Published in final edited form as:

Regen Med. 2014 March ; 9(2): 129–132. doi:10.2217/rme.14.1.

Stem cell-based therapies for multiple sclerosis: recent advances in animal models and human clinical trials

Sarah E Lutz[‡],

Department of Developmental & Cell Biology, University of California, Irvine, CA 92697, USA

Justin Lengfeld[‡], and

Department of Developmental & Cell Biology, University of California, Irvine, CA 92697, USA

Dritan Agalliu

Department of Developmental & Cell Biology, University of California, Irvine, CA 92697, USA,
dagalliu@uci.edu

Keywords

blood–brain barrier; experimental autoimmune encephalomyelitis; hematopoietic stem cells; mesenchymal stem cells; multiple sclerosis; neural stem cells; stem cell transplantation

“...much progress has been made in laying out the groundwork for stem cell-based therapies to be used for multiple sclerosis treatment. Further work is needed to explore the effects of stem cell transplantation with or without ablative therapies and to maximize the success of this approach.”

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the CNS, widely regarded to be autoimmune in nature, and a leading cause of disability among adults aged 20–40 years. Most patients present with a relapsing remitting profile, in which inflammatory flare-ups are interspersed with periods of baseline function. A minority of patients display a primary progressive disease characterized by a continually worsening clinical profile. Chronic MS is accompanied by cortical atrophy and loss of neurons, axons and oligodendrocytes. The most frequently employed animal model that recapitulates many pathological aspects of MS is experimental autoimmune encephalomyelitis (EAE), a predominantly CD4⁺ T-cell-mediated disease induced by immunization with myelin peptides. There are significant, unmet clinical needs in MS, including therapies that target its neurodegenerative component and those for patients who are refractory to current treatments. In this editorial, we focus on the most recent compelling reports describing stem cell transplantation therapies for both MS and EAE, and discuss promising future directions.

Correspondence to: Dritan Agalliu.

[‡]Authors contributed equally

Financial & competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Stem cells for blood–brain barrier repair

MS and its animal models are characterized by blood–brain barrier (BBB) breakdown, enabling inflammatory leukocytes and blood factors such as complement and fibrinogen to gain access to the CNS and promote disease. A frequent incidence of BBB dysfunction, demonstrated clinically by gadolinium-enhancing lesions in MRI, is associated with a more aggressive disease and severe neurodegenerative pathology. BBB dysfunction can even occur in normal-appearing white matter in MS [1]. Such microscopic vascular lesions may become hot spots for future tissue damage and are interesting therapeutic targets.

Few studies have directly assessed stem cell-mediated effects in BBB function for animal models of MS. However, stem cell restoration of damaged BBB has been explored in other CNS diseases. A high number of endogenous endothelial precursor cells (EPCs), a cell population that is increased in circulation in patients with acute stroke, correlates with improved clinical outcome [2]. Transplanted EPCs ameliorate cerebral edema, BBB permeability and behavioral deficits after traumatic brain injury owing to increased microvascular density and expression of endothelial tight junction proteins [3]. A prospective study of early ischemic stroke also found an inverse correlation between EPC number and serum ICAM-1 [4], an adhesion molecule that promotes leukocyte extravasation from endothelium. Therefore, EPCs may play an immune modulatory role in stroke. Human mesenchymal stem cell (MSC) treatment has also been effective for murine traumatic brain injury in reducing BBB permeability and preserving adherens and tight junctions, by secreting TIMP3 [5]. *In vitro* MSCs can reduce permeability of cultured human umbilical vein endothelial cells [6]. Finally, transplantation of hematopoietic stem cells (HSCs) enriched for CD34⁺ endothelial cells showed striking benefits in patients with aggressive, progressive MS [7]. Therefore, it is tempting to speculate that stem cells administered during chronic or progressive disease may attenuate vascular dysfunction, in addition to their immunomodulatory effects. The contribution of stem cells to functional BBB recovery for animal models and human MS is thus a potentially exciting but underexplored area of research.

Stem cells for remyelination

Several stem cells have shown great therapeutic promise for remyelination. In a recent study, MSCs or MSC-conditioned media reduced clinical signs in mice even when transplanted at the peak of disease severity [8]. HGF, a secreted factor from MSCs, was identified as an active disease-modifying component. A single dose of HGF was as effective in reducing both clinical and pathological symptoms as well as neuronal and oligodendrocyte loss as MSC transplantation. Therefore, MSCs may induce both neuroprotective and regenerative mechanisms by virtue of HGF secretion. However, the half-life of HGF is short and other unidentified MSC-derived factors may sustain the clinical benefits that persisted 2 weeks after treatment.

Neural stem cells have been extensively used to repair the demyelinating axons. Bai *et al.* reported that administration of NG2⁺ neural stem cells isolated from adult mouse spinal cord induce myelin repair and functional recovery when administered intravenously into mice

with MOG_{35–55}-induced EAE at the peak of disease [9]. Considerable functional recovery was observed within 5 days after cell administration, and maintained for the entire study. Labeled exogenous NG2⁺ cells were found in white matter tracts in transgenic PLP-eGFP recipient brains and spinal cords, in particular in regions of demyelination. Animals that received NG2⁺ cells had reduced demyelination, elevated levels of endogenous myelin expression and reduced immune cell infiltration into the CNS compared with controls. Interestingly, NG2⁺ cells preferentially differentiated into O1⁺ oligodendrocytes when exposed to EAE-derived conditioned medium *in vitro*. Therefore, the demyelinating environment may induce transplanted NG2⁺ neural stem cells to differentiate into oligodendrocytes that contribute to myelin repair.

Stem cells for attenuation of the immune response

One of the most clinically well-characterized stem cell therapies for MS has been HSC transplantation to repopulate a patient's immune system with nonpathogenic cells. Early clinical trials have used aggressive immunoablative therapies to deplete the pathogenic immune cell population prior to transplantation, whereas more recent trials have found success with a nonablative approach. MSC transplantation is less studied, although several clinical trials are currently ongoing or planned [10]. A goal of all transplant protocols is to reduce or eliminate pathogenic, autoreactive Th17 cells. Animal studies have established mechanisms by which HSC or MSC transplantation attenuates autoimmunity, including suppressing proliferation and differentiation of proinflammatory IL-17- and IFN- γ -producing CD4⁺ T cell populations within days after transplantation [11].

“Human mesenchymal stem cell treatment has also been effective for murine traumatic brain injury...”

Two of the most interesting results of the past year have examined immunological changes in MS patients 2 years after HSC transplantation. Darlington and colleagues reported on a Canadian MS HSCT study of 14 patients with aggressive MS who were treated with chemoablative therapy followed by autologous HSC transplantation [7]. The patients did not develop new gadolinium-enhancing lesions for 2 years after transplantation and had no worsening of clinical scores on the Expanded Disability Status Scale (EDSS), a widely used metric for quality of life. Immune ablation resulted in a persistent decrease in total circulating CD4⁺ cells, while CD8⁺ cells returned to baseline levels. The CD4⁺ T-cell population that was profoundly downregulated was the Th17 population implicated as the pathogenic T-cell subset in EAE. Abrahamsson and colleagues also reported long-term changes in the T-cell compartment for MS patients who received non-myeloablative, autologous HSC transplantation [12]. Samples obtained 6 months after transplantation were characterized by a shift toward regulatory and immunosuppressive T-cell subsets (CD4⁺ FoxP3⁺ regulatory T cells and CD56^{high} NK cells). Persistent depletion of the putatively pathogenic, mucosal-associated invariant T (MAIT) CD161^{high} CD8⁺ T-cell subset was found up to 2 years following transplantation. These MAIT cells express the CCR6 chemokine receptor, which mediates T-cell homing to the CNS in both MS and EAE, and are found in blood vessels and perivascular cuffs in acute inflammatory MS lesions.

A recent study showed that even neural stem cells NSCs attenuate the immune response. Payne *et al.* evaluated the therapeutic potential of two NSC lines (46C-NS and GS-N) in the EAE mouse model [13]. 46C-NS cells are a homogenous, symmetrically dividing NSC population whereas GS-N cells are heterogeneous in composition similar to neurospheres. Co-culture of these two cell populations with splenocytes reduced expression of key cytokines in EAE (e.g., IFN- γ) indicating that NSCs possess immunosuppressive capability. However, only GS-N cells were able to suppress T-cell proliferative responses upon exposure to MOG_{35–55}. Surprisingly administration (intravenous or intraperitoneal) of these NSC lines in MOG_{35–55}-induced EAE mice did not improve clinical score, likely owing to their inability to traffic to sites of inflammation. GS-N cells lack cell surface expression of many key homing molecules, including CD44 and integrin $\alpha 4$; by contrast, 46C-NS cells express CD44 and integrin $\alpha 4$. However, neither cell type expresses CXCR4, a chemokine receptor previously implicated in recruiting lymphocytes and NSCs to sites of CNS pathology via SDF-1 (CXCL12) [14–16]. CXCR4 is present on primary NSCs but its expression may be lost during *in vitro* expansion. Therefore, the lack of NSC homing ability, independent of their positive immunomodulatory effects, may be a key concern for their therapeutic use.

Conclusion & future perspective

In conclusion, much progress has been made in laying out the groundwork for stem cell-based therapies to be used for MS treatment. Further work is needed to explore the effects of stem cell transplantation with or without ablative therapies and to maximize the success of this approach. Animal models have also demonstrated the importance of proper expression of homing molecules in stem cells to reach area of pathology as well as the timing of stem cell delivery. Optimizing the procedure and timing of stem cell delivery to attenuate the immune response, and repair the damaged BBB and demyelinated axons, will be critical in maximizing the potential of stem cell-based therapies.

Acknowledgments

The authors would like to thank T Cutforth for help with the preparation of the editorial.

D Agalliu and J Lengfeld are supported by grants from the NMSS (RG4673A1/1) and NIH (1R01 HL116995–01). SE Lutz is supported by a NMSS postdoctoral fellowship (FG 2035-A-1).

Biography

Dritan Agalliu

References

1. Plumb J, McQuaid S, Mirakhur M, Kirk J. Abnormal endothelial tight junctions in active lesions and normal-appearing white matter in multiple sclerosis. *Brain Pathol.* 2002; 12:154–169. [PubMed: 11958369]
2. Bogoslovsky T, Chaudhry A, Latour L, et al. Endothelial progenitor cells correlate with lesion volume and growth in acute stroke. *Neurology.* 2010; 75:2059–2062. [PubMed: 21135380]
3. Huang XT, Zhang YQ, Li SJ, et al. Intracerebroventricular transplantation of *ex vivo* expanded endothelial colony-forming cells restores blood–brain barrier integrity and promotes angiogenesis of mice with traumatic brain injury. *J. Neurotrauma.* 2013; 30(24):2080–2088. [PubMed: 23957220]
4. Bogoslovsky T, Spatz M, Chaudhry A, et al. Circulating CD133⁺CD34⁺ progenitor cells inversely correlate with soluble ICAM-1 in early ischemic stroke patients. *J. Transl. Med.* 2011; 9:145. [PubMed: 21871109]
5. Menge T, Zhao Y, Zhao J, et al. Mesenchymal stem cells regulate blood–brain barrier integrity through TIMP3 release after traumatic brain injury. *Sci. Transl. Med.* 2012; 4 161ra150.
6. Pati S, Khakoo AY, Zhao J, et al. Human mesenchymal stem cells inhibit vascular permeability by modulating vascular endothelial cadherin/beta-catenin signaling. *Stem Cells Dev.* 2011; 20:89–101. [PubMed: 20446815]
7. Darlington PJ, Touil T, Doucet JS, et al. Diminished Th17 (not Th1) responses underlie multiple sclerosis disease abrogation after hematopoietic stem cell transplantation. *Ann Neurol.* 2013; 73:341–354. [PubMed: 23463494]
8. Bai L, Lennon DP, Caplan AI, et al. Hepatocyte growth factor mediates mesenchymal stem cell-induced recovery in multiple sclerosis models. *Nat. Neurosci.* 2012; 15:862–870. [PubMed: 22610068]
9. Bai L, Hecker J, Kerstetter A, Miller RH. Myelin repair and functional recovery mediated by neural cell transplantation in a mouse model of multiple sclerosis. *Neurosci. Bull.* 2013; 29:239–250. [PubMed: 23471865]
10. Darlington PJ, Boivin MN, Bar-Or A. Harnessing the therapeutic potential of mesenchymal stem cells in multiple sclerosis. *Expert Rev. Neurother.* 2011; 11:1295–1303. [PubMed: 21864075]
11. Rafei M, Berchiche YA, Birman E, et al. An engineered GM-CSF–CCL2 fusokine is a potent inhibitor of CCR2-driven inflammation as demonstrated in a murine model of inflammatory arthritis. *J. Immunol.* 2009; 183:1759–1766. [PubMed: 19592643]
12. Abrahamsson SV, Angelini DF, Dubinsky AN, et al. Non-myeloablative autologous haematopoietic stem cell transplantation expands regulatory cells and depletes IL-17 producing mucosal-associated invariant T cells in multiple sclerosis. *Brain.* 2013; 136:2888–2903. [PubMed: 23864273]
13. Payne NL, Sun G, Herszfeld D, et al. Comparative study on the therapeutic potential of neurally differentiated stem cells in a mouse model of multiple sclerosis. *PLoS ONE.* 2012; 7:e35093. [PubMed: 22514711]
14. Krumbholz M, Theil D, Cepok S, et al. Chemokines in multiple sclerosis: CXCL12 and CXCL13 up-regulation is differentially linked to CNS immune cell recruitment. *Brain.* 2006; 129:200–211. [PubMed: 16280350]
15. Liu KK, Dorovini-Zis K. Regulation of CXCL12 and CXCR4 expression by human brain endothelial cells and their role in CD4⁺ and CD8⁺ T cell adhesion and transendothelial migration. *J. Neuroimmunol.* 2009; 215:49–64. [PubMed: 19765831]
16. Imitola J, Raddassi K, Park KI, et al. Directed migration of neural stem cells to sites of CNS injury by the stromal cell-derived factor 1alpha/CXC chemokine receptor 4 pathway. *Proc. Natl Acad. Sci. USA.* 2004; 101:18117–18122. [PubMed: 15608062]