A long-sought needle in the haystack: the multiple endocrine neoplasia type 1 gene

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The recent identification of the gene underlying the pathogenesis of multiple endocrine neoplasia type 1 (MEN1) by Chandrasekharappa et al. is a significant advancement and will help to elucidate mechanisms of tumorigenesis in endocrine glands and provides more accurate tools to identify gene carriers at an early stage (1).

MEN1 is an autosomal dominant cancer syndrome predominantly characterized by tumors of the parathyroid glands (in 90 to 100% of cases), the anterior pituitary (in ∼50 to 65% of cases) and the neuroendocrine pancreas (in ∼30 to 75% of cases) (2). In addition, many other tumors occur at increased frequency in MEN1 patients. This impressive list includes, among others, thyroid adenomas, follicular thyroid carcinomas, adenocortical tumors, carcinoids in various locations, lipomas, angiofibromas, angiomyolipomas, and pinealomas. Besides the development of mass effects, these neoplasias may lead to altered secretion of hormones such as parathyroid hormone, prolactin, growth hormone, adrenocorticotropic hormone, vasoactive intestinal peptide, somatostatin, calcitonin, gastrin and a multitude of other biologically active peptides (e.g. chromogranins, pancreatic polypeptide, vasoactive intestinal peptide, somatostatin, calcitonin), resulting in the respective clinical pictures.

The association of four enlarged parathyroid glands and an eosinophilic pituitary adenoma was recognized at the beginning of the century by Erdheim (3). and Wermer proposed in 1954 an autosomal dominant defect with high penetrance based on the observation of a family in which the father and four of nine children presented with at least two of the classical MEN1 tumors (4). Zollinger-Ellison syndrome, gastrinomas causing hyperacidity, multiple and recurrent peptic ulcers and diarrhea, was described in 1955 (5). Although the prevalence of MEN1 is probably underestimated because of lack of recognition, it is estimated to range between 1 in 10 000 and 1 in 100 000. By age 50, the penetrance reaches almost 100% for parathyroid tumors which form the most common manifestation of the syndrome. What is the underlying genetic mechanism? Based on studies of sporadic and hereditary retinoblastomas, Knudson formulated the ‘two-hit model’ in 1971 (6). According to this concept, a tumor can develop when both copies of the retinoblastoma gene become defective in a retinal cell, either through two somatic events (sporadic retinoblastoma) or through somatic loss of the normal allele in an individual with an hereditary defect in the other allele (hereditary retinoblastoma). Cloning of the retinoblastoma gene subsequently confirmed the validity of this model. Analogous to the ‘two-hit model’ established in retinoblastomas, it was hypothesized that an early step of tumorigenesis in MEN1 involves loss of a tumor suppressor gene. The defective allele is inherited in a Mendelian fashion and present in the germline, the second hit consists in the loss of the wild-type allele as a somatic event in the affected tissue. The mode of inheritance thus follows a dominant pattern, but the tumorigenesis results from a recessive loss of the tumor suppressor gene in a given organ.

Following many detailed clinical descriptions, the mapping of the MEN1 locus to chromosome 11q13 in 1988 by classical linkage analysis in four Swedish families was a major step towards cloning of the gene (7). Moreover, two reports published in 1989 demonstrated that 50 to 60% of parathyroid tumors in MEN1 patients display allelic losses on chromosome 11 which include the MEN1 locus, and that the deleted allele originated from the unaffected parent (8, 9). These findings fully supported the concept of two genetic hits leading to the loss of a putative tumor suppressor.

Many of the steps leading to refinement of the mapping of this chromosomal region have been succinctly summarized by Larsson and Friedman (10). Pursuing a strategy of positional cloning (11) (genetic and physical mapping, identification of genes in the candidate region, detection of a mutated candidate gene, confirmation of the relationship between the mutated gene and the disease), Chandrasekharappa et al. have become the first group to report the isolation of the MEN1 gene (1). The MEN1 gene contains 10 exons and encodes an apparently ubiquitously expressed 2·8 kb transcript identified in roughly equivalent amounts in all adult tissues. The cDNA encodes a protein of 610 amino acids called menin. Remarkably, sequence analysis of menin does not reveal any clearcut similarities to previously known proteins. Neither a signal peptide nor a nuclear localization signal are present, and there is no unambiguous indication of hydrophobic transmembrane domains.

Sequencing of genomic DNA of patients from typical MEN1 families revealed the presence of mutations in 14 of 15 individuals and confirmed that mutations in this gene segregate with the disease. Two mutations were encountered twice, one of them in two families not known to be related. The twelve detected mutations consisted of five frameshifts, three nonsense mutations,
two in-frame deletions and two missense alterations. These defects were found in six different exons, indicating a considerable heterogeneity in their location. Sequence analysis of 71 normal controls did not reveal any of these molecular defects.

The identification of the MEN1 gene product menin will have considerable clinical impact and opens new avenues for exploring the mechanisms underlying tumorigenesis in endocrine glands. The knowledge of the gene will facilitate the identification of gene carriers in affected families which, so far, had to rely on polymorphic markers. Accurate determination of gene carriers at the preclinical stage will help to answer the crucial question of whether earlier diagnosis and treatment lead to reduced morbidity and mortality. It will be of interest to assess whether the clinical heterogeneity commonly observed among MEN1 kindreds correlates with the location and type of the mutation, thus providing insights into structure–function relationships of menin. Furthermore, the question arises whether menin also plays a role in sporadic forms of endocrine tumors. Given the absence of known proteins with a similar structure, the key question as to the functional role of menin in the regulation of the cell cycle becomes, of course, even more substantial. As was the case with Rb, the retinoblastoma gene product, the functional characterization of menin will undoubtedly provide many insights into normal and pathological regulation of growth and function in endocrine cell systems, areas of interest to the clinician and the basic scientist.

References