International Journal of Microbiology Research
ISSN: 0975-5276 & E-ISSN: 0975-9174, Volume 12, Issue 5, 2020, pp.-1832-1835.
Available online at https://www.bioinfopublication.org/jouarchive.php?opt=&jouid=BPJ0000234

Review Article

CYTOTHERAPY AND SCOPE IN VETERINARY MEDICINE

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Received: April 30, 2020; Revised: May 10, 2020; Accepted: May 11, 2020; Published: May 30, 2020

Abstract- Cytotherapy is one of the most exciting fields in translational medicine. It stands at the intersection of rapidly developing scientific disciplines. Blood transfusion and bone marrow transplantation are prime examples of cell-based therapy. The major types of stem cells used in cytotherapy are embryonic and adult stem cells. Adipose derived stem cells are preferred source of cells used in cytotherapy due to their numerous advantages. There are numerous advantages and limitations of cell therapy or cytotherapy. Cytotherapy is being searched for the treatment of various diseases and ailments in veterinary medicine.

Keywords- *Adipose Derived Stem Cells, Bone Marrow Transplantation, Cytotherapy*

Citation: Akhoon Z.A., *et al*., (2020) Cytotherapy and Scope in Veterinary Medicine. International Journal of Microbiology Research, ISSN: 0975-5276 & E-ISSN: 0975-9174, Volume 12, Issue 5, pp.-1832-1835.

Academic Editor / Reviewer: Sunil Sonu Hatkar, Abdel Raheem M. A., Kavit S Mehta, Kiranjot Kaur

Introduction

Cytotherapy is the prevention, treatment, cure or mitigation of disease or injuries by the administration of autologous, allogeneic or xenogeneic cells that have been manipulated or altered *ex vivo* (FDA). It stands at the intersection of a variety of rapidly developing scientific disciplines (stem cell biology, transplantation biology, regenerative medicine, etc.). Blood transfusion and bone marrow transplantation are prime examples of cell-based therapy. Cell-based therapy providing a dynamic, interactive, and individualized therapeutic approach that responds to the pathophysiological condition of the patient. Cells may provide innovative methods for drug delivery of biologics, immunotherapy, and tissue regenerative or replacement engineering [1]. Cell therapy originated in the nineteenth century when scientists experimented by injecting animal material in an attempt to prevent and treat illness [2]. Today two distinct categories of cell therapy are recognized [3]. The first category is cell therapy in mainstream medicine which is subject of intense research and the basis of potential therapeutic benefit [4]. However, such research can be controversial when it involves human embryonic material.

Mechanisms of Action

Main principles by which cells facilitate therapeutic action

Stem cells or progenitor cell engraftment, differentiation and long-term replacement of damaged tissue. An example of this is the use of cells to replace cardiomyocytes after myocardial infarction [5]. Cells that have the capacity to release soluble factors such as cytokines, chemokines growth factors act in a paracrine or endocrine manner. Example of this include cells that secrete factors which facilitate angiogenesis, antiinflammation and anti-apoptosis [6].

MSCs (Mesenchymal Stem Cell Therapy)

Immunomodulatory, multipotent and fast proliferating and these unique capabilities mean they can be used for a wide range of treatments including immunomodulatory therapy, bone and cartilage regeneration, myocardium regeneration and treatment of Hurler syndrome, a skeletal and neurological disorder [7].

Researchers have demonstrated the use of MSCs for the treatment of Osteogenesis Imperfecta (OI) [8]. A more recent clinical trial showed that allogenic fetal MSCs transplanted in utero in patients with severe OI can engraft and differentiate into bone in a human fetus [9].

Cytotherapy in alternative Medicine

In alternative medicine cell therapy is defined as the injection of non-human cellular animal material in an attempt to treat illness [3]. Human adipose derived mesenchymal stem cells showed significant improvement in rabbits and dogs in retinal injury[10].

More about stem cells

Stem Cells are unspecialized cells with an extraordinary ability to self-renew, capable of differentiating into one or more specialized cell types playing a crucial role in homeostasis and tissue repair [11].

Kinds of Stem Cells

Totipotent: Each cell can develop into a new individual eg: Cells from early (1-3 days) embryos.
Pluripotent: Cells can form any (over 200) cell types eg. Some cells of blastocyst (5 to 14 days).
Multipotent: Cells differentiated, but can form a number of other tissues eg.Fetal tissue, cord blood and adult stem cells.

The Major Types of Stem Cells

A. Embryonic Stem Cells

From blastocysts left over from *In-Vitro* Fertilization in the laboratory and from aborted foetus.

B. Adult Stem Cells

Stem cells have been found in the blood, bone marrow, liver, kidney, cornea, dental pulp, umbilical cord, brain, skin, muscle and salivary gland.

Embryonic S.C.

Pluripotent (can become any cell). Stable *i.e*., can undergo many cell divisions. Easy to obtain but blastocyst is destroyed. Possibility of rejection.

Adult S.C.

Multipotent (can become many but not any). Less Stable and capacity for self-renewal is limited. Difficult to isolate in adult tissue. Host rejection minimized.

Types of Adult stem cells: Hemopoetic SCs, from cord blood or peripheral blood, mesenchymal stem cells, mesoderm layer of fetus & in adult reside in a variety of tissues such as bone marrow SCs, adipose tissue SCs, hepatic stem cells, dermal stem cells *etc* [11].

Why ADSCs more preferred stem cell source?

Adipose tissue can yield large amounts of stem cells and can be obtained in abundance [12].1in 50 cells in adipose tissue are stem cells. whereas 1 in 100000 cells (.0001%) in bone marrow are stem cells. ADSCs easy to access, renewable source, easy to separate cells, contain heterogenous mixture of regenerative cells. ADSCs can be induced to differentiate *in vitro* into various other cell lines including chondrogenic [13], adipogenic, hepatic [14] and neurogenic lineages [15]. The following stem cell characteristics make them good candidate for cell-based therapies: Potential to be harvested from patients, high capacity of proliferation in culture, ease of manipulation to replace existing nonfunctioning genes via gene transfer methods, ability to migrate to host's target tissues, ability to integrate into host tissues [11].

Sources of stem cells for treatment

Autologous- Patient's own stem cells

Allogenic- Stem cells from another donor of same species

Xenogeneic- In this stem cells from different species are transplanted.

Lab test to identify ESC

Growing & sub culturing the ESC for many months, under microscope-look healthy & undifferentiated, presence of protein called oct-4 (transcription factor) which undifferentiated cells make, using specific techniques to determine presence of surface markers (Alkaline phosphate Oct-4).

Prospects of Cell based therapies

Stem cell based regenerative therapy, stem cell-based gene therapy, stem cells-based cancer therapy, stem cells based therapeutic cloning, cell-based drug delivery. Adipose derived regenerative cells contain endothelial progenitor cells and MSCs that assist in angiogenesis and neo vascularization by the secretion of cytokines, hepatic growth factor (HGF), vascular endothelial growth factor (VEGF), placental growth factor (PGF), transforming growth factor (TGFβ), fibroblast growth factor (FGF-2), and angiopoietin.

Anti-apoptosis

BM-MSCs express factors that support cell survival and avoid apoptosis thereby preserving cells that would otherwise be destroyed.

Genetically Modified-Sc Based Gene Therapies

Gene therapy: insertion of transgene (new genetic material with specific instruction) into an individual's cells to treat a disease either by altering the function of an abnormal gene or to provide a gene that adds new functions. The rationale is that a virus vector is able to invade the endogenous cell type of interest and alter its function by integrating an exogenous gene into its genome thus enabling the cells to overexpress an existing gene or express a gene novel to that cell type [16]. Genes can be delivered to the target cell in 1 of 2 ways. The target cell can be cultured *in vitro*, transfected with the gene(s) of interest, and then delivered to the patient, a process known as *ex vivo* gene transfer.

Virus vectors containing the gene(s) of interest can be injected directly into the patient where they seek out the target cells, invade the cells, and insert the gene into the cellular genome, so-called *in vivo* gene transfer.

Cancer stem cells & cancer therapy

Stem cell model of tumour formation- tumours originate in either long-lived tissue stem cells or progenitor cells through misregulation of the normally tightly regulated process of self-renewal leading to CSCs/tumour-initiating cells (TICs).It has been hypothesised that CSCs persist in tumours as a distinct population and may cause relapse and metastasis giving rise to new tumours. These cells may also explain why standard oncology treatments sometimes fail [17].

Characteristics of CSCs

CSCs undergo self-renewal → asymmetric division → CSCs+ transit-amplifying cell

Cancer transit-amplifying cells fail to differentiate normally and instead accumulate resulting in cancer growth. CSCs are either dormant or in a proliferative phase. Dormant CSCs, like normal stem cells exist in a quiescent state therefore, they might be more resistant to the cytostatics that target dividing cells whereas CSC proliferation would give rise to tumour mass/bulk. Self-protection ability through innate MDR transporters à energy-requiring efflux pumps with the function of pumping toxic hemotherapeutic drugs out of the cancer cells. Resistance to apoptosis and radiotherapy.

CSCs and perspectives in cancer therapy

Comparing gene expression profiles of CSCs, the bulk tumour cell population, normal stem cells and normal tissues, it may be possible to recognise therapeutic approaches that preferentially attack CSCs.

Two approaches

Differentiation therapy

One way to control the tumour progression is to treat cancer by inducing differentiation of CSCs. Differentiation therapy causes CSCs to differentiate and lose their self-renewal property Vitamin Aand its analogue [by upregulation of CRBP1 and CRABPs receptors) (Niles, 2004). Agents that act directly or indirectly to convert abnormal chromatin modifying enzymes into normal ones, enabling cancer cells to undergo terminal differentiation.

Elimination therapy

Another way to intensify the efficacy of cancer therapy is to eliminate CSCs. Exposure of CSCs to sufficiently high levels of conventional cytotoxic agents and the development of novel therapeutic agents that are targeted to CSCs can be used for this purpose [18].

Advantages and Limitations of Cytotherapy

Advantages

For the past several years MSCs including hUCB-MSCs have been applied in animal models or human clinical trials for various disease treatments such as osteoarthritis, multiple sclerosis, spinal cord injury and liver diseases [19]. In 1968, first successful allogenic stem cell graft in humans using donor bone marrow was undertaken in USA [20]. Bone marrow derived MSCs were first used in Rhesus monkeys for nervous tissue regeneration which appeared promising [21]. Mouse ES derived cardiomyocytes were engrafted in injured myocardium of rat resulting in angiogenetic effect and subsequently improved cardiac function during the 32 week observation period [22]. In race horses, the adipose derived MSCs were used to successfully treat experimental tendinitis [23].

Limitations

Putative fibrogenic potential of MSCs [24], heterogenicity, safety, dependence on donor, immunological barrier, outgrowth of transplanted cell, cell may not be simply grown but tumors or inappropriately differentiate tissue may developed, purity of material used to avoid transplant of unwanted cells, difficulty in identification of SC, contamination by viruses, bacteria, fungi, and Mycoplasma

possible, SC proliferation must be controlled once placed into patients, therapeutic failure: tissue rejection (major factor), pathological environment, inaccuracy in SC placement; SC fail to integrate/express function, more funds have to be generated for research and ethical controversy associated are some main limitations of cytotherapy.

Stem Cell Therapy in Veterinary Medicine

Currently in dogs stem cell therapy is commonly used to treat osteoarthritis, tendon and ligament injuries and neurological conditions. High density platelet rich plasma (HDPRP) defined as plasma with platelet concentrations > 4 times the levels found in circulating blood. Activated platelets – stromal cell derived factor 1 alpha (SDF-1α)- migration of mesenchymal stem/stromal cells [25]. Fibroblast growth factor (FGF), Insulin like growth factor (IGF), Interferons: alpha, Gamma (I-A, I-G), Interleukin-1 (IL-1), Platelet-derived angiogenesis factor (PDAF), Platelet-derived epidermal growth factor (PDEGF), Platelet factor 4 etc. play an important role.

Torricelli *et al*. [26] showed that racing horses who were given 1-4 x 100000 mononuclear bone marrow cells, combined with autologous platelet-rich plasma, applied directly on the lesion (located by USG) showed muscular regeneration after 12 months of follow up. Sharma and Jeong [27] demonstrated the possibilities of bovine mammary stem cell therapy offering significant potential for regeneration of tissues that can potentially replace or repair the diseased gland suggesting differentiation of stem cells isolated into epithelial, myoepithelial and/or cuboidal/columnar cells using iPS approach. Induced pluripotent stem cells (iPS) are defined as differentiated cells that have been experimentally reprogrammed to pluripotent cells to achieve an embryonic stem cell like state.

Advances in the Use of Stem Cells in Veterinary Medicine

Activation of a specific cellular signalling axis, homing (response as migration, proliferation and differentiation),hypoxia and release of hypoxia-inducible factor-1 (HIF-1), release of cytokines (stromal derived factor-1 (SDF-1), vascular endothelial growth factor (VEGF) [28],transmigration and release of reactive oxygen species influencing cell homing [29], bone marrow and adipose tissue still most widely used in therapeutics [30], paracrine effect withrelease of fibroblast growth factors (FGF) 2 and 7, hepatocyte growth factor (HGF), angiopoietin-1, transforming growth factor-beta (TGF-beta), matrix metalloproteinase-9 (MMP-9), tumour necrosis factor-alpha (TNF-alpha), Interleukin 1 and 6 and others [31].

Hong *et al* [32] reported the application of human umbilical cord blood derived mesenchymal stem cells (hUCB-MSCs) on bone regeneration in ovariectomzed rats with femoral defects.MSCs possessing characteristics like self-renewal and differentiation potential have been isolated from a variety of tissues sources including bone marrow, peripheral blood, umbilical cord blood, adipose tissue, fetal liver and lung, dental pulp and synovium [20].Canine adipose derived stem cells have been used in osteoarthritis and joint disorders in dogs [Stem cell international) [33].Adipose stem cells derived from subcut fat of young goat have been used in repairment of mastitic mammary gland in goat [34].

Conclusion

Cryopreservation and long-term storage of stem cells will greatly enhance the applicability of stem cell-based therapies. Cell-based therapy has substantial technological, regulatory and ethical barriers, the potential to develop innovative treatments for a large number of clinical disorders, including acute and chronic renal diseases is expanding rapidly.

Application of research: Study of cytotherapy or cell therapy.

Review Category: Cytotherapy.

Acknowledgement / Funding: Authors are thankful to Division of Clinical Veterinary Medicine, Faculty of Veterinary Sciences and Animal Husbandry, Shuhama, Sher-e-Kashmir University of Agricultural Sciences & Technology of Kashmir, Shalimar, 190019, Jammu and Kashmir, India

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Research project name or number: Review study

Author Contributions: All authors equally contributed

Author statement: All authors read, reviewed, agreed and approved the final manuscript. Note-All authors agreed that- Written informed consent was obtained from all participants prior to publish / enrolment

Study area / Sample Collection: Division of Clinical Veterinary Medicine, Faculty of Veterinary Sciences and Animal Husbandry, Shuhama

Cultivar / Variety / Breed name: Nil

Conflict of Interest: None declared

Ethical approval: Ethical approval taken from Division of Clinical Veterinary Medicine, Faculty of Veterinary Sciences and Animal Husbandry, Shuhama, Sher-e-Kashmir University of Agricultural Sciences & Technology of Kashmir, Shalimar, 190019, Jammu and Kashmir, India.
Ethical Committee Approval Number: Nil

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