Molecular Pathology of Gastric Cancer

Fátima Carneiro
IPATIMUP & FMUP/HSJ
Porto, Portugal
Twenty European countries with the highest incidence of gastric cancer

Stomach: both sexes, all ages

ASR (v) per 100,000

Portugal

Belarus, Albania, Ukraine, FYR Macedonia, Lithuania, Montenegro, Estonia, Latvia, Portugal, Republic of Moldova, Croatia, Slovenia, Italy, Bulgaria, Hungary, Slovakia, Romania, Bosnia Herzegovina, Poland

Incidence
Mortality

GLOBCAN 2008 (ARC) (1.12.2010)
Types and sub-types of gastric carcinoma

- Adenocarcinoma
- Adenosquamous carcinoma
- Anaplastic carcinoma
- Blue cell carcinoma
- Carcinoma with lymphoid stroma
- Carcinoma simplex
- Desmoplastic carcinoma
- Differentiated carcinoma
- Diffuse carcinoma
- Expanding carcinoma
- Glandular carcinoma
- Infiltrative carcinoma
- Intestinal carcinoma
- Intestinal cell type carcinoma
- Limitis plastica
- Lymphoepithelial carcinoma
- Lymphoepithelioma-like carcinoma
- Mixed carcinoma
- Medullary carcinoma with lymphoid stroma
- Mucinous adenocarcinoma
- Mucoid carcinoma
- Mucous cell type carcinoma
- Non-glandular carcinoma
- Papillary adenocarcinoma
- Parietal cell carcinoma
- Poorly-differentiated adenocarcinoma
- Pyloric-cardiac cell carcinoma
- Scirrhous carcinoma
- Signet-ring cell carcinoma
- Small cell carcinoma
- Solid carcinoma
- Solid medullary type
- Squamous cell carcinoma
- Tubular adenocarcinoma
- Types I, II, III and IV of Goseki et al.
- Unclassified carcinoma
- Undifferentiated carcinoma

Localization
Histotype

Changing epidemiology

Morphologic heterogeneity
Cholecystokinin
- Gall bladder contraction
- Gastrointestinal motility
- Pancreatic exocrine secretion
- Secretin
- Pancreatic exocrine secretion
- GIP
- Incretin activity
- Motilin
- Gastrointestinal motility

Ghrellin
- Hunger
- Growth hormone release
- Gastrin
- Acid secretion

Insulin and glucagon
- Glucose homeostasis
- Pancreatic polypeptide
- Gastric motility
- Satiation
- Amylin
- Glucose homeostasis
- Gastric motility

GLP-1
- Incretin activity
- Satiation
- GLP-2
- Gastrointestinal motility and growth
- Oxyntomodulin
- Satiation
- Acid secretion
- PYY₅₋₇
- Satiation

Major bacteria present:
- Esophagus: Lactobacillus
- Stomach: Lactobacillus
- Duodenum: Enterooccus, Lactobacillus
- Jejunum: Enterobacteria, Aerococcus, rods, lactobacilli
- Ileum: Enterooccus, lactobacilli, rods, lactobacilli
- Colon: Caudicides, Lactobacilli

Major physiological processes:
- Esophagus: Secration of acid (HCl)
- Stomach: Digestion of macromolecules (pH 2)
- Duodenum: Continued digestion
- Jejunum: Absorption of monooctropeptides, amino acids, fatty acids, water (pH 5)
- Ileum: Absorption of bile acids, vitamin B₁₂ (pH 11)
Any story about a human’s microbes tends to invoke impressive numbers. Take the 10 trillion or so microbial cells living in the gut, which exceed the number of human cells by 10 to 1. Between them, they harbour millions of genes, compared with the paltry 20,000 estimated in the human genome. To say that you are outnumbered is a massive understatement.

But that might not be a bad thing. There is strength in numbers; so much so, in fact, that some biologists regard a human as a ‘super-organism’ — a community that adds up to more than the sum of its parts. The body itself is merely one, albeit encompassing, component.
Evolution of Mammals and Their Gut Microbes

Ruth E. Ley,1 Micah Hamady,2 Catherine Lozupone,1,3 Peter J. Turnbaugh,1 Rob Roy Ramey,4 J. Stephen Bircher,5 Michael L. Schlegel,6 Tammy A. Tucker,6 Mark D. Schrenzel,6 Rob Knight,3 Jeffrey I. Gordon1*

Mammals are metagenomic in that they are composed of not only their own gene complements but also those of all of their associated microbes.
The stomach displays a diverse microbiota when *H. pylori* is absent or low in abundance.

Resident or transient populations of ingested microbes??

Andersson *et al.*, PLoS ONE 2008
Risk of gastric cancer development

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. pylori virulent genotypes</td>
<td>15 to 17</td>
</tr>
<tr>
<td>IL-1 gene polymorphism</td>
<td>3.3</td>
</tr>
<tr>
<td>H. pylori virulence &amp; IL-1B polymorphism</td>
<td>87</td>
</tr>
</tbody>
</table>

Gene-environment interaction

- Helicobacter pylori infection
- Diet
- Smoking

Machado et al, Gastroenterology 121: 823, 2001
Figueiredo et al, JNCI 94: 1680, 2002

Familial aggregation

- Polymorphisms: Mucin genes; Pro-inflammatory genes
- Mutations in “low” or “high” penetrant genes
Sporadic cancer
Hereditary cancer
Morphology
Molecular pathology
Intestinal (glandular) carcinoma

- Elderly patients, mainly males
- Decreasing incidence everywhere
- Blood-born metastases

Diffuse (isolated cell-type) carcinoma

- Young patients, mainly females
- Familial/hereditary conditioning
- Dissemination to the peritoneum
<table>
<thead>
<tr>
<th>Intestinal (glandular) carcinoma</th>
<th>Diffuse (isolated cell) carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CIN (Chromosomal instability)-Aneuploidy</strong></td>
<td><strong>Diploidy</strong></td>
</tr>
<tr>
<td># 3p, 7q, 13q (LOH)</td>
<td># 3p, 7q, 13q (LOH)</td>
</tr>
<tr>
<td># 6q (LOH)</td>
<td># 6q (LOH)</td>
</tr>
<tr>
<td># 1q, 5q, 17p (LOH)</td>
<td></td>
</tr>
<tr>
<td>RAS (overexpression/mutation)</td>
<td></td>
</tr>
<tr>
<td>ERBB-2 (amplification)</td>
<td></td>
</tr>
<tr>
<td>TPR-MET (rearrangement)</td>
<td></td>
</tr>
<tr>
<td>c-MET (6.0 Kb mRNA)</td>
<td>c-MET (6.0 Kb mRNA)</td>
</tr>
<tr>
<td>EGF (overexpression)</td>
<td>p 53 (LOH, mutation)</td>
</tr>
<tr>
<td>TGF-a (overexpression)</td>
<td></td>
</tr>
<tr>
<td>p 53 (LOH, mutation)</td>
<td></td>
</tr>
<tr>
<td>APC (LOH, mutation)</td>
<td></td>
</tr>
<tr>
<td>DCC (LOH)</td>
<td></td>
</tr>
<tr>
<td>p 16 (hypermethylation)</td>
<td>TGF-ß (overexpression)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MSI (Microsatellite Instability)</strong></td>
<td><strong>K-SAM (amplification)</strong></td>
</tr>
<tr>
<td>S-Tn, T, S-T</td>
<td>S-Tn, T, S-T</td>
</tr>
<tr>
<td>CDw75, S-Lex</td>
<td>CDw75, S-Lex</td>
</tr>
<tr>
<td>Laminin, collagen IV</td>
<td></td>
</tr>
<tr>
<td>u-PA, Cat-D</td>
<td></td>
</tr>
<tr>
<td>NM 23 (loss)</td>
<td>NM 23 (loss)</td>
</tr>
<tr>
<td>CD 44 (variants)</td>
<td>CD 44 (variants)</td>
</tr>
</tbody>
</table>
ERBB-2 amplification in intestinal carcinoma

**Blood born metastases**

**Poor prognosis**

**ERBB-2**

In gastric carcinoma

**ERBB-2 amplification**

in intestinal carcinoma

Blood born metastases
Poor prognosis

ToGA Trial

ERBB2 overexpression in 22% of advanced gastric cancers
Significantly improved survival with trastuzumab

David L et al; Mod Pathol 5:384, 1992
Barros-Silva J et al; Br J Cancer 100: 487, 2009

ASCO 2009 (LBA 4509)
EGFR mutations in sporadic gastric carcinoma

EGFR mutations
2/77 cases

EGFR amplification
4/30 cases

3'-UTR EGFR A13 REPEAT
20/63 (31.7%)
Microsatellite Instability (MSI) in gastric cancer

15-30% of the cases

Santos NR et al. Gastroenterology 110:38, 1996
Survival of patients

Univariate analysis

Multivariate analysis

- Staging (pTNM) (p< 0.0008)
- Venous invasion (p= 0.004)
- Histological classification (p=0.08)
- Microsatellite instability (p=0.04)

MSI is a molecular marker of good prognosis in sporadic gastric cancer

Mismatch Repair (MMR) gene mutations are rare in sporadic gastric carcinomas

(Do not explain most of the MSI cases)

MLH1 methylation

MSI-H
- Unmethylated 25%
- Methylated 75%

MSS
- Unmethylated 100%
- Methylated -

hMLH1 promoter hypermethylation is the main mechanism underlying MSI in SGC
**KRAS and BRAF in sporadic gastric carcinoma**

<table>
<thead>
<tr>
<th>MSI status</th>
<th>K-RAS Exon 1</th>
<th>BRAF Exon 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSI-H</td>
<td><strong>10/36 (28%)</strong></td>
<td>0/38 (0%)</td>
</tr>
<tr>
<td>MSS</td>
<td>0/46 (0%)</td>
<td>1/139 (0.72%)</td>
</tr>
</tbody>
</table>

\[ p=0.0001 \quad \text{NP} \]

Brennetot C et al, Gastroenterology 125, 2003
Orcein staining

<table>
<thead>
<tr>
<th>Venous invasion</th>
<th>High expression of $S$-$L$-$e^x$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>5.6%</td>
</tr>
<tr>
<td>Present</td>
<td>94.4%</td>
</tr>
</tbody>
</table>

$p = 0.0025$


High $S$-$L$-$e^x$ expression is a marker of poor prognosis in sporadic gastric cancer
## CD44v6 in sporadic gastric carcinoma

<table>
<thead>
<tr>
<th>Histotype</th>
<th>cases (n)</th>
<th>CD44v6 overexpression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal</td>
<td>14</td>
<td>7 (50.0)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>13</td>
<td>10 (76.9)</td>
</tr>
<tr>
<td>Mixed</td>
<td>16</td>
<td>10 (62.5)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>43</td>
<td>27 (62.8)</td>
</tr>
</tbody>
</table>
CD44v6 in precursor lesions of gastric carcinoma
### What about diffuse carcinoma?

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<th>Intestinal (glandular) carcinoma</th>
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<td><strong>CDw75, S-Le̅</strong></td>
<td><strong>E-cadherin (loss/mutation)</strong></td>
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</tr>
</tbody>
</table>

**E-cadherin gene (CDH1) plays the major role**
E-Cadherin changes in diffuse carcinoma

Somatic mutations

CDH1 mutations (50% - 70%)
E-cadherin gene alterations in sporadic gastric carcinoma

"1st HIT"

Mutation

"2nd HIT"

LOH

Promoter methylation

Inactivation of *CDH1* in sporadic gastric carcinoma

E-cadherin epigenetic and structural alterations in 246 gastric cancers.

<table>
<thead>
<tr>
<th>Clinicopathological features</th>
<th>Total n° cases N=246</th>
<th>With E-cadherin alterations N=77</th>
<th>Without E-cadherin alterations N=169</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN0</td>
<td>72</td>
<td>15</td>
<td>57</td>
<td>0.024</td>
</tr>
<tr>
<td>p(\geq N1)</td>
<td>172</td>
<td>62</td>
<td>112</td>
<td></td>
</tr>
<tr>
<td>Stage grouping</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>57</td>
<td>10</td>
<td>47</td>
<td>0.011</td>
</tr>
<tr>
<td>II+III+IV</td>
<td>187</td>
<td>66</td>
<td>121</td>
<td></td>
</tr>
</tbody>
</table>
Inactivation of \textit{CDH1} in sporadic gastric carcinoma
What about the mixed type of gastric carcinoma?
Mixed gastric carcinomas show similar chromosomal aberrations in both their diffuse and glandular components

Carvalho B et al. Cellular Oncology 28:283, 2006
What about the mixed type of gastric carcinoma?
E-cadherin mutations in mixed gastric carcinomas

<table>
<thead>
<tr>
<th>Component</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Intestinal&quot;</td>
<td>17%</td>
</tr>
<tr>
<td>&quot;Diffuse&quot;</td>
<td>83%</td>
</tr>
</tbody>
</table>

Machado JC et al: E-cadherin gene mutations provide a genetic basis for the phenotypic divergence of mixed gastric carcinomas

Lab Invest 79: 459, 1999
<table>
<thead>
<tr>
<th>Histological type</th>
<th>5-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glandular (n=89)</td>
<td>52%</td>
</tr>
<tr>
<td>Isolated cell (n=14)</td>
<td>67%</td>
</tr>
<tr>
<td>Solid (n=28)</td>
<td>48%</td>
</tr>
<tr>
<td>Mixed (n=82)</td>
<td>16%</td>
</tr>
</tbody>
</table>

### 4-1-02 - ICD-O Code

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>8140/3</td>
</tr>
<tr>
<td>Papillary adenocarcinoma</td>
<td>8260/3</td>
</tr>
<tr>
<td>Tubular adenocarcinoma</td>
<td>8211/3</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>8480/3</td>
</tr>
<tr>
<td>Signet-ring cell carcinoma</td>
<td>8490/3</td>
</tr>
</tbody>
</table>

**WHO - 3rd Edition**

**Some shortcomings:**

- Signet ring cell ca?
- Mixed ca?
4-1 Gastric carcinoma

Gregory Y. Lauwers
Fátima Carneiro
David Y. Graham
Maria-Paula Curado
Silvia Franceschi
Elizabeth Montgomery
Masae Tatematsu
Takenori Hattori

4-1-02 - ICD-O Code

| Tumour Type                               | Code  
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
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<tr>
<td>Tubular adenocarcinoma</td>
<td>8211/3</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>8480/3</td>
</tr>
<tr>
<td>Poorly cohesive carcinomas (including signet ring cell carcinoma and other variants)</td>
<td>8490/3</td>
</tr>
<tr>
<td>Mixed carcinoma</td>
<td>8255/3</td>
</tr>
</tbody>
</table>

WHO Classification of Tumours of the Digestive System Consensus and Editorial meeting IARC, Lyon, 10-12 December 2009

Major histological types

- pT
- pN
- pM
- Venous invasion

Poor prognosis
- Microsatellite instability
- Sialyl-Le\(^x\)
- ERBB-2
- E-cadherin

Good prognosis
Sporadic gastric carcinoma

**MSI**
- Intestinal GC, older age
- MLH1 methylation
- Good prognostic biomarker

**E-cadherin**
- Nodal metastization, Advanced stage
- Poor prognostic biomarker
- LOH+ Mut

**Oncogenic Mutations**
- KRAS negative
- EGFR positive
- BRAF negative
- Biomarker for targeted therapy (EGFR inhibitors?)

**CD44v6**
- Normal mucosa: neg
- Intestinal metaplasia & dysplasia: pos
- New diagnostic biomarker
Gastric cancer in hereditary cancer syndromes

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Genetic alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lynch syndrome (HNPCC)</td>
<td>$MMR$</td>
</tr>
<tr>
<td>• Li-Fraumeni syndrome</td>
<td>$TP53$</td>
</tr>
<tr>
<td>• Peutz-Jeghers syndrome</td>
<td>$STK1$</td>
</tr>
<tr>
<td>• Familial adenomatous polyposis</td>
<td>$APC$</td>
</tr>
</tbody>
</table>
GASTRIC CARCINOMA

- Sporadic (90%)

- Familial Aggregation (10%)
  - Familial Gastric Cancer (FGC)
  - Familial Intestinal Gastric Cancer (FIGC)
  - Familial Diffuse Gastric Cancer (FDGC)

- Hereditary (1%)
  - Hereditary Diffuse Gastric Cancer (HDGC)
Maori kindred

E-cadherin gene (CDH1) germline mutations

Hereditary Diffuse Gastric Cancer

E-cadherin changes in familial gastric cancer

1999
Familial gastric cancer: overview and guidelines for management.

2001
Prophylactic gastrectomies in asymptomatic carriers of germ-line E-cadherin mutations

2002
Functional analyses of E-cadherin (CDH1) germline missense mutations

2003
Model of development of HDGC

2004
Report of the first Portuguese family with HDGC

2005
Cleft lip/palate and CDH1 mutations in families with HDGC

2006
Experimental model in Drosophila

2007
Novel germline CDH1 mutations

2008
NMD mRNA surveillance downregulates aberrant CDH1 transcripts

2009
Second hit of CDH1 inactivation

2010
Novel germline CDH1 mutations

References:
- Hum Mutat 19:510, 2002
- J Pathol 203: 681, 2004
- Virchows Arch 446: 18, 2005
- Clin Cancer Res 11:5401, 2005
- Hum Mutat 28:203, 2007
- Oncogene 27: 4255, 2008
- Gastroenterology 136:2137, 2009
IDENTIFICATION OF FAMILIAL CASES

The story of hereditary diffuse gastric carcinoma
E-cadherin mutations in diffuse gastric cancer

**HEREDITARY – Germline mutations**

- **Sig**
- **Percursor**
- **Extracellular domain**
- **TM**
- **Cyto. domain**

**SPORADIC – Somatic mutations**

- **Sig**
- **Percursor**
- **Extracellular domain**
- **TM**
- **Cyto. domain**
Missense mutations (20%)

Functional Assays in CHO cells (aggregation & collagen invasion assays)
Missense mutations affect cell-cell adhesion, motility and invasion


Functional Relevant
Adhesion, Motility, Invasion

A617T, ....

Functional Irrelevant
“so-called variants”

Oliveira C, 2010

Bar chart showing the frequency of alterations in different protein domains:
- Signal: 13.4
- Precursor: 9.2
- Extracellular: 58.0
- Transmembrane: 1.7
- Cytoplasmic: 17.6
Oliveira C, 2010

Type of CDH1 alteration

Frequency of CDH1 alterations

- Promoter methylation: 0.8
- Large deletion: 5.0
- Small frameshift: 30.0
- Nonsense: 19.2
- Splice-site: 25.0
- In-frame insertion: 0.8
- Missense: 19.2

Truncating or non-expressing 80%
Familial gastric cancer: overview and guidelines for management
(International Gastric Cancer Linkage Consortium)

Carriers of germline E-cadherin truncating mutations

Intensive screening
Prophylactic gastrectomy

Caldas C, Carneiro F, Lynch H et al
Eur J Genet 36: 873, 1999
In 9 prophylactic gastrectomies from North America (Huntsman et al, 2001 and Chun et al, 2001), all exhibited foci of intramucosal diffuse carcinoma

E-cadherin germline mutations in HDGC

TRUNCATING

MISSENSE
In vivo validation of CDH1 germline missense mutations

Table 2: E-cadherin germline missense mutations used for the statistical analysis

<table>
<thead>
<tr>
<th>Variant</th>
<th>&lt;1% Co-segregation</th>
<th>Recurrence</th>
<th>SIFTa</th>
<th>Functional effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral (N)b</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>T118R</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>L214P</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>G239R</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<tr>
<td>A298T</td>
<td>+</td>
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<td>T340A</td>
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<td>W409R</td>
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<td>A617T</td>
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<td>A634V</td>
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<td>+</td>
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<tr>
<td>R732Q</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>P799R</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>V832M</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Suriano G et al
J Mol Med 84:1023, 2006
In vivo validation of in vitro assays of CDH1 missense mutations

Table 2. Patients’ characteristics and foci identified

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Germline mutation</th>
<th>Mutation type</th>
<th>Age at surgery (years)</th>
<th>Sex</th>
<th>Length of time in surveillance programme</th>
<th>Number positive endoscopic biopsies/total taken (months prior to surgery)</th>
<th>Number of signet ring cancer foci identified in gastrectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>M13A</td>
<td>641T&gt;C</td>
<td>Missense</td>
<td>23</td>
<td>F</td>
<td>6 Months</td>
<td>2/24 (2)</td>
<td>16</td>
</tr>
<tr>
<td>M13B</td>
<td></td>
<td></td>
<td>20</td>
<td>F</td>
<td>6 Months</td>
<td>6/24 (2)</td>
<td>66</td>
</tr>
</tbody>
</table>

Barber M et al
The highest number of foci was found in the fundus (44.7%) followed by the body (40.2%).

Barber M et al
70% of the total signet ring cell foci were located within the proximal 1/3 of the stomach

Rogers W et al
Gastrectomies in New Zealand in CDH1 carriers

Total gastrectomies in asymptomatic CDH1 mutation carriers (n=96) (prophylactic gastrectomies & gastrectomies for early carcinoma)

• Intramucosal SRC carcinoma 87 (91%)
• Total gastrectomies studied under research protocol 73
• Number of cases with intramucosal SRC carcinoma 70* (96%)

* 2/3 cases negative for SRC intramucosal carcinoma displayed in situ carcinoma
Intramucosal signet ring cell (diffuse) carcinoma
In situ (signet ring cell) carcinoma

**Pagetoid spread** of signet ring cells:

Two-layer structure:
- an inner layer composed of benign mucous cells
- an outer layer of signet ring cells.
Pagetoid spread of signet ring cells and early invasion of lamina propria
**In situ** (signet ring cell) carcinoma

Pagetoid spread of signet ring cells:
Two-layer structure: an inner layer composed of benign mucous cells and an outer layer of signet ring cells.

<table>
<thead>
<tr>
<th>TNM stage</th>
<th>Tis</th>
<th>T1a</th>
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</thead>
<tbody>
<tr>
<td>Mucosa</td>
<td><img src="A" alt="Image" /></td>
<td><img src="B" alt="Image" /></td>
</tr>
<tr>
<td>Muscularis mucosa</td>
<td><img src="A" alt="Image" /></td>
<td><img src="B" alt="Image" /></td>
</tr>
<tr>
<td>Submucosa</td>
<td><img src="A" alt="Image" /></td>
<td><img src="B" alt="Image" /></td>
</tr>
</tbody>
</table>

Carneiro F, Charlton A, Huntsman D
Development model of HDGC

Inactivation of second allele of CDH1

CDH1 germline mutation

Non-neoplastic mucosa with foveolar hyperplasia

In situ signet ring cell carcinoma

In situ signet ring cell carcinoma and pagetoid spread

Pagetoid spread of signet ring cell carcinoma

Early invasive (intramucosal) signet ring cell carcinoma

Carneiro F et al
CLINICAL HISTORY

HISTOLOGICAL CLASSIFICATION

MOLECULAR CLASSIFICATION

First Portuguese HDGC Family (Porto)

Second Portuguese HDGC Family (Coimbra)
Genetics, Pathology and Clinics of Familial Gastric Cancer

The story of Hereditary Diffuse Gastric Cancer (HDGC)
2\textsuperscript{nd} HIT of CDH1 silencing?

Methylation

DNA demethylating agents

Gene structure alterations

Modulators
E-cadherin expression

Partners of E-cadherin signalling
THANKS FOR YOUR ATTENTION
First Portuguese Family with HDGC (Porto)

Second Portuguese Family with HDGC (Coimbra)