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Editorial

Mesenchymal Stem Cell - A Ray of Hope in the Management of ILD

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Interstitial fibrosis is a devastating condition with no effective treatment yet now, however development of cell therapies as well as bio-engineering approaches for lung ailment has been highlighted over the past decade [1-3]. Although more than hundred different forms of interstitial lung disease (ILD) have been described in literature with numerous gene variants, IPF is the most common form among them, representing 45% of the total with high morbidity and mortality along with approximately 20% survival of 5-year [4,5]. Current evidence suggests that the areas of fibrosis seen in lungs of patients with IPF share many features with normal aging, such as genomic instability, telomere attrition, mitochondrial dysfunction, cellular senescence, and immune dysregulation. Because of the degenerative course of the disease, as well as lack of a definitive therapy for IPF other than lung transplantation, there is a continuous need to find new options for IPF treatment. Some pharmacological therapies e.g. corticosteroids, azathioprine, N-acetylcysteine, Pirfenidone and etanercept have also been under practice, despite of insignificant long term benefit. Therefore, cellular therapies have emerged as a promising option, and the use of MSCs is consistently being studied [6].

In current era, stem cell therapy represents the great covenant for the future of molecular medicine. In fact several diseases can be slowed or even blocked by stem cell transplantation (SCT) according to recent research. Among the various stem cell population, mesenchymal stem cells (MSCs), which were discovered by Friedenstein., *et al.* in 1968, belongs to a class of multipotent stem cells with self-proliferation and differentiation potential [7]. It found principally in the bone marrow of adults though can be isolated from different tissues e.g. adipose, liver, tendons, synovial membrane, amniotic fluid, placenta, umbilical cord, as well as teeth, and giving rise to skeletal muscle cells, blood, fat, vascular, uro-genital systems, in addition it also generate connective tissues throughout the body [8,9]. These cells are non-hematopoietic stem cells having a multilineage potential with capacity of differentiating into both mesenchymal and non-mesenchymal lineages, besides this adult bone marrow-derived stem cells have great plasticity and are able to differentiate into bronchial, alveolar and vascular endothelium, along with interstitial cell types, making them prime candidates for lung-tissue repair [10,11]. Apart from this, MSCs have two other extraordinary characteristics: they are able to migrate to sites of tissue injury and have strong immunosuppressive properties that can be utilized for successful autologous as well as heterologous transplantations, in addition it can also be administered by systemic or local routes into injured animals [1,12]. Moreover MSC may support the restoration of the alveolar epithelium and reduce fibrosis through their anti-apoptotic as well as anti-scarring properties even in the absence of a substantial and sustained structural engraftment [5]. In recent research the MSC effects on lung fibrosis have been investigated with syngeneic, allogeneic, or xenogeneic MSC administration in mouse or rat models of bleomycin-induced lung fibrosis, promulgate that MSC may be efficacious in the treatment of IPF [13].

The immunological properties that make MSCs an optimistic therapy in this pathology are several, perhaps secretion of growth factors as KGF, HGF, VEGF, and Ang-1 play a crucial role in the repair of the alveolar epithelium as well as endothelium. Additionally, through nitric oxide and indoleamine 2, 3-dioxygenase, MSCs suppress T-cell proliferation to avoid cytotoxic T cells and natural killer cells [14]. Furthermore; their capability of restoration of the injured tissue has been demonstrated through mitochondrial transfer, since mitochondrial dysfunction is linked to cellular senescence and inability to protect the lung from injury.

Apart from this MSCs also have potential to induce an anti-inflammatory response by enhancing IL-10 and soluble IL-1β receptor, resultantly decline in the titer of TNFα, IFNγ and IL-2. MSCs are immune privileged, escaping the immune response through the lack of expression of HLA class II and weak expression of HLA class I, which do not induce proliferation and activation of T lymphocytes, making them ideal in the setting of therapy [14], therefore these cells can be administered to an immunocompetent patient without the need for further immunosuppression. In addition to paracrine actions, the release of episomal or microsomal particles by MSCs can influence behavior of both surrounding structural cells and also surrounding inflammatory cells. MSCs can also act as antigen presenting cells and transfer cytosolic components through connexin bridges [8]. A recent report highlighted that MSCs may also promote repair through activation of endogenous distal lung airway progenitor cell populations in mouse models. Collectively, MSCs seem to exert pleiotropic effects, including anti-inflammatory, immunomodulatory, antifibrotic at the site of lung injury.

A recent single center, open-label phase 1b study by Tzouvelekis., *et al*. [6] assessed the safety profile of the end bronchial administration of adipose derived stromal cells-stromal vascular fraction in patients with mild to moderate IPF. There were no reported serious or clinically relevant side effects in the 24-month follow-up period after the first infusion. In another recent single center phase 1 study, by Chambers., *et al*. patients with IPF received intravenous placenta-derived hMSCs, were followed for 6 months reported mild and self-limiting adverse event. In a similar study, published by Glassberg., *et al.* constituted the first non-randomized, non-placebo single-centre clinical human trial designed to evaluate the safety of BM-derived human allogeneic MSCs (BM-hMSCs) in patients with mild to moderate IPF without any treatment -related serious AEs over a 60-week follow-up period [11]. Contrary to this Thangakunam., *et al.* proclaim that use of MSC treatment for extensive lung fibrosis has not shown positive results, rather has deleterious side effects though, it was merely a case report of a single subject [15].

However MSC seems a promising alternative for the therapy of IPF, particularly for their suitability to easily be isolated, expanded to big numbers in culture, though, a number of questions still have no answers: what is the most efficacious source of MSC? Whether allogeneic cells are as safe and efficacious as autologous MSC? Are MSC most effective in the lung when administered intra- tracheal, intravenously or by some other method? Which need to be addressed by the researchers yet, besides this biological variations between MSC from different lineage (BM-MSC, AD-MSC, UC-MSC, AM-MSC, etc.), inoculation routes (intravenous, intra-tracheal, etc.) and extent of the disease should be thoroughly considered when choosing a specific clinical application for these cells, although few researcher endorse that, intratracheal instillation of MSC obtained from perinatal tissues may have some advantages, however it need more robust data in support [9].

Perhaps the weak preclinical information that supports the use of MSCs in IPF creates the need for caution in future investigations that concern appropriate timing to use MSCs, the ideal dosage, and route of administration. Additionally, the potential for cancerous transformation and immunologic rejection is largely unexplored. These issues highlight the potential danger of implementing stem cell therapies before they have been adequately studied *in vitro* and *in vivo* in animal models. Though with advancement in technique and constant up gradation of existing knowledge by the clinical trials in this domain, we would be able to manage interstitial fibrosis by the help of "Mesenchymal stem cells" as a treatment of choice in near future with more precision and success.

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