Review Article

Cytotherapeutics: Emerging Tool of Clinical Application in Veterinary Sciences

Zul-I-Huma[1], Neelesh Sharma[1]*, Jyoti Misri [2], Amit Kumar Singh[3], Dong Kee Jeong[4] and Sung Jin Lee[5]

[1]Division of Veterinary Medicine, F.V.Sc. & A.H., SKUAST-J, R.S. Pura, Jammu, Jammu and Kashmir, INDIA
[2]Animal Science Division, ICAR, New Delhi, INDIA
[3]Laboratory for Animal Experiments, National Jalma Institute of Leprosy and other Mycobacterial Diseases, Agra, Uttar Pradesh, INDIA
[4]Department of Animal Biotechnology, Faculty of Biotechnology, Jeju National University, Jeju, REPUBLIC OF KOREA
[5]Department of Animal Biotechnology, College of Animal Bioscience and Technology, Kangwon National University, Chuncheon, REPUBLIC OF KOREA

***Corresponding author:** drneelesh_sharma@yahoo.co.in

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Abstract

Cytotherapeutics refers to prevention, treatment, cure or mitigation of disease or injuries by the administration of autologous, allogenic or xenogenic cells (manipulated or altered ex vivo). Cells with the power of unlimited self-renewal which when triggered can differentiate into advantageous specialized cell types, such types of cells are known as pluripotent stem cells. They provide an unprecedented hope in the treatment of many debilitating diseases of humans as well as animals and have enormous use in the animal cloning, drug discovery, gene targeting, transgenic animal, chimera production and regenerative therapy. Animal models are being used widely to study their properties and potential for possible future application in human medicine. In veterinary medicine, it continues to evolve rapidly both experimentally and clinically. Therefore, there's a lot of hope and emphasis is to be laid on the research of newly evolving field of human as well as veterinary regenerative medicine.

Key words: Stem cells, embryonic stem cells, ligament repair, liver progenitor cells, mammary epithelial cells.

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Introduction

Cells with the power of unlimited self-renewal which when triggered can differentiate into advantageous specialized cell types, such types of cells are known as pluripotent stem cells. They provide the basis for an unlimited source for innovative cell therapies (Kumar *et al*., 2015). Thus over a past decade, greater attention has been paid to stem cell research, which serves as an emerging area of significant interest for scientist/researchers/clinicians because of the potential in its application in regenerative medicine (Iacono *et al*., 2015). They provide an unprecedented hope in the treatment of many debilitating diseases of humans as well as animals (Gade *et al.*, 2012) and have enormous use in the animal cloning (Stice and Keefer, 1993) drug discovery, gene targeting (Zwaka *et al.*, 2003), transgenic animal (Saito *et al.*, 2001), chimera production (Jung *et al.*, 2007) and regenerative therapy. They have been classified into seven major classes in mammals including embryonic stem cells (ESCs) (Iacono *et al*., 2015). They are the most promising for cell based therapies that are being currently tested in pre-clinical trials for a wide range of ailments for their therapeutic potential in veterinary practice (Gade *et al.*, 2012) like the treatment of equine tendinopathies with mesenchymal stem cells (MSCs). Moreover, animal models are being used widely to study their properties and potential for possible future application in human medicine.

It all started in 1981, Martin Evans of Cardiff University, UK, then at the University of Cambridge, first identified embryonic stem cells– in mice. In 1997 Ian Wilmut and his colleagues at the Roslin Institute, Edinburgh unveiled Dolly the sheep, the first artificial animal clone. James Thomson and John Gearhart in 1998 isolated human embryonic stem cells and grew them in the lab. In 2001, US reduced the funding for research on human embryonic stem cells because of human embryos are destroyed in the process. However, US government allowed continued research on human embryonic stem cells lines that were created before the restrictions were announced. In 2005, Woo Suk Hwang of Seoul National University in South Korea reported that his team has used therapeutic cloning – a technique inspired by the one used to create Dolly – to create human embryonic stem cells genetically matched to specific people. Later that year, his claims turn out to be false. In 2006, Shinya Yamanaka of Kyoto University in Japan revealed a way of making embryonic-like cells from adult cells – avoiding the need to destroy an embryo. His team reprograms ordinary adult cells by inserting four key genes – forming "induced pluripotent stem cells". In 2007, Evans shared the Nobel Prize for medicine with Mario Capecchi and Oliver Smithies for work on genetics and embryonic stem cells. In 2009, President Barack Obama lifted 2001 restrictions on federal funding for human embryonic stem cell research. In 2010, a person with spinal injury became the first to receive a medical treatment derived from human embryonic stem cells as part of a trial by Geron of Menlo Park, California, a pioneering company for human embryonic stem cell therapies. In 2012, Human embryonic stem cells showed medical promise in a treatment that eased blindness. In 2012, Yamanaka won a Nobel Prize for creating induced pluripotent stem cells, which he shared with John Gurdon of the

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University of Cambridge. In 2013, Shoukhrat Mitalipov at the Oregon National Primate Research Center in Beaverton and his colleagues produced human embryonic stem cells from fetal cells using therapeutic cloning – the breakthrough falsely claimed in 2005. In 2014, researchers from Harvard Medical School and Riken Center for Developmental Biology in Kobe, Japan, announced a revolutionary discovery that any cell can potentially be rewound to a pre-embryonic state – using a simple, 30-minute technique, but later this hypothesis was challenged by various stem cell researchers and resulting authors found guilty. In 2014, Teams led by Dieter Egli of the New York Stem Cell Foundation and Young Gie Chung from CHA University in Seoul, South Korea, independently produced human embryonic stem cells from adult cells, using therapeutic cloning. Egli's team used skin cells from a woman with diabetes and demonstrated that the resulting stem cells could be turned into insulin-producing beta cells. In theory, the cells could be used to replace those lost to the disease. In 2014, Masayo Takahashi at the same Riken centre selected patients for what promised to be the world's first trial of therapy based on induced pluripotent stem cells, to treat a form of age-related blindness.

Source and Types of Stem Cells

Stem cells are commonly defined as "cells capable of self-renewal through replication and differentiating into specific cell lineages". The progenitor cells are defined by their ability to self-renew, to generate differentiated progenies and to express specific molecular marker/s and clonal assay. Stem cells are classified as adult and embryonic stem cells depending upon the sources (Fig. 1).

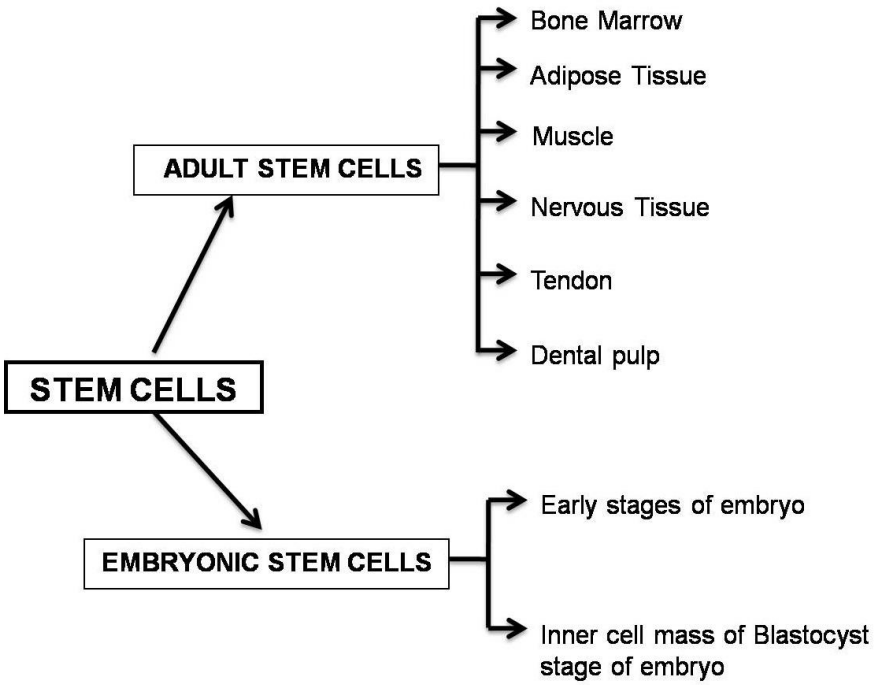

Fig. 1: Classification of stem cells on the basis of their sources.

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Here is a current list of the sources of different types of stem cells (Kogler *et al*., 2010; Nadig, 2010)-

a) ***Embryonic stem cells*** - are harvested from the inner cell mass of the blastocyst seven to ten days after fertilization. These are *pluripotent*, meaning they can give rise to every cell type in the fully formed body, but not the placenta and umbilical cord. These cells are incredibly valuable because they provide a renewable resource for studying normal development and disease, and for testing drugs and other therapies.
b) ***Fetal stem cells*** - are taken from the germ line tissues that will make up the gonads of aborted fetuses. Apart from that stem cells obtained from fetal blood and tissues are believed to have similar properties and immunophenotype to comparable adult tissue-derived stem cells, although their development potential is more restricted than pluripotent embryonic stem (ES) cells.
c) ***Umbilical cord stem cells*** - The concept of using umbilical cord blood as a source of stem cells for hematopoietic transplantation was first proposed by Edward Boyse in 1983. Umbilical cord blood contains stem cells similar to those found in bone marrow.
d) ***Placenta derived stem cells*** - up to ten times as many stem cells can be harvested from a placenta as from cord blood.
e) ***Adult stem cells*** – are undifferentiated cells, found throughout the body after development, which multiply by cell division to replenish dying cells and regenerate damaged tissues. Also known as somatic cells, they can be found in juvenile as well as adult animals and humans, unlike embryonic stem cells. Many adult tissues contain stem cells that can be isolated**.**

Stem cells have an important property that they also serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is alive. On the basis of property of differentiation, stem cells can be classified into three broad categories such as totipotent, pluripotent and multipotent stem cells (Fig. 2).

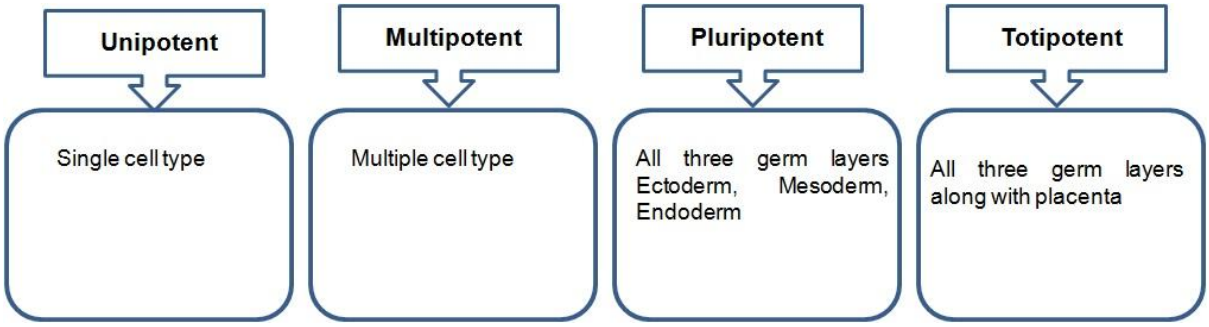

Fig. 2: Classification of stem cells on the basis of their plasticity.

Totipotent stem cells have form a complete organism (e.g., identical twins) and found in early embryos. Pluripotent stem cells exist in the undifferentiated inner cell mass of the blastocyst and can form any of the over 200 different cell types found in the body. Multipotent stem cells are derived from fetal tissue, cord blood and adult stem cells. Although their ability to differentiate is more limited than pluripotent stem cells, they already have a track record of success in cell-based therapies.

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Application of Stem Cell in Veterinary Medicine

A clear clinical picture of application of stem cells in veterinary medicine can be seen, they are being used well in equine orthopedics and small animals stem cell treatments which are being commercially offered. In veterinary medicine, it continues to evolve rapidly both experimentally and clinically. Technologies of assisted reproduction are being developed to apply the properties of spermatogonial stem cells to preserve endangered animal species. The same methods can be used to generate transgenic animals for the 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. It has been demonstrated that signals produced by damaged tissues are enabled by MSCs through special chemokine receptors (Guest *et al*., 2008). MSCs migrate to damaged tissue as a response to the signal and seem to induce regeneration of the respective tissue. Therefore, there's a lot of hope and emphasis is to be laid on the research of newly evolving field of human as well as veterinary regenerative medicine.

Tendon Injury

Apart from the in vitro studies and experimentation on small animals, horses are certainly the more focused subject with regard to veterinary research on stem cell treatment of tendon injuries (Ribitsch *et al*., 2010). Tendon injury is frequently encountered in equine athletes. After a clinical injury, there is a phase of small inflammatory response in tendon, which is followed by formation of fibrous scar tissue which lacks elasticity and thus, animal becomes more prone to re-injury (Smith, 2008). The possibility of regeneration of functional tendon is more with stem cell therapy than the conventional treatment, preventing the rate of re-injuries (Guest *et al*., 2008). Two possible theories regarding the effect of stem cells are discussed. One possibility is that they differentiate into tenocytes within the tendon environment and support healing via collagen production and remodeling activities. The second possibility is that the injected cells supply growth factors rather than differentiate terminally into the required tissue (Chong *et al*., 2008; Richardson *et al*., 2007). There are two different approaches to stem cell therapy that are clinically used for the treatment of equine tendon disease: one is to apply isolated and expanded bone marrow-derived MSCs, the other is to implant adipose-derived nucleated cell (ADNC) fractions or adipose derived expanded MSC (Richardson *et al*., 2007). In equine, autologous bone marrow derived MSCs after in vitro expansion were utilized and found effective for regeneration tendon matrix in superficial flexor tendon injury (Smith *et al*., 2003). In race horses, the adipose derived MSCs were used to successfully treat experimental tendinitis (Carvalho *et al*., 2011). Bone marrow derived autologous MSCs along with collagen gel were used to repair surgically induced patellar tendon defect in adult New

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Zealand White rabbits; treated group shows significant improvement in its biomechanical properties after 4 weeks (Awad *et al.*, 1999).

Mammary Gland

It has been suggested that the multipotent mammary stem cells (MaSCs) give rise to epithelial precursor cells, the progeny of which develop into either ductal or alveolar cells (Hennighausen and Robinson, 2005) (Fig. 3). The parenchyma is the portion of the mammary gland (udder) that is considered to be the functional aspect of the gland as this region contains the mammary epithelial cells (MECs) (Thorn *et al.*, 2008). MECs, responsible for producing milk, are the focus of the majority of research pertaining to mammary gland in cattle.

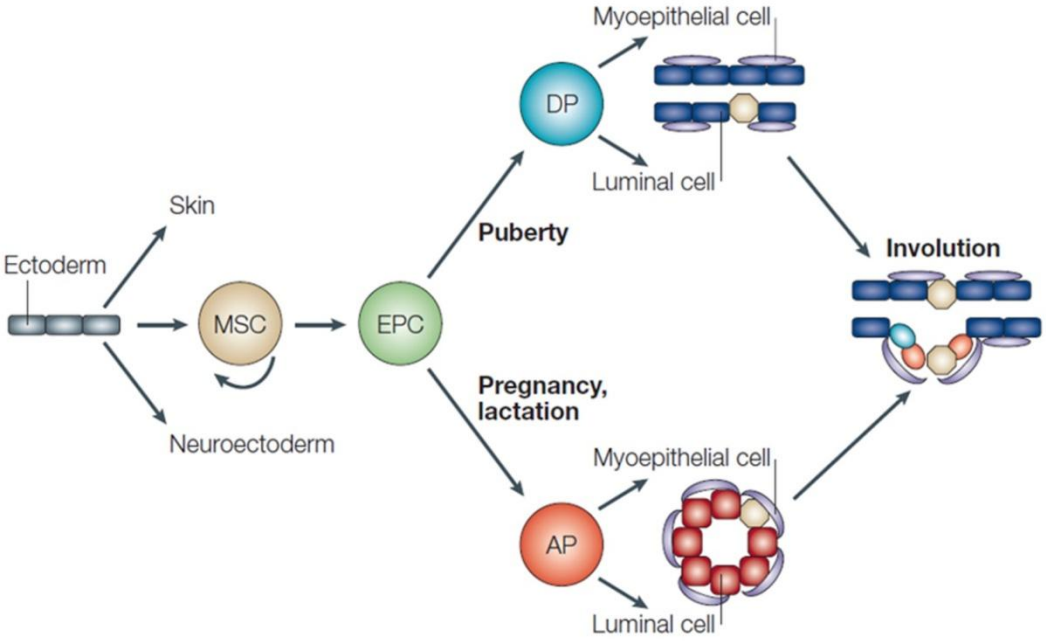

Fig. 3: Mammary gland epithelium cell lineages.

Myoepithelial cells and luminal cells are formed from ductal precursors (DP) as the ducts grow out postnatally, particularly during puberty. On initiation of pregnancy, alveolar precursor cells (AP) give rise to myoepithelial and luminal cells, the latter of which synthesize and secrete milk. After lactation, the alveolar cells are subject to programmed cell death during the process of involution. A simple ductal system containing multipotent (yellow) and committed ductal (green) and luminal (orange) precursor cells persist that will develop into a fully functional epithelium in subsequent pregnancies (Hennighausen and Robinson, 2005).

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Milk production is directly related to the number of the functional mammary epithelial cells, which produce and secrete milk, in the mammary glands (Tucker, 1981). Intramammary infection severely damages the internal structures of udder which results into significant decrease in milk production. Growth and maintenance of the mammary epithelium depend on the function of mammary stem cells and progenitor cells (Capuco and Ellis, 2013). An important attribute of the mammary gland is the regenerative capacity of mammary epithelium, which is evidenced by repair mechanism during the regression phase in successive reproductive cycles (Smith and Chepko, 2001).

Clinical mastitis has a deleterious effect on the udder and is also a welfare issue with large impact on the economy and quality of milk, reduction in production is no different to it as there is the destruction of epithelial cells. Bovine mammary epithelial cells (MECs) and their stem cells are very important in milk production and bioengineering. The inner layer of columnar/luminal cells of bovine MECs, is characterized by cytokeratin18, 19 (CK18, CK19) and an outer layer such as myoepithelial cells which are characterized by CK14, α-smooth muscle actin (α-SMA) and p63 (Sharma *et al.*, 2013). Much work has been done in mouse and human, on mammary gland stem cell research, particularly in cancer therapy, but stem cell research in bovine is still in its infancy. There is still some hope that these discoveries which are being applied in humans and mouse mammary gland will be applied in bovines to correct the structural/cytological defects in bovine udder suffering from mastitis. In a recent study of Sharma *et al.* (2015) which has been established bovine mammary epithelial stem cell under extra-cellular condition medium, which has opened the new avenue for further research in the direction of mammary gland repair. Mammary cell proliferation, turnover and tissue regeneration are functions of mammary stem cells.

Bone Regeneration

The natural repair or bone regeneration is a complex process with local MSCs generating essential components: chondroblasts, chondrocytes, fibroblasts and osteoblasts which form the callus (Carter *et al*., 1998). New extracellular matrix (ECM) is formed and comprises osteoids and cartilage that undergo enchondral ossification and bone formation until the fracture gap is bridged (Kraus and Kirker-Head, 2006). The newer tissue engineering process involves all those elements required for the natural repair process of osseous tissue and delivers them to the site of the larger defect. There are three general approaches have been applied to the art of tissue engineering of bone matrix based therapies that use factor based therapies that directly provide osteoinductive stimuli such as the family of bone marrow proteins (BMPs), scaffolding implants to replace the missing bone, and cell based therapies that transfer cells with osteogenic potential directly to the site of repair in damaged tissue. It is based on the implantation of unfractionated fresh bone marrow, culture expanded MSCs, MSCs differentiated towards osteoblastic and chondrogenic lineages or cells that have been modified genetically to express a rhBMP

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(Bruder and Fox., 1999). In general, less differentiated cells are easier to expand in vitro due to their high proliferation rate, while differentiated cells are more effective in vivo due to their higher and rapid production of mineralized ECM. Amongst all adult stem cells, bone marrow-derived stem cells are the most commonly used cell source for bone regeneration and repair in studies using different animal models. Richards and coworkers injected murine MSCs into distracted femoral bones of rats. After five weeks they observed significant increase of new bone volume, formation of new trabecular bone with marked osteoblastic activity and osteoid production. So far, repairments of various bones such as long bones, cranial bones, mandibular bone and alveolar bone as well as for the enhancement of spinal fusion using MSCs have been examined.

Liver Damage

The liver is known for its remarkable capacity to regenerate after acute injury, such as loss of liver mass. However, chronic hepatic damage due to continuous viral, toxic, or carcinogenic injuries compromises the regenerative capacity of hepatocytes through induction of replicative arrest. Liver progenitor cells (LPC) are hoped to be able to support liver regeneration. And these LPCs, undifferentiated epithelial cells which lie at the interface of the hepatic cords and the biliary tree, offer a promising target for therapeutic intervention in severe liver diseases.

The growing worldwide challenge of cirrhosis and hepatocellular carcinoma due to increasing prevalence of viral hepatitis, obesity, and the metabolic syndrome has sparked interest in stem cell-like liver progenitor cells (LPCs) as potential candidates for cell therapy and tissue engineering (Köhn-Gaone *et al.*, 2016). Activated LPCs can either differentiate into haematopoietic lineages or mature hepatocytes as well as cholangiocytes in order to regenerate the pathological changes in the liver (Arends *et al*., 1999). Mesenchymal stem cells are considered one of the best eligible sources for cell therapy (Horwitz *et al.*, 2005). Due to their immunosuppressive and tissue remodeling properties, MSCs are a promising therapeutic tool in a variety of diseases, including liver disease (Kuo *et al.*, 2008). Canines are a large animal model, in which the pathologies of liver diseases are similar to man (Malagola *et al.*, 2016). They have been reported canine liver MSCs markers such as CD274, PTGS-1, and PTGS-2.

Cardiac Damage

According to world health organization (WHO), cardiovascular diseases are the leading cause of death worldwide. Claiming 14.7 million lives in 1990 and 17 million in 1999 (Bonow *et al.*, 2002), therefore effective secondary treatments are urgently needed. All these issues insist the researchers to find out other alternative source/animal models of stem cells. Nguyen *et al.* (2014) have been claimed chicken can be used as animal model for the human cardiac diseases, as they have isolated and characterized cardiac

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differentiation potential of chicken spermatogonial cells. A number of adult stem cell therapies primarily MSCs have been explored for the repair and regeneration of damaged tissues and organs (Orlic *et al.*, 2001). They migrate to sites of inflammation when infused intravenously, although comprehensive understanding of how they act once they have lodged in a specific tissue is not available (Chapel *et al.*, 2003; Ortiz *et al.*, 2003). In preclinical studies, MSCs have been shown to improve myocardial function after myocardial infarction in rodents (Itescu *et al.*, 2003) and pigs (Amado *et al.*, 2005). In a recent study has been claimed that cardiac stem cells from young hearts could rejuvenate old hearts using animal model (Grigorian-Shamagian *et al.,* 2017). They injected cardio-sphere derived cells of young rat heards into old rat hearts and found improved functions of heart. Laflamme *et al.* (2005) injected differentiated cardiac-enriched human embryonic stem cells (hESC) progeny into the left ventricular wall of athymic rats and found that grafts consisted predominantly of cardiomyocytes by 4 weeks. Mouse embryonic stem cells derived cardiomyocytes were engrafted in the injured myocardium of rat this resulted in angiogenetic effect and subsequently improved cardiac function during the 32-week observation period (Min *et al.*, 2003). Since MSC have been shown to improve myocardial function after myocardial ischaemia in preclinical studies, the preferential homing of MSC to the infracted myocardium is important, since it enables the intravenous route of administration to be used, rather than the more invasive alternatives of intra-arterial or intra-myocardial administration.

Spinal Cord Injuries

Many dogs and cats are affected by the acute spinal injuries. Nearly 2% of the dogs that are being admitted in the clinical complexes suffer from injuries to spinal cord mostly involving intervertebral disc disease (Webb *et al*., 2004). Traumatic spinal cord injury causes loss of tissue, including myelinated fibre tracts responsible for carrying descending motor and ascending sensory information. Loss of myelinated cells or reduced oligodendrocyte myelin synthesis leads to reduced myelination (Dasari *et al*., 2007). Although a considerable amount of locomotor ability may be recovered after injury, however natural CNS capacity to recover is limited and besides that neuroanatomical difference between species also plays an important role in assessing the recovery of spinal cord.

Fetal- or adult-derived neural stem cells (NSCs)/progenitor cells are considered an attractive source for cell therapy because they are already committed to neural differentiation. Primary cultures (Johann *et al.*, 2007) and fetus-derived immortalized cell lines (Lee *et al.*, 2005), as well as progenitor stem cells from central nervous system (CNS) brain tissues, and have been used in animal studies. The remarkable developmental potential and replicative capacity of embryonic stem (ES) cells were utilized by transplanting neural precursors into the brain of immunosuppressed neonatal mice and no teratomas emerged within 8 weeks after implantation (Zhang *et al.*, 2001). The comparison of autologous and

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allogenic transplantation of canine bone-marrow derived MSCs in experimentally-induced spinal cord injury (SCI) revealed that both approaches could be utilized clinically (Jung *et al.*, 2009).

Future Prospects and Outlooks

Based on the reports it is obvious that regenerative medicine in the field of veterinary medicine is making great steps to become clinical reality. Though the promise of stem cells therapies is an exciting one, but significant technical hurdle remains there, that will only be overcome through years of intensive research. Instead of transplanting stem cell, attempts can be made to activate the individual's own stem cell to repair. Cell therapy has the potential to creatively leverage Mother Nature's billion years of research and development to provide new and much needed treatments to patients with acute and chronic diseases. The clinical use of stem cells in veterinary medicine is clearly in its early stages. Optimization of these stem cell-based therapies will focus on cellular origin, isolation, enrichment, and processing as well as on the timing, route of administration, formulation, and dosing of those therapies. Development of confirmed ES or iPS cells in domestic species would greatly facilitate the development of a wider range of clinical applications. Embryonic stem (ES) cells are pluripotent stem cells obtained from the inner cell mass of the blastocyst – an early-stage embryo. So far ES cells have been recovered and maintained from non-human primate, mouse and horse blastocyst. In addition, bovine ES cells have been grown in primary culture and there are several reports of ES cells derived from mink, rat, rabbit, chicken and pigs. Advances in the laboratories have led to development of feeder and animal-sera – free cells lines and could also help in preservation of germplasm of threatened species. Though they have immense potential in therapeutics, their clinical use requires extensive research for standardization of the treatment protocols, routes and doses. But the clinical application of ES cells remains faced with practical and ethical concerns. Therefore, it should be a collective goal of the veterinary community to use clinical trials, which include sufficient similar cases and a consistent and standardized panel of objective outcome measures (Stewart, 2011).

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