

Editorial

Mesenchymal Stem Cells: Novel Therapeutic Option Besides their Stem Cell Properties-Utilizing the Niche Effect

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Abstract

Mesenchymal Stem Cells (MSC's) are multipotent stem cells having diverse inflammatory, antimicrobial, antimicrobial and regenerative therapeutic efficacy because of which there is effect on damaged tissues and inflammation. MSC's may be used for direct clinical effects but its manipulation of host response in different occasions via cell-cell interactions including through production of bioactive secreted factors which include small proteins, chemokines, cytokines & other cellular regulators. The following factors can induce angiogenesis by chemotactic and induction of cellular recruitment manner. This differential can also be bettered in vitro before in vivo administration potentiating the versatility of the MSC's => active communication between newly administered cells & host tissue. Various clinical trials are on and studies conducted on MSC's ability for therapy in human disease. Still controversy exist and deeper insight required to bring them into therapeutic arena.

Editorial

Introduction

Mesenchymal stem cells constitute non-hematopoietic stromal cells which have the differentiation capacity along with leading to regeneration of mesenchymal tissue like bone, cartilage, muscle, ligament, tendon and adipose tissue, along with lungs, pancreas, CNS, GIT and the circulatory system [1]. In bone marrow, they are rare and represent 1 in 10,000 nucleated cells. They can enlarge multifold in culture while retain in their growth as well as multilineage potential. For identification of MSC's expression of certain molecules including CD105(SH2), and CD73(SH3/4), absence of hematopoietic markers CD34, CD45 and CD14 is required. These properties make these cells ideal candidates for tissue engineering. On systemic administration MSC's can migrate to sites of important role in tissue specific homing of leukocytes and

have been involved in trafficking of hematopoietic precursors into and through tissues. Functional expression of various chemokine receptors and adhesion molecules on human MSC's utilizing their chemokine-chemokine receptor interactions might be an important way of increasing their ability to correct inherited disorders of mesenchymal tissues or facilitate tissue repair in vivo [2]. Still there is controversy regarding their use in therapeutics and deeper understanding regarding their being important niche factors may help in developing them for till now unsuccessful use in therapeutic arena.

Wound Treatment by Stem Cells

For healing of wounds to occur there is interaction of mitosis, inflammation, synthesis, angiogenesis and remodeling of extracellular matrix [3]. Without treatment these wounds become chronic requiring further treatment [3]. Hence the pro and anti-

inflammatory responses besides angiogenesis [1] is offered by MSC's. Use of MSC's regarding wound treatment is both by direct as well as indirect delivery to the wound site. For indirect methods MSC's are infused into the circulating system [4]. MSC's home at sites of injury giving a therapeutic benefit [4]. MSC's reach the region of injury by trafficking to chemokine ligand 7 (CCL7) [5,6]. On reaching the injury area MSC's leave the vasculature in the connective tissue stromal region [4]. MSC's respond to the specific tissue milieu and themselves add to the milieu by secreting biomolecules [7]. By this interaction occurring between the tissue and MSC's gives the efficacy, potency and total therapeutic effects of MSC's. I/v delivery of MSC's means localization in the lungs. Based on this fact MSC's get used in treatment of lung diseases which are associated with marked inflammation like asthma and cystic fibrosis. Although initially MSC's are distributed in the lung they are hardly seen in lung after a week in most studies. This may be due to the proposal that localization of MSC's to tissue sites of damage followed by migration to the destined tissue occurs. Indirect delivery cause the risk that the MSC's may go to the spleen, liver and lung and if destined site for effect is not in these areas there may be a marked reduction in therapeutic efficacy. New way of getting the therapeutic effect of MSC at their site of impact have become important research issue involving direct application of MSC's to the wound areas [4]. The new methods include direct injection into the wound site as seen in new models of urinary incontinence, arthritic lesions along with different kind of neuronal diseases [7]. For use of this method MSC's need to be injected close to the wound site or put directly onto site of injury [4]. Stoff et al showed that human MSC's injected close to injury site in immunocompetent rabbits improved tissue function and decreased the amount of scarring [8]. They also found that no evidence of rejection of MSC's existed. Similarly, Falanga et al placed MSC's directly on the site of injury => wound betterment [9]. Stoff et al demonstrated that using fibrin MSC's sprayed in wound => healing much faster and a better histology as compared to wound not treated with topical MSC's [4,9]. This creates path for studying immunomodulation action of MSC's in wound healing. Previous studies have shown that MSC's can be activated by use of cytokines like granulocyte colony stimulating factor (GM-CSF), Tumor Necrosis Factor Alpha (TNF- α) or Interferon Gamma (IFN- γ) to increase activity and therapeutic efficacy. Once MSC's are activated using IFN- γ , MSC's secrete soluble factors which enhance killer T cells and early stage dendritic cells [4,10], as shown in these studies. As per the disease or specific setup MSC's maybe made even more potent with the aspect of application. Moreover, soluble factors developed by MSC's may also give new and innovative directions in cell therapy beyond treating wounds and in commercialization of studied products [4,11].

Orthopedic Use of Stem Cells

As shown earlier MSC's bear the capacity to move chemot-

actically to inflammation and infection sites in an organism's tissues [12]. They secrete variety of cytokines, which exert anti-inflammatory mechanisms in the micro environment [12]. There is an active role of MSC's in causing tissue regeneration like by giving them i/v they secrete soluble factors and regulate inflammatory response [12]. They also secrete factors which help in bone regeneration. For cartilage regeneration MSC's use is to repair damage. Shafiee et al in a rabbit model showed that full thickness cartilage defects showed improved healing as seen by macroscopic score [13]. 6 months following the study MSC's showed efficacy of chondrocyte transplantation along with tissue regeneration [13]. Overall clinical scores were markedly improved although no complete hyaline cartilage was found [14]. Scott et al used cellular allograft having MSC's for high risk foot and ankle reconstruction [14]. MSC's have come to be of use in vivo secondary to their osteogenic potential. Stem cells got grafted in hind foot and ankle surgery which improved healing and interval to partial weight bearing which suggests the use in foot and ankle surgery [14].

Biggest problems come in big bone defects due to infection, tumors, trauma, insufficient blood supply or due to post infection sequelae [15]. In these defects since blood supply is very limited they are difficult to treat by producing autologous bone grafts [15]. Also these bone graft cause a great level of morbidity in donors along with increased risk of disease transmission or rejection in recipients [15]. Granero-Motto in a mouse models showed bone marrow MSC's showed movement toward the site of fracture to begin regeneration after systemic application of MSC's [16]. Bone marrow MSC's increased tissue healing in the site and actively aided to a marked fracture promoting the production of angiogenic paracrine factors [15,16]. Lin et al used luminescence and fluorescence tagged MSC's and demonstrated that by whatever means MSC's are given they localize to areas of injury including bone damage. With time the MSC's became less dense but had the ability to localize to bone injury followed by some regenerative capacity [17]. Still more work is needed in terms of bettering wound healing by developing new and innovative scaffolds and increasing the production of soluble mediators.

Hematological Pathology and Stem Cells

Hematological Stem cells (HSC's) get used for hematological pathologies, but for many side effects like bleeding, Graft versus Host Disease (GvHD) and other ways of rejection [18]. MSC's can help in HSC engraftment and prevent rejection with their properties of immune suppression. Besides that MSC's produce cytokines which aid hematopoiesis and can improve the efficiency of MSC's in bone marrow recovery after chemotherapy and/or irradiation [18]. After MSC/HSC infusion in a patient having severe idiopathic aplastic anemia, most of these problems got resolved, although still there was no recovery of hematopoietic tissue [18]. Thus, MSC had the capability to be used as safe addition for use as

a co-infusion cellular therapeutic with HSC's [18]. There was further proof of MSC use in hematopoietic pathology in a phase 1 clinical trial. In the trial, hematopoietic recovery occurred for most patients with 50% of patients not developing GvHD [18,19]. The suggestions got from these studies using cultured expanded MSC's with the HSC's for transplantation could be an effective and safe process that could minimize the side effects to facilitate bone marrow recovery [19].

Neurological Diseases and Stem Cells

MSC's have the capacity to change into neurons and astrocytes [20]. Because of these findings mouse models have been tested for MSC transplantation on mice with acid sphingomyelin, a neurodegenerative disease. MSC infusion caused a delay in the initiation of neurological abnormalities and increased overall survival in the mouse model [18]. On this basis to study the effectiveness of MSC transplantation in human beings having amyotrophic lateral sclerosis characterized by degeneration of motor neurons and muscle functionality a study was started [18]. Taking bone marrow aspirates from every patient of the 7 patients MSC cultures were done over 3-4 weeks. On injecting MSC's into spinal cord of the patient Magnetic Resonance Imaging (MRI) was done at 3 and 6 months [20]. There was a pattern of increase in muscle strength slow though there is not enough data to conclude for how long the direct effect can be sustained. Various conditions like stroke, trauma or basic neurological conditions can produce situations mimicking that caused by Central Nervous System (CNS) injury. Neural MSC's (NSC's) and MSC's are used for the purpose of regeneration in CNS to prepare new cells which replace that were lost [21,22]. Still this has not been totally successful because of oxidative stress and toxic byproducts which have a bearing on MSC transplantation [22,23]. Because of this there is slowing of tissue regeneration along with decreased longevity. Carbon nanotubes (CNT's) are being used to help MSC differentiation in the field of Nanomedicine in this arena. CNT/MSComposites were put to use for increasing neurite growth after CNS damage. Both *In vivo* as well as *in-vitro* setting biocompatibility of the CNT's with the MSC's and NSC's was shown [22]. This could direct neuron function and promote healing of damaged neural tissue [21,22]. In Parkinson's disease MSC's have been shown to be useful for inhibiting inflammatory cytokine production, a main factor which contributes to the disease. Another way of giving MSC's was from nose as shown by workers in Tübingen, Germany. In Parkinson's induced rat model intranasal bone marrow MSC's were given [20]. MSC's were detected in olfactory bulb, cortex, striatum, cerebellum, brain stem and hippocampus up to 4-5 months after they were given in the rodents which gives data which suggests MSC's can multiply *in vivo* successfully. Intranasal administration increased tyrosine hydroxylase levels in the lesioned ipsilateral striatum & substantia nigra while levels of toxin 6 hydroxy dopamine got re-

duced [23]. Reduction of TNF- α , IL2, 6 & 12, & IFN- γ were seen in combination with cell therapy [23]. The *i/nasal* method of administration could change the face of MSC administration [23].

In case of genetically inherited diseases bone marrow MSCs have been used as therapeutic for Hurler syndrome & metachromatic leukodystrophy. After bone marrow transplantation from these sibling donors 11 patients having metachromatic leukodystrophy were given bone marrow MSC's from their sibling donors by injection significant improvements occur in nerve conduction velocities in 4/11 patients [23,24]. Still more studies are needed, before one can conclude success or failure of marrow MSC'S in situations of inherited diseases [24].

Diabetes & Stem Cells

In type 1 DM there is shortage of insulin producing cells in diabetic pancreas & with use of islet transplantation it has been tried to reduce the need for insulin injections on a regular basis [25]. The problem is that pancreas & islet cells are scarce & are rejected by recipients after transplantation. Use of ESC's has ethical issues besides high rates of rejection after use [21]. Thus, Autologous Stem Cells (ASC) became a good alternative because there is no risk of rejection & no ethical stigma of ESC's. Most attainable sets of ASCs' in peripheral blood which also contains the normal human insulin producing cells [24,25]. These cells can be isolated by ease from autologous blood based on this phenotype [25], Zhao et al conducted experiments where peripheral blood insulin containing cells could be isolated and preserved for future insulin production since they have the ability to cling onto polystyrene petri-dish and they show transcription and insulin production at protein & mRNA level [25], reviewed In KKK [26]. This technology could allow patients to generate their own insulin producing cells [25] & with this complication of rejection by immune system gets removed and decreases the time to transplant because of shortage of donors & has no ethical issues. Voltarelli et al did a clinical trial on newly diagnosed Type 1 DM patients who showed long periods of insulin independence in most participants after transplantation with MSC's [27]. Besides this MSC's can also be used in DM when defective wound healing & diabetic neuropathy [28] is there. Thus, MSC's may have marked effect in giving better care in DM.

Lung Diseases and Stem Cells

MSC's carry the capacity to affect damaged or inflamed lung areas by repairing the tissue or stimulating the host tissue to regenerate itself. In fibrotic lung disease, there is a possibility that MSC's may reverse ECM deposition and collagen synthesis. In case of Idiopathic Pulmonary Fibrosis (IPF), lung fibrosis => scarring and terminal pulmonary insufficiency [28-30]. In a Bleomycin model which shows morphology same as IPF, bone marrow MSC administration following bleomycin treatment showed decrease in both

collagen deposition & inflammation [29-31]. In another study, it was found that murine MSC's home to lung in response to injury and become epithelium like in phenotype while decreasing lung tissue inflammation [29,31-33]. There is great morbidity and mortality rate in Acute Lung Injury (ALI) [4,33]. Injury to alveolar epithelium, vascular endothelium and endotoxins are common effects. Treatment with MSC's decreased proinflammatory cytokines while the resolution response anti-inflammatory cytokine levels increased [31,34]. Also, mice receiving murine MSC's had decreased levels of alveolar capillary permeability, extravasation, edema and mortality [31]. MSC's in patients suffering from chronic obstructive pulmonary disease (COPD) characterized by severe lung and systemic inflammation in a placebo controlled study, MSC's got infused/v [35]. There was a marked decrease in Circulating Reactive Protein (CRP) with MSC treatment which created a basis for continuous clinical trials of MSC's for COPD [35], endotoxin induced lung injury [23,31,34]. The use of MSC's in ALI, COPD & IP-F can be a therapeutic option as suggested by these studies.

Cystic Fibrosis (CF) and Stem Cells

Cystic Fibrosis CF occurs secondary to mutations in Cystic Fibrosis Transmembrane Regulator (CFTR) gene. This mutation affects practically every organ in the body → main causes of morbidity & mortality is the inability to controlling infection and inflammation.

Bone Marrow MSC's have both anti-inflammatory and antimicrobial properties, studies were done to investigate properties of MSC's for use for therapeutic purpose in murine models of CF lung infection & inflammation [1,35,36]. In this model, CF mice lose considerable weight without resolution & often succumb to infection. Bone marrow MSC's used for treatment purposes in these model => weight changes same as control mice which improved gross lung pathology and decreased cellular recruitment into the lung. Bone marrow MSC's moved the pulmonary differential from mainly neutrophils to an equally distributed differential of both neutrophils & macrophages [36]. What is important is that even though inflammatory profile was decreased in severity there was no increase in bacterial as well. These studies have given the 1st series of preclinical data to support potential of using MSC as a new cell based treatment option in CF [35,37].

Allergy and Asthma & Stem Cells

Asthma is characterized by airway inflammation and reactivity which => lung injury finally. MSC's are properties of anti-inflammatory as well as growth promoting mechanism which make them an attractive treatment approach for chronic asthma. Studies in Weiss laboratory demonstrated that in ovalbumin asthma model given murine MSC'S has a marked decrease in airway hyper responsiveness and eosinophil levels in Broncho Alveolar Lavage (BAL) [33]. The direction of T-cell response shifting away from

Helper Cells (Th2) cytokines is also influenced [33] MSC's administered to mice decreased epithelial hyperplasia, inflammation, ECM deposition as shown by separate studies found in these models despite human MSC' being used in mice [31,37].

Immunomodulatory properties of MSC's give new way of treating allergy. In Sun laboratory mice received allergic inflammation in their upper and lower airways. With the use of murine MSC's the mice showed inhibited nasal eosinophilia and lung pathology [38] With the pathology suppressed along with balancing of immune response inflammation was markedly decreased in both upper and lower airways in the model after challenge with MSC's [38]. This may be relevant in hematopoietic stem cells source. Bone marrow stromal cells inhibit mast cell function though Cyclooxygenase (COX2) dependent mechanisms which suggest that there maybe potential applications of bone marrow MSC's towards the treatment of mast cell inflammatory diseases such as anaphylaxis [39] but the source of MSC's maybe important in these studies. These observations give credit to MSC use as an alternative cell source for the treatment of severe allergic diseases.

Cardiac Disease and MSC's

Williams & Hare reviewed the use of MSC's in cardiac diseases. Animal Models of myocardial infarction have shown the ability of transplanted MSC's to engraft and differentiate into cardiomyocytes and vasculature cells, recruiting endogenous cardiac stem cells and secrete a wide type of paracrine factors. These properties can be utilized for both avoiding and revert remodeling in the damaged ischemic ventricle. In phase I clinical trials MSC therapy improved left ventricular function, induce reverse remodeling and decrease [40].

Further Sahara et al reviewed how these discoveries of MSC's in cardiac regenerative medicine can be used for programming and reprogramming a human heart cell. Progress in this field has been affected by a lack of reproducible and convincing evidence which has given modest outcomes and is still far from clinical practice and have discussed current controversies and for making cardiac regenerative medicine forward cellular and molecular programs are discussed [41].

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