TheEducationCenter A RESOURCE FOR THE ASTUTE PRACTITIONER
A special advertising section

Stem cell therapy in immune-mediated disease

By Bob Harman, DVM, MPVM
For the Education Center

Immune-mediated diseases are some of the most refractory and difficult clinical challenges for the small animal practitioner. Immunology is complex, and our clinical tools are limited for trying to modulate aberrant immune system responses. Current therapy is still fundamentally rooted in immunosuppression, and the majority of these drugs are adopted from human medicine without a label for canine or feline veterinary use.[1] In recent years, mesenchymal stem cell (MSC) therapy has become prominent in the press and literature and is being tested for efficacy and safety in many areas of human clinical medicine as evidenced by the 738 clinical trials currently registered with clinicaltrials.gov, including 108 that are specific to immune system disorders.

In veterinary medicine, we have a large number of immune-mediated diseases that affect our patients. Table 1 lists briefly some of the more common ones by organ system. This article covers how MSCs may function in the treatment immune-mediated diseases.

Immune system cells

The immune system is commonly divided into two categories: the innate and the adaptive.

Innate immune system

The innate immune system generally is thought of as nonspecific, such as epithelial barriers, secreted antimicrobial substances, and the phagocytic and natural killer (NK) cells.[1] A central cell in the innate system is the dendritic antigen-presenting cell (APC). This cell interacts with any incoming foreign substance and will internalize, process, and present portions of the foreign substance to cells of the adaptive immune system for further action. Although part of the innate (nonspecific) arm of the immune system, it is now known that the interactions between dendritic cells and pathogens are quite specific and involve pattern-recognition receptors.[1] It is also believed that the APC interacts with foreign substances and activates many genes, leading to production of specific proteins that can take part in the interaction with the adaptive immune system.[2]

Adaptive immune system

The adaptive immune system is composed of T cells and B cells. The study of T cells has evolved rapidly in recent years with discovery of existence of a large number of subsets with specific functions. The APCs of the innate immune system deliver these foreign substance fractions to T cells located in regional lymph nodes. All veterinary students are taught that T cell subsets include T helper cells (also called CD4+), T cytotoxic cells, and T suppressor cells. More recently, knowledge of T helper cell functional subsets has broadened the understanding of the complex interactions between these specialized T cells. The most prominently studies subsets are the TH1/TH17 combination and the TH2/TH9 combination, and these have been specifically studied in dogs.[3,4] Another arm of the T helper cells subset includes the suppressor or regulatory cells that provide the offsetting balance in the system. These are particularly important for this discussion in the suppression/prevention of activation of autoreactive or allergen-reactive T cells.[1,5]

Autoimmunity

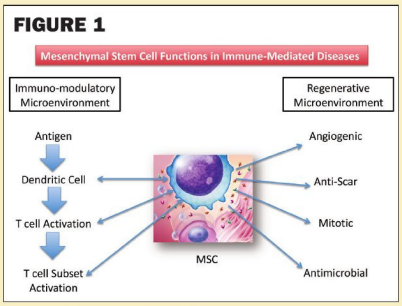
Autoimmunity occurs when the immune system somehow recognizes the host tissue as foreign. Whitley et al described autoimmunity as "Fundamentally, the latter may involve a lack of the Treg effect in parallel with an inappropriate presentation of autoantigen by APC that permits excessive activation of Th1 cells (for autoimmune diseases involving cytotoxic destruction of target tissue; *e.g.*, canine lymphocytic thyroiditis) or Th2 cells (for autoimmune diseases involving autoantibody production; *e.g.*, canine autoimmune hemolytic anemia or thrombocytopenia)."[1]

A significant predisposing factor in human and canine autoimmune disease is genetic background,1 with a common example being immune-mediated hemolytic anemia.[6] But the actual triggers are often cited as an infectious agent (*i.e.*, Babesia, Ehrlichia, virus, bacteria) or drug and vaccine administration.[1,7]

Let's now explore how the MSC functions in this environment and how therapy with MSCs might be indicated in immune-mediated diseases.

This author welcomes technical questions, comments, or reference list requests (bharman@vetstem.com).

FIGURE 1



Overview of the immune system

Table 1

COMMON SMALL ANIMAL IMMUNE-MEDIATED DISEASES	
Gastrointestinal	Inflammatory bowel disease
Hematology	Immune-mediated hemolytic anemia, immune-mediated thrombocytopenia
Oral	Feline chronic gingivostomatitis
Nervous	Myasthenia gravis
Ophthalmology	Keratoconjunctivitis secca
Orthopedic	Immune-mediated polyarthritis
Renal	Glomerulonephritis
Dermal	Pemphigus, lupus

MSC interaction with immune cells

In a comprehensive 2017 review of MSC immunomodualtory functions, Volarevik et al described MSCs "as new therapeutic agents in the treatment of immune-mediated diseases, particularly due to their immunomodulatory characteristics. In cell-to-cell contact and through the production of soluble mediators, MSCs can regulate the proliferation, activation, and effector function of T lymphocytes, professional antigen presenting cells, NK cells, NKT cells, and neutrophils."[8] Quite a mouthful, but it makes clear that there is evidence for the MSC being at the center of balancing the immune system and preventing or treating immune-mediated diseases.

The following are examples of immune-mediated diseases in dogs and cats that have supporting literature on the mechanisms, therapeutic approaches, and clinical outcomes.

Keratoconjunctivitis sicca (dry eye)

Keratoconjunctivitis sicca (KCS) is a common disease where dogs experience reduced or absent tear production.[9] In humans, patients with dry eye often are afflicted with other immune-mediated diseases such as rheumatoid arthritis, and these immune-mediated mechanisms contribute to cruciate ligament disease and osteoarthritis in humans and dogs.[10] Lifetime immunosuppression is the most common therapy for canine KCS.[9] Three recent peer-reviewed publications document the clinical use of adipose-derived stem cells in the therapy of KCS.[9,11,12] These authors used the approach of lacrimal gland/third eyelid site for injection. Successful improvement in the corneal pathology and improvement in tear production were seen in clinically affected dogs demonstrating proof of concept of this approach.

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a group of disorders of the GI tract of dogs and cats that are immunologically mediated, and therapy often involves dietary and pharmacologic interventions as well as use of antibiotics and soluble fiber supplements.[13] The literature contains numerous articles on the use of adipose stem cells in the therapy of human ulcerative colitis and Crohn's disease, and the European Medicines Agency recently recommended approval of the first adipose-stem cell product for therapeutic use in humans. Perez-Merino's 2015 article on use of allogeneic adipose-derived stem cells in IBD in dogs showed clinical remission in 9/11 dogs that had been treated with a single IV dose of 2 x 10^6/kg stem cells.[14] In a similar placebo-controlled study in cats with IBD and receiving a single IV dose of 2 x 10^6/kg stem cells, 5/7 treated cats showed significant improvement or complete remission while none of the placebo cats improved.[15]

Feline chronic gingivostomatitis

Feline chronic gingivostomatitis (FCGS) is a severe oral inflammatory disease of cats with an estimated prevalence of 0.7 to 12 percent of the U.S. cat population.[16-18] Clinical signs are moderate to severe oral pain and discomfort, including inappetence, reduced grooming, weight loss, and hypersalivation.[18,19] The most common treatment is full mouth extraction, with approximately 60 percent of cats responding. Approximately 20 percent of cats improve, and another 20 percent do not respond well to the extractions and require lifelong therapy with antibiotics, corticosteroids, and pain medication (refractory FCGS).[18] The pathogenesis of FCGS is not well understood but is proposed to be due to the host immune system responding inappropriately to chronic oral antigenic stimulation, possibly secondary to underlying oral bacterial or viral infections.[17] Arzi et al at UC Davis have conducted and published two studies on the use of adipose-derived stem cells to treat refractory FCGS in cats with full mouth extractions. The first study evaluated autologous adipose stem cells in a two-dose regimen of 20 million stem cells per dose intravenously. Five of seven cats had either complete remission or substantial clinical improvement.[20] In the second study, they used allogeneic (donor) adipose stem cells and found 4/7 cats responded with three cats as nonresponders.[21]

Summary

Immune-mediated diseases are complex and have limited therapeutic options. The discovery and research on the immune-modulatory functions of MSCs have now opened the door for new options for therapy of these difficult and chronic conditions. The above three diseases are examples immune-mediated disorders treated with stem cells, but many more have research data in human and animal species that suggest a broad range of conditions may be potential targets for cell therapy modalities. ●

This Education Center article was underwritten by VetStem Biopharma of Poway, Calif.