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Opportunities for Stem Cells Therapy in Veterinary Medicine

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Abstract
Animal contain stem cells in different parts of body that are involved in regeneration and repair process but regeneration and repair capacity of different animals is different. Stem cells can be classified on the basis of origin, potential of differentiation and cell surface markers. In addition to embryonic stem cells (ESCs), bone marrow derived mesenchymal stem cells (MSCs), circulating blood stem cells and umbilical cord blood stem cells are major source of stem cells for therapeutic purposes. Adipose derived MSCs have also proved to be rich and therapeutically important source of stem cells. Animal during lifetime suffer from various diseases that are treated by different therapeutical ways. With the advancement in research in area of stem cell biology, it provides a better alternative to treat several diseases including life threatening diseases. We provided information about current therapeutically potentials and future prospective of stem cells therapy in veterinary medicine. We collected information about stem cell research in various animals from peer reviewed journals using standard database. Stem cells therapy treat orthopedic lesions, disc regeneration, osteoarthritis, repair of cranial bone defects, cartilage defects, corneal stroma, tendon repair, ligament injury, liver injury, nerve regeneration etc. in various animals. Now a day's extensive research work is going in area of stem cells research in USA, Europe, Middle East and Asia. In future, stem cells therapy bears a scope to treat broad spectrum of animals ranging from rat, cats, and dogs to food and milk producing animals like goat, sheep, cow and buffaloes.
Keywords: Embryonic stem cells, regeneration, therapy, veterinary medicine.

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INTRODUCTION

Animals have ability to regenerate some parts of body which are accidentally lost i.e. tail of lizard during their course of life. Moreover repairing of body cells and tissues is normal phenomena both in animals and human. But variation in this regeneration process is seen in case of vertebrate and invertebrates; as invertebrates like hydra can regenerate whole tissue in rapid and precise manner while antler and liver regeneration in case of elks and human are examples of organ regeneration, healing of wounds is another example of regeneration in higher vertebrates. These tissue regeneration processes are done via activation of pre-existing stem cells or progenitor cells in body (Brockes, 1997). Due to this, research on ability of regeneration in living things through series of experimentations, scientists were able to recognize stem cells in different organs of body. It results in the development of different therapeutic approaches like bone marrow transplantation. Now-a-days scientists are involved in identification, extraction and potentially usage of different types of stem cells for therapeutic purpose. Stem cells are defined as cells that have the ability to self-renew as well can differentiate in different mature cells like hepatocytes, myocytes, neurons etc. In early embryos all cells are totipotent stem cells, as they have the ability to form all tissues of the organism. There are also stem cells in adult tissues that contribute to the renewal and regeneration of specific tissues.

In recent times, researchers have also discovered stem cells in umbilical cord and placenta. These stem cells have the ability to differentiate into all blood cells. Embryonic stem cells (ESCs) can be achieved from *in vitro* fertilization (IVF) and Somatic Cell Nuclear Transfer (SCNT) while adult stem can be affectively isolated from adult tissues of body. Three potential sources of stem cells to apply for transplants are bone marrow, the bloodstream, and umbilical cord blood. Bone marrow of the pelvis area has an affluent source of stem cells and used most frequently for bone marrow transplant. Usually, a small number of stem cells are found in the blood, the stem cells are usually activated to harvest them from circulating blood. Umbilical cord blood can be an additional possible source of stem cells. The above mentioned three sources of stem cells can be used for the similar objective like to treat the patients suffering from different diseases. Here might be few controversies to each source; however every source is generally capable to supply the desired number of stem cells for treatment options. In addition to adult stem cells single blastomere can be used for isolation of ESCs (Klimanskaya *et al.,* 2006). The inner cell mass (ICM) of blastocyst is the most common source of ESCs. For this purpose blastocyst can be produced *in vivo* and *in vitro* by insemination, direct sperm injection, SCNT and IVF (Klimanskaya *et al.,* 2005; Amit and Itskovitz-Eldor, 2006; Fletcher *et al.,* 2006). Induced Pluripotent stem cells (iPSCs) from different cell types (fibroblasts, hepatocytes etc.) had been produced by transfection of gene coding for Oct3/4, Sox2, c-Myc and Klf4 using similar cultural conditions as for ESCs (Takahashi and Yamanaka, 2006; Okita *et al.,* 2007; Wernig *et al.,* 2007) and these can be used as an alternative source of ESCs with minimal ethical issues.

Different strategies are used for the isolation of embryonic and adult stem cells from their sources for therapeutical purpose. Different approaches like mechanical dissection, immuno-selection are used for isolation of ICM from blastocyst in case of ESCs isolation. Adult stem cells are isolated from their sources by using mechanical digestion, enzymatic digestion, mononuclear cell fraction and centrifugation (Thomson *et al.,* 1998; Koch *et al.,* 2007). After isolation from blastocyst, culture and expansion of ICM can be achieved in tissue culture dish or petri plates having a mitotically inactivated feeder cell layer. But there are different views of scientist for the use of feeder layer and animal sera for culturing and expansion of ESCs. Contrary to ESCs, adult stem cells (ASCs) do not require feeder layer, they can be directly plated on plastic culture flasks or dish having material like polystyrene (Kang *et al.,* 2005; Amit and Itskovitz-Eldor, 2006; Fletcher *et al.,* 2006).

In case of stem cells like adipose derived-MSCs, angiogenesis and neovascularization is accelerated by secretion of cytokines such as hepatic growth factor (HGF), vascular endothelial growth factor (VEGF), placental growth factor (PGF), transforming growth factors-Beta (TGFβ), fibroblast growth factor (FGF-2) and angiopoietin and have been assisted by endothelial progenitor cells (Nakagami *et al.,* 2006). Stem cells shows diverse plasticity, which mean these cells, can be differentiate into adipose tissue, bone, cartilage, muscles, cardiac, neuron and hematopoietic lineage and this differentiation potential have been experimentally proved *in vitro* and animal models. Diseases in different animals like rabbits (Oliveira *et al.,* 2010), horses (MacLean *et al.,* 2012; Young, 2012), Caprine (Murphy *et al.,* 2003; Azari *et al.,* 2011), dogs (Zhao *et al.,* 2012) and mice (Cheng *et al.,* 2010) were treated by stem cell therapy. These cells like others progenitor cells can target distinctively their pathological area, when administrated into body via intravenous and parenteral routes due to their precise ability of chemotaxis, which help in migration of stem cells toward distant target sites (Chen *et al.,* 2001). Apart from these properties stem cell also have ability of revascularization, anti-apoptosis etc. which make stem cell a powerful candidate for therapy of veterinary diseases. Although stem cells research is focused on laboratory and large animals worldwide (Harding *et al.,* 2013; Khan *et al.,* 2013), recently, apart from goat (Dubey *et al.,* 2013), buffalo (Black gold of Pakistan) is also included in this list (Puri *et al.,* 2012; Sharma *et al.,* 2013) in India. In present review, the current therapeutically potentials and future prospective of stem cells therapy in various animals is discussed.

Types of stem cells

Stem cells can be differentiated on the basis of different potential paths, including their potency, origin and cell surface markers. With respect to potency of differentiation of stem cell, they are divided into three types including totipotent stem cell, pluripotent stem cell and multipotent stem cell. Totipotent stem cells are cells which can give raise every type of cell of body as well as complete organism. Cells from premature embryonic stages and zygote are considered as totipotent in their potency. While stem cells that can give raise any type of tissue but they cannot give rise a complete functional organism are known as pluripotent stem cells. They can form all cells of the body except trophoblast. ESCs are example of pluripotent stem cells as they can differentiate into cells of three germ layers. Third types of stem cells are more differential, so that they give rise only partial number of tissues or cell types. Mesenchymal stem cells are an excellent example of multipotent stem cells which contain classic trilineage segregation potential to chondrogenic, adipogenic and osteogenic pedigree (Koch *et al.,* 2008).

Stem cell with respect to their source of origin can divide them in two major types including embryonic stem cell and adult stem cells. ESCs are isolated from morulla or inner cell mass (ICM) of blastocyst of mammals while ASCs are localized in different parts of an organisms e.g. brain, liver, intestinal tissues, skin etc. ESCs can be produced by IVF, SCNT and more recently by forced expression of embryonic stem cells related gene in mature cells and are called iPSC. Moreover, most of the information related to ESCs came from two fields of investigation i.e. applied reproductive biology like IVF and fundamental research on mouse embryology. With the advancement in research related to stem cells, new concept are coming as in case of ASCs, a new term plasticity of ASCs is used, which mean it was considered commonly that hematopoietic stem cells from bone marrow can only be converted into blood and immune cells. But, now stem cell scientists are able to develop neurons and cells commonly found in brain from adult stem cells. Apart from division base on potency and origin, stem can be differentiate with respect to presence of surface markers like CD34, CD45, CD90, CD105, CD73, CD14, CD11b, CD79 and HLA-DR. As CD14, CD34 and CD45 are surface markers recognized on MSCs (Tyndall *et al.,* 2007).

Stem cells in animals

Stem cell therapy have vast application in animals especially in equine and canine family, apart from these other animals including sheep, goat, monkey, duck, golden hamster, pig, swine, rat, rabbit etc are used as laboratory animal to explore more treatment regimens for human being as well. MSC alone and in combination with Insulin-Like Growth Factor-I Gene (AdIGF) results in optimal improvement in injured tendon histological score both in experimental and impulsive lesions in equine (Smith *et al.,* 2003; Schnabel *et al.,* 2009). But some controversies have been seen with MSCs treatment, as in case of long term histological look or biochemical composition of cartilage lesions did not considerably improved in equine model while major healing has been seen at early stage in same animal (Wilke *et al.,* 2007). Autologous peripheral blood derived MSCs have been found to be affective for treatment of chronic degenerative joint disease (DJD) in horse (Spaas *et al.,* 2012). The effect of cell therapy products [adipose-derived stromal vascular fraction (SVF), bone marrow mononuclear cells (BMMNs), cord blood mononuclear cells (CBMNs) and platelet rich plasma] on MSCs function were studies in horse for acute orthopedic lesions treatment in vitro. They found all cell therapy product play role in proliferation of MSCs, while SVF play most significant role (Kol *et al.,* 2012). In a recent research on equine bone marrow, MSCs reported these stem cells can be proved as positive applicant for cell therapy in game animals (Adams *et al.,* 2012). Moreover, in recent study silica nano-particles were found as a very good labeling maker for canine Mesenchymal stem cells and this approach can be used for distribution and fate of transplanted MSCs (Han *et al.,* 2012).

Animal diseases potential candidates for stem cells therapy

Although there are several animals' diseases which can be treated with stem cell therapy, however, following are the few important veterinary diseases that can be treated with different types of stem cells as given in table 1.

Table1. List of animals' diseases can be treated with stem cell therapy.

Animal Type	Stem Cell Type	Disease/Disorder Treated	Reference
Dogs/ Canine	Mesenchymal stem cells (MSCs)	Canine Disc Degeneration	Serigano *et al.,* 2010
	Autologous adipose-derived (AD-D)-MSCs	Chronic osteoarthritis	Guercio *et al.,* 2012
	Bone marrow MSC associated with rhBMP2	Osteosarcoma	Rici *et al.,* 2012
	AD-D Mesenchymal Stem and Regenerative Cells	Chronic Osteoarthritis	Black *et al.,* 2008
	Adipose-derived MSCs	Peri-ocular and joint diseases	Wood *et al.,* 2012
	Allogenic muscle stem cells	Duchenne-muscular dystrophy	Rouger *et al.,* 2011
	Adipose derived stem cells and coral scaffold	Repair of cranial bone defects	Cui *et al.,* 2007
Rabbits	Autologous bone-marrow derived mesenchymal cell	Articular cartilage defects	Yanai *et al.,* 2005
	MSCs	Large osteochondral defect	Tatebe *et al.,* 2005
	Human MSCs	Incisional wound repair anterior	Alexander *et al.,* 2009
	MSCs or PDGF-B gene-transfected MSCs	Cruciate ligament reconstruction	Feng *et al.,* 2007
	Adipose-Derived Stem Cells	Therapy of the Corneal Stroma	Francisco *et al.,* 2008
	Fetal rabbit liver MSCs (fl-MSCs)	Congenital birth defects	Moreno *et al.,* 2012
	Infra-patellar fat pad derived MSCs	Osteoarthritis	Toghraie *et al.,* 2011
Horses	Autologous equine MSCs	Superficial digital flexor tendon	Smith *et al.,* 2003
	Fetal derived embryonic-like stem cells (fdESC)	Tendonitis	Watts *et al.,* 2011
	Arthroscopic MSCs	Articular Defects	Wilke *et al.,* 2007
	Bone marrow mononucleated cells (BMMNCs)	Musculoskeletal overuse injuries	Torricelli *et al.,* 2011
	Bone marrow-derived MSCs (BMSCs)	Chondral defects	McIlwraith *et al.,* 2011
Rat/ Mice	Allogeneic MSCs	Femoral segmental defect	Tsuchida *et al.,* 2003
	Mesoangioblasts	Alpa-sarcogycan null dystrophy	Sampaolesi *et al.,* 2003
	Multipotent cell population from human adipose	Dystrophin expression	Rodriguez *et al.,* 2005

	tissue		
	Allogeneic Bone Marrow MSCs	Collagen-Induced Arthritis	Augello *et al.,* 2007
	Bone-marrow stromal cells	Sciatic nerve regeneration	Dezawa *et al.,* 2001
	Adult bone marrow stromal cells	Traumatic brain injury	Lu *et al.,* 2001
	Allogeneic bone marrow-derived mesenchymal stromal cells	Injured skeletal muscle	Natsu *et al.,* 2004
	Autologous bone marrow cell therapy	Ischemia-induced angiogenesis	Claudio *et al.,* 2005
	Skin-Derived Stem Cells	Nerve Regeneration	Marchesi *et al.,* 2007
	Bone marrow stromal cell-derived Schwann cells	Nerve regeneration	Mimura *et al.,* 2004
	Bone marrow MSCs	Nerve regeneration	Tohill *et al.,* 2004
	Hematopoietic stem cell gene therapy	Neurological abnormalities	Miranda *et al.,* 2000
	MSCs	Acute myocardial infarction	Shyu *et al.,* 2006
	Adult stem cells	Bone Healing	Lee *et al.,* 2009
	MSCs	Therapy of Diabetes	Urban *et al.,* 2008
	MSCs	Obstructive sleep apnea	Carreras *et al.,* 2010
	Hematopoietic stem cell transplantation	Lethal stroke	Felfly *et al.,* 2010
Sheep/ Goat	Autologous MSCs	Large articular cartilage defects	Guo *et al.,* 2004
	MSCs	Bone regeneration	Niemeyer *et al.,* 2010
	Epidermal Adult Stem Cells	AFTSD* and LSCD**	Yang *et al.,* 2007
	MSCs	Cutaneous wound healing	Azari *et al.,* 2011
Buffalo	Embryonic stem cell	Chondrogenic differentiation	Sritanaudomchai *et al.,* 2013
Monkey/ Primate	Embryonic Stem Cell-Derived Neural Stem Cells	Parkinson's Disease	Muramatsu *et al.,* 2009
	Embryonic stem cells	Dopaminergic neurons generation	Takagi *et al.,* 2005
Avian/ Chicken	Neural stem cells	Reversal of neurobehavioral teratogenicity	Dotan *et al.,* 2010

*AFTSD = Acute full-thickness skin defect; **LSCD = Limbal stem cell deficiency

Prioritization of stem cell therapy in animals

Animals in their course of life suffer from different diseases which are treated by different therapeutical approaches. Apart from looking after of own health, humans also gave intention towards the good health of pet and domesticated animals as these animals are supportive for them in different daily life activities and excellent source of food as well. Veterinary medicine is a branch of science, in which we study about body of animal and its functions, moreover study about different therapeutic techniques beneficial for preservation and improvement of animals health (Fortier and Travis, 2011). Different therapeutic approaches like chemotherapy, acupressure, curative magnetism, bone setting, homeopathy, osteopathy, phytotherapy are some of the practice used in veterinary clinics. Traditional veterinary medicines are also used for treatment of animals. In traditional veterinary medication, body of patient divided into different parts like a physical set of organs, muscles, joints, and tissue systems and treatment is given according to this division with surgery, drugs, chemicals or radiation. Variable side effects have been faced by animals due to variable toxic nature, trauma due to destructive effect of these therapeutical approaches of chemical, radiation and surgery. So, in case of traumatic emergencies to prevent brain edema different supportive treatments like usage of steroids, intravenous solution along other medicines are essential for saving life of patient. Apart from steroid, non-steroid anti-inflammatory drugs (NSAIDs) are used in animals suffer from osteoarthritis (OA) but data depict that use of NSAIDs several times do not give full pain aid in case of a lot of dogs affected with osteoarthritis (Black *et al.,* 2008).

From above mention literature it is clear that these traditional veterinary therapeutical approaches are time consuming and having some limitations in the form of side effects i.e. tumor formation etc. So, there is immense need of such therapeutical approaches which can overcome the shortcomings of these traditional veterinary practices. Stem cell therapy is excellent candidate for the treatment of veterinary diseases. Stem cells are multipotent and can differentiate into tendon, ligament, bone, cartilage, cardiac, nerve, muscle, blood vessels, fat, liver tissues etc. Clinical research on stem cell therapy demonstrated positive results in treating animals like horses with tendon and ligament injuries, osteochondral defects and osteoarthritis. Likewise positive improvement in canines suffering with osteoarthritis of hip, defects of elbow and stifles have been reported (Verma *et al.,* 2007).

To date stem cell have been isolated from different sources, used for stem cell therapy, like bone marrow stem cells, AD-MSCs, mesoangioblast stem cells, infrapatellar fat pad derived MSCs, Hematopoietic stem cell, Epidermal stem cells, ESCs, neural stem cells, cardiac stem cells etc. Every type of stem cell mentioned above have its own benefits but AD-MSCs have been most successfully used in treatment of osteoarthritis, fractures, cerebral infarction, muscle dystrophy, autoimmune disorders etc. (Chen *et al.,* 2001; Murphy *et al.,* 2003; El-Badri *et al.,* 2004; Uccelli *et al.,* 2006). These stem cell having functions including limiting anti-inflammatory responses and promote anti-inflammatory pathways (Aggarwal and Pittenger, 2005) support angiogenesis, tissue remodeling, differentiation, and anti-apoptotic events by secreting bioactive level of cytokines and growth factors (Rehman *et al.,* 2004; Nakagami *et al.,* 2006). Authors give preference to AD-MSCs over traditional and regenerative cell derived from bone marrow because of their easy availability, can be collection in great concentration and contain heterogeneous mixture of MSCs, endothelial progenitor cells, immune cells, fibroblast etc. (Verma *et al.,* 2007). Furthermore still no systematic adverse actions have been reported in case of AD-MSC therapy. These information are sufficient to conclude that stem cell therapy is safe and having significant place in treatment of veterinary diseases.

Challenge, difficulties and ethical concerns in stem cell therapy

Stem cell research provides therapeutic profit in the fields of remedial cloning and regenerative medicine. This research approach provides great prospective in healing and therapy of illness related to human being and animal species. With the advancement in stem cell research, scientists were able to develop diverse body parts in laboratories for the aid in healing of diseases. Scientists were capable to identify defects related to birth, sterility, reproduction related diseases and diseases of other body organs. Apart from benefits of stem cell therapy, there is a chapter of controversies related to stem cell therapy both in human and animal population. Problem of contamination during cell therapy is a big issue as any invisible transfer defector stem cell can produce tumor in recipient body. Transmission of communicable diseases like viral, bacterial etc. during stem cell therapy is of particular concern. Specialized cells which are used for cell therapies in animals must be tested several times *in vitro* and *in vivo* in suitable experimental or laboratory animals before their clinical practices to illustrate that they can repair regular physiological role in sick animal. Another issue related to cell therapy is of tissue rejection. Questions have risen related to politics and religion status of stem cell therapy. As political and religious disagreements about stem cell therapy are everywhere but severity of issue varies from country to country.

CONCLUSION

In conclusion, currently we are using stem cell therapy for the treatment of different diseases in valuable animals like racing horses (having good genetic traits), cats, dogs etc. We hope, in future we will be able to use these stem cell therapeutical approaches widely for the treatment of different diseases and disorders related to common food producing animals like buffalo, cow, sheep, goat etc.

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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