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INVITED MEDICAL REVIEW

Unexpected roles for bone marrow stromal cells (or MSCs): a real promise for cellular, but not replacement, therapy

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Adult and embryonic stem cells have drawn a lot of attention in the last decade as new tools in regenerative medicine. A variety of such cells have been discovered and put forward as candidates for use in cell replacement therapy. Investigators hope that some, if not all, of our organs can be replaced or restored to function; that new livers, kidneys, and brain cells can be produced. Many reviews have already been written about stem cells and their potential use in regenerating tissues. In this study, we would like to call attention to a different application of a special group of adult stem cells, the stromal cells in the bone marrow (also called mesenchymal stem cells or MSCs). These cells have been discovered to modulate immune function. They can easily be expanded in culture and surprisingly, they also seem not to be immunogenic. Thus, they can be removed from donors, expanded, stored in freezers, and used as allogeneic transplants in a variety of diseases in everyday medicine.
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Stem cell research started with the realization that bone marrow (BM) contains cells that can replenish and continuously maintain the immune system and blood cells of a compromised recipient. This led to the application of BM transplants in certain diseases and radiation accidents in the early 1950s in Europe. As stem cells could not be isolated at that time, all of the cells in BM aspirates were administered to patients simultaneously (Thomas *et al*, 1957; Urso and Congdon, 1957). In his first report of six cases, Thomas described the results of giving marrow cells from unrelated donors. Although four of the patients died, there were surprisingly few immunological complications. The medical community did not have a deep understanding of human leucocyte antigen (HLA) compatibility at the time, and as a result, many of the early transplants failed. A BM transplant between identical twins guarantees complete HLA compatibility between donor and recipient. These were the first successful transplants in humans. It was not until the 1960s that physicians knew enough about HLA compatibility to perform transplants between siblings who were not identical twins. In 1973, a team of physicians performed the first unrelated BM transplant. Now that stem cells can be isolated from peripheral blood following a treatment that significantly increases the number of circulating HSCs, stem cell transplantation has replaced BM transplantation. Recent trials, however, have renewed the interest in BM transplantation and its possible advantages over stem cell transplants. To understand the difference between purified stem cells mobilized from marrow, and whole BM samples, it was important to characterize the various cells in BM. Friedenstein reported almost 35 years ago that there is a population of fibroblast-like precursor cells among the hematopoietic cells in the marrow. The former cells could be cultured, formed colonies, and could differentiate into bone, cartilage or adipose tissue. An *ex vivo* assay for examining the clonogenic potential of these multipotent stromal cells – named colony-forming unit-fibroblasts (CFU-F) – was described in the 1970s by Friedenstein *et al*, (1976, 1974). Since then a vast amount of data surfaced regarding these cells, but as of today there is still no one marker that can be used to characterize or select them in humans or any other species. To summarize these data, one has to grapple with the following problems:

1. Nomenclature: Friedenstein called these cells CFU-F based on their feature of forming colonies from single cells that originated in the BM. This name did not catch on, and when one attempts to find articles in the literature on the subject, it soon becomes obvious that there is confusion about the nomenclature of stromal stem cells. The cells have been called mesenchymal stem cells (MSCs), but the mesenchyme is an embryonic tissue that gives rise to hematopoietic cells.

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As far as we know today, the fibroblastoid cells do not do this. Bone marrow stromal cell (BMSC) might be a more appropriate name for the unit-fibroblasts, but these cells are defined by their adherence to the plate (as opposed to the non-adherent hematopoietic cells) and are a mixed population of cells (Bianco *et al*, 2006; Keating, 2006; Phinney, 2002, 2007; Phinney and Prockop, 2007). Multipotent stem cells appear to comprise a small fraction of the whole adherent population. For the sake of simplicity, in this review we will use the term MSCs and will only talk about those of BM origin. We would like to mention the fact that cells similar to MSCs have now been found in almost all tissues studied and have also been tested for their immunomodulatory and regenerative properties (Vayssade and Nagel, 2009; Garcia-Castro *et al*, 2008).

2. Culture conditions: After they are harvested from the marrow, MSCs are separated on the basis of their adherence to plastic, and then grown for a variety of passages before they are used. When using mouse BM, one must be very careful first to remove the macrophages. This is not commonly mentioned in published methods, but unless it is performed, effects seen in studies of 'MSCs' *in vitro* can be difficult to interpret. This is usually not a problem with human cells.

Below we try to summarize the actions of MSCs that have convinced us and others that they may have important roles to play as cellular therapeutics.

Classical role of MSCs

Since their discovery, the BM stromal cells (MSCs) were considered the 'wet nurses' of the hematopoietic system: they support proliferation and self-renewal of the hematopoietic cells. This hypothesis was supported by the facts that they 'cradle' the islets of hematopoietic cells in the marrow, and synthesize and secrete growth factors/cytokines that promote hematopoiesis (Maloney and Patt, 1975; Patt and Maloney, 1972). During the last decade, however, MSCs were found to have other actions; in both humans and animals, they appear to modulate the function and character of cells of the immune system. We will briefly summarize the evidence for this below.

Immunomodulatory characteristics of MSCs

Before much was known about the mechanisms responsible for the immunomodulatory effects of MSCs, Le Blanc *et al* (2004) used MSCs successfully to combat graft *vs* host disease. They did this because they had observed that MSCs suppress T cell proliferation (Le Blanc *et al*, 2003). In the last 5 years, a good deal more has been learned about how MSCs affect the functions of a variety of immune cell populations. Because of space limitations, we cannot describe the primary data in detail. Instead, we have tried below to summarize the results and point the reader at good, comprehensive reviews for further details.

MSCs affect T cells

The first population of immune cells shown to be regulated by MSCs was the T cells. Di Nicola *et al* (2002) used human MSCs in mixed lymphocytic reactions and observed a 60–90% reduction in T cell proliferation in the presence of autologous as well as allogeneic MSCs. They suggested that factors secreted by the MSCs act on T cells but do not cause their apoptosis. Bartholomew *et al* (2002) studied skin-graft in baboons. Following MSC treatment, there was an altered immunological response to the grafts and prolonged graft survival due to reduced T cell proliferation. Tse *et al* (2003) reported that MSCs actively suppressed the proliferation of responder peripheral blood mononuclear cells (PBMCs) stimulated by third-party allogeneic PBMCs, and the proliferation of T cells stimulated by anti-CD3 and anti-CD28 antibodies. They stated that these suppressive effects could not be accounted for by the production of interleukin (IL)-10, transforming growth factor-beta1 or prostaglandin E2 by the MSCs, or by depletion of tryptophan from the culture medium.

MSC interactions with B cells

It has been known for some time that B cell differentiation requires the proximity of stromal cells (Kierney and Dorshkind, 1987). In a 2006 study, Corcione *et al* (2006) isolated hMSCs from BM and co-cultured them with B cells purified from the peripheral blood of healthy donors. They found that hMSCs inhibit B cell differentiation as demonstrated by a significant decrease in immunoglobulin (Ig)M, IgG and IgA production. They suggested that soluble factors produced by the MSCs might be responsible for the effect; but this remains to be determined. Similar results were observed when mouse MSCs and B cells were co-cultured. Unknown factor(s) released by MSCs appeared to exert a suppressive effect on B cell terminal differentiation (Tabera *et al*, 2008; Asari *et al*, 2009).

MSC interactions with dendritic cells (DC) and natural killer (NK) cells

Aggarwal and Pittenger (2005) co-cultured hMSCs with purified subpopulations of immune cells and reported that hMSCs altered the cytokine secretion profile of dendritic cells (DCs), naive and effector T cells (T helper 1 [Th1] and Th2), and natural killer (NK) cells, and induced a more anti-inflammatory phenotype. Furthermore, MSCs blocked the differentiation and migration of DCs (Li *et al*, 2008; Jung *et al*, 2007; Jiang *et al*, 2005; English *et al*, 2008) and impaired their ability to present antigens (Ramasamy *et al*, 2007a). Human MSCs also altered NK cytokine secretion and the cytotoxic effects of the cells on HLA-I expressing targets (Sotiropoulou *et al*, 2006).

Testing the effects of MSCs in vivo

When MSCs had been shown to affect the functions of a variety of immune cells, workers in the field began to examine their actions in whole animals. Members of a number of groups studied MSCs in disease models (Table 1) and tried to determine whether the cells could

Table 1 Articles using MSCs in a variety of disease models

Immune system related disorders	
Tumor/cancer	Ramasamy *et al* (2007b); Djouad *et al* (2003); Ame-Thomas *et al* (2007); Khakoo *et al* (2006); Karnoub *et al* (2007)
Diabetes	Madec *et al* (2009); Vija *et al* (2009); Dong *et al* (2008); Chang *et al* (2008); Abdi *et al* (2008)
Rheumatoid arthritis	Inoue *et al* (2007); Augello *et al* (2007); Jones *et al* (2009); Chen and Tuan (2008); Zheng *et al* (2008); van Laar and Tyndall (2006)
Autoimmune encephalitis (EAE)	Zappia *et al* (2005); Gerdoni *et al* (2007); Rafei *et al* (2009); Lu *et al* (2009); Kassis *et al* (2008)
Skin-graft rejection	Aksu *et al* (2008); Sbano *et al* (2008); Bartholomew *et al* (2009)
Peritonitis/sepsis	Ringden *et al* (2007); Nemeth *et al* (2009); Gonzalez-Rey *et al* (2009)
Organ failure related disorders	
Heart	Orlic *et al* (2001); Mirotsou *et al* (2007); Casiraghi *et al* (2008); Psaltis *et al* (2008); Imanishi *et al* (2008)
Lung	Gupta *et al* (2007); Ortiz *et al* (2007); Iyer *et al* (2009); Erokhin *et al* (2008); Zhao *et al* (2008); Iyer and Rojas (2008); Yan *et al* (2007); Kanki-Horimoto *et al* (2006); Ortiz *et al* (2003)
Kidney	Togel *et al* (2005); Humphreys and Bonventre (2008); Crop *et al* (2009); Cavaglieri *et al* (2009); Behr *et al* (2009)
Liver	van Poll *et al* (2008); Parekkadan *et al* (2007a,b); Carvalho *et al* (2008); Abdel Aziz *et al* (2007)

MSC, mesenchymal stem cells

alter the courses of diseases associated with immune dysfunction. Several investigators (Uccelli *et al*, 2008; Nasef *et al*, 2008; Jones and McTaggart, 2008; Sotiropoulou and Papamichail, 2007; Nauta and Fibbe, 2007) have written excellent reviews on this subject. We provide a synopsis of recent experiments below.

Immune system related disorders

Cancer treatment

The discovery of the immunoregulatory effects of MSCs raised the question of their possible effect on tumor growth. There is no clear consensus about the answer to this question. Both inhibition and stimulation of tumor cell proliferation *in vitro* and/or tumor growth *in vivo* by MSCs have been reported. A number of studies have shown that MSCs exhibit potent antiproliferative activity on tumor cells (Ramasamy *et al*., 2007b, Khakoo *et al*, 2006). On the other hand, Ame-Thomas *et al* (2007) found that MSCs recruit primary follicular lymphoma cells and trigger their differentiation into fibroblastic reticular cells, which have a survival advantage. MSCs also increased the metastatic potential of otherwise weakly metastatic breast cancer cells when mixed together before implantation (Karnoub *et al*, 2007). In addition, MSCs stimulated the growth of tumors following subcutaneous injection of B16 melanoma cells in allogeneic recipients (Djouad *et al*, 2003).

Diabetes

As Type I diabetes is an autoimmune disease, using immunosupressive cells (MSCs) to inhibit the progression of the condition was a reasonable idea (see Abdi *et al*, 2008). Injected MSCs were shown to improve diabetes in pigs (Chang *et al*, 2008), as well as in non-obese diabetic mice, where MSCs were demonstrated to induce regulatory T cells to produce IL-10 and to inhibit the migration of autoreactive T cells into the pancreas (Madec *et al*, 2009).

Peritonitis/sepsis

Sepsis is a very complicated and frequently lethal disease with no cure in sight. The greatest medical challenge in sepsis is to inhibit the unbridled innate immune response that damages organs in the first phase of the disorder, without contributing to the immune paralysis that occurs later on. The biphasic character of the disease makes it especially hard to treat. Ringden and his coworkers tested allogeneic MSCs in 10 patients who – following BM transplants – developed severe infections (hemorrhagic cystitis, pneumomediastinum, perforated colon and peritonitis). One person with an antibiotic-resistant infection appeared to have been saved by this therapy (Ringden *et al*, 2007). Subsequently, Nemeth *et al* (2009) have demonstrated the beneficial effect of intravenously injected MSCs using cecal ligation and puncture in a mouse model of peritonitis and sepsis. The authors suggest that secretion of prostaglandin E2 by MSCs reprograms macrophages, decreasing their production of pro-inflammatory cytokines and increasing their production of anti-inflammatory (IL-10) ones. The authors also conclude that a cell-to-cell contact between MSCs and macrophages is necessary for the effect to take place.

Disorders characterized by organ damage and failure

Several organs can develop inflammatory disease, followed by fibrosis. Ultimately, this can cause organ failure and death. If the initial inflammation could be kept under control or the fibrotic changes could be prevented or reversed, patients could have a longer and better life.

Heart

The first report of the use of MSCs to repair heart damage suggested that the cells differentiate into cardiomyocytes (Orlic *et al*, 2001). This conclusion was subsequently debated. Most follow-up studies provided evidence that MSCs have beneficial effects on damaged hearts, but not the conclusion that they give rise to new heart tissue (Psaltis *et al*, 2008).

Imanishi *et al* (2008) found MSC transplantation to be useful following acute myocardial infarctions. Although the MSCs disappeared quickly, they seemed to trigger beneficial effect on the heart by releasing

vascular endothelial growth factor (VEGF). The increase in survival and decrease in the apoptosis of cardiomyocytes after ischemic injury were also suggested to be due to paracrine effects (Mirotsou *et al*, 2007). Finally, following allogeneic heart transplantation in mice, MSCs were found to increase immune tolerance by the expansion of donor-specific regulatory T cells (Casiraghi *et al*, 2008).

Lung

Mesenchymal stem cells were shown to home into the lungs of mice (Ortiz *et al*, 2003) and rats (Zhao *et al*, 2008) that were treated with bleomycin, and to reduce inflammation and collagen deposition there. The authors propose that this effect is mediated by the MSCs, which are a major source of an IL1 receptor antagonist and inhibit macrophage-derived tumour necrosis factor (TNF)α production by macrophages (Ortiz *et al*, 2007). Similar results were observed when an intratracheal administration of endotoxin was followed by MSC administration 4 h later. The MSCs decreased pulmonary edema and increased survival of mice by decreasing pro-inflammatory (TNFα) cytokine production by macrophages and increasing anti-inflammatory (IL-10) cytokine levels in the plasma (Gupta *et al*, 2007). There has been one publication describing the use of autologous MSCs in 27 patients with multi-drug resistant tuberculosis, 16 of them being followed for up to 2 years. After MSC administration, the authors reported a positive clinical outcome in all cases to a varying degree. Bacterial discharge stopped in 20 patients 3–4 months after treatment and the resolution of sustained lung tissue cavities was observed in 11 patients (Erokhin *et al*, 2008). A more comprehensive review of the possible uses of MSCs in lung injury has been published recently (Iyer *et al*, 2009).

Kidney

As kidney failure leading to death is commonly seen in patients with severe infections, improvement of kidney function has been an early target in the MSC field. In an ischemia-reperfusion model of acute kidney injury, intracarotid administration of MSCs significantly improved renal function by reducing the production of pro-inflammatory (IL1b, TNFα, interferon-γ, and inducible nitric oxide) and increasing the production of anti-inflammatory factors (IL-10, bovine fibroblast growth factor, and TGFα) (Togel *et al*, 2005) and VEGF (Togel *et al*, 2008) in the kidney. Subcapsular injection of MSCs in a rat model of kidney injury (partial nephrectomy) had a protective effect and significantly improved kidney function (Cavaglieri *et al*, 2009). In an ovine model of bilateral renal ischemia and reperfusion, sheep were injected autologous MSCs and the authors found no improvement of kidney parenchyma or any difference in cell death or cytokine release (Behr *et al*, 2009).

Liver

Liver damage is another common cause of death in infections or following chronic exposure to toxins. Carbon tetrachloride is generally used to mimic the latter. It induces liver fibrosis. In this model (i.e. Carbon tetrachloride induced fibrosis), intravenous injection of MSCs had a significant antifibrotic effect in rats (Abdel Aziz *et al*, 2007) although not confirmed in one subsequent study (Carvalho *et al*, 2008) and a similar effect together with an improvement of liver function in mice (Sakaida *et al*, 2004). MSCs were later demonstrated to affect the function and IL-6 production of stellate cells, inhibiting collagen synthesis. MSC-produced hepatocyte growth factor improved the survival of hepatocytes by decreasing apoptosis (Parekkadan *et al*, 2007a). Similarly, in D-galactosamine-induced fulminant hepatic failure, MSCs reduced leukocytic infiltrates and hepatocellular death. In this study, MSC-derived conditioned medium was shown to divert adoptively transferred leukocytes from the injured organ, suggesting that a change in leukocyte migration might be the reason for the absence of immune cells in liver tissue following treatment (Parekkadan *et al*, 2007b; van Poll *et al*, 2008). A recent review summarizes the use of MSCs in liver diseases (Dai *et al*, 2009).

Based on all the data we know so far, the MSCs are a unique population of cells that holds great promise in future therapy in many different fields of medicine. MSCs seem to work as biosensors. Depending on cues in their environment, they may be able to direct other immune cells to mount more beneficial responses in situations that are harmful to the host. MSC administration appears to have no deleterious side effects, and the cells may be 'smarter' and more specific in their actions than systemically administered drugs. Their uniqueness is further exemplified by the observation that they can be used without HLA typing – thus promising to be a 'universal donor' in cell therapy. Before we can start using them though, we still need to understand the details of their mechanism of action and the reasons for the contradictory results in the literature. If their promise holds, the use of adult stem cells could open an exciting new chapter in the history of medicine and many future patients will greatly benefit from their use.

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