Bone marrow mesenchymal stem cell-derived exosomes: A novel therapeutic agent for tendon-bone healing (Review)

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Abstract. In sports medicine, injuries related to the insertion of tendons into bones, including rotator cuff injuries, anterior cruciate ligament injuries and Achilles tendon ruptures, are commonly observed. However, traditional therapies have proven to be insufficient in achieving satisfactory outcomes due to the intricate anatomical structure associated with these injuries. Adult bone marrow mesenchymal stem cells possess self-renewal and multi-directional differentiation potential and can generate various mesenchymal tissues to aid in the recovery of bone, cartilage, adipose tissue and bone marrow hematopoietic tissue. In addition, extracellular vesicles derived from bone marrow mesenchymal stem cells known as exosomes, contain lipids, proteins and nucleic acids that govern the tissue microenvironment, facilitate tissue repair and perform various biological functions. Studies have demonstrated that bone marrow mesenchymal stem cell-derived exosomes can function as natural nanocapsules for drug delivery and can enhance tendon-bone healing strength. The present review discusses the latest research results on the role of exosomes released by bone marrow mesenchymal stem cells in tendon-bone healing and provides valuable information for implementing these techniques in regenerative medicine and sports health.

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1. Introduction

The tendon-bone interface is a transitional region of soft tissue-to-bone transformation composed of the tendon, uncalcified fibrocartilage, calcified fibrocartilage and bone. It is a highly specialized structure (1). The connection between the tendon or ligament and the bone is established. The tendon-bone interface transmits the force generated by skeletal muscle contraction to the bone, providing strong support for joint movement and facilitating the gradual transfer of intricate mechanical loads in an efficient manner. In addition, it also plays an essential role in maintaining homeostasis and intercellular communications. However, due to the enormous difference in elastic modulus between tendon and bone, the tendon is a stress-bearing area, which significantly increases the risk of injury (2). Tendon-bone insertion (TBI) injuries are a common musculoskeletal disorder, including the anterior cruciate ligament (ACL) and the rotator cuff (RC) and Achilles tendon injuries. Injuries of the ACL and RC are the most common (3). Survey data indicate that the incidence of RC tears in the general population is ~20.7%, and increases with age (4). ACL injuries occur in >2 million patients annually in the United States, accounting for more than half of all knee injuries (5). Local tendon swelling, pain and functional impairment typically accompany TBI injury. This condition severely affects the quality of life of affected individuals and is a significant cause of pain and disability (6).

Bone marrow mesenchymal stem cells (BMSCs) are adult stem cells derived from bone marrow with self-replication and multiple differentiation potential that can differentiate into various cell types, including osteoblasts, chondrocytes and adipocytes, and these entities possess the capacity to efficiently restore impaired tissues, thus rendering them ideal for regenerative medicine and tissue engineering repair (7,8). BMSCs have the advantages of convenient sampling, a potent proliferative ability, low immunogenicity, easy gene transfection and strong differentiation potential, and they are the optimal type of stem cells used in current research and clinical applications. With further research and the development of related technologies, BMSCs are widely used in the treatment

of orthopedic clinical diseases. Previous studies have indicated that BMSCs can promote bone, cartilage, muscle, ligament and tendon healing (9,10). BMSCs possess the ability to modulate the expression and release of growth factors and cytokines in the vicinity of the injury site, thereby facilitating the process of wound healing and regeneration of damaged tissues (11,12).

Exosomes (EXOs) are nanoparticles with lipid bilayers and membrane structures that are naturally released by cells through cytoplasmic exocytosis (13). Research has indicated that BMSCs release EXOs containing various bioactive substances in a paracrine manner to regulate the local microenvironment of tissues and physiological and pathological activities in cells and may be critical factors by which BMSCs play a therapeutic role (14).

2. Exosomes

EXO biogenesis and uptake. EXOs are derived from intracellular bodies termed multivesicular bodies (MVBs) and are nanoscale extracellular vesicles, with a diameter of ~30 to 150 nm (15,16) and a density between 1.1 and 1.2 g/ml. They are found in various cell types and extracellular fluids, such as plasma, synovial fluid, urine, amniotic fluid, saliva, cerebrospinal fluid and breast milk (17-21). The cell membrane invaginates to form early endosomes, which turn into late endosomes under the control of various cellular signaling pathways (22-24). Stage 2 refers to the budding of late endosomes to form MVBs. Stage 3 of the process entails the amalgamation of MVBs with the plasma membrane, followed by the selective recruitment of cytoplasmic elements, including proteins, RNA and lipids, to form intact EXOs. The process of EXO formation is relatively complex and is regulated by a number of factors, such as tetraspanins, cholesterol, endosomal sorting complexes responsible for transport, sphingomyelinases and adhesion molecules, after which they are released into the microenvironment (25,26). When EXOs were first discovered, scholars considered them a way to expel unwanted components from cells (27). As research progressed, receptor-ligand interactions with EXOs, and direct membrane fusions for the delivery of biomolecules to target cells and mediate intercellular communications have been verified (28).

Structure and function of EXOs. Exosomal vesicles are rich in lipids, proteins and various types of nucleic acids, such as DNA, mRNAs, microRNAs (miRNAs/miRs) and long non-coding RNAs, transcription factors and cytokine receptors. Organelles, such as ribosomes and mitochondria are typically absent. EXOs mediate cell-cell and cell-extracellular matrix (ECM) communications through the biologically active molecules within them to induce the necessary growth signals and transcriptional changes to cause phenotypic changes in the local environment (29,30). Various physiological and pathological mechanisms have been observed to exert an effect on recipient cells, including the amelioration of ischemic brain injury and the stimulation of angiogenesis, which leads to the acceleration of skin wound healing, thus holding promise as a potential therapeutic approach for addressing osteoarthritis (31-33). Depending on the cell type that produces the EXOs and changes in the cellular microenvironment, such as physiological and pathological states, the number of EXOs secreted and the composition of the contents of EXOs varies (34). For example, BMSC-derived EXOs (BMSC-EXOs) contain a variety of anti-inflammatory factors and growth factors, such as transforming growth factor-β (TGF-β), interleukin (IL)-10 and tumor necrosis factor (TNF)-stimulated gene ((TSG)-6 (35). It has been demonstrated that BMSC-EXOs contain miR-301a, miR-22 and miR-let-7, which are involved in immune-related pathways (36). Given their significant osmotic impact, EXOs possess the ability to traverse the blood-brain and blood-spinal cord barriers effectively. Moreover, they exhibit a selective propensity to infiltrate sites of inflammation within bodily tissues, thereby exerting regulatory control over the inflammatory response (37,38). In addition, the membrane transport process is involved in the production of EXOs. Several proteins that are closely related to this process, such as tetraspanins (CD9, CD63 and CD81), the membrane proteins, annexin and flotillin, heat shock proteins (HSP70 and HSP90) and markers of the endosomal sorting complex required for transport pathway, have been identified. Several proteins, including lysosomal-associated membrane protein 1 and TSG101, are highly enriched in various cell-derived EXOs (39). Therefore, they are often used as the marker proteins of EXOs and are widely used to extract and purify EXOs. The morphological and structural pattern of EXOs is illustrated in Fig. 1.

3. TBI

Physical structure and physiopathology of TBI. There are two types of TBI: Indirect insertion and direct insertion. For example, indirect insertion involves the insertion of the medial collateral ligament into the tibia. The ACL and RC are anatomical structures that are intricately integrated into the bone through a gradient structure comprising four consecutive layers of distinct tissue. These layers can be categorized from soft to hard, starting with the tendon, followed by noncalcified fibrocartilage, calcified fibrocartilage and ultimately bone tissue (40-42). Once the tendon-bone connection is damaged, restoring the natural anatomical structure is difficult (Fig. 2).

Tendon cells are responsible for synthesizing and secreting collagen, and are the basic units of tendon function. Healthy tendons primarily contain type I collagen, which provides mechanical strength and durability. Type II collagen is found in lower amounts and is typically concentrated where tendons connect to bones. Following a tendon injury, type III collagen is abundant in scar tissue and is crucial for tendon healing. An imbalance in type III and type I collagen in the tendons can cause mechanical damage. Notably, in addition to altering the phenotype and function of various cells, MSC-EXOs can also increase the content of type III collagen by increasing the level of TGF-β1, thus promoting tendon healing (43).

Tendon cells are closely associated with RC disease; studies have shown that they are involved in tendon repair through proliferation and migration (44). For example, tendon stem cell-derived EXOs induce tendon differentiation in mesenchymal stem cells via TGF-β (45), promote healing in injured tendons by balancing the synthesis and

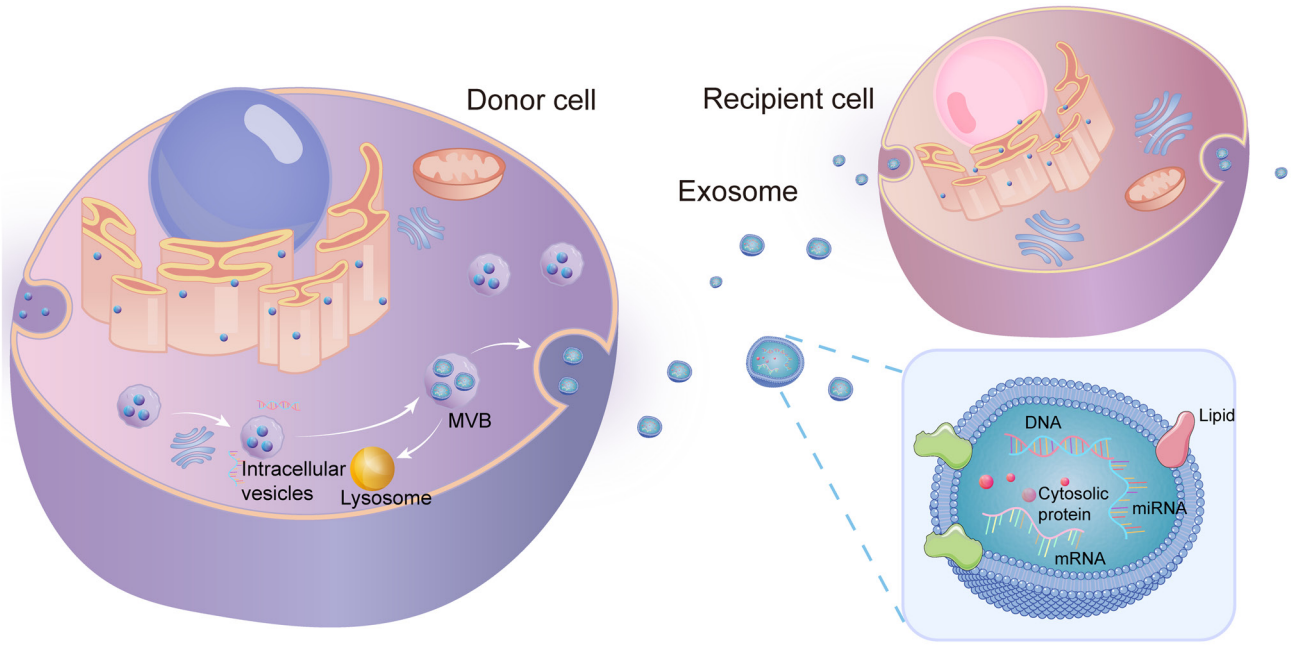

Figure 1. Morphological and structural pattern of exosomes. MVB, multivesicular body; miRNA, microRNA.

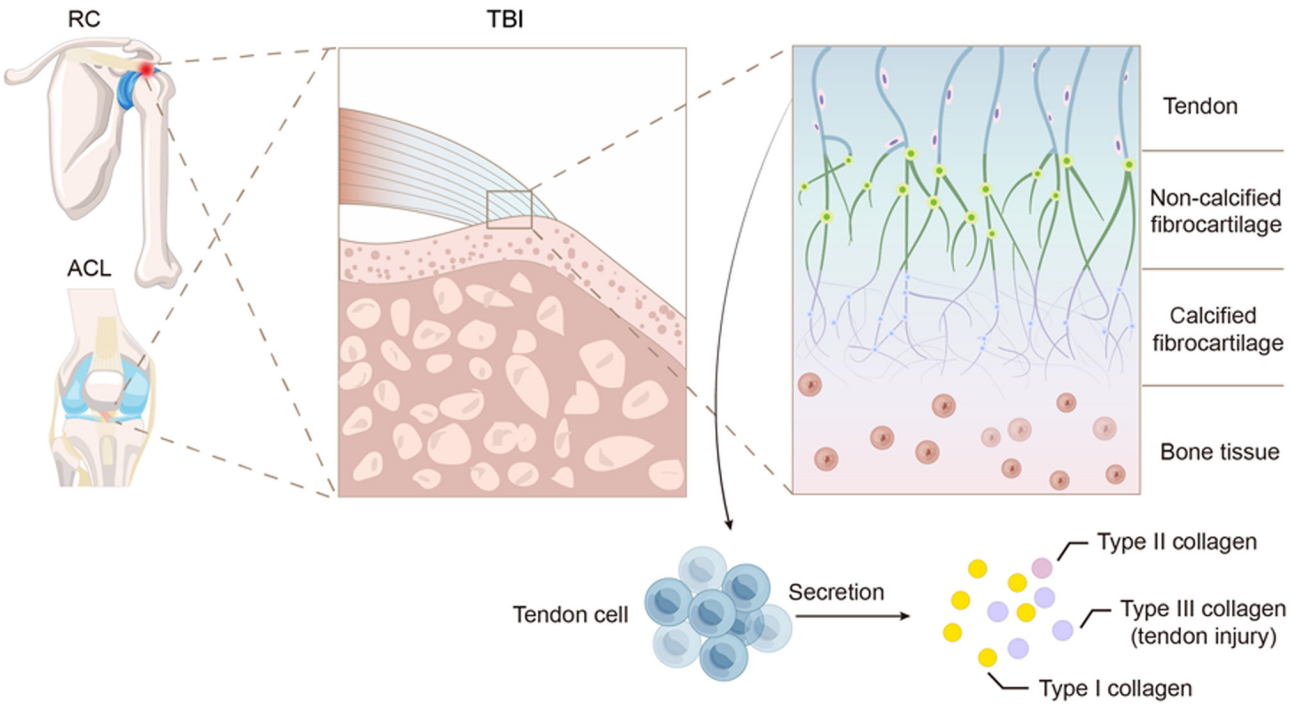

Figure 2. Four-layer structural model diagram of TBI. TBI, tendon-bone insertion; RC, rotator cuff; ACL, anterior cruciate ligament.

degradation of tendon extracellular matrix (6), and can regulate inflammation and promote high-quality healing of injured tendons (46).

TBI injuries are typically classified as acute and chronic. If not repaired in time, acute injury can gradually transform into chronic injury. The overuse or overload of tendons often leads to injury (42), while other factors such as age, metabolism and blood pressure can also exacerbate tendon injury (43). This condition severely affects the quality of life of affected individuals, and is a major cause of pain and disability (6). The distinguishing characteristics of the healing process between tendons and bones encompass the fusion of bone, heightened mechanical thresholds and the constricting of the bone tunnel (47,48). Tendon healing is divided into four phases: Inflammatory, proliferative, remodeling and maturation (49). During tendon healing, the levels of several growth factors, including TGF-β, platelet-derived growth factor, vascular endothelial growth factor (VEGF) and insulin-like growth factor-1, are increased and play critical roles in all stages of the recovery process (50).

TBI healing is very complex for several reasons. First, the region of fibrocartilage at the site of injury exhibits a deficiency in cells and blood supply, leading to a delayed or impaired healing process in TBI (51). Second, the regeneration of new bone is typically very slow, and strength and stiffness are correspondingly reduced (2). Third, during the healing of TBI, an initial inflammatory response occurs at the junction between the tendon and bone, and a large number of macrophages infiltrate, fibroblasts release extracellular matrix to form granulomas, and a large amount of collagen is deposited; the occurrence of fibrovascular scar tissue formation in the local area is a consequence that can be observed (52). In contrast to the initial anatomical arrangement, scar tissue has a significant impact on the process of new bone generation and the development of the interface between the tendon and bone. In comparison to the original physiological system, the presence of scar tissue has notable implications for the regeneration of new bone. The development of the tendon-bone interface and its ability to mediate load transmission and stress dispersion experiences a notable decline, which leads to decreased biomechanical properties in poorly regenerated tendons, impaired motor function, a shortened service life and a significantly reduced quality of healing (8,53).

Conventional treatment of TBI injuries

Surgical treatment. Non-surgical treatments often need to be revised. These strategies can only be used to control pain (54). Therefore, in the majority of cases, TBI injury requires surgical intervention. Thus, for decades, surgical reconstruction has been considered the standard treatment for attachment point injuries. The clinical treatment of ACL and RC injuries often involves tendon/ligament reconstruction surgery, in which the insertion of the tendon graft into the bone tunnel is essential for promoting tendon-bone healing. A critical aspect of this healing process is the regeneration of the fibrocartilage zone (55,56). During the surgical procedure of reconstruction, the graft is carefully positioned and subsequently maneuvered through a bone tunnel. The indigenous and directly implanted transitional tissue fails to undergo regeneration, instead giving rise to fibrovascular scar tissue at the interface of the graft and tunnel (57). Initially, this tissue exhibits a lack of organization. After 3-4 weeks, vertical fibers that resemble indirectly inserted threads begin to form. At ~1 year after surgery, the bone gradually grows into the graft-tunnel interface, enhancing the strength of graft attachment and facilitating the integration of the graft with the adjacent bone (57).

The process of fibrocartilage healing involves the formation of scar tissue following an injury, which is rich in type I collagen (40,58,59). The fibrocartilage zone plays a vital role in the absorption of stress that occurs between the tendon and bone (2). Nevertheless, scar tissue does not possess the inherent gradient structure and organized alignment of collagen fibers present in the native tendon-bone interface, resulting in low biomechanical properties, weak mechanical strength and increased re-tearing rate (60). There are data indicating high recurrence rates following TBI; for example, recurrent retear rates after RC repair are typically 20 to 30%, and can be as high as 94%, and ACL reconstruction has an average failure rate of 11.7% (40,61,62). For other commonly injured tendons and ligaments, such as the distal biceps tendon and lateral ankle sprain (anterior talofibular ligament, calcaneofibular ligament and posterior talofibular ligament), the rates of re-rupture were 1.6 and 18.1%, respectively (63). The most important cause of recurrent retears suboptimal tendon-bone healing. Promoting the healing of the connection between tendons and bones is crucial in the treatment of TBI injury and in preventing the occurrence of another tear after reconstruction. In contrast to interosseous recovery, the regeneration of fibrocartilage transitions is restricted, and TBI regeneration is particularly difficult. Insufficient osseointegration following surgical reconstruction is one of the main reasons for unsatisfactory clinical results (64). In addition, joint stiffness and pain caused by long-term post-operative immobilization can significantly affect the outcome of surgical treatment.

Tissue engineering therapy. Over the past few years, there has been a significant application of growth factors/cytokines, platelet-rich plasma, physiotherapy, tissue engineering, and different delivery and induction techniques (65-68). Currently, a diverse range of growth factors and cytokines, such as TGF-β, bone morphogenetic protein (BMP) and granulocyte colony-stimulating factor, have been employed to enhance the healing of tendon grafts within bone tunnels in different animal models. However, the implementation of these methods in clinical settings still has certain restrictions. Of note, retaining these biological factors at the specific location where the tendon or ligament injury occurred is challenging, and they are lost or rapidly removed (62).

Platelet-rich plasma (PRP) therapy. In recent years, multiple preclinical studies have demonstrated the role of PRP in promoting TBI interface healing and improving biomechanical properties (69-71). Several systematic reviews have reported that PRP can enhance tendon and ligament tissue by promoting tendon cell proliferation and angiogenesis, thus significantly promoting healing and controlling pain, and this treatment has exhibited sound therapeutic effects on RC and lateral elbow injuries (72-74). However, some studies have reported the potential limitations of PRP therapy; for example, the results of a randomized controlled trial suggested that injecting platelet-rich plasma did not improve tendon function or the quality of life in patients with severe acute Achilles tendon rupture. There was no evidence of any benefit from the injection of platelet-rich plasma (75). In addition, Bennell *et al* (76) used PRP therapy to treat patients with knee osteoarthritis and did not achieve significant efficacy. In summary, as a new technology, PRP therapy has the advantages of less trauma and fewer complications. It is a promising treatment strategy for TBI injury; however, its application scope, indications and efficacy warrant further investigation.

Stem cell therapy. Stem cell-based cell therapy is anticipated to emerge as a viable substitute for tissue engineering therapy. Mesenchymal stem cells can self-renew and differentiate into various cell types, including adipocytes, osteoblasts and chondrocytes, and exhibit low immunogenicity when transplanted. In the context of healing tendons and bones, the stem cells that are frequently utilized are typically obtained from either the bone marrow (BMSCs) or adipose tissue (adipose tissue-derived stem cells). It has been demonstrated that mesenchymal stem cells derived from the periosteum, synovium and tendon have been extensively employed to enhance the healing process at locations where tendons and

bones meet (77). Although the results of cell therapies are promising, they also have some limitations. For instance, the absence of a standardized protocol for the dosage and frequency of stem cell therapy hinders the attainment of optimal outcomes. This poses a significant challenge to the widespread clinical implementation of stem cells (55,78). The clinical application of stem cell transplantation therapy still needs to be improved, including factors such as cell dedifferentiation, low cell survival rate, immune rejection and ethical issues (79). To address these limitations, it is necessary to investigate an innovative treatment method that can effectively meet the clinical requirements and enhance the healing process of the tendon and bone. The conventional treatment methods for TBI injuries, as well as their advantages, disadvantages and clinical applications are presented in Table I.

4. Research progress on BMSC-EXOs in the repair of TBI injury

BMSCs-EXOs have been used to treat diseases of the respiratory system (such as the treatment of acute lung injury (ALI), circulatory system (such as the treatment of ischemic myocardial infarction), digestive system (such as the repair of liver damage), nervous system diseases (such as the treatment of brain injury and stroke), urinary system diseases (such as the treatment of ischemia reperfusion kidney injury), reproductive system diseases (such as repairing ovarian function) and breast diseases (such as breast cancer treatment). At present, BMSC-EXOs have been used in the research of diseases of multiple systems, providing new insight for the research and application of clinical drugs in the future. With extensive research on mesenchymal stem cells in recent years, BMSC-EXOs have also been widely used in the treatment of motor system diseases, and BMSC-EXOs have been used to treat TBI injury.

As natural cell products, EXOs have good biocompatibility, can penetrate biological barriers, exert therapeutic effects and can be used to treat bone-related diseases. It has been reported that mesenchymal stem cells from different sources can be used to promote tendon-bone healing, and in recent times, a substantial amount of evidence has indicated that the beneficial impacts of stem cell therapy could potentially occur through the release of extracellular vesicles termed EXOs from MSCs via a process known as paracrine signaling (2,58,80-83). This paracrine mechanism, which is known as stem cell conditioned medium (CM), secretome CM or secretome, is the medium in which stem cells are cultured and contains soluble proteins, lipids, nucleic acids and extracellular vesicles or microvesicles (84,85). These vesicles are further divided into EXOs and shedding vesicles. A summary of the advances in the promotion of tendon and bone healing by BMSC-EXOs is presented in Table II.

EXOs appear to be a more promising treatment option than stem cell therapy. The benefits of EXOs are mainly characterized by several aspects: i) EXOs are smaller and have a simple structure and composition, rendering them easier to separate and preserve, while exhibiting a lower immunogenicity; ii) EXOs can block the metastasis of cells that may contain immunogenic molecules or even mutated or damaged DNA; iii) EXOs can penetrate any organ and pass through it effortlessly due to their nanoscale size, unlike large cells that cannot migrate through capillaries to the injury site; iv) EXOs have the ability to move to different parts of the body as they have specific molecules on their surfaces that guide their migration; v) EXOs, being an integral part of the human body, possess biochemical characteristics that are akin to their originating cells. As a result, they are capable of evading phagocytosis, merging with cell membranes and lysosomal fusion (86,87).

5. Mechanisms through which BMSC-EXOs promote tendon-bone healing

Regulation of macrophage phenotypic polarization. Macrophages are derived from the bone marrow mononuclear cell line, are essential to the innate immune system and play an indispensable role in the immune response. Macrophages are divided into classically activated (M1) macrophages and alternately activated (M2) macrophages in response to various environmental stimuli. These two types of macrophages exhibit significant heterogeneity in phenotype and function. M1 and M2 macrophages are considered to have pro-inflammatory and fibrotic phenotypes, respectively (88,89). Previous studies have demonstrated that macrophages play a non-negligible role in the occurrence and development of TBI injury (90-92). In the early stages following tissue injury or tendon/ligament reconstruction, macrophages are recruited in large numbers to the graft-tunnel interface and are polarized toward the M1 type, inducing inflammatory responses and engulfing apoptotic cells, and removing cell debris (90). During this period, the expression of various pro-inflammatory factors, including TNF-α, IL-12, and inducible nitric oxide synthase, is significantly increased, thereby amplifying the inflammatory response in the affected area (90). The presence of inflammation in the surrounding environment helps attract additional cells from various locations to travel to the injured area and assist in the preparation of future tissue healing. In the advanced phase of the injury, M2 macrophages replace M1 macrophages in large numbers and secrete anti-inflammatory factors, such as IL-10 and TGF-β; by doing so, this decreases the localized inflammation and enhances the local regeneration and repair of tissues (93). Thus, accelerating macrophage polarization from M1 to M2 can accelerate tissue repair (94). If this is not achieved, it can lead to a prolonged inflammatory phase, increased apoptosis and decreased cell proliferation, resulting in slow healing. In addition, this condition can induce the excessive secretion of ECM by fibroblasts, leading to soft tissue fibrosis and scar tissue formation at the injury site, which hinders cartilage regeneration and graft remodeling (95-97). Therefore, regulating the polarization of macrophages may be key to promoting early tendon-bone healing.

Previous studies have reported that EXOs regulate inflammation through macrophage polarization, reduce cell infiltration and matrix deposition, promote collagen formation, and improve fiber continuity and alignment during tendon healing remodeling (46,98,99). In addition, EXOs derived from mesenchymal stem cells have been shown to modulate macrophage polarization in several *in vitro* and *in vivo* studies. For example, Huang *et al* (100) discovered that BMSC-EXOs were able to suppress inflammation by preventing the activation

Table I. Conventional treatment of TBI injuries.

Treatment	Advantage	Disadvantage	Clinical application
Surgical treatment	Surgical treatment is by far the most widely used. After years of development, the surgical technique is mature. It is almost the only effectivereatment for tsevere TBI injury.	The trauma is relatively large. Post-operativecomplications, such as infection, pain andjoint stiffness are common.	Traditional surgical treatment. Arthroscopic treatment.
Tissue engineering therapy	The trauma is minimal.	Bioactive factors have poor stability and are rapidly degraded and inactivated at the site of tendon/ligament injury.	Tissue engineering scaffold. Biological factor injection.
Platelet-rich plasma therapy	It has the advantages of low cost, simple operation and easy clinical promotion. There was no infection and immune rejection.	The efficacy of treatment has not been well established. The mechanism of action is not clear.	Autologous platelet-rich plasma injection.
Stem cell therapy	Stem cells can self-renew and have the potential of multidirectional differentiation. Stem cells can promote tissue repair through paracrine. Stem cells have a wide range of tissue sources and are relatively easy to isolate.	The biological mechanism of action remains unclear. The dose and duration of stem cell therapy have not been achieved to ensure the optimal result. The immune rejection of stem cells and the safety of genetically engineered stem cells cannot be completely guaranteed.	Bone marrow mesenchymal stem cells (BMSCs). Synovium-derived mesenchymal stem cells (SMSCs). Adipose-derived stem cells (ADSCs). Periosteum-derived periosteal stem cells (PSCs). ACL-derived stem cells.

Table II. Recent advances in the promotion of tendon and bone healing by BMSC-EXOs.

Author(s)	Affected tissue	Study type	Main results	Mechanism	(Refs.)
Huang *et al*	RC	*In vivo* and *in vitro*	BMSC-EXOs inhibited inflammation by inhibiting the polarization of M1 macrophages and the secretion of pro-inflammatory factors, confirming that BMSC-EXOs can increase the fracture load and stiffness of the RC after reconstruction, induce angiogenesis and inhibit inflammation around RC endpoints, thereby promoting tendon-bone healing after RC reconstruction in rats.	Regulation of macrophage phenotypic polarization.	(100)
Li *et al*	ACL	*In vivo* and *in vitro*	BMSC-EXOs promoted the polarization of M1 macrophages to M2 macrophages through miR-23a-3p, suggesting that early BMSC-EXOs treatment could inhibit the inflammatory response at the tendon-bone interface, promote fibrocartilage regeneration, and accelerate tendon-bone healing afterACL reconstruction. Moreover, the overexpression of miR-23a-3p could enhance the therapeutic effect.	Regulation of macrophage phenotypic polarization.	(8)
Shi *et al*	TBI	*In vivo* and *in vitro*	BMSC-EXOs improved the inflammatory microenvironment and promoted fibrocartilage regeneration at the tendon-bone interface by increasing M2 macrophage polarization, reducing the expression of proinflammatory cytokines IL-1β and IL-6, and enhancing the expression of anti-inflammatory cytokines IL-10, TGF-β, and insulin-like growth factor (IGF) during tendon healing. Thus, the biomechanical properties of tendon-to bone healing can be improved.	Regulation of macrophage phenotypic polarization.	(101)
Takayama *et al*	ACL	*In vivo* and *in vitro*	Inhibition of VEGF expression impairs revascularization and inhibits the biomechanical strength of tendon grafts after ACL reconstruction surgery. At the same time, overexpression of VEGF affects the enhancement of the biomechanical strength of tendon grafts.	Increase promotes angiogenesis.	(105)
Huang *et al*	RC	*In vivo* and *in vitro*	BMSC-EXOs can promote angiogenesis around the tendon-bone interface, increase the load and stiffness of RC rupturein rats after reconstruction, and promote the growth of thetendon-bone interface. BMSC-EXOs can activate the VEGF and Hippo signaling pathways and promote the proliferation,migration, and angiogenic tube formation of human umbilical vein endothelial cells (HUVECs) under *in vitro* culture conditions.	Increase promotes angiogenesis.	(100)

Table II. Continued.

Author(s)	Affected tissue	Study type	Main results	Mechanism	(Refs.)
Zhang *et al*	ACL	*In vivo* and *in vitro*	BMSC-EXOs promoted the formation of blood vessels around the graft and improved bone microstructure, which accelerated the healing of the transplanted tendon-bone tunnel after ACL reconstruction.	Regulation of bone metabolism.	(107)
Fang *et al*	BMSCs	*In vitro*	BMSC-EXOs containing tRNA-10277 could regulate the adipogenic and osteogenic potential of BMSCs.	Regulation of bone metabolism.	(108)
Zhang *et al*	BMSCs	*In vivo* and *in vitro*	miR-935-enriched EXOs produced by BMSCs directly enhanced osteoblast proliferation and activity by targeting signal transducer and transcription 1 (STAT1) activator to promote osteoblast proliferation and differentiation.	Regulation of bone metabolism.	(109)
Han *et al*	RC	*In vivo* and *in vitro*	BMP-2 and poly lactic acid (PLA) delivered by BMSC-EXOs of PASP-PLGA microcapsules promoted chondrogenic differentiation through the Smad/RUNX2 pathway, enhanced tendon interface stiffness and ultimate load strength, and promoted tendon-bone healing in rabbits with acute RC tears (RCT).	Regulation of bone metabolism.	(112)
Wu *et al*	RC	*In vivo* and *in vitro*	BMSC-EXOs pre-treated with low-intensity pulsed ultrasound stimulation (LIPUS) can improve fibrocartilage regeneration at the tendon-bone interface and reduce supraspinatus fat infiltration in a mouse RC repair model by delivering miR-140	Regulation of bone metabolism.	(113)
Cai *et al*	RC	*In vivo* and *in vitro*	Local injection of SAH with sustained KGN-EXOs release could effectively promote cartilage formation as well as collagen maturation and organization for enthesis regeneration, contributing to enhanced biomechanical properties after RCR.	Regulation of bone metabolism.	(114)
Li *et al*	RC	*In vitro*	EXOs derived from BMSCs promote the proliferation, migration, and fibrotic activity of RC tenocytes, and TGF-β1 is the crucial molecule mediating the effects of EXOs, pretreatment of BMSCs with TGF-β1 can significantly promote the secretion and release of EXOs.	Promotes tendon regeneration.	(117)
Li *et al*	RC	*In vitro*	TGF-β1 treatment promoted BMSCs-EXOs secretion, in which miR-29a promoted tendon cell proliferation, migration, and fibrosis by targeting FABP3, thus improving tendon injury and RCT.	Promotes tendon regeneration.	(118)

Table II. Continued.

Author(s)	Affected tissue	Study type	Main results	Mechanism	(Refs.)
Yu *et al*	BMSCs	*In vivo* and *in vitro*	BMSCs-EXOs significantly promoted the proliferation, migration and tenogenic differentiation ability of TSPCs. Moreover, by embedding BMSCs-EXOs into the fibrin gel, the control-released exosomes retained the ability of being internalized by TSPCs *in vivo* and promoted the regeneration of patellar tendon tissue in the defect area in rats.	Promotes tendon regeneration.	(116)
Li *et al*	BMSCs	*In vitro*	BMSC-derived exosomes promote fibroblast activation possibly through the PTEN and PI3K/Akt signaling pathways, which may serve as potential targets to further promote tendon-bone healing.	Promotes tendon regeneration.	(122)

BMSCs, bone marrow mesenchymal stem cells; EXOs, exosomes; BMSC-EXOs, exosomes derived from BMSCs; RC, rotator cuff; TBI, tendon-bone insertion; ACL, anterior cruciate ligament; IL, interleukin; TGF, transforming growth factor; miR, microRNA.

of M1 macrophages and the release of pro-inflammatory substances. Their study confirmed that BMSC-EXOs have the potential to enhance the fracture load and stiffness in the reconstructed RC, thereby inducing angiogenesis and inhibiting inflammation around RC endpoints, and promoting the healing of tendons and bones following RC reconstruction in rats. Li *et al* (8), in their groundbreaking study, demonstrated that BMSC-EXOs have the ability to induce the transformation of M1 macrophages into M2 macrophages through the involvement of miR-23a-3p. This finding suggests that early treatment with BMSC-EXOs may effectively suppress the inflammatory response at the interface between the tendon and bone. Furthermore, it was observed that BMSC-EXOs facilitated the regeneration of fibrocartilage and expedited the healing process of the tendon-bone junction following ACL reconstruction. Moreover, miR-23a-3p overexpression enhanced the therapeutic effect (8). Shi *et al* (101) demonstrated that BMSC-EXOs improved the inflammatory microenvironment and promoted fibrocartilage regeneration at the tendon-bone interface by increasing M2 macrophage polarization, thereby reducing the expression of the pro-inflammatory cytokines. IL-1β and IL-6. and enhancing the expression of the anti-inflammatory cytokines, IL-10, TGF-β and insulin-like growth factor during tendon healing. Furthermore, it is possible to enhance the biomechanical characteristics of the healing process between tendons and bones.

The characteristics of EXOs exhibit potential for reducing initial inflammatory reactions, which is necessary for effective tissue healing (102). However, the specific mechanism through which BMSC-EXOs control the polarization and function of M2 macrophages in TBI injury is not yet completely understood and warrants further investigation. The mechanisms of BMSC-EXOs in promoting tendon-bone healing are illustrated in Fig. 3.

An increase in VEGF promotes angiogenesis. After experiencing a traumatic brain injury, there is a decrease in blood flow to the area where the tendon connects to the bone. This decrease in blood flow means that important nutrients that are necessary for the healing of the tendon and bone are not being delivered properly. As a result, the biomechanical properties of the tendon and bone are negatively affected, which in turn affects the overall recovery of the tendon and bone (103). Numerous research studies have provided evidence that neovascularization plays a crucial role in facilitating the healing process of tendon-bone. It has been consistently demonstrated that following RC reconstruction, tendon-bone healing quality can be effectively improved by improving the blood supply at the tenodesis point or trough, where the blood supply is relatively poor (104).

VEGF is a key factor that regulates the natural formation of new blood vessels in the body. It plays a crucial role in activating, increasing in number and facilitating the movement of endothelial cells which line the inside of blood vessels and improve the circulation of blood to the transplanted tendon, which in turn facilitates the healing of the tendon-bone connection (103). Takayama *et al* (105) provided evidence that suppressing the expression of VEGF hindered the process of blood vessel formation and also hindered the mechanical integrity of tendon grafts following ACL reconstruction

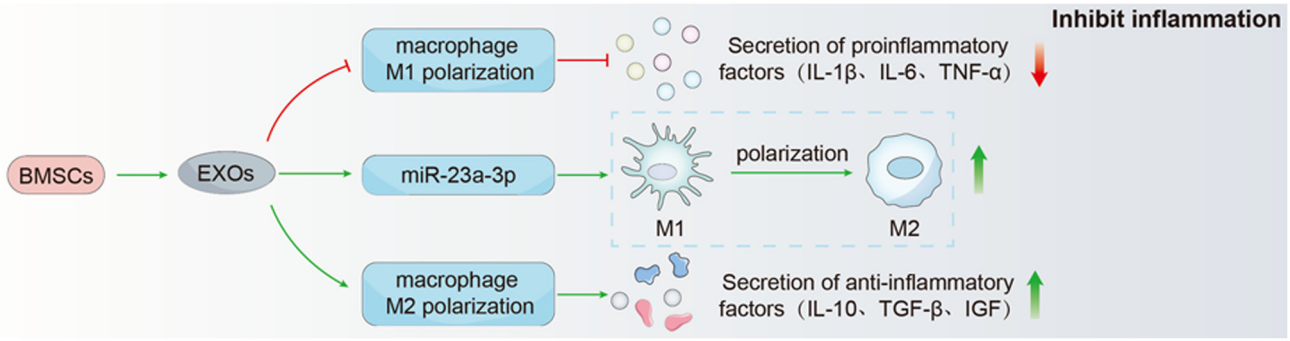

Figure 3. Mechanisms of BMSC-EXOs in promoting tendon-bone healing: Regulation of macrophage phenotype polarization and inhibition of the inflammatory response. BMSC-EXOs inhibit macrophage M1 polarization, and the secretion and release of pro-inflammatory factors. They promote macrophage M2 polarization and the secretion and release of anti-inflammatory factors. miR-23a-3p in BMSC-EXOs promotes the phenotypic conversion of macrophages from the M1 to M2 phenotype. BMSCs, bone marrow mesenchymal stem cells; EXOs, exosomes; BMSC-EXOs, exosomes derived from BMSCs; IL, interleukin; TGF, transforming growth factor; IGF, insulin-like growth factor.

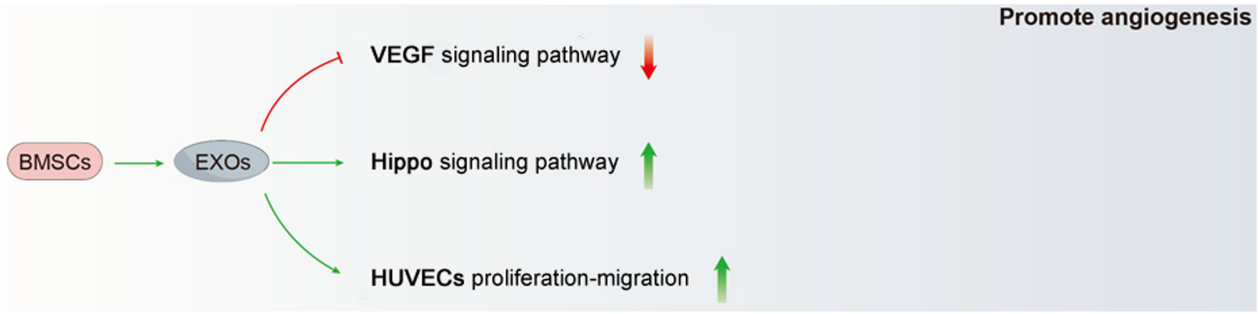

Figure 4. Mechanisms of BMSC-EXOs in promoting tendon-bone healing: Promotion of angiogenesis. BMSC-EXOs can activate the VEGF and Hippo signaling pathways, which are vital angiogenesis signaling pathways, to promote the proliferation and migration of HUVECs, thereby promoting angiogenesis around the tendon-bone interface. BMSCs, bone marrow mesenchymal stem cells; EXOs, exosomes; BMSC-EXOs, exosomes derived from BMSCs; VEGF, vascular endothelial growth factor; HUVECs, human umbilical vein endothelial cells.

surgery. Furthermore, the overexpression of VEGF affected the enhancement of the biomechanical strength of tendon grafts (105). Huang *et al* (100) discovered that BMSC-EXOs have the ability to enhance the formation of new blood vessels around the area where the tendon and bone meet. Additionally, they found that these exosomes can increase the strength and rigidity of the tendon in rats following reconstruction, as well as stimulate the growth of the tendon-bone junction (100). During further mechanistic analyses, the researchers verified that BMSC-EXOs have the ability to stimulate the VEGF and Hippo signaling pathways. Additionally, they can enhance the growth, movement and formation of blood vessels in human umbilical vein endothelial cells *in vitro* (100). Notably, the researchers discovered that the stimulation of the VEGF and Hippo signaling pathways by BMSC-EXOs could be separate. This indicates that the activation of the Hippo signaling pathway by BMSC-EXOs does not solely rely on the VEGF signaling pathway. This suggests that BMSC-EXOs have extensive and beneficial impacts on enhancing angiogenesis (Fig. 4).

Regulation of bone metabolism. Bone is a dynamic tissue that undergoes continuous remodeling by a delicate equilibrium between the creation of new bone by osteoblasts and the breakdown of old bone by osteoclasts. The process of bone formation is carefully regulated and involves the direct transformation of BMSCs into osteoblasts. Following surgical reconstruction, up to 25% of patients require revision surgery, partly due to traumatic, technical, bacterial and biological factors. A significant factor contributing to this issue is the deterioration of bone surrounding the graft, which directly affects the secure connection of the transplanted tendon to the bone tunnel. Therefore, reducing bone loss around the graft may be a therapeutic strategy with which to promote tendon-bone tunnel healing and reduce the rate of reconstruction failure.

The healing quality of the grafted tendon-to-bone tunnel is closely related to the formation of bone around the graft, which is inseparable from early post-operative angiogenesis. The blood vessels located at the boundary between the transplanted tendon and the bone tunnel supply an ample amount of oxygen and nutrients to the cells. As a result, this has a direct impact on the formation of new bone around the graft (100,106). Zhang *et al* (107) examined a rat ACL reconstruction model and demonstrated that BMSC-EXOs promoted the formation of blood vessels around the graft and improved bone microstructure, which accelerated the healing of the transplanted tendon-bone tunnel following ACL reconstruction.

BMSC-EXOs can participate in bone remodeling by directly regulating the proliferation and activity of osteoblasts. Fang *et al* (108) found that BMSC-EXOs containing

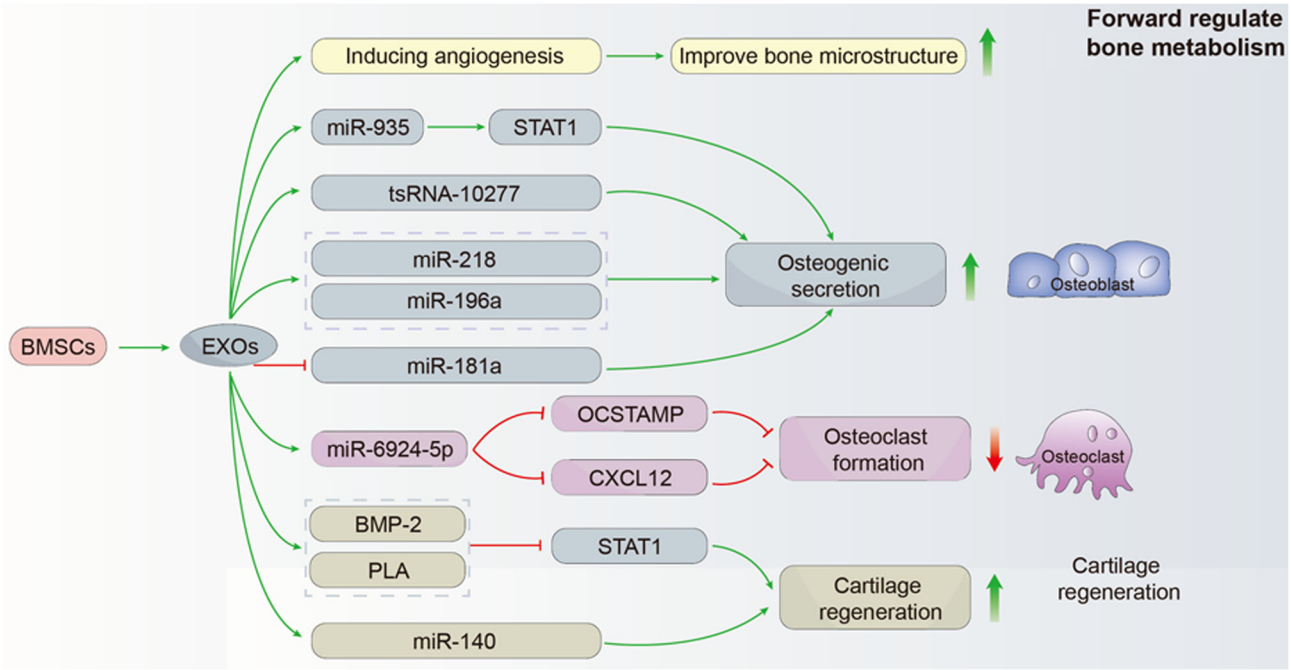

Figure 5. Mechanisms of BMSC-EXOs in promoting tendon-bone healing: Regulation of bone metabolism. BMSCs-EXOs promote the formation of blood vessels around grafts and improve bone microstructure. tsRNA-10277, miR-935, miR-218, miR-196a, and miR-181a in BMSCs-EXOs promote the proliferation and active osteogenic potential of osteoblasts. miR-6924-5p in BMSCs-EXOs targets OCSTAMP and CXCL12 to inhibit osteoclast formation. BMP-2 and PLA in BMSC-EXOs activate the Smad/RUNX2 pathway to promote chondrogenesis, and miR-140 in BMSC-EXOs promotes fibrocartilage regeneration. BMSCs, bone marrow mesenchymal stem cells; EXOs, exosomes; BMSC-EXOs, exosomes derived from BMSCs; OCSTAMP, osteoclast stimulatory transmembrane protein; CXCL12, chemokine (C-X-C motif) ligand 12; BMP-2, bone morphogenetic protein 2; PLA, polylactic acid; miR, microRNA; STAT1, signal transducer and activator of transcription 1.

tsRNA-10277 altered the adipogenic and osteogenic potential of BMSCs. Zhang *et al* (109) found that miR-935-enriched EXOs produced by BMSCs directly enhanced osteoblast proliferation and activity by targeting signal transducer and transcription 1 activation to promote osteoblast proliferation and differentiation. In addition, miR-218, miR-196a and miR-181a contained in BMSC-EXOs have been confirmed to exert positive regulatory effects on osteoblast differentiation (110).

In addition to targeting osteoblasts, BMSC-EXOs can regulate the activity of osteoclasts, thereby regulating bone metabolism at the tendon-bone interface. Feng *et al* (111) demonstrated that EXOs containing a high amount of miR-6924-5p, derived from platelet derived growth factor receptor α (+) BMSCs overexpressing Scleraxis, could be used as a novel type of nanotherapeutic agent. These EXOs were able to prevent the formation of osteoclasts by targeting two specific proteins: Osteoclast stimulatory transmembrane protein and chemokine (C-X-C motif) ligand 1. In addition, this treatment could effectively hinder the process of tunnel osteolysis and enhance the biomechanical stability of tendon-bone healing (111).

Fibrocartilage is an essential component of the tendon-bone interface. Recently, Han *et al* (112) reported that BMP-2 and polylactic acid delivered by BMSC-EXOs in polyaspartic acid-polylactic acid-glycolic acid copolymer microcapsules promoted chondrogenic differentiation through the Smad/RUNX2 pathway, enhanced tendon interface stiffness and ultimate load strength, and promoted tendon-bone healing in rabbits with acute RC tears. BMSC-EXOs that have undergone low-intensity pulsed ultrasound stimulation (LIPUS) have the potential to enhance the regeneration of fibrocartilage at the interface between the tendon and bone. Additionally, they can help reduce the infiltration of fat in the supraspinatus muscle in a mouse model of RC repair. This is achieved by delivering miR-140 (113). Cai *et al* (114) reported that the local injection of EXOs derived from kartogenin-preconditioned BMSCs had the potential to efficiently stimulate the development of cartilage, enhance the maturation of collagen, and facilitate the regeneration of tissues in the rotator cuffs of rats with chronic RC tears, and enhance biomechanical properties following RC repair (Fig. 5).

Promotion of tendon regeneration. The proliferation and migration of tendon cells are involved in tendon tissue repair and tendon-bone healing (115). Ample research has validated the positive impact of BMSC-EXOs in facilitating the restoration of tendons. For example, Yu *et al* (116) demonstrated that BMSC-EXOs promoted the proliferation, migration and tendon differentiation of tendon stem/progenitor cells (TSPCs) *in vitro*, and subsequent *in vivo* analyses further confirmed that BMSC-EXOs could be taken up and internalized by rat TSPCs, thereby promoting the proliferation and migration of TSPCs. This effect was characterized by improved histological scores of patellar tendons, the enhanced expression of Mohawk, tending-regulatory protein and type I collagen, and improved mechanical properties of the new tendons (116). Subsequent studies confirmed that exosomes derived from BMSCs promoted the proliferation, migration and fibrotic activity of rotator cuff tendon cells, and TGF-β1 was a key molecule that mediated the effect of exosomes (117).

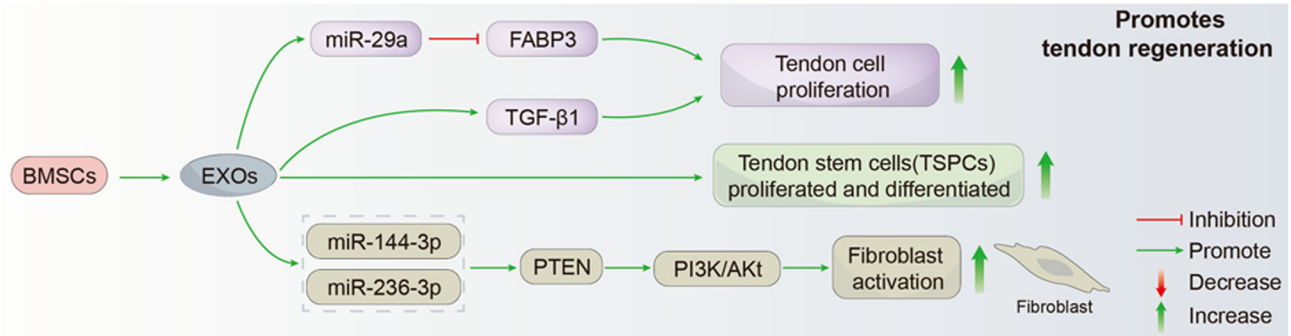

Figure 6. Mechanisms of BMSC-EXOs in promoting tendon-bone healing: Promotion of tendon cell proliferation. TGF-β1 in BMSCs promotes tendon cell proliferation, migration and fibrosis activity. miR-29a in BMSC-EXOs targets FABP3 to promote tendon cell proliferation, migration and fibrosis. BMSCs, bone marrow mesenchymal stem cells; EXOs, exosomes; BMSC-EXOs, exosomes derived from BMSCs; TGF, transforming growth factor; miR, microRNA; FABP3, fatty acid binding protein 3.

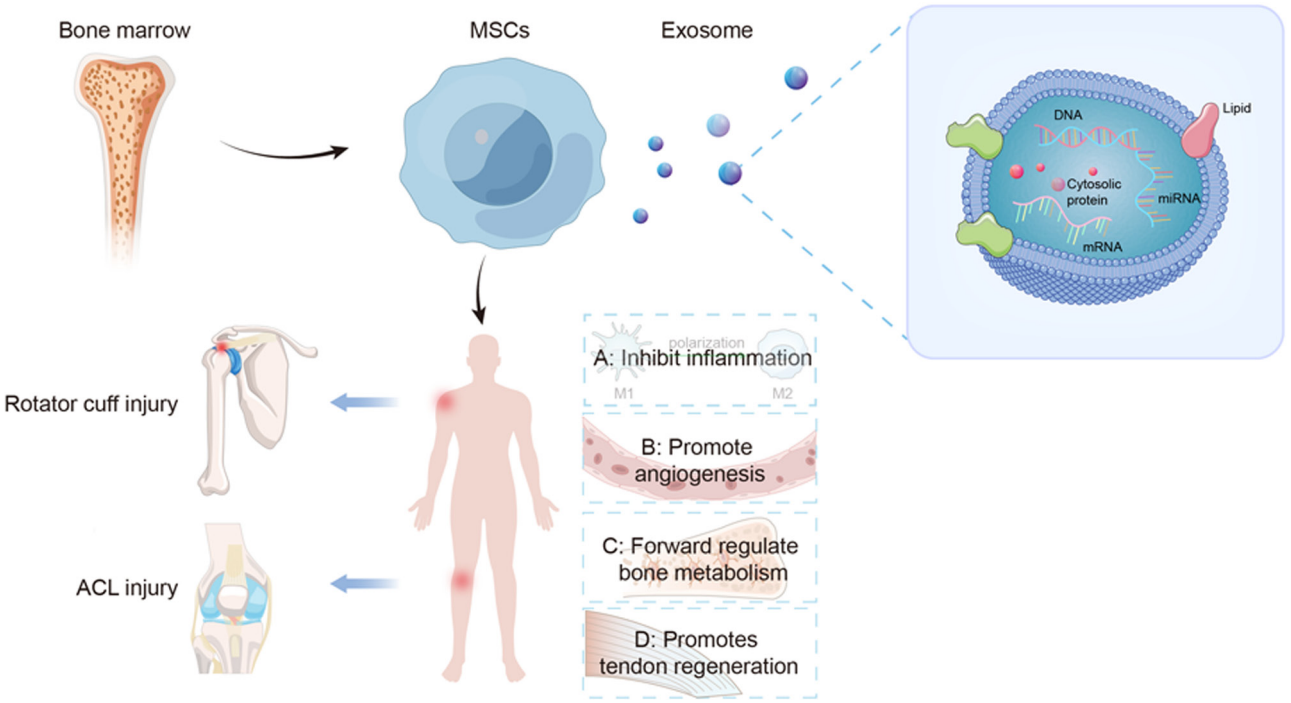

Figure 7. Conceptual diagram of exosomes derived from bone marrow mesenchymal stem cells acting on tendon-bone repairing. MSCs, mesenchymal stem cells; ACL, anterior cruciate ligament; miRNA, microRNA.

Pre-treatment of BMSCs with TGF-β1 can also significantly promote the secretion and release of EXOs from BMSCs. Li *et al* (118) first described that TGF-β1 treatment promoted BMSC-EXO secretion, and miR-29a promoted tendon cell proliferation, migration and fibrosis by targeting fatty acid binding protein 3, thereby improving tendon injury and RC tear. Several previous studies have shown that BMSCs-EXOs can promote skin wound healing by regulating the activation and proliferation of fibroblasts (119-121). Recently, Li *et al* (122) confirmed that BMSC-EXOs also play a critical role in promoting tendon-bone healing by promoting the proliferation and differentiation of fibroblasts. In addition, the downstream targets of miRNA, which is an active molecule in BMSCs-EXOs, have also been more fully verified in their study. According to the study conducted by Li *et al* (122), it was confirmed that miR-144-3p and miR-23b-3p enhanced the proliferation, migration and collagen synthesis of NIH3T3 fibroblasts through both bioinformatics analysis and *in vitro* experiments. Further analyses demonstrated that miR-144-3p and miR-23b-3p promoted fibroblast activation through the upregulation of the PTEN and PI3K/Akt signaling pathways (122). This discovery lays a theoretical foundation for RC tear therapy and provides a new avenue for further research (Fig. 6).

6. Conclusions and future perspectives

EXOs are small soluble vesicles secreted by various cells that can be found in cell cultures and bodily fluids. Their lipid bilayers protect proteins and nucleic acids from degradation in the extracellular environment, and facilitate intercellular communication by carrying contents across the cell membrane

to the cytoplasm of recipient cells. EXOs play a crucial role in regulating life activities (123,124). BMSCs have been known to promote tissue healing and regeneration due to their multipotent stem cell properties. BMSC-EXOs, which are key products secreted by BMSCs, have also been shown to possess regenerative qualities similar to those of parental BMSCs. BMSC-EXOs exhibit great promise in serving as diagnostic or prognostic biomarkers, drug delivery systems and carriers for gene therapy in the clinical setting. These findings provide a new perspective for the study of promoting tendon healing and bring new opportunities.

In recent years, with increasingly extensive and in-depth research on the treatment of TBI injury, an increasing number of new methods have been developed. Numerous studies have suggested that purified BMSC-EXOs offer several unique advantages over BMSCs in repairing damaged tissues. They have stable biological activity, long-term preservation, fast transportation, strong permeability, good biocompatibility, ease of engineering and the ability to avoid immune responses and tumorigenesis (8,14,125). Therefore, BMSC-EXO-based decellularized therapy is a promising therapeutic approach for maintaining the regenerative properties of BMSCs, while avoiding the potential downsides associated with cell therapy (126,127).

While the beneficial effects of BMSC-EXOs on tendon-bone healing have been initially confirmed, further extensive and in-depth studies are warranted. Clinical trials for safety and efficacy should be accelerated and performed as soon as possible. Additionally, the extraction and purification of EXOs needs to improved, as factors such as high cost, complex technology, low yield and the ease of destruction limit their broad clinical applications (128). The future of EXOs in biomedical engineering is an area that requires further investigation.

In summary, BMSC-EXOs have a vast potential for use in tendon-bone healing and repair. This breakthrough presents fresh possibilities for fundamental scientific investigation, the diagnosis of medical conditions, and the management of associated illnesses. However, further research is required in order to fully comprehend the mechanisms through which BMSC-EXOs promote healing and improve the clinical application of EXOs (Fig. 7).

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Availability of data and materials

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Authors' contributions

HZ provided a brief introduction to the article. YZ and GC were responsible for the writing of the manuscript. YZ prepared the tables. HZ and JY revised the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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