Molecular Mechanism of Muscle Wasting in CKD

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Abstract

Chronic kidney disease (CKD), a chronic catabolic condition, is characterized by muscle wasting and a decreased muscle endurance. Many insights have made into the molecular mechanisms of muscle atrophy in CKD. A persistent imbalance between protein synthesis and degradation causes a loss of muscle mass. A decrease in insulin/IGF-1-Akt-mTOR signaling and an increased ubiquitin-proteasome system (UPS) have emerged as inducers of muscle loss. During muscle wasting, abnormal levels of reactive oxygen species (ROS) and inflammatory cytokines are detected in skeletal muscle. These increased ROS and inflammatory cytokine levels induce the expression of myostatin. The binding of myostatin to its receptor ActRIIB stimulates the expression of Foxo-dependent atrogenes. An impaired mitochondrial function also contributes to reduced muscle endurance. Increased glucocorticoid, angiotensin II, parathyroid hormone, and protein-bound uremic toxin levels that are observed in CKD all have a negative effect on muscle mass and endurance. The loss of skeletal muscle mass during the progression of CKD further contributes to the development of renal failure. Some potential therapeutic approaches based on the molecular mechanisms of muscle wasting in CKD are currently in the testing stages using animal models and clinical settings.

Keywords

Atrogene · Myostatin · Mitochondria · Oxidative stress · Inflammation · Uremic toxin

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2.1 Introduction

Skeletal muscle atrophy, referred to as sarcopenia, and decreased exercise endurance are frequently observed in chronic kidney disease (CKD) and are correlated with the risk of morbidity and mortality in such patients [1–5]. Therefore, maintaining physical performance is considered to be an essential factor for improving the prognosis of CKD patients. Muscle tissue functions as a protein reservoir and a source of amino acids that can be used for energy production by various tissues during catabolic conditions. In catabolic conditions such as CKD, persistent imbalances between protein synthesis and degradation result in a substantial loss of muscular protein mass (cachexia). Impaired mitochondrial function also contributes to reducing muscle endurance. This chapter explores the available evidence for the molecular mechanism of muscle wasting and potential therapeutic agents that might be used to counteract muscle atrophy in CKD.

2.2 Molecular Mechanism of Muscle Atrophy in CKD

2.2.1 Protein Degradation in Muscle

2.2.1.1 Atrogenes: Atrogin-1, MuRF-1, and Autophagy-Related Genes

A balance between protein synthesis and degradation is important for the maintenance of muscle mass. Therefore, the decrease in muscle mass can be attributed to either an increase in protein degradation or a decrease in protein synthesis. Several molecular mechanisms have been proposed to explain CKD-induced skeletal muscle atrophy in which multiple intracellular signaling pathways stimulate the expression of atrogenes such as atrogen-1 (known as muscle atrophin F-box (MAFbx)) and muscle ring factor 1 (MuRF-1, known as TRIM63), a member of the muscle-specific ubiquitin ligase family, in addition to autophagy-related genes (Fig. 2.1) [6–8]. The increased expression of these atrogenes induces protein degradation via the activation of the ubiquitin-proteasome system (UPS) and autophagy. In a catabolic state such as CKD, increased oxidative stress, inflammation, the production of glucocorticoids, angiotensin II, parathyroid hormone, and defective insulin signaling can initiate these pathways [6–9]. Hemodialysis procedures can also reduce protein synthesis and stimulate protein degradation [10].

2.2.1.2 Myostatin and TGF-β

Myostatin, a member of the TGF-β family and an autocrine inhibitor of muscle growth, is produced predominantly in skeletal muscle and functions as a negative regulator of muscle growth [11, 12]. It binds to the activin A receptor type IIB (ActRIIB) followed by activation of the downstream pathway in which Smad2 and Smad3 are factors that mediate the effects of myostatin on muscle (Fig. 2.1) [13, 14]. In a study of the skeletal muscle of patients with CKD, Verzola et al. reported

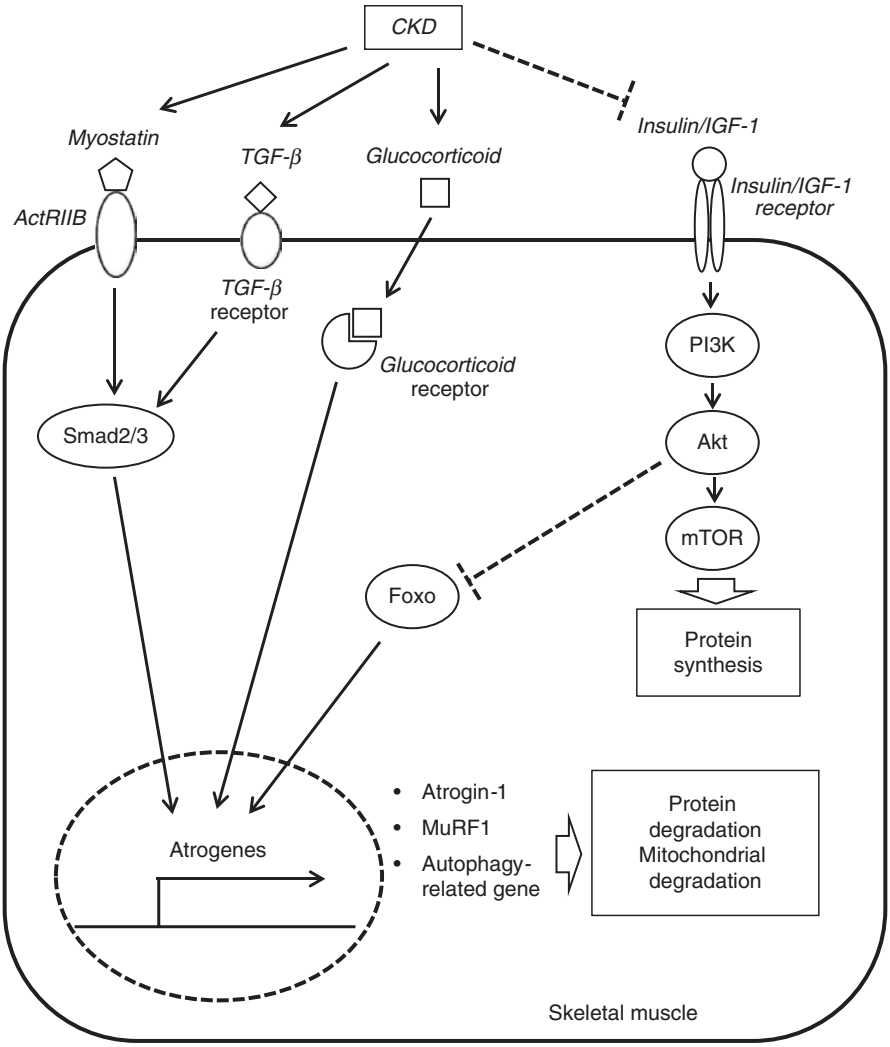

Fig. 2.1 Proposed molecular mechanisms for the muscle atrophy that develops in CKD. In a catabolic condition such as CKD, increased myostatin, TGF-β, and glucocorticoid levels induce atrogenes such as atrogin-1, MuRF1, and autophagy-related genes. The reduction in insulin/IGF-1-Akt-mTOR activity then results in a decrease in protein synthesis

that the mRNA expression of myostatin were upregulated [15]. Zhang et al. reported that the expression of myostatin in muscle was also increased in five-sixth nephrectomized mice (CKD mice) as well as CKD patients [16], and that the administration of an anti-myostatin anti-peptide to these mice suppressed the reduction in muscle mass [17]. Myostatin expression is enhanced by oxidative stress, inflammation, and glucocorticoids [18–20] through the forkhead box protein O (Foxo), NF-κB [21], and Smad2/3.

TGF-β also functions as a potent inducer of muscle wasting. In fact, Mendias et al. reported that the administration of TGF- β induced muscle atrophy and fibrosis through the induction of atrogin-1 [22]. TGF-β binds to TGF-β type II and type I receptors, which activate the Smad2/3 and TAK1/p38 MAPK signaling pathways to induce atrogenes (Fig. 2.1).

2.2.2 Protein Synthesis in Muscle

2.2.2.1 Akt-mTOR Signaling and Foxo Activation

The insulin or insulin-like growth factor (IGF-1)-PI3K-Akt pathway plays important roles in skeletal muscle hypertrophy by increasing muscle protein synthesis via mTOR and decreasing protein degradation via the inactivation of the Foxo family [8, 23–26]. Lee et al. reported that muscle atrophy was increased under conditions where insulin responsiveness was impaired, and suppressing PI3K activity increased atrogin-1 activity [27]. Sandri et al. reported that a decrease in Akt activity led to the activation of Foxo transcription factors and atrogen-1 induction. In addition, an IGF-1 treatment or the overexpression of Akt suppressed the expression of Foxo and atrogen-1 [28]. In this scenario, the expression of atrogenes such as atrogin-1, MuRF-1, and autophagy-related genes is suppressed by Akt via the inactivation of Foxo, a negative regulator of transcriptional factors for atrogenes [26–28].

2.2.3 Mitochondria

It is well known that exercise capacity is strongly related to mitochondrial function in skeletal muscle [29]. The amount of mitochondria is regulated by both mitochondrial biosynthesis and degradation [30, 31]. Tamaki et al. recently reported that muscle mitochondria and running distance were decreased in the early-stage of CKD model mice and that it was correlated with increased oxidative stress and inflammatory responses [32]. In fact, oxidative stress and inflammation cause the expression of the peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α), a master regulator for mitochondrial biosynthesis, to be reduced and to an increase in autophagy, a mitochondria degradation system. Interestingly, Brault et al. demonstrated that the overexpression of PGC-1α caused a resistance to muscle atrophy that was induced by denervation or fasting [33]. Similarly, Wenz et al. also showed that the overexpression of PGC-1α in mice prevented muscle atrophy, resulting in an extended life span [34]. In patients with stage 3~4 CKD, Balakrishnan et al. reported that the numbers of mitochondria in skeletal muscle were decreased [35]. They also demonstrated that the exercise increased the mitochondria content in skeletal muscle of CKD patients. Therefore, a decrease in the number of mitochondria in muscle appears to play a critical role in muscle endurance in CKD patients.

2.3 Initiating Factors Responsible for the Onset and Progression of Muscle Atrophy in CKD

2.3.1 Oxidative Stress and Inflammation

During muscle wasting, abnormally high levels of reactive oxygen species (ROS) and inflammatory cytokines are produced in skeletal muscle [21, 36]. Zhang et al. previously reported that an increase in ROS-induced TNF-α expression triggers myostatin production via a NF-κB dependent pathway, which further stimulates the production with the release of IL-6 in muscle tissue [16]. Sriram et al. also demonstrated that myostatin-induced TNF-α production via NF-κB signaling resulted in a further increase in ROS levels through the activation of NADPH oxidase [21]. Therefore, increased ROS production results in a feed forward loop that further increases the expression of myostatin via the NF-κB signaling of TNF-α.

Inflammatory cytokines such as TNF-α and IL-6, which were known to cause skeletal muscle breakdown, were also increased in muscle tissue of CKD mice [3, 37], whereas the inhibition of myostatin reduced the levels of these cytokines in the blood circulation [17]. In addition, Cheung et al. demonstrated that the infusion of TNF-α and IL-6 into mice resulted in the development of muscle atrophy, while it was attenuated by the neutralization of these cytokines [38]. Zhang et al. also reported that TNF-α activates myostatin, which further accelerates UPS-mediated catabolism [17]. Similar to myostatin, atrogin-1 was also found to be regulated by oxidative stress and inflammatory cytokines. These findings point to the conclusion that the development of skeletal muscle atrophy is mutually linked with myostatin, atrogenes, oxidative stress, and inflammation [21, 39–43].

2.3.2 Glucocorticoids

Increased levels of circulating glucocorticoids are associated with muscle atrophy. Watson et al. tested the direct contribution of a glucocorticoid receptor in skeletal atrophy by creating muscle-specific glucocorticoid receptor knockout mice. They subsequently showed that the knockout mice were resistance to glucocorticoid-induced muscle atrophy [44], suggesting that the glucocorticoid receptor was essential for muscle atrophy in response to glucocorticoids. Several reports have shown that myostatin expression is increased in the presence of glucocorticoids [45–48], thereby inducing protein breakdown by enhancing atrogenes (atrogine-1 and MuRF1) expression and decreasing protein synthesis by inhibiting the mTOR pathway. In particular, in the case of the IGF-1-PI3K-Akt-mTOR pathway, glucocorticoids were found to inhibit IGF-1 production [49, 50], accelerate the degradation of insulin receptor growth factor (IRS-1), followed by reducing PI3K activity [51–54]. Frost and Lang et al. showed that the constitutively activated form of Akt suppressed the negative effects of glucocorticoids on protein synthesis [55] and muscle mass [19]. Glucocorticoids also caused an increase in Foxo gene

expression [46, 56]. It therefore appears that glucocorticoid receptors and Foxo synergistically contribute to the upregulation of atrogene expression [57]. Glucocorticoid-induced muscle atrophy is characterized by fast-twitch (type II muscle fiber) atrophy and reduced protein mass in muscle [58]. On the other hand, it was also reported that the administration of glucocorticoid paradoxically exerted a positive effect on muscle function, probably due to suppressing inflammatory cytokine expression [59].

2.3.3 Angiotensin II

Increased levels of circulating angiotensin II are associated with the loss of lean body mass in CKD. Brink et al. reported that angiotensin II infusion to rats induced cachexia [60]. They found that, when rats were infused with angiotensin II, muscle mass became decreased but kidney and left ventricular weights were increased (Brink [61]. In these experimental conditions, circulating IGF-1 levels were reduced by about 30% in angiotensin II-treated rats. Zhang et al. also demonstrated that the infusion of angiotensin II increased the levels of circulating IL-6 and its hepatic production [62]. In addition, the infusion of angiotensin II stimulates the suppressor of cytokine signaling (SOCS3) in muscle which led to a loss of the insulin receptor substrate 1 (IRS-1), thus impairing insulin/IGF-1 signaling [62]. Benigni et al. reported that the mouse homolog of antgiotensin II type 1 (AT_1) knockout mice (agtr1a$^{-/-}$) showed a decrease in oxidative stress and an increase in the number of mitochondria. In addition, the mice had a prolonged life span [63]. Yabumoto et al. recently reported that the administration of irbesartan, an AT_1 receptor blocker, improved muscle repair and regeneration through the downregulation of the aging promoting C_{1q}-Wnt/β-catenin signaling pathway [64]. These data indicate that angiotensin II can stimulate muscle atrophy through a defect in insulin/IGF-1 signaling and an inflammatory mechanism via an AT_1 receptor.

2.4 Molecular Mechanism of Uremic Toxin-Induced Muscle Wasting

2.4.1 Uremic Toxin

Uremic toxins accumulate in the body under CKD conditions and exert biological actions. Among the uremic toxins, the presence of protein-bound uremic toxins, such as indoxyl sulfate, indole acetic acid, *p*-cresyl sulfate, hippuric acid, kynurenic acid, and 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid, etc., has been reported, due to the difficulty associated with their removal by hemodialysis because of their strong binding to serum albumin [65–68]. An accumulation of evidence has clarified that protein-bound uremic toxins are related to renal toxicity and CKD complications, including cardiovascular damage caused by enhanced oxidative

stress and inflammation [69–74]. In addition, Tamaki et al. reported that feeding a high protein diet not only exacerbates impaired renal function but also reduces exercise endurance in CKD mice [75], which is accompanied by an increased production of protein-bound uremic toxins [76]. These bodies of experimental evidence led us to hypothesize that protein-bound uremic toxins play an important role in the muscle atrophy and reduced endurance.

Several mechanisms have been proposed to explain the harmful actions of protein-bound uremic toxins. For example, protein-bound uremic toxins enter the target cell via specific transporters, such as an organic anion transporter (OAT) [77–83], and they then exert their toxicity via the activation of cellular NADPH oxidase, which results in the overproduction of ROS and inflammatory cytokines [71–73]. In addition, recent reports have shown that indole containing toxins, especially indoxyl sulfate, act as aryl hydrocarbon receptor (AHR) ligands and exert their toxicity via AHR [84, 85]. Interestingly, Ohake et al. reported that AHR functions as a component of the ubiquitin ligase complex [86]. We recently demonstrated that, among the protein-bound uremic toxins, indole containing compounds, namely, indoxyl sulfate, contributed to skeletal muscle wasting [87, 88].

2.4.2 The Distribution of Indoxyl Sulfate in Muscle Tissue

OAT such as Oat1 and Oat3 is responsible for the uptake of indoxyl sulfate by cells [77–79]. Western blotting analyses showed the mouse Oat1 and Oat3 are expressed in C2C12 mouse myoblast cells. In addition, when half-nephrectomized mice are administered indoxyl sulfate, the indoxyl sulfate is distributed to skeletal muscle (gastrocnemius) [87]. At the same time, the pattern of the immunostaining image of indoxyl sulfate was similar to that for ROS production, suggesting that indoxyl sulfate induces ROS production in skeletal muscle in vivo (Fig. 2.2).

2.4.3 Redox Properties of Indoxyl Sulfate in Skeletal Muscle

Indoxyl sulfate inhibits the proliferation and myotube formation in C2C12 myoblast cells. In addition, indoxyl sulfate caused an increased ROS production and inflammatory cytokine expression (TNF-α, IL-6, and TGF-β1) in C2C12 cells. It also enhances the expression of myostatin and atrogin-1. These effects which are induced by indoxyl sulfate were suppressed in the presence of an antioxidant, inhibitors of the Oat and AHR, or in the presence of siAHR. The chronic administration of indoxyl sulfate to half-nephrectomized mice significantly reduced their body weights and this reduction was accompanied by a loss in skeletal muscle weight. In these mice, indoxyl sulfate induced the expression of myostatin and atrogin-1, in addition to increasing the production of inflammatory cytokines by enhancing oxidative stress in skeletal muscle [87]. Indoxyl sulfate also induced mitochondrial dysfunction by decreasing the expression of PGC-1α and inducing autophagy (Fig. 2.2) [88].

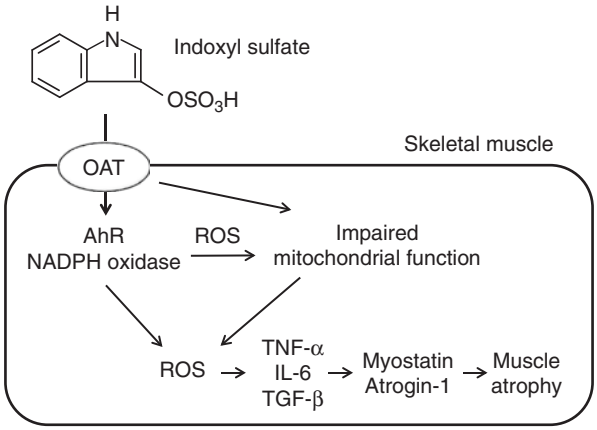

Fig. 2.2 Proposed mechanism for indoxyl sulfate-induced muscle atrophy. Indoxyl sulfate accumulates in muscle cells via Oat where indoxyl sulfate activates the AHR pathway and NADPH oxidase to cause increased ROS production. The enhanced ROS production, in turn, triggers the production of inflammatory cytokines to induce the expression of myostatin and atrogin-1, which are involved in muscle wasting. Indoxyl sulfate also impairs mitochondrial function

2.4.4 Effect of *p*-Cresyl Sulfate on Insulin Signaling in Skeletal Muscle

Koppe et al. demonstrated that, when mice are treated with *p*-cresyl sulfate, insulin signaling is altered in skeletal muscle where *p*-cresyl sulfate inhibited insulin-stimulated glucose uptake and decreased insulin signaling pathways through the activation of the ERK kinase [89]. Regarding the downstream pathway of insulin signaling, *p*-cresyl sulfate suppressed the insulin-induced phosphorylation of Akt. Since indoxyl sulfate had no effect on Akt phosphorylation [87], the effect of indoxyl sulfate or *p*-cresyl sulfate on muscle atrophy appears to be independent of each other (Fig. 2.3).

2.5 Muscle–Kidney Crosstalk: Skeletal Muscle Affects the Renal Pathology

Hanatani and Izumiya et al. investigated the effects of muscle growth on kidney disease using muscle-specific Akt transgenic mice [90]. They showed that unilateral ureteral obstruction (UUO)-induced renal interstitial fibrosis was significantly diminished in Akt transgenic mice via mediation by an increased level of eNOS signaling in the kidney. In a recent study, Peng et al. reported that the overexpression of muscle-specific PGC-1α resulted in reduced kidney damage and fibrosis in a mouse model of kidney disease [91]. These data suggest that skeletal muscle loss during kidney disease can affect the further progress of renal failure [90–92].

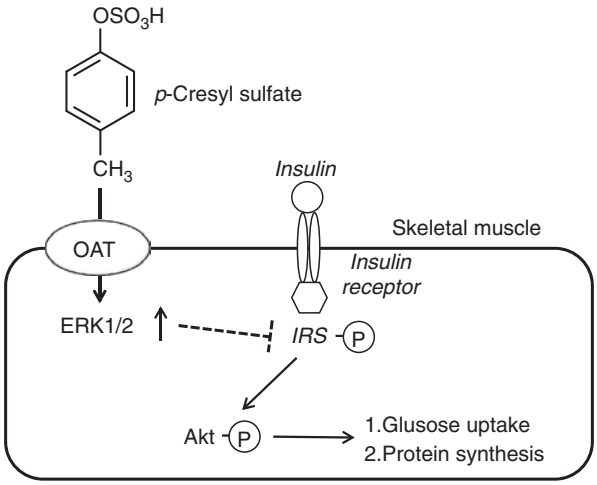

Fig. 2.3 Proposed mechanism for *p*-cresyl sulfate-induced insulin resistance. *p*-cresyl sulfate accumulates in muscle cells via Oat. *p*-Cresyl sulfate induces a resistance to insulin in muscle, accompanied by a decrease in insulin/IGF-1-Akt-mTOR activity through ERK1/2 activation

2.6 Kidney–Fat–Muscle Crosstalk: Parathyroid Hormone (PTH) Contributes to Muscle Atrophy Via PTH Receptor Expressed in Fat Tissue

Kir et al. demonstrated that the parathyroid hormone (PTH) is involved in stimulating the expression of thermogenic gene, such as UCP1, in five-sixth nephrectomized CKD mice [9]. In this mouse model, the expression of the atrogine-1, MuRF1, and myostatin genes was increased in gastrocnemius muscle tissue, whereas IGF-1 expression was decreased. Interestingly, they also showed that the loss of PTH receptors in fat tissue blocked the upregulation of thermogenic genes and prevented muscle atrophy. These data indicate that PTH/PHR receptor signaling in fat tissue is an important player in muscle atrophy in CKD.

2.7 Potential Therapeutic Interventions for CKD-Associated Sarcopenia in the Animal Model

2.7.1 Blocking Myostatin-ActRIIB Signaling

Myostatins are negative regulators of skeletal muscle mass, which are known to signal via the ActRIIB receptor on skeletal muscle, thereby inducing muscle wasting [11]. Morvan et al. recently showed that bimagrumab, acting as a human dual-specific anti-ActRIIA/ActRIIB antibody, neutralized muscle atrophy [93]. The activin decoy receptor ActRIIB also prevented skeletal muscle pathophysiology

[94, 95]. Endogenous circulating proteins such as follistatin and follistatin-like proteins are known to inhibit the binding of myostatin to ActRIIB [96, 97]. Lee et al. reported that transgenic mice expressing high levels of follistatin showed an increased muscle mass [98]. Chang et al. also demonstrated that the overexpression of muscle-specific follistatin enhanced skeletal muscle growth, due, at least in part, to myofiber hypertrophy [99]. Follistatin gene therapy against sporadic inclusion body myositis or facioscapulohumeral muscular dystrophy improved functional outcomes such as the distance traveled in a 6-min walk test [100]. Follistatin delivery systems such as nanoparticles and Fc fusion systems, etc. are under development in clinical settings [101–103]. In addition, the anti-myostatin peptibody that binds myostatin or blocks its receptor is also under development [17]. These data suggest that molecules that block myostatin-ActRIIB signaling would be potentially useful for enhancing muscle growth.

2.7.2 L-Carnitine

In CKD patients, restricted protein intake, decreased L-carnitine biosynthesis, and the easy removal of L-carnitine by dialysis result in an L-carnitine deficiency. Such a deficiency results in a decline in muscle power, the development of fatigue, non-ketotic hypoglycemia, or myocardial myopathy, while L-carnitine supplementation is effective for myopathy and for a decrease in muscle mass and power [104, 105]. An L-carnitine treatment ameliorates muscle atrophy and exercise capacity in CKD mice without affecting their renal function or the indoxyl sulfate levels in both plasma and muscle [88]. This can be attributed to the inhibition of mitochondrial dysfunction and decreased numbers of type I slow twitch fibers (Enoki [88].

2.7.3 DPP-4 Inhibitor

Teneligliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, has therapeutic potential for the treatment of CKD-induced muscular dysfunction without causing changes in indoxyl sulfate accumulation [88]. The DPP-4 enzyme catalyzes the degradation of incretin hormones such as GLP-1 and glucose-dependent insulinotropic polypeptide [106]. Kang et al. recently reported that GLP-1 increased mitochondrial membrane potential and oxygen consumption in addition to increasing PGC-1α expression [107]. Fukuda-Tsuru et al. reported that a teneligliptin treatment suppressed mitochondrial dysfunction in the livers of mice that had been fed a high-fat diet [108]. GLP-1 also ameliorated insulin resistance via the activation of the PI3K-Akt signal pathway in skeletal muscle [109]. In addition, Kimura et al. reported that teneligliptin acts as a hydroxyl radical scavenger [110]. Using human proximal tubular cells, Wang et al. also reported that diportin, another DPP-4 inhibitor, inhibited cell injury via the inhibition of indoxyl sulfate-induced ROS/p38MAPK/ERK activity, and the recovery of the PI3K-Akt signaling pathway without involving the

action of GLP-1[111]. Taking these findings into consideration, a DDP-4 inhibitor may exert cytoprotective activities not only indirectly via GLP-1 but also via its direct action against CKD-induced muscle atrophy.

2.7.4 AST-120

In clinical settings, AST-120 is used to suppress the progression of renal failure in CKD patients via inhibiting the accumulation of protein-bound uremic toxins. The administration of AST-120 to CKD mice resulted in a significant decrease in the plasma and muscular levels of indoxyl sulfate, which resulted in exercise capacity, muscle weight, and the number of type I slow twitch fibers to be restored and mitochondrial dysfunction was suppressed [88]. Nishikawa et al. also showed that the administration of AST-120 improved exercise capacity and mitochondrial biogenesis of skeletal muscle via reducing oxidative stress in CKD mice [112].

2.7.5 Ghrelin

Tamaki et al. reported that the administration of acylated ghrelin to five-sixth nephrectomized CKD mice increased muscle mass and muscle mitochondrial content through increasing PGC-1α expression [75, 113]. It has also been reported that the non-peptidergic ghrelin receptor agonist counteracts cachectic body weight loss under inflammatory conditions [114–116].

2.7.6 Blockade of Leptin Activity

Elevated serum leptin levels are correlated with changes in lean body mass in patients with CKD, suggesting that leptin signaling could be an important cause of CKD-induced muscle loss [3, 117]. Cheung et al. reported that a pegylated leptin receptor antagonist attenuated CKD-induced muscle loss [118]. Interestingly, they also found the pegylated leptin receptor antagonist was able to cross the blood–brain barrier.

2.7.7 Others

Increased miR27a/b was reported to negatively regulate the expression of myostatin [119]. Wang et al. investigated the role of miR-23a and miR-27a in the regulation of muscle mass. The injection of an adeno-virus encoding miR-23a and miR-27a or the overexpression of miR-23a and miR-27a in CKD mice suppressed muscle loss through increasing Akt phosphorylation [120]. miR1 is a muscle-specific microRNA which induces muscle atrophy by regulating HSA70. The antagonism of miR1 may be beneficial during muscle atrophy [121]. Hu et al. reported that a low frequency

electrical stimulation ameliorates CKD-induced muscle atrophy by upregulating the IGF-1 signaling pathway through decreasing the expression of miR1 and miR206 [122]. Interestingly, low frequency electrical stimulation induced the activation of M2 macrophage [122].

2.8 Conclusions

This chapter summarizes the available evidence for the molecular mechanism of muscle wasting in CKD. It is noteworthy that oxidative stress and inflammation appear to be strong contributors to the muscle atrophy caused by a decrease in muscle mass and mitochondrial dysfunction. Increased levels of glucocorticoids, angiotensin II, parathyroid hormone, and uremic toxin also contribute to this type of muscle atrophy and reduced muscle endurance. These data point to the importance of developing potential therapeutic agents for counteracting the muscle atrophy that is associated with CKD.

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