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Editorial
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Mesenchymal Stem Cell Therapy: An Alternative Approach to Treat Chronic Obstructive Pulmonary Disease

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Editorial

Chronic obstructive pulmonary disease (COPD)

COPD is a respiratory disorder characterized by abnormal inflammatory response of the lung to noxious particles or toxic gases; fortunately, is a preventable and treatable disease [1,2]. Narrowing of small airways, loss of lung elastic recoil and emphysema, results in this condition [3]. Emphysema is an anatomic alteration of the lung, where abnormal permanent enlargement of airspaces, distal to the terminal bronchioles and destruction, changes the alveolar walls [1]. Moreover, patients may also develop chronic bronchitis, airways disease, and epithelial abnormalities, among other respiratory conditions [4]. Even though lungs have regenerative capacity, constant injury inflicted by external factors exceeds the capacity of auto renovation causing the development of many respiratory diseases [5,6]. Cigarette smoking has been firmly established as the most important cause in development of COPD [1,7]. Although this habit causes airway inflammation in all users, only 15% to 20% develop airway obstruction and persistent inflammation leading to a clinically significant COPD. These statistics suggests genetic predisposition and environmental factors must be having strong influence on the pathobiology of this condition [1,4]. Prolonged exposition to cigarette smoking have negative impact on lung mesenchymal cell repair functions, inhibits lung fibroblast chemotaxis, proliferation and production of extracellular matrix [8]. Likewise, genetic mutations can predispose patients to develop COPD. Especially those genes involved in the production of proteases and anti-proteases (α1-ACT, SlPI, MMPs, Par-2), modulation of the metabolism of toxic substances (GSTs, EC-SOD), clearance of mucociliary secretions (CFTR) and genes that influence inflammatory mediators (VDBP, TNF-α, IL-1 family, TGFB1, HLA, etc.) [9-11]. Any epigenetic or acquired mutations may predispose the development of this condition, escalating the problem if the patient is a frequent smoker [12]. For example, cigarette smoking affects the air lung barrier through repeated oxidative stress, causing oxidative DNA damaged of lung epithelial barrier cells. In most cases, these somatic mutations can be repair by endogenous DNA mismatch repair system (MMR); nevertheless, free radicals may contribute to the accumulation of damaged DNA due to the post translational inactivation of repair enzymes [10,13]. The small airways obstruction observed in COPD patients, has been related to the thickening of the airway wall due to a remodeling process associated to tissue repair and a malfunction of the mucociliary clearance apparatus; all of this results in accumulation of inflammatory exudates in the lumen [7]. Along with the increase of infiltrating inflammatory cells, intern healing mechanisms cannot cope with the damage occurred in lungs; which results into an accumulation of neutrophils, macrophages, and CD8+ T cells. CD8+ T cells express several pro-inflammatory chemokine receptors, including CCR5 and CXCR3; but the pathway involved in the accumulation of this cells in lungs still remains unclear [4,7].

Mesenchymal stem cell (MSC) therapy in COPD

Pharmacology approaches to treat this condition focuses mainly on ameliorating the symptoms, rather than the causes; these include anti-inflammatory drugs, corticosteroids, theophylline and bronchodilators [14]. MSC therapy can regulate the main causes and symptoms via reduction of apoptosis and oxidative stress, regeneration of damaged tissue and exhibition of paracrine effects. Previous reports demonstrate that MSC therapy results into immunomodulation of smoke damaged lung and pulmonary function. The levels of pro-inflammatory mediators (TNF-α, IL-1β, MCP-1 and IL-6), MMP9 and MMP12 were reduced; while VEGF, VEGF receptor and TGFβ-1 level were up-regulated and this resulted into reduced lung cell apoptosis [15,16]. Moreover, different studies have shown the beneficial effects of MSCs on reducing the oxidative stress in variety of tissues. Further, MSCs also protect lung damage by inhibition of ROS mediated inflammatory response, and prevent alveolar wall thickening and neutrophil recruitment [17-19]. Several studies have been conducted

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in search for the optimal source of MSC regarding COPD and other related lung conditions. Adipose derived (A-MSC) and Bone Marrow (BM-MSC) are the most commons, although cord blood derived, amniotic fluid derived, induced Pluripotent Stem Cells (iPSC) and Lung derived (L-MSC) have also been used in animal models [20-23]. Results showed improvement in COPD and emphysema conditions regardless the source of stem cells. Nevertheless, L-MSC had higher expression of adhesion molecules, such as ICAM-1, integrin-α2 and PDGFRα, which may be the explanation to the higher retention rate observed in lung in comparison with BM-MSC [24]. Since isolation of L-MSC from COPD patients represents a great challenge, the use of A-MSC may be a better option to treat this disease. It is easily acquired in considerable quantities after a minor liposuction; and can interact directly with endothelial progenitor cells to form new blood vessels for tissue repair and regeneration, reducing the excessive apoptosis and even counteracting the suppressive effects of smoking [25,26]. MSC can be administered via different routes; injection of MSC *via* Intravenous (IV) and Intrathecal (IT) on a mouse model with induced emphysema, showed no difference on reducing the neutrophil infiltration and cell apoptosis. Both treatments increased the elastic fiber content, reduced the alveolar capillary membrane and endothelial ultra structural damage; and decreased the expression of KC (keratinocyte-derived chemokine) and TGF-β (transforming growth factor). Nevertheless, IV injection has been proven more efficient in achieving immunomodulatory effects (induction of macrophage polarization, endothelial cell proliferation, production of Vascular Endothelial Growth Factor [VEGF] and others). While IT administration acts more intense on reparative mechanisms (reduction in lung hyperinflation and fibrosis) [14,20]. In several studies, regardless the source of MSC or administration route, improvement on the causes and symptoms of COPD has been reported [22,23]. Nevertheless, patients must cease smoking and exposure to toxic gases, in order to stop cellular constant damage. Although some of the beneficial properties of MSC need more research on human trials, this therapy proved to be safe as an alternative option or in combination with other anti-oxidative and anti-inflammatory medications in COPD diagnosis [18].

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