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See related article, "Renal Angiotensin-Converting Enzyme Is Essential for the Hypertension Induced by Nitric Oxide Synthesis Inhibition," on pages 2752–2763.

Can Muscle-Kidney Crosstalk Slow Progression of CKD?

Helbert Rondon-Berrios,* Yanlin Wang,† and William E. Mitch†

*Renal-Electrolyte Division, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; and †Nephrology Division, Department of Medicine, Baylor College of Medicine, Houston, Texas

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Crosstalk refers to interactions between organs or cellular signal transduction pathways and how they influence the function of the target organ or cells. Over decades, nephrologists have developed familiarity with this phenomenon because disorders such as the hepatorenal or cardiorenal syndromes or lung injury after AKI are clinical examples of crosstalk; the mediators causing loss of kidney function in these conditions are unidentified.[1–3] Unexpectedly, accumulating evidence suggests that skeletal muscle is also involved in crosstalk with other organs.[4] The mechanisms for the interaction involve the muscle "secretome," consisting of a variety of growth factors and cytokines that are expressed and secreted by skeletal muscle.[4] Examples of potential mediators of crosstalk in the secretome include IGF-1, myostatin, IL-6, and TNF-α.[5–9] It is established that these factors are activated and influence the growth and function of skeletal muscles in catabolic conditions, including CKD. New information indicates that these mediators can influence the growth and function of other organs. The nicely crafted report by Hanatani and colleagues in this issue of *JASN*[10] supports this conclusion.

The investigators examined the evidence for crosstalk between skeletal muscle and the kidney by determining whether growing muscle mass can influence the responses of the kidney to unilateral ureteral obstruction (UUO) or to cisplatin nephrotoxicity. They studied mice with doxycycline-inducible, muscle-specific expression of Akt (Akt1 TG mice) because this model mimics what occurs in muscles responding to exercise.[11] Another reason for studying responses to Akt1 is that it can suppress TGF-β1, a major profibrotic cytokine.[12] The authors provided results from control experiments to show that hemodynamic measures were similar between wild-type (WT) and Akt1 TG mice, thereby excluding systemic responses to Akt1 signaling in the heart. They also demonstrated that doxycycline did not interfere with the development of

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Correspondence: Dr. William E. Mitch, Nephrology Division, Baylor College of Medicine, M/S: BCM 395, One Baylor Plaza, ABBR R705, Houston, TX 77030. Email: mitch@bcm.edu

renal fibrosis.[13] Their experimental plan was to determine whether muscle growth (*i.e.*, Akt1 overexpression) would improve functional and histologic defects in kidneys damaged by UUO. In Akt1 TG mice with UUO, the authors found that histologic evidence of tubular injury and interstitial fibrosis parameters was reduced by about 15%, while changes in the expression of mRNAs of collagen or fibronectin were reduced 25%–60% and the mRNAs of inflammatory genes (*e.g.,* IL-6, IL-1β, TNF-α) were suppressed even further.

To extend the relevance of their experimental findings to kidney damage, the investigators examined the influence of muscle growth on another example of kidney damage, namely cisplatin nephrotoxicity. In that case, the experiments were not as comprehensive but the authors did find that cisplatin caused a sharp decrease in creatinine clearance; in Akt1 TG mice, however, it was more than 3-fold higher than in values measured in WT mice. The difference was not statistically significant.

In the final set of experiments, the authors examined how the beneficial effects of skeletal muscle growth on preventing kidney damage following UUO might be explained. Specifically, they examined activation of endothelial nitric oxide synthase (eNOS) and found it was activated in the kidneys of Akt1 TG mice following UUO. Administration of the eNOS inhibitor, L-NG-nitroarginine, abolished the difference in activated eNOS. However, in Akt1 TG mice with kidneys damaged by UUO, the inhibitor raised the reduced levels of genes associated with inflammation and fibrosis- and myofibroblast-differentiation in kidneys to levels measured in WT mice with kidneys subjected to UUO. Although these responses are consistent with an eNOS-dependent mechanism that suppresses damage and fibrosis in the kidney, the investigators did not determine how eNOS in the kidney was activated by the overexpression of Akt1 in muscle. In addition, it would be interesting to explore whether partial blockade of eNOS activity will also suppress kidney fibrosis and tubular damage in the obstructed kidney and whether eNOS activation works in an all-or-none fashion.

Could other mechanisms influence the crosstalk between skeletal muscle and the damaged kidney? The likely answer is yes, based on potential mediators present in the muscle secretome.[4] First, it will be important to assess the expression of circulating mediators as well as those in muscle samples. This suggestion arises from a report demonstrating that certain inflammatory cytokines can exert important changes in kidney function. In fact, those authors reported that cisplatin-induced kidney injury is worsened by the expression of TNF-α and potentially other cytokines and chemokines.[14] This is relevant because mice with genetic deletion of TNF-α were found to be resistant to cisplatin injury. Second, Guo and colleagues[15] examined the role of TNF-α receptor in another fashion. Through use of mice with genetic deletion of the individual TNF-α receptors, TNFR1 or TNFR2, the responses of the kidney with UUO were examined. The investigators found significant decreases in collagen IV and smooth muscle actin-α mRNAs in obstructed kidneys of TNFR1 knockout mice versus results in WT or TNFR2 knockout mice. Mice with genetic deletion of TNFR1 or TNFR2 had impaired myofibroblast differentiation and reduced NFκB activity in the kidney responding to UUO. The authors concluded that kidney damage from UUO is mediated at least in part by TNF-α through activation of TNF-α receptors. Third, complex interactions among potential mediators may affect the function of the damaged kidney. For example, in CKD, another catabolic condition that leads to kidney fibrosis, TNF-α stimulates IL-6 expression in muscle, leading to a reduction in both the phosphorylation of Akt1 and its metabolic influence in muscle. This response leads to loss of muscle mass and, potentially, more inflammation with a "feed forward" response that raises the expression of inflammatory mediators.[8,9] Fourth, skeletal muscle can express and release IGF-1 and other growth factors into the circulation.[4] The growth factors can affect the function of cells nearby and, potentially, those at a distance (*e.g.,* in the damaged kidney) and therefore could limit reparative responses in the obstructed kidney.[5] This possibility is raised because CKD impairs the function of IGF-1. Fifth, in AKT1 TG mice, the authors found lower levels of circulating adiponectin. This is of interest because a recent report demonstrated that the kidneys of mice with genetic deletion of adiponectin are protected from the development of fibrosis that is induced by UUO or injury following ischemia-reperfusion.[16] Finally, Hanatani *et al.* concluded that the infiltration of macrophages into kidneys damaged by UUO is reduced in Akt1 TG mice. It is tempting to speculate that there is crosstalk between skeletal muscle and bone marrow cells leading to reduced accumulation of bone marrow–derived fibroblasts and reduced kidney fibrosis.[17]

In conclusion, Hanatani and colleagues propose a new paradigm, namely that skeletal muscle can affect the growth and regenerative properties in the damaged kidney. Documentation of these responses could form the basis for potential therapeutic strategies to limit progression of CKD. Clearly, using genetic methods to increase muscle mass in order to improve kidney function is not practical. However, there are potential approaches that might be developed to explore this new area of investigation. First, exercise training can help patients with kidney disease build muscle that could release molecules that protect the injured kidney. Second, drugs could be developed to block the function of specific inflammatory cytokines (*e.g.*, TNF-α) that seem to be central to the development of obstructive kidney damage. Finally, understanding how muscle interacts with the kidney could identify novel signaling pathways, leading to strategies that boost protective responses or block detrimental responses.

DISCLOSURES

None.

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See related article, "Akt1-Mediated Fast/Glycolytic Skeletal Muscle Growth Attenuates Renal Damage in Experimental Kidney Disease," on pages 2800–2811.

Asking Dialysis Patients About What They Were Told: A New Strategy for Improving Access to Kidney Transplantation?

Mark Unruh* and Mary Amanda Dew†

*University of New Mexico School of Medicine, University of New Mexico, Albuquerque, New Mexico; and †Departments of Psychiatry, Psychology, Epidemiology, Biostatistics, and Clinical and Translational Science, University of Pittsburgh School of Medicine and Medical Center, Pittsburgh, Pennsylvania

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Kidney transplant remains the optimal treatment for many patients with ESRD.[1] Providing timely and equitable access to kidney transplantation across age and ethnicity has been a challenge for many programs.[2] Although elegant descriptions of the transplant process have demonstrated stepwise systemic barriers to equitable access to transplantation,[3] few studies have examined patient–dialysis team interactions and communication, including the extent to which provision of information about kidney transplantation influences transplant listing and subsequent outcomes.

The research by Salter and colleagues[4] in this issue of *JASN* is significant and important because it is the first to examine reports of kidney transplantation provision of information (KTPI) by both the care provider and the patient and then relate them to listing for kidney transplantation. Their work takes advantage of an ongoing study of sudden death among incident hemodialysis patients. In their ancillary cohort study, the investigators thus had access to a well characterized group of 388 patients initiating dialysis within 6 months of enrollment. They collected provider-reported KTPI from the Centers for Medicare & Medicaid Services Form 2728 and patient-reported KTPI from surveys. A notable finding was that KTPI was reported by both the provider and the patient for only 56% of patients. In nearly 28% of the sample, only the provider reported KTPI; only the patient reported it in 8.3%. Further, in multivariable analyses the provider-reported KTPI was neither strongly nor significantly associated with subsequent transplant listing status, while patient-reported KTPI was associated with an almost 3-fold increased likelihood of listing. This finding prompted the investigators to argue that patient perception of KTPI is a novel and important factor that may drive the association between KTPI and ultimate listing for transplantation.

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Correspondence: Dr. Mary Amanda Dew, University of Pittsburgh School of Medicine and Medical Center, 3811 O'Hara Street, Pittsburgh, PA 15213. Email: dewma@upmc.edu