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Therapeutic Mechanisms of Mesenchymal Stem Cells (MSCs) and Their Exosomes in Skeletal Muscle Disorders

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Abstract. Skeletal muscle is crucial for daily activities, but various external risk factors can impair its normal physiological function, including aging, injury, and autoimmune disorders. Therefore, there is an urgent need for effective treatment interventions. MSC and mesenchymal stem cell-derived exosomes have great potential in the treatment of skeletal muscle-related diseases. This paper summarizes the therapeutic effects and potential mechanisms of MSCs and MSC exosomes in skeletal muscle-related diseases, including age-related sarcopenia (AAS), myasthenia gravis (MG), and rotator cuff injury (RCI). This paper mainly compares the efficacy and mechanism of MSCs and MSC exons in the treatment of skeletal muscle dysfunction, and explores the optimized pathways of MSC exons and MSCs in the treatment of sarcopenia. This study suggests that MSCs and MSC Exos exert therapeutic effects through multiple pathways, including anti-inflammatory, mitochondrial function enhancement, and apoptosis inhibition. This paper suggests that future research should explore drug treatment strategies that combine HUC MSCs and MSC Exos. The purpose is to explore the possible theoretical basis for the future application of MSCs and MSC Exos in the clinical treatment of skeletal muscle-related diseases, especially in the progression of sarcopenia, and to guide future related research to adjust treatment plans to adapt to patient progression and protect patients from the troubles caused by chronic diseases.

Keywords: skeletal muscle, exosomes, mesenchymal stem cells.

1. Introduction

Skeletal muscle is the core tissue that maintains the body's motor function, metabolic balance and energy homeostasis. Maintaining its normal physiological functions is vulnerable to exogenous adverse factors such as aging, accidental injury, and autoimmune disorders, which can lead to age-related sarcopenia (AAS), myasthenia gravis (MG), rotator cuff injury (RCI) and other diseases. The number of elderly people suffering from muscle atrophy worldwide is constantly increasing. Moreover, muscle atrophy is closely related to adverse outcomes such as falls, fractures, increased mortality rate, decline in cognitive ability, and complications after surgery, which has brought a huge economic burden to individuals and affected the further development of the country and society. And currently, there are no effective drugs available for preventing muscle atrophy or reversing its progression [1].

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Domestic and foreign scholars have conducted a large number of studies on the application of MSCs in skeletal muscle diseases, confirming that Human umbilical cord mesenchymal stromal cells (HUC-MSCs) have emerged as a promising therapeutic approach, thanks to their strong paracrine action, immunomodulatory properties, and ability to repair extracellular matrix (ECM) [1]. However, despite the therapies based on MSCs being beneficial, their shortcomings cannot be ignored, such as low grafting efficiency and low cell survival rate after transplantation. Moreover, there are still challenges in terms of standardization, long-term safety, and the potential carcinogenic risks associated with MSC treatment. Some studies have found that compared with the MSC itself, MSC-Exos offer significant advantages by effectively reducing adverse reactions [2]. Exosomes, which can transport proteins and lipids to the receptor cells, are of great importance in curing skeletal muscle diseases. However, there are a variety of challenges in marking the heterogeneity of MSC-Exos and purifying them [3].

Based on the current research status of MSCs and MSC-exosomes and the role they play in the health of skeletal muscles, using either of them as a separate therapeutic agent for the illness holds its own insurmountable limitations. Moreover, the existing studies lack comprehensive comparisons of the therapeutic mechanisms of the two, as well as discussions on their complementary advantages and combined application strategies. Therefore, the research motivation of this article is to systematically review the therapeutic effects and molecular mechanisms of MSCs and MSC-Exos in skeletal muscle-related diseases, compare their therapeutic effects and limitations, and seek more appropriate treatment options.

This paper summarizes the roles and mechanisms of MSCs and MSC-Exos in skeletal muscle diseases. The key comparison was made between the therapeutic mechanisms of MSCs and MSC-Exos in the treatment of muscular dystrophy, as well as the respective limitations of the two, aiming to find the optimal solution for treating skeletal muscle disorders. The use of the MSC therapy and MSC-Exos therapy alone has obvious limitations. This paper combine strategy of MSCs and MSC-Exos in musculoskeletal disorders, especially AAS, in order to enhance the therapeutic effect while reducing the treatment risk. This approach provides new ideas for safer treatment of senile muscle atrophy in the future.

2. Mechanisms of HUC-MSCs in age-related sarcopenia (AAS)

Featured by the degenerative reduction in muscle size and strength, AAS is a progressive systemic skeletal muscle disease that arises from the accelerated functional deterioration associated with aging [4]. The mechanisms by which HUC-MSCs treat sarcopenia are numerous, including anti-inflammatory effects, enhancing mitochondrial function, inhibiting protein degradation, activating muscle stem cells (MuSCs), restoring the ratio of fast and slow muscle fibers, promoting autophagy, reducing apoptosis, and repairing the ECM [1].

Specifically, the chronic inflammation caused by aging is a significant factor contributing to the occurrence of AAS, and HUC-MSCs reduce critical inflammatory factors (TNF-α, IL-6, IFN-γ) in SAMP10 mice, which are senescence-accelerated, thereby alleviating systemic and local inflammation responses, protecting muscle cells and improving age-related muscle function decline [1]. Meanwhile, the contraction of skeletal muscles mainly requires ATP provided by mitochondria. HUC-MSCs can activate the AMPK/Sirt1/PGC-1α signaling axis via tail-vein injection, increase the expression levels of related proteins such as PGC-1α and COX-IV, improve mitochondrial damage caused by aging and restore normal mitochondrial structure and function in vivo [1].

The muscle repair ability of the elderly declines mainly due to the reduction in the number of MuSC and functional exhaustion. HUC-MSCs intervention can effectively restore the number of

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MuSC, maintain the stability of the MuSC pool, and promote their proliferation and differentiation and help the muscle fibers to be repaired again [4]. Additionally, one characteristic of AAS is the reduction in the total amount of muscle fibers and fast muscle fibers being more prone to atrophy. This change directly leads to a decline in muscle strength and exercise tolerance. HUC-MSCs treatment regulates the ratio of fast and slow muscle fibers and significantly boosts skeletal muscle mass and enhances muscle contraction ability [4].

As people age, the function of cellular autophagy declines and damaged proteins and abnormal mitochondria accumulate continuously, accelerating the aging of muscle cells.; however, HUC-MSCs can enhance cellular autophagy, inhibit the aging-related pathways, slow the aging of muscle cells and provide sufficient energy for MuSC activation to promote muscle regeneration [4]. In muscle atrophy models, HUC-MSCs also exert a consistent inhibitory effect on cell apoptosis. The relevant detection results show that after treatment, the proportion of cell apoptosis has significantly decreased [1].

In terms of ECM integrity, aging-induced ECM remodeling weakens the stability of muscle fiber membranes and damages cell adhesion, but HUC-MSCs upregulate key ECM structural proteins' expression in AAS mice, preserving myocyte adhesion, optimizing the microenvironment of muscle and enhancing the toughness of muscle [1,4]. The in vivo experiments further confirm that clinical-grade HUC-MSCs stimulate the muscle strength of SAMP8 and D-galactose-induced aging mice and restore the morphological structure of skeletal muscles, with core sarcopenia functional metrics (grip strength and anti-fatigue tests) verifying significantly enhanced motor function compared with the PBS control group [4].

3. Therapeutic mechanisms of MSCs in myasthenia gravis (MG)

MSCs have strong immunomodulatory properties, which make them a promising treatment for autoimmune disorders, including MG [5]. Early experiments prove that in experimental autoimmune myasthenia gravis (EAMG) animal models, the transplantation of MSC improves the efficiency of neuromuscular junction (NMJ) signaling, and it also reduces the antibody titers of acetylcholine receptor (AChR) which is abnormally elevated and restores the homeostasis of immune cell subsets, laying a solid theoretical foundation for the clinical translational research on the treatment of MG with MSC therapy [5]. MG is an autoimmune disease whose onset is closely related to abnormal spleen function, and allogeneic MSC transplantation has dual therapeutic effects on skeletal muscle weakness caused by MG. MSCs can inhibit excessive pathological immune responses and reduce the damage to muscle fibers which is caused by the immune reaction. At the same time, they can also activate the body's own satellite cells, helping muscle fibers complete repair and regeneration. MSCs possess dual characteristics of inhibiting inflammation and promoting muscle tissue regeneration, which is a crucial feature. This is because by relying on dual effect, they can alleviate muscle weakness symptoms of patients with MG and slow down the further progression of the disease [5]. The obstruction of signal transmission at the NMJ is MG's core pathological characteristic. MSCs can secrete ciliary neurotrophic factor (CNTF) and brain-derived neurotrophic factor (BDNF), thereby exerting neuroprotective effects. Among these two factors, CNTF can maintain the survival status of motor neurons and promote the regeneration of nerve axons, and BDNF can regulate the function of synapses, making the signal transmission at the NMJ smoother [5]. The main cause of MG is that the human immune system attacks AChR at the NMJ. Researchers hypothesize that MSCs may promote the synthesis and enhance the release of ACh. At the same time, it can also competitively inhibit the pathogenic effects of acetylcholine receptor antibodies in

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the blood, thereby alleviating the clinical symptoms of MG. However, rigorous in vitro and in vivo experimental validation is required to support this potential mechanism [5].

4. Therapeutic mechanisms of MSCs in rotator cuff injury (RCI)

The reparative mechanisms of MSCs in RCI are multifaceted and systematic, involving both direct cellular differentiation and indirect paracrine regulatory effects [6]. In vitro and in vivo research have consistently confirmed that MSCs migrate to RCI sites and can also integrate into, and further differentiate into tenocytes, chondrocytes, and osteoblasts under the induction of the local injury microenvironment, directly resulting in the reconstruction of the normal architecture of tendon-bone tissue and the restoration of normal biomechanical properties of the rotator cuff [6]. Meanwhile, MSCs secrete various bioactive paracrine factors, including IGF-1, TGF-β, VEGF, and anti-inflammatory cytokines, which modulate the native injury microenvironment by way of promoting reparative cells' proliferation, inhibiting excessive inflammation after injury, and enhancing the synthesis and remodeling of ECM [6]. In addition, MSCs secrete angiogenic factors, including VEGF, at the injury site in order to facilitate neovascularization, and enhancing vascularization is critical for delivering nutrients and removing waste, which can satisfy the high metabolic needs of regenerative tissues and effectively accelerate tendon-bone healing [6]. Furthermore, MSCs release factors such as chemotactic and immunomodulatory to activate and recruit endogenous tissue progenitor cells, expand the bank of reparative cells that stay at the RCI site to amplify the internal regenerative response of the organization, and ultimately accelerate the repair and functional recovery of damaged rotator cuff tissue [6].

5. The therapeutic effects and mechanisms ofMSC-Exos on skeletal muscle disease

Previous studies have detected that HUC-MSC-Exos are indispensable for combating human skeletal muscle atrophy through anti-inflammatory, mitochondrial-enhancing, proteolysis-suppressing, autophagy-promoting and anti-apoptotic pathways [1]. For inflammatory inhibition, both hUC-MSCs and MSC-Exos effectively alleviate inflammation, which is induced by DEX in vivo and in vitro, as DEX significantly upregulates inflammatory cytokine secretion, while co-culture with HUC-MSCs/MSC-Exos markedly suppresses the release of these inflammatory mediators [7]. Regarding mitochondrial function and oxidative stress improvement, researchers inject HUC-MSC-Exos into the tail-vein of SAMP10 mice, results indicate that this way increases the protein expression of Sirt1 and PGC-1α in skeletal muscles of the laboratory mice, relieves the damage to aging-induced mitochondrial cristae, prevents the accumulation of lipid droplet and mitigates the injury of mitochondrial in the muscle; these studies collectively verify that HUC-MSC-Exos significantly enhance signaling pathways which are related to mitochondrial biogenesis in vivo [1,8]. HUC-MSC-Exos also inhibit abnormal skeletal muscle protein degradation by targeting the FOXO3 signaling axis, mainly through the pathway, which is miR-132-3p-mediated: miR-132-3p was transmitted by exosomes to target myocytes, downregulate FOXO3 expression, suppress the degradation of pathological protein, which is ubiquitin–proteasome-mediated, and promote the regeneration of myotube to alleviate muscle atrophy [1]. For the regulation of autophagy and apoptosis in the skeletal muscle atrophy, which is induced by DEX, disrupted autophagy flux and excessive apoptosis are core pathophysiological features, and MSC-Exos treatment restores the expression of Beclin1 (an autophagy initiation promoter) and reduces the accumulation of P62 (an autophagy degradation substrate) to reactivate autophagy, clearing damaged proteins and cellular debris to relieve atrophy; meanwhile, the Bcl-2/Bax ratio is normalized due to MSC-Exos, the

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expression of Caspase-3 is also suppressed by MSC-Exos. The most important point is that MSC-Exos can mitigate cell apoptosis [7]. For MG treatment, BMSC-Exos alleviate dysregulation of skeletal muscle protein metabolism by the combination of various mechanisms, including activating the autophagy pathway, which is AMPK/ULK1-mediated and specifically downregulating the expression of Atrogin-1 and MuRF1. Thereby, the pathological progression of MG-related skeletal muscle atrophy is effectively suppressed [5]. For RCI, BMSC-exos exert anti-inflammatory effects, promote angiogenesis, prevent scar formation and regulate bone metabolism; in the acute post-injury inflammatory phase, they induce M2 macrophage polarization to exert anti-inflammatory effects and promote RCI repair, although the specific signaling pathways remain to be further explored [9]. Additionally, BMSC-exos loaded with different miRNAs exert bidirectional angiogenesis regulation: promoting angiogenesis in the early RCI stage facilitates tendon interface healing, while inhibiting angiogenesis in the late stage improves the biomechanical strength of tendon-bone tissue, determining the optimal angiogenesis regulation time point, an urgent clinical issue to be addressed [9].

6. Comparison of MSCs therapy and MSC-Exos therapy for sarcopenia

Both MSCs and MSC-Exos target the multi-factorial pathogenesis of sarcopenia by regulating the immune mechanism, promoting autophagy, and resisting apoptosis, revealing a systematic mechanism of intervention measures for this age-related muscle disorder [7]. For MSCs therapy, several key clinical and practical limitations remain to be resolved: the optimal therapeutic dosage, administration frequency and transplantation route have not been uniformly standardized, the quality condition and biological functionality of HUC-MSCs are significantly affected by in vitro culture passage number, and the detailed downstream molecular mechanisms underlying their therapeutic effects still require further in-depth elucidation despite partially confirmed efficacy against skeletal muscle disorders. In the field of biology, the bidirectional difference between therapeutic MSCs and the host's immune microenvironment is the principal bottleneck [1,5,6]. Moreover, the potential tumorigenic risk of MSC transplantation is an unresolved safety concern that demands long-term and careful evaluation before large-scale clinical application [5]. For MSC-Exos therapy, despite its remarkable therapeutic potential and high biosafety, the complete mechanistic regulatory pathways have not yet been fully elucidated, and several core bottlenecks limit its clinical translation: intravenously injected MSC-Exos show poor skeletal muscle targeting efficiency and are difficult to precisely reach the target sites of atrophic skeletal muscles, there is a lack of direct in vivo experiments confirming whether MSC-Exos accelerate differentiation of skeletal muscle cells in mouse models and where this physiological phenomenon occur, and no research has conducted straightforward genetic or pharmacological inhibition experiments to further demonstrate the main signaling pathway of MSC-Exos [1,8].

7. Summary and optimization paths of MSC-Exos and MSCs in sarcopenia treatment

MSC-Exos are more suitable for early-stage sarcopenia interventions due to their superior tissue penetration, stability and targeted delivery efficiency, while HUC-MSCs are preferred for moderate-to-late-stage treatment owing to their sustained paracrine and immunomodulatory effects [1]. Notably, the therapeutic efficacy of both modalities mainly relies on paracrine mechanisms rather than direct cellular integration into host tissues [7]. To promote clinical translation, core optimization paths focus on three critical aspects: refining exosome extraction and targeted modification technologies, as well as optimizing HUC-MSC administration protocols to enhance

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cell homing and viability, exploring combined therapies with pharmacological or rehabilitation interventions to boost symptom control and patient quality of life and advancing personalized regimens, clinical trials, long-term safety monitoring and standardized production to accelerate clinical application [1,7,10].

8. Conclusion

This paper systematically reveals the therapeutic effects and molecular mechanisms of MSCs and MSC-exos in three skeletal muscle-related diseases, including AAS, MG, and RCI. It also compares and analyzes the advantages and limitations of these two approaches in treating Sarcopenia and explores the optimized treatment plans for such diseases using MSC-Exos and MSCs. Existing studies have verified that HUC-MSCs can effectively improve the muscle function and morphology of diseased mice through various means. It can reduce body inflammation, enhance the efficiency of mitochondria, activate MuSCs and repair the supporting structures outside muscle cells. When treating MG, MSCs can regulate the body's immune balance and repair the damage at nerve-muscle junctions. In the treatment of RCI, MSCs-Exos can directly differentiate into repair cells and accelerate the healing of the injured area by secreting substances. MSCs are the key carriers for MSCs' function, which achieve similar therapeutic effects as MSCs. Such effects can also alleviate inflammatory effects, improve mitochondrial function, and reduce cellular oxidative damage. Moreover, MSC-exos have higher safety and can effectively reduce adverse reactions after treatment. Additionally, for MG and RCI, MSC-Exos can also regulate protein metabolism and promote the growth of new blood vessels at the injured site, which makes the application scope of MSC-Exos therapy more extensive. This study systematically reviews and compares the therapeutic principles of MSCs and MSC-exos, and clearly identifies their complementary advantages. This also provides a complete theoretical basis for regenerative medical treatment of diseases which are related to skeletal muscles. However, this study has certain drawbacks. The research lacks in vitro and in vivo experiments that combine the application of MSCs and MSC-exos, and the specific signaling pathways of the two treatments have not been sufficiently explored. Future related research can focus on optimizing the combined treatment plan of MSCs and MSC-exos, and delving deeply into the core molecular targets that regulate skeletal muscle diseases. In the future, research on standardized production processes should be further advanced to solve the problems of low yield and insufficient purity of MSC-exos.

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