Cell Stem Cell
Perspective

The MSC: An Injury Drugstore

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Now that mesenchymal stem cells (MSCs) have been shown to be perivascular in vivo, the existing traditional view that focuses on the multipotent differentiation capacity of these cells should be expanded to include their equally interesting role as cellular modulators that brings them into a broader therapeutic scenario. We discuss existing evidence that leads us to propose that during local injury, MSCs are released from their perivascular location, become activated, and establish a regenerative microenvironment by secreting bioactive molecules and regulating the local immune response. These trophic and immunomodulatory activities suggest that MSCs may serve as site-regulated "drugstores" in vivo.

The Mesenchymal Stem Cell

In embryonic development, the mesodermal layer harbors multipotent progenitors that give rise to bone, cartilage, muscle, and other mesenchymal tissues. Based on this embryonic perspective and previous reports from our group and others, a hypothetical and comprehensive scheme, pictured in Figure 1, proposed that in adult bone marrow (BM), a population of mesenchymal stem cells (MSCs) could likewise give rise to a spectrum of mesenchymal tissues by differentiating along separate and distinct lineage pathways (Caplan, 1991). In the early iterations of this model, cells from the marrow were the main focus because orthopedic surgeons had long ago established that cells from this tissue could be used to stimulate bone formation and repair, and because it had been demonstrated that osteoprogenitor cells originated from BM (Friedenstein et al., 1966, 1987; Tavassoli and Crosby, 1968; Owen and Friedenstein, 1988). Using this same logic, we and then others successfully isolated and culture expanded MSCs from adult human BM and documented the multipotency for mesenchymal differentiation by these heterogeneous cell populations and by clones of these cells as predicted in the model pictured in Figure 1. This finding encouraged us and others to explore the use of MSCs as progenitors for use in tissue engineering to replace or repair damaged tissues of mesenchymal origin.

What we lost with this isolated focus on multipotency and tissue engineering was the question of what MSCs naturally do in BM and other tissues, and what intrinsic physiological roles these populations may play in vivo, beyond how their functional traits might be harnessed in response to artificial cues or settings. Indeed, it was recognized that MSCs can support hematopoiesis in culture, and this finding focused our attention on their potential to constitute the supportive BM stroma (Majumdar et al., 1998). With this capacity in mind, the first clinical trials conducted by our colleagues with culture-expanded MSCs were designed to augment and support BM transplantation (BMT) for cancer patients (Lazarus et al., 1995). Because of this focus on BMT and the aversion to the term "stem cells," others proposed (Horwitz et al., 2005) that MSCs be called "multipotential mesenchymal stromal cells," and sometimes just "marrow stromal cells," terms that keep the MSC abbreviation but, for us and some others, have always seemed to be inappropriate. The nomenclature issues, however, arise from the difficulties of reconciling in one term the fact that MSCs, at least from BM, do exhibit stemness properties, including self-renewal capacity under clonogenic conditions (Sacchetti et al., 2007; Dennis et al., 1999; Baksh et al., 2004; Bruder et al., 1997; Colter et al., 2000) and multipotential differentiation capabilities (Pittenger et al., 1999; Mackay et al., 1998; Dennis et al., 1999; Prockop, 1997; Giordano et al., 2007), once they are isolated from the nonparenchymal component ("stroma") of various tissues.

This logic would likewise apply to other tissue-derived cells, such as adipose-derived stem cells (ADSCs), which exhibit similar ex vivo multipotency (Rodeheffer et al., 2008; Tang et al., 2008). At least some of the current debate stems from the fact that while the multipotential capacity of MSCs has been proven in vitro (Pittenger et al., 1999), the in vivo counterpart is still not definitive. However, it is important to mention that in spite of the fact that multipotency should be strictly defined using clonogenic experiments, this single-cell approach does not necessarily reflect the in vivo situation. Additionally, the lack of an unambiguous in vivo MSC marker that identifies this cell population in different tissues highlights the possibility that different cell characteristics may be dictated by the local tissue microenvironment in which they reside (Bianco et al., 2008). This technical shortcoming also poses limitations when comparing the general performance of different isolated populations, given the inconsistencies often seen in terms of the isolation and characterization methods employed. To complicate the problem even further, the "pure" mesodermal origin of MSCs is still debatable, given the potential additional ectodermal origin through ectoderm-derived neural crest in craniofacial bones (Hall, 2008).

The Pericyte

As described above, the early studies of MSCs depended on their isolation, expansion, and characterization in vitro, and considerable effort has been expended toward identifying and localizing these cells in situ. There is a detailed and elegant literature (Hirschi and D'Amore, 1996; Crisan et al., 2008; Traktuev et al., 2008; Sacchetti et al., 2007) that supports the fact that for almost every blood vessel in the body, mesenchymal cells are observed in perivascular locations (on both arterial and venous vessels). These abluminal cells, called pericytes for

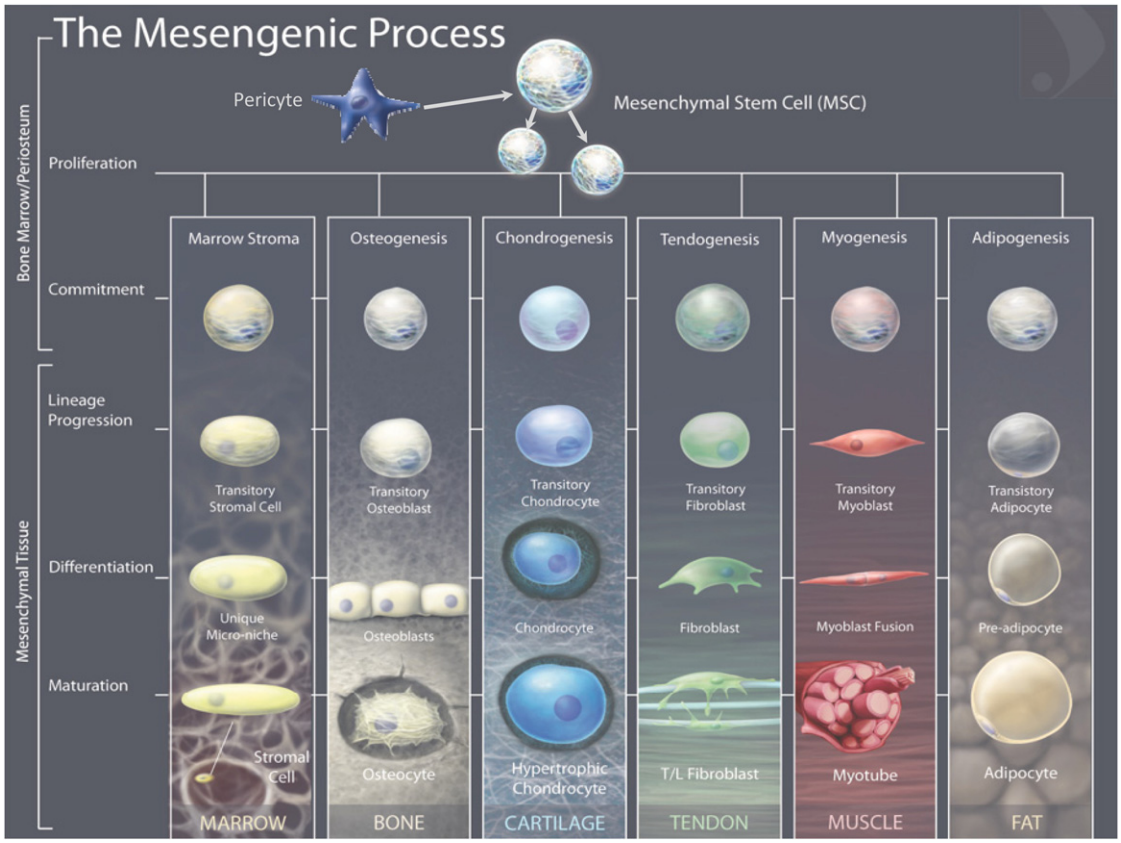

Figure 1. The Mesengenic Process

The original version of this figure was generated in the late 1980s (Caplan, 1991, 1994) and has been modernized in this rendition. The figure proposes that an MSC exists in the bone marrow and that its progeny can be induced to enter one of several mesenchymal lineage pathways. The lineage format was constructed from what was known about the hematopoietic lineage pathway, and this figure depicts the predicted differentiation hierarchy of the most prominent candidate lineages. (Current image graphics produced by Michael Gilkey, National Center for Regenerative Medicine).

convenience, are in intimate contact with the basement membrane and surrounding endothelial cells that comprise the microvasculature, from precapillary arterioles to small collecting venules. A continuum of phenotypic similarities is apparent across various vessel types in that pure pericytic cells are observed in the microvessels, while the smooth muscle cells that are typically present in terminal arterioles, venules, and larger vessels retain the expression of some pericytic markers such as NG2 and CD146 (Crisan et al., 2008; Díaz-Flores et al., 2009). It is now clear that isolated pericytes exhibit a panel of cell surface markers that are identical to those expressed by isolated MSCs (Crisan et al., 2008). Furthermore, as described in this issue of *Cell Stem Cell*, a novel cell surface-specific marker of ADSCs (WAT7, which corresponds to a cleavage product of decorin) is also expressed in vivo by perivascular cells that exhibit typical pericyte markers such as PDGFR-β and αSMA (Daquinag et al., 2011). These and other observations allowed us to speculate in a commentary in this journal that all MSCs are pericytes (Caplan, 2008). If most or all MSCs are indeed pericytes, it opens new possibilities regarding how to physiologically and therapeutically visualize the role of MSCs. In particular, if pericytes are the source of MSCs, do these cells have local functions in the tissue microenvironment beyond their mesenchymal differentiation capabilities?

Preclinical Animal Models and Clinical Trials

The potential therapeutic benefit of exogenous MSCs has been under preclinical investigation for many years. Between 1995 and 2011, both autologous and allogeneic MSCs from multiple sources have been injected into tissue sites such as heart or infused into the blood stream and have been observed to localize to tissue sites of injury involving broken or inflamed blood vessels. As of May 2011, the NIH website (http://clinicaltrials.gov) lists 19,364 cell-based therapies, and 206 of those are considered MSC-related. The list of MSC-related candidate applications includes diverse clinical targets, indications, or clinical conditions, such as BMT, graft versus host disease, acute myocardial infarct, stroke, spinal cord (cuts and contusions), lung (asthma and chronic obstructive pulmonary disease [COPD]), acute kidney failure, liver fibrosis, tendinitis, juvenile diabetes, radiation syndrome, burns and wound healing, osteoarthritis and rheumatoid arthritis, lupus, autism, inflammatory bowel disease, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), urinary incontinence, and sepsis. Consistent with the proposal that there is an ongoing change in philosophy with regard to the clinical potential offered by MSCs, almost all of these trials and preclinical models utilize MSCs in therapeutic and medicinal manners that are quite distinct from the capacity of the cells to differentiate into different phenotypic lineages.

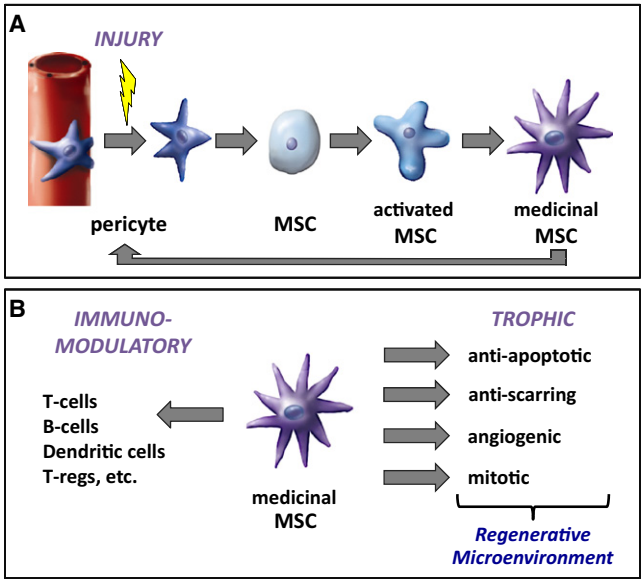

Figure 2. MSCs Are Immunomodulatory and Trophic

(A) The proposed sequential activation of pericytes as a response to injury. Local vessel damage affects resident pericytes and liberates them from functional contact with blood vessels to become activated MSCs. Upon immune activation, these mobilized, "medicinal" MSCs secrete factors that organize a regenerative microenvironment. Subsequent repair is reinforced when activated MSCs reacquire a stabilizing pericyte phenotype in the abluminal space. (B) The bioactive molecules secreted by medicinal MSCs are immunomodulatory and affect a variety of immune cell lineages (Aggarwal and Pittenger, 2005). Other secreted molecules establish a regenerative microenvironment by establishing a powerful trophic field (Caplan, 2010).

Indeed, all of these disorders and conditions appear to be muted or cured by the injected or infused MSCs based on two generalizable therapeutic activities (Caplan and Dennis, 2006): immunomodulation and trophic activities (Figure 2). The immunoactivity of these cells has been shown to be mediated by both secreted bioactive molecules and by cell-cell contact, and can involve dendritic cells and B and T cells, including T regulatory cells, killer cells, and a variety of T helper cells (Iyer and Rojas, 2008; Jones and McTaggart, 2008; Le Blanc et al., 2003). The trophic effects involve MSC-secreted molecules that inhibit apoptosis (especially caused by ischemia) and scar formation. They also involve stimulation of MSC-mediated angiogenesis by secretion of VEGF and by the MSC stabilization of new vessels by the return to their earlier pericyte phenotype (Sorrell et al., 2009). Lastly, MSC-secreted mitogens stimulate tissue-intrinsic progenitors to divide and appropriately differentiate (Wagner et al., 2009; Rehman et al., 2004). In this regard, we have published a compendium that identifies the molecular agents secreted by MSCs that contribute to these immunomodulatory and trophic effects (Meirelles Lda et al., 2009; Singer and Caplan, 2011).

The Drugstore

Based on the examples described above, we support the model that MSCs are clinically active at different tissue sites, that MSCs are pericytes and can be isolated from any vascularized tissue, and that MSCs secrete large quantities of a variety of bioactive molecules as part of their local trophic and immunomodulatory activities. We propose that this specific MSC tissue "regulatory" phenotype arises as a consequence of broken or inflamed blood vessels at sites of tissue damage. This model does not exclude the possibility that pericytes naturally have an on/off cycle in the noninjured situation. We envision that this active phenotype can be adopted in addition to their "constitutive" phenotype in which, as perivascular cells, this population expresses MSC markers both in vivo and ex vivo and functionally exhibits multipotential ex vivo differentiation capabilities (Crisan et al., 2008; Sacchetti et al., 2007; Pittenger et al., 1999; Mackay et al., 1998; Dennis et al., 1999; Prockop, 1997; Giordano et al., 2007). According to this paradigm, in situations of vessel damage, the released pericytes become MSCs, are activated by the injury, and respond to that tissue site by secreting a spectrum of bioactive molecules (i.e., drugs) that serve to, first, inhibit any immune cell coming to survey the tissue damage and, thus, prevent autoimmune activities from developing (Figure 2). In addition, these secreted bioactive molecules, through their trophic activities, establish a regenerative microenvironment to support the regeneration and refabrication of the injured tissue. In this context, the MSCs serve as site-regulated, multidrug dispensaries, or "drugstores," to promote and support the natural regeneration of focal injuries. If these injuries are large or occur in older individuals, the natural supply of MSCs must be supplemented by local or systemic delivery.

Although most existing clinical information has been generated to date using culture expanded marrow-derived MSCs, there is information to suggest that MSCs from fat, placenta, umbilical cord, and muscle have similar, but not identical, functional potential (Guilak et al., 2010; Moretti et al., 2010; Hass et al., 2011). However, the question of which tissue source of exogenously supplied MSCs might be optimal for a given clinical situation has not yet been established. What is quite clear, however, is that allogeneic human MSCs do not elicit a vigorous immune response that leads to their rejection even after multiple infusions (Aggarwal and Pittenger, 2005; Koç et al., 2002; Le Blanc et al., 2008; Ringdén et al., 2006). Moreover, we and others routinely utilize culture-expanded human MSCs from many human donors in animal models of disease (MS, asthma, inflammatory bowel disease, etc.) with reproducible efficacy (Bonfield et al., 2010; Bai et al., 2009). This pattern of clinical application does not question the potential efficacy of autologous MSCs, although one could envision that some autoimmune diseases might be initiated in response to a malfunction of these endogenous, resident MSCs should this population no longer provide adequate immunomodulation at the affected tissue site. Similarly, for select conditions, the provision of autologous MSCs might inadvertently exacerbate a targeted disease state, particularly if an autoimmune component is evident, for example, in MS. In this latter case, for the MSCs to be curative they must not only mute the inflammatory or autoimmune activity that causes demyelination, but they must stimulate the differentiation and site-specific functioning of oligodendrocytes from local progenitors to rewrap the denuded axons in the central nervous system as has been shown in animal models (Miller et al., 2010) .

Unanticipated Efficacy

The theme above centers on diseases where immunomodulation and trophic activities can affect the progression of the clinical

presentation. Completely unanticipated is the recent publication that human MSCs also make a protein that is a lethal antimicrobial for both gram-positive and gram-negative bacteria. The synthesis of this cathelicidin by MSCs, called hCAP-18/LL37, was shown to be a dose-of-bacteria-dependent antimicrobial when tested in an intratracheally (IT)-instilled mouse model of *E. coli*-induced pneumonia (Krasnodembskaya et al., 2010). In this work, IT-delivered MSCs reduced the growth of bacteria and promoted their clearance from the animals, as evaluated by lung homogenates and bronchoalveolar lavages. These results may be applicable to other devastating lung infections, such as the ones present in cystic fibrosis (CF) patients, where IT or aerosolized cell preparations may have potential therapeutic benefits. The control of these tissue-specific bacterial infections exerted by MSCs can now be added to their known systemic bacterial growth control in different models of induced sepsis (Németh et al., 2009; Gonzalez-Rey et al., 2009). We further speculate that this MSC-dependent antimicrobial activity is normally present in the lung, oral cavity, gut, etc. Thus, MSCs may be extremely useful in both local and disseminated infections.

Medical Applications

Given all of the above, we envision that the clinical use of MSCs may change the course of the practice of medicine. For instance, based on the known effects of infused MSCs on heart diseases (Schuster et al., 2004; Itescu et al., 2003; Minguell and Erices, 2006), it may be possible to develop an alternative therapeutic paradigm for use in third world countries or in situations in which adequate life-support is not readily available for patients suffering an acute myocardial infarct. Following this new approach, patients would be treated in a clinical facility that had frozen stores of bags of allogeneic MSCs available for infusion. This early therapy, combined with subsequent support treatments that are already in current use, would be expected to stop the progression of myocardium loss and serve to limit and minimize the long-term effects of the cardiac ischemia. Therefore, the scientific advance in our understanding of the properties of MSCs as a potential therapy for heart diseases, and their subsequent potential for clinical application, raises a central and important question: How long must we wait for this therapy to become widely available, given that it is based on the cells serving as drugstores that dispense secreted trophic factors? Because the current proposed clinical uses of MSCs have nothing to do with their multipotency, we have suggested that we call MSCs *m*edicinal *s*ignaling *c*ells (Caplan, 2010). It should be noted that both neural stem cells and hematopoietic stem cells likewise have the capacity to secrete a diverse set of bioactive molecules that have both immunomodulatory and trophic activities. Thus, we are careful to say that these local pro-regenerative activities may not be directly related to the specific differentiation capacity of multipotent progenitors, but instead may be a common feature of adult stem cell populations.

The Lesson Learned

Perhaps the most important lesson learned from the past 20 years of MSC research is that we must continually ask what the native, normal functions of these cells are. Of course, this line of investigation is particularly challenging in the absence of tools that allow the identification and tracking of specific, homogeneous populations of MSCs in vivo. Scientists are enormously clever in terms of the tricks we can make cells perform in the context of manipulated culture conditions. However, how to translate these tricks into successful clinical protocols has proven to be elusive. The powerful, natural capacities of these isolated cells when put back into the body either as freshly harvested cells or after culture expansion is the more important discovery, and these clinical observations provide a window into understanding their normal physiology and normal cell function. This insight helps us design more informative and revealing experiments that will lead to the eventual translation of our science into practical and effective clinical treatments. Much work needs to be done to carefully define the clinical circumstances where MSCs should be utilized and to more precisely define their mode of action.

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