Gut Neuroendocrine Disease

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Gastrointestinal endocrinology as a basic and clinical science has expanded substantially since the early days of Bayliss and Starling. The peptide chemistry period was followed by the immunocytochemistry period, and at present we have moved into the molecular biology era. In retrospect, relatively little progress has been made in our understanding and treatment of the common gastrointestinal diseases, while considerable knowledge has accumulated in regard to the rare gut neuroendocrine tumors. Currently, assay determination of tumor markers has made tumor diagnosis and localization a well-established routine at most medical institutions. The study of tumor tissue has also played an important role in allowing further characterization of these lesions, e.g., purification of peptides normally occurring in low concentration, isolation of peptide mRNA, and studies of receptor binding and activation.

The increased understanding of the nature of the area of hormone receptors/receptor binding has enabled the pharmaceutical engineering of new molecules with potent and durable agonist or antagonist actions. An excellent example is the somatostatin analog, octreotide, which effectively suppresses hormone secretion and has become a valuable therapeutic principle in gut neuroendocrine disease [1].

Surgery still remains the first option in the treatment of solid tumors (Fig. 1). Treatment of disseminated metastatic disease continues to be a matter of some controversy: expectance, chemotherapy, tumor ischemia, interferons, or somatostatin analogs have all been studied. Due to the relative rarity of these tumors, the clinical series of treatment evaluations are generally small, and comparison has usually utilized historical controls. Most recently, randomized multi-center trials have, however, been established and will no doubt produce valuable recommendations [2].

Another important issue is monitoring of the effectiveness of therapy: traditional tumor responses have been followed either radiologically (size) or biochemically by plasma levels of tumor markers. Some difficulties arise in this respect, since the novel treatment strategies may modulate hormone secretion without corresponding antiproliferative effects. Also, the sensitivity of tumor imaging varies among the different radiological techniques used. These problems are some of the topics that require further evaluation.

Perspectives in Clinical Research

Part of the discrepancy in progress between the basic and clinical fields may be due to the fact that, to date, interest has predominantly focused on the mature peptide

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Abbreviations: FGF: fibroblast-stimulating growth factor  IGF-I: insulin-like growth factor I  IL-2; interleukin 2  MEN: multiple endocrine neoplasia (syndromes)  NGF: nerve growth factor  NK: natural killer (cells)  PDGF: platelet-derived growth factor  TGF: transforming growth factor  TIL: tumor-infiltrating lymphocytes

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FIG. 1. To obtain optimal tumor reduction, all patients with midgut carcinoid syndrome were first treated surgically (one or two operations). This procedure resulted in total remission in 25 percent of the patients (cf. [2]). Patients with residual liver disease underwent subsequent embolization of the hepatic arteries and also received octreotide (100–200 μg daily) for palliation. With this combined treatment, half of the patients showed objective regression of their liver metastases (i.e., > 50 percent size reduction), accompanied by a substantial decrease in plasma levels of tumor markers for long periods (cf. Fig. 3). It is likely that this anti-tumor effect in responsive patients is multifactorial (tumor ischemia, suppression of tumor growth, by octreotide and probably further unknown factors).

produced by the normal endocrine cell. In the study of the diseased endocrine cell, it is likely that the synthesis of precursors may be equally important. Thus, future directions will probably include the development of processing-independent assays measuring the entire translation product [3].

The large number of tumor-produced peptides, amines, enzymes, granule, or membrane components detected in plasma and tissue samples have, in general, a low efficacy when used to distinguish the metastatic potential of a lesion. This impediment may suggest that these compounds have little to do with cell proliferation, invasiveness, or metastasis formation [4]. The first search for tumor markers was directed toward identification of the classical amines and peptide hormones associated with the clinical syndromes. The second search was focused on markers reflecting the neuroendocrine origin of the tumors (neuron-specific enolase, chromogranins, synaptophysin). It is likely that the third search will lead us to growth regulators and gene products. In this regard, the multiple endocrine neoplasia (MEN) syndromes and specific animal models (Mastomys) will be of benefit in enabling the study of the transformation of endocrine cells into neoplastic cells. The concomitant evaluation of gene products, growth factor expression, and hormone production should provide important information.

A further area of human clinical advance relates to the mapping of the gene
defects in the MEN syndromes. A significant contribution in this area will lead to
diagnosis of at-risk individuals and allow re-evaluation of the difficult problems of
prophylactic surgery versus reliable monitoring of the transition of endocrine hyper-
plasia into neoplasia. My perspective of the clinical future in neuroendocrine tumors
relates to three main areas: tumor cell receptors, growth factors, and immunology.

Tumor Cell Receptors

The identification of somatostatin receptors on gut endocrine tumor cells led to an
evaluation of their possible clinical utility [5]. The development of the novel imaging
techniques (iodine- or indium-labeled somatostatin analogs) has generated signifi-
cant new diagnostic perspectives. Thus, in vivo and in vitro demonstration of
somatostatin receptors not only serves diagnostic purposes but may also guide
potential treatment [6]. It is probable that these imaging techniques will not be
limited to somatostatin receptors alone. Accordingly, a likely possibility may be the
imaging of other receptors, for example, growth factors. The development of this
investigative modality may be more viable than tumor labeling with monoclonal
antibodies, which recognize domains that are often relatively nonspecific.

Growth Factors

A role of tumor-produced growth factors as paracrine or autocrine modulators of
tumor cell growth was originally proposed by Sporn and Todaro [7]. Endocrine
tumors have been reported to produce a number of diverse growth factors, including
transforming growth factor α and β (TGF), fibroblast-stimulating growth factor
(FGF), platelet-derived growth factor (PDGF), and probably also nerve growth
factor (NGF)-like molecules. In our laboratory, we have demonstrated that human
midgut carcinoids contain and secrete insulin-like growth factor I (IGF-I) (Fig. 2). In
tumors which exhibited IGF-I receptors, that is, those possessing a complete
autocrine loop, exogenous IGF resulted in a substantial mitogenic effect, which was
significantly reduced by octreotide [8]. Thus, cell culture studies may be a useful
model to investigate the possible mode of anti-proliferative action for octreotide and
other similar agents in individual tumors.

The hypothesis of a constitutive hypersecretion of IGFs from neuroendocrine
tumors is further supported by studies on pheochromocytomas. These tumors exhibit
an inverse expression of IGF, with almost exclusive production of IGF-II [9]. The
human genes of IGF-I and -II have been mapped to chromosomes 11 and 12 in
regions carrying the proto-oncogenes of the ras family [10,11]. More recently,
overexpression of IGF-I has been correlated with specific chromosome translocation
in individual neuroendocrine tumors [12].

Immunology

Natural killer (NK) cells have an important function in the defense against
neoplasms. Depressed NK-cell activity has been noted after injury and attributed to
the hormones released by the stress response [13]. In patients with neuroendocrine
tumors, the NK-cell activity can be augmented in patients responsive to treatment
with recombinant gamma interferon. Recent studies have suggested that the NK-cell
activity is independent of the individual hormones produced by the tumor and that
the course may be reflected by the NK-cell activity [14].

Rosenberg et al. [15,16] recently commented on the biological significance and
FIG. 2. Immunocytochemical demonstration of IGF-I (A) and its receptor (D) in cultured midgut carcinoid tumor cells. Consecutive sections from a surgical biopsy of a midgut carcinoid, showing positive reactions with antisera against IGF-I (C) and proliferating cell nuclear antigen-cyclin (B), respectively. Note that the proliferating cells contain IGF-I (co-existence between IGF-I and PCNA), suggesting an autocrine role of IGF-I (cf. [8]). Bars indicate 20 microns.

potential therapeutic implications of tumor-infiltrating lymphocytes (TIL cells) in metastases of advanced melanomas. If TIL cells were isolated from tumor biopsies by culture in the presence of exogenous interleukin 2 (IL-2), TIL cells were activated with IL-2, but maintained intact tumor recognition. When these activated TIL cells were administered to the patient, marked tumor regression was observed in individual patients. Liver metastases of midgut carcinoid tumors are also infiltrated by TIL cells, and IL-2 is contained within tumor cells (Fig. 3). We have hypothesized that
FIG. 3. Top: Urinary 5-HIAA studied over time in patients with midgut carcinoid syndrome (bilobar hepatic disease) subsequent to embolization therapy (mean ± SEM). Group I (open circles) showed objective tumor regression on CT scan, and group II (solid circles) did not. Three patients (arrows) in group II were excluded due to tumor progression. No patient in group I showed progressive hepatic disease. Bottom: Immunocytochemical demonstration of TIL cells in liver metastases of a midgut carcinoid tumor, using monoclonal antibodies. Inset: After cell culture (three months), IL-2 immunoreactive material was demonstrated in cytoplasmic granules of tumor cells, indicating endogenous synthesis of IL-2. Bars indicate 25 microns.
embolization and secondary tumor ischemia may liberate TIL cells and endogenous cytokines from ischemic lesions. This process would theoretically result in an enhanced immunological response against the tumor and would support the excellent clinical response noted in certain patients consequent upon embolization. Further studies are needed to elucidate the scientific and clinical application of such potentially useful mechanisms.

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