

SIGNIFICANCE STATEMENT

TonEBP (tonicity-responsive enhancer-binding protein), also known as Nfat5, is a transcription factor with a physiologic role in the response to osmotic stress in epithelial cells of the renal medulla. Recent evidence points to additional functions in macrophages. This study provides evidence that TonEBP constitutes a causal link between hyperglycemia and induction of proinflammatory gene expression in macrophages, renal infiltration by macrophages, and macrophage-mediated renal injury. Beyond this, the investigators find in a cohort of healthy humans that genetic variations in the TonEBP gene are associated with systemic inflammation and renal function. TonEBP is a novel target for therapy development for diabetic complications including diabetic nephropathy.