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Review

Skeletal Muscle and Kidney Crosstalk in Chronic Kidney Disease

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Key Words
Muscle atrophy • Crosstalk • Kidney • CKD

Abstract
The functioning of complex organisms requires a constant and delicate balance of processes both between and within cells, tissues, and organ systems. There is growing appreciation for the role of signalling crosstalk connecting different organ systems of the body, even from tissues traditionally classified as "inert" in terms of their capacity to produce chemical signals that can act on other organ systems. Many of these secreted molecules have been shown to contribute to, or exacerbate, a variety of functions and diseases in other organ systems, even if the two organs are not functionally linked. For example, there is a strong association with skeletal muscle atrophy and dysfunction in patients with chronic kidney disease (CKD). Identification of molecules produced and secreted by skeletal muscle has existed for some time, and there is emerging evidence that skeletal muscle may directly affect kidney function. Conversely, factors produced and secreted by the kidneys in various models of CKD have been shown to contribute to reduced muscle functionality. This review will focus on crosstalk in both directions between skeletal muscle and the kidneys. The emphasis will be on direct interaction between these organs using examples of secreted factors that are produced by the muscle or kidneys (including activin A, myostatin, microRNA's, irisin and mitsugumin 53), often under pathophysiological conditions. Our understanding of how the kidneys and skeletal muscle interact with each other is key to elucidating the pathophysiology processes that drive health and disease.

Introduction

The functioning of complex organisms requires a constant and delicate balance of processes both between and within cells, tissues, and organ systems. Our understanding of how hormones and cytokines can affect function in different organ systems has been pivotal to elucidating the physiology and pathophysiology behind many processes [1, 2]. There is growing appreciation for the role of signalling crosstalk connecting different organ systems of the body, even from tissues traditionally classified as "inert" in terms of their capacity to

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produce chemical signals that can act on other organ systems [3-5]. These bioactive proteins are often classified and grouped based on the tissue producing them - *adipokines* produced by adipose tissue, *hepatokines* from liver, and *myokines* from muscle. Essentially, many organs have much more of a functional interaction with other systems than what we once thought was possible.

Many of these secreted molecules contribute to, or can exacerbate, a variety of functions and diseases in other organ systems, even if the two organs are not traditionally considered as having a linked or shared function [6]. For example, there is a strong association with skeletal muscle atrophy and muscle dysfunction in patients with chronic kidney disease (CKD) [7, 8]. Inversely, patients with CKD who are able to maintain muscle mass and continue habitual exercise and can reduce disease progression and prevent renal function decline [9, 10]. Considering the large volume of blood filtered by the kidneys, and the substantial metabolic role and relative mass of skeletal muscle, it is unsurprising that there is evidence of physiological crosstalk between skeletal muscle and kidney. To date, research has primarily examined the role of kidney dysfunction on muscle atrophy via indirect factors such as metabolic acidosis [11], chronic inflammation [12], and impaired insulin signalling [8]. Muscle atrophy caused by metabolic acidosis present in CKD is perhaps one of the most well-understood examples of kidney-muscle cross talk. Metabolic acidosis is a milieu commonly associated with CKD, as the kidneys are unable to maintain their capacity to secrete endogenous acid generated from metabolic processes, resulting in an overall increase in hydrogen ion concentration in the body. Progressive impairment of kidney function causes metabolic acidosis, which subsequently drives muscle atrophy primarily through upregulation of muscle protein degradation via the suppression of the IRS-PI3K-Akt insulin signalling pathway, which subsequently increases FoxO transcription activity [8]. The IRS-PI3K-Akt pathway is not only responsible for insulin-mediated glucose uptake via GLUT4 (Glucose transporter type 4) in skeletal muscle, but also plays a pivotal role in protein degradation. The phosphorylation of Akt (Protein kinase B) causes subsequent phosphorylation of FoxO (Forkhead box class O), which excludes FoxO from the nucleus, decreasing its transcriptional activity of E3 ubiquitin ligases. If activation of the IRS-PI3K-Akt pathway is decreased, FoxO activity is subsequently increased, which stimulates transcription of E3 ubiquitin ligases including Atrogin-1 and MuRF-1 (Muscle Ring Factor-1) for targeting of proteins to be degraded by the ubiquitin proteasome system [7, 8, 13]. In CKD, acidosis contributes to downregulation of the IRS1-PI3K-Akt pathway and subsequently increases ubiquitin-proteasome mediated protein degradation. Glucocorticoids also induce atrophy via decreasing PI3K (Phosphoinositide 3-kinase) activity, affecting both protein synthesis and degradation in skeletal muscle [14].

Whilst the relationship between muscle wasting and CKD is complex and multifactorial in nature, it is only recently that specific signalling molecules that directly contribute to this kidney-muscle relationship have been identified. Identification of molecules that are produced and secreted by skeletal muscle have existed for some time, and Pedersen, et al. [15] coined the term "myokines" for these autocrine, paracrine and endocrine signalling factors originating from skeletal muscle, with IL-6 (Interleukin 6) being one of the first examples [4, 15]. A decade later, emerging evidence started to link the ability of myokines to *directly* affect kidney functioning in the context of chronic kidney disease [16-19]. More recently, in various models of nephropathy it has been demonstrated that the kidneys themselves can produce cachectic factors which directly mediate atrophy in skeletal muscle [5]. This review will focus on crosstalk in both directions between skeletal muscle and the kidney. The interaction of these organs in pathological conditions like Chronic Kidney Disease (CKD) and muscle atrophy, sarcopenia, and cachexia will be examined, as well inter-organ crosstalk in a non-disease state, where the beneficial effects of exercise will be examined in terms of kidney function. For the purposes of this review, the term "crosstalk" will refer to direct secreted humeral factors from kidney or skeletal muscle, which affects the other organ system. Our understanding of how the kidneys and skeletal muscle interact with each other is key to elucidating the pathophysiology processes that drive both health and disease.

The Impact of CKD on Skeletal Muscle Mass and Function

Chronic kidney disease (CKD) is a common condition, affecting 10-15% of the worldwide adult population [20]. CKD is disease defined as abnormalities in kidney structure (podocyte loss, tubular hypertrophy, fibrosis) or function (reduced glomerular filtration rate, elevated proteinuria, creatinine or BUN; Blood Urea Nitrogen) for three months or more [21]. CKD severity is clinically assessed in five stages, with Stage 1 being normal glomerular filtration rate, and minor structural damage or elevation of urine markers, to Stage 5, which is considered end stage kidney failure. CKD is a serious disease that once it progresses to Stage 5, can be fatal if not treated by continuing dialysis or kidney transplant [20]. CKD is often associated with other comorbidities, including diabetes, hypertension, cardiomyopathy, muscle atrophy, and muscle dysfunction [8, 10, 16, 21-23]. Muscle wasting conditions can encompass a spectrum of symptoms, from a loss of skeletal muscle mass, termed *muscle atrophy*, or progressive muscle weakness and loss with aging known as *sarcopenia*, to a complex metabolic syndrome known as *cachexia*, where patients exhibit involuntary and pathological weight loss of more than 5% of their body weight over 12 months [24].

Reduced muscle function and reductions in lean muscle mass are common outcomes for people living with CKD. Symptoms and treatment of CKD contributes to alterations in both the catabolic and anabolic processes which are required to maintain muscle mass. It is estimated that between 11-28% of patients with CKD have sarcopenia [25] - although the incidence may be as high as 54% depending on clinical definitions, cut off points, and diagnostic tools used to gauge incidence, as rates vary between experimental models and regions [26]. As the disease progresses, each stage of CKD increases the risk of sarcopenia by an additional 45% [27]. Protein degradation in skeletal muscle can be via the activation of the ubiquitin-proteasome (UPS), lysosome-autophagy, and calpain systems. In CKD patients, a loss of lean muscle mass and reduced muscle function is clinically important, as muscle atrophy and cachexia are both associated with a higher mortality rate [28]. Primary skeletal muscle cells obtained from CKD patients retain their cachexia phenotype *in vitro* [29], and dialysis has been shown to directly alter protein metabolism, stimulating protein breakdown in skeletal muscle during dialysis treatment, with proteolytic processes persisting for 2-hours post treatment [30]. Patients with more advanced CKD are often directed by medical professionals to lower their dietary intake of protein (or may do so spontaneously) in order to combat intraglomerular pressure and hyper-filtration, to help maintain and preserve renal function. However, dietary protein restriction may also contribute to the development of muscle atrophy and sarcopenia [16, 31, 32]. The causes of muscle atrophy and cachexia in CKD are multifaceted with several factors contributing to protein degradation, including malnutrition, inflammation and acidosis and are reviewed elsewhere [16, 33]. The following sections of this review will the factors activin A (released by the kidney), myostatin, microRNA's, irisin and mitsugumin 53 (released by muscle) during disease which have been shown to have a direct effect on the other organ.

Kidney-Derived Factors which Affect Muscle Mass and Function

Activin A

Activin A is a protein that was identified in the 1980s and characterised as an endogenous antagonist to the hormone inhibin [34]. Activin A belongs to the TGF-β (Transforming Growth Factor beta) superfamily of growth and differentiation factors, which elicits effects via two kinase receptors known as activin receptor II type A (ActRIIA) and B (ActRIIB) [34-37]. Overexpression of activin A can have detrimental effects on the normal structure and function of both the kidneys and skeletal muscle independently [35-41]. In the kidneys, overexpression of activin A during embryonic development can inhibit tubule and ureteric bud formation, and cause alterations in the proliferation and differentiation patterns of kidney cell populations via increased Pax-2 expression [40]. Indeed, inhibition of activin A via Follistatin reduced fibrosis caused by unilateral ureteral obstruction in rats [41]. *In vitro*

and *in vivo*, healthy kidney expresses activin A at low levels, or is not detected at all [5, 37, 41]. In humans, circulating levels of activin A in blood serum is negatively correlated with estimated Glomerular Filtrations Rate (eGFR) and positively correlated with renal fibrosis [5]. In various models of nephropathy, activin A is an autocrine factor which causes the upregulation of fibrotic factors such as α-smooth muscle actin (α-SMA) and collagen types I and IV, and increases the proliferation and differentiation of renal fibroblast cells into myofibroblasts [5, 37].

In skeletal muscle, activation of ActRIIB by activin A (and other endogenous ligands such as myostatin, TGF-β, and BMP-11) will initiate phosphorylation of Smad2/Smad3 and pAKT-FoxO signalling cascade (Fig. 1) that leads to muscle wasting and cachexia via transcription of E3 ubiquitin ligases MuRF1 and Atrogin-1, which upregulates ubiquitin-proteasome mediated protein degradation [36, 38, 42]. Through both Smad2/Smad3 and pAKT-FoxO signalling activin A expression also mediates reduced skeletal muscle growth and myogenesis [38, 43], and inhibition of activin A has been shown to mitigate weight loss (total body weight and lean body weight), improve skeletal muscle mass, and help retain muscle strength in cancer cachexia [35, 36]. Promisingly, the activin A inhibitor Follistatin instigates muscle hypertrophy and may have utility in combating atrophy, especially if effects can be localised to skeletal muscle [44, 45]. However, as Follistatin can inhibit both myostatin and activin A [45], it is unclear to what extent the potential anti-atrophic effects of Follistatin are due to activin A inhibition alone. To the best of the authors' knowledge, the effects of exogenous Follistatin has not been directly investigated in CKD-induced muscle atrophy and presents an intriguing future area of research.

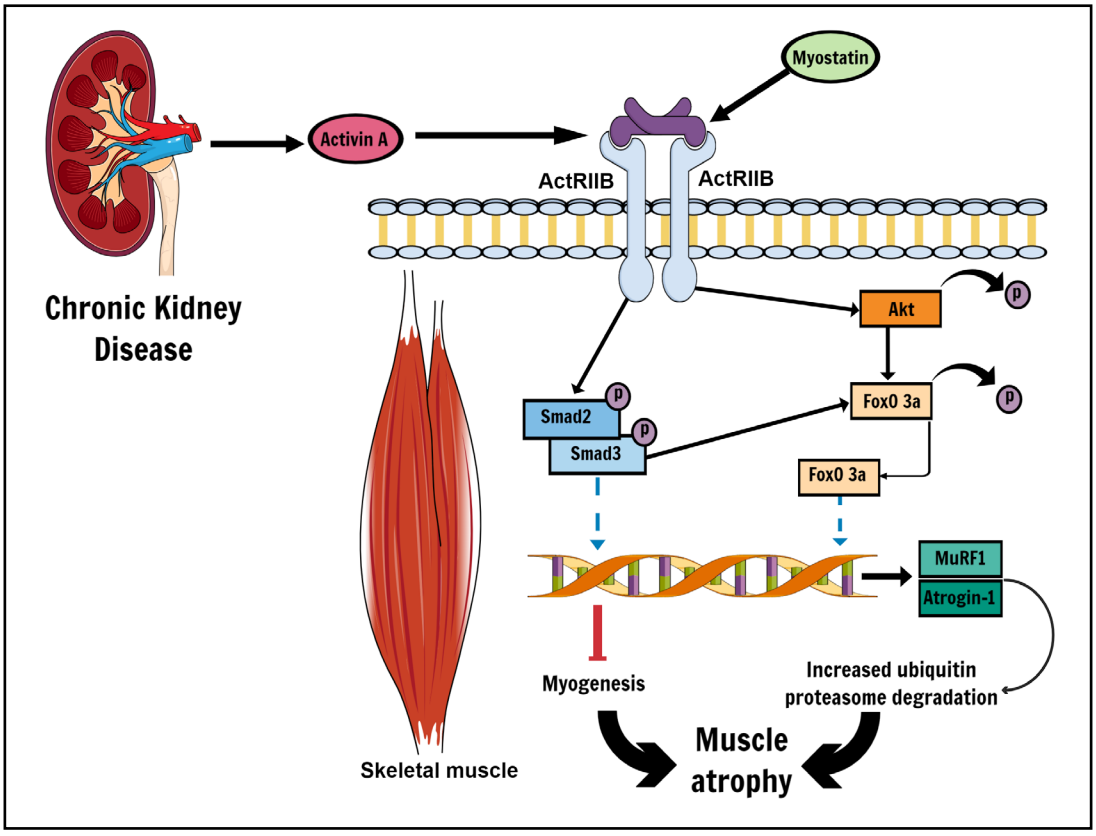

Fig. 1. Proposed role of kidney-derived activin A in skeletal muscle during chronic kidney disease. In chronic kidney disease and damage, activin A is produced by juxtaglomerular cells in the kidney (Solagna et al. [5]), which activates the activin receptor type-2B (ActRIIB). The activation of this receptor increases ubiquitin proteasome degradation through Akt-FoxO signalling and attenuates myogenesis through Smad2/3 phosphorylation (Han et al. [38]), leading to muscle atrophy.

There is emerging evidence of *direct* crosstalk between the kidney and skeletal muscle as a mechanism that promotes muscle atrophy in CKD. In comprehensive work recently published by Solagna, et al. [5], signalling cross-talk between skeletal muscle and kidneys was demonstrated using a number of different mouse models of nephropathy, and by examining cachexic factors of patients with CKD. In this study, activin A was shown to be near-exclusively produced by juxtaglomerular tubular cells and fibroblasts of the kidney in both human and rodent models of nephropathy, and higher levels of circulating activin A was positively correlated with worse outcomes for both kidney and skeletal muscle structure and function [5]. This work identified the role of kidney-derived activin A directly mediating muscle atrophy in a genetic mouse model (using the kidney-specific knockout of the kinase kif3a gene) and with a separate model of CKD, and demonstrated that pharmacologically blocking activin A in skeletal muscle also led to reduced renal fibrosis and improved renal function [5]. Pharmacological inhibition of activin A or blockade of activin A in skeletal muscle using an adenovirus vector in mice attenuated muscle mass loss, increased the cross-sectional area of muscle fibres, improved tetanic specific force and mitochondrial density in muscle fibres. The attenuation of muscle atrophy was shown to be mediated via a combination of increased protein expression via the mTOR pathway and the downregulation of FoXO-dependent gene transcription, which is involved in protein degradation. Simultaneously, inhibition of activin A in skeletal muscle alone improved kidney function and structure, highlighting that activin A crosstalk between kidneys and muscle is not unidirectional. Accumulation of activin A was also inversely associated with estimated GFR in CKD patients, suggesting that declining kidney function not only produced activin A, but also dampened the clearance of activin A. The emergence of this direct crosstalk mechanism between the kidneys and muscle is an exciting development and may be indicative that other kidney-derived factors, or "*renalkines*", could have some direct role in muscle physiology in CKD and renal failure; although mechanistic studies in humans are required.

The Role of Myokines in Skeletal Muscle and Kidney Function

Myostatin

Myostatin, or growth developmental factor-8 (GDF-8) belongs to the same TGF-β superfamily as activin A. Like activin A, myostatin elicits effects at target tissues using the same ActRIIB receptor, but also can bind with lesser affinity to the ActRIIA receptor. Myostatin is synthesised by skeletal muscle and can have paracrine, autocrine or endocrine effects, including influencing kidney function [38, 46]. Since its discovery in 1997 [47], myostatin as a negative regulator for skeletal muscle has been well-established. Myostatin elicits its effects in skeletal muscle via the phosphorylation of Smad2/3 and by increasing MuRF-1 and Atrogin 1; leading to suppression of muscle differentiation and increased protein degradation [38, 39, 48-50]. Rodent models of CKD exhibit 2-3 fold increase in myostatin expression in skeletal muscle [51]. In both a healthy population, and in people diagnosed with CKD, myostatin released by skeletal muscle occurs in response to stressors such as oxidative stress and inflammatory conditions; conversely, aerobic exercise has been shown to decrease circulating myostatin levels [46]. Human studies have also shown that muscle myostatin expression correlates well with inflammatory markers such as IL-6 in the later stages of CKD [52], but this association with inflammation is less clear when circulating myostatin levels in the blood are used as a marker [53]. In rodent and cell culture models, pharmacological inhibition of myostatin with a peptide antibody protected against skeletal muscle degradation and suppressed systemic inflammation compared to vehicle-treated controls [51].

Clinical trials for myostatin inhibitors have had some success at improving muscle function in disease states such as Duchenne's Muscular Dystrophy, cancer, and elderly populations, but many of these trials have been halted due to side effects (bleeding gums) or muscle function measurements improvements did not reach expected trial thresholds [46, 54]. In humans, pharmacological inhibition of myostatin in CKD has yet to be investigated,

but comprehensive work has been done which examines blood or muscle levels of myostatin in this population at various disease stages. In humans, plasma myostatin levels are elevated in the early stages of CKD, and is inversely associated with renal functional measurements eGFR and creatinine clearance [55]. However, while myostatin is elevated in the CKD milieu, the relationship between plasma level of myostatin and muscle function or mass has been inconsistent. In one study examining CKD patients on haemodialysis, blood myostatin levels was inversely associated with hand grip strength and muscle mass and was shown to be a good predictor of 1-year mortality risk [56]. However, in the RENEXC study (Randomised Controlled Trial of Exercise in CKD) which examined strength or balance-based exercise interventions in 151 non-dialysis CKD people, after one year all participants exhibited much higher levels of plasma myostatin (regardless of exercise type), even though only balance-based exercise group had an increase in lean muscle mass [57]. These differences may be partially explained by the fact that the two studies examined CKD patients in different stages of disease progression (dialysis-dependant vs non-dialysis dependant). However, given that myostatin levels have also been reported to be *higher* in the early stages of CKD [55] when the risk of sarcopenia and muscle wasting is lower, this factor warrants further investigation.

Most research in this area has focused on the skeletal muscle-based effects of myostatin in CKD, however very little is known about the kidney-specific effects of myostatin. It is clear that myostatin levels becomes dysregulated, even in the early stages of CKD [55], and this myokine has been shown to influence protein and glucose metabolism and play a role in obesity – all factors which can contribute to the pathogenesis of CKD. One study reported that higher levels of myostatin is expressed in the skeletal muscle of obese, insulin resistant, and diabetic patients as well as their relatives [58]. Myostatin, and its receptor ActRIIB are expressed in both glomerular and tubular kidney cell types, and expression of these are increased in diabetic nephropathy [59]. In cell culture, myostatin upregulates fibronectin and Smad2/3 phosphorylation; which contribute to the formation of tubulofibrosis during diabetic nephropathy [59]. These findings indicate there is some potential for myostatin to affect kidney function, but this hypothesis requires more clinical and pre-clinical evidence.

Micro RNA

The rapid expansion in knowledge regarding micro RNA (miR) in the past decade has led to the discovery of miRs being a potential myokine via their release from muscle and packaging into exosomes to enter the circulation. The miRs 23, 26, 27 and 29 have been demonstrated to participate in muscle to kidney crosstalk, affecting kidney fibrosis and function. In mice treated with STZ (which rapidly induces insulin-dependent diabetes), caused muscle loss and reduced kidney function, the injection of an adeno-associated virus (AAV) into the tibialis anterior muscle expressing miR23a/27a in the muscle, led to increased packaging of miR23a/27a exosomes and increased miR23a/27a in the kidneys [18]. The overexpression of kidney miR23a/27a, derived from skeletal muscle, improved kidney function as indicated by improvement in both blood urea nitrogen (BUN) and creatinine levels. This muscle-kidney crosstalk via miR23a/27a reduced fibrosis and fibrotic markers such TGFβ, alpha smooth muscle actin and fibronectin, which the authors contend to be through a mechanism including downregulation of Smad3 [18]. Interestingly, the upregulation of miR23a/27a also reduced the muscle atrophy through FoxO1 signalling. The same research group has also reported comparable findings with miR 26 and miR29. In work by Zhang, et al. [19], mice which had UUO performed had an injection of exogenous exosomes containing miR26a into skeletal muscle, causing packaging of miR26a into exosomes. The exogenous miR26a treatment decreased kidney fibrosis and TGFβ1, although kidney function was not specifically reported in this study. Finally, either exogenous miR29a [23], or an AAV encoding miR29a [60] injected into muscle not only reduced muscle atrophy caused by UUO, but promoted exosome packaging of mIR29a which reduced the UUO-induced kidney fibrosis through downregulation of Ying Yang 1 (YY1) and TGFβ.

The work by Wang's research group indicates that kidney damage and fibrosis, and the resulting effect on renal function, can be attenuated via the exogenous application of miRs 23,

26, 27 and 29 [23, 60]. Whilst this is an exciting development in terms of a potential treatment for renal damage, it is vital to note that these studies indicate that exogenously bolstering levels miRs 23, 26, 27 and 29 can participate in muscle-kidney crosstalk and improve renal function, and do not directly indicate that the *decline* in these miRs contributes to renal fibrosis and reduction in renal function in CKD. To investigate such a question would require muscle specific miR transgenic interventions, or other interventions which specifically inhibit muscle derived miRs. Considering the rapid rise of the CRISPR/Cas9 technique, such research is becoming more methodologically accessible. It is also important to note that there is a paucity of evidence that exercise, either acutely or chronically, consistently changes muscle or plasma levels of miRs 23, 26, 27 and 29. Exercise improves quality of life outcomes for CKD [9, 61, 62], and if these miRs were part of this crosstalk mechanism, the levels of miR23, 26, and 29 would be expected to be bolstered by exercise in the either the muscle or plasma. However, the findings of studies investigating these miRs after exercise are inconsistent. In one study, 14 days of exercise training caused no change in muscle miR29a in humans [63], nor did endurance exercise in rats alter miR 23a or 29a levels in skeletal muscle [64]. Conversely, another study found an increase in plasma miR29a in humans immediately after the completion of a marathon [65], and patients with Type 2 Diabetes Mellitus, who are at higher risk of kidney damage, had increased basal levels of miR29a in the muscle [66]. Twenty-four hours after a marathon, miR26a levels were reduced in the plasma. Taken together, it is apparent that the overexpression of muscle-derived miR23, 26, and 29 are unlikely to represent the mechanisms of how exercising muscle may improve renal function but do present an exciting new area of potential treatment for CKD.

Irisin

Irisin is predominately released by skeletal muscle during exercise or exposure to cold, through the stimulation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) [22]. Multiple studies have shown that irisin is lower in CKD patients, and reduction in circulating irisin levels correlate well with CKD disease progression [67-69]. In addition to these correlational studies, mechanistically, irisin may have beneficial effects directly within the kidney, improving kidney function through enhancing the oxidative capacity of renal tubular cells and reducing renal fibrosis via the TGFβ/Smad 2 pathway [22]. A comprehensive study by Peng, et al. [22] determined how irisin may work as a myokine which is able to mediate beneficial effects in kidney disease. Here, the authors utilised mice with muscle-specific overexpression of PGC1α, a pivotal transcription factor involved in processes such as mitochondrial biogenesis which is activated by exercise. When kidney function was examined, these mice exhibited reduced fibrosis and fibrotic markers, and improved renal function (serum creatinine) in response to stressors such as folic acid injection, UUO or subtotal nephrectomy. The serum from the mice with muscle specific overexpression of PGC1α also caused metabolic reprogramming in cultured tubule cells, increasing their oxygen consumption. To elucidate which myokines may have been responsible for these renal adaptations, 24 myokines were screened in muscle, with irisin one of the upregulated myokines in both skeletal muscle and serum. When the serum was fractionated, only the serum fraction ranging in size from 10-50 kDa, which included irisin (as confirmed by mass spectrometry), induced the metabolic reprogramming in the cultured tubule cells. Importantly, incubation of anti-irisin antibodies with the serum from the muscle specific PGC1α overexpression mice inhibited this change in oxygen consumption, indicating irisin was the specific myokine which was responsible for the renal adaptations. Further, recombinant irisin treatment alone was able to alleviate renal fibrosis and impairment in renal function with both folic acid treatment and subtotal nephrectomy. Peng, et al. [22] theorise that the mechanism behind the beneficial effects of irisin on tubule cell fibrosis is described in Fig. 2; Irisin binds to TGFBR 2, which subsequently interferes with the TGF-β1 mediated phosphorylation of Smad 2/3 [22]. It is noteworthy that similar to miRs 23, 26 and 29, irisin elicits its beneficial effects on renal tubules through inhibiting TGF-β and Smad 2/3 signalling, indicating the importance of this pathway for kidney fibrosis and its potential for targeting by myokines.

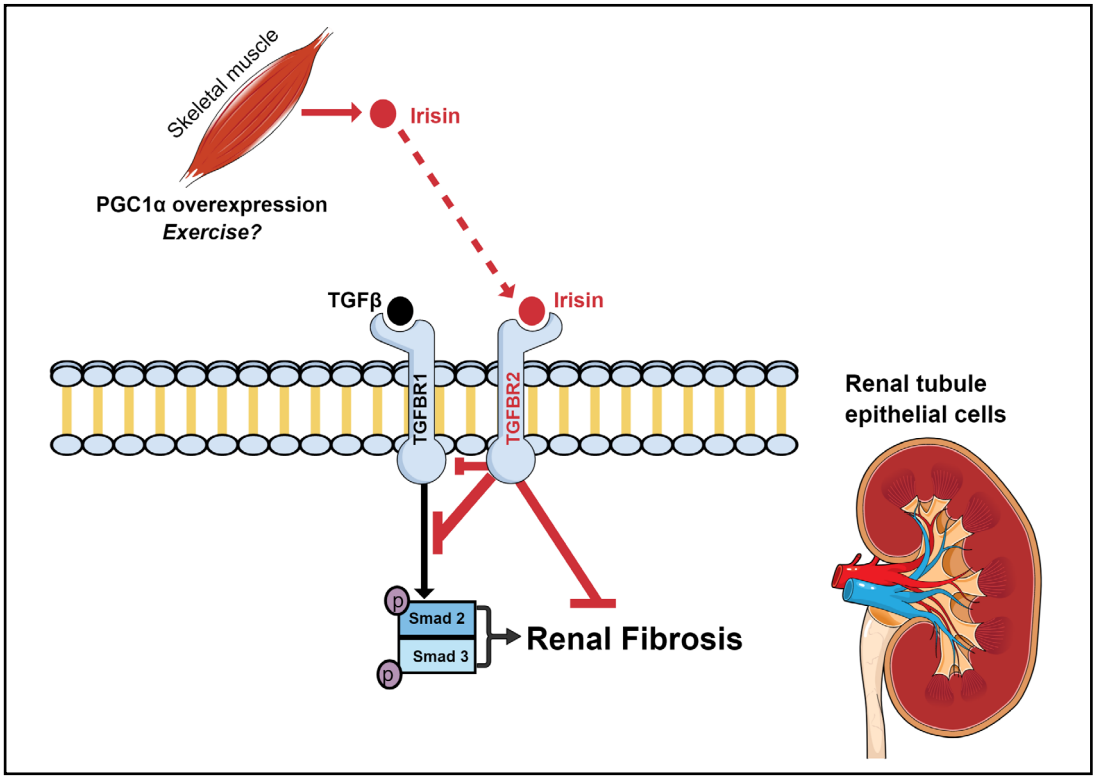

Fig. 2. Irisin released from skeletal muscle PGC-1α overexpression (and potentially exercise) binds to TGFβ receptor 2 (TGFBR2) and inhibits renal fibrosis via inhibition of TGFβ signalling including Smad2/3 phosphorylation. Schematic created from findings by Peng et al. [22]. It is currently uncertain whether Irisin derived from exercising skeletal muscle could recapitulate this signalling pathway in renal tubule cells.

Levels of circulating irisin have been shown to be modulated pharmacologically through the use of Metformin, Fenofibrate and Follistatin, compounds already used clinically and in pre-clinically to treat a range of diseases [70]. As such, irisin has been of interest for its potential role as a therapeutic target for the treatment of CKD, although it should be noted that research into this myokine has not been without controversy [71-74]. Irisin is a protein derived from fibronectin type II domain-containing (FNDC5) via proteolytic cleavage and can be released from muscle as a peptide hormone [75]. Timmons, et al. [76] note that increased FNDC5 mRNA expression following exercise is not consistent. Following exercise, younger participants did not have increased FNDC5 mRNA expression unlike older participants, despite the finding of increased mitochondrial gene expression [76]. Therefore, caution should be taken generalising that irisin is a ubiquitously expressed exercise-induced myokine in all populations. Since its discovery in 2012, many research groups have also identified issues with measuring irisin accurately in biological samples due to a range of factors. Irisin demonstrates cross reactivity with other proteins, has a short half-life, and various post-translational modifications by glycosylation and dimerization which can alter both stability and molecular weight of irisin [70, 72, 77]. While mass spectrometry may provide a more valid format of assessing irisin concentrations in samples, ELISA is a more commonly utilised method by research groups. Most available ELISA kits have been shown to lack specificity, which brings into question the validity of this method as a measure of irisin [70] - one research group reported that ELISA kits from the same manufacturer returned different concentrations of irisin when the same samples were repeatedly tested [72]. Hence, future research investigating irisin and kidney crosstalk need to robustly demonstrate their accuracy.

Mitsugumin 53 (MG53)

Mitsugumin 53 (MG53) is a protein first identified in 2005, alternately named TRIM72, as it belongs to the tripartite motif-containing (TRIM) family of proteins [78]. MG53 is highly expressed in striated muscle (cardiac and skeletal), and, to a lesser extent is expressed in lung, kidney, and immune cells [78-81]. One of the primary functions of MG53 is cell membrane repair following injury via the recruitment of vesicles to the plasma membrane, suppressing inflammation, and stimulating the production of stem cells [78, 82, 83]. In a number of different cell lines, it has been shown that following injury, MG53 expression is upregulated at the site of damage [82, 84], and exogenously applied MG53 will preferentially localise at injured cells [80]. MG53 is highly expressed in skeletal muscle tissue; exercise and insulin treatment can increase its expression and release into the systemic circulation, where MG53 can have effects as a myokine [78, 84]. MG53 is a soluble protein, but can tightly associate with a range of protein types, forming lipid rafts at the cell membrane during plasma membrane repair, or is exported from striated muscle by fusing with intracellular proteins at the sarcolemma [85]. MG53 has yet to be used in a clinical or pre-clinical setting [85, 86]; most of our current understanding about the physiology of MG53 is derived from rodent models and cell culture. Manipulation of MG53 can be via the use of recombinant human MG53 (rhMG53) or adenovirus vectors, these methods can restore or overexpress MG53 either systemically, or in a specific organ [78-80, 83, 84].

Mice with genetic knockout of MG53 ($MG53^{-/-}$) start exhibiting signs of muscular dystrophy at around 11 months of age, and decline in muscle function can be seen much earlier if stressed, as measured by muscle fibre contractility and ability to complete endurance exercise [82, 84]. In this model, decline in kidney function commences much earlier, with $MG53^{-/-}$ mice displaying proteinuria, elevated serum creatinine and worse renal structural integrity by 20 weeks of age [80]. Elevated levels of circulating MG53 in transgenic mice led to improvements in running capacity and endurance, but without changes to skeletal muscle fibre type or size [87]. In a mouse model of muscular dystrophy (*mdx*), systemic administration of rhMG53 demonstrated improvements in muscle fibrosis and histological structure in some muscle groups compared to vehicle-treated controls [84]. The effects of Cardiotoxin, an agent that can induce necrosis in skeletal tissue when injected, exacerbates muscle damage in $MG53^{-/-}$ mice; whilst tissue regeneration is improved in transgenic mice who have upregulation of MG53 in circulation [87].

A comprehensive study conducted by Duann, et al. [80] were the first to examine the effects of genetic deletion of MG53 on kidney function. In this model, it was observed that kidney function prematurely declines in $MG53^{-/-}$ mice, and when exposed to different models of acute kidney injury, exhibited worse renal function and abnormal kidney development compared to wild type controls [80]. In a cell model of acute injury using renal proximal tubule cells, MG53 protein expression was upregulated at the injury site. The presence or absence of MG53 in proximal tubule cells directly affected their viability, where MG53 expression was required for cell survival rate following injury [80]. This study also demonstrated application of rhMG53 intravenously is tolerated in larger animal models using rats and dogs, and that rhMG53 is freely filtered by the kidneys, appearing in urine samples within a few hours of treatment. Further work has shown that MG53 can protect against the development of renal fibrosis by inhibiting the NF-Kβ response [81]. Whilst markers of kidney damage appear in relatively young $MG53^{-/-}$ mice, further structural changes such renal macrophage accumulation, and formation of renal fibrosis starts appearing in mice of older age (5- 10 months) [81]. This study not only identified the signalling pathway by which MG53 elicits renal protection, but also recapitulated the work performed by Duann, et al. [80], showing in $MG53^{-/-}$ mice undergoing injury by unilateral ureteral obstruction (UUO), mice exhibited significantly higher levels of fibrosis compared to wild type controls. Renal damage following UUO was partially rescued by pre and post treatment with rhMG53 [81].

Whilst the potential therapeutic use of MG53 in the prevention and treatment of muscle and kidney disease has garnered interest, clinical translation has yet to be conducted and has somewhat been hindered by its role in insulin signalling; MG53 can act as an E3

ubiquitin ligase for proteins like insulin receptor substrate-1 (IRS-1). In this capacity, MG53 mediates the conjugation of ubiquitin to IRS-1, resulting in protein degradation, reduced IRS-1 expression, and potentially negatively affects insulin sensitivity in skeletal muscle [85, 88]. However, the role of MG53 in metabolic disorders such as diabetes is contentious. Some research groups have found increased expression of MG53 in skeletal muscle samples in rodent models of diabetes [89, 90]. Recently, a longitudinal study identified that people with higher blood serum concentrations of MG53 was associated with worse glucose tolerance and insulin response, and those with elevated blood levels of MG53 were more likely to progress to Type 2 Diabetes after 15 years [91]. Contrastingly, other research groups have not recapitulated these findings in animal models of insulin resistance [92, 93], or in human samples of skeletal muscle from diabetic patients [88]. While a transgenic mouse model with elevated circulating MG53 has been shown to react normally to glucose and insulin challenges [87]. Considering insulin resistance can be part of the contributing factors to muscle dysfunction in CKD, it is clear that further work needs to be done in order to understand the role of MG53 in metabolic disorders.

Conclusions and Future Recommendations

- Skeletal muscle can produce over 650 different myokines, with only approximately 5% having a defined biological function [4]; the number of kidney derived factors, or "renalkines" which may alter skeletal muscle mass and function is currently unknown.
- Activin A presents one such "renalkine" which promotes skeletal muscle atrophy, and whilst upregulated in CKD patients, its mechanistic role so far is dependent on preclinical animal models.
- The role of myostatin in CKD-induced atrophy has garnered substantial interest and promising findings, but further human clinical pharmacological interventions are required, and the potential role of myostatin on kidney function requires further mechanistic research.
- Micro RNA may present an exciting exogenous treatment for CKD-induced muscle atrophy, including miRs 23, 26, 27 and 29, especially if they can be localised to renal tissue.
- The myokine irisin may improve renal functioning, but the methodological concerns regarding the accuracy of irisin measurements need to be carefully considered in future research.
- Clinical translation of MG53 may prove difficult due to its role in potentially negatively affecting insulin signalling, therefore, further research needs to clarify that any anti-atrophic effects of MG53 are not accompanied by impaired insulin sensitivity.
- Smad2/3 signalling has been a common signalling target for many myokines mentioned in this review to improve renal fibrosis, and hence myokines which can affect this signalling pathway and affect the kidney may be a viable target of future research.

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