Inflammation and Tumor Development

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Disclosures

- None

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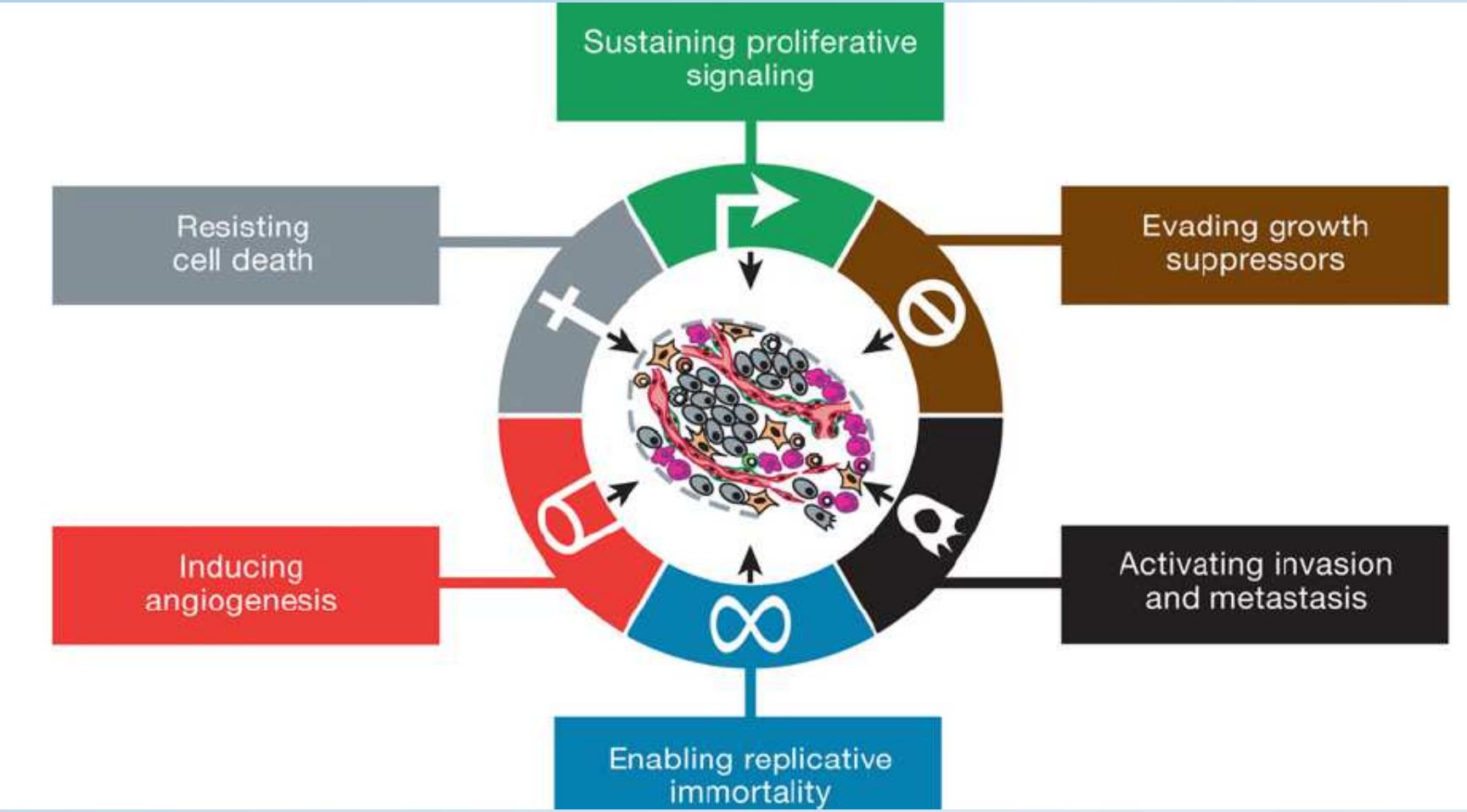
Objectives

- Understand the broad role inflammation plays in tumor development
- Appreciate the interaction of intrinsic and extrinsic factors in cancer growth
- Apply knowledge of immune players and tumor evolution to understanding clinical cancer prevention and treatment strategies

Key Concepts

- Malignant cells are often a minor part of tumors
- Cancer cells actively recruit stromal components to support growth
- Most cancers develop in the context of an “ineffective” chronic inflammatory reaction
- Inflammation can function as both a promoter and an initiator of tumor development

What is Cancer?



Cell *144*, March 4, 2011

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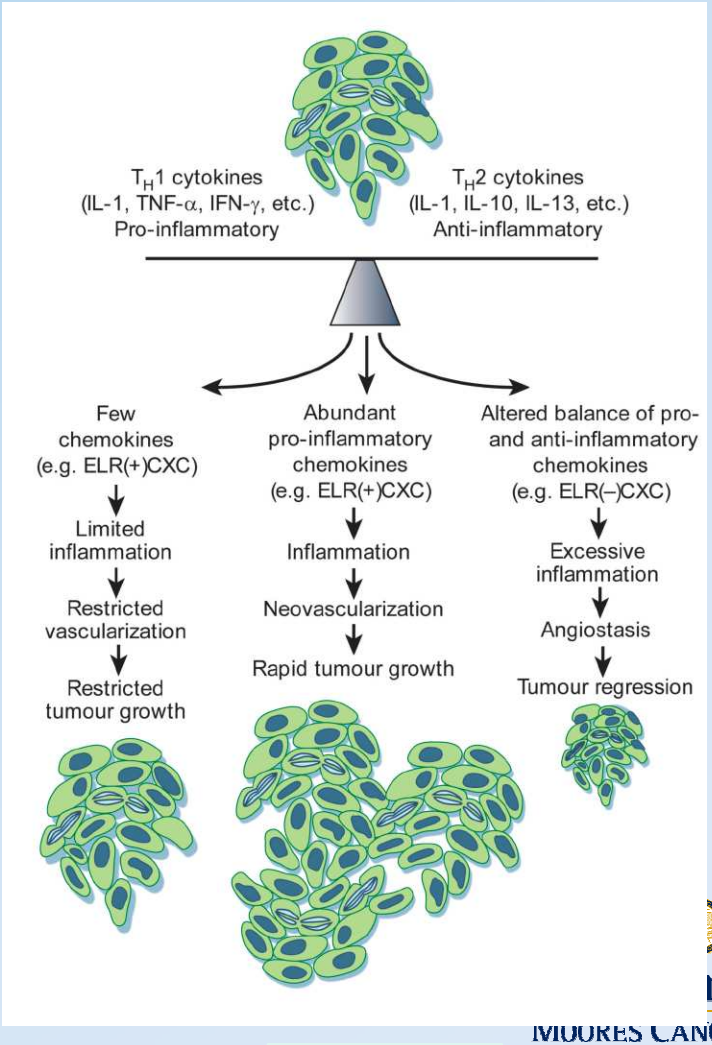
Seed and Soil

DISTRIBUTION OF SECONDARY GROWTHS IN CANCER OF THE BREAST.

BY STEPHEN PAGET, F.R.C.S.,
ASSISTANT SURGEON TO THE WEST LONDON HOSPITAL AND THE METROPOLITAN HOSPITAL.

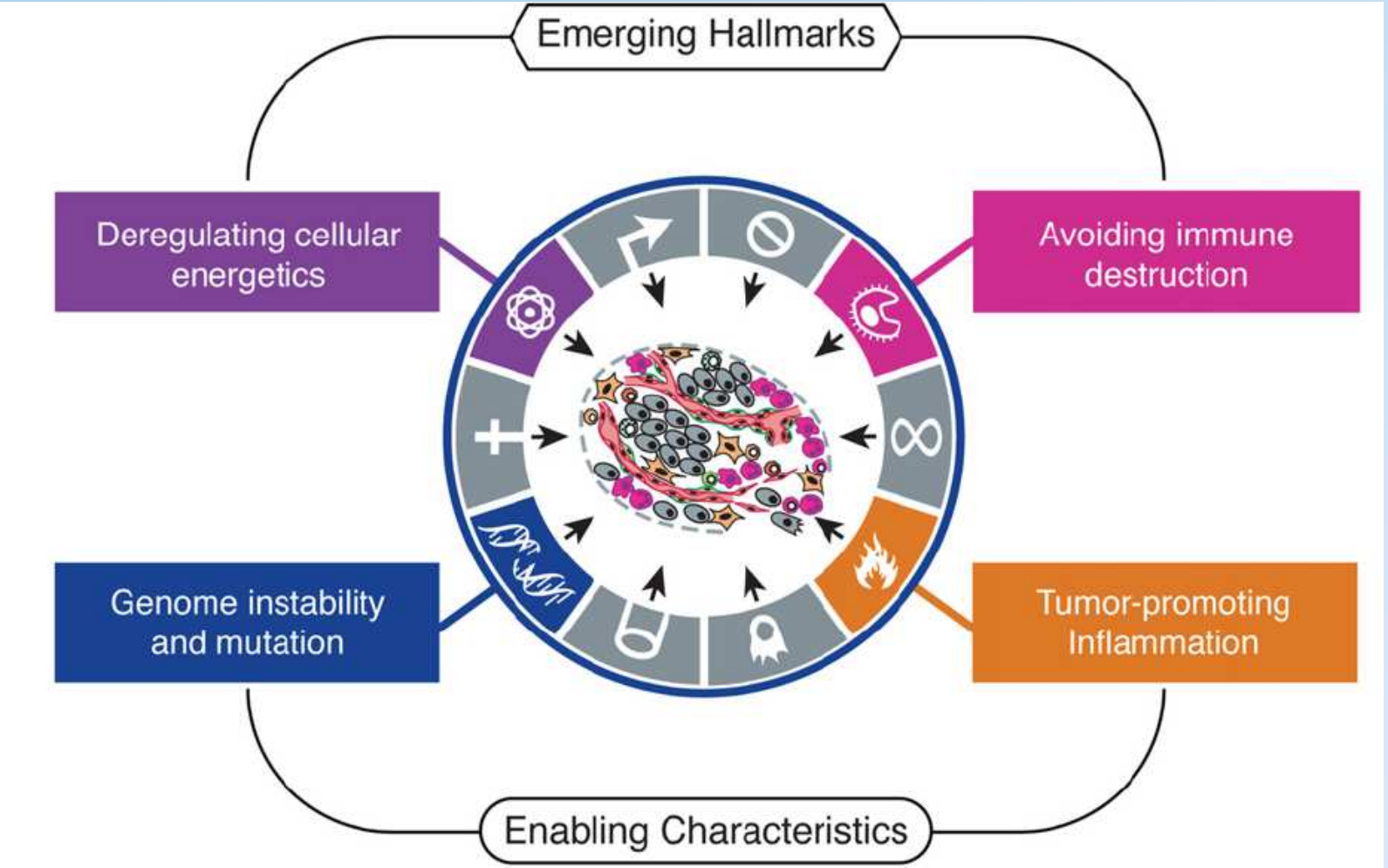
AN attempt is made in this paper to consider "metastasis" in malignant disease, and to show that the distribution of the secondary growths is not a matter of chance. It is urged both by Langenbeck and by Billroth that the question ought to be asked, and, if possible, answered: "What is it that decides what organs shall suffer in a case of disseminated cancer?" If the remote organs in such a case are all alike passive and, so to speak, helpless—all equally ready to receive and nourish any particle of the primary growth which may "slip through the lungs," and so be brought to them,—then the distribution of cancer throughout the body must be a matter of chance. But if we can trace any sort of rule or sequence in the distribution of cancer, any relation between the character of the primary growth and the situation of the secondary growths derived from it, then the remote organs cannot be altogether passive or indifferent as regards embolism.



Stephen Paget's paper reproduced from The Lancet, 1889

Nature. 2002 December 19; 420(6917): 860-867. doi:10.1038/nature01

Immune Reaction as the "Seventh" Hallmark of Cancer



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Two Competing Models

Virchow

- Inflammation predisposes to cancer
- Cancer often arises in the context of chronic inflammation
- Inflammatory cells present in tumors

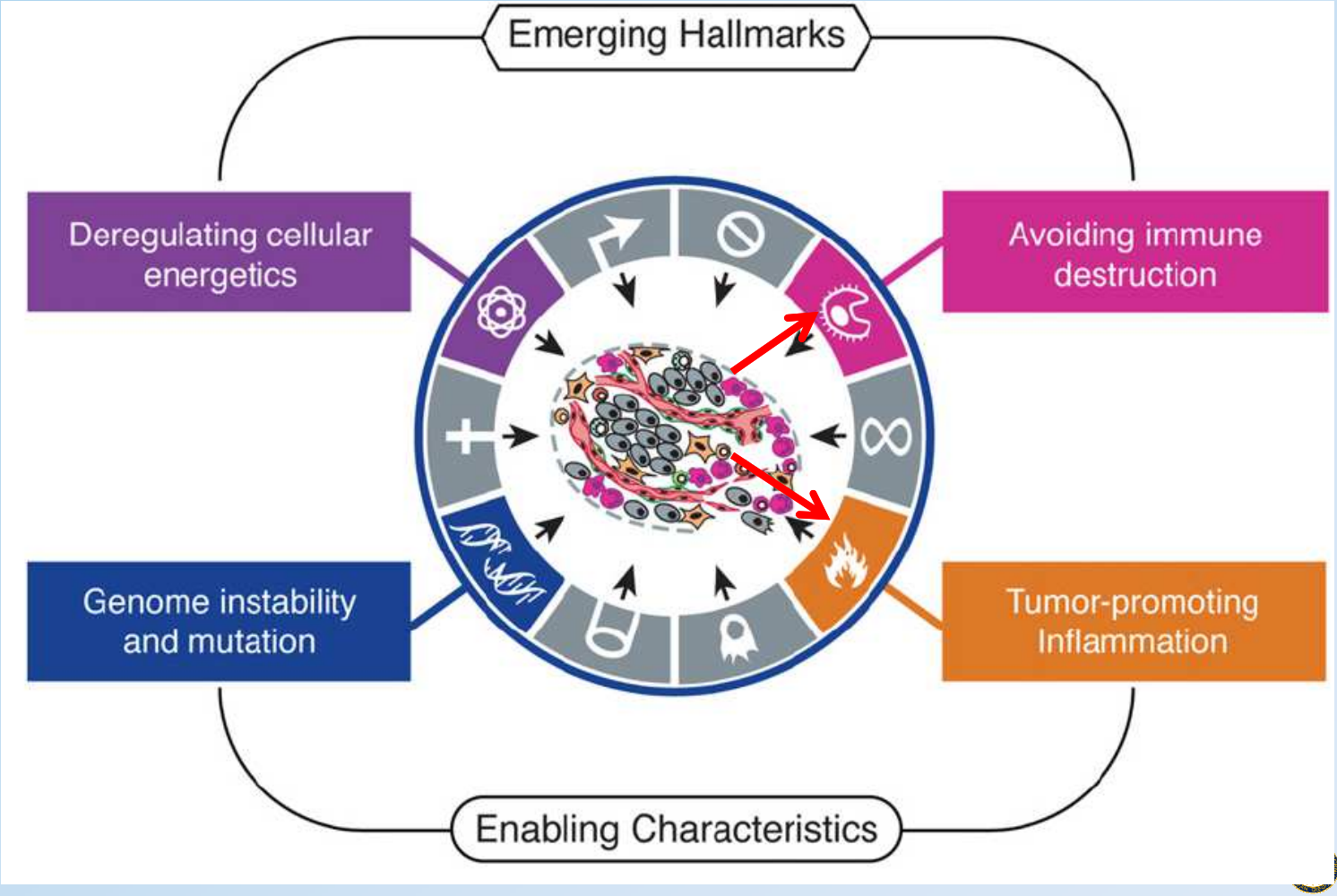
Immune system as positive requirement for cancer development.

Burnet

- Immunologic surveillance
- Immune system protects against cancer

Need to replace or enhance a defective response.

Tumor Manages Tumor Microenvironment (TME)



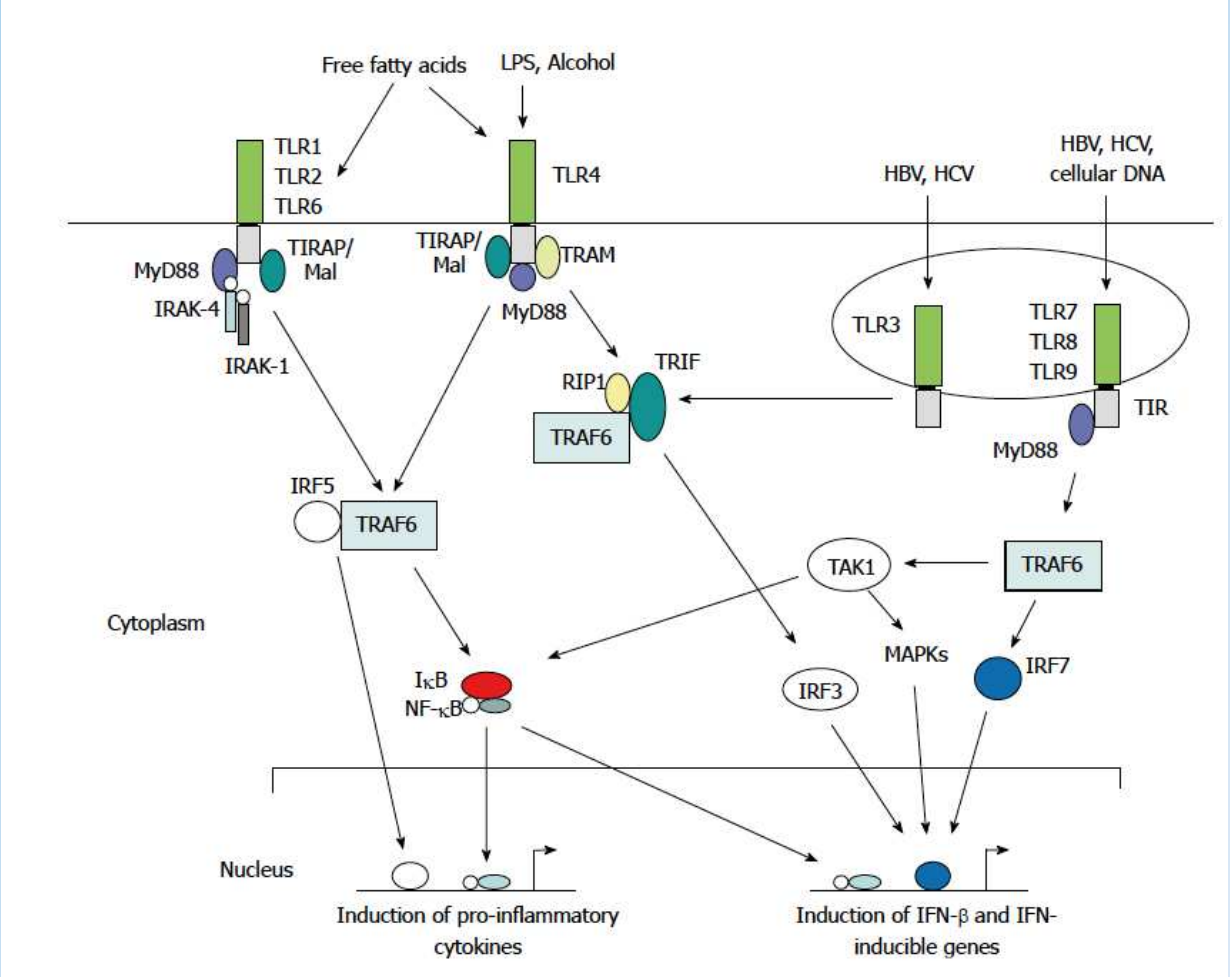
Cancer Development

- Wounds that do not heal
- Acute inflammation that leads to an aberrant ineffective chronic inflammatory state

Hepatocellular Carcinoma

- Third leading cause of cancer related death in the world
- Risk factors include viral hepatitis, obesity and toxins including alcohol, vinyl chloride and aflatoxin
  - Activation of Kupffer cells and Stellate cells
  - Necrosis
  - Regeneration (resolution of inflammation) vs fibrosis and cirrhosis (ongoing/ineffective chronic inflammatory response)

Toll-like receptor signaling in liver cells



Aravalli World J Gastroenterology 2013 (Review)

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How Does Fibrosis and Cirrhosis Support Cancer Development?

DIRECT (Intrinsic changes)

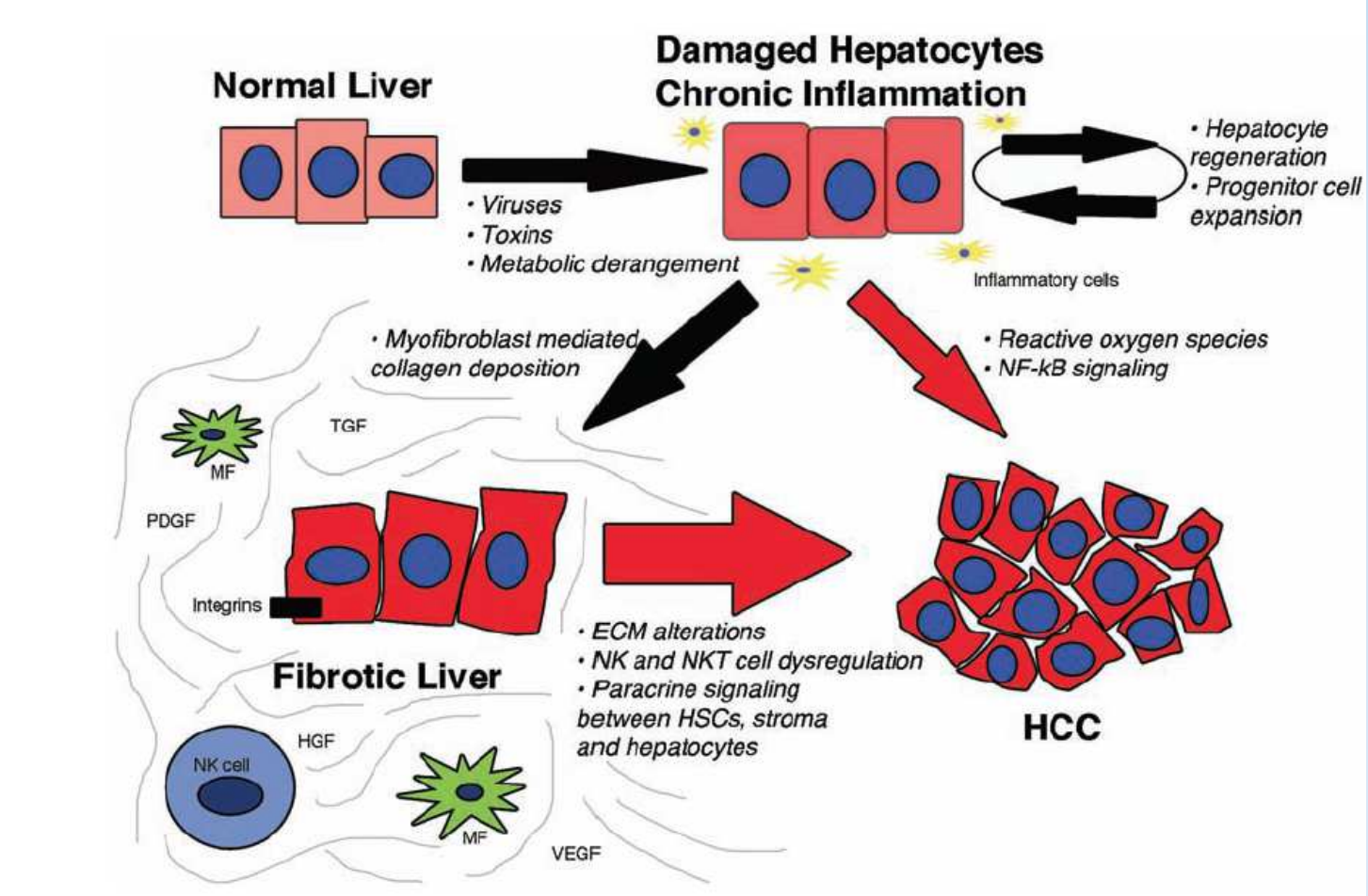
- Some of the *promoters* of inflammation are also tumor *initiators*—ie mutagens.
- Inflammation leads to elevated levels of ROS and other mechanisms that *enhance genetic instability and mutation rate*.

INDIRECT (TME)

- Fibroblasts, macrophages, endothelial cells, neutrophils, DCs, etc
  - *Growth factors, cytokines, chemokines*
- Shape a permissive niche by polarizing cells from "anti-tumor" to "pro-tumor"

Aravalli World J Gastroenterology 2013 (Review)

HCC Development



Wallace Gene Expression 2014 (Review)

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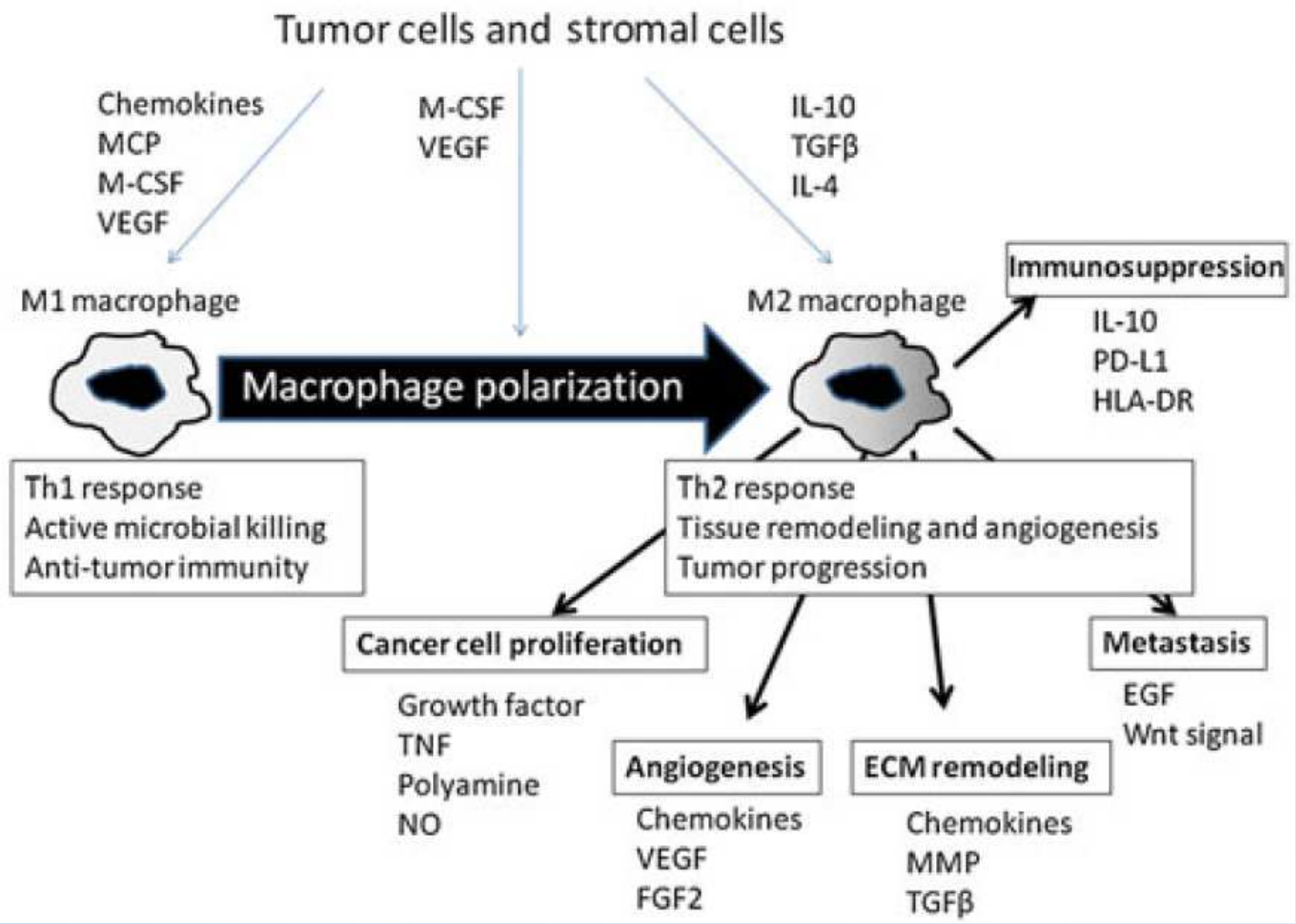
TME components



Shirabe Surgery Today 2012 (Review HCC)

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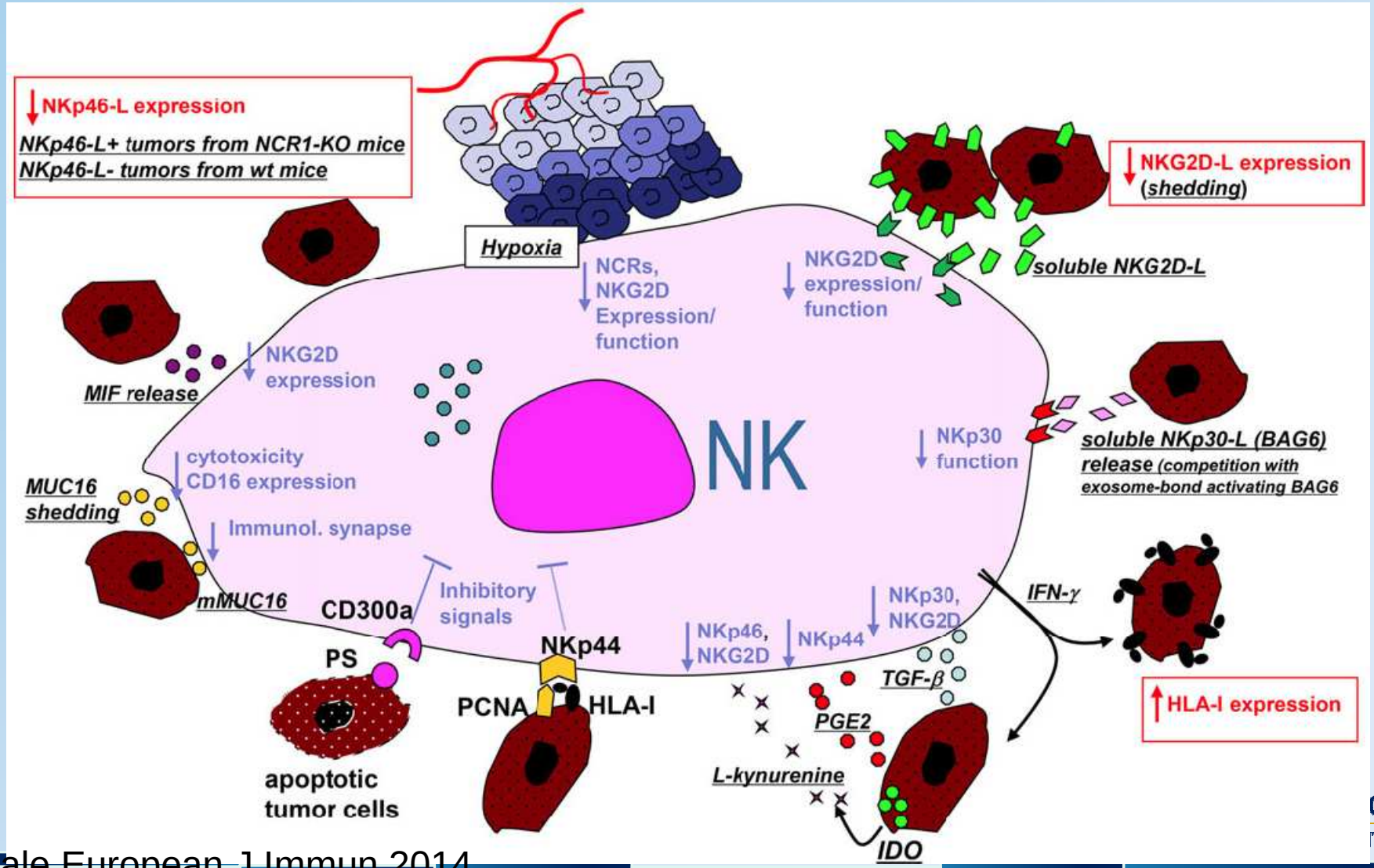
Multiple strategies employed



Vitale European J Immun 2014

Tumor Infiltrating Cells

- **Recruited** into tumors
  - Tumor associated macrophages (CCL2)
    - From circulating monocytes
    - M1 to M2 progression
      - Tolerogenic DCs, Regulatory T cells and Th2
      - IL10 and TGFb
  - Myeloid-derived suppressor cells, Tumor associated fibroblasts, NK, Treg, neutrophils etc
- Network of regulatory response with different tumors likely having different networks.

Cancer Shapes TME Immunity

- "Seed" conditions the soil.
- Immune cell composition will vary per tumor type, between patients and intrapatient
- Cancer cells manipulate natural immunity to provides growth support
  - Angiogenesis
  - Stromal support

Cancer and the TME

Tumor shapes the immune response and the immune response shapes the tumor

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- **Apply knowledge of immune players and tumor evolution to understanding clinical cancer prevention and treatment strategies**

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Preventable Causes of Cancer

- Tobacco
  - Lung, mouth, lips, pharynx, esophagus, stomach, pancreas, kidney, bladder, uterine cervix, and acute myeloid leukemia
  - In the United States, tobacco use is responsible for nearly 1 in 5 deaths
- Alcohol
  - Mouth, esophagus, pharynx, breast, liver, stomach, pancreatic
  - ?colorectal, ?prostate
- Ionizing radiation (A-bomb data vs medical radiation)
  - Leukemia, breast, lung, thyroid
- Viruses
  - HPV (cervix, oral), HepC, EBV, HTLV1, HIV
- Environmental toxins

Int J Radiat Biol. 2009 June; 85(6): 467–482.

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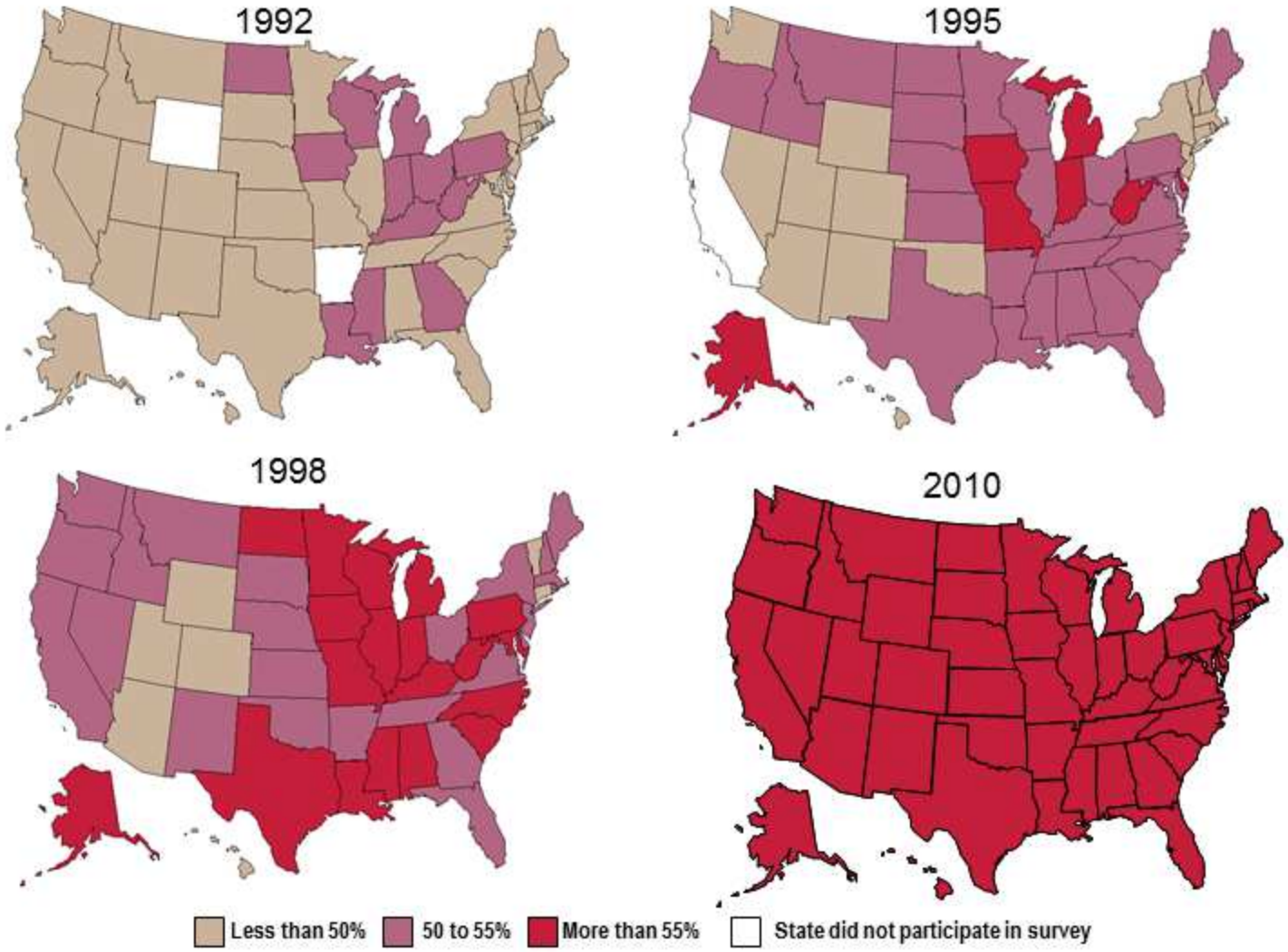
Clinician Point of View

	New cases per year (UK)*	n (%) cases attributable to overweight and obesity	Projected extra cases per year with a 1 kg/m² population-wide increase in BMI (99% CI)
Colon (C18)	26 725	2970 (11·1%)	559 (519–598)
Liver (C22)	4241	661 (15·6%)	145 (135–154)
Gall bladder (C23)	660	134 (20·3%)	36 (35–37)
Breast (post-menopausal, C50)	39 812	2035 (5·1%)	1441 (1417–1465)
Cervix (C53)	2851	214 (7·5%)	51 (50–53)
Uterus (C54–55)	8288	3384 (40·8%)	806 (784–829)
Ovaries (C56)	7011	512 (7·3%)	125 (118–133)
Kidney (C64)	9639	1597 (16·6%)	428 (414–442)
Thyroid (C73)	2654	51 (1·9%)	49 (48–51)
Leukaemia (C91–95)	8257	522 (6·3%)	150 (138–163)

Bhaskaran Lancet 2014
Getty images

Trends in Overweight* Prevalence (%), Adults 18 and Older, US, 1992-2010

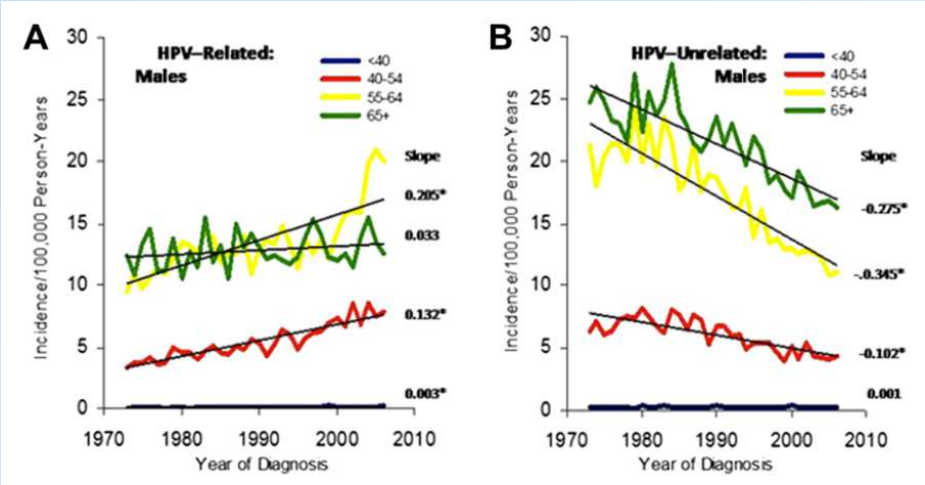


*Body mass index of 25.0 kg/m^{2}or greater. Source: Behavioral Risk Factor Surveillance System, CD-ROM 1992-2010), National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 2011.

HPV associated cancers

- 20 million people currently infected with genital HPV in the US
- Most sexually active adults become infected at some point
  - Most infections are asymptomatic and transient
  - Certain oncogene types persist—HPV 16 and HPV 18

- HPV is changing the epidemiology of oropharyngeal cancers



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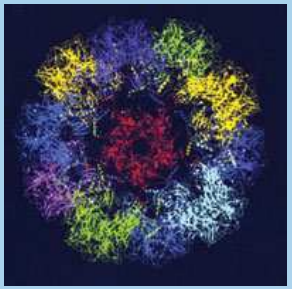

HPV-associated cancers

- HPV causes 5% of cancers worldwide
- Primary prevention
  - Vaccination
  - Protection
- Secondary prevention
  - PAP
  - Early detection

Table 1. Sites of HPV-associated cancers: Proportion of cancer due to HPV, presence of HPV-induced precancer, screening modality, and HPV vaccine efficacy

Cancer site	% attributable to HPV infection	HPV-induced premalignant lesion	Screening modality	Vaccine efficacy against persistent HPV16/18 infection[a]	Vaccine efficacy against HPV16/18-associated premalignant lesions[a]
Cervix	100	Cervical intraepithelial neoplasia (CIN)	Cytology, colposcopy, primary screening through HPV cotesting	91%–94%	93%–98%
Anus	90	Anal intraepithelial neoplasia (AIN)	Cytology, high-resolution anoscopy	95%	78%
Penis	40	Penile intraepithelial neoplasia (PIN)	Cytology/histology	90%	90%[b]
Vagina	40	Vaginal intraepithelial neoplasia (VAIN)	Cytology/histology	?	100%
Vulva	40	Vulvar intraepithelial neoplasia (VIN)	Cytology/histology	?	100%
Oropharynx	12–72	?	?	?	?

[a]In an according-to-protocol or per-protocol susceptible analytic cohort, which is typically restricted to individuals who were HPV DNA negative and seronegative at baseline and through the vaccination phase.
[b]Against a composite endpoint of penile, perianal, or perineal intraepithelial neoplasia.

http://www.cdc.gov/hpv/vaccine.html

HPV vaccination is recommended for preteen girls and boys at age 11 or 12 years

Cancer Prev Res; 4(9) September 2011

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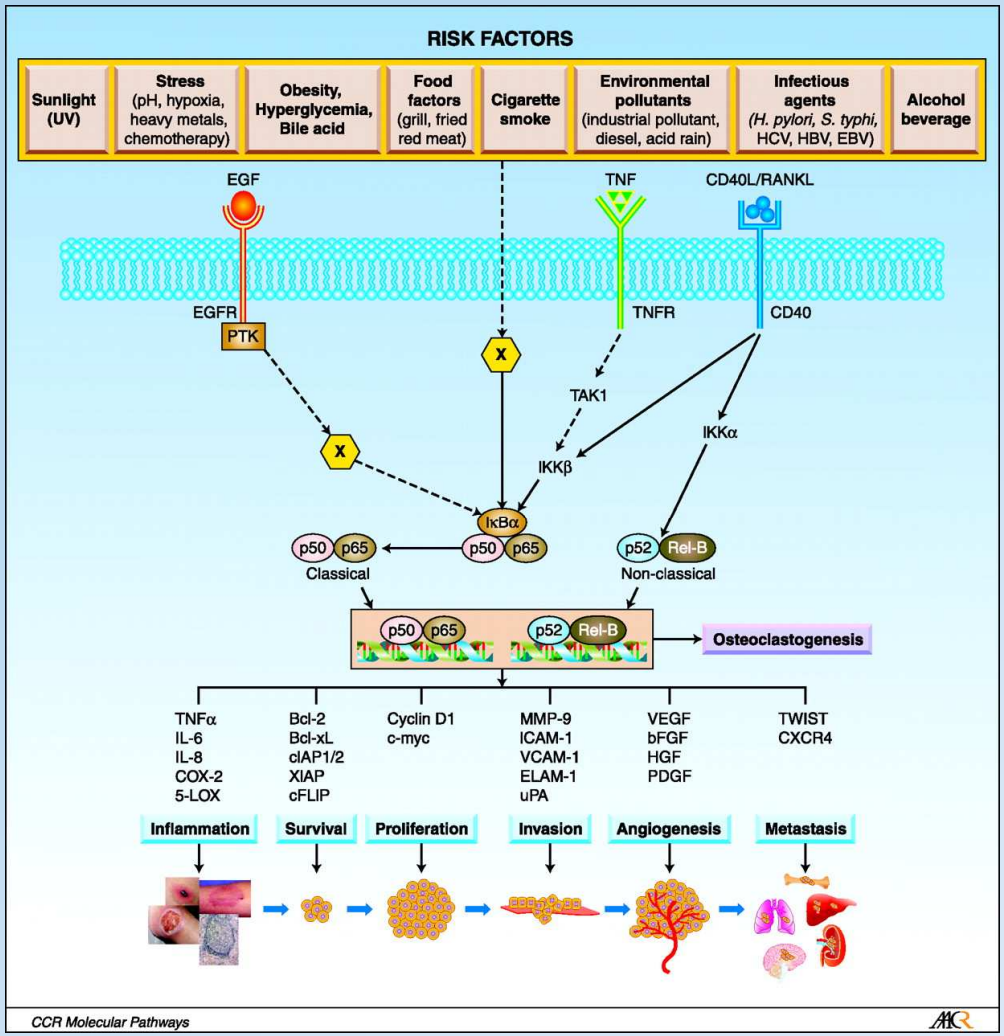
Inflammation as a Common Link of Tumor Promoters?



Aggarwal B B et al. Clin Cancer Res 2009;15:425-430

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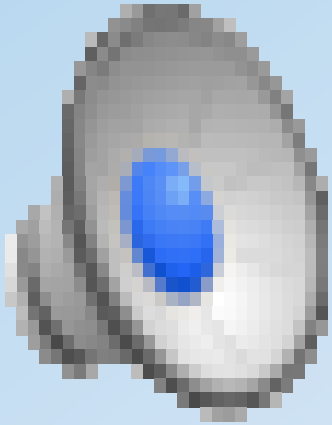
Clinical Reasoning

- If ineffective chronic inflammation initiates and promotes tumor development then strategies to lower chronic inflammation may lower the incidence of certain cancers

Big News



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Clinical Relevance of Inflammation and Tumor Development

- Cancer related symptoms
  - Appetite and weight loss, fatigue and pain
  - QOL
- Cancer associated inflammation decreases treatment efficacy
  - “B-symptoms”, CRP, neutrophil, lymphocyte and platelet count associate with response
  - Inflammation directly changes metabolism of drugs (P450)

Roxburgh BJC 2014 (review)

Quality of Life

- Corticosteroids reduce systemic inflammation and improve cancer-related symptoms in advanced cancer patients
- Non-steroidal anti-inflammatory drugs
  - Pain management
  - Risk reductin
- Statins
  - Immune modulatory
  - Associated with cancer reduction

Roxburgh BJC 2014 (review)

Take Away

- Cancer is largely a preventable disease
- Chronic inflammation links many cancer risk factors
- Strategies targeted to reduce tumor promoting inflammation may be effective preventative strategies broadly.

Questions

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