Journal of Orthopaedic Translation 45 (2024) 132–139

Contents lists available at ScienceDirect

Journal of Orthopaedic Translation

journal homepage: www.journals.elsevier.com/journal-of-orthopaedic-translation

Review article

The Revolution of exosomes: From biological functions to therapeutic applications in skeletal muscle diseases

Renwen Wan [a,1], Shan Liu [b,1], Xinting Feng [a,1], Wei Luo [a], Hanli Zhang [a], Yang Wu [a,**], Shiyi Chen [a,***], Xiliang Shang [a,*]

[a] Department of Sports Medicine, Huashan Hospital, Fudan University, Shanghai, 200040, China
[b] Department of Endocrinology, Huashan Hospital, Fudan University, Shanghai, 200040, China

ARTICLE INFO

Keywords:
Exosomes
Extracellular vesicle
Mechanism
Skeletal muscle diseases
Stem cell
Treatment

ABSTRACT

Skeletal muscle diseases, a broad category encompassing a myriad of afflictions such as acute muscle injury and muscular dystrophies, pose a significant health burden globally. These conditions often lead to muscle weakness, compromised mobility, and a diminished quality of life. In light of this, innovative and effective therapeutic strategies are fervently sought after. Exosomes, naturally extracellular vesicles with a diameter of 30–150 nm, pervade biological fluids. These microscopic entities harbor a host of biological molecules, including proteins, nucleic acids, and lipids, bearing a significant resemblance to their parent cells. The roles they play in the biological theater are manifold, influencing crucial physiological and pathological processes within the organism. In the context of skeletal muscle diseases, their potential extends beyond these roles, as they present a promising therapeutic target and a vehicle for targeted drug delivery. This potentially paves the way for significant clinical applications. This review aims to elucidate the mechanisms underpinning exosome action, their myriad biological functions, and the strides made in exosome research and application. A comprehensive exploration of the part played by exosomes in skeletal muscle repair and regeneration is undertaken. In addition, we delve into the use of exosomes in the therapeutic landscape of skeletal muscle diseases, providing a valuable reference for a deeper understanding of exosome applications in this realm. The concluding section encapsulates the prospective avenues for exosome research and the promising future they hold, underscoring the tremendous potential these diminutive vesicles possess in the field of skeletal muscle diseases.

The Translational Potential of this Article.

The comprehensive exploration of exosome's diverse biological functions and translational potential in the context of skeletal muscle diseases presented in this review underscores their promising future as a therapeutic target with significant clinical applications, thus paving the way for innovative and effective therapeutic strategies in this realm.

1. Introduction

The skeletal muscle is a substantial and adaptable tissue within the human body, constituting around 40 % of overall body weight and encompassing 50–75 % of the body's protein stores. The main functions attributed to skeletal muscle include facilitating body mobility, serving as a reservoir for protein storage, generating heat through thermogenesis, contributing to metabolic processes, and providing protection to visceral organs [1–3]. Skeletal muscle diseases encompass a diverse array of muscular ailments, characterized by their heterogeneity, such as injuries, atrophy, sarcopenia, and weakness, impacting individuals' health and functional abilities [4]. Skeletal muscles are sensitive to injury because they are frequently subjected to high contractile forces that may damage the sarcolemmal, especially during

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: rwwan22@m.fudan.edu.cn (R. Wan), shanliu22@m.fudan.edu.cn (S. Liu), fengxinting2022@163.com (X. Feng), weiLuo1027@163.com (W. Luo), 22211220069@m.fudan.edu.cn (H. Zhang), sonnewu@hotmail.com (Y. Wu), cshiyi@163.com (S. Chen), sxl00720@163.com (X. Shang).
[1] These authors contributed equally to this work and share the first authorship

https://doi.org/10.1016/j.jot.2024.01.001
Received 1 December 2023; Received in revised form 29 December 2023; Accepted 8 January 2024

eccentric muscle contraction [5]. The intensity of persistent inflammation following skeletal muscle injury is also one of the clinical concerns that need urgent attention. Generally, 50 % of acute injuries become chronic [6,7]. A multitude of causes can alter skeletal muscle homeostasis, resulting in skeletal muscular atrophy, such as diabetes, cancer and chronic obstructive pulmonary disease, weightlessness, denervation disuse state, fasting, and aging [8,9]. Aging is followed by a steady reduction in skeletal muscle mass and strength, which may lead to primary sarcopenia [10]. Skeletal muscle atrophy weakens the body's ability to cope with stress and chronic diseases, drastically diminishes people's quality of life, increases morbidity and mortality, causes huge social and economic burden, and alters the prognosis of patients [11]. Further research and advancements in treatment modalities are needed to improve outcomes for individuals affected by skeletal muscle diseases.

The treatment of skeletal muscle diseases involves various approaches, including pharmacological interventions, physical therapies, and regenerative medicine techniques [12–15]. These modalities aim to alleviate symptoms, promote healing, improve abilities, and enhance the quality of life. Understanding these approaches is essential for effective management and rehabilitation. Pharmacological treatments play a crucial role, with nonsteroidal antiinflammatory drugs (NSAIDs) used for muscle injuries, muscle relaxants for spasms, and medications for neuromuscular disorders [13,16]. Physical therapies restore function, strength, and mobility through exercises, manual therapy, stimulation, and modalities [17,18]. Regenerative medicine techniques, such as stem cell therapy, platelets-rich plasma (PRP) injections, and tissue engineering, hold promise for repairing and restoring muscle structure and function [19,20].

Exosomes, a specialized category of extracellular vesicles (EVs), have emerged as key players in redefining our comprehension of how cells communicate with each other. These diminutive, membrane-enclosed entities, which vary in size from 30 to 150 nm, are produced and released by a diversity of cell types. They are endowed with the extraordinary capability to carry and distribute a vast array of bioactive compounds. This includes an assortment of proteins, nucleic acids, lipids, and various metabolic byproducts, making them pivotal in cellular interactions and signaling [21–23]. The discovery and characterization of exosomes have provided valuable insights into their role in physiological and pathological processes. They are derived from a diverse range of cell types, including immune cells, stem cells, epithelial cells, and cancer cells [24]. The release of exosomes can be triggered by various stimuli such as cellular activation, stress, or injury. Exosomes have a diverse payload because they mirror the parent cells' traits and functions. Proteins, mRNA, miRNA, lipids, and other substances may be in this cargo. Exosomes transport bioactive chemicals from donor cells to receiving cells, affecting their behavior and phenotype [25]. They are involved in immunological control, tissue healing, angiogenesis, and neural signaling. Cancer progression, inflammation, and infectious agent propagation are also caused by exosomes. Exosome cargo can regulate gene expression, signaling pathways, and cellular responses in recipient cells, affecting cellular physiology [21]. The significance of exosomes in biomedical research lies in their ability to transport diverse molecules and their involvement in a wide range of physiological and pathological processes.

Skeletal muscle diseases present a significant obstacle in clinical treatment, prompting the exploration of exosome therapy as a potential avenue for novel approaches in regenerative medicine and targeted drug administration. This therapeutic modality holds considerable promise in its ability to influence muscle regeneration, facilitate tissue repair, and enhance the effectiveness of treatments. This review aims to investigate the involvement of exosomes in skeletal muscle illnesses and elucidate the possible therapeutic applications of exosomes in the management of such conditions.

1.1. A comprehensive explanation of exosomes

The exosome is a crucial subtype of EVs that originates from the multivesicular bodies that are produced from the endosomes. It was first described in 1983 by Pan and Johnstone, who subsequently attributed the term "exosome" to their work [26]. EVs can be categorized into three distinct groups according to their size and biological source: exosomes (30–150 nm), microvesicles (100–1000 nm), and apoptotic bodies (>1000 nm) [27,28]. The size and production mechanisms of EVs exhibit significant variation, resulting in specific characteristics for each vesicle. Exosomes are derived from endosomes, which are formed when the cell membrane undergoes invagination to produce early endosomes. The early endosomes undergo maturation to become late endosomes, which thereafter transform multivesicular bodies comprising intraluminal vesicles that ultimately differentiate into exosomes [29]. In due course, the release of exosomes into the extracellular space occurs when the multivesicular bodies fuse with the cell membrane and undergo exocytosis [30]. The generation of exosomes involves a distinct mechanism of creation. Despite the lack of a comprehensive understanding of the total molecular mechanism underlying exosome formation, existing research has revealed the involvement of various variables in the unique sorting of exosome contents. These components include the exosome sorting complex (ESCRT) for transportation, tetraspanin, ceramides, and lipids [31–34]. Upon secretion, exosomes can transport their contents to recipient cells via diverse pathways. The mechanisms involved in cellular uptake encompass fusion with the cell membrane, as well as other forms of endocytosis, including lipid raft-mediated, clathrin-mediated, caveolin-mediated, phagocytosis, and macropinocytosis (Fig. 1). Furthermore, exosomes possess the ability to establish direct communication with target cells via receptor–ligand interactions [35]. The degree to which various patterns of exosome internalization by recipient cells result in unique functional consequences remains unknown.

Exosomes derived from various cellular origins exhibit variations in terms of their size, composition, and impact on the function of recipient cells, displaying a notable level of heterogeneity [29]. The small vesicles described in the text include several components that originate from their parent cells. These components include growth factors, cytokines, signaling lipids, mRNA, miRNA, and proteins [35,36]. Exosomes contain a diverse array of proteins, encompassing both non-specific and particular protein components [24]. Proteins of a nonspecific nature are universally found in exosomes, irrespective of the cellular source of these exosomes. Examples of such proteins include ESCRT proteins, heat shock proteins, transport and fusion proteins (Rab proteins, Annexins, Flotillin), as well as cytoskeletal proteins (Actin, Cofilin). These proteins can serve as reliable indicators for the identification of exosomes. On the other hand, certain proteins that are linked to cells originating from exosomes, such as MHC class I and MHC class II proteins, as well as transferrin receptors, have the potential to indicate tissue and cell selectivity, and might potentially facilitate signaling processes. Exosomes are composed of a diverse array of lipids, such as sphingolipids, cholesterol, and ceramides. These lipids have the dual purpose of ensuring chemical stability and contributing to the manufacture of exosomes [27,37]. Furthermore, exosomes contain a diverse array of nucleic acids in their extracellular compartment, encompassing both DNA (single-stranded and double-stranded) and RNA (containing lncRNA, miRNA, mRNA, rRNA, among others), with miRNA being the predominant constituent [27]. The composition of exosomes exhibits similarities to their parent cells, indicating the presence of specific sorting processes involved in the process of exosome formation (Fig. 1).

Exosomes exhibit a diverse array of biological functions, and a more comprehensive comprehension of these functions would facilitate researchers in gaining deeper insights into the mechanisms underlying exosomal behavior in both physiological and pathological contexts. Firstly, signal transduction is a fundamental and critical biological process performed by exosomes. Exosomes function as mediators of

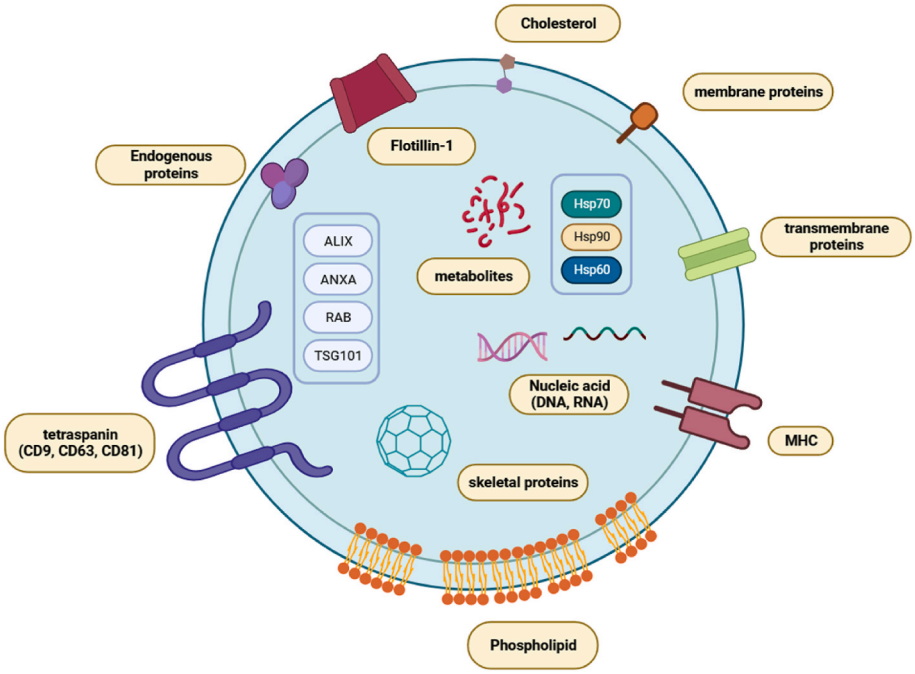

Figure 1. Exosomes are composed of lipid bilayers that transport numerous biomolecules, such as proteins, DNA, RNA, lipids, etc.

intercellular communication, enabling the delivery of their cargo to nearby or distant cells, thus exerting regulatory influence over a broad range of physiological and pathological [38]. Furthermore, exosomes play a significant role in the modulation of inflammation by their ability to either enhance or suppress the activation of inflammatory vesicles [39]. Numerous studies have demonstrated that exosomes released by cells under inflammatory contexts can stimulate the polarization of macrophages towards the M1 phenotype, while concurrently suppressing M2 polarization, thus facilitating the progression of inflammatory reactions [40–42]. Thirdly, exosomes derived from immune cells possess the potential to either enhance or suppress immune responses, largely contingent upon their composition and the specific cellular environment in which they are induced, thereby assuming significant roles in the modulation of immune reactions and immune tolerance. Additionally, exosomes can facilitate the process of tissue repair and regeneration. The utilization of exosomes produced from mesenchymal stem cells (MSCs) has been observed to exhibit beneficial properties in the context of wound healing, cartilage repair and tissue regeneration, displaying both protective and therapeutic benefits [43–45]. Finally, exosomes derived from various origins have the potential to elicit either stimulatory or inhibitory impacts on the process of autophagy. Moreover, exosomes have the potential to function as biomarkers and therapeutic vehicles for a wide range of illnesses. The molecular makeup of exosomes exhibits differences that are dependent on the specific cells from which they originate and is significantly impacted by the microenvironment of these cells. The diverse content of functional molecules in exosomes enables a wide range of biological functions to be assigned to them [46].

1.2. The role of exosomes in skeletal muscle repair and regeneration

The repair and regeneration processes of skeletal muscle are influenced by various elements, with exosomes assuming a significant part in these mechanisms. In the subsequent discourse, we will delve into the multifaceted role of exosomes in skeletal muscle biology. This exploration will encompass three primary areas: the involvement of exosomes in the proliferation, differentiation, and migration of skeletal muscle cells; their function in the immunoregulatory processes within skeletal muscles; and their significance in the induction of angiogenesis in skeletal muscle tissue. These dimensions collectively illuminate the critical importance of exosomes in the context of skeletal muscle repair and regeneration (Fig. 2).

1.3. Role of exosomes on cell proliferation, differentiation, and migration

During the process of skeletal muscle regeneration, satellite cells are stimulated and undergo activation, leading to their differentiation into myoblasts. These myoblasts then proceed to undergo terminal differentiation, ultimately resulting in the development of myotubes that possess multiple nuclei [47,48]. The study conducted by Luo et al. showed that exosomes produc ed from C2C12 myoblasts can enhance both myoblast proliferation and differentiation [41]. Cho et al. conducted a study wherein they extracted exosomes during the process of differentiating human skeletal myoblast cells (HSkMs) into myotubes. The researchers discovered that these exosomes exhibited a high concentration of multiple myogenic factors, such as insulin-like growth factor, hepatocyte growth factor, fibroblast growth factor-2, and platelet-derived growth factor-AA. Following this, the researchers proceeded to administer HSkM-Exos to the mouse model with a muscle tear, subsequently observing a notable improvement in muscle regeneration. This was accompanied by a substantial increase in the expression of myogenic proteins and genes, so demonstrating that exosomes had a key role in promoting both myogenic differentiation and regeneration [49]. The study conducted by Nakamura et al. revealed the presence of exosome markers in the context of muscle regeneration. Additionally, the researchers observed a significant increase in muscle cross-sectional area and a corresponding decrease in fibrotic area following the administration of exosomes. Furthermore, an assessment was conducted to examine the association between miR-494 and myogenesis. This was accomplished by introducing miR-494 into C2C12 myoblasts through transfection. The results revealed that the fusion index of myoblasts transfected with miR-494 exhibited a notably higher value compared to myoblasts transfected with siNega. These findings provide compelling evidence supporting the significant involvement of exosomes in the process of C2C12 myogenesis [23]. Similarly, Forterre et al. discovered that muscle-associated exosomes can stimulate myogenesis by transporting miRNA between proliferating myoblasts and mature myotubes [50]. Simultaneously, exosomes have the dual capacity of facilitating

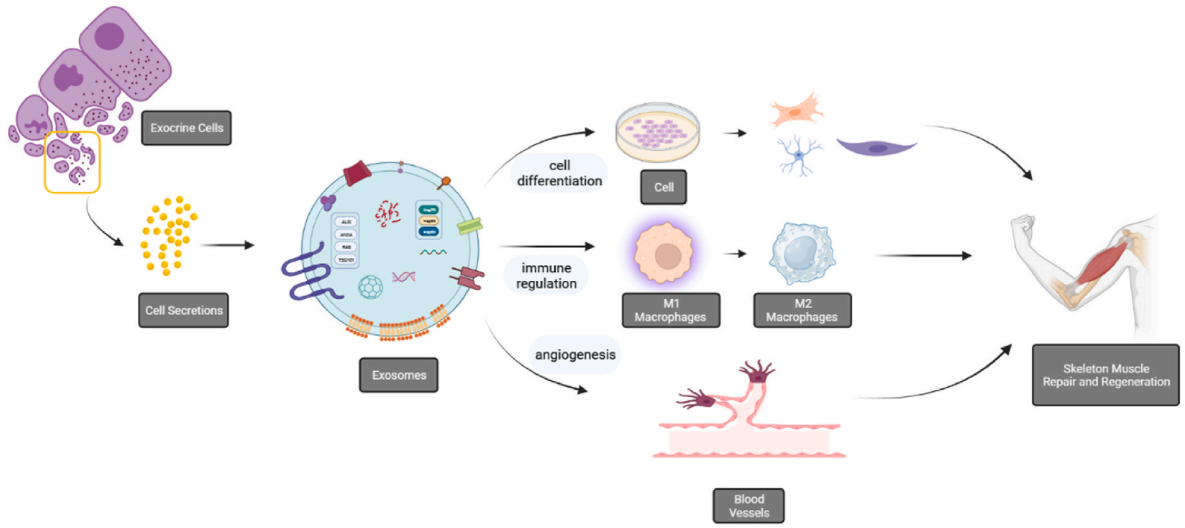

Figure 2. The role of exosomes in skeletal muscle repair and regeneration.

the growth of muscle fibers while impeding the programmed cell death of myoblasts, myocytes, and endothelial cells [51–53]. Numerous pieces of research have provided comprehensive confirmation of the advantageous impacts of exosomes in facilitating the development of satellite cells, suppressing cellular apoptosis, and enhancing the expression of myogenic genes inside skeletal muscle. Nevertheless, the precise mechanisms of the signaling pathways remain elusive and warrant more investigation in subsequent studies.

1.4. Role of exosomes in skeletal muscle immune regulation

Exosomes can modulate the process of skeletal muscle repair and regeneration through their ability to induce macrophage polarisation and suppress skeletal muscle inflammation comparably. Cavallari et al. originally reported on the action of EVs on inflammatory cells, discovering that serum EVs nearly entirely inhibited inflammatory cell infiltration in ischemic gastrocnemius muscle, but they did not investigate the specific mechanism [54]. Typically, M1 macrophages exhibit pro-inflammatory properties and are involved in the clearance of cellular debris. Conversely, M2 macrophages assume an anti-inflammatory and myogenic function in the week subsequent to injury. The latter process stimulates myogenic precursor cells, resulting in their union and subsequent production of muscle fibers. These muscle fibers play a crucial role in the repair and regeneration of muscle tissue. The initial study conducted by Lo Sicco et al. provided the first description of the impact of MSC-EV on macrophage polarisation. The study demonstrated that MSC-EV treatment resulted in the conversion of bone marrow-derived macrophages from an M1 to an M2 phenotype in an in vitro setting. In the in vivo setting, it was shown that the expression levels of IL-6 and NOS2 were notably decreased, while the expression levels of Arg1 and Ym1 were dramatically increased in cardiotoxin-injured skeletal muscle that was treated with MSC-EV. These findings imply that EVs possess the capacity to modulate macrophages towards an anti-inflammatory and reparative phenotype [55]. In the recent study conducted by Luo et al., it was found that both bone mesenchymal stem cells-Exos (BMSC-Exos) and C2C12-Exos exhibited a significant ability to decrease the expression levels of proinflammatory factors such as iNOS, TNF-a, IL-1b, and IL-6 [41,56]. Furthermore, Zhou et al. discovered that the application of M2-Exos to the damaged pubococcygeus muscle resulted in a notable enhancement of muscle regeneration. Conversely, the impact of M1-Exos on myoblast differentiation was shown to be minimal [57].

1.5. Role of exosomes in skeletal muscle angiogenesis

Exosomes have demonstrated a significant capacity to transport miRNA, proteins, and other particles to cells exhibiting elevated angiogenic activity. This pivotal biological function positions exosomes as key players in the mechanism of circulation angiogenesis [58]. The study conducted by Nakamura et al. revealed that exosomes produced from MSCs exhibited a significant enhancement of angiogenesis both in vitro and in vivo. The researchers subjected human umbilical vein endothelial cells (HUVECs) to several treatments, including DMEM, MSC-conditioned medium, MSC-Exo suspension in DMEM, and exosome-free MSC-conditioned medium. Their findings demonstrated a considerable increase in the migratory capacity of HUVECs following treatment with either MSC or MSC-Exo. This phenomenon is accompanied by the creation of tubes of increased size. Following the intramuscular administration of MSC-Exos, a notable enhancement in capillary density was seen in the MSC-Exo group during in vivo experimentation [23]. Simultaneously, Lo Sicco et al. conducted a study wherein they implanted matrix glue plugs containing MSC-EVHypo and MSC-EVNormo in a mouse model of cardiotoxin-induced skeletal muscle damage. Both experimental groups stimulated the development of tubular endothelial structures around embolization and increased the production of angiogenic factors, such as platelet and endothelial cell adhesion molecule (PECAM) and vascular endothelial growth factor A (VEGFA). In contrast, the MSC-Evhypo group, which consisted of MSCs exposed to hypoxic settings, exhibited elevated expression of pro-angiogenic factors and demonstrated a greater degree of angiogenesis in the injured tibialis anterior muscle as compared to the MSC-Evnormo group, which was released under normoxic conditions [55]. In their study, Figliolini et al. employed genetic detection techniques to conduct a comprehensive investigation and examination of the constituents within adipose-derived stem cells-extracellular vesicles (ASC-EVs). Their findings revealed the presence of mRNA encoding angiogenin, VEGFA(vascular endothelial growth factor A), HGF (hepatocyte growth factor), IGF1 (insulin-like growth factor-1), and EGF (epidermal growth factor) within these extracellular vesicles [51]. Interestingly, the effects of administering EVs on angiogenesis have been found to vary in different studies. Contrary to the prevailing findings of numerous investigations, Wang et al. discovered that ASCs-Exos exhibited a partial reduction in angiogenesis [53]. Inconsistencies in the effects of exosomes on skeletal muscle angiogenesis may potentially arise from variations in exosome origins, vectors, and concentrations/dosages. Furthermore, the facilitation of angiogenesis in the process of muscle regeneration may encompass several pathways, and

forthcoming research endeavors should prioritize the exploration of distinct methods for generating variably secreted proteomes.

1.6. Exosomes in the treatment of skeletal muscle injury

Skeletal muscle injury is a prevalent condition characterized by the damage of skeletal muscle fibers resulting from mechanical strain incurred during physical exertion or genetic disorders leading to muscle fiber vulnerability. Luo et al. employed bone marrow stromal cell-derived exosomes to treat skeletal muscle contusion in mice and discovered that BMSC-Exos reduced muscle contusion and improved muscle recovery by modifying macrophage polarization and reducing inflammatory responses [56]. In a separate investigation, Luo et al. showcased the significance of intercellular communication between myoblasts and macrophages via exosomes containing miRNA molecules. This communication was found to play a crucial role in regulating macrophage polarization as well as myogenic differentiation and proliferation during the process of muscle injury repair. Furthermore, the researchers devised a novel approach involving the use of M2 polarization-activated anti-inflammatory agents and miRNA-engineered exosomes [40]. This strategy holds promise as a potential therapeutic intervention for the treatment of muscle injury. Yan et al. discovered that the miR-421/FOXO3a axis is directly modulated by circHIPK3, with exosomes derived from umbilical cord mesenchymal stem cells (UC-MSCs) crucially downregulating miR-421 *via* circHIPK3 release. This mechanism not only elevates FOXO3a expression but also curtails pyroptosis and the release of IL-1β and IL-18, effectively mitigating ischemic skeletal muscle injury [59]. Simultaneously, a substantial body of research has demonstrated that exosome treatment of satellite cells or injured muscles leads to a notable upregulation of genes associated with muscle regeneration, such as MYOG, MYOD, myogenin, and Pax7. Furthermore, this intervention has been observed to enhance muscular function in vivo [60–63].

1.7. Exosomes in the treatment of skeletal muscle sarcopenia

Sarcopenia, a prominent characteristic of the aging process, poses significant challenges for older individuals, manifesting in various daily life difficulties [64]. This condition elevates the susceptibility to falls and fractures, thereby exacerbating adverse clinical outcomes and socioeconomic ramifications [65]. Notably, diminished muscle strength stands out as the primary attribute associated with sarcopenia. The therapeutic potential of exosomes in the management of sarcopenia has been increasingly acknowledged. The process of myogenesis is intricately regulated by the human body, necessitating coordinated intercellular interactions, with exosomes playing a vital role. Exosomes released by skeletal muscles not only promote myoblast proliferation and muscle formation but also transmit crucial signaling molecules across muscle cells, underscoring their significance in the crosstalk between myocytes and myoblasts. Research led by Aswad et al. has shown that feeding mice a high-fat diet triggers their skeletal muscles to secrete exosomes, which subsequently stimulate myoblast proliferation and alter gene expression related to muscle cell cycle and differentiation in vitro [66]. Exosomes from other cell types, such as those from MSCs, enhance the proliferation and differentiation of C2C12 cells, while adipocyte-derived exosomal miR-27a induces insulin resistance in skeletal muscle cells [67]. Research on the application of exosomes in muscle disease treatment is still evolving. Research on the application of exosomes in muscle disease treatment is still evolving. Skeletal muscle cells are rich in various miRNAs, including miR-31 and miR-23a, believed to regulate satellite cell activation, promote muscle regeneration, and reduce muscle atrophy. These miRNAs, secreted via exosomes, demonstrate their potential application in muscle disease treatment. Therapeutically, exosomes produced by human skeletal myoblasts and MSCs have been found to accelerate muscle regeneration [23,49]. For instance, MSC-derived exosomes, partially mediated by miR-494, enhance the proliferation and differentiation of skeletal muscle C2C12 cells [23]. Another study revealed that exosome therapy facilitates human muscle cell development through the transfer of exosomal miR-29c, with placenta-derived MSCs releasing exosomes high in miR-29 expression [68]. These findings highlight the immense potential of exosomes as therapeutic agents in skeletal muscle sarcopenia.

1.8. Exosomes in the treatment of skeletal muscle atrophy

The intricate biochemical mechanism underlying skeletal muscle atrophy remains incompletely understood. The perpetual turnover of muscle proteins is attributed to the equilibrium between the processes of protein synthesis and breakdown inside the muscular tissue [69]. Various disorders are known to induce skeletal muscle atrophy, and this process is believed to be initiated by significant factors such as heightened oxidative stress, inflammation, and impaired mitochondrial activity [70]. Wang et al. discovered that the introduction of an exosome vector carrying Lamp2b, a gene encoding an exosomal membrane protein fused with a muscle-specific surface peptide for targeted delivery to muscle cells, into muscle satellite cells, followed by the transduction of these cells with an adenovirus expressing miR-26a, resulted in the generation of an exosomal vector. The production of exosomes containing miR-26a (Exo/miR-26a) has the potential to enhance the cross-sectional area of skeletal muscle in mice [71]. Exosomes originating from differentiated human skeletal myoblasts have a notable enrichment of various myogenic factors, including TNF, IGF, and FGF2. The exosomes can stimulate the process of myogenic differentiation in human adipose-derived stem cells, resulting in a rise in both the fusion index and the expression of myogenic genes such as ACTA1, MYOD1, and DAG1, among others [49]. Li et al. discovered that human BMSCs-derived exosomes might prevent dexamethasone-induced muscle atrophy by increasing miR-486-5p expression and inhibiting FoxO1 nuclear translocation [72]. In a separate investigation, the targeted inhibition of miR-690, a tiny extracellular vesicle originating from atrophic skeletal muscle fibers inside the muscular system, was found to enhance the process of satellite cell development and mitigate muscle atrophy in elderly mice [73]. Exosomes have also been demonstrated to prevent muscle atrophy, fatty degeneration, inflammation, and vascularization in cases of extensive or chronic rotator cuff tears [74,75]. In their research on a rat model with severe rotator cuff tears, Wang et al. observed that injecting ASC-derived exosomes into the supraspinatus muscle significantly mitigated muscle weight loss, fatty infiltration, inflammation, and vascularization while enhancing myofiber regeneration and biomechanical strength compared to saline treatment over 8 and 16 weeks [53]. In a chronic rabbit rotator cuff tear model, ASC-Exos, when locally injected into damaged supraspinatus muscles, were found to notably decrease fatty degeneration, enhance tendon-bone healing with increased fibrocartilage, collagen II, and tenascin-C, and yield a more uniform healing with less fibrosis, also improving biomechanical strength [76]. Exosomes derived from cells in distinct physiological conditions exhibit distinct compositions and fulfill distinct functions. Hence, the development of engineered cellular exosomes with the ability to transport signaling molecules enclosed in vesicles directly to muscle cells represents a potentially fruitful avenue. This innovative technique holds promise for addressing the challenge of muscle atrophy and could potentially emerge as a novel therapeutic strategy. The biological role of exosomes in skeletal muscle diseases is summarized in Table 1.

1.9. Future direction and perspective

Natural exosomes encounter certain challenges as molecular delivery systems for therapeutics [27]. The therapeutic potential of natural exosomes is constrained by the absence of pharmacological constituents. Experimental investigations on animals have elucidated the limited tissue and cellular targeting capabilities of natural exosomes, resulting in the non-selective transportation of cargo to recipient cells [77].

Table 1
The role of exosomes in skeletal muscle diseases.

Skeletal muscle diseases	Origin of exosomes	Roles	References
Skeletal muscle contusion	Bone mesenchymal stem cells (BMSCs)	Promoted muscle recovery in mice by altering macrophage polarization and reducing inflammatory responses	[56]
Ischemic skeletal muscle injury	Umbilical cord mesenchymal stem cells (UC-MSCs)	Releasing circHIPK3 significantly downregulates miR-421, increases FOXO3a expression, reduces pyroptosis, and decreases the release of IL-1β and IL-1	[59]
Skeletal muscle injury	PRP and mesenchymal stem cells (MSCs)	Enhance the recuperation process following a muscle strain injury in a small-animal experimental model	[60]
Skeletal muscle defect	Mesenchymal stem cells (MSCs)	Promote skeletal muscle regeneration	[61]
Skeletal muscle injury	Mesenchymal stem cells (MSCs)	Enhances muscle regeneration by boosting myogenesis and angiogenesis, partly mediated by miRNAs like miR-494	[23]
Duchenne muscular dystrophy (DMD)	Mesenchymal stem cells (MSCs)	Cell therapy for DMD achieved through the targeted delivery of exosomal miR-29c	[68]
Skeletal muscle injury	Human skeletal myoblasts(HSkM)	Significant improvement in skeletal muscle regeneration	[49]
Muscle Atrophy	Bone mesenchymal stem cells(BMSCs)	Prevent dexamethasone-induced muscle atrophy by increasing miR-486-5p expression and inhibiting FoxO1 nuclear translocation	[72]
Muscle Atrophy	Atrophic muscle fibre	Atrophic muscle fiber-derived sEV miR-690 inhibits satellite cell differentiation by targeting myocyte enhancer factor 2	[73]
Muscle Degeneration Associated With Torn Rotator Cuffs	Adipose-derived stem cells (ASCs)	Decrease atrophy and degeneration, and improve muscle regeneration and biomechanical properties in torn rotator cuff muscles.	[53]
Muscle Degeneration Associated With Torn Rotator Cuffs	Adipose-derived stem cells (ASCs)	Promote the progress of fatty infiltration, enhance tendon-bone healing, and improve biomechanical properties.	[76]

However, the inherent modifiability of exosomes presents an auspicious opportunity to bolster their targeting precision, safety profile, and therapeutic efficacy, and enable loading of more potent functional molecules, aligning with the exigencies of clinical applications [78].

Currently, exosome engineering strategies can be classified into two distinct categories based on the temporal aspect of modification: “cell engineering” and “exosome engineering” [79]. The former entails genetic engineering of parent cells or co-incubation techniques to facilitate the transfection of nucleotides or protein importation into exosomes. Conversely, the latter focuses on direct post-secretion modification of exosomes and can be further subdivided into exosome membrane remodeling and content loading [80]. Outer membrane modification aims to augment exosome targeting precision, mitigate clearance rates, enhance concentration at the disease site, and maximize therapeutic efficacy while minimizing cytotoxicity and untoward reactions. Content loading facilitates the selective loading of specific nucleic acids, proteins, small molecule drugs, and other agents [81]. For instance, Zhang et al. employed extrusion and incubation methodologies to process neutrophil exosomes, culminating in the construction of engineered exosomes adorned with superparamagnetic iron oxide nanoparticles and adeptly loaded with chemotherapeutic drugs [82]. By capitalizing on the influence of an externally applied magnetic field, these engineered exosomes were adeptly guided and enriched at tumor sites, thereby exerting a dual effect on tumor treatment—effectively eradicating tumor growth, and significantly prolonging the survival of tumor-bearing mice. Furthermore, the development of biocompatible scaffolds, rife with exosome cargo, presents an appealing prospect for exosome carriers, facilitating targeted and batched delivery, sustained and regulated release, and augmenting therapeutic effects [82]. In an independent study, three distinctive loading methodologies—namely, incubation, sonication, and electroporation—were evaluated, with the findings attesting to the superior efficacy of sonication [83].

The engineering strategies employed for exosomes, together with the development of exosome carriers, by incorporating salient factors such as low immunogenicity, nanoparticles, targeted drug delivery, and drug delivery systems, serve to ameliorate exosome half-life and enable targeted enrichment. Such transformative advancements hold paramount importance for biomedical research and the clinical translation of exosome-based therapies.

2. Conclusion

Exosomes, small extracellular vesicles containing various bioactive molecules, have emerged as a promising avenue for the treatment of skeletal muscle-related disorders. Their remarkable potential lies in their ability to facilitate muscle repair and regeneration through the promotion of myofiber development, stimulation of satellite cell differentiation, and upregulation of key myogenesis genes. Moreover, exosomes have demonstrated their capacity to mitigate apoptosis in myoblasts, myocytes, and endothelial cells, thereby offering significant advancements in the regenerative process.

Nevertheless, the transition of exosome-based therapies from laboratory research to practical clinical applications presents a landscape riddled with formidable obstacles, particularly in the realm of treating skeletal muscle diseases. A central hurdle is the absence of uniform, reproducible methods for the extraction, purification, and detailed analysis of exosomes. Establishing stringent, consistent protocols and maintaining strict quality control are imperative to harness the full therapeutic capabilities of exosomes. Moreover, the complex cellular mechanisms through which exosomes contribute to muscle tissue repair are yet to be fully elucidated. There is a pressing need for comprehensive research to untangle the sophisticated network of interactions and signaling processes that are central to the regenerative efficacy of exosomes. Such investigative efforts are crucial to address the concerns regarding the effectiveness and safety of these therapies, ultimately paving the way for the development of dependable and potent strategies for exosome-based treatments.

The potential of exosomes in the treatment of skeletal muscle diseases is noteworthy, and their practical application in clinical settings warrants explicit discussion. Exosomes are emerging as significant agents in regenerative medicine, primarily due to their ability to efficiently transport an array of therapeutic molecules like miRNAs, growth factors, and cytokines directly to the targeted cells. In a clinical context, this could translate to more precise and effective treatments for muscle-related diseases, as exosomes can be engineered to carry specific therapeutic agents to the affected muscle tissues. Their minimal immune

response and ability to bypass biological barriers further enhance their suitability for clinical applications. For instance, these properties facilitate the systemic administration of exosomes, potentially enabling them to reach and repair damaged muscle tissues more effectively. Therefore, these unique characteristics of exosomes not only underscore their importance in advancing regenerative medicine but also highlight their practicality in developing innovative and targeted therapies for skeletal muscle regeneration in real-world clinical scenarios.

To conclude, exosomes present an alluring avenue for addressing skeletal muscle-related disorders and offer significant promise in the realm of regenerative medicine research. Future investigations should focus on optimizing exosome production and characterization methodologies, as well as unraveling the complex mechanisms underlying their regenerative effects. With continued progress, exosome-based therapies have the potential to revolutionize the field and instill renewed hope in individuals suffering from skeletal muscle disorders.

Author contributions

YW, SC and XS contributed to the conception and design of the study. SL and RW designed and wrote the whole manuscript. XF, HZ and WL completed subsequent revisions of the manuscript. RW, SL, XF and WL collected the references and prepared figures of the manuscript. All authors contributed to manuscript revision, and approved the final version of manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (Grant No. 82172511,81972125, and 82172510).

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

[1] Grgic J, Schoenfeld BJ, Mikulic P. Effects of plyometric vs. resistance training on skeletal muscle hypertrophy: a review. J Sport Health Sci 2021;10(5):530–6.
[2] Yamakawa H, Kusumoto D, Hashimoto H, Yuasa S. Stem cell aging in skeletal muscle regeneration and disease. Int J Mol Sci 2020;21(5).
[3] Greggio C, Jha P, Kulkarni SS, Lagarrigue S, Broskey NT, Boutant M, et al. Enhanced Respiratory chain supercomplex formation in response to exercise in human skeletal muscle. Cell Metabol 2017;25(2):301–11.
[4] Nie M, Deng Z-L, Liu J, Wang D-Z. Noncoding RNAs, emerging regulators of skeletal muscle development and diseases. BioMed Res Int 2015;2015:1–17.
[5] Demonbreun AR, McNally EM. Muscle cell communication in development and repair. Curr Opin Pharmacol 2017;34:7–14.
[6] Belasso CJ, Behboodi B, Benali H, Boily M, Rivaz H, Fortin M. LUMINOUS database: lumbar multifidus muscle segmentation from ultrasound images. BMC Muscoskel Disord 2020;21(1):703.
[7] Hildebrandt M, Fankhauser G, Meichtry A, Luomajoki H. Correlation between lumbar dysfunction and fat infiltration in lumbar multifidus muscles in patients with low back pain. BMC Muscoskel Disord 2017;18(1):12.
[8] Qiu J, Fang Q, Xu T, Wu C, Xu L, Wang L, et al. Mechanistic role of reactive oxygen species and therapeutic potential of antioxidants in denervation- or fasting-induced skeletal muscle atrophy. Front Physiol 2018;9:215.
[9] Shen Y, Li M, Wang K, Qi G, Liu H, Wang W, et al. Diabetic muscular atrophy: molecular mechanisms and promising therapies. Front Endocrinol 2022;13:917113.
[10] Nascimento CM, Ingles M, Salvador-Pascual A, Cominetti MR, Gomez-Cabrera MC, Vina J. Sarcopenia, frailty and their prevention by exercise. Free Radic Biol Med 2019;132:42–9.
[11] Wang W, Shen D, Zhang L, Ji Y, Xu L, Chen Z, et al. SKP-SC-EVs mitigate denervated muscle atrophy by inhibiting oxidative stress and inflammation and improving microcirculation. Antioxidants 2021;11(1).
[12] Jarvinen TA, Jarvinen TL, Kaariainen M, Kalimo H, Jarvinen M. Muscle injuries: biology and treatment. Am J Sports Med 2005;33(5):745–64.
[13] Yin L, Li N, Jia W, Wang N, Liang M, Yang X, et al. Skeletal muscle atrophy: from mechanisms to treatments. Pharmacol Res 2021;172:105807.
[14] Gilbert-Honick J, Grayson W. Vascularized and innervated skeletal muscle tissue engineering. Adv Healthcare Mater 2020;9(1):e1900626.
[15] Furrer R, Handschin C. Muscle wasting diseases: novel targets and treatments. Annu Rev Pharmacol Toxicol 2019;59:315–39.
[16] Page MJ, Green S, McBain B, Surace SJ, Deitch J, Lyttle N, et al. Manual therapy and exercise for rotator cuff disease. Cochrane Database Syst Rev 2016;2016(6):CD012224.
[17] Widmann M, Niess AM, Munz B. Physical exercise and epigenetic modifications in skeletal muscle. Sports Med 2019;49(4):509–23.
[18] Fyfe JJ, Hamilton DL, Daly RM. Minimal-dose resistance training for improving muscle mass, strength, and function: a narrative review of current evidence and practical considerations. Sports Med 2022;52(3):463–79.
[19] Srivastava S, Rathor R, Singh SN, Suryakumar G. Emerging role of MyomiRs as biomarkers and therapeutic targets in skeletal muscle diseases. Am J Physiol Cell Physiol 2021;321(5):C859–75.
[20] Feige P, Brun CE, Ritso M, Rudnicki MA. Orienting muscle stem cells for regeneration in homeostasis, aging, and disease. Cell Stem Cell 2018;23(5):653–64.
[21] Pegtel DM, Gould SJ. Exosomes. Annu Rev Biochem 2019;88:487–514.
[22] Whiteside TL. Stimulatory role of exosomes in the context of therapeutic anticancer vaccines. Biota 2017;1.
[23] Nakamura Y, Miyaki S, Ishitobi H, Matsuyama S, Nakasa T, Kamei N, et al. Mesenchymal-stem-cell-derived exosomes accelerate skeletal muscle regeneration. FEBS Lett 2015;589(11):1257–65.
[24] Doyle LM, Wang MZ. Overview of extracellular vesicles, their origin, composition, purpose, and methods for exosome isolation and analysis. Cells 2019;8(7).
[25] Pant S, Hilton H, Burczynski ME. The multifaceted exosome: biogenesis, role in normal and aberrant cellular function, and frontiers for pharmacological and biomarker opportunities. Biochem Pharmacol 2012;83(11):1484–94.
[26] Pan BT, Johnstone RM. Fate of the transferrin receptor during maturation of sheep reticulocytes in vitro: selective externalization of the receptor. Cell 1983;33(3):967–78.
[27] Feng X, Peng Z, Yuan L, Jin M, Hu H, Peng X, et al. Research progress of exosomes in pathogenesis, diagnosis, and treatment of ocular diseases. Front Bioeng Biotechnol 2023;11:1100310.
[28] Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol 2013;200(4):373–83.
[29] Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science 2020;367(6478).
[30] Skotland T, Hessvik NP, Sandvig K, Llorente A. Exosomal lipid composition and the role of ether lipids and phosphoinositides in exosome biology. J Lipid Res 2019;60(1):9–18.
[31] Thery C, Zitvogel L, Amigorena S. Exosomes: composition, biogenesis and function. Nat Rev Immunol 2002;2(8):569–79.
[32] van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. Nat Rev Mol Cell Biol 2018;19(4):213–28.
[33] Kalluri R. The biology and function of exosomes in cancer. J Clin Invest 2016;126(4):1208–15.
[34] Colombo M, Moita C, van Niel G, Kowal J, Vigneron J, Benaroch P, et al. Analysis of ESCRT functions in exosome biogenesis, composition and secretion highlights the heterogeneity of extracellular vesicles. J Cell Sci 2013;126(Pt 24):5553–65.
[35] Gurung S, Perocheau D, Touramanidou L, Baruteau J. The exosome journey: from biogenesis to uptake and intracellular signalling. Cell Commun Signal 2021;19(1):47.
[36] Mashouri L, Yousefi H, Aref AR, Ahadi AM, Molaei F, Alahari SK. Exosomes: composition, biogenesis, and mechanisms in cancer metastasis and drug resistance. Mol Cancer 2019;18(1):75.
[37] Minciacchi VR, Freeman MR, Di Vizio D. Extracellular vesicles in cancer: exosomes, microvesicles and the emerging role of large oncosomes. Semin Cell Dev Biol 2015;40:41–51.
[38] Wei H, Chen Q, Lin L, Sha C, Li T, Liu Y, et al. Regulation of exosome production and cargo sorting. Int J Biol Sci 2021;17(1):163–77.
[39] Noonin C, Thongboonkerd V. Exosome-inflammasome crosstalk and their roles in inflammatory responses. Theranostics 2021;11(9):4436–51.
[40] Luo Z, Qi B, Sun Y, Chen Y, Lin J, Qin H, et al. Engineering bioactive M2 macrophage-polarized, anti-inflammatory, miRNA-based liposomes for functional muscle repair: from exosomal mechanisms to biomaterials. Small 2022;18(34):e2201957.
[41] Luo ZW, Sun YY, Lin JR, Qi BJ, Chen JW. Exosomes derived from inflammatory myoblasts promote M1 polarization and break the balance of myoblast proliferation/differentiation. World J Stem Cell 2021;13(11):1762–82.
[42] Luo Z, Sun Y, Qi B, Lin J, Chen Y, Xu Y, et al. Human bone marrow mesenchymal stem cell-derived extracellular vesicles inhibit shoulder stiffness via let-7a/Tgfbr1 axis. Bioact Mater 2022;17:344–59.
[43] Chen W, Sun Y, Gu X, Cai J, Liu X, Zhang X, et al. Conditioned medium of human bone marrow-derived stem cells promotes tendon-bone healing of the rotator cuff in a rat model. Biomaterials 2021;271:120714.
[44] Bakhtyar N, Jeschke MG, Mainville L, Herer E, Amini-Nik S. Acellular gelatinous material of human umbilical cord enhances wound healing: a candidate remedy for deficient wound healing. Front Physiol 2017;8:200.
[45] Wu X, Wang Y, Xiao Y, Crawford R, Mao X, Prasadam I. Extracellular vesicles: potential role in osteoarthritis regenerative medicine. J Orthop Translat 2020;21:73–80.
[46] Hassanpour M, Rezabakhsh A, Rezaie J, Nouri M, Rahbarghazi R. Exosomal cargos modulate autophagy in recipient cells via different signaling pathways. Cell Biosci 2020;10:92.
[47] Charge SB, Rudnicki MA. Cellular and molecular regulation of muscle regeneration. Physiol Rev 2004;84(1):209–38.

[48] Anderson JE. Key concepts in muscle regeneration: muscle "cellular ecology" integrates a gestalt of cellular cross-talk, motility, and activity to remodel structure and restore function. Eur J Appl Physiol 2022;122(2):273–300.
[49] Choi JS, Yoon HI, Lee KS, Choi YC, Yang SH, Kim IS, et al. Exosomes from differentiating human skeletal muscle cells trigger myogenesis of stem cells and provide biochemical cues for skeletal muscle regeneration. J Contr Release 2016; 222:107–15.
[50] Forterre A, Jalabert A, Chikh K, Pesenti S, Euthine V, Granjon A, et al. Myotube-derived exosomal miRNAs downregulate Sirtuin1 in myoblasts during muscle cell differentiation. Cell Cycle 2014;13(1):78–89.
[51] Figliolini F, Ranghino A, Grange C, Cedrino M, Tapparo M, Cavallari C, et al. Extracellular vesicles from adipose stem cells prevent muscle damage and inflammation in a mouse model of hind limb ischemia: role of neuregulin-1. Arterioscler Thromb Vasc Biol 2020;40(1):239–54.
[52] Zhang X, Jiang Y, Huang Q, Wu Z, Pu H, Xu Z, et al. Exosomes derived from adipose-derived stem cells overexpressing glyoxalase-1 protect endothelial cells and enhance angiogenesis in type 2 diabetic mice with limb ischemia. Stem Cell Res Ther 2021;12(1):403.
[53] Wang C, Song W, Chen B, Liu X, He Y. Exosomes isolated from adipose-derived stem cells: a new cell-free approach to prevent the muscle degeneration associated with torn rotator cuffs. Am J Sports Med 2019;47(13):3247–55.
[54] Cavallari C, Ranghino A, Tapparo M, Cedrino M, Figliolini F, Grange C, et al. Serum-derived extracellular vesicles (EVs) impact on vascular remodeling and prevent muscle damage in acute hind limb ischemia. Sci Rep 2017;7(1):8180.
[55] Lo Sicco C, Reverberi D, Balbi C, Ulivi V, Principi E, Pascucci L, et al. Mesenchymal stem cell-derived extracellular vesicles as mediators of anti-inflammatory effects: endorsement of macrophage polarization. Stem Cells Transl Med 2017;6(3): 1018–28.
[56] Luo Z, Lin J, Sun Y, Wang C, Chen J. Bone marrow stromal cell-derived exosomes promote muscle healing following contusion through macrophage polarization. Stem Cell Dev 2021;30(3):135–48.
[57] Zhou M, Li B, Liu C, Hu M, Tang J, Min J, et al. M2 Macrophage-derived exosomal miR-501 contributes to pubococcygeal muscle regeneration. Int Immunopharm 2021;101(Pt B):108223.
[58] Floriano JF, Emanueli C, Vega S, Barbosa AMP, Oliveira RG, Floriano EAF, et al. Pro-angiogenic approach for skeletal muscle regeneration. Biochim Biophys Acta Gen Subj 2022;1866(2):130059.
[59] Yan B, Zhang Y, Liang C, Liu B, Ding F, Wang Y, et al. Stem cell-derived exosomes prevent pyroptosis and repair ischemic muscle injury through a novel exosome/circHIPK3/FOXO3a pathway. Theranostics 2020;10(15):6728–42.
[60] Iyer SR, Scheiber AL, Yarowsky P, Henn 3rd RF, Otsuru S, Lovering RM. Exosomes isolated from platelet-rich plasma and mesenchymal stem cells promote recovery of function after muscle injury. Am J Sports Med 2020;48(9):2277–86.
[61] Byun SE, Sim C, Chung Y, Kim HK, Park S, Kim DK, et al. Skeletal muscle regeneration by the exosomes of adipose tissue-derived mesenchymal stem cells. Curr Issues Mol Biol 2021;43(3):1473–88.
[62] Aswad H, Jalabert A, Rome S. Depleting extracellular vesicles from fetal bovine serum alters proliferation and differentiation of skeletal muscle cells in vitro. BMC Biotechnol 2016;16:32.
[63] Forterre A, Jalabert A, Berger E, Baudet M, Chikh K, Errazuriz E, et al. Proteomic analysis of C2C12 myoblast and myotube exosome-like vesicles: a new paradigm for myoblast-myotube cross talk? PLoS One 2014;9(1):e84153.
[64] Deutz NEP, Thaden JJ, Ten Have GAM, Walker DK, Engelen M. Metabolic phenotyping using kinetic measurements in young and older healthy adults. Metabolism 2018;78:167–78.
[65] Cesari M, Fielding RA, Pahor M, Goodpaster B, Hellerstein M, van Kan GA, et al. Biomarkers of sarcopenia in clinical trials-recommendations from the international working group on sarcopenia. J Cachexia Sarcopenia Muscle 2012;3(3):181–90.
[66] Aswad H, Forterre A, Wiklander OP, Vial G, Danty-Berger E, Jalabert A, et al. Exosomes participate in the alteration of muscle homeostasis during lipid-induced insulin resistance in mice. Diabetologia 2014;57(10):2155–64.
[67] Yue B, Yang H, Wang J, Ru W, Wu J, Huang Y, et al. Exosome biogenesis, secretion and function of exosomal miRNAs in skeletal muscle myogenesis. Cell Prolif 2020; 53(7):e12857.
[68] Bier A, Berenstein P, Kronfeld N, Morgoulis D, Ziv-Av A, Goldstein H, et al. Placenta-derived mesenchymal stromal cells and their exosomes exert therapeutic effects in Duchenne muscular dystrophy. Biomaterials 2018;174:67–78.
[69] Choi DH, Yang J, Kim YS. Rapamycin suppresses postnatal muscle hypertrophy induced by myostatin-inhibition accompanied by transcriptional suppression of the Akt/mTOR pathway. Biochem Biophys Rep 2019;17:182–90.
[70] Sun H, Sun J, Li M, Qian L, Zhang L, Huang Z, et al. Transcriptome analysis of immune receptor activation and energy metabolism reduction as the underlying mechanisms in interleukin-6-induced skeletal muscle atrophy. Front Immunol 2021;12:730070.
[71] Wang W, Li M, Chen Z, Xu L, Chang M, Wang K, et al. Biogenesis and function of extracellular vesicles in pathophysiological processes of skeletal muscle atrophy. Biochem Pharmacol 2022;198:114954.
[72] Li Z, Liu C, Li S, Li T, Li Y, Wang N, et al. BMSC-derived exosomes inhibit dexamethasone-induced muscle atrophy via the miR-486-5p/FoxO1 Axis. Front Endocrinol 2021;12:681267.
[73] Shao X, Gong W, Wang Q, Wang P, Shi T, Mahmut A, et al. Atrophic skeletal muscle fibre-derived small extracellular vesicle miR-690 inhibits satellite cell differentiation during ageing. J Cachexia Sarcopenia Muscle 2022;13(6):3163–80.
[74] Zhang X, Wang D, Wang Z, Ling SK, Yung PS, Tuan RS, et al. Clinical perspectives for repairing rotator cuff injuries with multi-tissue regenerative approaches. J Orthop Translat 2022;36:91–108.
[75] Sheng R, Cao M, Song M, Wang M, Zhang Y, Shi L, et al. Muscle-bone crosstalk via endocrine signals and potential targets for osteosarcopenia-related fracture. J Orthop Translat 2023;43:36–46.
[76] Wang C, Hu Q, Song W, Yu W, He Y. Adipose stem cell-derived exosomes decrease fatty infiltration and enhance rotator cuff healing in a rabbit model of chronic tears. Am J Sports Med 2020;48(6):1456–64.
[77] Tian T, Zhang HX, He CP, Fan S, Zhu YL, Qi C, et al. Surface functionalized exosomes as targeted drug delivery vehicles for cerebral ischemia therapy. Biomaterials 2018;150:137–49.
[78] Zhang H, Liu J, Qu D, Wang L, Wong CM, Lau CW, et al. Serum exosomes mediate delivery of arginase 1 as a novel mechanism for endothelial dysfunction in diabetes. Proc Natl Acad Sci U S A 2018;115(29):E6927–36.
[79] Lu M, Xing H, Xun Z, Yang T, Zhao X, Cai C, et al. Functionalized extracellular vesicles as advanced therapeutic nanodelivery systems. Eur J Pharmaceut Sci 2018; 121:34–46.
[80] Xu W, Wu Y, Hu Z, Sun L, Dou G, Zhang Z, et al. Exosomes from microglia attenuate photoreceptor injury and neovascularization in an animal model of retinopathy of prematurity. Mol Ther Nucleic Acids 2019;16:778–90.
[81] Liang Y, Duan L, Lu J, Xia J. Engineering exosomes for targeted drug delivery. Theranostics 2021;11(7):3183–95.
[82] Zhang J, Ji C, Zhang H, Shi H, Mao F, Qian H, et al. Engineered neutrophil-derived exosome-like vesicles for targeted cancer therapy. Sci Adv 2022;8(2):eabj8207.
[83] Kim MS, Haney MJ, Zhao Y, Mahajan V, Deygen I, Klyachko NL, et al. Development of exosome-encapsulated paclitaxel to overcome MDR in cancer cells. Nanomedicine 2016;12(3):655–64.