The Nucleocytoplasmic Shuttling of Tonicity-Responsive Transcription Factors

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Maintenance of tonicity balance is essential for cell survival. To counter the deleterious effects of hyper- or hypotonic conditions, cells have developed sophisticated mechanisms to mount an effective adaptive response. Part of this adaptation process involves rapid nucleocytoplasmic shuttling of transcription factors to regulate the expression of tonicity-responsive genes.

Nuclear Factor of Activated T-cells 5 (NFAT5) is one such example in mammalian cells. Hypertonicity triggers rapid nuclear import of NFAT5 to activate the transcription of multiple organic osmolyte transporters. In contrast, hypotonicity renders NFAT5 largely cytosolic, thus turning off the NFAT5-mediated transcription program. The molecular mechanism of this tonicity-regulated nucleocytoplasmic shuttling is not well understood.

Here we report molecular and structural studies to dissect the tonicity-regulated nucleocytoplasmic shuttling process of NFAT5. We first used siRNA screening to confirm that the nuclear import of NFAT5 under hypertonicity requires only karyopherin β1 (KPNB1), but not karyopherin α. We also used proteomics analysis to reveal that the nuclear export of NFAT5 under hypotonicity is driven by exportin-T (XPOT). We mapped an unconventional nuclear localization signal (NLS) in NFAT5 and investigated its interaction with KPNB1 by cryo-EM studies.

Overall, our studies reveal that NFAT5 undergoes tonicity-drive nucleocytoplasmic shuttling through unconventional routes involving KPNB1 and XPOT. Our findings may apply to other tonicity-responsive transcription factors.