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**Activated Protein C Protects Against Diabetic Nephropathy *In Vivo* Via Its Anti-apoptotic Properties**

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Data providing direct evidence for a causative link between endothelial dysfunction, microvascular disease and diabetic end-organ damage are scarce. Here we show that activated protein C (APC) formation, which is regulated by endothelial thrombomodulin, is reduced in diabetic mice and causally linked to nephropathy. Thrombomodulin-dependent APC formation mediates cytoprotection in diabetic nephropathy by inhibiting glomerular apoptosis. APC prevents glucose-induced apoptosis in endothelial cells and podocytes, the cellular components of the glomerular filtration barrier. APC modulates the mitochondrial apoptosis pathway via the protease-activated receptor PAR-1 and the endothelial protein C receptor EPCR in glucose-stressed cells. These experiments establish a new pathway, in which hyperglycemia impairs endothelial thrombomodulin-dependent APC formation. Loss of thrombomodulin-dependent APC formation interrupts cross-talk between the vascular compartment and podocytes, causing glomerular apoptosis and diabetic nephropathy. Conversely, maintaining high APC levels during long-term diabetes protects against diabetic nephropathy.