Interplay between TonEBP and calcineurin-NFATc signaling pathways: a means of optimizing water reabsorption? Focus on “Calcineurin-NFATc signaling pathway regulates AQP2 expression in response to calcium signals and osmotic stress”

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CORRECT REGULATION of renal water reabsorption and urinary concentration is critical for the proper maintenance of body fluid volume. In comparison to the established role of the transcription factor tonicity-responsive enhancer binding protein (TonEBP) in the urinary concentration mechanism, that played by nuclear factor of activated T cells (NFAT) is less obvious. Now, Li et al. (6) provide evidence that links calcium signaling and water reabsorption by showing that transcription of the aquaporin (AQP)2 water channel is enhanced by the calcineurin-NFATc pathway. The authors show that while TonEBP and calcineurin-NFATc pathways each directly induce AQP2 transcription, cross talk occurring between both pathways further enhances AQP2 expression.

The final checkpoint for renal water reabsorption occurs at the level of the collecting duct. High water permeability in this nephron segment is largely due to the presence of AQP2 inserted in the apical membrane of principal collecting duct cells. While the antidiuretic hormone (8-arginine)vasopressin (AVP) plays a major role in regulating AQP2 expression, several pieces of evidence indicate that this event is additionally influenced by hypertonicity (12). Water reabsorption increases along the osmotic gradient together with TonEBP expression. TonEBP is consequently highly expressed in the kidney medulla and the importance of TonEBP in renal physiology is well recognized. In contrast, while the calcineurin-NFATc pathway has been extensively described in such diverse areas as immune, nervous, and cardiovascular systems (3), relatively little is known of its role in the kidney. The NFAT family consists of five members, NFAT1–5, that share a highly conserved DNA-binding domain that confers a common specificity to a consensus binding sequence (8, 9). However, TonEBP (NFAT5) differs from NFATc (NFAT1–4) in several ways. While TonEBP binds DNA as a dimer, NFATc binds DNA as a monomer and often forms cooperative complexes with Fos and Jun. Changes in environmental tonicity increase TonEBP activity by increasing TonEBP nuclear localization, transactivation, and abundance (9). TonEBP contributes to the corticopapillary osmotic gradient by stimulating urea recycling between the ascending limb of Henle’s loop and the inner medullary collecting duct (11), by protecting cells from the deleterious effects of high urea, by regulating heat shock protein 70 expression (16), and by enhancing AQP2 expression (4). TonEBP also plays an outstanding role in protecting cells against hypertonicity by stimulating transcription of genes whose products help accumulate compatible osmolytes that lower intracellular ionic strength (15). NFATc activity, on the other hand, is mediated by a large number of environmental signals that induce a receptor-mediated rise of intracellular Ca²⁺. The ensuing activation of the protein phosphatase calcineurin diphosphorylates NFATc, leading to exposure of NFATc nuclear localization sequences and nuclear import of NFATc protein (3). Various observations led to the proposal that NFATc is implicated in salt and water homeostasis by decreasing, via a COX-2-dependent mechanism, sodium reabsorption as a consequence of decreased Na⁺-K⁺-2Cl⁻ cotransporter activity in the medullary thick ascending limb and decreased Na⁺-K⁺-ATPase activity in other nephron segments (1).

In this issue of the American Journal of Physiology-Cell Physiology, Li et al. (Ref. 6, see p. C1606) show that AQP2 transcription in cultured collecting duct principal cells (mpkCCD34) is not only controlled by TonEBP-mediated hypertonicity but also by the calcineurin-NFATc pathway. In addition, the authors provide evidence that the calcineurin-NFATc pathway can be activated by hypertonicity and that TonEBP expression can be induced by calcineurin activity. Such interplay between calcineurin-NFATc and TonEBP pathways most likely affects transcriptional activity in various physiological settings. For instance, the authors’ observation that the calcineurin-NFATc1 pathway enhances AQP2 transcription independently of hypertonic and TonEBP stimulation is, by itself, of substantial importance for our understanding of events that control AQP2 expression. However, the authors additionally show that hypertonic and calcineurin/AP-1 stimulation, acting independently of each other, induce binding of both TonEBP and NFATc1 to the AQP2 proximal promoter and increase AQP2 transcriptional activity. Moreover, both events were downregulated by cyclosporin A/FK506. Collectively, these observations indicate that AQP2 transcription is mediated by cross talk between calcium-dependent calcineurin signaling and hypertonicity-induced signaling pathways. Such control over AQP2 transcription may have important consequences in water handling in distal nephron segments.

The findings of Li et al. provide further insight into another aspect of clinical importance, that of the well-known nephrotoxic effects observed in patients who receive calcineurin inhibitors (2, 10). Previous observations, together with those of Li et al. (6), suggest that these effects may at least partly result from reduced TonEBP activity. Indeed, cyclosporin A treatment reduces TonEBP-dependent expression of several osmoprotective genes (13), urea transporters, and renal aquaporins, including AQP2, and promotes apoptotic cell death (7). As Li et al. point out, chronic toxicity of calcineurin inhibitors on
renal tubules may consequently result from loss of a calcineurin-mediated regulatory mechanism necessary for compatible osmolyte accumulation and transepithelial water transport. This suggests that calcineurin may play a key role in water homeostasis and osmoprotection in collecting duct principal cells. Calcineurin stimulation of TonEBP activity may represent a common phenomenon occurring in numerous cell types outside of the kidney. Many of the effects of modulated calcineurin activity on TonEBP-controlled transcription presented in the article by Li et al. (6) were additionally demonstrated in T lymphocytes (14). Since TonEBP is expressed in a wide variety of tissue types, including those that are not normally subject to conditions of elevated tonicity (5, 14), calcineurin-dependent induction of TonEBP may play a broader role in inducing genes distinct from those induced by hypertonicity. Interplay between TonEBP and calcineurin-NFATc pathways may confer greater regulatory control over gene expression in response to diverse environmental signals. For instance, exposure of cells to conditions of high osmolality initiates a series of events, including compatible osmolyte accumulation and cytokine elicitation, as part of an adaptation process that ultimately leads to cell survival. One can speculate that converging TonEBP and calcineurin-NFATc pathways may provide the cell with a means to adapt quickly to a hyperosmotic environment. We are only beginning to understand the complex interplay between these pathways. The article by Li et al. provides evidence that water reabsorption is modulated by both TonEBP and calcineurin-NFATc pathways via controlled AQP2 transcriptional activity. Our understanding of the consequences of integrated osmotic stress and calcium signaling will undoubtedly lend further insight into how cells optimally respond to diverse extracellular stimuli.

REFERENCES


