Identification of a Novel Nuclear Export Sequence of OREBP/TonEBP/NFAT5 that Controls Cytoplasmic Localization.

B. Ko,[1] E. H. Tong,[1] S. S. Chung[2]; [1]Department of Chemistry, The University of Hong Kong, Hong Kong, Hong Kong Special Administrative Region of China, [2]Department of Physiology, The University of Hong Kong, Hong Kong, Hong Kong Special Administrative Region of China

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The Osmotic-Response Element-Binding Protein (OREBP), also known as the Tonicity Enhancer-Binding Protein (TonEBP) or NFAT5, regulates the hypertonicity- induced expression of a battery of genes crucial for the adaptation of mammalian cells to extracellular hypertonic stress. Recently, it has been suggested that OREBP may play a role in metastasis. The nucleocytoplasmic trafficking of OREBP plays an important role in regulating its function. Here we show that, by immunocytochemistry and GFP fusion, the transactivation domain of OREBP is not necessary for the nucleocytoplasmic trafficking. Nuclear export of OREBP can be blocked by leptomycin B, suggesting that it is a Crm1-dependent process. However, two leucine-rich motifs located in the N-terminal of OREBP do not function as nuclear export signals (NES). In contrast, a protein domain N-terminal to the DNA-binding domain functions as NES and directs the localization to the cytoplasm. Recombinant OREBP devoid of the NES constitutively resides in the nucleus despite of extracellular hypotonicity.