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Mesenchymal Stem Cells as Therapeutics and Vehicles for Gene and Drug Delivery

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Abstract

Mesenchymal stem cells (MSCs) possess a set of several fairly unique properties which make them ideally suited both for cellular therapies/regenerative medicine, and as vehicles for gene and drug delivery. These include: 1) relative ease of isolation; 2) the ability to differentiate into a wide variety of seemingly functional cell types of both mesenchymal and non-mesenchymal origin; 3) the ability to be extensively expanded in culture without a loss of differentiative capacity; 4) they are not only hypoimmunogenic, but they produce immunosuppression upon transplantation; 5) their pronounced anti-inflammatory properties; and 6) their ability to home to damaged tissues, tumors, and metastases following in vivo administration. In this review, we summarize the latest research in the use of mesenchymal stem cells in regenerative medicine, as immunomodulatory/anti-inflammatory agents, and as vehicles for transferring both therapeutic genes in genetic disease and genes designed to destroy malignant cells.

Isolation and Characterization of MSC

In pioneering studies [1,2] performed over 30 years ago, Friedenstein demonstrated that fibroblastoid cells obtained from the bone marrow were capable of transferring the hematopoietic microenvironment to ectopic sites, thus establishing the concept that the marrow microenvironment resided within the so-called stromal cells of the marrow. Years later, scientists began to explore the full potential of these microenvironmental cells, and results of these studies led to the realization that this population harbored cells with properties of true stem cells. These cells were officially termed mesenchymal stem cells (MSC) [3]. MSC are now known to make up a key part of the stromal microenvironment that supports the hematopoietic stem cell and drives the process of hematopoiesis. Despite their essential role within the bone marrow, MSC only comprise roughly 0.001–0.01% of cells within the marrow [4]. The most straightforward method for obtaining MSC is to simply rely on MSC's plastic adherence and their ability to be passaged with trypsin to obtain a relatively morphologically homogeneous population of fibroblastic cells from a bulk mononuclear cell preparation within only two to three passages in culture [5–7]. While this method is certainly straightforward, true MSC account for only a small percentage of this highly heterogeneous population, making results obtained with cells prepared in this fashion difficult to interpret. To avoid this problem, numerous groups have worked to identify antigens that are unique to MSC. While there are currently no markers that

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specifically identify MSC, several markers have proven useful for obtaining highly enriched MSC populations. The first of these markers to be identified was Stro-1, an antibody that reacts with non-hematopoietic bone marrow stromal precursor cells [8]. Although the antigen recognized by this antibody has not yet been identified, we and others have found that by tri-labeling bone marrow cells with Stro-1, anti-CD45, and anti-GlyA, and selecting the Stro-1+CD45-GlyA- cells, it is possible to consistently obtain a homogeneous population that is highly enriched for MSC [9–15]. In addition to Stro-1, Table 1 provides a summary of some of the markers and characteristics which have been used to isolate MSC to date. As can be seen, human MSC do not express markers which have been associated with other stem cell populations (like hematopoietic stem cells) such as CD34, CD133, or c-kit. However, antibodies such as SB-10, SH2, SH3, and SH4 have been developed over the years and numerous surface antigens such CD13, CD29, CD44, CD63, CD73, CD90, CD166 have been used to attempt to isolate MSC [16–18]. Unfortunately, all of these antigens appear to be expressed on a wide range of cell types within the body in addition to MSC. This lack of a unique marker suggests that to obtain a pure population of MSC that are functionally homogeneous, investigators will likely either have to await the development of novel antibodies that recognize as yet unidentified antigens that are unique to primitive MSC, or employ strategies in which multiple antibodies are combined to allow for positive selection of MSC and depletion of cells of other lineages that share expression of the antigens recognized by the MSC antibody in question, as we have done with Stro-1, CD45, and GlyA.

Sources of MSC

Although much of the work to date has focused on MSC isolated from adult bone marrow, it is important to realize that cells that appear phenotypically and functionally to be MSC have now been isolated by our group and others from numerous tissues, including brain, liver, lung, fetal blood, umbilical cord blood, kidney, and even liposuction material [19–26]. The broad distribution of MSC throughout the body leads one to postulate that MSC are likely to play a critical role in organ homeostasis, perhaps providing supportive factors like in the bone marrow, and/or mediating maintenance/repair within their respective tissue. Importantly, although MSC from each of these tissues appear similar with respect to phenotype and overall differentiative potential, studies at the RNA and protein level have now revealed that subtle differences exist between MSC from these various tissues, with MSC from each tissue possessing a molecular fingerprint indicative of their tissue of origin [21,22,27–31]. Using a noninjury fetal sheep transplantation model, we showed that these differences result in a bias for human MSC to home to and give rise to cells of their tissue of origin in vivo [32,33]. This suggests that the ideal source of MSC may differ depending on the specific disease to be treated and the desired target organ.

Despite the apparent presence of MSC within many of the major organs of the body, the relatively non-invasive fashion with which adipose tissue or bone marrow can be obtained, and the fact that both these tissues could readily be obtained from each patient to be treated, combine to suggest that these two tissues will likely be the predominant source of MSC employed in clinical applications in the foreseeable future. However, additional in vitro and in vivo experiments will likely have to be performed to rigorously assess the inherent safety of adipose tissue-derived MSC before these cells will see widespread clinical use, since at least one recent study has suggested that they may be inherently less genetically stable than MSC isolated from bone marrow [34]. Indeed, two other studies showed that, upon prolonged in vitro expansion, adipose tissue-derived MSC can exhibit aneuploidy [35,36] and have now been shown to undergo transformation [37,38], raising the possibility that these cells could prove tumorigenic when used in vivo. In stark contrast, however, are results of a recent study investigating the inherent safety of adipose-derived MSC. This new

study has now shown that, even if genomic instability is intentionally induced with genotoxic agents, adipose tissue-derived MSC respond to this insult by undergoing terminal adipogenic differentiation rather than transformation [39]. While the reasons for the conflicting nature of the results from these different studies are not currently known, one can speculate that differing methods employed for isolating and culturing MSC, differing levels of contaminating non-MSC cells in the cultures, as well as the duration of the culture (i.e., the number of times the cells have been passaged) are likely to be contributing factors. Bearing this possible instability in mind, at this point it seems prudent, regardless of the source of MSC, to only make clinical use of cells that have been passaged fewer than 25 times in culture [40].

MSC in Regenerative Medicine

The in vitro and in vivo differentiation of MSC into the various mesenchymal cell types found within the bone marrow, i.e. bone, cartilage, and fat, has now been described by numerous laboratories, and the conditions to bring about each of these differentiative pathways have been delineated in detail [7]. Recent studies employing microarrays [30,41–43] have now begun to shed light on the molecular mechanisms responsible for commitment to and progression along each of these lineages, providing investigators with information that is vital for developing more efficient means of differentiating MSC along specific desired pathways. These studies have also begun to reveal some of the genes and signaling pathways that are important for maintaining MSC in an undifferentiated state, helping to better define this somewhat elusive stem cell population. Promising results from preclinical studies examining the use of MSC for bone and cartilage repair [44,45] quickly led to clinical trials using MSC to treat large bone defects [46], articular cartilage defects [47], and osteogenesis imperfecta [48–51], and these trials have thus far confirmed the exciting results from animal studies, highlighting the therapeutic potential of MSC.

Although the ability of MSC to produce cartilage and bone quickly established MSC as a promising therapeutic modality to treat a wide range of injuries and diseases of the skeletal system, further study into MSC biology revealed that these cells have far broader differentiative capabilities than was initially anticipated. For example, MSC also have the ability to generate what appear to be functional skeletal muscle cells in vitro [52] and in vivo [53,54], raising the possibility that MSC could one day be used to treat diseases like Duchenne Muscular Dystrophy [54]. Following the demonstration that MSC could give rise to all cells of the musculoskeletal system subsequent studies showed, quite remarkably, that MSC had the ability to give rise not only to cells of mesenchymal derivation, but in fact, to cells of all three germinal layers. The first of the studies to demonstrate that MSC had the ability to cross developmental boundaries and reprogram to differentiate into cells of another germ layer convincingly demonstrated that MSC could give rise to both neural and glial (ectoderm) cell types in vitro and in vivo [55–58]. These findings raised the exciting possibility that MSC could serve as a readily available source of cells for treating injuries or degenerative conditions within the central nervous system; clinical situations for which there are currently very limited, if any, options, other than simply masking the symptoms or slowing disease progression. Indeed, numerous in vivo transplantation studies have now confirmed these exciting in vitro results by showing that MSC have the ability to mediate repair following spinal cord injury [59–61], ischemic injury and stroke [62–72], demyelinating conditions [73–77], experimentally induced Parkinson's disease [78–80] and potentially treat a host of other injuries and degenerative diseases of the CNS [81–84]. Although questions have been raised as to the mechanism by which this apparent “trans-differentiation” occurs [85], the demonstration by numerous groups that MSC can indeed give rise to neural cells in various stages of differentiation and mediate functional improvement for a variety of injuries/diseases within the CNS provides the impetus for

further studies attempting to increase the efficiency and predictability of this process and harness this potential for therapy.

Having now established that MSC were able to interconvert from cells of one germinal layer to those of another, numerous groups began rapidly testing the ability of MSC to differentiate into yet other tissue-specific cell types. Studies were published showing that MSC could give rise in vitro to cells which appear, phenotypically and morphologically, and behave like cardiomyocytes [86–88] and to endothelium [89], engraft within the injured myocardium [90–106], and form Purkinje fibers in vivo [9,15,107]. These preclinical studies generated a tremendous amount of excitement in the field of regenerative medicine, since they strongly suggested that MSC could be used as therapy to mediate cardiac repair post-infarct, diseases within the conduction pathways of the heart, or even, perhaps, to treat chronic progressive cardiac diseases such as congestive heart failure [91,101,108–110]. These exciting results, coupled with preclinical animal studies showing functional cardiac improvement following MSC infusion (discussed in detail in the later section entitled “MSC as Trophic Factories”), were the driving force for launching several clinical trials to investigate whether MSC are able to mediate repair in the post-infarct heart [97,111–116].

As a last major example of MSC in regenerative medicine, we will address their use in liver repair. Liver failure is a life-threatening condition for which the only curative treatment is whole or partial organ transplantation. Given the crippling shortage of donor livers available for transplant and the high mortality and morbidity associated with the need for lifelong immunosuppression following liver transplantation, a major focus of regenerative medicine over the past several years has been to identify cells which could be used to repopulate and/or repair the damaged, failing liver. We and others have devoted a great deal of energy to demonstrating the ability of MSC from various sources to serve as therapeutics for liver disease [11,13,14,33,117–143]. It is now clear that, not only do MSC have the ability to generate, in vitro and in vivo, cells which are indistinguishable from native hepatocytes, but transplantation of MSC in a range of model systems can result in fairly robust formation of hepatocytes which repair a variety of inborn genetic defects, toxin-induced injuries, and even fibrosis. This wealth of supportive data in several different species has led to the utilization of MSC for liver disease in 3 clinical trials thus far [144–146]. While the patient numbers were low and the approaches employed were not curative, the patients’ clinical parameters have shown a trend of improvement, supporting further studies into the use of MSC in this context.

MSC as Trophic “Factories”

One issue which has complicated interpretation of the data generated from the aforementioned studies in liver as well as those conducted looking at the potential of MSC to mediate repair in the heart and other organ systems, is the fact that a therapeutic benefit is often observed in the absence of any evidence of sustained engraftment of the transplanted MSC within the damaged organ. Instead, it appears that the transplantation of MSC somehow stimulates the damaged host organ to repair itself without the donor cells actually having to persist long-term within the recipient. These findings initially led to a great deal of debate as to whether MSC can actually generate many of the cell types they appeared to produce in vivo or if, perhaps, all the effects they produce are simply mediated through release of soluble factors.

A variety of evidence from animal studies has now indicated that both MSC’s direct differentiation and their indirect effects through secretion of factors which stimulate the regeneration of endogenous cells are likely to play important roles in promoting tissue recovery [126,147–164]. A diagrammatic summary of these findings appears in Figure 1.

For example, studies have now shown that MSC protein extracts or conditioned medium collected from MSC cultures [153,154,162] can produce many of the same beneficial effects of MSC on the post-infarct heart and in the damaged/diseased liver [148,165]. Moreover, studies from other groups have now shown that MSC release paracrine factors which protect cardiomyocytes from apoptosis in a mitochondrial-dependent fashion [163]. Furthermore, MSC were recently shown to produce and release insulin-like growth factor I (IGF-I), which can then act upon neonatal cardiomyocytes to induce upregulation of c-kit and re-entry of these cells into cell cycle [164]. MSC further activated expression of hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), and insulin-like growth factor II (IGF-II) within the myocardium [161]. Further complicating matters, however, are other studies which have provided evidence that many of the beneficial effects of MSC on the injured heart may have little to do with the repair/regeneration of the damaged myocardium, but with the ability of MSC to promote angiogenesis [155]. Other studies have now provided clues as to how MSC may mediate this effect. MSC appear to secrete VEGF and basic fibroblast growth factor (bFGF) upon contacting the injured myocardium, which stimulates the formation of new vessels and increases capillary density to increase/restore blood flow to the infarcted region [158]. Recent evidence now suggests that many of these paracrine actions of MSC are mediated by their release of small 50–100nm exosomes [157], which contain not only potentially beneficial proteins, but also pre-microRNA's [152], the function of which still remains to be determined. It would thus seem that MSC may mediate therapeutic benefit not only by engrafting within the damaged tissue and producing tissue-specific cells to correct for the existing deficit, but also by acting as a sort of protein factory, churning out factors which act upon the endogenous cells within the damaged myocardium and encourage the injured heart to assume the task of mediating its own repair.

In addition to these paracrine and trophic activities, in the case of both the liver and the heart, it would seem that MSC have additional properties which help to not only reduce existing damage, but promote the healing process. In the case of the liver, recent studies have shown that MSC have the ability to enhance fibrous matrix degradation, likely through the induction of matrix metalloproteinases (MMP's), suggesting that MSC may be ideally suited for treatment of liver diseases involving fibrosis [130,131,138,142,166–169]. Likewise, in the heart, MSC release paracrine factors which attenuate fibroblast proliferation and inhibit collagen synthesis/deposition [159], apparently by stimulating cardiac fibroblasts to secrete MMP's 2 and 9 and express membrane type I MMP on their surface. These results in these two organ systems are very exciting, because they imply that MSC could potentially mediate beneficial effects even at more advanced stages of disease, once fibrosis had set in. The ability to apply therapy at later points in the disease would enable much larger numbers of patients to benefit from this treatment. However, these results must be interpreted carefully and with tempered enthusiasm, because other studies have suggested that under different conditions, transplanted MSC may actually contribute to the myofibroblast pool and thus enhance the fibrotic process, at least within the liver [128,169–173]. This has led to the current feeling within the field that the effect of MSC will probably vary with the nature of the injury/disease that is being treated, the specific experimental model in which the therapy is being tested, and perhaps even the time frame of MSC application, such that MSC could be beneficial if administered at certain stages of disease progression and harmful if administered at other stages.

MSC as Vehicles for Delivering Therapeutic Genes

While MSC possess tremendous therapeutic potential by virtue of their ability to lodge/engraft within multiple tissues in the body and both give rise to tissue-specific cells and release trophic factors that trigger the tissue's own endogenous repair pathways, gene therapists have realized that these properties are just the beginning of the therapeutic

applications for MSC [24,174,175]. By using gene therapy to engineer MSC to either augment their own natural production of specific desired proteins or to enable them to express proteins outside of their native repertoire, it is possible to greatly broaden the spectrum of diseases for which MSC could provide therapeutic benefit. Unlike hematopoietic stem cells which are notoriously difficult to modify with most viral vectors while preserving their in vivo potential, MSC can be readily transduced with all of the major clinically prevalent viral vector systems including those based upon adenovirus [176–178], the murine retroviruses [178–182], lentiviruses [183–188], and AAV [189,190], and efficiently produce a wide range of cytoplasmic, membrane-bound, and secreted protein products. This ease of transduction coupled with the ability to subsequently select and expand only the gene-modified cells in vitro to generate adequate numbers for transplantation combine to make MSC one of the most promising stem cell populations for use in gene therapy studies and trials.

To date, the majority of studies using gene-modified MSC have been undertaken with the purpose of enhancing the natural abilities of MSC to mediate repair within various tissues. Using the heart as an example, once investigators discovered the identity of some of the key trophic factors responsible for MSC's beneficial effect on the injured myocardium, they undertook studies using MSC engineered to overexpress a number of these factors [93,183,191–196]. As anticipated, the “gene-enhanced” MSC were substantially more effective than their unmodified counterparts. Studies of this nature have not been limited to the heart. On the contrary, similar studies have also been performed to repair the damaged CNS using MSC engineered to produce neurotrophic factors [64,69,70,197–199], and to repair the injured liver using MSC expressing proteins involved in hepatocyte differentiation and/or proliferation [132,200]. In each case thus far, MSC engineered to express higher levels of proteins known to be beneficial for the tissue in question have produced even better results than unmodified MSC.

Despite the many advantages of using MSC as gene delivery vehicles, few studies have thus far explored this potential for the treatment of genetic diseases. One disease for which MSC are being actively pursued for delivery of a therapeutic gene is hemophilia A. Both hemophilia A and B are rather unique among the genetic diseases because expression of the missing coagulation factor (FVIII or FIX, respectively) does not need to be expressed in either a cell- or tissue-specific fashion to mediate correction. Although the liver is thought to be the primary natural site of synthesis of FVIII and FIX, expression of these factors in other tissues exerts no deleterious effects. As long as the proteins are expressed in cells which have ready access to the circulation, they can be secreted into the bloodstream and exert their appropriate clotting activity. The hemophilias are also unique in that very low levels of gene correction/expression are actually required to exert a pronounced therapeutic benefit. To convert a patient from a severe, life-threatening phenotype to a moderate phenotype and thus greatly improve their quality of life, levels of FVIII or IX of only 2–3% of normal are required. From the standpoint of feasibility, studies have already shown that MSC can be transduced with FVIII-expressing viral vectors and secrete high levels of FVIII protein. Importantly, FVIII purified from the conditioned medium of the transduced MSC was proven to have a specific activity, relative electrophoretic mobility, and proteolytic activation pattern that was virtually identical to that of FVIII produced by other commercial cell lines [201]. Given the widespread distribution and engraftment of MSC following their systemic infusion and their ability to efficiently process and secrete high amounts of biologically active FVIII, they are, not surprisingly, being viewed as ideal vehicles for delivering a FVIII transgene throughout the body and thus providing long-term/permanent correction of hemophilia A [201–203]. Extrapolating the work thus far on using MSC to deliver therapeutic genes for the hemophilias, and combining this with the large amount of evidence we have summarized herein demonstrating the abilities of MSC to give rise to cells

of numerous tissue types from all three germinal layers, one can envision MSC soon being used as vehicles to deliver gene therapy vectors to numerous tissues in the body, thus promising to provide a permanent cure for a diverse range of diseases.

Use of MSC as Immunomodulatory/Anti-Inflammatory Agents

In addition to their broad differentiative capabilities and their potential utility as gene delivery vehicles, MSC represent a rather unique cell from an immunological standpoint, since MSC are known to be relatively hypoimmunogenic. They do not normally express MHC class II or the co-stimulatory molecules CD80 and CD82, unless they are stimulated with IFN- γ . As such, they do not seem to serve as very good targets for lysis by cytotoxic T cells or NK cells, and do not really stimulate the proliferation of allogeneic lymphocytes when used as stimulators in a traditional mixed lymphocyte reaction. Given these properties, it is perhaps not surprising that a large body of evidence is now accumulating that MSC can be readily transplanted across allogeneic barriers without eliciting an immune response [204,205]. Thus, if one wished to use MSC to treat an inherited genetic defect within a given tissue, MSC from an unrelated donor could be used for transplantation, greatly increasing the feasibility of using these stem cells for therapy. Perhaps even more important from the standpoint of their potential use as therapeutics, more recent studies have provided evidence that MSC are not only relatively non-immunogenic, but they also appear to have the ability to exert both immunosuppressive and anti-inflammatory properties both in vitro and in vivo. These properties appear to result from MSC's ability to intervene, at multiple levels, with the generation and propagation of an immune response. To name just a few examples, MSC have been demonstrated to interfere with the generation and maturation of cytotoxic T cells and helper T cells [206–215], dendritic cells (and thus antigen presentation) [216–219], and B cells [220], effectively crippling each arm of the adaptive immune system. In addition to actively shutting down the generation of immune effector cells, MSC also appear to indirectly suppress the generation of an immune response by inducing the formation of potent Tregs, although the mechanism by which this comes about is still the subject of active research [40,221–223]. MSC are also known to express an arsenal of factors [40] such as transforming growth factor- β 1 [210,211], prostaglandin-E2 [221], nitric oxide [224], IL-10 [209,225], HLA-G [226], hepatocyte growth factor [210], and, following stimulation with IFN- γ , indoleamine 2,3-dioxygenase [227,228]. The combined effects of these various factors serve to reduce local inflammation, blunt immune response, and counteract the chemotactic signals released to recruit immune cells to the site of injury/inflammation. Scientists and clinicians have already begun exploring whether it is possible to exploit these properties and use MSC as an adjunct in HSC or solid tissue transplantation to prevent GVHD or graft rejection in the event that the cells/tissue to be transplanted are not ideally matched [40,229–232]. Proof of this principle has come from recent clinical trials in which it was demonstrated that co-transplanting MSC with the HSC graft led to a significant reduction in both acute and chronic GVHD [233–236]. Collectively considering all of these immunomodulatory properties, MSC can be viewed as one of the few universal donor cell types that could likely be transplanted to treat numerous injuries/diseases without the necessity of exquisite HLA-matching between the donor and the recipient. Moreover, their use appears to promote the acceptance and survival of mismatched cells and tissues following transplantation, further extending their therapeutic utility.

In addition to their numerous differentiative, trophic, and immunomodulatory properties, a large number of preclinical animal studies examining the potential of MSC isolated from adult tissues have also highlighted another interesting and clinically valuable characteristic of MSC; their ability to selectively navigate to sites of injury and/or inflammation within the body. Once reaching these specific sites, the MSC then mediate repair both by engrafting and generating tissue-specific cells within the injured tissue (but contributing very little if at

all to other tissues that are functionally normal [94–96]), and by releasing trophic factors that blunt the inflammatory response and often promote healing by activating the tissue's own endogenous repair mechanisms. While the mechanisms responsible for this trafficking to sites of injury are currently not well understood, this observation has raised the exciting prospect of using MSC to treat a wide array of diseases in which inflammation plays a key role such as stroke [62–72], rheumatoid arthritis [237], asthma [238–240] and allergic rhinitis [241], and both acute and chronic lung injury [242]. Recently, these valuable anti-inflammatory properties at sites of injury have been explored as a possible adjunct or first line treatment for muscular dystrophy [54], since the constant damage to weakened muscle fibers creates a hostile environment which frequently induced apoptosis of transplanted muscle progenitors or stem cells, precluding their ability to repair the damaged muscle. It is hoped that transplanting MSC systemically will allow their migration to sites of active muscle degeneration, thereby rendering the local microenvironment more receptive to cells transplanted to regenerate the defective muscle fibers. Studies exploring this possible use of MSC are still relatively early in development, so the true clinical utility of this approach will not likely be defined for some time.

Based on the widespread distribution of MSC and their demonstrated ability to mediate repair in a wide range of injuries/diseases, it is intriguing to speculate that MSC may in fact represent a latent pool of pluripotent stem cells, distributed ubiquitously throughout the body [10], potentially capable of migrating to sites of injury/inflammation and generating tissue-specific cells and/or releasing trophic/immunomodulatory factors to repair the damage in question. The issue that needs to be resolved to tap this reservoir of potentially therapeutic cells is the delineation of methods for mobilizing the MSC from their places of residence into the circulation, from which they could theoretically traffic wherever they were needed. Such methods could one day allow the patient's own MSC to repair the injury, obviating the need for transplantation.

MSC as Anti-Cancer Agents

Cancer represents another condition in which there is a selective need for new cells created by the forming tumor. Studies over the last several years have now revealed that MSC have the ability to “sense” this need, migrate to the forming tumor following intravenous administration, and contribute to the newly forming tumor “stroma”. While this may not seem ideal, since the MSC could, in fact, provide support to the growing tumor, this property has now been realized to present a very powerful and unique means of selectively delivering anti-cancer gene products to tumor cells in vivo [243,244]. Three of the gene products which have thus far received the most attention are IL-2 [245,246], IFN- β [243,244], and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [247–250]. Unfortunately, the utility of these and many other biological agents that could be used for cancer therapy is often limited by both their short half-life in vivo and their pronounced toxicity due to effects on normal, non-malignant cells within the body. Using MSC to deliver these therapeutics promises to solve both of these problems, since the MSC can selectively migrate to the tumor site and release their therapeutic payload locally. This greatly increases the agent's concentration within the tumor and significantly lowers its systemic toxicity. In addition, by genetically modifying the MSC with viral vectors, the engrafted MSC will steadily release the therapeutic agent, allowing a single administration to result in long-lasting effects. Other studies have now provided evidence that MSC have the ability to not only selectively home to solid tumors [243,244,247], but also to actively seek out metastases at sites far removed from the primary site of the tumor [244,248,250,251]. This ability has recently been proven to be of great therapeutic value in the treatment of lung metastases arising from both breast cancer and melanoma in a murine xenograft model [244]. Given the difficulty and frequent lack of success using traditional

approaches such as surgery, radiotherapy, and chemotherapeutic agents to treat tumors which are either highly invasive or prone to metastasis, this property of MSC will likely prove to be of great clinical value in the near future. One form of cancer for which the use of MSC is receiving a great deal of attention is glioblastoma multiforme (GBM). GBM represents the most common form of malignant glioma. Despite decades of research and many advances in the treatment of this disease with conventional surgery, radiotherapy, and chemotherapy, there is no cure, and the current prognosis is dismal, with a median survival of only 6–18 months. The failure of current therapies to cure this disease arises predominantly from the highly invasive nature of this cancer and the inability of these agents to effectively target tumor cells which have disseminated into the normal parenchyma of the brain, at sites distant from the main tumor mass. Given the ability of MSC to home to tumors and their ability to track to metastases, a number of studies have been performed evaluating the ability of gene-modified MSC to treat GBM. These studies have now shown that MSC migrate through the normal brain parenchyma towards gliomas [246,249,250,252] and to track microscopic tumor deposits and individual tumor cells which have infiltrated the normal brain parenchyma [246,249–252]. While these migratory properties are certainly interesting, even more exciting are the dramatic therapeutic benefits these same studies have shown, with reduction in tumor size, and pronounced improvements in survival. It is important to note that these studies used MSC as the sole therapy, and definite benefits were observed. In the clinical setting, the current plan is to use gene-modified MSC as an adjunct after surgical resection. In this scenario, the majority of the tumor mass would be surgically removed, and the MSC would then be transplanted to remove the residual malignant cells at the site of the tumor and to hunt down any invasive tumor cells that have migrated away from the site of the primary tumor. In this context, one would imagine that the therapeutic benefit of the MSC will likely be even more pronounced, since their anti-tumor effects could be focused only on the small number of residual tumor cells that evaded removal during surgery. Thus, the remarkable success seen in studies aimed at treating GBM, one of the most devastating forms of cancer, highlight the tremendous potential MSC harbor as gene delivery vehicles for the treatment of many forms of cancer for which current therapeutic strategies are ineffective.

Conclusions

With numerous investigators around the globe having established and verified that MSC harbor the ability to cross embryonic germ layers and give rise to a wide range of what developmental biology had taught were tissue-specific cells, it is now clear that the differentiative capacity of MSC is far broader than anyone would have foreseen at the time Friedenstein originally described his bone marrow-derived CFU-F. In addition to this tremendous differentiative potential, the relative ease with which MSC can be isolated, propagated in culture, and modified with a variety of viral-based vectors, and their intrinsic ability to seek out sites of injury/inflammation within the body argues that MSC may be ideally suited as cellular therapeutics and gene delivery vehicles for numerous diseases/injuries affecting each of the major organ systems of the body. Figure 2 provides a diagrammatic summary of some of the key properties of MSC which make them one of the ideal cell types for use as therapeutics and vehicles for gene and drug delivery.

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- Direct contribution to hepatocyte pool through cellular reprogramming
- Reduction in hepatocyte apoptosis.
- Divert immune cells from sites of injury, reducing inflammation.
- Produce MMP's which enhance fibrous matrix degradation.
- Stimulate endogenous expression of factors which promote hepatocyte proliferation.
- Secrete angiogenic factors which increase/restore blood flow to sites of injury/fibrosis.
- Can be engineered to deliver proteins involved in hepatocyte differentiation and/or proliferation

- Release of paracrine factors which protect cardiomyocytes from apoptosis, attenuate fibroblast proliferation, and inhibit collagen synthesis/ deposition.
- Release of IGF-I, inducing re-entry of cardiomyocytes into cell cycle.
- Activation of endogenous expression of HGF, VEGF, and IGF-II within the myocardium.
- Secretion of VEGF and bFGF, stimulating the formation of new vessels which increases/restores blood flow to infarcted region.
- Release of small exosomes with proteins and/or pre-microRNA's which mediate paracrine actions.

Figure 1.
MSC as Trophic Factories

Figure 2.
Overview of Key Properties of MSC

Table 1

Properties/Markers for Isolating/Identifying MSC

	<u>Exhibited/Expressed by MSC</u>
Plastic Adherence	Yes
Passagable with trypsin	Yes
Stro-1	Yes
form CFU-F colonies	Yes
SB-10	Yes
SH2	Yes
SH3	Yes
SH4	Yes
CD13	Yes
CD29	Yes
CD44	Yes
CD63	Yes
CD73	Yes
CD90	Yes
CD166	Yes
CD45	No
Gly-A	No
CD34	No
CD133	No
c-kit	No