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MORPHOLOGICAL AND CLINICAL CHANGES OF PODOCYTES IN DIABETIC GLOMERULOPATHY

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Diabetic nephropathy (DN) is a significant and severe complication of diabetes mellitus. Central to its progression is injury to the glomerular visceral epithelial cells – the podocytes. These highly specialized, terminally differentiated cells feature primary and secondary processes that culminate in foot processes. Interdigitating foot processes from neighboring podocytes form narrow filtration slits spanned by the slit diaphragm, an extracellular structure that acts as a size-selective barrier preventing protein leakage. Beyond this structural role, podocytes produce vital glomerular basement membrane (GBM) components, including type IV collagen, laminin, entactin, and agrin. Given that DN is characterized by clinical proteinuria and histopathological changes such as glomerular enlargement, GBM thickening, and foot process effacement, podocytes are a key focus of research. Human biopsy studies confirm that podocytes sustain early functional and structural damage during DN development.

The pathogenesis of podocyte injury begins with the chronic diabetic milieu – hyperglycemia, accumulation of advanced glycation end-products (AGEs), and increased mechanical stress from systemic and intraglomerular hypertension. Elevated intracellular glucose drives mitochondrial reactive oxygen species (ROS) production, activating the polyol pathway, PKC, and the AGE-RAGE axis. This metabolic stress, together with angiotensin II (ANG II), directly disrupts the podocyte actin cytoskeleton.

A critical early event is the reduction of nephrin, a key slit diaphragm protein with antiapoptotic properties. Nephrin downregulation – mediated by hyperglycemia, ROS, and ANG II – causes foot process effacement (FPE) and enhances protein leakage. ANG II plays a pivotal role by further downregulating nephrin and activating cytokine pathways such as transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF). TGF-β1 fosters mesangial matrix expansion and GBM thickening, and can induce podocyte apoptosis or detachment. VEGF, produced by podocytes in an autocrine manner, influences podocyte function, glomerular blood flow, and endothelial permeability; its dysregulation is crucial in the development of albuminuria.

As FPE progresses, podocytes detach from the GBM due to downregulated integrins (α3β1) and dystroglycans. Detachment is irreversible. Metabolic dysregulation also triggers podocyte apoptosis via upregulation of Bax/p53 and downregulation of Bcl-2, along with lipotoxicity-induced endoplasmic reticulum stress. The diabetic environment directly or indirectly causes podocyte hypertrophy, apoptosis, structural alterations, and increased type IV collagen production.

Loss of podocytes (podocyturia) denudes the GBM, which then adheres to Bowman's capsule, forming synechiae and tuft adhesions. This initiates segmental and global glomerulosclerosis, along with tubulointerstitial fibrosis. Proteinuria, once a consequence of podocyte injury, further exacerbates tubular damage. Ultimately, the degree of podocyte loss correlates directly with the rate of renal function decline. Research indicates that abnormal hemodynamics and growth factor activity drive these changes. Thus, preserving podocyte integrity and targeting pathways involving nephrin, ANG II, TGF-β, and VEGF represent central therapeutic strategies in diabetic kidney disease.