The growing importance of mTORC1-S6K1 signaling in kidney

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RENAL HYPERTROPHY, which aptly describes the condition of increased kidney mass attributable to enlargement more so than proliferation of tubular and glomerular cells, can occur under many circumstances, but the underlying mechanism(s) remain poorly understood. Diabetes mellitus is a common disease associated with a pronounced renal cellular hypertrophy that can progress to chronic fibrotic changes. Because diabetic nephropathy is the leading cause of chronic renal failure in the U.S. and renal hypertrophy is an early event, elucidating the mechanisms involved in renal hypertrophy may not only provide significant advancement in understanding a fundamental question in renal biology but may also offer new therapeutic inroads. Decades ago, increased single nephron glomerular filtration rate and increased nephron size had been observed after uninephrectomy. Despite significant effort by many groups, the sequence of these events, whether one causes the other, and the molecular signals that lead to these changes remain unclear.

In an article by Chen et al. (3), the authors demonstrate the requirement of S6 kinase 1 (S6K1) for the development of compensatory and diabetes-induced renal hypertrophy in mice. S6K1 is a principal downstream effector of mammalian target of rapamycin (mTOR), a serine/threonine protein kinase that regulates many cellular events including growth, proliferation, motility, survival, protein synthesis, and transcription. mTOR activity is modulated by a large variety of factors including hormones, growth factors, availability of amino acids, presence of energy stress, and hypoxia. mTOR exists in two structurally and functionally distinct multiprotein complexes, mTOR complex 1 (mTORC1) and mTORC2, regulating different downstream events. The same group has previously shown that pharmacological inhibition of mTORC1 (which specifically activates S6K1) by rapamycin prevents compensatory hypertrophy (2). Now the group presents the first genetic evidence for the involvement of mTORC1 signaling in the renal hypertrophic process, further supporting the assertion that mTORC1 has an important mechanistic role in this response. Specifically, the present study suggests that the role of mTORC1 in renal hypertrophy is mediated by S6K1 and not by its homolog S6K2, which appears to be upregulated in the absence of S6K1 but does not functionally compensate in the hypertrophic process. Although both S6K1 and 2 are substrates of mTORC1, their differential regulation and separable roles in cell signaling are not fully understood. In addition, rapamycin, an allosteric inhibitor of mTORC1 approved for prophylaxis of organ transplant rejection with experimental use treating renal cell carcinomas, has been shown to differentially inhibit S6K1 and 4E-binding protein 1 (4E-BP1) (4). Thus continued study of mTORC1 function in models of renal hypertrophy may further the overall understanding of this important signaling pathway and provide information that can be applied to other areas (such as cancer biology) where mTORC1 signaling is also important.

Another highlight of this study is the demonstration that S6K1 is required for renal hypertrophy that is induced both by loss of functioning nephrons and diabetes. In these two conditions, the detected increase in kidney size is either due to almost “pure” hypertrophy (compensatory renal growth) or mixed hypertrophy and hyperplasia (diabetes mellitus). Previous studies have suggested that the mechanisms underlying kidney growth associated with these two conditions might not completely overlap because additive hypertrophy was observed in remnant kidneys of uninephrectomized rodents with induced diabetes (14). Thus studies of the combination of diabetes and uninephrectomy in the S6K1 knockout mouse may provide critical information as to the mode of mTORC1-S6K1 activation in each case.

The finding that the mTORC1 pathway mediates at least a significant portion of renal hypertrophy is important for several reasons. First, positioning mTORC1 signaling in the renal hypertrophic process may provide clues to the signals that initiate the structural adaptation. mTORC1, the rapamycin-sensitive mTOR complex composed of mTOR, regulatory associated protein of mTOR (raptor), mammalian LST8/G protein β-subunit-like protein, and PRAS40, functions as a cellular sensor of energy level, nutrient availability, and redox status (7, 8). As such, its activity can be stimulated by insulin, growth factors, and amino acids to initiate protein synthesis through activation of S6 ribosomal protein by S6K1 and release of suppression of the eukaryotic initiation factor 4E (eIF4E) by 4E-BP1. On the basis of this understanding of mTORC1 signaling, it is plausible that mTORC1-mediated renal hypertrophy may be driven by increased growth factor delivery or nutrient availability to the remaining kidney after uninephrectomy or by their altered equilibrium in other hypertrophic conditions. However, this convergence of multiple signals into mTORC1 is not the only cascade activated as underscored by the discovery that an S6K1-independent, rapamycin-insensitive component exists that contributes to renal hypertrophy associated with uninephrectomy or diabetes. In particular, growth factors are well known to transmit their signals through multiple pathways. One example is transforming growth factor (TGF)-β, which has been shown to promote hypertrophy and regulate cell cycle in compensatory renal growth. Unfortunately, TGF-β also increases extracellular matrix deposition and promotes glomerulosclerosis. In this respect, it is important to note that larger reductions of nephron number (i.e., experimentally in 5/6 nephrectomy) can lead to progressive renal fibrosis. It could be contemplated whether
this is attributable to an imbalance of signals shifting the cellular response from appropriate compensatory renal growth to “inappropriate” progressive renal fibrosis. The dissection of these pathways by studies like the one by Chen et al. (3) certainly will improve our understanding of this network. In addition, it may be possible to utilize the activation of S6K1 as an early read out in search of a stimulus that initiates renal hypertrophy, further enhancing the overall value of this finding.

Another potentially important upshot of the involvement of mTORC1 signaling in renal hypertrophy is that the pathway is very targetable. mTORC1 activity is specifically and effectively inhibited by the drug rapamycin, a macrolide first developed as an antifungal that is now widely used for immunosuppression and more recently as an antiproliferative in cancer therapy (5, 11, 12). mTORC1 inhibition may be a treatment option in situations where renal hypertrophy is detrimental and/or pathogenic, such as diabetes. In fact, there is already some precedent for this idea. Studies have shown that mTORC1 inhibition with rapamycin can prevent diabetes-induced renal hypertrophy and attenuate the subsequent kidney disease in rats and mice (10, 13, 15). Alternatively, in light of the involvement of mTORC1-S6K1 in compensatory renal hypertrophy, it may also be necessary to avoid (or at least closely monitor the use of) drugs that target the mTORC1 pathway in situations where renal hypertrophy is desirable. Thus an important question might be whether mTORC1 inhibition might impair recruitment of the renal reserve. As an interesting corollary, what if repair of acute renal injury can occur through similar mechanisms to compensatory hypertrophy? If a patient is on rapamycin for immunosuppression and is also exposed to other nephotoxic drugs (nonsteroidal anti-inflammatory drugs, for example), mTORC1 inhibition might impair the ability of the kidney to respond to the insult. This would suggest that activity of S6K or a related pathway could be extremely useful as a marker of disease or for progression. The availability of a sensitive marker would clearly facilitate monitoring the development of renal hypertrophy and possibly benefit the discovery of new and appropriate interventions.

It is likewise important to note, because of the complex signal integration network in which mTORC1-S6K1 is involved, that we cannot conclude that its specific inhibition would not exhibit other unwanted effects in the kidney. Findings in cancer models suggest a link between inhibition of mTOR and ERK activation, possibly reflecting interruption of an S6K1-dependent negative feedback loop (1, 6, 9). It remains to be determined whether this is also significant in renal hypertrophy.

The study presented by Chen et al. (3) is the latest, and perhaps provides the most direct evidence supporting the involvement of mTORC1-S6K1 signaling in renal hypertrophy, which is a significant step forward in understanding the mechanisms behind this phenomenon. This discovery raises many important questions about the signaling network responsible for mediating renal hypertrophy and its role in different types of renal injury. Examining the role of another downstream target of mTORC1, 4E-BP1, in hypertrophic renal growth will likely contribute much because 4E-BP1 controls translation of capped mRNAs by keeping the eIF4E inactive. Also, what about the persistence of the effect? Does mTORC1 remain hyperactive indefinitely, or is it transiently activated? The forthcoming answers to these and other related questions will likely add clarity to a longstanding observation in renal biology and provide the groundwork for improved therapeutic approaches.

ACKNOWLEDGMENTS

The authors thank Drs. John J. Bissler (CHMC) and Thomas H. Hostetter (AECOM) for helpful discussions in the preparation of this editorial.

GRANTS

M. Bitez is supported by the AMGEN Nephrology Institute, the Nephcure Foundation, and the American Society of Nephrology. B. Siroky is supported by the PKD foundation.

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