Chronic Inflammation and gastric cancer

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Esophago-Gastro-Intestinal Barrier

- Pre-epithelial barrier
- Epithelial barrier
- Postepithelial barrier

Modulators
- Luminal agents
- Commensals
- Pathogens
- Inflammation
The barrier succumbs to *H. pylori* infection

- Mucolytic enzymes
- Cytotoxins

- Mucus
- Epithelial cells
- Submucosa
- Blood vessels
- Pain
- Inflammatory mediators
- Granulocytes
- Macrophages
- Cytokines
H. pylori attacks the epithelial cell
Pathogenesis of *H. pylori*-infection

- Autoantibodies
- Le^x^ and Le^y^ antigens
- VacA, signal-transduction, CagA, adhesion, antigens
- Receptor phosphorylation, activation of Rac1, Cdc42, MAP-kinases, transcription
- Inhibition of Src-kinase
- Modulation of Actin-polymerisation
- IL-8, PMNs, chemotaxis
- IL-1, IL-6, IL-12
- Proinflammatory cytokines
- IFN-γ, TNF-α
- PMN=Polymorphonuclear cells
- Th1= Lymphocytes
- M=Monocytes//Macrophages

The *cag* pathogenicity island encodes a type IV secretion system.
**H. pylori affects adherens- and tight junctions**

*In vivo*

- E-cadherin ↓↓↓ (Terres et al., 1998)
- α-catenin ↓↓↓ (Ebert et al., 2000)
- β-catenin (impaired) (Ebert et al., 2002)

**Adherens junction**

- E-cadherin
- actin
- α-catenin
- β-catenin

**Tight junction**

- Occludin
- ZO-1
- CagA
- PTP-ζ

**VacA targets PTP-zeta**

- Gastric Ulcer ↑↑↑ (Fujikawa et al., 2003)

**Amieva et al. 2003**
Epithelial barrier disruption by H. pylori
Epithelial barrier disruption by *H. pylori*

**Course of infection**

- **Tight junctions**
  - Secretion of PAI-independent factors

- **Adherens junctions**
  - Apical adherence
  - Early signaling
  - Vacuolization
  - Initial (mild) disruption of junctions
  - Transcystosis of integrins

- **Focal adhesions**
  - Mild apical injection of CagA and PG
  - Disruptions of junctions
  - Release of cytokines↑
  - Recruitment of immune cells
  - Tissue damage↑

- **Apical membrane**

- **Basal membrane**

- **Integrins**

- **Neutrophils**

- **Macrophage**

- **Lymphocytes**

Wessler and Backert, Trends Microbiol. 2008
Epithelial barrier disruption by H. pylori

Course of infection

Loss of cell polarity

Host-cell proliferation↑

Massive disruption of cell-to-cell junctions

Intercellular invasion of H. pylori

Apoptosis

Massive injection of CagA

Host-cell motility and elongation↑

Lumen

Lamina propria

Wessler and Backert, Trends Microbiol. 2008
Gastritis criteria

- H. pylori Activity
- Chronicity
- Atrophy
- Intestinal Metaplasia
Common topographical patterns of chronic gastritis

Non-atrophic

Initial infection

Antrum predominant, Minimal corpus Involvement

Atrophic

Multifocal accompanied by metaplasia

Auto immune Corpus-predominant with antrum normal

Duodenal ulcer

gastric cancer
Atrophy and Intestinal Metaplasia
GASTRIC CANCER
Intestinal type
Gastric cancer

location subcardial

Histology: intestinal type
The role of *H. pylori* in gastric cancer

- H. pylori infection and gastric cancer link

- **Epidemiology**

- **Histological cascade**

- **Molecular events in gastric carcinogenesis**

- **Experimental models (cell biology, animal models)**

- **Clinical facts, clinical trials**
<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n 68</td>
<td></td>
<td></td>
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</table>

**Exclusion:**
- T4 gastric cancer
- Serum taken < 90 days following gastrectomy
- Cag A not considered if H. pylori negative

**Results:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>OR</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. pylori - Cag -</td>
<td>3.7</td>
<td>18.3</td>
</tr>
<tr>
<td>H. pylori + Cag +</td>
<td>5.7</td>
<td>28.4</td>
</tr>
</tbody>
</table>


H. pylori is the essential condition
Inflammation is the origin of cancer

Many common gastrointestinal cancers develop as a consequence of chronic inflammation over years

Moss SF, Blaser MJ. Nat Clin Pract Oncol. 2005
Atrophy-Metaplasia-Dysplasia-Carcinoma-Sequence

Chronic Hp-Gastritis

Multifocal Atrophy

Intestinal Metaplasia

Dysplasia

Cancer

Adaptiert nach Correa Cancer Res 48: 3554-60, 1988
diffuse gastric cancer
transmitted, 10 – 20 % genetic deviation

Methylation: CDH1, DAP-K, HRASLS, LOX, MGMT, p14, RAR-β
Amplification: C-MET, K-SAM
Mutation: CHD1, TP53
Expression: hTERT

H. pylori

non atrophic surface

gastritis

„genetic disposition“
transmitted CHD1-mutation

intestinal gastric cancer
purchased, 80 – 90 % genetic deviation

CIMP/Microsatellite-Instability
Methylation: p16, COX-2, GSTP1, hMLH1, MGMT, RASSF1A, RUNX3, TFF1
Amplification: ERBB2
Mutation: K-RAS, TP53
LOH: APC, MCC, TP53

Mutation: APC, TP53
Methylation: APC, CDH1, DAP-K, hMLH1, p14, THBS1, TIMP-3
Expression: EGFR, TGF-α

Expression: CDX1/2, COX-2, hTERT

atrophic gastritis
intestinal metaplasia

Pathological sequence in gastric adenocarcinoma

At which point does eradication of *H. pylori* interrupt the cascade?

Fox et al, Journ of Clin Investigation 2007
H. pylori and Gastric cancer

- The bacterium
- The host
- The environment
Mechanisms involved in carcinogenesis

**Helicobacter pylori-related:**

- **H. pylori virulence factors**
  - Pathogenicity island (PAI)
  - Genetic variation (recombination, point mutations, horizontal transfer of genetic elements)
  - CagA+ strains
  - VacA sl, VacA ml genotypes

- **Regulation of growth factors receptors by H. pylori**
  - Epidermal growth factor (EGF)
  - EGFR-related receptor (Her2-Neu)
  - c-Met receptor

- **Enhancement of cell motility**
  - c-Met receptor
  - Adaptor protein
  - Tyrosine phosphatase SHP-2
  - Phospholipase Cγ

- **Evasion of apoptosis**
  - Activation of nuclear hormone receptor peroxisome proliferators activates receptor-δ (PPAR-δ)

- **Increased angiogenesis**
  - induction of vascular endothelial growth factor-A (VEGF-A)

- **Disruption of cell-cell contacts**
  - Decreased ZO-I and tight junctional adhesion protein (JAM)
  - Phosphorylation of Git I
## Importance of Cag A / PAI

<table>
<thead>
<tr>
<th>Cag A status</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>1 (referent)</td>
</tr>
<tr>
<td>Positive</td>
<td>15 (7.4 to 29)</td>
</tr>
</tbody>
</table>

Figueiredo *et al* JNCI 2002;94:1680
H. pylori and Gastric cancer

- Cell pathophysiology
- Organ physiology
*H. pylori* activates and modulates receptor tyrosine kinases

- c Met
- EGFR
- Her2/Neu

**Motogenic response**

- CagA
- *Keates et al., 2001*
- *Wallasch et al., 2002*
- *Churin et al., 2003*

**Proliferation**
**H. pylori and gastric cancer**

**Biological effects**

- **↑ Gastrin**
- **↓ Somatostatin**
- **↑ Mucosal proliferation**
- **↑ ROM**
- **↑ Mutation**
- **↑ Gastric glandular atrophy**
- **↓ Acid secretion**
- **↓ Ascorbic acid**
- **↑ Nitroso compounds**

**VacA**
- **S1m1**
- **CagA**
Common topographical patterns of chronic gastritis

- **Non-atrophic**
- **Initial infection**
- **Atrophic**
  - Multifocal accompanied by metaplasia
- **Antrum predominant, Minimal corpus Involvement**
- **Auto immune Corpus-predominant with antrum normal**
- **Duodenal ulcer**
- **Gastric cancer**
H. pylori and Gastric cancer

- The host susceptibility
Risk factors of gastric cancer

1351 patients, 30–74 years, recruited 1987–88

**H. pylori** prevalence

- **Gastric cancer**: 69.9%
- **Control group**: 44.0%

Familial risk is due to **H. Pylori** infection

- multiple regression analysis
- aOD 2.7 (95% CI 1.3–5.9)
- < 55 y
- aOD 5.1 (95% CI 1.6–16.1)

Brenner et al, Gastroenterology 2000
**H. pylori and gastric cancer**

- Relatives of gastric cancer patients (n100), *H. pylori* prevalence 63%
- Control subjects (n 100), *H. pylori* prevalence 64%

There is still genetic predisposition.
## Cytokine Polymorphisms in H. pylori seropositive

### Non Cardia Gastric Cancer

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>H. pylori seropositive OR</th>
<th>Cag seropositive OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1 β 511 T</td>
<td>4,2</td>
<td>9,9</td>
</tr>
<tr>
<td>IL-1 RN *2 /*2</td>
<td>1,6</td>
<td>2,9</td>
</tr>
<tr>
<td>IL-10 ATA/ATA</td>
<td>2,9</td>
<td>5,2</td>
</tr>
<tr>
<td>TNF-A-308*</td>
<td>2,9</td>
<td>6,2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HpAb + Cag Ab</th>
<th>1 marker OR</th>
<th>2 markers OR</th>
<th>3 markers OR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5,4 - 6,6</td>
<td>8,3 - 19,5</td>
<td>42 - ∞</td>
</tr>
</tbody>
</table>

*El’Omar et al, Gastroenterology 2003*
Host related factors
IL-1β Polymorphisms & Hypoacidity

IL-1 Gen Cluster
IL-1A, IL-1B, IL-1RN

IL-1B-31T+
IL-1RN*2/*2
Gastric Cancer

Inhibits acid secretion
Factors contributing to H. pylori-related gastric cancer

Pro-inflammatory cytokine gene polymorphisms
- IL-1B-511*T
- IL-1RN*2*2
- IL-10 ATA haplotype
- TNF-A-308*A

Innate immune response gene polymorphisms
- TLR4+896*G

Bacterial factors
- Cag A
- Vac A s1/m1

Environmental factors
- Smoking
- Diet
Risk of Gastric Cancer is greatest in subjects with both bacterial and host „highrisk-genotypes“.
Gastric Cancer and H. pylori infection

Risk factors - Memo for the clinician

- Familial history
- H. pylori infection
  - bacterial virulence
  - host genetic determinants
  - environmental factors
Statement:

*H. pylori* infection is the most common proven risk factor for human non-cardia gastric cancer.

Eradication has the potential to prevent

Level of Evidence: n.a.  
Grade of Recommendation: A

Values in percentage

Malfertheiner et al Gut 2007
H. Pylori eradication reduces incidence of gastric cancer

Systematic review of randomized controlled trials from Cochrane-, Medline- und EMBASE-data:

- 5 studies with 5,676 patients
- 3 from China, 2 from Japan
- Follow up 2, 4 – 12 years
- 130 cancers detected

Moayyedi et al DDW 2008
Helicobacter-Eradication in gastric cancer

- Reduced gastric cancer risk following eradication (RR=0.56, 95% CI=0.4-0.8)

NNT=227

Moayyedi et al DDW 2008
Eradication H. pylori infection in a general population prevents gastric cancer: A 7-year prospective randomized placebo-controlled study.

Gastric cancer in subjects with no preneoplastic changes on entry.

Wong et al. JAMA2004
H. pylori eradication for gastric cancer prevention

- Cave!!
- The point of no return
H. Pylori eradication in patients with EMR of early gastric cancer reduces further GC.

K. Fukase et al, Lancet 2008,

![Graph showing cumulative incidence rate of new carcinoma](image)
Probability of regression of the pre-neoplastic lesions

H. pylori and gastric cancer

Infection with *H. pylori*

- Chronic active gastritis
- Atrophic gastitis
- Intestinal metaplasia

Dysplasia

Gastric cancer

- Months
- Years
- Decades
$H. pylori$-Eradication and GC-Prevention: Screening Cost-effectiveness

**\(^{13}\text{C-UBT} + \text{Eradication}\)**

- Once-only chemo-prevention
- Age: 30 years
  (Worse cost-effectiveness if later)
- Costs: $17,044 /life-year gained

**Serum Pepsinogen + Endoscopic confirmation**

- Annual high-risk screening
- Age: 50 years
- Costs: $29,741 /life year gained

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Lee et al, Cancer Epidemiol Biomarkers Prev 2007
**H. pylori-Eradication and GC-Prevention Hazards**

- Complex therapy (multi-agent) → **Compliance?**
- Availability (Developing countries) → strict indication
- Increasing **resistance** (Clarithromycin/Metronidazole)
- Critical **point of time** for eradication

Current H. pylori therapies need to improve

Perspectives

- new antibiotics
- vaccine
- genome targeting drugs

probiotics additional

New drug development