Stem Cell Therapy in Feline Chronic Enteropathy

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Adult stem cells were first discovered approximately fifty years ago. Although much remains unknown about them, it is thought that the cells remain in specialized ‘niches’ in adult animals for use in tissue repair and replacement throughout the life of the animal. There are two main types of adult stem cells: hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSC).

MSCs are derived from a multitude of adult tissues. They are less controversial than other stem cell types as they are derived from adult tissues such as adipose tissue, and MSC have limited self-renewal capacity. MSCs are thought to be immunologically-privileged cells that can be given as an allogeneic and even xenogeneic transplant without inducing a clinically noted immune response. They have homing capabilities, which make them appealing for regenerative therapies as they can tract towards areas of inflammation. They also have immunomodulatory functions. Due to these properties, MSCs have been considered in many medical applications including tissue regeneration, as cell vehicles for gene therapy, to enhance HSC engraftment, and for treatment of immune diseases. In terms of regenerative therapies, there is little direct evidence that MSCs actually engraft and become new tissue to any notable degree. However, there is a great deal of evidence that MSCs have many immunomodulatory functions. MSCs have trophic effects in that they secrete cytokines and growth factors with both paracrine and autocrine effects. MSCs induce local immunosuppression as they avoid allorecognition, suppress T and B cell proliferation, alter dendritic cell (DC) maturation and function, and modulate natural killer (NK) cells and macrophage function. MSCs can also inhibit fibrosis and apoptosis, enhance angiogenesis, and stimulate mitosis and differentiation of tissue-intrinsic reparative or stem cells. In 2002 three different investigators discovered that MSCs suppress lymphocyte proliferation in vitro, which highlighted the potential application of the cells to treat immune disease.

Inflammatory bowel disease (IBD) affecting domestic cats is defined by Washabau et al. in the ACVIM Consensus Statement in 2010 as a chronic (>3 weeks) condition with persistent and/or progressive gastrointestinal symptoms. Definitive diagnosis requires histopathology. IBD is an idiopathic disease so other potential causes of the symptoms need to be ruled-out. The patient has inadequate response to dietary, antibiotic, and/or antihelmintic therapy alone. Clinical response is seen to anti-inflammatory or immunosuppressive therapy. It has been shown that the clinical severity and response to therapy in affected cats does not necessarily correspond to the histopathologic changes or their severity. Treatment often involves a change in diet, antibiotics, supplements such as cobalamin, and immunosuppressive drugs such as prednisolone or chlorambucil. Unfortunately, some cats do not have
adequate resolution of their symptoms with this therapy, and affected cats generally require life-long medication.

Humans also suffer from IBD, which has two main forms: Crohn’s disease and ulcerative colitis (UC). As in cats it is an idiopathic disease with chronic inflammation. Nearly all patients require surgery at some point, and the disease generally continues to progress even despite surgery. In about 10% of human cases of UC, there is persistent disease despite therapy. IBD in humans is a major cause of morbidity and increased health care costs. New therapies are needed to help with this disease, especially considering the disease starts in childhood for some individuals. Currently, there is no cure for IBD.

Due to the chronic inflammatory nature of IBD and the severity of the disease in some affected people, application of the immunomodulatory effects of stem cells has recently been investigated. MSCs, as discussed, are relatively immunologically inert, can migrate to the site of disease, have the ability to suppress immune responses, actively participate in tissue repair processes, alter cytokine secretion profiles, effect differentiation of monocytes into DCs, downregulate co-stimulatory molecules, reduce activation of T cell proliferation, and secrete prostaglandin (PGE2) in response to inflammation. Several initial studies looked at bone marrow-derived MSCs for treatment of refractory Crohn’s disease and saw induction of remission with autologous hematopoietic cell transplantation in some or most of the treated individuals. In fact, Phase I, II, and III human trials of stem cell therapy for human IBD are completed or underway. In 2014 an article published in the World Journal of Gastroenterology noted that “MSCs have immune regulatory and regenerative properties, and low immunogenicity...MSCs have been used via the systemic route in IBD with promising results...though it is still too soon to draw firm conclusions.” Additionally, Duijvestein et al. showed that azathioprine, methotrexate, and anti-TNF compounds do not change the phenotype, morphology, viability, differentiation, and functional capabilities when incubated with MSCs in physiological concentrations. And, MSCs did not hamper the immunosuppressive effect of those medications for treatment of CD. Dalal et al. in 2012 noted that “thus far MSC have proven to be safe and have not resulted in toxicity or ectopic tissue growth in an increasing number of human trials,” although concern over cell transformation in later passages remains.

Application of MSC therapy to cats with chronic enteropathy was based on these studies in human IBD. The Winn Feline Foundation funded a pilot study to evaluate the safety and clinical efficacy of MSC treatment of feline chronic enteropathy to determine if such a novel therapy deserved further study. The results of the study have been published in the Journal of Feline Medicine and Surgery (2015). The blinded, placebo-controlled study enrolled client-owned cats with chronic enteropathy. Initial workup included physical examination, CBC, chemistry profile, total T4, and urinalysis to assess for concurrent disease. Concurrent diseases were not an exclusion criteria if the disease was stable and treatment was not changed during the course of the study. Treatment for the chronic enteropathy also had to
remain stable throughout the course of the study. At Day 0 of the study, owners filled out a questionnaire, bloodwork was collected for screening and a Texas GI panel. The first MSC/placebo injection was given at this time. The cats returned in two weeks for the second MSC/placebo injection. An additional two weeks later, the cats returned for a repeat Texas GI panel and questionnaire. One month later, a follow-up phone call was performed.

In total 10 cats were treated with MSCs. They received two injections two weeks apart of 2x10^6 MSC/kg body weight. The cells were allogeneic and all derived from adipose tissue from the same healthy specific pathogen free female cat. The cells were culture-expanded, freshly-cultured, and between passage 2 and 4. No adverse events were noted during the study period. Seven of the treated cats were blinded to their treatment group. Of these cats, 5/7 had significant improvement or resolution of their clinical signs. Two of the seven cats had modest but persistent improvement. Of the four blinded placebo cats, no change or some worsening was seen in their clinical signs during the course of the study. Three cats were not blinded to their treatment. Of these cats, one was lost to follow-up (adopted), one had marked improvement, and one had no change in clinical signs. Significant improvement was noted in mean fecal consistence in the MSC-treated group.

This pilot study supports further investigate the use of MSC for treatment of feline chronic enteropathy. Many questions remain to be answered in the potential clinical application of MSC to feline chronic enteropathy including optimization of treatment (donor selection, recipient selection, pretreatment or pre-conditioning of the cells, dose, interval, frequency, and total number of treatments) as well as investigation into the mechanism of action of the cells.

Currently, MSC therapy is a research procedure that is not approved by the FDA. The veterinary regenerative field is still working on two major issues with the application of MSCs to clinical disease: demonstrating safety and efficacy. Much still remains unknown about MSCs. Regulation of MSC and other regenerative therapies is still not fully established in veterinary medicine, although there are new FDA requirements and Guidelines. Although there are several promising studies to encourage continued investigation into the application of MSC to veterinary clinical diseases such as IBD, continued research is crucial.

References: