Hypothesis

Production of SARS-CoV-2 Specific IFN-γ/IL-10 Co-producing CD4 T Cells from Convalescent Donors to Treat COVID-19: A Hypothesis

Alejandro Núñez Nolasco*

Independent Researcher, La Vega, Dominican Republic

Keywords: SARS-CoV-2 specific T cells; IFN-γ/IL-10 co-producing Th1 cells; Living-drug; COVID-19 treatment; Hypothesis.

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has alarmed people worldwide as an emerging coronavirus, which to date remains a major global public health challenge. Patients are being treated with different therapies; however, no evidence of a single therapy has been found to improve the clinical outcomes significantly; therefore, there is currently no single effective treatment against COVID-19. The research related to virus-specific T cell therapy has provided positive results when treating Epstein-Barr virus (EBV) and cytomegalovirus (CMV). Therefore, when facing a new virus, it is necessary to continue innovating the therapeutic strategies that have worked to treat viral infections previously, adapting to the pathogenesis of this new disease, to treat patients infected with SARS-CoV-2 effectively and safely. This proposal presents the research idea of creating SARS-CoV-2 specific interferon-gamma (IFN-γ) and interleukin-10 (IL-10) co-producing CD4 T cells to determine the cytokine secretion and viability of their production for virus-specific T cell therapy.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which began in Wuhan, a central city in China, in December 2019, has alarmed people worldwide as an emerging coronavirus, which to date remains a major global public health challenge. In the first few days, patients that are infected with SARS-CoV-2 might develop the disease in several stages starting from an asymptomatic state. In the following days, the virus travels through the upper airways, where it spreads and migrates along the conductive airways, and a more robust immune and innate response is triggered, in approximately 80% of patients with COVID-19 the disease will be mild and mainly restricted to the upper and conductive airways. Approximately 20% of infected patients will progress to the next stage and develop pulmonary infiltrates, and some of them will develop severe diseases, such as hypoxia and progression to acute respiratory distress syndrome (ARDS). The pathological result of severe acute respiratory syndrome (SARS) and COVID-19 is diffuse alveolar damage with fibrin-rich hyaline membranes and some giant multinucleated cells, and aberrant wound healing could lead to scarring and fibrosis that is more severe than other forms of SARS. Other typical symptoms of COVID-19 include fever, dry cough, and shortness of breath; gastrointestinal symptoms, such as nausea, vomiting, abdominal pain, and diarrhea have been reported, and neurologically related symptoms, in particular, anosmia, hyposmia, and dysgeusia.

Currently, there is no single effective treatment against COVID-19. Hydroxychloroquine does not have any benefit, and thera-
Hypocytokinaemic immune dysregulation in COVID-19, which is known as cytokine storm syndrome, has been described as immune deregulation that is characterized by the continuous activation of immune cells, which are secretors of large amounts of cytokines that lead to overwhelming systemic inflammation and high-mortality multiorgan insufficiency.16,17 This could be mediated by interferon (IFN), tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) in various cells type; and it prevents the maturation of dendritic cells by blocking IL-12.16 IL-10 levels increase in the second week after the onset of symptoms; although they have not associated with the immune drawback, it is an indication of latent immune efforts to control the cytokine storm.17,18

Interferon-gamma (IFN-γ) is a type II interferon that is produced by various cells, such as CD4 T cells. IFN-γ participates in numerous immunological and adaptive functions, promotes macrophage activation and antigen presentation, and is highly involved in antibacterial and antiviral immunity and the transduction of signals.16,17 The inflammatory response to COVID-19 results in the formation of fibrosis in patients; it has been suggested that early intervention of antiviral infection using IFN-γ could be substantial in inhibiting fibrosis for a better functional recovery.19

Effector memory T cells that co-produce IFN-γ and IL-10 perform an essential role in regulating pulmonary inflammatory development and fatal injury in acute infections that are caused by respiratory viruses.20 Effector memory CD4 T cells that co-produce IFN-γ/IL-10 accumulate in peripheral tissues in areas where the infection is persistent to prevent local damage; however, despite its IL-10 production, these cells express especially high levels of IFN-γ.21 In addition, when these cells are cultivated with macrophages that have been infected with Toxoplasma gondii, the pathogen is efficiently eradicated, which indicates that their simultaneous production of IL-10 does not compromise the effector function of these T-helper type 1 (Th1) cells.22,23

By focusing on the capabilities and therapeutic potential of these Th1 cells, it is essential to consider their use to combat the disease that is caused by SARS-CoV-2 (Fig. 1). In addition, it is necessary to determine the viability of its production and analyze the IFN-γ and IL-10 secretion of these cells. Therefore, the methods that support the study design of this research hypothesis are explained in detail in the following section.

**Proposed methods for the hypothesis**

**Donor eligibility**

Donor eligibility must be performed under all criteria set by PAHO/WHO. People between the ages of 21 and 65 years, with registered COVID-19 positive documentation of reverse-transcription-polymerase chain reaction (RT-PCR) nasopharyngeal samples from when they had the disease; however, at the time of this study, they must show negative results of the same RT-PCR tests. People using immunosuppressive treatments and that have diseases, such as human immunodeficiency virus (HIV), Hepatitis C virus (HCV), and Hepatitis B Virus (HBV) infection do not qualify as donors. In addition, informed consent will be required for the use of blood components from the donor and approval from the institutional bioethics committees for the study’s development must be obtained.

**Cell processing to obtain SARS-CoV-2 specific IFN-γ T cells**

Following extraction of PBMCs, the cells will undergo a fully automated process that uses the CliniMACS Prodigy IFN-γ Cytokine Capture System (CCS) (Miltenyi Biotec, Germany). The cells will be stimulated with PepTivator Prot-S SARS-CoV-2 that contains the amino acids sequence domains 304-338, 421-475, 492-519, 683-707, 741-770, 785-802, and 885-1273; PepTivator Prot-M and Prot-N SARS-CoV-2, each comprises a set of peptides, which consist mainly of 15-mer sequences with 11 amino acids overlap that covers the complete sequence of the nucleocapsid phosphoprotein (N) and the complete sequence of the SARS-CoV-2 membrane glycoprotein (M) respectively (GenBank MN908947.3, Protein QHD43416.1, Protein QHD43419.1, Protein QHD43423.2) (Miltenyi Biotec, Germany). Then, the cells will be labeled with the Catchmatrix reagent (Miltenyi Biotec, Germany) that contains biospecific antibodies for CD45 and specific for IFN-γ, which will be secreted by the target cells on stimulation. Briefly, IFN-γ bound to the cell surface will be guided by the CliniMACS enrichment reagent; this IFN-γ specific antibody is conjugated to MACs MicroBeads, which leads to cell separation. Finally, the cells that secrete IFN-γ labeled with the microbeads will be isolated by the built-in magnetic column of the CliniMACS Prodigy; however, the unlabeled cells pass through this and the microbead-labeled cells are retained in the magnetic field, and then diluted in the target cell bag.24

**Isolation of IFN-γ-secreting CD4 T cells**

Effector memory CD4 T cells will be isolated from the previous procedure’s target cell bag, using the effector memory CD4 T cell isolation kit (Miltenyi Biotec, Germany), with the autoMACS Pro Separator (Miltenyi Biotec, Germany) following the manufacturer’s protocols.

**Re-stimulation of IFN-γ Th1 cells for IL-10 secretion**

In this step, 10⁷ cells/mL will be restimulated with the SARS-CoV-2 in a peptide pool previously described at a concentration of

DOI: 10.14218/ERHM.2021.00008 | Volume 7 Issue 1, March 2022
5 µg/mL, in TexMACS medium (Miltenyi Biotec, Germany), with 1% penicillin/streptomycin (Thermo Fisher Scientific, USA), 5% AB serum (Thermo Fisher Scientific), 60 ng/mL IL-12 (Miltenyi Biotec, Germany) at 37°C, 5% CO₂ for 4–6 h. To study the secretion of IL-10, a parallel sample cultured without peptides and IL-12 as control must be performed. After stimulation, the cells will be labeled with the IL-10 Secretion Assay-Detection Kit Capture Reagent, human (Miltenyi Biotec, Germany) composed from antibodies specific for IL-10 secreted by the target cells. Therefore, after the secretion phase, the IL-10 bound to the cell surface could be attacked using the IL-10 PE antibody included in the kit for their respective magnetic separation; therefore, obtaining the target cells.

**Cell irradiation**

Harvested effector memory IFN-γ/IL-10 co-producing CD4 T Cells will be irradiated by the RS 1800 Q Biological Irradiator (Rad Source Technologies Quastar, USA) at 7.5 Gy, for the inhibition of cell proliferation. A dose of 0 Gy will be used as a control sample.

**IFN-γ and IL-10 secretion assay**

IFN-γ/IL-10 co-producing Th1 cells will be simultaneously analyzed for the production of two different cytokines by combining two different cytokine secretion assays, using the IFN-γ Secretion Assay Detection Kit (PE) (Miltenyi Biotec, Germany) and the IL-10 Secretion Assay Detection Kit (PE) (Miltenyi Biotec, Germany), following the manufacturer’s protocol (Two-color Cytokine Secretion Assays, Miltenyi Biotec, Germany).

**Cell proliferation assay**

The CellTrace CFSE Cell Proliferation Kit (Invitrogen) (Thermo Fisher Scientific) will be used for flow cytometry, following the manufacturer’s specifications to analyze cell proliferation.

**TCRVβ spectratyping**

For evaluation of T cell receptor (TCR) spectra, the complementary-determining region 3 (CDR3) coding region of the T cell receptor variable (TCRV) gene will be expanded using 24 specific primers of the TCRV subfamily and a primer conjugated per carboxyfluorescein region (FAM). The PCR products will be denatured with Hi-Di formamide (Applied Biosystems, Carlsbad, CA) and electrophoresed along with the standard size Gene Scan-600 LIZ (Applied Biosystems) on a SeqStudio Genetic Analyzer (Applied Biosystems).
Flow cytometry panels for immune cell purity and composition

To analyze the cell composition, two antibody panels must be performed with MACSQuant Analyzer (Miltenyi Biotec, Germany) using the express mode. The first panel, CCS_Immune_Cell_Composition_h_01 (Panel A) will be used to determine immune cell composition and target cell number with CD45-VioBlue, CD4-VioGreen, CD3-FITC, CD16/CD56-PE, CD19-PEVio770, CD14-APC, CD8-APC-Vio 770, and 7-AAD; the second panel, CCS_Purity_h_01 (Panel B) will be used to determine phenotype and frequency of target cells with CD45-VioBlue, CD3-FITC, IFN-γ-PE, CD45RO-PEVio770, CD62L-APC, and CD8-APC-Vio770.12

Evaluation of the hypothesis and the proposed methods

COVID-19 is a disease that remains a major global public health challenge.1 Vaccine development and implementation is accelerating and the number of vaccines that are entering phase IV clinical trials is increasing;23 however, there is currently no single effective treatment against COVID-19.7 One of the strategies used to treat patients with COVID-19 has been CPT, which is composed of neutralizing antibodies specific for SARS-CoV-2.7,24 The Food and Drug Administration (FDA) currently approves CPT for use in patients with COVID-19 for research purposes; observational studies have shown treated patients have significantly improved oxygen saturation, CRP, 30-day survival rate, and reduced need for mechanical ventilation.7 However, CPT requires active compatible donors for urgent transfusion, which for some people could be difficult to obtain if a donor is not available at the right time.

T cell therapy might be a promising strategy when treating patients infected by SARS-CoV-2 based on the evidence and positive results of this therapy previously.8,9,25,26 and could give us the possibility to create a reperitory of cells samples, because they can be cultured and stored in a biobank.27 Therefore, haploidentical patients might obtain a living drug to be treated quickly and efficiently, an idea that has initiated multinational research into this approach.11–14 The recommended doses are approximately >2.5×10^10/kg of the recipient’s body weight for perfusion of virus-specific T cells in incompatible/haploidentical donors.28 The use of third-party virus-specific T cells in biobanks is a feasible and safe method to treat severe viral infections rapidly; previous studies reflect the efficacy of virus-specific cells, even when combined with a single relevant human leukocyte antigen (HLA) allele with the receptor, as long as this allele presents antigens derived from viruses.27

The acute hyperinflammatory response, the phenomenon that has been implicated in critically ill patients that are infected with SARS-CoV-2,15,16,19,30 could be regulated by IL-10; a cytokine that these proposed effector cells secrete. IL-10 is a mediator cytokine of the immune response; this inhibits the secretion of other pro-inflammatory cytokines, such as IL-1, IL-1α, IL-1β, IL-6, IL-8, IFN-γ, and TNF-α, and blocks IL-12,16,31,32 In addition, the modulatory effect of IL-10 in the inflammatory responses is associated with the inhibition of the nuclear factor-kappa B (NF-κB) pathway.33,34 The NF-κB coordinates the activation of numerous genes in response to pathogens and pro-inflammatory cytokines and is; therefore, critical in the development of acute and chronic inflammatory diseases.34,36 In COVID-19, the NF-κB activation in various cells, such as macrophages of the lung, liver, kidney, central nervous system, gastrointestinal system, and cardiovascular system leads to pro-inflammatory cytokines and chemokines production.37 Various authors proposed that the inhibition of the NF-κB pathway as a potential target for therapeutic strategies to treat severe COVID-19.37–39 IL-10 blocks NF-κB activity at two levels; through the suppression of I kappa B kinase (IKK) activity and through the inhibition of NF-κB DNA binding activity.34

These proposed cells secrete IFN-γ, which is an essential antiviral cytokine in the immune response to viral infections and eradicating pathogens.16,19 In addition to its antiviral activity, IFN-γ has antifibrotic properties.19 IFN-γ increases the destruction function of CD8 T cells by inducing major histocompatibility complex (MHC) class I; in addition, it improves the immune response by stimulating the MHC class II receptors.40 IFN-γ amplifies antigen presentation through antigen-presenting cells (APCs) by enhancing antigen recognition via cognate T cell interaction.46,41 It has been suggested that early intervention in antiviral infection using IFN-γ could be substantial in inhibiting fibrosis for better functional recovery,19 and a study with results that were limited to a small number of patients obtained data on the positive effect of IFN-γ on the rate of clinical stabilization and recovery of patients with moderate COVID-19.42 IFN-γ/IL-10 coproducing CD4 T cells express T-box transcription factor (TBX21), which is known as T-box expressed on T cells (T-bet).21,22,43 T-bet plays a critical role in defending against Vaccinia virus (V) infection in mice; it is required to control IFN-γ production in CD4 T cells and natural killer (NK) cells.43 NK cells play a central role in maintaining immune homeostasis, which is a critical requirement when facing the challenge of a novel pathogen; SARS-CoV-2 infection impedes NK cell function, and therefore, disrupts this vital balance.42 IL-10 has previously been associated with the inhibition of NK cell production of IFN-γ due to its ability to suppress accessory cell production of pro-inflammatory cytokines.44–46 However, IL-10 increases NK cell production of IFN-γ when combined with interleukin-18 (IL-18).46 which is a cytokine presented in the cytokine storm in COVID-19.47,48 In addition, IL-10 enhanced the ability of IL-18 to stimulate NK cell cytotoxicity and proliferation,46 and plays a role on the stimulation of IFN-γ production by CD8 T cells.16 IL-10 is an influential factor for the growth and differentiation of mastocytes, thymocytes, and B cells;18 IL-10 supports the differentiation of B cells in the complete absence of IL-2.49

In the proposed process (Fig. 2), PBMCs samples will be extracted from convalescent patients (Fig. 2.1). Recovered COVID-19 patients consistently generated a substantial CD4 T cell response against SARS-CoV-2.19 After extraction of the PBMCs, lymphocytes will be automatically processed with specific peptides of the SARS-COV-2 for IFN-γ secretion (Fig. 2.2), this process takes approximately 12 h, is fully automatic, and it requires limited human input for its development.52 In brief, the cells will be isolated to obtain the effector memory CD4 T cells that secretes IFN-γ (Fig. 2.3) along with an automated magnetic cell separation with the autoMACS Pro Separator for fast and gentle isolation; therefore, the target cells will be separated without requiring density gradient centrifugation. In the re-stimulation process (Fig. 2.5), the cells will be re-stimulated with SARS-COV-2 peptides and IL-12; IFN-γ/IL-10 co-producing Th1 cells require a high dose induced phosphorylation of antigen and IL-12 induced signal transducer and activator of transcription 4 (STAT-4) activation.50 After re-stimulation (Fig. 2.4), the harvest cells will be irradiated to ensure perfusion and attenuate the alloreactivity to avoid GVHD. 7.5 Gv was a safe dose used in previous studies to inhibit cell proliferation in treatments as donor lymphocyte infusion (DLI), 7.5 Gv likewise preserves the cells for their secretion.
Future directions

No data or results exist for the proposed idea; therefore, its development is required to determine its viability and initiate further research to study its therapeutic efficacy. This research idea implementation and therapy’s direct practice will require an interdisciplinary approach, which should include but not be limited to biotechnologists, immunologists, geneticists, hematologists, oncologists, and other biomedical professionals.
Due to the global transmission of the virus, a large number of SARS-CoV-2 variants have appeared, especially the emerging strains that have been discovered in the UK (variant 20I/501Y.V1, lineage B.1.1.7), South Africa (variant 20H/501Y.V2, lineage B.1.351), Brazil (variant 20S/501Y.V3, lineage P.1), California (variant 20C, lineage B.1.427/B.1.429), India (variant G/452R.V3 or VUI-21APR-01, lineage B.1.617.1) (Kappa), and India (variant G/452R.V3 or VUI-21APR-02, lineage B.1.617.2) (Delta).

In addition to the peptides shown in the methods section of the research idea (PepTivator SARS-CoV-2 Prot_S B.1.1.7, Prot_N B.1.1.7, Prot_S B.1.351, Prot_S P.1, Prot_S B.1.427/B.1.429, Prot_S B.1.525, Prot_S B.1.617.1 and Prot_S B.1.617.2) (Milenyi Biotec, Germany) could stimulate the target cells to broaden their specificity.

Conclusions

When facing a new virus, it is necessary to continue innovating the therapeutic strategies that have worked to treat previous viral infections, adapting to the pathogenesis of this new disease, to treat patients infected with SARS-CoV-2 effectively and safely. This proposal presents the research idea of creating SARS-CoV-2 specific IFN-γ and IL-10 co-producing CD4 T cells to determine its viability and cytokine secretion of the target cells. Target cell samples could be stored in a biobank; therefore, haploidentical patients might obtain the living drug to be treated quickly and efficiently.

Acknowledgments

I would like to thank Dr. Bienvenido A. Veras for his valuable mentorship and his advice when writing this article, Mr. Daniel A. Khoury for supporting me economically when writing it, and help when registering the invention. Ms. Andrea J. Vazquez for helping me drawing the figures presented in it, and Mr. Luis A. Reyes for his help when registering the invention. I also want to thank Mr. Eddyon Núñez, Mr. Tommy Roman, and especially my father, Mr. Silfredo A. Núñez, for supporting me all the time. Moreover, I thank the reviewers and editors for taking the time and effort necessary to review the manuscript and provide me with exceptional experience in the entire editorial process; I sincerely appreciate all valuable comments and suggestions, which helped me improve the manuscript’s quality.

Funding

None to declare.

Conflict of interest

ANN registered the invention for a patent.

Nolasco A.N.: SARS-CoV-2 specific CD4 T cells: a hypothesis

Author contributions

ANN was the only author.

References

[1] Zheng J. SARS-CoV-2: an Emerging Coronavirus that Causes a Global Threat. Int J Biol Sci 2020;16(10):1678–1685. doi:10.7150/ijbs.45053.
[2] Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. Eur Respir J 2020;55(4):2000607. doi:10.1183/13993003.00607-2020.
[3] Wu Z, McGooagan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323(13):1239–1242. doi:10.1001/jama.2020.2648.
[4] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8(4):420–422. doi:10.1016/S2213-2600(20)30076-X.
[5] Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. Am J Pathol 2007;170(4):1136–1147. doi:10.2353/ajpath.2007.061088.
[6] Azer SA. COVID-19: pathophysiology, diagnosis, complications and investigational therapeutics. New Microbes New Infect 2020;37:100738. doi:10.1016/j.mmi.2020.100738.
[7] Dong Y, Shamsuddin A, Campbell H, Theodoratou E; on behalf of UNCOVER. Current COVID-19 treatments: rapid review of the literature. J Glob Health 2021;11:10003. doi:10.7189/jogh.11.10003.
[8] McLaughlin LP, Bollard CM, Keller MD. Adoptive T Cell Therapy for Epstein-Barr Virus Complications in Patients with Primary Immunodeficiency Disorders. Front Immunol 2018;9:556. doi:10.3389/fimmu.2018.00556.
[9] Feuchttinger T, Opherk K, Bethe WA, Topp MS, Schuster FR, Weissinger EM, et al. Adoptive transfer of pp65-specific T cells for the treatment of chemorefractory cytomegalovirus disease or reactivation after haploidentical and matched unrelated stem cell transplantation. Blood 2010;116(20):4360–4367. doi:10.1182/blood-2010-03-262089.
[10] Grifoni A, Weiskopf D, Ramirez Sl, Mateus J, Dan JM, Moderbacher CR, et al. Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals. Cell 2020;181(7):1489–1501.e15. doi:10.1016/j.cell.2020.05.015.
[11] Children's National Hospital. T-cells from recovered COVID-19 patients show promise to protect vulnerable patients from infection: Immunotherapy experts apply proven model to grow SARS-CoV-2-fighting T-cells from convalescent donors. ScienceDaily 2020. Available from: www.sciencedaily.com/releases/2020/10/201026114218.htm. Accessed December 8, 2020.
[12] Leung W, Soh TG, Linn YC, Low JG, Loh J, Chan M, et al. Rapid production of clinical-grade SARS-CoV-2 specific T cells. Adv Cell Gene Ther 2020;3(4):e101. doi:10.1002/acg2.101.
[13] Cooper RS, Fraser AR, Smith L, Burgoyne P, Imlich SN, Jarvis LM, et al. Rapid GMP-Compliant Expansion of SARS-CoV-2-Specific T Cells from Convalescent Donors for Use as an Allogeneic Cell Therapy for COVID-19. Front Immunol 2021;12:598402. doi:10.3389/fimmu.2020.598402.
[14] Ferreras C, Pascual-Miguélez B, Mestre-Durán C, Navarro-Zapata A, Clares-Villa L, Martín-Cortésar C, et al. SARS-CoV-2-Specific Memory T Lymphocytes From COVID-19 Convalescent Donors: Identification, bank, and Large-Scale Production for Adoptive Cell Therapy. Front Cell Dev Biol 2021;9:620730. doi:10.3389/fcell.2021.620730.
[15] Chen LY, Holland RL, Stukas S, Wellington Cl, Seshon MS. Facing the controversy: interleukin-6 and the COVID-19 cytokine storm syndrome. Eur Respir J 2020;56(4):2003006. doi:10.1183/13993003.03006-2020.
[16] Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodríguez L. SARS-CoV-2 Infection: The Role of cytokines in COVID-19 Disease. Cytokine Growth Factor Rev 2020;54:62–75. doi:10.1016/j.cytogfr.2020.06.001.
[17] Fara A, Mitrev Z, Rosalia RA, Assas BM. Cytokine storm and COVID-19: a chronicle of pro-inflammatory cytokines. Open Biol 2020;10(9):
Wang P, Wu P, Siegel MI, Egan RW, Billah MM. Interleukin (IL)-10 inhibits factor kappa B (NF-kappa B) activation in human monocytes. IL-10 and IL-4 suppress cytokine synthesis by different mechanisms. J Biomed 1995;270(16):9558–9563. doi:10.1074/jbc.270.16.9558.

Hariharana A, Hakeem AR, Radhakrishnan S, Reddy MS, Rela M. The Role and Therapeutic Potential of NF-kappa-B Pathway in Severe COVID-19 Patients. Inflammopharmacology 2021;29(1):91–100. doi:10.1007/s10787-020-00773-9.

Kirchges M, Haasbach E, Lueftenerg D, Heyken WT, Ocker M, Planz O. NF-kB Pathway as a Potential Target for Treatment of Critical Stage COVID-19 Patients. Front Immunol 2020;11:598444. doi:10.3389/fimmu.2020.598444.

Kandasamy M. NF-kB signalling as a pharmacological target in COVID-19: potential roles for IKK beta inhibitors. Naunyn Schmiedebergs Arch Pharmacol 2021;394(3):561–567. doi:10.1002/ps.202055.

Kak G, Raza M, Tiwari BK. Interleukin-10 (IFN-y): exploring its implications in infectious diseases. Biomed Concepts 2018;9(1):64–79. doi:10.1515/bmc-2018-0007.

Haji Abdolvahab M, Moradi-Kalbodani S, Zarei M, Bose D, Majidzadeh A-K, Farahmand L. Potential role of interleukin-10 in treating COVID-19 patients. Int Immunopharmacol 2021;98:107171. doi:10.1016/j.intimp.2020.107171.

van Eeden C, Khan L, Osman MS, Cohen Tervaert JW. Natural Killer Cell Dysfunction and Its Role in COVID-19. Int J Mol Sci 2020;21(7):16351. doi:10.3390/ijms210716351.

Matsui M, Moriya O, Yoshimoto T, Akatsuka T. T-bet is required for protection against vaccinia virus infection. J Virol 2005;79(20):12798–12806. doi:10.1128/JVI.79.20.12798-12806.2005.

Tripp C, WS, Wolf SF, Unanue ER. Interleukin 12 and tumor necrosis factor alpha are costimulators of interferon-gamma production by natural killer cells in severe combined immunodeficiency mice with listeriosis, and interleukin 10 is a physiologic antagonist. PNAS 1993;90(8):3725–3729. doi:10.1073/pnas.90.8.3725.

O’Andrea A, Aste-Amezaga M, Valiente NM, Ma X, Kubin M, Trinchieri G. Interleukin 10 (IL-10) inhibits human lymphocyte interferon gamma production by suppressing natural killer cell stimulatory factor/IL-12 synthesis in accessory cells. J Exp Med 1993;178(3):1041–1048. doi:10.1084/jem.178.3.1041.

Cai G, Kastelein RA, Hunter CA. IL-10 enhances NK cell proliferation, cytotoxicity and production of IFN-gamma when combined with IL-18. Eur J Immunol 1999;29(9):2658–2665. doi:10.1002/(SICI)1521-4141(19990909)29:9<2658::AID-IJIM2658-3.0.CO;2-G.

Tian LH, Furukawa K, Nagano T, Kiriu T, Nishimura M, Arii J, €et et al. Early Differences in Cytokine Production by Severity of Coronavirus Disease 2019. J Infect Dis 2021;223(7):1145–1149. doi:10.1093/infdis/jiaa005.

Satoh S, Özger HS, Aysor Yıldız P, Hizel K, Gulbahar Ö, Erbaş G, et al. Prognostic value of interleukin-18 and its association with other inflammatory markers and disease severity in COVID-19. Cytokine 2021;137:155302. doi:10.1016/j.cyto.2020.155302.

Itoh K, Hirohata S. The role of IL-10 in human B cell activation, proliferation, and differentiation. Immunol Rev 1995;149:341–430. doi:10.1111/j.1600-065X.1995.tb00947.x.

Sarafia M, Christensen JR, Veldhoven M, Murphy TL, Murphy KM, O’Garra A. Interleukin-10 production by Th1 cells requires interleukin-12-induced STAT4 transcription factor and ERK MAP kinase activation by high antigen dose. Immunity 2009;31(2):209–219. doi:10.1016/j.immuni.2009.05.012.

Wei YQ, Cen XN, Liu HH, Sun YH, Shi YL, Liu W, et al. Irradiation of peripheral blood mononuclear cells with 7.5 Gy X-rays prior to donor lymphocyte infusion inhibits proliferation while preserving cytotoxicity, and improves the effectiveness of HSC in patients with hematological malignancies. Oncol Lett 2017;13(6):4101–4108. doi:10.3892/ol.2017.7596.

Jia Z, Gong W. Will Mutations in the Spike Protein of SARS-CoV-2 Lead to the Failure of COVID-19 Vaccines? J Korean Med Sci 2021;36(18):e124. doi:10.3346/jkms.2021.36.e124.

McCallum M, Bassi J, de Marco A, Chen A, Walls AC, Di Iulio J, et al. SARS-CoV-2 immune evasion by variant B.1.427/B.1.429. bioRxiv (Preprint) 2020;2021.03.31.437925.

Public Health England. SARS-CoV-2 variants of concern and variants under investigation in England, Technical briefing 15 (11 June 2021). Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/993879/variants_of_concern_voc_technical_Briefing_15.pdf. Accessed June 27, 2021.

DOI: 10.14218/ERHM.2021.00008 | Volume 7 Issue 1, March 2022