

Cellular Therapy: The Hope for Covid-19

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Abstract

Coronaviruses (CoVs) are a group of very diverse viruses that cause a broad spectrum of diseases from mild to severe enteric, respiratory, systemic diseases, and common cold or pneumonia among humans and animals. This virus is associated with Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS), and lung disease that lead to Acute Respiratory Distress Syndrome (ARDS). In December 2019, researchers identified a novel coronavirus type, called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2), which was associated with symptoms of high fever, dry cough, headache, diarrhea, and reduction of White Blood Cells (WBC). Coronavirus-associated acute respiratory disease was named Coronavirus Disease 19 (COVID-19). No proven treatment has been discovered for COVID-19 so far, but researchers are trying to find the best effective way to treat this disease. Therefore, therapeutic strategies that facilitate the recovery of COVID-19 patients and reduce life-threatening complications are urgently needed now. Today, Mesenchymal Stem Cells (MSCs) and their secretion are utilized as one of the most applied tools to treat various diseases such as inflammation and cancer. MSC-derived vesicles are rich in various growth factors, cytokines, and interleukins that are produced and secreted under different physiological or pathological conditions. These vesicles were considered a suitable and effective tool in regeneration medicine because of their high power in repairing damaged tissues and modulating immune responses. Recently, evidence has shown MSC-derived vesicles through reduced expression of pro-inflammatory cytokines could improve damaged tissues in COVID-19 patients. In addition to MSCs and MSC-derived exosomes, Natural Killer (NK) cells, T cells, and platelet lysates were used against viral infection. In this review, we tried to provide an overview of MSC secretion and immune cells for COVID-19 therapy.

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Introduction

Stem cells are undifferentiated cells that can differentiate into mature specialized cells. Some of the stem cells such as Mesenchymal Stem Cells (MSCs), Hematopoietic Stem Cells (HSCs), and skeletal muscle stem cells play a crucial role in cell therapy ¹.

Recently, cell therapy has become a beneficial tool for disease treatment as well as a strategy for replacing, repairing, and enhancing the biological function of damaged tissue. The use of cell therapy in treatment of diseases such as cancer, autoimmune disease, joint injuries, and infectious diseases has been proven ².

The COVID-19 disease is caused by a positive-stranded RNA virus named SARS-CoV2. This virus

binds to host Angiotensin-Converting Enzyme 2 receptors (ACE2) through the viral spike protein, leading to excessive stimulation of immune system and consequently damaging body organs ³⁻⁵. ACE2 by converting Angiotensin II (AngII) increases the levels of Tumor Necrosis Factor-alpha (TNF- α) and Interleukin 6 (IL-6) in the cells that lead to upregulating Nuclear Factor kappa B (NF- κ b) and activating the inflammasome ⁶. ACE2 receptors are present in many tissues including the lungs, heart, blood vessels, kidneys, liver, and gastrointestinal tract, and also are abundant in human Alveolar Type II cells (AT2) ⁷.

The replication of SARS-CoV2 in target cells in-

duces the release of large amounts of inflammatory factors from host immune cells, causing a cytokine storm. This exaggerated immune response is responsible for different complications in the host and eventually leads to multiple organ failure⁸. Numerous researches have shown higher plasma levels of Granulocyte Colony-Stimulating Factor (GCSF) and TNF- α in severe COVID-19 patients, and on the other hand, increasing GCSF and TNF- α levels induce cytokine storm and lead to Acute Respiratory Distress Syndrome (ARDS)⁹. So, suppressing immunological response and regeneration of the lung tissue can be an effective treatment modality for COVID-19 patients¹⁰.

Researchers are trying to recommend the best treatment for COVID-19 disease. Several studies show that the use of MSCs and their secretion can treat coronavirus-induced pneumonia¹¹. MSCs therapy offers a promising approach for reducing the harmful effects in COVID-19 patients. This therapeutic approach reduces the expression of pro-inflammatory cytokines as well as repairs damaged tissues in COVID-19 patients⁹. Except for MSCs, immune system cells, including Natural Killer (NK) cells and platelet lysates play an important role in the body's defense against disease¹². This review has been organized to put forward the positive arguments and implications in support of cell therapy as a necessary approach for treating COVID-19 patients (Figure 1).

Role of mesenchymal stem cells (MSCs) in respiratory virus-induced lung injury

Despite the development of stem cell-based therapy, important limitations such as immunogenicity, limited cell source, and ethical issue have not been solved yet. Among these, MSCs have attracted attention due to: easily accessible with a high proliferation rate, low invasive procedures, and being free of ethical issues¹³. MSCs are spindle multipotent stromal cells. These stem cells are derived from different adult tissue and express special cell surface markers (positive for CD73, CD90, and CD105; negative for CD45, CD34, CD14 or CD11b, CD79 or CD19, and HLA-DR). MSCs have self-renewal capability and are differentiated into several cell-types¹⁴. MSCs as non-hematopoietic cells are normally found in the bone marrow and make up about 0.001-0.01% of all bone marrow nucleated cells. MSCs are easily accessible and derived from multiple tissues such as bone marrow and adipose tissues, umbilical cord, dental pulp, menstrual blood, buccal fat pad, etc. These stem cells demonstrate similar phenotypes but have different functions and variable markers in each tissue¹⁵. MSCs can easily expand to clinical volume in a suitable period and can be stored for repetitive therapeutic usage¹¹.

The immunoregulatory properties and the tissue reparative ability of MSCs are relied on express immunosuppressive molecules as well as the secretion of inflammatory cytokines, and various growth factors that induce tissue repair and maintain immune homeostasis

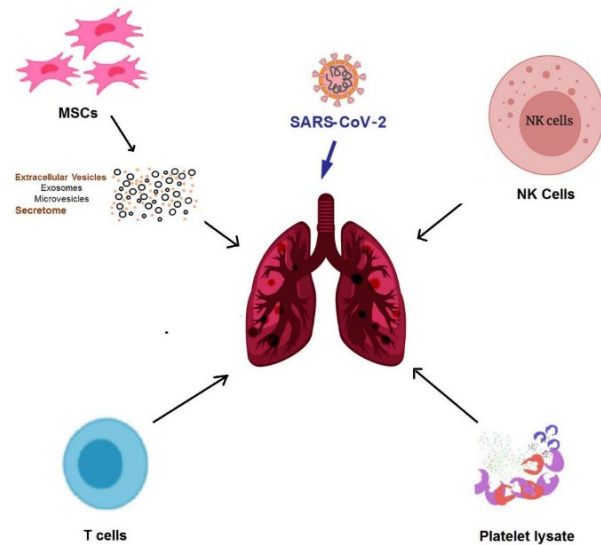


Figure 1. Schematic representation of cell-based therapeutic approaches against covid-19.

16,17. Furthermore, MSCs are capable of activating other resident stem cells to participate in the healing process and can stimulate neo-angiogenesis, tissue repair, and cell survival in surrounding tissues¹⁸. MSCs could retain Dendritic Cells (DCs) in an immature state by suppressing pro-inflammatory cytokine secretion and *via* inhibiting the expression of Major Histocompatibility Complex (MHC) class II, CD1- α , CD40, CD80, and CD86 markers¹⁹. MSCs through increasing secretion soluble factors, such as TGF- β and Prostaglandin E2 (PGE2) can inhibit the function of DCs, NK cells, and macrophages²⁰. These stem cells decrease IL-2- or IL-15-driven NK cell proliferation²¹.

MSCs have been already known to inhibit T-cell proliferation in adaptive immune responses²². Besides, they can decrease B-cell proliferation *via* cell-cell contact and secret growth factors²³. MSCs induce IL-10-secreting macrophages in both *in vitro* and *in vivo* researches²⁴. When MSCs have entered the microenvironment of damaged tissues, several different cytokines such as TNF- α , IL-1, IFN- γ , toxins of infectious agents, viruses, and hypoxia can trigger the secretion of critical soluble growth factors by MSCs, including Epidermal Growth Factor (EGF), Fibroblast Growth Factor (FGF), Insulin Growth Factor-1 (IGF-1), Transforming Growth Factor- β (TGF- β), Vascular Endothelial Growth Factor (VEGF), Hepatocyte Growth Factor (HGF), Platelet-Derived Growth Factor (PDGF), Angiopoietin-1 (Ang-1), Keratinocyte Growth Factor (KGF) and Stromal cell-Derived Factor-1 (SDF-1). These growth factors increase the development of fibroblasts, integrity of endothelial cells and promote angiogenesis through regulating endothelial cell proliferation and extracellular matrix production and subsequently tissue repair accrue²⁵⁻²⁸. These cells play their role by direct cell to cell contact and secretion of

growth factors⁷. MSCs can release extracellular vesicles containing numerous mRNAs, regulatory miRNAs, multiple bioactive proteins and compounds, and the production and secretion of a large number of regulatory substances rather than MSC direct differentiation and cell replacement^{29,30}.

The basic therapeutic effects of MSCs are now attributed to the stimulation of several endogenous repair processes in injured tissues *in vivo* by secreted factors as well as the modulation of an immune response, which translates into a positive outcome of MSC-based therapies^{31,32}. Therefore, MSCs have been mentioned as an effective cell source for cell therapy approach³³.

A lot of clinical trials using MSCs in different aspects have been done³⁴⁻³⁷. MSC-based therapies are superior to other treatments due to their source potential, high proliferation, low invasiveness, and being free of ethical issues¹³. Additionally, MSCs based immunomodulation treatment has been one of the promising tools in various diseases and several clinical trials have begun in this regard³⁸. MSC administration can significantly reduce lung injury in respiratory viruses such as influenza strains H5N1 and H9N2³⁹.

After the entry of COVID-19 into the body an exaggerated immune response is induced through the production of large amounts of inflammatory agents, including cytokines, chemokines, and immune cell responses. Evidence has shown MSCs in lung cells can release different soluble mediators including cytokines, antimicrobial peptides, angiogenic factors, and extracellular vesicles⁴⁰⁻⁴². In systemic administration MSCs lodge in the pulmonary vascular. MSCs clearance from capillary endothelial cells *via* apoptosis and phagocytosis by resident inflammatory, immune cells, and macrophages is around 24-48 hr^{43,44}.

Numerous reports strongly focus on MSC paracrine properties in ARDS patients, as well as, introducing MSCs as a therapeutic approach for use in the treatment of COVID-19⁴⁵. Leng *et al* performed a clinical trial study (ChiCTR2000029990) using human Umbilical Cord-Derived MSCs (hUCMSCs) in seven COVID-19 patients for 14 days and then observed that the population of CD14⁺, CD11c⁺, CD11b^{Mid} and regDCs markedly increased and levels of TNF- α decreased, while levels of IL-10 increased in the MSC treatment group compared to the control group⁹. Recent experiments

on rat lungs have shown that MSCs can be modulate inflammatory reactions that lead to acute lung injury and pulmonary fibrosis⁴⁶. MSCs, inhibit tissue fibrosis and stimulate angiogenesis by producing anti-fibrotic and angiogenic factors⁴⁷. The summary of MSCs mechanisms of therapy is given in table 1.

Despite MSCs attracting a lot of attention in regeneration medicine, it seems MSCs therapies are complicated and their outcomes should be followed-up in long term. Also during MSCs transplantation potential risks such as pro-tumorigenic, immune response, disturbed differentiation capacities, differentiation into desirable tissue, short survival after transplantation, unspecial optimal dose and route of cell administration should be considered^{2,48,49}. Some evidences demonstrated that the quality of MSCs in cell therapy depends on the age, genetic traits, and medical history of the donor^{50,51}. Another complicated issue in the use of MSCs in autologous transplantation is how to expand MSCs from elderly patients to obtain a suitable number of interest cells. Also, it is difficult to isolate an effective population of MSCs from patients with some diseases because cells isolated from the patient may be affected by the disease⁵².

Extracellular vesicles derived- MSCs

Extracellular Vesicles (EVs) are small circulating membrane-enclosed entities shed from cell surfaces of variant cell types in response to cell conditions⁵³. EVs measure 0.01-4 μm and are generated by various processes. The secretion of EVs depend on chemical and mechanical stimuli. In addition gamma-ray, calcium ionosphere, heparinase, statins, hypoxia, and acidic condition can also increase the secretion of EVs^{54,55}. EVs are divided into three categories based on size and cell sources such as 1) Ectosomes or Microvesicles (MVs) (200~1000 nm) that originate from the plasma membrane, 2) Exosomes (40~100 nm) are composed of the germination of intracellular secondary endosomes that are secreted out of the cell after fusion with the cell membrane, and 3) apoptotic bodies (50~500 nm) are released from a cell that has been in apoptosis⁵⁶.

Stem cell secretome induces the neighboring cells to modulate various downstream pathways, including immunomodulation, suppression of apoptosis, prevention of fibrosis, and remodeling of the injured tissues⁵⁷. Stem cells release these secretomes by common secre-

Table 1. The summary of MSCs mechanisms of therapy

Mechanisms	Factors
Immunomodulation	TGF- β , HGF, IL10, PGE2, IDO, NO, FAS/FASL
Tissue regeneration	EGF, FGF, PDGF, IGF-1, SDF-1, TGF- β , TNF, IFN- γ , IL1, PGE2, IDO, NO
Anti-inflammatory effects	\uparrow IL10, \downarrow IFN γ , TNF α , β or IL6
Activation of resident stem cells	VEGF, HGF, IGF-1
Neo angiogenesis	VEGF, HGF, FGF, IGF, PIGF, PDGF, Ang, SDF-1, IL-6, MCP-1
Anti-microbial effects	LL-37, Lipocalin-2, BD
Anti-apoptotic activity	VEGF, HGF, IGF, TGF- β , FGF, GM-CSF, IL-6
Migration activity	EGF, IGF, PDGF, VEGF, SDF-1, TNF- α , IL-1,6,8, VCAM-1, MCP, G-CSF

tory mechanisms. When secretomes are injected into the patients, the near cells absorb the molecules by paracrine signaling⁵⁸. MSCs secretome can repair damaged tissue, reduce tissue fibrosis, express antiviral miRNA genes to improve the function of immunity by directly affecting viral replication⁵⁹. As mentioned MSCs exosomes are types of EVs that have shown significant potential in recent decades⁶⁰. Indeed, researchers found that plasma EVs can affect directly patients' host cells and modulate immune systems⁶¹. MSC-Exos can inhibit T^{CD8+} and T^{CD4+} via inhibiting T cells expression IL-17 and induced IL-10-expressing⁶². MSC-Exos could suppress differentiation of T^{CD8+} and T^{CD4+} cells via releasing TGFβ and inhibit inflammation *in vivo* model⁶³. MSCs exosomes can repair the muscles by the process of myogenesis and angiogenesis with function depending on miR-494 in the exosomes⁶⁴.

MSCs exosomes, by inducing gene expression in the target cell can regenerate bone marrow stroma and lead to an increase in the function of angiogenesis in target cells. EVs are one of the ideal carriers for drug or gene delivery to the target tissue because they are rich in various growth factors⁶⁵. Evidence shows direct use of MSCs should increase the risk of rejection but EVs are successful in transplantation with no rejection. EVs can be a good alternative for MSCs in the treatment and repair of tissues⁶⁶.

Faisal A. Alzahrani *et al*, showed ExoFlo™, a bm-MSC-derived exosome agent, significantly improved neutrophilia and lymphopenia including increased CD3+, CD4+, and T^{CD8+} lymphocytes in addition to reducing the severity of diseases⁶⁷. MSCs mediate these kinds of effects by direct contact, where it releases the regulatory cytokines, such as Interferon-gamma (IFN-γ), indoleamine 2,3-dioxygenase, TGFβ, IL-10, and PGE2⁶⁸. Moreover, MSCs can hinder the proliferation and/or functions of the CD4+ Th1 and TH17 cells, T^{CD8+} lymphocytes, and the NK cells, mainly by secreting soluble factors and vesicles, such as TGFβ1 and HGF⁶⁹. MSCs secretome has a direct and indirect effect on modulating immune responses. MSC injection in Acute Lung Injury (ALI) and ARDS preclinical

models resulted in improved lung tissue recovery. MSCs secretome increase the level of anti-inflammatory molecules such as IL-10 while decreasing inflammatory cytokines, including TNF-α, macrophage inflammatory protein 2 (MIP-2), IL-1β, TGF-β, VEGF, IL-6, IFN-γ, Myeloperoxidase (MPO), Regulated upon Activation Normal T Cell Expressed and Presumably Secreted (RANTES), and Nitric Oxide Synthases (NOS) levels^{70,71}. The list of extracellular vesicles derived-MSCs used in COVID19 clinical trial is given in table 2.

It should be noted that despite the therapeutic effectiveness of MSC-EV in preclinical studies, the use of EV in clinical treatments has several critical issues such as (i) isolation methods and large-scale-production, (ii) rapid and accurate characterization method, (iii) precise content characterization of the cargo, (iv) pharmacokinetics, targeting and transfer mechanisms of EV to the accurate sites, and (v) safety profiles to access the best clinical dosage and possible toxicities upon repeated administration⁷².

Natural killer cell (NK) based therapy in Covid-19

NK cells are the first responder's defense system against viral infections because of their role in cytotoxicity and chemokine releases. The NK cells are cytotoxic lymphocytes that contain 10-15% of total peripheral blood leukocytes in humans. These cells play a crucial role in linking innate and adaptive immune system activity⁸². They are present in the peritoneal lymph node, thymus, spleen, liver, peritoneal hollow area, and gravid uterus. Their function is well mediated by the ligand-receptor interaction. NK cells' role in tumorigenic, asthma, autoimmune diseases, and HIV-AIDS have been well defined⁸³. The interaction of NK cells in viral infections amplifies their potential role in showing the innate immune response; increasing the IFN-γ release; direct cytotoxicity of target cells and viral replication inhibition⁸⁴. After attachment of virus-infected cells to the Natural Killer Group 2D (NKG2D) receptor, major activating NK cell receptor NKG2D, NK cells are activated and produce anti-microbial and immunoregulatory cytokines and ultimately kill the infected cells. All NKG2 receptor families are type II

Table 2. MSC-EV in the treatment of COVID-19

Clinical trial number	Clinical outcome	Source	References
NCT04276987	Reduce pneumonia and recovery of COVID19 patients	MSCs- derived exosomes	(67,73)
NCT04493232	Reduce inflammation, fibrosis, and pulmonary hypertension in COVID19 patients	MSCs EV-derived bone marrow and MSCs EV-derived umbilical cord	(74,75)
ChiCTR2000030484	Increasing expression of IL-10, TGF1, and T cell activation	MSCs EV-derived bone marrow MSCs	(76)
NCT04361942	Decrease expression of cytokine n lung	MSCs EV-derived mouse bone marrow MSCs	(77)
NCT04371393	Reduce inflammation in COVID19 patients	MSCs EV-derived adipocyte	(39,78)
NCT01902082	Improve lung function of COVID19 patients	MSCs EV-derived adipocyte	(79)
NCT04276987	Improve lung function of COVID19 patients	MSCs- derived exosomes	(80)
ChiCTR2000029990	Increase CD ^{11bMid} , CD ¹⁴⁺ , and CD ^{11c+} after 14 days and improve lung function of COVID19 patients	MSCs- derived exosomes	(9)
ChiCTR2000030261	Improve lung function of COVID19 patients	MSCs- derived exosomes	(81)

transmembrane glycoproteins. Also activating receptor NKG2D (CD314) is expressed in NK. This finding describes the rational function of the NK cell in COVID-19⁸⁵. In COVID-19 patients' number of NK cells are decreased which is associated with development and severity of COVID-19⁸⁶.

The most common symptoms of coronavirus infections include significant morbidity and mortality related to pulmonary lesions and acute respiratory syndrome due to an exaggerated immune response, where NK cells are a critical mediator. Along with their effective antiviral function, NK cells have also been related to immunopathology in infections like Respiratory Syncytial Virus (RSV), influenza, and hepatitis B^{87,88}.

The natural immunity response is triggered by molecular structures -called Pathogen-Associated Molecular Patterns (PAMPs) that are recognized by Pathogen Recognition Receptors (PRRs). In respiratory RNA viruses, epithelial cells, which express certain PRRs, are infected and have a primary role in the first line of defense. Toll-Like Receptor (TLR3), TLR7, TLR8, Melanoma Differentiation-associated protein 5 (MD-5), and Retinoic acid-inducible gene I (RIGI) are PRRs predominantly expressed by immune and non-immune cells against RNA respiratory viruses, like coronaviruses. Following identifying PRRs, production type I interferons (IFNs), (IFN- α/β) and other components involved in the inflammatory response, are the main stage in antiviral responses.

Also, decreased NK cell levels have been inversely associated with the severity of COVID-19 patients. One of the possible mechanisms by which NK cells can also emerge as hyporesponsive in fighting coronavirus is interference with type I IFN pathways⁸⁹.

IFNs type I is released by both immune and non-immune cells and besides stimulating interstice antiviral defense mechanisms, are critical to natural and adaptive lymphocytes, such as NK cells. In patients with Natural Killer cell Deficiency (NKD) and immune-compromised who are highly sensitive to viral infections, the importance of NK cells as a first-line antiviral responder is highlighted. Some studies proposed that neutrophils and inflammatory monocyte-macrophages accumulate in the lungs in acute coronavirus infections such as, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) and release the chemokines and cytokines that result in NK cell activation and migration⁹⁰.

Additionally, adoptive NK cells and CAR-NK cells are candidates for cell-based therapy as an alternative treatment of COVID-19 patients. In a new report, Novocellbio has confirmed that its autologous NK cell treatment agent Novo-NK, an autologous natural killer cell treatment, is effective in killing SARS-CoV-2 in a cellular and preclinical study. Recently, five clinical trials have been registered at the Clinical level based on using of Peripheral Blood Mononuclear Cell (PBMC) derived NK cells in COVID-19 patients, alt-

hough, there have been no published clinical reports yet. In one of these trials (Identifier: NCT04344548), patients were treated with three different injections of NK cells 48 hr apart with 1, 10, and 20, 106 cells/kg body weight, but the protocols are unknown and clinical trials are in phases 1 and 2⁹¹.

T cell-based therapy in COVID-19

The T lymphocytes are one of the important blood cells which play a critical role in adaptive immune response. T lymphocytes driven from hematopoietic stem cells in bone marrow, then migrate to the thymus gland for maturation. T cell exhaustion is a broad term that was known as the response of T cells to chronic antigen stimulation, bacterial, and parasitic infections as well as human cancers⁹². Lately, two backgrounds have shed light on the comprehension of T cell exhaustion. Firstly, both intrinsic negative regulatory pathways (such as PD-1) and extrinsic regulatory pathways (along with immunoregulatory cytokines) have the main role in T cell exhaustion⁹³. T cells play a main role in development of COVID-19 patients. Transient lymphopenia is a typical characteristic in many respiratory viral infections, including influenza A H3N2 virus, human rhinovirus, or respiratory syncytial virus. Lymphopenia is related to the severity of the COVID-19 and some studies have shown reduction of CD³⁺, CD⁴⁺, CD⁸⁺ T lymphocyte, B cells, and NK cells in COVID-19 patients. Similarly, the most recent RNA-seq upper respiratory tract reported that the participation of cytotoxic T lymphocytes in patients with COVID-19 lymphocytes significantly decreased compared to mild disease. Several kinds of research demonstrated lymphopenia as an eminent feature of the SARS-CoV-2 infection⁹⁴. Thus, finding out how lymphopenia could influence T cell hyperactivation in patients with COVID-19 is a crucial aim in therapeutic approaches. There are some studies that strongly suggest the formation of immunological memory of T cells following improvement from SARS-CoV-2. This evidence highlights the important role of T cells in the diagnosis and treatment of severe patients⁹⁵.

Platelet lysate based therapy in COVID-19

Human blood is known as a source of many therapeutic agents which can be classified into cellular and protein-based blood products. The cellular blood products include buffy coat derived, red blood cells, and apheresis platelets, whereas protein-based products are cryoprecipitate, fresh frozen plasma, and plasma fractionation products. Platelet lysate is an acellular product consisting of regenerative molecules released from a cluster of platelets and considered as a regenerative immunomodulatory agent to combat COVID-19⁹⁶. The critical role of platelets in wound regeneration and tissue reconstruction is feasible by the use of human platelet derivatives products in regenerative medicine⁹⁷.

Platelet lysate decreases immune reaction with the introduction of growth factors, cytokines, and proteins.

Cytokines and factors in platelet granules will be released naturally by stimulation of thrombin and coagulation or artificially by sonication, chemical agents or freeze/thaw-mediated platelet lysis. Platelet lysate can be used in nebulized form for such acute respiratory distress conditions in COVID-19 elderly patients. Evidence has shown the effect of the platelet in COVID-19-associated pathophysiology.

Furthermore, platelet lysate can be used for treating problems such as chronic obstructive pulmonary disease, acute lung injuries, and asthma. In this manner, as adjuvant therapy for the treatment of COVID-19 associated acute respiratory syndrome, it can be useful because it triggers inflammatory processes⁹⁸. Platelets release proinflammatory cytokines that promote inflammatory immunomodulation. There is a multiplex interplay between the intrinsic and adaptive immunological components of platelets in the clearance of pathogens. The role of platelets in defending against viral infections has been reported by research and requires accurate interaction of the receptor-ligand. The role of platelets and their interaction in viral infection has been characterized. Furthermore, it can increase the oxygen saturation range for patients with COVID-19⁹⁹.

Platelets are stimulated either by direct or indirect stimuli and undergo degranulation. In addition, it releases numerous growth factors and biomolecules that are active in mediating host defensive mechanisms. New chemokines that also exert direct antimicrobial activity have been termed kinocidins. Platelet factor 4 (PF-4/CXCL-four) has been listed as the most effective minocycline. CCL-five has been reported to be active in the viral affected lung, and this has been shown in viral infection of influenza A in mice, where it provides (anti-apoptotic) signalling for macrophages. Likewise, platelet lysate can grow to be a key participant in viral lysis¹⁰⁰.

The platelet lysate processing produces a rich material content of growth factors with a limited volume of white cell antigens. The platelet lysate will provide a beacon of desire in cell regeneration by stimulating cell proliferation and angiogenesis with the supply of supraphysiologic doses of platelet factors. This trait can be further analyzed to act as an adjuvant in patients with COVID-19.

Platelets have bioactive molecules that, once platelets are used in the form of platelet-rich plasma, cause the quiescent cells to perform the target effects. The next application of platelet technology is platelet lysate obtained from the ruptured platelet membrane, and these acquired bioactive molecules are then based on using lyophilization to manufacture powdered form; the mission here is the lyophilization and immunogenicity process. The advantage of platelet lysate is the quantification of bioactive molecules present in it. However, in multiple diseases, it is an expanded way to verify dosage and control strategies¹⁰¹.

Conclusion

There is no specific treatment for COVID-19 now, and the recent treatment methods for COVID-19 are confined to the previous therapeutic techniques for similar viruses and previous generations of coronaviruses, including SARS- and MERS-CoVs. Such a situation calls attention from various medical fields including stem cell therapy and immune-modulatory methods. COVID-19 can damage various systems at the same time, including the central nervous system, the gastrointestinal system, and the respiratory system, and this will depend on its profound effects on the immune system. The improving features of MSCs, including their regenerative properties and ability to differentiate into diverse cell lineages, have generated considerable interest among researchers whose work has offered intriguing perspectives on cell-based therapies for various diseases. Immunomodulatory and anti-inflammatory properties of MSCs in the treatment of respiratory diseases were confirmed. However, the cost-effectiveness and speed of therapeutic preparation are the capable discussed issue for MSC-based therapy for COVID-19. Besides, the clinical use of MSCs therapy to treat COVID-19 is still some time away, but there are some promising reports to utilize it in the clinical trial. Stem cell therapy and especially MSCs maybe be one of the most ideal therapeutics or a combination of treatments to treat COVID-19 patients. However, scientists are trying incessantly to develop a vaccine for COVID-19, as well as therapeutics to treat this disease. The immunomodulatory effects of MSCs, which may assist in inhibiting cytokine storm and lung inflammation, are of particular interest for COVID-19 therapy. Besides, the potentials of NK cells to exert cytotoxic effects on infected cells and induce interferon production perhaps make NK cells a promising candidate for COVID-19 cell therapy. Cell-derived exosomes can be used as transfers for various macromolecules, which can modulate immune cells and signaling pathways, and therefore, become interesting for COVID-19 therapy. Finally, induced Pluripotent Stem Cells (iPSCs) can help the development of a personalized approach to COVID-19 therapy.

Generally, it has been shown cell-based therapies may be applicable in specific pathogenesis of COVID-19. However, there are some limitations to cell therapies that must be considered including immune rejection, dosing of the cells, number of injections, cell delivery approaches, cell survival/retention, and age of patients¹⁰². The appropriate route of administration is very important in effectiveness of cell therapies. Furthermore, multiple strategies are being addressed to boost cell viability, amend functional features of individual cells, and to elongate cell retention. For instance, integrating pharmacotherapy and cell therapy, genetic modification and preconditioning cells are strategies which are being studied to enhance cell therapy efficiency. Another alternative strategy is the use

of a combination of several cell types. For example, epithelial cells and pulmonary endothelial cells have been investigated for their synergistic effect with MSCs¹⁰³. In sum, the present comprehension of cell based therapy and the finding strategies will certainly progress cell-based therapy and treat patients with Covid-19.

Conflict of Interest

The authors have no financial or non-financial conflicts of interest to declare.

References

- Mastri M, Lin H, Lee T. Enhancing the efficacy of mesenchymal stem cell therapy. *World J Stem Cells* 2014;6(2):82-93.
- Lukomska B, Stanaszek L, Zuba-Surma E, Legosz P, Sarzynska S, Dreła K. Challenges and controversies in human mesenchymal stem cell therapy. *Stem Cells Int* 2019;2019:9628536.
- Li X, Ma X. Acute respiratory failure in COVID-19: is it “typical” ARDS? *Crit Care* 2020;24(1):198.
- Meftahi GH, Jangravi Z, Sahraei H, Bahari Z. The possible pathophysiology mechanism of cytokine storm in elderly adults with COVID-19 infection: the contribution of “inflammation-aging”. *Inflamm Res* 2020;69(9):825-39.
- Neghab HK, Azadeh SS, Soheilifar MH, Dashtestani F. Nanoformulation-based antiviral combination therapy for treatment of COVID-19. *Avicenna J Med Biotechnol* 2020;12(4):255-6.
- Zbinden-Foncea H, Francaux M, Deldicque L, Hawley JA. Does high cardiorespiratory fitness confer some protection against proinflammatory responses after infection by SARS-CoV-2? *Obesity (Silver Spring)* 2020;28(8):1378-81.
- Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* 2020;98(1):219-27.
- Li N, Wang X, Lv T. Prolonged SARS-CoV-2 RNA shedding: not a rare phenomenon. *J Med Virol* 2020;92(11):2286-2287.
- Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, et al. Transplantation of ACE2-mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. *Aging Dis* 2020;11(2):216-8.
- Sleem A, Saleh F. Mesenchymal stem cells in the fight against viruses: Face to face with the invisible enemy. *Curr Res Transl Med* 2020;68(3):105-10.
- Golchin A, Seyedjafari E, Ardeshtyrlajimi A. Mesenchymal stem cell therapy for COVID-19: present or future. *Stem Cell Rev Rep* 2020;16(3):427-33.
- Bonam SR, Kaveri SV, Sakuntabhai A, Gilardin L, Bayry J. Adjunct immunotherapies for the management of severely ill COVID-19 patients. *Cell Rep Med* 2020;1(2):100016.
- Golchin A, Farahany TZ, Khojasteh A, Soleimanifar F, Ardeshtyrlajimi A. The clinical trials of mesenchymal stem cell therapy in skin diseases: an update and concise review. *Curr Stem Cell Res Ther* 2019;14(1):22-33.
- Maleki M, Ghanbarvand F, Behvarz MR, Ejtemaei M, Ghadirkhomi E. Comparison of mesenchymal stem cell markers in multiple human adult stem cells. *Int J Stem Cells* 2014;7(2):118-26.
- Cosenza S, Ruiz M, Toupet K, Jorgensen C, Noël D. Mesenchymal stem cells derived exosomes and micro-particles protect cartilage and bone from degradation in osteoarthritis. *Sci Rep* 2017;7(1):16214.
- Ma S, Xie N, Li W, Yuan B, Shi Y, Wang Y. Immunobiology of mesenchymal stem cells. *Cell Death Differ* 2014;21(2):216-25.
- Waterman RS, Tomchuck SL, Henkle SL, Betancourt AM. A new mesenchymal stem cell (MSC) paradigm: polarization into a pro-inflammatory MSC1 or an immunosuppressive MSC2 phenotype. *PloS One* 2010;5(4):e10088.
- Pansky A, Roitzheim B, Tobiasch E. Differentiation potential of adult human mesenchymal stem cells. *Clin Lab* 2007;53(1-2):81-4.
- Jiang XX, Zhang Y, Liu B, Zhang SX, Wu Y, Yu XD, et al. Human mesenchymal stem cells inhibit differentiation and function of monocyte-derived dendritic cells. *Blood* 2005;105(10):4120-6.
- Sotiropoulou PA, Perez SA, Gritzapis AD, Baxeavanis CN, Papamichail M. Interactions between human mesenchymal stem cells and natural killer cells. *Stem Cells* 2006;24(1):74-85.
- Spaggiari GM, Capobianco A, Becchetti S, Mingari MC, Moretta L. Mesenchymal stem cell-natural killer cell interactions: evidence that activated NK cells are capable of killing MSCs, whereas MSCs can inhibit IL-2-induced NK-cell proliferation. *Blood* 2006;107(4):1484-90.
- Svobodova E, Krulova M, Zajicova A, Pokorna K, Prochazkova J, Trosan P, et al. The role of mouse mesenchymal stem cells in differentiation of naive T-cells into anti-inflammatory regulatory T-cell or proinflammatory helper T-cell 17 population. *Stem Cells Develop* 2012;21(6):901-10.
- Corcione A, Benvenuto F, Ferretti E, Giunti D, Cappiello V, Cazzanti F, et al. Human mesenchymal stem cells modulate B-cell functions. *Blood* 2006;107(1):367-72.
- Németh K, Leelahavanichkul A, Yuen PS, Mayer B, Parmelee A, Doi K, et al. Bone marrow stromal cells attenuate sepsis via prostaglandin E₂-dependent reprogramming of host macrophages to increase their interleukin-10 production. *Nat Med* 2009;15(1):42-9.
- Shi Y, Su J, Roberts AI, Shou P, Rabson AB, Ren G. How mesenchymal stem cells interact with tissue immune responses. *Trends Immunol* 2012;33(3):136-43.
- Ma XL, Liu KD, Li FC, Jiang XM, Jiang L, Li HL. Human mesenchymal stem cells increases expression of α -tubulin and angiopoietin 1 and 2 in focal cerebral ischemia and reperfusion. *Curr Neurovasc Res* 2013;10(2):103-11.

27. Aguilar S, Scotton CJ, McNulty K, Nye E, Stamp G, Laurent G, et al. Bone marrow stem cells expressing keratinocyte growth factor via an inducible lentivirus protects against bleomycin-induced pulmonary fibrosis. *PLoS One* 2009;4(11):e8013.
28. Hung SP, Yang MH, Tseng KF, Lee OK. Hypoxia-induced secretion of TGF- β 1 in mesenchymal stem cell promotes breast cancer cell progression. *Cell Transplant* 2013;22(10):1869-82.
29. Gong M, Yu B, Wang J, Wang Y, Liu M, Paul C, et al. Mesenchymal stem cells release exosomes that transfer miRNAs to endothelial cells and promote angiogenesis. *Oncotarget* 2017;8(28):45200-12.
30. Soheilifar MH, Neghab HK, Basiri P. Biological impacts of microRNAs in covid-19: Implications for anti-viral miRNA-based therapies. *Arch Clin Infect Dis* 2020;15.
31. Jiang W, Xu J. Immune modulation by mesenchymal stem cells. *Cell Prolif* 2020;53(1):e12712.
32. Kim S, Lee SK, Kim H, Kim TM. Exosomes secreted from induced pluripotent stem cell-derived mesenchymal stem cells accelerate skin cell proliferation. *Int J Mol Sci* 2018;19(10):3119.
33. Brown C, McKee C, Bakshi S, Walker K, Hakman E, Halassy S, et al. Mesenchymal stem cells: cell therapy and regeneration potential. *J Tissue Eng Regen Med* 2019;13(9):1738-55.
34. Cao Y, Sun H, Zhu H, Zhu X, Tang X, Yan G, et al. Allogeneic cell therapy using umbilical cord MSCs on collagen scaffolds for patients with recurrent uterine adhesion: a phase I clinical trial. *Stem Cell Res Ther* 2018;9(1):192.
35. Galstian GM, Parovichnikova EN, Makarova PM, Kuzmina LA, Troitskaya VV, Gemdzian E, et al. The results of the Russian clinical trial of mesenchymal stromal cells (MSCs) in severe neutropenic patients (pts) with septic shock (SS)(RUMCESS trial). *American Society of Hematology* Washington, DC; 2015.
36. Infante A, Gener B, Vázquez M, Olivares N, Arrieta A, Grau G, et al. Reiterative infusions of MSCs improve pediatric osteogenesis imperfecta eliciting a pro-osteogenic paracrine response: TERCELOI clinical trial. *Clin Transl Med* 2021;11(1):e265.
37. Oh SK, Choi KH, Yoo JY, Kim DY, Kim SJ, Jeon SR. A phase III clinical trial showing limited efficacy of autologous mesenchymal stem cell therapy for spinal cord injury. *Neurosurgery* 2016;78(3):436-47.
38. Joyce N, Annett G, Wirthlin L, Olson S, Bauer G, Nolte JA. Mesenchymal stem cells for the treatment of neurodegenerative disease. *Regen Med* 2010;5(6):933-46.
39. Li Y, Xu J, Shi W, Chen C, Shao Y, Zhu L, et al. Mesenchymal stromal cell treatment prevents H9N2 avian influenza virus-induced acute lung injury in mice. *Stem Cell Res Ther* 2016;7(1):159.
40. Lee RH, Pulin AA, Seo MJ, Kota DJ, Ylostalo J, Larson BL, et al. Intravenous hMSCs improve myocardial infarction in mice because cells embolized in lung are activated to secrete the anti-inflammatory protein TSG-6. *Cell Stem Cell* 2009;5(1):54-63.
41. Krasnodembskaya A, Song Y, Fang X, Gupta N, Serikov V, Lee JW, et al. Antibacterial effect of human mesenchymal stem cells is mediated in part from secretion of the antimicrobial peptide LL-37. *Stem Cells* 2010;28(12):2229-38.
42. Hu S, Park J, Liu A, Lee J, Zhang X, Hao Q, et al. Mesenchymal stem cell microvesicles restore protein permeability across primary cultures of injured human lung microvascular endothelial cells. *Stem Cells Transl Med* 2018;7(8):615-24.
43. Armitage J, Tan DB, Troedson R, Young P, Lam KV, Shaw K, et al. Mesenchymal stromal cell infusion modulates systemic immunological responses in stable COPD patients: a phase I pilot study. *Eur Respir J* 2018;51(3):1702369.
44. Galipeau J, Sensébé L. Mesenchymal stromal cells: clinical challenges and therapeutic opportunities. *Cell Stem Cell* 2018;22(6):824-33.
45. Metcalfe SM. Mesenchymal stem cells and management of COVID-19 pneumonia. *Med Drug Discov* 2020;5:100019.
46. Vagnozzi RJ, Maillot M, Sargent MA, Khalil H, Johansen AKZ, Schwanekamp JA, et al. An acute immune response underlies the benefit of cardiac stem cell therapy. *Nature* 2020;577(7790):405-9.
47. Pashoutan Sarvar D, Shamsasenjan K, Akbarzadehlaleh P, Movassaghpour A, Timari H, Aqmasheh S. The application of Mesenchymal stem cell-derived vesicles in regenerative medicine. *Sci J Iran Blood Transfus Organ* 2017;14(3):237-48.
48. Ankrum JA, Ong JF, Karp JM. Mesenchymal stem cells: immune evasive, not immune privileged. *Nat Biotechnol* 2014;32(3):252-60.
49. Joswig AJ, Mitchell A, Cummings KJ, Levine GJ, Gregory CA, Smith R, et al. Repeated intra-articular injection of allogeneic mesenchymal stem cells causes an adverse response compared to autologous cells in the equine model. *Stem Cell Res Ther* 2017;8(1):42.
50. Dufrane D. Impact of age on human adipose stem cells for bone tissue engineering. *Cell Transplant* 2017;26(9):1496-504.
51. Liu M, Lei H, Dong P, Fu X, Yang Z, Yang Y, et al. Adipose-derived mesenchymal stem cells from the elderly exhibit decreased migration and differentiation abilities with senescent properties. *Cell Transplant* 2017;26(9):1505-19.
52. Pachón-Peña G, Serena C, Ejarque M, Petriz J, Duran X, Oliva-Olivera W, et al. Obesity determines the immunophenotypic profile and functional characteristics of human mesenchymal stem cells from adipose tissue. *Stem Cells Transl Med* 2016;5(4):464-75.
53. Nomura S, Ozaki Y, Ikeda Y. Function and role of microparticles in various clinical settings. *Thromb Res* 2008;123(1):8-23.
54. Ciardiello C, Cavallini L, Spinelli C, Yang J, Reis-Sobreiro M, De Candia P, et al. Focus on extracellular vesicles: new frontiers of cell-to-cell communication in cancer. *Int J Mol Sci* 2016;17(2):175.

55. Alberro A, Sáenz-Cuesta M, Muñoz-Culla M, Mateo-Abad M, Gonzalez E, Carrasco-García E, et al. Inflammation and frailty status do not result in an increased extracellular vesicle concentration in circulation. *Int J Mol Sci* 2016;17(7):1168.
56. Nomura S. Extracellular vesicles and blood diseases. *Int J Hematol* 2017;105(4):392-405.
57. Bari E, Ferrarotti I, Saracino L, Perteghella S, Torre ML, Corsico AG. Mesenchymal stromal cell secretome for severe COVID-19 infections: premises for the therapeutic use. *Cells* 2020;9(4):924.
58. Deffune E, Prudenciatti A, Moroz A. Mesenchymal stem cell (MSc) secretome: A possible therapeutic strategy for intensive-care COVID-19 patients. *Med Hypotheses* 2020;142:109769.
59. Jamshidi E, Babajani A, Soltani P, Niknejad H. Proposed mechanisms of targeting COVID-19 by delivering mesenchymal stem cells and their exosomes to damaged organs. *Stem Cell Rev Rep* 2021;17(1):176-92.
60. Cai S, Cheng X, Pan X, Li J. Emerging role of exosomes in liver physiology and pathology. *Hepatol Res* 2017;47(2):194-203.
61. Jayaramayya K, Mahalaxmi I, Subramaniam MD, Raj N, Dayem AA, Lim KM, et al. Immunomodulatory effect of mesenchymal stem cells and mesenchymal stem-cell-derived exosomes for COVID-19 treatment. *BMB Rep* 2020;53(8):400-12.
62. Lai P, Chen X, Guo L, Wang Y, Liu X, Liu Y, et al. A potent immunomodulatory role of exosomes derived from mesenchymal stromal cells in preventing cGVHD. *J Hematol Oncol* 2018;11(1):135.
63. Álvarez V, Sánchez-Margallo FM, Macías-García B, Gómez-Serrano M, Jorge I, Vázquez J, et al. The immunomodulatory activity of extracellular vesicles derived from endometrial mesenchymal stem cells on CD4+ T cells is partially mediated by TGFβ. *J Tissue Eng Regen Med* 2018;12(10):2088-98.
64. Motawi TM, Sabry D, Maurice NW, Rizk SM. Role of mesenchymal stem cells exosomes derived microRNAs; miR-136, miR-494 and miR-495 in pre-eclampsia diagnosis and evaluation. *Arch Biochem Biophys* 2018;659:13-21.
65. Sharma A. Role of stem cell derived exosomes in tumor biology. *Int J Cancer* 2018;142(6):1086-92.
66. Akbari A, Rezaie J. Potential therapeutic application of mesenchymal stem cell-derived exosomes in SARS-CoV-2 pneumonia. *Stem Cell Res Ther* 2020;11(1):356.
67. Alzahrani FA, Saadeldin IM, Ahmad A, Kumar D, Azhar EI, Siddiqui AJ, et al. The potential use of mesenchymal stem cells and their derived exosomes as immunomodulatory agents for COVID-19 patients. *Stem Cells Int* 2020;2020:8835986.
68. Thanunchai M, Hongeng S, Thitithyanont A. Mesenchymal stromal cells and viral infection. *Stem Cells Int* 2015;2015:860950.
69. Zhao Q, Ren H, Han Z. Mesenchymal stem cells: Immunomodulatory capability and clinical potential in immune diseases. *J Cell Immunother* 2016;2(1):3-20.
70. Güldner A, Maron-Gutierrez T, Abreu SC, Xisto DG, Senegaglia AC, da Silva Barcelos PR, et al. Expanded endothelial progenitor cells mitigate lung injury in septic mice. *Stem Cell Res Ther* 2015;6(1):1-8.
71. Liang ZX, Sun JP, Ping W, Qing T, Zhen Y, Chen LA. Bone marrow-derived mesenchymal stem cells protect rats from endotoxin-induced acute lung injury. *Chinese Med J (Engl)* 2011;124(17):2715-22.
72. Gowen A, Shahjin F, Chand S, Odegaard KE, Yelamanchili SV. Mesenchymal stem cell-derived extracellular vesicles: challenges in clinical applications. *Front Cell Develop Biol* 2020;8:149.
73. Ma ZJ, Yang JJ, Lu YB, Liu ZY, Wang XX. Mesenchymal stem cell-derived exosomes: Toward cell-free therapeutic strategies in regenerative medicine. *World J Stem Cells* 2020;12(8):814-40.
74. Cruz FF, Rocco PR. Stem-cell extracellular vesicles and lung repair. *Stem cell investigation*. 2017;4.
75. Yahaya BH. ID2008 Aerosol-based cell delivery as an innovative treatment for lung diseases. *Biomed Res Ther* 2017;4(S):S41-S.
76. Pocsfalvi G, Mammadova R, Juarez APR, Bokka R, Trepiccione F, Capasso G. COVID-19 and extracellular vesicles: an intriguing interplay. *Kidney Blood Press Res* 2020;45(5):661-70.
77. Choudhery MS, Harris DT. Stem cell therapy for COVID-19: Possibilities and challenges. *Cell Biol Int* 2020;44(11):2182-91.
78. Du YM, Zhuansun YX, Chen R, Lin L, Lin Y, Li JG. Mesenchymal stem cell exosomes promote immunosuppression of regulatory T cells in asthma. *Exp Cell Res* 2018;363(1):114-20.
79. Zheng G, Huang L, Tong H, Shu Q, Hu Y, Ge M, et al. Treatment of acute respiratory distress syndrome with allogeneic adipose-derived mesenchymal stem cells: a randomized, placebo-controlled pilot study. *Respir Res* 2014;15(1):39.
80. Nile SH, Nile A, Qiu J, Li L, Jia X, Kai G. COVID-19: Pathogenesis, cytokine storm and therapeutic potential of interferons. *Cytokine Growth Factor Rev* 2020;53:66-70.
81. Yin G, Zhang C, Jin H. Current status on clinical trials and treatments for COVID-19.
82. Bertzbach LD, van Haarlem DA, Härtle S, Kaufer BB, Jansen CA. Marek's disease virus infection of natural killer cells. *Microorganisms* 2019;7(12):588.
83. Le Gars M, Seiler C, Kay AW, Bayless NL, Starosvetsky E, Moore L, et al. Pregnancy-induced alterations in NK cell phenotype and function. *Front Immunol* 2019;10:2469.
84. Liu Y, Zheng J, Liu Y, Wen L, Huang L, Xiang Z, et al. Uncompromised NK cell activation is essential for virus-specific CTL activity during acute influenza virus infection. *Cell Mol Immunol* 2018;15(9):827-37.
85. Denaeghel S, De Pelsmaeker S, Van Waesberghe C, Favoreel HW. Pseudorabies virus infection causes downregulation of ligands for the activating NK cell receptor NKG2D. *Viruses* 2021;13(2):266.

86. He R, Lu Z, Zhang L, Fan T, Xiong R, Shen X, et al. The clinical course and its correlated immune status in COVID-19 pneumonia. *J Clin Virol* 2020;127:104361.
87. Zimmer CL, Rinker F, Höner zu Siederdisen C, Manns MP, Wedemeyer H, Cornberg M, et al. Increased NK cell function after cessation of long-term nucleos (t) ide analogue treatment in chronic hepatitis B is associated with liver damage and HBsAg loss. *J Infect Dis* 2018; 217(10):1656-66.
88. Farsakoglu Y, Palomino-Segura M, Latino I, Zanaga S, Chatziandreou N, Pizzagalli DU, et al. Influenza vaccination induces NK-cell-mediated type-II IFN response that regulates humoral immunity in an IL-6-dependent manner. *Cell Rep* 2019;26(9):2307-15.
89. Maucourant C, Filipovic I, Ponzetta A, Aleman S, Cornillet M, Hertwig L, et al. Natural killer cell immunotypes related to COVID-19 disease severity. *Sci Immunol* 2020;5(50):eabd6832.
90. 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(17):6351.
91. Golchin A. Cell-based therapy for severe COVID-19 patients: clinical trials and cost-utility. *Stem Cell Rev Rep* 2020;17(1):56-62.
92. Blank CU, Haining WN, Held W, Hogan PG, Kallies A, Lugli E, et al. Defining 'T cell exhaustion'. *Nat Rev Immunol* 2019;19(11):665-74.
93. Beltra JC, Manne S, Abdel-Hakeem MS, Kurachi M, Giles JR, Chen Z, et al. Developmental relationships of four exhausted CD8+ T cell subsets reveals underlying transcriptional and epigenetic landscape control mechanisms. *Immunity* 2020;52(5):825-41.
94. Liu R, Wang Y, Li J, Han H, Xia Z, Liu F, et al. Decreased T cell populations contribute to the increased severity of COVID-19. *Clin Chim Acta* 2020;508:110-4.
95. Stephen-Victor E, Das M, Kamam A, Pitard B, Gautier JF, Bayry J. Potential of regulatory T-cell-based therapies in the management of severe COVID-19. *Eur Respir J* 2020;56(3):2002182.
96. Jeyaraman M, Muthu S, Khanna M, Jain R, Anudeep TC, Muthukanagaraj P, et al. Platelet lysate for COVID-19 pneumonia-a newer adjunctive therapeutic avenue. *Stem Cell Investig* 2021;8:11.
97. Sandri G, Bonferoni MC, Rossi S, Ferrari F, Mori M, Cervio M, et al. Platelet lysate embedded scaffolds for skin regeneration. *Expert Opin Drug Deliv* 2015;12(4): 525-45.
98. Beitia M, Delgado D, Sánchez P, Vallejo de la Cueva A, Cugat JR, Sánchez M. Platelet lysate nebulization protocol for the treatment of COVID-19 and its sequels: Proof of concept and scientific rationale. *Int J Mol Sci* 2021;22(4):1856.
99. Zaid Y, Puhm F, Allaey I, Naya A, Oudghiri M, Khalki L, et al. Platelets can associate with SARS-Cov-2 RNA and are hyperactivated in COVID-19. *Circ Res* 2020;127 (11):1404-18.
100. Kalungi A, Kinyanda E, Akena DH, Kaleebu P, Bisangwa IM. Less Severe cases of COVID-19 in Sub-Saharan Africa: Could co-infection or a recent history of Plasmodium falciparum infection be protective? *Front Immunol* 2021;12:360.
101. Klatte-Schulz F, Schmidt T, Uckert M, Scheffler S, Kalus U, Rojewski M, et al. Comparative analysis of different platelet lysates and platelet rich preparations to stimulate tendon cell biology: an in vitro study. *Int J Mol Sci* 2018;19(1):212.
102. Zaki MM, Lesha E, Said K, Kiaee K, Robinson-McCarthy L, George H, et al. Cell therapy strategies for COVID-19: Current approaches and potential applications. *Sci Adv* 2021;7(33):eabg5995.
103. Suzuki G, Young RF, Suzuki H. Where are cell-based therapies heading? Current limitations and future directions. *Heart Res Open J* 2017;4(3):71-7.