Human bone marrow-derived mesenchymal stem cells

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Abstract: Mesenchymal stem cells (MSCs) have elicited a great clinical interest, particularly in the areas of regenerative medicine and induction of tolerance in allogeneic transplantation. Previous reports demonstrated the feasibility of transplanting MSCs, which generates new prospects in cellular therapy. Recently, injection of MSCs induced remission of steroid-resistant acute graft-versus-host disease (GVHD). This review summarizes the knowledge and possible future clinical uses of MSCs.

Key Words: *mesenchymal stem cells, plasticity, immunomodulation, cancer, gene therapy.*
Abbreviations: *BM: Bone Marrow; GVHD: graft-versus-host disease; HSC: hematopoietic stem cells; PMNC: peripheral mononuclear cells; MSCs: mesenchymal stem cells; NOD/SCID: nondiabetic severe combined immune deficiency; OI: osteogenesis imperfecta*

Introduction

Isolation of bone marrow (BM) cells that could form new bone when transplanted to an ectopic site was demonstrated using the guinea pig model [1,2]. These derived stromal cells, named mesenchymal stem cells (MSCs), were expanded from adherent stromal cells in bone marrow culture. The results were confirmed later in both rabbit and rat bone marrow cells [2-4].

MSCs are adult clonal multipotential stem cells localized in the medullary stroma [5-7]. The human body contains many stem cells, i.e. hematopoietic (HSC) [8], neural [9], epithelial [10,11] and embryonic stem cells [12]. MSCs do not fulfill all true stem cell criteria. In contrast to HSC, single MSCs cannot regenerate a whole tissue compartment, and they do not have indefinite self renewal capacity.

MSC cells represent 1/10,000 to 1/100,000 of all mononuclear cells in the BM, and they can be expanded 500-fold through as many as 50 generations to produce billions of cells [13-16]. Colonies derived from a single MSC vary to some extent in differentiation capacity and expansion potential [17-20]. Entry of MSC into senescence is almost undetectable, and they lose their stem cell characteristics and differentiation potential from the sixth passage onwards [21].

Haynesworth *et al* developed a reliable *in vivo* bone-forming assay and were able to isolate and expand human MSCs for therapeutic purposes [22].

The ability to expand MSCs *in vitro* for clinical applications has recently facilitated the development of clinical trials designed to assess the safety, feasibility, and efficacy of transplanting MSCs for a variety of diseases [14]. Neither toxicity nor malignancy was associated with infusion of expanded autologus MSCs into patients with advanced breast cancer, with Hurler syndrome, or with metachromatic leukodystrophy [23-25].

In this review we will discuss the following:

1- Characterstics of MSCs
2- MSCs isolation and culture expansion
3- Transplantibility and engrafment of MSCs
4- Role of MSCs in support of hematopoiesis
5- MSCs plasticity, differentiation, possible uses in regenerative medicine and treatment of various diseases
6- Role of MSCs in immunomodulation
7- MSCs and solid organ graft
8- Role of MSCs in irradiation injuries or burns
9- MSCs in gene therapy
10- MSCs in cancer

Characteristics of MSCs

MSCs are unspecialized cells that lack tissue-specific characteristics and can maintain their undifferentiated phenotype. Under the influence of specific biological signals, MSCs can differentiate into specialized cells with a phenotype that is fully distinct from that of the precursor.

MSCs express neither the hematopoietic markers CD34, CD45, CD14, CD11 (7,26), nor the co-stimulatory molecules CD 80, CD 86, CD40, CD 40 ligand and CD 154 (27). MSCs are positive for CD73, CD105 and CD90 (28). MSCs express adhesion molecules, including VCAM (CD 106), ICAM (CD54), and LFA-3 (29). It has been demonstrated that human MSC MHC (HLA-DR) is localized in the submembranous space near the nucleolus (30), but cell surface expression of class I and class II MHC requires activation by interferon-γ (IFN-γ) (27, 31).

MSCs secrete respectively Interleukin-6 (IL-6), IL-7, IL-11, IL-12, IL-14, IL-15, leukemia inhibitory factor (LIF), macrophage colony-stimulating factor (M-CSF), stem cell factor (SCF), and flt-3 ligand [32].

Minimal criteria for defining multipotent mesenchymal stromal cells according to the International Society for Cellular Therapy are the ability to regenerate and differentiate into tissues of mesodermal origin (osteocytes, adipocytes and chondrocytes), and the absence of expression of haemopoietic molecules [28].

MSC isolation and culture expansion

MSCs have been isolated from adipose tissue, fetal liver, blood, lung, postnatal marrow, cord blood, brain, spleen, kidney, bone marrow,

muscle, thymus, pancreas, and from human peripheral blood mobilized with Granulocyte-Colony stimulating factor (G-CSF) [33-36]. However, long-term cultures of MSCs can be generated only from blood vessels [37].

Human MSCs are isolated from the total nucleated cell population in a BM aspirate, which is often harvested from the superior iliac crest of the pelvis, after separation by discontinuous density gradient centrifugation [6,38,39]. Mononuclear cells (MNC) are then cultured in a medium, such as Dulbecco's modified Eagle's medium (DMEM), or alpha MEM (α-MEM) supplemented with 10% fetal calf serum (FCS), platelet-rich plasma (PRP), or a commercial substitute of human serum [15,40,41].

In culture, the non-adherent MNC are washed away to leave behind small, adherent fibroblast-like cells. Cultures have an initial lag phase of three to five days [42], followed by rapid proliferation with an average initial doubling time ranging from 12 to 24 h and varying from one donor to another [15]. MSCs have a spindle shape (Figure1), and they can be expanded for about three weeks. At confluence, MSCs enter a stationary phase [15]. They are then detached by trypsinization and subcultured for many passages, giving long-term cultures. Using this method, comparable and reproducible populations of MSCs have been generated in many laboratories [4,7,26,37].

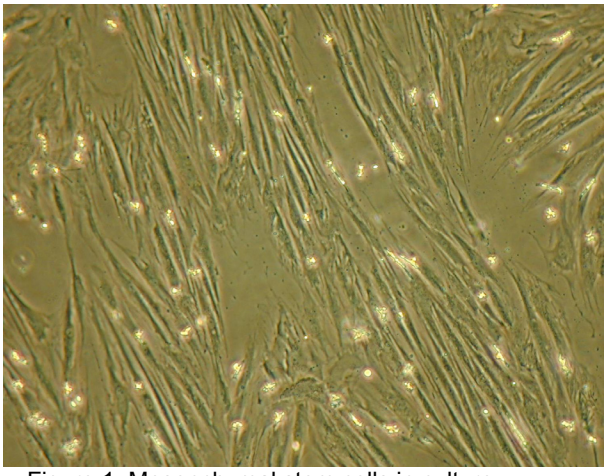

Figure 1: Mesenchymal stem cells in culture.

Transplantability and engraftment of MSCs.

Numerous studies have demonstrated migration and multiorgan engraftment of MSCs both in animal models and in human clinical trials [43-48].

Direct injection of human marrow stromal cells into the corpus striatum of rat brain showed engraftment of 20% of the infused cells [48].

Injection of MSCs into the lateral ventricle of neonatal mice migrated throughout the forebrain and cerebellum [44]. Rat bone marrow stromal cells infused distally into areas of occluded ascending aorta migrated after eight weeks into the scar and periscar tissue [47].

MSCs injected intravenously into irradiated primates could engraft in different injured tissues, such as bone marrow, skin, digestive tract, and muscle [49,50]. MSCs infused into mice homed into thymus [46].

In rat models, rat MSC have been engrafted in multiple organs, such as lung, liver, kidney and spleen. However, homing of labeled MSCs to the marrow of long bones was significantly increased by pre-treatment with vasodilators [51].

Human MSCs engrafted into sheep [52,53] or mouse [54-56] show site-specific differentiation. The ability of MSC to engraft was influenced neither by the route of adminstration nor by the difference in conditioning protocols [57].

Both autologous and allogeneic MSCs have been given to patients [25,58,59]. Allogeneic HLA-mismatched male foetal cells injected into HLA-incompatible female fetal cells with osteogenesis imperfecta (OI) engrafted and differentiated into bone [60]. Haploidentical MSCs had a low level of engraftment in a patient with aplastic anemia, but there was a partial restoration of the bone marrow microenvironment [61]. In contrast, infused allogeneic MSCs did not expand substantially in patients. [59,62].

Role of MSCs in support of hematopoiesis

MSCs support medullary hematopoiesis structurally and functionally by providing growth factors and extracellular matrix [63-67, 42].

Co-transplantation of HSCs along with MSCs ameliorated hematopoietic reconstitution [25,68,69]. MSCs maintain the expansion of lineage, specific colony-forming units of marrow CD34+ HSC. MSCs enhance engraftment of dose limited allogeneic and umbilical cord-derived HSC in NOD/SCID and in fetal sheep [70-72]. This promoting effect of MSCs was present even though MSCs were not detected in the BM of the host [73].

Co-transplantation of human MSCs enhances human myelopoiesis and megakaryocytopoiesis in NOD/SCID mice [72] and increases the functional hematopoietic microenvironment [74]. In humans, rapid hematopoietic recovery was demonstrated after co-infusion of autologous-blood stem cells and culture-expanded MSCs in advanced breast cancer patients receiving high-dose chemotherapy [23].

Co-transplantation of HLA-identical (sibling) culture-expanded MSCs with an HLA-identical (sibling) HSC transplant induced hematopoietic recovery on peripheral mononuclear cells (PMNC) and platelets [24,75].

MSC plasticity, differentiation, and prospective use in regenerative medicine and treatment of various diseases

Human MSCs are multipotent and easily expanded. They represent potential clinical tools for tissue repair and gene therapy.

MSCs have a plastic potential. Plasticity means the ability of cells to convert from one type to another, which is also known as horizontal progression (synonomous to differentiation). *In vitro* and *in vivo* studies have indicated the ability of MSCs to differentiate into muscle, neural precursors, myocardial tissues, cardiomyocytes, bone, tendon, cartilage, and possibly other cell types (Figure 2). MSCs also produce appreciable amounts of lysosomal enzyme activity, which could correct metabolic derangements when given to enzyme-deficient patients with lysosomal storage diseases and other neurometabolic illnesses [76].

Here we will outline briefly the results of several studies demonstrating the ability of MSC to differentiate into different tissues.

Muscle and heart

Repeated endomyocardial transplantation of high doses of allogeneic MSCs appeared safe in Yorkshire swine models [77]. Adult human MSCs showed persistent engraftment into infarcted rat myocardium [78]. MSCs enhanced the survival of existing myocytes in mice through paracrine mechanisms [79]. In murine models, single clonally purified MSCs seem to be more beneficial than unpurified transplantated MSCs in cardiac repair [80].

Transplantation of MSC combined with treatment with erythropoietin in rat models of acute myocardial infarction leads to enhancement of capillary density, and reduction of infarct size and fibrotic areas, as compared to groups that received only MSCs [81]. Transplantation of genetically engineered MSCs expressing an anti-apoptotic and angiogenic peptide improved cardiac function after myocardial infarction significantly more than MSCs alone [82]. MSCs implanted in a rat myocardial infarct heart improved cardiac structure and function through the combined effect of myogenesis and angiogenesis [83]. Fischer rats transplanted with MSCs transduced with an adenovirus expressing the *Ang*-1 and *Akt* genes were more resistant to anoxia and restored global cardiac function [84]. However, MSC proliferation *in vitro* was inhibited by aspirin, which is used extensively to treat cardiovascular diseases [85].

MSCs can differentiate into smooth muscles in rat models [86] and skeletal muscles in rat and mouse models, respectively [87,88]. Human fetal MSCs transplanted into the uterus of mice with Duchenne muscular dystrophy distributed widely and differentiated into muscle cells. However, this did not cure the disease [89].

Nervous and renal system

Implantation of MSCs into injured spinal cords of rhesus monkeys elicited *de novo* neurogenesis and promoted functional recovery, as determined by tests of cortical somatosensory-evoked potential (CSEP) and motor-evoked potential (MEP). This also led to nearly normal sensory responses three months after transplantation [90]. Following spinal cord injury (SCI), MSCs had a positive effect on behavioural outcomes and histopathological assessments. They induced better recovery of hind limb sensitivity and increased the spared white matter in rat models [91]. In mice, transdifferentiated MSCs implanted into devitalised muscle grafts could support peripheral nerve regeneration to some extent [92]. Intrastriatal transplantation of MSCs promoted functional improvement on the rotarod test in murine models of Parkinson's disease [93]. Addition of MSCs to degenerative disc cells with anulus fibrosis (AF) *in vitro* resulted in changes in extracellular matrix biosynthesis with an up-regulation of proteoglycan synthesis [94].

In murine models of experimental autoimmune encephalomyelitis, administration of MSCs at onset and at the peak of disease decreased inflammatory infiltrates and demyelination in the central nervous system [95]. In rhesus monkeys, implantation of a cellular allogenic nerve grafts and autologous MSCs repaired extended peripheral nerve lesions [96].

In humans, MSCs transdifferentiated into neural stem cells and improved the electrical and functional recovery of two patients with chronic spinal injury [97]. MSC infusion into patients suffering from metachromatic leukodystrophy and Hurler Syndrome was associated with significant improvement in nerve conduction velocities [25].

Transplanted MSCs accelerated glomerular healing in experimental rat models with glomerulonephritis [98]. In mice, MSCs reduced interstitial fibrosis, but did not delay progression of chronic kidney disease [99]. MSCs may protect against acute renal injury and promote the recovery of morphological and functional alterations of tubular epithelial cells [54]. In murine

models, MSCs improved tissue damage triggered by renal ischemia and reperfusion injury [100].

Skin and related tissue

Human MSCs derived from the early human embryo can transform into epidermal cells *in vitro* and *in vivo* [101]. Injection of autologous biograft composed of autologous skin fibroblasts on biodegradable collagen membrane (Coladerm) in combination with autologous MSCs into the edges of the wound decreased wound size and increased the vascularity of the dermis of diabetic foot wounds [102]. Infusion of MSCs promoted the survival of allogeneic skin grafts in mice [103] and baboons [104].

Injection of human MSCs derived from umbilical cord blood into four men with Buerger's disease relieved ischemic rest pain in their affected extremities, led to healing of necrotic skin lesions within four weeks, and improved peripheral circulation [105].

Bone, cartilage and tendons

MSCs expanded in an osteoconductive carrier regenerated a critical segmental defect in the femur of dogs as effectively as autogenous cancellous bone. Mismatched allogeneic stem cells regenerated bone without eliciting an immunologic response. This finding raised the possibility of establishing allogeneic MSC banks for bone regeneration [106]. MSCs were able to reconstitute different layers in the femoral condyle [107]. In a canine model, transplantation of MSCs with partially demineralized bone matrix restored bone defects and enhanced bone growth [108]. In a rabbit model, MSCs regenerated full-thickness defects of articular cartilage defects, repaired Achilles tendon [107,109], and helped to strengthen osteoporotic bone [110]. Implantation of rat demineralised bone matrices (DBM) with MSCs led to the formation of bone [111]. MSCs engrafted in mice with OI led to a significant increase in bone collagen and mineral content [112]. In an ovine model, spraying autologous MSCs onto grooved hydroxyapatite-coated collars of segmental bone tumor implants increased bone growth [113]. However, naive MSCs injected in mouse knee joints could not differentiate to restore cartilage tissue [114]. In addition, MSCs transplanted to ectopic sites in mice underwent alterations related to endochondral ossification rather than adopting a stable chondrogenic phenotype [115].

Use of MSCs in five children with OI disease lead to a signifincat increase in the total body mineral content and increased growth velocity [116,117]. Three-dimensional tissue scaffolds promoted MSC ectopic bone formation [118]. MSCs that were used to fill bone defects during revision total joint replacement survived normal impact force during this procedure [119].

Retina tissues, liver and teeth

MSCs formed structures similar to the photoreceptor layer and expressed a photoreceptor-specific marker in rats [120], and could provide a beneficial effect in retinitis pigmentosa [121]. Murine MSCs integrated into retinal pigment displayed neuronal and glial morphologies and preserved photoreceptor cells in the rhodopsin knockout mouse [121].

Human MSCs grown *in vitro* gain the characteristic morphology and function of hepatocytes after transplantation into livers of immunodeficient mice; they engrafted and retained function of hepatocytes [122].

In vitro and in vivo studies demonstrated that MSCs can differentiate into functional odontoblast-like cells [123]. New populations of stem cells isolated from the root papilla of human teeth transplanted with periodontal ligament stem cells (PDLSCs) generated a root/periodontal complex capable of supporting a porcelain crown and resulting in normal tooth strength and appearance [124].

Role of MSCs in immunomodulation

Coculture of MSCs with allogeneic lymphocytes failed to stimulate their proliferation, indicating that these cells are innately not immunogeneic [125,126,104]. Recent reports suggest that MSCs have immunomodulatory properties and can inhibit lymphocyte antigen presenting cells, natural killer cells, and cytotoxic lymphocyte proliferation in mixed-lymphocyte reactions (MLR) [27,30,70,104,125-128].

MSCs inhibit CD2, CD4 and CD8 subsets of T lymphocytes [127,128]. Despite the expression of HLA by MSCs, they were well tolerated without side effects in allogeneic hosts [27,61,104,129].

Reports on the underlying mechanisms of MSC-mediated inhibitory effects are contradictory. Soluble inhibitory factors, such as hepatocyte growth factor [127], transforming growth factor-B [127], indoleamine oxidase [130], human leukocyte antigen-G [131] and interleukin-10 [132] have been implicated as mediators of the MSC inhibtory effect. However, the implication of TGF-B, interleukin-10 and indoleamine oxidase has not been demonstrated by others [27].

The importance of cellular contact between MSCs and lymphocytes in enhancement of MSCs inhibtory effect is contradictory [127,132,133].

Co-transplantation of MSCs may prevent lethal graft-versus-host disease (GVHD) in MHC-mismatched murine HSC transplantation [129]. In a baboon model, MSC injection led to prolonged skin allograft survival [104]. Intravenous administration of MSCs prolonged the survival of transplanted hearts [134].

In humans, MSCs were used to treat severe acute GVHD [135]. MSCs derived from autoimmune disease (AD) patients exhibited extensive anti-proliferative properties against lymphocytes *in vitro*. This could be investigated as a form of immunomodulatory cellular therapy for AD patients [136].

In contrast, allogeneic and transgeneic MSCs were rejected by mismatched recipient mice [137,138]. In addition, concurrent treatment with low-dose cyclosporine A and MSCs accelerated allograft rejection [139]. MSCs failed to prevent acute GVHD in mice [140].

MSCs and solid organ graft

MSCs revitalized cryopreserved allogeneic grafts used to repair large musculoskeletal defects [141]. They incorporated within the tissue sheath around the tendon, and adopted the characteristic spindle-shaped morphology of tenocyte-like cells [141].

MSC transplantation into heart enhanced cell survival, improved angiomyogenesis, and restored global cardiac function [84]. The vascular protheses, the inner surfaces of which are covered with MSCs that overexpress nitric oxide synthase, may have longer graft patency and vasculoprotective effects [142]. Injection of MSC enhanced xenochimerism in murine models, thereby showing promise as a strategy to achieve whole organ xenograft tolerance [143].

Role of MSCs in irradiation injury and in burns

Exposure of living cells to irradiation induces DNA damage and results in immediate tissue aplasia, or long term secondary effects resulting in induction of cancer [144,145]. Acute radiation syndrome affects hematopoietic, gastrointestinal, neurovascular and cutanous systems [146]. Therapeutic irradiation can induce a significant decrease of both mature and immature progenitors in human BM and peripheral blood immediately after low-dose total body irradiation (TBI) (147). A dose of 2-8 Gy causes the hematopoietic component of the acute radiation syndrome in humans [148-150]. It has been demonstrated that growth of irradiated CD34+ cells was enhanced by co-culture with MSCs [151]. Injection of MSCs could help in the management of therapeutic irradiation side effects. Radiation enteritis is a functional disorder of the intestine that can occur during or after a course of radiotherapy of the abdomen, pelvis or rectum.

Radiation enteritis can present either as an acute or a chronic form, both of which have life threatening sequelae. The increasing use of radiotherapy in the treatment of solid organ malignancies in the abdomen and pelvis is likely to increase the incidence of radiation enteropathy in the future [152]. Moreover, it can damage normal tissues during the course of therapy for a few weeks after therapy, or even for months or years [153].

The first challenge in therapeutic MSC transplantation is how to efficiently deliver it to the sites of intended action. TBI increased human MSC engrafment in BM and muscle and further led to engraftment in brain, heart and liver [50]. Local irradiation in addition to TBI induces homing of human MSCs to exposed sites and promotes widespread engraftment to multiple organs in murine models [50]. It seems that inflammation and tissue injury due to irradiation activate molecular pathways that increase the release of tissue chemokines. This attracts MSCs to injured tissue, where they engraft and differentiate into different tissues to replace the injured areas and repair damage. MSCs accelerate structural recovery and favour healing of irradiated tissues [154]. Human MSCs were shown to support the structural regeneration of the small intestine in NOD/SCID mice after abdominal irradiation [154]. Amazingly, MSCs are resistant to irradiation [155]. Cells expressing the MSC phenotype were more prevalent in the peripheral blood of burn patients than in healthy donors. The percentage of MSCs correlated with the size and severity of burns, and with patient age [156]. Human MSCs favour healing of cutaneous radiation syndrome in a xenogenic transplant model [157].

MSCs in gene therapy

Transplantation of interleukin-7 (IL-7) gene-engineered MSCs into lethally irradiated mice led to a significant increase in thymopoiesis and homeostatic expansion of peripheral T lymphocytes. It also protected the host from GVHD and enhanced immune reconstitution [158].

In a murine model, MSCs transfected *ex vivo* with the hepatocyte growth factor gene were more therapeutically efficient than MSCs alone in protecting brain tissues from acute ischemic damage in the midcerebral artery occlusion [159].

Transduction with the brain-derived neurotrophic factor gene further enhanced the protective efficacy against ischemic damage [160].

Hypoxia-regulated HO-1 vector modification of MSCs enhanced the tolerance of engrafted MSCs to hypoxia-reoxygen injury *in vitro* and improved their viability in ischemic hearts [161].

MSCs in cancer

MSCs possess excellent migratory ability and exert inhibitory effects on the proliferation of glioma cells [162]. Modification of MSCs by gene therapy with therapeutic cytokines augments the anti-tumor effect and prolongs the survival of tumor-bearing animals [163]. MSCs transfected with the epidermal growth factor receptor exhibit enhanced therapeutic potential against murine brain tumors [164].

In a model of Kaposi's sarcoma, human MSCs injected intravenously homed to sites of tumorigenesis and potently inhibited tumor growth [165]. In a murine model, MSCs adenovirally-engineered to secrete interleukin-12 prevented revival and recurrence of tumor cells, which had escaped from conventional treatment [166].

MSC-engineered hydroxyapatite used to fill the patient's bone cavity after tumor curettage demonstrated healing potential without adverse reactions [167].

Genetically modified MSCs expressing the vascular endothelial growth factor receptor (tsFlk-1) gene can inhibit growth of Burkitt's lymphoma in a murine model [168]. MSCs can target tumour cells [162] and have been suggested as a possible approach for the delivery of therapeutic agents [169]. MSCs transduced with an adenoviral expression vector carrying the human IFN-beta gene suppressed the growth of pulmonary metastases, presumably through the local production of IFN-beta in the tumor microenvironment [170].

By contrast, it has been demonstrated that MSCs could favour tumour growth in murine models [126,171], but they do not interfere with the kinetics of tumor development [171]. MSCs recruit primary follicular lymphoma (FL) cells and trigger their differentiation into fibroblastic reticular cells, making them able to support malignant B-cell survival [172].

MSCs target microscopic tumors and contribute to the formation of a significant portion of tumor stroma development *in vivo* [173].

Tumor cells, when mixed with MSCs and transplanted subcutaneously, exhibited increased capability of proliferation and angiogenesis in tumour tissues and highly metastatic ability. When human marrow-derived MSCs were injected into tail veins of SCID mice bearing human malignant melanoma, human cells incorporated into tumor vessels and participated in angiogenesis [174]. Interaction of Multiple Myeloma cells with MSCs resulted in the formation and persistence of osteolytic bone lesions. However, 6-bromoindirubin-3'-monoxime treatment reduces the MSCs-stimulated proliferation of Multiple Myeloma cells and may enable MSCs to repair existing osteolytic lesions [175].

These results are contradictory, and further experimental and clinical studies are needed to evaluate the benificial effects of MSCs in cancer therapy.

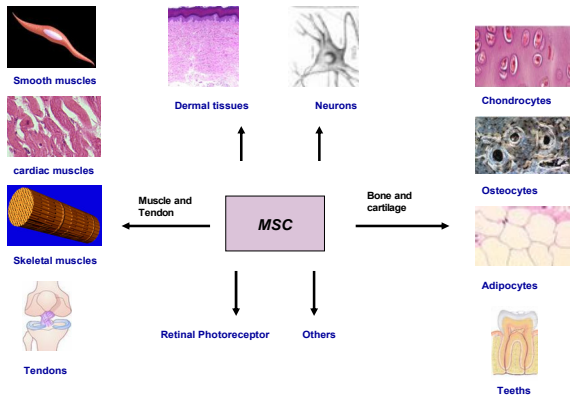

Figure 2 Different possible cells that could be obtained from MSCs

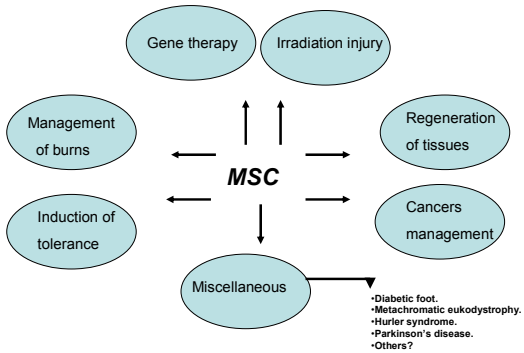

Figure 3 Possible future therapeutic application of MSCs.

Conclusion

MSCs have a multipotent capacity. They support hematopoiesis and have immunomodulatory activity. Experimental and clinical studies have implicated MSCs in tissue repair. These characteristics make MSCs particularly attractive for therapeutic exploitation, such as regeneration of various tissues, induction of tolerance in solid organ graft, and BM transplantation. Figure 3 summarizes the possible therapeutic applications of MSCs. However, the beneficial versus deleterious effects of MSCs

remain controversial. For instance, some studies showed the tolerogeneic effect of MSCs in recipients, while others showed that MSCs tended to promote rejection. Some reports demonstrated that MSCs had favourable effects on tumour growth, while others found that MSCs reduced the delay for tumour occurrence.

MSCs could provide opportunities for future clinical use in cellular therapy. However, more studies are needed on engraftment capacity, differentiation, and possible adverse effects in vivo.

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