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Stem Cell Therapy against COVID -19

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ABSTRACT

The term corona virus (Latin: Corona, crown) is coined due to presence of spikes glycoproteins on the surface that gives it a crown-like appearance. Coronaviruses came from the family Coronaviridae and the order Nidovirales.
Novel Corona Virus Disease outbreak happened in January 2020 subsequently dispersed around the world and reason for death of several million people worldwide. Currently, no effective treatment for severe COVID-19 patients is present. Now days, patients are only treated symptomatically. Scientific community working to develop novel antiviral drugs, vaccines, immunomodulatory medications. In the recent scenario of COVID-19 pandemic, we lack any better therapeutic option for treatment of severe COVID-19 patients. MSCs may be a better option for providing emergency therapy. Vast number of studies and clinical trials are warranted regarding the safety and efficacy stem cell therapy in COVID-19 and other respiratory disorders.

Key words: COVID-19, Mesenchymal cells, Stem cell therapy, Novel corona virus

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INTRODUCTION

Novel Corona Virus Disease outbreak happened in January 2020, subsequently dispersed around the world and reason for death of several million people worldwide [1,2].

As COVID-19 confirmed cases rises up, global shortage of medical resources become a challenge in the treatment of critically ill patients. We can avoid the shortage of resources and preserve medical ecosystem by using protective mask and social distancing. Integration of telemedicine in medical system may eliminate unnecessary exposure for both vulnerable patients and healthcare workers [3].

Death risk and morbidities in COVID-19 cases created a horrible situation worldwide and changed the mode of work, examination, celebration, business and of course medical education. During pandemic, most of the medical colleges are running online lectures. However, online lectures are not the substitute of face-to-face classroom lectures (FFCL) [4].

The term corona virus (Latin: Corona, crown) is coined due to presence of spikes glycoproteins on the surface that gives it a crown-like appearance. Coronaviruses came from the family Coronaviridae and the order Nidovirales [5]. This virus broadly distributed in several mammals including humans, with a large

Positive-sense RNA encapsulated in a protein coat. Coronaviruses majorly affect animals and depict transmission from animals to humans. These coronaviruses can be classified in to four groups, alpha, beta, gamma and delta, causing illness which range from mild fever, cold to severe disease like SARS (Severe Acute Respiratory Syndrome & MERS (Middle East Respiratory Syndrome).

Human Coronaviruses cause mild infection in majorly cases but in past two decades Coronaviruses of beta family viz. (SARS-CoV) and MERS-CoV, are responsible for more

than 10,000 cumulative cases with fatality rate of 10 % and 37% respectively [6,7].

Recently, a new member of the beta group Coronaviruses, SARS-CoV-2 caused pandemic disease (COVID-19) worldwide. As like SARS-Co-V, SARS-CoV-2 also affects lower respiratory system to cause viral pneumonia. In addition, many studies reported a disturbance GIT, heart liver, kidney and CNS (central nervous system) that ultimately lead to MOF (multiple organ failure).

The SARS-CoV-2 virus stimulates a profusion of cytokines for example TNF-alpha, MIP1A, MCP1, IP10, IL-2, IL-6, IL-7, G-SCF.

This inflammatory response is called cytokines Storm. It is followed by ARDS, EDEMA, dysfunction of air exchange, acute cardiac injury, secondary infection like mucormycosis or other fungal or bacterial infection may occur.

In severe cases, sometimes Cytokine Storm becomes extraordinary and out of control, leads to MOF (multiple organ failure) and death [8,9].

Therapeutics are used in order to control Cytokine Storm may play a preponderant role in treating COVID -19 patients. MSCs possess immunomodulatory properties and ACE-2 receptor absent in it, that's why there is minimum probability of contamination with SARS-COV-2 [4].

Cytokine Storm (CS) appears to be one of the most common cause behind COVID-19 infected patients death. Cytokine storm takes place whenever the immune system is exaggerated in COVID -19 infected patients [10]. Several therapeutic approaches might be able to manage CS and decrease the mortality and morbidity rates associated with COVID-19 [11].

Additionally, drug repositioning has also been approved to be effective for COVID -19 patients [5].

Besides stem cell therapy, use of exosomes has also been studied as they have hypoimmunogenic properties and are enclosed in a lipid bilayer. These qualities make the exosomes extremely stable and fit to migrate to the target organ of damage instead of accumulating via blood stream. Combined strategy of antiviral drugs along with immunomodulatory, tissue protective and highly healing potential of stem cells and their exosomes may be proven an effective therapy for COVID-19 cases and may also reduce the severity of COVID-19 [25].

If we talk about application of stem cell therapy in bones and joints disorders, stem cell therapy can be a better substitute for hardware, implants and arthroplasty. Moreover, no single method or approach ideal for all types of fractures (e.g. Pilon fracture) or we can say every method has its own benefits and drawbacks. Hence, Stem cell therapy can provide better options for number of bone disorders with least risks and complications [14-17].

Generally, Spine surgeons perform two procedures ACDF (Artificial cervical discectomy and fusion) and ACDR (Artificial cervical disc replacement) in case of CDDD (cervical disc degeneration disease) patients.

ACDF having risk of ASD (Adjacent segment degeneration), while ACDR is a 'Double Edged Sword' having motion sparing benefits but potential drawback of Heterotopic ossification, device failure etc. [18].

Mesenchymal stem cells are immunomodulatory in function and ability to differentiate in to cartilage, which is essential part for Intervertebral Disc Regeneration [19].

Moreover, Stem Cell Regenerative medicine (SCRM) and gene therapy can be optimised with the use of Artificial Intelligence Techniques and we can predict the clinical outcomes in Pediatric patients [20].

Therefore, artificial intelligence able to fulfil the need of the patient in several branches of medicine, such as radiology, pathology, oncology, surgery, Traumatic Brain Injury (TBI) [21]. Contrarily, the huge clinical trials are essential for ensuring the safety, accuracy and efficiency of Artificial Intelligence in Medicine [22].

This review talks about application of stem cell regenerative medicine (SCRM) in the treatment of COVID-19 patients. Additionally, other applicable and possible type's therapeutic modalities against COVID-19 (corona virus) will also be discussed.

MATERIAL AND METHODS

Methods: Online search was conducted on PubMed, Embase, Scopus, Semantic Scholar, Google Scholar, Clinicaltrials.gov for suitable studies till 10 September 2021 using keywords, stem cells, stem cell therapy, Mesenchymal stem cells, cell therapy, corona virus treatment, COVID-19, Novel corona virus, SARS CoV-2, treatment methods against COVID -19 virus.

Inclusion criteria

We included studies where stem cells or exosomes were used as therapy in order to modify the clinical outcome in COVID-19 cases (Novel corona virus) lung injury animal model, ARDS.

Exclusion criteria

We excluded studies involving other corona-viruses which do not cause severe human disease (HKU1, 229E, NL63, OC43) and studies in- silico studies, and studies using methods other than stem cell therapy to treat COVID -19 cases and lung injury animal model.

RESULTS

Table 1 and Table 2 showing results.

Table 1: In-vivo stem cell therapy in SARS CoV-2 and acute respiratory distress syndrome (ARDS).

Author / Year	Condition /Goal of study	Outcome
Masterson etal [23]	E.coli and ventilator induced lung injury./ To evaluate the effect of syndecan 2 (CD 362)- expressing human mesenchymal stromal enhance resolution after ventilator induced lung injury.	E.coli induced Lung injury attenuated,improved arterial oxygenation and lung compliance, reduction in bacterial load and improved structural injury.resolved lung inflammation,lung histological structure restored.
Kumamoto etal [24]	Bleomycin induced lung injury /To test engraftment of minimally cultured BMMSCs on improvement of progressive fibrotic lung injury.	Weight restored and animal survived.Down regulation of type 1 pro- collagen indicating reduction of inflammation and lung fibrosis
Zhao et al [25]	Bleomycin induced lung injury / to determine the effect of MSC therapy in lung protection.	Alveolar wall thickness, collagen quantity in lung interstitium reduced singificantly.Most alveoli were intact.Laminin, hyaluronan and hydroxyproline reduced remarkably, indicating improvement in lung fibrosis and injury.
Zhang etal. [26]	LPS induced lung injury / To study the therapeutic effects of ASC based therapy	Anti-inflammatory effects are seen, leukocyte migration in to alveoli was decreased (for instance neutrophil). Enhanced anti-inflammatory Cytokine (IL-10) levels and proinflammatory cytokines suppressed.
Chen etal [27]	LPS induced lung injury / To explore the effects of Hemeoxygenase (HO-1-) modified bone marrow derived MSCs (MSCs-HO- 1)	Survival rate significantly increased in all groups in comparison to NS, further improved in MSC-HO -1group. Lung injury reduced with decreased counts of neutrophil in BALF and reduction in lung water content. TNF-alpha and IL- 1 beta levels reduced.

Table2: Clinical studies of stem cell therapy in COVID-19 and ARDS patients.

Author / study design	Condition	Outcome
Leng et al [8]/ pilot Study	COVID-19	Primary outcome: All symptoms (high fever, low oxygen saturation level, breathlessness, weakness) disappeared in all the patients 2-4 days after stem cell therapy with no adverse effect.RT-PCR turned negative for COVID -19. Chest CT: Showed ground glass opacity and decreased pneumonia infiltration. Incase of severe patients, decrease in CRP, increase in oxygen saturation, respiratory rate came back to normal.
Zhang et al [28]/ case report	COVID-19	Recovery of patient with decrease breathlessness, increased lymphocyte count, decreases CRP level. No adverse effect. Patient discharged with negative RT- PCR for COVID-19.
Wilson [29] et al. /Multicentre open-label, dose-escalation, phase 1 clinical trial	ARDS	Well tolerated, 3 patients showed ADR not related to MSC, out of which 2 patients died. Mean lung injury score improved from baseline till day 3 in all 3 groups. Greatest decrease in high dose and lowest in low dose. Similar results in SOFA (sequential organ failure assessment) score: (High dose 7 to 3.7 (-48%) and low dose 8 to 7.7 (-4%)
Matthay et al [30]/controlled phase 2a trial	ARDS	Infusion of MSCs caused lethal cardiopulmonary arrest but death not related to MSC.
		Mortality at day 28 and 60 was non-significantly higher in MSC group than placebo.
		Oxygenation index had non-significant decrease in MSC group compared to placebo.
Alturi et al [31]/case report	COVID-19	Vital signs stabilised, after infusion patient was reported negative for virus on throat swabs after 2 days.
Singh et al. [32]/ case series	COVID -19 (6 patients with critical condition)	No ADR reported. 4 patients improved clinically with exception of 2 who remained critically ill but stable.6 (18%) death in control group
Sengupta et al [13]/ prospective nonblinded non randomized primary safety trial.	COVID -19	.71 % patients recovered, 83% survival rate, 13 % remained critically ill but stable, 16 % death unrelated to treatment. No ADR (Adverse Drug reaction) reported.

Stem cells application in respiratory disorders

Stem cells having the capability to differentiate in to other type of cells [33]. In some organs, the stem cells produce progeny that maintain tissue homeostasis and also perform same function as the cells that are not generated from this differentiation [34]. These stem cells depict their applications in many disorders including lung disease. For the treatment of ARDS and sepsis, several types of stem cells such as mesenchymal stem cells (MSCs), epithelial progenitor cells (EpPCs).

Mesenchymal stem cells are involved in most of clinical studies, however Induced pluripotent stem cell (iPSC) are also used in the treatment of Acute Respiratory distress syndrome (ARDS) [35].

Stem cells can be isolated from bone marrow and expanded on a wide extent in vitro. They play a key role in repair process of injured lung [36,37]. MSCs transplantation may initiate simultaneously, where MSCs differentiate in to lung epithelial cells and can directly take place of damaged alveolar cells during ARDS treatment [38,39]. Their applications in treating cardiovascular, pulmonary [37,40] and severe inflammatory disorders [41,42] have also been reported. Moreover, these characteristics showing immunomodulatory/immunosuppressive function [43,44] of MSCs, which increases Keratinocytes Growth Factor (KGF) on epithelial cells and in lung injury study models. So, they play a key role in protection through inducing type II cell proliferation and clearance of Edema [45]. Additionally, MSCs also play an anti-inflammatory role by secreting several mediators, which decrease the inflammatory process [46] and secrete growth factors, including KGF [47,48].

Potential bio markers for disease progression in COVID-19 patients are lymphopenia and higher levels of cytokines. A "Cytokine Storm" takes place in severely ill patient due to high level of cytokines, and as a result, several adverse reactions are observed in human body [49]. Cytokine storms include the interleukins IL-1 beta, IL-2, IL-6, IL-7, IL-8, IL-10, G-CSF (Granulocyte colony stimulating factor), GM- CSF(Granulocyte macrophage colony stimulating factor), IP10 (Interferon gamma inducible protein), MCP1 (monocyte chemo attractant protein-1) MIP-1 Alpha (Macrophage inflammatory protein -1 alpha), TNF-alpha, IFN-gamma [49-53]. IL-6 plays as a key mediator in development of Cytokine Storm [54]. After getting infection,CD4 +T cells can be quickly activated in pathogenic helper T cells (Th) 1 secreting GM-CSF, which further induces CD14+, CD16+monocytes providing high levels of IL-6, enhancing the inflammation process [49,55]. Study suggested that monoclonal antibodies that target the GM- CSF or IL-6 receptor may have potential to control immunopathology caused by COVID -19 and consequently spare more time for virus clearance [55].

Several studies highlighted different mechanisms showing important role of stem cell therapy in restoration of lung function. Stem cell therapy reserves an important place in the treatment of COVID-19 cases. Several case reports also show the safety and efficacy in of stem cell therapy in COVID -19 cases, especially in critically ill patients, which can't be treated by conventional therapy methods. Remarkable benefits noticed from several stem cell therapy based studies include decreased Cytokine levels without any allergic reactions. Therefore, current evidences from in-vitro/in-vivo and clinical studies show huge potential of MSCs in the treatment of COVID-19 patients. Additionally, large scale trials of stem cell therapy should be conducted for ruling out correct efficacy. Last but not the least, it will be too early to predict potential therapeutic role of MSCs in COVID-19 [56].

MSC based acellular therapeutic methods for COVID -19

MSCs can exert their immunomodulatory effects through multiple mechanisms as these cells have paracrine role in lung regeneration. MSCs are promising candidate for the treatment of variety of disorders including ARDS & COVID-19, however safety cell viability etc. issues raises concern about their usefulness in treatment.

MSCs exert their beneficial effects primarily by paracrine mechanisms in which they release extracellular vesicles i.e. micro vesicles and exosomes. Exosomes contain a variety of chemokine's, messenger RNA, & micro RNA. Products of extracellular vesicles have anti-inflammatory and immunomodulatory qualities and hence act as regulator of immune system [57,58].

Furthermore, exosomes also possess a surprising regenerative potential for damaged tissues and organs. Several preclinical studies have shown encouraging results of exosomes in animal models of ARDS & other inflammatory and respiratory disorders.

Exosomes injections in these studies showed reduced alveolar inflammation, rapid Edema clearance restored leaky epithelial membranes. In a nutshell, Cytokine Storm can be managed with Exosomes injections [59-62].

LIMITATIONS

Due to limited data availability, there is limited information regarding MSC based therapies in this review article. Additionally, COVID -19 is a new disease and we have limited number of studies. Due to the current wave of COVID -19, number of mortalities and new cases change every day. Unfortunately, we lack solid data based on Multi-centre trial and Randomised controlled trial (RCT) etc.

Secondly, Adverse Drug Reaction is not studied regarding safety of MSC administration in severely ill COVID -19, ARDS patients and other respiratory disorders.

Finally, language itself a Barrier for information. Due to which, we may miss important studies published in other languages.

CONCLUSION

In the recent scenario of COVID-19 pandemic, we lack any better therapeutic option for treatment of severe COVID-19 patients. MSCs may be a better option for providing emergency therapy. Vast number of studies and clinical trials are warranted regarding the safety and efficacy stem cell therapy in COVID-19 and other respiratory disorders.

LIST OF ABBREVIATION

- ARDS: Acute Respiratory Distress syndrome
- COVID -19: Novel corona virus disease happened in 2019

- RCT: Randomised controlled trials
- MSC: Mesenchymal stem cell
- G-CSF: Granulocyte colony stimulating factor
- GM- CSF: Granulocyte macrophage colony stimulating factor
- IP10: Interferon gamma inducible protein
- MCP1: Monocyte chemoattractant protein -1
- MIP-1: Alpha Macrophage inflammatory protein -1 alpha
- TNF-alpha: Tumor necrosis factor-alpha
- IFN-gamma: Interferon-gamma.
- KGF: Keratinocytes Growth Factor.
- iPSC: Induced pluripotent stem cell
- EpPCs: Epithelial progenitor cells (EpPCs).
- BMMSCs: Bone marrow mesenchymal stem cells.
- FFCL: Face- to -face classroom lectures.

REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. New England J Med 2020.
2. https://covid19.who.int/
3. Oropallo A, Lantis J, Martin A, et al. Wound care during the COVID-19 pandemic: Improving outcomes through the integration of telemedicine. J Wound Care 2021; 30:12-17.
4. Dwivedi A, Qiu XM, Dwivedi SS, et al. Impact of online lectures on medical students during COVID-19 pandemic. J Res Med Dent Sci 2021; 9:433-437.
5. Banerjee A, Kulcsar K, Misra V, et al. Bats and coronaviruses. Viruses 2019; 11:41.
6. https://www.who.int/publications/m/item/summary-of-probable-sars-cases-with-onset-of-illness-from-1-november-2002-to-31-july-2003
7. https://www.who.int/health-topics/middle-east-respiratory-syndrome-coronavirus-mers
8. Leng Z, Zhu R, Hou W, et al. Transplantation of ACE 2-Mesenchymal Stem Cells Improves the outcome of patients with COVID-19 Pneumonia. Aging Diseas 2020; 11:216.
9. Bari E, Ferrarotti I, Saracino L, et al. Mesenchymal stromal cell secretome for severe COVID-19 infections: Premises for the therapeutic use. Cells 2020; 9:924.
10. Coperchini F, Chiovato L, Croce L, et al. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth Factor Rev 2020; 53:25-32.
11. Ragab D, Salah Eldin H, Taeimah M, et al. The COVID-19 cytokine storm; What we know so far. Frontiers Immunol 2020; 11:1446.
12. Fajgenbaum DC, Khor JS, Gorzewski A, et al. Treatments administered to the first 9152 reported cases of COVID-19: A systematic review. Infectious Diseas Therapy 2020; 9:435-449.
13. Sengupta V, Sengupta S, Lazo A, et al. Exosomes derived from bone marrow mesenchymal stem cells as treatment for severe COVID-19. Stem Cells Develop 2020; 29:747-754.
14. Dwivedi A, Dwivedi SS, Tariq MR, et al. Stem cell regenerative medicine-A new hope in orthopaedics-Review article. J Stem Cell Biol Transplant 2019; 3:1-4.
15. Dwivedi A, Dwivedi SS, Su Zhenhong, et al. Open reduction and internal fixation (ORIF) of posterior pilon variant fractures with Butteress plate through posterolateral approach. Int J Contemporary Med Res 2018; 5:1-5.
16. Dwivedi A, Jian WX, Dwivedi SS, et al. Pilon fracture: An unsolved riddle an updated review. IJCMR 2017; 4:718-25.
17. Dwivedi A, Dwivedi SS, Tariq MR, et al. General idea about the reach of stem cell regenerative medicine: Evidence based review. J Res Med Dent Sci 2020; 8:57-64.
18. Dwivedi A, Jian WX, Dwivedi SS, et al. Artificial cervical disc replacement: A double edged sword-A clinical review. IJCMR 2017; 4:1163-1168.
19. Sakai D, Mochida J, Iwashina T, et al. Differentiation of mesenchymal stem cells transplanted to a rabbit degenerative disc model: Potential and limitations for stem cell therapy in disc regeneration. Spine 2005; 30:2379-87.
20. Sniecinski I, Seghatchian J. Artificial intelligence: A joint narrative on potential use in pediatric stem and immune cell therapies and regenerative medicine. Transfusion Apheresis Sci 2018; 57:422-424.
21. Dwivedi A, Dwivedi SS, Tariq MR, et al. Brain injury and stem cell therapy. J Res Med Dent Sci 2020; 8:94-96.
22. Dwivedi A, Dwivedi SS, Tariq MR, et al. Scope of artificial intelligence in medicine. J Res Med Dent Sci 2020; 8:137-140.
23. Masterson C, Devaney J, Horey S, et al. Syndecan-2 positive, bone marrow-derived human mesenchymal stromal cells attenuate bacterial induced acute lung injury and enhance resolution of ventilator-induced lung injury in rats. Anaesthesiol 2018; 129:502-516.
24. Kumamoto M, Nishiwaki T, Matsuo N, et al. Minimally cultured bone marrow mesenchymal stem cells ameliorate fibrotic lung injury. Eur Respiratory J 2009; 34:740-748.
25. Zhao F, Zhang YF, Liu YG, et al. Therapeutic effects of bone marrow-derived mesenchymal stem cells engraftment on bleomycin-induced lung injury in rats. In Transplantation proceedings Elsevier 2008; 40:1700-1705.
26. Zhang S, Danchuk SD, Imhof KM, et al. Comparison of the therapeutic effects of human and mouse adipose-derived stem cells in a murine

model of lipopolysaccharide-induced acute lung injury. Stem Cell Res Therapy 2013; 4:1-3.

27. Chen X, Wu S, Tang L, et al. Mesenchymal stem cells overexpressing heme oxygenase-1 ameliorate lipopolysaccharide-induced acute lung injury in rats. J Cellular Physiol 2019; 234:7301-7319.
28. Zhang Y, Ding J, Ren S, et al. Intravenous infusion of human umbilical cord Wharton's jelly-derived mesenchymal stem cells as a potential treatment for patients with COVID-19 pneumonia. Stem Cell Res Therapy 2020; 11:1-6.
29. Wilson JG, Liu KD, Zhuo H, et al. Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. Lancet Respir Med 2015; 3:24-32.
30. Matthay MA, Calfee CS, Zhuo H, et al. Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome (START study): A randomised phase 2a safety trial. Lancet Respirator Med 2019; 7:154-62.
31. Orleans LA, is Vice H, Manchikanti L. Expanded umbilical cord mesenchymal stem cells (UC-MSCs) as a therapeutic strategy in managing critically ill COVID-19 patients: The case for compassionate use. Pain Phys 2020; 23:e71-e83.
32. Singh S, Chakravarty T, Chen P, et al. Allogeneic cardiosphere-derived cells (CAP-1002) in critically ill COVID-19 patients: Compassionate-use case series. Basic Res Cardiol 2020; 115:1-1.
33. Sengupta V, Sengupta S, Lazo A, et al. Exosomes derived from bone marrow mesenchymal stem cells as treatment for severe COVID-19. Stem Cells Develop 2020; 29:747-54.
34. Zakrzewski W, Dobrzyński M, Szymonowicz M, et al. Stem cells: Past, present, and future. Stem Cell Res Therapy 2019; 10:1-22.
35. Bond AM, Ming GL, Song H. Adult mammalian neural stem cells and neurogenesis: Five decades later. Cell Stem Cell 2015; 17:385-95.
36. Guillamat-Prats R, Camprubí-Rimblas M, Bringué J, et al. Cell therapy for the treatment of sepsis and acute respiratory distress syndrome. Annals Translational Med 2017; 5.
37. Mei SH, McCarter SD, Deng Y, et al. Prevention of LPS-induced acute lung injury in mice by mesenchymal stem cells overexpressing angiopoietin 1. PLoS Med 2007; 4:e269.
38. Mei SHJ, Stewart DJ. Stem cells as vehicles for gene therapy in lung repair. Cell Therapy Lung Dis 2010; 287-311.
39. Prockop DJ. Marrow stromal cells as stem cells for nonhematopoietic tissues. Science 1997; 276:71-4.
40. Grove JE, Lutzko C, Priller J, et al. Marrow-derived cells as vehicles for delivery of gene therapy to pulmonary epithelium. Am J Respir Cell Mol Biol 2002; 27:645-51.
41. Barry FP, Murphy JM. Mesenchymal stem cells: Clinical applications and biological characterization. Int J Biochem Cell Biol 2004; 36:568-584.
42. Ware LB, Matthay MA, Parsons PE, et al. Pathogenetic and prognostic significance of altered coagulation and fibrinolysis in acute lung injury/acute respiratory distress syndrome. Critical Care Med 2007; 35:1821.
43. Nijnik A, Hancock RE. The roles of cathelicidin LL-37 in immune defences and novel clinical applications. Curr Opinion Hematol 2009; 16:41-47.
44. Stewart DJ, Mei SH. Cell-based therapies for lung vascular diseases: lessons for the future. Proceedings Am Thoracic Society 2011; 8:535-40.
45. Xu F, Hu Y, Zhou J, et al. Mesenchymal stem cells in acute lung injury: Are they ready for translational medicine?. J Cell Mol Med 2013; 17:927-35.
46. Matthay MA, Goolaerts A, Howard JP, et al. Mesenchymal stem cells for acute lung injury: preclinical evidence. Critical Care Med 2010; 38:S569.
47. Ghannam S, Bouffi C, Djouad F, et al. Immunosuppression by mesenchymal stem cells: Mechanisms and clinical applications. Stem Cell Res Therapy 2010; 1:1-7.
48. Boyle AJ, McNamee JJ, McAuley DF. Biological therapies in the acute respiratory distress syndrome. Expert Opinion Biol Therapy 2014; 14:969-981.
49. Walter J, Ware LB, Matthay MA. Mesenchymal stem cells: Mechanisms of potential therapeutic benefit in ARDS and sepsis. Lancet Respir Med 2014; 2:1016-1026.
50. Yang L, Liu S, Liu J, et al. COVID-19: Immunopathogenesis and Immunotherapeutics. Signal Transduction Targeted Therapy 2020; 5:1-8.
51. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395:497-506.
52. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020; 395:507-513.
53. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Diseas 2020; 71:762-768.
54. Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. E Bio Med 2020; 55:102763.
55. Yip MS, Leung HL, Li PH, et al. Antibody-dependent enhancement of SARS coronavirus

infection and its role in the pathogenesis of SARS. Hong Kong Med J 2016; 22:25-31.

56. Zhou Y, Fu B, Zheng X, et al. Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+ CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus. Bio Rxiv 2020.
57. Mahendiratta S, Bansal S, Sarma P, et al. Stem cell therapy in COVID-19: Pooled evidence from SARS-CoV-2, SARS-CoV, MERS-CoV and ARDS: A systematic review. Biomed Pharmacotherap 2021; 111300.
58. Chen TS, Lai RC, Lee MM, et al. Mesenchymal stem cell secretes microparticles enriched in pre-microRNAs. Nucleic Acids Res 2010; 38:215-24.
59. Lai RC, Tan SS, Teh BJ, et al. Proteolytic potential of the MSC exosome proteome: implications for an exosome-mediated delivery of therapeutic proteasome. Int J Proteomics 2012; 2012.
60. Zhu YG, Feng XM, Abbott J, et al. Human mesenchymal stem cell microvesicles for treatment of Escherichia coli endotoxin-induced acute lung injury in mice. Stem Cells 2014; 32:116-25.
61. Tang XD, Shi L, Monsel A, et al. Mesenchymal stem cell microvesicles attenuate acute lung injury in mice partly mediated by Ang-1 mRNA. Stem Cells 2017; 35:1849-1859.
62. Katsha AM, Ohkouchi S, Xin H, et al. Paracrine factors of multipotent stromal cells ameliorate lung injury in an elastase-induced emphysema model. Mol Therapy 2011; 19:196-203.
63. Lee JH, Park J, Lee JW. Therapeutic use of mesenchymal stem cell–derived extracellular vesicles in acute lung injury. Transfusion 2019; 59:876-883.