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The evolving role of TonEBP as an immunometabolic stress protein

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Tonicity-responsive enhancer binding protein (TonEBP), also known as nuclear factor of activated T cell 5 (NFAT5), was discovered 21 years ago as a transcriptional regulator of the response to hypertonic (hyperosmotic salinity) stress in the renal medulla. TonEBP stimulates transcription of AQP2 and UT-A transporter genes as well as membrane transporters and biosynthetic enzymes for cellular accumulation of organic osmolytes. Animals deficient in TonEBP suffer from nephrogenic diabetes insipidus with severe renal medullay hypotrophy consistent with the role of TonEBP in the urinary concentration and protection of renal medullary cells from local hypertonic stress. Numerous studies since then have uncovered that TonEBP is a pleiotropic stress protein involved in a variety of immunometabolic diseases. Single nucleotide variations in the introns of the TonEBP gene are associated with the risk of type 2 diabetes, diabetic nephropathy, inflammation, blood pressure, and serum sodium suggesting that variations in the level of TonEBP expression are responsible for the various phenotypes. In addition, functional studies have shown that TonEBP is involved in the pathogenesis of rheumatoid arthritis, atherosclerosis, diabetic nephropathy, hyperlipidemia and insulin resistance, autoimmune diseases including type 1 diabetes and multiple sclerosis, salt homeostasis linked to resolution of hypertension, hepatocellular carcinoma, and repair of DNA damage. An emerging theme is that TonEBP is a stress protein responding to a variety of pathological insults including excess calorie intake, inflammation, and oxidative stress.