Citation: Clinical and Translational Gastroenterology (2017) 8, e82; doi:10.1038/ctg.2017.7
 2155-384X/17

www.nature.com/ctg

TRANSLATIONAL MEDICINE: BENCH TO BEDSIDE

Stem Cell Therapy for Inflammatory Bowel Disease

Amy L. Lightner, MD[1]

Clinical and Translational Gastroenterology (2017) **8,** e82; doi:10.1038/ctg.2017.7; published online 16 March 2017

Introduction

Inflammatory bowel disease (IBD) can be categorized as Crohn's disease (CD) or ulcerative colitis (UC). Both are chronic inflammatory diseases of the bowel resulting in significant alterations in quality of life due to remitting and relapsing symptoms of pain, increased stool frequency, and anemia. Before the era of biologic therapy, with the US Food and Drug Administration (FDA) approval of infliximab in 1998, the cornerstone of medical therapy was corticosteroids. Since 1998, however, biologic therapy has taken a prominent role in the treatment of IBD, and drugs in the anti-tumor necrosis factor a (infliximab, adalimumab, certolizumab pegol, golimumab), anti-integrin (natalizumab, vedolizumab), and anti-interleukin (ustekinumab) classes have since been FDA-approved for the treatment of IBD. However, all have side effect profiles that limit their use, potential to develop a loss of response, potential for adverse reactions, and, most importantly, are only effective in up to half of IBD patients. Patients who become refractory to medical management eventually require surgery; up to 60% of patients with CD will require a bowel resection,[1] and 15% with UC undergo a colectomy.[2]

There is a clear need for improved treatment practices in order to avoid systemic complications with medical management and surgical intervention. Stem cell therapy is emerging as a promising treatment alternative. Herein we review key basic science articles to discuss important mechanistic aspects as to why stem cell therapy may be an effective treatment strategy to bring to the bedside.

Immunosuppressive Properties

In IBD, the immune system is in an overactive state. Mesenchymal stem cells (MSCs), multipotent stromal cells that can be isolated from many tissues, including bone marrow and adipose tissue, have been studied extensively for the treatment of IBD due to their immunomodulatory capability. One of the mechanisms through which MSCs modulate the immune system is via the promotion of regulatory T-cell (Treg) formation, a cell population found to be deficient or devoid of function in IBD patients.[3] As Treg cells are the most potent immunosuppressive T cells, with great ability to distinguish self from non-self antigens,[4] therapies that promote the production of Treg cells could foreseeably benefit IBD patients.

Melief *et al.*[5] used an *in vitro* culture system to focus on the molecular pathways underlying the promotion of Treg cells by MSCs. Peripheral blood mononuclear cells (PBMCs) were cocultured with MSCs, the phenotype of monocytes was analyzed through staining for surface receptors, and cytokine secretion from monocytes was determined by enzyme-linked immunosorbent assay. Antibody neutralization studies identified MSC-produced transforming growth factor β1 (TGF-β1) mediates the induction of Tregs. Because TGF-β1 is constitutively secreted by MSCs, the generation of Tregs by TGF-β1 appears independent of the interaction between MSCs and PBMCs. The group then showed that MSCs induced differentiation of monocytes toward macrophage type 2 cells that secrete high level of interleukin10 (IL-10) and chemokine motif ligand 18 (CCL18). CCL18 secreted by these monocytes induced the production of Treg cells. Therefore, MSCs promote the generation of Tregs directly by constitutive production of TGF-β1 and indirectly by influencing the differentiation of monocytes toward CCL18-producing type 2 macrophages. These mechanistic pathways may provide potential areas for improved therapeutic targets for the treatment of IBD.

[1]Division of Colon and Rectal Surgery, Mayo Clinic, Rochester, Minnesota, USA
Correspondence: Amy L. Lightner, MD, Mayo Clinic, Colon and Rectal Surgery, 200 1st St SW, Rochester, Minnesota 55905, USA. E-mail: Lightner.amy@mayo.edu

Intestinal Migration

Targeted delivery of stem cells is needed for CD and UC since both involve specific regions of the intestine. CD may affect any area from the mouth to the anus, but often presents with skip lesions, or limited regions of the bowel are affected, whereas UC is characteristically seen as continuous inflammation from rectum to cecum. Optimal stem cell-based therapy would allow for targeted delivery of MSCs to hone and engraft only in involved segments of the bowel as opposed to systemic distribution of cells.

Khalil *et al.*[6] sought to determine if stem cells facilitate epithelial repair in IBD through improved microcirculation and in doing so demonstrated localization of stem cells upon systemic delivery. Moderate to severe colitis was induced in mice by dextran sulfate sodium treatment. Once colitis was present, two million human $CD34^{-}$ stem cells were infused twice via the tail vein. The group found that the stem cells significantly reduced the colitis severity score in moderate ($P = 0.0003$) and severe ($P < 0.0001$) colitis after 35 days. Importantly, the group also found that the stem cells homed to the damaged digestive tract tissue—on histology, stem cells were detected predominately in the submucosa of the damaged colonic epithelium following killing. This secondary discovery that the stem cells selectively traveled and engrafted at sites of colonic inflammation and injury has important implications for the systemic use of stem cells to treat IBD.

Francois *et al.*[7] used a mouse model to investigate if MSCs, a stem cell used in most clinical trials, also selectively travel to sites of injury. Tissue damage was induced in nonobese diabetic/severe combined immunodeficient mice by whole-body radiation. Additional local irradiation was then superimposed to the total body irradiation (TBI) to create pockets of localized inflammation. MSCs were transplanted via tail vein injection into four groups of mice: Group 1 (no irradiation), Group 2 (TBI only), Group 3 (TBI and local irradiation to abdomen), and group 4 (TBI and local irradiation to the leg). Fifteen days after irradiation, quantitative and spatial distribution of MSCs was studied using histological analysis. In non-irradiated mice, MSCs homed at a very low level to various tissues (lung, bone marrow, and muscles) with no specific sites of engraftment, whereas TBI induced increased engraftment of MSCs in the brain, heart, bone marrow, and muscles. Additional abdominal and leg irradiation increased MSC engraftment in the specifically exposed areas (the gut, liver, and spleen, or the leg). Thus, MSCs specifically migrate to areas of damaged tissue, which is of significance in patients with CD and UC who have specific segments of bowel affected.

Alleviation of Experimental Colitis With MSCs

CD is characterized by activated T-helper cells promoting an exaggerated macrophage and neutrophil infiltration whose activation then leads to uncontrolled production of inflammatory cytokines and chemokines. Gonzalez *et al.*[8] sought to characterize the therapeutic effect of both human and mouse adipose-derived MSCs on restoring immune tolerance and inhibiting the inflammatory response *in vivo*. Trinitrobenzene sulfonic acid in ethanol was administered intrarectally in BALB/c mice to induce colitis. MSCs were then delivered intraperitoneally. The group found that systemic infusion of either human or mouse MSCs ameliorated the clinical and histopathologic severity of colitis. This effect was mediated by downregulating T-helper responses, impairing T-helper expansion, and inducing Treg expansion. This study demonstrated the effectiveness of MSCs for the treatment of an IBD model of colitis, again underscoring the importance of Treg cells.

Conclusions

Taken together, MSCs offer a promising emerging therapy for patients with IBD due to their immunosuppressive properties, ability to migrate to areas of injury, and demonstration of colonic healing in a mouse model. Future research will expand these basic science findings by translating them to bedside clinical trials for the treatment of IBD, a disease whose pathogenesis remains unknown and is notoriously difficult to treat.

CONFLICT OF INTEREST

Guarantor of the article: Amy L. Lightner, MD.
Financial support: None.
Potential competing interests: None.

1. Peyrin-Biroulet L, Harmsen WS, Tremaine WJ *et al.* Surgery in a population-based cohort of Crohn's disease from Olmsted County, Minnesota (1970–2004). *Am J Gastroenterol* 2012; **107**: 1693–1701.
2. Targownik LE, Singh H, Nugent Z *et al.* The epidemiology of colectomy in ulcerative colitis: results from a population-based cohort. *Am J Gastroenterol* 2012; **107**: 1228–1235.
3. Mayne CG, Williams CB. Induced and natural regulatory T cells in the development of inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19**: 1772–1788.
4. Himmel ME, Yao Y, Orban PC *et al.* Regulatory T-cell therapy for inflammatory bowel disease: more questions than answers. *Immunology* 2012; **136**: 115–122.

5. Melief SM, Schrama E, Brugman MH *et al.* Multipotent stromal cells induce human regulatory T cells through a novel pathway involving skewing of monocytes toward anti-inflammatory macrophages. *Stem Cells* 2013; **31**: 1980–1991.
6. Khalil PN, Weiler V, Nelson PJ *et al.* Nonmyeloablative stem cell therapy enhances microcirculation and tissue regeneration in murine inflammatory bowel disease. *Gastroenterology* 2007; **132**: 944–954.
7. Francois S, Bensidhoum M, Mouiseddine M *et al.* Local irradiation not only induces homing of human mesenchymal stem cells at exposed sites but promotes their widespread engraftment to multiple organs: a study of their quantitative distribution after irradiation damage. *Stem Cells* 2006; **24**: 1020–1029.
8. Gonzalez MA, Gonzalez-Rey E, Rico L *et al.* Adipose-derived mesenchymal stem cells alleviate experimental colitis by inhibiting inflammatory and autoimmune responses. *Gastroenterology* 2009; **136**: 978–989.