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 protein are expressed in all normal studied tissues, unexplaining the endocrine predominance of neoplasms. Mutations in the MEN1 gene frequently predict protein truncation possibly leading to inactivated function consistent with the idea of a tumor suppressor gene. Menin interacts with AP1 transcription factor JunD, Smad3 and inhibits NFkB-mediated transactivation. Moreover, menin also interacts with pem, nm23, GFAP, the 32-kDa subunit of RFPA, and nonmuscle myosin IIA heavy chain. Menin uncouples Elk-1, JunD, and c-Jun phosphorylation from MAPK activation. The effects of MEN1 in human neuroendocrine cells and its role in gene regulation remain still elusive. We studied the role of MEN1 mRNA and menin protein in the global gene expression network in skin fibroblasts from three MEN1 patients with heterozygote truncating mutation of gene and from healthy individuals: two sisters with a frame-shift, 738del4 (exon 3), introducing a premature stop codon, and a MEN1 individual with a nonsense mutation, R460X (exon 10). Densitometric analysis revealed a reduction of MEN1 mRNA expression in fibroblasts from patients vs 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.