

從基礎腎臟學研究探討臨床腎臟疾病各種挑戰—糖尿病腎病變

A look from basic research of pathogenetic mechanism to see the growing challenges  
in clinical nephrology: focused on diabetic nephropathy

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Diabetic nephropathy is one of leading cause of end-stage renal disease that becomes a tremendous healthcare burden in Taiwan. Dysfunction of mesangial cells and podocytes in renal glomerular micro-compartments contribute to diabetic nephropathy. Compared with conventional mechanisms of diabetic nephropathy, the Dickkopf-1(DKK1)/Wnt/  $\beta$ -catenin signaling pathway is virgin land in this field. By searching the PubMed at that time (2006), there is no research group in the world studies on molecular mechanism of DKK1/Wnt/GSK-3 $\beta$ / $\beta$ -catenin developmental signaling pathways that mediated diabetic nephropathy. We have previously demonstrated that excessive fibrosis and apoptosis via DKK1/Wnt pathway in mesangial cells and Notch1 mediated angiogenic reactions in podocytes are important cellular events underlying diabetes-mediated renal injury. Imbalance between Wnt signaling, CB1 and reactive oxygen stress were found to impede homeostasis and function in diabetic renal microenvironments. In recent JASN publication, we clearly demonstrated that miR-29a and HDAC4 is an important regulator in the maintenance of podocyte ultra-structure integrity and renal homeostasis. This study highlights an emerging view of an epigenetic mechanism underlying nephrin acetylation in podocytes and suggests that the addition of the miR-29a function is beneficial for improving diabetic podocytopathy. Our hypothesis in this paper was selected to be the cover page of this top journal which recognized the importance of our theory. Our groups in recent 10 year have demonstrated that the disturbance of developmental pathways including Notch1/DKK1/Wnt/ $\beta$ -catenin signaling and epigenetic modulation by miR-29a and HDAC4 plays a critical role in diabetic mesangial cell and podocyte injury. Its activation or depression in diabetic animals contributes to the development of diabetic glomerular disease. The Yin–Yang theory from traditional Chinese medicine, which is an analogy with depression and activation in signaling pathways, is important for diagnosis and treatment of chronic disease. These concepts not only characterize the molecular mechanism and the functional consequences of stem cell signaling activation in glomeruli, but also suggest that these tissue regeneration processes including DKK1 activation may ameliorate diabetic glomerular sclerosis. To our knowledge, few academic groups in the world have attributed diabetic nephropathy to the fibrosis products of tissue regeneration at that time. The proposed paradigm contradicts previous concepts which indicate that tissue regeneration and fibrosis are totally different cases. Such paradigm shift would provide screen platform for new drug discovery against diabetic kidney disease and exciting new venues for improving renal outcome by retarding the progression of diabetic nephropathy, which are regarded as the therapeutic hope in the future.