Chapter 5
MSCs as Therapeutics

Arnold I. Caplan

Abstract Marrow has long been recognized as a source of osteoprogenitor cells. Such cells are a member of a heterogeneous group of cells that I have termed mesenchymal stem cells (MSCs) because they can be induced to form a number of differentiated mesenchymal cell types. With the realization that many of these MSCs are perivascular cells, pericytes, also comes the realization that they secrete a large array of bioactive molecules that are immunomodulatory and trophic. In this context, the differentiation capabilities are less important than their medicinal capacity and their regenerative potential in a number of diseases and medical conditions. Thus, we propose the suggestion that they could be called medicinal signaling cells (MSCs).

Introduction

The twenty-first century brought the "Age of the Stem Cell" into sharp focus. Started in the 1950s and 1960s with the experimental demonstration of adult hematopoietic stem cells (HSCs) in human bone marrow, the focus on the turnover and control elements in hematopoiesis reemphasized the spectrum of molecules and factors contributing to embryonic tissue development and how all of life was a genomically controlled temporal pattern of change [1–5]: The temporal pattern of change is initiated when the sperm fertilizes the egg, then to form a primitive tri-layered embryo, then to form all the organs and specialized tissues, to have the newly configured organism grow and mature into an adult, and then the obvious genetic and environmental basis for late onset disease and the new biologic complexity associated with

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longevity [4, 5]. Clearly, a bone-fracturing fall for a 5-year old has hugely different consequence compared to a fall of an 80-year old: The orthopedic consequence of very rapid bone-fracture repair in the young compared to that of the older adult has both a molecular and cellular basis [6]. It is within this context that I invented the term "mesenchymal stem cell," the MSC, to account for both the embryonic formation of diverse skeletal tissues and the implications for their functioning in adult tissues as the controlling cellular elements of turnover, maintenance, and repair [7, 8]. Indeed, orthopedic surgeons long ago recognized that adding extra amounts of autologous bone marrow had associated osteogenic units that could add value to fracture repair or spinal fusions [9].

How the lessons learned in studying adult bone marrow MSCs ramified into deeper understanding of MSC function is the focus of this chapter with emphasis on orthopedics. It is safe to say that current clinical uses of adult MSCs represent the new and startling insight into their normal in vivo functions. These new clinical uses are the "new medicine" which will change the way healthcare is delivered. Although bone marrow MSCs, because of their relationship to HSCs, are well studied, the fact that adult MSCs can be isolated from almost every tissue and organ in the body implicates these cells in a broader context [10]. This broad context challenges us to understand how MSCs naturally function and, more importantly, how to optimally manage these cells both outside and inside the body for clinical benefit.

Historic Perspective

Marrow has long been recognized as a source for osteogenic cells [9, 11, 12]. The quality of the marrow, fatty yellow marrow compared to red marrow, is likewise associated with bone degradation and loss and bone formation and maintenance, respectively. The bone-forming units, osteoblasts, are present in vivo as monolayer sheets of electrically coupled and coordinately controlled secretory cells that form laminar sheets of organic matrix, osteoid, that eventually become mineralize into bone. The orientors of these sheets of osteoid-secreting cells are the blood vessels, the vasculature. This leads me to infer that vasculature is both the driver and orientor of bone formation [13, 14]. Likewise, in the chick embryo, we established that there was a sequential series of differentiation steps between the osteoprogenitor cells and these secretory osteoblasts and, thus, established the details of an osteogenic lineage progression [15]. The link between the osteoprogenitor cells (i.e., MSCs) and vasculature becomes more obvious in the sections below.

The experimental findings of the orthopedic surgeon and clever scientist Marshall Urist in describing the bone-forming effects of demineralized bone matrix (DBM) when implanted into the muscle of adult rodents also infers that in muscle (or in other sites such as subcutaneous pouches) that DBM attracted osteochondrogenic progenitor cells (i.e., MSCs) from the surrounding adult host tissue [16, 17]. Indeed, by implanting chips of DBM in subcutaneous pouches, these osteochondrogenic progenitors were, likewise, in association with the host vasculature: with the vasculature

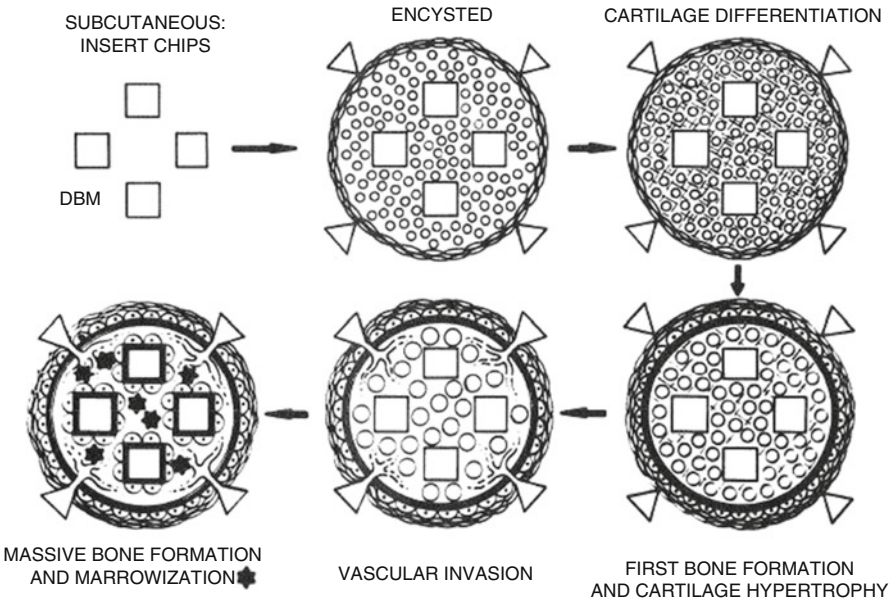

Fig. 5.1 Diagrammatic representation of low-magnification view of the sequence of cellular and tissue events involved with the implantation of DBM (*empty squares*) into a subcutaneous location [18]. The DBM particles are surrounded by mesenchymal cells (presumably MSCs), and this composite field is walled off by a three- or four-cell thick layer of "stacked-cells" to encyst the host cell-implanted particles of DBM. Outside the encysting layer (also probably MSCs) are blood vessels (*empty triangles*). The cells within the cyst differentiate into chondrocytes due to the bioactive factors released from the DBM [19]. From the bottom of the stacked cell layer, vascular-driven osteogenesis produces a layer of mineralized bone (*black circle*). The osteoid bony layer inhibits nutrient entrance which cases the internal chondrocytes to become hypertrophic and then to expire. These expiring chondrocytes secrete VEGF that causes the vasculature to erode through the bony layer bringing in resorptive cells that remove the cartilage ECM and replace it with newly forming blood vessels and new pericytes (MSCs) that form the first bony layer (*bold squares*) on the surface of the DBM particles. Eventually, marrow is established around the newly fabricated bone (With permission from [18])

orienting a 3–4-cell layer that encysted the DBM particles and, subsequently, the internal, expiring hypertrophic chondrocytes secreting chemoattractants to bring the host vasculature with new MSCs to replace the cartilage matrix with bone and eventually newly formed marrow (see Fig. 5.1) [18, 19]. The experiments of Reddi and his colleagues established both the cellular and molecular details as the implanted DBM experienced the sequential temporal phases of acute inflammatory events, the encysting, chondrogenesis, osteogenesis, and finally the formation of marrow [19].

Based on the above, in the late 1980s, I proposed that marrow contained an adult skeletal stem cell that I called a mesenchymal stem cell (MSC) that was capable of entering different expressional lineages to form, separately, bone, cartilage, muscle, the highly differentiated marrow stromal (marrow connective tissue) that houses hematopoiesis, tendon/ligament, fat, and other connective tissues; I summarily

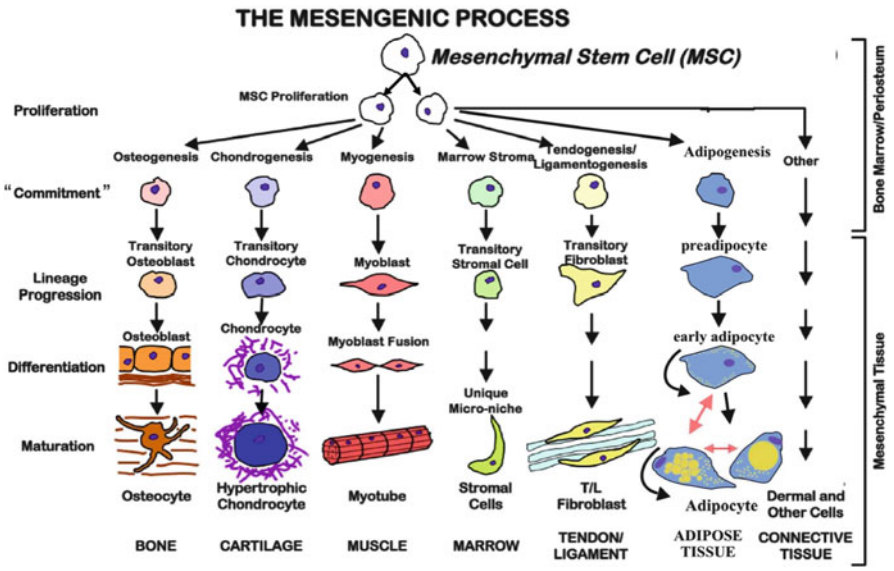

Fig. 5.2 The Mesengenic Process: Originally conceived in the late 1980s, the scheme was hypothesized to represent the existence of a stem cell whose progeny could separately lineage progress into a variety of mesenchymal phenotypes. The basis for the figure was the details known for hematopoiesis and the existence of an osteogenic lineage [7, 8, 20–22]

referred to this pathway as "mesengenesis" (see Fig. 5.2). The proposition of a widely distributed adult stem cell, the MSC, was quite contrary to the dogma of the 1980s that held that HSCs were the only progenitor cell in marrow. Based on this initial mesengenic hypothesis, Stephen Haynesworth and I developed the technology to isolate and culture expand human MSCs in a scale that could allow the clinical uses of MSCs [23].

Although unknown to me at that time, it was Alexander Friedenstein who first documented that osteogenic cells could be isolated and cultured from marrow [11, 12]. However, it was Maureen Owen who first put the lineage progression of MSCs into the same format as was pictured for HSC lineage progression [20]. Indeed, it was Owen who popularized Friedenstein's early work. In this context, Friedenstein is often recognized as the first to isolate a mesenchymal-like progenitor from marrow. By the mid-1990s, we published studies showing that MSCs from marrow (and also periosteum and synovium [24, 25]) could form bone [26, 27], cartilage [28], muscle [29], hematopoietic supportive stroma [30], tendon [31], and fat [21].

Also, the first use of MSCs in humans as a support for bone marrow transplantation in cancer patients documented their safety [32] and, eventually, their efficacy [33]. Based on these reports and on several patent applications, Osiris Therapeutics, Inc. was started in December 1992 as a "BioOrthopedic" company committed to the tissue-engineered restoration of skeletal tissues using MSCs.

Also by the mid-1990s, we published two reports in which, I am embarrassed to say, we overlooked the key biologic implications until many years later. The first was a study of the bioactive molecules secreted into the growth medium in 24 h by

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. 5.3 The media from 24-h incubation of human MSCs initiated into osteogenic or marrow stromagenic pathways compared to cells in growth were analyzed by ELISA for specific bioactive molecules listed on the *left*. The relative percent change was scored with +, ++, +++ representing fold increase over baseline (Taken from [34])

hMSCs in growth, in osteogenesis, or in stromagenesis [34]. An ELISA assay for each molecule listed in Fig. 5.3 allowed us to vertically identify a comparative molecular signature for these three cell states. What we missed is that the MSCs innately secreted massive quantities of various bioactive molecules (to be discussed below). The second publication documented that some MSCs were localized on or integrated with blood vessels in human skin of young donors [35]. Again, the implications of this observation eluded us until 2007–2008 [10].

From the late 1980s until 2006–2008, the focus of the MSC technology was within a tissue engineering context. Inherent in this approach was the supposition that MSCs were the natural progenitors for skeletal tissue turnover, maintenance, and repair. This is certainly the case for marrow-derived MSCs and bone and to some extent bone marrow itself [36]. However, the presence of the muscle satellite cells compared to muscle-derived MSCs both challenges and confuses the issue of which is the "true" turnover progenitor for muscle [37, 38].

Fracture Repair

Fracture repair in long bones had been the subject of numerous studies [22]. What is agreed upon is that a "blastema" (high-cell-density fracture-spanning tissue) is the key element of the repair process. If the fracture is mechanically stable, newly forming blood vessels can span the break, can span the blastema, and spanning bone will form

as driven by these mechanically stable blood vessels. If the fracture is mechanically unstable, the blastema forms a spanning avascular plug of cartilage in a connective tissue sheath [6, 7]. Outside this plug of cartilage, a vascular-driven outer shell of bone forms (much like the encysted DBM referred to earlier). This outer mineralized bony callus mechanically stabilizes the fracture, and the central cartilage becomes hypertrophic; these hypertrophic cells expire and cause blood vessels and new MSCs to invade that eventually forms bridging endochondral bone [18, 19]. Eventually, the callus and over-repaired bone are remodeled to provide weight-bearing bone spanning the previous fracture site. For emphasis, we now recognize this close relationship between MSCs and newly forming blood vessels, as will be discussed next.

MSCs Are Pericytes?

It was long ago recognized that all blood vessels, large and small, arterial or venous, have cells of mesenchymal origin in ablumenal locations; for simplicity, I refer to these perivascular cells as pericytes. Over the last few years, we now recognize that if one purifies or immunostains cells using pericyte markers, one obtains cells that also have MSC cell surface markers [10, 39, 40]. This observation leads me to hypothesize that "all MSCs are pericytes." The reverse that all pericytes are MSCs is not correct since some pericytes are so highly differentiated that they cannot exhibit the multipotent properties of MSCs. Recently, pericytes (i.e., MSCs) have been isolated from the thick connective tissue surrounding major blood vessels (these cells have distinctive markers compared to pericytes from capillaries) [41]. The fact that *every* blood vessel in the body has MSCs in perivascular locations explains the fact that MSCs can be isolated from every vascularized tissue of the body; the best characterized MSCs are from marrow [42, 43], fat [44, 45], and muscle [37, 38], but also from placenta [46] and from umbilical cord [47]. This latter source is quite interesting in that there are no MSCs in cord blood; a few MSCs can be isolated and expanded from cord blood probably resulting from the needle which is inserted thru the external tissue to enter the lumen of the cord to harvest the blood. I suspect that this needle pushes a pericyte or two into the collection stream. This also accounts for the fact that 30–60 % of cord blood specimens do not yield expandable cultures of MSCs.

The new hypothesis that all MSCs are pericytes now explains the close association of MSCs and blood vessels in fracture repair, DBM-controlled bone formation, endochondral bone formation, and in the embryology of bone formation. Moreover, the issue of "what do MSCs do naturally?" can be addressed relative to their close association with blood vessels.

Clinical Use of MSCs: The New Medicine

We like to say that we scientists take our bench work and translate it to the bedside, to clinical utility. In the case of MSCs, we have, indeed, done that but because of the new clinical information derived from the use of MSCs [48], we must take them

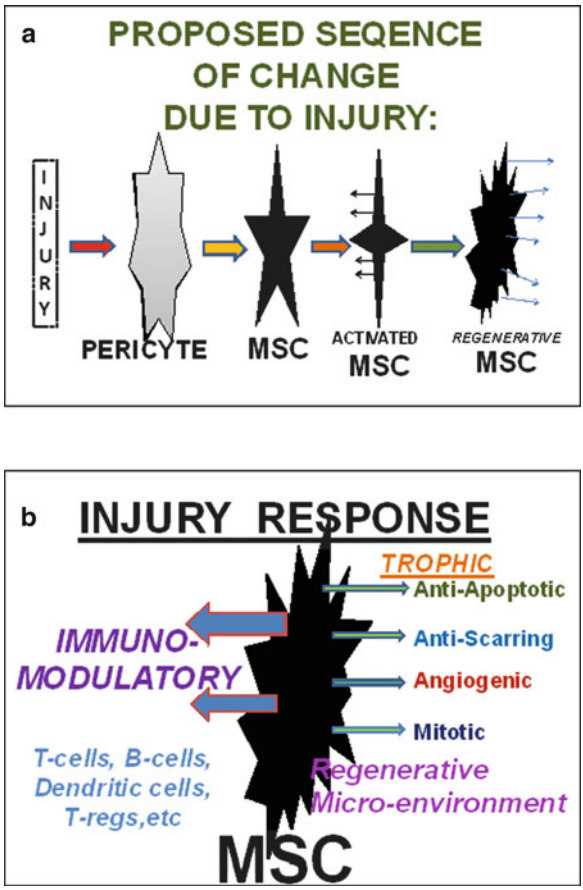

Fig. 5.4 Proposed sequence of cellular events following injury where pericytes are released from their ablumenal positions (**a**). These released pericytes become MSCs that are activated to secrete (**b**) bioactive molecules that are immunomodulatory and trophic [42, 43, 49]

back to the bench to determine how they function clinically since these results have nothing to do with their multipotency nor lineage progression pictured in Fig. 5.2. Without detailing all of the data now available, it is clear that MSCs have both an immunomodulatory and trophic function [49]. The immunomodulation allows allogeneic MSCs to be used clinically and allows the use of human MSCs in mouse models of disease such as asthma [50], MS [51], or inflammatory bowel disease [52]. The immunomodulation can affect a variety of immunocompetent and surveillance cells by shutting them down [53]. My hypothesis is that this is how the MSCs function once an inflamed or injured blood vessel releases the pericyte from its ablumenal surface. In this case, the injury site activates the MSC to interfere with the inflammatory process at its residency site (see Fig. 5.4). This inhibits immunosurveillance of the damaged tissue and, thus, inhibits autoimmune reactions from developing.

The trophic activity is much more complicated and probably involves different secreted molecules at different anatomic or diseased sites [42]. It seems obvious that MSCs function in the brain of a stroke patient differently from the same MSC

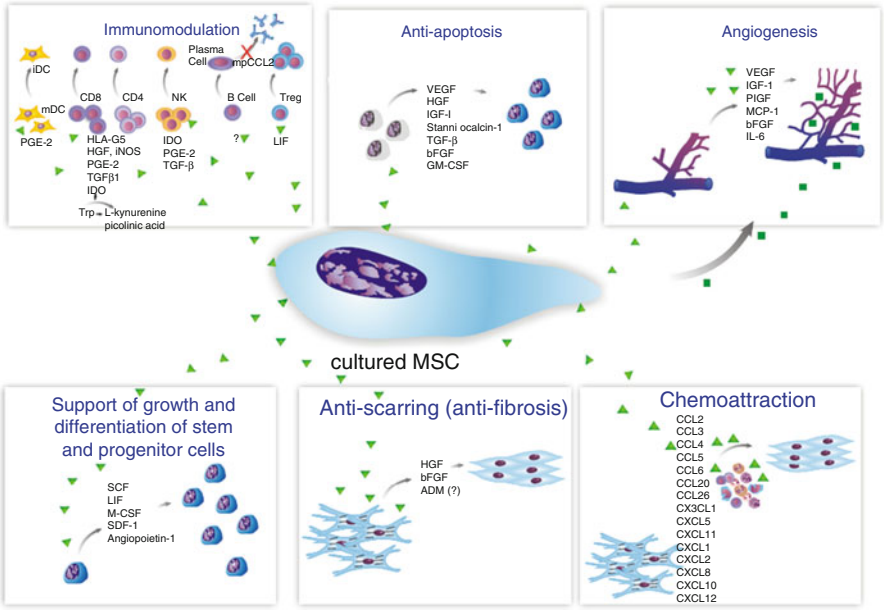

Fig. 5.5 The listing of bioactive molecules that have been identified [42] to contribute to MSC-controlled immunomodulation, anti-apoptosis, angiogenesis, mitosis of tissue-specific progenitors, anti-scarring, and chemotaxis

functioning at the infarct site of a heart attack patient. However, the trophic activity is similar at these different anatomic sites: anti-apoptotic (ischemic cells do not undergo apoptosis because of protective factors secreted by MSCs), anti-scarring (either by inhibiting the entry or functioning of myofibroblasts to form scar tissue), angiogenic (not only do MSCs secrete a huge amount of VEGF that attracts vascular endothelial cells, but MSCs again become pericytes and stabilize newly forming blood vessels), and mitotic for tissue intrinsic progenitors such as cardiac stem cells (see Fig. 5.5) [42, 43, 49].

It is now clear that our previous observations that MSCs intrinsically secrete massive quantities of bioactive molecules [34] account for both the immunomodulation and trophic activities observed clinically. Indeed, it is both of these activities that allows MSCs to structure regenerative microenvironments and provides the generalized mechanism for their clinical utility. Thus, one could foresee that in rural areas of Georgia, bags of MSCs for infusion could be stored at local urgent care or health centers and, thus, be a realistic way to treat heart attack patients; the challenge is to make this therapy at a few pennies per bag. This *new medicine*, delivered intravenously, will provide immune-silent allogeneic MSCs to home to sites of injury or inflammation.

Given the above, we can now more clearly understand the relationship between MSCs and blood vessels in fracture repair: Whether cells will form bone or cartilage will depend on the stability of the fragile, newly forming vessels. Moreover, the

regeneration of muscle, tendon, skin, and other well-vascularized tissues is not only dependent on the local microenvironments but also on the local vascular density and, thus, MSC titers. Regeneration of excised or damaged neonatal or pediatric (less than 3 years of age) skeletal tissues including the joints of fingers has been reported [54]; this regeneration will not occur in older individuals or in wounds that have been sutured. Like amphibians that can regenerate arms or legs, if the natural repair process is interrupted with sutures, regeneration will not occur. I would infer that a blood clot to close the wound followed by the acute inflammatory response followed by a sequence of MSC activity and vascular penetrance is required for regeneration. The interruption of this will result in nonunions, scarring, and lack of wound closure. The role of endogenous MSCs in these processes is the subject of current experimentation.

Conclusions

Based on the over 200 clinical trials now going on using MSCs from marrow, fat, and other tissues, it is clear that the principal use of MSCs clinically is not in the tissue-engineered fabrication of replacement tissues as we originally envisioned. Quite the contrary, the immunomodulatory and trophic properties of MSCs are now being investigated for graft-versus-host-disease, Crohn's disease, multiple sclerosis, diabetes, amyotrophic lateral sclerosis (ALS), tendonitis, osteoarthritis, rheumatoid arthritis, spinal cord injury, stroke, acute myocardial infarction and chronic cardiac insufficiency, asthma, and other indications. Based on these clinical uses, I would assert that MSCs are the "New Medicine" of this era, and cell-based therapies will change the course of healthcare delivery. For example, someday if someone has an infarct or stroke, they can receive a bag or two of allogeneic MSCs as a primary therapy, perhaps without major hospitalization. It is possible that this new use will make the "Miracle Drugs" of the last century seem insignificant by comparison. The new use of MSCs in orthopedics will likewise generate new products and approaches including smarter tissue-engineered tissue fabrication and implantation schemes that not only optimize the lineage translation and differentiated properties of MSCs, but also their medicinal activities (immunomodulation and trophic). With this in mind, I have recently suggested for non-tissue engineering uses that the MSC be renamed as the Medicinal Signaling Cell [55]. Thus, the future holds great promise when considering this new medicine both for the use of MSCs for specific disease states and also for aspects of longevity where vascular density plays a key role.

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