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Review

Muscle wasting from kidney failure—A model for catabolic conditions☆

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SUMMARY

Purpose: Muscle atrophy is a frequent complication of chronic kidney disease (CKD) and is associated with increased morbidity and mortality. The processes causing loss of muscle mass are also present in several catabolic conditions. Understanding the pathogenesis of CKD-induced muscle loss could lead to therapeutic interventions that prevent muscle wasting in CKD and potentially, other catabolic conditions.
Major findings: Insulin or IGF-1 resistance caused by CKD, acidosis, inflammation, glucocorticoids or cancer causes defects in insulin-stimulated intracellular signaling that suppresses IRS-1 activity leading to decreased phosphorylation of Akt (p-Akt). A low p-Akt activates caspase-3 which provides muscle proteins substrates of the ubiquitin–proteasome system (UPS). A low p-Akt also leads to decreased phosphorylation of forkhead transcription factors which enter the nucleus to stimulate the expression of atrogin-1/MAFbx and MuRF1, E3 ubiquitin ligases that can be associated with proteolysis of muscle cells by the UPS. Caspase-3 also stimulates proteasome-dependent proteolysis in muscle.
Summary: In CKD, diabetes, inflammatory conditions or in response to acidosis or excess glucocorticoids, insulin resistance develops, initiating reduced IRS-1/PI3K/Akt signaling. In CKD, this reduces p-Akt which stimulates muscle proteolysis by activating caspase-3 and the UPS. Second, caspase-3 cleaves actomyosin yielding substrates for the UPS and increased proteasome-mediated proteolysis. Third, p-Akt down-regulation suppresses myogenesis in CKD. Fourth, exercise in CKD stimulates insulin/IGF-1 signaling to reduce muscle atrophy. Lastly, there is evidence that microRNAs influence insulin signaling providing a potential opportunity to design therapeutic interventions.

This article is part of a Directed Issue entitled: Molecular basis of muscle wasting.

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1. Introduction

Patients with chronic kidney disease (CKD) have an increased risk of mortality and morbidity which is associated with losses of body fat and lean mass (Carrero et al., 2008). Two patient groups are at even higher risk of morbidity and mortality, elderly subjects with CKD and those being treated by dialysis. But, the development of muscle wasting is not limited to abnormalities induced by CKD, the pathogenesis of muscle protein losses in CKD is similar to that arising from other chronic diseases (*e.g.*, cancer, diabetes, *etc.*) (Doyle et al., 1998).

In patients with CKD, the most frequently used marker of depleted protein stores is hypoalbuminemia and some investigators have concluded that this means that patients with CKD suffer from protein malnutrition (Carrero et al., 2008; Getz and Reardon, 2004; Kelly and Garavan, 2005). This is unfortunate because malnutrition is defined as abnormalities caused by an insufficient amount of food eaten or to an imbalance of nutrients. Consequently, if inadequate dietary protein was the cause of signs of protein malnutrition in patients with CKD, then these associations should be reversed by simply increasing the amount of food eaten by these patients (Mitch, 2002). Unfortunately, CKD-induced hypoalbuminemia and lost protein stores are not generally corrected by raising protein intake. For example, estimates of the protein eaten by CKD patients are above values recommended by the World Health Organization (Berry et al., 2013; Karlsson et al., 2012). Second, providing dietary supplements have not corrected hypoalbuminemia or lost protein stores in patients with CKD. Perhaps the signs of protein depletion might be ameliorated by increasing dietary calories but this has not been systematically evaluated. In short, assigning the risks of morbidity and mortality documented in patients with kidney disease to protein malnutrition is not helpful. Instead available evidence indicates that the metabolic abnormalities caused by CKD are the result of mechanisms that are not eliminated by solely altering the diet (Mitch and Goldberg, 1996; Olsburgh et al., 2013; Thomas et al., 2013).

What physiologic abnormalities initiate loss of muscle mass in CKD? In rodents with experimentally-induced uremia, we identified that the metabolic acidosis that generally complicates CKD stimulates the breakdown of muscle proteins resulting in loss of muscle mass (Hu et al., 2013). In this study, uremia was created in rats or mice by subtotal nephrectomy and feeding a high protein diet; the latter resulted in rats with a blood bicarbonate level of 16 mM and the blood urine nitrogen (BUN) above 80 mg/dL, signifying accumulation of unexcreted waste products. Results from uremic rats were compared to those obtained from sham-operated, pair-fed control rats or from pair-fed, uremic rats that had sodium bicarbonate (NaHCO3) mixed in their diet. In uremic, acidotic rats, there was a sharp increase in the rate of muscle protein degradation compared to results from control rats and this catabolic condition was eliminated by $NaHCO_3$ to correct acidosis. Subsequently, it was demonstrated that metabolic acidosis stimulates protein degradation in patients with CKD who were not being treated by dialysis and those being treated by hemodialysis or peritoneal dialysis (Graham et al., 1996, 1997; Wu et al., 2012). In one report patients were treated by peritoneal dialysis throughout a year-long evaluation when metabolic acidosis was fully corrected. In non-acidotic patients, body weight and estimated muscle mass increased and there was reduced hospitalization of the non-acidotic patients (Hammad et al., 2007).

The cellular mechanisms mediating protein degradation were subsequently determined to involve the ubiquitin–proteasome system (UPS) (Bailey et al., 1996; Isozaki et al., 1996; Mitch et al., 1994). The importance of the UPS in mediating biological processes was recognized by awarding the Nobel Prize in Chemistry to Avram Hershko, Aaron Ciechanover and Irwin Rose (http://nobelprize.org/chemistry/laureates/2004/). Besides increasing protein degradation, the activation of the UPS was accompanied by increased levels of the mRNAs that encode different components of the UPS. An increase in ubiquitin (Ub) following correction of acidosis demonstrated that suppression of the activity of the UPS in muscles (Pickering et al., 2002). How does acidosis activate protein degradation in the UPS? To address this question, we examined rats with acute acidosis or uremia with chronic acidosis (Bailey et al., 1995). The goal of these experiments was to determine if intracellular pH measured by NMR decreased in response to acidosis. If so, it would imply that hydrogen ions activate a potential receptor stimulating the UPS to initiate the highly coordinated process of protein degradation and the transcription of genes encoding components of the UPS. There were no statistically significant differences in the intracellular pH of uremic rats that had the same characteristics as those uremic, acidotic rats that were exhibiting accelerated breakdown of muscle protein by the UPS (Bailey et al., 1996). This negative result stimulated us to search for other signals that would stimulate protein degradation in muscle.

The stimulus for the loss of muscle mass in CKD is frequently attributed to inflammation because CKD is associated with an increase in circulating levels of inflammatory cytokines (Miyamoto et al., 2011; Stenvinkel et al., 2005). However, the mechanism by which inflammatory cytokines cause losses of muscle mass has been difficult to establish. In rats, it was shown that treatment with IL-6 stimulates muscle protein degradation but the intracellular pathways that cause loss of protein stores and muscle mass was not identified (Goodman, 1994). Subsequently, it was shown that inflammation can cause defects in the intracellular signaling that is initiated by insulin or IGF-1 (Shoelson et al., 2006). A mechanism from inflammation to impaired insulin signaling in muscle to protein degradation was identified during evaluations into the mechanism by which angiotensin II, a stimulus for inflammation causes protein degradation in muscle (Song et al., 2005). Angiotensin II stimulates production of IL-6 and the acute phase protein, serum amyloid A (Zhang et al., 2009). These factors activate the suppressor of cytokine signaling3 (SOCS3) to phosphorylate Serine307 of the insulin receptor substrate-1 (IRS-1). An increase in phosphorylated Serine307 of IRS-1 was shown to lead to the degradation of IRS-1, causing interference with insulin/IGF-1 intracellular signaling. In fact, insulin-induced intracellular signaling is impaired not only by angiotensin II but also by CKD, metabolic acidosis or inflammation, resulting in acceleration of muscle protein breakdown.

2. CKD stimulates proteolytic mechanisms in muscle

Several proteolytic processes can contribute to loss of muscle mass, including the uptake and degradation of certain extracellular or cell surface proteins or some cytosolic proteins by endocytosis into autophagic vacuoles that fuse with lysosomes (Lecker and