Renal and Non-renal Function of TonEBP/NFAT5 Transcriptional Activator

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TonEBP (tonicity-responsive enhancer (TonE) binding protein) is a member of the Rel family of transcriptional activators that include NF κ B and NFAT (nuclear factor of activated T-cells). A transcriptional activator binds to its cognate sites located near the promoter and stimulates transcription. The Rel family is defined based on structural similarity in the Rel-homology domain (RHD) involved in DNA binding. The RHD's of TonEBP and NFAT isoforms share 43% of amino acids. On this basis, TonEBP is also called NFAT5. Interestingly, however, the RHD of TonEBP forms a dimer like the RHD of NF-κB even though they share minimal amino acid identities, i.e., less than 20%. Thus, structure of TonEBP resembles that of NF-κB even though sequence of TonEBP is similar to NFAT.

Analyses of genome databases reveal that the Rel proteins first appeared in invertebrates such as the *Drosophila*. There are several NF-κB members and a homolog of TonEBP named *MSER1* in the *Drosophila* genome. *MSER1* appears to be the ortholog of TonEBP because its RHD displays higher homology to the RHD of TonEBP than NFAT, and it has two glutamine repeats like TonEBP. Based on analyses of exon structures of the Rel proteins, it is believed that TonEBP is the direct evolutionary ancestor of the NFAT subfamily that exists only in vertebrates.

TonEBP was initially cloned from the kidney medulla as the key regulatory protein that stimulates genes in response to ambient hypertonicity, i.e., hyperosmotic salt. Osmolality of the mammalian kidney medulla is very high, often 10 times the blood or higher, due to high concentration of salt and urea. The hyperosmolality provides driving force for water reabsorption and urinary concentration, and thereby, contributes to the maintenance of body fluid volume and blood pressure. Because of the hypertonicity, TonEBP activity in the kidney medulla is high. By stimulating its target genes, TonEBP contributes to the function of the kidney medulla. TonEBP enhances expression of the vasopressin-regulated urea transporter, a key molecule in generation of the high urea concentration in the kidney medulla. Thus, hypertonicity is ultimately responsible for generation of the high urea concentration in the renal medulla.

Unfortunately, the hyperosmolality imposes a great deal of stress to the renal medullary cells causing double stranded DNA breaks and cell death. TonEBP also plays a major role in protection of cells in the kidney medulla in two ways. First, TonEBP stimulates several genes encoding plasma membrane transporters and aldose reductase that catalyze cellular accumulation of organic osmolytes. Major organic osmolytes in the mammalian kidney include inositol, betaine, taurine, sorbitol, and glycerophosphorylcholine. High concentration of intracellular organic osmolytes protects cells from the deleterious effects of hypertonicity by lowering the cellular ionic strength. Second, TonEBP stimulates expression of heat shock protein 70 that protects cells from the deleterious effects of high urea.

In mammals, TonEBP is abundantly expressed

throughout fetal development and in most adult tissues outside the kidney such as brain, heart, and thymus. Function of TonEBP is understood in the thymus. T cell receptor activation leads to an increased TonEBP expression in T cells. In transgenic mice expressing a dominant inhibitory form of TonEBP in the thymus, the number of T cells is significantly reduced. It appears that the osmoprotective function of TonEBP is required for proliferation and/or survival of T cells in the thymus. In mature T cells, TonEBP stimulates expression of TNF α and lymphotoxin β. Function of TonEBP in other organs is unknown except that TonEBP appears to participate in the integrin-mediated carcinoma invasion. In *Drosophila*, recessive lethal mutations of *MSER1* have been reported. Overexpression of *MSER1* resulted in suppression of the RAS signaling and axon guidance/synaptogenesis phenotypes.

In conclusion, TonEBP is a newly recognized Rel protein. TonEBP plays a major role in differentiation of the renal medulla by stimulating genes involved in urea accumulation and protection of cells from high osmolality. Much of TonEBP function in non-renal tissues remains to be learned.