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3

Aetiology, molecular pathogenesis and genetics

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Endocrine tumours of the gut and pancreas originate from cells of the diffuse endocrine system and are characterised by the production of a wide variety of bioactive substances including growth factors. Two major tumour categories are distinguished-well-differentiated and poorly differentiated neoplasms-with distinct phenotypes and significantly diverse clinical behaviour. Here, genetic background data are summarised on an anatomical basis for tumours of foregut, midgut and hindgut derivatives. For well-differentiated tumours, independent techniques identified the abnormality of multiple chromosomal sites and genes, pointing to a complex genetic background. Differences in foregut tumours compared with midgut and hindgut tumours are, however, outlined. The multiple endocrine neoplasia syndrome type 1 (*MEN1*) gene is reported to be involved in about one-third of sporadic foregut endocrine tumours and exceptionally in midgut and hindgut tumours. Similarly, X chromosome markers are associated with malignant behaviour in foregut tumours only. For poorly differentiated carcinomas, a high degree of chromosomal instability is the common genetic trait independent of tumour site and frequently involving the *p53* gene.

Key words: pancreas; gut; endocrine cells; hormones; immunohistochemistry; molecular genetics; loss of heterozygosity.

AETIOLOGY

Histogenesis

The endocrine tumours of gut and pancreas are made by cells displaying a phenotype similar to that of the cells of the so-called diffuse endocrine system. In normal

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conditions, at least 14 endocrine cell types are described and characterised by the production of a wide variety of hormonal peptides, biogenic amines and other bioactive substances, including growth factors.[1,2] Diffuse endocrine system cells proliferate and differentiate according to constitutive tissue-specific programmes. In the gastrointestinal tract, endocrine cell homeostasis is maintained by specific physiological stimuli on multipotent cells, with the entry of new cells along the differentiation path.[3] Conversely, in the pancreas, the mechanism of endocrine cell self-maintenance entails the duplication of terminally differentiated endocrine cells.[4] In both cases, the endocrine-committed cells and the adult endocrine cells are prone to transforming agents, as demonstrated by the heritable development of endocrine tumours in transgenic mice.[5–7] It can be reasonably accepted that, in man, a similar mechanism may occur, resulting in endocrine tumour disease.

When talking about endocrine tumours of the gut, most clinicians refer to so-called 'carcinoids', a word that in reality encompasses a wide variety of different tumour diseases of the well-differentiated type (see the chapter by Klöppel in this volume), with clinical behaviour spanning from benign (well-differentiated endocrine tumour, WDET) to low-grade malignant (well-differentiated endocrine carcinoma).[8] In any case, WDETs/carcinomas are mostly slow-growing malignancies with a relatively low mitotic index and a low proliferation index. In addition, poorly differentiated endocrine carcinomas (PDECs) must be considered, especially given their severe histology and high-grade malignant behaviour. PDECs are considered to be derived from a more primitive, endocrine-committed although as yet incompletely differentiated endocrine cell, thus possessing an elevated proliferative and metastatic capacity.

Endocrine tumour cell functional phenotype

The endocrine differentiation of tumour cells is assessed by the identification of general markers of neuroendocrine differentiation by immunohistochemistry (Table 1).[9] Useful markers include the cytosol antigens neurone-specific enolase[10] and protein gene product 9.5,[11] the membrane-bound neural cell adhesion molecules,[12,13] the granule markers chromogranin A and the ATP-dependent vesicular monoamine transporters-1 and -2,[14–19] and the vesicle antigen synaptophysin.[20–22] Well-differentiated tumour cells express diffusely and intensely most of the above-mentioned markers, like their normal endocrine cell counterparts. Conversely, PDECs are overall diffusely positive for neurone-specific enolase, protein gene product 9.5 and synaptophysin, although negative for chromogranin A because of the rarity of large, dense-core granules.[23] The loss of chromogranin A expression in PDEC cells indicates their incomplete or abortive endocrine differentiation, in keeping with the 'on/off' switch function of the chromogranin A gene for endocrine differentiation in mammalian cells.[24]

Specific tumour cell types are identified by specific hormone immunohistochemistry. In general, WDETs are composed of one or more endocrine cell types that reflect the normal endocrine cell population of the organ of origin. In keeping with this, enterochromaffin-like (ECL) cell tumours are observed only in the stomach, insulinomas in the pancreas, etc.[1] In contrast, PDECs may be present at any site in the gut and pancreas, again supporting an origin from a less-differentiated, albeit endocrine-committed, cell type. Indeed, as a rule, PDECs display only occasional hormone-producing tumour cells.

In addition to hormones and biogenic amines, WDETs of the gut and pancreas often produce growth factors and express their related specific receptors (Table 2).