

당뇨병증신장병증에서 TonEBP 전사조절인자의 역할: 치료제와 발병위험진단 개발

울산과학기술대학교

권혁무

TonEBP/NFAT5 Transcription Factor Promotes Diabetic Nephropathy Via Local Inflammation: Implications in Therapy and Risk Assessment

Hyug Moo Kwon

Ulsan National Institute of Science and Technology

Diabetic nephropathy is the leading cause of chronic kidney disease and end-stage renal disease. Low-grade, chronic inflammation in the kidney is associated with the development of nephropathy in patients with type 1 diabetes.¹⁾ Since the TonEBP transcription factor is critical in chronic inflammation in the setting of rheumatoid arthritis²⁾ and atherosclerosis,³⁾ we ask whether TonEBP plays a role in diabetic nephropathy. We find that hyperglycemia is a powerful pro-inflammatory stimulus as it promotes the pro-inflammatory phenotype (M1) of macrophages while it suppresses the anti-inflammatory phenotype (M2). TonEBP is involved in both of these processes. Macrophages whose TonEBP expression is reduced by siRNA-mediated knockdown or genetic haploinsufficiency (TonEBP(+/ Δ) mice (heterozygotes) display a dramatic shift toward M2 phenotype away from M1. In patients with <30 years of type 1 diabetes, those patients with proteinuria shows 70% higher activity of TonEBP in their monocytes compared to those without proteinuria.⁴⁾ In a mouse model of diabetic nephropathy (endothelial nitric oxide synthase null mice), streptozotocin-induced diabetes leads to a dramatic nephropathy – proteinuria, glomerular injury, and interstitial fibrosis. All the aspects of injury is dramatically ameliorated in the TonEBP heterozygotes in association with smaller number of M1 macrophages in the kidney and lower expression of inflammatory cytokines. In two Caucasian cohorts, HAPI (healthy Amish adults)⁵⁾ and CDKGen,⁶⁾ we find that single nucleotide polymorphisms (SNPs) in the TonEBP genes display significant association with inflammation and eGFR, a marker for renal insufficiency, suggesting that genetic variations in the TonEBP gene determines inflammation and nephropathy. In aggregate, these observations provide two interesting insights: 1) inhibitors of TonEBP would be useful therapeutic agents for diabetic nephropathy, and 2) specific sequence variation(s) in the TonEBP gene might predispose nephropathy among patients with diabetes and would be useful in assessing the risk of nephropathy at early stages of diabetes.

References

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