

# Dual Role of the Immune System in Protection and Pathogenesis

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Deputy Editor, Cancer Vaccines (De Gruyter Open)

Special Edition Editor, Vaccine (Elsevier)

Chair, SAB, TapImmune Inc. Seattle, WA

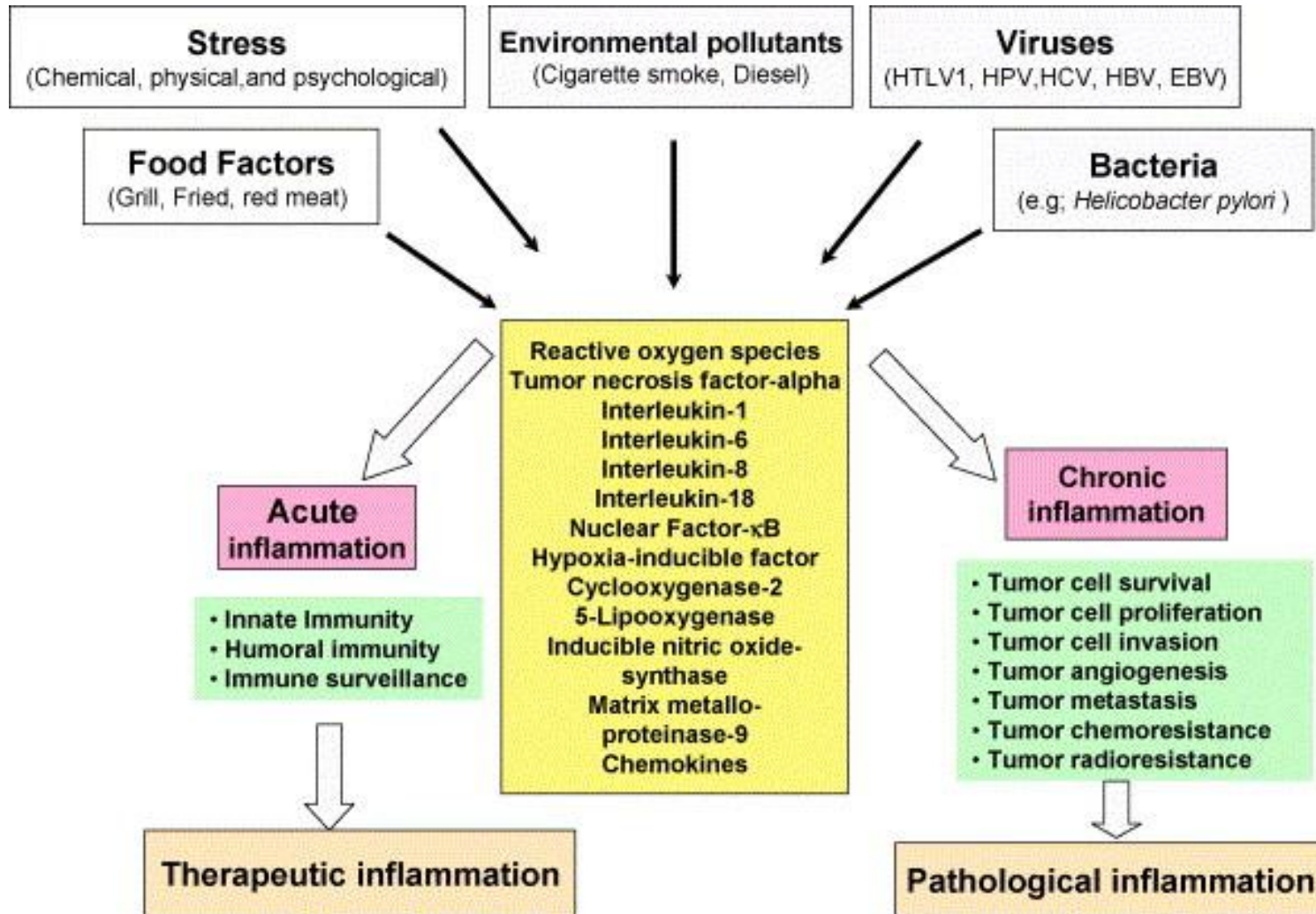
SAB, Antigen Express, Boston, MA

# Paradoxical roles of the immune system in cancer development

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1. The key functions of the mammalian immune system:
  - (1) Protect from infectious pathogens
  - (2) Monitor tissue homeostasis => Eliminate damaged cells (e.g. tumor cells) and induce wound healing.
2. Mechanisms against cancer development:
  - (1) Cellular immunity- T, NK, & Other innate immune cells
  - (2) Humoral immunity- Cytokines, Abs, etc.
3. Mechanisms promoting cancer development:
  - (1) Homeostatic Inflammation => Angiogenesis & Tissue remodeling
  - (2) Enhance survival pathways (NF-kB activation)
  - (3) Suppression of anti-tumor immune responses

# Acute vs. Chronic Inflammation: Role in Cancer Pathology



# The difference between acute and chronic inflammation

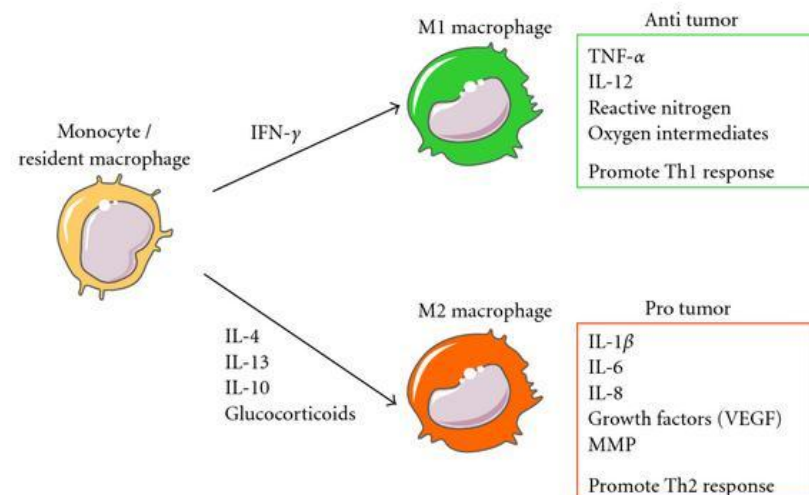
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## Acute Inflammation

- Type I response
- Cell and tissue destruction
- **Antigen or insult elimination**
- M1 Macrophages
- Neutrophils
- Activated DCs
- Cytotoxic T cells
- Antibodies
- Th1 T cells
- Resolution and wound repair

## Chronic Inflammation

- Type 2 response
- Antigen or insult persistence
- Remodeling programs
- M2 Macrophages
- Th2 T cells IL-13
- Treg T cells
- Suppressive myeloid cells



# Association of inflammation with cancers

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- Tobacco Use: 30%
- Diet: 35%
- Obesity: 20%
- Infectious Agents: 18%
- Radiation or Environmental Pollutants: 7%

# Association of chronic inflammation with cancers

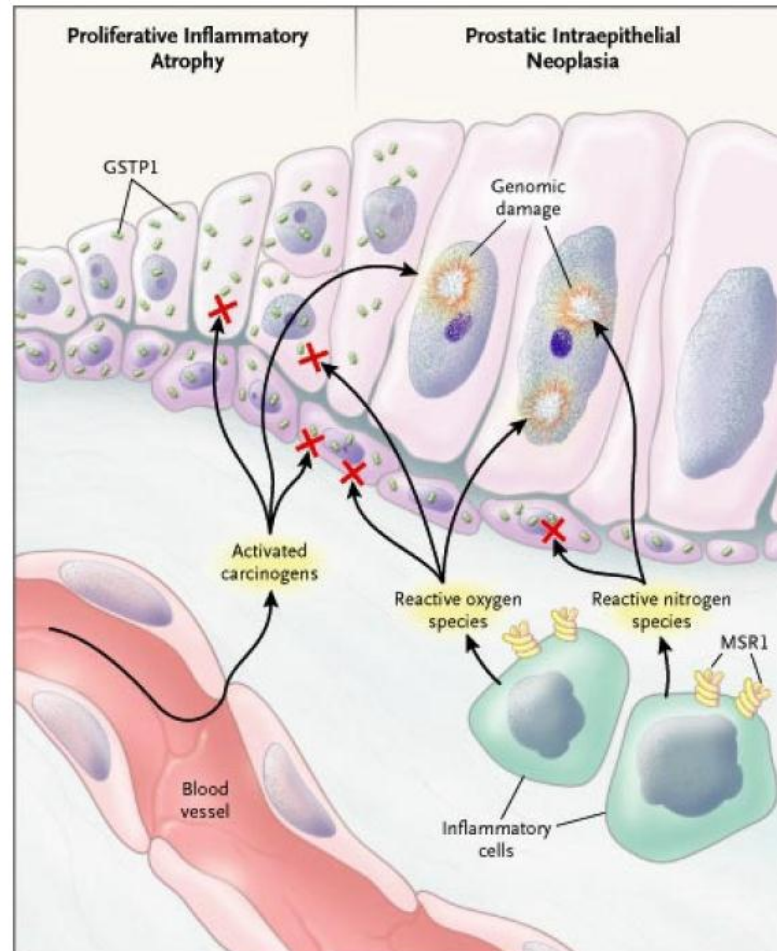
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Inflammation that causes insults or pathological conditions	Associated malignancy
Silica, asbestos, smoking-associated silicosis and bronchitis	Lung carcinoma
Pelvic inflammatory disease	Ovarian carcinoma
Chronic indwelling urinary catheter	Bladder carcinoma
<i>TRYP1</i> mutation-associated pancreatitis and alcoholism-associated pancreatitis	Pancreatic carcinoma
UV irradiation-associated skin inflammation	Melanoma
Asbestos	Mesothelioma
Bile acids	Cholangiosarcoma and colorectal carcinoma
Gastric acid-associated Barrett's metaplasia and reflux oesophagitis	Oesophageal carcinoma
Gall bladder stone-associated cholecystitis	Gall bladder carcinoma
Lichen sclerosus (a skin condition)	Vulvar carcinoma
Inflammatory bowel disease	Colorectal carcinoma
Hashimoto's thyroiditis (an autoimmune disease of the thyroid) and Sjögren's syndrome (an autoimmune disease of exocrine glands)	Mucosa-associated lymphoid tissue lymphoma
Gingivitis (inflammation of the gum tissue) and lichen planus	Oral squamous cell carcinoma
Sialadenitis (inflammation of the salivary gland)	Salivary gland carcinoma

*TRYP1*, trypsinogen 1; UV, ultraviolet.

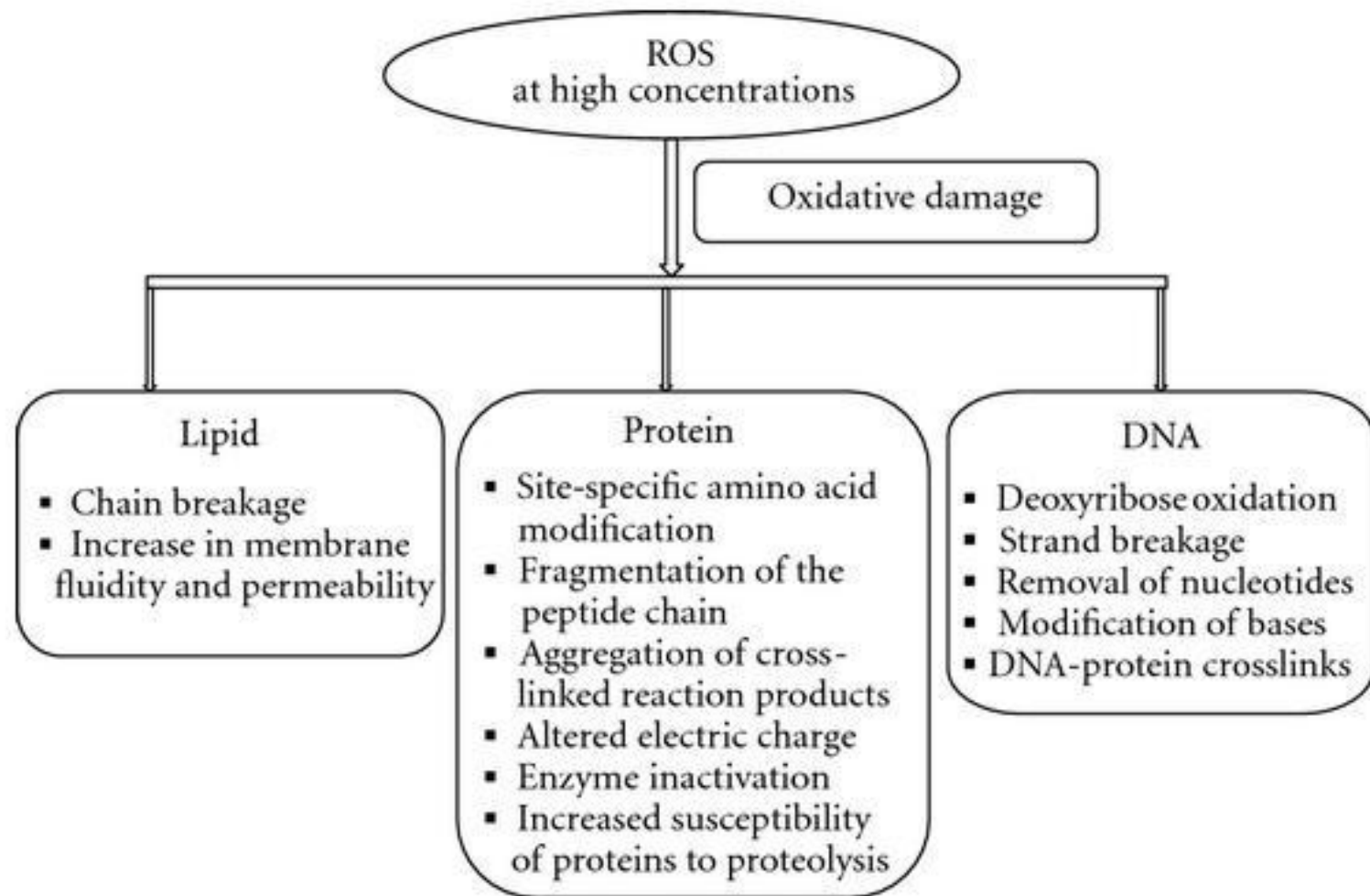


# Chronic inflammation causes genomic damage through reactive oxygen and nitrogen



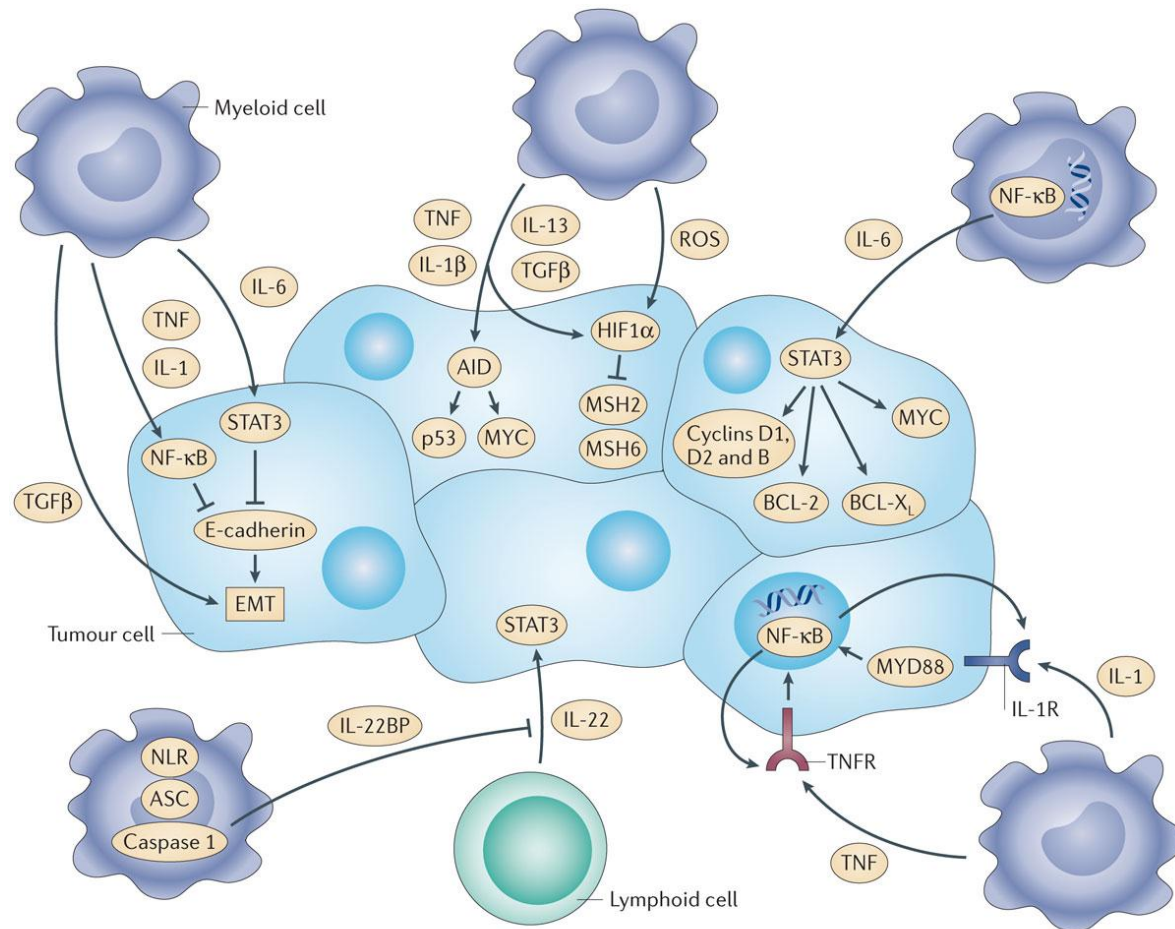
Nelson WG *et al.*  
New Engl J Med  
349: 366-81 (2003).

# Chronic inflammation causes lipid and protein damage through reactive oxygen and nitrogen

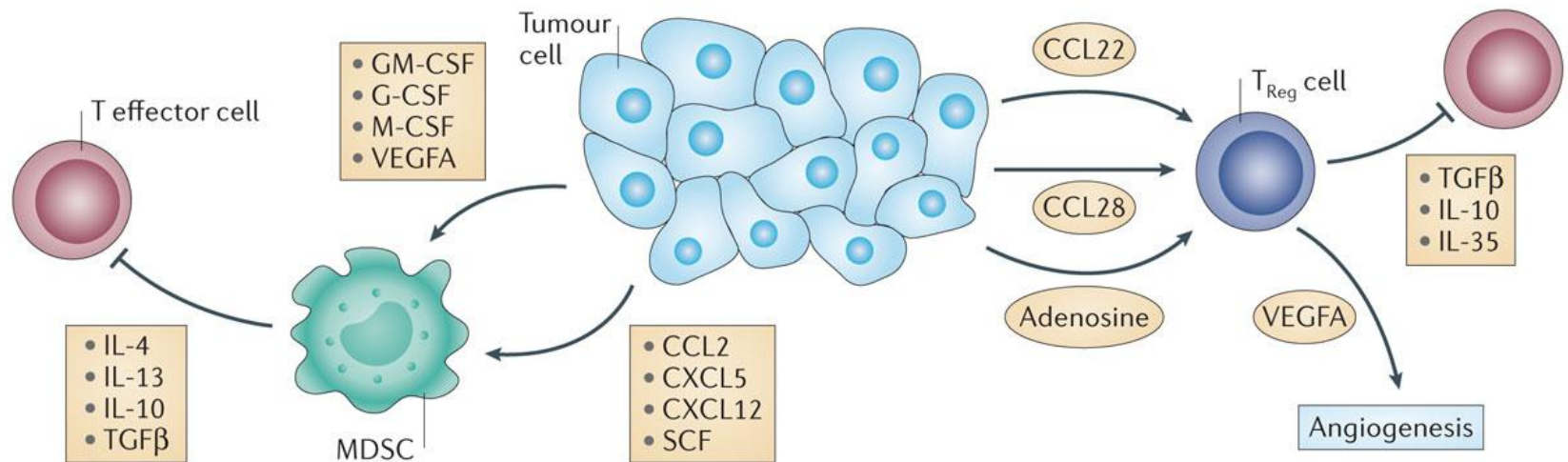




# Inflammation elevates cytokines that activate transcription factors which promote tumor formation and progression.



# Inflammation induces immune suppressive cells which prevent adaptive cellular immunity



# Chronic inflammation can act locally or at a distance

Carcinogenesis vol.0 no.0 pp.1–4, 2012  
doi:10.1093/carcin/bgs112  
Advance Access publication February 26, 2012

## Periodontal disease, *Porphyromonas gingivalis* serum antibody levels and orodigestive cancer mortality

Jiyoung Ahn\*, Stephanie Segers and Richard B. Hayes

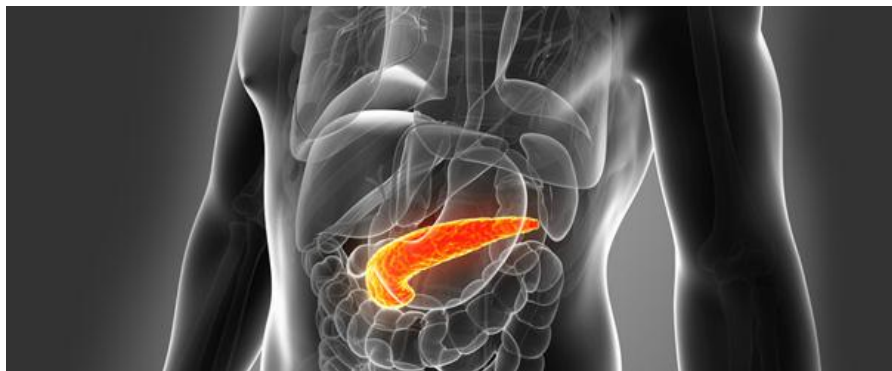
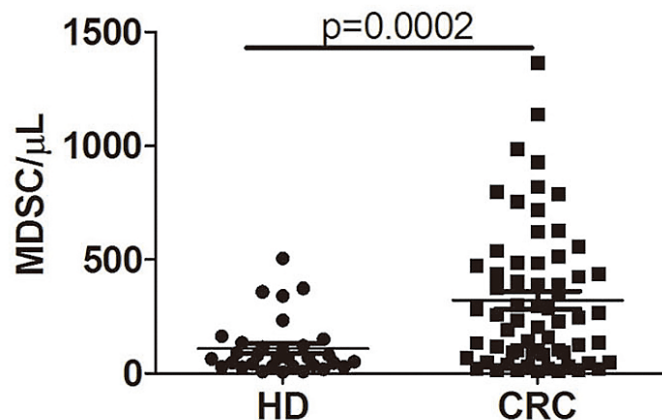
Division of Epidemiology, Department of Environmental Medicine, New York University School of Medicine, 650 First Ave, New York, NY 10016, USA

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Fax: +1 212 263 8570;  
Email: Jiyoung.Ahn@nyumc.org

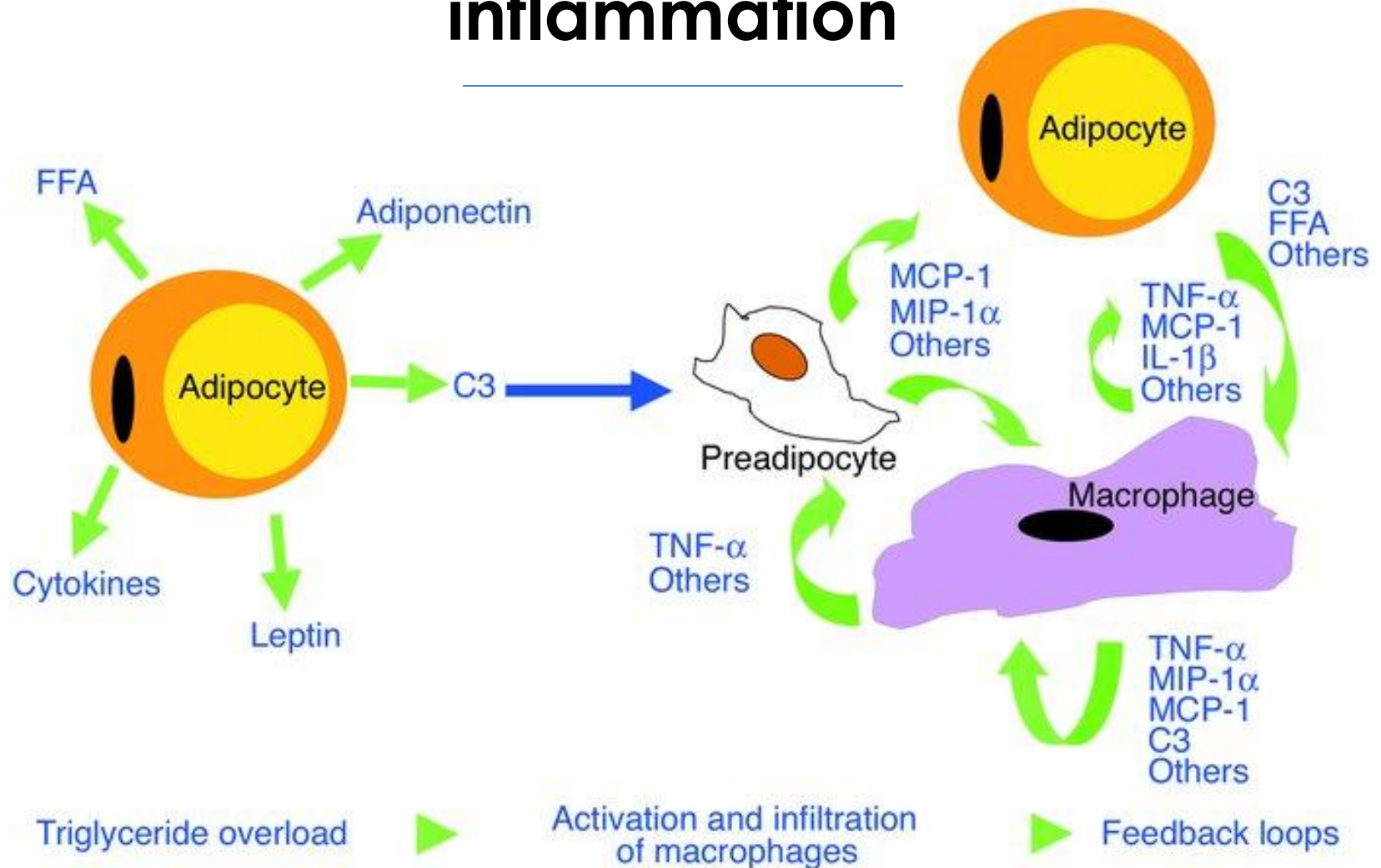
### Materials and methods

#### Study population

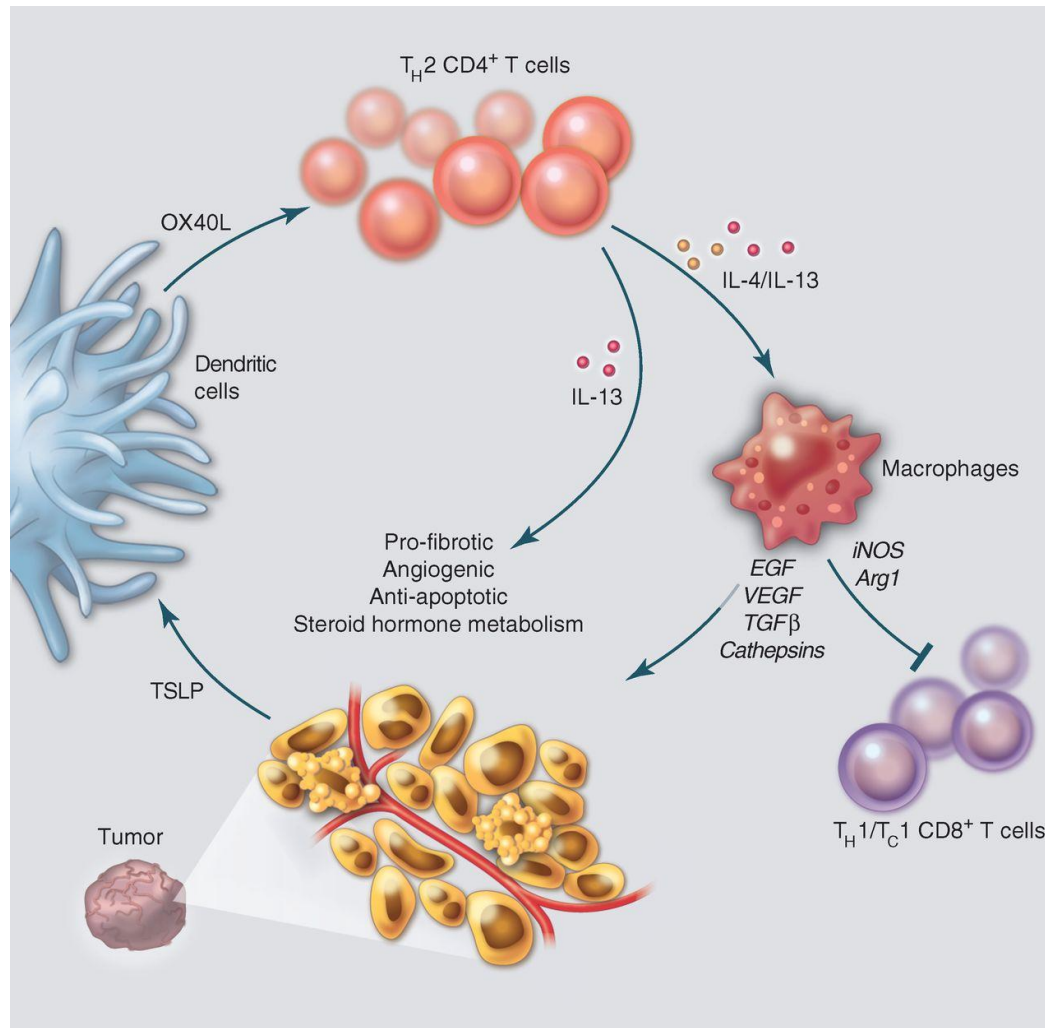
The National Health and Nutrition Examination Survey III (NHANES III) survey, which was conducted in two phases between 1988 and 1994 by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC), was designed to examine the health and nutritional status of the non-institutionalized USA population (6), including estimates for



# Large volumes of white fat activates inflammation



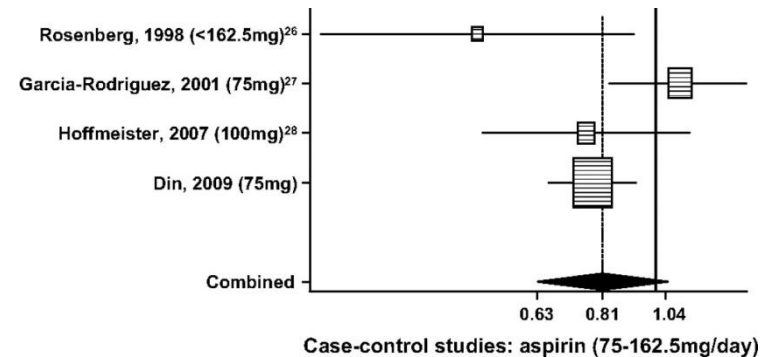
# Malignant cells foster development of wound healing responses





# Preventing Tumor-inducing Inflammation

- **Life style changes:** lose weight, quit smoking, quit drinking.
- **Non-steroidal anti-inflammatories:** colorectal, bladder, ovarian.
- **Vaccination:** HBV, MUC1
- **Phytochemicals:** Variety of inhibitors (Natural Cox and Stat3 inhibitors).



Published OnlineFirst December 17, 2012; DOI: 10.1158/1940-6207.CAPR-12-0275

Research Article

Cancer  
Prevention  
Research

## MUC1 Vaccine for Individuals with Advanced Adenoma of the Colon: A Cancer Immunoprevention Feasibility Study

Takashi Kimura<sup>1</sup>, John R. McKolanis<sup>1</sup>, Lynda A. Dzubinski<sup>2</sup>, Kazi Islam<sup>3</sup>, Douglas M. Potter<sup>4</sup>, Andres M. Salazar<sup>5</sup>, Robert E. Schoen<sup>2</sup>, and Olivera J. Finn<sup>1</sup>



# Preventing Tumor-inducing Inflammation with Aspirin

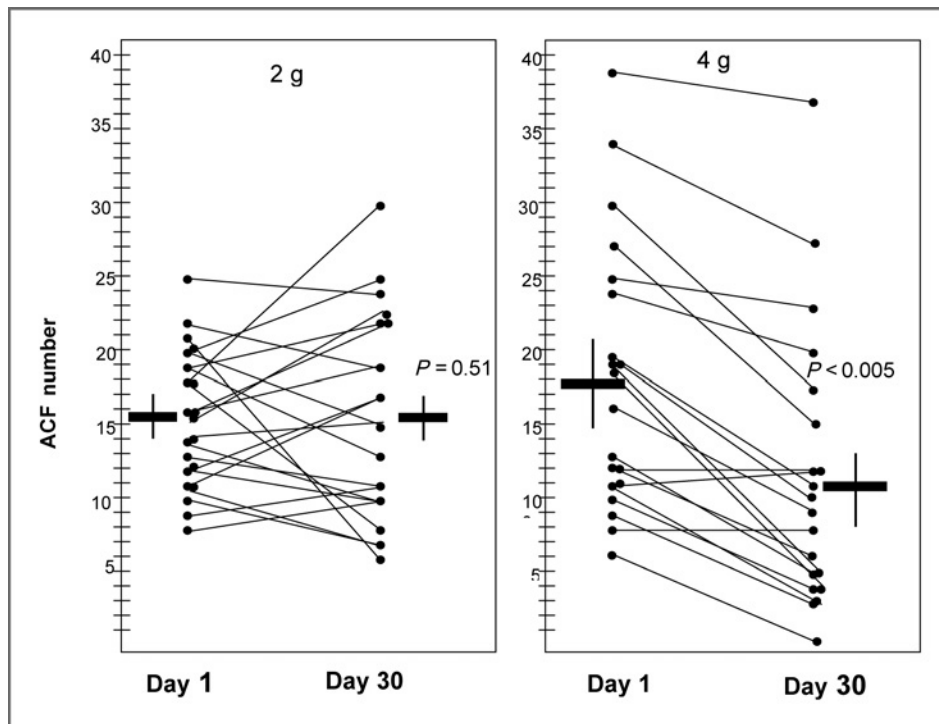
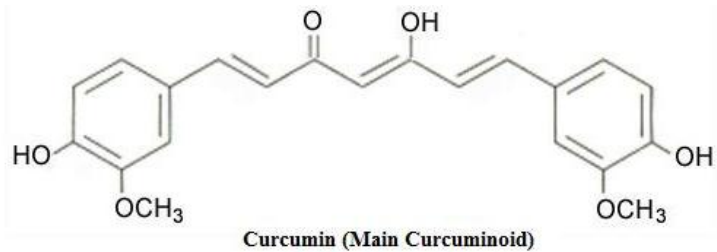
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- **Overall benefit:** 12% overall reduction in incidence. 19% at 5 year or more duration. 24% if used for 3 or more years. Lancet 2012
- **Site Specific** Curr Oncol Res 2013
  - Colorectal: 20-38%
  - Esophageal: 27-43%
  - Gastric: 29-39%
  - Breast: 8-18%
  - Prostate: 9-14%
  - Lung: 19%

## **Risk Benefit**

Intracranial Bleeding  
Ulcers  
Diabetes  
Smoking  
Cholesterol

# Preventing Tumor-inducing Inflammation with Curcumin



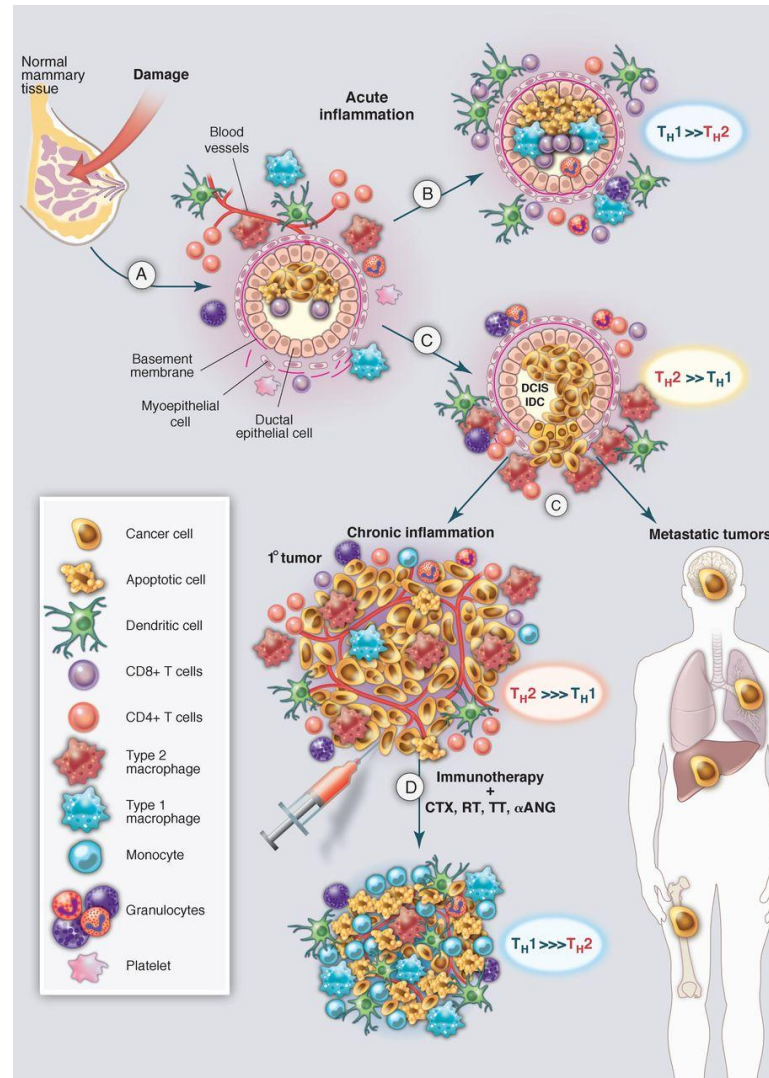
## Mechanisms of action

Blocks NFkB activation  
Blocks Jak-Stat pathways

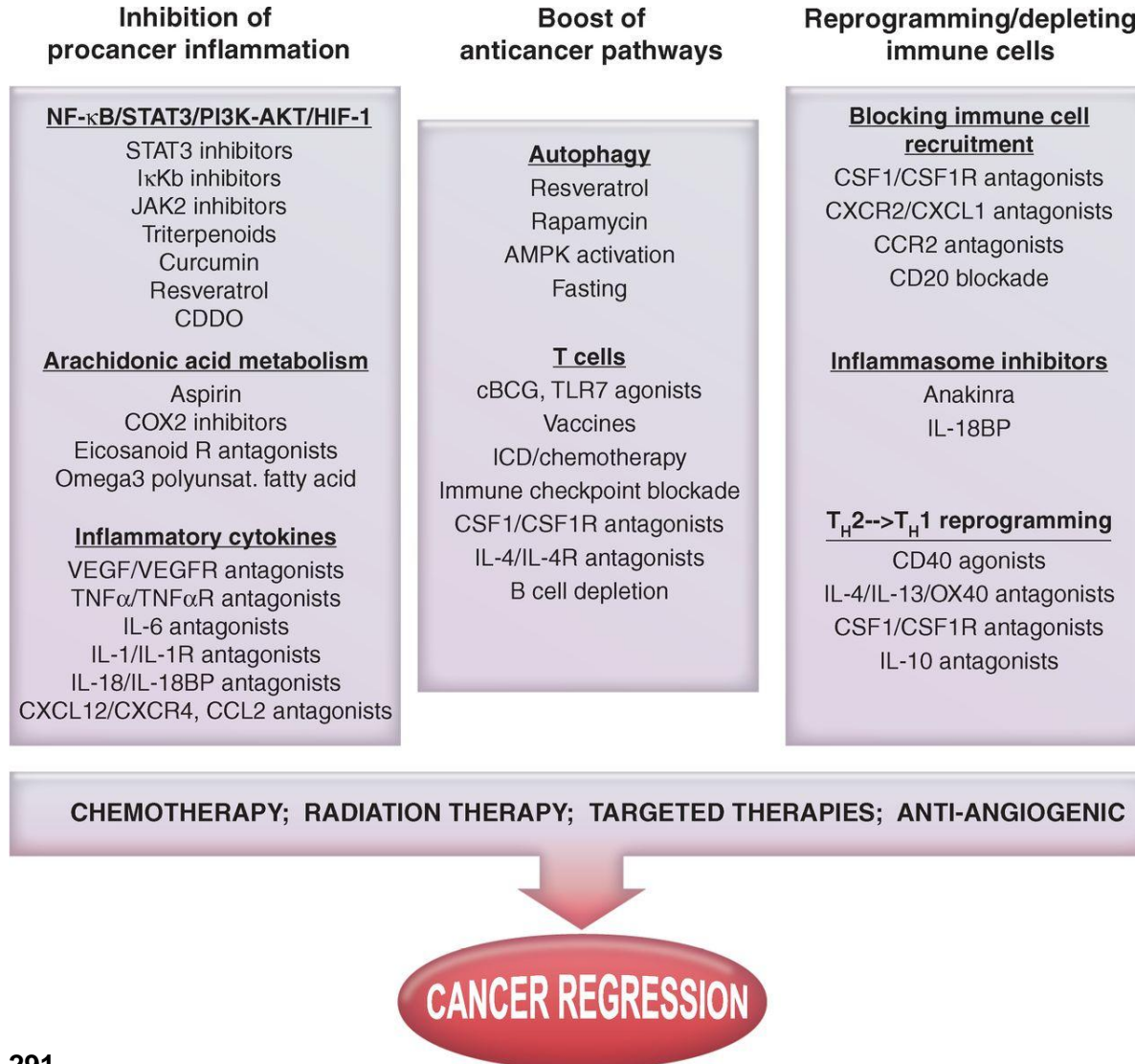
## Risk Benefit

Low grade only  
Diarrhea  
Distension  
Reflux  
Iron deficiency (susceptible people)

# Converting chronic to acute inflammation



# Reversing Tumor-Associated Chronic Inflammation



# Reversing from a chronic to an acute inflammatory response

## **Boosting adaptive Th1 immunity**

- Vaccines
- T cell therapy
- Radiation
- Cytokines
- Viral therapy

## **Reversing immune suppression/regulatory mechanisms**

- Checkpoint Blockade
- Tregs
- MDSCs