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Meeting abstract

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The neuron-specific protein, p42^{IP4} (Centaurin-α1) is localized in mitochondria, interacts with 2',3'-cyclic nucleotide 3'-phosphodiesterase and is involved in regulation and control of mitochondrial Ca^{2+}

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p42^{IP4} is a brain-specific protein also called centaurin-α1. This protein specifically recognizes two second messengers, the membrane lipid PtdIns (3,4,5)P3 and the soluble inositol phosphate Ins(1,3,4,5)P4. Previously, expression of p42^{IP4} protein in non-neuronal CHO cells stably transfected with pcDNA-p42^{IP4} was shown in cytosol, membranes and nucleus. The membrane fraction in that study also contained mitochondria. The yeast protein Gcs1p, which is structurally and functionally related to p42^{IP4}, is localized in mitochondria and is involved in maintenance of mitochondrial morphology. The program PSORT II had predicted a high probability for mitochondrial localization of p42IP4. Therefore, localization of p42^{IP4} in mitochondria was suggested.

We show here for the first time that p42^{IP4} is localized in mitochondria, isolated from cells transfected with p42^{IP4}, CHO cells and mouse neuroblastoma (N2a) cells. In CHO cells, p42^{IP4} is localized predominantly in the intermembrane space side of the mitochondrial inner membrane. p42^{IP4} is also found in mitochondria isolated from rat brain.

Previously, 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP) has been shown to be associated with mitochondria, but the exact role of CNP in mitochondria is still obscure. We show the localization of CNP in both mitochondrial membrane fractions by sub-fractionation of rat brain mitochondria (RBM). We additionally found interaction of p42^{IP4} with CNP in RBM by pull-down binding assay and by immunoprecipitation.

Cellular Ca^{2+} signals are crucial in the control of most physiological processes, cell injury and programmed cell death. In neurons, mitochondria dampen changes in cytosolic Ca^{2+} loads and sustain cellular Ca^{2+} homeostasis that is required for normal neuronal function. However, mitochondria take up a limited amount of calcium up to a certain threshold. Accumulation of Ca^{2+} above this threshold leads to increased permeability of the inner mitochondrial membrane due to formation of a unselective pore at the contact site between outer and inner membranes. Since permeability transition pore (PTP) opening is important in mitochondrial events leading to cell death, we studied whether p42^{IP4} is involved in Ca^{2+}-induced Ca^{2+} release and consequently PTP. We determined the Ca^{2+}capacity and lag-phase for PTP opening in mitochondria isolated from p42^{IP4}-transfected and from control N2a cells. Overexpression of p42^{IP4} led to significant decrease of these functional mitochondrial Ca^{2+} parameters. Thus, we suggest that due to involvement in the regulation of Ca^{2+} transport in mitochondria, p42^{IP4},

destabilizes mitochondria by promoting Ca^{2+}-induced PTP opening.