The treatment of articular cartilage injuries with mesenchymal stem cells in different animal species

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Abstract
One of the major problems observed in veterinary practice is articular cartilage injuries in animals. In terms of agriculture, it leads to their culling from the herd, even if they are highly productive animals. With companion animals, owners usually have to decide between euthanasia or long-term sometimes lifelong treatment of the injury by a veterinarian. The use of mesenchymal stem cells (MSCs) for the treatment of cartilage injury in veterinary medicine is based on the good results observed in preclinical studies, where large animals have been used as experimental models to study the regenerative activity of MSCs. According to the literature, MSCs in veterinary medicine have been used to treat cartilage injury of dogs and horses, whereas sheep and goats are generally models for reproducing the disease in preclinical experimental studies.
Keywords: Mesenchymal stem cells, Cartilage tissue, Animals, Regeneration, Therapy.

Introduction

Mesenchymal stem cells (MSCs) are precursors of human and animal tissues. MSCs are detected within, and can be separated from, various sources including bone marrow (BM), adipose tissue (AT), cord tissue (CT), cord blood (CB), Wharton's jelly (WJ), the pulp of milk teeth, the endometrium, and other sources. Modern researches have shown that MSCs process regenerative activities within damaged body tissues (Zakirova *et al*., 2017, 2019) and can be differentiated into four lines. This therapeutic effect is due to their ability to affect injured tissues with biologically active substances secreted by MSCs (Ragni *et al*., 2020).

The research into veterinary regenerative medicine has focused mainly on domestic and sporting animals, but a critical reading of the published results, combined with selected articles published for domestic animals, allows us to gain valuable insights about the future use of regenerative medicine in farming. Among all domesticated animals, cattle play a crucial role in the farming economy. There are several diseases, such as mastitis, lameness, and monomeric fractures to limb bones, which can negatively affect the production of meat and milk, in addition to the reduction in reproductive efficiency in cattle. For cows with high economic or genetic potential, these losses create significant costs for the owner, and the owner is obliged to use expensive and effective treatment methods to restore the animal's health (Jean and Anderson, 2014). According to literature data, osteoarthritis (OA) affects about 20% of dogs (Pigareva, 2016), and in horses, it is one of the most common causes of lameness. It is shown that approximately 33% of horses have cartilage injury associated with OA (Nifontov, 2009). Therefore, it is important to develop therapeutic approaches to stimulate the regeneration of hyaline tissue for better joint rehabilitation (Juneau et al., 2016).

The aim of this review is to scrutinize the modern achievements of regenerative veterinary medicine in the treatment of joint injuries in animals.

The peculiarities of the structure and regeneration of cartilage tissue concerning MSC use

Articular cartilage is mainly composed of hyaline tissue which in itself is a specialized tissue present in most joints, providing low abrasion and amortization. It also provides a structural and biological barrier between the two bone surfaces, for an unimpeded, even range of motion in the joints. It should be noted that the cartilage is devoid of blood vessels, lymph nodes, and nerves and is generally split into the superficial, middle, and deep zones with calcified cartilage situated next to the subchondral bone (Duarte Campos, 2012) (Fig. 1).

Cartilage tissue mainly comprises 70%–80% of water, 10%–15% of organic substances, and 4%–7% mineral salts. Collagen is found between 50% and 70% of the dry matter, which gives tensile strength, and also in proteoglycans, which provide functional resistance to compression (Francis *et al*., 2018). The thickness of articular cartilage depends on the type of joint and the age of the animal, in addition to the species type. The average thickness of knee cartilage in adult rabbits, sheep, dogs, goats, horses, and humans is 0.3, 0.4–0.5, 0.6–1.3, 0.7–1.5, 1.5–2.0, and 2.2–2.5 mm, respectively (Frisbie *et al*., 2006). Due to its basic structure,

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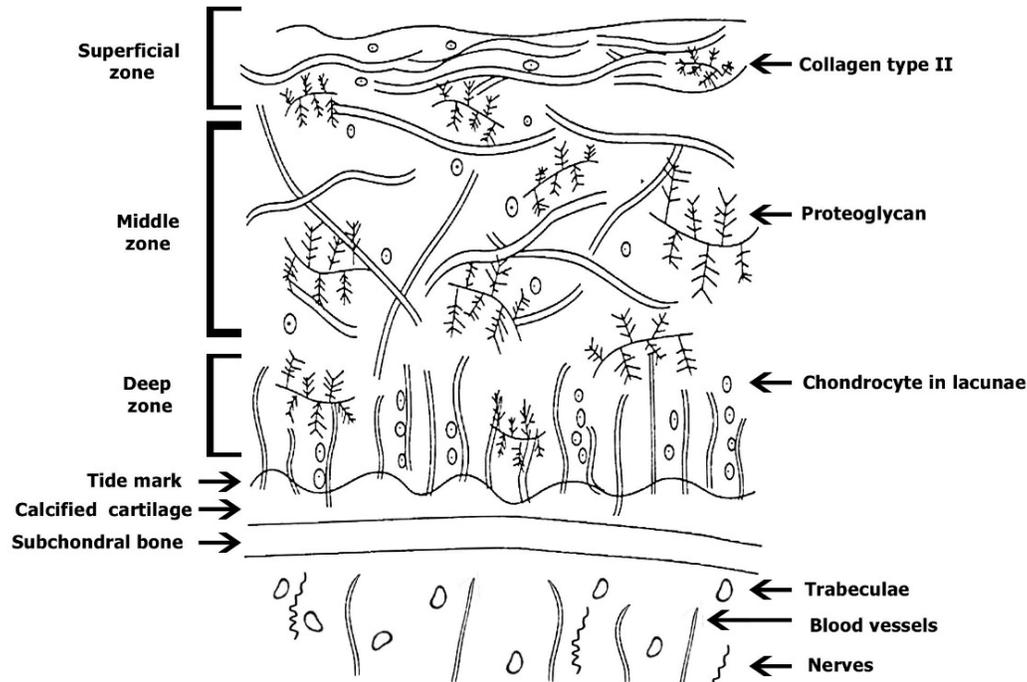
Fig. 1. Structure of cartilage tissue.

damaged hyaline cartilage has low regenerative abilities. This is a serious problem in orthopedics, both with and without treatment; cartilage injuries are filled with fibrous tissue, but this does not have the necessary specialized properties of hyaline cartilage and, therefore, compromises structure and function (Redman *et al*., 2005). Cartilage defects can penetrate throughout the entire thickness of the cartilage into the subchondral bone, or be limited to the cartilage itself (Gugjoo *et al*., 2016). Defects penetrating partially through the cartilage do not heal spontaneously due to the absence of a fibrin clump and, consequently, of reparative stem cells, although full thickness injuries heal spontaneously as they are filled in mechanically with structurally diminished fibrous tissues that do not integrate with native cartilage (Tiwary *et al*., 2014). However, one risk is that if the treatment is ineffective, the injury can lead to OA (Fig. 2). It should be noted that cartilage degeneration and inflammation are key signs of OA, which can affect the entire joint and cause pain, deformation, and loss of function (Toh *et al*., 2016).

Studies on animals show that MSCs obtained from adult tissues are prospective candidates for the treatment of injuries because they have low immunogenicity and high anti-inflammatory potential (Gao *et al*., 2015; Mount *et al*., 2015). *In vivo* studies using MSCs for cartilage therapy have been carried out on almost all domesticated species of mammals, including sheep, goats, dogs, horses, cattle, cats, and pigs. Both allogeneic and autogenic cells have been used in these studies. Researchers have noted that allogeneic MSCs transplanted once or several times are safe and do not cause any reactions from the immune system (Ardanaz *et al*., 2016; Vega *et al*., 2015). The cells are detected *in vivo* in the implantation zone even after 14 weeks (Feng *et al*., 2018). At present, it is recommended that MSCs be administered after anti-inflammatory therapy during the treatment of injured joint surfaces (Ando *et al*., 2012; Zayed *et al*., 2016).

Transplantation of MSCs in sheep and goats for cartilage injury treatment

At present, there are many articles devoted to the treatment of cartilage injury with MSCs originating from BM and AT, as they were extensively used to show the impact of MSCs transplantation in cartilage injury in sheep and goats which were used as models. The methods of administration of MSCs-AT and MSCs-BM are different but both intra-articular and systemic administration is recommended. However, all published studies have shown positive effects and an absence of complications in the animals following the introduction of MSCs (Caminal *et al*., 2014).

Some researchers recommend that to strengthen the regenerative potential of MSCs-BM, they should be pre-differentiated in the chondrogenic direction. In a model of surgically induced OA in sheep, pre-differentiated MSCs-BM were introduced intra-articularly and compared against a positive control group where intact MSCs-BM were introduced and negative control group animals were given a basal environment without cells. According to histological studies in the experimental group, the thickness and
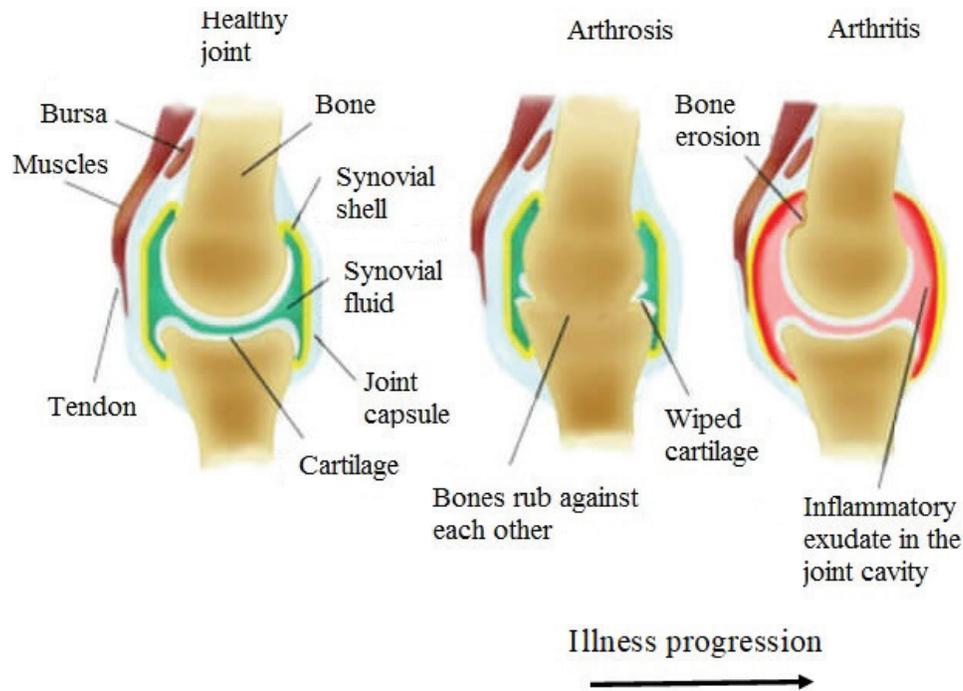
Fig. 2. Development of arthritis.

quality of cartilage tissue were comparable to intact knee joint cartilage. In the positive control group, the researchers also noted positive effects from MSCs-BM introduction, and in the negative control group, severe OA and meniscus damages were observed. Thus, a single intra-articular injection of intact or pre-differentiated *in vitro* MSCs-BM may slowdown the progression of OA in the sheep model, but pre-differentiated cells showed better results, especially in the process of meniscus regeneration (Al Faqeh *et al.*, 2012).

Bornes et al. (2018) studied the effects of oxygen concentration on the regenerative potential of MSCs-BM differentiated in the chondrogen direction. At the same time, native MSCs-BM was grown on scaffolds (cell matrices) made of hyaluronic acid. Before transplantation, MSCs were injected into the damaged joint and then placed in a differentiation medium and cultured at 21% oxygen (normoxia) or 3% (hypoxia) for 4 days. Cells were not transplanted into animals in the control group having damaged joints. According to the results obtained from the experiments, the researchers concluded that when cells were cultured *in vitro* in a chondrogenic environment in hypoxic samples, the expression of aggrecan and type 2 of collagen increased. However, after *in vivo* implantation, the difference between normoxic and hypoxic samples on histological morphology was not detected, but in comparison with acellular controls in the two experimental groups, there were higher percentages of filling within injuries with a hyaline-like tissue (Bornes *et al.*, 2018).

Abdalmula *et al*. (2017) studied the regenerative potential of MSCs which were obtained from the ovary of a sheep on a model of sheep monoarthritis. They received collagen-induced hock monoarthritis of the joint, and then animals were given intravenous MSCs derived from ovarian mesenchyma. As a result of the experiments, a positive regenerative effect of the selected MSCs was shown. The publication notes significant reductions in lameness, pain in the affected joints, and edema as compared to the animals in the control group. Besides, histological studies showed decreased cartilage erosion in the experimental group along with activation of the synovial stromal cells and angiogenesis. These effects were accompanied by a decrease in the infiltration of synovial tissues by CD4 + lymphocytes and CD14 + monocytes/macrophages. Within 3 days of induction in the MSCs injected in articular arthropathy animals, a significant decrease in the numbers of circulating neutrophils in the blood and the concentration of activin A in the blood plasma was observed. From the results obtained, it was concluded that MSCs isolated from the ovaries can soften the clinical signs of arthritis and reduce the concentration of certain inflammatory mediators in the blood responsible for the destruction of joint tissue (Abdalmula *et al.*, 2017).

In a model of medial condyle defect of the femoral bone and trochlear notch in goats, MSCs-AT therapy and stromal vascular fraction (SVF) were used. The cells were seeded on a type I/III collagen scaffold and transplanted into animals. This procedure led to

stimulation and regeneration of cartilage compared to animals treated with scaffolds of cell-free collagen I/III. The researchers reported that there were no significant differences in the rate of regeneration between animals that received a collagen scaffold with MSCs-AT or SVF (Jurgens *et al*., 2013).

Regenerative therapy of cartilage injury in dogs by MSCs transplantation

In contrast to most studies in goats and sheep, dogs are not only used as model animals in preclinical research when developing MSCs therapies, but also as species-specific treatments which are being developed for their own healthcare needs (Kazemi *et al*., 2017).

Kazemi et al. (2017) conducted a series of experiments on 12 adult dogs in which osteochondral defects were created on the medial condyles of the femoral bone, into which MSCs-BM mixed with a thrombocyte mass were placed. In control animals, the defect was not filled in. According to the results of the experiment, the use of autologous cultures of MSCs-BM with thrombocyte masses stimulated cartilage regeneration in dogs. Thrombocyte masses are rich with fibrin and create a suitable environment for proliferation and differentiation of MSCs by releasing endogenous growth factors that lead to the creation of hyaline-like reparative tissue (Kazemi *et al*., 2017).

The treatment of nine dogs with natural OA on the background of joint dysplasia also showed interesting results. The animals had not received any treatment for 2 months prior to a single intra-articular injection of autologous MSCs-AT. Observations noted over the ensuing 6 months showed that lameness and severe pain disappeared for 3 months, but thereafter the symptoms of the disease began to reappear (Vilar *et al*., 2014). However, studies conducted by Shah et al. (2018) have shown a positive effect of intravenous or intra-articular administration of MSCs in dogs with natural degenerative arthritis. Of the 203 dogs treated, 88% had a significant reduction in clinical symptoms, while the remaining 12% had no reaction following cell administration. At the same time, it should be noted that the positive effects of the introduced MSCs-AT also correlated with the age of the animals. Significant improvements occurred in 90% of the younger dogs (up to 9 years old), which reduced to 60% of older dogs (Shah *et al*., 2018).

Intra-articular introduction of allogeneic MSCs in 0.5% hyaluronic acid to dogs suffering from elbow joint dysplasia and OA showed significant improvements in the condition of animals. Researchers noted the absence of lameness or reduction to just low-grade lameness for 1 year. Control arthroscopy of the first group of dogs with the absence of lameness showed that the cartilage was restored. Histological analyses of the cartilage biopsy also confirmed that the regenerated cartilage was of the hyaline type. These results demonstrate that allogeneic MSCs-AT transplantation is a new, non-invasive, and highly effective therapeutic tool in the treatment of canine dysplasia of the elbow joint (Kriston-Pal *et al*., 2017).

The influence of species-specific MSCs umbilical cords of dogs was studied in animals with naturally occurring OA in the elbow joint. The presence of changes in the dog's joint following treatment was confirmed by computer tomography. After collecting CB from dogs during planned cesarean section, MSCs were isolated from the umbilical cord and cultured *in vitro*. Each of the 28 dogs was given 7 million cells intra-articularly, and the 28 control dogs were given a saline solution. None of the dogs in either group developed worse lameness after treatment; therefore, none of the dogs had to be removed from the study. No adverse local side effects (increased pain, the appearance or increase of edema, and the appearance of secretions from the joints) were observed. The overall results of this study demonstrated an improvement of clinical signs over 6 months in dogs treated with intra-articular injections of the umbilical cord. This fact is very attractive because other treatments of OA, such as corticosteroids, lead to risks associated with cytotoxicity, anaphylactic reactions, or septic arthritis (Kim *et al*., 2019).

Therapy of cartilage injury MSCs in horses

Most studies of MSC treatment in horses, whether preclinical or clinical, indicate incomplete regeneration of damaged horse cartilage, but MSCs therapy did produce a decrease in the severity of clinical signs in these animals (Broeckx Sarah *et al*., 2019; Kovac *et al*., 2018). According to literature data, animal recovery was more effective when MSCs were introduced in the early stages of the disease but decreased when introduced at later stages (Wilke *et al*., 2007). Similar to autologous MSCs, a single intra-articular transplantation of allogeneic MSCs-BM also did not stir an immune response (Ardanaz *et al*., 2016), but repeated intra-articular transplantation led to adverse reactions following the introduction of allogeneic MSCs (Joswig *et al*., 2017).

MSCs-BM and AT have contributed toward the regeneration of damaged meniscus of horses, by restoring cartilage tissue (Gonzalez-Fernandez *et al*., 2016). In this model of horse femoral knee disease, MSCs seeded in an autogenously self-polymerizing fibrin carrier were used with better results in the early stages compared to a cell-free fibrin carrier. In equids, improvements in arthroscopic parameters of the damaged horse meniscus cartilage were observed 30 days after MSCs transplantation (Kovac *et al*., 2018). However, after a longer follow-up period (8 months), histological indicators in the group with MSCs were comparable to the control group (Wilke *et al*., 2007). Nevertheless, after 12 months, there was a slight improvement in clinical and histological indicators compared to the control group animals. In general, the use of MSCs-BM resulted in improved cartilage quality (McIIwraith *et al*., 2011). The ability of MSCs-BM to stimulate the regeneration of cartilage tissue is

considered to be better than that of the SVF of adipose tissue (SVF-AT). The use of MSCs-BM in comparison with SVF-AT leads to better clinical, biochemical, and histological results in the treatment of horse joints with OA on day 70 following treatment (Frisbie *et al*., 2009). In the search for effective treatments for degenerative joint disease, Broeckx Sarah et al. (2019) conducted a study involving 75 adult horses that had early signs of joint damage. Fifty animals were given intravenous allogeneic MSCs induced in the chondrogen direction with equine allogeneic plasma, and 25 horses were given a control drug having 0.9% NaCl. Long-term observation of animals after MSCs transplantation (1 year) showed that a significant number of horses subjected to cell therapy worked at the training level or returned to the previous level (Broeckx Sarah *et al*., 2019).

Due to the presence of a considerable number of sources of MSCs, Zayed et al. (2018) conducted comparative studies of MSCs-BM and MSCs from synovial fluid (MSCs-SF) of horses *in vitro*. The results showed that MSCs-SF had similar proliferative activities to MSCs-BM and expressed the membrane markers CD29, CD44, and CD90, but demonstrated different chondrogenesis characteristics. In addition to this, MHC II was positively expressed in all MSCs, while in MSCs-BM the expression was negative. When both autologous and allogeneic MSCs were administered *in vivo*, an increment in the level of total protein and in the total number of nucleated cells was observed in the horse's ankle joint. Therefore, further experiments to assess *in vivo* acute or chronic responses to allogeneic or autologous MSCs from various sources are necessary (Zayed *et al*., 2018).

Conclusion

The articular cartilage after damage tends to deteriorate every day due to its typical location and limited innate healing potential. With limited success of modern surgical methods, the inclusion of stem cells in regenerative drug therapy is intensively studied to ensure better rehabilitation of cartilage. Various stem cells derived from AT and BM MSCs are studied to assess their clinical use. This technology promises to develop a mechanically strong border between cartilage and cartilage, and includes mesenchymal condensation into cell bodies under the influence of growth factors. However, this method is yet to be tested *in vivo* (clinical conditions). The clinical use of MSCs has mainly been applied in dogs and horses, while in sheep and goats MSCs has mainly been studied in preclinical experimental models. MSCs chondrogenesis greatly varies in terms of cell sources, methods of cultivation, number of passages, number of implants required, and the inclusion of growth factors, and hence requires further research. In general, the best treatment is observed in the treatment of MSCs compared to the control. However, there are various problems with the treatment of MSCs, such as the lack of hyaline tissue regeneration, integration of the regenerated tissue matrix with the native cartilage or subchondral bone of the host, and its comparable effectiveness in all cases. Thus, the use of the unique regenerative properties of MSCs from autologous AT, BM, CB, CT, and WJ can be considered fully effective, clinically applicable, safe, and dependable for improving the clinical results and therapeutic doses of injected cells.

Conflict of interest
The authors declare that there is no conflict of interest.

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