Cellule neuroendocrine

- Adenoipofisi
- Paratiroidi
- Cellule di Merket della cute
- Insule pancreatiche
- Cellule NE gastrointestinali
- Miscellanea di cellule NE: prostata, vescica, laringe, mammella...
- Cellule NE del timo
- Cellule NE del polmone
- Midollare surrenatica e paragangli
CELLULE SNED

Contenuto di granuli secretori
Circulating CGA, 5HT and others non specific secretion markers

Insulin, gastrin, PP, glucagon and other specific secretion markers

Chromogranins, Synaptophysyns, VCAM 2

Secretory process

Cytosol

Rough endoplasmic reticulum with attached ribosomes

PGP 9.5-NSE

Neuron

Menin

CD 44

CD 56

CD 171

CD 24

Adhesion molecules

Receptors

CD 57

Citolysis

Circulating NSE

from Ferolla et al. modified
SSTR

cAMP

cAMP

Ca++

Phosphatase

Calcineurin

SSTR

Ser/Thr Phosp.

PTP

Carcinoid Tumors: History

Oberndorfer: introduced the term “Karzinoid” to describe a class of intestinal tumors that behave less aggressively than adenocarcinomas

• 1914 Gosset and Masson: using silver impregnation techniques demonstrated that carcinoid tumors might arise from enterochromaffin cells (Kulchitsky’s cell) within glands of Lieberkuhn

• 1928 Masson: established characterization of carcinoids as Argentaffin cell tumors

• 1954 Waldenstrom’s group: described a series of patients with “carcinoid syndrome”

• 1968 Pearse: Concept of APUD System

• 1980 WHO classification: applied the term carcinoid to all tumors of the diffuse endocrine system (synonymous with neuroendocrine cell system).
Classificazione dei tumori neuroendocrini

1. Tumori endocrini ben differenziati:
   - a comportamento benigno (carcinoide tipico)
   - a comportamento incerto (carcinoide atipico)
2. Carcinoma endocrino ben differenziato
3. Carcinoma endocrino scarsamente differenziato
   (a piccole, intermedie e grandi cellule)
4. Tumori misti esocrini-endocrini

(Solcia et al., 2000)
• **Typical Carcinoid (TC)**
  “with fewer than two mitoses per 2 mm² of viable tumour and lacking necrosis.”
  *(ten high-power fields)*

• **Atypical Carcinoid (AC)**
  “with between two and ten mitoses per 2 mm² and/or with foci of necrosis.”
  *(ten high-power fields)*
### Clinical features

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Schrevens et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lung cancer 2004</td>
</tr>
<tr>
<td>– Asymptomatic</td>
<td>23%</td>
</tr>
<tr>
<td>– Recurrent infections*</td>
<td>42%</td>
</tr>
<tr>
<td>– Cough / Hemoptysis *</td>
<td>21%</td>
</tr>
<tr>
<td>– Chest pain</td>
<td>7%</td>
</tr>
<tr>
<td>– Dyspnea / Wheezing *</td>
<td></td>
</tr>
</tbody>
</table>

*All had central tumors demonstrable by bronchoscopy

**Endocrine symptoms:** 12%  
(Uppsala material) carcinoid syndrome, atypical carcinoid s., cushing, acromegalia

**Endocrine secretion:** 15%  
(Perugia material) carcinoid syndrome, atypical carcinoid s., cushing, acromegalia
Carcinoid Tumours

<table>
<thead>
<tr>
<th>Frequency %</th>
<th>Secretory Products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Foregut (10-15%)</strong></td>
<td>ACTH, CRF, GHRH, ADH</td>
</tr>
<tr>
<td>Thymus</td>
<td>Serotonin, Histamine, Gastrin, Calcitonin, Tachykinins, CgA, HCGα/β</td>
</tr>
<tr>
<td>Lung</td>
<td>CgA, Histamine, Gastrin, Serotonin, Gastrocalcin?</td>
</tr>
<tr>
<td>Stomach</td>
<td>Gastrin, Somatostatin, CgA</td>
</tr>
<tr>
<td>Duodenum</td>
<td>No known secretory product</td>
</tr>
<tr>
<td><strong>Midgut (20-60%)</strong></td>
<td>Serotonin, Tachykinins, CgA</td>
</tr>
<tr>
<td>Appendix</td>
<td></td>
</tr>
<tr>
<td>Ileum</td>
<td></td>
</tr>
<tr>
<td>Caecum</td>
<td></td>
</tr>
<tr>
<td>Colon ascendance</td>
<td></td>
</tr>
<tr>
<td><strong>Hindgut (25-30%)</strong></td>
<td>CgA, PP, HCGa</td>
</tr>
<tr>
<td>Colon</td>
<td>PYY, Somatostatin</td>
</tr>
<tr>
<td>Rectum</td>
<td></td>
</tr>
</tbody>
</table>
NEUROENDOCRINE FUNCTIONING TUMORS

- CARCINOIDS
- INSULINOMAS
- GASTRINOMAS
- VIPOMAS
- GLUCAGONOMAS
- SOMATOSTATINOMAS
- GRF-OMAS

Clinical syndrome correlated to peptide hyperproduction
La “Sindrome da Carcinoide”
CARCINOID SYNDROME

TYPICAL 95%
- Flushing
- Diarrhea
- Wheezing
- Cardiac fibrosis

ATYPICAL 5%
- Prolonged flushing
- Headache
- Lacrimation
- Bronchoconstriction
GASTRINOMA and Zollinger Ellison Syndrome

SYMPTOMS and SIGNS
- Ulcers
- Reflux symptoms
- Diarrhea

TUMOR DISTRIBUTION
- < 10%
- 20%
- 60-80%
VIPOMA

SYMPTOMS and SIGNS

Watery Diarrhea
Hypokaliemia
Hypoachlorhydria
Hypercalcemia
Flushing

TUMOR DISTRIBUTION

~90%

~5-10%
GLUCAGONOMA

SYMPTOMS and SIGNS

Migratory Necrolityc Erythema
Diabetes
Weight loss

TUMOR DISTRIBUTION

14% 51%
22%
SOMATOSTATINOMA

SYMPTOMS and SIGNS

Cholelithiasis
Diabetes
Diarrhea/Steatorrhea

TUMOR DISTRIBUTION

57%
43%
NEUROENDOCRINE FUNCTIONING TUMORS

- CARCINOIDS
- INSULINOMAS
- GASTRINOMAS
- VIPOMAS
- GLUCAGONOMAS
- SOMATOSTATINOMAS
- GRF-OMAS

Clinical syndrome correlated to peptide hyperproduction
M.E.N. (Multiple Endocrine Neoplasia)

Definizione

Gruppo di Neoplasie che hanno in comune le seguenti caratteristiche:

1. Secernono uno o più Peptidi o BioAmine
2. Sono Tumori in genere benigni, con effetti clinici indotti da ipersecrezione di ormoni
3. I Tumori compaiono abbastanza precocemente interessando spesso più organi endocrini
4. Esiste la possibilità di trasformazione maligna
5. Eredità con modello autosomico dominante
## M.E.N. type 1: common features

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroids hyperplasia</td>
<td>(85-90%)</td>
</tr>
<tr>
<td>Pituitary adenomas</td>
<td>(15-50%)</td>
</tr>
<tr>
<td>Pancreatic tumours</td>
<td>(30-80%)</td>
</tr>
<tr>
<td>Carcinoids</td>
<td>(5% ?)</td>
</tr>
<tr>
<td>Lipomas</td>
<td>(5%)</td>
</tr>
<tr>
<td>Adrenocortical adenomas</td>
<td>(10-15%)</td>
</tr>
<tr>
<td>Thyroid adenomas</td>
<td>(5-20%)</td>
</tr>
<tr>
<td>Thymic Carcinoid</td>
<td>?</td>
</tr>
</tbody>
</table>
“two hit” model of tumour development

inherited (germline) inactivation of one copy of a tumour suppressor gene

(FIRST HIT)

subsequent (somatic) mutation

(SECOND HIT)

inherited syndrome associated tumor development
MEN 2A

Carcinoma midollare della tiroide 90-100%

Iperplasia delle paratiroidi 10-50%

Feocromocitoma bilaterale 40-50%

MEN 2B

Carcinoma midollare della tiroide 90-100%

Feocromocitoma bilaterale 50-70%

Neuromi mucosi 90%
Extracellular region

GDNF

GDNF-α

ligand-binding domain

Plasma membrane

C634

tyrosine kinase domains

Intracellular region

M918
GDNF

GDNFR-α

RET

Cys-rich

634

TM

TK

918

GDNF

918
**Germline ret mutation in multiple endocrine neoplasia type 2 families**

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
<th>Codon Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN 2A</td>
<td>98%</td>
<td>Codon 634 in 85% (usually TGC to CGC)</td>
</tr>
<tr>
<td>FMTC</td>
<td>88%</td>
<td>Codon 634 in 30% (usually TCG to TAC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Codon 634 TGC to CGC not found</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Codon 618 in 33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Codon 768 and 804 rarely</td>
</tr>
<tr>
<td>MEN 2B</td>
<td>95%</td>
<td>Codon 918(ATG to ACG) in 100%</td>
</tr>
</tbody>
</table>

(data from the International Ret Mutation Consortium)