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See related article, "Role of Receptor Protein Tyrosine Phosphatase γ in Sensing Extracellular CO_2 and HCO_3^-," on pages 2616–2621.

Glucocorticoid-Regulated Kinase: Linking Azotemia and Muscle Wasting in CKD

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A reduction in the protein content of muscle, observably reflected as loss of muscle mass, is a frequent accompaniment of aging and inflammatory and catabolic diseases, including progressive CKD.[1,2] In patients with CKD, aside from the risk of progression to ESRD, all-cause mortality is an important competing risk[3] and has been related to loss of muscle mass.[2] Progressive resistance training in patients with CKD has been shown to restore muscle hypertrophy (albeit incompletely) and improve health–related quality of life.[4] Oddly, the muscle wasting from advanced CKD seems to involve mechanisms independent of nutrition alone, which was shown in a trial of patients on dialysis given intradialytic parenteral nutrition for an extended period of time.[5] These data would suggest that methods to inhibit ongoing muscle loss in CKD together with augmentation of nutritional intake may improve health–related quality of life and reduce mortality.

Protein turnover is constantly ongoing, with an estimated 4% of total body protein undergoing degradation and synthesis every day in homeostasis. The rate of proteins lost and gained (*i.e.*, the turnover rate) depends on the nature and site of a specific protein's function within the cell, its distribution in cell and tissue types, and the existing pathologic state. Simply put, a net loss in muscle mass can result from reduced protein synthesis in muscle cells, increased protein breakdown, or the presence of both concurrently. Experimental and clinical data suggest that, although the CKD milieu impairs synthesis of myosin and nonmyosin proteins within myocytes,[6] it may have a greater effect on promoting protein catabolism.[7] Metabolic acidosis, insulin resistance and impaired insulin/IGF signaling, and inflammation, all of which are encountered in CKD, seem to play important and direct roles in the muscle loss of CKD (reviewed comprehensively in ref. 8). Excess proinflammatory cytokine productions (TNF-α, IL-6, IL-1, serum amyloid protein A, and IFN-α) have been associated with muscle protein loss in CKD.[9] Hemodialysis has complex effects on protein synthesis, catabolism, and inflammation, affecting muscle mass in multiple ways.[10] The function of muscle satellite cells, which usually remain quiescent but contribute to myocytes in response to injury, may also be affected by CKD through myogenic regulatory signals, such as Myf-5 and myoblast determination protein-1.[11]

Other than from nonspecific increases in protein catabolism in CKD, specific and targeted ubiquitin-proteosome system (UPS) –mediated degradation of myocyte proteins is well recognized to play a key role in CKD–induced muscle loss. TGF-β as well as myostatin and activin A (of the TGF-β family) and their downstream SMAD2/3 signaling have been shown to suppress AKT phosphorylation and enhance forkhead box O phosphorylation in mycocytes. These signals, in turn, stimulate the expression of E3-ubiquitin ligases (Atrogin and MuRF-1) and UPS-mediated proteolysis that is responsible for muscle loss in CKD.[12,13] Similarly, impaired IGF-1 signals associated with insulin resistance in CKD affect phosphoinositide 3-kinase

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activity and AKT phosphorylation, promoting UPS-mediated proteolysis.[14]

In this issue of the *Journal of the American Society of Nephrology*, Luo *et al.*[15] examined the role of Serum Glucocorticoid–regulated kinase-1 (SGK-1), a downstream target for phosphoinositide 3-kinase and insulin signaling, in CKD–induced muscle wasting. SGK-1, which has sequence similarity to Akt, was previously known to have multiple homeostatic metabolic regulatory functions, and it plays a role in the preservation of muscle mass in hibernating animals. Luo *et al.*[15] initially made the observation that SGK-1 expression and activation are reduced at the RNA and protein levels in myocytes of murine and human CKD biopsies. Using a global *SGK-1* knockout mouse, they observed accentuated weight loss in response to CKD (by 5/6th nephrectomy model) compared with in control mice subjected to the same procedure.[15] This weight loss was associated with a reduced cross–sectional area of muscle fibers in the tibialis anterior/gastronemius muscle groups in SGK-1 knockout mice. In the *SGK-1* knockout mice, interestingly, they observed that forkhead box O3 activation and SMAD2/3 phosphorylation were enhanced, leading to the upregulation of ubiquitin ligases Atrogin and MuRF-1 (markers of ongoing UPS activation).[15] *In vitro*, using C2C12 myocyte cell lines with *SGK-1* knockdown, the dependence of the upregulation of E3-ubiquitin ligases in response to inflammatory signals as well as TGF-β on SGK-1 was confirmed. In addition, Luo *et al.*[15] further identified a direct interaction between NDRG and SMAD2/3, which inhibited the phosphorylation of SMAD2/3. This NDRG-mediated inhibition of phosphorylated SMAD3 was also dependent on the presence of activated SGK-1 in myocytes. Most interestingly, local injection of an adenoviral *SGK-1* overexpression plasmid into muscle restored myocyte cross–sectional area in these *SGK-1* knockout mice subjected to uremia, implying a local role of SGK-1 in CKD–induced muscle disease. Furthermore, *in vitro*, stretch–responsive muscle fiber hypertrophy observed in myocytes seemed to be dependent on the presence of SGK-1. Although wild–type uremic mice showed significant increases in muscle fiber size on treadmill training, knockout mice exhibited persistent upregulation of UPS proteolysis and did not regain muscle fiber size in the absence of *SGK-1*. Through these elegant series of experiments, Luo *et al.*[15] concluded that SGK-1 plays a critical role in CKD–induced muscle wasting and that SGK-1 might be a mechanical sensor necessary for mediating exercise-induced improvement in muscle wasting in CKD.

These novel data link SGK-1 to CKD–induced muscle disease and suggest that SGK-1 agonism or excess could be a potential strategy to combat CKD–induced muscle disease. However, it is important to note that *SGK-1* is widely expressed in different cell types and has disparate effects. For instance, the weight loss observed in the global knockout murine model may not necessarily reflect a myocyte-exclusive effect. Specifically, SGK-1 is important in inhibiting insulin release in response to glucocorticoids, and adipose tissue alterations may account for some of the excess weight changes in these animals.[16] Indeed, a relatively common gene variant of *SGK-1* has been associated with increased body weight.[16] Furthermore, SGK-1 mediates the salt-sensitizing effects of hyperinsulinism, and in the context of CKD, nontissue–specific SGK-1 excess may lead to aggravated hypertension.[17] Similarly, *SGK-1* is potently upregulated by mineralocorticoids, and volume expansion and salt retention *via* epithelial sodium channels could emerge as a concern with global SGK-1 agonism.[18] Hence, to truly quantify any potential benefit of SGK-1 agonism without off-target effects, a myocyte-specific model of SGK-1 excess in the context of CKD will need to be examined in subsequent studies. Additionally, although Luo *et al.*[15] observed that SGK-1 agonism through NDRG may inhibit TGF-β SMAD2/3 signaling and epithelio-mesenchymal transition, conflicting data have been reported in renal fibrosis,[19] and the ultimate effect of *SGK-1* on CKD itself needs additional clarification.

In spite of these concerns regarding the potential future applications of SGK-1 agonism, the study by Luo *et al.*[15] describes a novel mechanism for CKD–induced muscle disease that may have still wider applicability. The data by Luo *et al.*[15] suggest that inflammatory cytokines accompanying CKD downregulate *SGK-1*. Therefore, if *SGK-1* plays a role in myopathy of other chronic inflammatory diseases, a potential target for muscle weakness and frailty (a major current epidemiologic problem in an aging population) may have been uncovered.

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DISCLOSURES

None.

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See related article, "Serum Glucocorticoid–Regulated Kinase 1 Blocks CKD–Induced Muscle Wasting *Via* Inactivation of FoxO3a and Smad2/3," on pages 2797–2808.

Challenges in Rare Variant Association Studies for Complex Kidney Traits: *CFHR5* and IgA Nephropathy

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With the first successful genome–wide application of linkage disequilibrium mapping in 2005,[1] genome–wide association studies (GWASs) have now surpassed their 10th anniversary. GWASs have been applied extensively to dissect contributions of common variants to complex disease, and thousands of robust disease associations have been identified using this approach.[2] Important discoveries have also been made in nephrology, where GWASs provided new insights into the regulation of BP,[3] renal function,[4] and albuminuria.[5] In addition, several landmark studies have shown strong contribution of common variants to the risk of glomerular disease, providing novel clues about human biology of these disorders. For example, the discovery of African *APOL1* risk alleles explained a large fraction of racial disparities in kidney disease and pointed to a completely new disease mechanism for FSGS.[6] GWAS findings for IgA nephropathy (IgAN) established the pathogenic role of the intestinal network for IgA production and the alternative complement pathway.[7–9] These findings led to a significant refinement of the disease pathogenesis model and provided novel clues about the disease geoepidemiology.[10–12] Similarly, the genetic interaction between variants in *PLA2R1* and *HLA* arising from GWAS solidified the pathogenesis model for membranous nephropathy, highlighting the antigen-HLA interplay as central to the disease process.[13]

Despite this progress, however, a large portion of the genetic contribution to many complex traits remains unexplained, including traits for which very large GWAS meta–analyses have already been performed. This issue has been identified as the missing heritability problem. The missing heritability has many potential explanations, including the possibility that low-frequency variants substantially contribute to the inherited risk of disease. Such rare alleles are not well captured on popular microarray genotyping platforms and thus, have been

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