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Post-COVID pulmonary fibrosis: therapeutic efficacy using with mesenchymal stem cells – How the lung heals

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Abstract. – COVID-19 is an acute respiratory infectious disease caused by SARS-COV 2 (Severe Acute Respiratory Syndrome Coronavirus) that has become a global pandemic. COVID-19 mainly causes the respiratory complications of Acute Respiratory Distress Syndrome (ARDS), cytokine storm, and severe immune disruptions. The assays depict that though people recuperate from COVID-19, there are still symptoms that persists in the body causing discomfort, which is the consequence of the viral infection due to severe immune disruptions. Upon various difficulties of post COVID-19, the pulmonary fibrosis is the stumbling block in the lungs causing severe damage. In this review, we have shown the effectiveness and importance of the Hepatocyte Growth Factor (HGF) secreted by Mesenchymal Stem Cell (MSC) therapy on selective stoppage of the Transforming Growth Factor-Beta (TGF-β) signalling pathway by causing immunomodulatory effects that ameliorate the pulmonary fibrosis through paracrine signalling. However, more pilot studies have to be carried out to determine the efficacy and outcomes of the re-emerging complication.

Key Words:
COVID-19, Pulmonary fibrosis, TGF-β, MSCs, HGF.

Introduction

On December 31, 2019 World Health Organisation (WHO) has been notified by China about the unknown pneumonia cases from Wuhan, Hubei Province[1]. The clinical presentations resembled viral pneumonia accompanied by severe symptoms of respiratory illnesses, including persistent fever, cough, fatigue, dysgeusia, and dyspnoea. It has been announced as global pandemic by WHO and named as Coronavirus Disease 2019 (COVID-19). COVID-19 has symptoms more severe than the Severe Acute Respiratory Syndrome (SARS) or the Middle East Respiratory Syndrome (MERS). It severely damage the respiratory tract causing cytokine release syndrome, ARDS, and pulmonary fibrosis. However, analysing patients recovered from COVID-19, it has shown the persistence of at least one symptom of fatigue and dyspnoea[2]. The post-COVID manifestations have symptoms similar to the SARS and, in severe cases, it leads to pulmonary fibrosis and myocarditis.

COVID-19 and Its Pathogenesis

The SARS-COV 2 belongs to the family coronaviridae of the order nidovirales. Approximate length of virus genome is 29.9 kb and 80 to 120 nm diameter. The COVID-19 virus has enhanced transmissibility and high affinity to enter into the host cells and it utilises a highly glycosylated heteromeric protein. It has a Receptor Binding Domain (RBD) in its spike binds with the ACE2 receptor of the host cell. It is mediated by the Transmembrane Protease Serine 2 (TMPRSS2) cathepsin. ACE2 receptors are widely expressed in the endothelial cells of alveolar, tracheal, bronchial cells, monocytes, and macrophages of the immune system. The virus replicates its genome, assembles and releases large number of viral particles.

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Post COVID-19 Pulmonary Fibrosis

The clinical, radiographic and autopsy reports have shown that COVID-19 primarily affects the respiratory system resulting in pulmonary fibrosis. It is a sequela of persistent severe damage to the lungs. Though patients survive the acute phase of the disease and even discharged, a major proportion of the affected individuals die from pulmonary fibrosis. The ARDS has a dysregulation of matrix metalloproteinase in its inflammatory phase that could lead to a complex combination of the epithelial and endothelial damage thus resulting in uncontrolled fibrosis[3]. The continuous and aberrant activation of the cells of epithelium could lead to the cellular senescence and over active secretion of chemokines, vascular inhibitors, pro-fibrotic growth factors, and pro-coagulant mediators. These kinds of factors are collectively called Senescence Associated Secretory Phenotype factors (SASP). These cells will lead to abnormal wound healing process that is characterized by the dysregulated crosstalk between epithelial cells and mesenchymal cells and also the consequent accumulation of the myofibroblasts. The fibrotic lungs having the fibroblasts and myofibroblasts are the markers of stress and senescence which also causes resistance to apoptosis and excessive production of Extra Cellular Matrix components (ECM).

Non-Specific Immunity Prompted by Post-COVID Pulmonary Fibrosis

The COVID-19 upon entering the body immediately activates the non-specific immunity mainly by macrophages, NK cells and gamma cells. The COVID patients generally have the aggressive hypoxemia and massive amount of frozen mucus in the lung. It has been reported that the hypoxemia conditions promote the fibrosis by Epithelial Mesenchymal Transition (EMT). Therefore, during the late stage of the ARDS the lung tissue-damage repair mechanism is activated by collagen deposition and increased fibroblast cells.

The viruses are identified through Pathogen Associated Molecular Factors (PAMP). Lung macrophages are induced by γ-interferon and T helper cells 1 (Th1) secretes Tumour Necrosis Factor-α (TNF-α) that polarises into M1 macrophages secreting IL-1, IL-12, IL-23, IL-1β, and other inflammatory active substances resulting in tissue damage and triggers inflammation. If M1 activation is not controlled, it then results in continued lung tissue damage. In contrast, T helper cells 2 (Th2) polarizes M2 macrophages resulting in the secretion of IL-4, IL-10, IL-13, TGF-β, and Vascular Endothelial Growth Factor (VEGF). The Th2 cytokines have anti-inflammatory effects and stimulate human fibroblast synthesis of collagen. Under normal conditions these subgroups Th1 and Th2 antagonize each other and maintain negative feedback effect. During infectious state, this negative feedback gets altered which in turn activates Th2 alone that subsequently leads to fibrin proliferation and collagen production. Among all the inflammatory factors secreted by Th2, the TGF-β signalling plays a major role in ECM formation by synthesizing collagen deposition factors, such as EMT and Endothelial Mesenchymal Transition (EnMT)[4].

TGF-β Signalling Pathway

The anti-inflammatory factor TGF-β super family includes diverse range of functionally related proteins, such as Bone Morphogenetic Proteins (BMPs), activins, inhibins, and Growth Differentiation Factors (GDFs). It multifunctionally regulates wide range of biological processes, such as immune regulation, morphogenesis, wound healing, inflammation, and embryonic development. This TGF-β in turn signals through type I and type II serine/threonine kinase receptors (TβRI and TβRII). The TGF-β on reaching the target cell binds with the homodimer of TGF-β Type II Receptors (TβRII) which provides the structural interface that facilitates the formation of the stable complex with the homodimer of the TGF-β Type I Receptor (TβRI) that has been shown in Figure 1. The active receptor complex TβRII autophosphorylates and catalyzes the transphosphorylation of TβRI which in turn activates kinase activity.

The substrates for TβRI kinases, Small Mothers against Decapentaplegic (SMADs), operate the signalling function. The SMADs are expressed ubiquitously throughout the tissues and some of them are produced from spliced mRNAs. The TGF-β activates the TβRI kinase resulting in the phosphorylation of the SMAD2 and SMAD3. The activated SMAD2 and SMAD3 subsequently form oligomeric complexes with SMAD4[5]. The resultant complex of SMADs moves into the nucleus and interacts with the transcription factors of TGF-β responsive genes which take part in the regulation of the cell proliferation and differentiation.

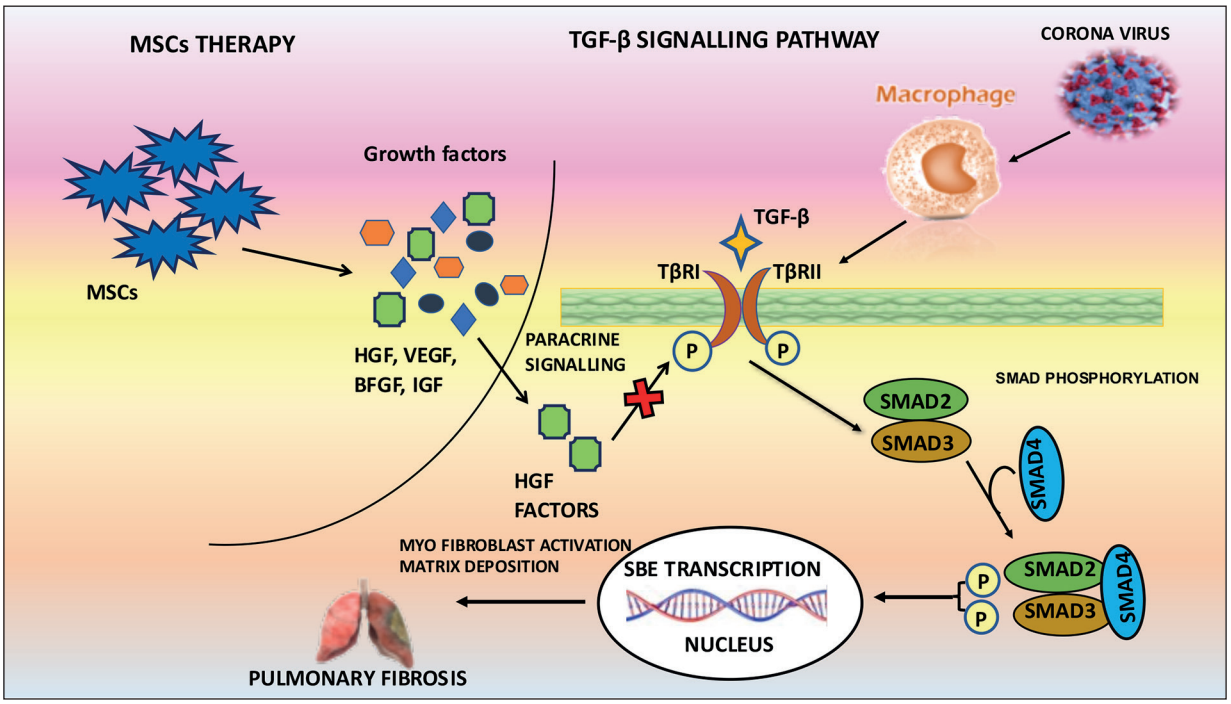

Figure 1. COVID-19 activates non-specific immunity by macrophages. The macrophage in turn initiates the TGF-β signalling pathway. The TGF-β undergoes phosphorylation with the help of homodimer TβRI and TβRII. TGF-β undergoes further phosphorylation by SMAD2 and SMAD3. SMAD2 and SMAD3 subsequently form oligomeric complexes with SMAD4 resulting in myofibroblasts activation and matrix deposition. This results in severe pulmonary fibrosis. Upon intravenous injection the MSCs secretes growth factors of HGF, VEGF, BFGF, IGF. Among all the factors, the HGF inhibits the SMAD2 phosphorylation by paracrine signalling.

Mesenchymal Stem Cell Therapy

Mesenchymal stem cell (MSCs) directly reaches the sites of injury, inhibit the inflammation, and contribute to epithelium repair. MSCs have potential as a completely unique therapeutic agent in multiple diseases and they are safely administered during a number of clinical trials. Research has shown that MSCs have specific cytokines that drive immunomodulation and anti-fibrotic properties, which may be useful against SARS CoV-2. MSCs were initially isolated from Bone Marrow (BM) and further it has been followed by isolation from diverse kind of tissues including adipose fat pads, dental pulp, umbilical cord, and placenta. The MSCs secrete various paracrine soluble factors, such as the HGF, EGF, Angiopoietin 1 Precursor (ANGPT1), and Interleukin-10 (IL-10). These factors aid in the amelioration of the epithelial and endothelial repair and results in reduced inflammation. The HGF inhibited the TGF-β induced phosphorylation of SMAD2 by paracrine signalling. HGF has therapeutic potential in preventing tissue fibrosis and disturbing TGF-β signalling (Figure 1). The formation of cascade of the collagen is stopped and prevents the pulmonary fibrosis. This method has been implemented in *in vitro* studies of pulmonary fibrosis. Therefore, the MSC therapy is one of the primary targets for treating fibrosis in a pool of anti-fibrotic therapies.

Conclusions

Of all the therapies touted for COVID-19, the mesenchymal stem cell therapy is the most significant. It plays a major role in the amelioration of the pulmonary fibrosis and improving lung function. The preclinical studies are being carried out at different phases. The COVID-19 has no reductionistic drugs to cure the ARDS, pulmonary fibrosis and sub-sequent complications. These conditions have no comprehensive information on its effectiveness, yet MSCs are effective alternatives for treating viral infections and has promising results in safety and efficacy. To improve the outcome, further studies have to be carried out to confirm the effect of MSCs at optimal dosage, source and timing of administration.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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