Sestrin 2: a regulator of the glomerular parietal epithelial cell phenotype

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FOR A LONG TIME, glomerular parietal epithelial cells (PECs) have mainly been considered to be “innocent bystanders” in the pathology and physiology of the glomerulus. More recently, important functions of PECs have been proposed (for a review, see Ref. 16). PECs have been suggested to be (1) an intrinsic progenitor population to replenish podocytes or proximal tubular cells (15), (2) a second glomerular barrier (13), and (3) important cells involved in the pathogenesis of glomerulonephrosis and crescent formation (5, 17, 18).

PECs are very flat cells with a flat condensed nucleus. Usually, they exhibit very little proliferative activity. In glomerular disease, however, PECs can become activated, develop a larger cytoplasm and a larger round nucleus, and express de novo the marker protein CD44 (18). PEC activation plays an important role in two seemingly different glomerular diseases: (1) rapidly progressing glomerulonephritis and 2) focal and segmental glomerulosclerosis. In rapidly progressing glomerulonephritis, activated PECs primarily exhibit increased proliferation, leading to the formation of early cellular crescents. These, in turn, cause acute and often irreversible loss of renal function by blocking the flow of the primary filtrate into the proximal tubule, leading to degeneration of the entire nephron (12). In focal and segmental glomerulosclerosis, migration and matrix production by activated PECs appear to be more prominent (17, 18). These observations suggest that PECs may become activated in different fashions. However, so far, it is unknown which processes or mediators trigger PEC activation and by which pathways activated PECs are regulated. Elucidation of the crucial mediators and mechanisms may potentially provide new and specific therapies that attenuate the progression of glomerular disease.

A study by Hamatani et al. (9), published in a recent issue of the American Journal of Physiology-Renal Physiology, identified sestrin 2 as one such potential regulator of PEC phenotypes (9). Sestrin 2 is a member of a family of stress-inducible proteins that counteract oxidative stress. Specifically, sestrin 2 represses cell proliferation and growth by inhibition of mammalian target of rapamycin (mTOR) signaling (2). By virtue of these actions, sestrins can maintain cellular and metabolic homeostasis. In contrast to other cell types, where sestrin 2 expression is related to stressors (3), normal adult PECs constitutively express sestrin 2. In addition, in different models of glomerular injury leading to transient proteinuria, glomerulosclerosis, or crescentic glomerulonephritis, sestrin 2 expression in PECs is decreased. By immunohistochemistry and in vitro experiments, Hamatani and coworkers demonstrated that reduced PEC sestrin 2 expression was associated with de novo expression of the activation marker CD44, proliferation, and/or apoptosis. Moreover, decreased expression of sestrin 2 was accompanied by increased expression activity of mTOR. The authors concluded that sestrin 2 and mTOR may represent a yin-yang system in PECs, with high sestrin 2 and low mTOR activity in health possibly contributing to the maintenance of normal homeostasis of PECs. In injured and/or activated PECs, decreased expression of sestrin 2 led to increased mTOR activity, which resulted in either PEC activation, proliferation, and/or apoptosis.

The results from this study suggest that the mTOR signaling network plays an important role in the switch from normal resting to activated PECs seen in progressive glomerular disease. Although these exciting observations will require further followup studies, including transgenic PEC-specific targeting of sestrin 2 and target of rapamycin complex (TORC1)/TORC2 in vivo, mTOR signaling might become a pharmaceutical target to prevent or reduce PEC activation and subsequently to dampen and halt the process of glomerulosclerosis and crescent formation.

mTOR inhibitors are commonly used to prevent transplant rejection and as antiproliferative agents in different cancers. However, with regard to the kidney, the effects of mTOR inhibition are inconsistent. Experimentally, mTOR inhibition can delay or reverse glomerular diseases (1, 11) and diabetic nephropathy (6), but inhibition of mTOR frequently causes proteinuria in humans (4). These conflicting findings probably result from the tight regulation of mTOR activity within kidney epithelial cells, where even minimal changes in activity may have dramatic effects. Moreover, the effects are context dependent, as reduced mTOR activity may lead to different cell responses in health or disease (10). This presumably also holds true for PECs. Hamatani et al. showed that despite a common loss of sestrin 2 and increased mTOR activity in PECs in different models of glomerular injury, the effects on PECs were different. In adriamycin and puromycin rat models of glomerulosclerosis and transient proteinuria, respectively, reduced numbers of PECs were observed. In contrast, in crescentic glomerular nephritis, they merely observed proliferation of PECs.

In addition, mTOR inhibition might not be specific enough to target activated PECs selectively. Next to modulating the immune system, mTOR activity is a key pathway that regulates cellular growth, cell division, lipid and mitochondrial biogenesis, and tubular electrolyte in epithelial cells of the entire nephron (6–8, 14, 19). Since fine-tuned mTOR activity is crucial for most if not all kidney epithelial cells, it is comprehensible that systemic inhibition of mTOR affects the survival and regeneration not only of PECs but also of other cells.

Nevertheless, present study by Hamatani et al. provides new and important clues on the molecules regulating the fate of...
PECs in glomerular disease, and it is imperative to further study and gain insights into the upstream regulators of mTOR activity, like sestrin 2. In addition, further understanding and identification of cell-specific downstream targets of mTOR, including autophagy, might allow the development of specific therapies to halt glomerulosclerosis and crescent formation by PECs.

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