Tumor and Inflammation - two Sides of the Coin

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Tumor & Inflammation

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Cancer, infection and inflammation

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

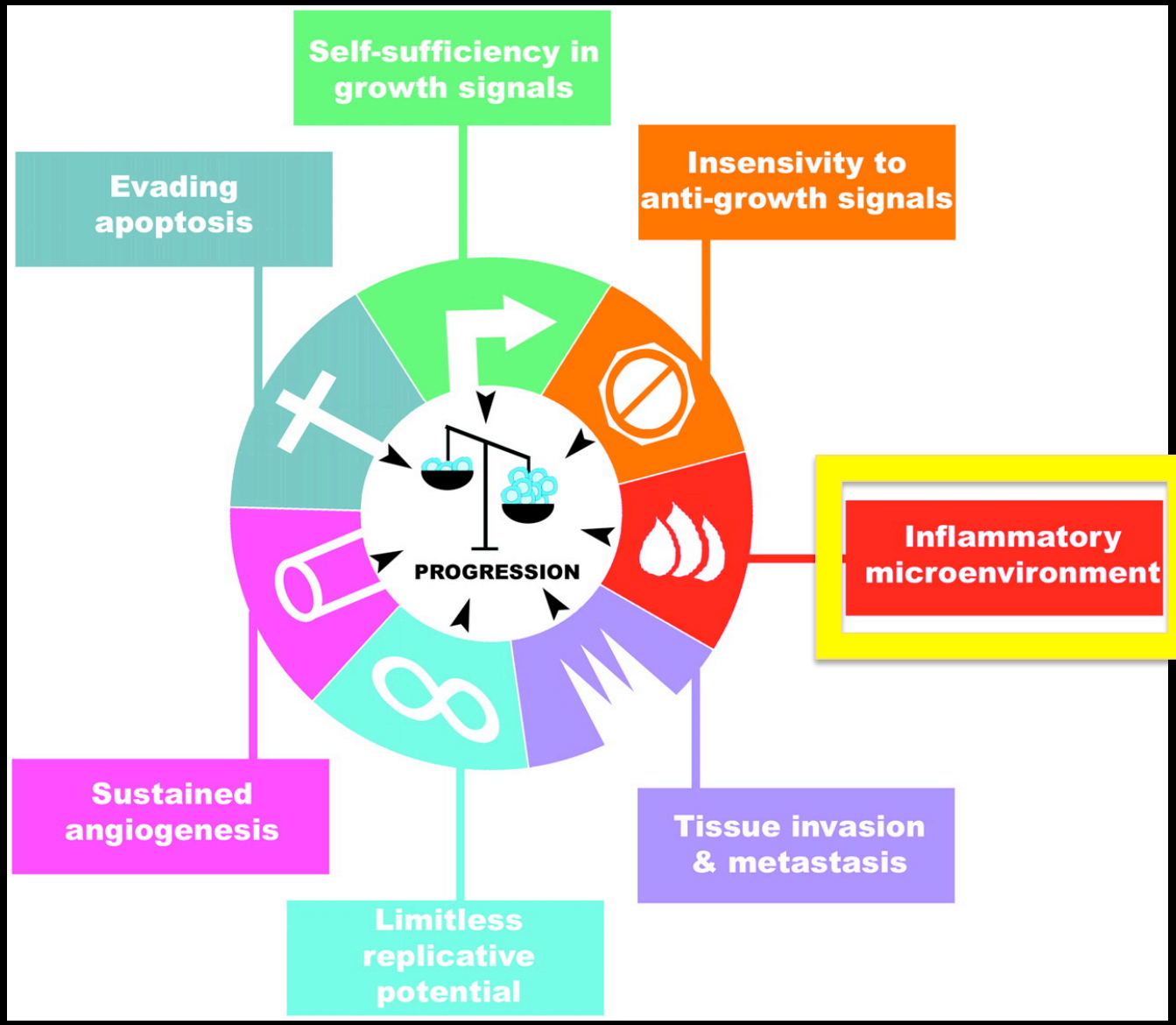
→ diseases due to defects in individual cells of the body

→ **all diseases (cancer) start from inflammation**

Robert Koch: funding father of modern bacteriology

→ **all diseases (cancer) start from infections**

The seven hallmarks of cancer



Colotta et al, *Carcinogenesis* **30**:1073 (2009)

Cellular composition of tumors

non malignant cells
tumor stromal cells

- fibroblasts
- endothelial cells
- blood/lymphatic vessels
- immune-competent cells

→ macrophages, lymphocytes

malignant cells

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

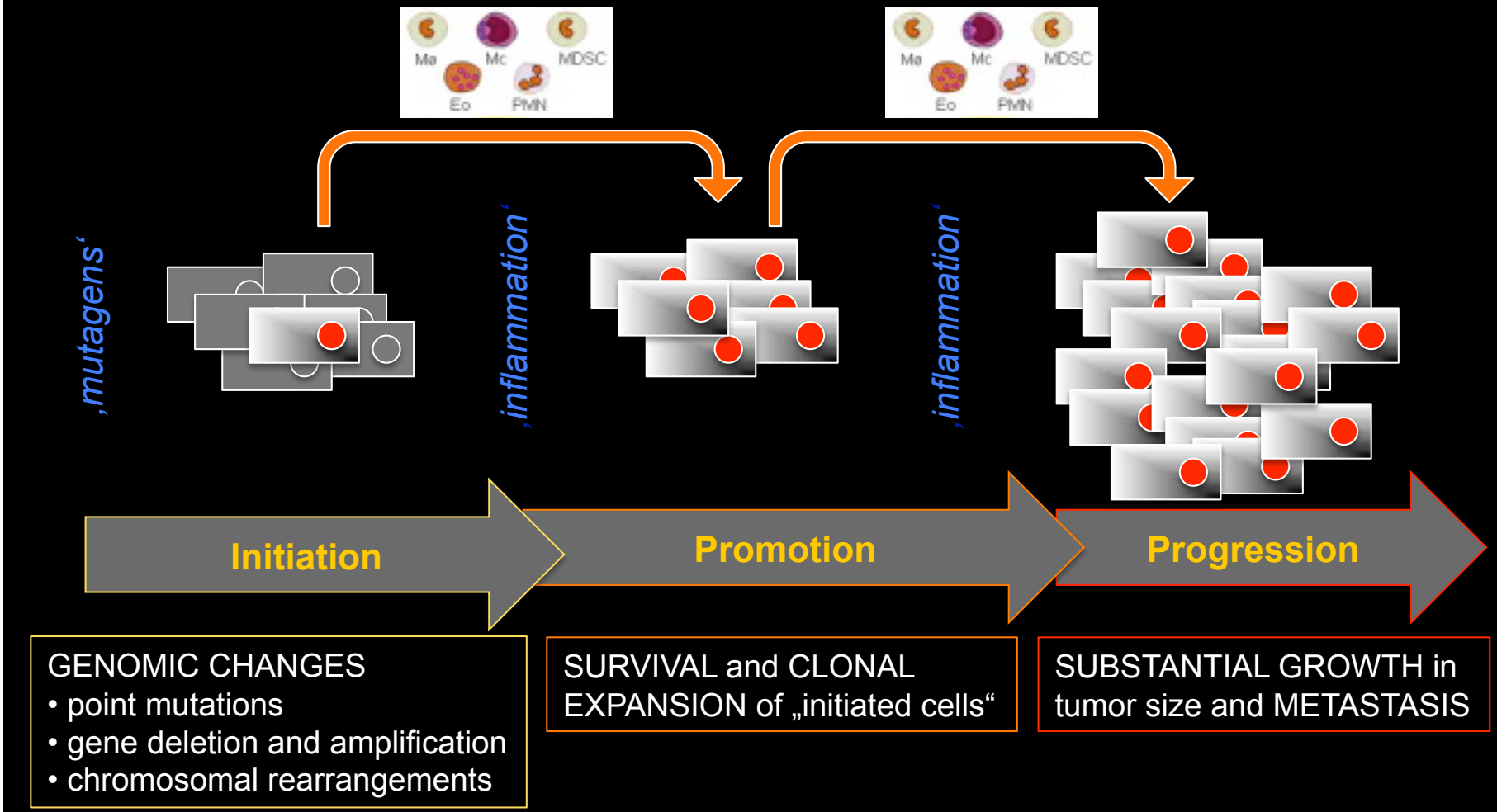
inflammation

Cancer

Inflammation can cause Cancer

Cancer can cause Inflammation

Cancer Development steps



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

SURVIVAL and CLONAL EXPANSION of „initiated cells“

SUBSTANTIAL GROWTH in tumor size and METASTASIS

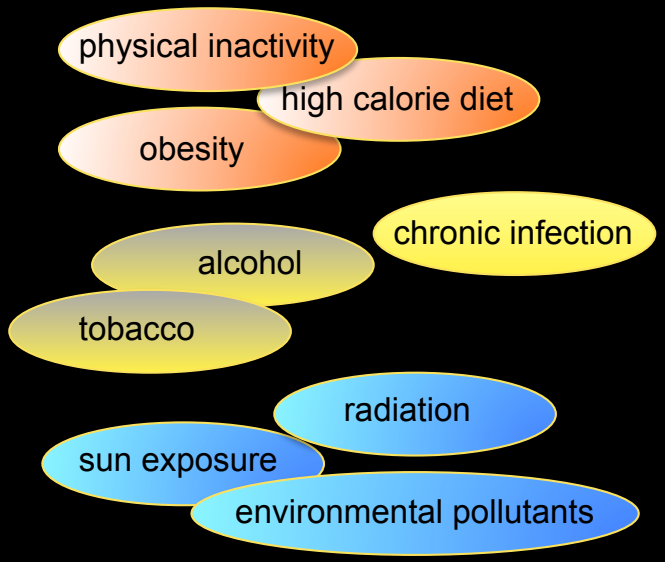
Role for inflammation in Cancer

- 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 -



chronic Inflammation

activation of: NFκB, AP-1, STAT3

Chronic Inflammation: predisposition for tumor development

Clinical Evidence (some examples)

Disease	associated tumors	Etiology
Colitis ulcerosa, M. Crohn	Colon-Ca.	Autoimmune Disease
Chronic Gastritis	Gastric-Ca., MALT	Helicobacter pylori
gastroesophageal reflux Disease	Esophagus-Ca.	Gastric acid
Hepatitis	Hepatocellular Ca.	Hepatitis B und C virus
Chronic Pancreatitis	Pancreas-Ca.	Alcoholism
Asbestosis	Mesotheliom, Lung-Ca.	Asbestos
COPD	Lung-Ca.	tobacco
Schistosomiasis	Bladder- and Liver-Ca.	Vermin

Gastric Carcinoma

Stomach ulcer and stress

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

Top 10 most stressful jobs	Top 10 least stressful jobs
Inner City HS Teacher	Forester
Police Officer	Bookbinder
Miner	Telephone line worker
Air traffic controller	Toolmaker
Medical intern	Millwright
Stockbrocker	Repairperson
Journalist	Civil engineer
Customer Service	Therapist
Secretary	Natural Scientist
Waiter	Sales Representative

according to Health Magazine

Treatment of ulcers with antacids...

... and by reducing stress

Helicobacter pylori (*H.p.*) induced gastric cancer and MALT lymphoma

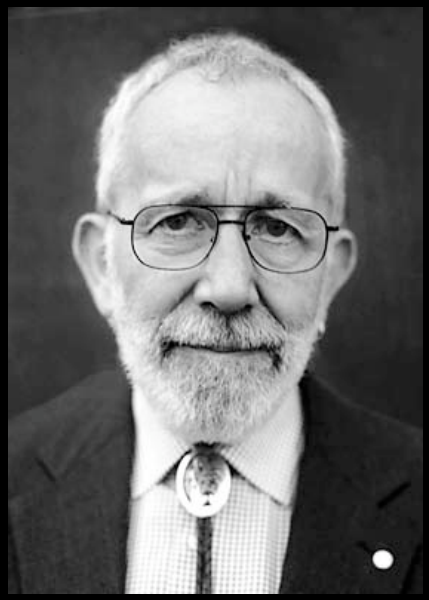
The Nobel Prize in Physiology or Medicine 2005

... but not everybody thought that ulcers were stress related but induced by bacteria (1983)

was awarded jointly to
Barry Marshall and
J. Robin Warren

Barry J. Marshall

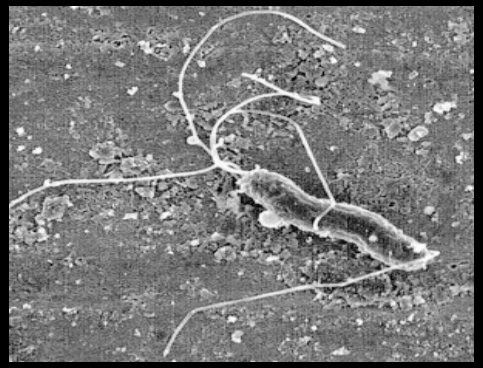
"for their discovery of the bacterium Helicobacter pylori and its role in gastritis and peptic ulcer disease“



J. Robin Warren

Mode of action of *H.p.*

- *H.p.* helix-shaped, gram-negative, microaerophilic bacterium
- highly motile due to 4-6 flagella
- *H.p.* 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%)

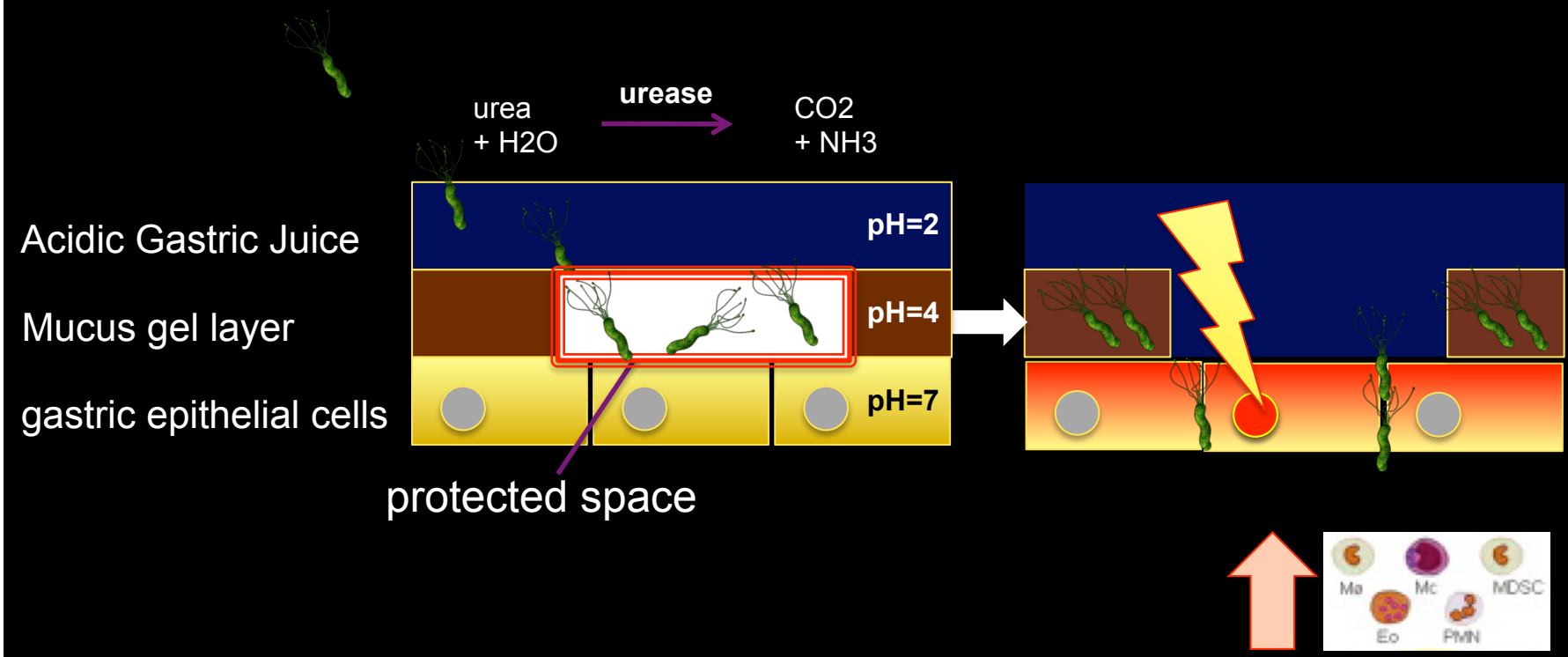
- Asymptomatic colonization 80%
  → but always detectabel gastritis histologically

- 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



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

indirect effects

Gastric epithelial cell damage by:

- **proteases**
- **phospholipases**
- **ammonia (NH_3)**
- **toxins (VacA)**

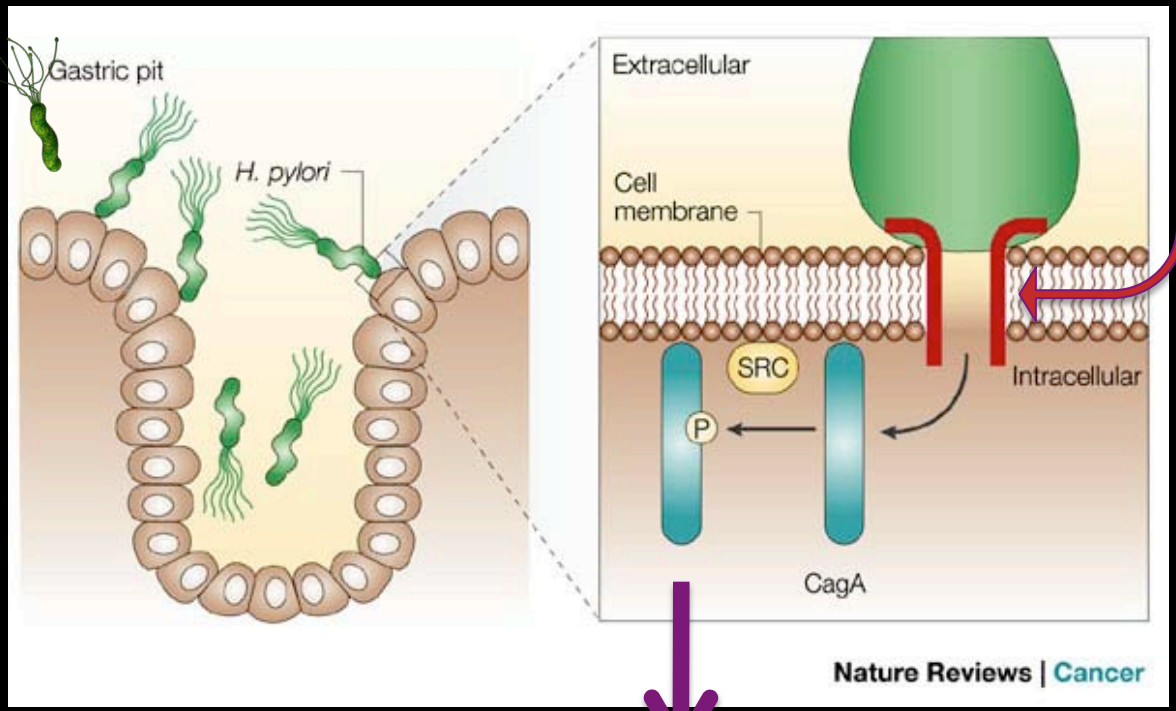
induction of an inflammatory response by *H.p.*

- **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)**

Induction of a chronic inflammatory response by *H.p.* CagA protein

The Cag pathogenicity island encodes a secretory system



p50 p65 → *activation of inflammatory genes*

Host cell Transcriptional Response to *H.p.* CagA

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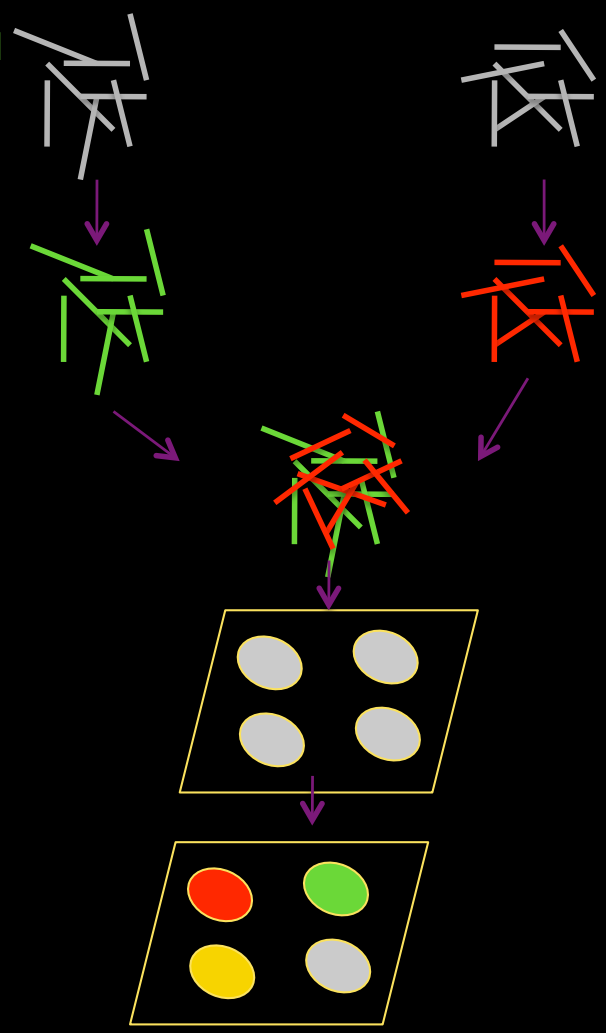
Reference RNA from **uninfected** gastric epithelial cells

RNA from *H.p.* **infected** gastric epithelial cells

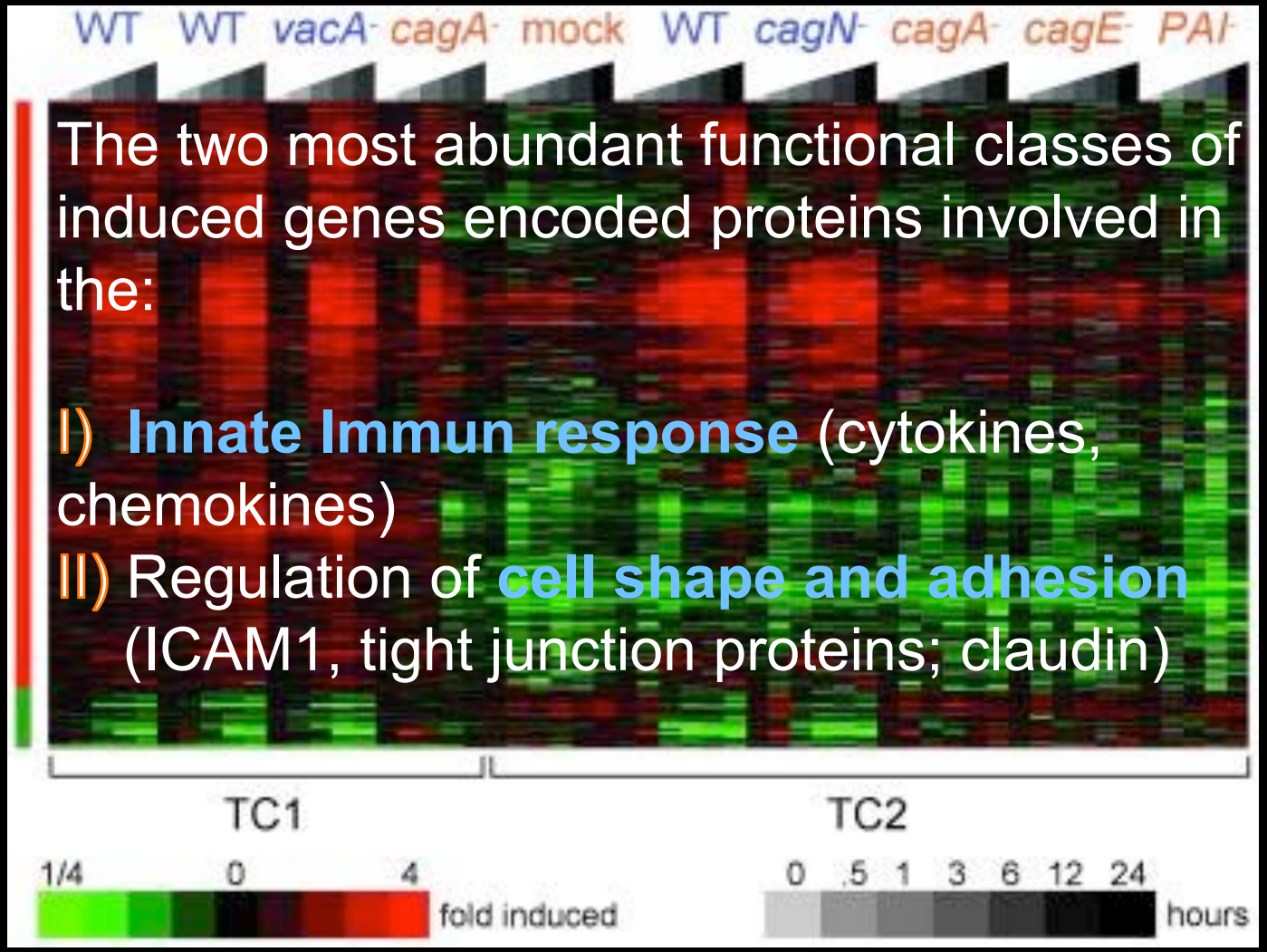


Which genes are differently regulated between *H.p.* treated and untreated epithelial cells

- RNA downregulated in infected cells
- RNA unchanged in infected cells
- RNA upregulated in infected cells

Nachmittag der Wissenschaft January 14, 2011

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)

Guillemin et al (2002) PNAS *USA* 99(23): 15136–15141.

Colon Carcinoma

Colitis associated Colorectal cancer

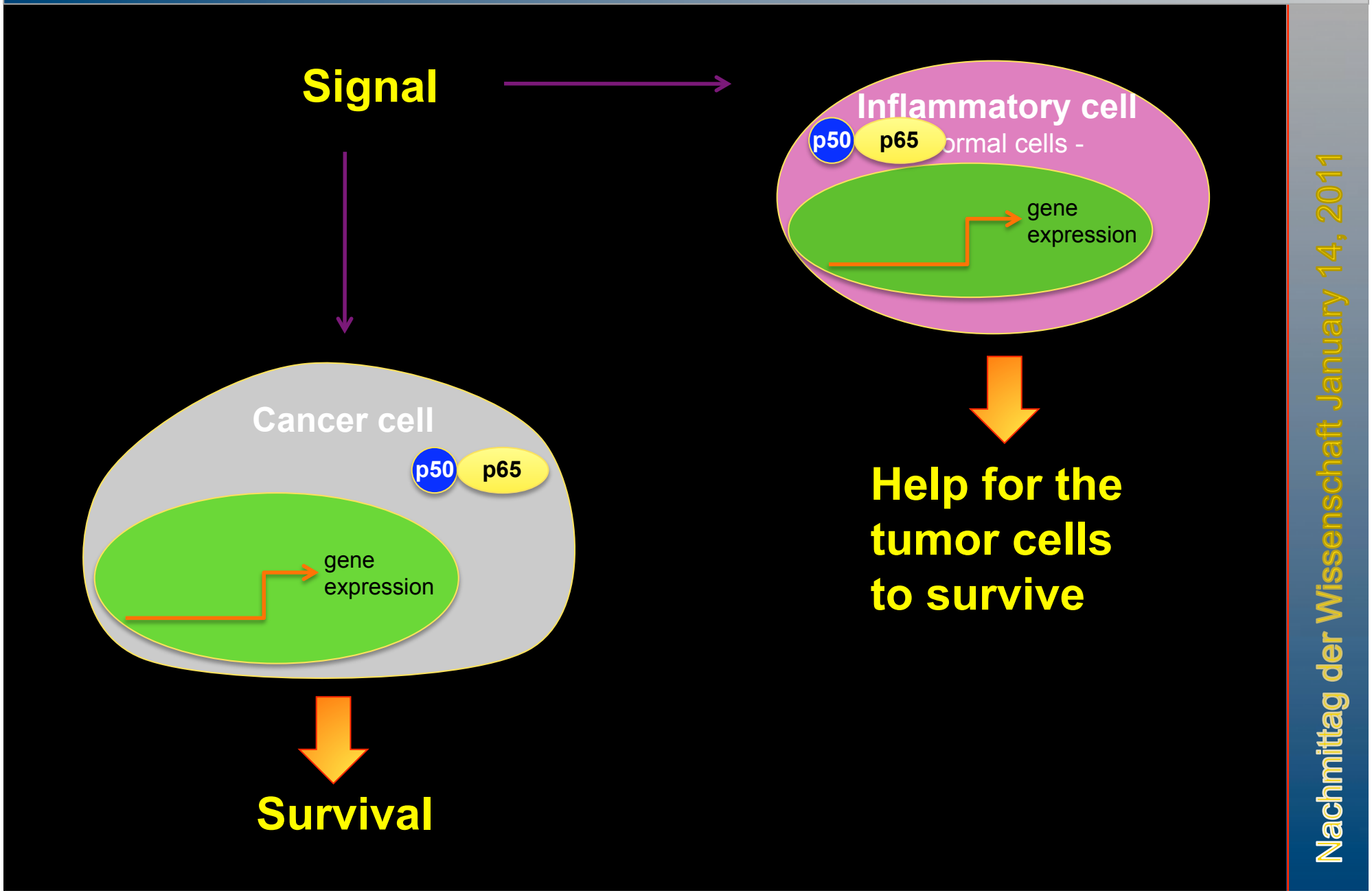
- a chronic (auto-) inflammatory bowel disease
- have a 1 % increased risk to develop cancer for every year of disease; that means that patients suffering from colitis for 30 years have a 30% increased risk to develop colorectal cancer
- activation of NFκB plays a dominant role in this cancer

Colitis associated cancer (CAC) mouse model

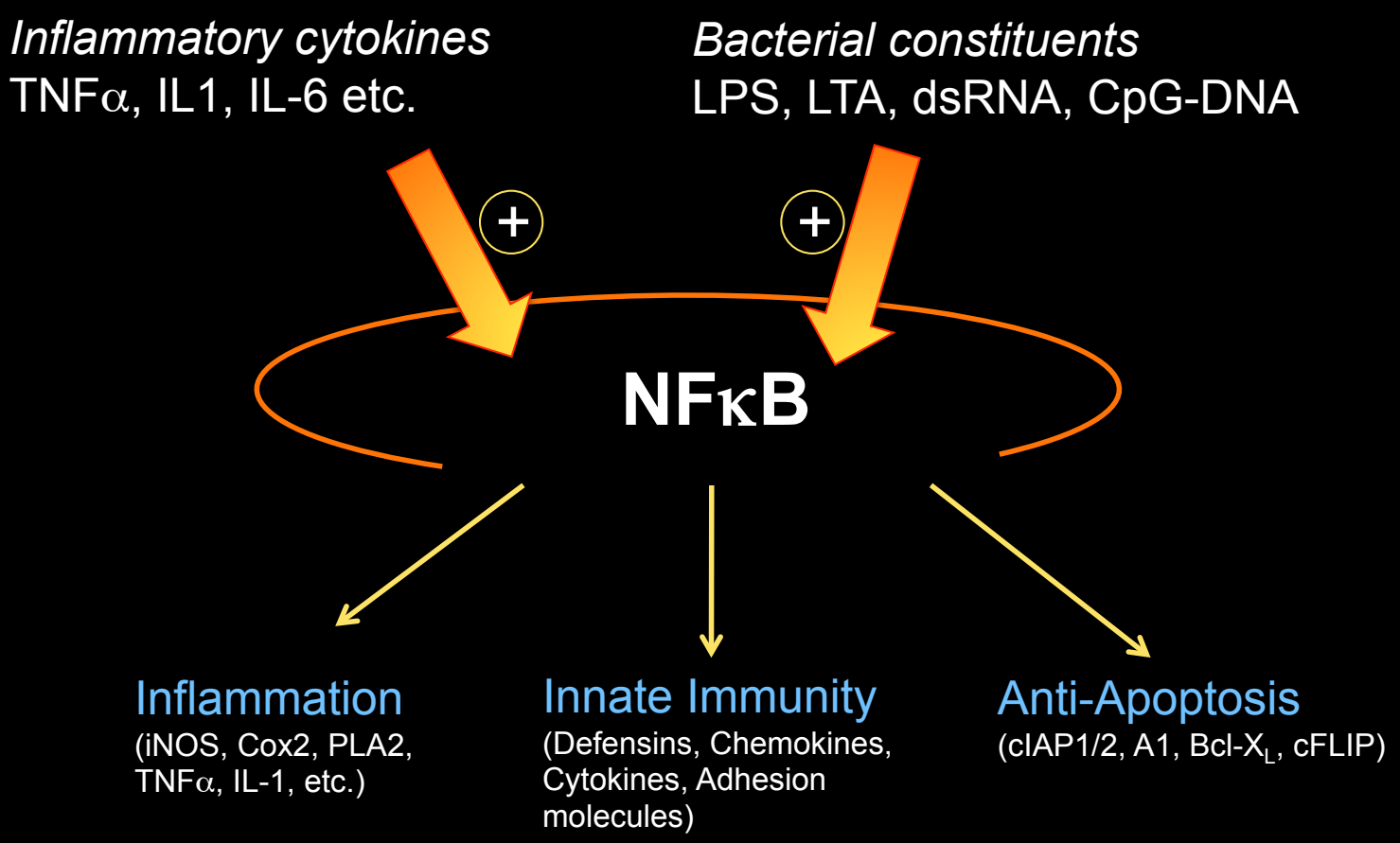
1. induce mutations — apply a carcinogen (e.g. azoxymethane; AOM) intraperitoneally

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

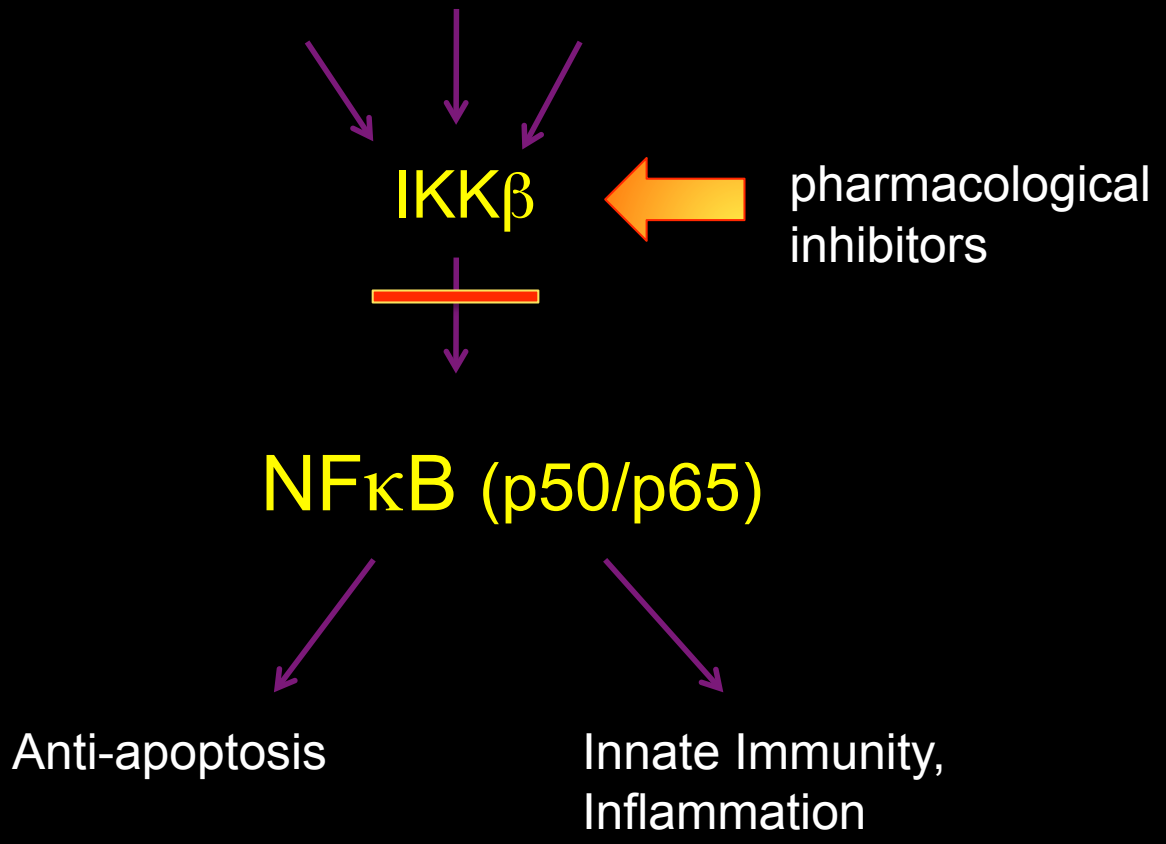
NFκB: a central transcription factor I



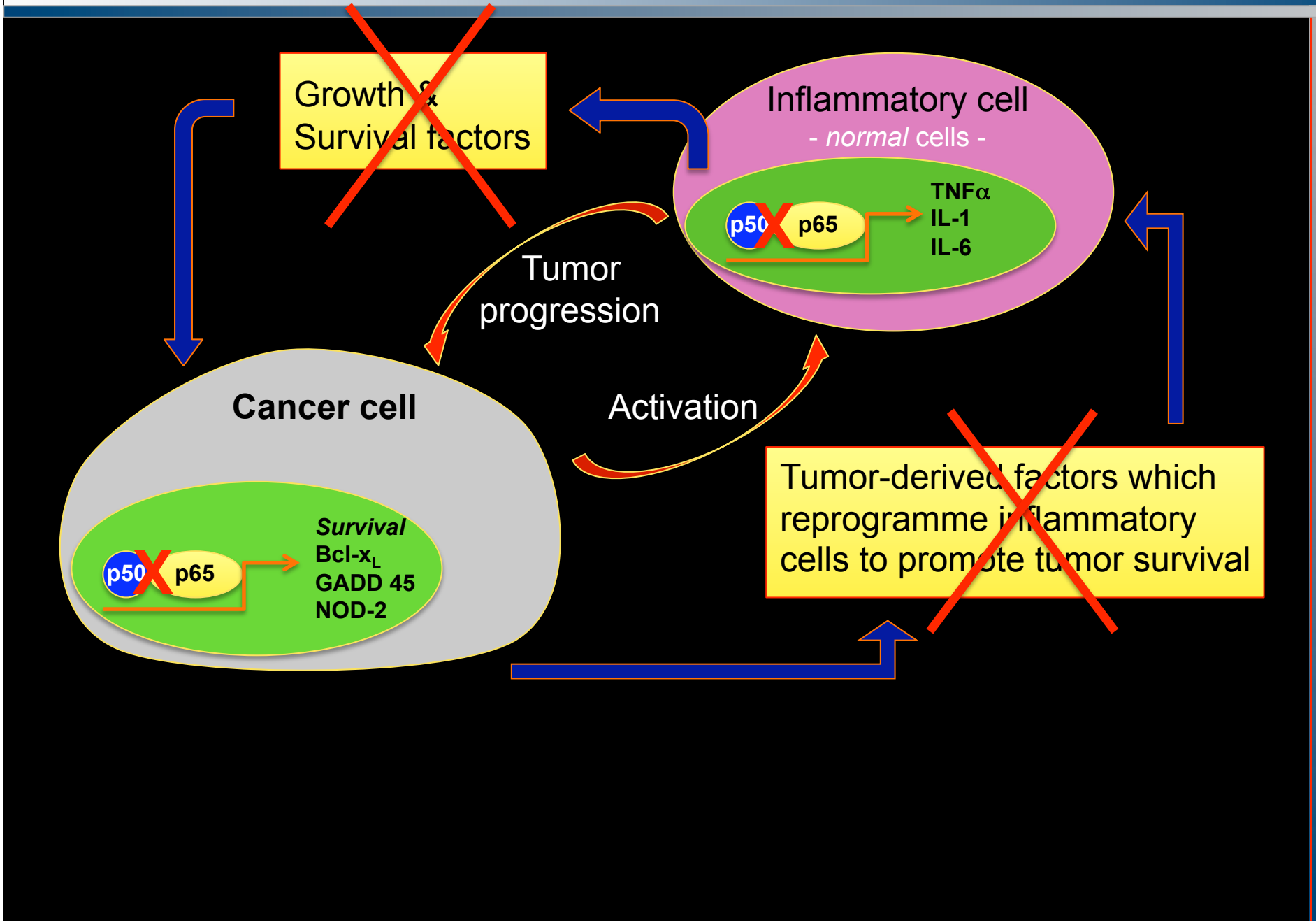
NFκB: a central transcription factor II



NFκB: a central transcription factor III



NFκB as a taget for Colon cancer therapy

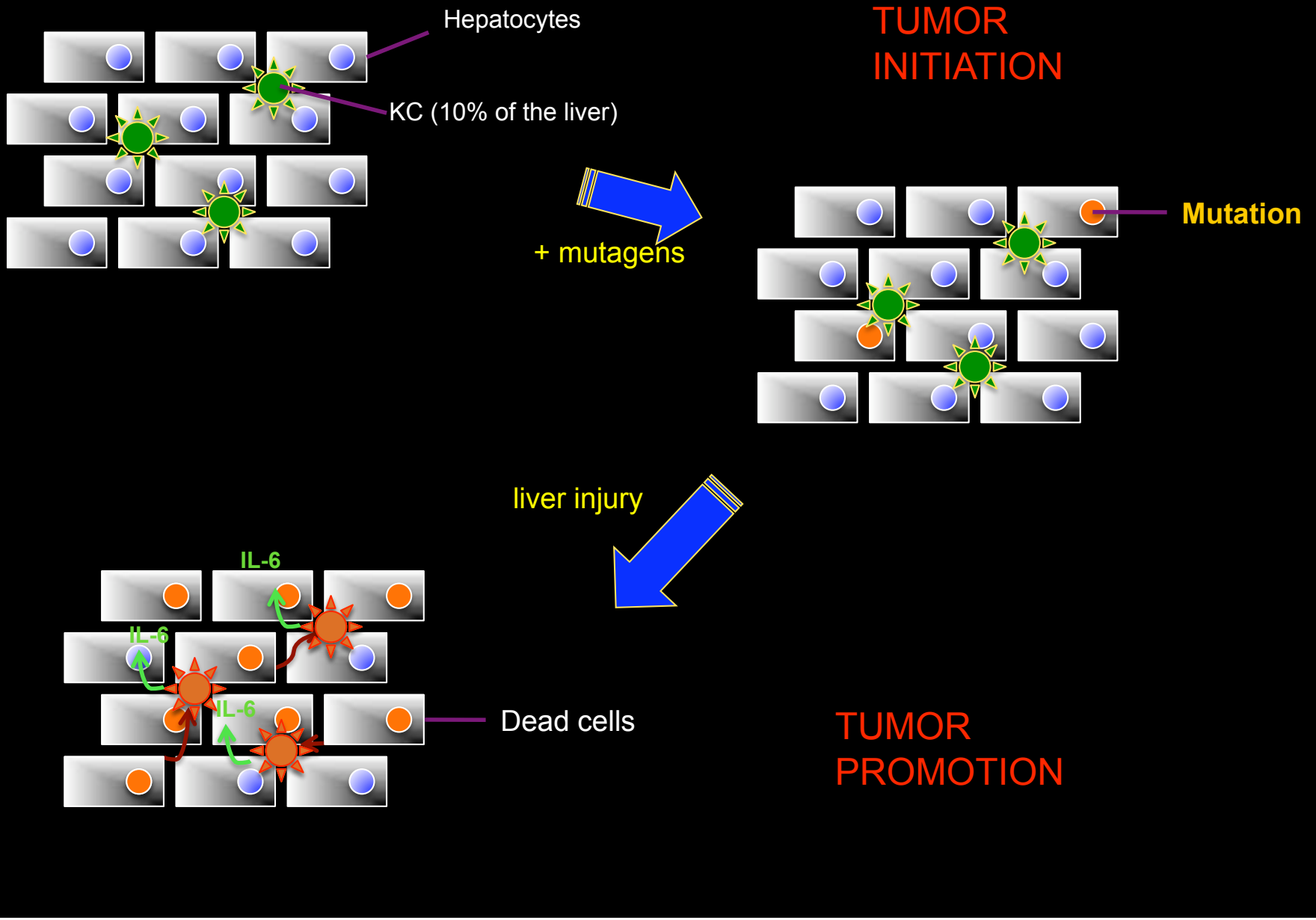


Colon carcinoma

Colon → NFκB → increase of apoptosis
thereby
inhibition of tumor cell growth

Hepatocellular Carcinoma

Role for Compensatory Proliferation in Hepatocellular Carcinoma



Role for NFκB in different tumor models

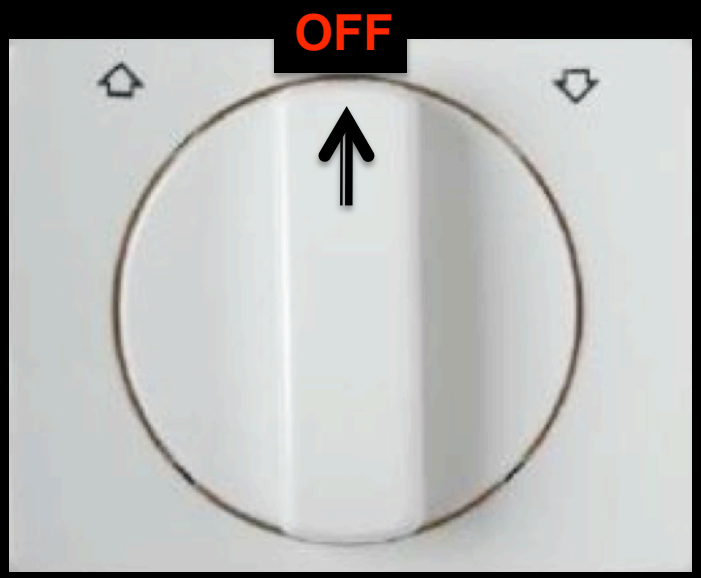
Colon	NFκB → inhibition of proliferation in malignant cells → let them die	increase of apoptosis thereby inhibiting of tumor cell growth	Colon carcinoma
Hepatocytes	NFκB → induction of proliferation in initiated cells → generate space for cell proliferation	increase of apoptosis but support of tumor cell growth	Hepatocellular carcinoma
Macrophages	NFκB → inhibition of tumor supportive actions → turn off help	inhibition of tumor cell growth	in both tumor models

Maeda...Karin Cell **121**:977 (2005).
Karin & Greten Nat Rev Immunol **5**:749 (2005).

Take home message

Inflammation

Innate Immune cells

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Thank you for Your attention