

SITC - Primer on Tumor Immunology and Biological Therapy of Cancer

Innate Immunity and Inflammation

Willem Overwijk, Ph.D.

MD Anderson Cancer Center

Center for Cancer Immunology Research

Houston, TX

THE UNIVERSITY OF TEXAS
MD Anderson
Cancer Center

Making Cancer History™

www.allthingsbeautiful.com

Innate Immunity and Inflammation

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

Innate Immunity and Inflammation

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

- **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.

- **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)

“Innate Immunity” and “Inflammation” are vague terms

- Specific cell types and molecules orchestrate specific types of inflammation

“Innate Immunity” and “Inflammation” are vague terms

- Specific cell types and molecules orchestrate specific types of inflammation
- Innate Immunity A \neq Innate Immunity B
- Inflammation A \neq Inflammation B

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

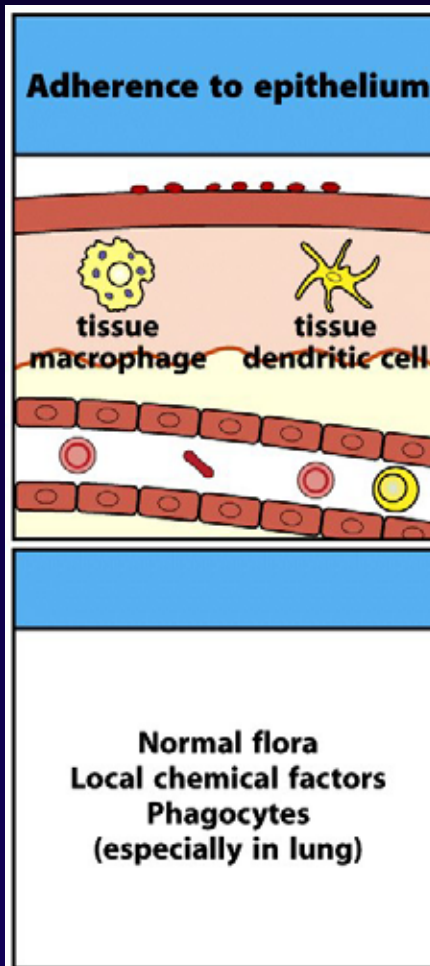
- Specific cell types and molecules orchestrate specific types of inflammation
- Innate Immunity A \neq Innate Immunity B
- Inflammation A \neq Inflammation B
- Some immune responses promote cancer, others suppress it

Innate Immunity and Inflammation

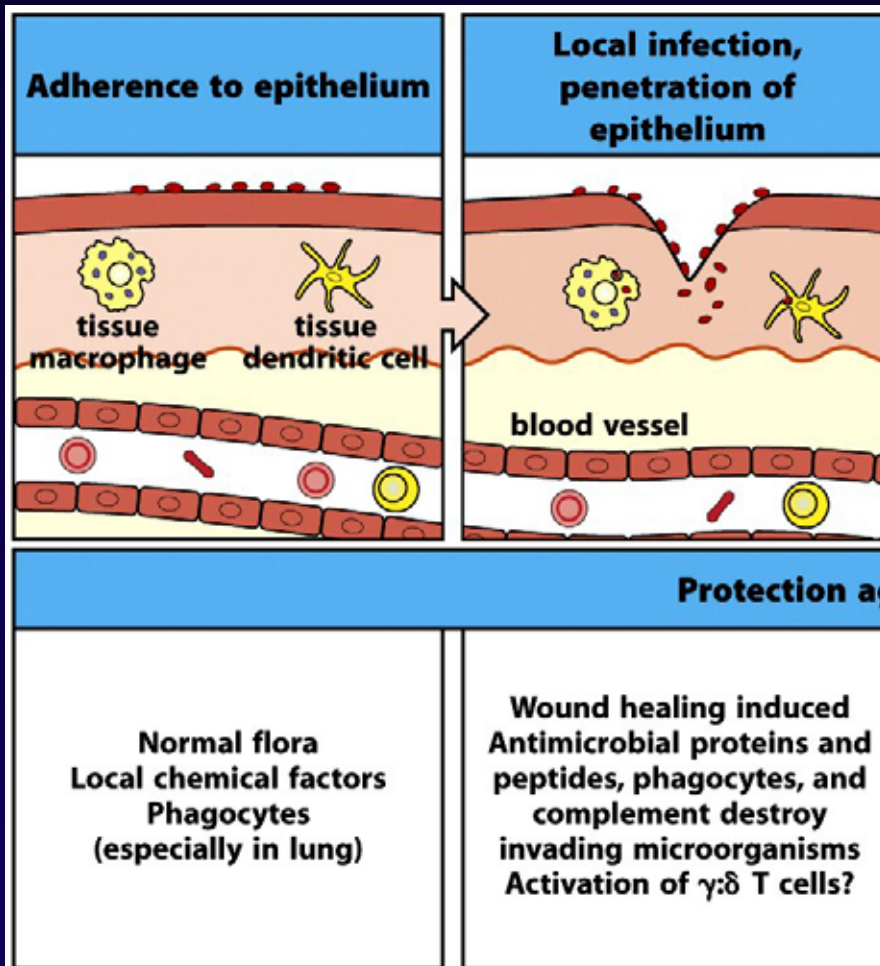
Functions:

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

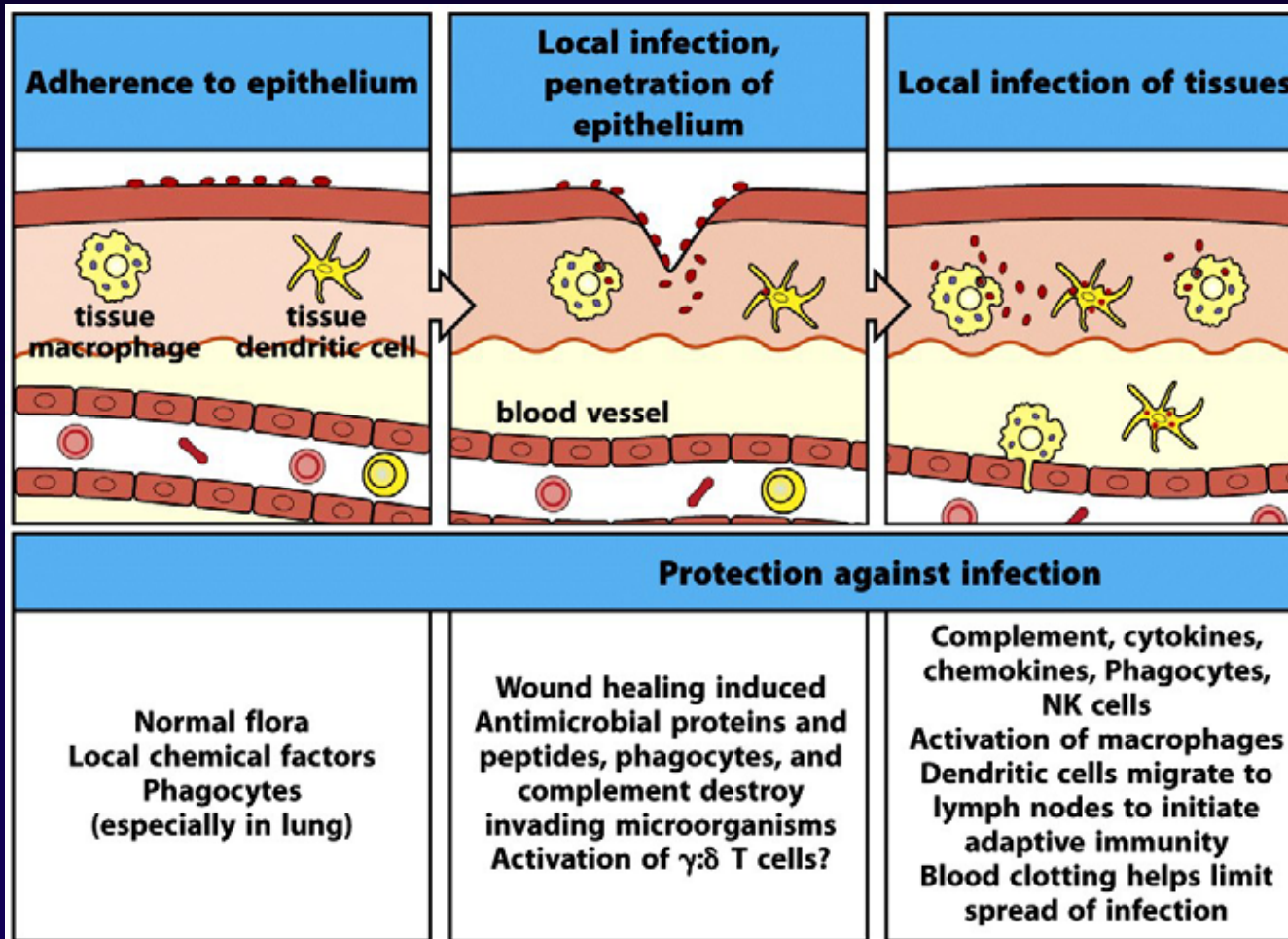
Innate Immunity and Inflammation: A Paper Cut



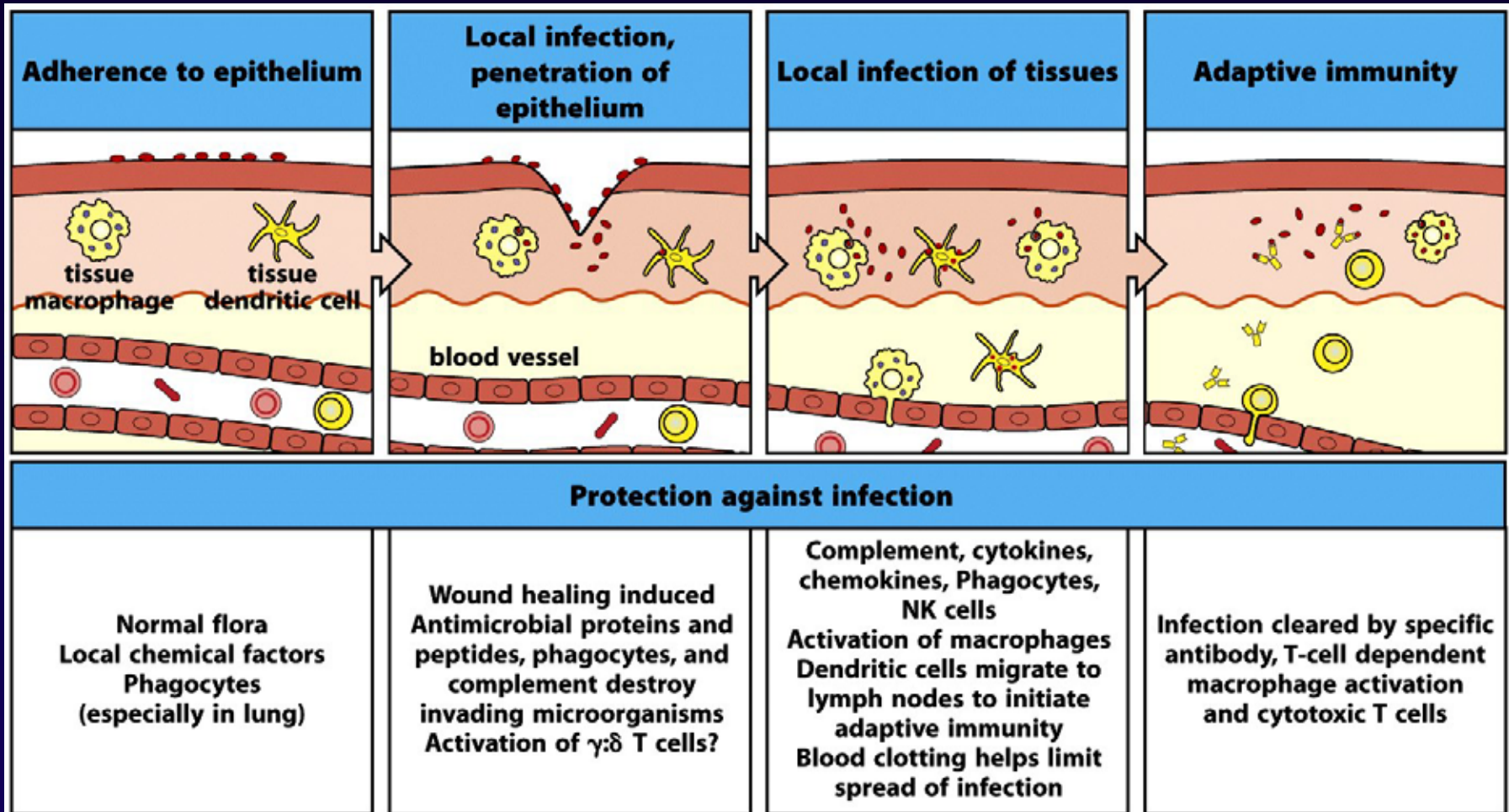
Innate Immunity and Inflammation: A Paper Cut



Innate Immunity and Inflammation: A Paper Cut



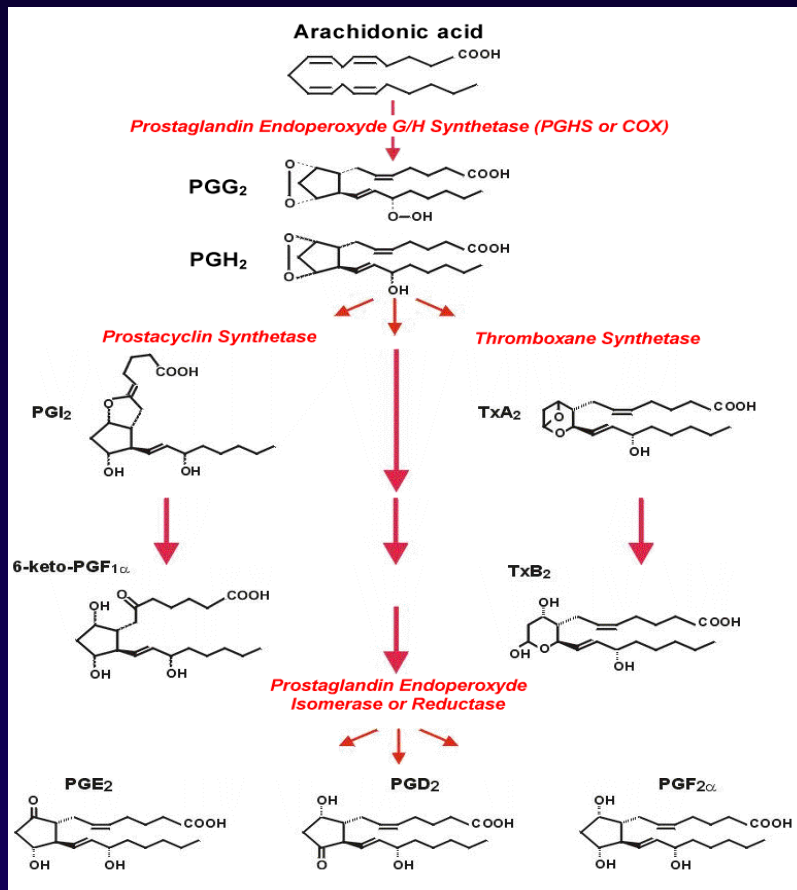
Innate Immunity and Inflammation: A Paper Cut



Innate Immunity and Inflammation

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

Innate Immune Molecules: Cyclooxygenase-2 (COX-2)



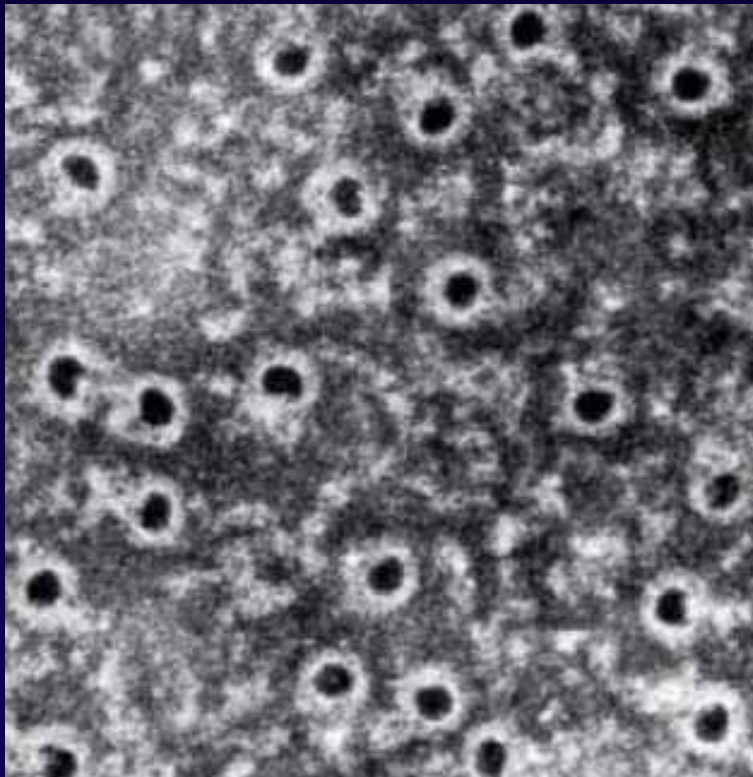
Recognize

- inflammation

Cause

- inflammation

Innate Immune Molecules: Complement System



Recognize

- pathogens
- antibodies
- lectins

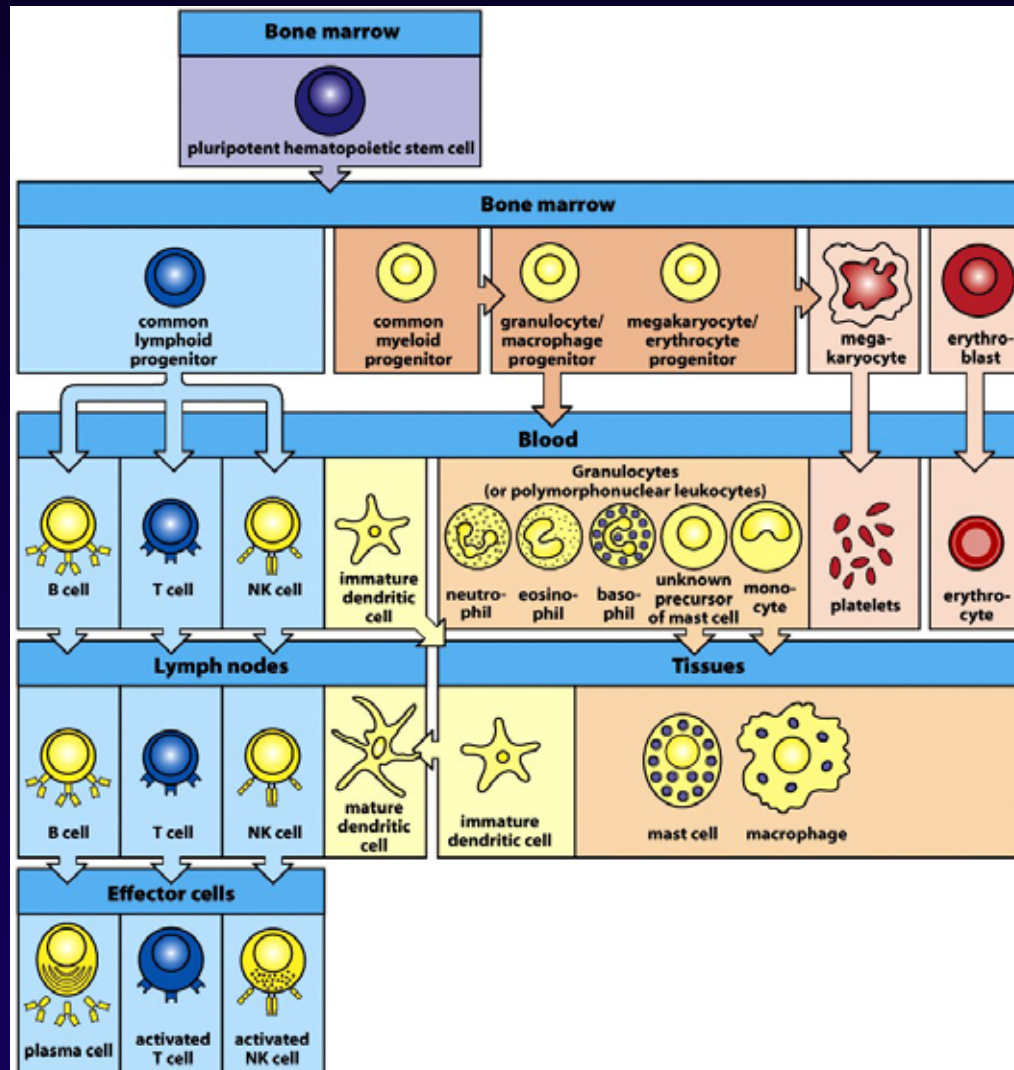
Cause

- pathogen clearance
- chemotaxis
- inflammation

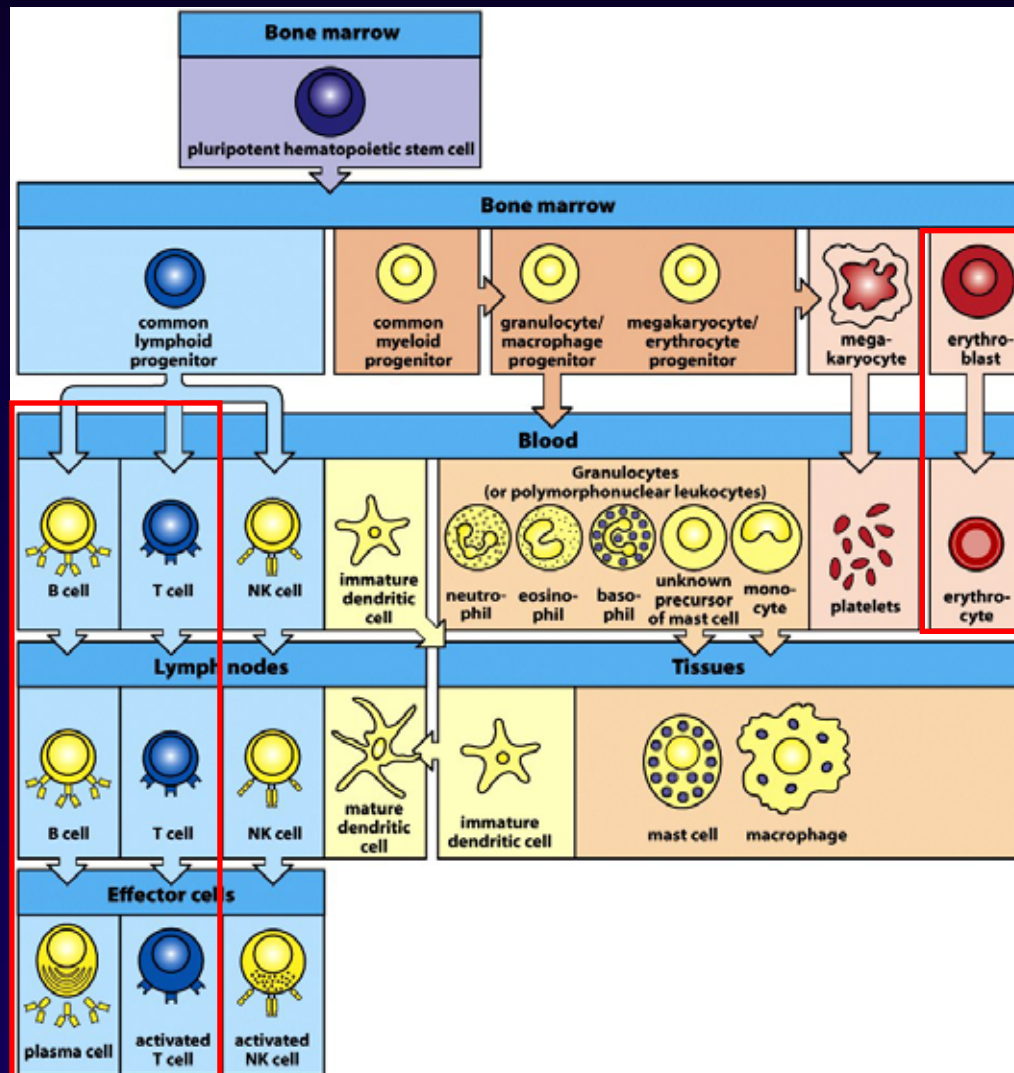
Innate Immune Molecules: type I IFN(- α , β)

- Induced by infection/damage
- Antiviral/Antiproliferative
- Increase innate and adaptive immunity
- Cause inflammation

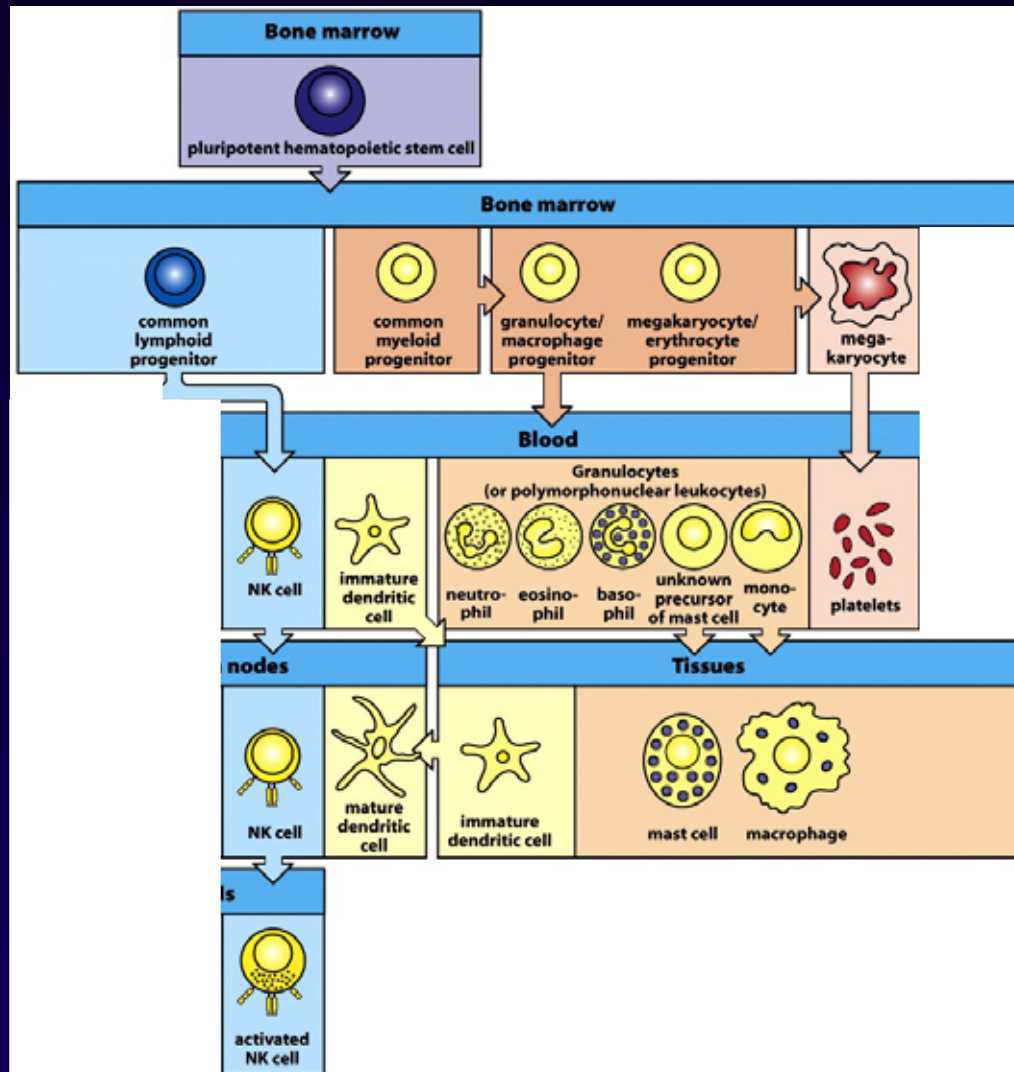
Innate Immune Cells




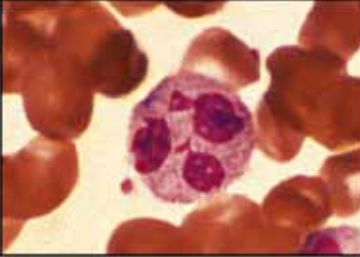

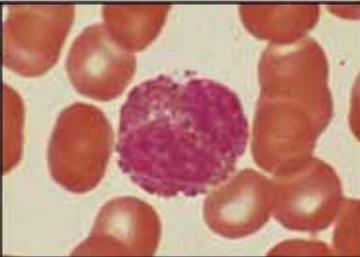

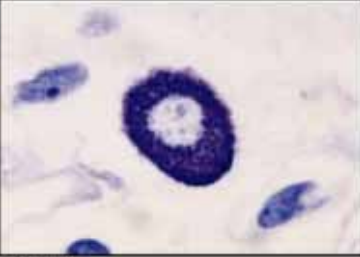

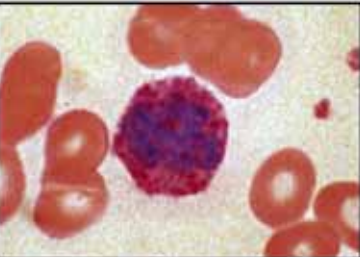
Innate Immune Cells



Innate Immune Cells



Innate Immune Cells: granulocytes

Cell		Activated function
Neutrophil 		Phagocytosis and activation of bactericidal mechanisms
Eosinophil 		Killing of antibody-coated parasites
Mast cell 		Release of granules containing histamine and active agents
Basophil 		(Unknown) <i>Antigen Presentation</i>

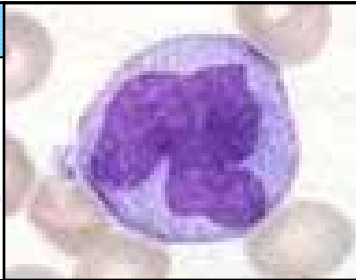
Recognize

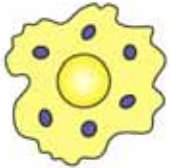

- pathogens
- antibodies

Cause

- pathogen clearance
- inflammation

Innate Immune Cells: phagocytes

Cell		Activated function
Monocyte Deeply Indented Nucleus		<i>Blood precursor of tissue Macrophages and Dendritic Cells</i>

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

Innate Immune Cells: NK, NKT and $\gamma\delta$ T cells

Recognize

- pathogens
- stressed cells
- “altered self”

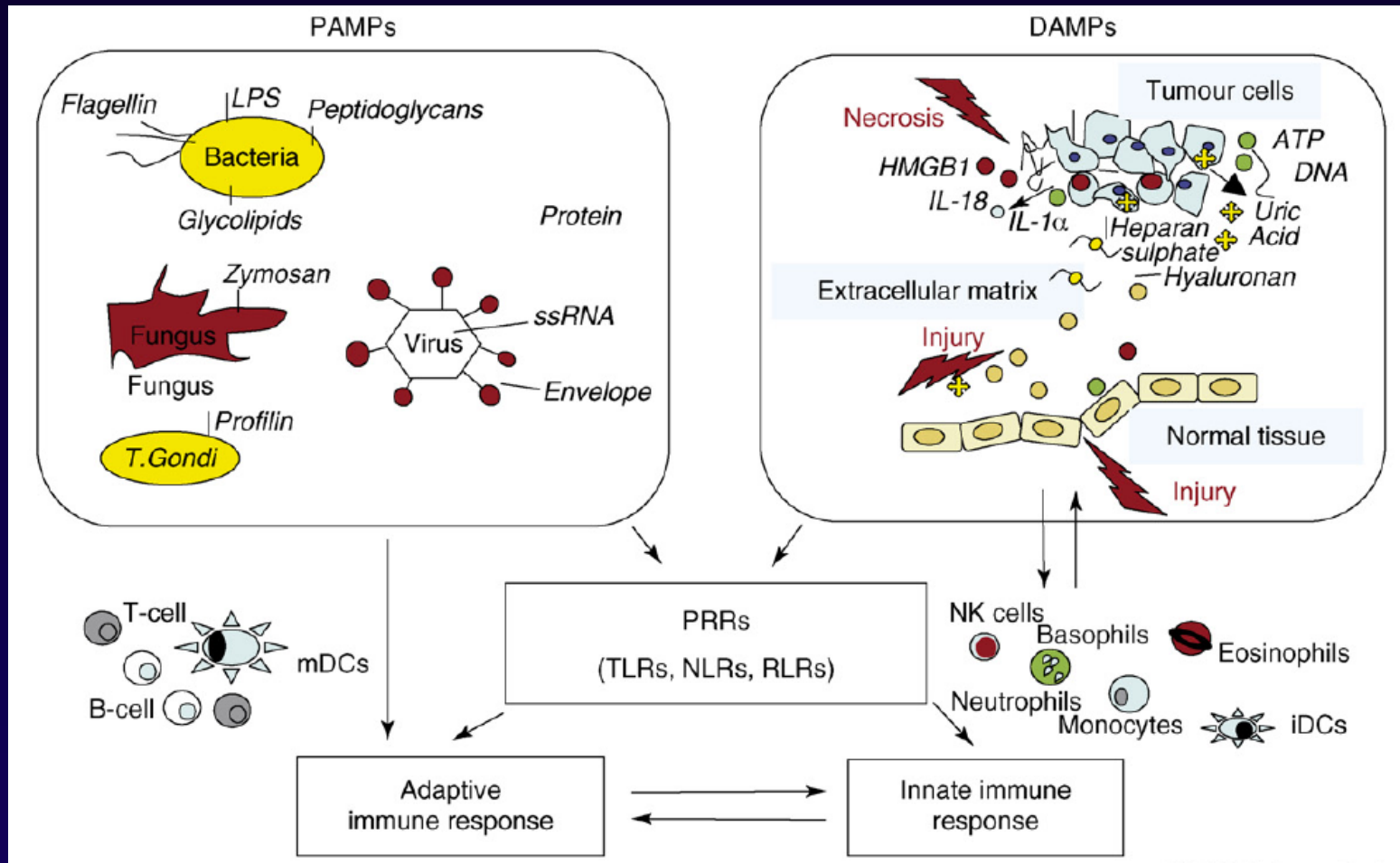
Cause

- pathogen clearance
- stressed/abnormal cell clearance
- inflammation

Danger signals start inflammation

PATHOGENS

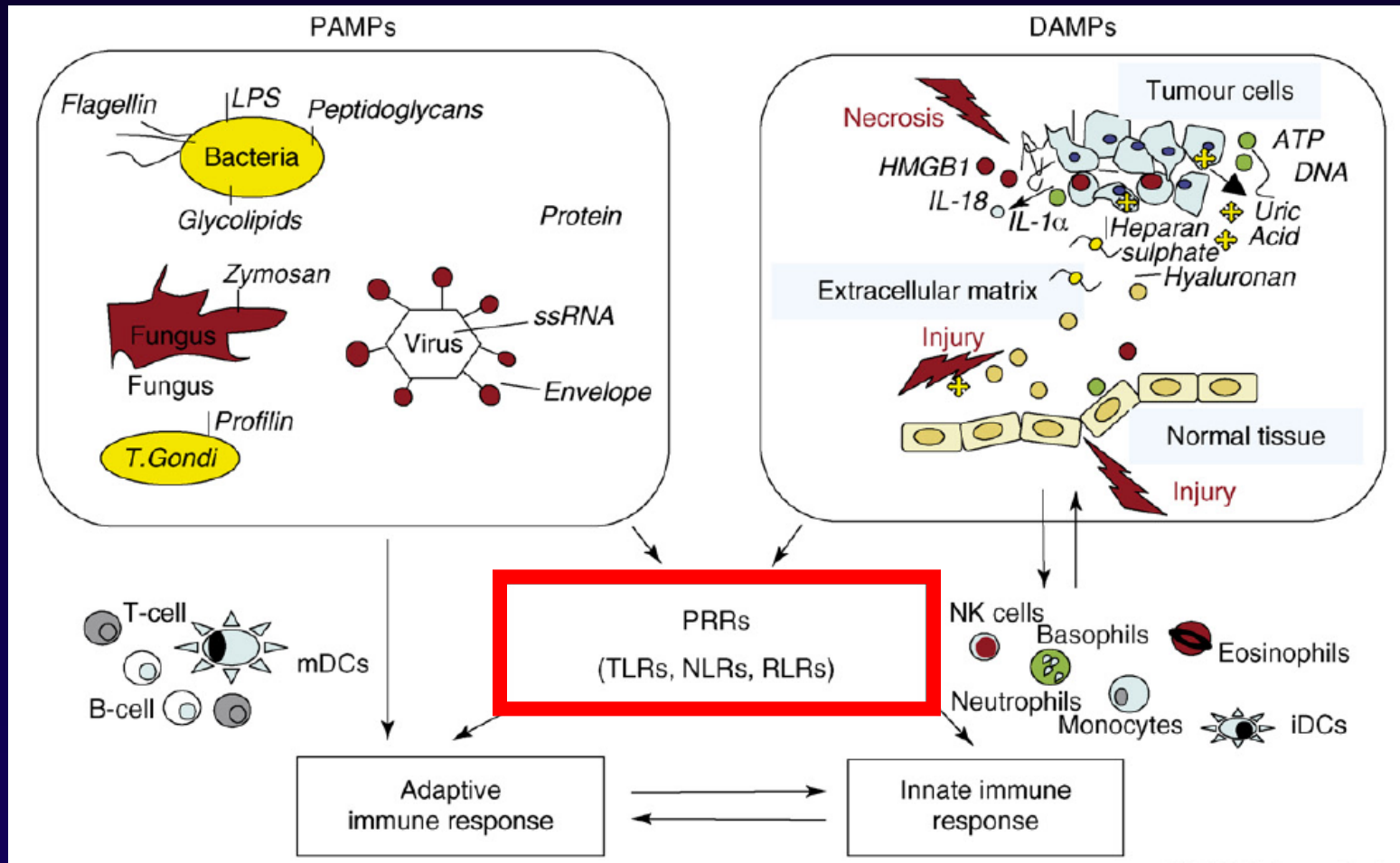
DAMAGE



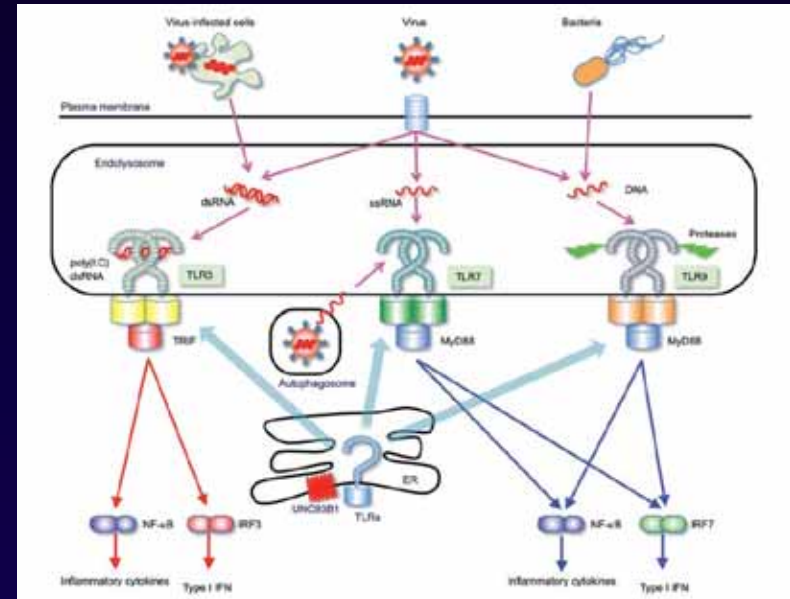
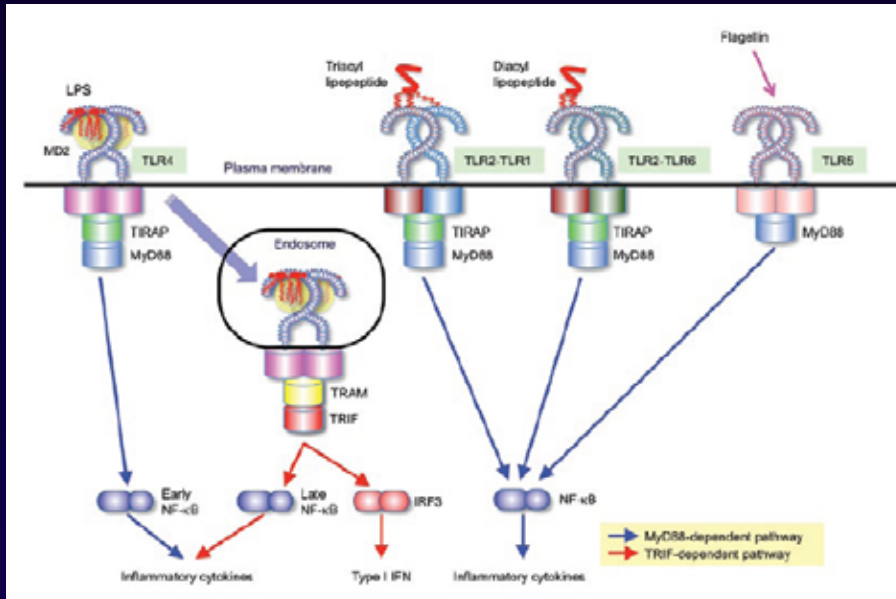
Danger signals start inflammation

PATHOGENS

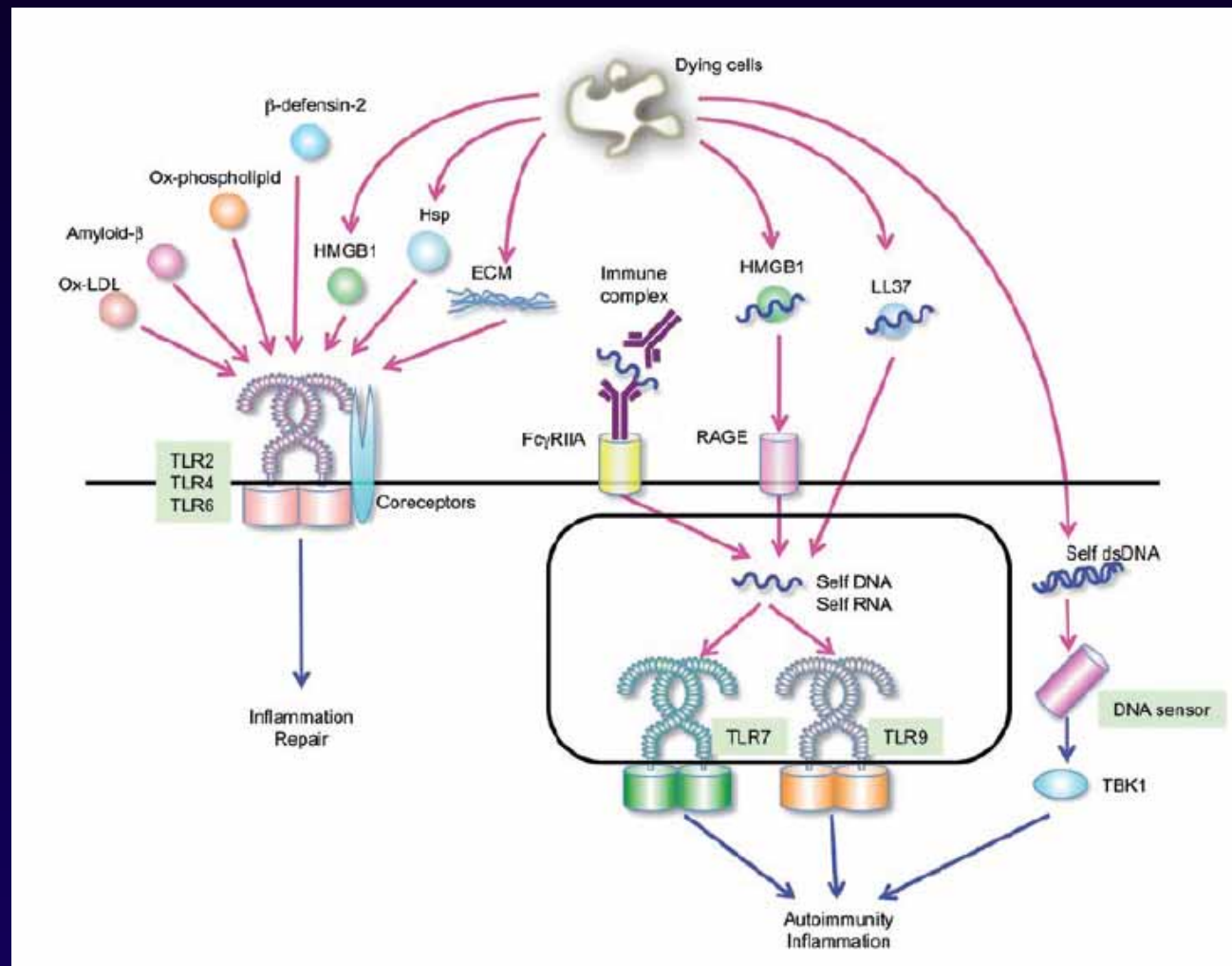
DAMAGE



Receptors sense Danger: Pathogens



Receptors sense Danger: Damage



Innate Immunity and Inflammation

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

Innate Immunity and Inflammation in Cancer

- Outcomes vary:
 - Promote cancer (Bad inflammation)
 - Suppress cancer (Good inflammation)

Innate Immunity and Inflammation

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

Bad Inflammation Causes Cancer

DANGER

cellular damage caused by

- pathogens
- physical damage
- chemicals
- UV
- etc

DANGER



**IMMUNE RESPONSE
INFLAMMATION**

~~DANGER~~



IMMUNE RESPONSE
INFLAMMATION

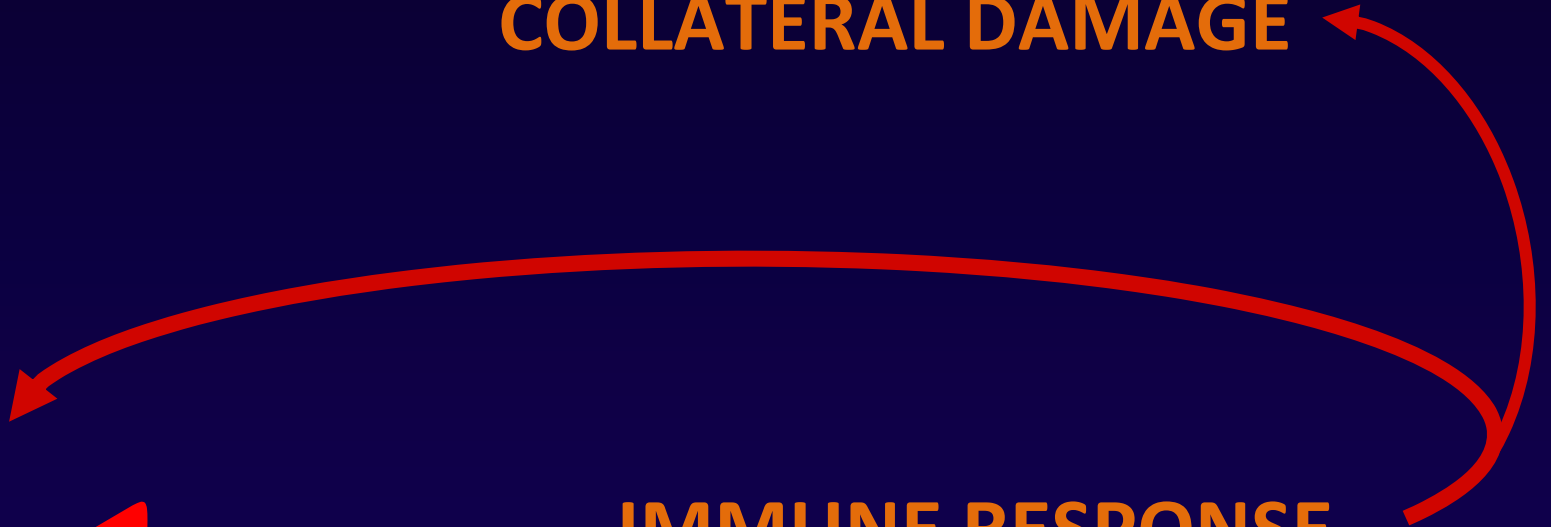


COLLATERAL DAMAGE

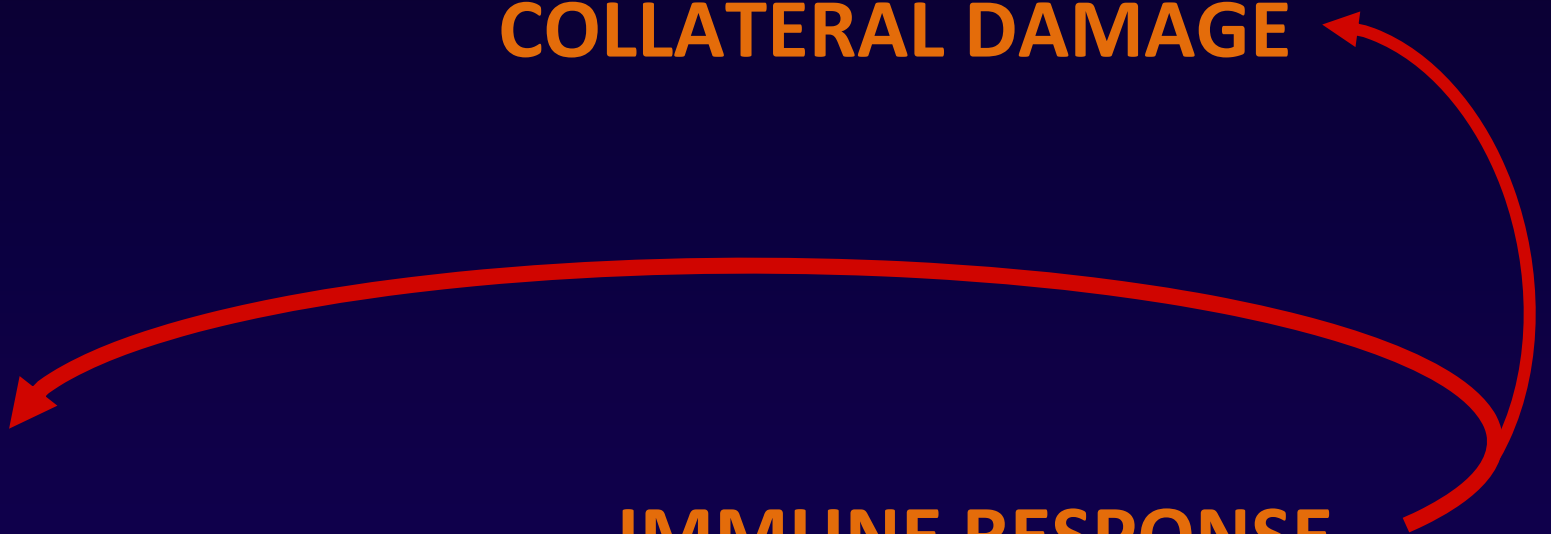
~~**DANGER**~~



**IMMUNE RESPONSE
INFLAMMATION**



COLLATERAL DAMAGE



**IMMUNE RESPONSE
INFLAMMATION**



DANGER



**IMMUNE RESPONSE
INFLAMMATION**

COLLATERAL DAMAGE



**CHRONIC
DANGER**



**IMMUNE RESPONSE
INFLAMMATION**

COLLATERAL DAMAGE

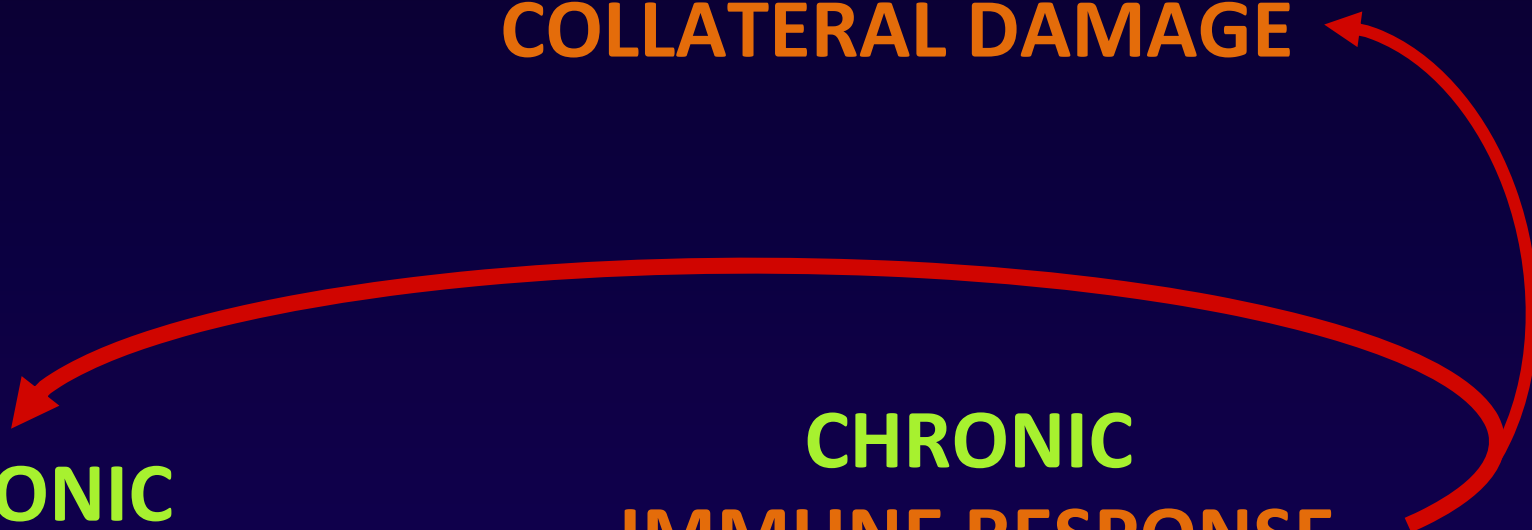


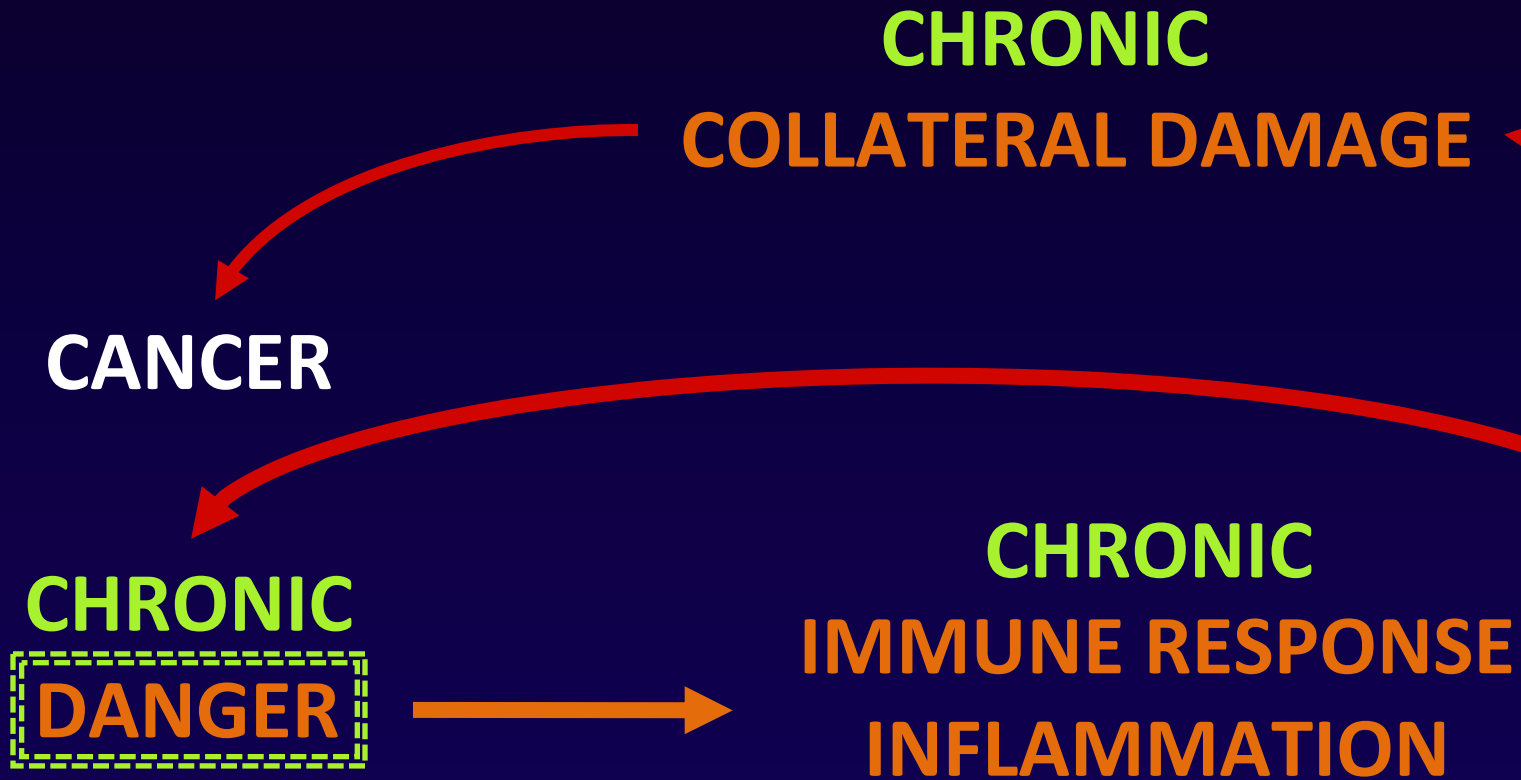
CHRONIC
DANGER

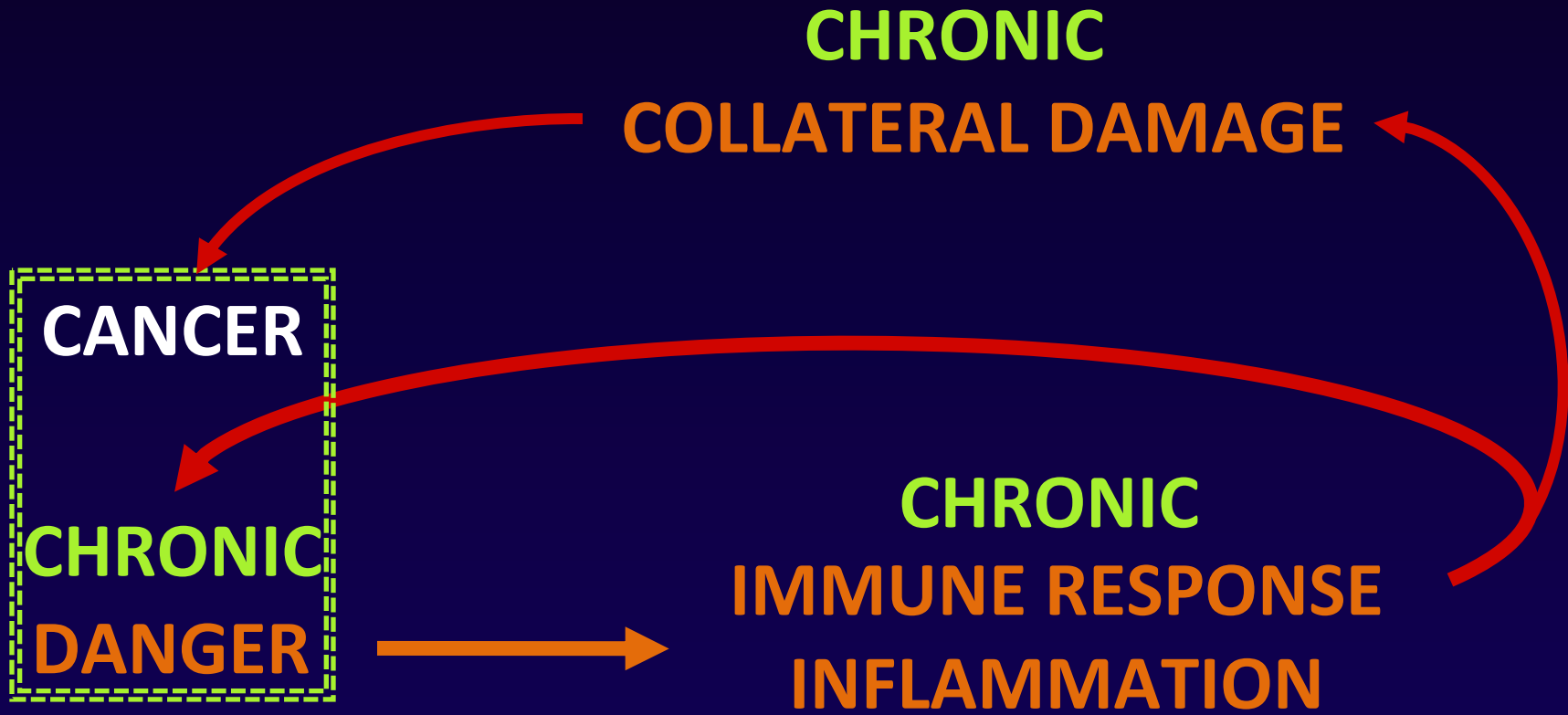


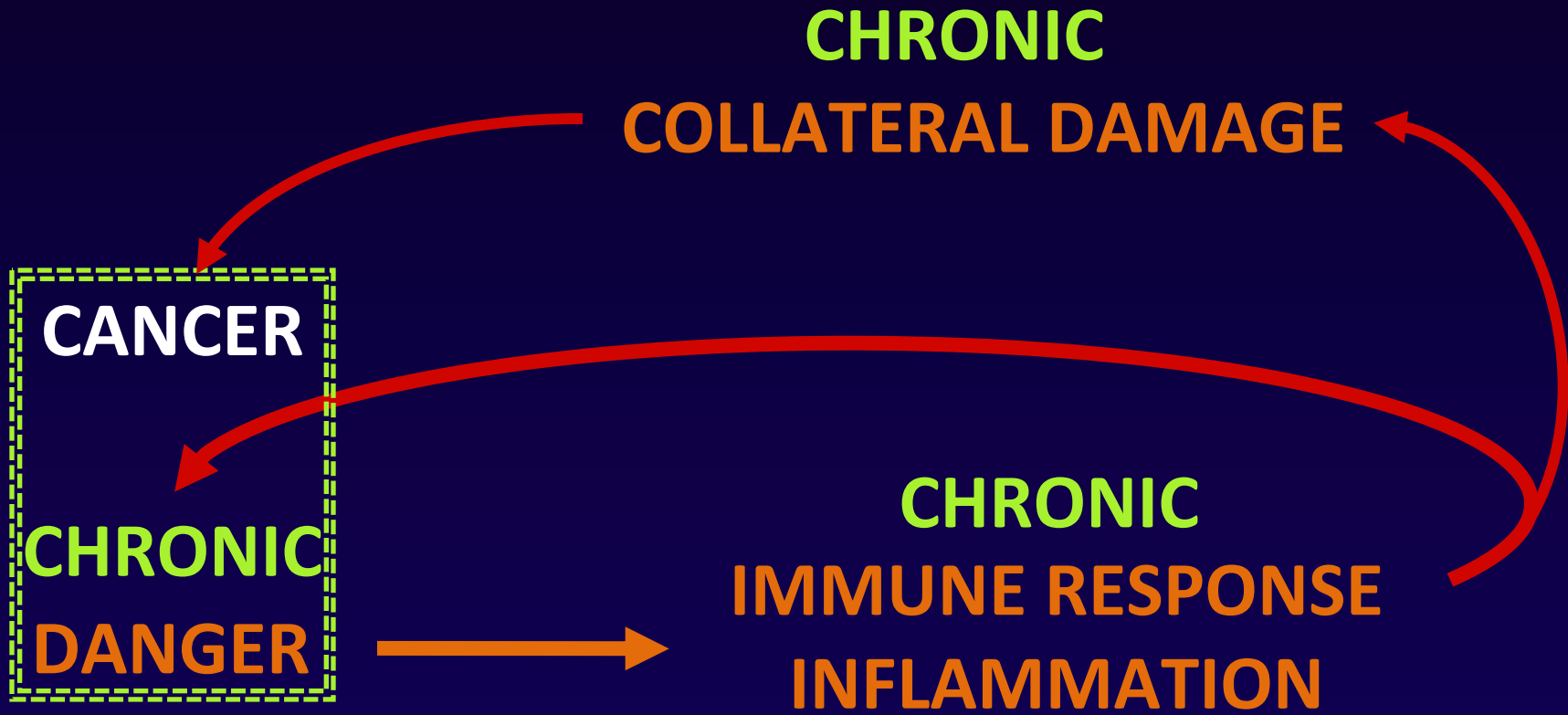
CHRONIC
IMMUNE RESPONSE
INFLAMMATION

CHRONIC
COLLATERAL DAMAGE





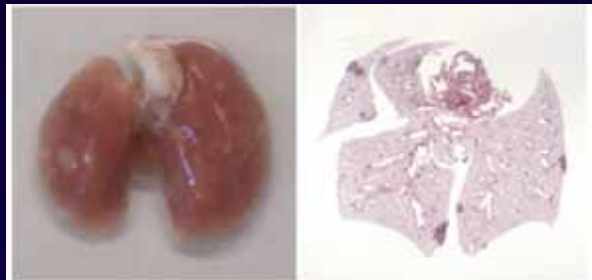




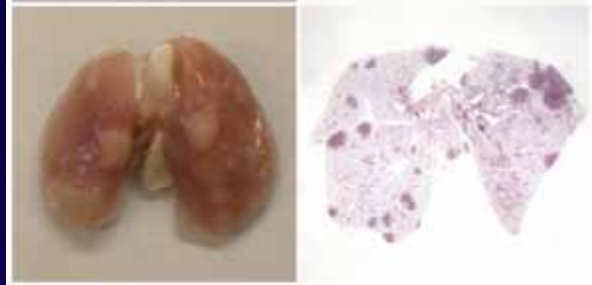
cancer: a “never-healing wound”

Inflammation can Promote Cancer: collaboration with K-ras mutation

no
smoking



4 cigarettes
per day

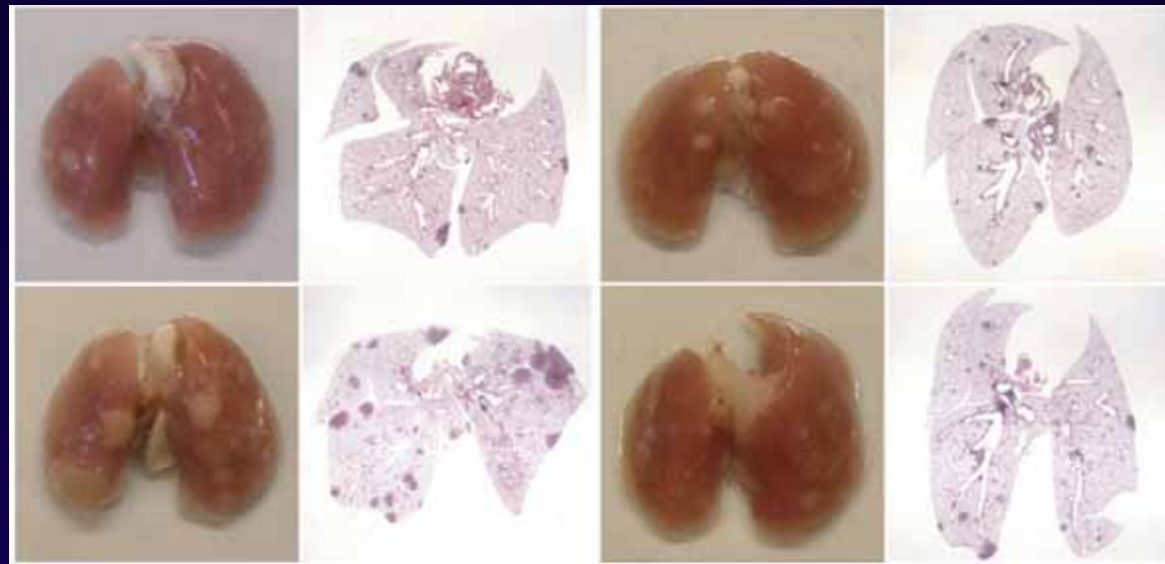


K-ras mutation
&
normal myeloid cells

Inflammation can Promote Cancer: collaboration with K-ras mutation

no
smoking

4 cigarettes
per day



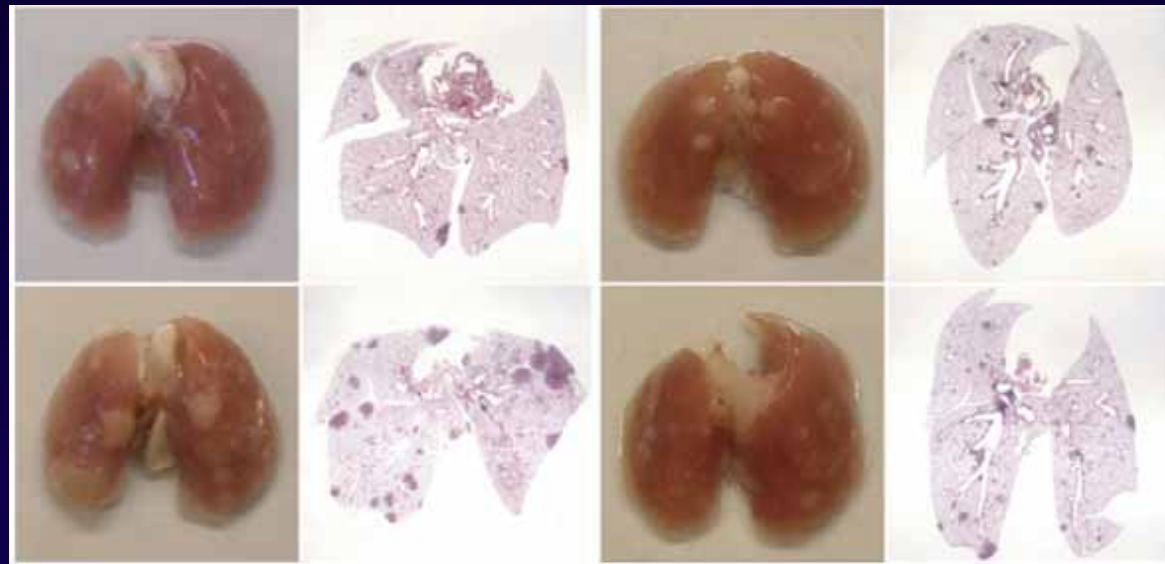
K-ras mutation
&
normal myeloid cells

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

Inflammation can Promote Cancer: collaboration with K-ras mutation

no
smoking

4 cigarettes
per day

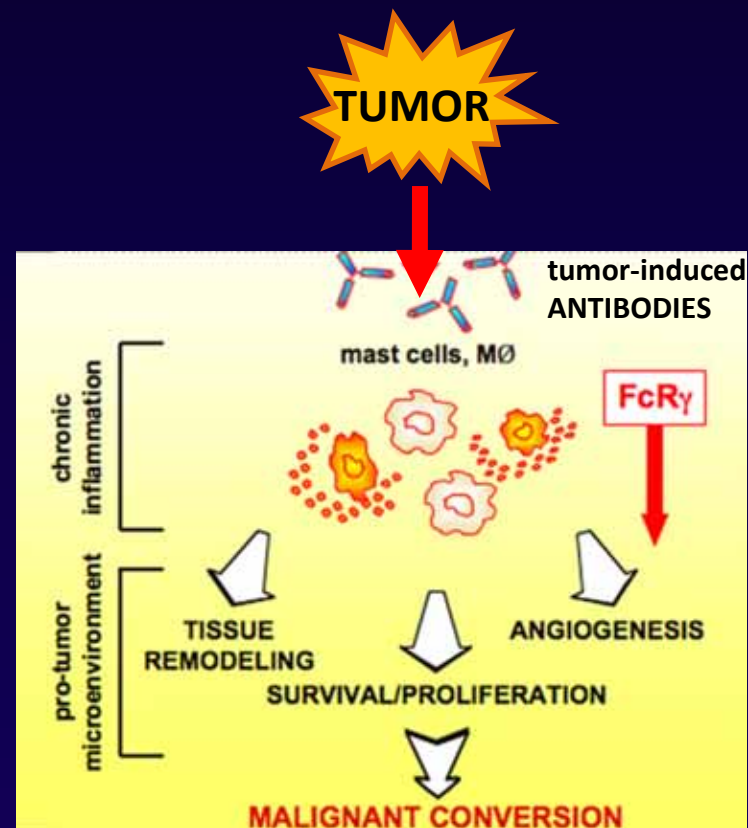


K-ras mutation
&
normal myeloid cells

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

- ↓ NF- κ B
- ↓ pSTAT3
- ↓ IL-6
- ↓ neutrophils
- ↓ angiogenesis

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



Tumors can induce bad inflammation

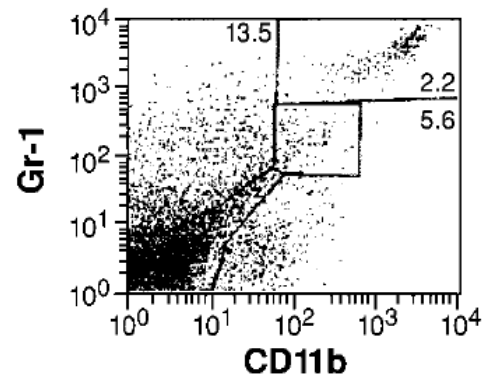
**Apoptotic Death of CD8⁺ T Lymphocytes After Immunization:
Induction of a Suppressive Population of Mac-1⁺/Gr-1⁺ Cells¹**

Vincenzo Bronte,^{2*} Michael Wang,[†] Willem W. Overwijk,^{*} Deborah R. Surman,^{*}
Federica Pericle,[‡] Steven A. Rosenberg,^{*} and Nicholas P. Restifo^{3*}

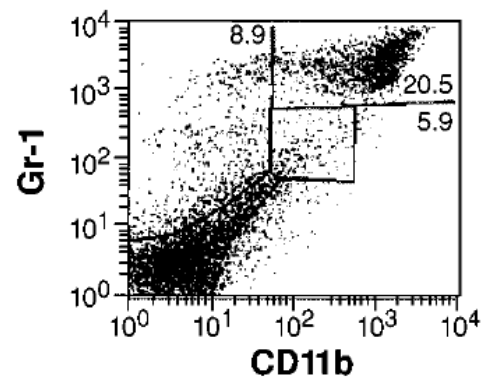
The Journal of Immunology, 1998, 161: 5313–5320.

Tumors can induce bad inflammation

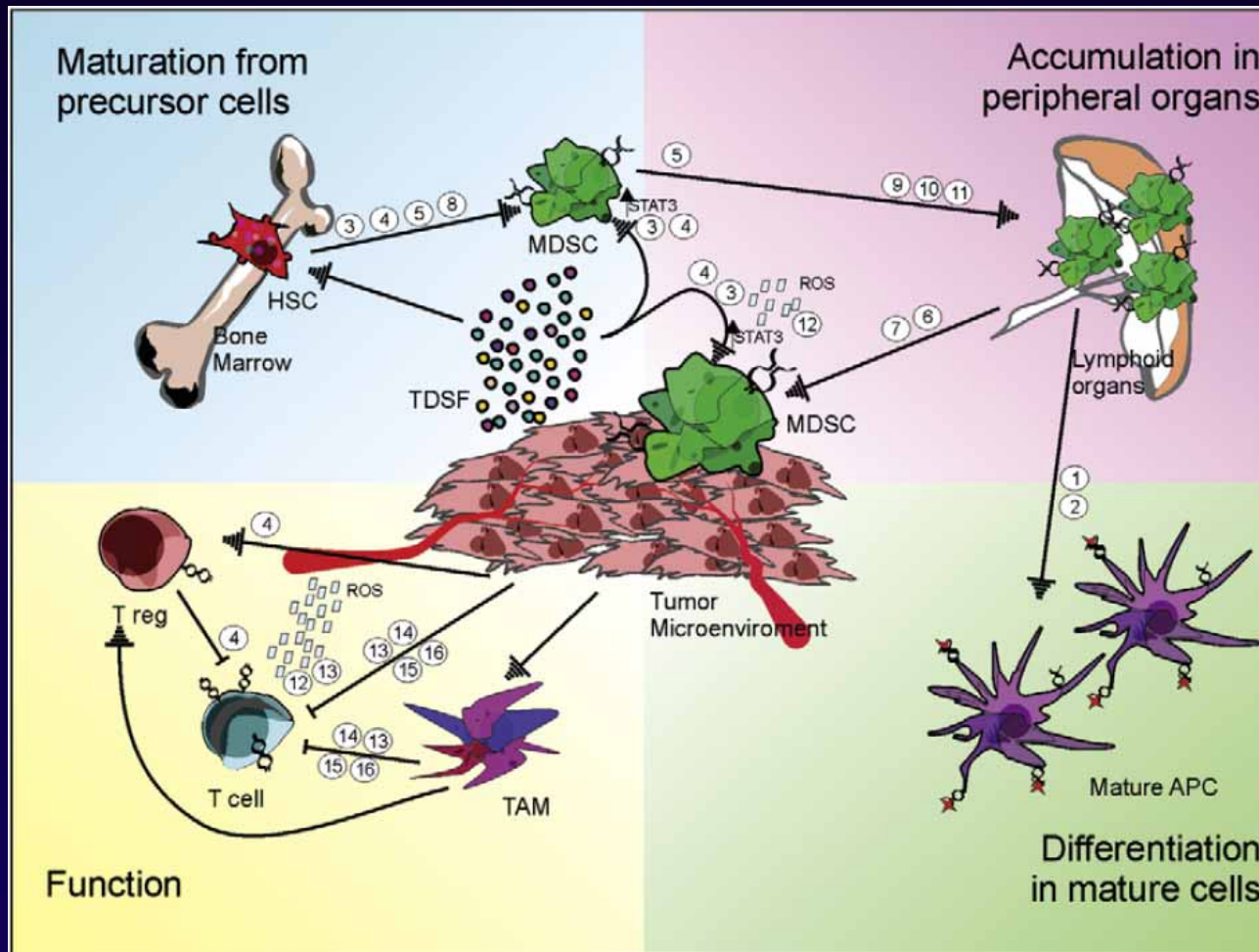
Spleen (no tumor)



Spleen (subcut. tumor)

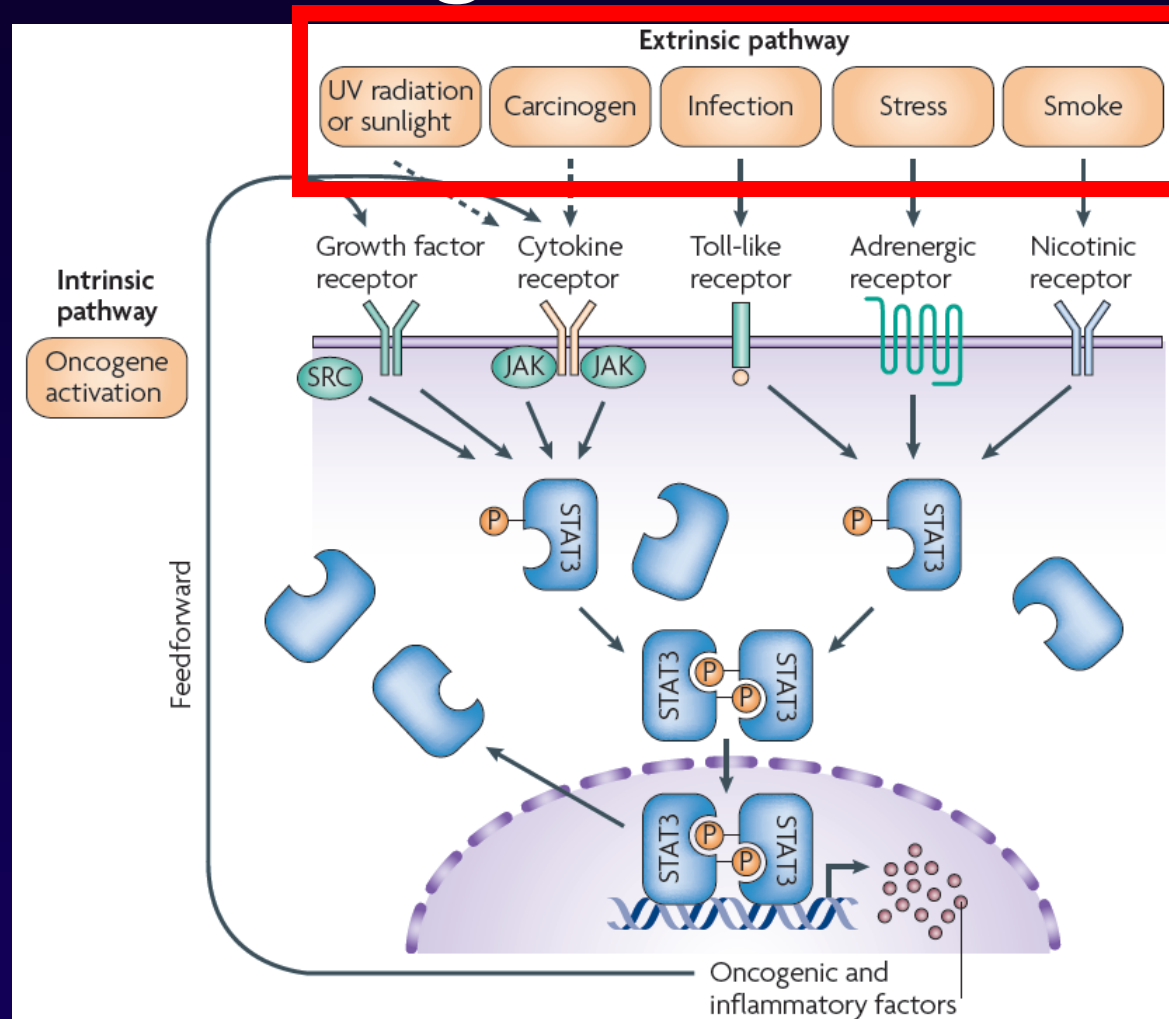


Tumors can induce bad inflammation



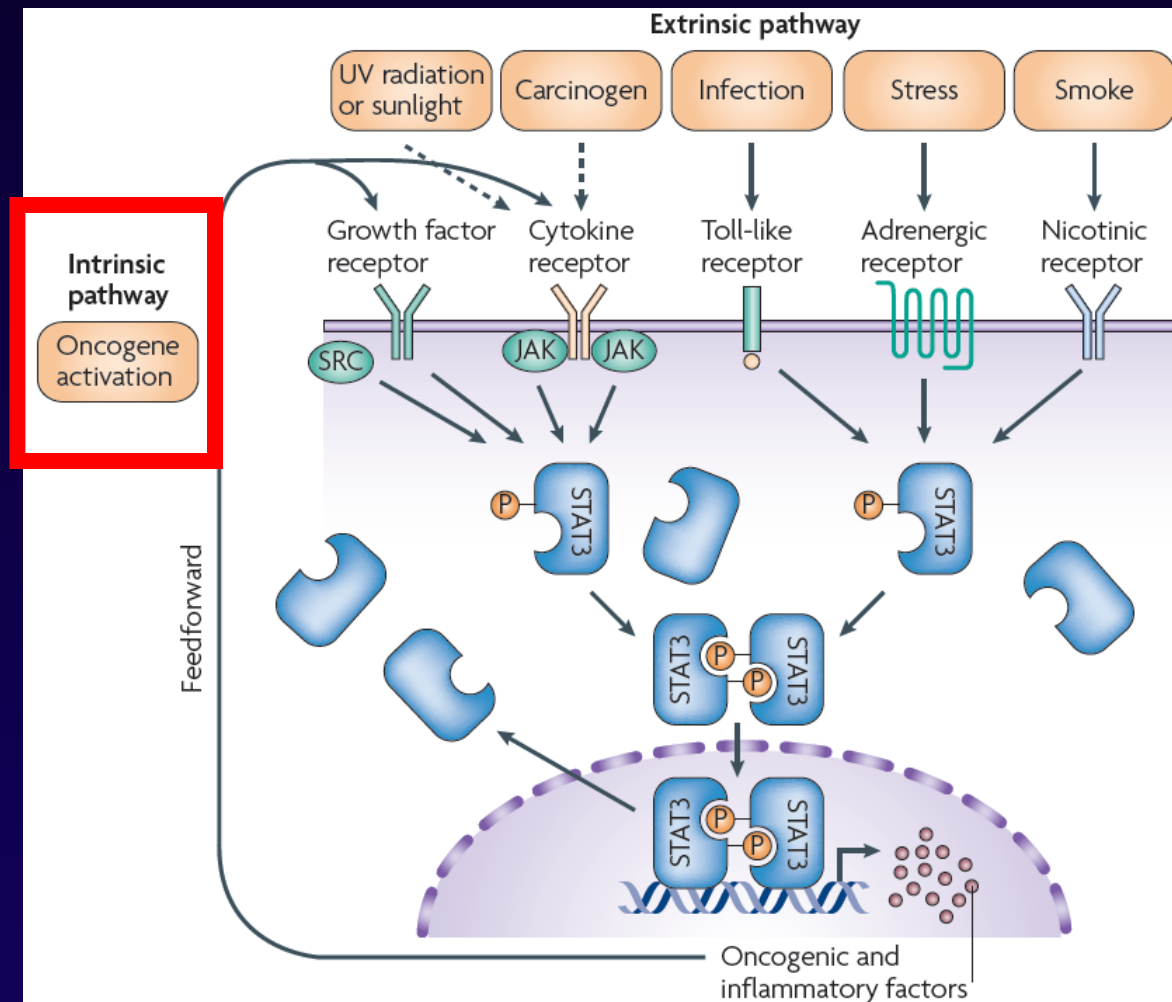
Tumors can induce bad inflammation

Oncogenic STAT3



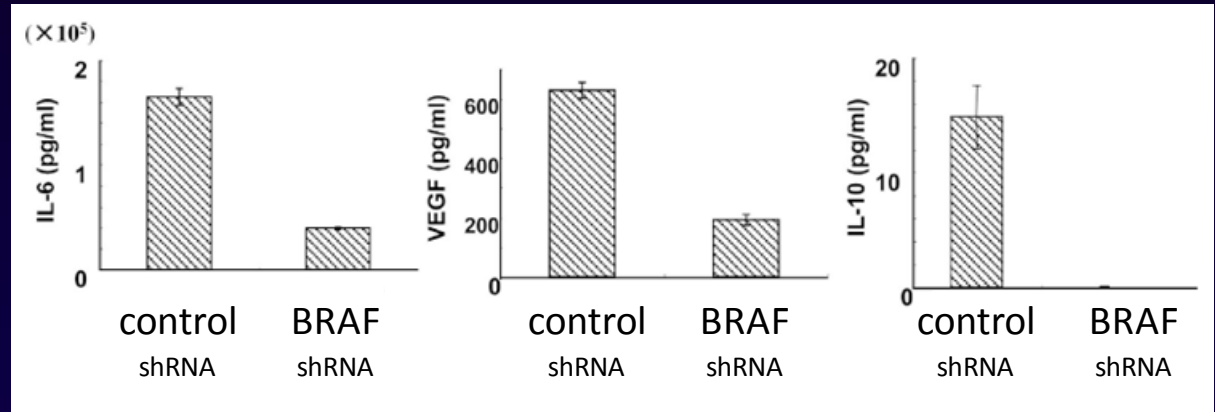
Tumors can induce bad inflammation

Oncogenic STAT3



Mutations can Drive Bad Inflammation

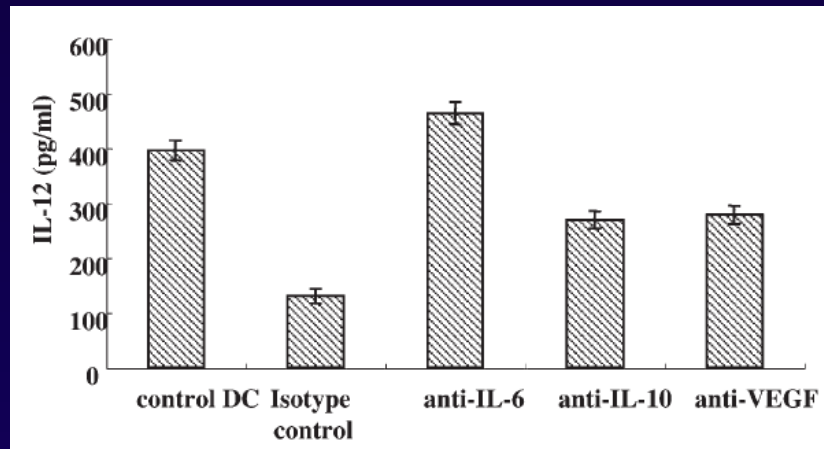
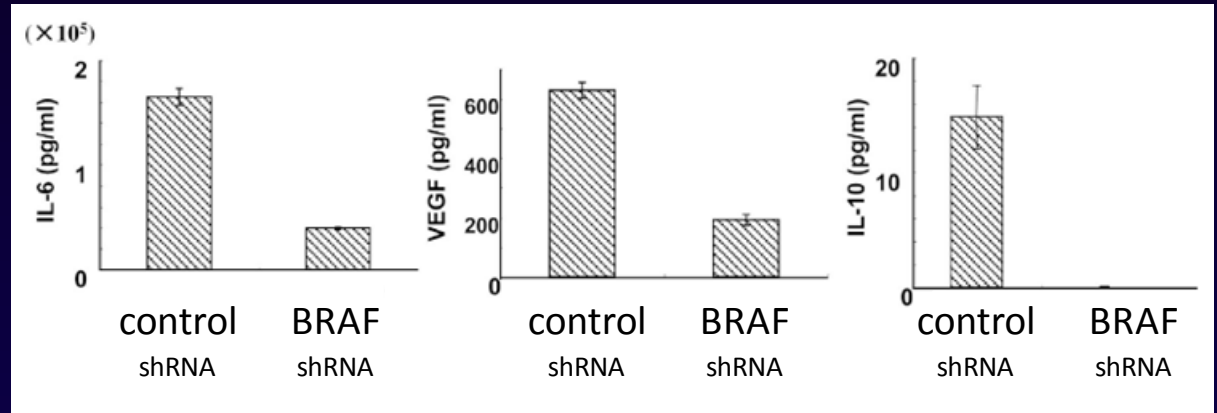
Mutated BRAF → tumor cells produce bad, immunosuppressive cytokines



Mutations can Drive Bad Inflammation

Mutated BRAF → tumor cells produce bad, immunosuppressive cytokines

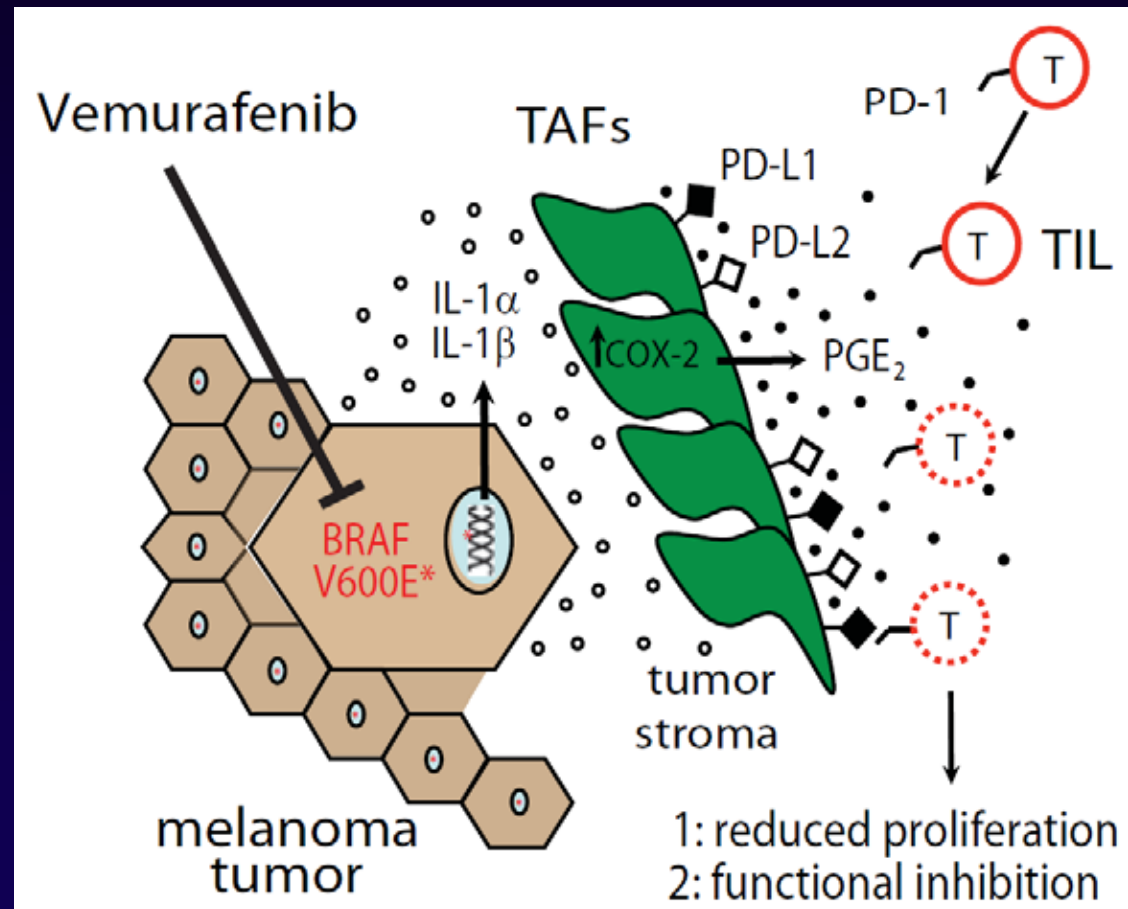
↓
block production of good cytokines in DCs



Mutations can Drive Bad Inflammation

Mutated BRAF → tumor cells produce bad, immunosuppressive cytokines

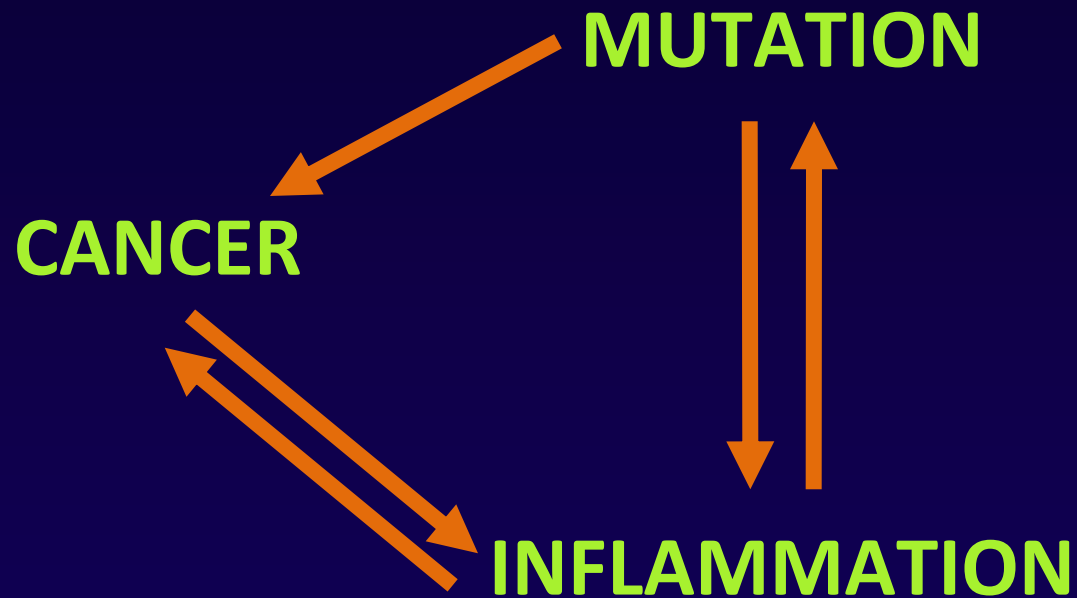
↓
promote expression of immunosuppressive molecules



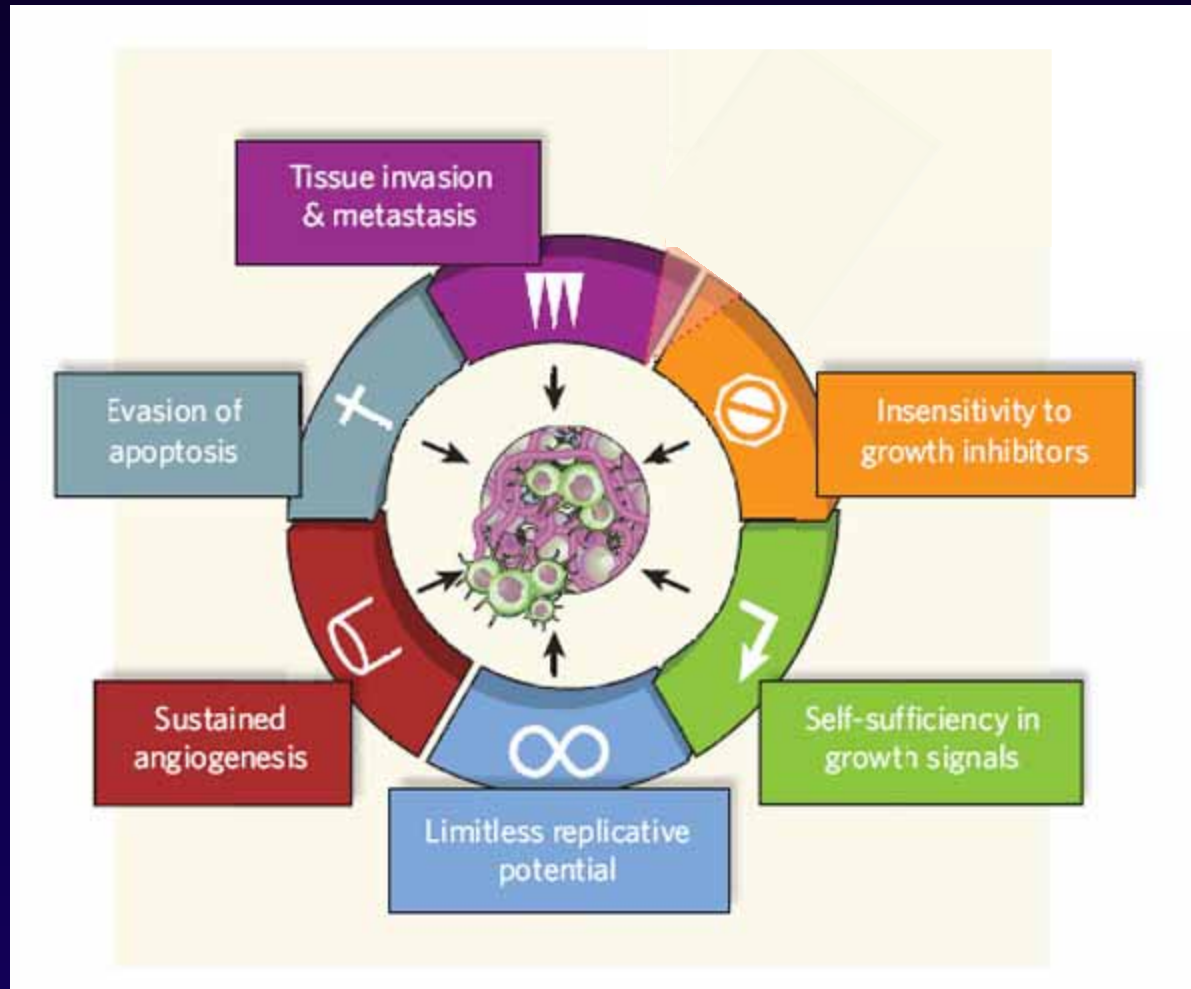
Conclusion: Inflammation and Cancer

- Inflammation can Cause Cancer
- Inflammation can Cause Mutation
- Mutation can Cause Inflammation
- Mutation can Cause Cancer
- Cancer can Cause Inflammation

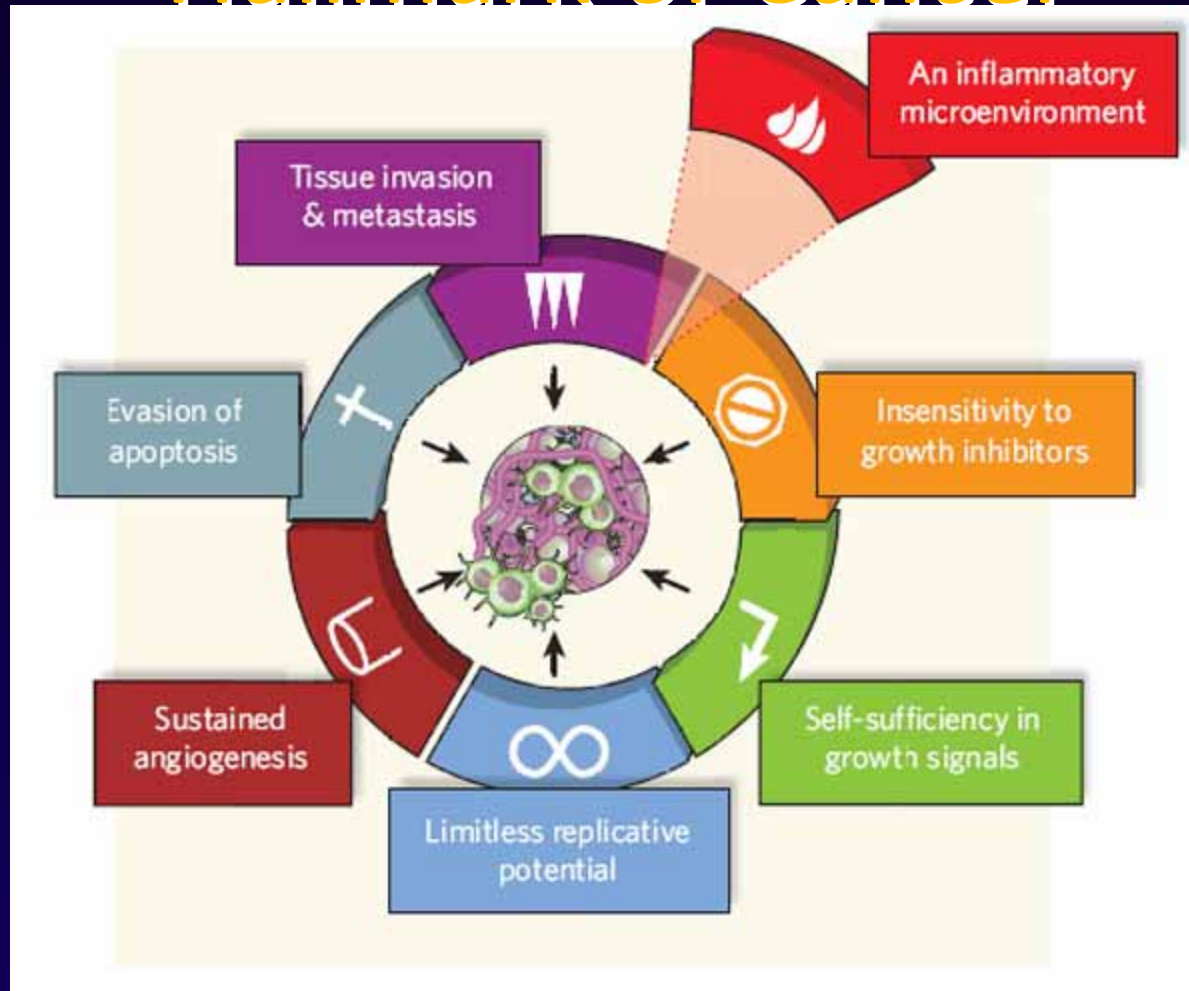
Inflammation and Cancer: A Vicious Cycle



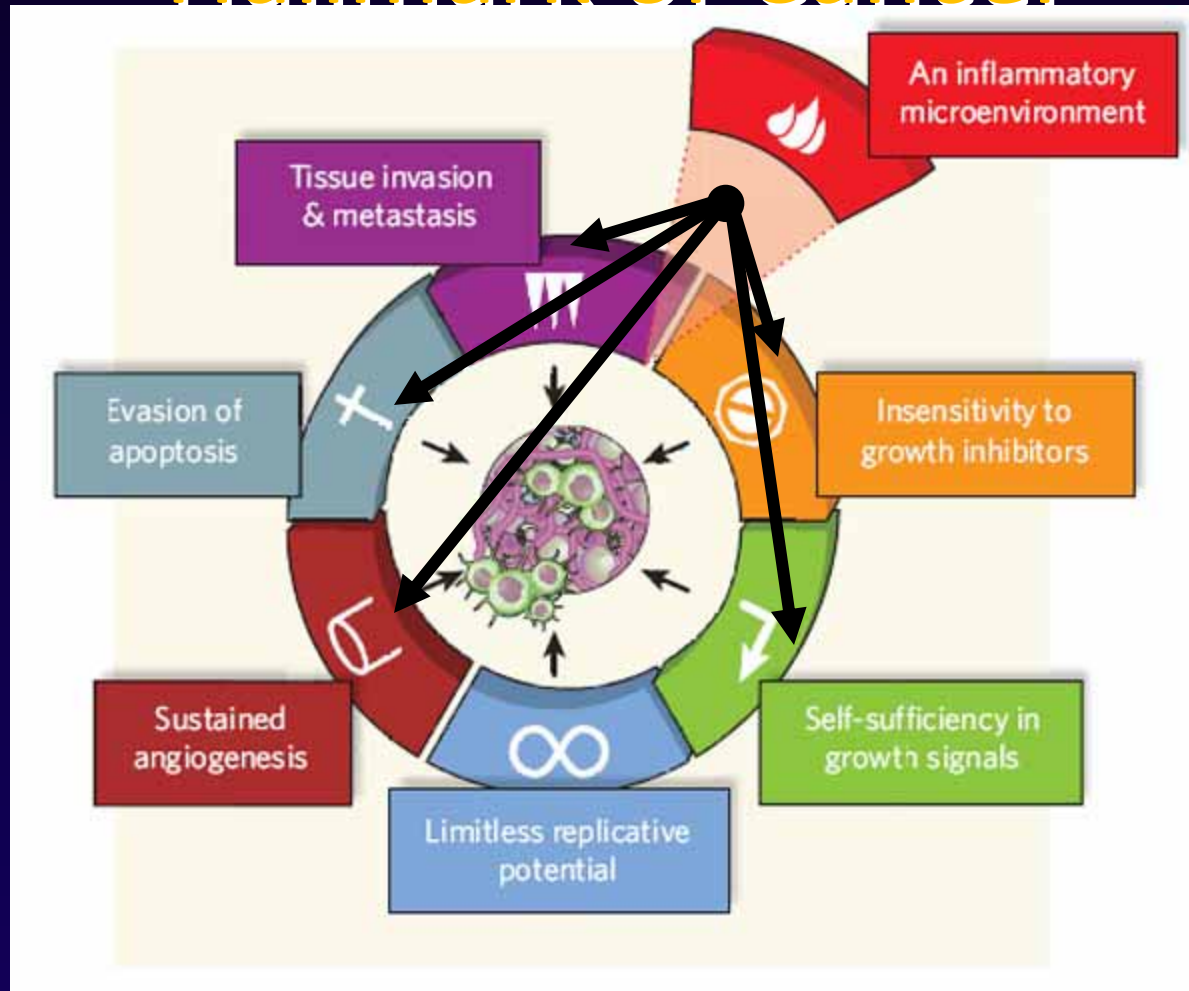
Classic Hallmarks of Cancer



Inflammation is (now) a Classic Hallmark of Cancer



Inflammation is (now) a Classic Hallmark of Cancer



Innate Immunity and Inflammation

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

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

IFN- γ Suppresses Human Tumor Development

Multiple cutaneous squamous cell carcinomas in a patient with interferon γ receptor 2 (IFN γ R2) deficiency

IFN- γ Suppresses Human Tumor Development

Multiple cutaneous squamous cell carcinomas in a patient with interferon γ receptor 2 (IFN γ R2) deficiency

At 17 years of age, the patient developed multifocal Squamous Cell Carcinomas on the face and both hands. Despite local tumour excision, multiple lesions occurred and the patient died at 20 years of age of disseminated SCC. Inherited disorders of IFN- γ -mediated immunity may predispose patients to SCC.

Human Immune System can Suppress Existing Tumors for Years

1982: patient with primary, resected melanoma

1997: declared disease-free and “cured”

1998: died of brain hemorrhage, donated kidneys

2000: - kidney recipient 1 died of metastatic donor melanoma

- kidney recipient 2 taken off immunosuppression; start IFN- α

- kidney recipient 2 rejects kidney and melanoma

Human Immune System can Suppress Existing Tumors for Years

1982: patient with primary, resected melanoma

1997: declared disease-free and “cured”

1998: died of brain hemorrhage, donated kidneys

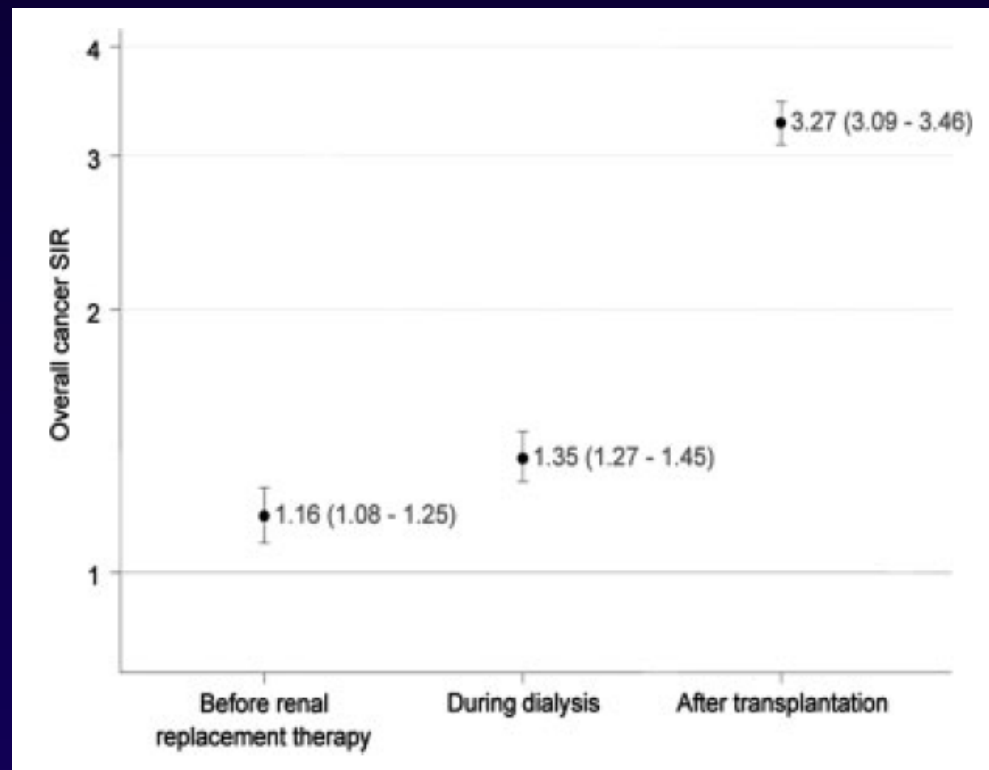
2000: - kidney recipient 1 died of metastatic donor melanoma

- kidney recipient 2 taken off immunosuppression; start IFN- α

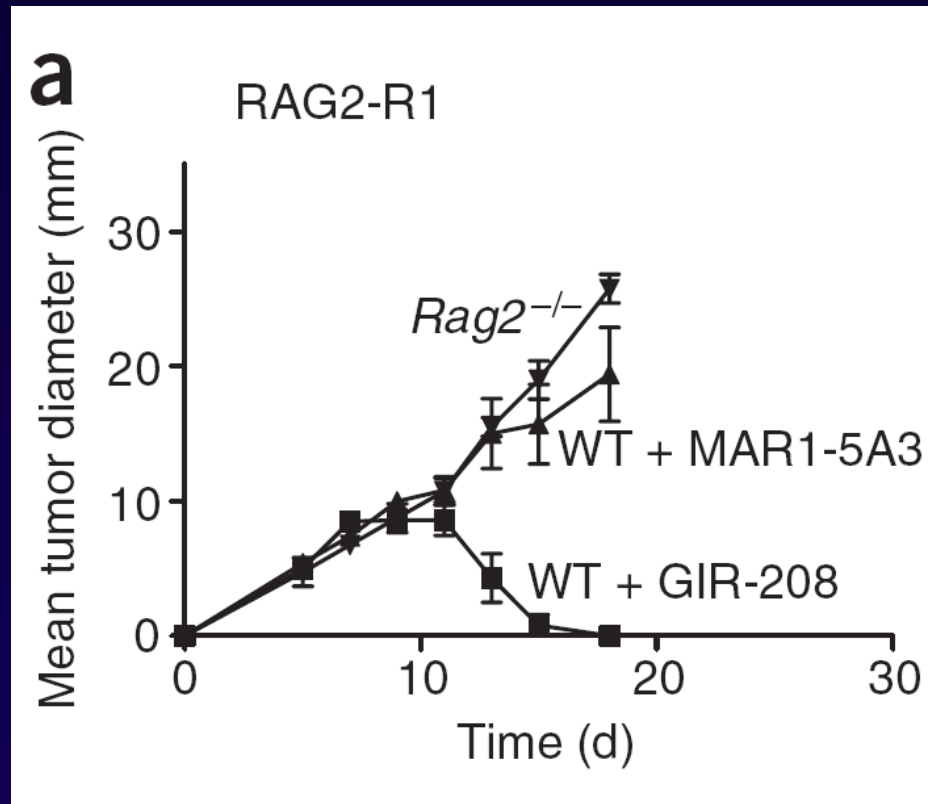
- kidney recipient 2 rejects kidney and melanoma



Post-transplant Immunosuppression Increases Cancer Incidence



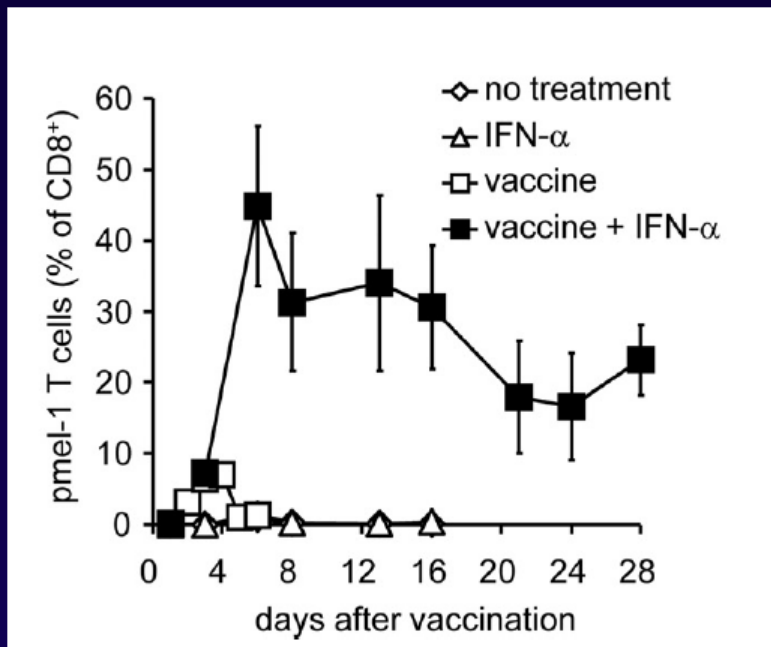
Type I IFNs Suppress Growth of Transplanted Tumors



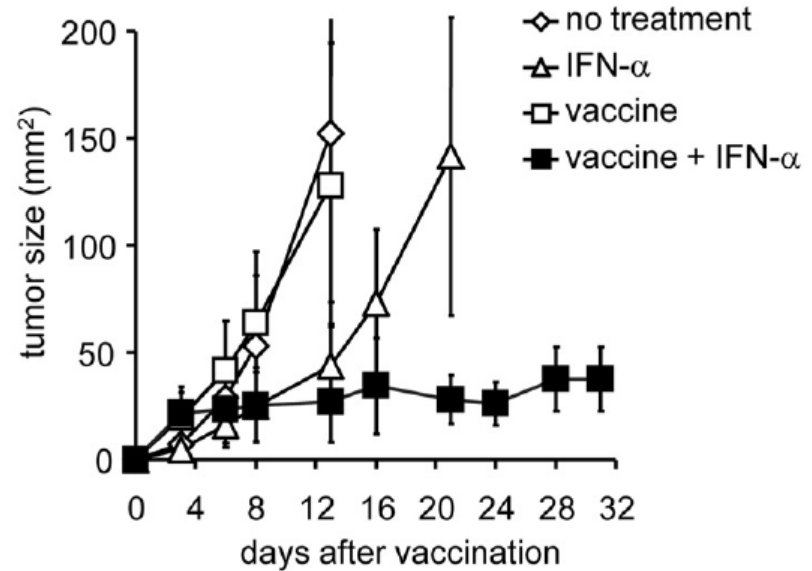
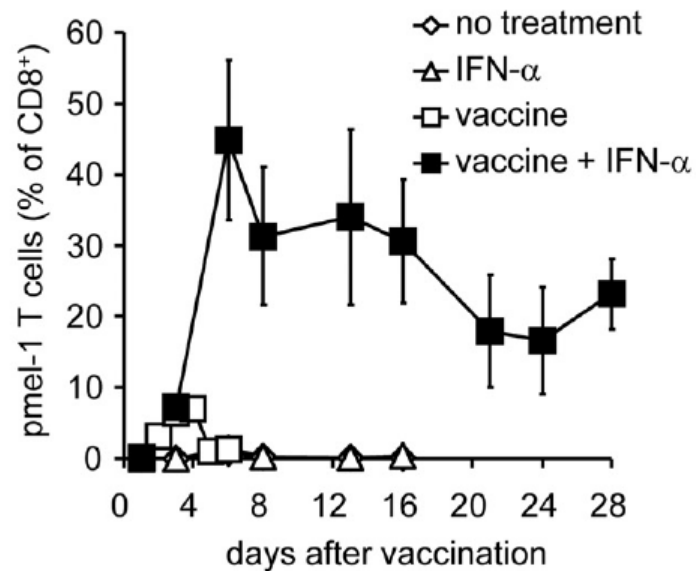
IFN- α receptor
blocking mAb

control mAb

IFN- α treatment enhances anti-cancer vaccination



IFN- α treatment enhances anti-cancer vaccination

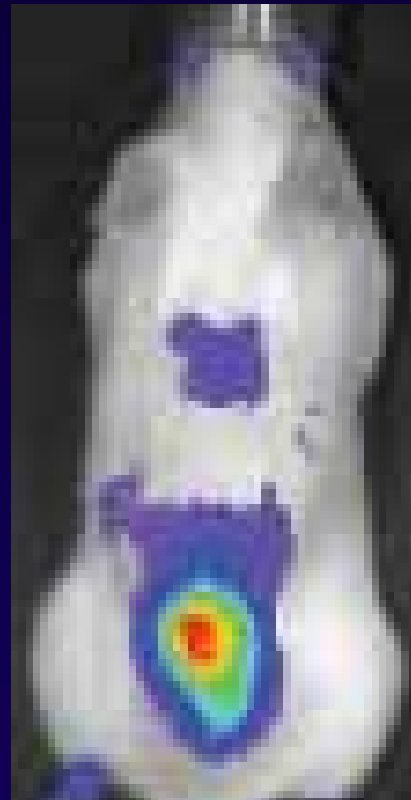


CpG Causes Tumor Inflammation and Intratumoral T cell Accumulation

Intratumoral PBS



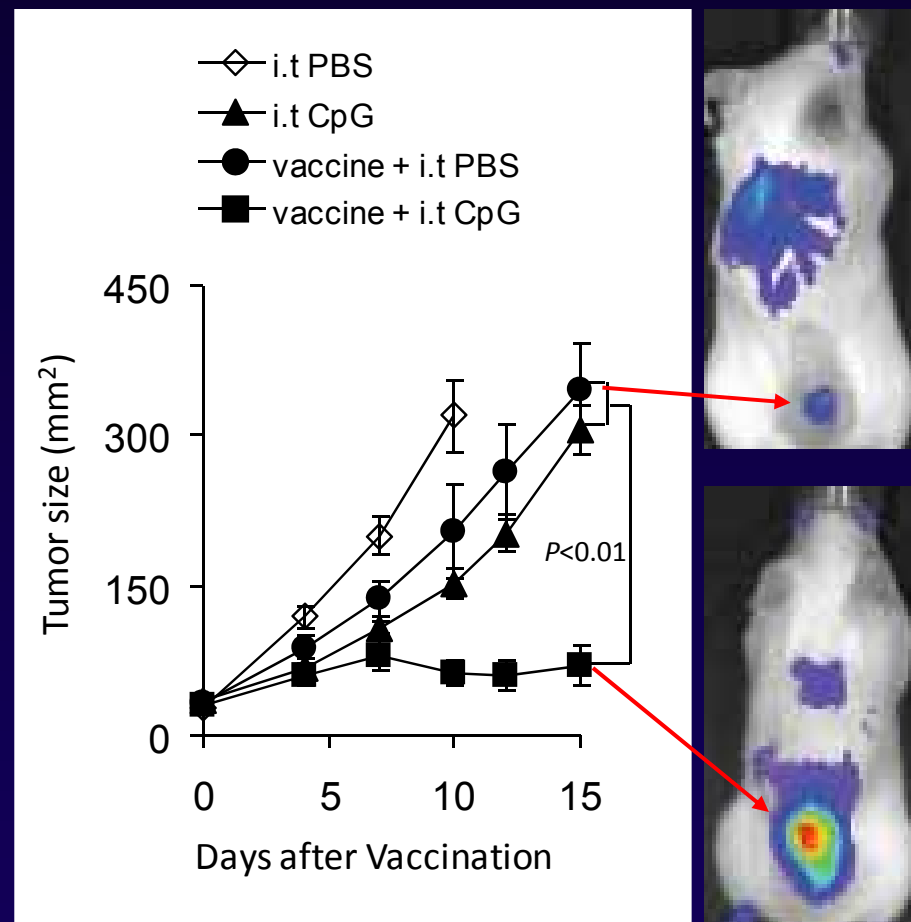
Intratumoral CpG

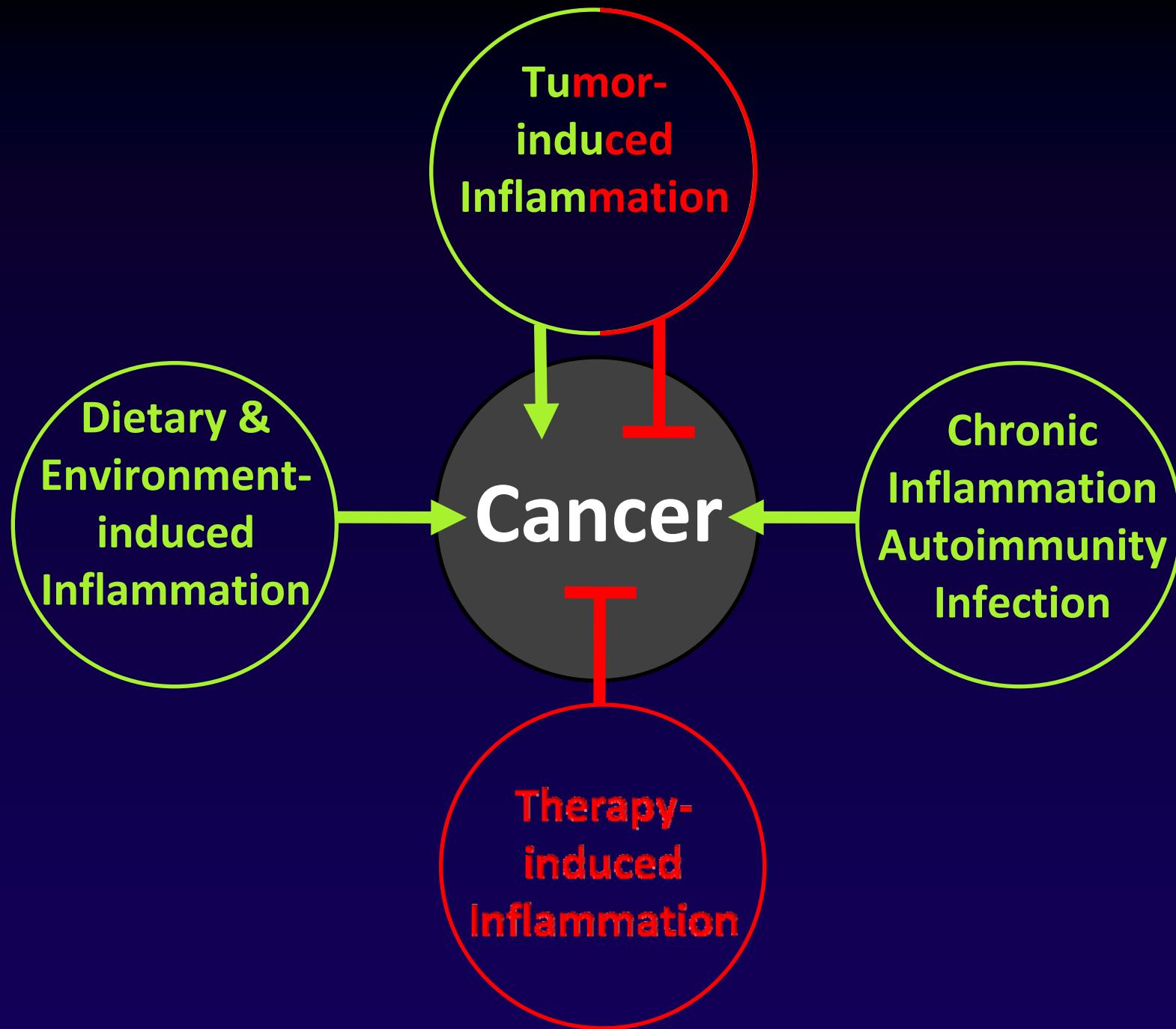


Intravenous CpG



CpG Causes Tumor Inflammation and Intratumoral T cell Accumulation





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 γ)	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

In the Clinic: Cancer Therapies that Block Bad Inflammation

In the Clinic: Cancer Therapies that Block Bad Inflammation

- COX-2 inhibitor Aspirin, Celecoxib (colorectal)

In the Clinic: Cancer Therapies that Block Bad Inflammation

- COX-2 inhibitor Aspirin, Celecoxib (colorectal)
- VEGF blocker Bevacizumab, Sorafenib (several)
- IL-1 β blocker IL-1Ra (MM)

In the Clinic: Cancer Therapies that Block Bad Inflammation

- COX-2 inhibitor Aspirin, Celecoxib (colorectal)
- VEGF blocker Bevacizumab, Sorafenib (several)
- IL-1 β blocker IL-1Ra (MM)
- Cytokine Regulators Lenalidomide (MDS, MM)

In the Clinic: Cancer Therapies that Block Bad Inflammation

- COX-2 inhibitor Aspirin, Celecoxib (colorectal)
- VEGF blocker Bevacizumab, Sorafenib (several)
- IL-1 β blocker IL-1Ra (MM)
- Cytokine Regulators Lenalidomide (MDS, MM)
- Kill Helicobacter Pylori Clarithrom./Amoxicillin (gastric)

In the Clinic: Cancer Therapies that Block Bad Inflammation

- COX-2 inhibitor Aspirin, Celecoxib (colorectal)
- VEGF blocker Bevacizumab, Sorafenib (several)
- IL-1 β blocker IL-1Ra (MM)
- Cytokine Regulators Lenalidomide (MDS, MM)
- Kill Helicobacter Pylori Clarithrom./Amoxicillin (gastric)
- Remove suppressors Cycl/Fludar + T cells (melanoma)

In the Clinic: Cancer Therapies that Block Bad Inflammation

- COX-2 inhibitor Aspirin, Celecoxib (colorectal)
- VEGF blocker Bevacizumab, Sorafenib (several)
- IL-1 β 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)

In the Clinic: Cancer Therapies that Block Bad Inflammation

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

In the Clinic: Cancer Therapies that Induce Good Inflammation

In the Clinic: Cancer Therapies that Induce Good Inflammation

- Bacteria BCG (bladder)

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)

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)

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)

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)

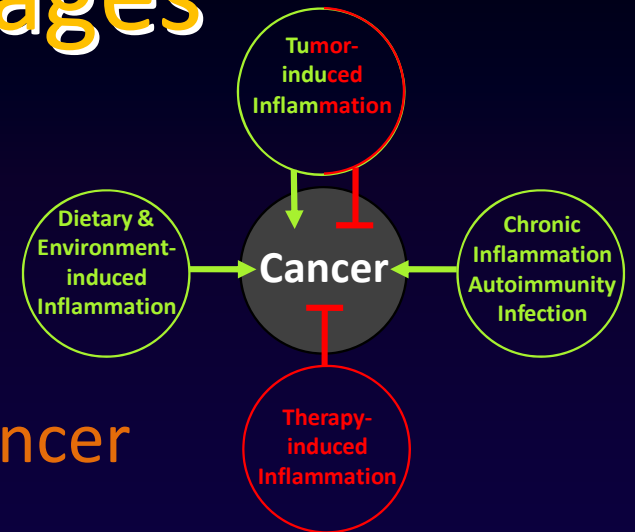
In the Clinic: Cancer Therapies that Induce Good Inflammation

- 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)

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