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REVIEW ARTICLE

Umbilical cord mesenchymal stem cells and their secretome: a new frontier in orthopedic medicine

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ABSTRACT

Umbilical cord mesenchymal stem cells (UC-MSCs) have gained significant attention in regenerative medicine due to their unique biological properties, including high proliferation capacity, low immunogenicity, and potent immunomodulatory effects. These characteristics make UC-MSCs particularly promising for orthopedic applications, where the repair and regeneration of musculoskeletal tissues such as bone, cartilage, tendons, ligaments, and nerves are critical for restoring function. The secretome of UC-MSCs—comprising bioactive molecules such as exosomes, cytokines, and growth factors—offers a powerful, cell-free therapeutic option through paracrine signaling, further enhancing their therapeutic potential. A literature search was conducted in major databases (PubMed, ScienceDirect, SpringerLink, Google Scholar) for English articles from 2010–2025 using keywords related to UC-MSCs and orthopedic regeneration. This review explores the role of UC-MSCs and their secretome in orthopedic tissue repair, focusing on their application in bone healing, cartilage regeneration, tendon-ligament repair, and nerve regeneration with their innovative delivery. Despite the promising potential of UC-MSC therapies, several challenges remain, including regulatory hurdles, long-term safety concerns, and the scalability of cell-based and secretome-based therapies for widespread clinical use. Although umbilical cord MSCs are not yet widely applied in clinical practice, increasing evidence suggests that they offer significant therapeutic potential, especially in the treatment of autoimmune and neurodegenerative diseases. The UC-MSCs and their secretome represent a transformative approach in orthopedics, offering new avenues for treating complex musculoskeletal injuries and degenerative diseases. Ongoing advancements in this field will likely unlock their full potential, making them viable options for clinical use in the near future.

Keywords: Umbilical cord-mesenchymal stem cells (UC-MSCs), secretome, orthopedics, neurodegenerative diseases

Abbreviations
ACL: Anterior Cruciate Ligament

BDNF: Brain-Derived Neurotrophic Factor
BMPs: Bone Morphogenetic Proteins
ECM: Extracellular Matrix
EMA: European Medicines Agency
EVs: Extracellular Vesicles
FDA: Food and Drug Administration
GDNF: Glial Cell-Derived Neurotrophic Factor
GMP: Good Manufacturing Practices
HSCs: Hematopoietic Stem Cells
HUVECs: Human Umbilical Vein Endothelial Cells
IGF: Insulin-Like Growth Factor
IL-10: Interleukin-10
IL-6: Interleukin-6
MHC: Major Histocompatibility Complex
miRNA: MicroRNA
MSCs: Mesenchymal Stem Cells
NGF: Nerve Growth Factor
NK cells: Natural Killer Cells
OA: Osteoarthritis
PDGF: Platelet-Derived Growth Factor
RNA: Ribonucleic Acid
TGF-β: Transforming Growth Factor-Beta
TNF-α: Tumor Necrosis Factor-Alpha
UC-MSCs: Umbilical Cord-Derived Mesenchymal Stem Cells
VEGF: Vascular Endothelial Growth Factor

INTRODUCTION

Orthopedic medicine, that may be applied for addressing musculoskeletal disorders, such as bone fractures, osteoarthritis, tendon injuries, intervertebral disc degeneration, and peripheral nerve lesions, has currently modality therapeutic options on surgical intervention, mechanical support, and pharmacological management. These therapeutic options may not always lead to optimal healing and can be associated with complications such as infection, implant rejection, or limited long-term efficacy, and often result in chronic pain, disability, and decreased quality of life.[1] As a result, there is a growing need for advanced, biologically based therapeutic approaches that can enhance tissue regeneration and repair.[2,3]

In recent years, mesenchymal stem cells (MSCs), particularly umbilical cord-mesenchymal stem cells (UC-MSCs), have emerged as a promising option for addressing orthopedic challenges. Their ability to differentiate into bone, cartilage, and tendon cells and Schwann cell-like cells makes them particularly suitable for treating a wide range of musculoskeletal injuries and conditions.[4] Furthermore, UC-MSCs secrete bioactive molecules (the secretome) that enhance tissue healing by modulating inflammation, promoting angiogenesis, and stimulating cell proliferation and differentiation.[5]

Umbilical cord mesenchymal stem cells and their secretome are being explored in preclinical and clinical studies for their potential to accelerate bone healing, regenerate cartilage, repair damaged tendons and ligaments, as well as to repair and regenerate peripheral nerves. Their non-invasive harvesting process, robust regenerative capacity, and low risk of immune rejection make them particularly promising in the field of orthopedics, where effective and long-lasting tissue repair is crucial for patient recovery.[6,7]

The aim of this review was to provide a comprehensive analysis of the use of MSCs, specifically UC-MSCs, with their secretome, as a potential for regenerative medicine in treatment approaches for orthopedic tissue repair. This paper highlights the unique properties of UC-MSCs that make them suitable for regenerative therapy and innovative delivery, and also discusses the challenges and limitations of UC-MSC therapies in orthopedics.

METHODS

This narrative review synthesized current evidence on the therapeutic use of UC-MSCs and

their secretome in orthopedic applications, including bone, cartilage, tendon, joint, and nerve repair. A comprehensive search of PubMed, Scopus, ScienceDirect, and Google Scholar was performed for articles published between January 2015 and March 2025 using the terms: "umbilical cord mesenchymal stem cells" OR "UC-MSCs" AND "secretome" AND ("orthopedics" OR "bone" OR "cartilage" OR "tendon" OR "joint" OR "nerve" OR "musculoskeletal") AND ("regeneration" OR "repair" OR "healing").

Eligible articles focused on UC-MSCs or their secretome in orthopedics-related tissues or conditions, were original studies, reviews, or clinical trials in English, and reported mechanistic or therapeutic outcomes. Studies on non-orthopedic systems, abstracts, editorials, conference posters, and unpublished material were excluded. The following data were extracted: study type and model (in vitro, in vivo, clinical), source and characterization of UC-MSCs, application site (e.g., bone defect, osteoarthritis, nerve lesion), role of secretome or exosomes, outcome measures (histological, molecular, functional), key findings and limitations. The data were summarized narratively, categorized by tissue type (bone, cartilage, tendon, nerve), and discussed in the context of regenerative mechanisms and translational potential. The study selection process for a systematic review of umbilical cord–derived mesenchymal stem cells (UC-MSCs) in orthopedics was conducted according to the PRISMA guidelines, as diagrammed in Figure 1. Records were identified through database searching of PubMed, Scopus, ScienceDirect, and Google Scholar between 2015 and 2025 (n = 280). After removal of duplicate records (n = 50), 230 reports were screened for retrieval. Thirty reports could not be retrieved due to access limitations or unavailability of full-text articles, leaving 200 reports for full-text eligibility assessment based on predefined inclusion and exclusion criteria. Of these, 96 reports were excluded (31 non-orthopedic studies, 25 abstracts without full text, 20 editorials or conference posters, and 20 articles on irrelevant topics). A total of 104 studies met the eligibility criteria and were included in the qualitative synthesis, comprising studies on bone regeneration, cartilage repair, tendon/ligament regeneration, and nerve regeneration (Fig. 1).

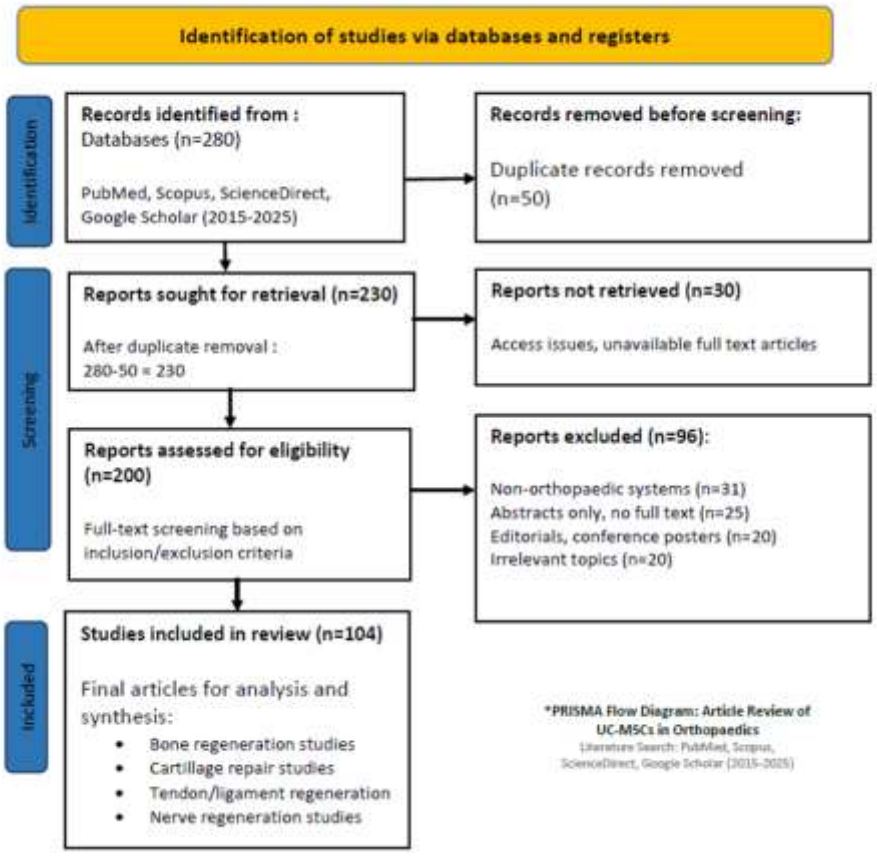

Figure 1. PRISMA flow diagram: article review of UC-MSCs in orthopedics

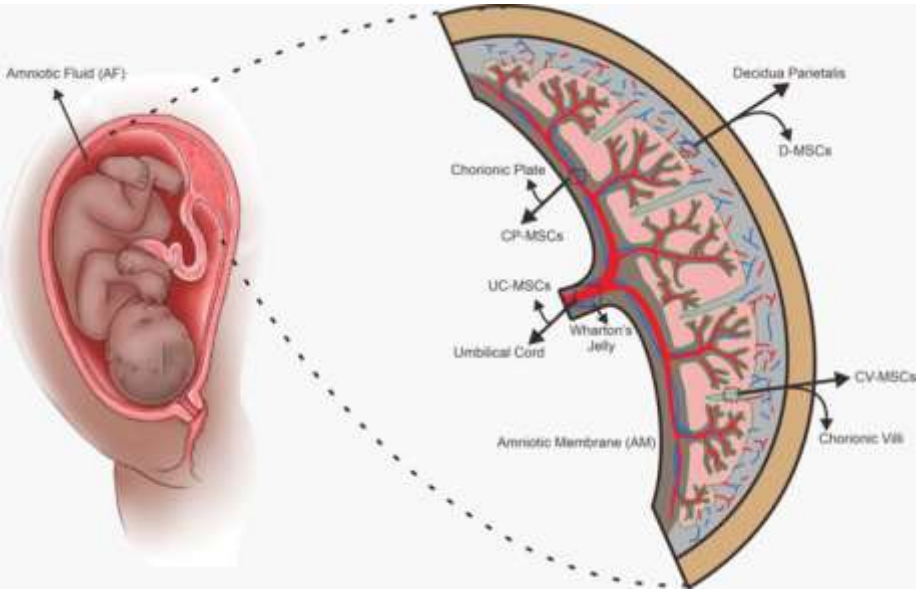

Figure 2. Anatomical structure of the fetus in the uterus and a cross section of the placenta showing the various sources of mesenchymal stem cells (MSCs). The placenta, along with associated tissues such as the umbilical cord and amniotic membrane, is an important source of stem cells that can be used for regenerative therapies. The different types of stem cells shown in the image include : UC-MSCs (mesenchymal stem cells from the umbilical cord), CP-MSCs (stem cells from the chorionic plate), CV-MSCs (stem cells from the chorionic villi), D-MSCs (stem cells from the parietal decidua/maternal layer), AF-MSCs (stem cells from amniotic fluid), and stem cells from Wharton's Jelly a mucoid tissue in the umbilical cord that is rich in MSCs. The extraembryonic tissues such as the placenta not only play a role in supporting fetal growth but are also a potential source of multipotent stem cells for future medical applications

Characteristics of UC-MSCs

The umbilical cord is a highly accessible, ethically favorable source of mesenchymal stem cells (MSCs), as it is routinely discarded after birth and can be collected non-invasively without risk to mother or infant. UC-MSCs are mainly isolated from Wharton's jelly, a gelatinous matrix within the cord that is particularly rich in MSCs. As illustrated in Figure 2, the placenta and related extraembryonic tissues also provide diverse MSC populations, including UC-MSCs from Wharton's jelly, CP-MSCs from the chorionic plate, CV-MSCs from chorionic villi, D-MSCs from the maternal decidua, and AF-MSCs from amniotic fluid, all of which are routinely discarded material that may be transformed into valuable, ethically acceptable reservoirs of multipotent stem cells for regenerative medicine.[8]

Isolation of UC-MSCs starts with cord collection after delivery, followed by cleaning, disinfection, and dissection to obtain Wharton's jelly. MSCs are then isolated either by enzymatic digestion (e.g., collagenase) to release cells from the matrix or by explant culture, where tissue pieces are placed in medium and the cells migrate out. The harvested cells are subsequently expanded in vitro in appropriate culture media to obtain sufficient numbers for therapeutic applications.[9,10]

Umbilical cord mesenchymal stem cells (UC-MSCs) have potent immunomodulatory capacity, suppressing proliferation and activation of T cells, B cells, and NK cells to reduce inflammation. They also secrete anti-inflammatory cytokines, creating a favorable healing microenvironment and enabling their use in allogeneic transplantation with minimal need for intensive immunosuppression. [11]

Umbilical cord mesenchymal stem cells have the capacity to differentiate into various mesenchymal lineages (Fig.2), including osteocytes (bone cells), chondrocytes (cartilage cells), tenocytes (tendon cells),[12] and Schwann-cell like cells.[13] This makes them highly suitable for orthopedic applications, as they can contribute directly to the repair of musculoskeletal tissues. Their osteogenic differentiation supports bone healing and regeneration, while their chondrogenic potential is crucial for cartilage repair in conditions such as osteoarthritis. Their ability to differentiate into tenocytes and also into Schwann-cell like cells allows UC-MSCs to play a role in tendon and ligament repair, as well as in peripheral nerve repair and regeneration.[14,15]

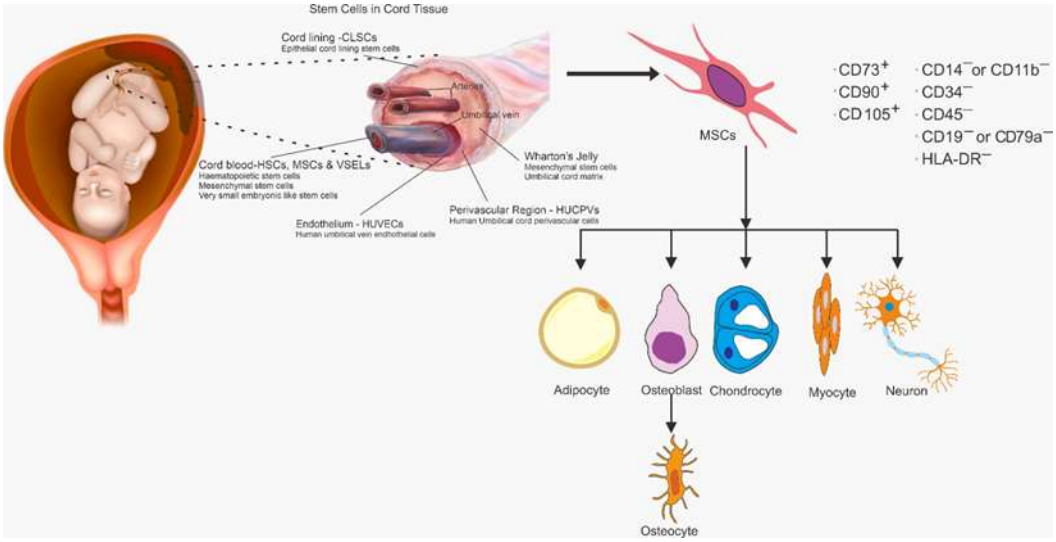

Figure 3. This image shows the different types of stem cells that can be obtained from human umbilical cord tissue and their differentiation capabilities. The umbilical cord, previously considered medical waste, is now known to be a rich source of mesenchymal stem cells (MSCs) and other cell types with high therapeutic potential. The main sites that produce stem cells include : Cord lining/LSCs (contains epithelial stem cells from the inner lining of the umbilical cord), Cord blood (contains hematopoietic stem cells/HSCs, mesenchymal stem cells/MSCs, and very small embryonic-like stem cells/VSELs), Wharton's Jelly (contains MSCs in the mucoid matrix of the umbilical cord), Perivascular region/HUCPVs (contains stem cells from the area surrounding blood vessels), Endothelium/HUVECs (Endothelial cells from the human umbilical vein). Immunophenotypic features of MSCs shown include: positive for CD73+, CD90+, CD105+; negative for CD14-/CD11b-, CD34-, CD45-, CD19-/CD79a-, HLA-DR-. These MSCs are able to differentiate into various cell types including: adipocytes/fat cells, osteoblasts and osteocytes/bone cells, chondrocytes/cartilage cells, myoblasts/myocytes (muscle cells), neurons/nerve cells. With their multipotent differentiation capabilities and favorable immunological profile, these cells have great potential for applications in regenerative therapies and cell-based medicine

Compared with other MSC sources, UC-MSCs show lower immunogenicity, largely due to reduced expression of MHC class I and II molecules. This makes them particularly suitable for allogeneic, off-the-shelf therapies with less need for strict donor–recipient matching.[16] Umbilical cord mesenchymal stem cells have a higher proliferation rate compared to MSCs derived from sources such as bone marrow or adipose tissue. They can be expanded more rapidly in culture, allowing for the generation of larger cell numbers in a shorter time frame (Fig.3). This is particularly advantageous for clinical applications that require high doses of MSCs for effective treatment.[17] Additionally, UC-MSCs maintain their stemness and differentiation potential for a longer period compared to other MSC sources, making them more viable for long-term regenerative therapies.[18]

Umbilical cord mesenchymal stem cells secrete a variety of bioactive molecules, including growth factors and cytokines, which play a crucial role in promoting tissue repair and regeneration.[5,19] These secreted factors (UC-MSC secretome), include vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), and various interleukins, which help stimulate angiogenesis, reduce inflammation, and enhance the proliferation and differentiation of resident cells in damaged tissues.[20] The UC-MSC secretome is particularly important for paracrine signaling, where UC-MSCs influence nearby cells and tissues to promote healing, even in situations where direct differentiation into target cells is not the primary mode of action.[21,22]

Overall, the combination of low immunogenicity, high proliferation rates, and a rich secretome makes UC-MSCs a highly attractive candidate for use in regenerative medicine, particularly in the field of orthopedics, where effective tissue repair and regeneration are paramount.[23,24]

The role of UC-MSCs in orthopedic applications

Umbilical cord mesenchymal stem cells (UC-MSCs) contribute significantly to

osteogenesis by differentiating into osteoblasts that produce bone matrix and support mineralization (Fig. 4). They secrete growth factors such as BMPs, VEGF, and TGF-β, which promote osteogenic differentiation, stimulate angiogenesis, and recruit additional regenerative cells to the injury site, thereby enhancing bone remodeling and repair.[25]

The UC-MSCs have shown great promise in treating bone fractures, particularly in cases of delayed union or non-union where normal healing processes are impaired.[7,26] Umbilical cord mesenchymal stem cells can be applied directly to the fracture site or delivered through scaffolds, where they assist in forming new bone tissue by differentiating into osteoblasts and releasing their regenerative secretome.[27] Studies have shown that UC-MSCs accelerate bone healing by promoting the deposition of new bone matrix, reducing inflammation, and stimulating angiogenesis, which improves the blood supply to the injured area.[28,29] In preclinical and clinical settings, UC-MSCs have demonstrated the potential to enhance healing in cases of severe fractures or in patients with compromised healing capacity, such as those with osteoporosis or advanced age.[26,30]

Cartilage repair is a significant challenge in orthopedics, particularly for degenerative diseases such as osteoarthritis, where the cartilage in the joints breaks down and leads to pain and loss of function.[31,32]. The UC-MSCs have been explored as potential therapy for regenerating damaged cartilage due to their ability to differentiate into chondrocytes and secrete bioactive molecules (Fig.5) that promote tissue repair.[33,34] When applied to areas of cartilage damage, UC-MSCs can differentiate into chondrocytes and contribute to the regeneration of the extracellular matrix, which is essential for cartilage function and durability.[35]

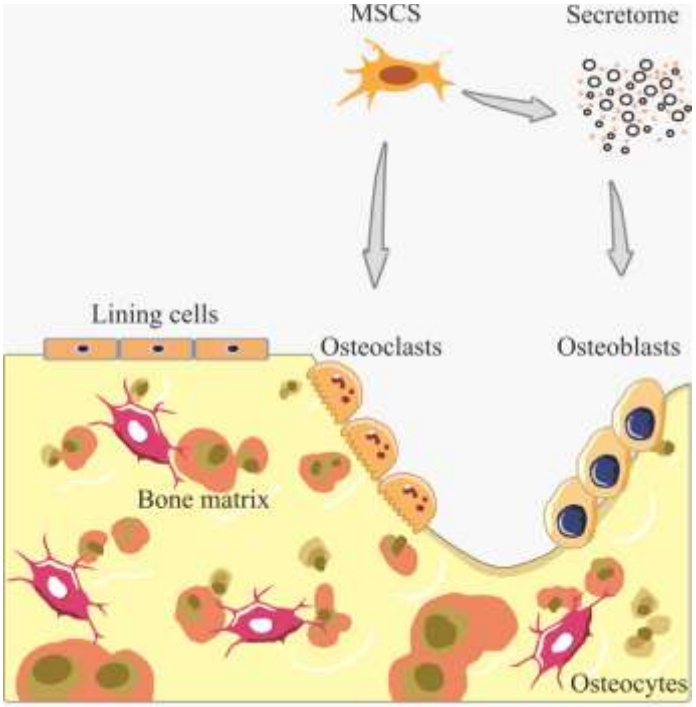

Figure. 4 This illustration provides a visual representation of the role of Mesenchymal Stem Cells (MSCs) and their secretome in the process of bone remodeling. MSCs are shown as the origin of both direct cellular influence and the production of a biologically active substance (secretome), play crucial roles in intercellular communication and regulation within the bone microenvironment.
MSCs and their secretome impact osteoclasts that are responsible for bone resorption, breaking down the bone matrix and facilitating the removal of old or damaged bone tissue; and osteoblasts, involved in bone formation, synthesizing new bone matrix and contributing to bone regeneration. Over time, some osteoblasts become embedded within the matrix they produce, differentiating into osteocytes, which act as mechanosensors and regulators of bone remodeling. Lining cells on the bone surface originate from osteoblasts and regulate mineral exchange, as well as support bone remodeling activities. Within the bone matrix, osteocytes and various other cells maintain homeostasis and coordinate the dynamic balance between bone resorption and formation

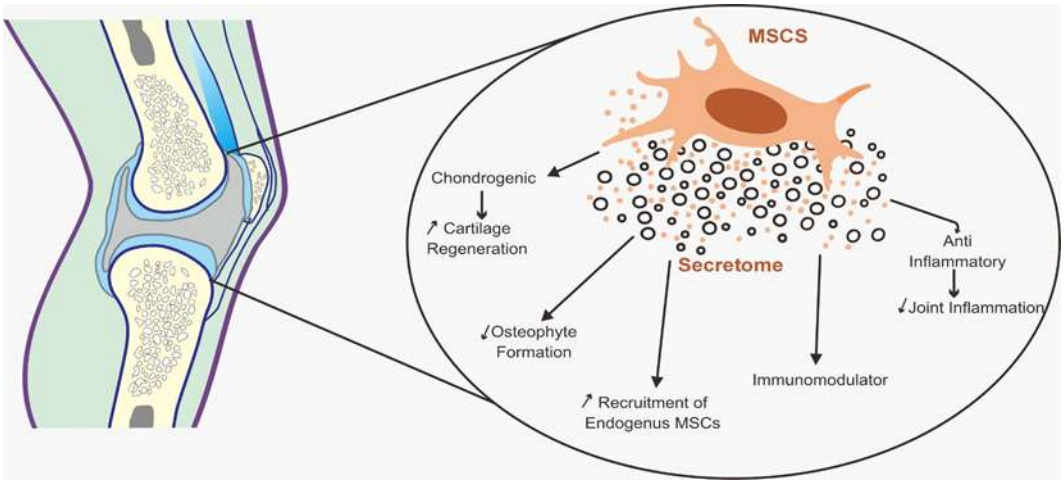

Figure 5. This illustration highlights the therapeutic potential of Mesenchymal Stem Cells (MSCs) and their secretome in the context of joint disease, particularly osteoarthritis (OA).
The left image shows a degenerative joint—likely the knee—where cartilage breakdown and inflammation are key pathological features. On the right, the focus shifts to the MSCs and their secretome, which encompasses a variety of bioactive molecules including cytokines, growth factors, and extracellular vesicles.
Chondrogenic Activity: The secretome promotes chondrogenesis, leading to enhanced cartilage regeneration, a critical factor in restoring joint function and preventing further degeneration.
Reduction in Osteophyte Formation: By modulating the joint environment, MSC secretome helps suppress the formation of osteophytes (bony outgrowths), which are a hallmark of OA and contribute to joint stiffness and pain.
Recruitment of Endogenous MSCs: The factors released by MSCs can attract the body's own stem cells to the site of injury, amplifying regenerative processes and aiding long-term healing.
Immunomodulation: The secretome exhibits immunomodulatory effects, helping to balance the immune response and prevent chronic inflammation that would otherwise damage joint tissues.
Anti-Inflammatory Effects: Through the secretion of anti-inflammatory mediators, MSC secretome reduces joint inflammation, providing symptomatic relief and slowing disease progression.
This diagram underscores how MSC-derived secretome acts as a cell-free therapy capable of addressing multiple pathological aspects of joint degeneration—structural damage, inflammation, and impaired repair—making it a promising strategy for regenerative medicine in osteoarthritis and related joint disorders.

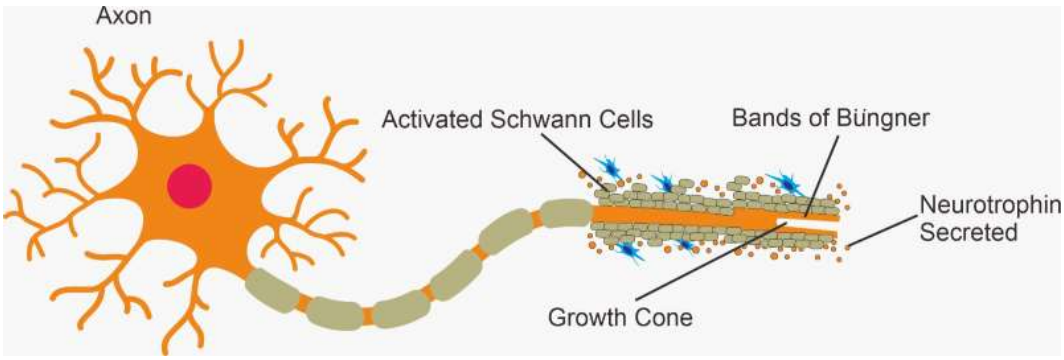

Figure 6. This illustration depicts the critical steps and cellular components involved in **peripheral nerve regeneration** following injury, highlighting the role of Schwann cells and neurotrophic signaling in axonal repair. After injury, Schwann cells become activated and begin to proliferate and clear debris from the damaged axon and play a pivotal role in guiding axonal regrowth. **Bands of Büngner are** longitudinal columns formed by aligned Schwann cells and their basal lamina, provide a **physical and molecular scaffold** that directs the regenerating axon toward its target, ensuring proper orientation and connectivity. At the tip of the regenerating axon, the growth cone explores the microenvironment, responding to molecular cues for directional growth. **Neurotrophin secretion**, the secretion from activated Schwann cells (NGF, BDNF, and GDNF) enhance neuronal survival, stimulate axon elongation, and support synaptic reconnection.

The UC-MSCs undergo chondrogenic differentiation in response to specific signals such as TGF-β and insulin-like growth factor (IGF). These factors promote the expression of key chondrogenic markers, including collagen type II and aggrecan, which are essential components of the cartilage matrix.[36,37] Additionally, UC-MSCs' paracrine activity—mediated through the secretion of anti-inflammatory cytokines and growth factors—can modulate the local environment to reduce cartilage degradation and stimulate tissue repair.[24,38] Preclinical studies and clinical trials have demonstrated that UC-MSCs can improve cartilage repair, reduce pain, and improve joint function in osteoarthritis patients, suggesting their potential as a novel therapeutic approach for cartilage regeneration.[39]

Tendon and ligament injuries, such as rotator cuff tears and anterior cruciate ligament (ACL) ruptures, are common orthopedic conditions that often require surgical intervention.[40] Umbilical cord mesenchymal stem cells have been explored as biological therapy to improve tendon and ligament repair due to their ability to differentiate into tenocytes and their potential to enhance the healing process.[41,42] When applied to injured tendons or ligaments, UC-MSCs can promote tissue regeneration by increasing collagen synthesis, reducing inflammation, and stimulating the repair of the extracellular matrix. Their ability to secrete growth factors, such as platelet-derived growth factor (PDGF) and TGF-β, helps in creating a favorable environment for tendon and ligament healing.[43]

In preclinical studies, UC-MSCs have shown success in improving the healing of tendon and ligament injuries. Animal models with induced tendon or ligament injuries that were treated with UC-MSCs demonstrated improved biomechanical properties, reduced inflammation, and enhanced tissue regeneration compared to untreated controls.[44] Early-phase clinical trials have also shown promising results, with UC-MSC-treated patients experiencing faster recovery times, improved functional outcomes, and reduced re-injury rates. These findings suggest that UC-MSCs could become an important adjunct to surgical repair techniques for tendon and ligament injuries.[45]

Spinal disc degeneration and the need for spinal fusion surgery represent significant challenges in orthopedic care. Current treatments for degenerative disc disease often involve spinal fusion, which eliminates motion between vertebrae but does not address the underlying degeneration of the intervertebral discs.[46] Umbilical cord mesenchymal stem cells offer a potential regenerative solution by promoting the regeneration of the nucleus pulposus and annulus fibrosus. The UC-MSCs can differentiate into discogenic cells and produce extracellular matrix proteins, such as collagen and proteoglycans, that are essential for disc function.[47,48]

In the context of spinal fusion, UC-MSCs can enhance bone healing and fusion at the surgical site. By promoting osteogenesis and releasing bioactive molecules that stimulate bone formation, UC-MSCs may help achieve a more robust and successful fusion.[49] Early studies suggest that UC-MSCs could reduce recovery times and improve outcomes in spinal fusion surgeries, potentially offering a regenerative approach to disc degeneration and improving the long-term function of the spine.[50,51]

Wallerian degeneration is a process that occurs after peripheral nerve injury in the peripheral nerve repair and regeneration, where the part of the axon distal to the injury site degenerates and the myelin sheath breaks down. This process is essential for clearing damaged cells and preparing the nerve for regeneration, but it also involves significant inflammation and immune cell activation.[52,53] The UC-MSCs play a critical role in modulating this process by exerting immunomodulatory and anti-inflammatory effects that can enhance the repair of peripheral nerves.[45,53]

Umbilical cord mesenchymal stem cells have been shown to influence the Wallerian degeneration process by reducing the inflammatory response and promoting an environment conducive to nerve regeneration (Fig.6). Through the secretion of bioactive molecules such as interleukin-10 (IL-10) and TGF-β, UC-MSCs can attenuate the activation of immune cells such as macrophages, which are involved in clearing debris but can also contribute to further nerve damage if overly activated.[20] Additionally, UC-MSCs release neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), which support the survival and growth of neurons during the regeneration process.[54] By modulating the local immune response and promoting neuroprotection, UC-MSCs help to create an environment that facilitates axonal regrowth,

remyelination, and ultimately functional recovery of the nerve after injury.[55,56]

Peripheral nerve injuries and lesions, such as those resulting from trauma, compression, or surgical procedures, often lead to a loss of motor or sensory function, presenting a significant clinical challenge. [57] Conventional treatments for peripheral nerve injuries, including nerve grafts or surgical repairs, often have limited success, especially in cases of large nerve gaps or delayed treatment. UC-MSCs offer a promising therapeutic alternative due to their regenerative properties and ability to promote nerve repair.[45,58]

The UC-MSCs can enhance peripheral nerve regeneration by promoting the differentiation of Schwann cells, which are critical for axonal regrowth and remyelination. Schwann cells provide physical support to growing axons and secrete factors that aid in nerve repair. When UC-MSCs are applied to injured peripheral nerves, they can promote Schwann cell proliferation and function, thus supporting the natural regenerative processes of the nerve.[54,59]

Additionally, UC-MSCs can secrete neuroprotective and angiogenic factors, such as VEGF, which help to restore blood supply to the injured area, further enhancing the repair process. This is especially important in cases of nerve crush injuries or other forms of ischemic damage, where restoring proper blood flow is essential for nerve survival and regeneration.[60]

In cases of more severe nerve lesions, such as nerve transection or extensive damage, UC-MSCs can be applied in combination with bioengineered scaffolds or nerve conduits to bridge the nerve gap and facilitate axonal regeneration. The scaffolds provide physical guidance for the regenerating axons, while UC-MSCs contribute to the biochemical signals necessary for nerve regrowth. This combination has shown promise in preclinical models, with evidence of improved nerve regeneration and functional recovery compared to standard surgical repairs alone.[61,62]

The UC-MSCs have also been shown to reduce scar tissue formation at the injury site, which is a common barrier to successful nerve regeneration. By limiting the extent of fibrosis and promoting a pro-regenerative environment, UC-MSCs can enhance the likelihood of successful nerve repair and functional recovery.[63,64]

In preclinical studies and animal models of peripheral nerve injury, UC-MSCs have demonstrated the ability to accelerate nerve regeneration, improve axonal regrowth, and enhance functional recovery.[65] Early clinical trials are exploring the use of UC-MSCs in treating peripheral nerve injuries, particularly in cases where conventional treatments have failed or are insufficient. The results thus far suggest that UC-MSCs hold great potential for improving outcomes in peripheral nerve repair, offering a new avenue of treatment for patients with traumatic nerve injuries or chronic nerve lesions.[45,66]

UC-MSCs secretome: clinical studies for the treatment of orthopedic conditions

The **secretome** refers to the collection of bioactive molecules secreted by cells, including proteins, lipids, nucleic acids, and other factors that influence surrounding cells and tissues.[28] In the context of UC-MSCs, the secretome is composed of a variety of substances that contribute to tissue repair and regeneration through paracrine signaling mechanisms. [67,68]

The major components of the UC-MSC secretome include exosomes, cytokines, and growth factors. Exosomes are small extracellular vesicles that carry proteins, RNA, and microRNAs (miRNAs). These vesicles play a key role in cell communication and deliver signals to target cells to modulate their behavior.[69] Cytokines are signaling proteins that regulate immune responses and inflammation, such as IL-10, IL-6, and tumor necrosis factor-alpha (TNF-α).[70] Growth factors are molecules such as VEGF, TGF-β, PDGF, and IGF, that stimulate tissue repair, angiogenesis, and cell proliferation.[71] These components collectively contribute to the therapeutic potential of the UC-MSC secretome in promoting healing in musculoskeletal injuries and diseases.

The UC-MSC secretome exerts its regenerative effects primarily through paracrine signaling**,** in which secreted factors from UC-MSCs influence neighboring cells and tissues to promote repair and regeneration without the need for direct cell-to-cell contact.[72] The key mechanisms of action of the secretome include anti-inflammatory effects, anti-fibrotic effects, and angiogenic effects. The secretome contains cytokines and growth factors, such as IL-10 and TGF-β, that help reduce inflammation by modulating immune responses (anti-inflammatory effects**)**. These factors inhibit the activation of pro-inflammatory immune cells, such as macrophages and T-cells, which is critical in preventing chronic inflammation and creating a conducive environment for tissue repair.[28,73]

The UC-MSC secretome can reduce scar tissue formation (anti-fibrotic effects) by limiting the deposition of extracellular matrix proteins, such as collagen, that contribute to fibrosis. This is particularly important in the context of musculoskeletal injuries, where excessive scar tissue can impede functional recovery.[23,74]

The secretome is rich in angiogenic factors, such as VEGF and PDGF, which promote the formation of new blood vessels (angiogenic effects). This enhanced vascularization is crucial for delivering oxygen and nutrients to damaged tissues, thus accelerating the healing process in bone, cartilage, and soft tissue injuries.[75]

Secretome in bone and cartilage repair

Studies have shown that the UC-MSC secretome plays a pivotal role in bone and cartilage regeneration.[27] Preclinical research has demonstrated that the secretome can enhance osteogenesis and chondrogenesis through several pathways.[27,35] The UC-MSC secretome promotes bone healing by stimulating the proliferation and differentiation of osteoblasts, the cells responsible for bone formation. It also enhances the recruitment of endogenous stem cells to the site of injury and promotes the release of growth factors that accelerate bone repair. Studies in animal models have shown that the application of UC-MSC-derived exosomes can improve bone healing in fractures, especially in cases of delayed or impaired healing.[28,68]

The UC-MSC secretome has demonstrated the ability to stimulate chondrocyte activity and promote the deposition of cartilage matrix, which is essential for cartilage repair. In models of osteoarthritis, the secretome has been shown to reduce inflammation, slow cartilage degradation, and improve the regeneration of cartilage tissue. This suggests a potential therapeutic application in treating cartilage defects and degenerative joint diseases.[76,77] The secretome in peripheral nerve regeneration and repair. The UC-MSCs secretome plays a crucial role in peripheral nerve repair and regeneration following injury or lesion. Instead of relying solely on the differentiation of MSCs into nerve cells, researchers have found that their paracrine effects—specifically the bioactive factors that they secrete—are key drivers of regeneration.[66]

The crucial roles in peripheral nerve repair and regeneration, including neuroprotection, neuroregeneration, immunomodulation, angiogenesis, and recruitment - activation of endogenous cells. The MSCs secrete factors such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and glial cell-derived neurotrophic factor (GDNF). These support neuron survival, prevent apoptosis, and maintain axonal integrity after injury.[78] Exosomes and EVs from MSCs can transfer miRNAs that modulate gene expression in injured neurons and Schwann cells. These promote axon sprouting, axon elongation, and myelin sheath restoration.[79] The MSC secretome reduces local inflammation by secreting anti-inflammatory cytokines (e.g., IL-10, TGF-β) and suppressing pro-inflammatory cytokines (e.g., TNF-α, IL-1β). This creates a more favorable environment for nerve regeneration and minimizes secondary damage.[11,80] The UC-MSCs release VEGF and other angiogenic factors that promote the formation of new blood vessels. Improved vascularization supports nutrient and oxygen supply to regenerating nerve tissue. [81] The UC-MSCs secretome can recruit Schwann cells, macrophages, and endogenous stem cells to the injury site. Schwann cells are essential for guiding axonal regrowth and remyelination.[82]

Advantages over whole-cell therapy

The UC-MSC secretome offers several practical advantages over whole-cell therapy, making it an attractive alternative for regenerative medicine applications. The secretome can be easily stored, handled, and administered without the need for complex cell culture techniques. Unlike live cells, the secretome can be stored as an "off-the-shelf" product in frozen or lyophilized (freeze-dried) form, allowing for greater convenience and broader clinical applicability.[83]

While UC-MSCs themselves exhibit low immunogenicity, the secretome has an even lower risk of triggering an immune response because it lacks the cellular components (e.g., cell membranes, nuclei) that could be recognized as foreign by the recipient's immune system. This makes the secretome an ideal candidate for allogeneic applications (using donor-derived products) without the need for immunosuppression.[5,73]

The secretome avoids several potential risks associated with cell-based therapies. Live stem cells have a theoretical risk of uncontrolled proliferation and tumor formation (tumorigenicity) when transplanted into patients. The secretome, consisting of non-cellular components, eliminates this risk.[84] The

secretome can be derived from discarded umbilical cords, making it ethically uncontroversial, unlike some other sources of stem cells.[23] The secretome is easy to regulate and standardize for therapeutic use, providing a more controlled and predictable treatment approach compared to cell-based therapies, where the behavior of live cells can vary depending on patient conditions.[85]

Orthopedic medicine: innovative stem cells and secretome delivery

In regenerative orthopedics, injectable hydrogels serve as protective carriers for therapeutic agents, shielding them from rapid enzymatic degradation and clearance in vivo. They enable controlled and sustained release of bioactive components over days to weeks, improving therapeutic efficacy while reducing dosing frequency. Hydrogels can also promote integration of the therapeutic payload into host tissue by facilitating cell migration, matrix deposition, and vascular ingrowth at the defect site.[86] Table 1 briefly overviews the clinical use of the UC-MSC secretome in orthopedics, mainly intra-articular injections for knee osteoarthritis, including product type, study design, patient number, dosing, and key outcomes, and shows that these treatments appear safe, and reduce pain and improve function, while bone-defect and disc-degeneration applications of UC-MSC secretome/exosomes remain preclinical (Table 1). Some injectable hydrogels are three-dimensional, water-rich polymeric networks that closely mimic the structural and biochemical properties of the extracellular matrix (ECM). Their high water content and tunable mechanical properties create a biocompatible and hydrated environment, making them ideal for encapsulating living cells, stem cell secretome, or bioactive molecules. By resembling the native ECM, hydrogels provide physical support and biochemical cues that enhance cell survival, proliferation, and differentiation in regenerative applications.[91]

Formulations such as chitosan-based gels, collagen solutions, and Pluronic F127 undergo a sol–gel transition at physiological temperature (thermosensitive hydrogels). These can be injected as liquids into irregular cartilage defects, where they solidify in situ, enabling precise, localized delivery of stem cells or secretome.[92]

Hydrogels integrated with nanoparticles (e.g., hydroxyapatite, silica, or polymeric nanocarriers) allow dual delivery of cells and growth factors (nanocomposite hydrogels). This strategy has shown promise in enhancing bone healing by providing both osteoconductive scaffolding and sustained biochemical stimulation.[93]

Injectable hydrogels offer a minimally invasive delivery method that conforms to complex tissue geometries without requiring open surgery. Once injected, they undergo gelation at the target site, ensuring localized retention of therapeutic agents and reducing systemic side effects. Their tunable degradation rates and release kinetics allow for customized treatment regimens tailored to specific orthopedic conditions.[86]

The scaffold-based localized delivery involves the use of biodegradable, three-dimensional matrices that function both as structural frameworks for tissue regeneration and as reservoirs for therapeutic agents such as stem cell secretome.[94] These scaffolds mimic the architecture of native extracellular matrix (ECM), providing an environment that supports cell adhesion, proliferation, and differentiation while gradually degrading to be replaced by newly formed tissue.[95]

In orthopedic applications, scaffolds serve a dual role for mechanical stability, in that they firstly fill and reinforce bone or cartilage defects, maintain the space needed for tissue ingrowth, and prevent collapse of the defect site, and secondly they provide biological stimulation when loaded with UC-MSCs or their secretome scaffolds act as a localized delivery depot and gradually release regenerative signals (e.g., growth factors, cytokines, exosomes) that promote angiogenesis, osteogenesis, or chondrogenesis.[96]

Collagen and fibrin scaffolds (natural polymer scaffolds), valued for their biocompatibility and bioactivity, can be impregnated with UC-MSCs or secretome for bone regeneration, enabling both osteoconductive support and paracrine signaling.[97] Bio-ceramic scaffolds that are composed of hydroxyapatite, β-tricalcium phosphate, or other calcium phosphate ceramics, are osteoconductive and mechanically strong, making them suitable for load-bearing bone defect repair.[98] Scaffolds can be fabricated with patient-specific shapes and controlled porosity to match irregular defect geometries (3D-printed porous scaffolds) by using additive manufacturing for ensuring a snug fit and optimal tissue integration.[99] Scaffold-based delivery offers the synergistic benefit of combining

mechanical reinforcement with targeted biological stimulation. This integration enhances structural integrity, guides tissue regeneration, and supports long-term healing without the need for additional fixation materials once the scaffold degrades.[100]

Challenges and limitations of UC-MSC therapies in orthopedics

One of the primary challenges facing the clinical application of UC-MSC therapies is navigating the complex regulatory landscape and addressing ethical concerns. Regulatory challenges arise in the standardization of UC-MSC-based products for clinical use. The process of isolating, expanding, and delivering UC-MSCs is complex, and ensuring consistent quality, potency, and purity of cells across different batches is difficult. Regulatory agencies, such as the US FDA and European Medicines Agency (EMA), have established strict guidelines for cell-based therapies, including ensuring that manufacturing processes are compliant with Good Manufacturing Practices (GMP). This includes defining stringent protocols for cell source, handling, storage, and expansion, but these vary between countries, making global standardization a challenge.[101] The secretome presents additional regulatory hurdles. As a cell-free product composed of secreted factors, the secretome lacks standardization in terms of defining its components, dosage, and storage. Regulatory agencies must also address how to regulate these biologically complex products to ensure safety and efficacy.[28,64] Although UC-MSCs are derived from non-invasive sources, such as discarded umbilical cords after childbirth, there are still ethical concerns to consider. These primarily revolve around ensuring informed consent from the donor's parents and ensuring that the donation process is voluntary and free from exploitation.[102]

While UC-MSCs are considered ethically more acceptable than other stem cell sources (such as embryonic stem cells), public perception and concerns over the potential commercialization of human biological materials remain. There may also be questions surrounding the long-term risks of using stem cell-derived products in clinical applications, which may require further ethical review.[84]

Though UC-MSC therapies have shown promise in early clinical trials, there remain several safety concerns that need to be addressed, particularly regarding long-term efficacy. While UC-MSCs are known for their low immunogenicity, there remains a small risk of triggering an immune response in recipients, particularly in allogeneic (donor-derived) applications. This is why UC-MSC therapies are being closely monitored for any signs of immune rejection or inflammatory reactions. However, due to the immunomodulatory nature of UC-MSCs, these risks are typically low and manageable.[28]

There is a theoretical risk of tumor formation when using live stem cells in regenerative medicine, as stem cells have the ability to proliferate and differentiate. Although UC-MSCs are not considered highly tumorigenic, their proliferative capacity still raises concerns, especially in long-term follow-up studies. Researchers have focused on minimizing this risk by selecting and culturing cells in a way that avoids uncontrolled growth or mutations, but vigilance is required in clinical applications.[84]

While short-term results from UC-MSC therapies in orthopedics are promising, there is still limited data on the long-term outcomes of these treatments. It remains uncertain whether the beneficial effects, such as improved tissue regeneration or pain relief, persist over time, or if additional treatments are required to maintain these effects. Long-term studies are critical to understanding the durability of UC-MSC-based therapies.[26,39]

Another significant challenge for UC-MSC-based therapies is the ability to scale up production for widespread clinical use while maintaining quality and consistency. Expanding UC-MSCs for large-scale clinical applications presents several challenges. UC-MSCs need to be cultured and expanded under strict GMP conditions to ensure that the cells retain their therapeutic properties, but scaling this process can lead to changes in cell characteristics, such as reduced differentiation potential or altered secretory profiles. As demand for stem cell-based therapies grows, it will be necessary to develop reliable and efficient methods for expanding cells without compromising their quality. The production of the secretome requires careful control of the cell culture conditions to ensure that the correct therapeutic molecules are produced in sufficient quantities. This is complicated by the fact that the secretome's composition can vary depending on how UC-MSCs are cultured, how long they are cultured, and the environmental conditions they are exposed to.[23]

Ensuring quality control during the production process is critical to the success of UC-

MSC-based therapies. Variability in the biological properties of UC-MSCs, such as their immunomodulatory or differentiation potential, can occur due to differences in donor characteristics (e.g., age, health) or in vitro culture conditions. This variability can make it difficult to produce a consistent, standardized product that performs the same way across different batches and patients.[103] For secretome-based therapies, ensuring the reproducibility of the composition of secreted factors (such as exosomes, cytokines, and growth factors) is an ongoing challenge. The complexity of the secretome and its dynamic nature during cell culture makes it difficult to characterize and standardize for clinical use.[64] Moreover, methods for quality control, such as potency assays, need to be developed and validated to ensure that the secretome maintains its therapeutic efficacy across different production runs.[104]

CONCLUSION

Umbilical cord mesenchymal stem cells are a promising tool in orthopedics, offering non-invasive sourcing, low immunogenicity, and high proliferation. They show strong potential in bone, cartilage, tendon, ligament, and nerve regeneration, aided by their immunomodulatory, anti-inflammatory, and angiogenic effects. The UC-MSC-derived secretome, rich in bioactive molecules, provides a cell-free alternative with easier storage and lower tumorigenic risk. While early studies are encouraging, future research must address regulatory, safety, and manufacturing challenges to ensure clinical translation.

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Authors' Contributions

TTO suggested the original manuscript's topic and wrote its first draft. ROM and MJD made revisions and edits to the manuscript. RTM and ASP provided contextual input on the updated paper. TTO oversaw the manuscript and made significant edits to the draft. Every author has approved the manuscript's final edit.

Conflict of Interest

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The authors declare that they have not used AI-generated work in this manuscript.

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