Role of the podocyte signal-transduction systems in the pathogenesis of diabetic nephropathy

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Diabetic nephropathy, which develops in 30–40% of diabetic patients, is a leading cause of end-stage renal disease (ESRD), accounting for more than 40% of new ESRD cases undergoing treatment in the USA and other developed countries [1, 2]. In its initial stage, diabetic patients excrete macromolecules such as albumin, indicating an abnormality in the glomerular permeability barrier, followed by a gradual decline of GFR with the appearance of overt proteinuria [3]. The glomerular permeability barrier consists of endothelial cells, the glomerular basement membrane, and podocytes. Podocytes are highly specialized epithelial cells with interdigitating foot processes that participate in the prevention of proteinuria [4]. In the early stage of diabetic nephropathy, effacement of the foot processes is observed in podocytes, resulting in the leakage of macromolecules, including albumin, into the urine [4]. Loss of trace amounts of albumin in the urine, microalbuminuria, has been regarded as an early marker of diabetic nephropathy, although microalbuminuria is also observed in patients with metabolic syndrome, indicating that insulin resistance may cause podocyte injury [5].

To examine the role of podocyte insulin signaling in the pathogenesis of diabetic nephropathy, Welsh et al. [6] recently analyzed mice with podocyte-specific deletion of the insulin receptor. They showed that these mice developed significant proteinuria by 5 weeks of age; histological

glomerular changes resembling those of diabetic nephropathy, for example effacement of podocyte foot processes, thickening of the basement membrane, accumulation of mesangial matrix, and glomerulosclerosis in a normoglycemic environment, were also observed. In in-vivo and in-vitro analysis of podocytes lacking the insulin receptor, both the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase/Akt pathways, the two major pathways downstream of the insulin receptor, were shown to be abrogated. It was also reported that insulin-induced reorganization of actin cytoskeleton in podocytes, which, in investigations of familial nephritic syndromes, was revealed to be important in the maintenance of the glomerular permeability barrier [7], was affected by the absence of the insulin receptor. These findings suggested that impaired insulin signaling in podocytes is sufficient for development of some pathological features of diabetic nephropathy, although its molecular mechanism was not fully investigated. In addition, in these mice, the role of other insulin-regulated pathways important for the maintenance of podocyte function, such as autophagy and mammalian target of rapamycin (mTOR) pathways were not evaluated [8, 9].

Autophagy is a biological process that plays a crucial role in maintaining cell integrity by degradation and recycling of cytosolic proteins and organelles [8]. As podocytes are terminally differentiated postmitotic cells, autophagy is critically important for maintenance of cellular homeostasis. In fact, podocyte-specific deletion of autophagy-related 5 (Atg5), a key regulator of the autophagic process, led to a glomerulopathy in aging mice that was accompanied by accumulation of oxidized and ubiquitinated proteins, ER stress, and proteinuria [10]. This autophagic pathway is inhibited by insulin, and by other growth factors and nutrients, for example

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glucose and amino acids, via a rapamycin-sensitive protein complex, termed mTOR complex 1 (mTORC1), containing an evolutionarily conserved serine/threonine protein kinase, mTOR [9]. Animal studies have revealed that experimental inhibition of mTORC1 activity upregulated in diabetic state via rapamycin has a beneficial effect on the treatment of diabetic nephropathy [11]. According to these findings, Inoki et al. [12] recently generated mice with podocyte-specific ablation of an upstream negative regulator of mTORC1, TSC1, to analyze the effects of constitutive mTORC1 activation on glomerular function. Podocyte-specific mTORC1 activation caused thickening of the glomerular basement membrane, proteinuria, and mesangial expansion, in addition to podocyte loss. These diabetic nephropathy-like features were ameliorated by rapamycin treatment or genetic suppression of mTORC1 activity by podocyte-specific knockout of Raptor, an essential component of mTORC1 [12]. Conversely, Gödel [13] analyzed mice lacking podocyte mTORC1 activity by podocyte-specific knockout of Raptor, and demonstrated that loss of podocyte mTORC1 activity also caused albuminuria and progressive glomerulosclerosis. They also showed that additional loss of podocyte mTORC2 activity by podocyte-specific knockout of Rictor, an essential component of mTORC2, aggravated the glomerular lesions, indicating that both of the two mTOR complexes are involved in the maintenance of podocyte function [13]. These studies convincingly showed that podocyte mTOR activity is essential to the maintenance of glomerular function, although the extent to which these mTOR pathways are involved in the pathogenesis of nephropathy in diabetic patients remains unclear. Moreover, taking into account that patients with tuberous sclerosis caused by TSC1 or TSC2 mutations do not develop glomerular lesions resembling those of diabetic nephropathy [14], these findings in animal models should be cautiously examined for future clinical applications in the treatment of diabetic nephropathy.

Collectively, recent animal studies manipulating podocyte insulin-regulated signal transduction have verified that perturbation of this system in podocytes is sufficient to cause development of pathological changes similar to those of diabetic nephropathy. Further investigation is needed to clarify the molecular mechanisms of human diabetic nephropathy.

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