Glucagon cell adenomatosis

Homozygous P86S Mutation of the Human Glucagon Receptor Is Associated With Hyperglucagonemia, α Cell Hyperplasia, and Islet Cell Tumor

Cuiqi Zhou, PhD,* Deepti Dhall, MD,† Nicholas N. Nissen, MD,‡§ Chun-Rong Chen, MD, PhD,* and Run Yu, MD, PhD* (Pancreas 2009;38: 941–946)

• One patient with glucagon cell adenomatosis
• Homozygous mutation of the glucagon cell receptor gene
Glucagon cell adenomatosis


5 adult patients (3 men, 2 women) with multiple pancreatic glucagon-expressing neoplasms

-morphologically – all pts had microadenomas
  - in addition three pts had single macrotumors

-clinically heterogeneous (one pt with glucagonoma syndrome, 4 without)

-- no metastases, no family history
Glucagon cell adenomatosis

- Micro adenomas
- Macrotumors
Glucagon cell adenomatosis (pat. 5)
Glucagon cell adenomatosi

No LOH of 11q13 & C11

pat. 3
Glucagon cell adenomatosis (pat. 1)
Whole genom sequencing in 5 cases with GCA

3 pts with germ line mutations in the glucagon receptor gene
   2 x homozygous
   1 x heterozygous

2 pts without germ line mutations in the gr-gene

Henopp, Anlauf, Klöppel, Sipos, 2012-13
Lower blood glucose, hyperglucagonemia, and pancreatic α cell hyperplasia in glucagon receptor knockout mice


Departments of ††Diabetes Biology, *Pharmacological Research 4, **Pharmacological Research 2, and ††Pharmacological Research 3, Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark; Departments of ‡Biochemistry, §Medicine (Endocrinology), and ‖Physiology and Biophysics, Albert Einstein College of Medicine, Bronx, NY 10461; †Department of Developmental Biology, Hagedorn Research Institute, DK-2820 Gentofte, Denmark; and †Department of Medical Physiology, Panum Institute, DK-2200 Copenhagen, Denmark

Communicated by Bruce S. McEwen, The Rockefeller University, New York, NY, November 21, 2002 (received for review February 21, 2002)

• Gcgr-/- mice were generated
• lower blood glucose levels
• improved glucose tolerance
• similar insulin levels compared to control animals.
• elevated glucagon levels
• postnatal enlargement of the pancreas with hyperplasia of islets, predominantly composed of alpha cells
Ablation of the Glucagon Receptor Gene Increases Fetal Lethality and Produces Alterations in Islet Development and Maturation


Departments of Pediatrics (P.M.V.) and Biochemistry (P.M.V., L.C., R.W.G., M.J.C.), Albert Einstein College of Medicine, Bronx, New York 10461; Department of Anatomy and Cell Biology (M.H.K., Y.G., M.N., G.T.), State University of New York-Downstate Medical Center, Brooklyn, New York 11203; and Metabolex Inc. (R.W.G.), Hayward, California 94545

- mice were generated with a global deletion of the glucagon receptor.
  - displayed elevated glucagon levels
  - **hyperplasia of islets consisting predominantly of alpha cells**, and to a lesser extent delta cells
  - increased number of islets
  - lower blood glucose level
  - improved glucose tolerance
  - similar insulin level compared with control animals.
Natural history of Pan NENs

Tumor size - cm

Time course - years

1 cm

2 cm

3 cm

metastases

simple genetics

complex genetics
Genetic aberrations in PanNETs: chromosomal gains and losses

C G H

0 - 5 aberrations
6 - 10
11 - 36

follow up

Tumor free survival

1-, 11q-, 9q+: < 2 cm
3p-, 6pq-, 10pq-, 5q+, 12q+, 18q+, 20q+: >2cm

..., 4+, 7+, 21q-: mets

Zhao et al 2001
Speel et al 1999
Perren et al 2007
### Mutated genes and survival in 68 sporadic PanNENs

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation Rate</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEN 1</strong></td>
<td>- 44 %</td>
<td>histone remodelling</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
</tr>
<tr>
<td><strong>DAXX/ATRX</strong></td>
<td>- 43 % (25%+18%)</td>
<td>chromatin assembly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TSC2 (mTOR pathway)</strong></td>
<td>- 9 %</td>
<td>GTPase act. p.</td>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td>- 7 %</td>
<td></td>
</tr>
<tr>
<td><strong>PIK3CA</strong></td>
<td>- 1 %</td>
<td></td>
</tr>
<tr>
<td><strong>Rarely mutated genes</strong></td>
<td>- 3 %</td>
<td>VHL, NF1, KRAS, P53, SMAD4, P16</td>
</tr>
</tbody>
</table>

Jiao et al, Science 2011
Pancreatic Neuroendocrine Tumors

- Defining subgroups
  well and poorly differentiated histology
  G 1, G 2, G 3
  tumor spread (i.e. TNM)
  functioning and nonfunctioning
  genetic alterations

- by entity - histologically, functionally and biologically defined
  genetic signature
GEP-NETs: Clinical classification

- **Functioning** (active, syndromic)
  - Insulinoma  
  - Gastrinoma – panc.  
  - Glucagonoma  
  - VIPoma  
  - Somatostatinoma  
  - Others (ACTH, GFRH, serotonin, calcitonin, MEN1)

- **Non-functioning** (inactive, clinically silent)
  - PP (pancreatic polypeptide) , Glucagon – producing NETs
  - ECL – cell NETs – gastric
  - Somatostatin-producing NETs
  - Others (MEN1)
## Pancreatic Neuroendocrine Tumors

### New entities

- **insulinomatosis**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulinoma</td>
<td>solitary sporadic benign</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>solitary sporadic malignant</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>multiple hereditary MEN1</td>
</tr>
<tr>
<td>Insulinomatosis</td>
<td>multiple non MEN1</td>
</tr>
</tbody>
</table>
benign insulinoma

malignant insulinoma
Insulinomatosis

Serotonin producing PanNETs are sclerosing tumors usually involving the main pancreatic duct

- Genetics?
Small Serotonin-producing Duct-obstructing PanNET

Shi et al., Radiology. 2010;257:107-14
Somatostatin producing PanNETs frequently show a paraganglioma-like pattern.
Pan-NETs are seemingly homogenous:

1. Heterogeneous
2. Subgroup separation by grade, stage, entity, genetics
3. Phenotype meets genotype
Martin
Anlauf
Bence
Sipos
Anlauf
Philipp
Heitz
Aurel
Perren
Paul
Komminoth
Mutated genes and survival in 68 sporadic PanNENs

Jiao et al, Science 2011

**MEN 1** - 44 %
**DAXX/ATRX** - 43 %
**Genes in mTOR pathway** - 16 %

Significant better survival in pts with **MEN 1** and/or **DAXX/ATRX** mutations than in pts with wild type **MEN1/DAXX/ATRX**

Mutations in **MEN 1** and/or **DAXX/ATRX** may identify a biologically specific subgroup

Loss of **PTEN** and **TSC2** expression correlates with shorter disease free and overall survival
mTOR pathway involvement

*Somatic mutations* in mTOR pathway - 16% predicting to result in aberrant mTOR signaling (cell growths, proliferation, anabolic metabolism)

RADIANT – 3 trial showed that more than 16% of the pts responded to everolimus suggesting additional mechanisms activating PanNETs growth.

Loss of ATRX/DAXX function might impact PanNET initiation and/or progression

*DAXX/ATRX* encode proteins involved in
- heterochromatin assembly
- heterochromatin maintenance at telomeres

Jiao et al, Science 2011