Tumor and Inflammation - two Sides of the Coin

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Tumor & Inflammation

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Rudolf Virchow: father of modern pathology and founder of the „cellular pathology“ theory

→ diseases due to defects in individual cells of the body

→ all diseases (cancer) start from inflammation

Robert Koch: funding father of modern bacteriology

→ all diseases (cancer) start from infections
The seven hallmarks of cancer

- Self-sufficiency in growth signals
- Insensitivity to anti-growth signals
- Evading apoptosis
- Inflammatory microenvironment
- Sustained angiogenesis
- Limitless replicative potential
- Tissue invasion & metastasis
Cellular composition of tumors

- Tumor
  - malignant cells
  - non malignant cells
    - tumor stromal cells
      - fibroblasts
      - endothelial cells
      - blood/lymphatic vessels
      - immune-competent cells
        - macrophages, lymphocytes

The tumor microenvironment
Inflammatory tumor environment

Extrinsic pathway:
driven by inflammatory cells and mediators

Intrinsic pathways:
genetic alterations

- mutations in onco- and/or suppressor genes

Cancer

Inflammation

Inflammation can cause Cancer
Cancer can cause Inflammation

Inflammation can cause Cancer
Cancer can cause Inflammation
Cancer Development steps

Initiation

- GENOMIC CHANGES
  - point mutations
  - gene deletion and amplification
  - chromosomal rearrangements

Promotion

- SURVIVAL and CLONAL EXPANSION of "initiated cells"

Progression

- SUBSTANTIAL GROWTH in tumor size and METASTASIS

"mutagens" → "inflammation" → "inflammation"
Role for inflammation in Cancer

→ approx. only 5 – 10% of all cancer cases can be attributed to genetic defects,

→ the remaining 90 - 95% have their roots in the environment and lifestyle

→ approx. 20% of all malignancies are initiated or exacerbated by inflammation
Role for inflammation in Cancer

Cancer risk factors - environmental and lifestyle -

- physical inactivity
- high calorie diet
- obesity
- alcohol
- tobacco
- radiation
- sun exposure
- environmental pollutants

chronic Inflammation

activation of: NFκB, AP-1, STAT3
# Clinical Evidence (some examples)

<table>
<thead>
<tr>
<th>Disease</th>
<th>associated tumors</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colitis ulcerosa, M. Crohn</td>
<td>Colon-Ca.</td>
<td>Autoimmune Disease</td>
</tr>
<tr>
<td>Chronic Gastritis</td>
<td>Gastric-Ca., MALT</td>
<td>Helicobacter pylori</td>
</tr>
<tr>
<td>gastroesophageal reflux Disease</td>
<td>Esophagus-Ca.</td>
<td>Gastric acid</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Hepatocellular Ca.</td>
<td>Hepatitis B und C virus</td>
</tr>
<tr>
<td>Chronic Pancreatitis</td>
<td>Pancreas-Ca.</td>
<td>Alcoholism</td>
</tr>
<tr>
<td>Asbestosis</td>
<td>Mesotheliom, Lung-Ca.</td>
<td>Asbestos</td>
</tr>
<tr>
<td>COPD</td>
<td>Lung-Ca.</td>
<td>tobacco</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>Bladder- and Liver-Ca.</td>
<td>Vermin</td>
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</table>
Gastric Carcinoma
Tumor & Inflammation

Twenty years ago we thought of stomach ulcers as a stress related disease

<table>
<thead>
<tr>
<th>Top 10 most stressful jobs</th>
<th>Top 10 least stressful jobs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner City HS Teacher</td>
<td>Forester</td>
</tr>
<tr>
<td>Police Officer</td>
<td>Bookbinder</td>
</tr>
<tr>
<td>Miner</td>
<td>Telephone line worker</td>
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<tr>
<td>Air traffic controller</td>
<td>Toolmaker</td>
</tr>
<tr>
<td>Medical intern</td>
<td>Millwright</td>
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<tr>
<td>Stockbroker</td>
<td>Repairperson</td>
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<tr>
<td>Journalist</td>
<td>Civil engineer</td>
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<tr>
<td>Customer Service</td>
<td>Therapist</td>
</tr>
<tr>
<td>Secretary</td>
<td>Natural Scientist</td>
</tr>
<tr>
<td>Waiter</td>
<td>Sales Representative</td>
</tr>
</tbody>
</table>

generated by Health Magazine
Treatment of ulcers with antacids...
... and by reducing stress
Helicobacter pylori (*H.p.*) induced gastric cancer and MALT lymphoma

... but not everybody thought that ulcers were stress related but induced by bacteria (1983) was awarded jointly to Barry Marshall and J. Robin Warren 

"for their discovery of the bacterium Helicobacter pylori and its role in gastritis and peptic ulcer disease"
Mode of action of *H. pylori*.

- *H. pylori* helix-shaped, gram-negative, microaerophilic bacterium
- Highly motile due to 4-6 flagella
- *H. pylori* colonize the stomach, burrows into the mucus
- Neutralization of the gastric acid by urease

*H. pylori*: Electron-microscopical photo
Philip Sutton, Immunology and Cell Biology 2001
Epidemiology of *H. pylori*

- Half of the world’s population are infected by *H. p.*
  (Third world approx. 80%, Western countries around 25%)

- Asymptomatic colonization 80%
  → but always detectable gastritis histologically

- approx. 20% will develop gastric and duodenal ulcer

- 1 – 2% lifetime risk of stomach cancer and approx. 1% risk for gastric MALT lymphoma

  → the risk of getting gastric cancer from *H. p.* is as high as getting lung cancer from smoking

  → *H. p.* is detectable in 95% (!) of all MALT lymphoma and

  → *H. p.* eradication with antibiotics induces regression of low-grade MALT lymphomas

  → *H. p.* has been classified as a CARCINOGEN by the WHO
Chronic inflammatory states associated with *H. p.* infection

Urea + H$_2$O $\xrightarrow{\text{urease}}$ CO$_2$ + NH$_3$

Acidic Gastric Juice (pH=2)

Mucus gel layer (pH=4)

Gastric epithelial cells (pH=7)

Protected space

Attracting and activation of immune cells ➔ chronic inflammation
How does *H. p.* damage stomach tissue

50 – 70% of *H. p.* express the **CagA** pathogenecity island

**direct effects**

Gastric epithelial cell damage by:

- proteases
- phospholipases
- ammonia (NH$_3$)
- toxins (VacA)

**indirect effects**

induction of an inflammatory response by *H. p.*

- bacterial peptidoglycan and **CagA** protein is injected into the epithelial cells
- inflammatory cytokine release, recruitment of inflammatory cells (granulocytes, macrophages); activation of EGFR (altered signal transcription)
The Cag pathogenicity island encodes a secretory system that induces a chronic inflammatory response by H. pylori CagA protein. This protein activates inflammatory genes through its interaction with the H. pylori cell membrane, leading to the activation of p50 and p65, which are key components in the inflammatory response.

The diagram illustrates the process, showing the secretion of CagA from the H. pylori bacterium into the extracellular environment, where it interacts with the host cell membrane, leading to the intracellular activation of inflammatory genes.
Host cell Transcriptional Response to *H.p.* CagA

- Reference RNA from **uninfected** gastric epithelial cells
- RNA from *H.p.* **infected** gastric epithelial cells

Which genes are differently regulated between *H.p.* treated and untreated epithelial cells

- Green: RNA downregulated in infected cells
- Yellow: RNA unchanged in infected cells
- Red: RNA upregulated in infected cells
Specific expression profile of epithelial cells of the stomach upon *H.p.* infection

The two most abundant functional classes of induced genes encoded proteins involved in the:

I) **Innate Immun response** (cytokines, chemokines)

II) Regulation of **cell shape and adhesion** (ICAM1, tight junction proteins; claudin)

Colon Carcinoma
• a chronic (auto-) inflammatory bowel disease

• have a 1 % increased risk to develop cancer for every year of disease; that means that patients suffering from colitis for 30 years have a 30% increased risk to develop colorectal cancer

• activation of NFκB plays a dominant role in this cancer
Colitis associated cancer (CAC) mouse model

1. induce mutations
   apply a carcinogen (e.g. azoxymethane; AOM)
   intraperitoneally

2. induce inflammation
   mice are fed with dextran sulfate sodium (DSS)
   which is a toxin for colonic epithelial cells,
   thereby inducing leukocyte infiltration

\[1 + 2 = \text{Tumor}\]
NFκB: a central transcription factor I

Signal

Cancer cell

NFκB complex p50 p65

gene expression

Survival

Inflammatory cell

Gene expression

Help for the tumor cells to survive
NFκB: a central transcription factor II

*Inflammatory cytokines*
TNFα, IL1, IL-6 etc.

*Bacterial constituents*
LPS, LTA, dsRNA, CpG-DNA

NFκB

- **Inflammation**
  (iNOS, Cox2, PLA2, TNFα, IL-1, etc.)

- **Innate Immunity**
  (Defensins, Chemokines, Cytokines, Adhesion molecules)

- **Anti-Apoptosis**
  (cIAP1/2, A1, Bcl-X_L, cFLIP)

+ +
NFκB: a central transcription factor III

IKKβ

NFκB (p50/p65)

Anti-apoptosis

Innate Immunity, Inflammation

pharmacological inhibitors
NFκB as a target for Colon cancer therapy

**Cancer cell**
- p50
- p65
- Survival
  - Bcl-xL
  - GADD 45
  - NOD-2

**Inflammatory cell**
- Normal cells
- p50
- p65
- TNFα
- IL-1
- IL-6

**Growth & Survival factors**

**Tumor progression**

**Activation**

Tumor-derived factors which reprogramme inflammatory cells to promote tumor survival
Colon carcinoma

Colon \xrightarrow{\text{NF}_{\kappa}B} \text{increase of apoptosis thereby inhibition of tumor cell growth}
Hepatocellular Carcinoma
Role for Compensatory Proliferation in Hepatocellular Carcinoma

Hepatocytes

KC (10% of the liver)

+ mutagens

Liver injury

Dead cells

TUMOR INITIATION

Mutation

TUMOR PROMOTION
Role for NFκB in different tumor models

**Colon**
- NFκB
  - inhibition of proliferation in malignant cells
  - let them die
- increase of apoptosis
  - thereby inhibiting of tumor cell growth

**Hepatocytes**
- NFκB
  - induction of proliferation in initiated cells
  - generate space for cell proliferation
- increase of apoptosis
  - but support of tumor cell growth

**Macrophages**
- NFκB
  - inhibition of tumor supportive actions
  - turn off help
- inhibition of tumor cell growth

**Colon carcinoma**
- Hepatocellular carcinoma

Maeda...Karim Cell 121:977 (2005).
Take home message

Inflammation
Innate Immune cells

OFF