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The endothelial thrombomodulin protein C system mediates nephroprotection *via* inhibition of mitochondrial apoptosis in glomerular cells

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Thrombomodulin (Thbd) dependent protein C (PC) activation on endothelial cells exerts anti-coagulant, anti-inflammatory and anti-apoptotic activities. It has been shown that endothelial thrombomodulin protein system is impaired in diabetic individuals, as shown by increased levels of soluble thrombomodulin and decreased levels of activated protein C (APC). To determine whether impaired Thbd-dependent PC activation is mechanistically linked with endothelial and glomerular capillary dysfunction we employed mice with genetically altered levels of APC. Wild-type (Wt) mice, mice with a loss of Thbd-dependent PC-activation ($Thbd^{Pro/Pro}$), and mice with a gain of function mutation (APC^{high}) were maintained diabetic for 6 months. Markers of diabetic nephropathy were determined and tissue samples were collected for morphological and *ex vivo* expression studies. Supplementary *in vitro* experiments were performed with endothelial cells, podocytes and mesangial cells.

Compared to Wt mice, diabetic nephropathy was aggravated in $Thbd^{Pro/Pro}$ mice, while APC^{high} mice were protected. Glomerular apoptosis and depletion of podocytes was markedly increased in diabetic Wt and $Thbd^{Pro/Pro}$ mice where as diabetic APC^{high} mice were protected. APC modulates both mitochondrial and endoplasmic reticulum stress mediated apoptosis *in vivo*. In addition we provide an independent evidence for the first time that inhibition of apoptosis is sufficient to protect against diabetic nephropathy. APC protected endothelial cells; podocytes from hyperglycemia and puromycin induced apoptosis, but had no anti-apoptotic effect in mesangial cells *in vitro*. The cytoprotective effects of APC in endothelial cells are mediated via EPCR/PAR-1 where as in podocytes it requires PAR-3. In conclusion, our data link endothelial dysfunction and a loss of Thbd-dependent PC-activation with a loss of podocyte. This implies the existence of a cross talk between vascular system and podocytes, which is crucially involved in modulating diabetic nephropathy.