STUDY OF MENIN FUNCTION BY SIRNAS INHIBITION OF MEN1-mRNA IN CULTURED CELLS

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Multiple endocrine neoplasia type 1 (MEN1) is characterized by the occurrence of tumors of the parathyroids, neuroendocrine cells of the gastro-entero-pancreatic tract, and the anterior pituitary, including more than 20 other endocrine and nonendocrine tumor combinations. MEN1 gene, a tumor suppressor gene, encodes a protein, menin. Loss of heterozygosity (LOH) at 11q13 has been found in MEN1 tumors, but also in sporadic pituitary tumors and in 30-70% of sporadic parathyroids and endocrine pancreas tumors, a subset of those with LOH at 11q13 exhibiting mutations in the MEN1 gene. MEN1 mRNA and p ot in are expressed in all normal studied tissues, unexplaining the endocrine predominance of n sopuls no. Nutations in the MEN1 gene frequently predict protein truncat on possibly leading to inact va au furction consistent with the idea of a tumor suppressor gene. Men, interacts with AP 1 rens ription factor JunD, Smad3 and inhibits NFkB-mediated transportation. Moreover, menial list interacts with pem, nm23, GFAP, the 32-kDa subunit of REP \, and nor muscle myc sin UA heav; chain. Menin uncouples Elk-1, JunD, and c-Jun phosphorylation from MAPK active ion The effects of MEN1 in human neuroendocrine cells and its role in ger e egulation remain still elusive. We studied the role of MEN1 mRNA and menin protein in the global (ene expression rework in skin fibroblasts from three MEN1 patients with heterozyacte trupatin mutation of gene and from healthy individuals: two sisters with a frame-shift, 738del4 (ex-), in oducing a premeture stop codon, and a MEN1 individual with a nonsense mutation, R460X (exch 10). Densitemetri a alaysis revealed a reduction of MEN1 mRNA expression in fibroblasts from patients v: healthy donor as also confirmed by Real Time RT-PCR. Contrarily, menin protein seems to be similarly expressed in the three MEN1 patients as also in the healthy control. These preliminary data show a discrepancy between menin-mRNA and menin protein expression: reduced menin-mRNA expression does not fit with the observed equal expression of menin protein. A mechanism of compensation at mRNA and/or protein levels may explain our results. The down-regulation of the wild-type allele by siRNA and ribozymes in heterozygous MEN1 mutants should give more informations about this hypothetical mechanism.