특별 강연 IV

MicroRNAs in Diabetic Nephropathy

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Diabetic nephropathy (DN) is a frequent renal complication of diabetes that can also lead to end stage renal disease. Transforming Growth Factor-β (TGF-β) has been implicated as a key player in DN since it is associated with major hallmarks of DN such as the accumulation of extracellular matrix (ECM) proteins and increased hypertrophy in the kidney mesangium and tubulointerstitium. Evidence shows that several signaling mechanisms and transcription factors are involved in TGF-β actions in renal cells. We demonstrated that a microRNA circuit can mediate TGF-β induced expression of ECM genes like collagen in mesangial cells (MC). We observed that microRNA-192 (miR-192) was upregulated by TGF-β in cultured glomerular MC and in kidney glomeruli from diabetic mice, and enhanced collagen expression by targeting E-box repressors, Zeb1/2. miR-192 was also involved in MC hypertrophy and cell survival by activating Akt kinase via upregulating downstream miRNAs (miR-216a and miR-217) that target PTEN (Akt kinase inhibitor). miR-216a could also upregulate collagen via downregulation of an RNA-binding protein, Ybx1 that regulates mRNA stability and translation. miR-192 and TGF-β also increased the expression of miR-200 family members which can target Zeb1/2. This could promote an autoregulation of TGF-β itself in MC via de-repression at E-boxes in the TGF-β promoter. Since miR-192 is a key upstream regulator of other renal microRNAs (such as miR-216a, miR-217, miR-200b/c), we examined its potential as a therapeutic target for DN. For this we evaluated for the first time the efficacy of a Locked nucleic acid (LNA)-modified inhibitor of miR-192 (LNA-antimiR-192) in mouse models of DN. We first confirmed accumulation of LNA-antimiR-192 in renal compartments, and the specific and efficient reduction of miR-192 by subcutaneous injection of LNA-antimiR-192 in normal mice at 6, and 24hr post injection. Next, we tested the efficacy of LNA-antimiR-192 in Streptozotocin (STZ)-induced diabetic mice at three different time points post LNA-antimiR-192 treatment. We observed specific reduction of renal miR-192, decreased renal fibrosis and hypertrophy, and improved renal functions in the LNA-antimiR-192-injected diabetic mice. In summary, a miRNA-mediated amplifying cascade initiated by miR-192 in response to TGF-β in diabetic kidney MC may enhance ECM expression and hypertrophy related to DN. Together these data suggest that renal microRNAs may play major modulatory roles in the development of chronic kidney diseases.