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Review

Gastroenteropancreatic endocrine tumors

Alan Meeker *, Christopher Heaphy

The Johns Hopkins University School of Medicine, Department of Pathology, Bond Street Research Annex Bldg., Room B300, 411 North Caroline Street, Baltimore, MD 21231, United States

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ABSTRACT

Gastroenteropancreatic endocrine tumors (GEP-NETs) are relatively uncommon; comprising approximately 0.5% of all human cancers. Although they often exhibit relatively indolent clinical courses, GEP-NETs have the potential for lethal progression. Due to their scarcity and various technical challenges, GEP-NETs have been understudied. As a consequence, we have few diagnostic, prognostic and predictive biomarkers for these tumors. Early detection and surgical removal is currently the only reliable curative treatment for GEP-NET patients; many of whom, unfortunately, present with advanced disease. Here, we review the genetics and epigenetics of GEP-NETs. The last few years have witnessed unprecedented technological advances in these fields, and their application to GEP-NETS has already led to important new information on the molecular abnormalities underlying them. As outlined here, we expect that "omics" studies will provide us with new diagnostic and prognostic biomarkers, inform the development of improved pre-clinical models, and identify novel therapeutic targets for GEP-NET patients.

Contents

1. Introduction

Gastroenteropancreatic endocrine tumors arise from cells of the diffuse neuroendocrine system throughout the gut, pancreas, and bronchiopulmonary system (Kloppel, 2011). A common feature of these tumors is their expression of both neural and endocrine markers; thus, they are often referred to as Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET) (Oberg, 1999). Collectively, GEP-NETs are relatively rare, accounting for approximately 0.5% of all human cancers, although there is evidence that their incidence is increasing, likely due to increased awareness as well as increased detection through new endoscopic and imaging techniques (Yao et al., 2008a; Niederle et al., 2010; Modlin et al., 2007,2008). In the U.S., data from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) cancer registry shows that the overall age-adjusted incidence of GEP-NETs increased from 1 case per 100,000 individuals in the period 1973 to 1977 up to 3.65 cases per 100,000 between 2003 and 2007 (Lawrence et al., 2011). Annual incidence of GEP-NETs in the U.S. is approximately

* Corresponding author. Tel.: +1 410 502 3398, +1 410 790 7354.
E-mail address: ameeker1@jhmi.edu (A. Meeker).

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10,000, with a median age at diagnosis for all GEP-NETs of 63 years and a peak incidence of 80 years. Notably, rectal NETs have a significantly earlier incidence peak at approximately 50 years of age (Lawrence et al., 2011).

The study of these tumors has been challenging, due in large part to their relative scarcity; consequently, our knowledge of their cellular and molecular biology has laggedbehind that of other, more common cancers. Encouragingly, this is beginning to change – particularly through the recent application of modern molecular techniques such as high throughput (“next generation”) DNA sequencing to GEP-NETs. Thus, for the first time, details of the genetic landscapes of well-differentiated pancreatic neuroendocrine tumors (PanNETs), poorly-differentiated pancreatic neuroendocrine carcinomas (PanNECs) and small intestinal NETs (GI carcinoids) have recently been published (Yachida et al., 2012). Complementing these detailed genetic studies is an increased focus on the epigenetic aspects of GEP-NETs; for example, the roles played by cancer-related alterations in DNA methylation, histone protein modifications and the differential expression of non-coding RNAs, such as microRNAs.

Individual GEP-NET cases can exhibit widely different clinical courses, presumably reflecting anunderlying heterogeneity at the genetic, molecular and cellular levels that impact the biological behavior of the tumor (Mignon, 2000; Modlin et al., 2006). In keeping with this view, several published studies have identified specific genetic and epigenetic changes that are associated with clinically-relevant histopathologic tumor characteristics (e.g. tumor size, grade and stage), anatomic location of the tumor, or clinical outcomes, such as patient survival. The literature on GEP-NETs has been somewhat confusing due to the existence of multiple systems of tumor nomenclature and clinicopathologic categorization. Historically, different GEP-NETs have been grouped into three subcategories, based on embryology; nomenclature that is still commonly encountered. These categories include: foregut tumors (bronchial, duodenal, gastric and pancreatic NETs), midgut tumors (appendiceal, cecal, ascending and right transverse colon,ileal and jejunal NETs), and hindgut tumors (left transverse colon and rectal NETs) (Kloppel, 2011; Williams and Sandler, 1963). Traditionally, GEP-NETs have been referred to as carcinoid tumors or carcinoids; terminology introduced by the German physician and pathologist Siegfried Oberndorfer over 100 years ago, to describe tumors of the small intestine which he believed to be benign “cancer-like” entities (Modlin et al., 2004). Use of the term carcinoid has therefore been criticized due to its emphasis on an implied benign behavior. However, it is now clear that, despite a typically relatively indolent disease course, a large percentage of these tumors have lethal malignant potential. Despite this objection, the term carcinoid continues to enjoy widespread usage.

Regarding the histopathological and clinicalcharacterizations of GEP-NETs, several systems have been proposed for this heterogeneous group of tumors, and use of these systems remains mixed. These classification systems have recently been thoroughly reviewed by Klimstra et al. and Capelli et al (Capelli et al., 2012; Klimstra et al., 2010). Current guidelines typically feature tumor grading based on the degree of histomorphological differentiation and proliferation rates. For example, the most recent World Health Organization guidelines (Bosman FT, Carneiro F, Hruban RH, Theise ND, eds. *WHO Classification of Tumors of the Digestive System*. Lyon, France: IARC Press) stratify pure GEP-NETs into 3 grades (G1, G2, G3) defined by increasing proliferation rates, as assessed by mitotic count or Ki-67 immunostaining index. This has clinical utility, as proliferative rate is a highly significant prognostic indictor for GEP-NETs that is associated with thetumor’s biological aggressiveness and is widely used in therapeutic decision making (Oberg et al., 2004a; O’Toole et al., 2010; Pelosi et al., 1992; Ekeblad et al., 2008). Grade 3 tumors are highly proliferative (Ki-67 index >20%), usually poorly differentiated, and referred to as neuroendocrine carcinomas (NECs). Cytologically, NECs resemble small cell or large cell neuroendocrine carcinomas of other organs, such as the lung, with similar treatment approaches being applied (e.g. cisplatin and etoposide) (Fjallskog et al., 2001). In addition to grade, tumor stage also provides important prognostic information, with locally advanced and metastatic disease portending a poor prognosis, as complete surgical resection – currently the only reliable curative treatment – is impossible in such cases (Yao et al.,2008a; Modlin et al., 2008; Kaltsas et al., 2004a; Metz and Jensen, 2008). Modified clinical staging systems have recently been proposed by the European Neuroendocrine Tumor Society (ENETS), as well as the American Joint Committee on Cancer (AJCC) and feature site-specific TNM classification with the goal of improving prognostic capabilities (Kulke et al., 2010; Strosberg et al., 2010; Rindi et al., 2007; Scarpa et al., 2010). Although largely congruent, these systems do differ in some respects, and their relative merits are currently being evaluated (Rindi et al., 2012).

Some GEP-NET tumors secrete bioactive peptides or amines (e.g. insulin, gastrin, and somatostatin) which can cause recognizable clinical syndromes caused by the specific substance secreted (Kindmark etal., 2007; Larsson et al., 1977). Such tumors are termed functioning NETs; a clinical definition based on the existence of symptoms, whereas those that do not secrete are termed non-functioning tumors. The majority of GEP-NETs are non-functioning; which, unfortunately, often leads to significant delays in their detection. As a consequence, the majority of GEP-NET patients present with advanced, often metastatic, disease for which the prognosis is bleak due to a current lack of effective systemic therapies (Walter et al., 2012). For example, 70–85% of non-functioning pancreatic NETs (PanNETs) present with unresectable disease, often with liver metastases, and their 5-year survival rate is only 30–40%, the lowest survival rate of the GEP-NETs, with a median survival interval of only 24 months (Lawrence et al., 2011; Khasraw et al., 2009; Frilling etal., 2010). Likewise, 75% of patients with small intestinal NETs either harbor liver metastases at presentation, or will develop them during the course of their disease (Kaltsas et al., 2004a; Frilling et al., 2010; Oberg and Eriksson, 2005; Halfdanarson et al., 2008; Modlin et al., 2003). This frequent presentation with advanced disease, coupled with the lack of curative non-surgical treatments is reflected in the fact that GEP-NET mortality has remained essentially unchanged for decades (Modlin et al., 2003, 2007; Lepage et al., 2007). In contrast, the 5-year survival rate for insulinomas of the pancreas is 85–95%. These tumors are usually detected while small and localized, thus cure via surgical resection is possible.

The treatment options for GEP-NETs with associated liver metastases haverecently been reviewed by Demirkan and Eriksson (Demirkan and Eriksson, 2012). Most GEP-NETs express somatostatin (SST) receptors on their cell surfaces, and SST analogues have been found to be useful in controlling clinical symptoms arising from hormone secretion (Oberg et al., 2004b). Interestingly, SST analogues have also been found to increase time to disease progression, as well as to achieve stable disease in subsets of GEP-NET patients; both in functional, as well as non-functional tumors (Oberg et al., 2004b; Rinke et al., 2009; Strosberg and Kvols, 2010).

Traditional cytotoxic chemotherapies have been used in advanced GEP-NET; however, most GEP-NETs are well-differentiated with only low to moderate proliferation rates, thus showing limited degrees of responsiveness to theseagents. Streptozotocin is an alkylating agent displaying islet-cell specific toxicity and is approved for the treatment of islet cell tumors, where it is used in combination with other agents, such as 5-fluorouracil or doxorubicin (Kaltsas et al., 2001). Temozolomide, another alkylating agent, in combination with other agents, such

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