HIGHLIGHT

Mechanisms of multiple endocrine neoplasia type 1: evidence for regulation of the AP-1 family of transcription factors by Menin

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The autosomal dominant disorder, multiple endocrine neoplasia type 1 (MEN 1), in which there is an association of parathyroid, enteropancreatic, neuroendocrine and anterior pituitary tumours, was demonstrated to be caused by germline mutations in the tumour-suppressor MEN 1 gene. This gene, located on chromosome 11q13, was cloned by positional cloning in 1997 (1). It encodes a 67 kDa protein, Menin, that does not show homology with previously identified proteins. Although the function of Menin was unknown, its nuclear localization was established (2). As expected from Knudson's hypothesis, Menin seems to be implicated, not only in MEN 1 tumours, but also in sporadic endocrine tumours with loss of heterozygosity at 11q13 (1). Somatic MEN 1 mutations are common in sporadic bronchial carcinoids (36%), gastrinomas (33%), parathyroid adenomas (21%) and insulinomas (17%).

Using a yeast two-hybrid screen of a human brain cDNA library with Menin as the bait, Agarwal *et al.* (3) identified the transcription factor JunD as interacting directly with Menin. JunD is a member of the activating protein-1 (AP-1) family of transcription factors. AP-1 consists of various combinations of Fos, Jun and activating transcription factor (ATF2, ATF3, ...) bZIP proteins (4); they dimerize via the leucine zipper domain and bind to DNA via the adjacent basic region. The Fos family is made up of four gene products, c-Fos, FosB, Fra1 and Fra2, and there are three protein members of the Jun family of proteins: c-Jun, JunB, JunD. Jun proteins form heterodimers with Fos- and ATF-family members, and can also homodimerize.

AP-1 binds to the consensus TRE (tetradecanoyl phorbol acetate-responsive element) site, which is found in the promoter of many genes, such as cell-cycle regulators. AP-1 is a major target of cell growth, differentiation and stress signalling pathways. The Ras-dependent Raf–MEK–mitogen-activated protein (MAP) kinase cascade is one of the key signalling pathways in the regulation of AP-1 (Fig. 1). Unlike c-Jun and JunB, JunD is not classified as an immediate-early gene, as its expression is constitutive and poorly affected by growth factors and external stimuli. Moreover,

among the AP-1 family of transcription factors, JunD functions in an opposing manner in regulating growth and cell division, as it has been found to be non-transforming (5). This difference in transformation ability maps to the amino (N)-terminal region.

Menin N-terminal region and a separate central domain are required for interaction with the N terminus of JunD. Moreover, study of several naturally occurring MEN 1 missense mutations has demonstrated a region between amino acids 139 and 242 that is critical for Menin–JunD interaction (3). *In vitro* study of Menin–JunD

Figure 1 Interactions between Menin and AP-1: the growth factor signalling pathway from the cell surface to the nucleus through Ras and the MAP kinase cascade. The transcription factors of the AP-1 family are shown in the nucleus. The factors of this family bind the AP-1/TRE found in the promoter of numerous genes regulating cellular proliferation. As shown, Menin interacts with JunD, leading to its inactivation.

interactions has demonstrated repression of JunD transactivation by Menin (3). Interestingly, the majority of naturally occurring mutations found in MEN 1 families independently of the abolition of the Menin–JunD interaction were unable to repress JunD-mediated transcription. The interaction between Menin and JunD seems unlikely to interfere with JunD DNA-binding ability or JunD homo- or heterodimerization. Menin could itself be a repressor, or it could recruit a repressor protein to JunD. Thus the repressive effect of the tumour-repressive gene, Menin, on the non-transforming factor, JunD, seems paradoxical, and remains to be explained.

These findings give an insight into the role of the tumour-suppressor gene, Menin, in endocrine tumours and offer the first clues to the action of the MEN 1 gene product. They seem to establish a central role for transcription factors of the AP-1 family in endocrine tumorigenesis. Further investigations will help to understand Menin–JunD interactions, and might lead to the identification of specific target genes for the

Menin–JunD complex that are involved in endocrine tumorigenesis.

References

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