Role of Translationally Controlled Tumor Protein in the Pathogenesis of Hypertension

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The alpha subunit of rat Na,K-ATPase forms 3rd cytoplasmic domain (CD3) between H4 and H5 bordered on both sides by multiple transmembrane segments. The CD3 includes the phosphorylation site (Asp371) and ATP interaction site (Lys503). To identify proteins that might interact with the CD3 of Na,K-ATPase and affect the function of the pump, the yeast two-hybrid system was used to screen a rat skeletal muscle cDNA library. We isolated cDNA clones for translationally controlled tumor protein (TCTP), also known as IgE-dependent histamine-releasing factor which was found to cause histamine release from IgE+ basophils of chronic allergic patients by an unknown mechanism. In this study, we demonstrated that TCTP interacts only with the 3rd cytoplasmic domain but not with the 2nd, 4th, and 5th cytoplasmic domains or the cytoplasmic region of the b subunit of Na,K-ATPase. We also demonstrated that TCTP is a Na,K-ATPase binding protein that increases [Na+]i and plasma membrane depolarization, indicating that TCTP is a Na+ pump inhibitor. It has been reported that Na,K-ATPase inhibition by digitalis glycosides and potassium-deprivation causes hypertension as well as cardiac hypertrophy. Since TCTP functions as a Na pump inhibitor like ouabain as shown in our study, we hypothesized that the overexpression of HRF in the cell might be associated with the pathogenesis of hypertension. Thus, we generated TCTP transgenic mouse to test if the overexpression of TCTP is able to cause hypertension disease. We recently confirmed that this is the case by measuring the tail-cutoff systolic blood pressure of HRF transgenic mouse. Taken together, our new findings have led us to propose that when TCTP binds to Na/K-ATPase, it converts the enzyme to a signal transducer and causes hypertension.