Is there a link between inflammation and cancer?

**Seminar Structure:**

I. Introduction: What is the evidence that inflammation may lead to cancer?
II. Gastric cancer: a paradigm of inflammation-driven tumor initiation.
III. Hepatocellular carcinoma, NF-κB and cancer.
IV. The role of immune system in inflammation-driven cancer.

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**Evidence 1:** Infectious agents or chemicals that cause inflammation also cause cancer.

<table>
<thead>
<tr>
<th>Inflammatory condition</th>
<th>Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. Pylori</em> infection</td>
<td>Gastric Cancer</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>Pancreatic Cancer</td>
</tr>
<tr>
<td>Chronic viral hepatitis</td>
<td>Hepatocellular Cancer</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Lung Cancer</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>Bladder Cancer</td>
</tr>
<tr>
<td>Actinic keratosis</td>
<td>Squamous Cell carcinoma</td>
</tr>
</tbody>
</table>

* 15% of all tumours can be attributed to chronic inflammation (1.2 million deaths per year worldwide).
Is there a link between inflammation and cancer?

Evidence 1: Infectious agents or chemicals that cause inflammation also cause cancer.

2. Chronic inflammatory conditions enhance pre-disposition to cancer development (e.g. colitis → colorectal cancer).

3. Long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) reduces cancer risk.

4. Polymorphisms in genes that regulate immune balance (i.e. TNF, IL10, IL1b etc) influence cancer risk.

5. Immunosuppressed individuals display increased risk of cancer development (e.g. AIDS → Kaposi sarcoma)

6. In breast and lung adenocarcinomas, infiltration of tumors with innate-immune cell types, such as macrophages, correlates with unfavourable prognosis.

Helicobacter pylori and inflammation-driven cancer

- 1940: gastric cancer was the second leading cause of cancer in USA
- 1984- present: Epidemiological and animal data support this link.
- Inoculation of 2 humans with H. pylori resulted in chronic gastritis, an early precursor lesion of gastric cancer: restoration with antibiotics!
- 1994: WHO classifies H. pylori as definitive (type I) carcinogen
- 2005: Warren and Marshall are awarded the Nobel prize in Physiology or Medicine

Helicobacter pylori and inflammation-driven cancer

- A bacterium that colonizes the stomach in about 50% of all humans
- Strain differences display different pro-inflammatory capacity
- Infection of the corpus region of the stomach results in widespread inflammation that causes gastric ulcer.
- In general, acid secretion appears protective against gastric cancer: gastric cancer risk is decreased in duodenal ulcer patients (high acid secretion) and increased in gastric ulcer patients (low acid secretion)
Helicobacter pylori, inflammation and cancer: a complex relationship

H. Pylori initial infection:
- recruitment of inflammatory cells
- apoptosis is increased throughout the epithelium (surface cells and cells in proliferative zone)
- increase in proliferation (proliferative zone expands)

H. Pylori persistent infection:
- lesions become metaplastic
- dysplasia and cancer within 2 yrs

What is the evidence that inflammation is really linked to gastric cancer?

- T cell-deficient mice are resistant to epithelial damage or pre-neoplastic changes.
- SNPs in IL1β, IL1R, TNFa, IL10 confer a 27-fold increased risk of gastric cancer.
- Strong Th1 (IFNγ) response confers susceptibility to metaplasia. Th2 confers resistance. Explains the 'African enigma'.
- Inflammation in the stomach mucosa is also a risk factor for a lymphatic neoplasm in the stomach, MALT (mucosa-associated lymphoid tissue) lymphoma.
- Eradication with antibiotics!!

From Helicobacter pylori to cancer: a model of carcinogenesis

Lethally irradiated Mouse → Mouse lymphoid system → Regenerated

Bone marrow from C57BL6 or β-gal expressing mouse
**Question:** Is there a role for BMDC (stem cells) in inflammation-driven gastric cancer?

**Rationale:**
1. Y chromosome is found in the peripheral tissue of female patients having undergone transplantation with bone marrow derived from male donors (up to 7% of intestinal/liver cells) after graft-vs-host disease.
2. Bone marrow-derived epithelial cells have been identified in the lung, gastrointestinal tract, and skin of mice 11 months after transplantation of a single purified hematopoietic BMD stem cell.
3. Indications about the existence of 'cancer stem cells'.

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**Question:** Is there a role for BMDC (stem cells) in inflammation-driven gastric cancer?

**Rationale (cont.):**
- A tumor can be viewed as an aberrant but heterogeneous organ in which only a small subset of cancer cells—'cancer stem cells'—are capable of extensive proliferation and metastatic spread.
- These 'cancer stem cells' give rise to tumor cells of varying proliferative potential and with heterogeneous phenotypes similar to the differentiation and maturation of normal cells within an organ.
- This is a theory but tantalizing relevant observations exist:
  (a) only 0.001% of cancer cells tested have the ability to form colonies in soft agar— a trait indicative of transformation.
  (b) cancer therapy may initially shrink tumor bulk but it rarely eliminates the tumor completely and tumor mass is rapidly reestablished after drug withdrawal. One possible explanation for this is that cancer stem cells—like normal stem cells—are relatively chemotherapy resistant because they share the same protective mechanisms.
From *Helicobacter pylori* to cancer: a model of carcinogenesis

- Lethally irradiated Mouse
- Bone marrow from C57BL6 or b-gal expressing mouse
- Mouse lymphoid system Re-generated
- Administration of Helicobacter Felis

**Conclusion:** BMDC are recruited and engrafted in gastric mucosa.

Gastric cancer within a year. All tumor cells were gal-positive.

*Houghton et al. Science, 2004*
From *Helicobacter pylori* to cancer: a model of carcinogenesis

Lethally irradiated Mouse

Bone marrow from C57BL/6 or b-gal expressing mouse

Mouse lymphoid system

Regenerated

Administration of Helicobacter Felis

Acute injury

Acetic acid

Recovered. No blue cells.

Chronic injury

Repopulation with BMDC

Gastric cancer; Tumor cells are BMDC-derived.

Houghton et al. Science, 2004

NF-κB: a major link between inflammation and cancer

- a family of transcription factors (p65/RelA, RelB, cRel, p52 NF-κB2, p50 NF-κB1)
- Rel members function as homo- or heterodimers.
- Inhibition of NF-κB ameliorates inflammation-driven gastric cancer and colitis-related colorectal cancer. Therefore inhibition of NF-κB cures cancer?
The NF-κB pathway suppresses carcinogenesis!!

Maeda et al., Cell 121: 977, 2005
NF-κB links chronic inflammation and hepatocellular cancer: The complexity deepens.

- Loss of IKKβ in hepatocytes increases hepatocellular death and compensatory proliferation.
- Mediated in part by TNFα.
- Deletion of IKKβ in both hepatocytes and haemopoietic cells reduces susceptibility to chemical-induced carcinogenesis.

(Maeda et al., Cell 121:977, 2005)

NF-κB controls production of hepatomitogens & pro-inflammatory mediators by Kupffer cells.

- Depletion of IKKβ from Kupffer cells suppresses compensatory proliferation of hepatocytes and carcinogenesis.
NF-κB links chronic inflammation and hepatocellular cancer: a proposed model.

Roles for inflammatory mediators that affect either the target tissue directly or the recruitment of BMD stem cells.

NF-κB integrates apoptotic and proliferative signals.

Suppression of NF-κB in liver cells enhances HCC.

But, suppression of NF-κB in gastric cells or enterocytes attenuates tumourigenesis.

NF-κB may have different roles in different tissues acting either as a tumour promoter or a tumor suppressor.
The role of the immune system in inflammation-driven cancer

The facts:
1. In cancers, an abundance of infiltrating lymphocytes correlates with favourable prognosis.
2. In cancers, an abundance of infiltrating innate immune cells (macrophages, mast cells, neutrophils) correlates with angiogenesis and poor prognosis.
3. Tumor immunotherapy has limited success: for well established tumors, activation of endogenous T cell responses is insufficient to induce tumor regression.
4. Mouse models in which immune cells have been depleted display altered cancer progression. Also, immunosuppressed patients (AIDS, transplant) display enhanced risk of cancer.
5. B lymphocytes are positive regulators of skin carcinogenesis in mouse models.
Inflammation & Cancer: a summary of complex relationships

Inflammatory signals: minimizing the effort, maximizing the result.
Inflammatory signals: minimizing the effort, maximizing the result.

Suggested reading


Thank you!