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Regenerative Approaches in Veterinary Orthopaedics: Stem Cells and Bioactive Molecules in Bone Tissue Engineering

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Abstract:

Bone and cartilage disorders are among the most common causes of lameness, pain, and reduced performance in veterinary patients. Conventional treatments such as fixation, grafting, and pharmacological management often fail to restore complete structure and function, particularly in large bone defects and degenerative joint diseases like osteoarthritis. Bone tissue engineering (BTE) has emerged as a promising regenerative approach that combines stem cells, bioactive molecules, and scaffolds to promote true tissue regeneration rather than simple repair. Mesenchymal stem cells (MSCs), derived from sources such as bone marrow, adipose tissue, dental tissues, and umbilical cord, play a central role due to their regenerative, paracrine, and immunomodulatory properties. Bioactive molecules including bone morphogenetic proteins (BMPs), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) further enhance osteogenesis and angiogenesis. Although cost, technical complexity, and regulatory issues currently limit widespread clinical use in veterinary practice, stem cell based therapies are increasingly being adopted as adjunctive treatments. This article provides a popular overview of stem cell sources, mechanisms of action, and their applications in veterinary bone and cartilage tissue engineering.

Introduction:

Musculoskeletal disorders significantly affect the quality of life of animals, ranging from companion animals such as dogs and cats to large animals used in farming and sports. Fractures, bone defects, delayed union, non-union, and degenerative joint diseases such as osteoarthritis (OA) remain major clinical challenges in veterinary orthopaedics. Traditional treatment options, including internal fixation, bone grafts, and anti-inflammatory drugs, are often limited in their ability to fully restore damaged bone and cartilage.

Bone tissue engineering (BTE) represents a modern regenerative strategy that aims to regenerate functional bone by combining three essential components:

- Cells (stem cells)
- Bioactive molecules (growth factors and cytokines)
- Scaffolds (natural or synthetic matrices)

Among these, stem cells particularly mesenchymal stem cells (MSCs) have attracted immense attention in veterinary medicine due to their availability, safety profile, and multifunctional regenerative effects. Along with stem cells, bioactive molecules play a crucial role in directing cell behaviour, enhancing blood vessel formation, and improving integration with host tissues. This article discusses the role of stem cells and bioactive molecules in veterinary BTE, with special emphasis on their sources, mechanisms of action, and applications in bone and cartilage repair.

BONE TISSUE ENGINEERING: OVERVIEW

Bone tissue engineering seeks to mimic natural bone healing by creating a favorable biological environment. Successful bone regeneration depends on:

- Osteogenic cells capable of forming new bone
- Osteoinductive signals that stimulate bone formation
- Osteoconductive scaffolds that support cell attachment and growth
- Adequate vascular supply, which is essential for nutrient delivery

In large bone defects, natural healing is often insufficient due to poor blood supply and mechanical instability. Therefore, engineered constructs incorporating stem cells and bioactive molecules are designed to overcome these limitations.

SOURCES OF STEM CELLS IN VETERINARY MEDICINE

Stem cells used in veterinary regenerative medicine are derived from a variety of tissues, each source offering distinct biological advantages and clinical applications. Among these, mesenchymal stem cells (MSCs) are the most extensively studied and commonly used due to their multipotency, immunomodulatory properties, and relative safety.

Bone marrow derived mesenchymal stem cells (BM-MSCs) represent one of the earliest and most thoroughly investigated stem cell populations in bone tissue engineering. These cells possess a strong osteogenic potential and can readily differentiate into osteoblasts, chondrocytes, and adipocytes under appropriate conditions. Their biological behavior, differentiation pathways, and safety profile are well documented in experimental and clinical studies. However, the clinical use of BM-MSCs is limited by several factors, including the invasive nature of bone marrow collection, lower cell yield compared to adipose tissue, and a decline in proliferative and differentiation capacity with increasing age of the donor. Despite these limitations, BM-MSCs continue to be regarded as the gold standard in experimental veterinary bone tissue engineering studies.

Adipose-derived mesenchymal stem cells (AD-MSCs) have emerged as a highly practical and popular alternative source of stem cells in veterinary practice. Adipose tissue can be harvested from subcutaneous or intra-abdominal fat deposits with minimal morbidity, making the procedure less invasive and more acceptable in clinical settings. AD-MSCs offer a high cell yield and demonstrate rapid expansion in culture, which is advantageous for therapeutic applications. Clinically, these cells are widely used in dogs and horses for the management of orthopedic conditions such as osteoarthritis, ligament injuries, and tendon disorders. Their therapeutic efficacy is largely attributed to their strong immunomodulatory and paracrine effects rather than direct tissue replacement.

Dental tissue–derived stem cells, isolated from dental pulp, periodontal ligament, and exfoliated deciduous teeth, have also shown promising regenerative potential. These cells are of neural crest origin and exhibit strong osteogenic and angiogenic capabilities, making them particularly suitable for craniofacial and mandibular bone regeneration. Although their application in veterinary medicine is still largely experimental, dental stem cells represent a novel, ethically acceptable, and biologically potent source for future regenerative therapies.

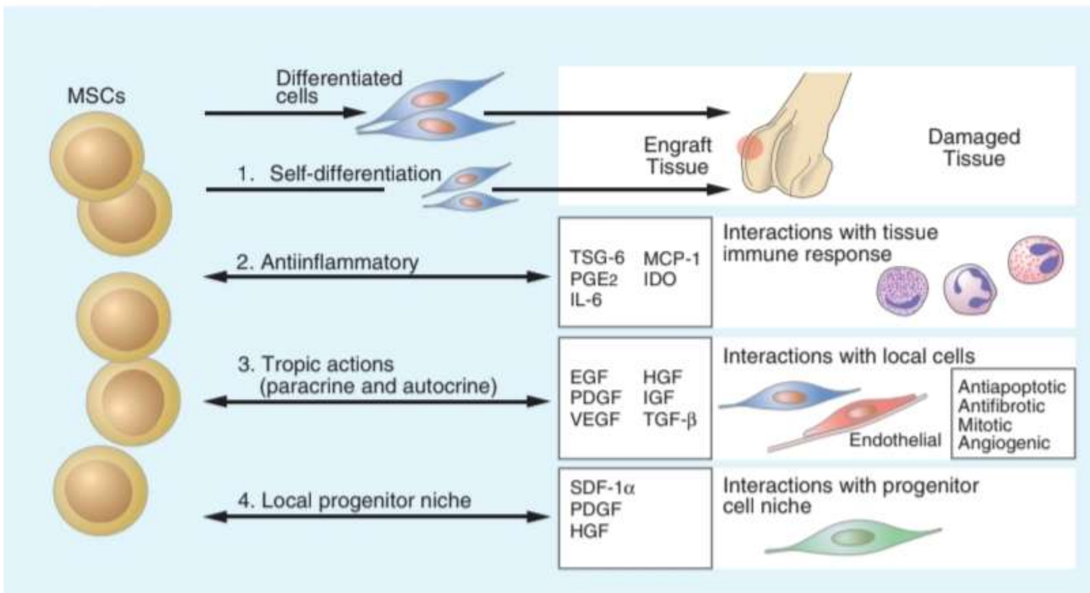
Perinatal tissues such as the umbilical cord, Wharton's jelly, and placenta are increasingly recognized as rich sources of primitive mesenchymal stem cells. Stem cells derived from these tissues can be obtained through non-invasive collection methods and exhibit high proliferative capacity along with low immunogenicity. These properties make them especially attractive for allogeneic, donor derived stem cell therapies, particularly in large animal practice where autologous cell harvesting may be impractical. Interest in perinatal stem cells is growing steadily as veterinary regenerative medicine moves toward off-the-shelf therapeutic solutions.

MECHANISMS OF ACTION OF STEM CELLS

The therapeutic effects of stem cells in bone and cartilage regeneration are mediated through multiple mechanisms, which may act independently or synergistically depending on the disease environment. One potential mechanism involves the engraftment and integration of transplanted stem cells into host tissues. When favorable conditions such as adequate vascularization, mechanical stability, and sufficient nutrient availability are present, stem cells can survive, engraft, and differentiate into bone- or cartilage-forming cells, thereby contributing directly to tissue reconstruction. However, in chronic degenerative conditions such as osteoarthritis, this mechanism is often limited or absent due to poor blood supply, excessive mechanical stress, and the presence of high concentrations of degradative enzymes that disrupt the extracellular matrix. As a result, direct tissue replacement is not considered the primary therapeutic mechanism in most clinical scenarios.

Instead, the predominant mode of action of stem cell therapy is their paracrine and trophic activity. Mesenchymal stem cells secrete a wide array of bioactive molecules, collectively referred to as the MSC secretome, which includes growth factors, cytokines, chemokines, and extracellular vesicles. These secreted factors stimulate local cell proliferation, enhance angiogenesis, inhibit apoptosis, and promote extracellular matrix remodeling, thereby creating a regenerative microenvironment. Platelet-rich plasma (PRP) and conditioned media derived from stem cell cultures exert their therapeutic effects largely through similar paracrine mechanisms. Together, these bioactive products influence the local stem cell niche, activate resident progenitor cells, and accelerate tissue repair.

In addition to their trophic effects, MSCs exhibit potent immunomodulatory and anti-inflammatory properties, particularly in damaged or inflamed tissues. In response to inflammatory signals within the tissue microenvironment, MSCs are induced to release immunoregulatory molecules such as inducible nitric oxide synthase, interleukin-1 receptor antagonist, and TNF stimulated gene 6. These substances suppress excessive inflammation, reduce tissue degradation, and promote a shift from a destructive inflammatory phase toward a regenerative healing response.



(Source: Small animal surgery / Theresa Welch Fossum, 5th edition chapter no. 31 (Principles of Orthopedic Surgery and Regenerative Medicine) page no. 973)

ROLE OF BIOACTIVE MOLECULES IN BONE TISSUE ENGINEERING

Bioactive molecules play a crucial role in directing stem cell behavior and enhancing regenerative outcomes in bone tissue engineering. Growth factors such as bone morphogenetic proteins act as strong osteoinductive signals that promote osteoblast differentiation and bone formation. Vascular endothelial growth factor is essential for angiogenesis, ensuring the development of an adequate blood supply to newly formed tissue, while platelet-derived growth factor enhances cell migration, proliferation, and tissue remodeling. In scaffold-based bone tissue engineering, the incorporation of angiogenic and osteogenic factors is particularly important, as insufficient vascularization remains a major limiting factor in the regeneration of large bone defects.

STEM CELLS IN CARTILAGE REPAIR AND OSTEOARTHRITIS

Osteoarthritis is one of the most prevalent musculoskeletal disorders in veterinary patients and is characterized by progressive cartilage degeneration, synovial inflammation, and changes in subchondral bone. Articular cartilage is avascular and possesses minimal intrinsic repair capacity, making spontaneous healing following injury extremely limited. Consequently, osteoarthritis represents a prime target for regenerative therapies. Stem cells contribute to cartilage repair primarily by modulating the joint environment rather than directly forming new cartilage tissue. Their therapeutic effects include reduction of synovial inflammation, stimulation of extracellular matrix synthesis such as collagen and proteoglycans, and protection of existing chondrocytes from apoptosis and catabolic stress. Through these mechanisms, MSCs help slow disease progression, alleviate pain, and improve joint function.

Stem cells can be administered using different delivery methods depending on the clinical condition. Intra-articular injection is a minimally invasive and commonly used technique in veterinary practice, particularly for the management of osteoarthritis. Surgical or arthroscopic implantation allows precise placement of stem cells or cell-loaded scaffolds into focal cartilage or osteochondral defects and is often used in combination with biomaterial scaffolds to enhance repair.

CLINICAL CHALLENGES AND FUTURE PERSPECTIVES

Despite the encouraging outcomes reported in experimental and clinical studies, the routine application of stem cell–based bone tissue engineering in veterinary practice remains limited. Major challenges include high treatment costs, regulatory constraints, variability in cell sources and treatment protocols, and a lack of long-term clinical outcome data. Current research efforts are therefore focused on the development of cell-free therapies using stem cell secretome or exosomes, combination approaches integrating stem cells with bioactive gels or scaffolds, standardization of therapeutic protocols, and the expanded use of allogeneic stem cells. These advances are expected to improve accessibility, consistency, and clinical effectiveness of regenerative therapies in veterinary medicine.

Conclusion

Stem cells and bioactive molecules represent a powerful regenerative approach in veterinary bone and cartilage tissue engineering. By combining osteogenic cells, angiogenic signals, and suitable scaffolds, BTE offers the potential to overcome the limitations of conventional treatments. Although widespread clinical application is still evolving, stem cell–based therapies are steadily gaining acceptance as safe and effective adjuncts in veterinary orthopaedics. Continued research and technological refinement are expected to make these advanced regenerative strategies more accessible in routine veterinary practice.