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Molecular Mechanisms, Therapeutic Targets and Pharmacological Interventions: An Update

Mohit Kwatra, Sahabuddin Ahmed, Samir Ranjan Panda, Vegi Ganga Modi Naidu and Nitika Gupta

Abstract

Muscles are the enriched reservoir of proteins in the body. During any workout or exercise, the demand in the form of energy is essentially required by the muscle. Energy expenditure of skeletal muscle is more dependent on the type of demand. There is particular homeostasis within the body that avoid surplus energy expenditure and this prevents any muscle loss. Muscle atrophy is termed as the loss of skeletal muscle mass due to immobility, malnutrition, medications, aging, cancer cachexia, variety of injuries or diseases that impact the musculoskeletal or nervous system. Hence, atrophy within the skeletal muscle initiates further cause fatigue, pain, muscle weakness, and disability in human subjects. Therefore, starvation and reduced muscle mass further initiate numerous signaling pathways including inflammatory, antioxidant signaling, mitochondria bio-energetic failure, AMP-activated protein kinase (AMPK), Sirtuin 1(SIRT1), BDNF/TrkB/PKC, Autophagy, ubiquitin-proteasome systems, etc. Here, in this chapter, we will mention molecular mechanisms involved in therapeutic targets and available Pharmacological Interventions with the latest updates.

Keywords: molecular mechanisms, therapeutic targets, pharmacological Interventions

1. Introduction

Muscles are enormous protein reservoirs within the body. It is a profound source of various amino acids required for energy production used by various organs (such as brain, liver, heart) during energy demand and disease conditions (cancer, AIDS, burn, heart failure). However, extensive protein requirement does not consider good in case of cachexia which might lead to increased morbidity and mortality. Skeletal muscle is an organ with plastic characteristics and regulated by several signaling pathways that control cell and protein turnover. The skeletal muscle atrophy may be due to lower muscle mass, disease. However, disuse muscle mediated acute atrophy is reversed through exercise. Furthermore, chronic atrophy such as sarcopenia features as loss of muscle mass strength with age. Moreover, other chronic diseases such as diabetes or disease of muscles (muscle dystrophy) cause

nerve damage to innervate to the muscle [1]. In muscle atrophy, a proteolytic system gets activated while contractile proteins and organelles are removed results in the shrinkage of muscle fibers.

Spinal muscular atrophy (SMA), a kind of intense neuromuscular disease depicts as chief genetic cause of death in infants. It is featured as alpha motor neuron degeneration within the anterior horn region of the spinal cord and brain stem that is the leading cause of progressive muscle weakness. SMA is inherited as autosomal recessive disorder and the most common form (95% cases) caused by certain mutations in the survival motor neuron 1 ($SMN1$, SMN^T) gene localized on chromosome 5q12.2. The genetic deletion or carries a mutation of the SMN1 gene resulting SMN protein deficit. On the other hand, the SMN2 gene develops a relatively small amount of functional SMN protein and SMN2 copy numbers further determine the severity of the disease. The incidence of SMA is approx. 1 in 10,000 live births while prevalence estimates 1–2 in 100,000 affected individuals with extremely shortened life expectancy. SMA characterizes in various forms depending on the age of inception such as Infants being severely hypotonic possess feeding problems, further reach growing age of children does found with difficulty climbing stairs proceeded with frequent falls. The clinical manifestation of SMA is usually heterogeneous and scored to a range from severe to mild phenotype which is further divided into mainly 3 subtypes as Type I (also known as Werdnig-Hoffmann disease), type II and, type III (also called Kugelberg Welander disease). SMA categorized as type 0, a serious and rigorous form, lower/absent movements, abnormal muscle contractions, and immediate need for ventilation support. SMA type IV, a mild late (adult) onset [2]. Hence, improve understanding regarding the molecular pathogenesis mechanisms cause for muscle atrophy or muscle wasting attribute the efforts to designate the safe and effective therapy for affected human subjects.

2. Molecular key mechanisms in muscle and spinal muscular atrophy

Various signaling pathways participate in molecular pathogenesis of muscle atrophy (**Figure 1**).
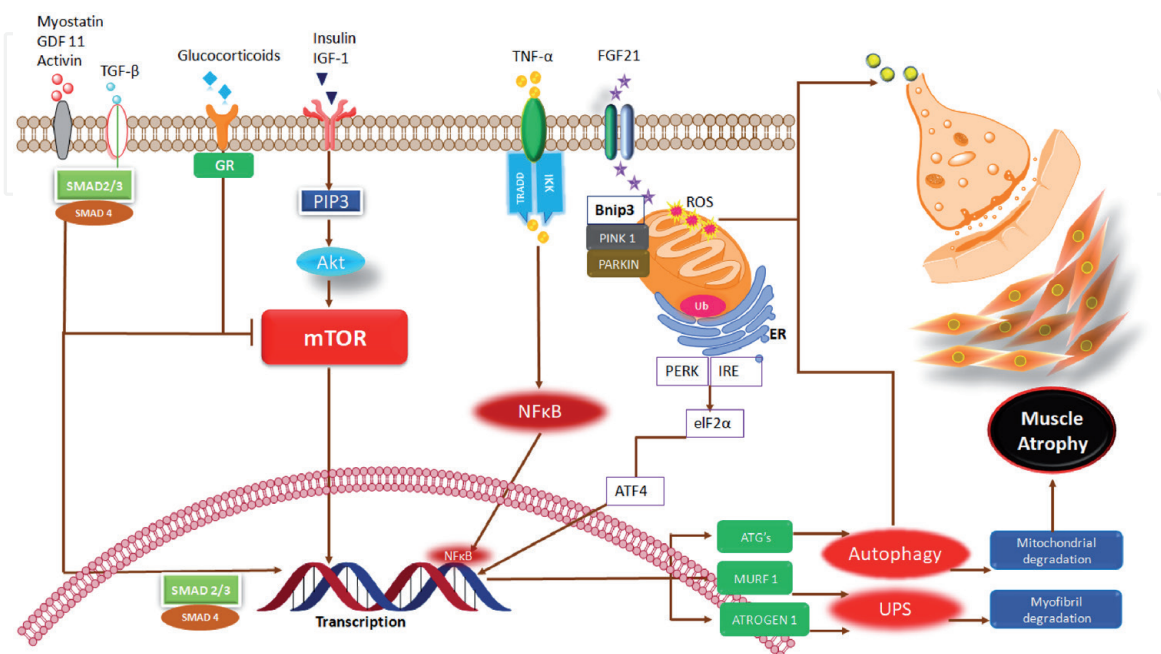

Figure 1.
Signaling Cascade Events in Muscle Atrophy.

2.1 Oxidative stress and inflammatory signaling

Oxidative stress and inflammation are considered the foremost molecular mechanisms responsible for muscle atrophy [3]. Raised levels of reactive oxygen species (ROS) production within skeletal muscles substantially promote mitochondrial function impairment, stimulate forkhead box class O (FoxO) transcription factors leads to inactivity induced muscle atrophy [4]. Inflammation perturbs the muscle homeostasis and process of myogenesis via activating the family of FoxO transcription factors significantly contribute to skeletal muscle atrophy [5]. FoxO activation is vital for the muscle atrophy induced through denervation/fasting, which upon activation (FoxO3) cause induction of ubiquitin–proteasome system (UPS) and autophagy–lysosomal system (ALS) in a coordinate manner, especially lysosomal proteolysis [6]. Shreds of evidence, state that FoxO knockout was able to reverse the muscle degeneration process loss, also the markers of increased UPS process and autophagy dysfunction in streptozotocin-diabetes induced mice (O'Neill et al., 2019). Therefore, necessary steps must be taken to find an intervention that can curb the atrophy. During muscle wasting or cachexia, NFκB transcription factors activate with certain stimulants or facilitators (such as TNF-α). Upon TNFα response, the IκB complex gets phosphorylates by IκB kinase (IKKβ), ensuing ubiquitylation followed by its proteasomal degradation which further causes nuclear translocation of NFκB and induce transcription of inflammatory mediators [7]. Transgenic mice showing muscle-specific overexpression of IKKβ results in drastic muscle wasting due to ubiquitin ligase MuRF1 and not by atrogin-1 [8]. Furthermore, muscle-specific inhibition of NFκB through transgenic expression of a typically active IκB mutant generated partial results due to denervation atrophy get substantially reduced [9]. Besides, mice deficient with p105/p50 subunit of NFκB reduced hindlimb unloading induced muscle atrophy [4, 10]. The pro-inflammatory cytokines including TNF-α cause insulin resistance and repress the Insulin-like growth factor-AKT (IGF1-Akt) pathway [11]. Furthermore, hyperphosphorylation of AKT was found in IKKβ knockout mouse which develops resistance against muscular atrophy [12]. These findings signify the important crosstalk of two pathways, and further future studies are desirable for elucidating respective links of the IKKβ-NFκB and Akt-FoxO pathways in muscle atrophy.

Moreover, an inflammatory cytokine strongly concerned for muscle-wasting disease is the TNF-like weak inducer of apoptosis (TWEAK), which binds on the surface receptor FN14 and induces NF-κB activation. TWEAK deficient mice ablate atrophy upon denervation, a process that generally activates TWEAK [13, 14]. Furthermore, the TWEAK-F14 axis may be a potential therapeutic target in muscle wasting diseases [15].

2.2 Mitochondrial dysfunction

Mitochondrial functional impairment is a critical regulatory event that brings on activation of atrophic programs in inactivity-induced muscle atrophy. Prolonged muscle inactivity induces mitochondria suffers from prompt reduction in the respiratory capacity, coupling, lower mitochondrial volume, mitochondrial ROS overload, and destruct mitochondrial architectures. Muscle inactivity, promotes mitochondrial fission rather than fusion and therefore decays energy level and leads to muscle atrophy [16, 17].

Mitochondrial fusion and fission process need excessive refinement due to mitochondrial lipid bilayer hence need synchronization at inner as well as outer membrane. Upon fusion process, mitofusin1 and 2 (MFN1 and MFN2) proteins facilitate fusion by attaching to an outer membrane in adjoining mitochondria, while the

inner membranes by optic atrophy 1 (OPA1). Additionally, MFN 1 and 2 also functions over junctions to create membrane-associated-sarcoplasmic reticulum membranes (MAM) to play keen role in mitochondrial Ca^{2+} management. Further, a major regulative component that regulate fusion with MFN proteins is the E3 ligase Parkin, which ubiquitinates MFN1 and MFN2 cause its extraction from the outer membrane of mitochondria with subsequent degradation and thereby prevent mitochondrial fusion [18, 19]. The mitochondrial fission is largely coordinated by dynamin-related protein 1 (DRP1). DRP1 locates in the cytosol and upon certain signaling event, process induce it translocate to the outer mitochondrial membrane. Phosphorylation at Ser616 is believed to activate DRP1, while phosphorylation at Ser637 and Ser693 inactivate DRP1 and prevention of mitochondrial fission activity altered through sumoylation and S-nitrosylation [20]. The muscle inactivity results in alterations of the proteins involve in both fusion and fission [21]. Inactivity-mediated muscle atrophy leads to increased total as well as phosphorylated (i.e., pDRP1-S616, active) DRP1 which explains it as an essential mediator of the mitochondrial division. Additionally, MFN1, MFN2, and OPA1 function as fusion promoters is found lower in protein content and hence limit the mitochondrial fusion process while promote mitochondrial fission.

Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a key regulator of mitochondrial biogenesis is found significantly decreased with prolonged muscle immobility. PGC-1α, a transcriptional coactivator assists the regulation of genes involved in mitochondrial biogenesis, fatty acid oxidation, and glycolysis. The reduction in PGC-1α abundance markedly impaired mitochondrial biogenesis negatively influences mitochondrial structure and function. However, PGC-1α overexpression preserved mitochondria and improved muscle performance [22]. Furthermore, overexpression of PGC-1α ameliorates decreased MFN1, MFN2, and OPA1 in muscle wasting. This further outlooked the importance of upstream transcriptional activators [23, 24]. Importantly, muscle inactivity-induced dysfunctions in skeletal muscle mitochondria through elevations in mitochondrial ROS emission, the release of proteolytic-activating mitochondrial proteins, and triggering apoptotic cellular signaling cascade caused due to mitochondrial fragmentation [24].

2.3 TrκB/BDNF/PKC pathway

Neurotrophins always have been thought to work within neuronal cells and function as differentiators, nerve growth, neuronal survival, and apoptosis regulators [25–27]. Various evidence state that these neurotrophins have a diverse function in numerous cell populations across multiple tissue compartments than earlier thought. Among these, skeletal muscle seeks great importance as it act as a plentiful source with neurotrophic support throughout the development process. Neurotrophin knockout mice show unique defects in muscle growth and function. For instance, NT (4/5), NT-3 implicates for muscle fiber transformation and spindle formation and nerve growth factor (NGF) in muscle dystrophy [25]. Brain-derived neurotrophic factor (BDNF), a well-known member of the neurotrophin family, plays an utmost vital role in differentiation, synaptic plasticity, development, neuronal survival via activating tropomyosin-related kinase receptor B (TrkB) receptor. BDNF potentiates TrkB autophosphorylation leading to initiation of some signaling pathways, including the PI3K/Akt, Ras/Raf/ERK, and PLCγ/PKC.

Initially, BDNF is produced as a precursor (pro-BDNF), further cleaves to mBDNF (a mature isoform) by Intra/extracellular proteases. These two isoforms stimulate different and even opposite functions via interacting especially to low-affinity nerve growth factor receptor (p75) or the tropomyosin-related kinase B

receptor (TrkB). Furthermore, alternative splicing of TrkB mRNA gives rise to a full-length TrkB isoform (TrkB.FL) and truncated TrkB isoforms T1 and T2 (TrkB.T1 and TrkB.T2) [28, 29]. TrkB.T1 is considered to be main truncated isoform in skeletal muscle tissue while TrkB.T2 (variant) chief variant function within brain regions. Growing evidence mentions that exercise training ensures CNS health, such as improving synaptic function. BDNF is secreted in an activity-dependent and its expression in the rodent spinal cord and skeletal muscle surges after a physical workout. Correspondingly, normal levels of neuromuscular activity are required to maintain basal levels of BDNF within the neuromuscular structure. Lastly, one study found that contracting cultured myotubes stimulated to release the BDNF and justify the postsynaptic origin (Matthews et al., 2009). However, the skeletal muscles release BDNF in *in-vivo* models, after contraction, either synaptic activity provokes its liberation, or a combination of both, the exact mechanisms remains elusive. Exogenous BDNF intensifies acetylcholine (ACh) discharge at neuromuscular junction via coupling with TrkB receptor This supports well where neuromuscular activity endorses BDNF/TrkB retrograde signaling in maintaining neuromuscular function [28, 30]. Furthermore, the nerve-stimulated muscle contraction is a chief regulator of the BDNF/TrkB signaling pathway, retrogradely activate conventional protein kinase C (cPKC) isoforms (in particular cPKCβI) in modifying synaptic function [31].

With embryonic development, primordial skeletal muscle cells express comparative higher BDNF levels and later downregulates with maturation. Furthermore, expression of BDNF does associate with myofibers development, which later expresses myosin heavy chain IIB. BDNF was also found regulating food intake and blood glucose level in genetically modified (*db/db*) obese mice [32]. Thus, it is obvious that BDNF drivesregulatory role in neurobiology and metabolism. Recent reports established the fact that physical activity (exercise) raises the circulating BDNF levels in healthy humans as well as patients of multiple sclerosis, nevertheless cellular sources still vague. Certain reports evidenced the increased BDNF mRNA transcriptome within skeletal muscle in response to muscle contraction, however, this substantiates the fact with BDNF source within neurons does innervate skeletal muscle compartments. A Contrasting study explains the BDNF mRNA expresses in skeletal muscle of murine and was found increased with inhibiting histone deacetylases (HDACs) [33]. Physical exercise also tends to block histone deacetylases and contracted muscles release BDNF and mentions as novel contraction-induced myokine [34]. Moreover, BDNF was found to possess metabolic activity in the skeletal muscle. It increased phosphorylation of AMPK, acetyl-coenzyme A carboxylase β (ACCβ), and raised the level of fatty acid oxidation studied *in vitro*, *in-vivo* (sex-dependent), and *ex vivo*. The impact of BDNF over fatty acid oxidation was AMPK-dependent, however, this increased energy regulation was found to repress inC2C12 cells infected with either AMPK dominant-negative form of adenovirus or employed AMPK inhibitor (Compound C). BDNF injected via electroporation within the tibialis cranialis muscle raises BDNF production and tropomyosin-related kinase B (TrkBTyr$^{706/707}$) and extracellular signal-regulated protein kinase (p44/42 Thr^{202}/Tyr^{204}) phosphorylation. Also, phosphorylation of ACCβ was also noticed in BDNF electroporated muscles [35, 36]. This raises the possibility that BDNF analogs or BDNF mimetic drugs can be a possible therapeutic intervention in metabolic diseases.

In the case of spinal bulbar muscular atrophy (SBMA) which is an androgen-dependent neuromuscular disorder associates with polyglutamine expansion mutation in androgen receptor gene [37]. SMBA affects people with middle young age and is featured through persistent muscle weakness with lower androgen sensibility. The muscle-derived neurotrophic factors such as vascular

endothelial growth factor (VEGF), neurotrophin-4, insulin-like growth factor-1 etc. expression is usually reduced in pathological condition and experimentally strengthen its expression within muscle improvised the condition in SBMA affected mice [37]. Further, a possible mechanism by which muscle-derived neurotrophic factors combat disease is by ameliorating it in retrograde axonal transport. The motor impairment in SBMA may disapprovingly depend upon lower levels of muscle-derived BDNF, concludes that neuromuscular function can be salvaged in disease condition via reloading with muscle BDNF. Probable locations of BDNF action for endorsing neuromuscular function are Schwann cells, motoneurons, and muscles. Despite muscle fiber or motor neurons gets damage, BDNF tends to promote regaining the function of residual motoneurons and muscle fibers as well. Nonetheless, the satellite cell population mobilize within muscle tissue is also induced by BDNF action [37].

2.4 SIRT1/AMPK/PGC-1α signaling

Starvation or energy deprivation limits glucose availability compensated by accelerating mitochondrial fatty acid oxidation within the skeletal muscle or peripheral tissues to reserve blood glucose amount and stream to the brain and red blood cells. Further, shortage of metabolic flexibility appropriately acclimatizes as per energy demands and nutrient availability forms a burden on energy homeostasis, resulting in the development of the metabolic disease. Such, metabolic transformations within the muscle are pushed towards synchronized transcriptional responses promote mitochondrial utilization of lipids as their substrates for the energy source. The variations in gene expression patterns are attained via the modulation of some transcriptional regulators such as coactivator PGC-1α and FOXO family of transcription factors, both are closely associated with the regulation of mitochondria and fatty acid metabolism [38, 39]. The activities of PGC-1α and FOXOs are seriously influenced by controlling their acetylation levels through the silent information regulator/Sirtuin (SIRT1) type III (NAD^+-dependent deacetylase). SIRT1 knock-down averts induction of mitochondrial/fat oxidation genes in glucose-limited myocytes.

AMP-activated protein kinase (AMPK), metabolic sensing protein is found robustly influence the transcriptional responses. It is a heterotrimeric Ser/Thr kinase consists of one catalytic (α) with another non-catalytic subunits (β and γ). Further, two different isoforms are the α and β subunits (α1 and α2 or β1 and β2), and the γ subunits are determined by different genes (γ1, γ2, and γ3). The γ subunits usually interact with AMP/ATP competitively and work jointly. The AMP binding surges the catalytic activity of complex and augments phosphorylation of Thr^{172}, crucial for activity. AMPK enhances SIRT1 activity by raising intracellular NAD+ levels. This leads to deacetylation of SIRT1 targets (NF-κB, PGC-1α, FOXO1) which corresponds physiological or pharmacological AMPK activation [40, 41]. Enhanced organ fibrosis comprises organ to malfunction in a variety of diseases. Tissue fibrosis is also an eminent pathological feature of dystrophic skeletal muscle seen in Duchenne muscular dystrophy (DMD) human subjects. Further, repression of muscle fibrosis may be a beneficial treatment strategy in patients suffers from muscular atrophy and dystrophy. Treatment with active flavonoid resveratrol suppresses interstitial fibrosis in the biceps femoris of *mdx* mice.

The muscle cells find to activate SIRT1 that reduces oxidative stress by preventing transforming growth factor-*β*- (TGF-*β*-) induced upregulation of NADPH oxidase (NOX), which congruently generates reactive oxygen species (ROS) [42]. SIRT1 inhibits inflammatory cascade mediator's transcription factors via carrying

deacetylation of acetyl NF-κB to P-NFκB and repress inflammation within muscles. Furthermore, deacetylation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) via SIRT1 induces transcription of mitochondrial and HIF2αgenes and hence promotes fast to slow fiber shift [43–45]. Tissue fibrosis is reduced by SIRT1 which function by two mechanisms in fibroblasts. One is SIRT1-mediated deacetylation and inhibition of Smad transcription factors. Secondly, p300 deacetylation by SIRT1 following p300 protein degradation by the ubiquitin-proteasome pathway. Hence, the anti-fibrotic effect linked to SIRT1 activation may be valuable in treating muscular dystrophies [44].

Silent information regulator 1 or sirtuin 1 (SIRT-1) have seemed as the auspicious target of these pathways. It was found inhibiting differentiation of mouse C2C12 myoblasts and then reduce myogenin expression, a chief regulator with myogenic speciality and differentiate activate satellite cells. Furthermore, SIRT-1 directly involves in proliferating satellite cells. The outcomes propose that SIRT-1 impart significant role to sustain or raise satellite cells proliferation [44]. Overexpression of SIRT-1 activates the PI3K/AKT/mTOR pathway or increases levels of JunB or PGC-1α and able to induce rapid growth. SIRT-1 excites growth within muscles by inhibiting basal protein degradation with minimal or no change in overall protein synthesis [46]. Though FoxOs induction is critical for proteolysis enhancement either by autophagy or ubiquitin-proteasome system (UPS) through muscle atrophy and hence, FoxO3 inhibition was observed with hypertrophy induction by increasing protein synthesis. SIRT1 activation inhibits atrophy while promote rapid muscle growth through inhibition of FoxOs and parallel activating PGC-1α, with appropriate therapeutic implication in muscle wasting diseases [46].

2.5 Ubiquitin-proteasome systems

Within muscles, the ubiquitin-proteasome system (UPS) functions as removing sarcomeric proteins with changing muscle performance [4]. Lower muscle mass is related to (1) raised attachment of ubiquitin to muscle proteins; (2) overactive proteasome ATP dependent activity; (3) higher proteolysis (4) increased transcripts encoding ubiquitin, some ubiquitin-conjugating enzymes (E2), a few ubiquitin-protein ligases (E3) along with several proteasome subunits. E1 enzymes induce ubiquitin proteins after cleaving ATP to AMP [4]. The ubiquitin-protein makes a transfer to E2 via the E1 enzyme. The last step of the ubiquitylation reaction is finally catalyzed by E3 enzyme members. E3 interacts with E2 and the protein substrate; bring the ubiquitin transfer from E2 towards the substrate. As substrate becomes polyubiquitylated, with ZNF216 (upregulated by FoxO in muscle atrophy) recognition it is cropped to the proteasome systems following degradation during muscle atrophy. ZNF216-deficient mice are rather found resistant to muscle loss undergoing denervation. ZNF216 deficits in muscle cause accumulation of polyubiquitylated proteins [47]. Polyubiquitin protein chains can be detached through de-ubiquitylating enzymes [ubiquitin-specific processing proteases (USPs): USP14, USP19]. Atrogin-1 (specific ubiquitin ligase: MAFbx) regulates the t1/2 of the MyoD transcription factor and eIF3f (protein synthesis activator), which is a critical step in protein synthesis. The atrogin-1 knockdown avoids muscle loss during starvation in rodents [4, 48] while MuRF1 knockout (and not atrogin-1 knockout) are resilient against dexamethasone-provoke muscle atrophy [49]. Fbxo40 (ubiquitin ligase) regulates the t1/2 of IRS1, a necessary factor for IGF1/insulin signaling, while MuRF1 (specific ubiquitin ligase) regulates the t1/2 of several sarcomeric proteins [50].

2.6 Autophagy pathway

The discovery of autophagy in the year 1992 by Yoshinori Ohsumi changed the revolution of the machinery involved in orderly degradation and recycling of cellular components [51]. From then on enormous research has been done proving the importance of autophagy in eliminating invading pathogens, damaged organelles and toxic protein clearance in neurodegenerative disorders, attenuating neuroinflammation in dementia, Parkinson's, Alzheimer's [52, 53]. Furthermore, autophagy imparts a crucial role in the production of nutrients (amino acids, lipids, nucleic acids) during fasting [54]. The involvement of autophagy in muscle proteolysis during atrophy was recognized long back after the initial discovery of the mechanism of autophagy. Early studies significantly exhibit evidence that cathepsin L (lysosomal protease) was found with increased expression during muscle atrophy and lysosomal degradation was involved in protein breakdown in denervated muscles [55–57]. Molecular imaging techniques for visualization of autophagosome formation have improved the characterization of autophagy in atrophying muscles and normal cells. Multiple intracellular signaling mechanisms in diverse catabolic states and the role of atrogenes expression, protein degradation through the proteasome and autophagy pathways were studied.

The three major mechanisms involved in mammals for delivering autophagic cargo to lysosomes are macroautophagy, chaperone-mediated autophagy (CMA), and microautophagy [4]. The role of macroautophagy in muscle has been widely studied and microautophagy's role is yet to be discovered although some findings reveal the potential role of microautophagy for glycogen uptake within lysosomes at a time when macroautophagy is blocked [58, 59]. Macroautophagy generally is facilitated by activation of a regulatory complex (composed of Ambra1, Vps34, Vps15, Beclin 1, and Atg14) which further leads to recruit LC3 towards nascent autophagosome. Mitophagy (a selective form of macroautophagy) requires PINK1 and Bnip3 translocation factors. Scaffold protein p62 delivers the lysosomal degradation proteins (BAG3 and filamin) labeled by polyubiquitin chains to the autophagosome [60]. CMA majorly was studied for its crucial effects on neurodegenerative disorders, aging, and lysosomal storage diseases. In CMA, the damaged proteins due to excess ROS production express a definite amino acid sequence (KFERQ motif) which gets recognized by the Hsc70 chaperone and interacts with Lamp2a receptors delivers them to the lysosome [61]. Microautophagy engulfs small cytoplasmic portions into the lysosomes apart from breaking down glycogen in skeletal muscles. All three subtypes are involved contributing to protein degradation and remove organelle in skeletal muscles.

Autophagy is considered as a non-selective degradation pathway but with the advancement, in research, it has been shown that it can promote selective eradication of specific organelles (mitochondria) via mitophagy [62]. Skeletal muscles display the highest amount of vesicle formation when compared to other tissues during fasting conditions, confirming that in fasting conditions autophagosome formation is higher in glycolytic muscles rather than β-oxidative muscles [4]. Increased ROS production due to oxidative stress and impairment in the antioxidant defense systems is frequently seen in pathological conditions of muscle atrophy thus causing an imbalance in protein synthesis and degradation [63]. High ROS levels result in inhibition of insulin's actions acting as a putative mediator in the development of insulin resistance [63]. The increased oxidative stress in the muscle cells promotes the expression of autophagy proteins activating proteolytic pathways like calpain and ubiquitin-proteasome system. Dodd et al., 2010 conferred in their work that ROS might be the activator of the FOXO pathway and NF-kB in skeletal muscle atrophy [64].

The genes that regulate mitophagy are parkin, PINK1, Bnip3L, Bnip3 and inactivation in these genes may cause impaired mitochondria synthesis [65]. PINK1 assists the recruitment of parkin to mitochondria, parkin promotes mitophagy through ubiquitylation of mitochondrial membrane proteins recognized by p62 and adds autophagic vesicles for ubiquitylated mitochondrial proteins [66]. Autophagosome recruitment to mitochondria occurs as a result of Bnip3 and Bip3L binding to the LC3 domain [67]. Mitochondria network is remodeled during fasting and denervation via Bnip3 promoting autophagy. Inhibiting mitochondrial fission in mice was sufficient to prevent muscle atrophy during denervation providing significant insights in the importance of mitochondrial fission machinery, an impairment in basal mitophagy may lead to a disruption in the muscle homeostasis [16]. Besides mitophagy, nucleophagy may prove to be essential for the nuclear remodeling of muscle fibers [68].

3. Therapeutic targets and pharmacological interventions

The growing era of both synthetic and natural agents, characterized for targeting different aspects of NF-κB signaling. Targeting activators of NF-κB activation, such as TNF-α, monoclonal antibodies against TNF-α (infliximab) or decoy TNF receptors (e.g., etanercept), both drugs were found putting useful effects in the mdx model of DMD – decreasing myonecrosis and inhibits overall inflammation. The patients, who suffer from myositis, find with the raised expression of TNF-α in the muscle, anti-TNF therapies are not preferred. NEMO-binding domain (NBD) peptide interrupts the association of the IKK complex – which thwarts canonical NF-κB pathway activation [69]. NBD peptide in the mdx model of DMD decreases the macrophage infiltration into muscle and prevented overall membrane damage/lysis. Salicylates tend to inhibit NF-κB activation and ameliorate muscle damage. Natural compounds (curcumin, *Aloe vera*, berberine, apigenin, Quercetin, resveratrol, 7,8-dihydroxyflavone, aspalathin, hesperidin, naringin, Epigallocatechin gallate, luteolin, rutin, Sulforaphane can target NF-κB signaling and harbors anti-NF-κB properties [70]. The use of antioxidants prevents inactivity-induced oxidative stress within skeletal muscles. Furthermore, antioxidants treatment to rodents could promote protein synthesis ad inhibits proteolysis. Numerous studies suggested that selected antioxidants such as vitamin E, Trolox and mitochondrial-targeted antioxidants, can lower inactivity-induced muscle atrophy in limb and respiratory muscles as well [71].

BDNF mimetic natural compound (7,8-dihydroxyflavone), chronically activate muscular TrkB modulates cellular energy expense and prohibit the development of excess body weight in female mice. These results reveal the molecular mechanism of targeting the TrkB receptor regulates cellular energy metabolism and improved motor activity [36, 72].

Certain evidence from *in vitro* studies concludes that Ferulic acid (polyphenolic compound), quercetin, luteolin, kaempferol, baicalin, rutin, naringin, and hesperidin regulates muscle fiber formation via activating Sirt1/AMPK signaling pathway. It activates Sirt1, which further activates LKB1 and AMPK. Sirt1 and AMPK congregate on enhancing the expression of PGC-1α and endorsing slow oxidative muscle fiber formation [72, 73]. Furthermore, Ex229 (a small molecule 991), PF-739, and MK-8722 activates AMPK within skeletal muscle [74].

Proteasome inhibitor such as MG132 significantly inhibits IκBα degradation and prevents NFκB activation *in vitro*. MG132 conserved muscle and its myofiber cross-sectional area via downregulating muscle-specific ubiquitin ligases: atrogin-1/MAFbx and MuRF-1 mRNA studied *in vivo* [75]. Furthermore, proteasome

inhibitor Velcade (also known as PS-341 and bortezomib) directly inhibits the proteasome complex without directly impacting ubiquitination. This compound is usually orally active and is currently approved for treating multiple myeloma. Velcade utilization reduces skeletal muscle atrophy observed in denervated skeletal muscle in rats [76].

Myostatin and activin A antagonists: Myostatin, autocrine factor which normally confines muscle size. With growing evidence, increased generation of myostatin and its analog, activin A, contribute to several forms of atrophy. Inhibition of myostatin–activin A–GDF11 signaling is a hopeful therapy for multiple types of systemic wasting.

The SMA disease management utilizes a multidisciplinary and supportive approach, include neurologists (adult and pediatric), geneticists, respiratory physicians, gastroenterologists, orthopedic surgeons, palliative care physicians, rehabilitation specialists, and allied health services [2] (**Table 1**). Furthermore, **Table 2** describes the list of clinical trials with different approaches to treat SMA. There are

Complications	Assessments	Interventions
Respiratory	Cough effectiveness; respiratory muscle function tests; overnight oximetry; forced vital capacity (> 6 yrs)	Routine immunizations
		Annual influenza vaccination
	Overnight polysomnography if disordered breathing suspected; Acute respiratory infections	
		Airway clearance techniques and cough assistance- chest physiotherapy, postural drainage, mechanical or manual cough assistance
		Noninvasive ventilation
		Antibiotics intensified airway clearance
		Increased ventilation support
Gastrointestinal and nutritional	Feeding and swallowing assessment	Nutritional supplementation, modifying food consistency, optimal oral intake
		Nasogastric, nasojejunal or percutaneous gastronomy – as reduced oral intake is observed
		Nissen fundoplication
	Assess caloric intake	
	Assess for signs of reflux or aspiration	Hydration
	Assess for constipation	
Orthopedic and rehabilitation	Posture, mobility, function, Contractures, Scoliosis	Equipment to assist with mobility, self-care and function
		Physiotherapy, standing frames, Spinal Surgery
Psychological	Assess for depression or anxiety	Counseling, Antidepressants, Antianxiety drug managements

Table 1.
Current Management of Spinal Muscular Atrophy.

Study	Status	Type	Methods	Trial number	Sponsor
Gene Transfer Clinical Trial for Spinal Muscular Atrophy Type 1	Completed	Phase I, nonrandomized, open-label	Functional SMN gene is delivered intravenously using AAV9 The study involves three cohorts and escalating doses to evaluate safety and efficacy	NCT02122952	AveXis, Inc.
A Study to Assess the Efficacy and Safety of ISIS-SMNRx in Patients with Later-onset Spinal Muscular Atrophy	Completed	Phase III, RCT	ISIS-SMNRx is administered by intrathecal injections with small needle prick on the lower back	NCT02292537	Biogen
An Open-label Safety, Tolerability, and Dose-range Finding Study of ISIS-SMNRx in Patients with Spinal Muscular Atrophy	Completed	Phase I, nonrandomized, open-label	ISIS-SMNRx is administered as a single intrathecal injection	NCT01494701	Biogen
A Study to Assess the Safety and Pharmacokinetics of ISIS-SMNRx in Infants with Spinal Muscular Atrophy	Completed	Phase II, nonrandomized, open-label	Multiple doses of ISIS-SMNRx administered into the spinal fluid three times over the duration of the trial	NCT01839656	Biogen
An Open-label Safety, Tolerability and Dose-range Finding Study of Multiple Doses of ISIS-SMNRx in Patient with Spinal Muscular Atrophy (SMNRx-CS2)	Completed	Phase II, nonrandomized, open-label	Escalating doses of ISIS-SMNRx administered multiple times with intrathecal injections	NCT01703988	Biogen
An Open-label Safety and Tolerability Study of ISIS-SMNRx in Patients with Spinal Muscular Atrophy Who Previously Participated in ISIS 396443-CS1	Completed	Phase I, nonrandomized, open-label	Single dose of ISIS-SMNRx administered as a single intrathecal injection in patients who previously participated in ISIS 396443-CS1	NCT01780246	Biogen
An Open-label Safety and Tolerability Study of ISIS-SMNRx in Patients with Spinal Muscular Atrophy Who Previously Participated in ISIS SMNRx-CS2 or ISIS SMNRx-CS10	Completed	Phase I, nonrandomized, open-label	Multiple doses of ISIS-SMNRx administered as an intrathecal injection in patients who previously participated in ISIS 396443-CS2 or ISIS 396443-CS10	NCT02052791	Biogen
A study to assess the efficacy and safety of nusinersen (ISIS 396443) in infants with SMA (ENDEAR)	Terminated	Phase III, randomized, quadruple (participant, care provider, investigator, outcomes assessor)	ISIS-SMNRx* is administered by intrathecal injections with small needle prick on the lower back	NCT02193074	Biogen

Study	Status	Type	Methods	Trial number	Sponsor
A study for participants with SMA who previously participated in nusinersen (ISIS 396443) investigational studies (SHINE)	Active, Non recruiting	Phase III, nonrandomized, open-label	Administered by intrathecal (IT) injection to evaluate long term safety and tolerability	NCT02594124	Biogen
A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants With Genetically Diagnosed and Pre-symptomatic Spinal Muscular Atrophy (NURTURE).	Active, Non recruiting	Phase II, open-label	Intrathecal administration of multiple doses of nusinersen in infants with genetically diagnosed and pre-symptomatic SM	NCT02386553	Biogen
A study of RO6885247 in adult and pediatric patients with SMA (MOONFISH)	Terminated	Phase I, randomized double (participant, investigator)	Patients receive either RO6885247 or placebo in oral solution once daily for 12 weeks	NCT02240355	Hoffmann-La Roche
A study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of RO7034067 (RG7916) given by mouth in healthy volunteer	Completed	Phase I, randomized, double (participant, investigator)	Oral administration of RO7034067 in healthy subjects to investigate safety, tolerability, pharmacokinetics and pharmacodynamics	NCT02633709	Hoffmann-La Roche
A study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of RO7034067 in participants with type 2 and 3 spinal SMA (Sunfish)	Active, Non recruiting	Phase II, III, randomized, double (participant, investigator)	Oral administration of RO7034067 in adult and pediatric patients with SMA2 and SMA3. The two-part study consists of an exploratory dose-finding part for 12 weeks and a confirmatory part for 24 months	NCT02908685	Hoffmann-La Roche
A study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of RO7034067 in infants with type 1 SMA (Firefish)	Active, Non recruiting	Phase II, III, nonrandomized, open-label	Oral administration of RO7034067 in infants with SMA1. The two-part study consists of an exploratory dose-finding part and a confirmatory part for 24 months at the dose selected in part 1	NCT02913482	Hoffmann-La Roche
A study of RO7034067 in adult and pediatric participants with SMA (Jewelfish)	Active, Non recruiting	Phase II, open- label	Oral administration of RO7034067 in adults and children with SMA2 and SMA3 previously treated with a SMN2targeting therapy	NCT03032172	Hoffmann-La Roche

Study	Status	Type	Methods	Trial number	Sponsor
An open-label study of LMI070 in type 1 SMA	Active, Non recruiting	Phase I, II nonrandomized, open-label	Oral administration of LMI070 to investigate, the dose is safe for long term use or not	NCT02268552	Novartis Pharmaceuticals
Safety and efficacy of olesoxime (TRO19622) in patients with SMA aged 3–25 years	Completed	Phase II, randomized, quadruple (participant, care provider, investigator, outcomes assessor)	Administration of liquid suspension formulation (10 mg/kg) of olesoxime once a day with food at dinner to non-ambulant 3–25-year-old patients with SMA2 or SMA3	NCT01302600	Hoffmann-La Roche
A study to evaluate long term safety, tolerability, and effectiveness of olesoxime in participants with SMA	Completed	Phase II, open-label	Administration of 10 mg/kg suspension of olesoxime once a day either orally or via a nasogastric or gastrostomy tube in patients with SMA who participated in previous TRO19622 studies	NCT02628743	Hoffmann-La Roche
A study of CK-2127107 in patients with SMA	Completed	Phase II, randomized, triple (participant, investigator, treatment assessor)	Oral administration of multiple doses of CK-2127107 to ambulant and non-ambulant patients with SMA2, SMA3 and SMA4	NCT02644668	Cytokinetics
A Study to Assess the Safety and Tolerability of Nusinersen (ISIS 396443) in Participants With Spinal Muscular Atrophy (SMA). (EMBRACE)	Terminated	Phase II, randomized, quadruple (participant, care provider,investigator, outcomes assessor)	Multiple doses of Nusinersen administered as an intrathecal injection	NCT02462759	Biogen
An Active Treatment Study of SRK-015 in Patients with Type 2 or Type 3 Spinal Muscular Atrophy (TOPAZ)	Active, Non recruiting	Phase I, nonrandomized, open-label	Administration of SRK-015 intravenous infusion in SMA Type 2 and Type 3 in pediatric and adult patients, to investigate the safety and efficacy	NCT03921528	Scholar Rock,Inc.

Based on trials listed in https://www.clinicaltrials.gov/ and http://www.curesma.org/.

Table 2.
Clinical trials list with different approaches to treat Spinal Muscular atrophy.

Drugs	Disease	Route of Delivery	Outcomes	References
ActRIIB decoy	Lung and Bowel cancer	Subcutaneous injection	Reversed skeletal and cardiac muscle wasting and prolonged survival	[79]
Myostatin-specific antibody	Lung cancer	Subcutaneous injection	Inhibited muscle wasting and improved muscle function	[80]
Myostatin-specific peptibody	Kidney failure	Subcutaneous injection	Prevented Muscle wasting	[81]
JA-16 (myostatin-specific antibody)	Cardiac failure	Intraperitoneal Injection	Inhibited Muscle wasting	[82]
Myostatin-specific antibody	Disuse (hindlimb immobilization in plaster cast	Subcutaneous injection	Inhibited muscle wasting	[83]
Myostatin-specific antibody	Sarcopenia	Subcutaneous injection	Inhibited muscle wasting	[83]
STAT3 small-molecule inhibitor (C188–9)	Kidney failure	Subcutaneous injection	Inhibited muscle wasting	[84]

Table 3.
Studies of myostatin–activin pathway inhibitors in rodents.

Drug/target	Disease Process	Trial details	Outcomes	Ref. or Clinical Trials.gov.identifier
TNF-α				
Etanercept (TNFα ligand bound to Fc-IgG1	Cancer	IV administration RCT	No inhibition of muscle wasting	[85]
Infliximab (TNF-α specific mAb)	Non-small-cell lung cancer	IV administration RCT	Trial ceased early stages due to reduced patient quality life in infliximab-treated group	[86]
IL-6				
ALD518 (BMS-945429; IL-6 – specific mAb	Lung cancer	IV administration Phase I/II	No inhibition of muscle wasting	[87]
Myostatin/activin				
BYM338 (bimagrumab; ActRIIB-specific mAb)	Sarcopenia	IV administration RCT	In Progress	NCT01669174
	COPD	IV administration RCT	In Progress	NCT01601600

Drug/target	Disease Process	Trial details	Outcomes	Ref. or Clinical Trials.gov.identifier
	Cancer	IV administration RCT	In Progress	NCT01868685
	Mechanical ventilation	IV administration RCT	In Progress	NCT01433263
	Sporadic inclusion body myositis	IV administration RCT	In Progress	NCT01925209 (RESILIENT trial)
LY2495655 (myostatinspecificmAb)	Pancreatic cancer	IV administration Phase II	In Progress	NCT01505530
Ghrelin receptor				
Ghrelin	COPD	IV administration RCT	Improvement in quality of life but not physical activity	[88]
Anamorelin (growth hormone secretagogue receptor agonist)	Cancer	Oral administration RCT	Improved symptoms	[89]
	Non-small-cell lung cancer	Oral administration RCT	In Progress	NCT01387282
SUN11031 (ghrelin agonist)	COPD	Subcutaneous administration	Increased muscle mass but not function	NCT00698828
Androgen receptor				
Enobosarm	Aging	Oral administration Phase II	Increased muscle mass and function	[90]
	Cancer	Oral administration RCT	Increase muscle mass but not function	NCT01355484 and NCT01355497 (POWER trials); NCT00467844
MT-102 (SARM)	Non-small-cell lung cancer	Oral administration RCT	In Progress	ACT-ONE trial
GSK2849466 (SARM)	Healthy volunteers	Oral administration Phase I	Non-serious adverse events	NCT01696604
LGD-4033 (SARM)	Healthy volunteers	Oral administration Phase I	Non-serious adverse events	[91]

ActRIIB, activin A receptor, type IIB; COPD, chronic obstructive pulmonary disease; IgG1, immunoglobulin G1; IV, ntravenous; IL-6, interleukin-6; mAb, monoclonal antibody; RCT, randomized controlled trial; SARM, selective androgen receptor modulator

Table 4.
Clinical trials assessing treatments for muscle wasting.

some preclinical and clinical trials evaluating treatments for muscle wasting [77, 78] mentioned in **Tables 3** and **4**.

The Stem-cell-related therapies provide prominent therapeutic benefits in the reversal of condition in muscle atrophy thereby promoting muscle regeneration. Stem cell therapy (e.g., umbilical cord blood stem cell transplantation) showed helpful results for treating Duchenne muscular dystrophy (DMD). In the setting of a first-in-class approved therapy, progress in developing second generation and combination therapies will be requisite for novel approaches in trial design [92, 93]. Also, current new challenges are for developing therapies, together with difficulties access to treatment allied with complications, costs, and expertise which is required for intrathecal administration. Further efforts to ascertain optimal routes of drug delivery, body distribution, and limit safety therapeutic window must be essential.

4. Conclusion

Further, future directions are needed for developing novel safe, efficacious therapies with innovative therapeutic approaches for establishing a quality life in patients. The foremost challenge with developing therapies that grow muscle is preventing misuse for enhancing athletic performance, particularly anabolic steroids and growth hormones. Novel methods along with specific guidelines must be developed to monitor the numerous agents with potential remedial benefits of such therapies are likely to be considerable.

Acknowledgements

Abbreviations

ALS	autophagy lysosomal system
AMPK	AMP activated protein kinase
BDNF	brain-derived neurotrophic factor
CMA	chaperone mediated autophagy
cPKC	protein kinase C
DMD	Duchenne muscular dystrophy
DRP1	dynamin related protein 1
FoxO	forkhead box transcription factors
IKKβ	IκB kinase
MFN	mitofusin
MAM	membrane associated-sarcoplasmic reticulum membranes
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NGF	nerve growth factor
OPA1	optic atrophy 1
PGC-1α	proliferator-activated receptor gamma coactivator 1-alpha
ROS	reactive oxygen species
SBMA	spinal bulbar muscular atrophy
SMA	spinal Muscular Atrophy
SIRT1	silent information regulator/Sirtuin 1

TrkB	tropomyosin-related kinase B receptor
TGF-β	transforming growth factor-β
TNF-α	tumor necrosis factor-α
TWEAK	TNF-like weak inducer of apoptosis
UPS	ubiquitin–proteasome system
VEGF	vascular endothelial growth factor

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