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®

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.

Adapted from *Merriam-Webster Medical Dictionary*

- **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” 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 ≠ Innate Immunity B
- Inflammation A ≠ Inflammation B

"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

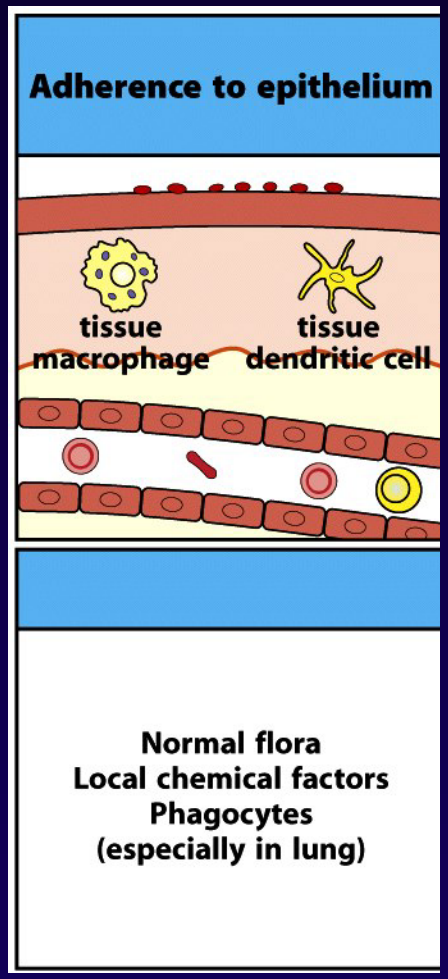
- Some immune responses promote cancer, others suppress it

Innate Immunity and Inflammation

Functions:

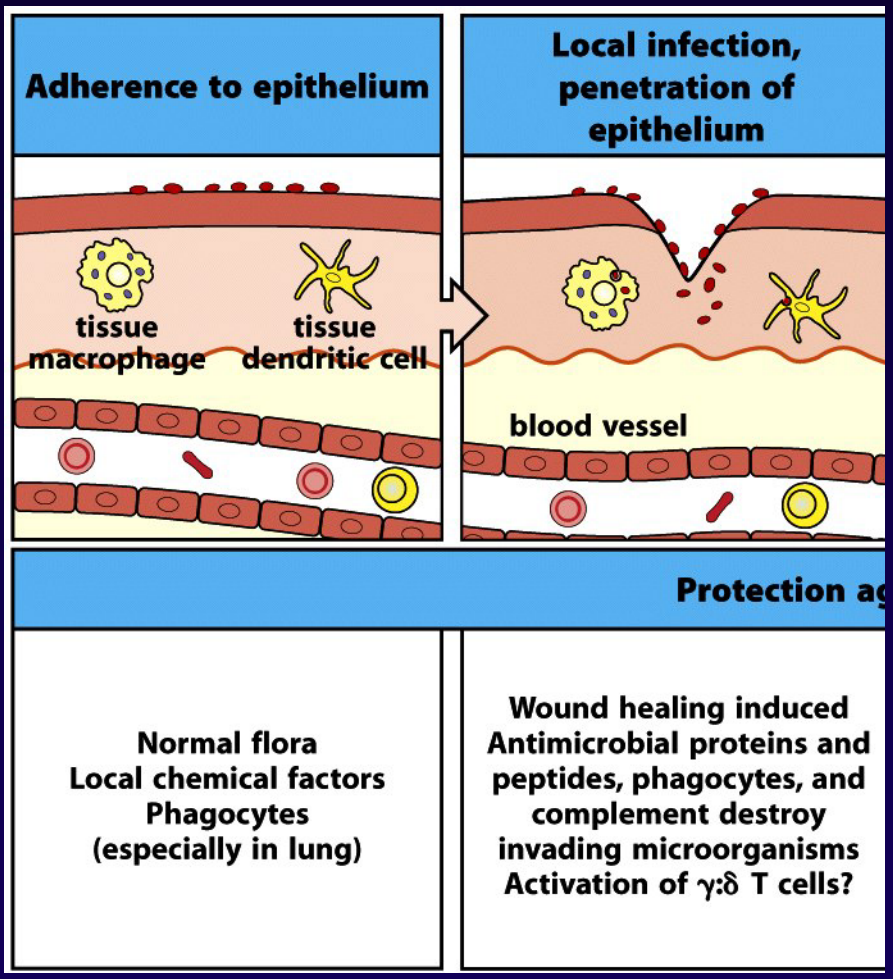
- Rapid response to tissue damage
- Limit spread of infection
- Initiate adaptive immune response (T, B)
- Initiate tissue repair

Innate Immunity and Inflammation: A Paper Cut



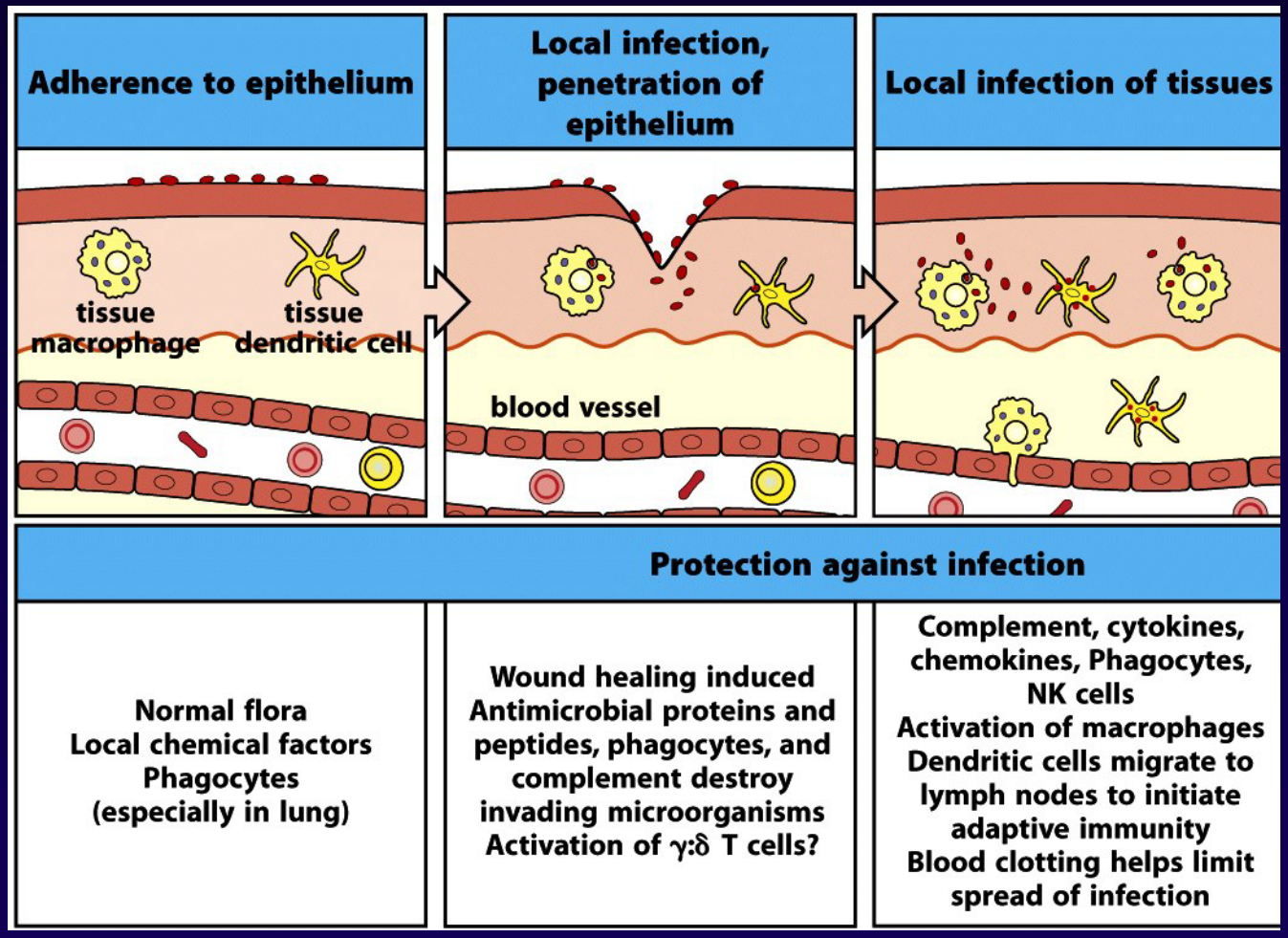
Janeway, *Immunobiology, 7th Ed.*

Innate Immunity and Inflammation: A Paper Cut



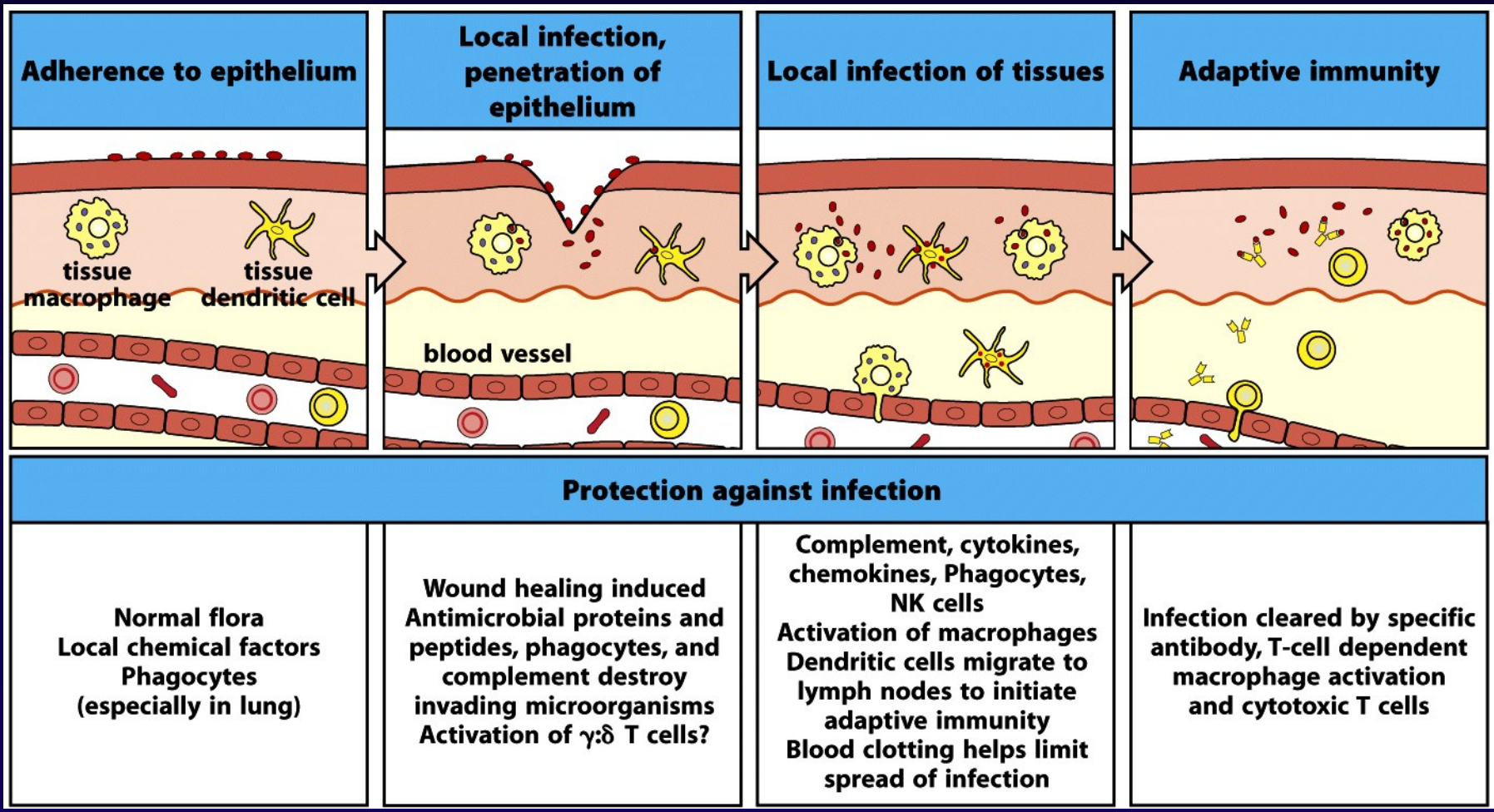
Janeway, *Immunobiology, 7th Ed.*

Innate Immunity and Inflammation: A Paper Cut



Janeway, *Immunobiology, 7th Ed.*

Innate Immunity and Inflammation: A Paper Cut

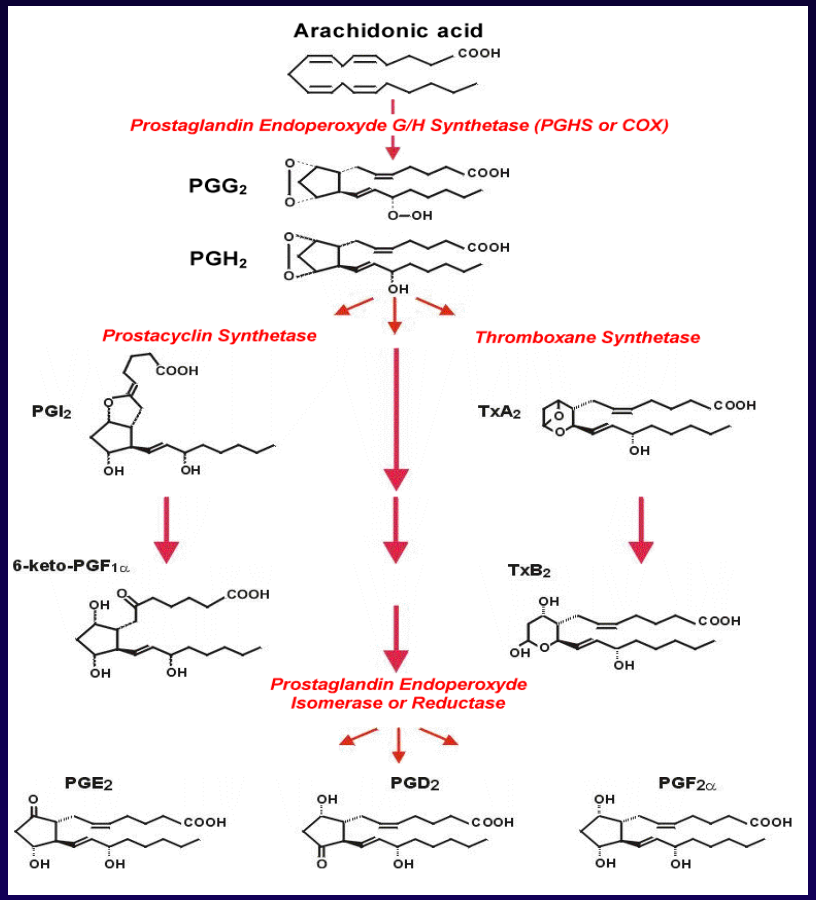


Janeway, *Immunobiology, 7th Ed.*

Innate Immunity and Inflammation

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

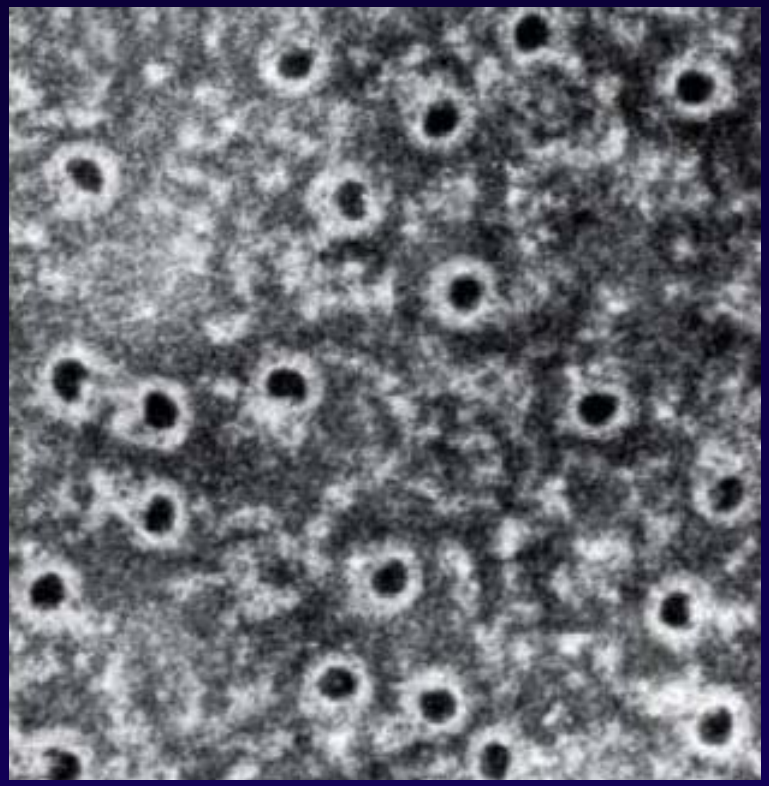
Innate Immune Molecules: Cyclooxygenase-2 (COX-2)



Recognize
- inflammation

Cause
- inflammation

Innate Immune Molecules: Complement System



Recognize

- pathogens
- antibodies
- lectins

Cause

- pathogen clearance
- chemotaxis
- inflammation

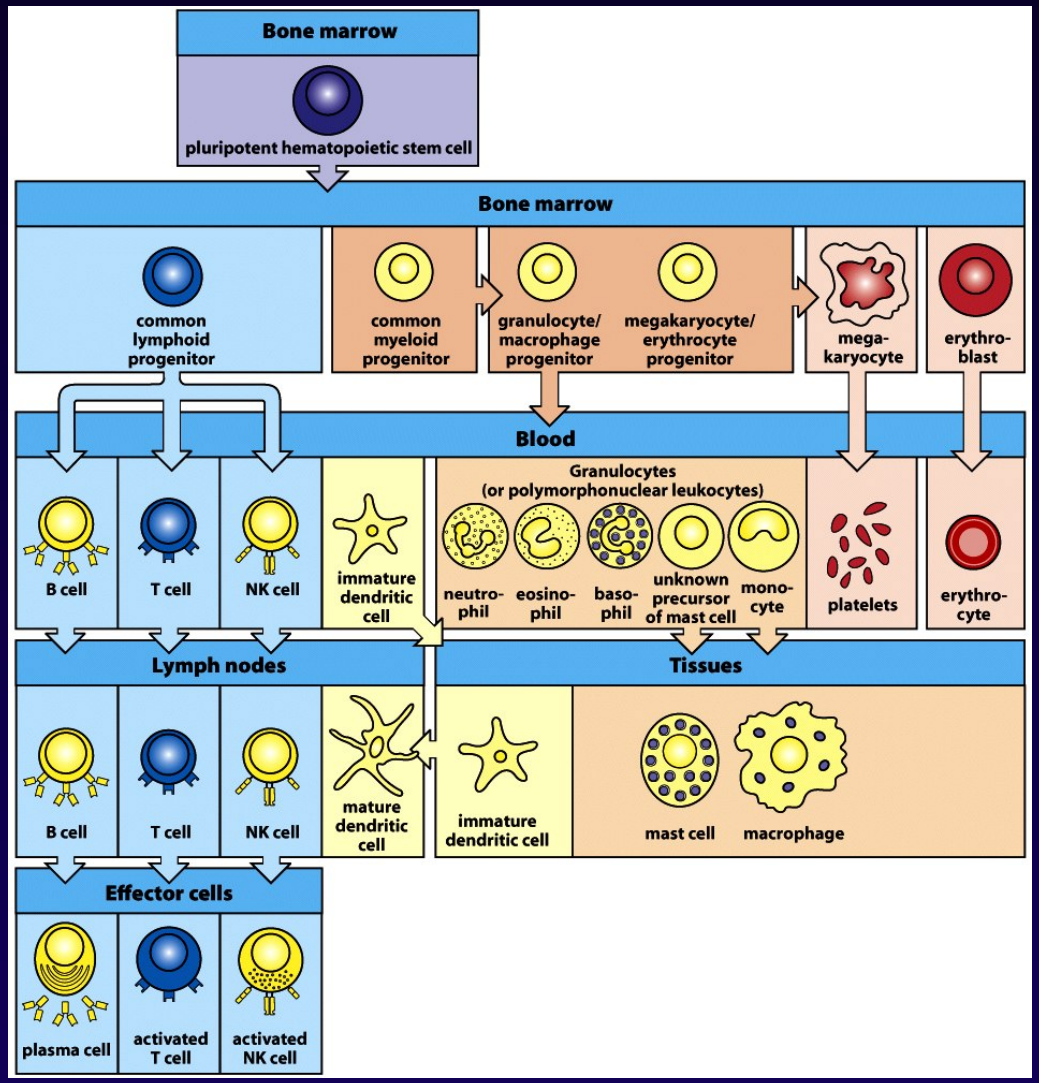
Janeway, *Immunobiology, 7th Ed.*

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

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

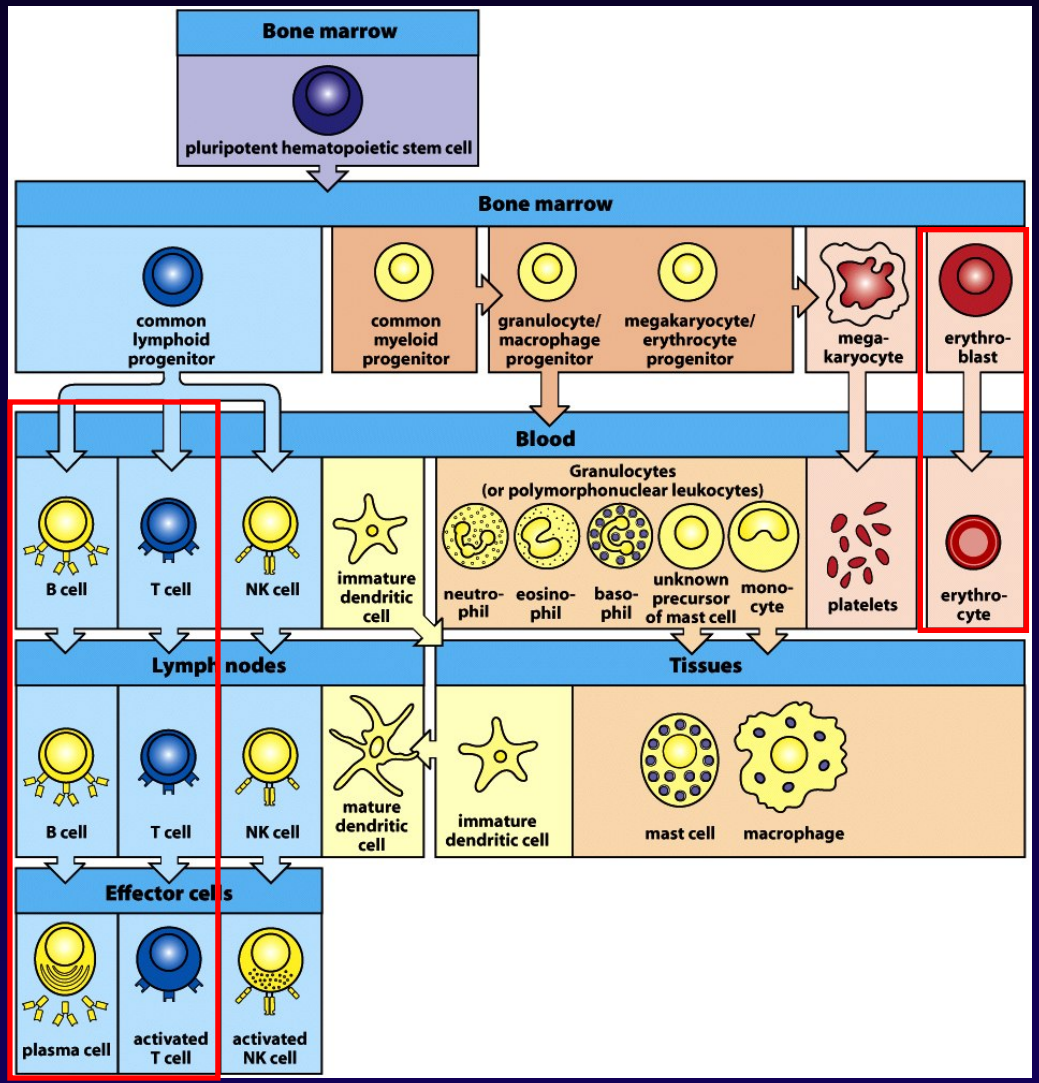
- Cause inflammation

Innate Immune Cells



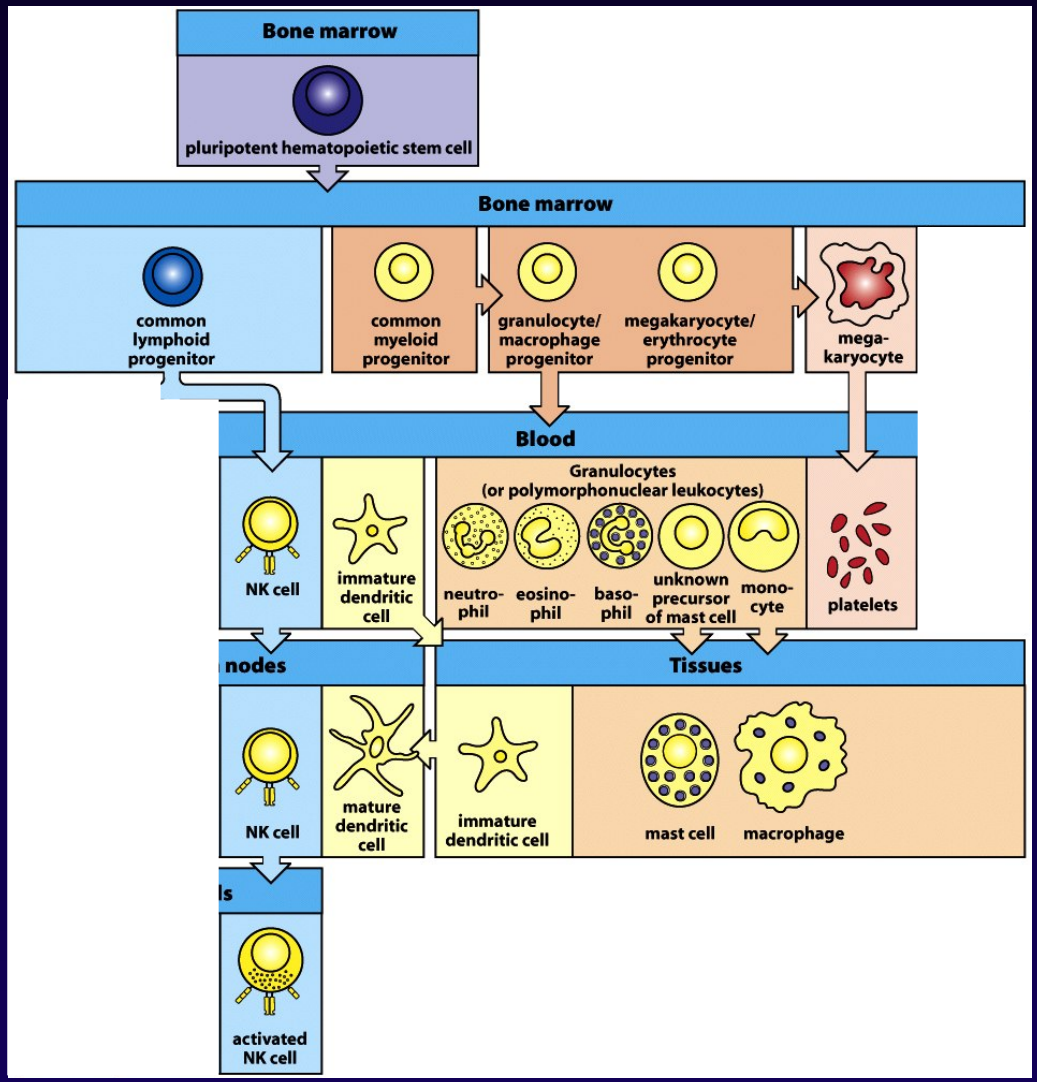
Janeway, *Immunobiology, 7th Ed.*

Innate Immune Cells



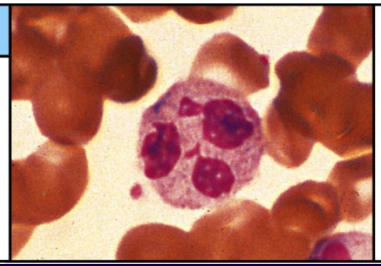
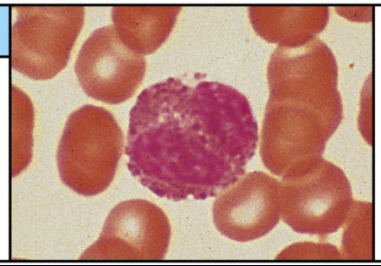
Janeway, *Immunobiology, 7th Ed.*

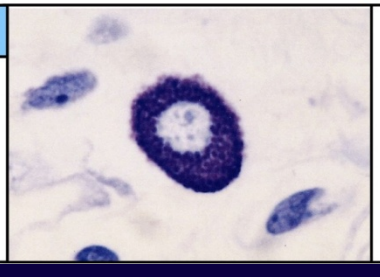
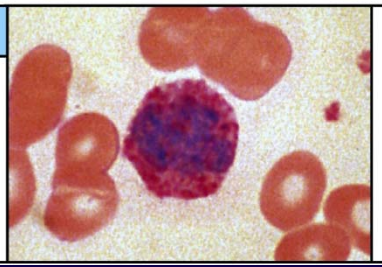
Innate Immune Cells



Janeway, *Immunobiology, 7th Ed.*

Innate Immune Cells: granulocytes

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

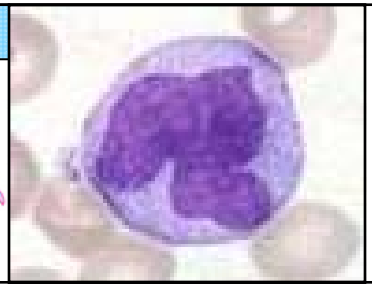
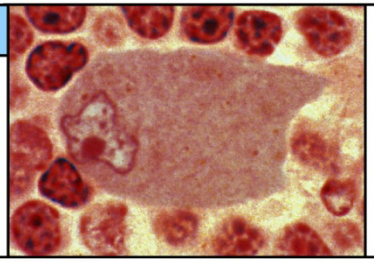
Cell		Activated function
Mast cell		Release of granules containing histamine and active agents
Basophil		(Unknown) Antigen Presentation

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”

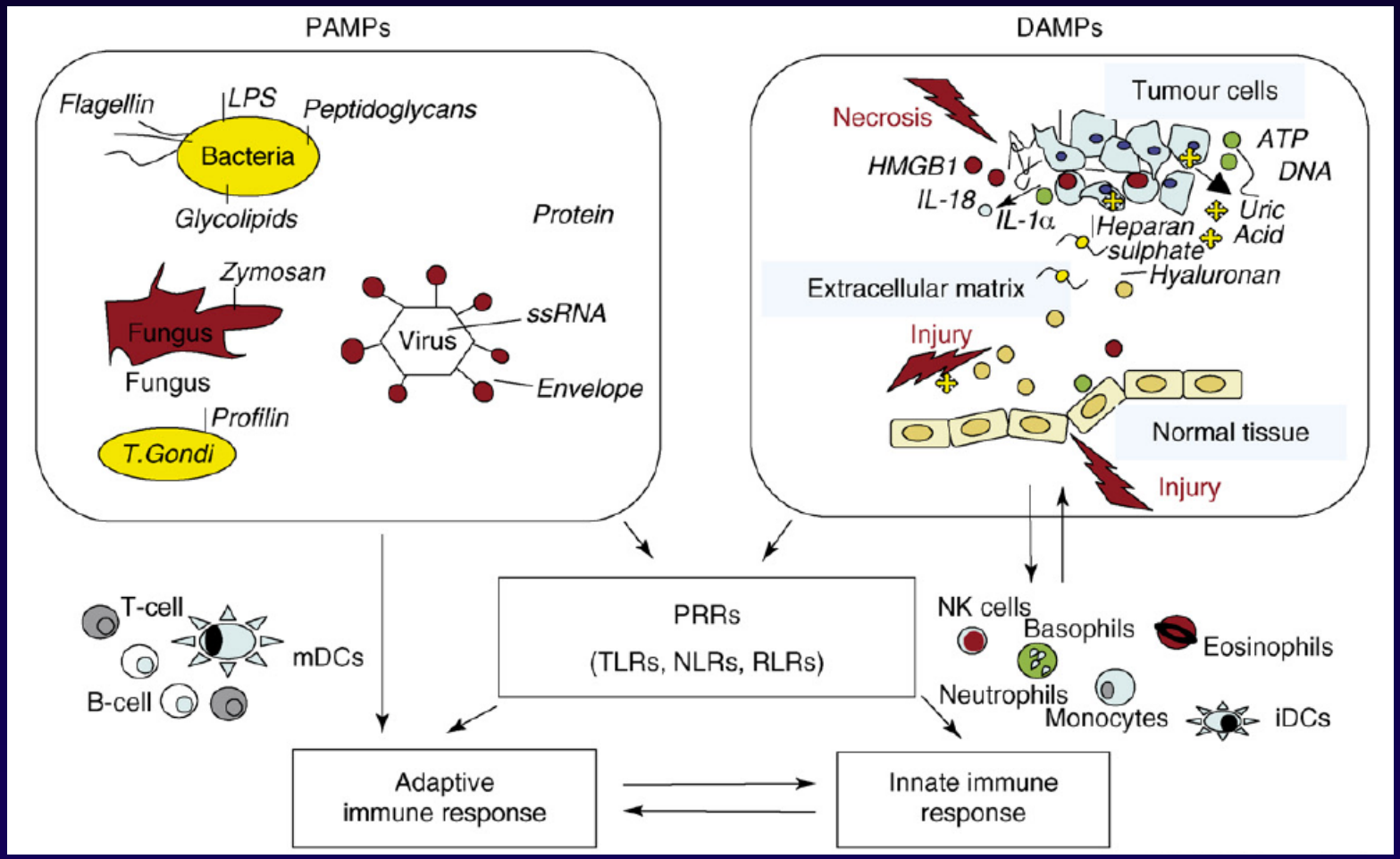
Cause

- pathogen clearance
- stressed/abnormal cell clearance
- inflammation

Danger signals start inflammation

PATHOGENS

DAMAGE

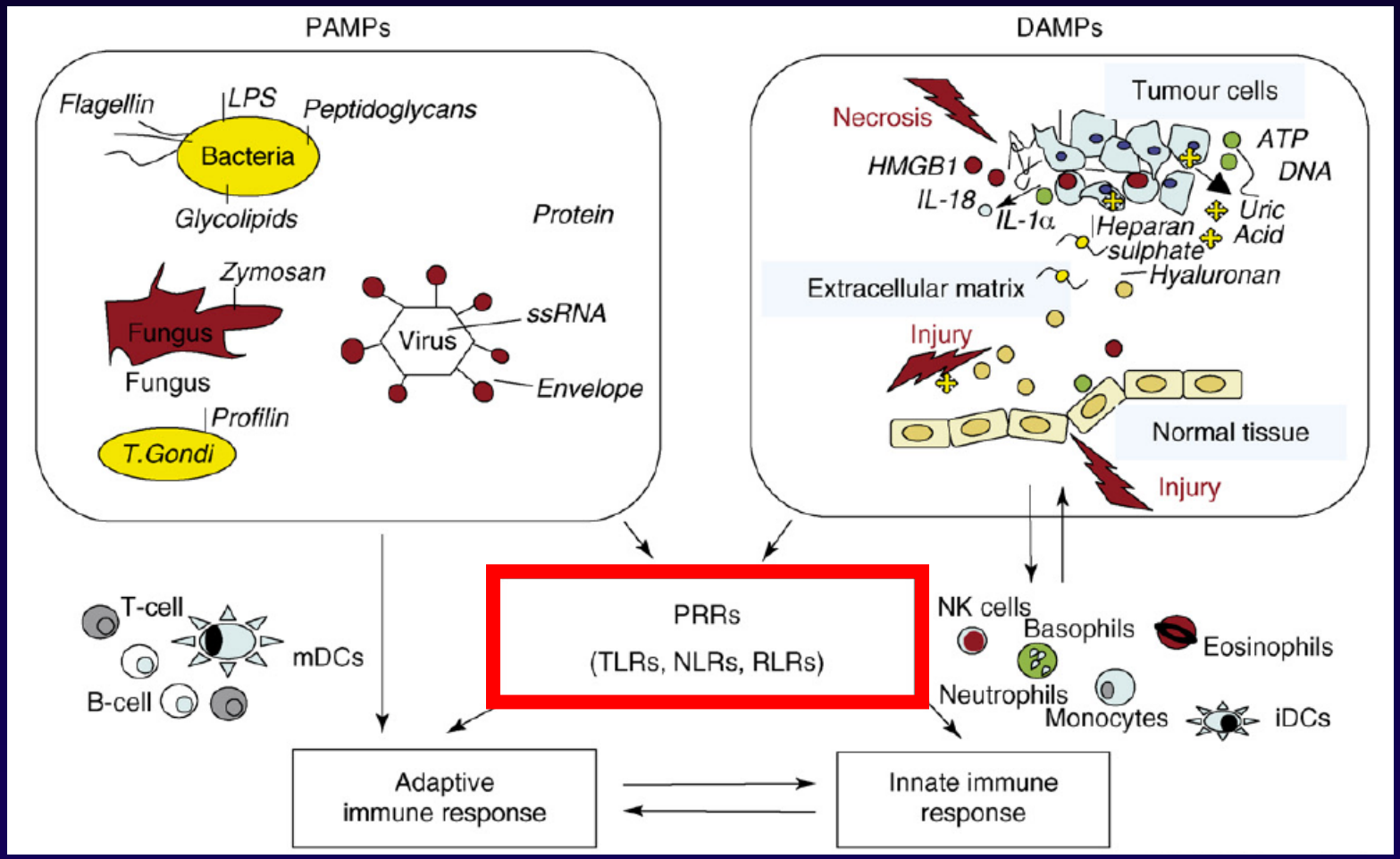


Rubartelli & Lotze, *Trends in Immunology 2007*

Danger signals start inflammation

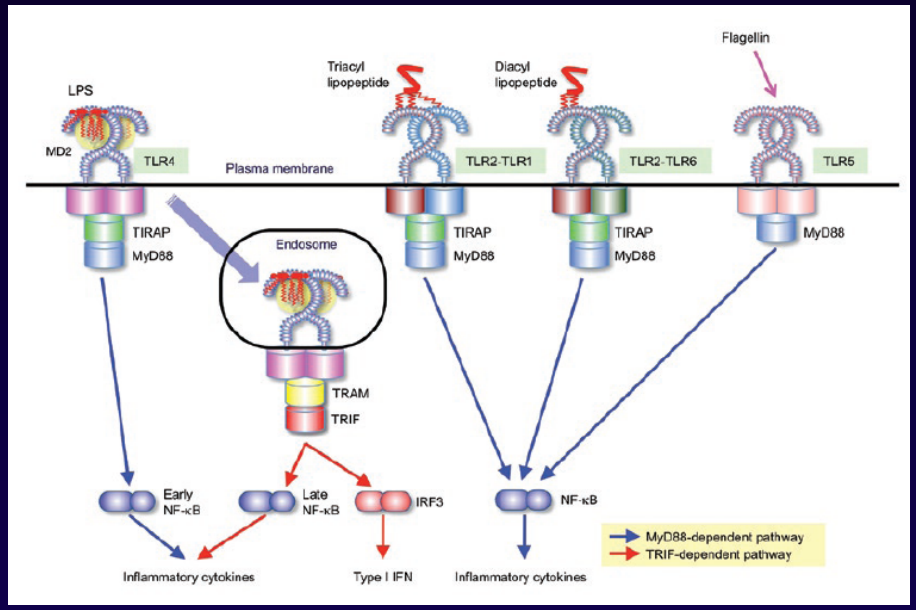
PATHOGENS

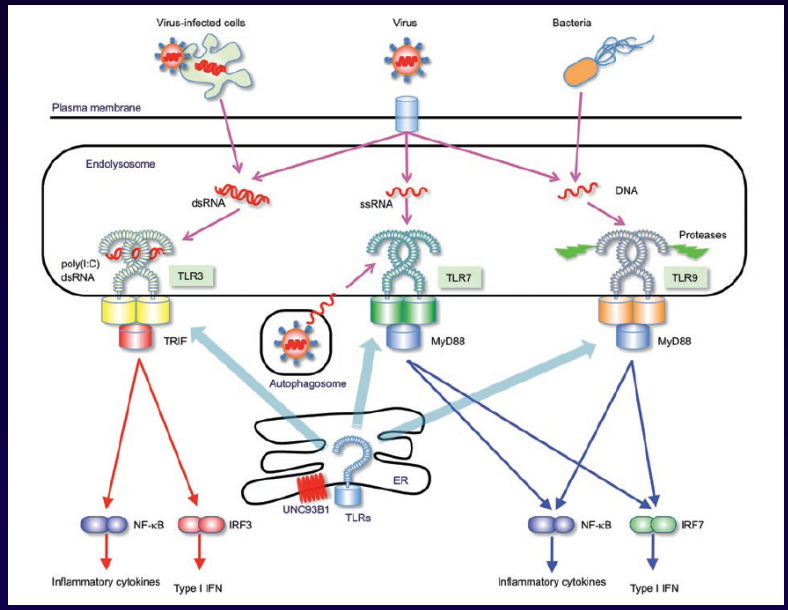
DAMAGE



Rubartelli & Lotze, *Trends in Immunology 2007*

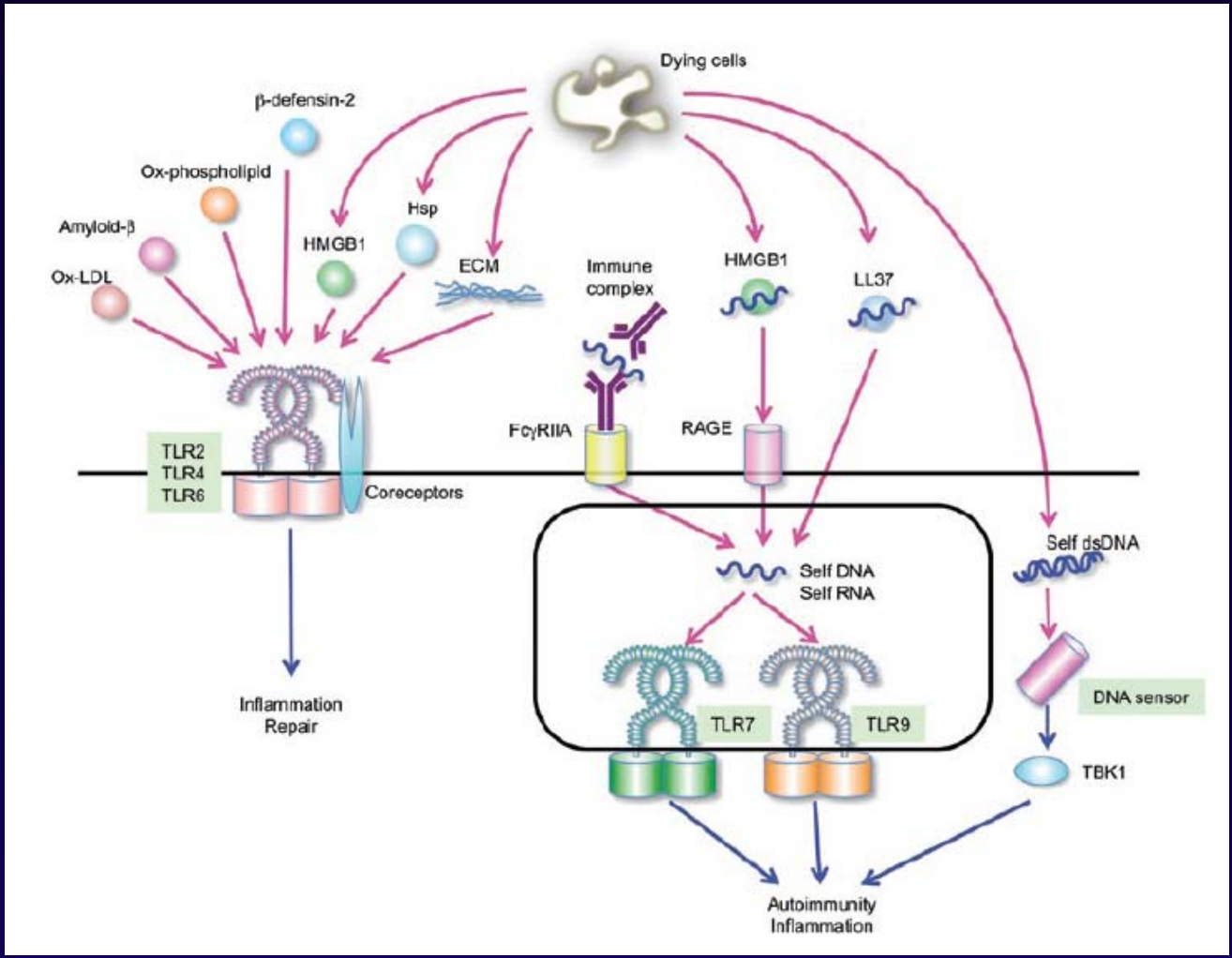
Receptors sense Danger: Pathogens





Kawai & Akira, *Nat. Immunol. 2010*

Receptors sense Danger: Damage



Kawai & Akira, *Nat. Immunol. 2010*

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

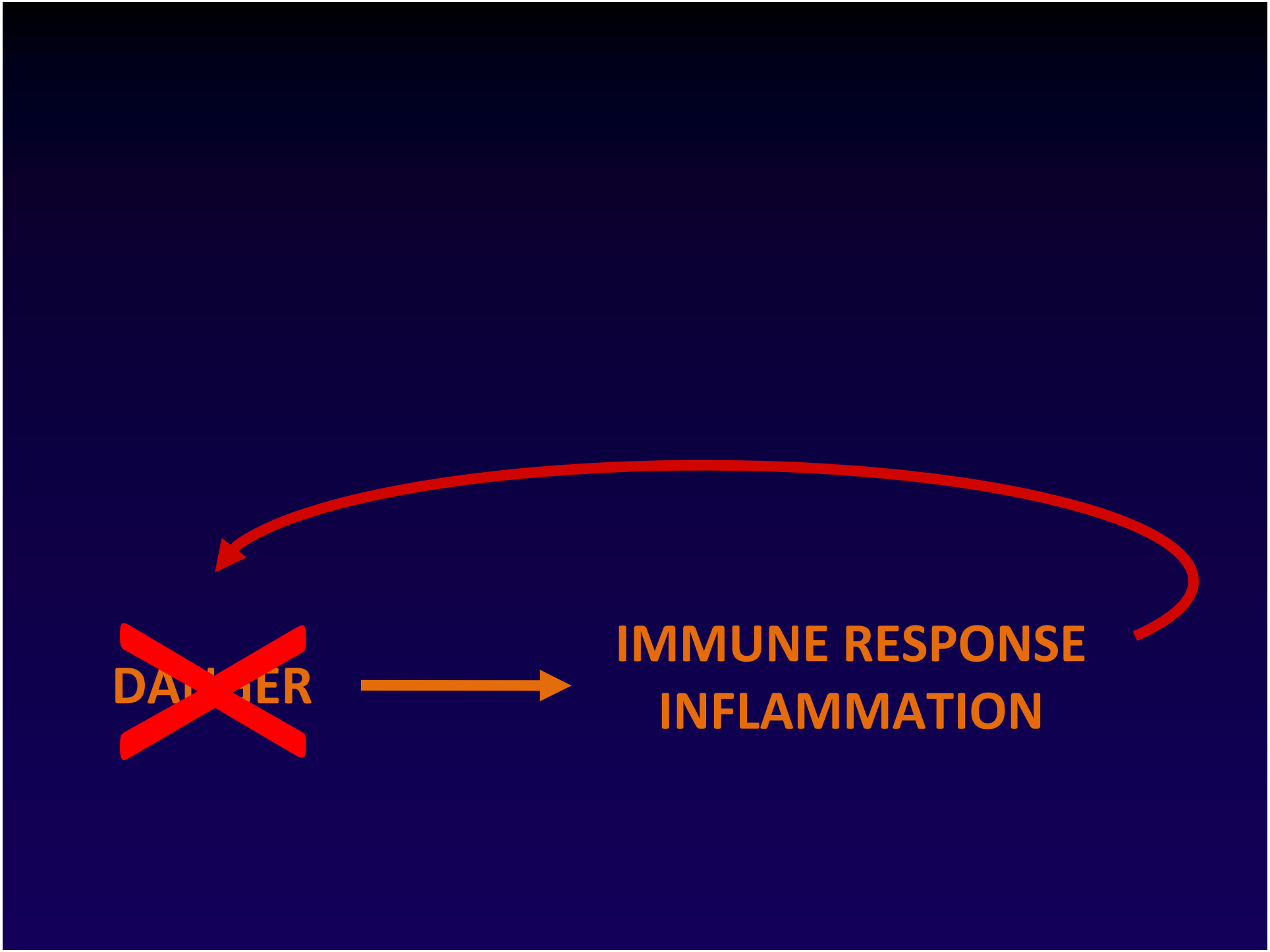
Bad Inflammation Causes Cancer

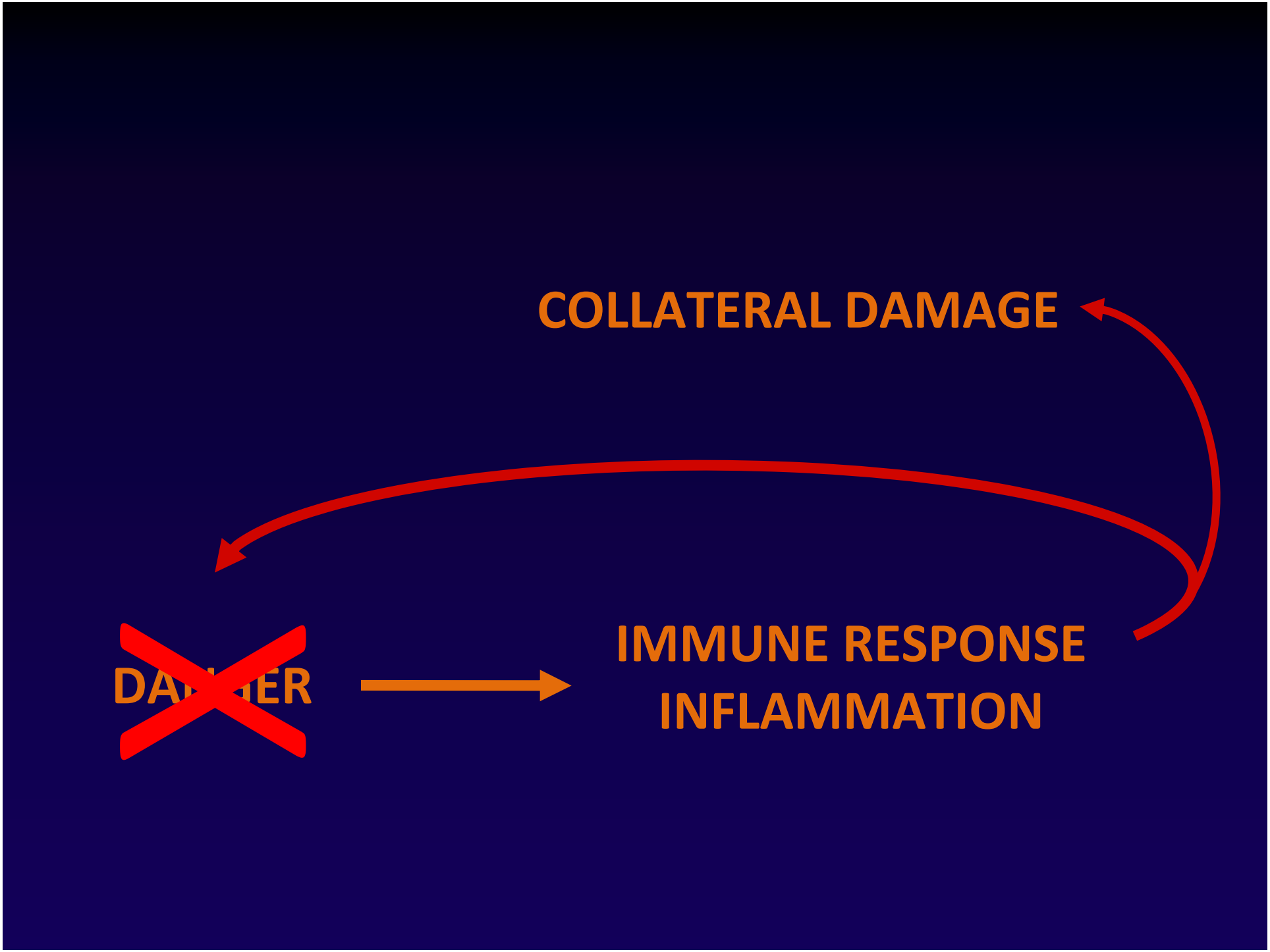
DANGER

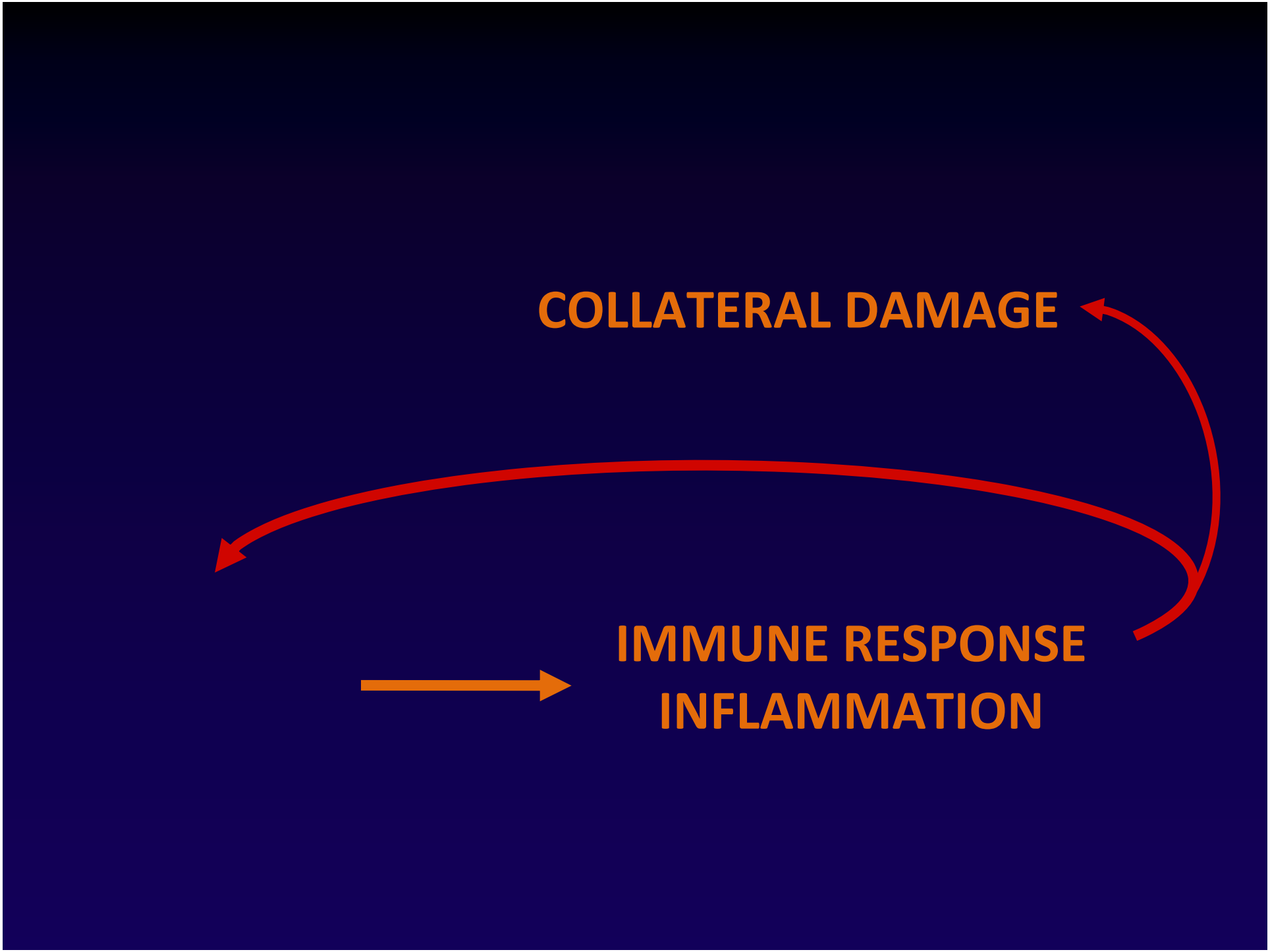
cellular damage caused by

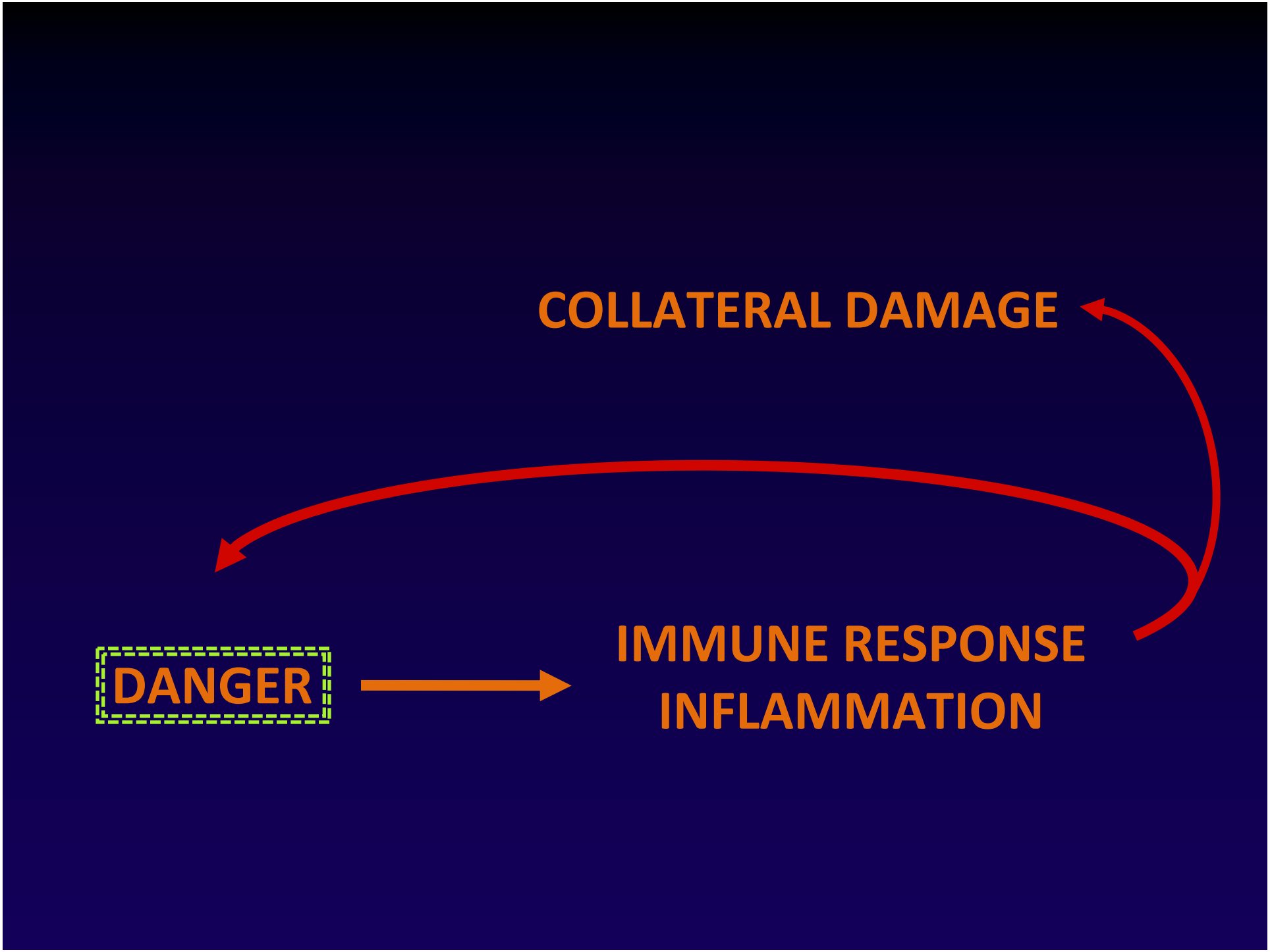
- **pathogens**
- **physical damage**
- **chemicals**
- **UV**
- **etc**

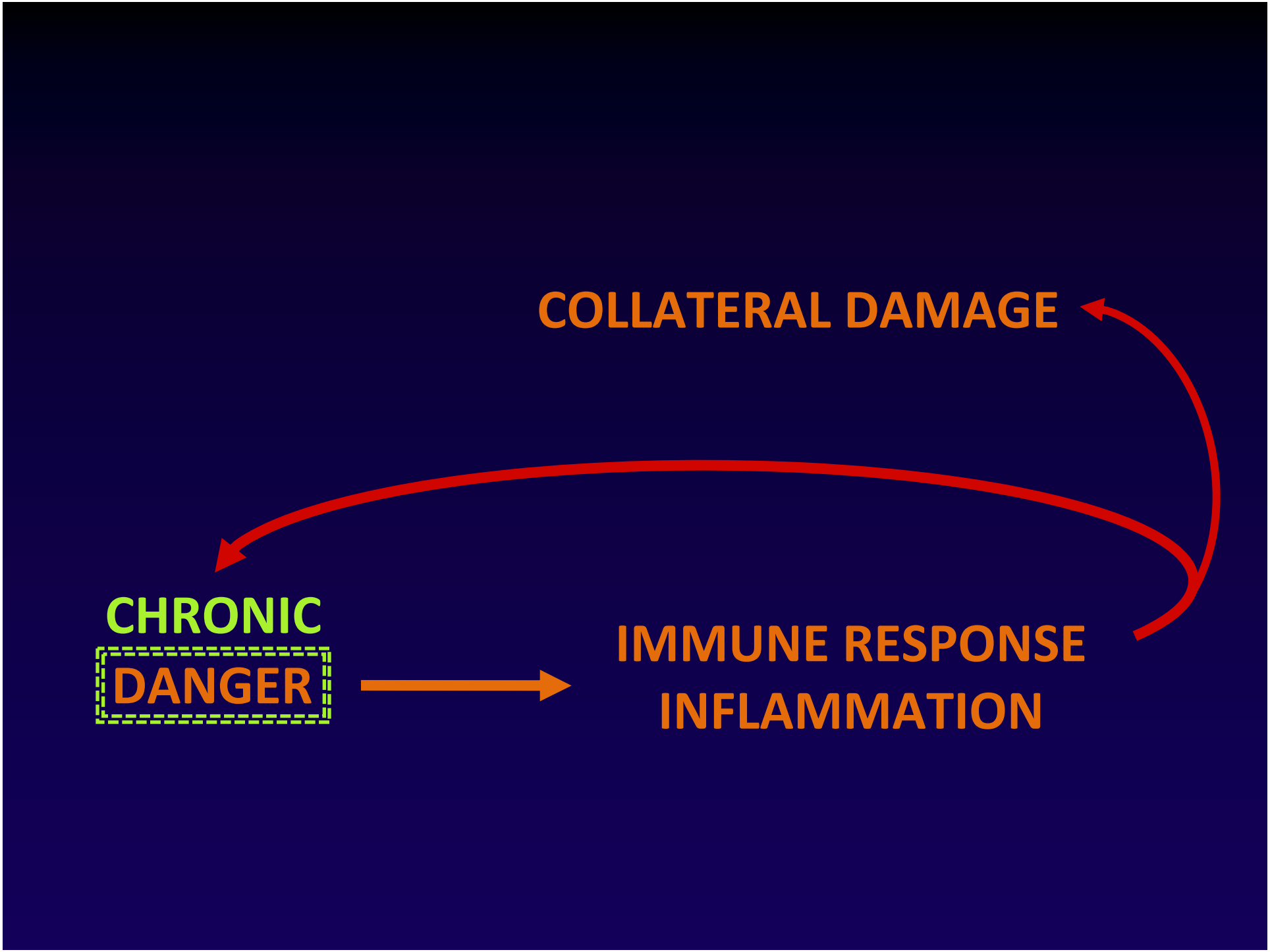
DANGER → IMMUNE RESPONSE
INFLAMMATION

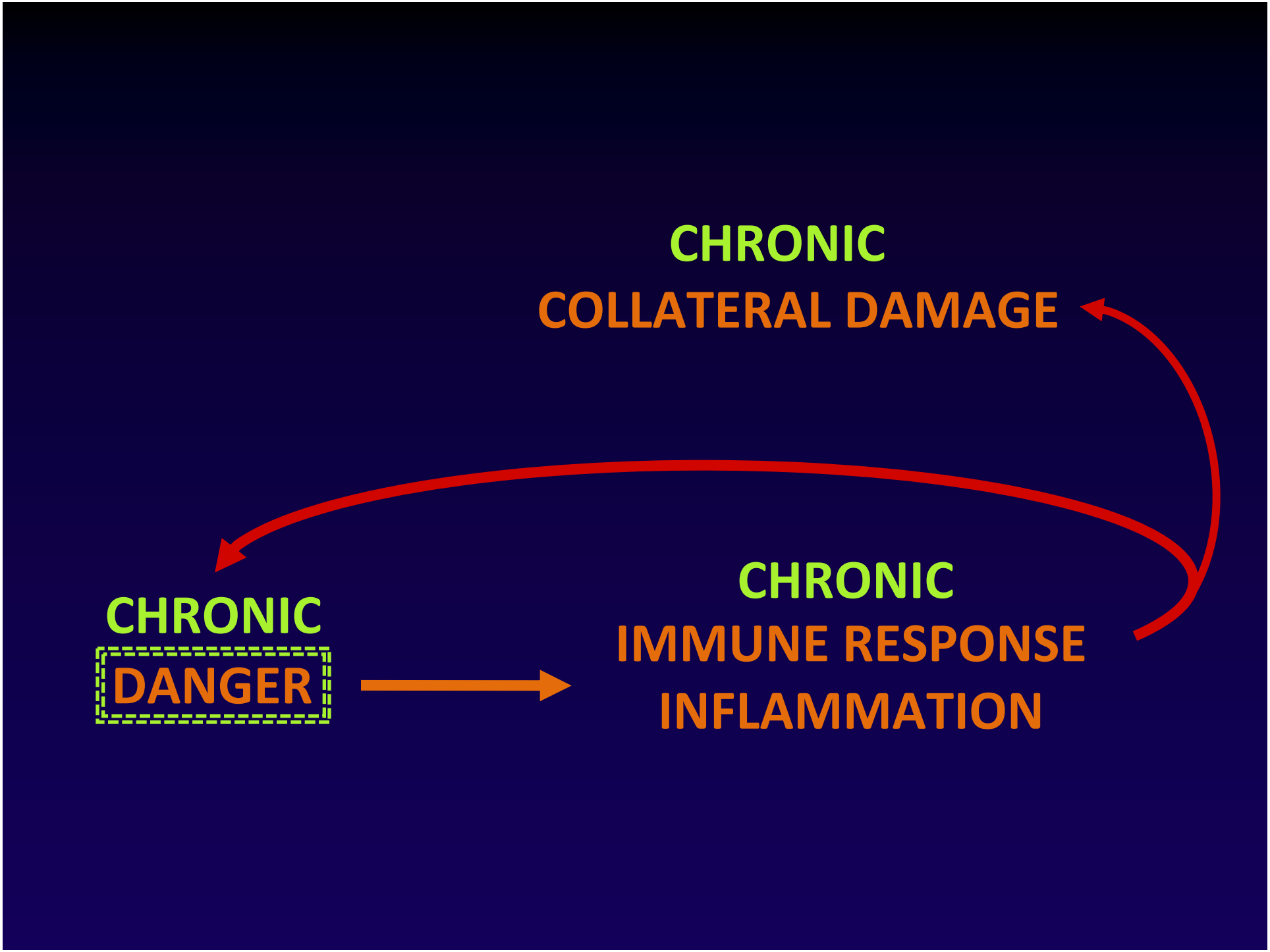

DANGER
IMMUNE RESPONSE
INFLAMMATION

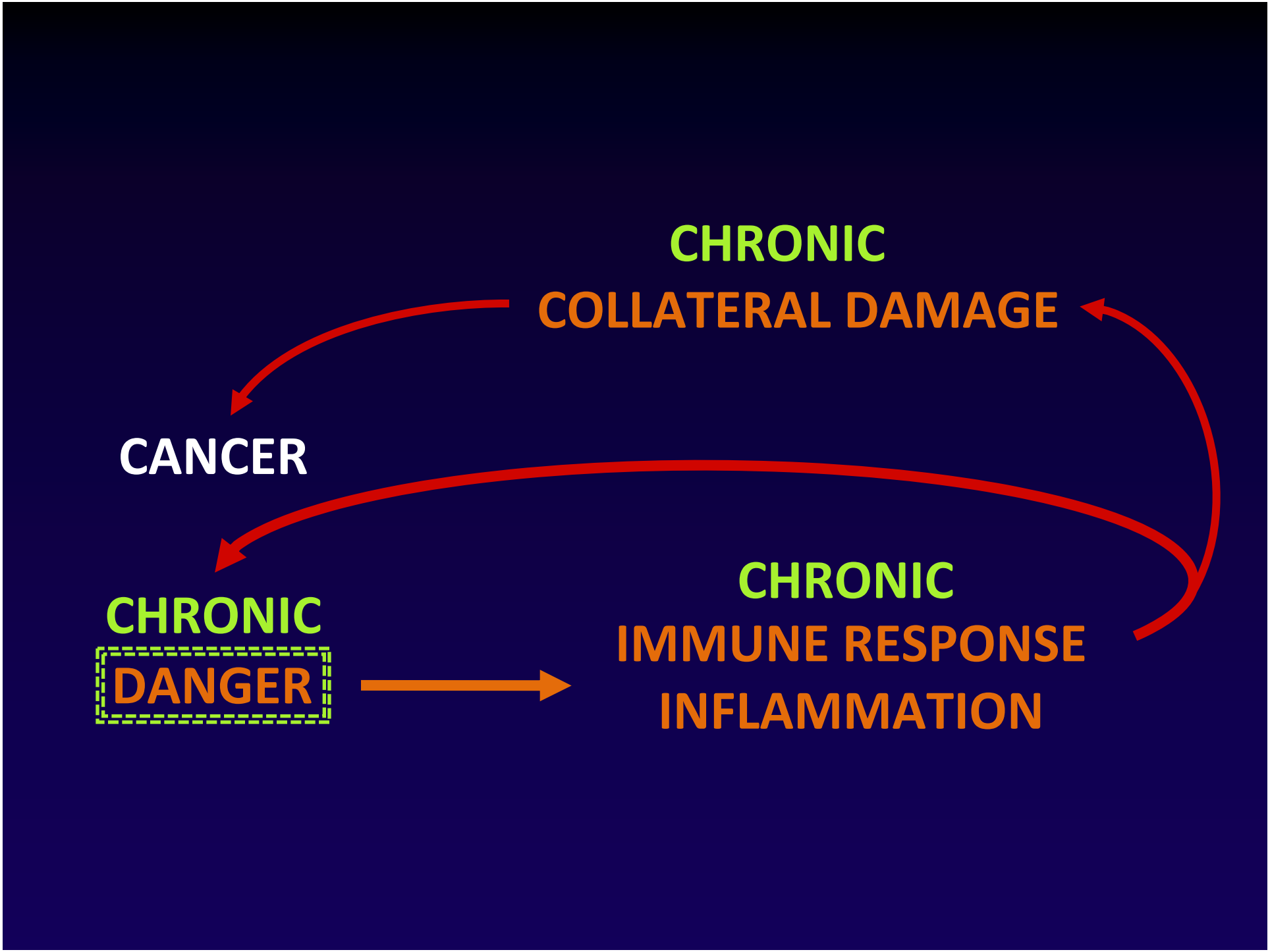

COLLATERAL DAMAGE
DANGER
IMMUNE RESPONSE
INFLAMMATION

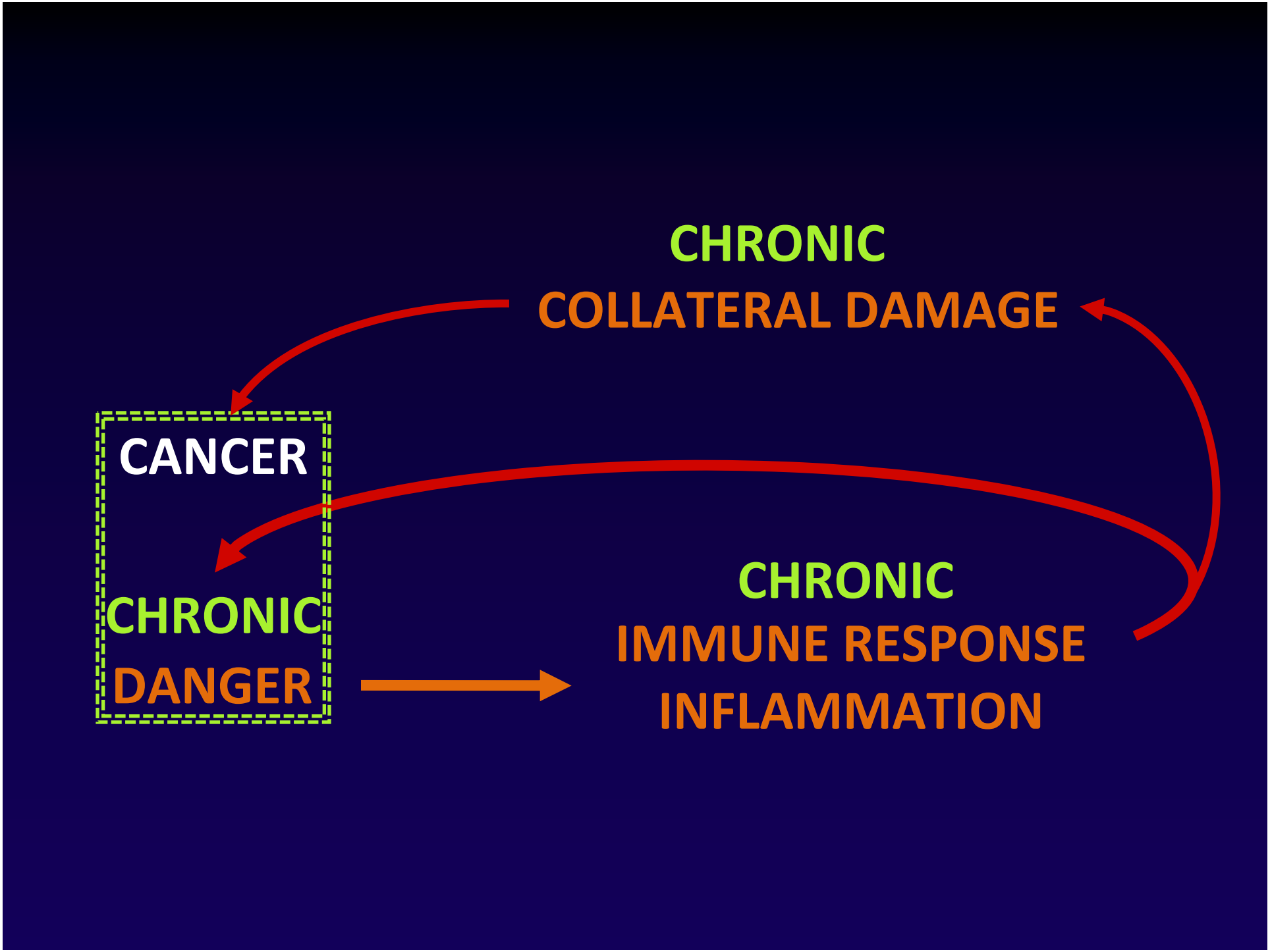

COLLATERAL DAMAGE
IMMUNE RESPONSE
INFLAMMATION

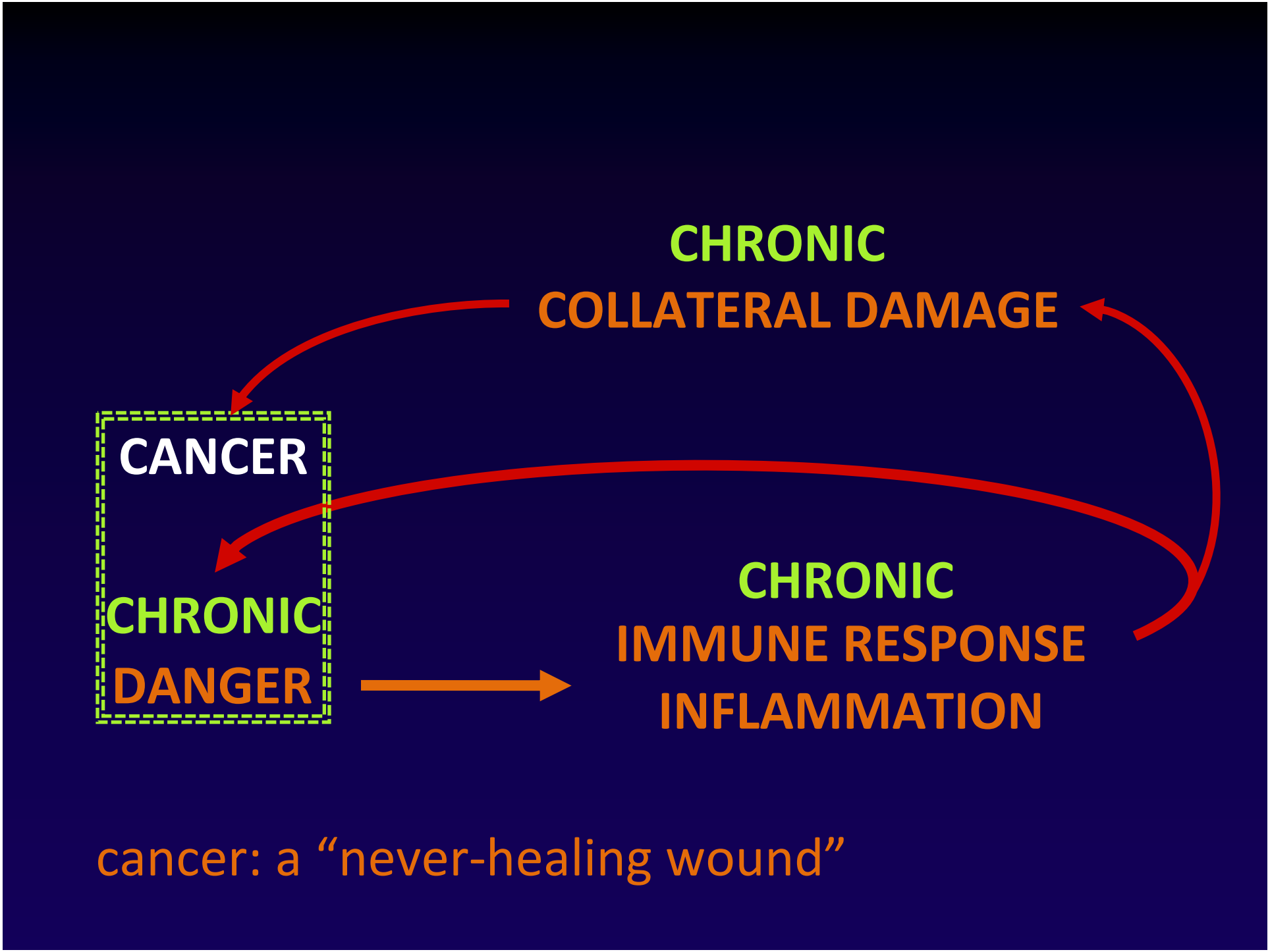

COLLATERAL DAMAGE
DANGER
IMMUNE RESPONSE
INFLAMMATION


COLLATERAL DAMAGE
CHRONIC
DANGER
IMMUNE RESPONSE
INFLAMMATION


CHRONIC
COLLATERAL DAMAGE
CHRONIC
IMMUNE RESPONSE
INFLAMMATION
CHRONIC
DANGER


CHRONIC
COLLATERAL DAMAGE
CANCER
CHRONIC
DANGER
CHRONIC
IMMUNE RESPONSE
INFLAMMATION


CHRONIC
COLLATERAL DAMAGE
CANCER
CHRONIC
DANGER
CHRONIC
IMMUNE RESPONSE
INFLAMMATION

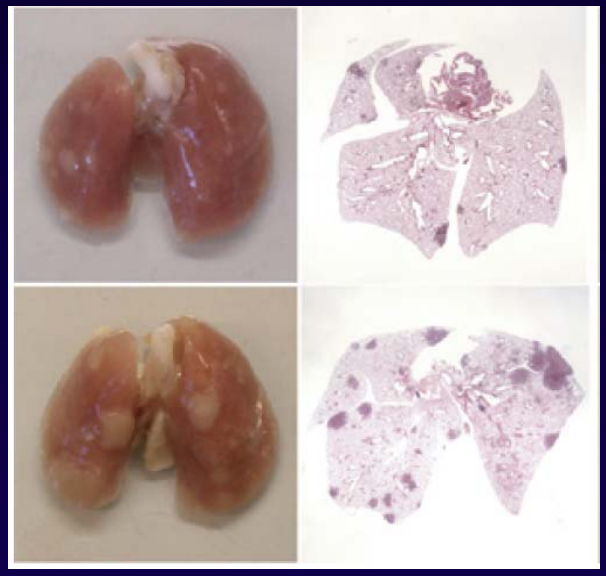


cancer: a “never-healing wound”

Inflammation can Promote Cancer: collaboration with K-ras mutation

no smoking

4 cigarettes per day



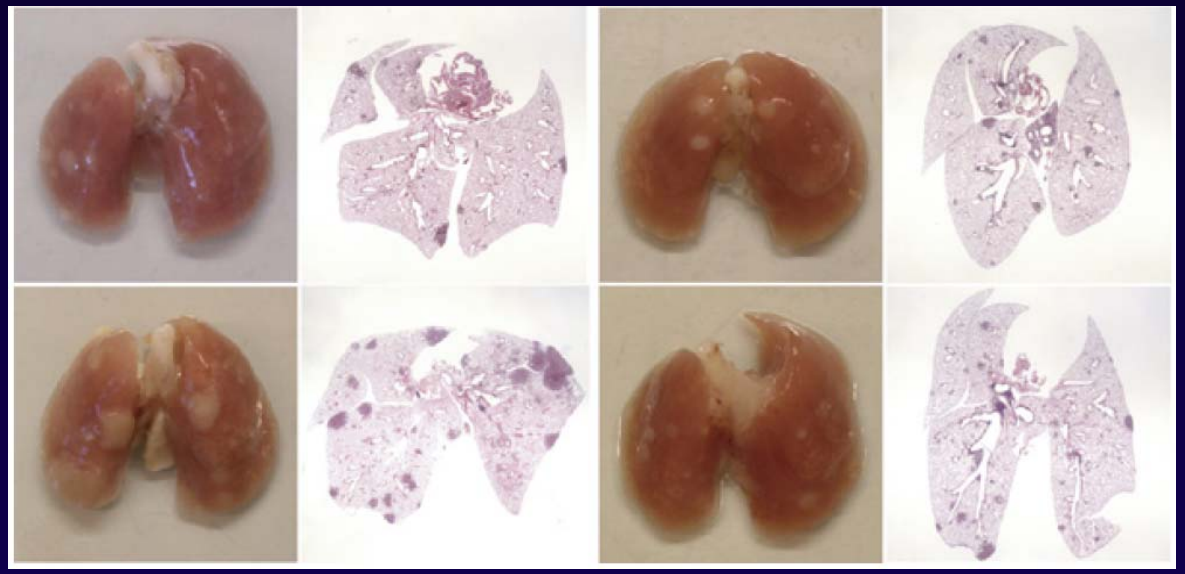
K-ras mutation
&
normal myeloid cells

Takahashi et al. , *Cancer Cell* 2010

Inflammation can Promote Cancer: collaboration with K-ras mutation

no smoking

4 cigarettes per day



K-ras mutation & normal myeloid cells

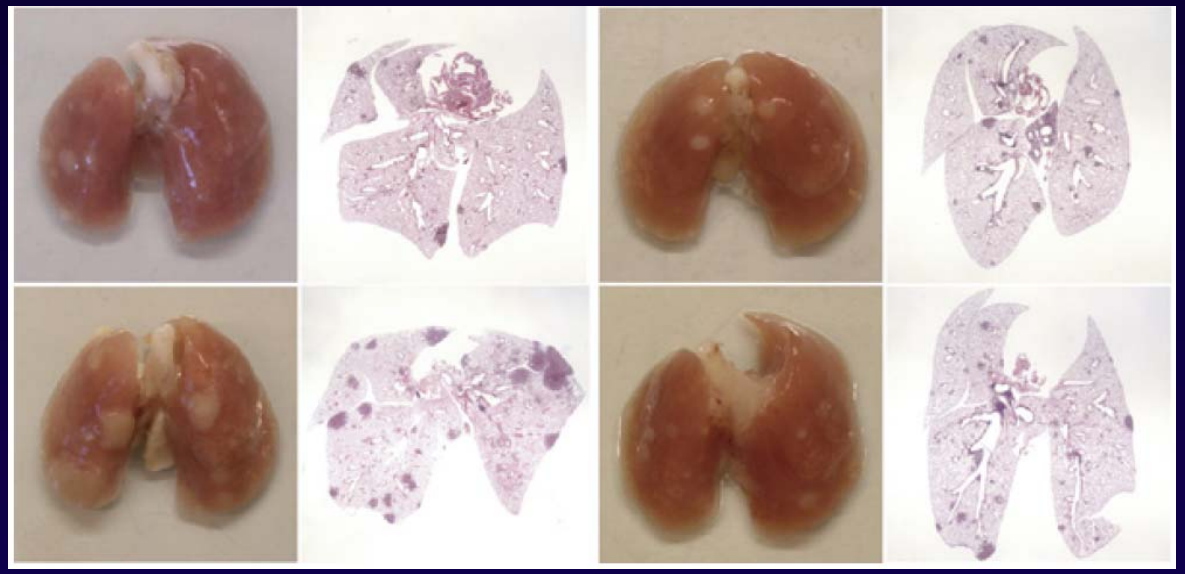
K-ras mutation + $IKK^{-/-}$ myeloid cells

Takahashi et al. , *Cancer Cell* 2010

Inflammation can Promote Cancer: collaboration with K-ras mutation

no smoking

4 cigarettes per day



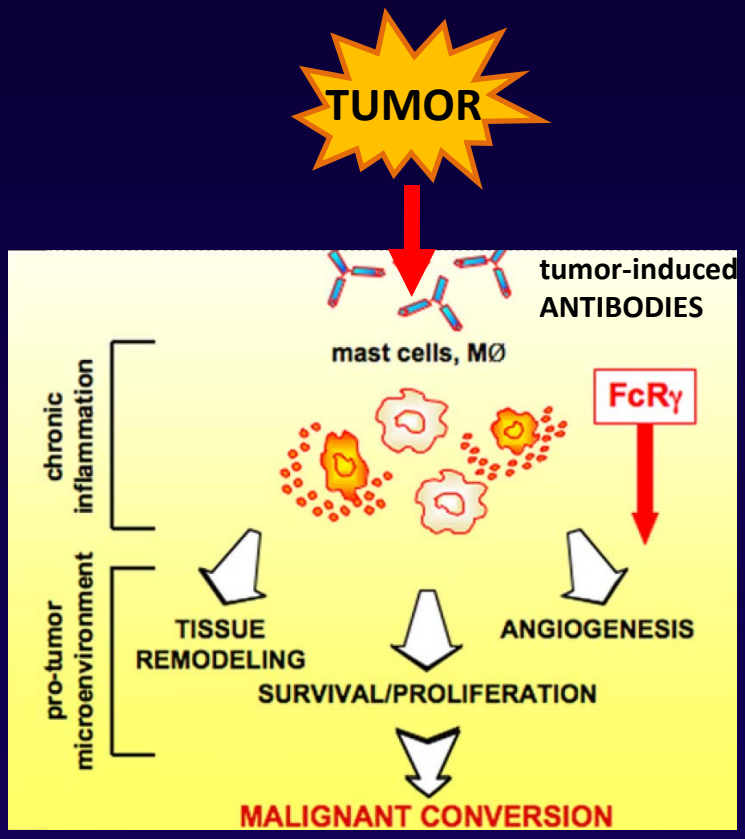
K-ras mutation & normal myeloid cells

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

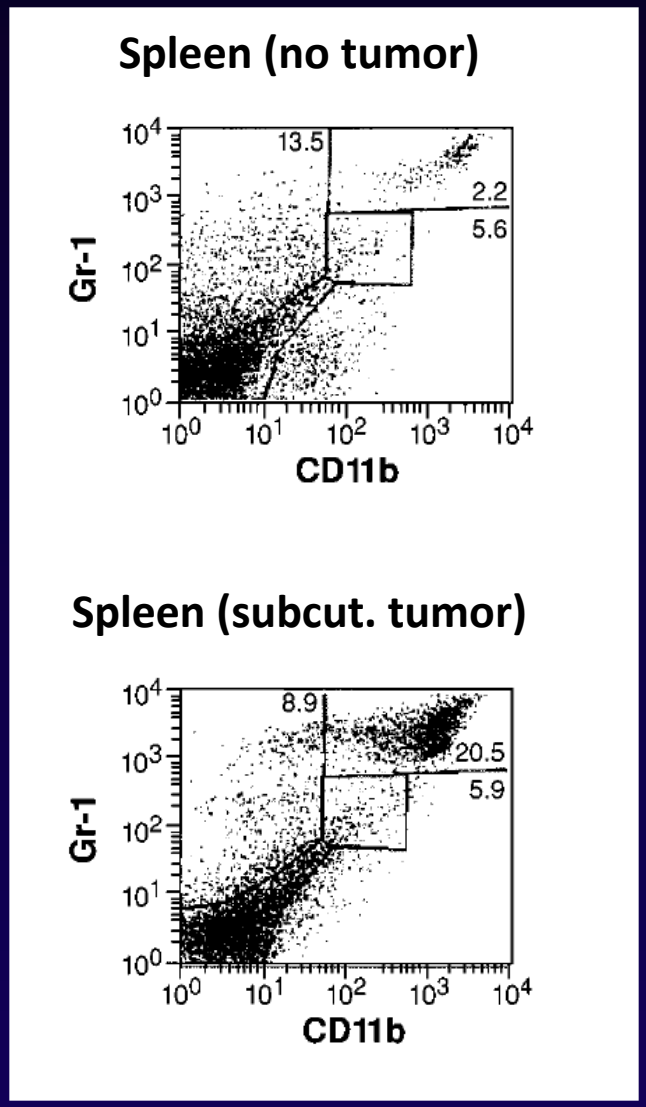
Tumors can induce bad inflammation

Apoptotic Death of CD8$^+$ T Lymphocytes After Immunization: Induction of a Suppressive Population of Mac-1$^+$/Gr-1$^+$ Cells[1]

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

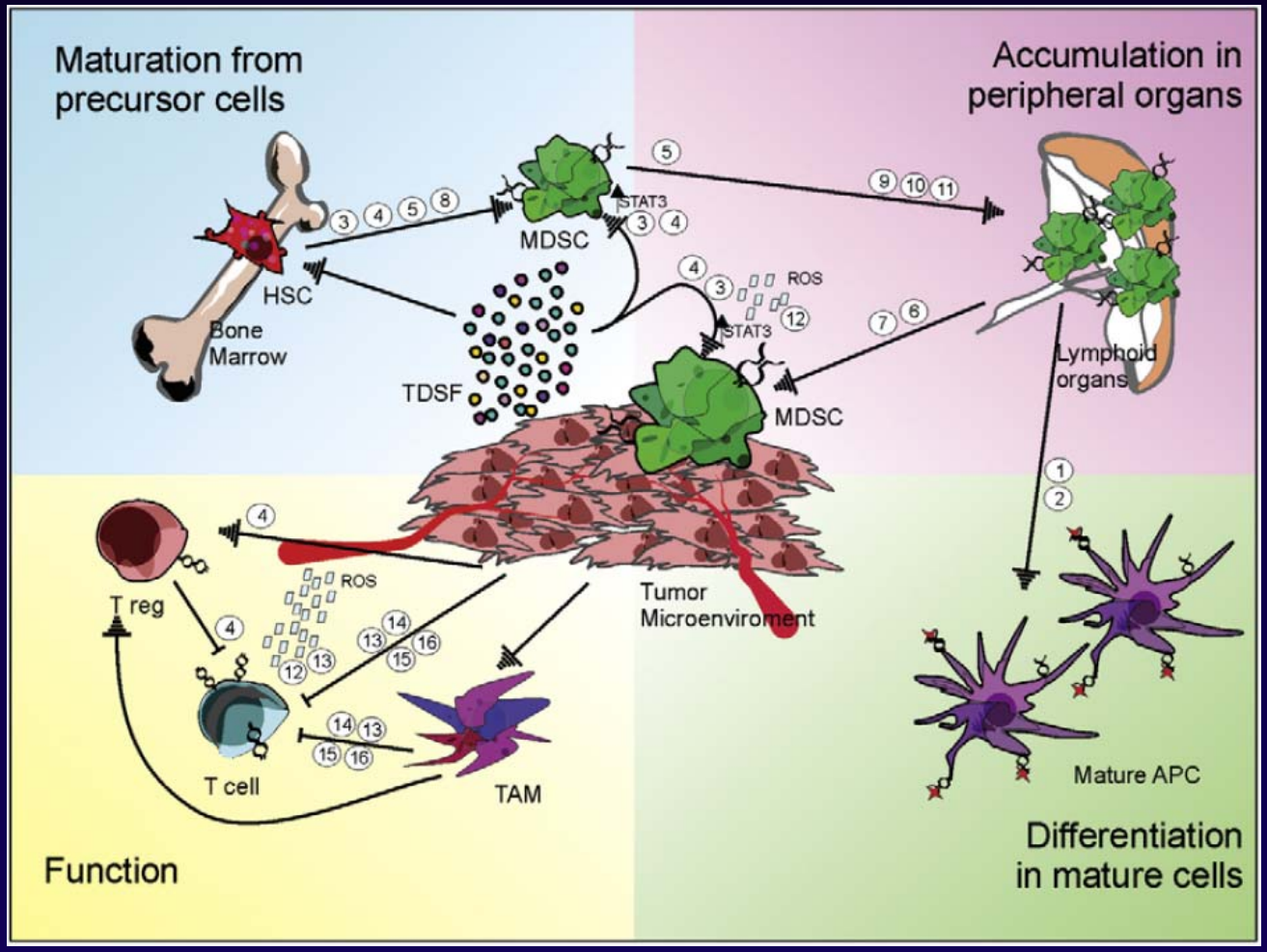
The Journal of Immunology, 1998, 161: 5313–5320.

Tumors can induce bad inflammation



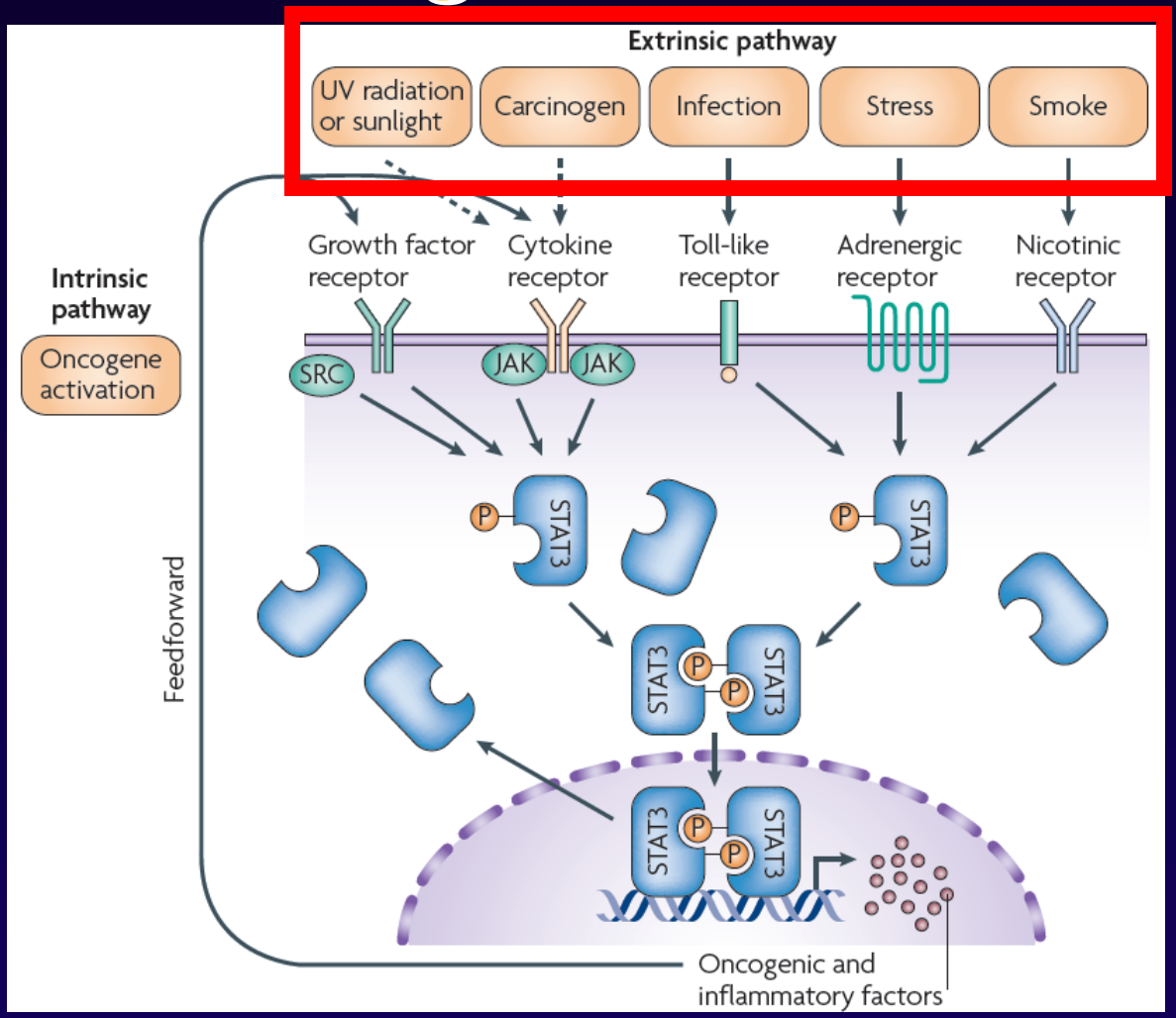
Bronte et al., *J. Immunol.* 1999

Tumors can induce bad inflammation



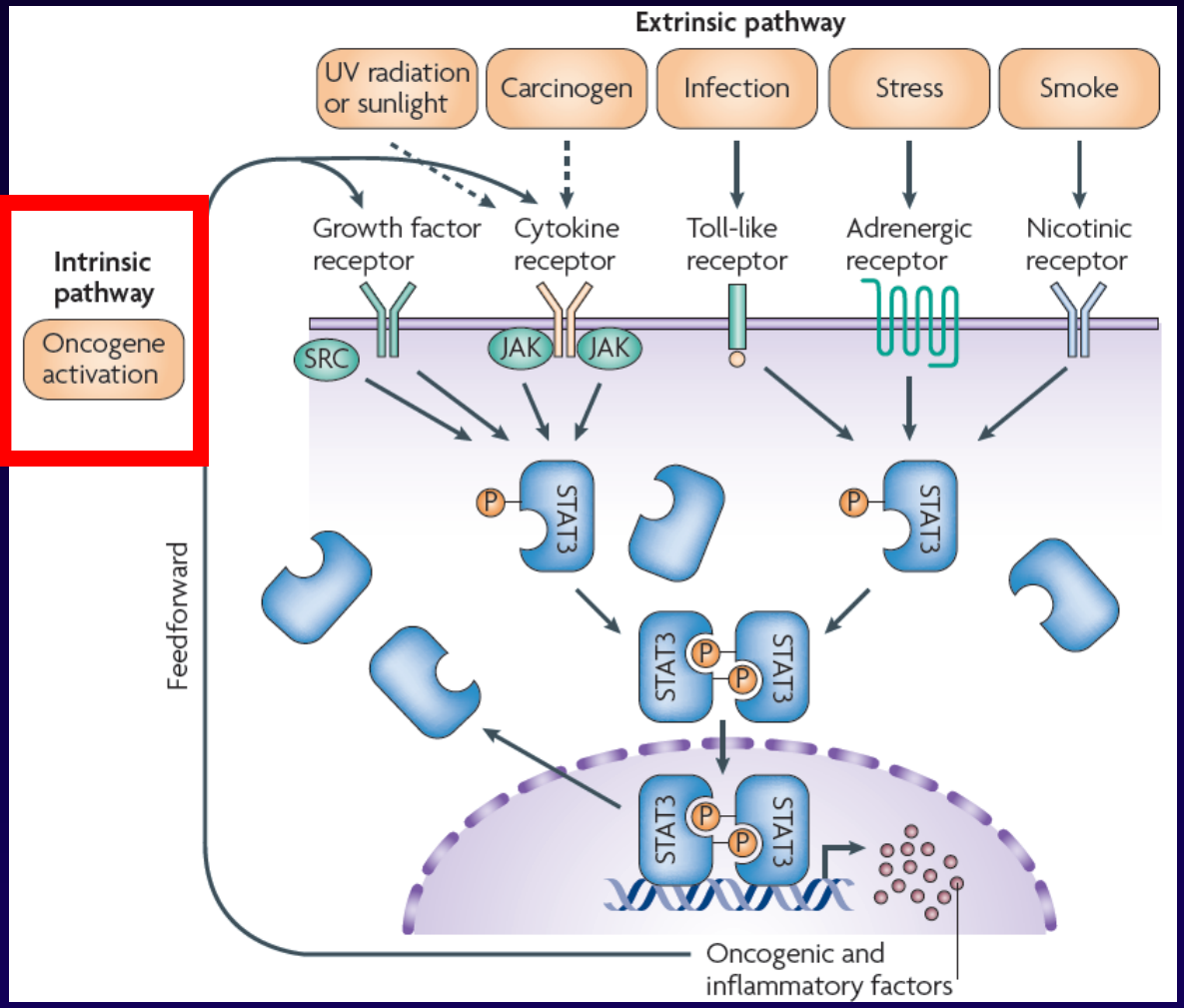
Ugel et al., *Curr. Opin. Pharmacol.* 2010

Tumors can induce bad inflammation
Oncogenic STAT3



Yu et al., *Nat. Rev. Cancer* 2009

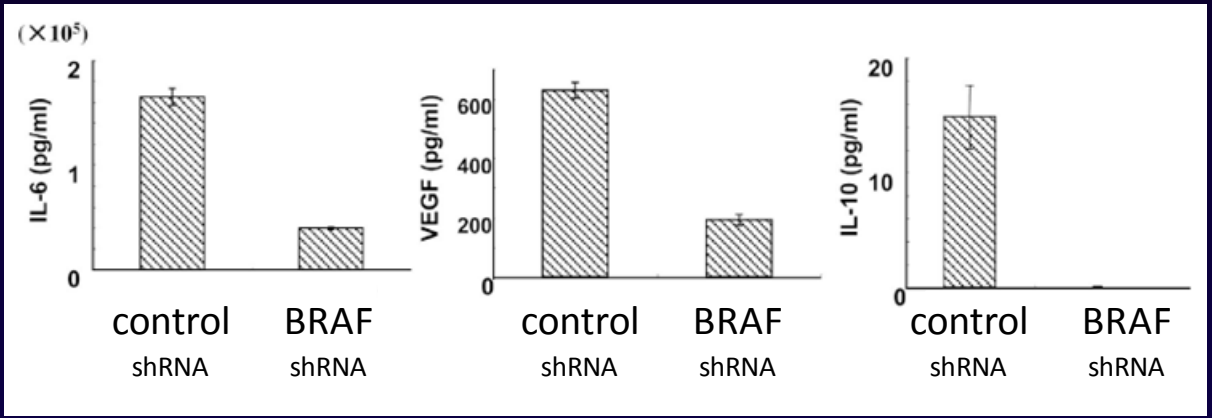
Tumors can induce bad inflammation
Oncogenic STAT3



Yu et al., *Nat. Rev. Cancer* 2009

Mutations can Drive Bad Inflammation

Mutated BRAF → tumor cells produce bad, imunosuppressive cytokines

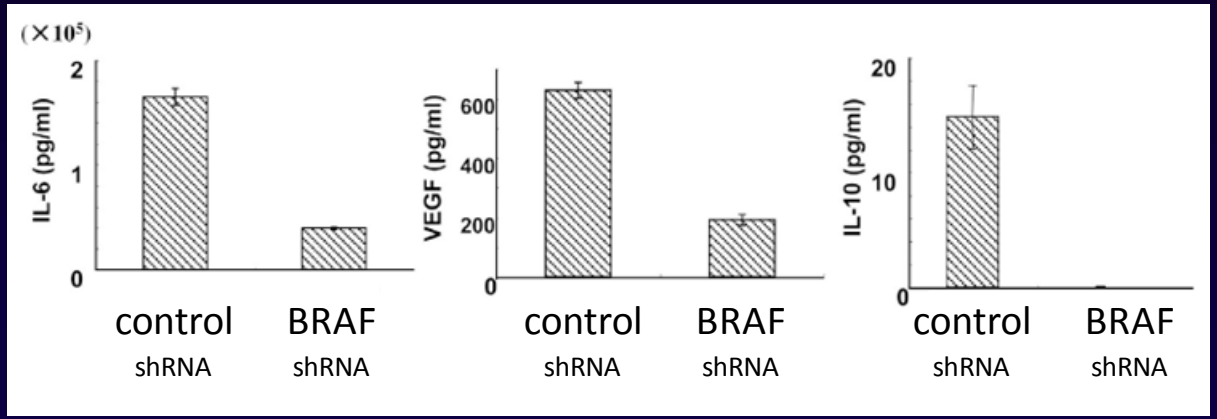


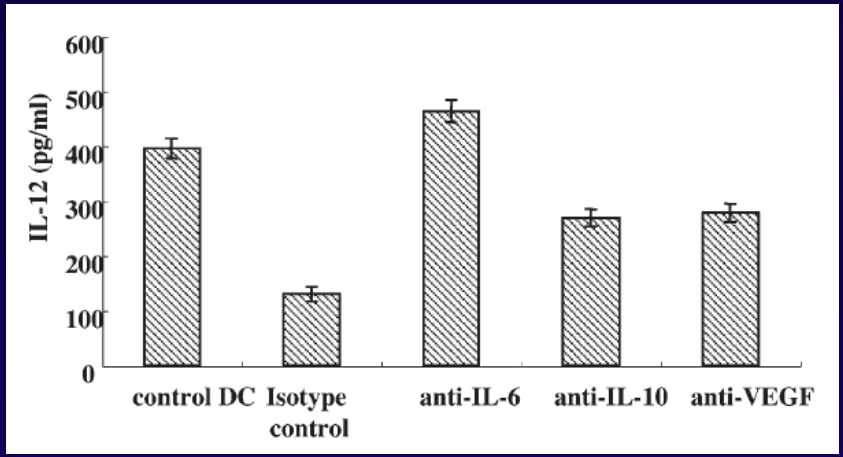
Sumimoto et al., *J. Exp. Med.*. 2006

Mutations can Drive Bad Inflammation

Mutated BRAF → tumor cells produce bad, imunosuppressive cytokines

block production of good cytokines in DCs



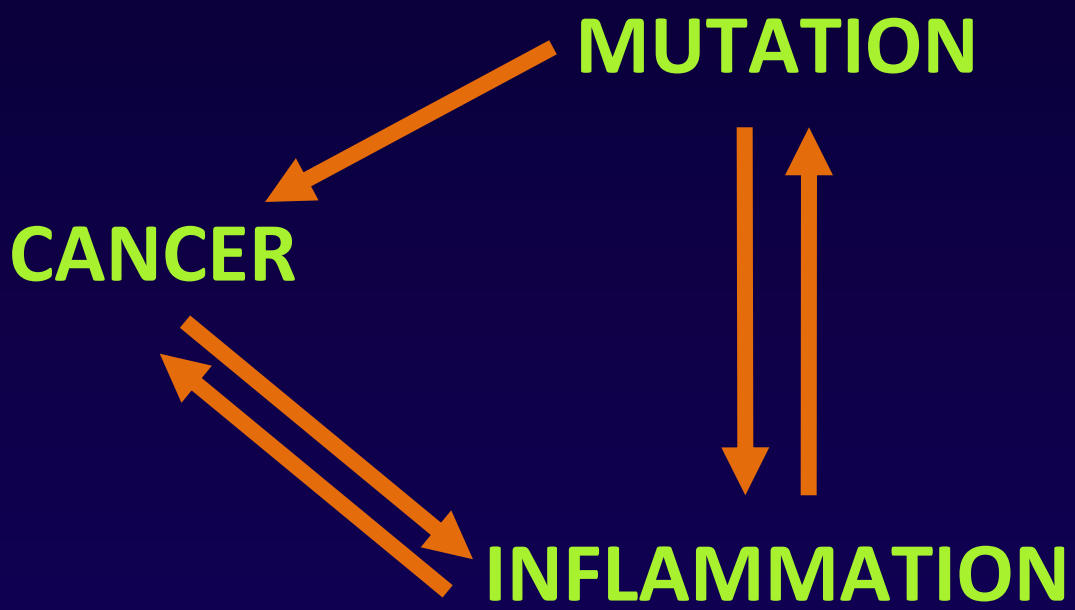


Sumimoto et al., *J. Exp. Med.*. 2006

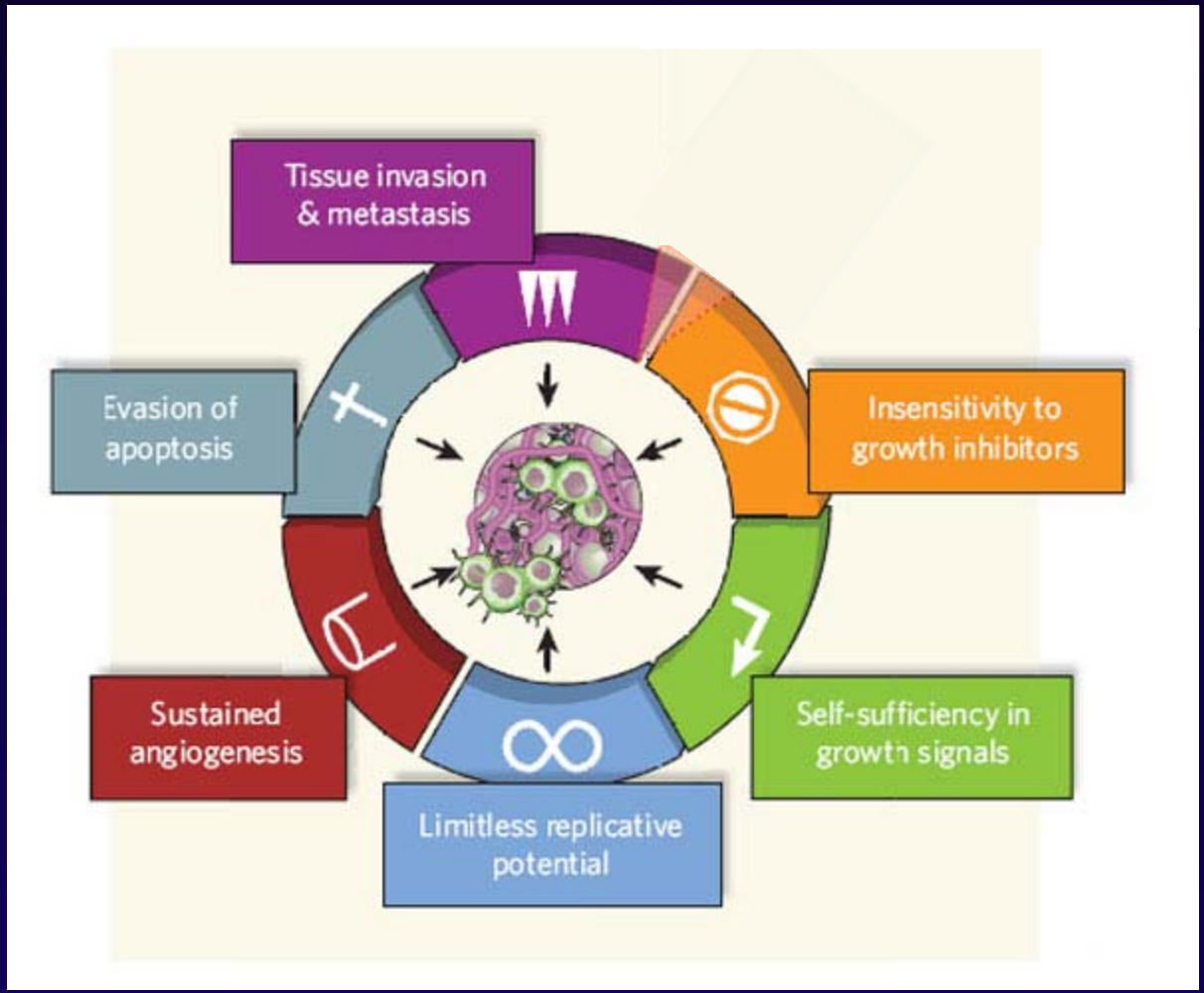
Conclusion: Inflammation and Cancer

- 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

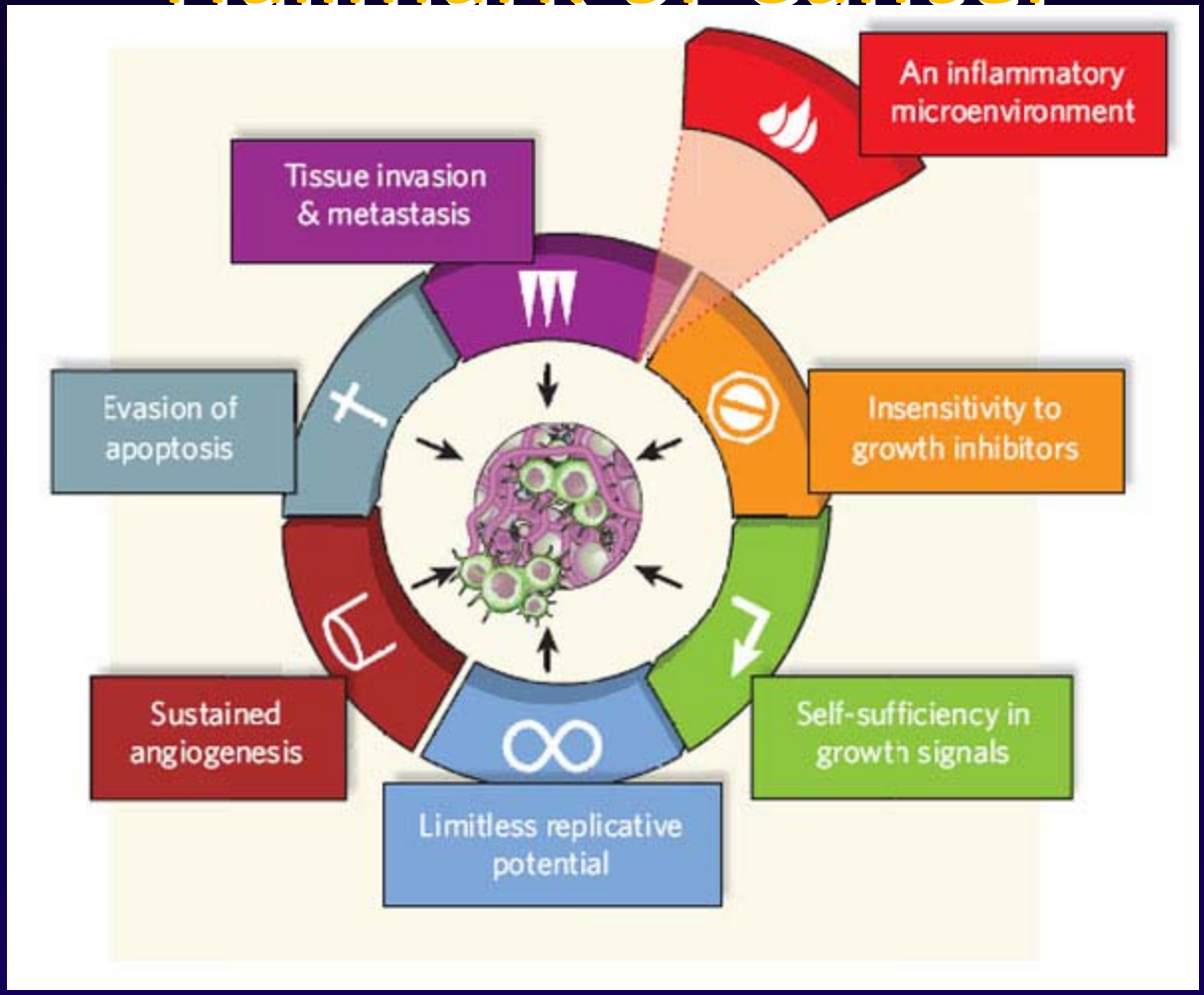


Classic Hallmarks of Cancer



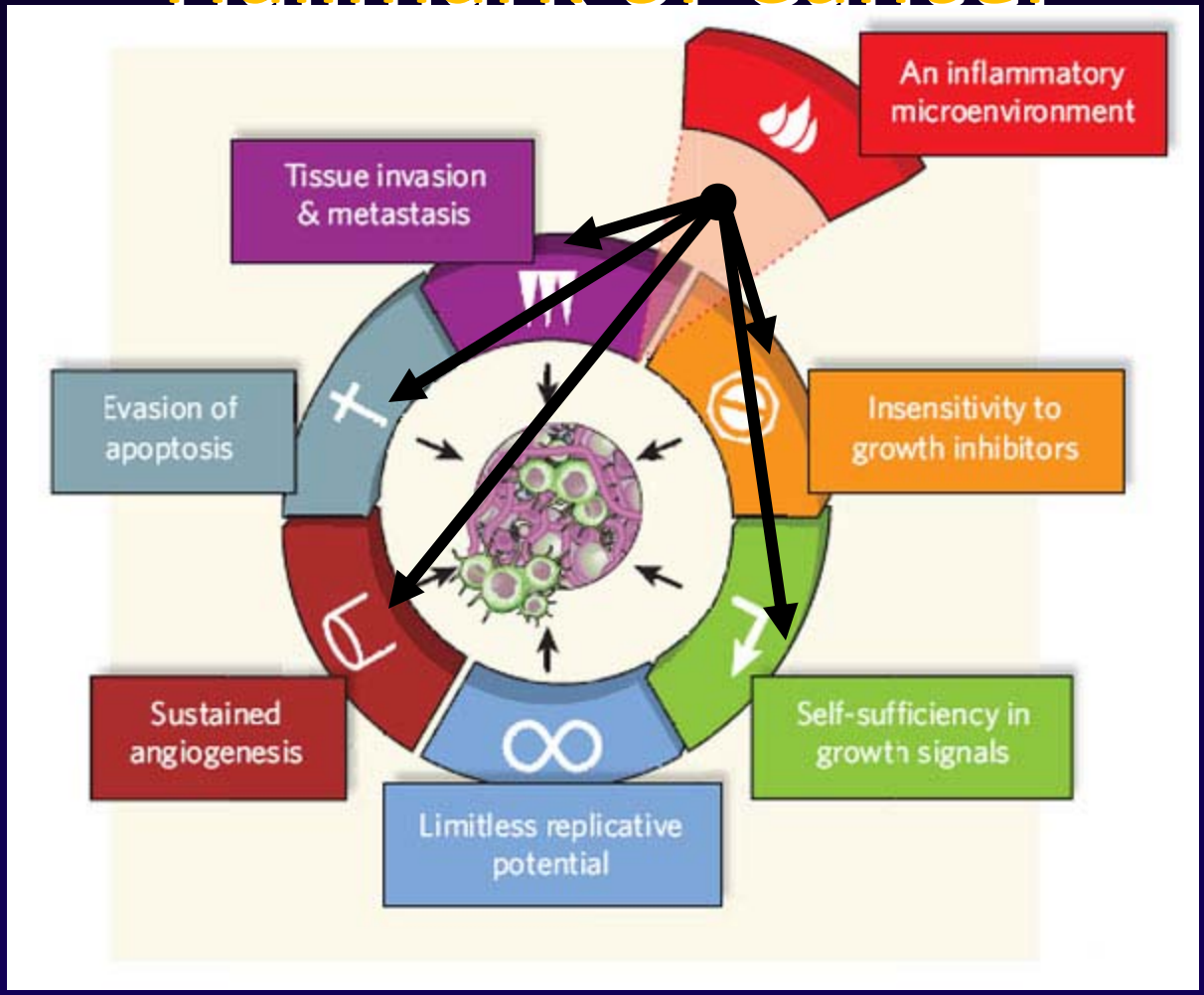
Mantovani et al., *Nature* 2009
Hanahan & Weinberg, *Cell* 2000

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



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

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 (IFNγR2) deficiency

Toyoda et al., *J. Med. Genetics* 2010

IFN-γ Suppresses Human Tumor Development

Multiple cutaneous squamous cell carcinomas in a patient with interferon γ receptor 2 (IFNγR2) 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.

Toyoda et al., *J. Med. Genetics* 2010

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

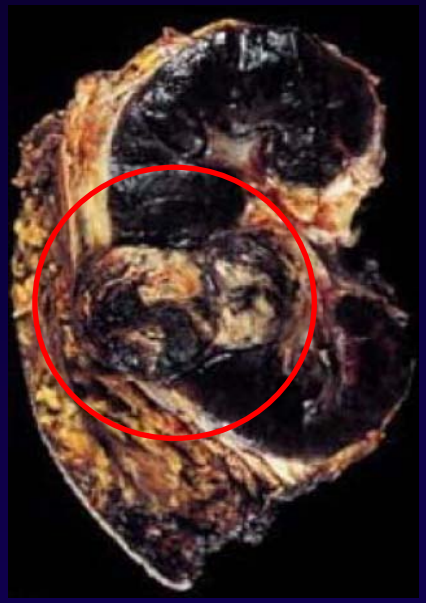
2000: - kidney recipient 1 died of metastatic donor melanoma

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

- kidney recipient 2 rejects kidney and melanoma

MacKie et al., *NEJM* 2003

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

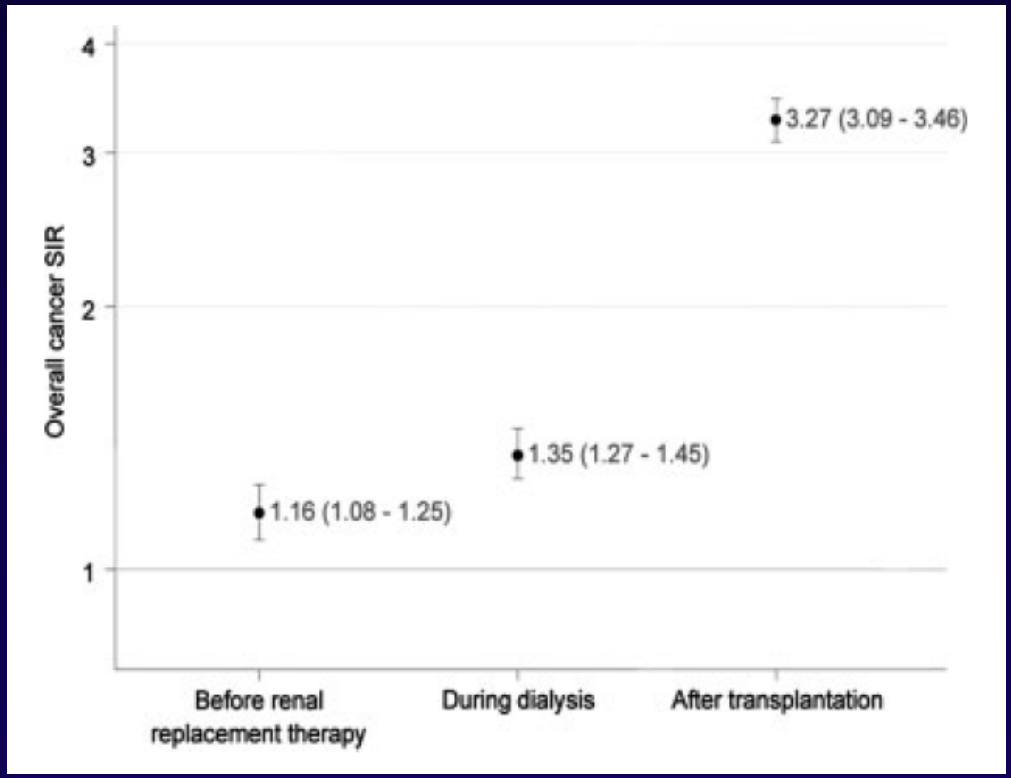
2000: - kidney recipient 1 died of metastatic donor melanoma

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

- kidney recipient 2 rejects kidney and melanoma

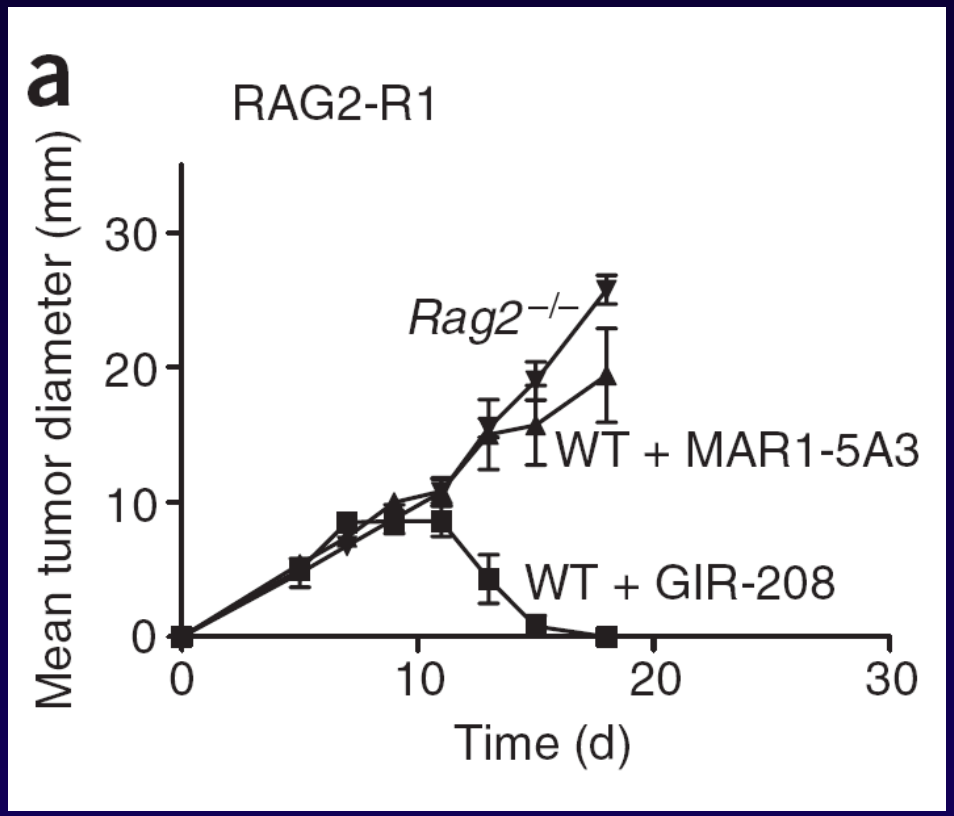
MacKie et al., *NEJM* 2003

Post-transplant Immunosuppression Increases Cancer Incidence



Vajdic & Van Leeuwen , *Int. J. Cancer 2009*

Type I IFNs Suppress Growth of Transplanted Tumors

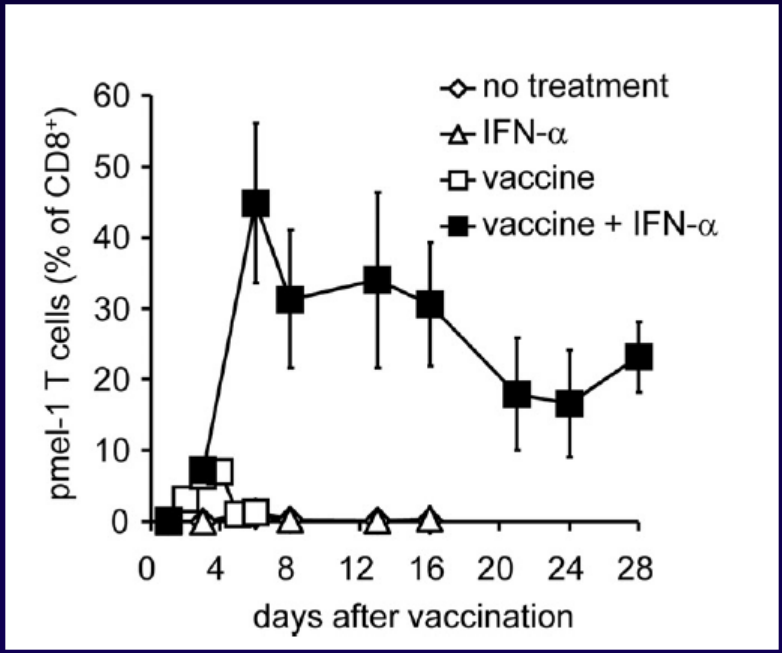


IFN-α receptor blocking mAb

control mAb

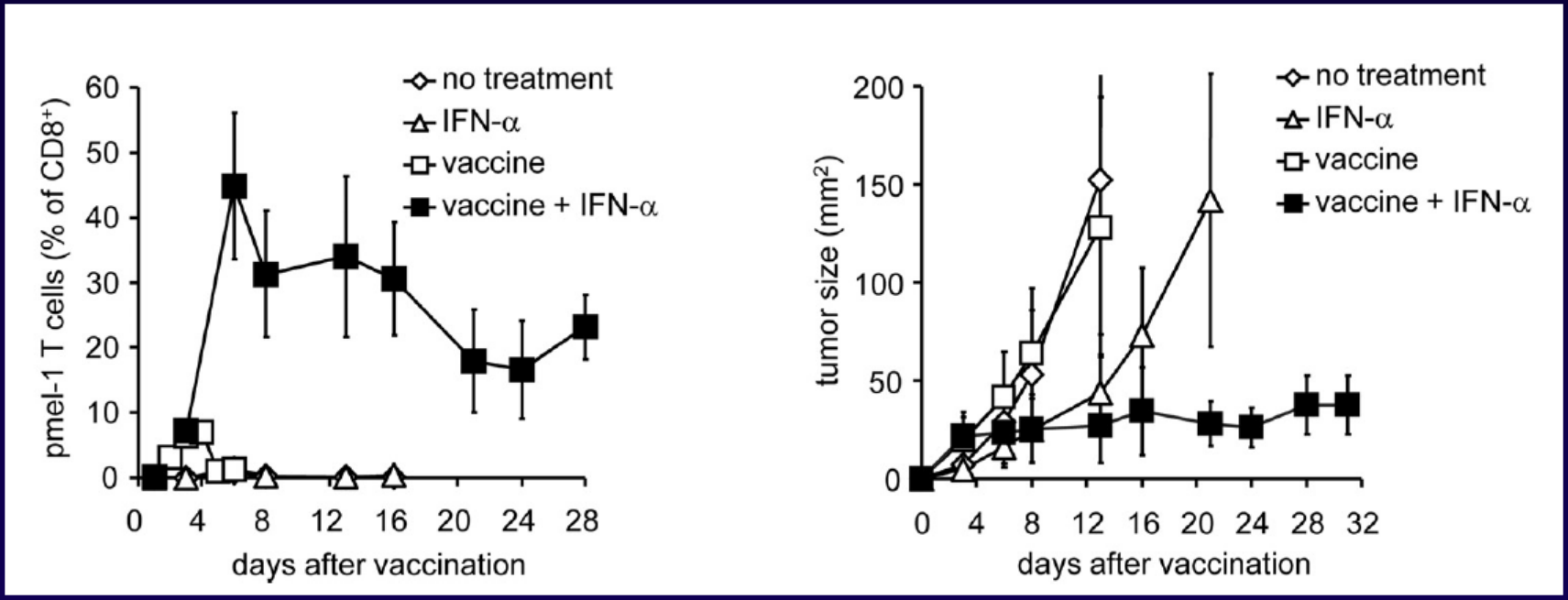
Dunn et al. *Nat. Immunol.* 2005

IFN-α treatment enhances anti-cancer vaccination



Sikora et al. *J. Immunol.* 2009

IFN-α treatment enhances anti-cancer vaccination



Sikora et al. *J. Immunol.* 2009

CpG Causes Tumor Inflammation and Intratumoral T cell Accumulation

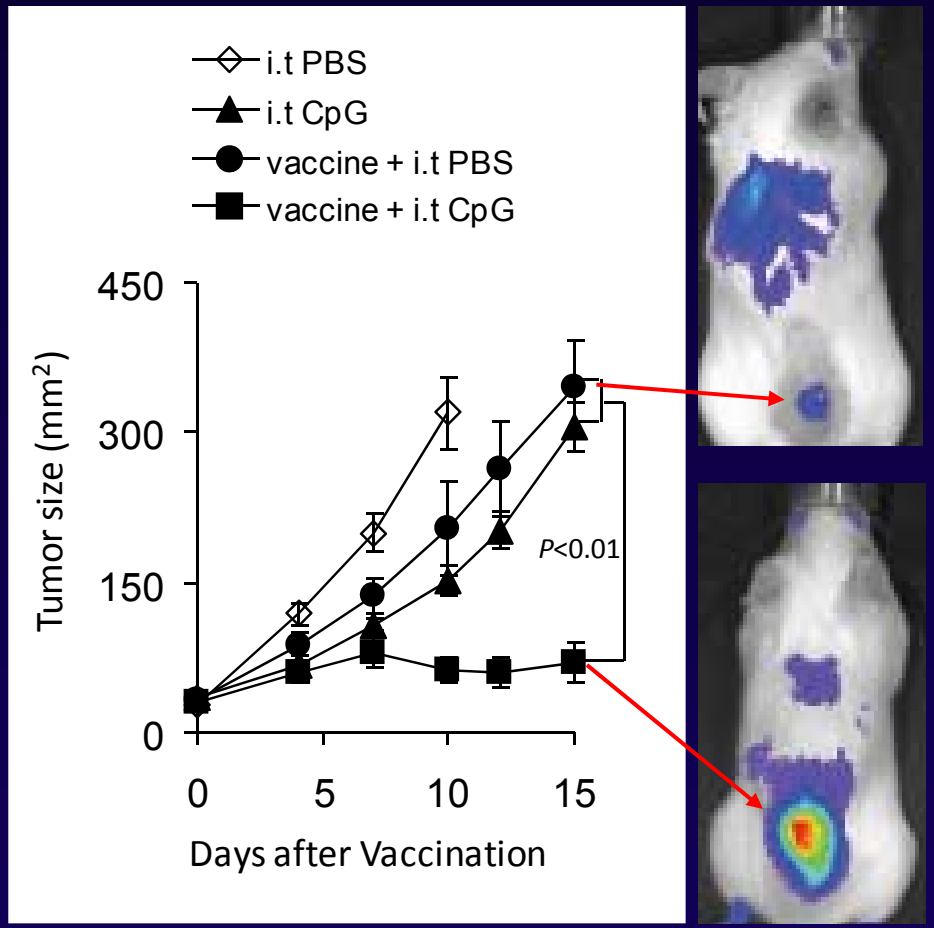
Intratumoral PBS

Intratumoral CpG

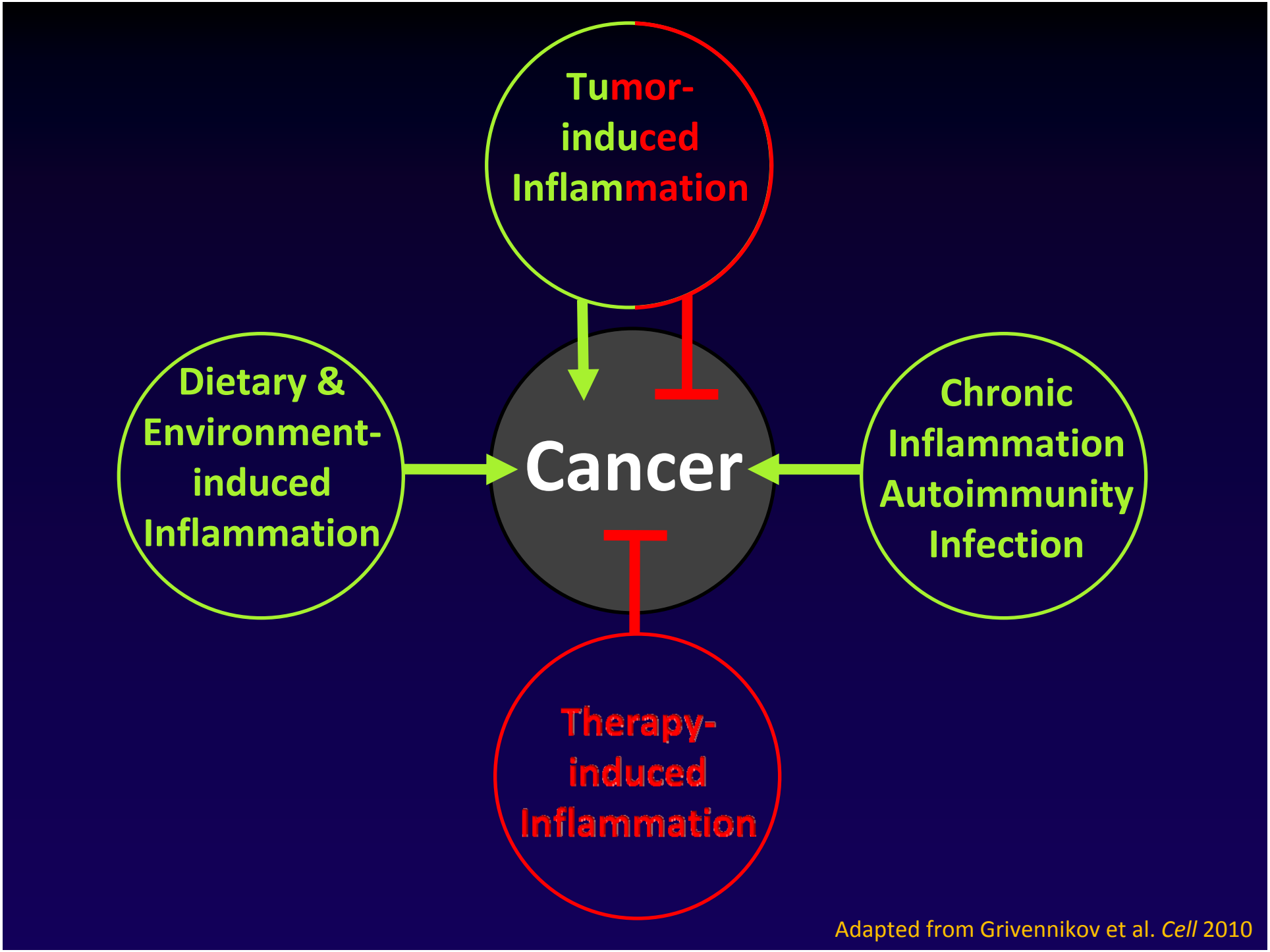
Intravenous CpG

Lou et al. , *J. Immunother*. 2011

CpG Causes Tumor Inflammation and Intratumoral T cell Accumulation



Lou et al. , *unpublished results*



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 (IFNγ)	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

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)

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)

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)

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)

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)

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)

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

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)

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 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 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 mAb (melanoma)
- Surgery — Danger/inflammation? (cervical)
- Hem. Stem Cells — Stem Cell Transpl. (leukemia, lymphoma)

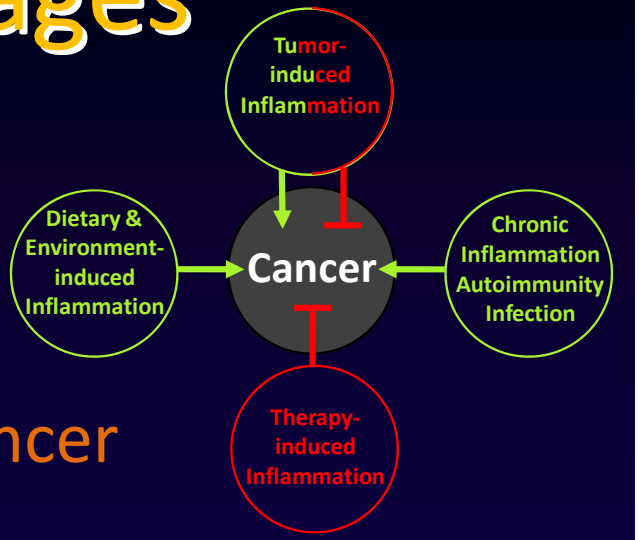
In the Clinic: Cancer Therapies that Induce Good Inflammation

- 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 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 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