

Stem cell therapy independent of stemness

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Abstract

Mesenchymal stem cell (MSC) therapy is entering a new era shifting the focus from initial feasibility study to optimization of therapeutic efficacy. However, how MSC therapy facilitates tissue regeneration remains incompletely characterized. Consistent with the emerging notion that secretion of multiple growth factors/cytokines (trophic factors) by MSC provides the underlying tissue regenerative mechanism, the recent study by Bai *et al* demonstrated a critical therapeutic role of MSC-derived hepatocyte growth factor (HGF) in two animal models of multiple sclerosis (MS), which is a progressive autoimmune disorder caused by damage to the myelin sheath and loss of oligodendrocytes. Although current MS therapies are directed toward attenuation of the immune response, robust repair of myelin sheath likely requires a regenerative approach focusing on long-term replacement of the lost oligodendrocytes. This approach appears feasible because adult organs contain various populations of multipotent resident stem/progenitor cells that may be activated by MSC trophic factors as demonstrated by Bai *et al*. This commentary highlights and discusses the major findings of their studies, emphasizing the anti-inflammatory function and trophic cross-talk mechanisms mediated by HGF and other MSC-derived trophic factors in sustaining the treatment benefits. Identification of multiple functionally synergistic trophic factors, such as HGF and vascular endothelial growth factor, can

eventually lead to the development of efficacious cell-free therapeutic regimens targeting a broad spectrum of degenerative conditions.

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Key words: Mesenchymal stem cell; Hepatocyte growth factor; Multiple sclerosis; Trophic action; Stem cell therapy

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COMMENTARY ON HOT TOPICS

Clinical trials of human bone marrow mesenchymal stem cells (MSC) have been initiated for cardiovascular and immune disorders^[1,2]. The therapeutic utility of MSC stems in part from the recognition that MSC possess immunomodulatory properties that can be explored for non-autologous (allogeneic) stem cell therapy. Emerging evidence indicates that although MSC exhibit prominent multi-lineage potential, this cellular feature appears to bear little relevance to their therapeutic effects. Instead, the secretion of multiple growth factors/cytokines (trophic factors) by MSC provides the underlying regenerative capacity^[3,4]. These findings broach a novel concept of stem cell trophic factor-mediated tissue repair independent of stemness. The work performed by Bai *et al*^[5] studying the therapeutic role of MSC-derived hepatocyte growth factor (HGF) in two animal models of multiple

sclerosis (MS) provides yet another convincing evidence for this concept.

MS is a progressive autoimmune and inflammatory disorder caused by damage to the myelin sheath, which is produced by oligodendrocytes and provides the protective covering surrounding nerve cells^[6]. The demyelinating process renders axons functionally impaired and susceptible to insult, contributing to physical and cognitive disabilities^[7]. Several therapeutic modules are currently in use or under investigation for treating MS^[8]. These include oral drugs that disrupt purine and pyrimidine metabolism, modulate sphingosine-1-phosphate receptor, or attenuate oxidative stress. Also used are humanized monoclonal antibodies directed against various immune cell receptors such as CD20, CD25 and CD52, which are intended to rebalance the immune system in favor of tissue regeneration. However, many of these new MS treatments have been found to trigger serious adverse events, and their long-term safety data remain lacking^[8]. It should be noted that since these MS therapies are directed toward attenuation of the immune response, robust repair of myelin sheath, which requires a regenerative approach focusing on long-term replacement of the lost oligodendrocytes, may not be effectively achieved. Thus, recent cell-based therapeutic approaches for MSC treatment have received much attention. These cell therapies have used neural stem cells, oligodendrocyte progenitors, and most notably MSC^[5,9-11]. This therapeutic strategy is attractive because the adult central nervous system is known to harbor populations of multipotent neural stem cells and oligodendrocyte precursors^[12,13] that may be activated by the administered stem cells. In the adult heart, indeed, MSC administration has been found to activate cardiac stem/progenitor cells, contributing to myocardial regeneration^[14,15].

The MS therapeutic study demonstrated by Bai *et al*^[5] is based on the use of human MSC-conditioned medium (MSC-CM), which contains a myriad of therapeutically relevant trophic factors. They showed that exposure of neurosphere cultures to MSC-CM resulted in reduced astrocytes and increased oligodendrocyte precursor cells, oligodendrocytes, and neurons. This *in vitro* finding is mirrored by intravenous infusion of MSC-CM in their MS mice, which was found to reduce functional deficits and accelerate development of oligodendrocytes and neurons in the context of improved remyelination. Further insights came from their biochemical fractionation and characterization of MSC-CM, demonstrating that HGF and its receptor cMet are primarily responsible for the therapeutic benefits. Indeed, both MSC-derived HGF and exogenously supplied HGF promoted regeneration and functional recovery. This conclusion is further strengthened by the use of an HGF-neutralizing antibody and a cMet-blocking antibody, each of which negated the therapeutic effects. Taken together, their studies highlight the critical role of the HGF/cMet axis in MSC therapy for MS and possibly other tissue degenerative conditions.

MSC have long been known to provide stromal sup-

port for the growth and differentiation of bone marrow hematopoietic stem cells through cell contact-dependent and -independent mechanisms, the latter of which is mediated by MSC trophic factors^[16], which include many hematopoietic growth factors including granulocyte/macrophage colony-stimulating factor (GM-CSF), G-CSF, M-CSF, and interleukin (IL)-7 as well as IL-6-type cytokines^[4,17]. Production of these MSC trophic factors can be further enhanced following exposure to Toll-like receptor (TLR) ligands such as lipopolysaccharide and the double-stranded RNA mimetic polyinosinic-polycytidylic acid [poly(I:C)]^[18,19]. Although TLR activation of the immune system is associated with chronic inflammation, Cole *et al*^[20] demonstrated an unexpected beneficial role for TLR3 in the arterial wall upon systemic administration of poly(I:C). Further, Packard *et al*^[21] found poly(I:C) administration to be protective against cerebral ischemia-reperfusion injury. Since MSC are widely present *in vivo* and their perivascular origin in multiple human organs appears certain^[3,22,23], it is possible that these prophylactic benefits of poly(I:C) may be mediated through its trophic stimulatory effect on the endogenous MSC niches.

Therapeutically, MSC trophic factors can be functionally redundant and synergistic, mediating immune regulation, cytoprotection, host stem cell activation and mobilization, and extracellular tissue remodeling. MSC also interact with cells of both the innate and adaptive immune systems, leading to immunomodulation of their effector functions^[24]. The anti-inflammatory property of MSC was indeed highlighted in the study by Bai *et al*^[5], showing that the therapy reduced the levels of multiple inflammatory cytokines and enhanced the levels of multiple anti-inflammatory cytokines produced by the mononuclear cells from the spinal cords. Along this line, Osiris Therapeutics is currently conducting a Phase III trial of MSC in treating several immune disorders such as graft-versus-host disease and Crohn's disease (www.osiris.com). Although how HGF might singly modulate the host immune response remains unclear, the authors speculated that HGF might alter the balance of pro- and anti-inflammatory T cells possibly by influencing the function of dendritic cells, which express cMet and therefore can be modulated by HGF. However, the immunomodulatory function of MSC alone does not appear to lead to effective tissue repair as demonstrated in our recent MSC therapy for the failing hamster heart, which shows that while a low-dose MSC regimen suppressed myocardial inflammation, it failed to promote cardiac repair. On the other hand, the low-dose cell therapy combined with poly(I:C) conditioning of MSC, which amplified HGF and other trophic factors, suppressed inflammation and stimulated myocardial regeneration^[18].

Another important point regarding the therapeutic use of MSC trophic factors is that these soluble mediators typically exhibit a short half-life. Vascular endothelial growth factor (VEGF), for instance, possesses a half-life of about 3 min in circulation^[25]. Given a short half-life of HGF^[26], the authors raised the question of how this treatment might result in long-term therapeutic

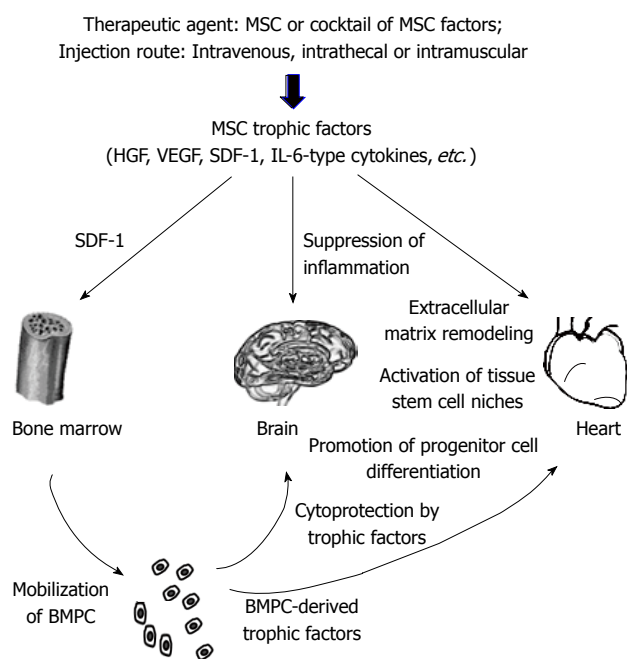


Figure 1 Current model of mesenchymal stem cell therapy for brain and heart regeneration. Mesenchymal stem cell (MSC) therapies for brain and heart repairs have been conducted using either MSC or MSC-derived trophic factors. Successful trials have been obtained based on multiple injection regimens, such as intravenous (for brain and heart), intrathecal (for brain), and intramuscular (for heart) administration routes. Major MSC trophic factors that have been found to be critical in mediating tissue regeneration include hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), stromal cell derived factor (SDF)-1, and interleukin (IL)-6-type cytokines. The SDF-1/CXCR4 axis has been found to mobilize bone marrow progenitor cells (BMPC). These heterogeneous BMPC populations are also capable of producing trophic factors, which likely act in concert with MSC trophic factors in suppressing tissue inflammation, normalizing extracellular matrix remodeling, promoting cell survival, activating local stem cell niches, and directing progenitor cell differentiation. In addition, myocardial recruitment of BMPC after MSC therapy has been documented.

benefits. It has previously been found that exogenously administered HGF could result in sustained elevation of endogenous HGF through a positive feedback loop^[27]. This finding may not be unexpected given that the growth factor network often exhibits a cross-talk mechanism, enabling induction and amplification of more than one growth factor by another. This trophic cross-talk mechanism has been illustrated in our cardiac therapeutic studies based on intramuscular injection of MSC^[4,15]. This MSC therapeutic strategy is coupled to the inherent ability of skeletal muscle to produce beneficial trophic factors in response to exercise and injury^[28,29]. Although the injected MSC are trapped in the hamstrings, their trophic actions induce mobilization of bone marrow progenitor cells (BMPC) through the SDF-1/CXCR4 axis and promote increased growth factor levels in the quadriceps, liver, and brain^[4,15]. We further demonstrate that the mobilized BMPC are also capable of trophic actions^[30], contributing to the systemic increase in trophic factors, which may be explored for MS therapy (Figure 1). Consistent with these preclinical findings, the clinical trials with MS patients revealed similar benefits mediated by either intrathecal or intravenous MSC with no

consensus on the best cell delivery route^[31]. Note that intravenous infusion of MSC has been adopted for clinical trials of neurodegenerative and heart diseases^[2,32]. Although the intravenously infused MSC are largely distributed to the lungs, their trophic actions underlie the observed therapeutic benefits independent of MSC stemness. These findings illustrate the significance of formulating a minimally invasive stem cell delivery approach for patient care.

HGF, like VEGF, also possesses a potent angiogenic function^[33]. Administration of HGF, either as a recombinant protein or DNA vector, has been shown to promote angiogenesis without increased vascular permeability or inflammation^[34]. Further, HGF can decrease VEGF-mediated leukocyte activation and co-administration of HGF and VEGF more potently promotes angiogenesis than either growth factor alone^[35], suggesting that exploring interactions of MSC trophic factors for therapeutic application may be warranted. Coordinated induction of HGF and VEGF following intramuscular administration of MSC is observed in our stem cell and growth factor therapeutic trials for hamster heart failure^[4,15,30,36]. This cross activation mechanism may explain why intramuscular injection of VEGF or HGF alone also repairs the failing heart^[36,37]. Thus, the beneficial effects observed in the HGF therapy for MS^[5] are likely mediated and coordinated by HGF and the many downstream trophic factors induced by HGF. This trophic cascade can also be initiated by MSC-derived IL-6-type cytokines, which signaling through JAK/STAT3 induce HGF, VEGF and many other trophic factors as demonstrated in our MSC therapeutic study^[4].

A cautionary note is warranted here because the potent angiogenic function of HGF and VEGF may be associated with a risk of cancer. Indeed, MSC are known to express cancer/testis antigen^[38], and MSC-derived VEGF has been reported to promote breast cancer cell migration^[39]. However, as noted in a recent review, MSC can also have the potential of diminishing tumor growth, and may be used as “Trojan horses” to deliver anti-cancer therapeutics into the tumor stroma^[40]. This controversy may be due to the heterogeneity nature of MSC prepared from differences tissue sources and the use of various experimental models. Interestingly, MSC have been found to be differentially primed by TLR4 and TLR3 ligands to adopt a pro-inflammatory [mesenchymal stem cell (MSC) 1] and anti-inflammatory (MSC2) status, respectively^[41]. The MSC1 and MSC2 phenotypes attenuate and promote tumor growth/metastasis, respectively^[42]. Along this line, we recently demonstrated that MSC TLR3 activation prominently suppressed tissue inflammation caused by myocyte cell death and promoted myocardial regeneration^[18]. These studies thus indicate that the cytokine secretion profile of MSC plays a decisive role in dictating the therapeutic potency and outcome.

In summary, despite encouraging results from numerous preclinical studies, ongoing clinical trials of stem cell therapy have thus far demonstrated moderate

and inconsistent benefits^[43-45], indicating an urgent need to optimize the therapeutic platform. Identification of multiple functionally synergistic trophic factors, such as HGF and VEGF, can eventually lead to the development of an efficacious cell-free therapeutic regimen. The study by Bai *et al*^[5] paved the way for this logistically attractive approach.

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