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Review

Novel treatment strategies for feline chronic kidney disease: A critical look at the potential of mesenchymal stem cell therapy

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ABSTRACT

Stem cell therapy is an innovative field of scientific investigation with tremendous potential for clinical application that holds promise for the treatment of a variety of diseases in veterinary medicine. Based on the known desirable properties of mesenchymal stem cells, the therapy has potential for treatment of both acute kidney injury and chronic kidney disease in cats. This review details terminology commonly used in this field of study, sources of mesenchymal stem cells and their proposed mechanism of action particularly as it relates to renal repair. Studies performed in rodent models of chronic kidney disease and feline clinical trial results are also summarized with the aim of providing an overview of the current status of this treatment modality and its potential for the future.

Introduction

Regenerative medicine refers to the process of using living cells or tissues to repair or replace tissues or organs that are functionally damaged. It is an innovative field of scientific investigation with tremendous potential for clinical applications in veterinary as well as human medicine. Regenerative medicine strategies currently under investigation for kidney disease include (but are not limited to) exploring the use of stem cells and resident renal progenitor cells and their by-products (microvesicles), reprogramming stem cells into renal progenitor cells or reprogramming of renal cells into a more pluripotent cell type, and the use of decellularized kidney scaffolds for renal regeneration with or without induced pluripotent stem cells to seed the scaffolds (Aggarwal et al., 2013).

Recent years have brought increased interest in the potential use of adult stem cells in the treatment of disease through both their regenerative properties and their ability to alter the tissue environment in injured and diseased organs. In particular, adult stem cells known as mesenchymal stem cells (MSCs) can migrate to affected areas and support the growth of other stem cells, as well as modulate immune responses. Based on the known desirable properties of MSCs, MSC therapy has potential for treatment of both acute kidney injury (AKI) and chronic kidney disease (CKD) in cats.

This review describes what is currently known about the application of MSC therapy for feline CKD. We begin by defining MSC terminology and potential sources of stem cells in veterinary medicine, as well as the therapeutic implication of these sources. The proposed mechanism of action of MSCs is also discussed, particularly as it relates to renal regeneration and repair. We then review studies that have been performed in rodent models of CKD as well as clinical trials in pet cats and conclude with a summary of the current status of this potential therapy.

What are mesenchymal stem cells?

A stem cell is a generic term referring to any unspecialized cell that is capable of long-term self-renewal through cell division but that can be induced to differentiate into a specialized, functional cell. Stem cells are generally divided into two groups, embryonic stem cells and adult stem cells. Adult stem cells can be obtained from many differentiated tissues including (but not limited to) bone marrow, bone, fat, and muscle tissues. Obtaining adult stem cells also does not raise ethical concerns, and most commonly stem cells are obtained from bone marrow or adipose sources.

For many studies that use the label 'stem cell therapy', the cells being used are actually MSCs, also referred to in some publications as mesenchymal stromal cells. MSCs are multipotent but not pluripotent, which means they can differentiate primarily into adipose, cartilage and bone tissues, but do not readily differentiate into other cell lineages. (Reinders et al., 2010). MSCs have the ability to home to injured tissues and can produce tropic factors that can promote repair and regeneration, giving them tremendous therapeutic potential.

MSC sources

MSCs can be isolated from virtually every tissue in the body. In cats, sources of MSCs that have been utilized for expansion and

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clinical therapy include bone marrow, adipose, testicular and ovarian tissue salvaged from routine sterilization procedures, and fetal membrane tissues discarded from pregnant ovariohysterectomy (Martin et al., 2002; Iacono et al., 2012; Webb et al., 2012; Quimby et al., 2013; Zhang et al., 2014). As the tissue source with the highest MSC proliferation potential appears to vary from species to species (Ribitsch et al., 2010; Kisiel et al., 2012), a recent study in cats compared the proliferative capacities of MSCs from different sources (Webb et al., 2012). In addition to a relatively easier collection procedure, adipose-derived MSCs (aMSCs) were found to be superior in proliferative potential than bone marrow-derived MSCs (bmMSCs) and were considered therefore to be the preferred source for MSC therapy in cats (Webb et al., 2012).

Although most MSC therapies in AKI and CKD rodent models utilize bmMSCs, more recent studies indicate similar efficacy with aMSCs (Furuichi et al., 2012; Kim et al., 2012). The surface phenotype and immunologic properties of bmMSCs and aMSCs appear to be similar (Strioga et al., 2012), with recent literature even suggesting an added advantage of using aMSCs for immunomodulatory indications (Ivanova-Todorova et al., 2009).

Two different types of MSC products are currently being investigated as a novel therapy for CKD in cats; aMSCs expanded in culture and stromal vascular fraction (SVF) cells (also known as non-expanded aMSCs). SVF is the initial product of adipose tissue enzymatic digestion and is the type of cellular product produced from point of care tissue processors and by several private stem cell companies. In contrast to aMSC cultures which contain a relatively homogeneous population of activated and proliferating MSCs, the SVF product is a mixture of multiple cell types, primarily cell types such as adipocytes and endothelial cells that do not give rise to MSCs. These are thought to include MSCs as well as a mixture of B and T lymphocytes, endothelial cells, fibroblasts, macrophages, pericytes, and pre-adipocytes (Gimble et al., 2012).

Currently, not enough information is known about SVF to determine if such a product with a mixed cellular composition offers a therapeutic advantage or disadvantage for the intended applications. Culture-expanded MSCs (both bmMSCs and aMSCs) are the type predominantly used in the rodent model literature, however more recent rodent studies have started to explore the therapeutic potential of the SVF cellular product with promising results (Riordan et al., 2009; Yasuda et al., 2012).

Stem cells that are harvested from a patient with the intention of administering them back to that patient are termed autologous MSCs. Stem cells that are harvested from healthy donors for administration to a different, genetically unrelated patient are termed allogeneic MSCs. The relative efficacy of autologous vs. allogeneic cells is an area of controversy. Although allogeneic MSCs traditionally are thought to be immune-privileged and are not expected to incite an immune response, more recent evidence suggests that the terminology 'immune-evasive' may be more appropriate as antibody formation against and rejection of allogeneic donor MSCs have been documented (Ankrum et al., 2014). As a result it is argued that autologous MSCs may survive longer in the body in comparison to allogeneic cells, resulting in improved efficacy over the latter (Togel et al., 2009a). Decreased efficacy of allogeneic MSCs in comparison to autologous MSCs has been observed in one acute renal failure rodent study (Togel et al., 2009b). However, allogeneic MSCs have been widely used in experimental stem cell transfer investigations in rodents, as well as clinical trials in humans, with positive results (McTaggart and Atkinson, 2007; Togel et al., 2009b).

The advantages of using allogeneic MSCs include sparing the patient from undergoing the harvest procedure as well as the use of MSCs from young healthy donor animals. Recent studies in humans and rodents support the view that MSCs obtained from young healthy individuals have greater proliferation potential and have greater therapeutic potential than those collected from elderly diseased individuals (Lei et al., 2007; Kretlow et al., 2008; Scruggs et al., 2013; Wang et al., 2013).

Another concern about autologous MSC administration in animals with kidney disease is the growing body of literature supporting the theory that MSCs are adversely affected by uremia (Noh et al., 2012; van Koppen et al., 2012; Idziak et al., 2014; Klinkhammer et al., 2014; Yamada et al., 2014). Recent studies have documented that MSCs obtained from uremic rats have reduced proliferation in culture, caused loss of regenerative potential, premature senescence, decreased capacity to induce angiogenesis, and an altered secretome (Noh et al., 2012; van Koppen et al., 2012; Idziak et al., 2014; Klinkhammer et al., 2014).

Uremic effects also have been documented in vitro as a reduced capacity of MSCs from uremic individuals to ameliorate renal damage in experimentally-induced CKD in comparison to MSCs from healthy rats (van Koppen et al., 2012; Klinkhammer et al., 2014). Observations have been mixed as to whether this affects both bmMSCs and aMSCs. However one study offers evidence that aMSCs are not as susceptible to uremic effects as bmMSCs (Roemeling-van Rhijn et al., 2012).

Although there is a concern regarding the effects of uremia on MSC function, clinical trials performed with allogeneic aMSCs should circumvent these concerns and give the best opportunity for efficacy. This information does imply, however, that uremic patients are not the best MSC source, which is a concern for autologous MSC therapy. Little data have been gathered on whether MSCs transplanted into a uremic recipient environment will become compromised. The success of MSCs in palliation of AKI and CKD in rodent models argues against this being an issue.

Characterization

MSCs are plastic adherent and assume a fibroblast-like morphology during culture (Fig. 1). They proliferate easily in culture and can be cryopreserved without loss of phenotype or differentiation potential (Martinello et al., 2011); however whether cryopreservation affects their immunomodulatory capabilities has not been fully investigated. Cell surface marker characterization via flow cytometry can be used to distinguish MSCs from hematopoietic cells, but no truly unique MSC molecule has been identified (Schaffler and Buchler, 2007).

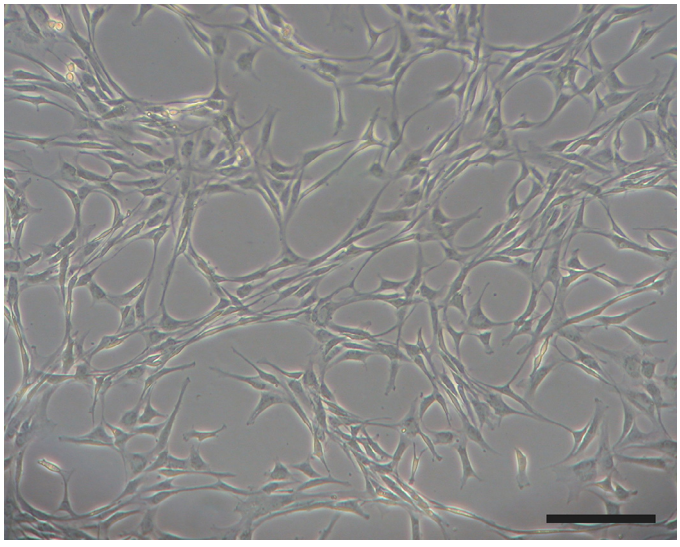

Fig. 1. Phenotype of feline adipose derived mesenchymal stem cells. Stem cells are plastic adherent and assume a fibroblast-like morphology during culture. Scale bar = 100 μm.