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Muscle wasting in chronic kidney disease: Mechanisms and therapeutic strategies

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Muscle wasting is triggered by complications of chronic kidney disease (CKD) including metabolic acidosis, insulin resistance, glucocorticoids, angiotensin II and inflammation (e.g., IL-6). These conditions activate caspase-3 and the ubiquitin proteasome system (UPS) to stimulate the degradation of protein; protein synthesis may also be reduced. Unfortunately, there are no approved, regularly effective treatments for the muscle wasting that occurs frequently in patients with CKD. We have found that CKD-stimulate myostatin expression in muscle. Myostatin is a negative regulator for muscle growth. Inhibition myostatin using humanized peptibody, we found the increased body and muscle weight in mice even with CKD. Inhibition of myostatin improved IGF1/insulin signaling pathway in muscle, increases satellite cell activation. It also inhibited CDK-stimulated pro-inflammatory cytokine production including IL-6. In CKD patients, morbidity and mortality correlate with circulating IL-6 levels. In rodent, IL-6 injection causes wasting and IL-6 inhibition partially ameliorates it. Since IL-6 activates Signal transducer and activator of transcription 3 (STAT3), we examined this molecule in muscle of CKD mice. In skeletal muscle of mice with CKD, we find increased p-STAT3 and expression of its target genes, including SOCS3 and C/EBPδ. C/EBPδ then stimulates expression of myostatin. Experimentally, we find that constitutively activated STAT3 is sufficient to cause myofiber protein wasting and when we inhibited STAT3 with a small molecule STAT3 inhibitor, there was suppression of IL-6-induced myotubes wasting as well as CKD-induced muscle atrophy in mice. Taken together, our results strongly implicate STAT3 as a causative trigger of CKD-induced muscle wasting. The STAT3 inhibitor is useful not only for uncovering cell signaling that causes muscle proteolysis but also could become a therapeutic strategy to reverse the muscle atrophy induced by CKD and potentially other conditions.

Biography

Dr. Liping Zhang received her PhD from Zhejiang University of China in 1996. She got her postdoc training from Pennsylvania State University, University of Kansas Medical Center, University of Texas Medical Branch at Galveston. Dr Zhang currently is an Assistant Professor at Baylor College of Medicine. Dr Zhang focuses her research in determining how kidney failure and other catabolic disease cause muscle wasting. Specifically, she and her colleagues study transgenic mice and mice with defects in gene expression to identify the mechanisms underlying abnormalities in insulin and IGF-1 signaling. Mice with genetic alterations in these signaling pathways are used to create chronic kidney disease so that mechanisms causing loss of lean body mass can be identified.

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