Role of myostatin protein in sarcopenia (aging muscle) after conditioned medium umbilical cord mesenchymal stem cells (secretome) therapy: mini review

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ABSTRACT

Umbilical Cord Mesenchymal stem cell (UC-MSCs) /secretome has been applied for treating several diseases, such as cardio-protection and diabetes. Secretome-derived paracrine modulating effects of various growth factors, cytokines, chemokines, angiogenic factors, and exosomes are used in aging therapy. In recent clinical trials on sarcopenia therapy such as pharmaceutical interventions, nutrition, and physical exercise are reported to be effective strategies to reduce sarcopenia. The pathomechanism of the secretome in the treatment of sarcopenia is unclear. This study looked into how secretome might affect myostatin, a biomarker of sarcopenia, at the molecular level. Myostatin, a member of the TGF-family, significantly increases muscle growth when it is absent while suppressing muscle growth when it is present. A bioactive substance called secretome is secreted by MSCs in conditioned conditions. It is rich in growth factors and cytokines, which are crucial for speeding up tissue regeneration. Secretome intervention is a promising approach for treating sarcopenia as shown by its ability to prevent muscle loss and to improve molecular biomarkers.

Keywords: Myostatin, molecular biomarker, skeletal muscle loss, secretome.


INTRODUCTION

Loss of muscular mass is a common side effect of aging. Sarcopenia is the term for the progressive decline in skeletal muscle size, strength, and/or function with aging. The aged will experience lower quality of life as a result of sarcopenia. In middle age, human skeletal muscle mass is at its peak; after that, it gradually declines. Sarcopenia is the severe and persistent loss of muscular mass, strength, and/or function with advancing age.¹ In the elderly, sarcopenia will lower skeletal muscle activity, physical function, and metabolism. Although the exact biological cause of sarcopenia is still unknown, it is believed to be influenced by a variety of factors, including as hormonal changes, sex steroids, physical activity, and coexisting diseases like heart failure, cancer, and diabetes. Myostatin, also known as growth and differentiation factor-8 (GDF-8), is a powerful inhibitor of muscle growth, and its involvement in the molecular pathway has been suggested as one cause of sarcopenia.² Therefore, a deeper knowledge of sarcopenia’s biology and the development of therapeutic strategies to stop or slow down the disease’s progression are both highly beneficial.³ Myostatin is a potential mediator of sarcopenia and a therapeutic target because it is known to be a negative growth regulator in skeletal muscle.⁴,⁵ Secretome research in inhibiting myostatin protein in sarcopenia is a challenge in the aging process. This review’s objectives are to discuss the challenges of the secretome in preventing the progression of sarcopenia and to highlight potential applications of myostatin inhibition as a sarcopenia prevention strategy.

Myostatin in Sarcopenia

Myostatin is a cytokine that is selective and has the potential to inhibit myogenesis. The in vivo mechanism of action of myostatin is anabolic growth hormone on skeletal muscle growth. Increased lean body mass and improved aerobic performance, as measured by maximal oxygen uptake and ventilation threshold, are the results of GH’s inhibitory action on myostatin. Parallel in vitro tests on skeletal muscle cells showed that myotube response to GH significantly reduced myostatin expression relative to vehicle treatment. In contrast, myostatin is upregulated in myoblasts when GH receptor antagonism occurs. Given the strong catabolic effects of myostatin, our findings imply that myostatin might be a crucial target for GH-induced anabolism.⁴ The molecular regulators of atrophy and hypertrophy are affected both directly and indirectly by the principal negative regulator of muscle mass in both humans and animals, myostatin. As a result, it can have an impact on physical fitness and function. Chronic disability-related disorders may cause myostatin to be increased (eg limb paresis in stroke). Myostatin is present in sarcopenic aged
people. When compared to individuals without sarcopenia, mRNA expression is typically lower (29%) (68.6 vs. 96.18 AU, \(P=0.09\)). Sarcopenia and muscle atrophy both depend on myostatin expression to progress.\(^5\)

**Myostatin Signals in Skeletal Muscles**

Myostatin is a protein of the TGF-beta superfamily, where the main expression is in skeletal muscle and to a lesser extent in adipose tissue and cardiac muscle.\(^6\) ActRIIB is a myostatin receptor that is co-expressed with kinase 4 such as activin (ALK4) or kinase 5 (ALK5). Furthermore, Smad2 and Smad3 will be phosphorylated by the intracellular serine/threonine kinase domains of ALK4 and 5 with the aim of forming a complex with Smad4. The formation of this complex will enter the nucleus to regulate the transcription of genes involved in the proliferation and differentiation of skeletal muscle precursor cells. In addition, this precursor will break down proteins in mature muscle cell myofibers.\(^7\) In addition to activating Smad 2 and 3, myostatin has mTOR inhibitory effects on the response to pro-growth signals such as insulin and IGF-1, which will stop protein synthesis. This inhibition of protein synthesis will prevent cell growth and differentiation as well as intracellular catabolic and anabolic signaling pathways. In the aging process, skeletal muscle development is affected by myostatin. Skeletal muscle hypertrophy results from mutation of myostatin which loses its function. Hence the notion that myostatin inhibition could be used to enhance skeletal muscle regeneration and reduce or prevent skeletal muscle loss in the context of cachexia and sarcopenia (muscle loss caused by the aging process).\(^8\)

**Effect of Myostatin in Skeletal Muscle**

Myostatin, also known as growth differentiation factor 8, was first identified by Se-Jin Lee and colleagues in 1997. One well-known highly conserved member of the TGF beta protein family is the myostatin gene\(^9\) which is highly expressed in skeletal muscle and to a lesser extent expressed in cardiac muscle and adipose tissue.\(^9,10\) Myostatin levels have been found to significantly fall in the plasma of healthy young men 24 hours after exercise compared to rest. A rise in plasma IL-6 levels is positively correlated with this drop in myostatin levels.\(^11\) Patients with spinal cord injury have also been shown to have higher serum myostatin levels after aerobic exercise.\(^12\) Circulating myostatin shows a marked increase in sarcopenia in women than in men.\(^13\)

The universally expressed activin receptor type IIB (ActRIIB) mediates the effects of myostatin.\(^14\) Smad2 and Smad3 are downstream mediators of myostatin that are phosphorylated and join forces with Smad4 to form complexes. The complex will also activate genes regulated by FoxO that are involved in skeletal muscle precursor cells’ proliferation and differentiation, as well as mature
myofibers’ autophagy and ubiquitin-proteasome-mediated protein degradation pathways. Myostatin inhibits muscle protein synthesis through Smad signaling and the Akt-mediated mTOR signaling pathway. Myostatin inhibits myogenesis by acting as a negative regulator of muscle growth, which causes muscle cells to differentiate and grow more slowly.

Increased activin and myostatin Analogs of A cause muscular wasting. Muscle mass significantly rises when myostatin activity is blocked (myofiber hypertrophy rather than hyperplasia). Animals lacking myostatin had roughly twice as much muscle mass as mice with normal myostatin levels. When compared to healthy people, people who have mutations in both copies of the myostatin gene show noticeable increases in both muscle mass and strength. Myostatin is one possible target molecule in the treatment of muscle wasting. Studies on substances like follistatin (a myostatin antagonist) and particular antibodies targeting ActRIIB, myostatin, and activin A were done to suppress myostatin signaling. In studies using common muscular dystrophies like Becker muscular dystrophy (BMD) and facioscapulohumeral dystrophy, the myostatin antibody MYO-029/stamulumab showed the ability to boost muscle strength in pathological circumstances. Myostatin may therefore be a target for the treatment of human muscle atrophy.

Myostatin Inhibition as Therapy for Sarcopenia

To reduce myostatin activity, a variety of methods have been developed, including neutralizing antibodies, propeptides, soluble ActRIIB receptors, and interacting proteins. Different characteristics can be therapeutic targets for sarcopenia. Aged mice receiving injections of myostatin-neutralizing antibodies experienced a 4-week rise in relative muscle weight of up to 17% as well as an improvement in index muscle performance and overall body metabolism. Dissolved single dose ActRIIB enhances postmenopausal women’s total lean body mass by >1 kg. Effect of target myostatin inhibition is very specific for skeleton muscle. Impaired myostatin signaling may directly or indirectly contribute to age-related alterations in other organs. Age-related resistance to diet-induced obesity, dyslipidemia, atherogenesis, hepatic steatosis, and macrophage infiltration/activation in adipose tissue and skeletal muscle was observed in older mice with altered or missing myostatin genes. As a result, myostatin levels dropped.

Increasing skeletal muscle mass with myostatin inhibition may also be a promising strategy for the treatment of type 2 diabetes and metabolic diseases associated with the aging process. Myostatin inhibition may increase skeletal muscle insulin sensitivity in aged rats, potentially as a therapeutic approach for age-related sarcopenia and metabolic disease.

Protein myostatin can be used as a therapeutic target for sarcopenia. The use of neutralizing antibodies will reduce total myostatin activity as a therapeutic target for sarcopenia. Strategy inhibits myostatin by neutralizing specific antibodies and propeptides myostatin targets, which are proteins that interact with myostatin. A specific transgenic muscle overexpression of follistatin will be provided by follistatin as an anabolic intervention, and this will result in myostatin causing muscle mass. It demonstrates that follistatin boosts skeletal muscle growth in part via different mechanisms in contrast to myostatin inhibition.

These results emphasize the importance of identifying additional factors that affect muscle growth in addition to myostatin. Interacting proteins and soluble ActRIIB are some of these factors. They have the potential to either (1) stimulate muscle growth and, if specifically targeted, potentially increase intervention efficacy, or (2) negatively affect the health of other tissues and, if specifically avoided, increase intervention safety. Naturally, risk tolerance varies depending on the indication, the therapeutic approach, and the desired outcomes. For elderly patients with sarcopenia, for example, a slightly higher risk may be acceptable for short-term treatment.

Role of Myostatin Inhibitors on Muscle Satellite Cells

In vitro studies have shown that circulating myostatin can positively influence satellite cell regenerative capacity and proliferation in aged mice. It was also reported that negative regulators of muscle mass can function to balance signals that affect satellite cell activation and regeneration capacity in the aging process. Myostatin protein will have a negative effect on myogenesis, inhibiting satellite cell activation and muscle regeneration. Young myostatin-null muscle fibers are characterized by massive hypertrophy and hyperplasia and an increase in type IIB fibers. This will result in a more glycolytic muscle. With aging, muscles will be increasingly oxidative and atrophic. The effect of aging on satellite cell count appears to be minimal, however, satellite cell activation is significantly decreased in myostatin-null muscle. In vivo studies of young, myostatin-deficient mice will result in a decreased number and activation of satellite cells. So myostatin inhibitors can prevent age-related sarcopenia and loss of muscle regenerative capacity.

Secretome of umbilical cord mesenchymal stem cells promotes skeletal muscle regeneration through Myostatin Inhibitor

Because stem cells have the potential to recognize injured tissue and specialize into particular cell types that will replace damaged cells, mesenchymal stem cells (MSCs) have a regenerative mechanism. Recent research has demonstrated that MSC secretomes, which are substances contained in extracellular vesicles (EVs), are in charge of tissue repair. The secretome’s miRNA content. Adipose-derived mesenchymal stem cells’ secretomes strongly influence cellular functions that encourage tissue regeneration and speed up the recovery of injured skeletal muscle (Figure 2).

Adipose tissue and skeletal muscle produce bioactive proteins continuously or sporadically, unlike endocrine organs, which are known to be experts in secreting proteins into the bloodstream. A significant group of physiologically active molecules known as secretomes are released into the bloodstream to support the communication between organ systems. Secretome profiles for the myostatin and TGF-beta signaling pathways in primary human skeletal muscle cells.
Conditioned media from both umbilical cord and adipose cells have potential on acute insulin release from normal β-cell cultures, non-diabetic islets and Type-2 diabetic islets. This is related to increased mitochondrial substrate oxidation as a strong antioxidant. So the secretome also functions as a strong antioxidant in the prevention of sarcopenia.17

Myostatin is also known as a growth differentiation factor. Termination of the myostatin pathway in the aging process is effective in increasing skeletal muscle mass. Decorin protein, a member of the leucine-rich proteoglycan family, is a metalloprotein that has been shown to bind and deactivate myostatin. In addition, binding of myostatin located at the N-terminal domain of decorin will affect the anti-myostatin activity of short and soluble decorin fragments. Previous studies have shown that murine decorin peptides DCN48-71 and 42-65 can inactivate myostatin in vitro. It has also been reported that the interaction of mDCN48-71 with myostatin is highly zinc dependent. The binding of myostatin to activin type II receptors results in Smad2/3 phosphorylation. The addition of decorin peptides DCN48-71 and 42-65 has also been reported that the interaction of DCN48-71 with myostatin is highly zinc dependent. The binding of myostatin to activin type II receptors results in Smad2/3 phosphorylation.


CONCLUSION

The TGF beta superfamily member myostatin is a potent inhibitor of skeletal muscle growth and development. Skeletal muscle atrophy results from myostatin activating an increase in the ubiquitin-proteasome pathway. Through the activation of the muscle-specific E3 ligases Atrogin-1 and MuRF1, as well as increased activity of the ubiquitin-proteasome pathway, treatment of C2C12 myotubes with C26 conditioned media caused myotubular atrophy. Activin A, Thrombospondin-1, and Insulin Growth Factor Binding Protein 3 (IGF-BP3), which are all produced in reaction to myostatin, cause skeletal muscle atrophy. These proteins, known as the secretome, are released by human major myotubes.

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CONFLICT OF INTERESTS

All the authors declared no conflict of interest.

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AUTHOR CONTRIBUTION

All authors contributed equally in this article.

REFERENCES


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