The multi-talented podocyte

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The podocyte has long been viewed as a fascinating cell. It was first appreciated for its exquisite anatomy with primary, secondary and tertiary foot processes enveloping the glomerular capillary loops in a complex meshwork. Karnovsky described the highly specialized cell junctions at the glomerular basement membrane, the slit diaphragm, further highlighting its complex and highly specialized anatomy [1]. The podocyte was recognized as a key element of the capillary wall barrier to maintain normal permeability, and podocyte abnormalities, i.e. foot process effacement, were recognized early on to be key corollaries of proteinuria. The next era of interest in the podocyte began with the discovery by Tryggvason et al. that a key slit diaphragm structural molecule, i.e. nephrin, was mutated in congenital nephrotic syndrome of Finnish type [2]. This discovery launched an explosion of interest in many structural molecules of the podocyte that when affected by mutations or polymorphisms are linked to nephrotic syndrome and sclerosis. Examples include podocin, α-actinin4, phospholipase C ε, CD2-AP and more recently the transient receptor potential channel-6 (TRPC-6) [3]. Thus, we now have an example of a podocyte channel that responds to alterations in angiotensin II by altering calcium signalling that profoundly affects the podocyte’s cytoskeleton [4]. In parallel, the slit diaphragm is now recognized not merely as a mechanical barrier to filtration, but also as a sensing device [5] that responds dynamically to alterations in the ultrafiltrate that passes through it, with changes in signalling cascades that also affect the cytoskeleton.

Injurious and pro-fibrotic events are also recognized to directly affect the podocyte. Thus, the podocyte expresses key components of the renin–angiotensin system and also responds to transforming growth factor-β (TGF-β) [6,7]. Importantly, the podocyte is not isolated, as it sits on the urinary aspect of the GBM. Through complex mechanisms, podocyte-specific production of vascular endothelial growth factor-A (VEGF-A) reaches the endothelium, which is key for maintenance of the glomerular endothelial cell [8]. Autocrine effects of VEGF, involving direct actions of VEGF-A via a podocyte receptor, have also been suggested [9].

The loss of the podocyte is thought to be a key event in progressive sclerotic injury in many diseases [10–12]. The podocyte has very limited regeneration capacity [13]. Although regeneration may be possible from niche stem cells, such as specialized parietal-like epithelial cells [14], podocyte detachment and/or apoptosis are closely correlated with loss of normal permeability function and ultimately, sclerosis. In recent years, the podocyte has also been shown to be capable of responding to insulin, transporting glucose via the glucose transporters GLUT1 and GLUT4 [15]. This action was found to be dependent on nephrin expression. The current studies by Lennon et al. reveal the expanded talents and responsiveness of the podocyte [16]. The authors show that free fatty acids induce profound changes in cultured podocytes, including decreased insulin receptor IRS1, PKB and lesser translocation of GLUT4 to the cytoplasmic membrane. In the absence of cytotoxicity, there was a corresponding downregulation of VEGF-A and of key insulin receptor signalling pathways, investigated by the focused gene array and protein signalling and trafficking.

The authors previously showed that the response of podocytes to insulin and glucose transport was dependent on nephrin expression [15]. The authors suggest that the NCK adaptor protein may mediate the linkage of nephrin to actin and thus play a role in glucose transporter translocation. Of key importance therefore is the downregulation of the adaptor protein NCK1 by palmitate, suggesting a direct fatty acid effect on glucose transport. In related studies, Ijaz et al. showed that podocytes from db/db diabetic mice lost their ability to respond to insulin as albuminuria developed, in association with increased phosphorylation of C-jun N-terminal kinase (JNK). However, when phosphorylation of JNK was inhibited in db/db mice in vivo, although insulin sensitivity improved and glucose levels were lower, there was no improvement in albuminuria. Similarly, knockout of either JNK1 or JNK2 did not improve the streptozotocin-induced diabetic phenotype, and albuminuria was actually worse in JNK2 knockout mice. However, whether JNK phosphorylation was specifically altered in podocytes, or whether podocyte differentiation and insulin sensitivity were altered in response to JNK inhibition, was not specifically investigated.

The above studies indicate that there may be complex interrelationships between events of insulin signalling and other components of podocyte injury and ultimate diabetic nephropathy. In vivo multiple mechanisms are
simultaneously activated. Reactive oxygen species are increased in diabetes, and are linked to podocyte apoptosis and podocyte depletion at the onset of diabetic nephropathy [18]. The renin–angiotensin system is activated in diabetes, and not only increases collagen production by podocytes, but also augments both TGFβ and VEGF-A, while decreasing nephrin. Augmented VEGF is linked to increased permeability and albuminuria, but depletion of VEGF is also detrimental to the glomerulus, being linked to cell death and sclerosis [19]. Particularly in diabetic nephropathy, augmented VEGF may play a pathophysiologic role in microalbuminuria [20]. Overall, the downregulation of VEGF induced in vitro by free fatty acids may thus not be the dominant net effect seen in vivo. In conjunction with other deleterious stimuli, free fatty acids may well contribute to a multi-hit assault on the podocyte from which it cannot recover. Further investigation, including both in-depth in vitro evidence as done in the current study and in vivo animal model studies and ultimately extrapolation and translation to human conditions, will be necessary to fully understand the significance of these findings.

Unfortunately, such efforts are greatly hampered by the current lack of rodent diabetic models that faithfully capture the key elements of human diabetic nephropathy [21]. We must thus at the present time continue to build our understanding of the multi-talented podocyte and its role in development of diabetic nephropathy in stepwise fashion; the current studies by Lennon et al. add yet another dimension to the evolving concepts of pathogenesis of diabetic nephropathy.

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References


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