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The Therapeutic Potential of Bone Marrow-Derived Stromal Cells

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ABSTRACT

Since the replacement of the hematopoietic system became feasible through bone marrow (BM) transplantation, the idea of how to replace other organs of the body has been in the forefront of medical research. Scientists have been searching for the ideal stem cell that could be manipulated to differentiate into any tissue. Although the embryonal stem cells seemed to have the ability to do this, the difficulties surrounding their use prevented them from becoming therapeutically useful. Thus, the field turned to adult stem cells, particularly stem cells of BM origin. We have learnt a lot during the last decade about the potential of the BM-derived stromal (also called mesenchymal stem) cells (BMSCs). The first studies suggested them as cell replacement tools, but later it turned out that their usefulness is more likely due to paracrine effects due to a large variety of secreted factors that induce growth and differentiation of the tissue-specific stem cells as well as prevent injured cells from apoptotic death. Finally, a whole new field emerged when many groups confirmed that these cells are also capable of regulating immune function in a so far unknown, dynamic manner. When BMSCs are injected they seem to be able to sense the environment and respond according to the actual need of the organism in order to survive. This plasticity can never be done by the use of any drugs and such a ''live'' cell therapy could open a whole new chapter in clinical care in the future. J. Cell. Biochem. 112: 2683–2687, 2011.

KEY WORDS: BONE MARROW STROMAL CELLS; TISSUE REPAIR; IMMUNE REGULATION

The organs of the body constantly renew themselves until we get old and this renewal process begins to fail. In addition, organ damage caused by trauma or disease, can result in regeneration or the need for replacement. Around the middle of the 20th century people realized that organs can be transplanted from one person into another—but problems associated with organ transplantation quickly surfaced. Work initiated by Sir Peter Brian Medawar's work on graft rejection eventually allowed clinicians to match donated organs to recipients and/or use immunosuppression to prevent rejection [Medawar, 1969]. Soon there were too few organs to meet the demand, and scientists began to wonder whether they could be manufactured in vitro. This gave birth to the field of regenerative medicine. To imagine making organs one has to understand how they develop in the embryo and how tissues are maintained physiologically. When embryonal stem (ES) cells were discovered, they seemed to be obvious candidates to use for tissue engineering because these cells generate every organ in the body. Histocompatibility problems as well as restrictions on the use of ES cells have hampered efforts to study them, however, and scientists who were interested in tissue regeneration turned their attention to the cells that rejuvenate specific organs in adults. These cells are adult stem cells (ASCs). By now we know that almost all organs contain tissue-specific stem cells that are capable of recreating their various components. The problem with this approach is the difficulty of isolating, characterizing and culturing a sufficient supply of ASCs to use for tissue repair except in the case of blood (hematopoietic) stem cells (HSCs). The latter are reasonably easy to isolate and have been used for some time to replenish all the elements of the blood. In a few other instances, tissue-specific stem cells have also been used to generate human tissue (i.e., skin, trachea), but these applications of stem cells are not yet as routinely practiced as bone marrow (BM) transplantation because they are currently more expensive and technically daunting. Furthermore, it has proven to be quite difficult to identify and culture stem cells from some organs. While these difficulties may be overcome, scientists have begun to look for other ''general'' ASCs that might be used for regeneration of multiple tissues. A logical choice was cells that are known to—or that potentially could—circulate and thus reach all organs of the body. Such cells could potentially originate in the BM or in the lymphatic system. Since lymphatic cells (lymphocytes) also derive from BM stem cells, the only unique stem cells that belong to the lymphatic system might be the stromal

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cells in the lymph nodes. These cells have not been widely studied. The BM, on the other hand, is known to have two populations of stem cells: the hematopoietic (HSC) and the stromal (BMSC) stem cells. HSCs are generally accepted to give rise to the different classes of blood cells (myeloid, erythroid, lymphoid, platelets, and mast cells), while BMSCs give rise to the structural elements of the skeleton, such as bone, cartilage, and marrow fat. A very interesting feature of these cells is that they do seem to be immune-privileged [Nauta and Fibbe, 2007] thus in most instances enabling the use of allogeneic cells that can be collected from volunteers, cultured and then kept as frozen aliquots for later use. During the last decade numerous studies have focused on the possibility of using these BMSCs to repair tissue. This repair might involve one or more of the following mechanisms (Fig. 1):

(1) Although there is no solid evidence yet, but one can imagine that BMSCs (like HSCs) might be induced to enter the circulation, infused into the bloodstream, or injected locally at the site of an injury. Such cells might become tissue-specific stem cells that proliferate and regenerate the tissue. This process could potentially allow tissue regeneration to occur following injury or replenish pools of stem cells in organs when they have been exhausted.

(2) BMSCs might enter organs and secrete paracrine factors that induce the proliferation and/or differentiation of stem cells in the local pools.

(3) BMSCs might get to sites of need and secrete anti-apoptotic factors that help injured cells survive.

(4) BMSCs may regulate the function of the immune system by inducing (or inhibiting) migration of the different immune cells into tissues, and altering their patterns of cytokine production.

For all of the above effects to take place, BMSCs need to get to the site of the injury/damage, but we still lack proof that these cells leave the BM and circulate to reach the injured organs. This has not been excluded though because there is no specific marker for BMSCs, and the number in the circulation is likely to be very low. Consequently, detecting them is a significant technical challenge. To complicate matters are also some interesting data suggesting that HSCs might actually give rise to BMSCs [Ogawa et al., 2010]. Many studies, on the other hand, have shown that if pre-labeled or gender-

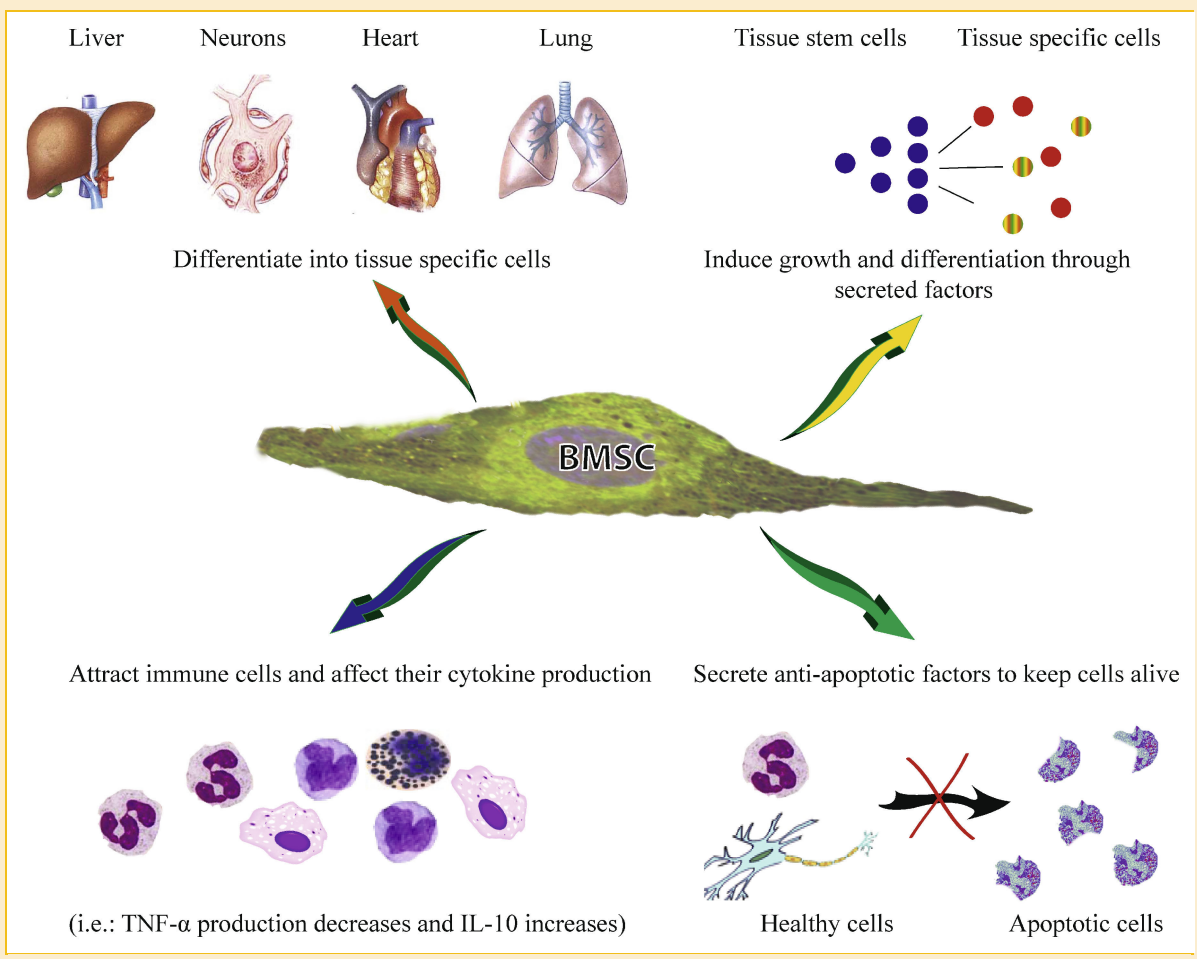

Fig. 1. Bone marrow stromal cells might help regenerate tissues or restoring healthy physiological state using a variety of mechanisms that are summarized above.

mismatched BMSCs are administered, they do indeed find their way to sites of injury [Spaeth et al., 2008]. Whether this happens physiologically remains to be determined. We do know that, BMSCs can adhere to the vascular endothelium and pass through vessel walls to reach the extravascular space. Furthermore, human BMSCs have a variety of chemokine receptors that should enable them to respond to signals from the injured tissues [Wynn et al., 2004; Honczarenko et al., 2006; Augello et al., 2010]. Once they get to sites of injury, it appears they can differentiate into organ-specific stem cells to speed up or enable regeneration. This process is called transdifferentiation if the target organ is not mesodermal in origin, and whether it actually occurs has been debated for a long time but finally the phenomenon of transdifferentiation seems to have been accepted. What is clear, however, is that the cells that are "born" this way do not seem to be numerous enough to repair any major damage. For information about this phenomenon, the reader should consult recent reviews [Phinney and Prockop, 2007; Jopling et al., 2011; Mezey, 2011; Sugimoto et al., 2011].

There is evidence from studies of both animals and humans that BMSCs indeed help damaged tissue recover by secreting growth and differentiation factors that stimulate regeneration mediated by local stem cell pools [Barker et al., 2010]. These factors are listed in Table I; many have been examined extensively in models of neuronal regeneration and skeletal repair [Crigler et al., 2006; Granero-Molto et al., 2008]. As reported recently, pericytes in a number of organs also seem to have many of the features of BMSCs [Feng et al., 2010]. This is not surprising since the BMSCs have been shown to be BM pericytes themselves [Bianco et al., 2008, 2010]. If tissue pericytes have actions that resemble those of BMSCs, they may mount beneficial responses to local injury. It will be important to do a rigorous comparison of organ-derived pericytes and BM-derived BMSCs to understand their similarities and differences.

TABLE I. A summary of agents that BMSCs produce and use to regenerate/restore tissues to health.

Name of factor made by BMSC	Known function of factor	Reference to factor in BMSC
Trophic		
Angiopoietin	Growth/angiogenesis	1, 2
BDNF	Growth/differentiation/anti-apoptotic	3
bFGF (FGF2)	Growth/differentiation	3, 4
BMI-1	Regulates self-renewal	5
EGF	Growth/proliferation/differentiation	1
Erythropoietin	Red cell production	1
GMFB	Nerve growth	6
HGF	Mitogenesis, cell motility	4, 7, 8
Keratinocyte growth factor (FGF7)	Growth	1
Macrophage inflammatory factor	Leukocyte migration/induce pro-inflammatory cytokines	1
MCP-1	Monocyte migration	3
PEDF	Antiangiogenesis/neurotrophic	6
TGF-β	Growth/proliferation/differentiation	7, 8
VEGF	Vasculogenesis, migration	2, 4, 5, 8
Anti-apoptotic agents		
CNTF	Anti-apoptotoic	5
IL-6	Anti-apoptotic	3, 9
IGF (IGF-1)	Anti-apoptotic/proliferation	1, 4
NGF	Growth/anti-apoptotic	5, 6
Attractants		
Eotaxin-3 (CCL-26)	Recruits eosinophils, basophils	10
Fractalkine (CX3CL1)	Recruits T cells and monocytes	10
GRO α, β (CXCL-1, CXCL-2)	Recruits neutrophils	10
i-TAC (CXCL-11)	Recruits activated T cells	10
IL-8 (CXCL-8)	Recruits neutrophils	9, 10
IP-10 (CXCL-10)	Recruits monocytes/macrophages, T cells, NK cells, dendritic cells	9, 10
MCP-1 (CCL2)	Recruits monocytes, memory T cells, dendritic cells	9, 10
MCP-3 (CCL7)	Recruits monocytes	10
MIF	Macrophage migration inhibition	6
MIP1 (CCL4)	Recruits monocytes, NK cells	10
MIP3-a (CCL20)	Recruits lymphocytes	10
RANTES (CCL5)	Recruits T cells, eosinophils, basophils	10
SDF-1 (CXCL-12)	Lymphocyte migration	1, 10
Immunomodulators		
ENA 78 (CXCL-5)	Activates neutrophils	10
Galectins	Anti-inflammatory	11, 12
HLA-G5	Immune suppression	13
IDO	Inhibits T cell proliferation	14
IL-1α, β	Cytokines; affect function of a variety of immune cells	9
INF1 β	Anti-inflammatory	9
LL-37	Anti bacterial	15
PGE-2	Immune suppression	16, 17
TNF-α*	Pro-inflammatory cytokine	9
TSG-6	Anti-inflammatory	18

1. Chen et al. [2008], 2. Wu et al. [2007], 3. Crigler et al. [2006], 4. Kinnaird et al. [2004], 5. Crisostomo et al. [2008], 6. Di Nicola et al. [2002], 7. Rehman et al. [2004], 8. Munoz et al. [2005], 9. Tomchuck et al. [2008], 10. da Silva Meirelles et al. [2008], 11. Sioud [2011], 12. Gieseke et al. [2010], 13. Selmani et al. [2008], 14. Meisel et al. [2004], 15. Krasnodembskaya et al. [2010], 16. Aggarwal and Pittenger [2005], 17. Nemeth et al. [2009], 18. Lee et al. [2009].

[a]*Only one study showed its' presence in mouse BMSCs, while many other groups could not detect its presence.

Some of the paracrine factors secreted by BMSCs have anti-apoptotic effects (Table I). Thus, in addition to speeding up the production of new cells in a damaged area by inducing proliferation and differentiation, the anti-apoptotic factors might also rescue cells thereby contributing to faster healing. This effect has been clearly demonstrated in the CNS following injuries [Crigler et al., 2006]. CTF and NGF released by BMSCs seem to restore some damaged nerve cells to health there. Similarly, IL-6 produced by BMSCs in the blood, inhibits apoptosis of neutrophils, increasing their lifespan and allowing them to fight infection for longer periods. This is one of many immune-modulatory actions of BMSCs.

It was first reported in 2002 [Di Nicola et al., 2002] that BM stromal cells suppress T cell proliferation. In the same year an in vivo study in monkeys demonstrated that the infusion of BMSCs increase the time of survival of skin grafts [Bartholomew et al., 2002]. These reports opened a new field of research on the possibility of using BMSCs for immunosuppression. In fact, patients were given allogeneic BMSCs to counter GVHD following BM transplantation [see Le Blanc, 2006]. Since the results of clinical trials were encouraging, basic scientists began to explore the mechanisms by which BMSCs alter immune function. Members of a number of groups including my own have worked on this problem, but we are still far from understanding all the interactions between BMSCs and members of the immune system. It appears that cell/cell interactions between the BMSCs and their target cells are required for some of the actions of the stem cells [Nemeth et al., 2009]. Other studies suggest that soluble factors secreted by the BMSCs (see Table I) are responsible for the effect [see Granero-Molto et al., 2008; Nasef et al., 2008; Uccelli et al., 2008; Caplan, 2009; Newman et al., 2009]. At present, we believe that the BMSCs can "sense" their environment. Perhaps they monitor a variety of cytokines in the serum and respond accordingly, because their responses seem to be context dependent. They can change a pro-inflammatory environment into an anti-inflammatory one by secreting anti-inflammatory regulators (Table I), such as INT-1β, galectins, and TSP-6 [Lee et al., 2009]. In septic animals [Nemeth et al., 2009], as in GVHD, they can induce pro-inflammatory macrophages to become less aggressive or even anti-inflammatory by secreting PGE2. In addition, in a model of asthma, they can rebalance the established inflammatory, allergic, Th2 dominant environment, helping to create a more anti-inflammatory environment by the release of TGF-β [Nemeth et al., 2010] and by recruiting regulatory T cells.

Finally, it seems that in addition to affecting the function of immune cells, BMSCs can also produce anti-bacterial agents, such as LL-37 [Krasnodembskaya et al., 2010] that could directly attack bacteria invading the body.

CONCLUSIONS

BM-derived stromal cells (and possibly stromal cells of other tissues including pericytes) have a surprising ability to participate in tissue repair in a variety of ways. They can differentiate into cells of other tissues; and they can secrete growth factors, anti-apoptotic agents, and factors that attract immune cells. Once the immune cells and the BMSCs are nearby, the BMSCs can affect the function of the immune cells and help the body to regain balance from whatever injury or damage occurred. Through all of the above actions they potentially provide a new kind of dynamic cellular therapy that cannot be replaced by any drugs. (The cells are much smarter and more adaptive than individual molecules.) Our job is to understand these cells and their actions well enough to use them safely and effectively.

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