Introduction to Innate Immunity

Willem Overwijk, Ph.D.
Dpt. of Melanoma Medical Oncology
MD Anderson Cancer Center, Houston, TX

SITC Primer 2015

Piled Higher and Deeper ***by Jorge Cham*** **www.phdcomics.com**

Seminar BINGO!

To play, simply print out this bingo sheet and attend a departmental seminar.

Mark over each square that occurs throughout the course of the lecture.

The first one to form a straight line (or all four corners) must yell out BINGO!! to win!

SEMINAR BINGO

Speaker bashes previous work	Repeated use of "um…"	Speaker sucks up to host professor	Host Professor falls asleep	Speaker wastes 5 minutes explaining outline
Laptop malfunction	Work ties in to Cancer/HIV or War on Terror	"…et al."	You're the only one in your lab that bothered to show up	Blatant typo
Entire slide filled with equations	"The data *clearly* shows…"	FREE Speaker runs out of time	Use of Powerpoint template with blue background	References Advisor (past or present)
There's a Grad Student wearing same clothes as yesterday	Bitter Post-doc asks question	"That's an interesting question"	"Beyond the scope of this work"	Master's student bobs head fighting sleep
Speaker forgets to thank collaborators	Cell phone goes off	You've no idea what's going on	"Future work will…"	Results conveniently show improvement

WWW.PHDCOMICS.COM

title: "Seminar Bingo" - originally published 4/9/2007

Innate Immunity and Inflammation

- Definitions
- Cells and Molecules
- Innate Immunity and Inflammation in Cancer
- Bad Inflammation
- Good Inflammation
- Therapeutic Implications

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- **Innate Immunity:** Immunity that is naturally present and is not due to prior sensitization to an antigen; generally nonspecific. It is in contrast to acquired/adaptive immunity.

- **Inflammation:** a local response to tissue injury
  - Rubor (redness)
  - Calor (heat)
  - Dolor (pain)
  - Tumor (swelling)

Adapted from *Merriam-Webster Medical Dictionary*

“Innate Immunity” and “Inflammation” can mean many things

- Specific cell types and molecules orchestrate specific types of inflammation

- Innate Immunity A ≠ Innate Immunity B
- Inflammation A ≠ Inflammation B

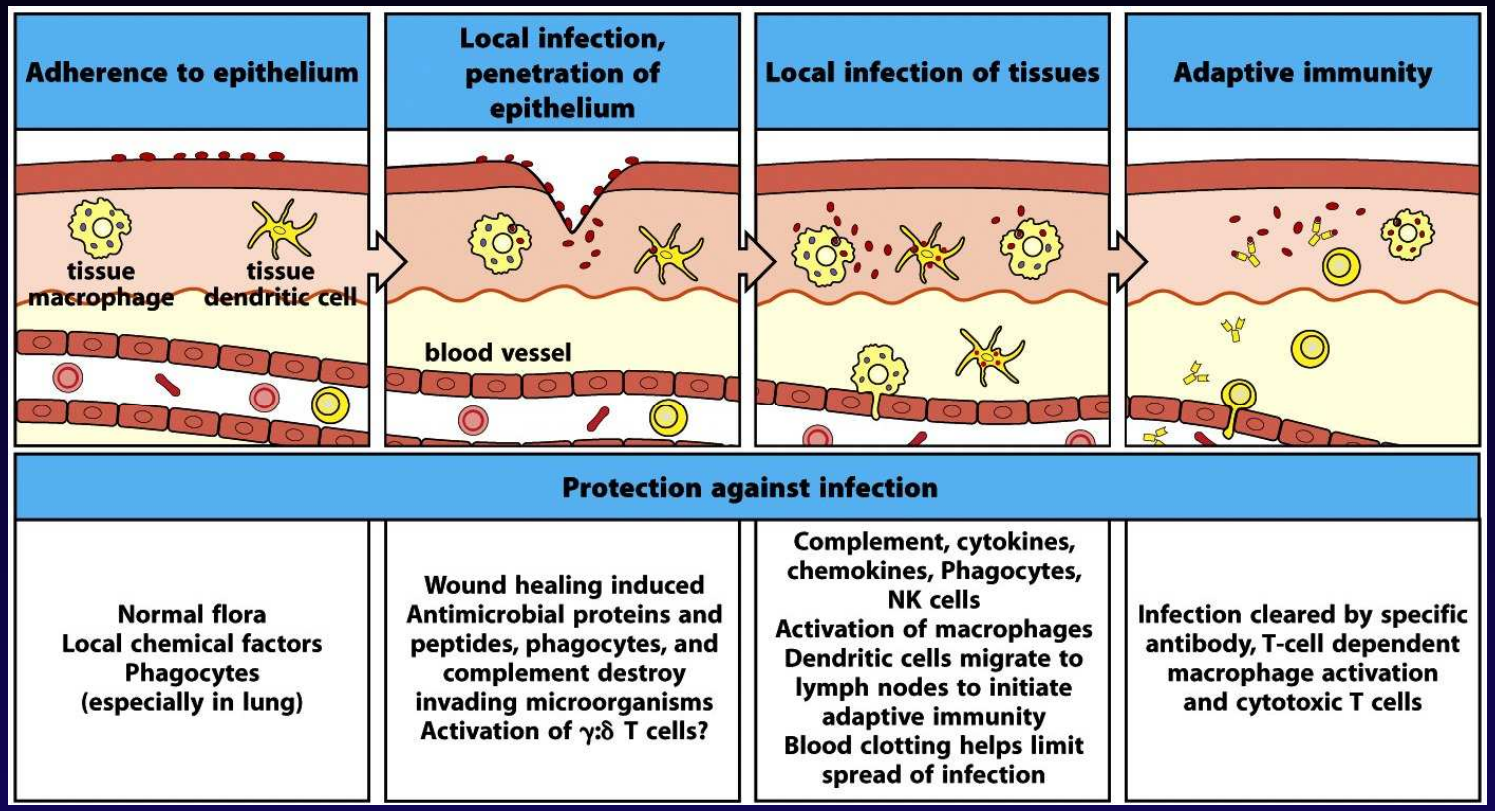
- Some immune responses promote cancer, others suppress it

Innate Immunity and Inflammation

Functions:

- Rapid response to tissue damage
- Limit spread of infection
- Initiate adaptive immune response (T, B)
- Initiate tissue repair

Innate Immunity and Inflammation: A Paper Cut



Janeway, *Immunobiology, 7th Ed.*

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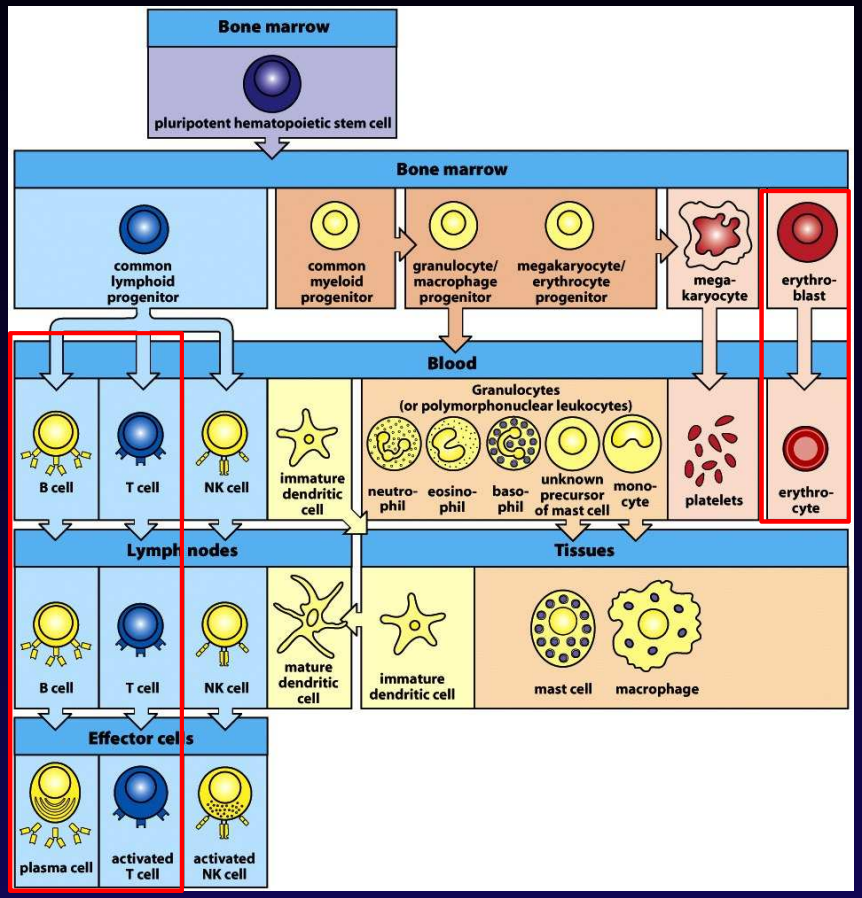
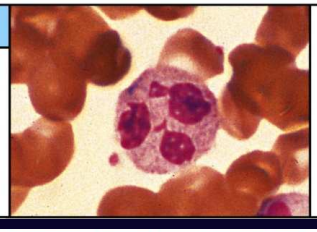
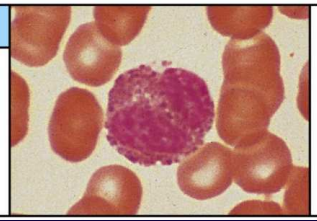
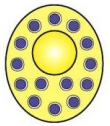
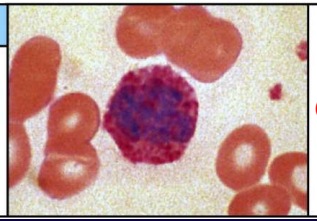
Innate Immune Cells



Janeway, *Immunobiology, 7th Ed.*

Innate Immune Cells: granulocytes

Cell		Activated function
Neutrophil 		Phagocytosis and activation of bactericidal mechanisms
Eosinophil 		Killing of antibody-coated parasites

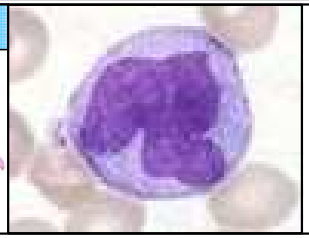
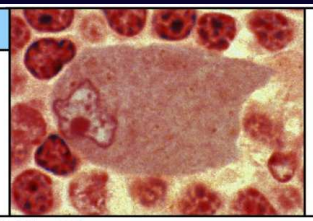
Cell		Activated function
Mast cell 		Release of granules containing histamine and active agents
Basophil 		(Unknown) **Antigen Presentation**

Recognize
- pathogens
- antibodies

Cause
- pathogen clearance
- inflammation

Janeway, *Immunobiology, 7th Ed.*

Innate Immune Cells: phagocytes

Cell		Activated function
Monocyte Deeply Indented Nucleus		Blood precursor of tissue Macrophages and Dendritic Cells
Macrophage		Phagocytosis and activation of bactericidal mechanisms Antigen presentation
Dendritic cell		Antigen uptake in peripheral sites Antigen presentation

Recognize
- pathogens
- antibodies

Cause
- pathogen clearance
- adaptive immunity
- inflammation

Janeway, *Immunobiology, 7th Ed.*

Innate Immune Cells: NK, NKT and γδ T cells

Recognize

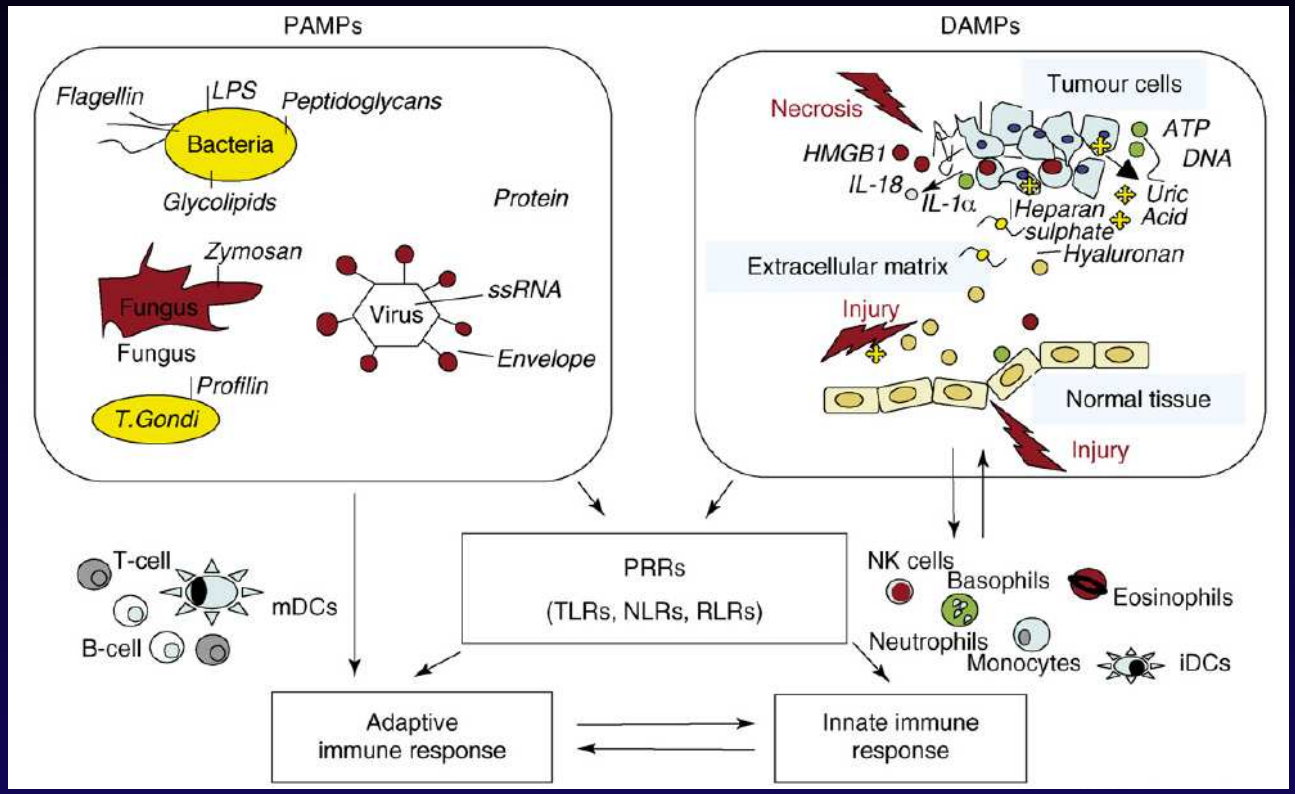
- pathogens
- stressed cells
- “altered self”

Cause

- pathogen clearance
- stressed/abnormal cell clearance
- inflammation

Danger signals start inflammation

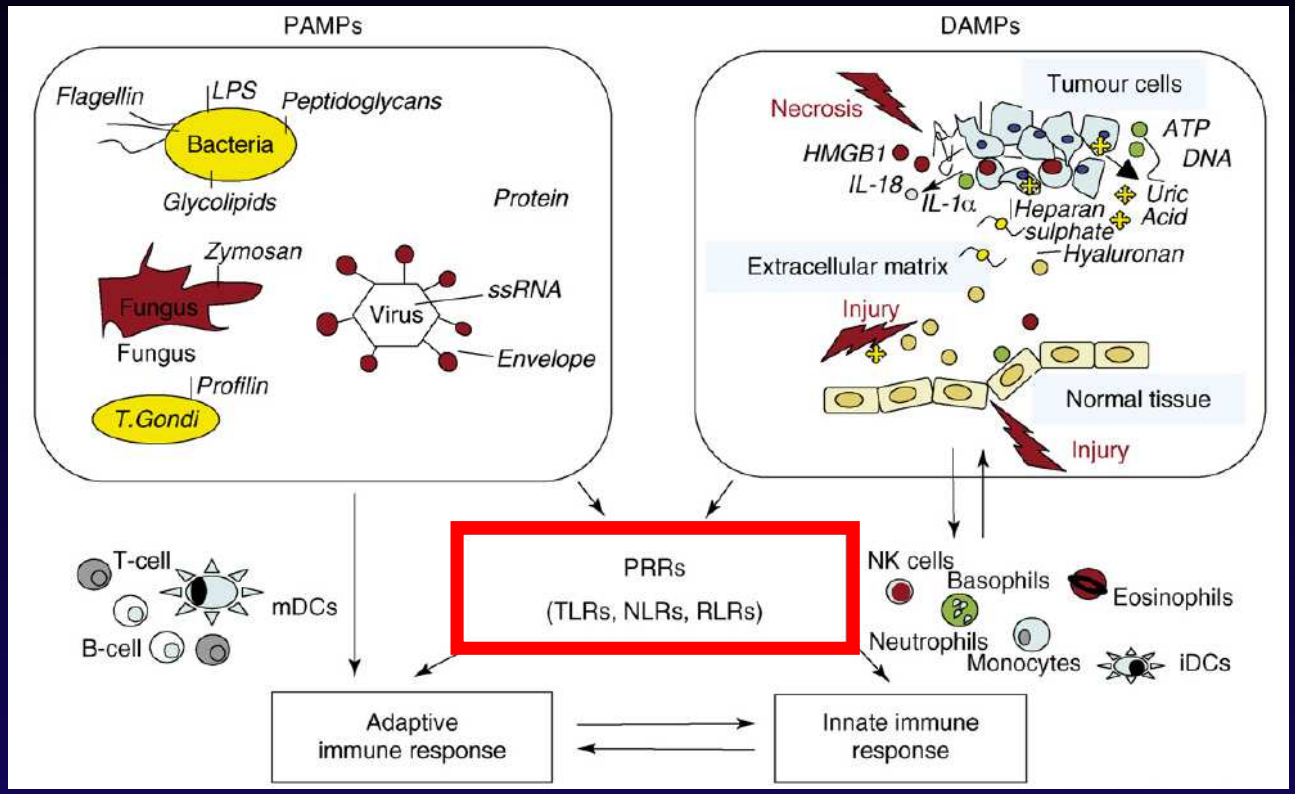
PATHOGENS **DAMAGE**



Rubartelli & Lotze, *Trends in Immunology 2007*

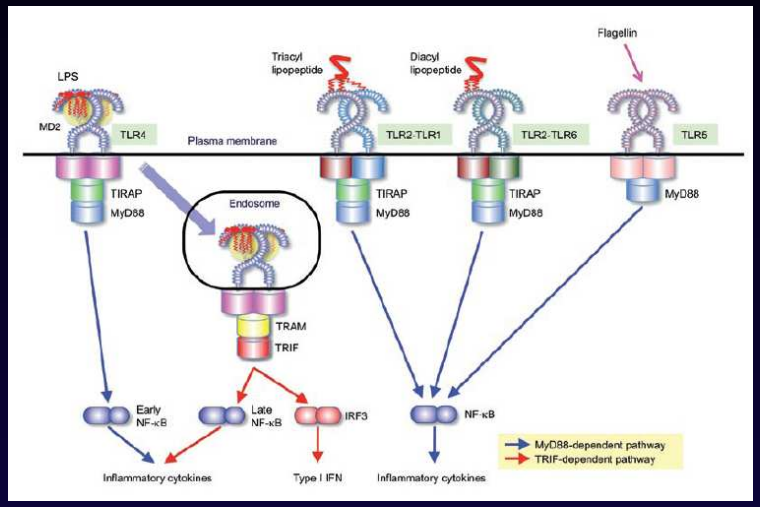
Danger signals start inflammation

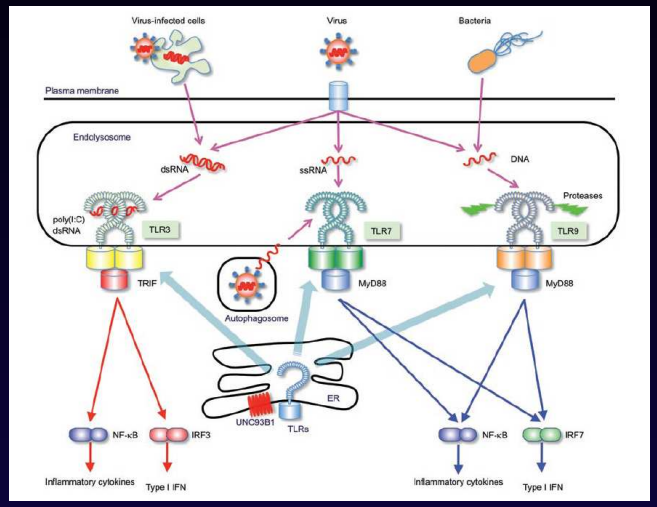
PATHOGENS **DAMAGE**



Rubartelli & Lotze, *Trends in Immunology 2007*

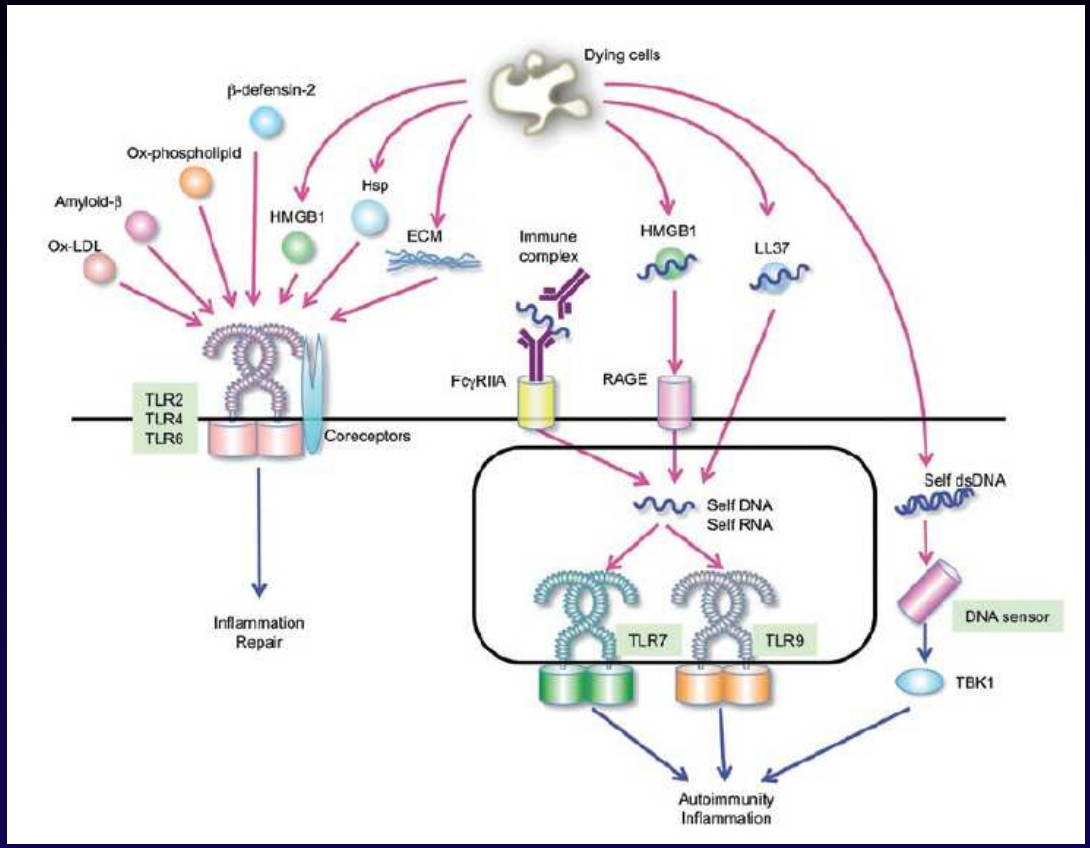
Receptors sense Danger: Pathogens





Kawai & Akira, *Nat. Immunol. 2010*

Receptors sense Danger: Damage



Kawai & Akira, *Nat. Immunol. 2010*

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Innate Immunity and Inflammation in Cancer

- Outcomes vary:

  - Promote cancer (Bad inflammation)

  - Suppress cancer (Good inflammation)

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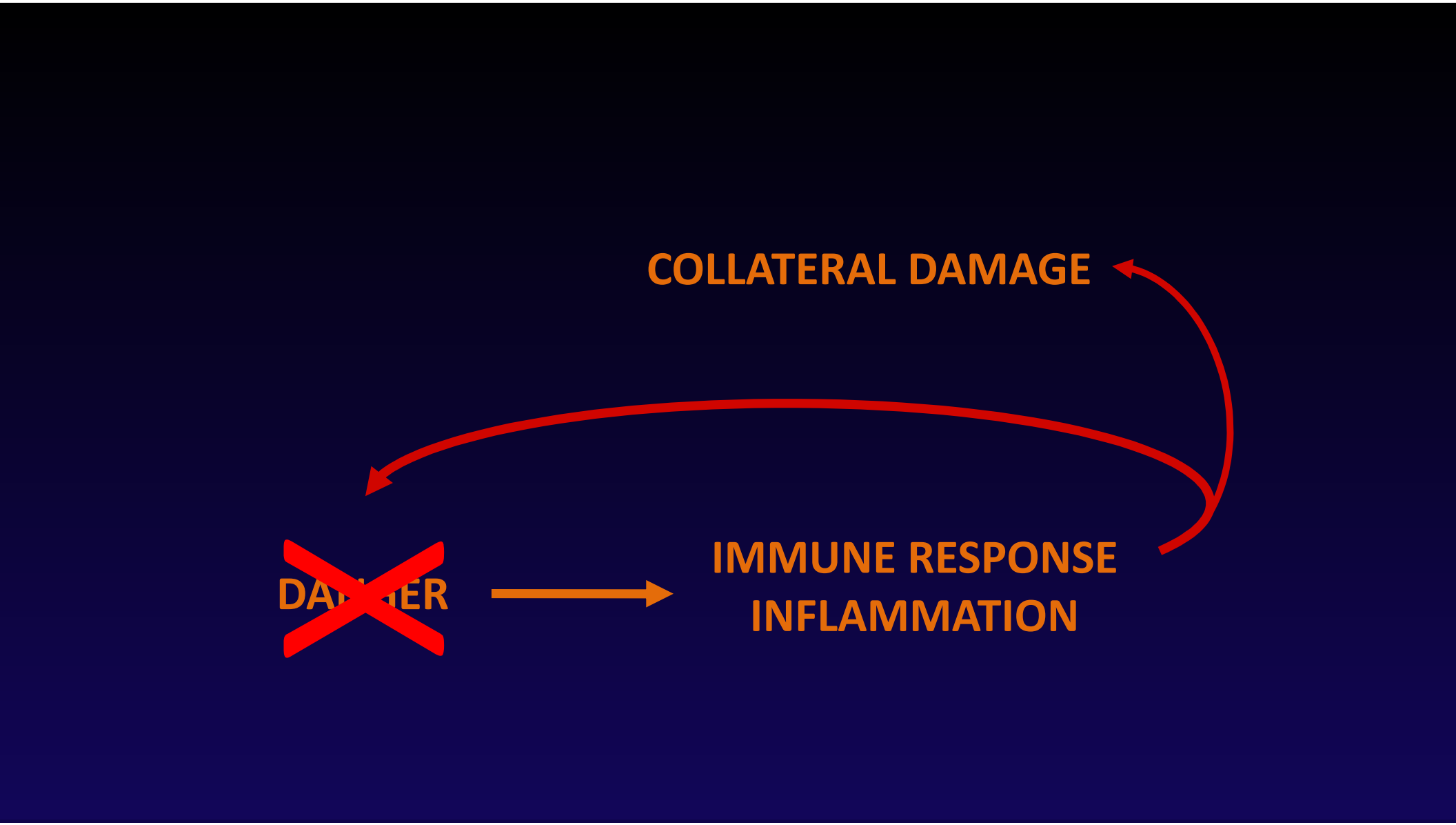
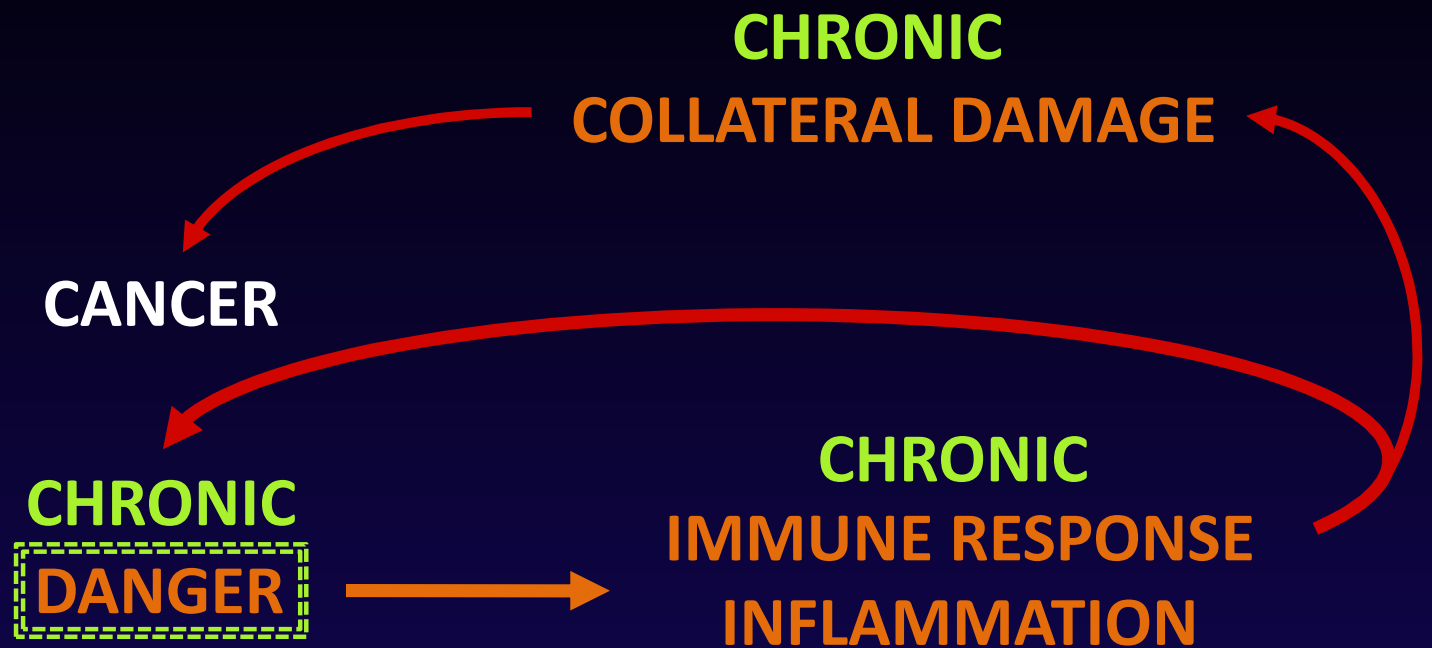
Bad Inflammation Causes Cancer

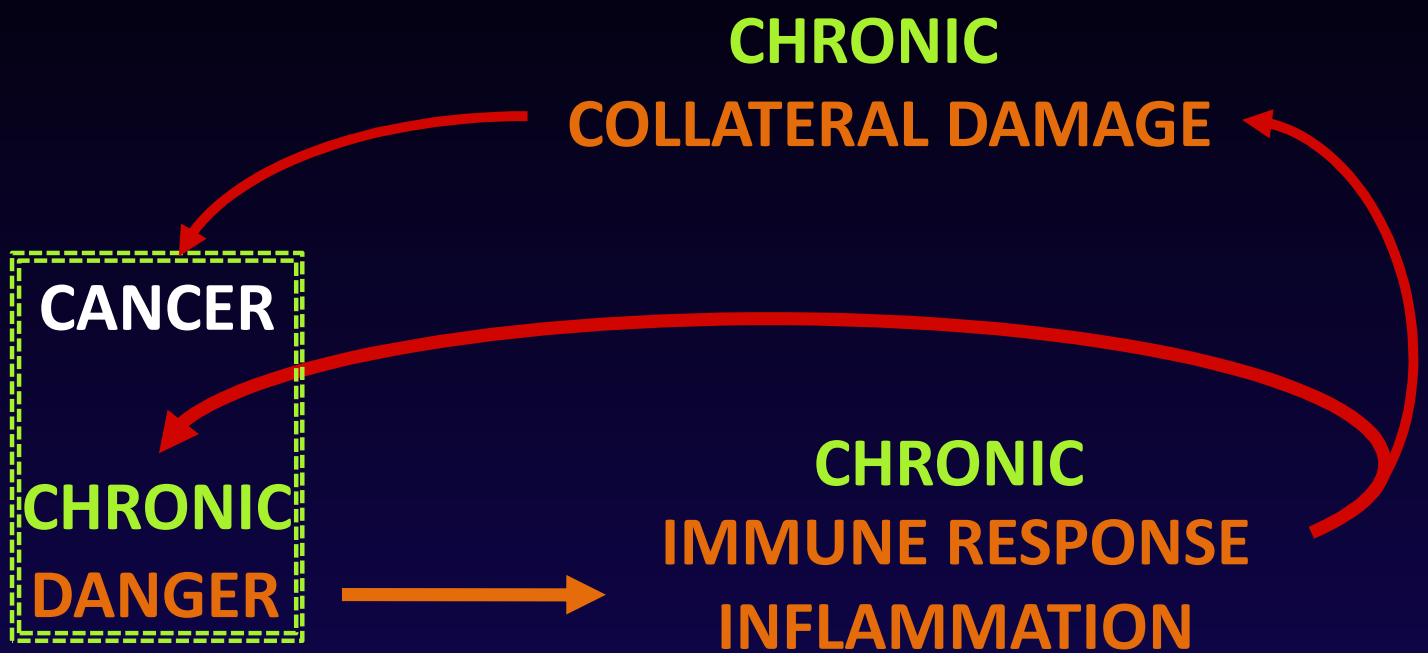
DANGER

cellular damage caused by

- **pathogens**
- **physical damage**
- **chemicals**
- **UV**
- **etc**


COLLATERAL DAMAGE
IMMUNE RESPONSE
INFLAMMATION


CHRONIC
COLLATERAL DAMAGE
CANCER
CHRONIC
DANGER
CHRONIC
IMMUNE RESPONSE
INFLAMMATION



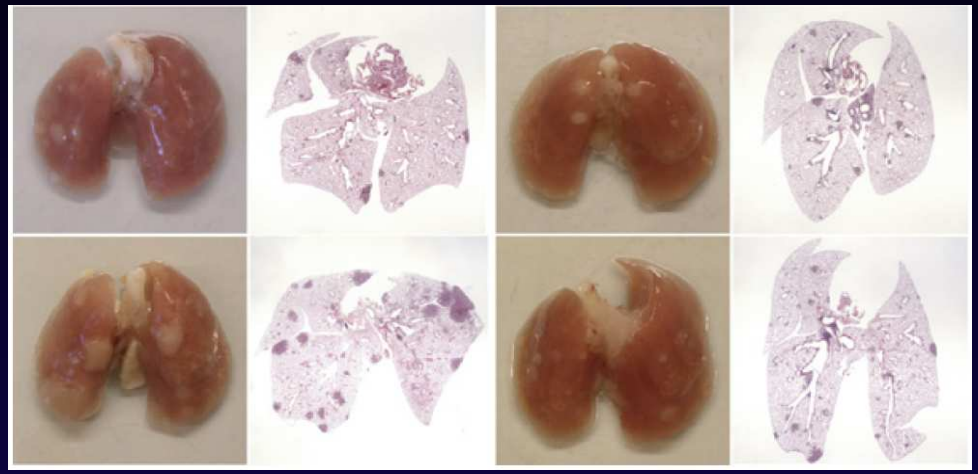
cancer: a “never-healing wound”

Dvorak , *NEJM* 1986

Inflammation can Promote Cancer: collaboration with K-ras mutation

no smoking

4 cigarettes per day



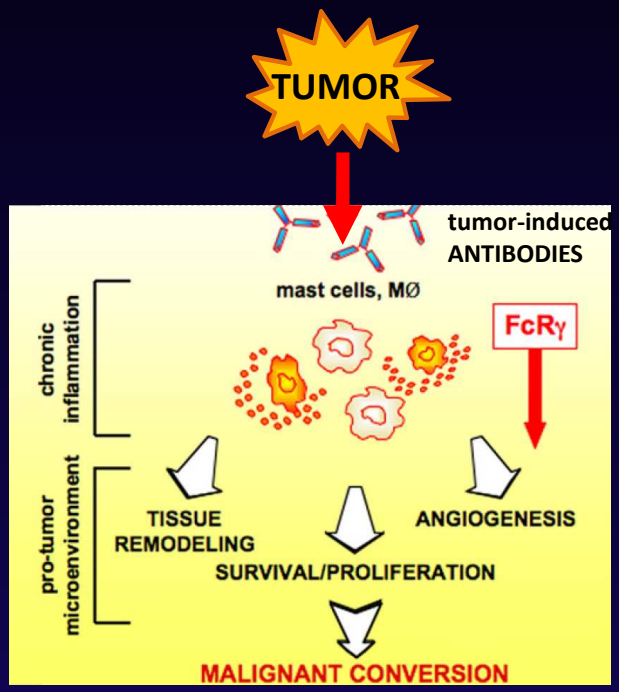
K-ras mutation & normal myeloid cells

K-ras mutation + $IKK^{-/-}$ myeloid cells

- ↓ NF-κB
- ↓ pSTAT3
- ↓ IL-6
- ↓ neutrophils
- ↓ angiogenesis

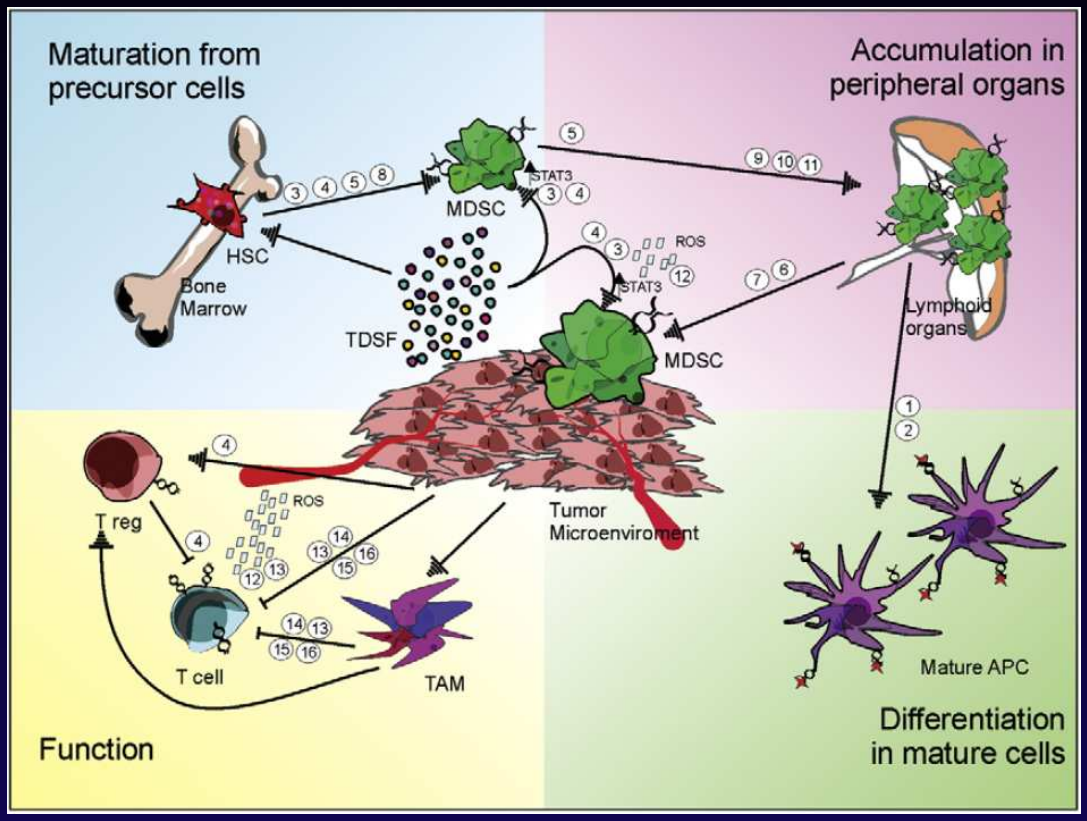
Takahashi et al. , *Cancer Cell* 2010

Inflammation can Promote Cancer: collaboration with HPV E6/E7 oncogene



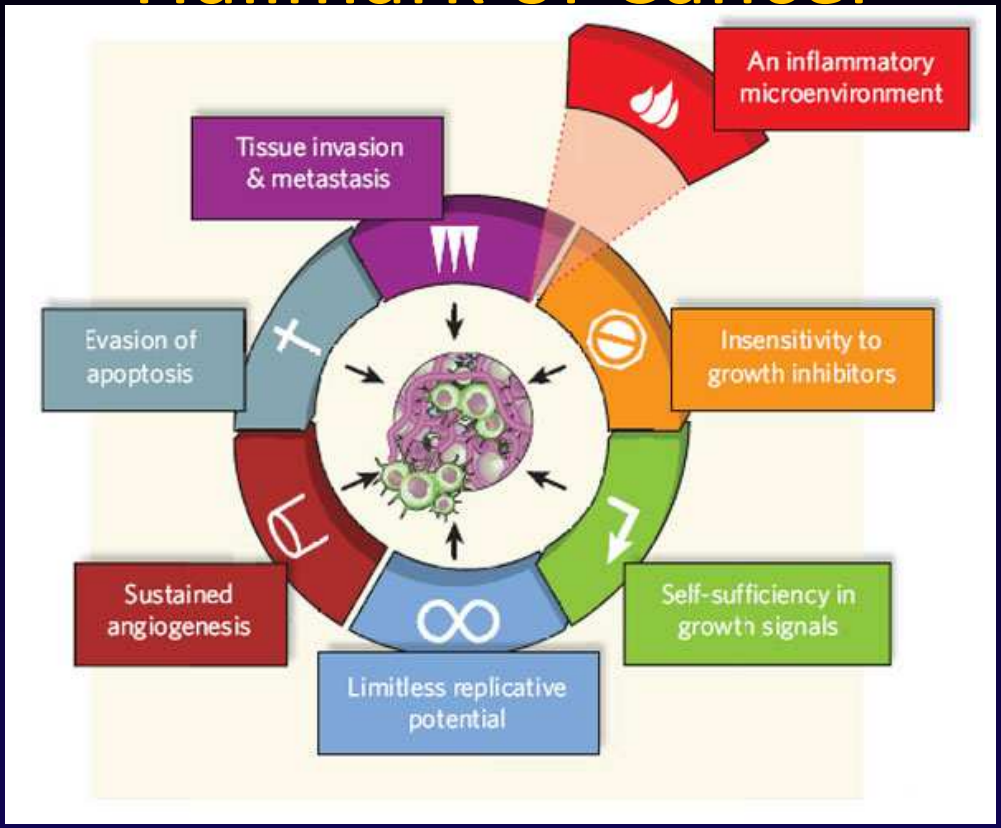
De Visser et al., *Cancer Cell* 2005
Andreu et al., *Cancer Cell* 2010

Tumors can induce bad inflammation



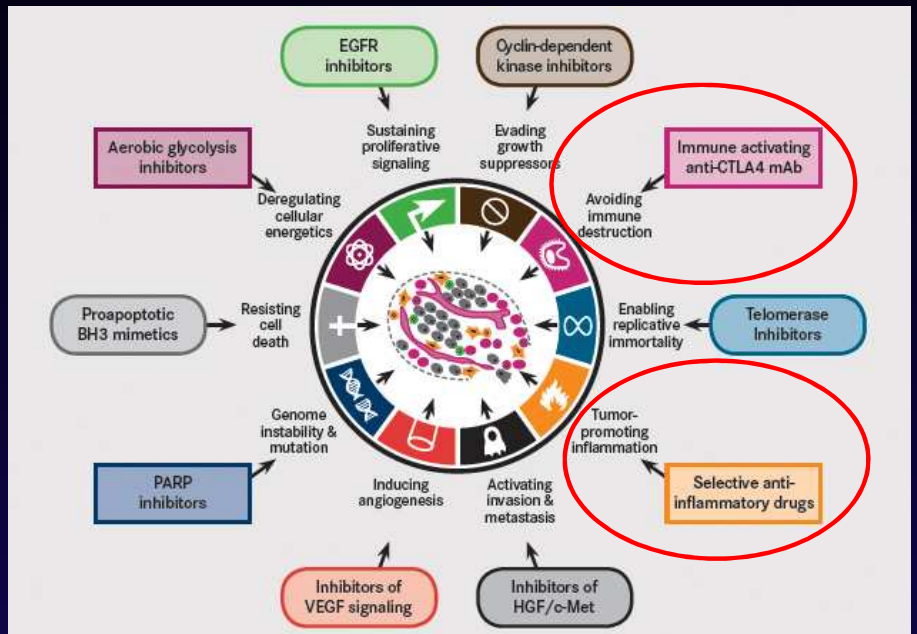
Ugel et al., *Curr. Opin. Pharmacol.* 2010

Inflammation is (now) a Classic Hallmark of Cancer



Mantovani et al., *Nature* 2009
Hanahan & Weinberg, *Cell* 2000

Inflammation is (now) a Classic Hallmark of Cancer



This figure illustrates some of the many approaches employed in developing therapeutics targeted to the known and emerging hallmarks of cancer.

EGFR indicates epidermal growth factor receptor; CTLA4, cytotoxic T lymphocyte-associated antigen 4; mAb, monoclonal antibody; HGF, hepatocyte growth factor; VEGF, vascular endothelial growth factor; PARP, poly-(ADP ribose) polymerase.

Source: Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646-674. Reprinted with permission.

Hanahan & Weinberg, *Cell* 2011

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Good *vs.* Bad Inflammation in Cancer

Immunity, Inflammation, and Cancer

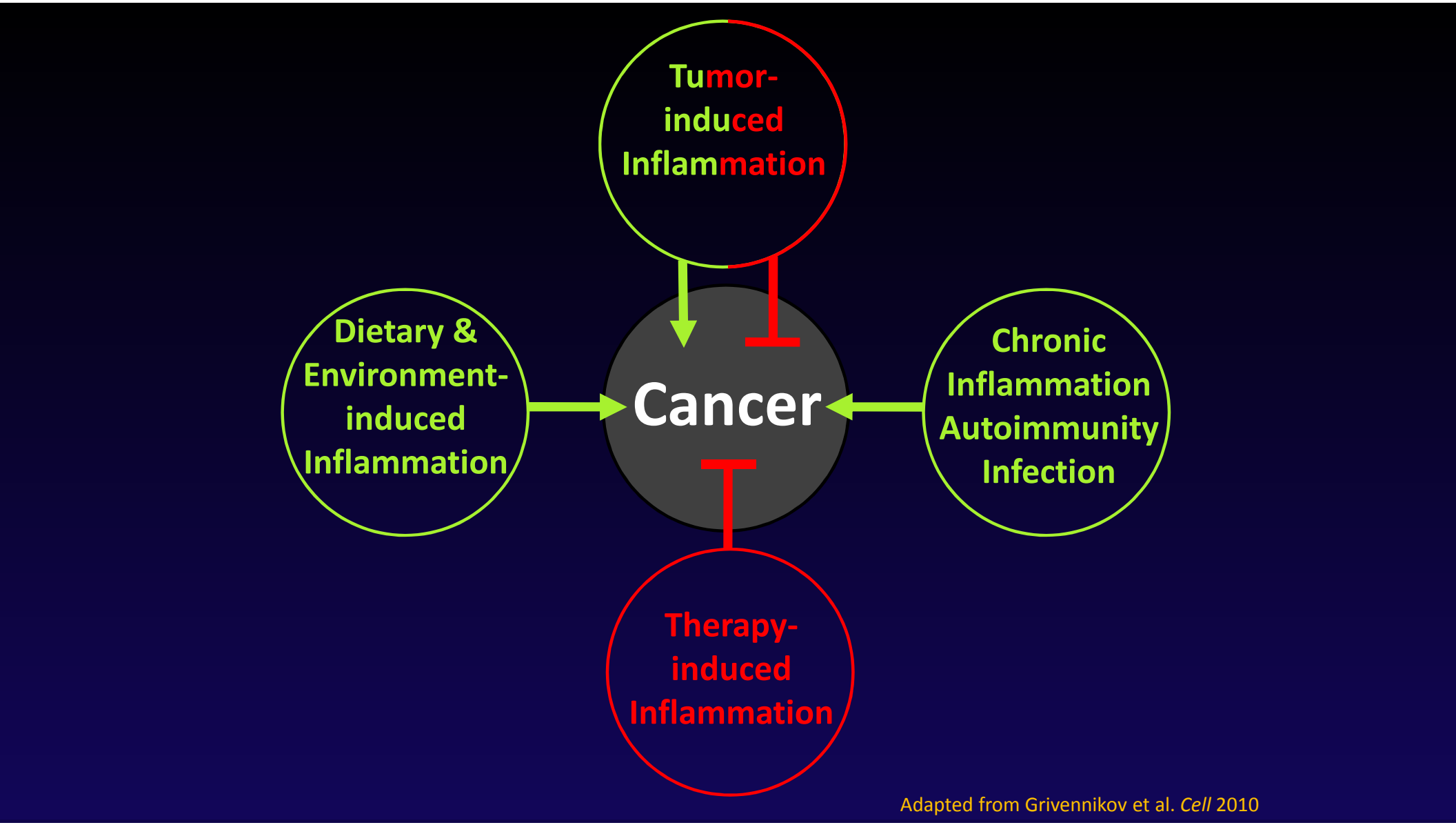
Sergei I. Grivennikov,[1] Florian R. Greten,[2] and Michael Karin[1,*]

Cell *140*, 883–899, March 19, 2010

Cancer and Inflammation: Promise for Biologic Therapy

Sandra Demaria, Eli Pikarsky,† Michael Karin,‡ Lisa M. Coussens,§ Yen-Ching Chen,‖ Emad M. El-Omar,¶ Giorgio Trinchieri,# Steven M. Dubinett,** Jenny T. Mao,†† Eva Szabo,‡‡ Arthur Krieg,§§ George J. Weiner,‖‖ Bernard A. Fox,¶¶ George Coukos,## Ena Wang,*** Robert T. Abraham,††† Michele Carbone,‡‡‡ and Michael T. Lotze§§§*

J Immunother • Volume 33, Number 4, May 2010



Adapted from Grivennikov et al. *Cell* 2010

Bottom Line: Inflammation can be Good or Bad: Pro or Anti-Tumor

Table 1. Roles of Different Subtypes of Immune and Inflammatory Cells in Antitumor Immunity and Tumor-Promoting Inflammation

Cell Types	Antitumor	Tumor-Promoting
Macrophages, dendritic cells, myeloid-derived suppressor cells	Antigen presentation; production of cytokines (IL-12 and type I IFN)	Immunosuppression; production of cytokines, chemokines, proteases, growth factors, and angiogenic factors
Mast cells		Production of cytokines
B cells	Production of tumor-specific antibodies?	Production of cytokines and antibodies; activation of mast cells; immunosuppression
$CD8^+$ T cells	Direct lysis of cancer cells; production of cytotoxic cytokines	Production of cytokines?
$CD4^+$ Th2 cells		Education of macrophages; production of cytokines; B cell activation
$CD4^+$ Th1 cells	Help to cytotoxic T lymphocytes (CTLs) in tumor rejection; production of cytokines ($IFN\gamma$)	Production of cytokines
$CD4^+$ Th17 cells	Activation of CTLs	Production of cytokines
$CD4^+$ Treg cells	Suppression of inflammation (cytokines and other suppressive mechanisms)	Immunosuppression; production of cytokines
Natural killer cells	Direct cytotoxicity toward cancer cells; production of cytotoxic cytokines	
Natural killer T cells	Direct cytotoxicity toward cancer cells; production of cytotoxic cytokines	
Neutrophils	Direct cytotoxicity; regulation of CTL responses	Production of cytokines, proteases, and ROS

Grivennikov et al. *Cell* 2010

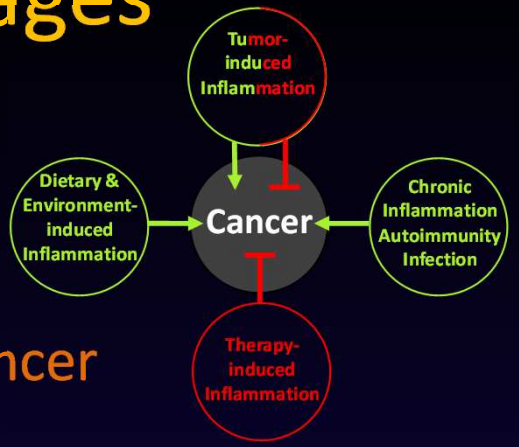
In the Clinic: Cancer Therapies that Block Bad Inflammation

• COX-2 inhibitor	Aspirin, Celecoxib (colorectal)
• VEGF blocker	Bevacizumab, Sorafenib (several)
• IL-1β blocker	IL-1Ra (MM)
• Cytokine Regulators	Lenalidomide (MDS, MM)
• Kill Helicobacter Pylori	Clarithrom./Amoxicillin (gastric)
• Remove suppressors	Cycl/Fludar + T cells (melanoma)
• Cytotoxic Therapy?	Radiation/Chemother. (all cancers)
• Targeted Therapy?	TKI inhibitors (many cancers)

In the Clinic: Cancer Therapies that Induce Good Inflammation

• Bacteria	BCG (bladder)
• TLR agonists	Imiquimod (basal cell carcinoma)
	CpG (B cell lymphoma)
• Cytokines	IL-2 (melanoma, renal)
	IFN-α (melanoma, renal, CML)
• Antibodies	aCTLA4/aPD(L)-1 mAb (melanoma)
• Surgery	Danger/inflammation? (cervical)
• Hem. Stem Cells	Stem Cell Transpl. (leukemia, lymphoma)
• T cells	Adoptive T cell Transfer (melanoma)
• Vaccine	PAP-loaded DCs (prostate)

Take Home Messages



- Inflammation is a classic hallmark of cancer
- Innate Immunity & Inflammation can promote or suppress cancer
- Manipulating immunity can promote or suppress cancer
- Understanding of inflammatory cells & molecules in cancer is limited but growing, allowing therapeutic intervention