MEN1 in pancreatic endocrine tumors: analysis of gene and protein status in 169 sporadic neoplasms reveals alterations in the vast majority of cases.

Pancreatic endocrine tumors (PETs) may be part of hereditary multiple endocrine neoplasia type 1 (MEN1) syndrome. While MEN1 gene mutation is the only ascertained genetic anomaly described in PETs, no data exist on the cellular localization of MEN1-encoded protein, menin, in normal pancreas and PETs. A total of 169 PETs were used to assess the i) MEN1 gene mutational status in 100 clinically sporadic PETs by direct DNA sequencing, ii) immunohistochemical expression of menin in normal pancreas and 140 PETs, including 71 cases screened for gene mutations, and iii) correlation of these findings with clinical-pathological parameters. Twenty-seven PETs showed mutations that were somatic in 25 patients and revealed to be germline in 2 patients. Menin immunostaining showed strong nuclear and very faint cytoplasmic signal in normal islet cells, whereas it displayed abnormal location and expression levels in 80% of tumors. PETs harboring MEN1 truncating mutations lacked nuclear protein, and most PETs with MEN1 missense mutations showed a strong cytoplasmic positivity for menin. Menin was also misplaced in a significant number of cases lacking MEN1 mutations. In conclusion, the vast majority of PETs showed qualitative and/or quantitative alterations in
menin localization. In 30% of cases, this was associated with MEN1 mutations affecting sequences involved in nuclear localization or protein-protein interaction. In cases lacking MEN1 mutations, the alteration of one of the menin interactors may have prevented its proper localization, as suggested by recent data showing that menin protein shuttles between the nucleus and cytoplasm and also affects the subcellular localization of its interactors.