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The use of in situ bone marrow stem cells for the treatment of various degenerative diseases ☆

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Summary The potential for tissue repair and regeneration is encouraging in the light of novel research on the plasticity of adult stem cells. Intense research efforts over the last 3 years have provided solid evidence for the continuous generation of many types of tissue cells from adult stem cells as a normal part of our physiology throughout development and adult life in mammals, including humans. This opens new therapeutic avenues for many clinical problems and provides alternative opportunities at a time when much attention has been brought to the issue of using embryonic stem cells for research purposes and for the development of treatments for various diseases. Embryonic stem cells are pluripotent cells characterized by nearly unlimited self-renewal and differentiation capacity. However, evidence has accumulated over the past few years, indicating that adult bone marrow stem cells might have pluripotent properties similar to those of embryonic stem cells. Based on a review of the literature we propose the hypothesis that in situ mobilization of stem cells from the bone marrow and their migration to various tissues is a normal physiological process of regeneration and repair and that therapeutic benefits can be generated with less invasive regimens than the removal and re-injection of stem cells, through the stimulation of normal stem cell migration. We further propose that effort should be made to identify natural compounds characterized by their ability to augment this normal process of mobilization and re-colonization of bone marrow stem cells for the potential treatment of various degenerative diseases.

INTRODUCTION

Spurred by political considerations, much attention has been recently brought to the issue of using adult stem cells (ASC) instead of embryonic stem cells (ESC) for research purposes and for the development of treatments for various diseases. Even though stem cell research started more than three decades ago (1–4), therapy using stem cells is still at an early and experimental stage. The belief has been that only ESC held the potential of providing multi- or pluripotent cells that could regenerate various types of adult tissues. ESC are pluripotent cells harvested from undifferentiated embryonic cells characterized by nearly unlimited self-renewal and differentiation capacity (5,6). Treatment with ESC has either been shown or is suspected to improve various degenerative diseases such as Parkinson's diseases (7,8), diabetes (9), and heart diseases (10), as well as degeneration of the nervous system (11). However, research involving ESC has received significant opposition over the years because of the obvious ethical nature of harvesting cells from live human embryos and because of the door it opens to research involving genetic manipulation of humans (12–15). An alternative to this ethical dilemma has developed, as evidence has accumulated over the past few years, indicating that adult bone marrow stem cells (ASC) might have pluripotent properties similar to

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☆ *Abbreviations used:* ASC: Adult stem cells; BM: Bone marrow; BMSC: Bone marrow stem cells; ESC: Embryonic stem cells.

ESC. Based on this research, we propose the hypothesis that stimulation of in situ release and homing of bone marrow stem cells could constitute an effective treatment for various degenerative diseases without the intervention of removing stem cells from the body for in vitro manipulation and later re-introduction into the patient. This paper provides a review of the available data on mobilization and recirculation of ASC as a means of self-repair mechanisms, leading to a hypothesis of induction of stem cell mobilization as one possible mechanism behind many clinical cases of recovery and as one possible treatment modality for many chronic illnesses.

BONE MARROW STEM CELLS

Traditionally, somatic tissue-derived stem cells of mammalian adults have been viewed as pluripotent precursors capable of lifelong maintenance of cellular compartments typical of the tissue in which they reside. Stem cells have been found to be present in various tissues, including the brain, muscles, liver, skin, and bone marrow, where they play an important role in healing and regeneration of the tissue they occupy. Stem cells are referred to as multi- or pluripotent because of their ability to differentiate in a variety of cell types present in a given tissue. Until recently, the differentiation potential of stem cells in tissues of the adult has been thought to be limited to cell lineages present in the organ from which they were derived.

Among all types of stem cells, bone marrow stem cells (BMSC) are unique with regard to their abundance and their role in the continuous lifelong physiological replenishment of blood cells. As traditionally seen, BMSC develop into hematopoietic and non-hematopoietic stem cells or marrow stromal cells, which are progenitors of skeletal tissue components such as bone and cartilage, as well as blood components. However, a comprehensive review of recent studies related to stem cells suggests that in normal healthy individuals ASC may hold the capacity to differentiate into a far broader variety of cell types and play a fundamental role in the healing and regeneration processes of various tissues and organs in the body. Data suggest that there is in mammalians an innate phenomenon of regeneration whereby BMSC would sense distant injury, exit the marrow and circulate to a target organ, migrate into the site of damage, and undergo tissue-specific differentiation, promoting structural and functional repair (Fig. 1).

To validate this hypothesis and its possible clinical application, three phenomena must be evidenced:

(1) The ability of adult BMSC to undergo differentiation within a target organ and adopt the target-specific phenotype and function;
(2) the ability of adult BMSC to naturally migrate into the target organ;
(3) the ability to mobilize BMSC and stimulate their release into the circulation to increase their availability to the target organ.

Items (1) and (2) are described jointly since many studies investigated both differentiation and migration capabilities.

PLURIPOTENT PROPERTIES AND MIGRATION CAPABILITIES OF ASC

ASC were recently shown to have the ability to migrate to a damaged target organ, differentiate, and become functional myocytes, cardiomyocytes, hepatocytes, osteocytes, and even glial cells and neurons.

Myocytes and cardiomyocytes

In postnatal life, growth and repair of skeletal muscle fibers are mediated by a resident population of mononuclear myogenic precursors called satellite cells. These cells, which are located between the sarcolemma and the basal lamina of the muscle fiber, divide at a slow rate to sustain both self-renewal and growth of differentiated tissue. In response to muscle injury or in individuals with chronic degenerative myopathies, satellite cells divide and fuse to repair or replace the damaged fibers. However, the self-renewal potential of adult satellite cells is limited, decreases with age, and can be exhausted by a chronic regenerative process such as that characteristic of severe muscular dystrophies, in which most muscle tissue is eventually lost and is replaced by connective tissue.

Interestingly, the number of resident satellite cells in adult muscle is much smaller than the number of committed myogenic precursors that populate the muscle tissue soon after an injury. Investigating the possibility that non-myogenic stem cells are involved in the regeneration of injured or damaged muscle fibers, Ferrari et al. (16) demonstrated the existence of bone marrow-derived cells able to migrate into areas of induced muscle degeneration, participate in the regeneration process, and give rise to fully differentiated muscle fibers. Data indicated that these cells appeared to be recruited by long-range, possibly inflammatory, signals originating from the degenerating tissue, and they appear to access the damaged muscle from the circulation, together with granulocytes and macrophages.

Orlic et al. (17) induced myocardial infarction by coronary ligation in rats and reported that 9 days after injection of BMSC in the ventricular wall nearby the infarcted area, newly formed BMSC-derived myocardium occupied 68% of the infarcted portion, which was com-

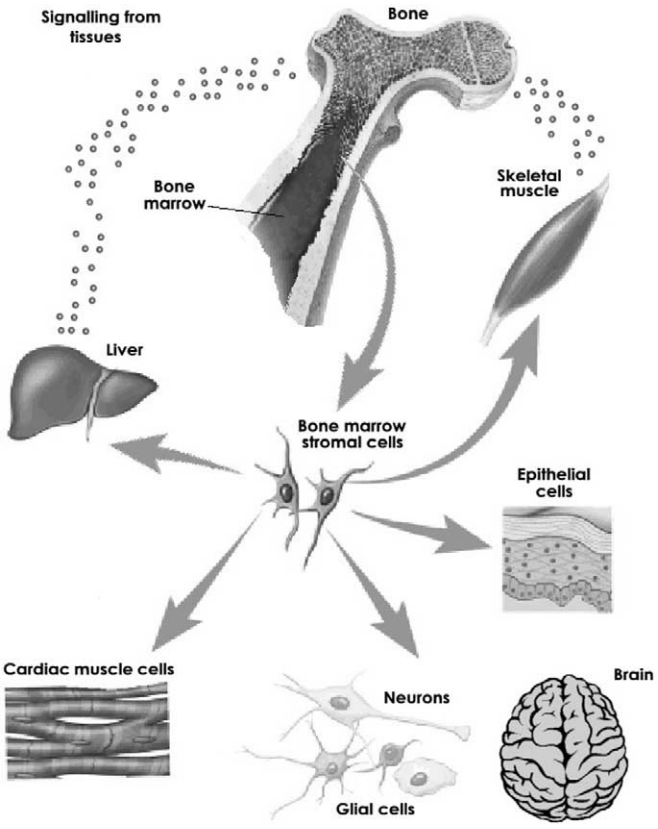

Fig. 1 Mobilization and migration of endogenous stem cells seem to be normal physiological phenomena. Subsequent to a signal sent by an inflamed or degenerating tissue, possibly eicosanoids or other endogenous inflammatory compounds, bone marrow stem cells would migrate out of the bone marrow and then through the bloodstream to target organs. In the target organs, stem cells undergo differentiation into fully functional target cells.

prised of myocytes and vascular structure. In post-infarct neoangiogenesis, often the capillary vasculature is unable to support the greater demands of the hypertrophied myocardium, resulting in progressive loss of viable tissue, infarct extension, and fibrous replacement. BMSC were shown to induce new blood vessel formation in the infarct-bed and proliferation of preexisting vasculature after experimental myocardial infarction (18,19).

Goodell et al. (20) recently described how BMSC can migrate from the bone marrow and contribute to cardiac muscle repair and neovascularization after ischemic injury. Highly purified BMSC were transplanted into lethally irradiated mice that subsequently were rendered ischemic by coronary artery occlusion and reperfusion. The engrafted stem cells or their progeny differentiated into cardiomyocytes and endothelial cells and contributed to the formation of functional tissue.

Hepatocytes

Hepatic oval cells are known to proliferate when hepatocytes are prevented from proliferating in response to liver damage and they may be considered stem cells for hepatocytes and bile duct cells or the intermediate progeny of a hepatic stem cell. Oval cells express CD34, Thy-1, c-kit mRNAs, proteins, and flt-3 receptor mRNA, all of which are also found in hematopoietic stem cells (HSC) (21).

Recent data indicate the ability of BMSC to home to liver tissue in animal models. Lagasse et al. (22) reported that intravenous injection of adult bone marrow cells in the FAH(–/–) mouse, an animal model of tyrosinemia type I, rescued the mouse and restored the biochemical function of its liver.

The hypothesis that oval cells and other liver cells may arise from a cell population originating from the BM was tested by Petersen et al. (21). They tested this hypothesis using two different approaches:

(1) Bone marrow transplantation from male rats into lethally irradiated syngeneic females and detection of donor cells in the recipients by means of DNA probes to the Y chromosome *sry* region;
(2) whole liver transplantation with Lewis rats that express the L21-6 antigen as recipients and Brown–Nor-

way rats that do not express this antigen as allogeneic donors to confirm that an extrahepatic source (L21-6^+ cells) could repopulate the transplanted (L21-6^- cells) liver.

In brief, female rats were lethally irradiated and rescued with a BM transplant from a male animal. Thirteen days after the intervention, Y chromosomes were detected in the hepatocyte fraction. At that time point, an estimated 9.9×10^5 mature hepatocytes that originated from transplanted BMSC had integrated into the liver parenchyma. This was confirmed by the widespread presence of L21-6^+ cells in the Brown–Norway livers transplanted into Lewis rats.

Osteocytes

Marrow stromal cells from wild-type mice were infused into transgenic mice that had a phenotype of fragile bones resembling osteogenesis imperfecta. In mice that were irradiated with potentially lethal or sublethal levels, DNA from the donor BMSC was detected consistently in marrow, bone, cartilage, and lung either 1 or 2.5 months after the infusions. There was a small but statistically significant increase in both collagen and mineral contents of bone 1 month after the infusion (23). In experiments in which male BMSC were infused into a female osteogenesis imperfecta-transgenic mouse, fluorescence in situ hybridization assays for the Y chromosome indicated that, after 2.5 months, donor male cells accounted for 4–19% of the fibroblasts or fibroblast-like cells obtained in primary cultures of cartilage, long bone, tail, and skin. These data indicate a prolonged and sustained integration and differentiation of BMSC into these tissue types.

Glial cells and neurons

Certain diseases of the nervous system are characterized by the degeneration and loss of specific brain cells. Alzheimer's disease is characterized by a loss of cholinergic neurons, whereas Parkinson's disease is characterized by a loss of dopaminergic neurons in the substantia nigra. Multiple sclerosis is characterized by a loss of myelin on motoneurons.

In a study designed to investigate whether BMSC had the ability to differentiate into brain cells, human BMSC were infused into the corpus striatum of rats. Five to 72 days later, brain sections were examined for the presence of the donor cells. About 20% of the infused cells had engrafted. The cells had migrated from the injection site along known pathways for migration of neural stem cells to successive layers of the brain. After infusion into the brain, the human BMSC lost their immunoreactivity to antibodies for collagen I (24,25). Similarly, Kopen et al. (26) injected BMSC into the lateral ventricle of neonatal mice and found that BMSC participated in many aspects of normal brain development, including proliferation, migration along established routes, nondisruptive integration within striatal, cortical, and cerebellar regions, and differentiation into astrocytes and perhaps neurons.

A double-blind study with 40 patients suffering from Parkinson's disease showed that disease progression was slowed in all of the 20 patients whose brains were transplanted with ESC derived from 7- to 8-week-old embryos (27). Likewise, there is evidence indicating that stem cells could reverse symptoms of Alzheimer's disease (28,29).

Studies were conducted to investigate whether stem cells injected intravascularly or endogenously released from the bone marrow could cross the blood brain barrier, migrate, and differentiate into brain cells. BMSC, along with monocytes and macrophages, have been shown to have the ability to cross the blood brain barrier and reach the brain (30–33). Intravascular delivery of genetically marked adult mouse BMSC into lethally irradiated normal adult hosts led to the development in the central nervous system of donor-derived cells expressing neuronal proteins (neuronal phenotypes) (34). After 8–12 weeks, it was estimated that about 0.2–0.3% of the total number of neurons was derived from the bone marrow. Brazelton et al. (34) wrote, 'Our results clearly show that adult cells from the marrow can gain access to the adult brain and assume characteristics of CNS neurons.' Similarly, Mezey et al. (32) showed that transplanted adult mouse BMSC migrated into the brain and differentiated into cells expressing neuron-specific antigens. Between 2.3 and 4.6% of all neurons were donor-derived. Some neurons were observed with axonic projections and apparent dendritic trees. Mezey et al. (32) suggested that, 'there may be a continuous influx of bone marrow stem cells into the ependymal and subependymal zones that give rise to a variety of CNS neural cell types,' thus, implicating a greater potential for CNS regeneration than traditionally expected.

Similar discoveries have been done regarding the ability of ASC to migrate to the brain and differentiate into glial cells, which provide physiological support to neurons and repair neuronal damage due to injury or disease. Egletis and Mezey (35) transplanted adult female mice with donor bone marrow cells genetically marked either with a retroviral tag or by using male donor cells. Using in situ hybridization histochemistry, a continuing influx of hematopoietic cells into the brain was detected. Marrow-derived cells were already detected in the brains of mice 3 days after transplant and their numbers increased over the next several weeks,

exceeding 14,000 cells per brain in several animals. Marrow-derived cells were widely distributed throughout the brain, including the cortex, hippocampus, thalamus, brain stem, and cerebellum, and were found in the parenchyma. Double-labeling analyses showed that at least some bone marrow-derived cells acquired microglial antigenic markers. Interestingly, marrow-derived cell numbers detected in the brain increased over time and continued to increase until the end of the study. No burst of marrow-derived brain cells was observed as a consequence of the surgery. The authors concluded that, 'The appearance of marrow-derived astroglia seems a normal process in these animals' (35). In conclusion, the recruitment and homing of BMSC from circulation to a wide variety of anatomical sites appear to be a normal aspect of mammalian physiology.

MOBILIZATION OF ADULT MSC

The existing scientific literature clearly established the capability of ASC to migrate from bone marrow to target organs where they can penetrate the organ, differentiate, and become fully functional cells. This characteristic of ASC may be used for the treatment of various degenerative diseases by mobilizing ASC and triggering their release from the bone marrow.

From the research data discussed above emerges the fact that, under healthy conditions, the human body holds the potential for generating stem cells for repair and regeneration. New therapeutic strategies involve stimulating stem cell mobilization and homing to enhance this natural phenomenon. At first, this approach would not be targeted and would enhance regeneration and repair throughout the body. Therapeutic tools could be developed to target stem cell migration to specific target organs where regeneration is needed. The existing pharmaceutical methods to produce stem cell mobilization are drastic and while they are great tools to prepare for autologous stem cell transplantation, they are not safe for prolonged use. Furthermore, in any pharmaceutical mobilization strategy, it is of concern whether the mobilized cells remain fully capable of tissue-specific homing and further differentiation. Some current therapeutical strategies in cancer treatment use growth factor injections to produce a prolonged increase of circulating stem cells for harvest prior to chemotherapy and re-injection of autologous stem cells. However, there are other clinical situations, including many chronic degenerative illnesses, where it appears a tempting alternative to substitute this drastic intervention by improving the patient's own reservoir of stem cells in situ, through a milder, more prolonged mobilization of stem cells, and to coach these into increased circulation and homing.

Another therapeutic strategy involves identifying why a patient's stem cells are failing to perform the inherent repair process in many types of chronic degenerative diseases, including Alzheimer's, Parkinson's, and multiple sclerosis, and to adapt therapy towards normalizing this process of regeneration.

During our research involving the effects of botanical extracts on recirculation of human leukocytes, we have gathered preliminary data indicating the ability of oral consumption of certain botanicals to significantly stimulate in healthy humans, within 2–3 h, the release of BMSC and to increase the number of circulating CD34+ cells.

CONCLUSION

Based on the data available in the scientific literature, it is clear that ASC have the ability to migrate and undergo differentiation and repair in a broad variety of tissue. This ability seems to be a normal phenomenon whereby a signal would be sent by an inflamed or degenerating tissue. This signal could be eicosanoids or other inflammatory endogenous compounds. Such a signal would induce the migration of ASC from the marrow into the circulation, and subsequently from the bloodstream into the damaged area, probably through events at the endothelial surfaces of the damaged tissue. Once within the target tissue, ASC would undergo differentiation into fully integrated tissue-specific functional cells. This migration presumably takes place in a manner similar to the migration of leukocytes into damaged or inflammed tissue, following a chemotactic gradient.

To enhance this apparently innate physiological regenerative ability, we propose the investment of research efforts in finding compounds that would specifically mobilize BMSC and trigger an increase in circulation and homing of stem cells. Such compounds could constitute potential treatments for various diseases such as multiple sclerosis, diabetes (36), traumatic brain injury (37), stroke (38), Parkinson's (27), and Alzheimer's diseases (28,29), cardiac infarct (20), and liver degeneration (22).

Therefore, we suggest that both endogenous and exogenous compounds exist that will trigger the mobilization of BMSC and increase the concentration of circulating SC, increasing the probability of migration into various tissues and repair. We also propose that contrary to the current use of pharmaceuticals for stimulating BMSC release, the ideal situation is to provide a series of smaller transient waves of stem cell mobilization, as not to exhaust the bone marrow environment thereby working within the parameters of homeostasis and maintaining normal stem cell phenotype and homing capacity. Thus, novel botanical and pharmaceutical

compounds could hold great promise in new strategies involving the mobilization of the patient's own stem cells and their migration to various tissues, by a non-invasive approach that facilitates their inherent capacity of repair and regeneration.

NOTE ADDED IN PROOF

Since this paper was written, the following article strongly supports our hypothesis, see (39).

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