Journal of Cellular Physiology

Adult Mesenchymal Stem Cells for Tissue Engineering Versus Regenerative Medicine

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Adult mesenchymal stem cells (MSCs) can be isolated from bone marrow or marrow aspirates and because they are culture-dish adherent, they can be expanded in culture while maintaining their multipotency. The MSCs have been used in preclinical models for tissue engineering of bone, cartilage, muscle, marrow stroma, tendon, fat, and other connective tissues. These tissue-engineered materials show considerable promise for use in rebuilding damaged or diseased mesenchymal tissues. Unanticipated is the realization that the MSCs secrete a large spectrum of bioactive molecules. These molecules are immunosuppressive, especially for T-cells and, thus, allogeneic MSCs can be considered for therapeutic use. In this context, the secreted bioactive molecules provide a regenerative microenvironment for a variety of injured adult tissues to limit the area of damage and to mount a self-regulated regenerative response. This regenerative microenvironment is referred to as trophic activity and, therefore, MSCs appear to be valuable mediators for tissue repair and regeneration. The natural titers of MSCs that are drawn to sites of tissue injury can be augmented by allogeneic MSCs delivered via the bloodstream. Indeed, human clinical trials are now under way to use allogeneic MSCs for treatment of myocardial infarcts, graft-versus-host disease, Crohn's Disease, cartilage and meniscus repair, stroke, and spinal cord injury. This review summarizes the biological basis for the in vivo functioning of MSCs through development and aging.

J. Cell. Physiol. 213: 341–347, 2007.

Theme

Adult bone marrow contains rare, yet powerful multipotent progenitor cells, which I refer to as mesenchymal stem cells (MSCs). These cells have two important capacities. First, MSCs can differentiate into distinctive end-stage cell types, such as those that fabricate specific mesenchymal tissues including bone, cartilage, muscle, bone marrow stroma, tendon/ligament, fat, dermis, and other connective tissues as diagrammed in Figure 1 (Caplan, 1989, 1991, 2005). Hence, these cells can be used for reforming these mesenchymal tissues through the principles and practices of tissue engineering. Second, MSCs, themselves, secrete a broad spectrum of bioactive macromolecules that are both immunoregulatory and serve to structure regenerative microenvironments in fields of tissue injury. I refer to this capacity of MSCs to home to injured tissues or to participate in the injury response by providing a broad array of paracrine factors as their "trophic activity;" these capacities define and embody, for me, the concept of Regenerative Medicine. This essay attempts to delineate the key biological principles in Regenerative Medicine by comparing and contrasting its logics with those of tissue engineering.

The Developmental Program

It is obvious that the transitions and changes in morphology and tissue function observed from fertilization of an egg by a sperm to the birth of an individual organism is an exquisitely controlled process of sequential changes. This developmental process is genetically controlled and results in tissues and organs with precise locations, morphologies, and integrated functions. The hallmarks of this process are the conversion of groups of multipotent cells to cells that form differentiated, highly specialized, and very narrowly functioning tissues. The structures and functions of heart, lung, liver, kidney, skeletal muscles, bones, etc., are all uniquely different, and each is connected to the other by neural and vascular networks for their cooperative and coordinated functioning. For emphasis, it is also quite obvious that the individual genetic information specifically determines the timing, the structure, and the functioning of these groups of cells within their differentiated tissues and organs.

Since a newborn, a 5 year-old, a 10-, 30-, 50-, 70-, or 90-year-old all have different performance and functional demand of these groups of cells and organs, it follows that these age-related changes are also exquisitely controlled by the organism's genetic information. Thus, the process of aging is a direct consequence of the Developmental Program embedded in the DNA of every cell. Once liver, kidney, or muscle forms in the embryo, how is it changed as a function of age?

One of the mechanisms for age-related change is depicted in Figure 2 and is predicated on the fact that every cell in the body has a specific half-life; every cell comes to maturation and will, predictably, drop dead in due course. Figure 2 shows that mature phenotypes arise from progenitor cells in a time-limited sequence of developmental transitions summarily referred to as a lineage. Red blood cells, for example, have half-lives of 60–90 days and arise in a multi-step lineage from the hematopoietic stem cell (HSC). When the cell reaches its lifespan limit, it expires as seen in the left-hand (solid line) curve of Figure 2. To maintain red blood cell numbers, the red blood cell (rbc) progenitors must be proceeding toward maturation, so that, as an existing rbc expires, its replacement has just reached maturity (Owen, 1985; Wagers and Weissman, 2004). If the right-hand (dashed line) curve in Figure 2 is moved a bit to the right, the individual would become slightly anemic because the total number of rbc's would be reduced. Likewise, the relative position of these two curves to one another defines growth, steady-state, or atrophy depending on when the first

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Received 1 June 2007; Accepted 4 June 2007

DOI: 10.1002/jcp.21200

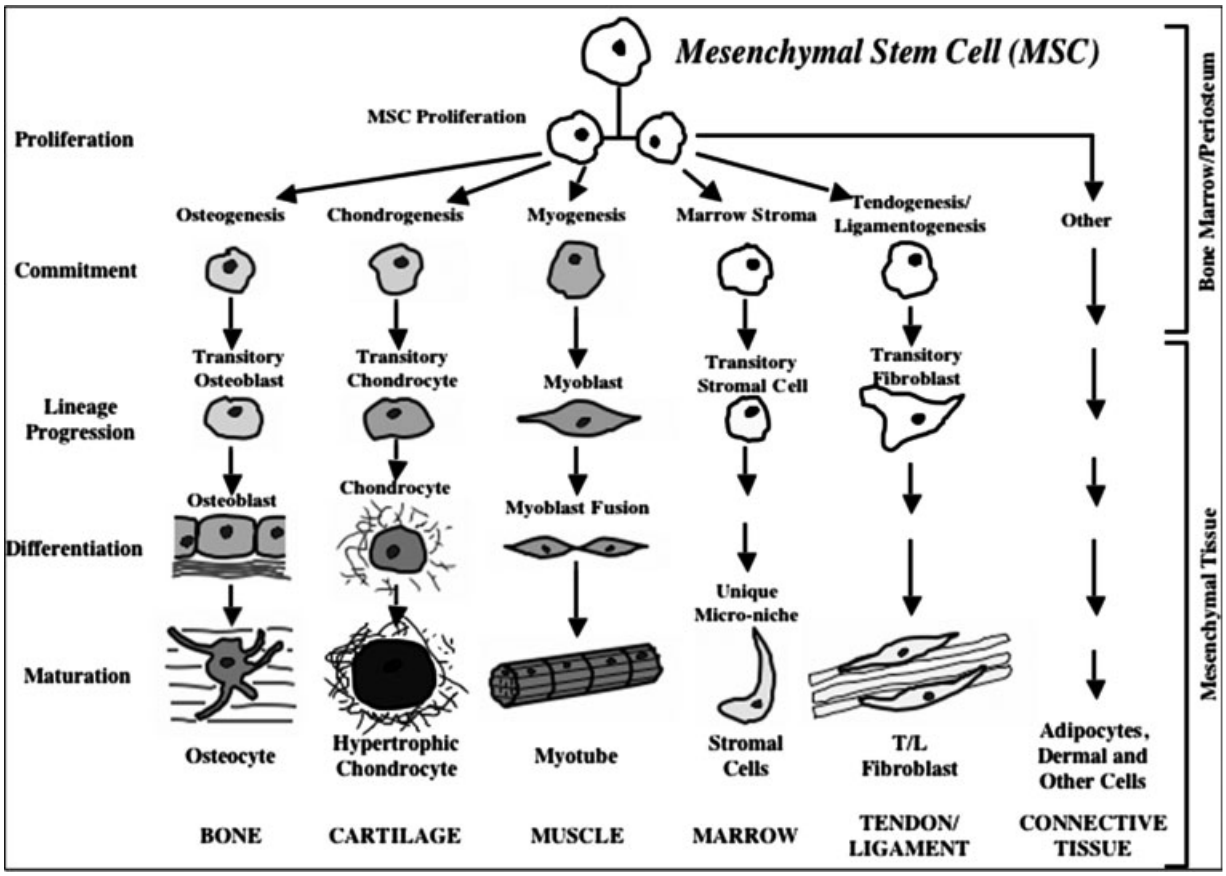


Fig. 1. The Mesengenic Process diagram originated in the late 1980s as a hypothesis based on what was known about mesenchymal progenitors in embryos. The format was designed to mirror the lineage pathways of hematopoiesis with the bone lineage (Owen, 1985) on the left reflecting the state of knowledge, while the lineages at the right were largely unstudied. The original diagram appeared first in Caplan (1989).

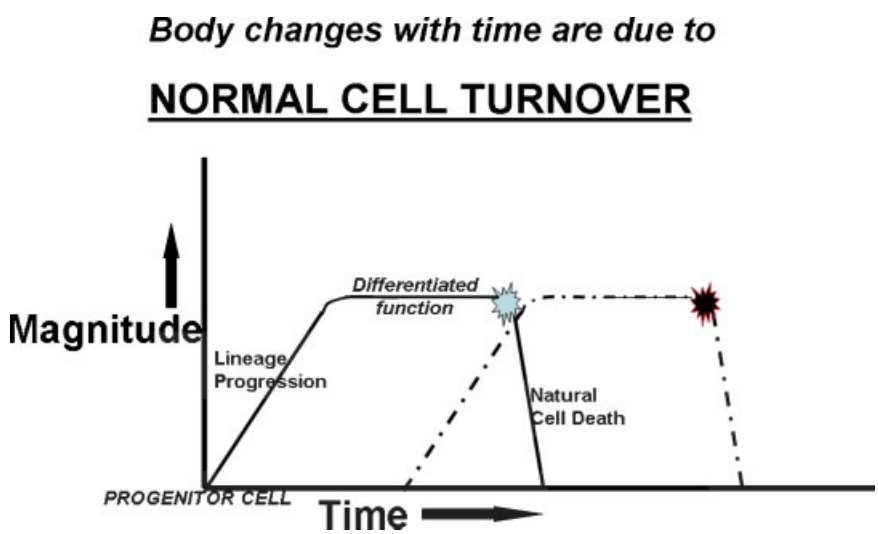


Fig. 2. Developmentally and genomically regulated changes in tissues occur in postneonatal organisms because every cell has a lifespan. Thus, the solid line represents the lineage progression that results in a cell exhibiting a differentiated function and, at a fixed time, the mature cell naturally expires. To maintain tissue mass and function, the replacement cell must be ascending the lineage progression (dashed line) prior to the expiration of the mature cell. If the dashed curve is shifted to the left, this represents tissue expansion or growth, while if the dashed curve is shifted in time to the right, this represents tissue atrophy. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

cell dies and when its replacement, the second cell, comes online.

This process is how all animals remain vital and how they constantly rejuvenate their tissues. This turnover sequence is the mechanism used to introduce small, genomically controlled changes in key structural components (isoforms) of various tissues, so that as we continue to exist, changes are programmed into the new, replacement cells and, thus, the tissues exhibit, over-extended time periods, age-related change (Caplan et al., 1983).

This sequence of turnover demands that, in adults, there must exist the progenitor cells that give rise to various mature phenotypes observed in complex tissues and organs such as heart, cartilage, bone, and liver. These progenitor cells are referred to as *adult stem cells* and they furnish the replacement units for the normal cell death. The normal half-lives of mature cells, thus, provide a mechanism for rejuvenating living tissue with fresh, functional cell units. This allows the replacement of cells that could be non-functional or that contain mutations. In addition, this allows the replacement cells to be slightly different from the expired cells. These changes through age are summarily referred to as aging. More specifically, adult MSCs are responsible for the replacement of, for example, osteoblasts that have half-lives of 8–10 days in humans. Loss of bone mass occurs because of the diminution of regenerative units in the marrow housed in various bones. Importantly, in our hands, the capacity of culture-expanded marrow-derived MSCs to differentiate into bone, cartilage, etc., is independent of the age of the donors, although MSC titers change with age (Haynesworth et al., 1994).

MSC Numbers

Figure 3 shows an estimate of marrow titers of human MSCs as judged by colony forming units-fibroblastic (CFU-f). The low MSC titers of elderly individuals are the primary cause for the long time periods required to mend broken bones, since the callus that spans the bone break is derived from MSCs. The local titers of MSCs are very low and, thus, cells must transit to the bone break site, divide, and differentiate into osteoblasts

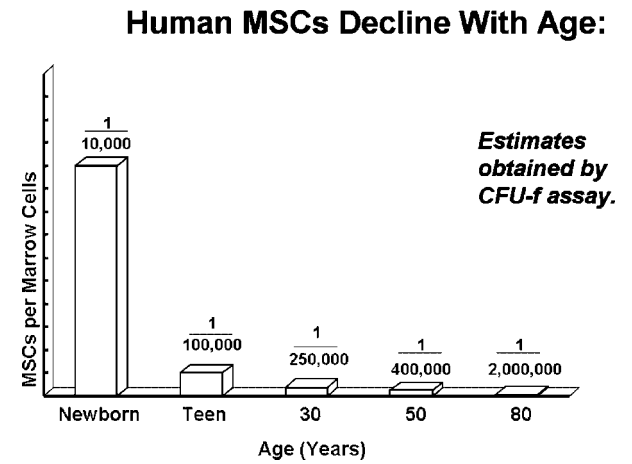


Fig. 3. The colony forming units-fibroblastic (CFU-f) assay is an estimate of the number of MSCs in marrow. These data are crude, at best, because the attachment to tissue culture dishes is not quantitative, so that upon the first medium change, the discarded medium still contains some MSCs (unpublished data). However, the three orders-of magnitude decrease in MSC titers between newborn and 80-year-old matches other estimates and clinical functionality.

to fabricate bone or cartilage that will stabilize the bone break and allow the callus to mineralize and form bony struts at the outer edge of the callus. Likewise, bone density and bone mass are dependent on the conversion of MSCs into osteoblasts that fill the pits of osteoclast-resorbed bone.

What controls the titers of MSCs in marrow and why these titers appear to change with age are not known. Moreover, the MSC niche, where MSCs actually reside in marrow, is also not known. This issue is further confused by the fact that there is no unique marker for MSCs, although several cell surface antigens have proven useful in separating MSCs from hematopoietic cells. For human MSCs, SH2, 3, and, 4 (Haynesworth et al., 1992; Barry et al., 2001), Stro-1 (Simmons and Torok-Storb, 1991) and $CD34^{-}/45^{-}$ (Herzog et al., 2003) have been used for this separation. The primary tests for MSCs have been in vitro assays for bone, cartilage, fat, and marrow stroma (hematopoietic support cells) and an in vivo porous calcium phosphate-ceramic cube implantation assay (Dennis et al., 1992, 1998; Ohgushi and Caplan, 1999).

The problem with in vitro differentiation assays for MSCs is that we and others have shown that distinctive differentiated cells such as adipocytes or chondrocytes can transdifferentiate into completely different lineage phenotypes such as osteoblasts (Tallheden et al., 2003; Farrington-Rock et al., 2004). This introduces the concept of phenotypic plasticity and challenges the validity of in vitro assays for MSCs. The plasticity issue, thus, requires the horizontal or diagonal arrows seen in Figure 4 as a refinement of Figure 1. Although the plasticity of MSCs has been documented in vitro, it is clear that some differentiated mesenchymal cells, such as human dermal fibroblasts, are neither plastic nor multipotent. We have used these human dermal fibroblasts to dilute human marrow-derived MSCs and then conducted both in vitro and in vivo implantation assays for MSC differentiation (Lennon et al., 2000). The presence of non-MSCs in the cell population causes a dose-dependent diminution of differentiation until no differentiation was observed at high percentages of dermal fibroblasts in the mixture. However, this diminution of differentiation was not observed until 25–50% of the mixture was dermal fibroblasts. In a very optimistic interpretation, one could say that implanted pure MSCs could sustain a 25–50% dilution by host non-MSCs, yet a full differentiation response could be expected.

The MSC Niche

The issue of where MSCs reside in marrow is addressed by considering the other tissues from which human MSC-like cells have been isolated. The other tissues, in addition to marrow, are adipose and muscle tissue. The adipose-derived stem cell (ADSC) preparations from both human and animals and muscle-derived stem cells (MDSCs) have been characterized (Zuk et al., 2001; Qu-Petersen et al., 2002; Shi and Gronthos, 2003; Lee et al., 2004). Cell preparations from both adipose and muscle tissue exhibit MSC-like differentiation properties and distinctive cell surface markers (Lee et al., 2000; Katz et al., 2005). The differentiation characteristics, the purity, and the yields are quite different for all of the stem cell preparations from different tissues. The impression is that these MSC-like cells are associated with blood vessels (Tavian et al., 2005). Indeed, every blood vessel in the body has a mesenchymal cell on the tissue side of endothelial cells of large and small vessels. This endothelial layer in contact with mesenchymal cells is found in every tissue of the body including non-mesenchymal tissues like liver or kidney. These vascular-associated mesenchymal cells are referred to as pericytes, smooth muscle cells, vascular support cells, etc. When isolated and assayed in culture, these cells have MSC-like characteristics. Conversely, marrow MSCs have characteristic markers of

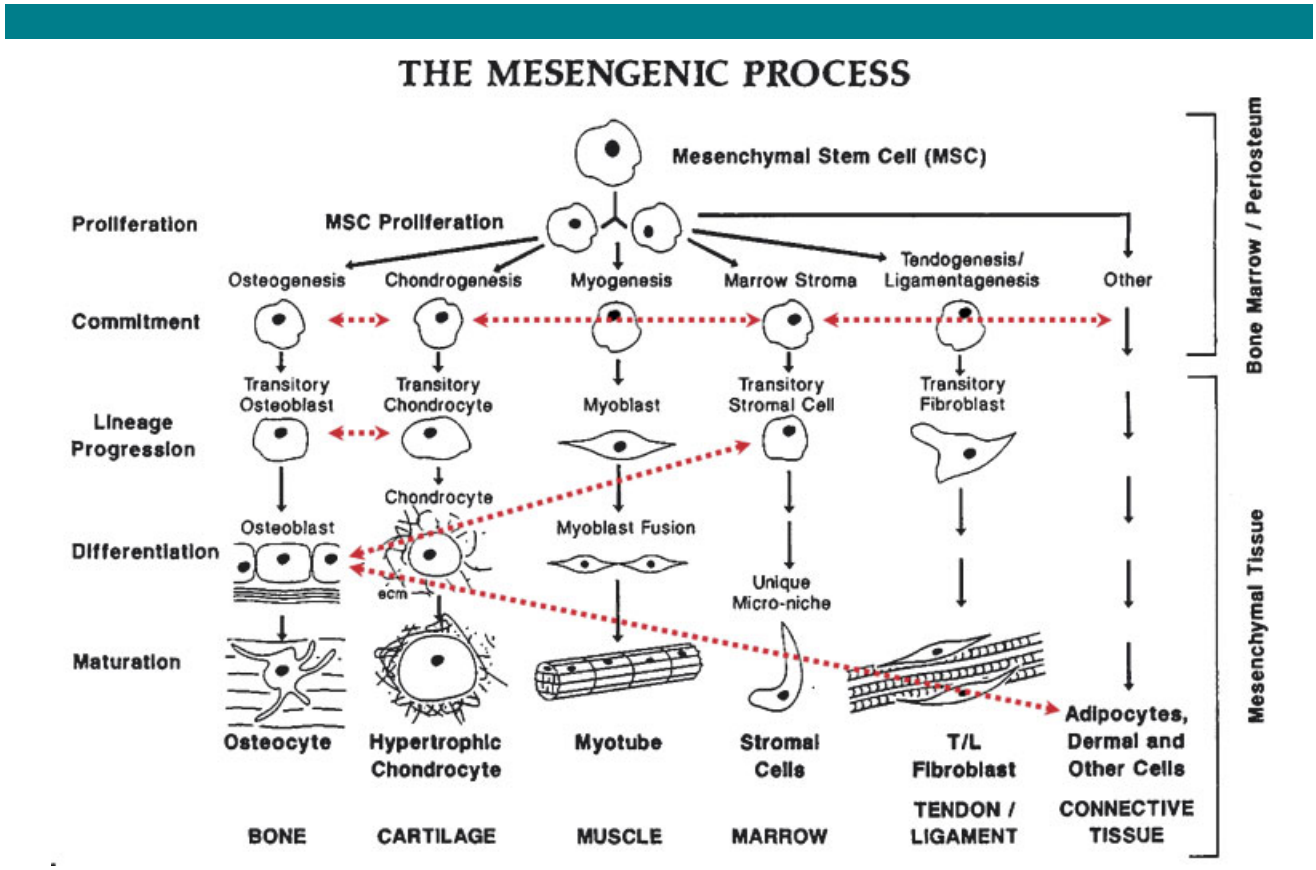


Fig. 4. The Mesengenic Process diagram of Figure 1 is overlaid with horizontal or diagonal arrows (dotted lines) depicting the plasticity of mesenchymal cells and the transdifferentiation of mature phenotypes into wholly different cell types (Caplan, 1989, 1991, 2005). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

pericytes, smooth muscle cells, etc. (Meirelles et al., 2007, personal communication).

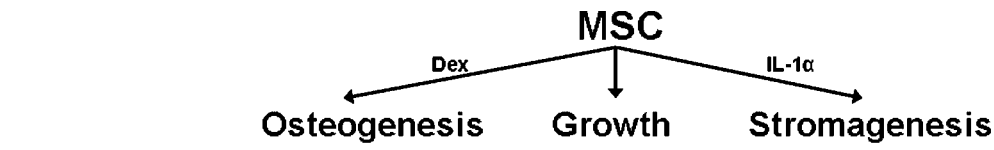
We have recently completed a very preliminary experiment with equine adipose tissue as the source of MSCs (e.g., ADSC) and have correlated the CFU-f from primary isolates of ADSCs supplied to us by Vet-Stem, Incorporated (12120 Tech Center Drive, Suite D, Poway, CA) and a morphometric estimate of vascular density. Fat specimens were obtained from two different locations in two different horses; one horse was athletically fit and the other was unfit. The fat specimens were from a highly vascular site and a relatively poorly vascularized site from both horses. Interestingly, the unfit horse had CFU-f numbers several-fold less than the fit horse, and there was a linear correlation between CFU-f and vascular density in all of the fat samples. We interpret this linear correlation to imply a relationship between vascularity and local MSC titers (Kubis et al., 2006; Meirelles et al., 2006).

Tissue Engineering

Since MSCs can differentiate into distinctive mesenchymal phenotypes, they have been used to reform tissues when encased in tissue-specific scaffolds and implanted into different tissue sites. For example, in rodents, dogs, and humans autologous marrow MSCs have been delivered to long-bone repair sites in calcium phosphate porous ceramics to produce morphologically and biomechanically superior bone (Liebergall et al., 1994; Bruder et al., 1998; Kon et al., 2000). Likewise, we and others have published the use of marrow MSCs in hyaluronan and polymeric scaffolds for cartilage repair (Solchaga et al., 2005). There are at least three different modes that have been employed for using MSCs in scaffolds. MSCs have been loaded into the scaffolds in vitro and, after a short incubation to insure attachment, the cell-scaffold composites were implanted (Dennis et al., 1992, 1998; Ohgushi and Caplan, 1999; Solchaga et al., 2000). Second, the cell-scaffold composite was incubated in differentiation medium to stimulate MSC progression into a specific lineage; after 7–14 days, the composite was implanted into orthotopic sites (Ohgushi et al., 1993, 2005). The last approach is to implant scaffolds to which targeted cells are able to attach to docking sites or to implant scaffolds with the included cells in protective coats and allow the scaffold to mature in vivo (hydrogels; Kirker et al., 2002; Park et al., 2007). All of these techniques have resulted in well integrated, newly differentiated tissue such as bone (Kadiyala et al., 1997). Although these approaches have been described in various animal models and in limited numbers in human (Kon et al., 2000), no human MSC-based tissue engineering technology is currently clinically available.

Trophic Activity of MSCs

We long ago published (Haynesworth et al., 1996) studies of cytokine/growth factor secretion activity of hMSCs in culture as depicted in Figure 5. Human MSCs in Growth, in Osteogenesis (+dex, +ascorbate) or in Stromagenesis (+IL-1α) were analyzed by collecting the culture medium after 24 and 48 h following a fresh medium change, the medium being DMEM, high glucose containing 10% fetal bovine serum from a selected batch (Lennon et al., 1996). Clearly, each column in Figure 5 has a signature profile of bioactive factor secretion as observed with quantitative ELISA kits. The absolute amounts of each



G-CSF	+	+	+++
GM-CSF	O	O	+++
M-CSF	+	+	+++
LIF	-	+	+++
IL-6	-	+	+++
IL-11	-	+	+++
SCF	+	+	+
IL-3	O	O	O
TGFβ2	O	O	O
OSM	O	O	O

Fig. 5. Simplified summary of data on 24-h conditioned medium of MSCs in growth, switched into osteogenesis medium (growth medium plus dexamethasone [Dex] and ascorbate) or stromagenesis (IL-19). Taken from Haynesworth et al. (1996).

bioactive factor varied from donor to donor, but the percent difference between the three conditions (columns in Fig. 5) very tightly grouped. What we missed in this previous study is the fact that hMSCs intrinsically synthesize and secrete very large amounts of these bioactive factors. For emphasis, the human MSCs in growth in 10% fetal bovine serum secrete an array of molecules yet to be characterized. I postulate that these human MSCs in logarithmic growth are comparable to MSCs that arrive at sites of tissue injury or ischemia to assist in the recuperation of that injured tissue. These cells are likely to be initially mitotic, since the acute inflammatory phase of injury is associated with a large array of mitogenic cytokines/growth factors in the injury field, such as PDGF.

Immunoregulation

When the medium conditioned for 24–48 h by MSCs in growth phase was subjected to various immunoassays, such as a mixed lymphocyte assay, strong immunosuppressive effects were noted (Pittinger et al., 1999; Devine et al., 2001; Maitra et al., 2004; Beyth et al., 2005). These immunoregulatory effects strongly inhibit T-cell recognition and expansion by inhibiting TNF-α and INF-γ production and, thus, increasing IL-10 levels as schematically represented in Figure 6. Although all of the immunomodulatory effects of the hMSC-secreted bioactive factors are yet to be described, the data available clearly support the concept that allogeneic MSCs can be used as therapeutic agents. In this regard, Osiris Therapeutics, Inc.* has clinical trials in progress to use allogeneic MSCs to combat graft versus host disease (GVHD) and Crohn's Disease, both involving the strong immunoregulatory capacity of the MSCs.

*I was one of the founders of Osiris, I have a very small amount of stock in Osiris, but have been separated from Osiris since 1997.

Regenerative Microenvironments

The intrinsic secretory activity of MSCs also establishes a regenerative microenvironment at sites of tissue injury or damage. Initially this was tested in the context of cancer therapy by adding culture-expanded human MSCs to bone marrow transplantations with the assumption that the MSCs would home to and rejuvenate the bone marrow stroma of chemotherapy/radiation-treated patients (Lazarus et al., 1995, 2005; Koc et al., 2000). Successful animal and human data for both auto- and allogeneic MSCs have been reported by us (Lazarus et al., 1995) and Osiris (Koc et al., 2000; Lazarus et al., 2005), although the detailed mechanism for how MSCs improve these transplants is not clear. More recently, animal or human MSCs have been used in animal models to affect heart infarct ischemia (Shake et al., 2002), stroke ischemia (Li et al., 2005), meniscus regeneration (Murphy et al., 2003), tendinitis (Harman et al., 2006), and spinal cord interruption (contusion or cuts), (Lange et al., 2005; Keilhoff et al., 2006). The mechanism governing all of these cases seems to be the same: the MSCs secrete bioactive factors that inhibit scarring, inhibit apotosis (narrow or contain the field of injury), stimulate angiogenesis, and stimulate the mitosis of tissue-intrinsic stem or progenitor cells. This complex, multifaceted activity caused by the secretory activity of MSCs is referred to as "trophic activity" as distinctive from the capacity of MSCs to differentiate. The word trophic broadly means nutritional, but was used by developmental neurobiologists to define the enhancing secretions by nerve terminals to end organs that were distinct from the electrical/chemical mediators of axon

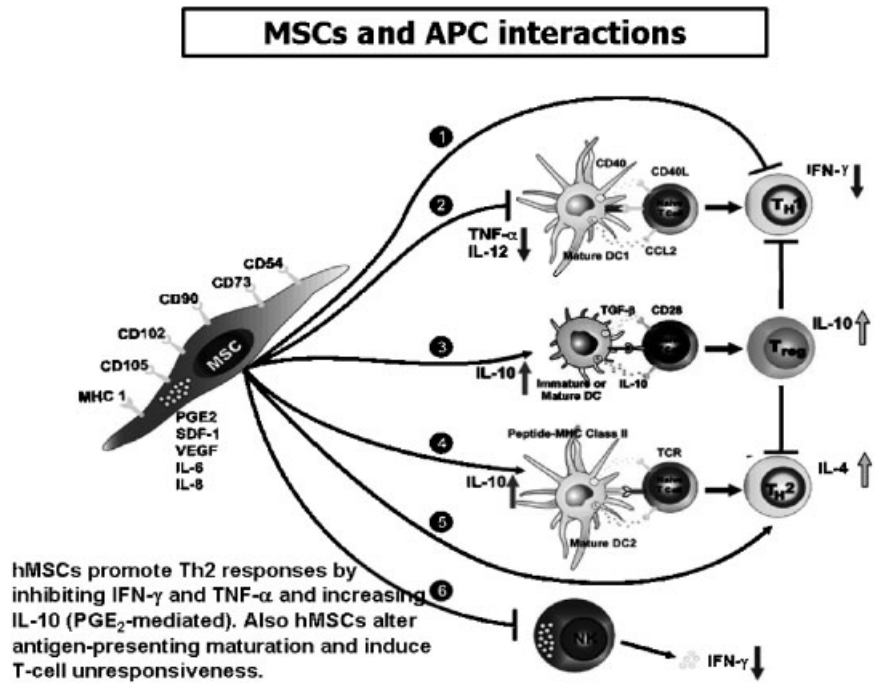


Fig. 6. MSCs are immunoregulatory because they secrete large amounts of bioactive agents as depicted here and in Figure 5. These agents cause the muting or inhibition of T-cell responses to allogeneic cells (Beyth et al., 2005). Figure originally composed by Aggarwal and Pittinger (2005).

conduction. Osiris is currently involved in clinical trials to study the use of allogeneic MSCs for infarct and meniscus regeneration as a clinically relevant management of this trophic capacity of MSCs.

In this regard, we have recently reported (Bai et al., 2007) that the conditioned medium from human MSCs in logarithmic growth not only is immunoregulatory, but also influences neural stem cells in culture to differentiate into oligodendricytes. Furthermore, in mice with a demyelinating disorder induced by treatment with a peptide derived from myelin, intravenous administration of human MSCs (without whole animal immunosuppression) caused a reversal of the observed neurological disorder. Presumably, the xeno-MSCs inhibited their immunorejection and caused local neural progenitor cells to form functional oligodendricytes which remylinated the afflicted neurons. We are currently testing this presumption.

Impressively, Mark Penn and his collaborators (Shake et al., 2002; Askari et al., 2003) have started to provide detailed molecular and cellular characterizations of the mechanisms governing the mobilization, attraction, and functioning of MSCs at heart infarct sites in rodents. They describe the fact that SDF-1 is secreted from the ischemic heart tissue, and this mobilizes and attracts to the tissue damage zones intrinsic marrow MSCs that have CRCX4 receptors. Other molecular mediators of homing have also been implicated in these rodent models (Schenk et al., 2007).

The Future

For the purposes of this review, it seems sufficient to point out that natural chemo-attractive mechanisms can bring MSCs from far and near to sites of tissue damage to establish reparative/regenerative microenvironments. The age of the individual, the extent of tissue damage, and the local and whole body titers of MSCs probably play a role in the rate and extent of the repair and/or regeneration of damaged tissue. Clearly, by direct delivery or manipulative targeting of MSCs to sites of tissue injury, we could profoundly control the extent of damage, cell death, scarring, and subsequent regeneration of various tissues. The mechanisms governing this immunosuppressive and trophic activity is quite distinct from those used in the tissue-engineered replacement of specific mesenchymal tissues. Indeed, one could envision the coupling of both tissue engineering and these trophic activities to massively regenerate tissues and to assist in their seamless integration into the body. Although we have worked with MSCs for more than 20 years, we are only now appreciating their true potential for clinical uses. Clearly, the use of MSCs for tissue engineering versus trophic and immunoregulatory activities requires very different logics. It now seems that these latter activities will be used in the clinics before tissue engineering approaches become practical.

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