treatment planning of COVID-19: Rationale and hypothesis for the use of multiple immunosuppressive agents: Anti-antibodies, immunoglobulins, and corticosteroids. *International Immunopharmacology*, 84, 106560. <https://doi.org/10.1016/j.intimp.2020.106560>
- Schietering, A., & Greenberg, P. D. (2014). Tolerance and exhaustion: defining mechanisms of T cell dysfunction. *Trends in Immunology*, 35(2), 51–60. <https://doi.org/10.1016/j.it.2013.10.001>
- Seguin, A., Galicier, L., Boutboul, D., Lemiale, V., & Azoulay, E. (2016). Pulmonary involvement in patients with hemophagocytic lymphohistiocytosis. *Chest*, 149(5), 1294–1301. <https://doi.org/10.1016/j.chest.2015.11.004>
- Shindo, Y., Unsinger, J., Burnham, C.-A., Green, J. M., & Hotchkiss, R. S. (2015). Interleukin 7 and anti-programmed cell death 1 antibody have differing effects to reverse sepsis-induced immunosuppression. *Shock*, 43(4), 334–343. <https://doi.org/10.1097/shk.0000000000000317>
- Sureda, X., F., Junyent, F., Verdager, E., Auladell, C., Pelegri, C., Vilaplana, J., ... Camins, A. (2011). Antiapoptotic drugs: A therapeutic strategy for the prevention of neurodegenerative diseases. *Current Pharmaceutical Design*, 17(3), 230–245. <https://doi.org/10.2174/138161211795049732>
- Tan, L., Wang, Q., Zhang, D., Ding, J., Huang, Q., Tang, Y.-Q., ... Miao, H. (2020). Lymphopenia predicts disease severity of COVID-19: A descriptive and predictive study. *Signal Transduction and Targeted Therapy*, 5(33), <https://doi.org/10.1038/s41392-020-0148-4>
- Thevarajan, I., Nguyen, T. H., Koutsakos, M., Druce, J., Caly, L., van de Sandt, C. E., ... Kedzierska, K. (2020). Breadth of concomitant immune responses prior to patient recovery: A case report of non-severe COVID-19. *Nature Medicine*, 26(4), 453–455. <https://doi.org/10.1038/s41591-020-0819-2>
- Walsh, K. B., Teijaro, J. R., Wilker, P. R., Jatzek, A., Fremgen, D. M., Das, S. C., ... Oldstone, M. B. A. (2011). Suppression of cytokine storm with a sphingosine analog provides protection against pathogenic influenza virus. *Proceedings of the National Academy of Sciences of the United States of America*, 108(29), 12018–12023. <https://doi.org/10.1073/pnas.1107024108>
- Wandrer, F., Falk, C. S., John, K., Skawran, B., Manns, M. P., Schulze-Osthoff, K., & Bantel, H. (2016). Interferon-mediated cytokine induction determines sustained virus control in chronic hepatitis C virus infection. *The Journal of Infectious Diseases*, 213(5), 746–754. <https://doi.org/10.1093/infdis/jiv505>
- Yang, X., Yu, Y., Xu, J., Shu, H., Liu, H., Wu, Y., ... Shang, Y. (2020). Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. *The Lancet Respiratory Medicine*, 8(5), 475–481. [https://doi.org/10.1016/s2213-2600\(20\)30079-5](https://doi.org/10.1016/s2213-2600(20)30079-5)
- Yi, J. S., Cox, M. A., & Zajac, A. J. (2010). T-cell exhaustion: Characteristics, causes and conversion. *Immunology*, 129(4), 474–481. <https://doi.org/10.1111/j.1365-2567.2010.03255.x>
- Ying, T., Li, W., & Dimitrov, D. S. (2016). Discovery of T-cell infection and apoptosis by Middle East respiratory syndrome coronavirus. *Journal of Infectious Diseases*, 213(6), 877–879. <https://doi.org/10.1093/infdis/jiv381>
- Zhang, F., Zhou, X., DiSpirito, J. R., Wang, C., Wang, Y., & Shen, H. (2014). Epigenetic manipulation restores functions of defective CD8+ T cells from chronic viral infection. *Molecular Therapy*, 22(9), 1698–1706. <https://doi.org/10.1038/mt.2014.91>
- Zheng, M., Gao, Y., Wang, G., Song, G., Liu, S., Sun, D., ... Tian, Z. (2020). Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cellular & Molecular Immunology*, 17(5), 533–535. <https://doi.org/10.1038/s41423-020-0402-2>

Zheng, H.-Y., Zhang, M., Yang, C.-X., Zhang, N., Wang, X.-C., Yang, X.-P., ... Zheng, Y.-T. (2020). Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. *Cellular & Molecular Immunology*, 17(5), 541–543. <https://doi.org/10.1038/s41423-020-0401-3>

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