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## MESENCHYMAL STEM CELL'S IN THERAPY- A REVIEW

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### Abstract

Stem cells are relatively unique and characteristic in comparison with the rest of mammalian cells especially in terms of lacking tissue specificity and undifferentiated phenotype unless exposed to specific selective signals. Mesenchymal stem cells are multipotent stromal cells derived from the mesoderm of embryonic connective tissue. Mesenchymal stem cells which are found and isolated from bone marrow, adipose tissue, umbilical cord blood are the precursors of any tissues of mesenchymal lineage including bone, tendon, cartilage, fat and muscle. Though many aspects of these cells such as commitment, differentiation, transdifferentiation and plasticity of cell population are not yet decoded and are yet to be brought into limelight, a broad spectrum of therapeutic potential and clinical applications seems to be transparent. Currently mesenchymal stem cell therapy is being assessed and analysed for numerous disease targets which are presently under pre-clinical and clinical trials. This article especially focuses on current status of mesenchymal stem cell therapy assessed for various disease conditions and the relevant properties of these cells aiding in therapy .

**Key Words:** Undifferentiated phenotype, Mesoderm, Mesenchymal stem cell, Transdifferentiation.

### Introduction

Stem cells are the specialised cells characterised by division, differentiation and self-renewal properties. Both embryonic and adult stem cells are autologous differing only in their origin where the former is derived from inner cell mass of blastocyst and the later are found in various tissues especially in the bone marrow and adipose tissue. These cells are the progenitors or the precursors of many cells for

example a hematopoietic stem cell produces cells of entire myeloid and lymphoid lineages which explains their role in tissue repair, regeneration and healing .[1]

Mesenchymal stem cells are a type of stem cells which are multipotent in nature and can divide and differentiate into any cell of mesenchymal lineage including chondrocytes, osteoblasts, adipocytes[2] . This phenomenon can be implicated for therepeutic potential of mesenchymal stem cells in repair and regeneration of above tissues as well as their associated disease conditions . Morphologically these cells are constituted of small cell bodies with a large nucleus and a prominent nucleolus . Though rigorous study is still required, this therapy is found to be effective and safe for multitude of disease conditions such as osteoarthritis , myocardial - infarction , muscular dystrophy , lung fibrosis , spine fusion , craniotomy defect , segmental bone defect , tendon defect , meniscus , large bone defect , osteogenesis imperfecta , severe idiopathic aplastic anemia and many more.

Up-to-date information clearly implies the applications of mesenchymal stem cells in therapy of many acute and chronic disease conditions. But a lot more studies must be performed to understand and obtain the pharmacological and toxicological data.

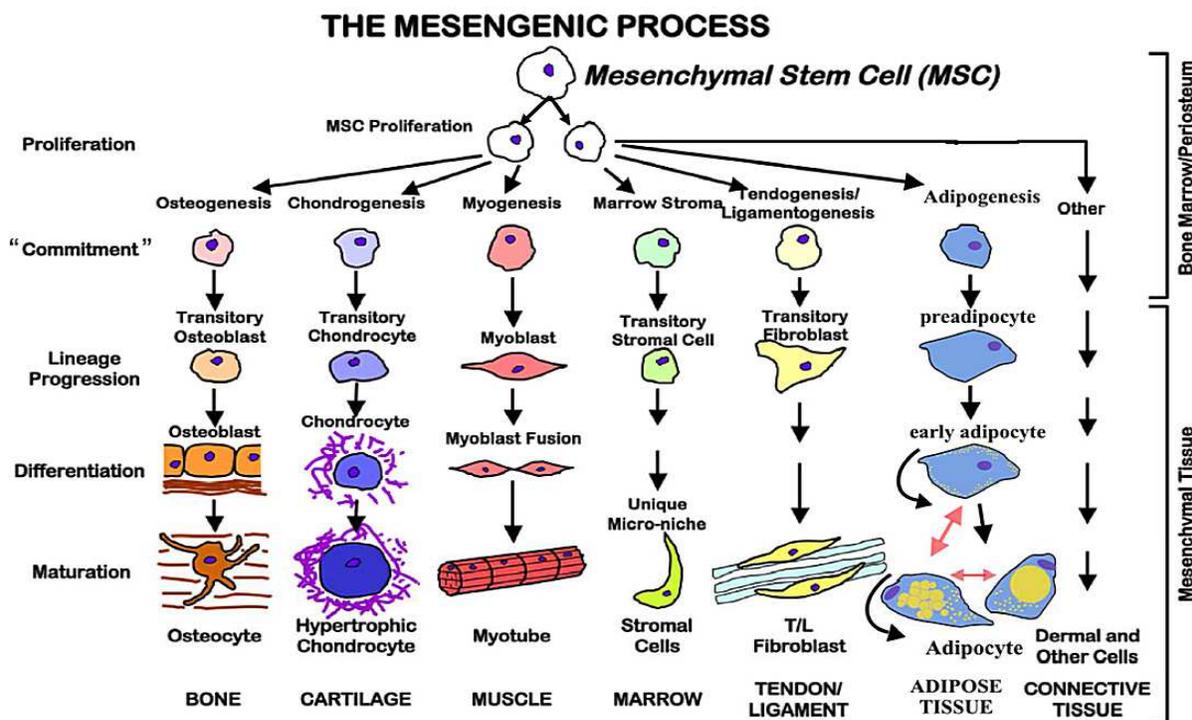


Figure 1/1 [19]

## Source and Isolation

Primitive MSCs ( mesenchymal stem cells ) are generally obtained from Wharton's jelly (umbilical cord tissue ) and umbilical cord blood. Hence preservation of umbilical cord (personal banking) after birth is being followed in the present days due to its rich source of pluripotent stem cells which can be used for autologous transplantation procedures in future whenever required[3].

Developing tooth bud of the mandibular third molar is an extremely rich source of MSCs particularly obtained within 10 years of age prior to complete calcification[4].

Adult MSCs are obtained and isolated from aspirated bone marrow and adipose tissue . Density of MSCs is usually around 500 times more in adipose tissue to that of bone marrow[5].

## Properties

The two properties of MSCs which are of prime importance are ,

- Repairative.
- Hypoimmunogenic or immunosuppressive .

Repair and healing are generally the inborn properties of any stem cells based upon their relative potency i.e they might be totipotent, pluripotent , multipotent or unipotent . Whereas the hypoimmunogenic property was confirmed based on several studies[6] .

## Applications in Therapy

Stem cell therapy is the transplantation of autologous or allogenic stem cell into patient either by surgical means or by systemic infusion. Here are some disease conditions for which MSCs therapy is being applied and investigated:

**In regeneration of infarcted myocardium:** Delivery of bone marrow MSCs in the infarct zone of patients suffering from myocardial infarction suggested healing of the infarct and the suburban myocardial tissue. The practical utility of this approach was demonstrated by stamm et al. Suggested mechanisms of regeneration were, connective tissue remodelling that forms the chronic scarring , neovascularisation and paracrine effects. However further clinical studies were required and dose escalation studies were yet to be performed to ensure myocardial safety[7][8].

### **In Bleomycin induced lung injury**

Pulmonary fibrosis is the most serious complication of anticancer, glycopeptide antibiotic bleomycin which is mostly used to treat hodkins lymphoma and testicular cancer . Bleomycin induced inflammation and fibrosis causes acute respiratory distress syndrome characterised by significant loss of lung tissue leading to altered pulmonary physiology, causing significant morbidity and mortality. Augmenting lung tissue repair by MSCs might be the key for advancement in treatment for this condition. Yuben moodley et al demonstrated the use of human umbilical cord MSCs isolated from Wharton's jelly on bleomycin induced lung injured mice and found that uMSCs have antifibrotic property. The infusion of uMSCs was given and traced over the interval of 7, 14 and 28 days respectively and was observed that the cells were especially localised only at the sites of injury or fibrosis but not at the regions of healthy tissue. Moreover there was reduced inflammation and inhibition of expression of transforming growth factor- $\beta$  , proinflammatory cytokines , interferon- $\gamma$  and tumor necrosis factor- $\alpha$ . These changes were also followed by significant reduction in collagen concentration. Similarly Mauricio rojas et al determined the use of bone marrow derived MSCs in repair of lung injury[9][10].

### **IN CNS repair and reconstitution**

MSCs can also be indirectly applied for autologous neuroreplacement therapies. Generation of neural stem cell like cells using bone marrow derived human mesenchymal stem cells was demonstrated by Fox et al . These NSC-like cells are capable of proliferating into different cells such as neurons , oligodendrocytes and so on and also express neural markers. This property of hMSCs derived NSC-like cells can be applied for treatment of cerebral palsy in repair and reconstitution of cerebral tissue to limit and reverse the motor impairment. Though still at baseline MSCs were found to be effective in treatment of parkinsons disease. This phenomenon was explained by Takuya Hayashi et al who performed autologous engraftment of A9 dopaminergic neuron-like cells induced from MSCs in hemiparkinsonian macaques and found improvement and of motor function followed by restoration of neurons at the site of engrafted striatum. Bone marrow derived MSCs when engrafted at the zone of traumatic region in spinal cord with schwann differentiating factor shown significant increase in brain derived neutrophic factor and vascular endothelial growth factor

in-vitro , this growth promoting and neuroprotective effect was depicted in cervical spinal cord injured mice by Novikova LN et al[11][12][13].

### **IN Alloantigen tolerance**

Graft-versus-host disease is the most common manifestation associated with allogenic hematopoietic stem cell transplantation causing significant mortality in children. Bone marrow and adipose tissue derived MSCs were showing promising performance of immune tolerance specifically by inhibiting T-cell proliferation in-vitro. Currently these studies are in phase-2 clinical trials. These might drastically minimise mortality due to graft rejection and are also an alternative for steroid resistant transplantations. *PROCHYMAL* is the first MSC preparation developed by Osiris therapeutics inc. On september 28<sup>th</sup> 2012 was licensed for treatment of acute graft-versus-host disease in Canada and New Zealand. It was categorised as an orphan drug and is yet to gain world wide acceptance and approval[14][15][16].

### **In articular cartilage repair**

MSCs efficiently differentiate into bone , muscle , cartilage and adipose tissue. These cell lineages were successfully implemented in animal models and found to regenerate articular cartilage. Percutaneous introduction of MSCs were found to be highly efficient in articular cartilage repair[17][18].

### **Conclusions**

Although a lot of research and multitude of clinical trials are yet to be carried on , a superficial understanding clearly implicates the indefinite breakthroughs of MSCs in the field of medicine and health. Applications of MSCs are not confined only to a single branch and can bring a tremendous change in the fields of cardiology , orthopedic , neurology and many others either directly or indirectly.

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