The Clinical Relevance of Chromogranin A as a Biomarker for Gastroenteropancreatic Neuroendocrine Tumors

Ben Lawrence, MBChB, MSc[a], Bjorn I. Gustafsson, MD, PhD[b,c], Mark Kidd, PhD[a], Marianne Pavel, MD[d], Bernhard Svejda, MD[a], Irvin M. Modlin, MD, PhD, DSc, FRCS(Eng & Ed)[a,*]

KEYWORDS

• Chromogranin • Granin family • Neuroendocrine tumor
• Carcinoid • Enterochromaffin cell • Tumor marker

THE BIOCHEMICAL DIAGNOSIS OF NEUROENDOCRINE TUMORS

An accurate tumor marker is a critical tool in tumor management because it establishes an uncertain diagnosis, offers a basis for individual prognostication, signals response to therapy, and identifies relapse. In classical terms, a high-quality tumor marker should represent a biologic attribute unique to the tumor cell or its local environment. Although this has proved manageable in a homogenous tumor population, the goal has been difficult to attain in gastroenteropancreatic neuroendocrine tumors (GEP-NETs) because they comprise an extremely heterogeneous group of cancers. Thus, the conundrum of identifying a global marker for NETs has remained a considerable technical challenge.

The identification of chromogranin A (CgA) in secretory vesicles in the adrenal medulla,[1] the development of a specific antibody,[2] and localization to extra-adrenal neuroendocrine cells[3,4] provided a partial solution. The clinical utility of this tool is blunted, however, by the ubiquity of CgA in normal tissue, the variable methodology

[a] Gastrointestinal Pathobiology Research Group, Department of Surgery, Yale University School of Medicine, 310 Cedar Street, PO Box 208602, New Haven, CT 06520-8062, USA
[b] Department of Gastroenterology, St Olavs Hospital, 7006 Trondheim, Norway
[c] Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Prinsesse Kristinas Gate 1, 7006 Trondheim, Norway
[d] Med. Klinik m.S. Hepatologie und Gastroenterologie, Charité - Campus Virchow Klinikum, Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany
* Corresponding author. Department of Gastroenterological Surgery, Yale University School of Medicine, 333 Cedar Street, PO Box 208062, New Haven, CT 06520-8062.
E-mail address: imodlin@optonline.net

Endocrinol Metab Clin N Am 40 (2011) 111–134
doi:10.1016/j.ecl.2010.12.001 **endo.theclinics.com**
0889-8529/11/$ – see front matter

of its measurement, and the diverse disease processes and physiologic events that perturb the granin family of peptides. To assess the utility of CgA measurement for clinical application, a basic understanding of essential CgA biology is necessary. This article provides an overview of the strengths and limitations of CgA as a tumor marker. It encompasses the physiologic role of CgA and evaluates the causes of CgA elevation in non-NET disease states and assesses the test platform variations and the impact on clinical care of NETs.

THE BIOLOGY OF CHROMOGRANIN A IN NORMAL CELLS

The Neuroendocrine Cell

Neuroendocrine cells aggregate in classical endocrine glands (eg, adrenal, pituitary, and parathyroid) but also in the diffuse neuroendocrine system (DNES)—the diaphanous, ill-defined, and poorly understood neuroendocrine syncytium integrated throughout the bronchopulmonary and gastrointestinal (GI) systems.[5] Although the overarching role of the DNES as a wide-ranging regulator of secretion, absorption, and motility is broadly understood, the precise mechanistic basis of its function and its cell lineage remains, for the most part, opaque.

The cellular origins of GEP-NETs are diverse and reflect the numerous neuroendocrine cell types of the DNES in the GI tract.[6] Certain neuroendocrine cells are localized to a single organ (eg, gastric enterochromaffin-like [ECL] cells) whereas others (eg, the enterochromaffin [EC] cells), are ubiquitous throughout the GI tract (**Table 1**). Neuroendocrine cells share several common features, including production of secretory granules, maturation, and exocytosis as well as the synthesis of specific proteins and the presence of electron-dense or translucent secretory granules that are prototypical of the neuroendocrine cell type.[6] Of particular interest is the synthesis and biologic role of the granin family of proteins and peptides, especially that of CgA.[7]

The Granin Family

Granins are found as major, or principal, components of the soluble core of dense-core secretory granules in neuroendocrine cells and are secreted in a physiologically regulated manner.[8–11] There are 8 members in granin family, including CgA, CgB, CgC (secretogranin [Sg] II), SgIII, SgIV, SgV (7B2), Sg VI (NESP55), and VGF nerve growth factor–inducible (VGF) (**Fig. 1**). Granins have been proposed as playing important roles in secretory granule formation, processing, and development. The precise function, however, of individual granins is dependent on the presence of other granins and hormones produced by a specific neuroendocrine cell, the presence of proteolytic processing enzymes, and their inhibitors and activators as well as the density and localization of calcium pumps and exchangers. Of critical relevance to their clinical utility is the observation that irrespective of the cellular type, processing milieu, or expression of other granins, all are cosecreted with a variety of peptide and amine hormones depending on the neuroendocrine cell type.

Neuroendocrine Cell Types and CgA Secretion

Each neuroendocrine cell type in the DNES produces different amines, peptides, and proteins with a variety of biologic functions. At the same time, neuroendocrine cells cosecrete CgA during the secretory granule exocytotic process. Based on this biologic event, CgA has come to represent a common denominator peptide with the putative ability to be a marker of neuroendocrine cell activity (see **Table 1**). CgA was the initial member of the granin family identified, and its name represents the