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Skeletal muscle atrophy is the consequence of protein degradation exceeding protein synthesis because of disease, aging, and physical inactivity. Patients with skeletal muscle atrophy have decreased muscle mass and fiber cross-sectional area, thereby experiencing reduced survival quality and motor function. The forkhead box O (FOXO) signaling pathway plays an important role in the pathogenesis of skeletal muscle atrophy by regulating E3 ubiquitin ligases and some autophagy factors. However, the mechanism of FOXO signaling pathway leading to skeletal muscle atrophy is still unclear and needs to be further explored. The development of treatment strategies for skeletal muscle atrophy has been a thorny problem. FOXO-targeted therapy to treat skeletal muscle atrophy is a promising approach, and an increasing number of relevant studies have been reported. In this article, we reviewed the mechanism and therapeutic targets of the FOXO signaling pathway mediating skeletal muscle atrophy, and provided some new ideas for the clinical treatment of this condition. (Am J Pathol 2022, 180: 1–10; https://doi.org/10.1016/j.ajpath.2022.09.003)
activated by many types of cellular stimulation or toxic injury, regulates essential cellular functions, such as transcription, translation, proliferation, growth, and survival. Besides essential cellular functions aforementioned, the IGF-1/PI3K/AKT signaling pathway regulates the gain and loss of skeletal muscle mass. When AKT is activated, it can control key cellular processes by phosphorylating the substrates involved in apoptosis, protein synthesis, metabolism, and the cell cycle. Downstream factors of the IGF-1/PI3K/AKT signaling pathway include glycogen synthase kinase-3β, mammalian target of rapamycin (mTOR), and forkhead box O (FOXO), which are all key regulatory proteins involved in protein synthesis and atrophy.

FOXOs are the evolutionarily conserved transcription factors of metabolic and stress responses. There are four types of FOXO existing in the human body (namely, FOXO1, FOXO3, FOXO4, and FOXO6). Among them, what are involved in skeletal muscle atrophy are mainly FOXO1 and FOXO3. By summarizing the regulatory role of FOXO signaling pathway in the pathogenesis of skeletal muscle atrophy and the possible therapeutic strategies to treat skeletal muscle atrophy through the FOXO signaling pathway, this article aimed to provide reference ideas for future clinical treatment.

Balance of Skeletal Muscle Atrophy and Hypertrophy

Causes of skeletal muscle atrophy include primary muscle atrophy and secondary muscle atrophy. Primary muscle atrophy includes muscular dystrophy, congenital myopathy, mitochondrial myopathy, and metabolic myopathy, whereas pathologic conditions leading to secondary muscle atrophy include neuromuscular diseases, cancer, chronic inflammatory diseases, and acute critical illness. Regardless of the pathogenesis, the stability of skeletal muscle mass is basically the result of the balance between protein anabolism and catabolism, covering both direct and indirect regulation of various factors. Muscle anabolism is driven by growth hormone, insulin, IGF-1, and testosterone, and muscle catabolism is regulated by endocrine, inflammatory, and oxidative stress factors.

Four proteolytic systems are known to be involved in muscle atrophy [namely, the ubiquitin proteasome system (UPS), the autophagy lysosome system, the cysteine aspartic proteases, and the calpain system]. Among them, the FOXO signaling pathway in this review is mainly related to the UPS and the autophagy lysosome system. The various types of FOXOs can regulate many genes in UPS and autophagy. UPS is composed of ubiquitin activase, ubiquitin-binding enzyme, ubiquitin protein ligase (E3), ubiquitin, and 26S proteasome, among which, the ubiquitin E3 ligase muscle ring finger 1 (MuRF-1) and another ligase that ubiquitiniates desmin muscle atrophy, F-box (MABx)/Atrogin-1, are also downstream regulatory genes of the FOXO signaling pathway; MuRF-1 is the most significant UPS factor in skeletal muscle atrophy and plays a part in myofibril degradation; besides, Atrogin-1 can also be involved in skeletal muscle atrophy. Ubiquitin forms compounds with ubiquitin activate and ubiquitin-binding enzyme in sequence, and then transfers the protein to E3 for processing, where the protein is finally degraded in the 26S proteasome, leading to peptide degradation and ubiquitin release for recycling. FOXO3 regulates some essential autophagy genes in the autophagy lysosome system, including Bnip3, Gabarap, LC3, and Atg12.

The IGF-1/PI3K/AKT signaling pathway plays an important role in various molecules and pathways related to skeletal muscle mass homeostasis. The two main downstream branches of the AKT pathway involved in muscle hypertrophy are the AKT-activated mTOR pathway and the AKT-blocked glycogen synthase kinase-3β, both of which control protein synthesis. Glycogen synthase kinase-3β can block the eukaryotic initiation factor 2B, which is involved in protein synthesis. When glycogen synthase kinase-3β is inhibited by AKT, the translation initiation factor 2B will be activated, resulting in increased protein synthesis. mTOR kinase interacts with several proteins to form two different complexes: one is the rapamycin-sensitive mTORC1 complex containing Raptor and the other one is the rapamycin-insensitive mTORC2 complex containing Rictor. The mTORC1 complex is mainly involved in protein synthesis. Phosphorylation of mTORC1 is mediated by the Raptor interacting protein to inhibit the eukaryotic cell initiation factor 4E binding protein 1, and mTORC1-mediated inhibition of 4E binding protein 1 will further lead to activation of the eukaryotic cell initiation factor 4E, thereby increasing protein synthesis.

Characteristics of FOXO Signaling Pathway

FOXOs are one of the major targets of the IGF-1/PI3K/AKT signaling pathway. The first gene containing the forkhead region was discovered in 1989 by Weigel et al while studying Drosophila. FOXOs are the evolutionarily conserved transcription factors of metabolic and stress responses, responsible for regulating the genes associated with autophagy, oxidative stress, energy metabolism, and muscle atrophy. There are four types of FOXOs existing in the human body (namely, FOXO1, FOXO3, FOXO4, and FOXO6), all of which belong to the large family of forkhead box transcription factors that share a highly conserved 100 amino acid DNA binding domain called the forkhead domain. More specifically, FOXO1 and FOXO3 are extensively expressed in skeletal muscle; FOXO4 is highly expressed in the skeletal and cardiac muscle; and FOXO6 is mainly expressed in the brain.
FOXOs can be regulated by a variety of external stimuli, such as insulin, IGF-1, other growth factors, neurotrophic factors, cytokines, and oxidative stress stimuli. The regulation of FOXOs through these stimuli is achieved by alterations in the posttranslational modifications of FOXOs, including phosphorylation, acetylation, and ubiquitination modifications. Among them, phosphorylation is the predominant posttranslational modification regulating the FOXO activity and can be mediated by several kinases, including AKT, AMPK, JNK, PRMT, SGK, ERK, p38, CDK2, CK1, and MST1, each recognizing a specific sequence in the FOXO. The most particular input to FOXO activity is the AKT activation signal in the presence of growth factors. FOXOs will translocate to the cytoplasm to be inactivated when they are phosphorylated by the IGF-1/PI3K/AKT signaling pathway. However, on induction of other kinases (eg, AMP-activated protein kinase/AMPK), FOXOs will be transferred to the nucleus where they can perform transcriptional functions. The dephosphorylated FOXOs can up-regulate the target genes in various cellular processes (eg, p21 and p27, which regulate the cell cycle; FasL, Bim, and Atg, which lead to apoptosis and autophagy; G6P, which involves glucose metabolism; Ponce and AgRP, which regulate food intake; and Atrogin-1, which causes muscle atrophy).
FOXO Signaling Pathway Regulates Skeletal Muscle Atrophy

As mentioned above, the FOXO signaling pathway is one of the major pathways regulating skeletal muscle atrophy. It mainly causes skeletal muscle atrophy through protein degradation. Then, what are the underlying mechanisms that link the FOXO signaling pathway with skeletal muscle atrophy?

In 2004, Kamei et al. demonstrated that FOXO1 negatively regulates the skeletal muscle mass and function by establishing specific FOXO1 overexpression mouse models. However, the specific mechanism by which FOXOs regulate skeletal muscle atrophy remains unclear. Meanwhile, Sandri et al. first demonstrated that FOXOs induced the ubiquitin ligase Atrogin-1 and caused skeletal muscle atrophy. They concluded that, in the normally growing skeletal muscle, the upstream AKT could suppress the FOXO-mediated expression of ubiquitin ligase Atrogin-1, thereby inhibiting skeletal muscle atrophy. Later, it was further demonstrated that the specific mechanism of the action of AKT was attributed to the phosphorylation of FOXOs, which were transferred to the cytoplasm and were then inactivated. In addition, Kang et al. established a rat model of Cushing syndrome and proposed a mechanism by which the glucocorticoid receptor and FOXO3 acted as a regulator of muscle atrophy in Cushing syndrome. The authors further pointed out that FOXO3 was involved in muscle atrophy by regulating MuRF-1 and Atrogin-1. A new group of novel ubiquitin ligases regulated by FOXO, MUSA1, SMART, FBXO31, and Itch, were identified in recent studies and were shown to be closely associated with skeletal muscle atrophy. FOXOs induce skeletal muscle atrophy also by regulating the related autophagy genes in addition to the UPS system described above. Mamucari et al. demonstrated that FOXO3 controlled the transcription of autophagy-related genes, including LC3 and Bnip3, of which Bnip3 is the main gene accounting for skeletal muscle atrophy. O'Neill et al. further demonstrated that FOXOs regulated the skeletal muscle autophagy in streptozotocin-diabetes mice by regulating both UPS and autophagy. Recently, Oyabu et al. identified novel FOXO1 target genes by modeling FOXO deletion, and CCAAT/enhancer-binding protein δ was shown to be a mediator and cofactor in the induction of UPS by FOXO1. As claimed by Ratti et al., the FOXO3-regulated histone deacetylase (HDAC) 6 was also a skeletal muscle atrophy gene associated with UPS, which possesses a ubiquitin binding domain interacting with Atrogin-1 to induce skeletal muscle autophagy. The detailed mechanism is shown in Figure 1.

FOXO not only acts on downstream genes, but also aggravates the status of skeletal muscle atrophy by exerting synergistic effects with a variety of factors. Reed et al. developed several different models of muscle atrophy and found that simultaneous blockade of the IκB kinase—mediated NF-κB activity and the FOXO transcriptional activity completely eliminated the disuse-induced muscle fiber atrophy, possibly because some atrophy genes contain both κB sites and FOXO binding elements in their regulatory regions. Recently, a potential FOXO synergistic partner, SMAD, which is a transcription factor activated by the muscle growth inhibitor (MYOSTATIN) and transforming growth factor-β, has also been identified. SMAD3 was shown to enhance the activity of FOXO-induced ubiquitin ligases, including MuRF-1 and MUSA1. In addition, the inhibition of FOXO activity in normal muscle concomitantly decreases the transcriptional activity of SMAD, which may be the result of a diminished synergistic effect. In 2007, Nakashima and Yakabe stimulated C2C12 myotubes using the AMPK activator (5-aminimidazole-4-carboxamide-1-β-D-ribonucleoside) AICAR and detected increased degradation of proteins, as well as increased levels of FOXOs and expressions of MuRF-1 and Atrogin-1 genes in C2C12 myotubes. mTORC1, a downstream branch of the AKT signaling pathway, has been mentioned earlier as a branch that leads to increased protein synthesis. However, recent studies have revealed that, when AKT signaling is inactive, mTORC1 can control a fine-tuned feedback loop to inhibit AKT and increase protein degradation. The specific mechanism above is shown in Figure 1. Recently, Fujimaki et al. identified a new target for the treatment of muscle wasting diseases, the endothelial Delta-like ligand-4. By silencing Delta-like ligand-4 or knocking out MUSC2 axis, and demonstrated that Notch2 was an upstream regulator of the FOXO signaling pathway.

In 1993, Lee et al. identified a noncoding small RNA (miRNA) in nematodes. The miRNAs regulate the proliferation, differentiation, and progression of various diseases by binding to the 3′-untranslated region of target genes. An increasing number of miRNAs have been shown to play a regulatory role in skeletal muscle atrophy. Among them, miRNAs that act on skeletal muscle atrophy through the FOXO signaling pathway have also been identified in large numbers. Specifically, miR-182 and miR-1290 were shown to directly inhibit the FOXO3 expression in C2C12 myotubes, and miR-486 and miR-27 were shown to inhibit FOXO1 to reduce the E3 ubiquitin ligase expression. The regulation of miR-23 with FOXOs is more complex, as miR-23 not only increases phosphorylation of AKT and inactivates FOXOs by decreasing PTEN (phosphatase and tensin homolog deleted on chromosome 10), but also...
directly inhibits the expressions of E3 ubiquitin ligases MuRF-1 and Atrogin-1. However, elevated miR-18 expression can lead to increased myotubular atrophy because miR-18 can increase the E3 ubiquitin ligase expression by down-regulating the IGF-1/P38K/akt signaling pathway. Wei et al also found that FOXO3 was regulated by hsa-miR-1207-5p, but further experimental validation is needed to confirm this finding. All of these miRNAs may be new targets for the treatment of skeletal muscle atrophy.

FOXO Signaling Pathway as a Therapeutic Target for Skeletal Muscle Atrophy

As a signaling pathway that activates the pathologic process of skeletal muscle atrophy, the FOXO signaling pathway may also function as a potential pathway for the treatment of skeletal muscle atrophy. In this article, several therapeutic targets surrounding FOXOs were summarized as follows.

AKT Activator and Its Upstream Molecular Activator

As mentioned earlier, AKT is the most common stimulatory signal for FOXO phosphorylation; it phosphorylates and translocates FOXOs to inactivate them in the cytoplasm. Therefore, activators of various types of AKT as well as their upstream molecular agonists can be potential therapeutic targets. Obestatin is a peptide consisting of 23 amino acids that activates the AKT signaling pathway through the G-protein-coupled receptor 39 and promotes the AKT signaling pathway in cell function, among other elements. By investigating the role of obestatin in the AKT downstream FOXO-regulated UPS and autophagy lysisome system, Cid-Díaz et al demonstrated that the obestatin-G-protein-coupled receptor 39 system inhibited protein degradation through inactivation of FOXO1 and FOXO4. In 2021, the team further found that the FOXO expression could also be activated through the neuronal precursor cell-expressed developmentally down-regulated 4/Krüppel-like factor (KLF) 15 axis, and obestatin not only stimulated the AKT signaling pathway but also down-regulated the neuronal precursor cell-expressed developmentally down-regulated 4/KLF15 axis expression to attenuate skeletal muscle atrophy. In addition, obestatin was also shown to promote the AKT signaling pathway in gastric cancer. Sestrins can prevent the progression of fat accumulation during aging. Recently, sestrin2 was found to activate the AKT signaling pathway by inducing P3K and mTORC2. Further demonstrated that sestrins could regulate the balance of mTOR complex, induce the mTORC2 activity, and suppress the FOXO-dependent skeletal muscle atrophy gene expression by up-regulating AKT. A potential direction for future research may lie in sestrin/mTOR modulators, such as NV-5138, which has been found to activate mTORC1 to produce rapid antidepressant effects. Moreover, a mitochondrial-derived peptide was also recently identified (namely, the mitochondrial open reading frame of the 12S ribosomal RNA type-c, which was shown to increase AKT phosphorylation and thus decrease the FOXO1 expression by increasing mTORC2). In addition to medication, safe alternatives, such as pulsed electromagnetic fields (PEMFs), are coming into view. PEMFs were first applied in 1974 to accelerate fracture healing, and have been widely used since then with increasing evidence on their ability to promote osteogenesis. PEMFs were found to promote activation of the mTOR signaling pathway by up-regulating the proteins AKT and MAPK kinase. Subsequently, Yang et al treated rats with streptozotocin-induced diabetic muscle atrophy using PEMFs and found that PEMFs significantly activated AKT and increased the cross-sectional area of muscle fibers in rat models. These studies have laid important foundation for the clinical application of PEMFs.

IGF-1 can be activated by a variety of signals, including angiotensin. By examining a murine mesangial cell line used to determine the mechanisms of the renin-angiotensin system and the IGF axis in elevated glucose levels, Davis et al reported that the exogenous angiotensin II treatment directly induced an increase in the IGF binding protein 2. In addition, Morales et al demonstrated that angiotensin exerted an anti-atrophic effect through its receptor to activate IGF-1. Liu Wei Di Huang is a traditional Chinese medicine consisting of six herbs, and has been shown to up-regulate the IGF-1 expression. In diabetic rat models, Liu Wei Di Huang decoction up-regulated the expressions of brain-derived neurotrophic factor and IGF-1 in the brains of rats with diabetic encephalopathy. Tseng et al. on such a basis, investigated the effect of Liu Wei Di Huang decoction on skeletal muscle atrophy in diabetic mice models and demonstrated that Liu Wei Di Huang decoction could improve the condition of skeletal muscle atrophy by activating IGF-1. Epigallocatechin 3-gallate is a polyphenolic flavonoid that is thought to have similar effects to IGF-1 and insulin. An earlier study found that the epigallocatechin 3-gallate treatment significantly restored the phosphorylated forms of P3K and AKT and inhibited the FOXO1 expression. Wimmer et al examined the nuclear-cytoplasmic translocation of green fluorescent protein-tagged FOXO1 by utilizing the confocal fluorescence imaging of adult mouse skeletal muscle fibers and found that epigallocatechin 3-gallate might not only directly activate P3K but also indirectly activate P3K phosphorylation via reactive oxygen species. Activation of the IGF-1/P3K/AKT signaling pathway by epigallocatechin 3-gallate also stimulates the growth and neuronal differentiation of cochlear neural stem cells, which can be used in the treatment of hearing impairment. The general AKT analogs as well as chemical activators have low selectivity and high toxic adverse effects and are often used only in in vitro experiments and scientific studies; continuous exploration is therefore needed before using these substances as clinical...
treatments. In addition to AKT kinases, activators of AMPK and IGF-1 and inhibitors of myostatin can also indirectly inhibit FOXO (Table 1).86–90

**Direct Inhibitors of FOXOs**

There are also inhibitors that act directly on FOXOs, some by blocking the nuclear localization of FOXOs, whereas others by inhibiting FOXOs directly. Leucine is a branched-chain amino acid that is thought to promote protein synthesis and reduce protein degradation.81 The glucocorticoid-induced leucine zipper (GILZ) is a protein isolated from a thymic subtractive DNA library as a dexamethasone-responsive gene.92 In 2004, Asselin-Labat et al92 found that GILZ could inhibit the FOXO3 transcriptional activity and reduce the *Bim* expression. To elucidate the molecular mechanism of GILZ in inhibiting FOXOs, the team studied the effect of GILZ on FOXO3 using a dual-luciferase reporter assay system and found that the expression of GILZ caused the Crm-1-dependent nuclear rejection of FOXO3, demonstrating that GILZ exerts its inhibitory effect by preventing FOXO factors from reaching the nucleus.93 Later, leucine was also shown to attenuate skeletal muscle atrophy by blocking the nuclear localization of FOXO3.94

Vitamin D deficiency may exacerbate skeletal muscle aging, but vitamin D supplementation does not seem to significantly reverse age-related muscle aging.95 The 1,25(OH)2 vitamin D3 is the active form of vitamin D, and the vitamin D receptor has been shown to alter the activity of different isoforms of FOXOs.95,96 Eelen et al95 investigated the effect of 1,25(OH)2 vitamin D3 on FOXOs in MC3T3-E1 osteoblasts and found that 1,25(OH)2 vitamin D3 induced the expression of FOXO3 and down-regulated the expression of FOXO1, while having no effect on FOXO4.95 Consistently, Xiong et al96 also demonstrated in a diabetic rat model that 1,25(OH)2 vitamin D3 inhibited the activity of FOXO1. Hirose et al97 further confirmed that 1,25(OH)2 vitamin D3 inhibited the expression of the FOXO1 target atrophy gene in C2C12 muscle cells. The opposite effect of 1,25(OH)2 vitamin D3 on the FOXO subtype may be the reason why vitamin D does not significantly reverse age-related muscle aging. The peroxisome proliferator-activated receptor γ coactivator 1 (PGC-1α) family of coactivators, which are major regulators of the mitochondrial content and oxidative metabolism, plays a key role in maintaining muscle and energy homeostasis.96,99 PGC-1α is a peroxisome proliferator-activated receptor γ-interacting protein, whose interaction with FOXO3 in endothelial cells regulates mitochondrial protection from oxidative stress.98 PGC-1α is also able to inhibit the activity of FOXO1 and FOXO3 to improve the structural and functional integrity of mitochondria.100 Back in 2006, Sandri et al101 reported that PGC-1α inhibited the transcriptional activity of FOXO3 and suppressed the skeletal muscle atrophy target gene expression and protein degradation. Geng et al101 further demonstrated that PGC-1α could both reduce the muscle atrophy target gene expression by inhibiting FOXO and reduce the reactive oxygen species–induced protein oxidation by enhancing the expressions of antioxidant genes.

There are also several potential therapeutic targets for reversing FOXO-induced skeletal muscle atrophy. There are acetylated, they are also translated to the cytoplasm to lose transcriptional activity.102 The histone acetyltransferase protein p300/CBP is one of the proteins that acetylate FOXOs, whereas HDACs reverse acetylated FOXOs and allow them to resume their transcriptional role.102 HDACs are central regulators of gene expression that control various cellular processes.50 A total of 18 HDAC proteins have been identified, which can be classified into four major groups according to their different structures and functions. Among them, HDAC1 has been shown to be a major regulator of FOXOs in skeletal muscle atrophy, and its inhibitor MS-275 plays the role of inhibiting FOXO-induced skeletal muscle atrophy.102 In addition, HDAC6 has also been shown to be a skeletal muscle atrophy gene, and FOXO3 up-regulates its expression to accelerate skeletal muscle atrophy during the disease.50 At present, breakthroughs have been achieved in elucidating the pathogenesis of HDAC in diseases such as tumors and cancer, and some HDAC inhibitors, such as vorinostat and panobinostat, have been already used in clinical treatment.103 However, further experiments and studies are needed with respect to the treatment of skeletal muscle atrophy using these inhibitors.

### Table 1: Indirect Inhibitors of FOXO Regulation

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>Models</th>
<th>Target (Results)</th>
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<tbody>
<tr>
<td>S-Rg386</td>
<td>C2C12 myoblast</td>
<td>AKT* (FOXO1)</td>
</tr>
<tr>
<td>Mountain ginseng87</td>
<td>Rat myoblast (L6) cells</td>
<td>AKT*, FOXO3* (Atrogin-1*, MuRF-1*)</td>
</tr>
<tr>
<td>GAD, GTDF88</td>
<td>Dex-IMA rat models, C2C12 myoblast</td>
<td>AMPK*, AKT* (PGC-1α*, FOXO1*)</td>
</tr>
<tr>
<td>Magnolol89</td>
<td>T24 bladder cancer cells</td>
<td>IGF-1* (FOXO3*, Atrogin-1*, MuRF-1*)</td>
</tr>
<tr>
<td>Formononetin90</td>
<td>CKD rat models, C2C12 myoblast</td>
<td>MYOSTATIN* (FOXO3*, Atrogin-1*, MuRF-1*)</td>
</tr>
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</table>

*Up-regulated.

*Down-regulated.

CKD, chronic kidney disease; Dex-IMA rat models, dexamethasone-induced myotube atrophy rats models; FOXO, forkhead box 0; GAD, globular adiponectin; GTDF, 6-C-β-D-glucopyranosyl-(2S,3S)-5,7,3′,4′-tetrahydroxydihydroflavonol; IGF-1, insulin-like growth factor-1; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; S-Rg3, 20(s)-ginsenoside-Rg3.
KLFs are a class of DNA-binding zinc finger transcription factors that play a role in regulating biological processes, such as development and metabolism. Among them, the activity of KLF5 was shown to be inhibited by the synthetic retinoic acid receptor agonist AM80, whereas KLF4 has been identified as a target gene of the FOXO signaling pathway. Recently, Liu et al. also found that KLF5 coregulated the dexamethasone-induced Atrogin-1 transcription with FOXO1, and the retinoic acid receptor agonist AM80 inhibited the dexamethasone-induced Atrogin-1 activation by suppressing both KLF5 and FOXO1. Inhibitors of KLF5, such as AM80, may occupy a key position in the future treatment of skeletal muscle atrophy. The mechanisms underlying the relationships between other KLFs and FOXO-transcribed genes need to be further clarified.

Conclusion

The FOXO signaling pathway is an important signaling pathway leading to skeletal muscle atrophy. In 2004, Sandri et al. first demonstrated that FOXOs induced the ubiquitin ligase Atrogin-1 and caused skeletal muscle atrophy. In 2022, Oyabu et al. discovered that the FOXO1 target gene CCAAT/enhancer-binding protein δ promoted the Atrogin-1 expression. Despite the ongoing exploration, the mechanism of FOXO-regulated skeletal muscle atrophy has not been fully elucidated. Therapeutic strategies, such as beostatin and sestrins, which eliminate FOXOs by activating AKT, have generally low selectivity and high toxic adverse effects, so there is still a long way to go from scientific experiment to clinical application. The inhibitors that directly inhibit FOXOs include vitamin D and leucine, which are common drugs in clinical practice, but their detailed FOXO inhibition mechanisms have not been well developed either. The HDAC inhibitors that acetylate FOXOs, such as vorinostat and panobinostat, have been used in cancer and tumor treatment, but whether they can be used in skeletal muscle atrophy treatment remains a question to be addressed urgently.

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Author Contributions

L.L. and Z.D. conceptualized this review and decided on the content; K.C. wrote the article and drew the figure; P.G. and Z.L. edited and wrote the article; A.D., M.Y., Z.D., and L.L. made corrections to the article. All the authors read and approved the final version of the article.

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