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Therapeutic potential of stem cells

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Abstract
The stem cell field in veterinary medicine continues to evolve rapidly both experimentally and clinically. The same methods can be used to generate transgenic animals for production of pharmaceuticals or for use as biomedical models. Small and large animal species serve as valuable models for preclinical evaluation of stem cell applications in human beings and in veterinary patients in areas such as spinal cord injury and myocardial infarction. However, these applications have not been implemented in the clinical treatment of veterinary patients. Reviews on the use of animal models for stem cell research have been published recently. Therefore, in this review, animal model research will be reviewed only in the context of supporting the current clinical application of stem cells in veterinary medicine.

Keywords: Therapeutic, potential, stem, transgenic, animal

Introduction
Regenerative medicine is a branch of medicine that develops methods to grow, repair, or replace damaged or diseased cells, organs or tissues. It has gained significant momentum in recent years. At present, stem cell therapies in veterinary patients are not rigorously supervised by regulatory agencies in any country [1]. It is unclear whether stem cells ultimately function once differentiated into a tissue-specific cell such as a tenocyte or whether they primarily improve tissue repair through secretion of immunomodulatory and bioactive trophic factors or whether a combination of the two mechanisms occurs [2]. Safe and efficacious applications of allogeneic stem cells would imply that off-the-shelf stem cell products could be developed for increased availability and rapid implementation of stem cell therapies early in a disease course.

They are classified by their source as
a. Embryonic (ESC)
b. Adult,
c. Induced pluripotent stem cells (IPSC) [2, 3].

Considering their phase of development and differentiation, they are further classified as totipotent, pluripotent, or multipotent cells [4]. The first isolation of human ESC was reported in 1998 [5]. Another alternative to ESCs presents the stem cells which are present in the adult organism. Bone marrow and umbilical cord blood contain hematopoietic stem cells (HSCs) and non-hematopoietic or mesenchymal stem cells (MSC), the latter residing also in numerous other tissues.

Stem cell Sources
Tissue origin of stem cells
To date, MSCs were successfully isolated from various tissues, and based on the source they have different properties, which should be considered when choosing the optimal stem cell therapy approach aiming at the tissue healing. In dogs, horses and cats, the most common companion veterinary patients, MSCs have been isolated from bone marrow, adipose tissue, synovium, synovial fluid, synovial membrane, infrapatellar fat pad, umbilical cord, umbilical cord blood, Wharton's Jelly, muscle and periosteum, gingiva and periodontal ligament, peripheral blood, endometrium and placenta [6].

Autologous and allogeneic stem cells
Based on the donor-recipient relationship, stem cells can be classified as autologous, allogeneic, or xenogeneic stem cells.

Autologous stem cells are collected from and administered to the same individual, allogeneic stem cells are collected from a donor and used in a recipient of the same species, whereas xenogeneic stem cells are those that are transplanted across species [7].

Therapeutic potentials of MSC

Paracrine effects

Increasing evidence suggests that the primary mechanism of action of MSC relies on paracrine signaling which results in functional changes in the immune cells, such as monocytes/macrophages, dendritic cells, T-cells, B-cells, and natural killer cells. Several factors have been reported to contribute to the immunomodulatory effects of MSC. Among them are well-established effectors such as transforming growth factor-beta (TGF-β), indolamine-2,3-dioxygenase (IDO), prostaglandin E2 (PGE2), interleukin 10 (IL-10) and tumor necrosis factor-(TNF) stimulated gene-6 (TSG-6) [8].

Secretion of extracellular vesicles (ECV)

The paracrine action of MSCs is not limited solely to the secretion of soluble factors since MSCs have the capability to transfer various molecules through the extracellular vesicles (ECV). ECVs are vesicles arising from the plasma membrane by outward or inward budding. They are carriers of miRNA, mRNA, proteins, and mitochondria that are protected by the membrane. This enables ECVs to move long distances inside the body. ECV include exosomes, which are 30-150 nm large plasma membrane coated vesicles of endocytic origin, microvesicles, which are 100-1000 nm large vesicles of non-endocytic origin, and apoptotic bodies, 50 nm−5 μm large vesicles released during membrane blebbing of apoptotic cells [9].

Apoptosis-mediated immunomodulation

Apoptosis might also play an important role in the immunomodulatory effect of MSC. Phagocytic clearance of dying cells (efferocytosis) takes part not only in resolving inflammation and restoring the function of damaged tissue but also in the adaptive and immune responses in inflamed tissues [10].

Mitochondrial transfer

The mitochondrial transfer has been proposed as another mechanism of MSC action. In addition to transferring molecules via ECVs, MSCs seem to be capable of intercellular transfer of organelles via tunneling nanotubes. In 2006 the first mitochondria transfer between MSC and somatic cells was observed [11]. This study revealed that active transfer of mitochondria from adult stem cells to somatic cells can rescue aerobic respiration in mammalian cells with non-functional mitochondria. In a mouse model of pneumonia, human BMMSC could transfer their mitochondria through the tunneling nanotubes to alveolar macrophages, which led to the enhanced phagocytosis of macrophages and antimicrobial effect of MSC [12].

Clinical use of MSC in veterinary medicine

To date, stem cells have been used, mostly experimentally, for treatments of a variety of diseases in different animal species. The initial focus of regenerative veterinary medicine was directed to the orthopedic diseases, but the focus is now rapidly expanding to other areas such as orodental and digestive tract diseases, liver, renal, cardiac, respiratory, neuromuscular, dermal, olfactory and reproductive system diseases.

It was shown that intraarticularly injected autologous BMMSCs engraft to the site of the injured cranial crucial ligament and have an anti-inflammatory effect. Post-operatively intraarticular or IV injection of autologous MSC in dogs with the same condition resulted in a decreased level of CD8+ T-cells, decreased serum and synovia CRP, and decreased synovial IFN-γ levels that persisted over 8 weeks after BMMSC injection. In cases of partial tears with no destabilization of the stifle joint, where surgery is not the optimal solution, promising results were collected from the retrospective study, where autologous treatment in combination prevented progression of further degenerative changes in the joint and contralateral ligament rupture in dogs [13]. Stem cell therapy in treating musculoskeletal disorders has proven remarkably effective, especially in horses with tendon injuries, bone spavin, and meniscal damages, and in dogs with osteoarthritic conditions. Such positive outcomes of stem cell therapies are thus decreasing the need for prolonged local or systemic use of anti-inflammatory drugs with their known toxic side effects. However, additional studies are needed to broaden our knowledge on mechanisms of action of stem cells, and especially allogeneic stem cells, as not all studies provided positive results on their safety when used in the therapy. Stem cells derived ECVs might represent a promising alternative to the allogeneic stem cell therapy as they mimic several biological actions of stem cells. ECV therapy has already been tested for treating suspensory ligament injury in a stallion, rendering positive results shown as increased lesion filling, improved angiogenesis, and elasticity of the damaged tendon [14].

Due to their immunomodulatory and anti-inflammatory effects, stem cells seem to be a suitable alternative therapy for dogs and cats with digestive tract disease. Results of preliminary studies are promising, but significant follow-up studies and further research is needed to establish stem cell treatment as a safe and effective method for treating digestive tract disease in animals. Chronic kidney disease (CKD) is a common medical condition in geriatric cats and is characterized by chronic tubulointerstitial nephritis, tubular atrophy, and interstitial fibrosis. Currently, renal transplantation is the only therapy that may restore renal function [15]. Petechiae and Soonleewong investigated the effect of IV administration of puppy deciduous teeth derived stem cells on the degenerative valvular disease [16]. Their results showed an improvement in the left ventricular ejection fraction, but this was a small study, and more studies will be needed to establish any potential positive effects. Single intratracheal administration of autologous cells and oral therapy with dexamethasone showed that bone marrow-derived mononuclear cells improved clinical signs and the inflammatory response in horses suffering from RAO. Levels of IL-10 increased after the cell treatment and were significantly higher than in the control group treated with dexamethasone. The results of this study correlate with positive results of experimental studies with induced respiratory conditions in dogs and cats [17].

Conclusion

Despite considerable advancements in veterinary regenerative medicine in recent years, this field is still in its infancy and much more work is needed to resolve many questions before proven, standardized therapies could be offered to the clinical

patients. We live in exciting times as new regenerative therapies are on the rise. One can be hopeful that the continuous research in this area will lead us to the point when the stem cell treatments for many currently untreatable diseases will not be a mere possibility but a realistic and accessible choice for the patients in both veterinary and human medicine.

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