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Popular Article

Stem Cell Therapy in Veterinary Practice: An Overview

Umang J Dubariya[1]*, Monali B Bhaesaniya[2], S. H. Zalavadiya[3]
[1]Department of Veterinary Surgery &Radiology, College of Veterinary Science & Animal Husbandry, Kamdhenu University, Navsari, Gujarat-396450, India
[2]Department of Veterinary Anatomy, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Junagadh, Gujarat-362001, India
[3]Department of Veterinary Surgery &Radiology, College of Veterinary Science & Animal Husbandry, Kamdhenu University, Junagadh, Gujarat-362001, India
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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. Stem cells are undifferentiated cells with the capability to self—renew and differentiate into tissue cells with specialized functions. Stem cell therapies are therefore used to overcome the body's inability to regenerate damaged tissues and metabolic processes after acute or chronic insult.

The concept of stem cell therapy was first introduced in 1991 by Caplan, who proposed that massive differentiation of cells into the desired tissue could be achieved by isolation, cultivation, and expansion of stem cells in in vitro conditions. Among different stem cell types, mesenchymal stem cells (MSC) currently seem to be the most suitable for therapeutic purposes, based on their simple isolation and culturing techniques, and lack of ethical issues regarding their usage. Because of their remarkable immunomodulatory abilities, MSCs are increasingly gaining recognition in veterinary medicine.

TYPES OF STEM CELLS

By definition, stem cells are undifferentiated cells capable of self—renewal and transformation into different specialized cells.

They are classified by their source as (a) embryonic (ESC), (b) adult, and (c) induced pluripotent stem cells (IPSC).

Considering their phase of development and differentiation, they are further classified as

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totipotent, pluripotent, or multipotent cells.

1) Totipotent stem cells are present only in a very early embryo during the morula stage before gastrulation starts. They are capable of developing into all embryonic and extra-embryonic tissues.
2) Subsequent divisions of cells during early embryonic development led to the emergence of the blastocyst with pluripotent ESC being present in the inner cell mass. ESC can give rise to all tissue cells in the body, with the exception of extra-embryonic tissues and germ cells. With further cell development, pluripotent ESC gradually loses their pluripotency and become multipotent.
3) The multipotent stage is characterized by the ability of cells to differentiate into limited types of specific cells, often depending on their germ layer origin

The first isolation of human ESC was reported in 1998.

This triggered numerous studies about gene expression and function during embryonic development and cell differentiation processes, as well as attempts to identify gene targets for new drugs that might be useful in tissue regeneration therapies. However, broad-spectrum therapeutic capabilities of human ESC collided with ethical, moral, and cultural dilemmas because their harvesting is associated with the destruction of human embryos. Other sources of stem cells, therefore, had to be explored to continue the research into stem cell— based therapies. One alternative was developed in 2006 by Takahashi and Yamanaka, who reprogrammed adult mouse fibroblasts into pluripotent stem cells by retroviral transduction of four specific genes: OCT4, c-Myc, SOX2, and KLF4.

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. These cells are multipotent because they can differentiate into specific body cell types.

HSCs can differentiate into different cells of the immune system, erythrocytes and platelets, and MSCs into cells of bone, cartilage, ligaments, tendons, fat, skin, muscle, and connective tissue. MSCs are activated endogenously when needed to replace dead, injured, or diseased tissue cells.

MSC SOURCES

Tissue Origin of MSC

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,

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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.

Currently, the most commonly used sources of MSC for stem cell therapies are bone marrow and adipose tissue because they offer larger number of MSCs than other tissues.

Autologous and Allogeneic MSC

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

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

When aiming to choose the most appropriate type of cells for particular stem cell therapy, choosing between autologous vs. allogeneic sources may prove challenging, and advantages and disadvantages for one over the other option should be considered.

The isolation and expansion of autologous stem cells are time-consuming and associated with the costly procedure. Moreover, the potency of autologous MSC could be affected by patient age and existing disease. The need for allogeneic off-the-shelf stem cell products derived from young and healthy donors is, therefore, on the rise.

The main concern with allogeneic stem cell therapy is the possibility that

- MHC I surface molecules on allogeneic MSCs are recognized by recipient CD8+T cells, leading to direct cytotoxicity of foreign cells.
- In addition, MHC II molecules can be recognized by recipient CD4+ T cells, leading to either cytotoxic or humoral immune response.

Therapeutic Potentials of MSC

Although stem cells were initially thought to be the source of cells that would differentiate and replace damaged or diseased tissues, it has become evident that the therapeutic properties of MSC are achieved mainly through their immunomodulatory functions, which operate in the interaction with the immune system cells. Complex immunomodulation activity of MSC includes:

- Paracrine Effects
- Secretion of Extracellular Vesicles (ECV)
- Apoptosis-Mediated Immunomodulation
- Mitochondrial Transfer

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- MSC homing
- MSC Preconditioning with Proinflammatory Cytokines

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 orthopaedic 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.

1) **Musculoskeletal System Diseases**
   - Tendons and Ligaments Diseases
   - Joint Diseases
2) **Orodental Diseases**

Oral diseases such as dental caries, periodontal disease, permanent tooth loss, oral mucosal lesions, oropharyngeal cancer, and dental trauma are also one of the major public health problems worldwide.

3) **Liver Diseases**
4) **Digestive tract Diseases**

Inflammatory bowel disease (IBD) is an autoimmune condition with chronic hypersensitivity reaction in the intestinal mucosa of unknown etiology.

5) **Renal Diseases**

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.

6) **Cardiac Diseases**

In human medicine, cardiac stem cell therapies directed toward myocardial repair following the acute or chronic myocardial infarction are being used for several years. Primary myocardial infarction is rarely observed in the companion animals. However, in large and giant dog breeds, dilated cardiomyopathy is a fairly common disease.

7) **Respiratory Diseases**

Respiratory diseases are a common problem also in veterinary medicine. Especially in horses, asthma, comprised of several diseases such as recurrent airway obstruction (RAO) or inflammatory airway disease, is a severe medical condition for which there is no successful treatment available.

8) **Neuromuscular Diseases and Injuries**

One of the most common neuromuscular injuries in both humans and animals are spinal cord

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injuries (SCI) and other includes paraplegia, degenerative intervertebral disc disease etc.

9) **Skin Diseases and Wound Healing**
10) **Eye Diseases**
11) **Reproductive System Diseases**

SAFETY AND REGULATORY ASPECTS OF STEM CELL THERAPIES IN VETERINARY MEDICINE

- The European Medicines Agency's (EMA) Committee for Medicinal Products for Veterinary Use (CVMP) has proposed some basic guidelines for stem cell-based medications for veterinary use.
- Since the use of allogeneic MSC in dogs and horses is increasing, so are the raising questions for manufacturers, authorities, and users. Currently, no specific guidance is available.
- Safety aspects of extraneous agents concerning veterinary medicinal products are included in the guidelines for the production and control of immunological veterinary medicinal products.
- In these guidelines is a list of viruses and bacteria for horses and dogs that should not be present in the medicinal products, and this should be adhered to also with the allogeneic MSC.
- Furthermore, as a general guideline, it is recommended that cell donors are always clinically healthy. If cells from new born animals or placental tissues are used, it is advisable to test mothers for the presence of any infectious agents.
- To demonstrate the absence of disease-causing agents. A combination of donor screening using anamnesis and clinical information, donor testing for the presence of specific disease agents and product (cells ready for therapy) testing should be applied.
- All material with biological origin needed for collection, selection, culture, and modification of cells should also be clearly specified and evaluated for the absence of any potentially harmful agents.
- Furthermore, aseptic manufacturing is necessary for reducing the presence of extraneous agents.
- In 2015 the USA Food and Drug Administration (FDA) published recommendations for the use of cell-based products in animals.
- According to this, cell-based products, including animal stem cell-based products (ASCP) that are intended for use in the diagnosis, mitigation, treatment, or prevention of diseases, are regulated as new animal medicines and require a premarket review to be legally marketed.
- The requirements for approval include the demonstration of safety, effectiveness, and manufacturing quality.

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- Evaluation of tumorigenicity, immunogenicity, donor selection criteria, the transmission of infectious agents, long term safety, cell survival, biodistribution, and ectopic tissue formation are required.
- In the future, additional regulatory guidelines can be expected.

It is unclear whether these new regulations will significantly affect the advancement of stem cell trials and the development of novel therapies, but any new regulations should be prepared and approved by experts from various fields, from cell biology to clinical veterinary medicine.

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