A. Eliopoulos

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.

A. Eliopoulos

Is there a link between inflammation and cancer ?

Inflammation & Cancer: a century of debate
'lymphoreticular infiltrate' in sites of chronic inflammation (Virchow, 1863)
'*the wound that will not heal*' (Dvorak, *NEJM*, 1986)

The topic :
• Acute injury and inflammation associated with healing are usually self-limited.

• Chronic injury or inflammation leads to proliferation and pre-disposes to malignant conversion.

Is there a link between inflammation and cancer ?

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

Inflammatory condition	Malignancy
H. Pylori infection	Gastric Cancer
Chronic pancreatitis	Pancreatic Cancer
Chronic viral hepatitis	Hepatocellular Cancer
Inflammatory bowel disease	Colorectal cancer
Cigarette smoking	Lung Cancer
Schistosomiasis	Bladder Cancer
Actinic keratosis	Squamous Cell carcinoma

* 15% of all tumours can be attributed to chronic inflammation (1.2 million deaths per year world-wide).

Is there a link between inflammation and cancer ?

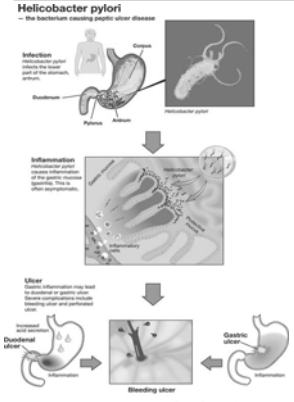
Evidence 1: Infectious agents or chemicals that cause inflammation also cause cancer.

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
- 1982: Warren and Marshall isolate *H. pylori* from human gastric cancer biopsies.
- 1983: causal relationship between *H. pylori* and gastric cancer proposed.
- 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)

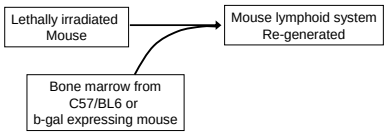
H. Pylori persistent infection:

- lesions become metaplastic
- dysplasia and cancer within 2 yrs

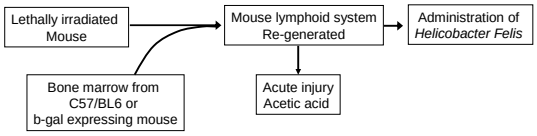
What is the evidence that inflammation is really linked to gastric cancer?

- 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



From *Helicobacter pylori* to cancer: a model of carcinogenesis



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'.

From *Helicobacter pylori* to cancer: a role for stem cells?

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

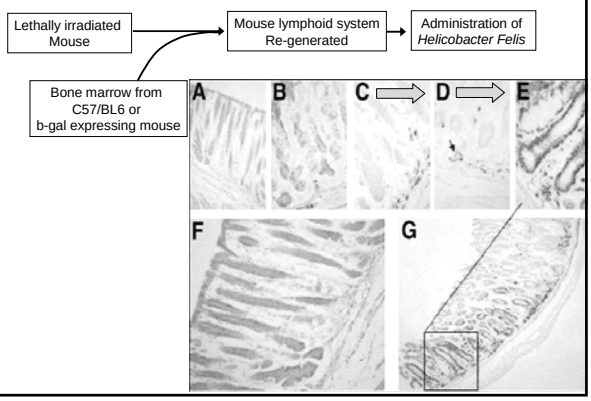
Rationale (cont.):

- 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.

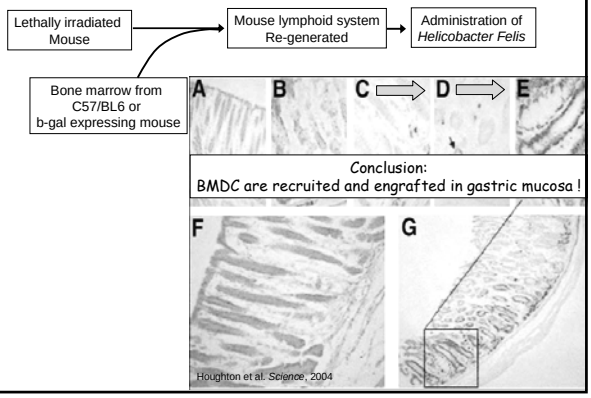
- These "cancer stem cells" give rise to tumor cells of varying proliferative potential and with heterogenous phenotypes similar to the differentiation and maturation of normal cells within an organ.

- 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.

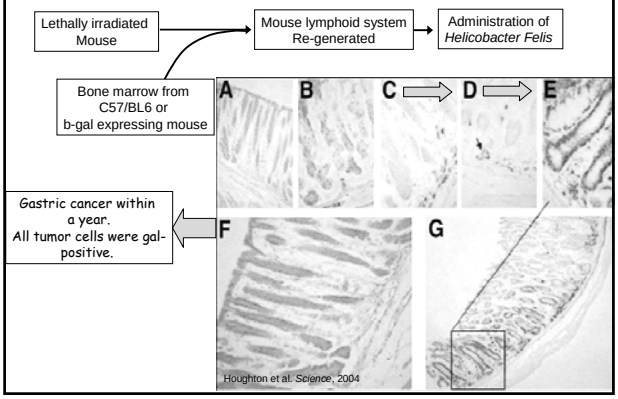
From *Helicobacter pylori* to cancer: a model of carcinogenesis



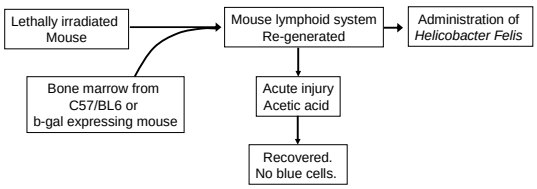
From *Helicobacter pylori* to cancer: a model of carcinogenesis



From *Helicobacter pylori* to cancer: a model of carcinogenesis

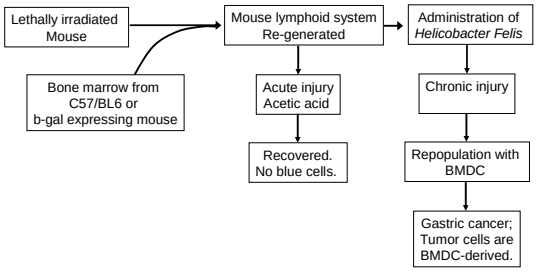


From *Helicobacter pylori* to cancer: a model of carcinogenesis



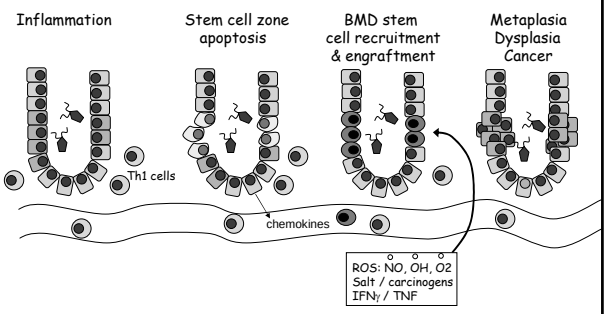
Houghton et al. Science, 2004

From *Helicobacter pylori* to cancer: a model of carcinogenesis



Houghton et al. Science. 2004

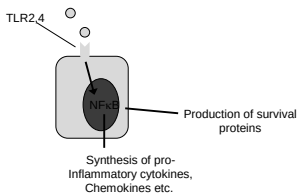
From *Helicobacter pylori* to cancer: a model of carcinogenesis



Multistage:
Inflammation ⇒ chronic inflammation ⇒ tissue injury & apoptosis ⇒ BMD stem cell differentiation failure & transformation ⇒ progression to cancer

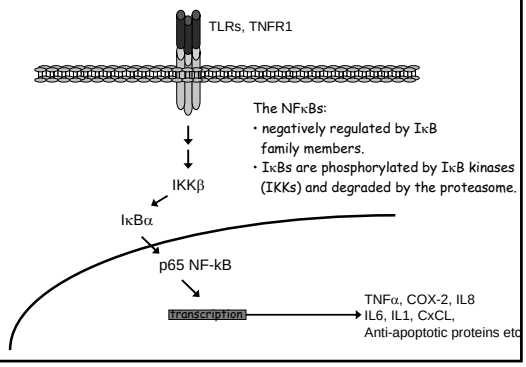
Houghton et al. Science. 2004

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-kB ameliorates inflammation-driven gastric cancer and colitis-related colorectal cancer. *Therefore inhibition of NF-κB cures cancer ?*

NF-κB signaling

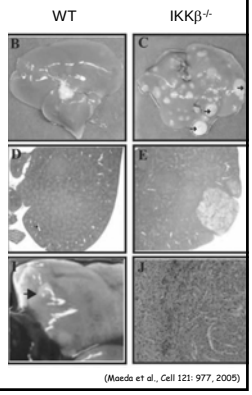


NF-κB links chronic inflammation and hepatocellular cancer: *The complexity deepens.*

•

• HCC risk factors: diet (i.e. aflatoxin B1)
viruses (HBV, HBC)
environmental pollutants
cirrhosis

• *Role for NF-κB ?*



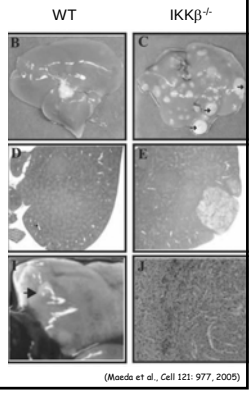
(Maeda et al., Cell 121: 977, 2005)

NF-κB links chronic inflammation and hepatocellular cancer: *The complexity deepens.*

•

• HCC risk factors: diet (i.e. aflatoxin B1)
viruses (HBV, HBC)
environmental pollutants
cirrhosis

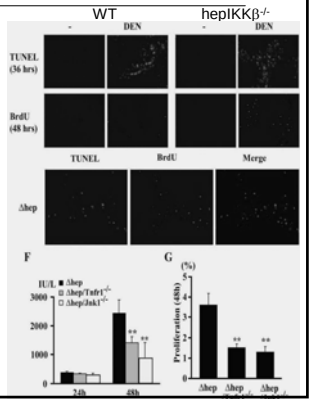
• *Role for NF-κB ?*
IKKβΔhep KO mice are highly susceptible to carcinogen-induced HCC; therefore:
the NF-κB pathway suppresses carcinogenesis !!



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

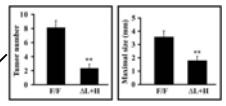
NF-κB links chronic inflammation and hepatocellular cancer: *The complexity deepens.*

- Loss of IKKβ in hepatocytes increases hepatocellular death and compensatory proliferation.
- Mediated in part by TNFα.



NF-κB links chronic inflammation and hepatocellular cancer: *The complexity deepens.*

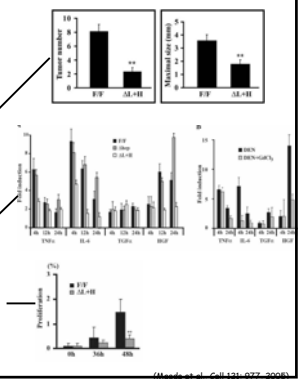
- Loss of IKKβ in hepatocytes increases hepatocellular death and compensatory proliferation.
- Mediated in part by TNFα.
- deletion of IKKβ in both hepatocytes and haemopoietic cells reduces susceptibility to chemical-induced carcinogenesis.



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

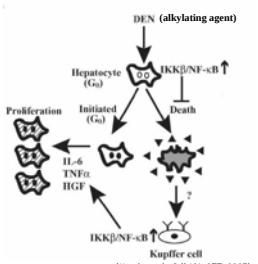
NF-κB links chronic inflammation and hepatocellular cancer: *The complexity deepens.*

- 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.
- Role for mitogens produced by Kupffer cells ?
  - ✓ NF-κB controls production of hepatomitogens & pro-inflammatory mediators by Kuppfer cells.
  - ✓ Depletion of IKKβ from Kuppfer cells suppresses compensatory proliferation of hepatocytes and carcinogenesis.



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

NF-κB links chronic inflammation and hepatocellular cancer: *a proposed model.*



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

Inflammation and cancer: a dualistic view

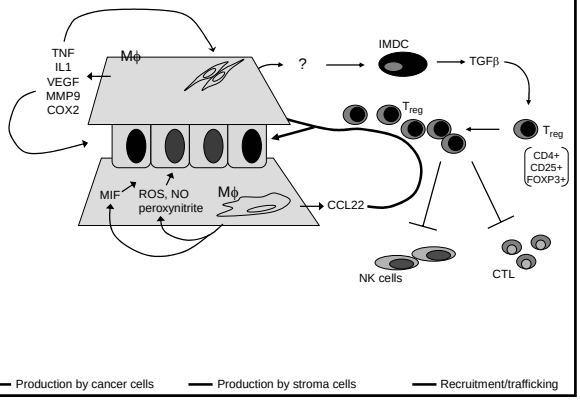
- In both gastric cancer and HCC, more apoptosis potentiates rather than attenuates carcinogenesis.
  Critical for tumour promotion is compensatory proliferation in tissues with high regenerative capacity.
- Role for inflammatory mediators that affect either the target tissue directly or the recruitment 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 as a tumor suppressor.

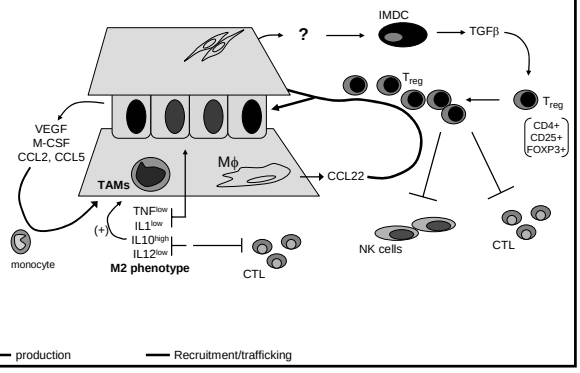
The role of the immune system in inflammation-driven cancer

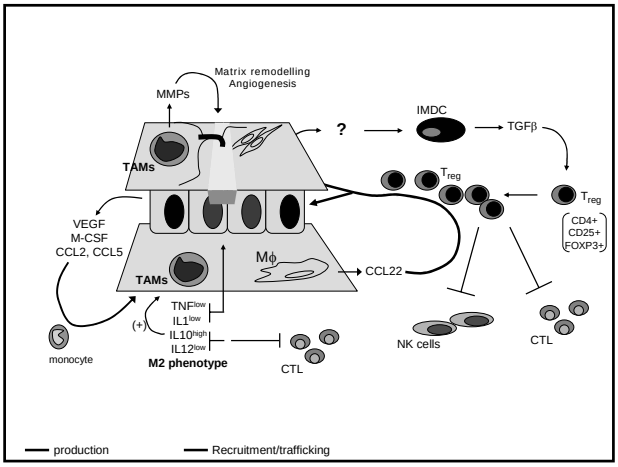
The facts:

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.

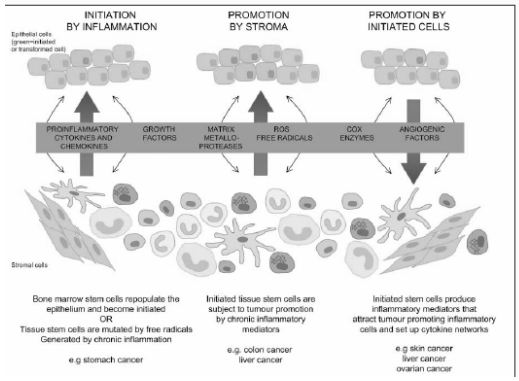
The role of the immune system in inflammation-driven cancer



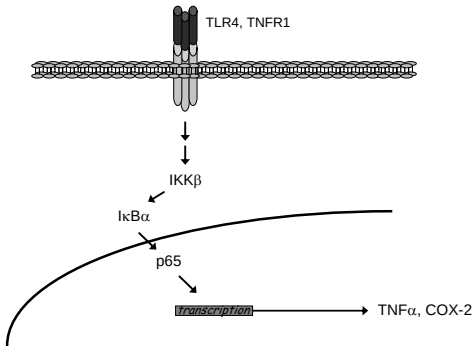




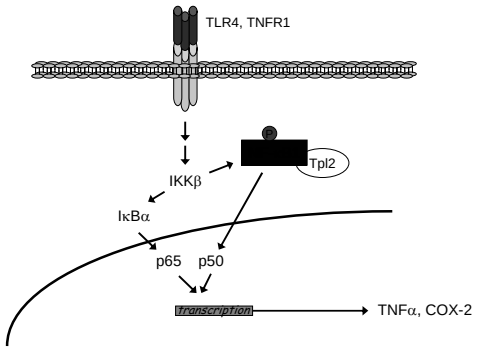
Inflammation & Cancer: a summary of complex relationships



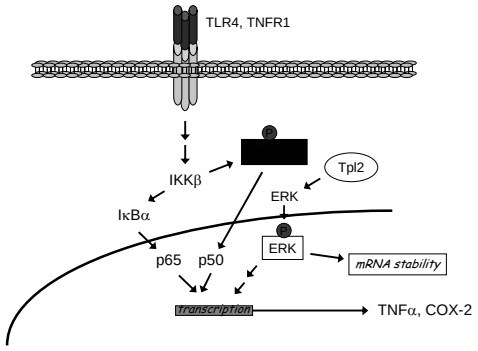
Inflammatory signals: minimizing the effort, maximizing the result.



Inflammatory signals: minimizing the effort, maximizing the result.



Inflammatory signals: minimizing the effort, maximizing the result.



Suggested reading

1. LM. Coussens & Z. Werb. Inflammation & cancer. *Nature* 420: 860-865, 2002.

2. J-M. Houghton et al. Gastric Cancer Originating from Bone Marrow–Derived Cells. *Science* 306:1568-1571, 2004.

3. J-M. Houghton and T. Wang. *Helicobacter pylori* and Gastric Cancer: A New Paradigm for Inflammation-Associated Epithelial Cancers. *Gastroenterology* 128: 1567-1578, 2005.

4. S. Maeda, et al. IKK couples hepatocyte death to cytokine-driven compensatory proliferation that promotes chemical hepato-carcinogenesis. *Cell*, 121: 977–990, 2005.

5. K. De Visser et al. Paradoxical roles of the immune system during cancer development. *Nature Rev. Cancer*, 6: 24-37, 2006.

Thank you!