

The Molecular Genetics of Gastroenteropancreatic Neuroendocrine Tumors

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The pathobiology of neuroendocrine tumors (NETs) is hampered by the lack of scientific tools that define their mechanisms of secretion, proliferation, and metastatic and, currently, there are no accurate means to assess tumor behavior and disease prognosis. Molecular biologic techniques and genetic analysis may facilitate the delineation of the molecular pathology of NETs and provide novel insights into their cellular mechanisms. The current status and recent advances in assessment of the molecular basis of tumorigenesis of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) were reviewed (1981–2004). The objectives of this retrospective study were to provide a cohesive overview of the current state of knowledge and to develop a molecular understanding of these rare tumor entities to facilitate the establishment of therapeutic targets and rational management strategies. Multiple differences in chromosomal aberration patterns were noted between gastrointestinal (GI) neuroendocrine and pancreatic endocrine tumors (PETs). Divergence in gene expression patterns in the development of GI carcinoids and PETs was identified, whereas examination of the PET and GI carcinoid data demonstrated only few areas of overlap in the accumulation of genetic aberrations. These data suggest that the recent World Health Organization classification of GEP-NETs may require updating. In addition, previous assumptions of tumor similarity (pancreatic vs. GI) may be unfounded when they are examined at a molecular level. On the basis of the evolution of genetic information, enteric neuroendocrine lesions (carcinoids) and PETs may need to be classified as two distinct entities rather than grouped together as the single entity “GEP-NETs.” *Cancer* 2005;104:2292–309. © 2005 American Cancer Society.

KEYWORDS: carcinoid, DNA, genetics, gastroenteropancreatic neuroendocrine tumor, methylation, neuroendocrine, pancreatic endocrine tumor, comparative genomic hybridization.

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a poorly understood group of lesions that encompass a broad category of neoplasms derived from neuroendocrine cells of the gastrointestinal (GI) mucosa and the pancreas (for review, see Solcia et al.¹). The lesions are grouped based on the acceptance that they have a common cell lineage and produce similar secretory products: chromogranin A (CgA),² synaptophysin,³ and neuron-specific enolase (NSE).⁴ The GEP-NET classification includes carcinoids, insulinomas, gastrinomas, tumors that secrete vasoactive intestinal peptide, glucagonomas, somatostatinomas, and nonfunctional pancreatic endocrine tumors (PETs). Although they are rarer than adenocarcinomas, the estimated incidence of PETs is ~ 5 per 1,000,000 population, whereas carcinoids (bronchopulmonary and GI) comprise ~ 0.46% of all malignancies.⁵ Although they are categorized together, their clinical behaviors are strikingly divergent in terms of both symptoms and

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Address for reprints: Irvin M. Modlin, M.D., Ph.D., Department of Surgery, Yale University School of Medicine, 333 Cedar Street, P.O. Box 208062, New Haven, CT 06520-8062; Fax: (203) 737-4067; E-mail: imodlin@optonline.net

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Molecular And Cell Biological Aspects Of Gastroenteropancreatic Neuroendocrine Tumor Disease

DJ Losen



Molecular And Cell Biological Aspects Of Gastroenteropancreatic Neuroendocrine Tumor Disease:

Molecular and Cell Biological Aspects of Gastroenteropancreatic Neuroendocrine Tumor Disease Bertram Wiedenmann, 1994 New molecular and cell biological approaches in the fields of neurobiology and neuroendocrinology have identified a large number of molecules that can be assigned structurally and functionally to various subcellular structures such as secretory vesicles the Golgi complex the trans Golgi network and endosomes It has become evident that neurons and neuroendocrine cells share many properties such as the expression of very similar secretory vesicles and molecules including cell adhesion molecules neurotransmitters hormones neurotransmitter receptors and hormone receptors Various molecules discovered and characterised in basic research have been found to be increasingly applicable for improved diagnosis and therapy of neuroendocrine tumour disease This volume reviews current research in both basic science and clinical research from the viewpoint of its direct applicability to clinical medicine Gastroenteropancreatic Neuroendocrine Tumor Disease Bertram Wiedenmann, 2004 At the beginning of the last century the development of the Neuroendocrine Concept sparked intensive and worldwide research efforts leading to fascinating insights into the complex and diverse system of neuroendocrine cells and its importance in human physiology and disease Recent developments in new and expanding research areas including developmental biology regulation of angiogenesis cellular signaling and transcription and impressive results obtained by application of genomics and proteomics warranted a reevaluation of the neuroendocrine concept impact of the current understanding of neuroendocrine biology and pathobiology in these research areas In particular new discoveries are presented in neuroendocrine developmental biology with special emphasis on transcription factors controlling neuroendocrine differentiation of endodermal stem cells controlling formation and proliferation of blood and lymphatic vessels and molecular determinants of hematogenous and lymphatic tumor dissemination Given their central importance for the establishment and maintenance of the neuroendocrine phenotype signal transduction cascades and their cellular targets related to the regulation of adhesion processes receptor mediated endocytosis and cell cycle events as well as secretory activation and membrane trafficking are discussed in the context of neuroendocrine physiology and neuroendocrine tumor disease Since many of the recent discoveries made in basic research can be directly linked to clinical applications this volume summarizes and discusses innovative treatment and or diagnostic approaches for neuroendocrine tumor disease

Endocrine Neoplasms Andrew Arnold, 2012-12-06 Andrew Arnold The past several years have been a time of intense excitement and have brought major advances in the understanding and treatment of endocrine neoplasms This is therefore an excellent point at which to undertake a broad based overview of the state of the art in endocrine neoplasia for the Cancer Treatment and Research series Because of the wide and interdisciplinary readership of this series our aim for each chapter has been to provide ample background for those not highly familiar with the topic while emphasizing the most recent advances Furthermore the chapters have been written with the clinician in mind whether she or he is an oncologist

endocrinologist surgeon generalist pathologist or radiologist As such the authors mission has been to focus on clinically relevant issues and to present the scientific basis of current or potential future advances in a manner easily digestible to the nonexpert Endocrine tumors often cause problems for the patient by virtue of their hormonal activity which may frequently but certainly not always overshadow the adverse consequences related to their mass per se In fact it is important to keep in mind that endocrine tumors can manifest two biologically separable but often intertwined properties namely increased cell mass and abnormal hormonal function These need not go hand in hand and their distinction has definite clinical relevance in for example the increasingly recognized problem of incidentally discovered adrenal or pituitary masses Hybrid SPECT/CT Imaging in Clinical Practice Ora Israel, Stanley J. Goldsmith, 2016-04-19 Exploring a technology that is significantly impacting the noninvasive evaluation of the physiology and anatomy of tumors as well as the diagnosis of infectious processes and cardiac diseases this source presents recent advances and clinical applications of sequential single session single photon emission computed tomography and computed tomography imaging This source is written by pioneers in hybrid imaging and offers authoritative sections on state of the art breakthroughs in sentinel lymph node identification cardiac imaging and the study and treatment of a variety of disorders including lymphoma thyroid and parathyroid tumors neuroendocrine tumors prostatic cancer and bone metastases Radiotherapy in practice - radioisotope therapy Peter J Hoskin, 2007-02-08 Radioisotope therapy is an internal form of radiation used to treat cancer it may be administered orally or intravenously and represents the nearest treatment option to the magic bullet specifically targeting sites of disease whilst sparing surrounding normal tissues Radioisotope therapy has an important role to play in modern medicine particularly in the treatment of thyroid disease neuroendocrine tumours bone metastasis and non Hodgkin s lymphoma It is found in both the diagnostic setting and in therapy but recently there has been a renaissance in the application of radioisotope unsealed sources in therapeutic indications It is an active area of research with the quest for new compounds that will be specific for therapeutic targets This book is an essential practical guide to the use of radioisotope therapy and also includes the background and developmental biology which underpins its use Individual tumours and diseases are explored with specific focus given to radioisotope treatment options The barriers to radioisotope therapy such as ease of access acquisition of radioisotopes radiation protection regulations and cost are also discussed ABOUT THE SERIES Radiotherapy remains the major non surgical treatment modality for the management of malignant disease with over 50% of patients receiving treatment at some time during the management of their malignant disease It is based on the application of the principles of applied physics radiobiology and tumour biology to clinical practice Each volume in this series takes the reader through the basic principles of different types of radiotherapy and then develops these by individual sites This series of practical handbooks are aimed at physicians both training and practising in radiotherapy as well as medical physicists dosimetrists radiographers and senior nurses Oxford Textbook of Endocrinology and Diabetes John A.H. Wass, Paul M. Stewart, 2011-07-28 Now in its second

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