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Therapeutic strategies against muscular dystrophy and related atrophic disorders

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Abstract

Skeletal muscles represent approximately 30–40% of total body weight and are important for proper movement; whole body homeostasis, including temperature control and metabolism, such as insulin sensitivity and glucose and lipid metabolism; and inter-organ crosstalk. Skeletal muscles are highly plastic and have remarkable regenerative capacity. There are multiple disorders that affect skeletal muscles. Muscular dystrophies are devastating muscular disorders. Atrophy of skeletal muscle is the most prominent pathoetiology of muscular dystrophy. Furthermore, as skeletal muscles are one of the major targets of insulin action, muscular disorders often affect whole body metabolism. With the rapidly aging population worldwide, sarcopenia, characterized by a decline in skeletal muscle tissue mass and muscle strength with aging, is becoming a major problem. Sarcopenia leads to restriction of physical activities, it affects the quality of life, and is sometimes lethal in elderly individuals. Prevention of and interventions against muscular atrophy and related disorders, like genetic disorders such as muscular dystrophy, sarcopenia, and cachexia, are clinically important as they impact millions of older adults and patients. In particular, Duchenne muscular dystrophy is a genetic disorder that is primarily characterized by progressive muscle weakness and loss. In this mini-review, we briefly review the potential therapeutic strategies against Duchenne musclular dystrophies and related atrophic disorders.

Muscle wasting disorders such as muscular dystrophies, sarcopenia, and cachexia, induce skeletal muscle atrophy. Muscular dystrophies are devastating disorders and therapies to prevent muscle atrophy and recover skeletal muscle mass and muscle strength are desired.

In the case of Duchenne muscular dystrophy (DMD), the most severe form of muscular dystrophy, dystrophin genes in the X chromosome are mutated. In DMD, repeated cycles of cell death and regeneration of myofibers are evident, and myofibers are replaced with fat and connective tissues, causing muscle weakness. Cardiac muscles and the diaphragm are also affected, leading to respiratory problems and mortality.

Effective fundamental and radical therapies for DMD are not yet realized [1]. For DMD, restoring dystrophin is the main therapeutic strategy [1]. Further, exon-skipping therapies for dystrophin genes, several nucleotide-based modified chemicals and morpholinos, and adeno-associated virus (AAV)-mediated skipping of dystrophin [2, 3] have revealed promising results for the treatment of DMD. Eteplirsen and NS-065 are still in the clinical trial stage [2]. Furthermore, dual exon skipping of both dystrophin and myostatin is also worth considering as a treatment option for DMD [3,4]. Co-delivery of micro-dystrophin and the myostatin/activin antagonist follistatin has also been reported to restore muscle function in the DMD model [5].

In another type of muscular dystrophy, namely, congenital muscular dystrophy, the splicing defect can be corrected by the CRISPR/Cas9 system [6].

With the rapidly aging society worldwide, coping with aging-related disorders has become very important both medically and socially. Sarcopenia, involving a severe loss of skeletal muscle mass, is one of the major disease etiologies related to aging. Although the precise pathophysiology of sarcopenia is still unknown, it impairs the quality of life and is lethal in elderly individuals [7]. Nutritional status is also a problem in sarcopenia [7]. Cachexia is observed in end-stage cancers, chronic obstructive pulmonary disease, chronic kidney disease, heart failure, and severe infectious diseases, leading to weight loss, fatigue, loss of appetite, adipose tissue loss, and muscle wasting [7,8].

Therefore, multiple diseases can lead to muscle atrophy. As effective fundamental and radical therapies against sarcopenia and muscle wasting diseases are not yet available, it is important to establish therapies to prevent skeletal muscle loss.

Myostatin and related cytokines affecting skeletal muscle mass

Myostatin inhibitors are promising drug candidates for muscle wasting disorders. Myostatin belongs to the transforming growth factor-β (TGF-β) superfamily, including TGF-βs, activin, growth differentiation factors (GDFs), and bone morphogenetic proteins (BMPs) [9-11]. Among them, myostatin and GDF11 are structurally similar and play an important role in the negative regulation of muscle growth and determine the mass and size of skeletal muscles and their regenerative capacity. In primates, it has been reported that activin A plays a more important role than myostatin in determining

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skeletal muscle mass [12]. Blockade of myostatin and related TGF-β superfamily members is a promising therapeutic strategy for restoring muscle mass and strength in muscle wasting disorders like muscular dystrophy, sarcopenia, and cachexia. Myostatin blockers include myostatin antibodies, myostatin propeptide, follistatin and follistatin-related proteins, soluble myostatin/activin receptors, siRNA against myostatin or myostatin/activin receptors, and chemicals [9]. Several antibodies and antagonists against myostatin have been developed and used to treat muscular wasting [13,14]. Furthermore, antibodies against the myostatin receptors such as activin type II receptors (ActRIIB and ActRIIA), namely, bimagrumab (BYM338), and soluble forms of activin receptor-Fc (sActRIIB-Fc), ACE-083 or ACE-031, have a marked effect in increasing skeletal muscle mass [14-17]. A dual anti-ActRIIA/IIB antibody is critical in promoting maximal skeletal muscle hypertrophy because of inhibition of myostatin and related TGF-β family members affecting skeletal muscle [16]. A combination of myostatin/activin blockade with the wheel running exercise is effective in correcting aerobic gene expression profiles of dystrophic muscle toward healthy profiles [17]. Anti-activin receptors are also effective for the treatment of sarcopenia [18, 19].

Furthermore, follistatin was initially identified as an activin-binding protein to neutralize activin function, and follistatin-related proteins were revealed to inhibit not only activins but also multiple members of the TGF-β family, including myostatin and GDF11 [9]. The follistatin gene therapy trial for BMD and sporadic inclusion body myositis has been carried out with improvement of functional recovery [20]. Structure–function relationships of follistatin–activin or follistatin–myostatin complexes may lead to suitable peptides for myostatin inhibition [21].

Interestingly, givinostat, one of the histone deacetylase (HDAC) inhibitors is reported to be effective in reducing fibrotic tissue and fatty degeneration and increases the fraction of muscle tissue in DMD patients [22-24]. HDAC inhibitors play a role in treating muscle wasting, but this mechanism is yet to be determined. Induction of follistatin could be one of the molecular mechanisms for preventing muscle loss [24].

Recent studies have shown that gene transfer of siRNA or short interfering hairpin RNA-induced myostatin inhibition are effective in increasing skeletal muscle mass [25, 26]. In this scenario, a combination of siRNA-induced myostatin inhibition with exercise or co-administration of ActRIIB-Fc fusion proteins is effective for skeletal muscle homeostasis and skeletal muscle hypertrophy [26,27]. Recently, genome-editing technology has also been applied to treat muscle wasting. CRISPR/Cas9-mediated disruption of myostatin prevents muscle wasting in vivo [28]. The cutting-edge genome editing technology is rapidly expanding and could be useful for therapy against muscle wasting and treatment of genetic muscular disorders.

LDN-193189, a small-molecule inhibitor chemical, was also reported to inhibit myostatin signaling and promote functional myoblast differentiation [29]. Since these chemicals inhibit multiple TGF-β family members, care must be taken to minimize their side effects.

Conclusion

Muscular dystrophies and sarcopenia affect skeletal muscles and cause muscle atrophy. Currently, effective therapies against them are limited. In DMD, exon skipping of dystrophin genes is effective and promising as clinically applicable therapeutic strategy. TGF-β family members, including myostatin and activins, are involved in muscle atrophy, and blockade of their signaling is effective in the recovery of muscle mass and inducing muscle regeneration. Muscle mass recovery through these therapeutic modalities could be promising for genetic muscle diseases and sarcopenia. A combination of exon skipping and inhibition of TGF-β signaling could be effective synergistically. Increase of skeletal muscle over a short period may cause an unexpected burden on bones in elderly people. Therefore, care must be taken to choose the proper treatment and to consider the pathology behind the inhibition of TGF-β family members for treating muscle atrophy.

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Competing Interests

We declare no competing interests.

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