Gastroenteropancreatic and Bronchopulmonary Neuroendocrine Tumors

Overview

Edda Gomez-Panzani, M.D.
Genes and chromosomes

- The genes are the coded messages in a cell that guide its behavior; they are packed in bundles called chromosomes.

http://dels-old.nas.edu/plant_genome/images/DNA.jpg
Normal cell cycle

http://www2.le.ac.uk/departments/genetics/vgec/diagrams/22-Cell-cycle.gif

http://www.cbp.pitt.edu/faculty/yong_wan/images/main_cell_cycle.jpg
Errors during the cell cycle

- Sometimes, mutations occur. Mutations are changes in the genes that result in the cells changing their behavior.
- These changes can involve losses, alterations or gains in the important cell control systems related to growth, interaction with other cells and even cells’ life span
- Once damage occurs, it can be:
  - Reversed
  - Removed
  - Tolerated
Mutations


Own work by uploader, http://bjornfree.com/galleries.html
Author=Bjørn Christian Tørrissen Date=2010-04-10

Muhammad Mahdi Karim (www.micro2macro.net)
Apoptosis (Programmed Cell Death)

Some times, when the damage is significant and it cannot be repaired or removed, the cell goes through a process of programmed cell death called apoptosis.

Apoptosis: A normal, genetically regulated process leading to the death of cells and triggered by the presence or absence of certain stimuli, as DNA damage.

www.dictionary.com

http://www.microbiologybytes.com/virology/kalmakoff/baculo/pics/Apoptosis.gif
How does cancer develop?

When a mutation cannot be repaired and the abnormal cells continue to multiply and become resistant to death (apoptosis), cancer occurs.
Mutations


Photo by Gary Bachman
Different cancers behave differently depending on the type of cell involved and the degree of uncontrolled cell growth.
Looking at degrees of cell growth

Mitotic count
- How many cells are undergoing mitosis (cell division)

Ki-67
- Immunohistochemical stain that identifies cells in any non-resting stage of the cell cycle (anything but GO). The result is given as the percent of cells that have entered the cell cycle.

http://www.gistsupport.org/media/Understanding Pathology Report/mitoses-marked-575pix.jpg
Neuroendocrine Tumors
Neuroendocrine Tumors (NETs)

Merkel cell tumors (skin)

Anterior pituitary gland
- Adenoma

Endocrine tumors in miscellaneous sites
- Ovary, cervix, endometrium
- Breast
- Prostate
- Medullary thyroid carcinoma
- Kidney
- Larynx, paranasal sinuses, salivary glands

Pheochromocytomas and Paragangliomas

Bronchopulmonary and Thymic endocrine tumors
- Thymic carcinoid
- Tumorlets
- Typical and atypical lung carcinoid
- Small cell lung cancer
- Large cell lung cancer

GI endocrine tumors
- Carcinoid Tumors
- Undifferentiated NE carcinomas

Pancreatic endocrine tumors
- Non-functional
- Insulinoma
- Gastrinoma
- VIPoma
- Glucagonoma
- Somatostatinoma
- ACTH-oma

NEUROENDOCRINE TUMORS

Merkel cell tumors (skin)

- Larynx, paranasal sinuses, salivary glands
Neuroendocrine Tumors (NETs) – Incidence

Gastro-Entero-Pancreatic (GEP) and Bronchopulmonary (BP) NETs – Incidence

Classification of GEP and BP NETs

- Pathological classification
- Where do they come from
  - Foregut (bronchus, lung, thymus, stomach, first portion of duodenum, pancreas and ovary) – 41%
  - Midgut (second portion of the duodenum, jejunum, ileum, appendix and ascending colon) – 26%
  - Hindgut (transverse colon, descending colon and rectum) – 19%
- What do they make
  - Functional
    » Classified by the peptide predominantly secreted
    » Can change secretory patterns over time
  - Non-Functional

Carcinoid Tumors
Non-Functional PNETs
Insulinomas
Gastrinomas
VIPomas
Glucagonomas
Somatostatinomas
Mixed islet cell/exocrine

Gastroenteropancreatic 60.5%
BP 27.3%
Other 12.2%

Adapted from Handbook of Gastroenteropancretic and Thoracic Neuroendocrine Tumors. Edited by Martyn Caplin and James Yao. 2011. With permission from J. Yao.
At least 13 gut neuroendocrine cells exist, all of which produce various bioactive peptides or amines (ie. serotonin, somatostatin, substance P, melatonin, histamine, gastrin, ghrelin, cholecystokinin, GLP, motilin, neurotensin, VIP etc.)

Metz D. and Jensen R. Gastroenterology 2008;135-1469-1492
## GEP-NETs

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Incidence per $10^6$ persons per year</th>
<th>Primary location</th>
<th>Malignant (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid&lt;sup&gt;1&lt;/sup&gt;</td>
<td>20-50</td>
<td>Gastrointestinal: 67%</td>
<td>70-100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bronchopulmonary: 25%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other: 8%</td>
<td></td>
</tr>
<tr>
<td>Gastrinoma&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.5-1.5</td>
<td>Pancreas: 60%</td>
<td>60-90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duodenum: 30%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other: 10%</td>
<td></td>
</tr>
<tr>
<td>Insulinoma&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1.2</td>
<td>Pancreas 99-100%</td>
<td>5-15</td>
</tr>
<tr>
<td>VIPoma&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.05-0.2</td>
<td>Pancreas: 90%</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other: 10%</td>
<td></td>
</tr>
<tr>
<td>Glucagonoma&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.01-0.1</td>
<td>Pancreas 99-100%</td>
<td>60</td>
</tr>
<tr>
<td>Somatostatinoma&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Very rare&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Pancreas: 56%</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duodenum/jejenum: 44%</td>
<td></td>
</tr>
<tr>
<td>GRFoma&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Very rare&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Pancreas: 30%</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung: 54%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jejunum: 7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other: 13%</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> Modlin et al. *Cancer* 2003 ;97(4):934-959

<sup>2</sup> Metz D. and Jensen R. *Gastroenterology* 2008;135-1469-1492.

<sup>3</sup> < 0.1/million
## GEP-NETs

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Peptide</th>
<th>Symptoms/Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>Serotonin Tachy and bradykinins</td>
<td>Carcinoid syndrome</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>Insulin</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>VIPoma</td>
<td>VIP</td>
<td>Verner-Morrison</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Glucagon</td>
<td>DM, NME*, cachexia</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Somatostatin</td>
<td>Bile stones, steatorrhea, DM</td>
</tr>
<tr>
<td>GRFoma</td>
<td>GH releasing factor</td>
<td>Acromegaly</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>Gastrin</td>
<td>Zollinger-Ellison Syndrome: Abdominal pain, diarrhea, GERD, ulcers</td>
</tr>
</tbody>
</table>

* Necrolytic migratory erythema

Carcinoid Tumors

©Edda Gomez-Panzani
Carcinoid (Karzinoide)

Siegfried Obendorfer 1907

Benign Tumors --- Malignant Tumors

Adenoma ↔ Carcinoid ↔ Carcinoma
Origin of Carcinoid tumors: Enterochromaffin cells

Crypts of Lieberkühn
Kulchitzsky cells
Intestinal Carcinoid tumors
Local effects - Carcinoid Tumor in Distal Ileum

Common findings:
- Mural thickening
- Considerable desmoplastic reaction
- Substantial kinking

Intestinal obstruction
- From primary tumor
- From sclerosing reaction in the surrounding mesentery

Radiographics 2007;27:236-236
©2007 by Radiological Society of North America
Serotonin Production by Carcinoid Tumors

CNS  GI  Platelets

Carcinoid syndrome
Carcinoid crisis

L-tryptophan

tryptophan hydroxylase

5-hydroxytryptophan

aromatic amino acid decarboxylase

5-hydroxytryptamine (5-HT)

serotonin

Wikipedia.org
Functional vs. Non-Functional

What role does the liver play?
The liver

From: Biomedical Communications
Arizona Health Sciences Center
Liver metastases
Carcinoid Syndrome

- The occurrence and severity of the syndrome is directly related to tumor bulk in an area that drains into the systemic circulation.
- In the vast majority of cases this correlates to hepatic metastases.
Syndrome without liver metastases

- Exceptions include:
  - Peritoneal carcinomatosis
  - Primary ovarian carcinoids
  - Broncopulmonary carcinoids

Glockzin et al. World Journal of Surgical Oncology
Serotonin and Carcinoid Tumors

- Foregut carcinoids have few serotonin granules (ie. Lung, Stomach, Pancreas)
- Mid-gut carcinoids are rich in serotonin containing granules and are frequently associated with carcinoid syndrome (small bowel, appendix)
- Hind-gut carcinoids have very few serotonin granules (distal colon and rectum)

Carcinoid Syndrome

- In 10% of patients with carcinoid tumors
- 1954 – Thorson and Waldenstrom
  - Malignant carcinoid of the small intestine
  - Metastases to the liver
  - Peripheral vasomotor symptoms (flushing)
  - Diarrhea
  - Valvular disease of the right side of the heart (pulmonary stenosis and tricuspid regurgitation without septal defects)
  - Bronchoconstriction
  - Abdominal pain
Frequency of Carcinoid Syndrome by Primary Organ site location of Carcinoid Tumor

Adapted from Gustafsson B. et al. Current Opinion in Oncology 2008;20:1-12.
Most Frequent Signs/Symptoms of Carcinoid Syndrome

Carcinoid Syndrome - Flushing

Flushing (~92%)

- Caused by vasodilatation
- May be brief (ie. 2-5 min) or may last for several hours
- May be accompanied by tachycardia
- Precipitated by:
  - Stress (physical and/or mental)
  - Infection
  - Alcohol
  - Certain foods (spicy)
  - Drugs (ie. Catecholamines, calcium, pentagastrin etc.)

Carcinoid Syndrome - Diarrhea

Diarrhea (~78%)

- Serotonin and Substance P stimulate small bowel and colonic motility
- Post-prandial transit times in the small bowel and colon have been reported (von der Ohne et al.) to be 2 to 6 times faster in carcinoid patients than in healthy individuals. Fasting colonic times are normal.
- Malabsorption can result in fluid and electrolyte imbalance, malnutrition, pellagra etc.
- May be accompanied by borborygmi, cramping and or pain

Carcinoid Syndrome – Carcinoid Heart Disease

Valvular Heart Disease (~52%)

- Most often in the presence of consistently high levels of 5-HIAA
- Excess serotonin (5-HIAA) stimulates proliferation of fibroblasts, myofibroblasts and a matrix-rich fibrous stroma devoid of elastic fibers covered by endothelium
- This proliferation results in the formation of plaques that are deposited primarily on the tricuspid and pulmonary valves causing them to thicken and retract
- Eventually the patient develops right sided ventricular failure which accounts for approximately 20-30% of deaths in patients with carcinoid tumors

Carcinoid Syndrome – Telangiectasia

Telangiectasia (~25%)

- Small dilated blood vessels near the surface of the skin or mucous membranes, measuring between 0.5 and 1 millimeter in diameter

- Lesions can develop anywhere on the body but are commonly seen on the face around the nose, cheeks and chin.

Carcinoid Syndrome – Pellagra

- Tryptophan, an essential amino acid, is required for the synthesis of niacin (B3)
- In the presence of a functional carcinoid tumor tryptophan is diverted from niacin to serotonin synthesis resulting in niacin deficiency
- Niacin deficiency leads to Pellagra
Carcinoid Syndrome – Pellagra

Pellagra (~7%)

- Pelle agra (pelle=skin; agra= rough).
- Symptoms:
  - Diarrhea, dermatitis, dementia and death
  - Photosensitivity
  - Aggression
  - Red skin lesions
  - Alopecia
  - Edema
  - Glossitis
- Treatment:
  - Niacinamide (niacin produces flushing) 200-500 mg daily in divided doses

Other Signs/Symptoms of Carcinoid Tumors

- Dyspnea
- Palpitations
- Low blood pressure
- Fatigue/Asthenia
- Dizziness
- Myopathy
- Changes in mental state

Carcinoid Crisis

- Immediate onset of a debilitating and life-threatening condition associated with carcinoid syndrome
- May occur spontaneously or may be precipitated by anesthesia, chemotherapy, infection, stress, catecholamines, tumor manipulation or embolization procedures
- Symptoms include prolonged severe flushing, diarrhea, hypotension/hypertension, tachycardia, severe dyspnea, peripheral cyanosis and sometimes hemodynamic instability, hyperthermia and bronchospasm.
- Most often seen with large tumor load, high levels of circulating serotonin, elevated CGA and 5-HIAA
- Appropriate precautions include immediate therapy and close monitoring before, during and after surgical treatment.

Natural History of Carcinoid Tumors

Diagnosis: Irritable Bowel, Menopause, Vague symptoms

Diarrhea

Flushing

Metastases

Primary Tumor Growth

0  2  4  6  8  10  12  14  16  18  20

Years

Death

NET Diagnosis

The problem, however, remains that diagnostic investigation is usually initiated by symptomatology, and in the vast majority of patients, symptomatology is indicative of metastasis.

50% of NETs Present with Regional or Distant Metastases at Diagnosis

SOURCE: SEER Database

Extent of Disease at Diagnosis by Site of Origin

- Given the time it takes to make the diagnosis, the probability of metastatic disease, is dramatically increased.

- Median age at diagnosis for NETs: Rectum - 56 years, lung - 64 years and jejunum/ileum - 66 years.

Sites of Metastatic Dissemination of Midgut NETs

Pancreatic Islet Cell Tumors
Origin of Pancreatic Islet Cell Tumors

- **Gastrinoma 30%**
- **Somatostatinoma 44%**
- **GRFoma 7%**

**GRFoma**

- 54%

**Somatostatinoma**

- 56%

**VIPoma**

- 90%

**Glucagonoma**

- >99%

**Insulinoma**

- >99%

References:

Insulinomas – 17% of all PETs

Hyperinsulinemia
- Neuroglycopenia (90%)
  - Amnesia or coma (47%)
  - Confusion (80%)
  - Visual changes (59%)
  - Convulsions (17%)
  - Altered consciousness (38%)
- Sympathetic overdrive (60-70%)
  - Weakness (56%)
  - Sweating (69%)
  - Tremors (24%)
  - Palpitations (12%)
  - Hyperphagia (14%)
- Obesity (<50%)

Whipple triad
- Episodic (symptomatic) hypoglycemia
- CNS dysfunction temporally related to hypoglycemia (measured at the time the symptoms were present)
- Dramatic reversal of CNS abnormalities by glucose administration

Metz D. and Jensen R. Gastroenterology 2008;135-1469-1492
Gastrinomas – 15% of all PETs

Gastrinoma → Gastrin → Zollinger-Ellison syndrome (ZES)

- Ulcers
- GERD
- Diarrhea
- Malabsorption

Hypergastrinemia (fasting 97-99%)

Metz D. and Jensen R. Gastroenterology 2008;135-1469-1492
VIPomas – 2% of all PETs

VIPomas ➔ VIP ➔ Diarrhea

- Electrolyte disturbances
  - Hypokalemia (70-100%)
- Dehydration (45-95%)
- Hyperglycemia (20-50%)
- Hypercalcemia (25-50%)
- Hypochlorhydria (35-76%)
- Flushing (15-30%)

Metz D. and Jensen R. Gastroenterology 2008;135-1469-1492
Glucagonoma – 1% of all PETs

Glucagonoma

Glucagon

Hyperglucagonemia

- Glucose intolerance (DM)
- Weight loss
- Necrolytic migratory erythema
- Hypoaminoacidemia
- Chelitis
- Normocytic anemia
- Vein thrombosis
- Neuropsychiatric manifestations


Courtesy of Prof. Raimo Suhonen
Non-functional NETs – ~33%

- Most secrete amines and peptides but do not result in an identifiable clinical syndrome
- Local mass effects: obstruction and pain
- Removal of the primary tumor has been reported to prolong survival in all patients (median 1.2 vs. 8.4 years; p<0.001) and in those with metastases (1.0 vs. 4.8 years; p<0.001)


Bronchopulmonary Carcinoid Tumors
Bronchopulmonary (BP) Neuroendocrine Tumors

- Comprise ~20% of all lung cancers
- R. Laennec’s report (published posthumously in 1831) of an intrabronchial mass could be the first written description of a BP carcinoid

Clinical presentation

- Cough
- Hemoptysis
- Obstructive pneumonia
- <5% Carcinoid syndrome
Bronchopulmonary (BP) Neuroendocrine Tumors

- WHO (2004) histologic classification:
  - Low-grade typical carcinoid tumor (TC) – G1
  - Intermediate-grade atypical carcinoid tumor (AC) – G2
  - High-grade large-cell neuroendocrine carcinoma (LCNEC) – rare (<3%) – G3
  - High-grade small-cell lung carcinoma (SCLC) – most common – G4

- SRS sensitivity in detection of BP-NETs: 93-87% for primary tumors and 59% for metastases

- 5 year survival:
  - TC ~88-90%
  - AC ~50-60%

Gustafsson B. et. Al. Cancer 2008;113:5-21
Thank You