Innate Immunity, Inflammation and Cancer

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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.

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 $\neq$ 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 ≠ Innate Immunity B
- Inflammation A ≠ Inflammation B

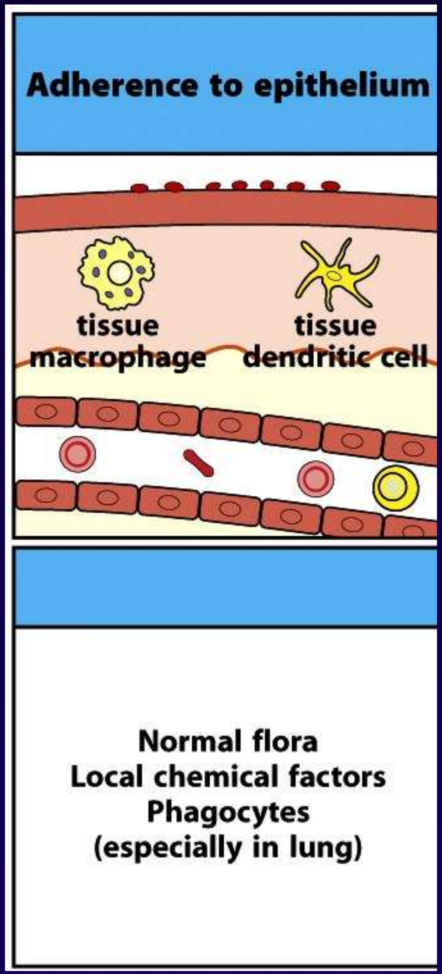
- Some immune responses promote cancer, others suppress it

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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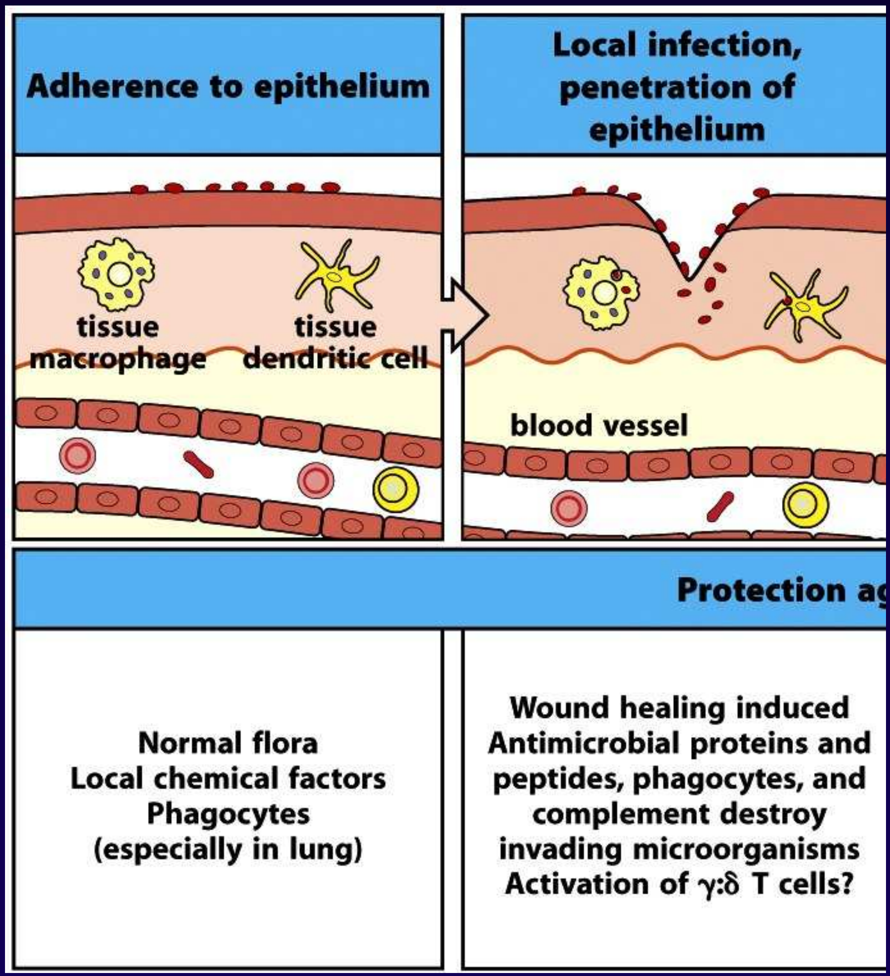

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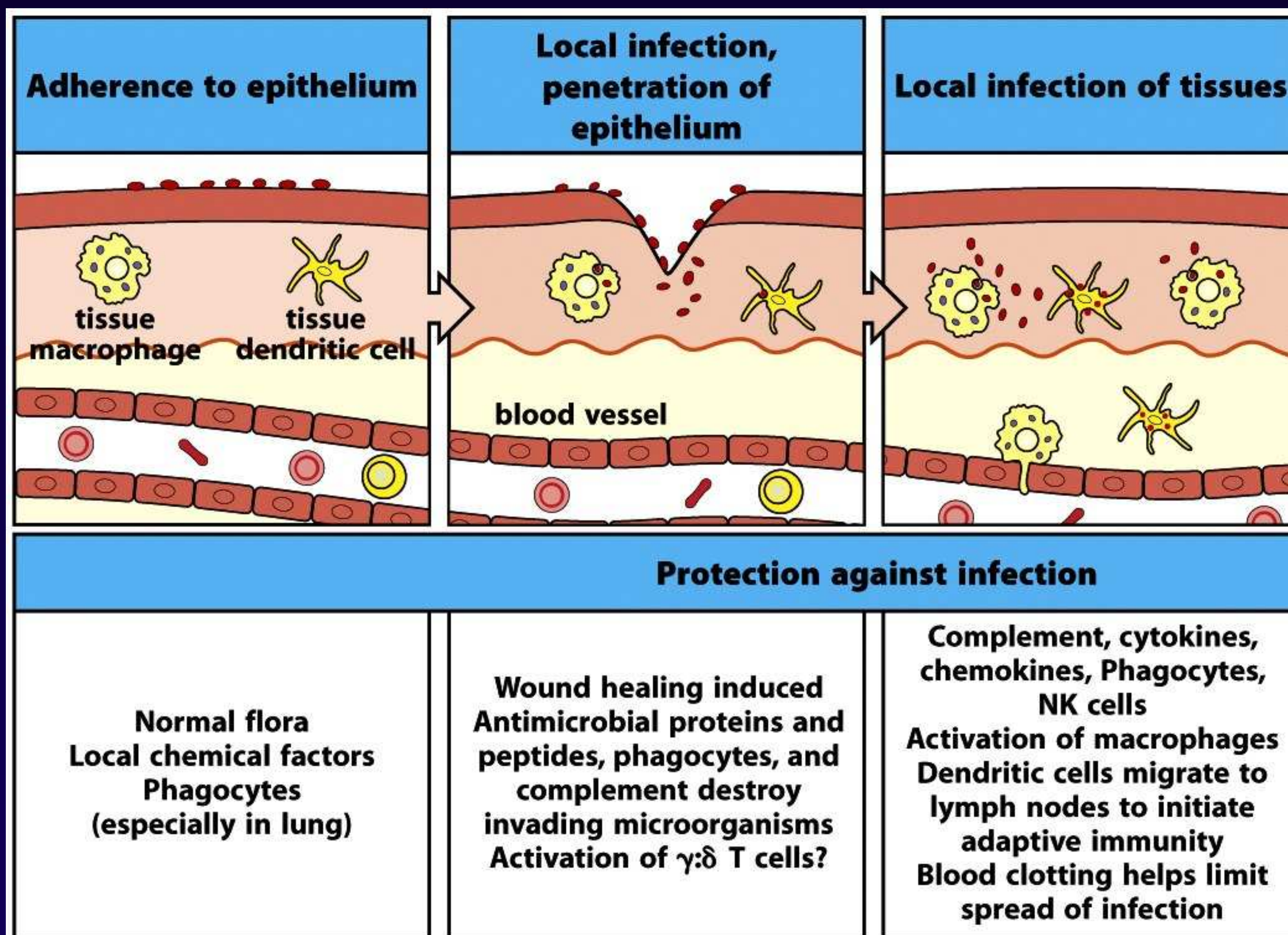

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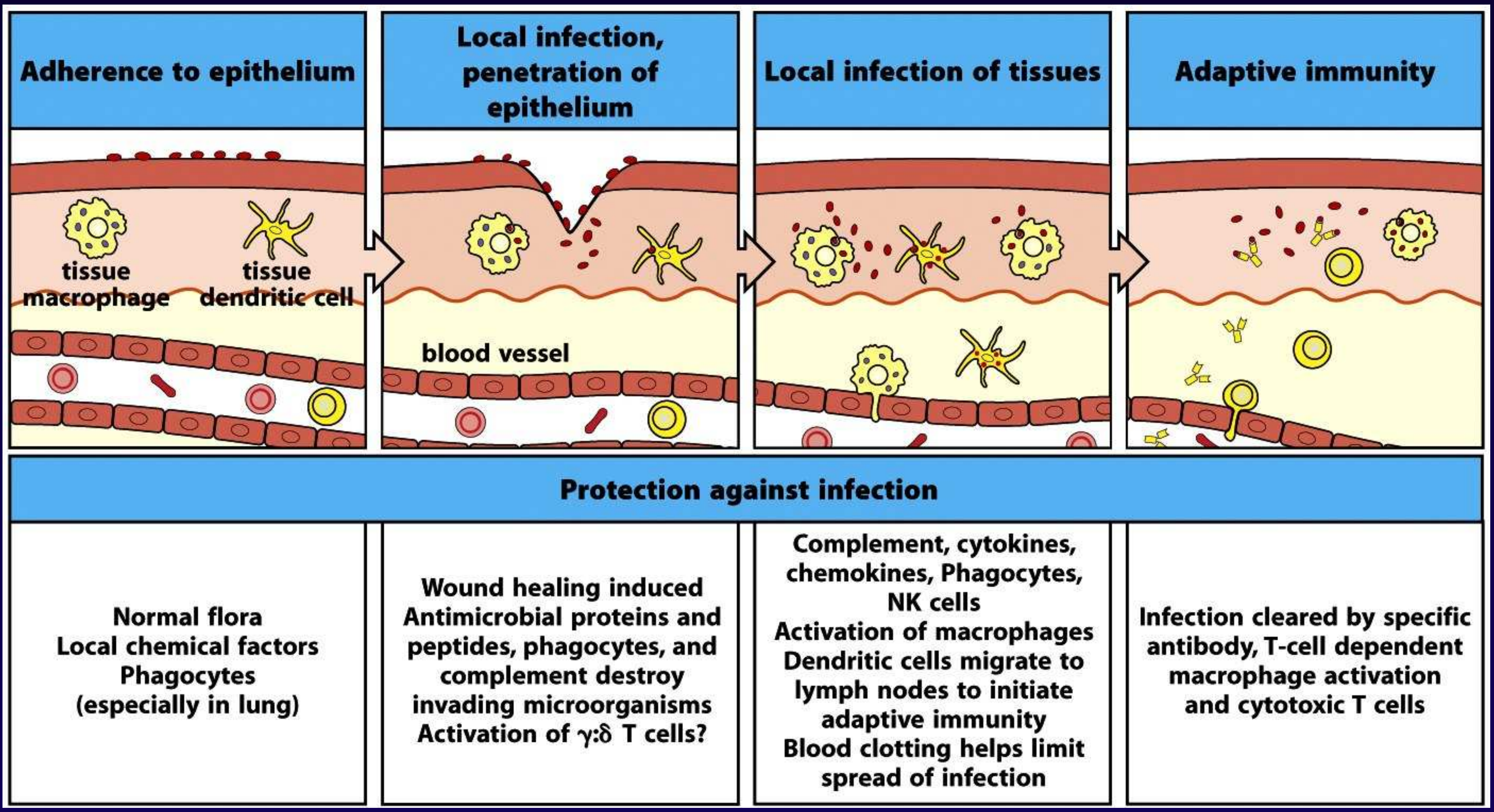

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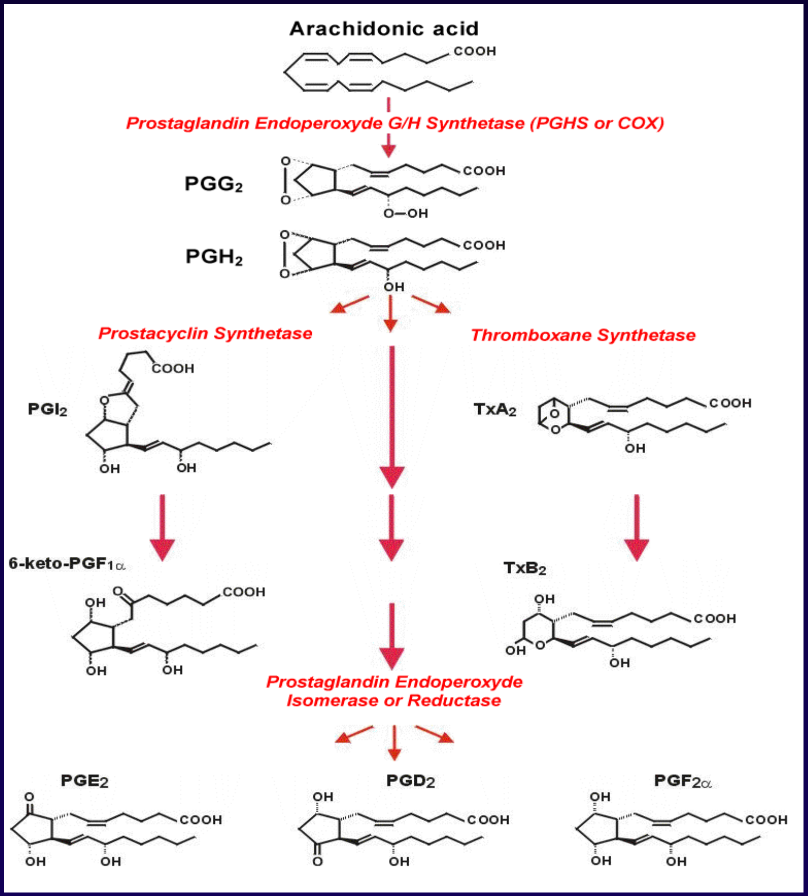
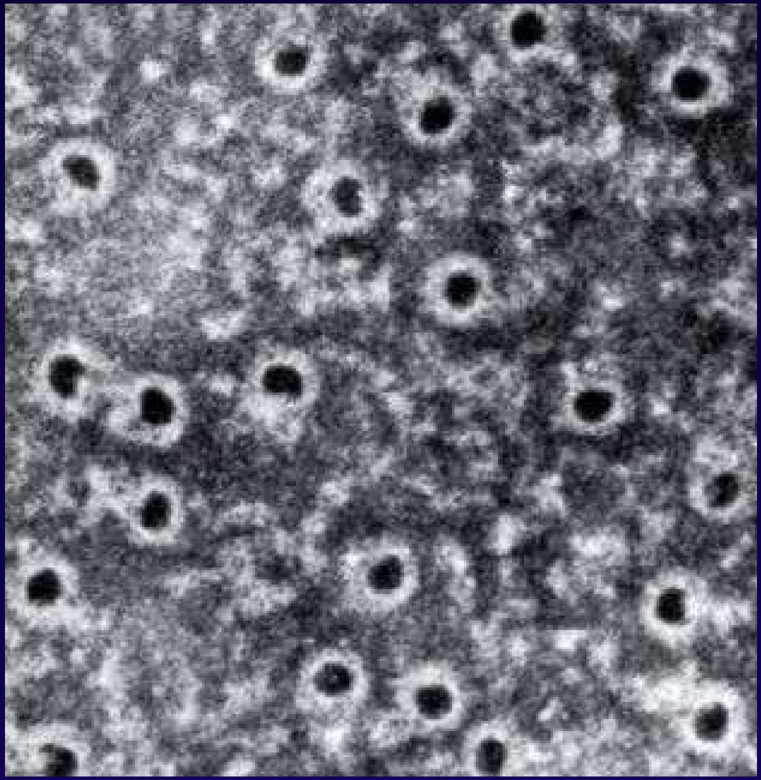
Innate Immune Molecules: Cyclooxygenase-2 (COX-2)



Recognize
- inflammation

Cause
- inflammation

Innate Immune Molecules: Complement System



Recognize
- pathogens
- antibodies
- lectins

Cause
- pathogen clearance
- chemotaxis
- inflammation

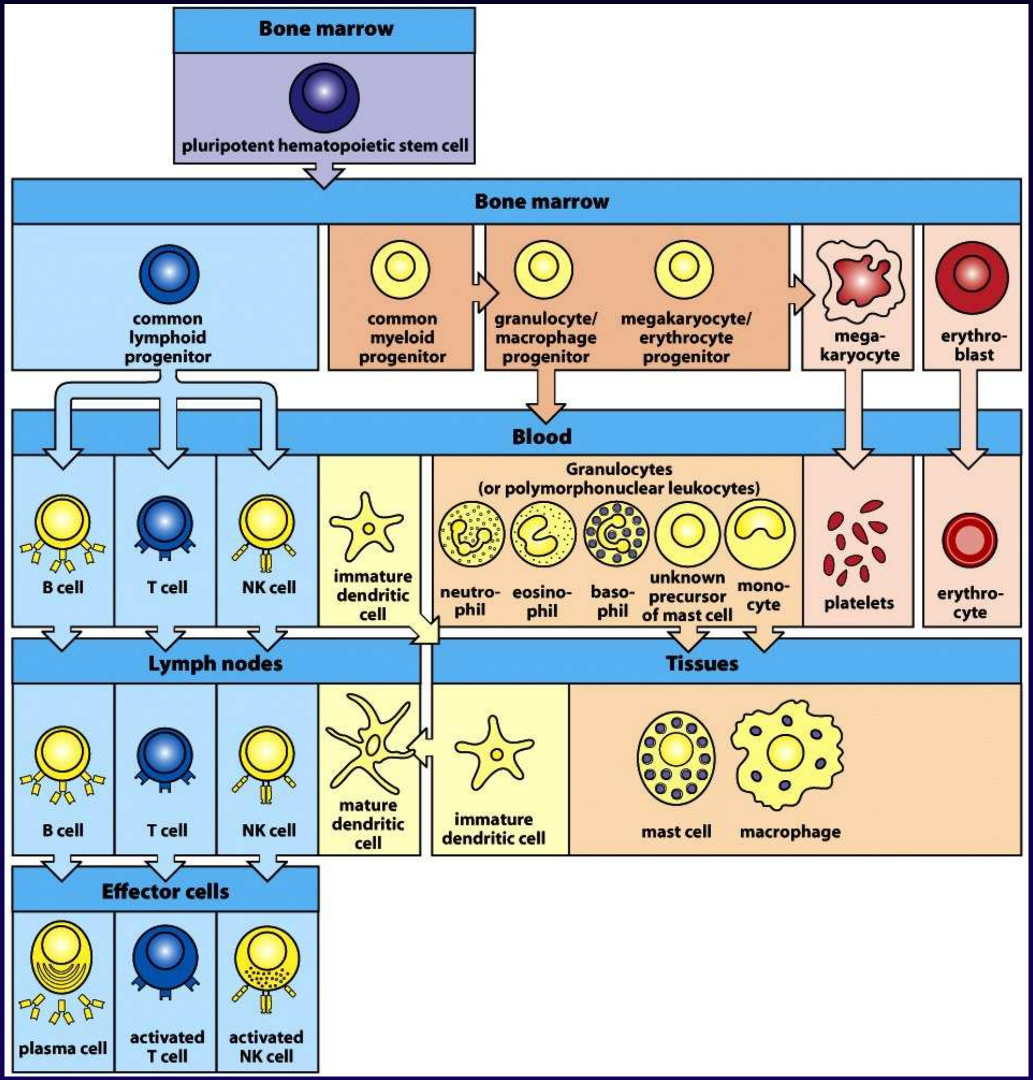
Janeway, *Immunobiology, 7th Ed.*

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

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

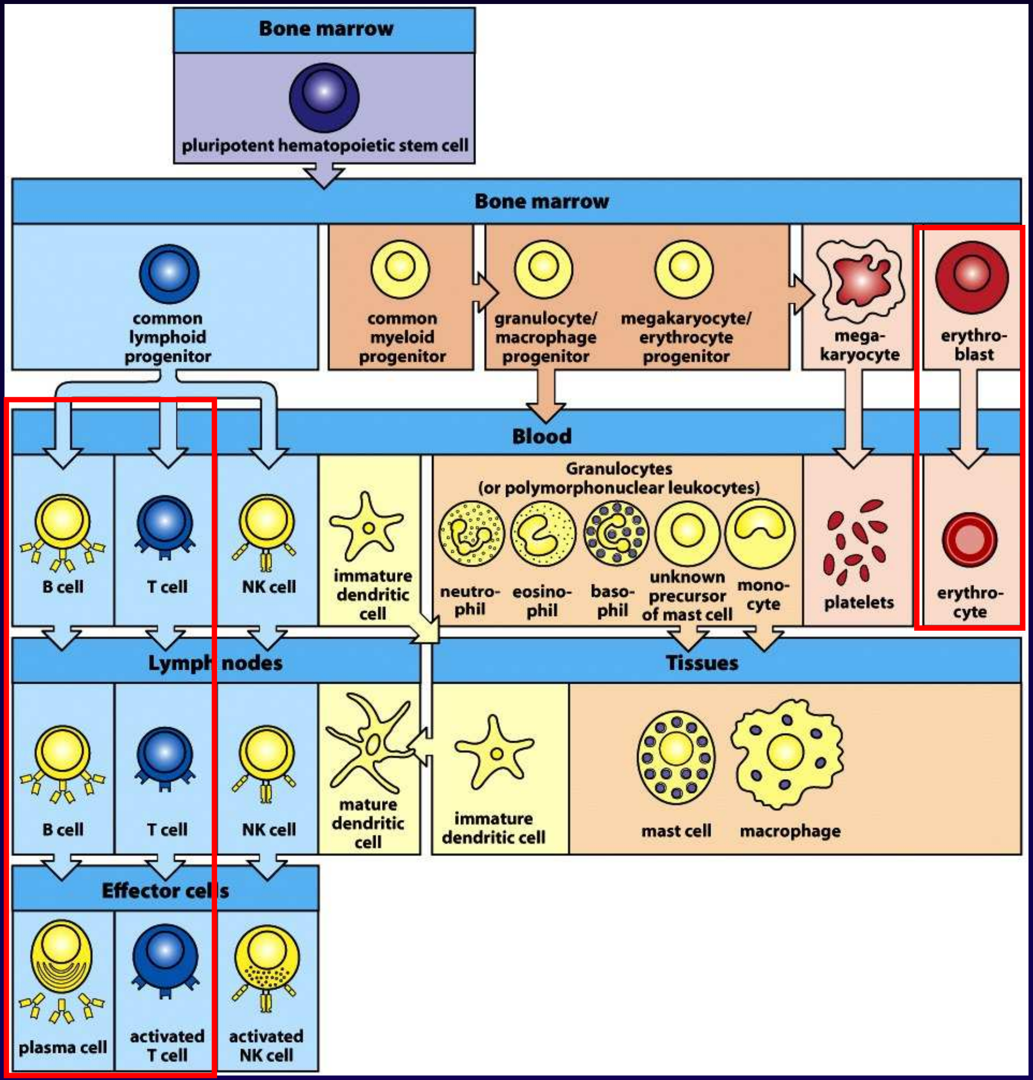
- Cause inflammation

Innate Immune Cells



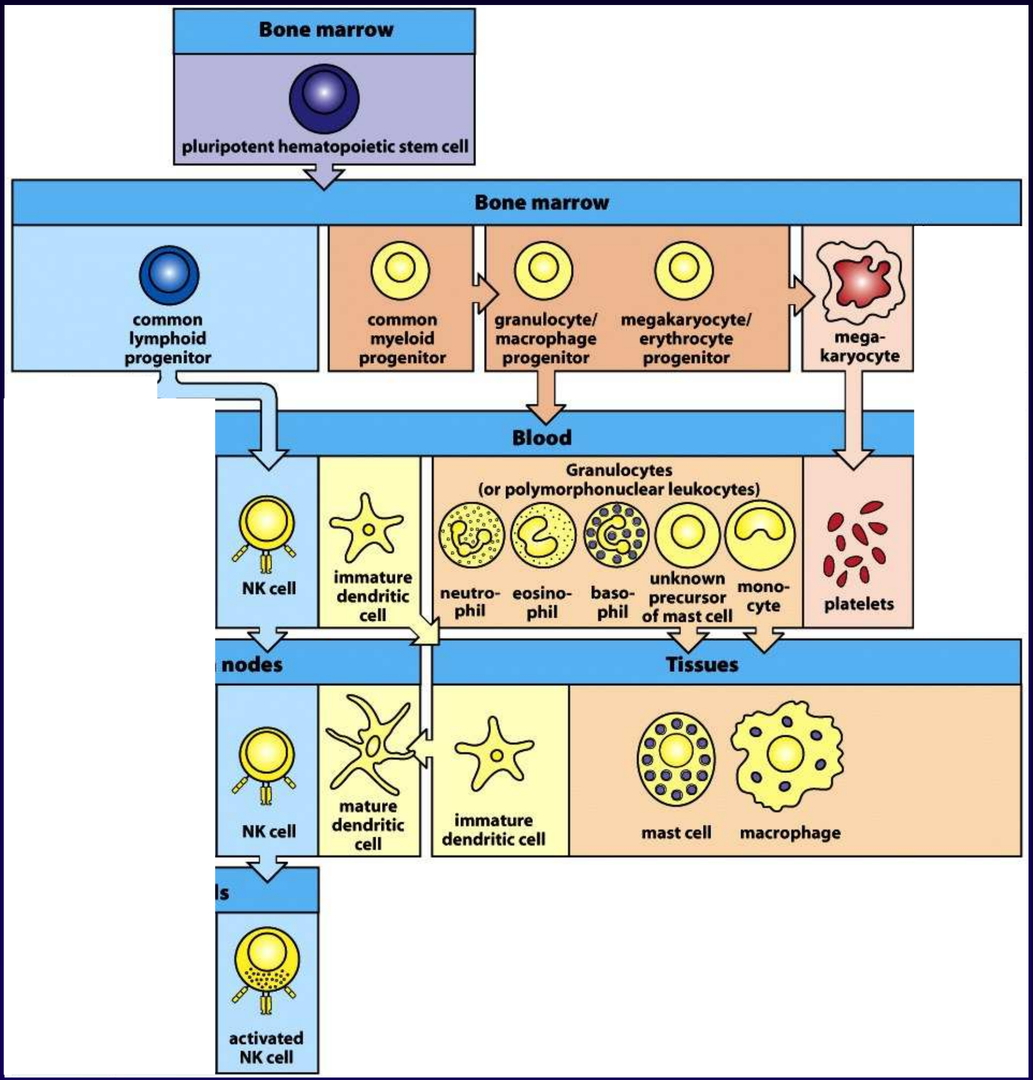
Janeway, *Immunobiology, 7th Ed.*

Innate Immune Cells



Janeway, *Immunobiology, 7th Ed.*

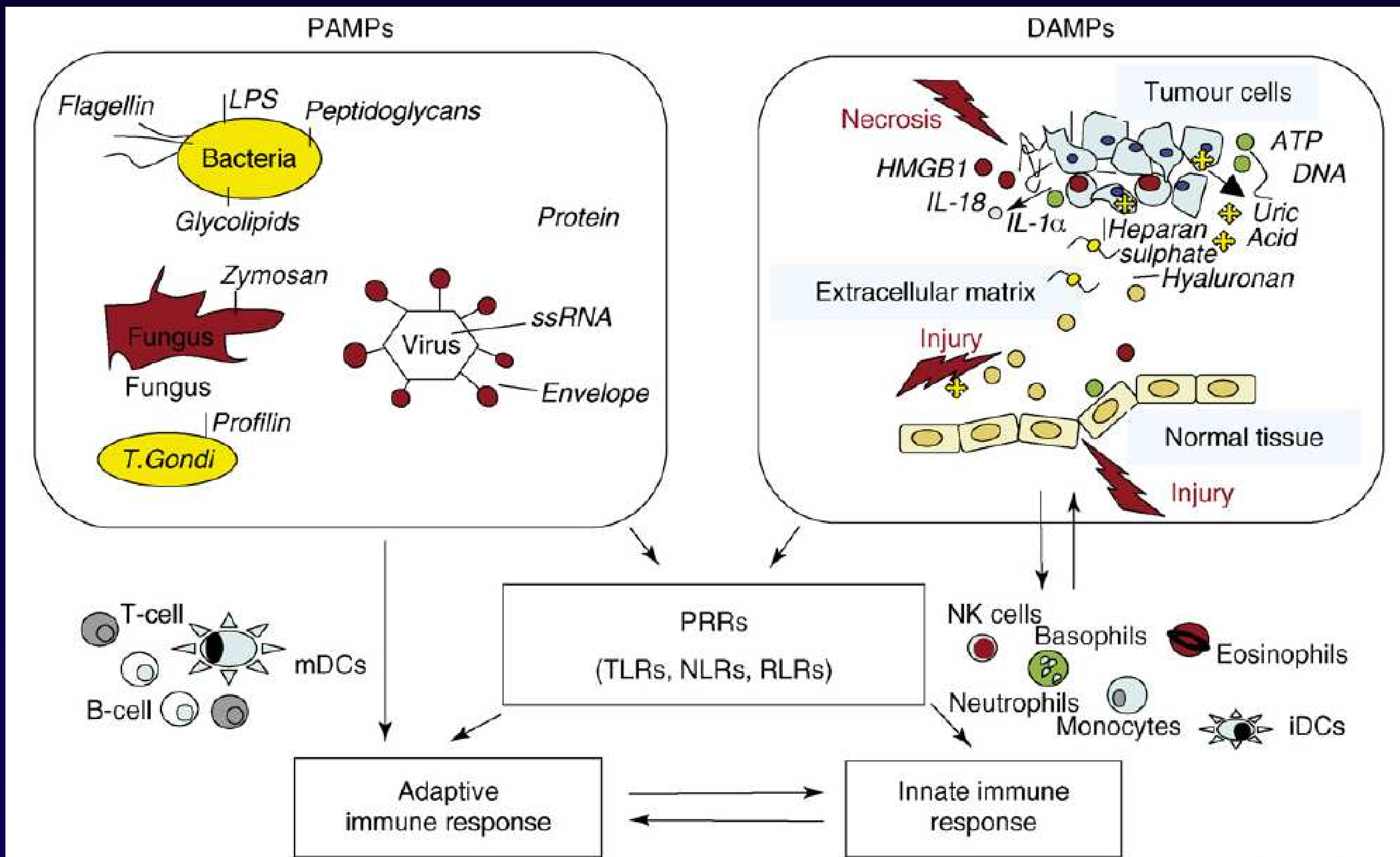
Innate Immune Cells



Janeway, *Immunobiology, 7th Ed.*

Danger signals start inflammation

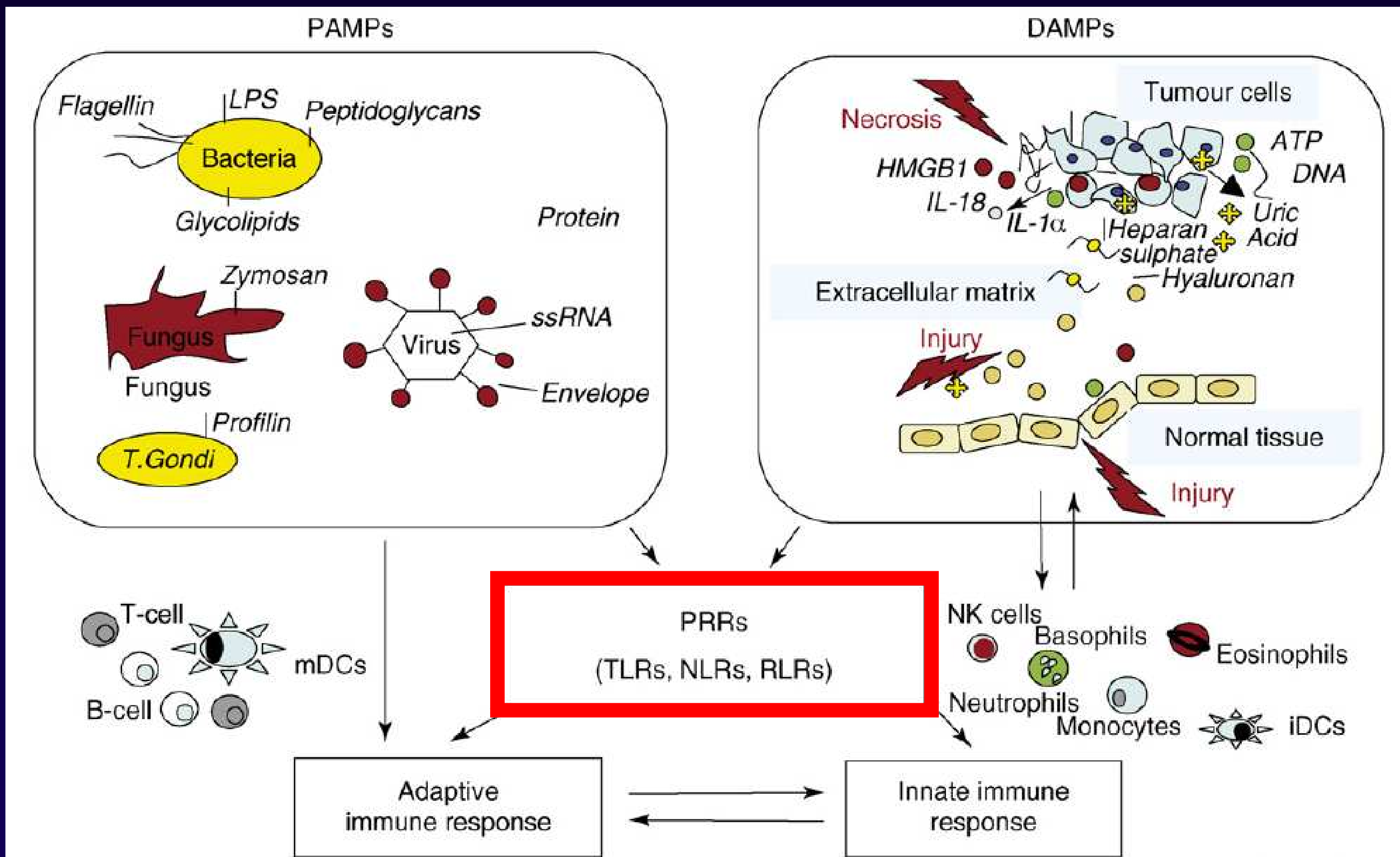
PATHOGENS — DAMAGE



Rubartelli & Lotze, *Trends in Immunology 2007*

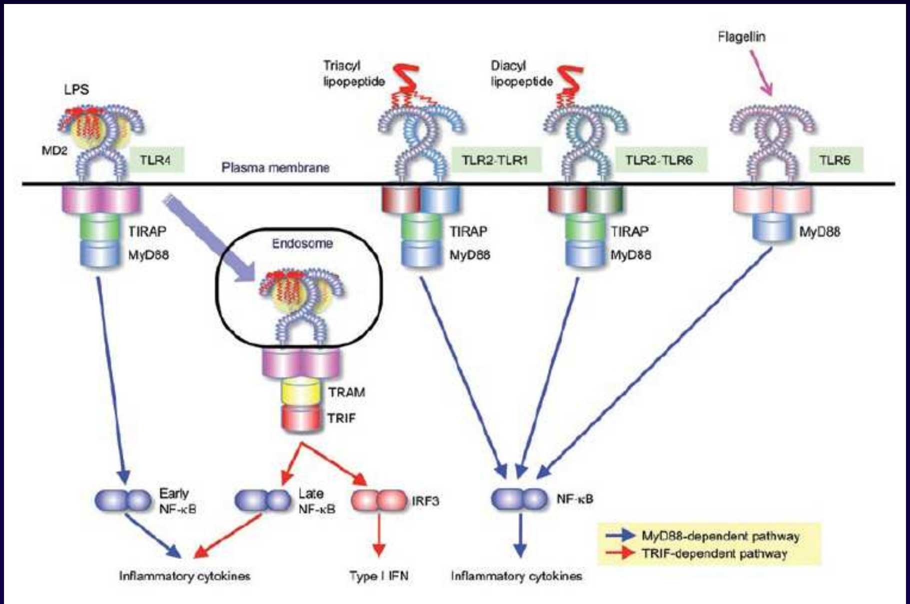
Danger signals start inflammation

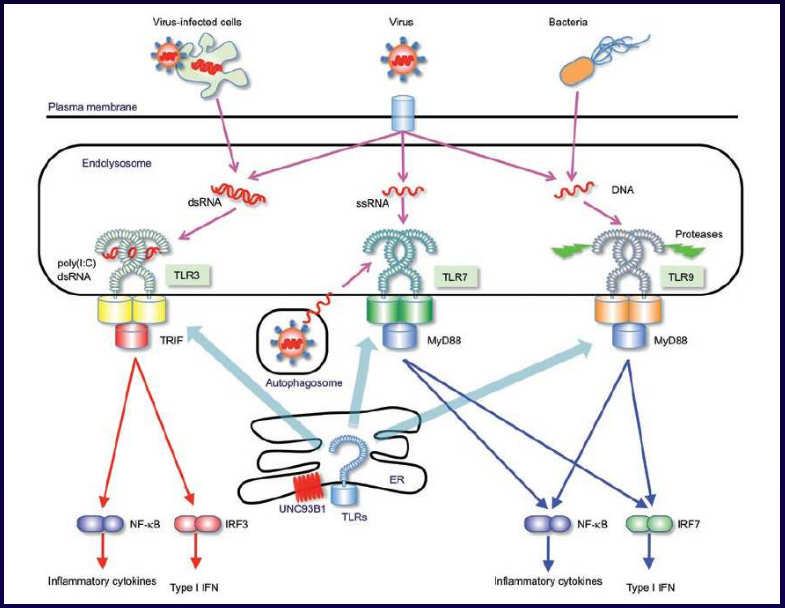
PATHOGENS   DAMAGE



Rubartelli & Lotze, *Trends in Immunology 2007*

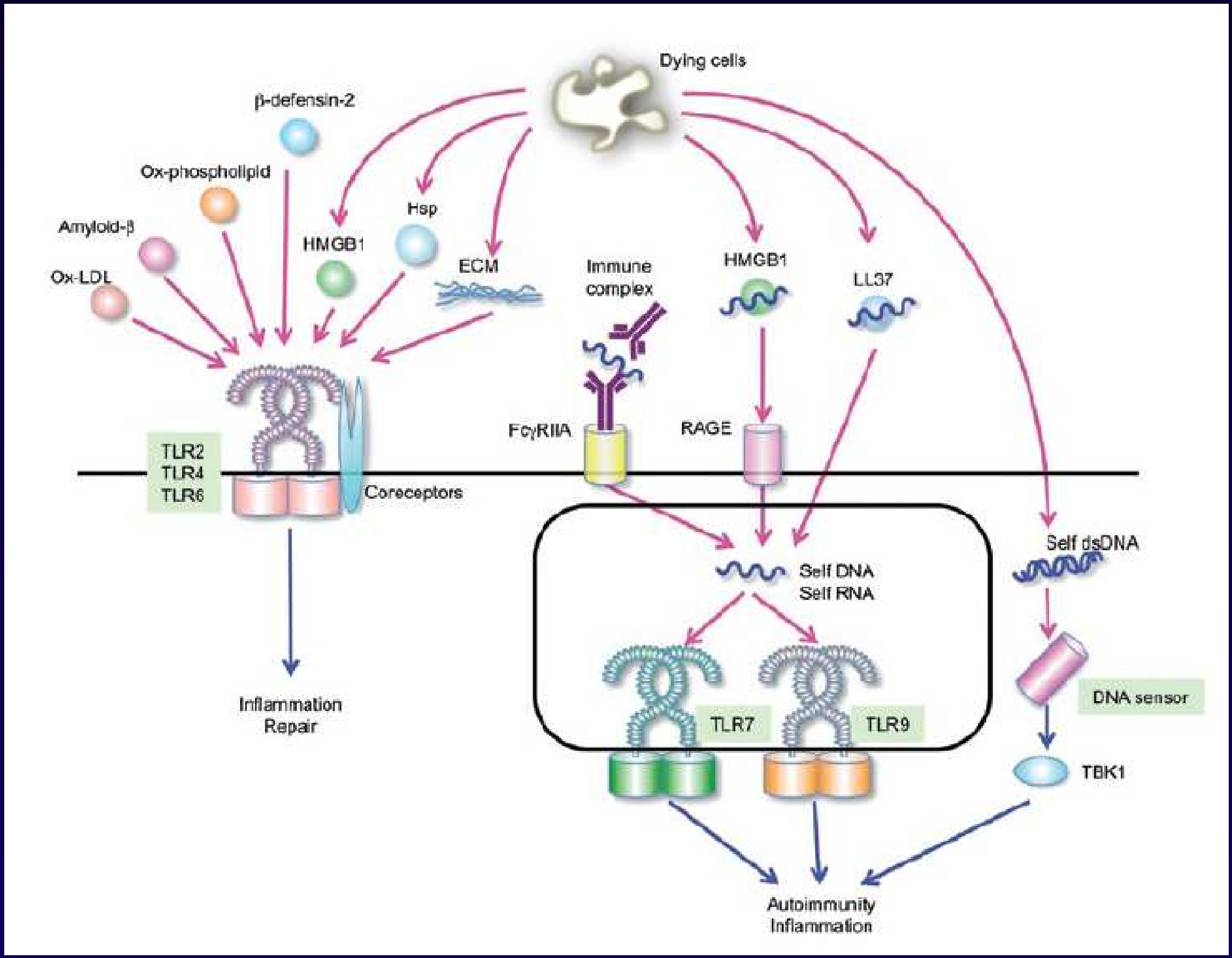
Receptors sense Danger: Pathogens





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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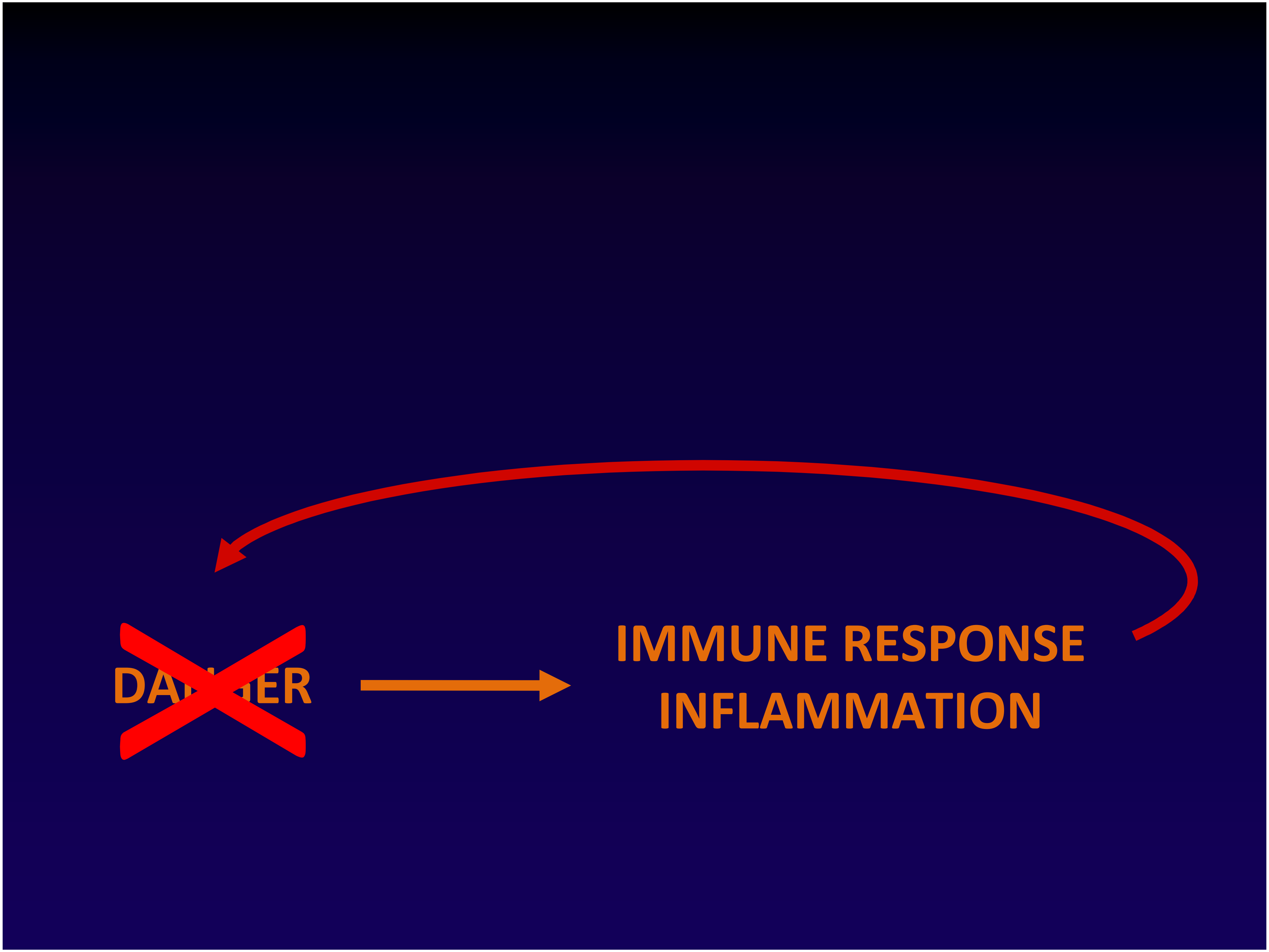
Bad Inflammation Causes Cancer

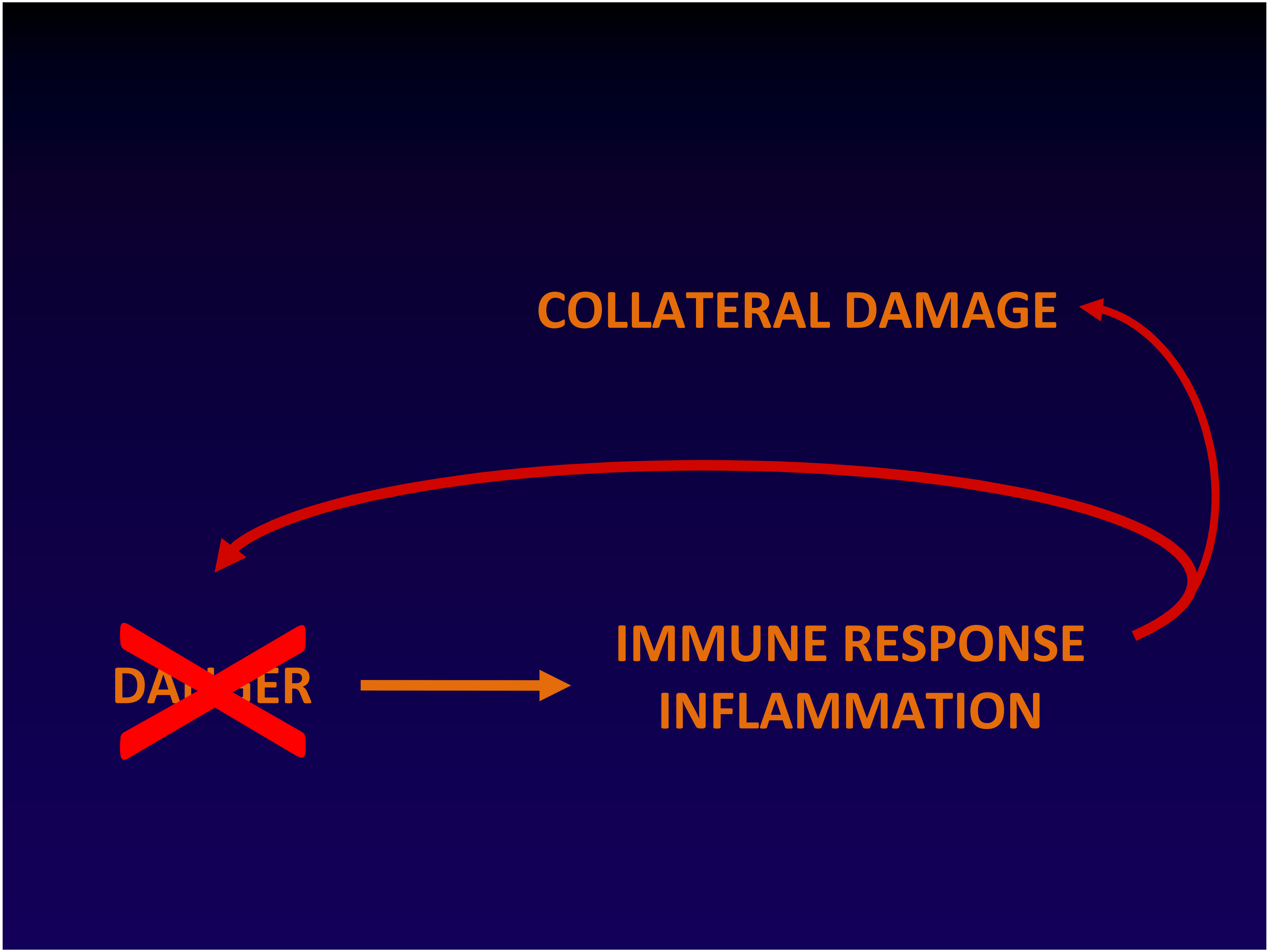
DANGER

cellular damage caused by

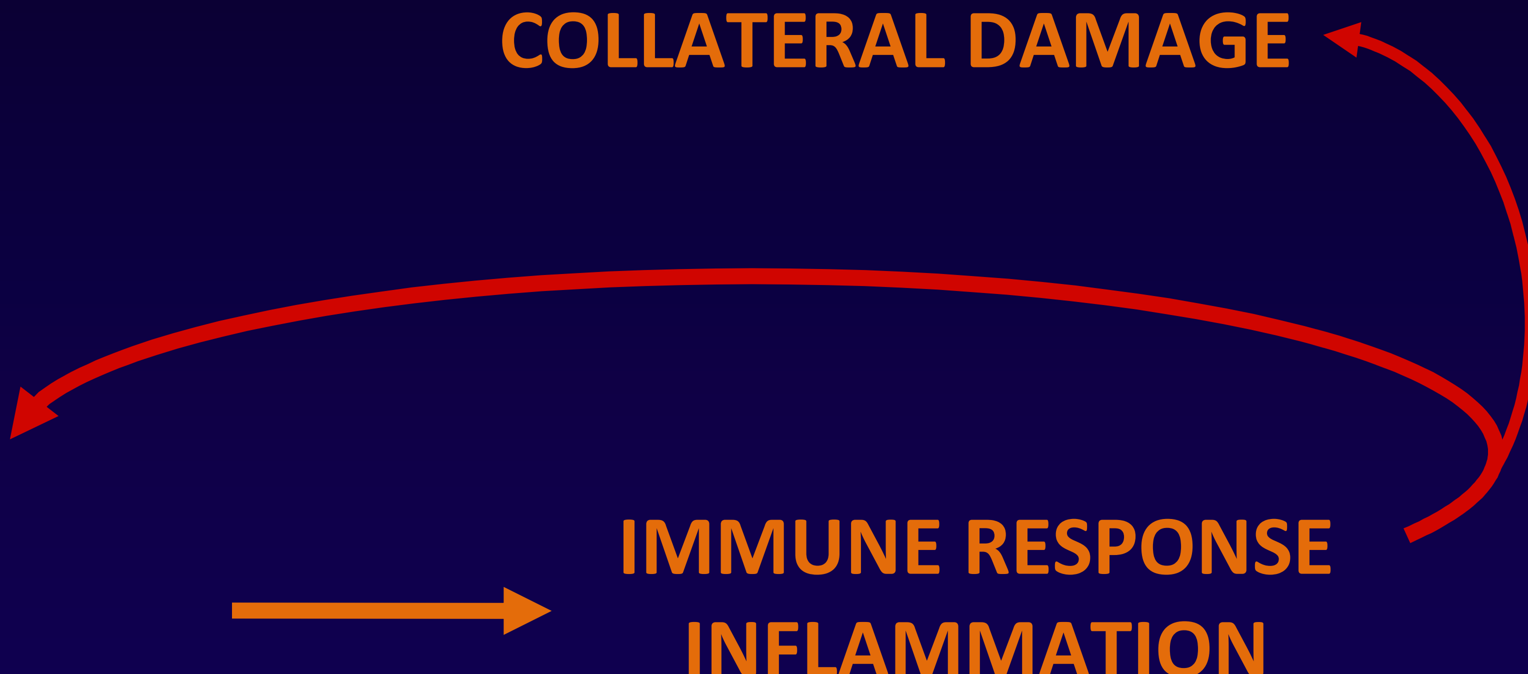
- **pathogens**
- **physical damage**
- **chemicals**
- **UV**
- **etc**

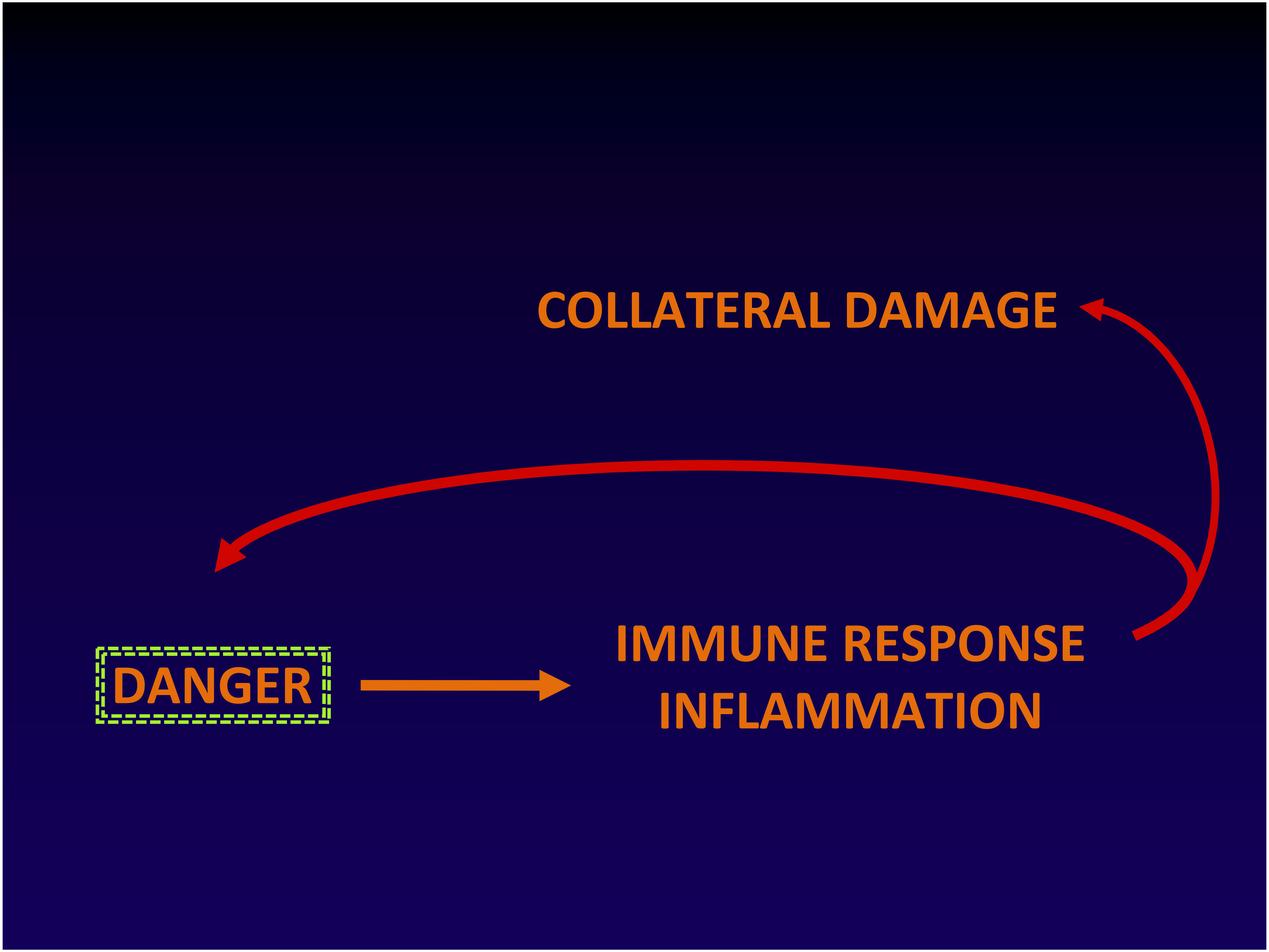
DANGER → IMMUNE RESPONSE
INFLAMMATION

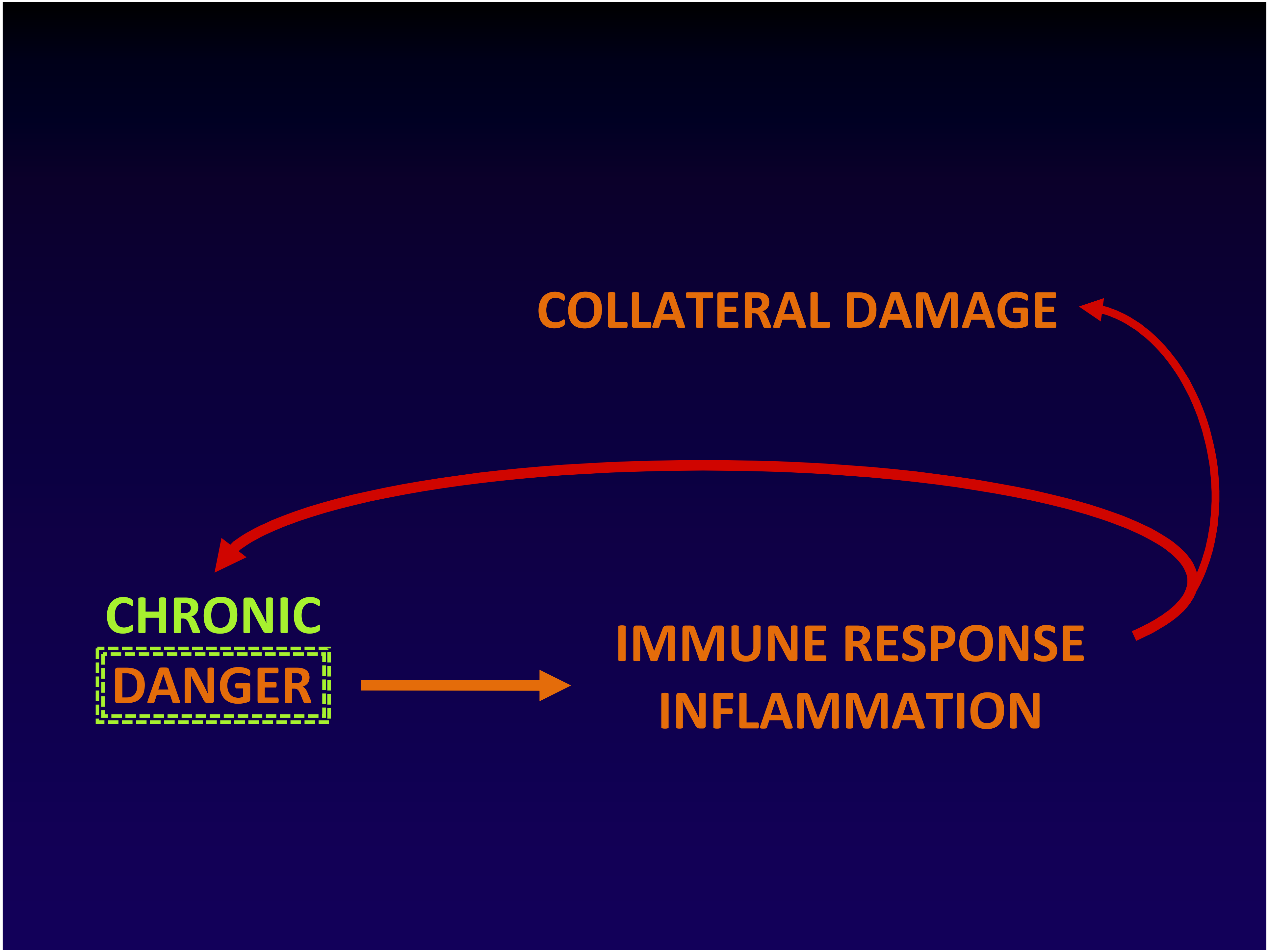

DANGER
IMMUNE RESPONSE
INFLAMMATION

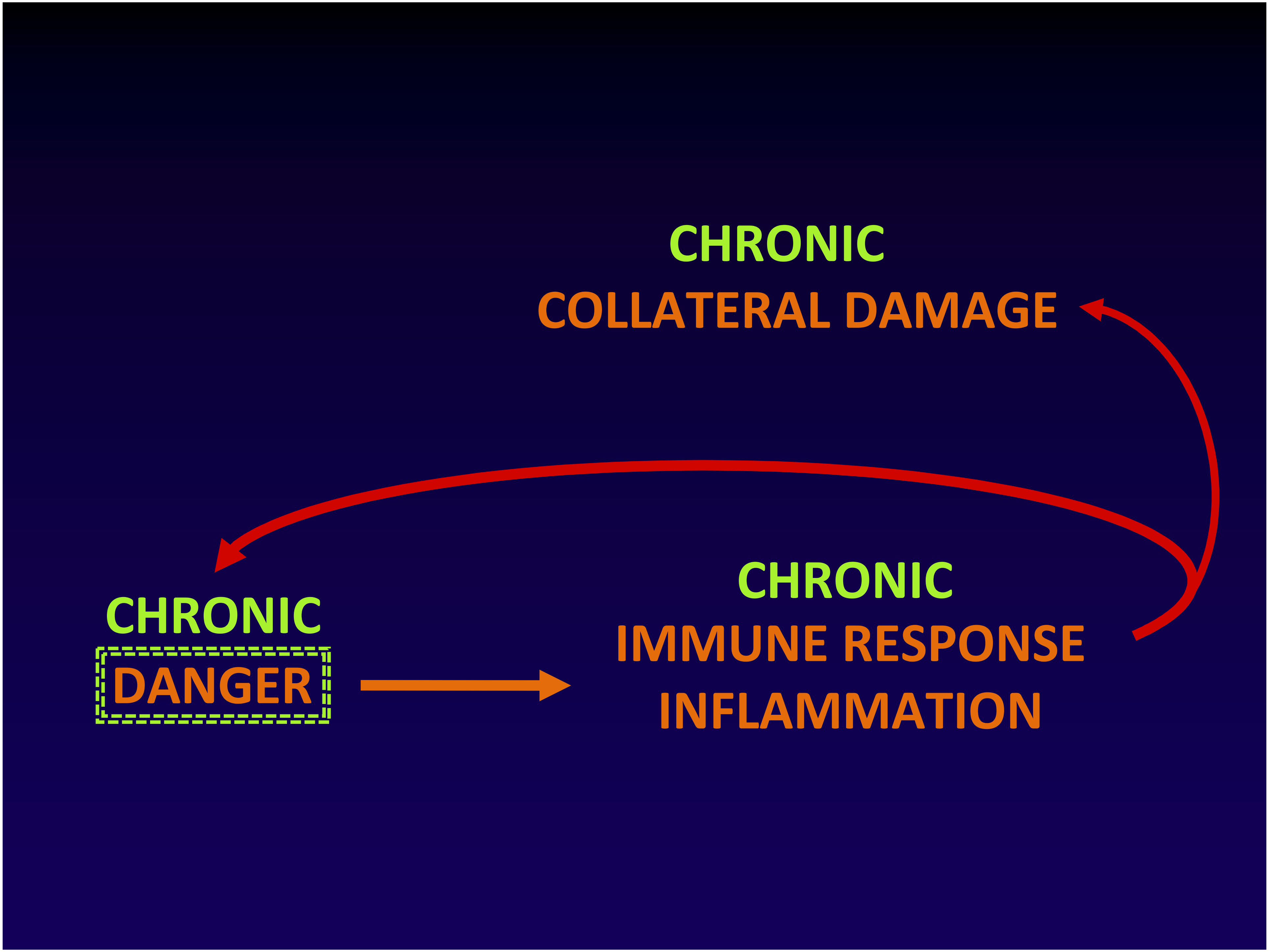


COLLATERAL DAMAGE
~~DANGER~~
IMMUNE RESPONSE
INFLAMMATION


COLLATERAL DAMAGE
IMMUNE RESPONSE
INFLAMMATION


COLLATERAL DAMAGE
DANGER
IMMUNE RESPONSE
INFLAMMATION


COLLATERAL DAMAGE
CHRONIC
DANGER
IMMUNE RESPONSE
INFLAMMATION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COLLATERAL DAMAGE
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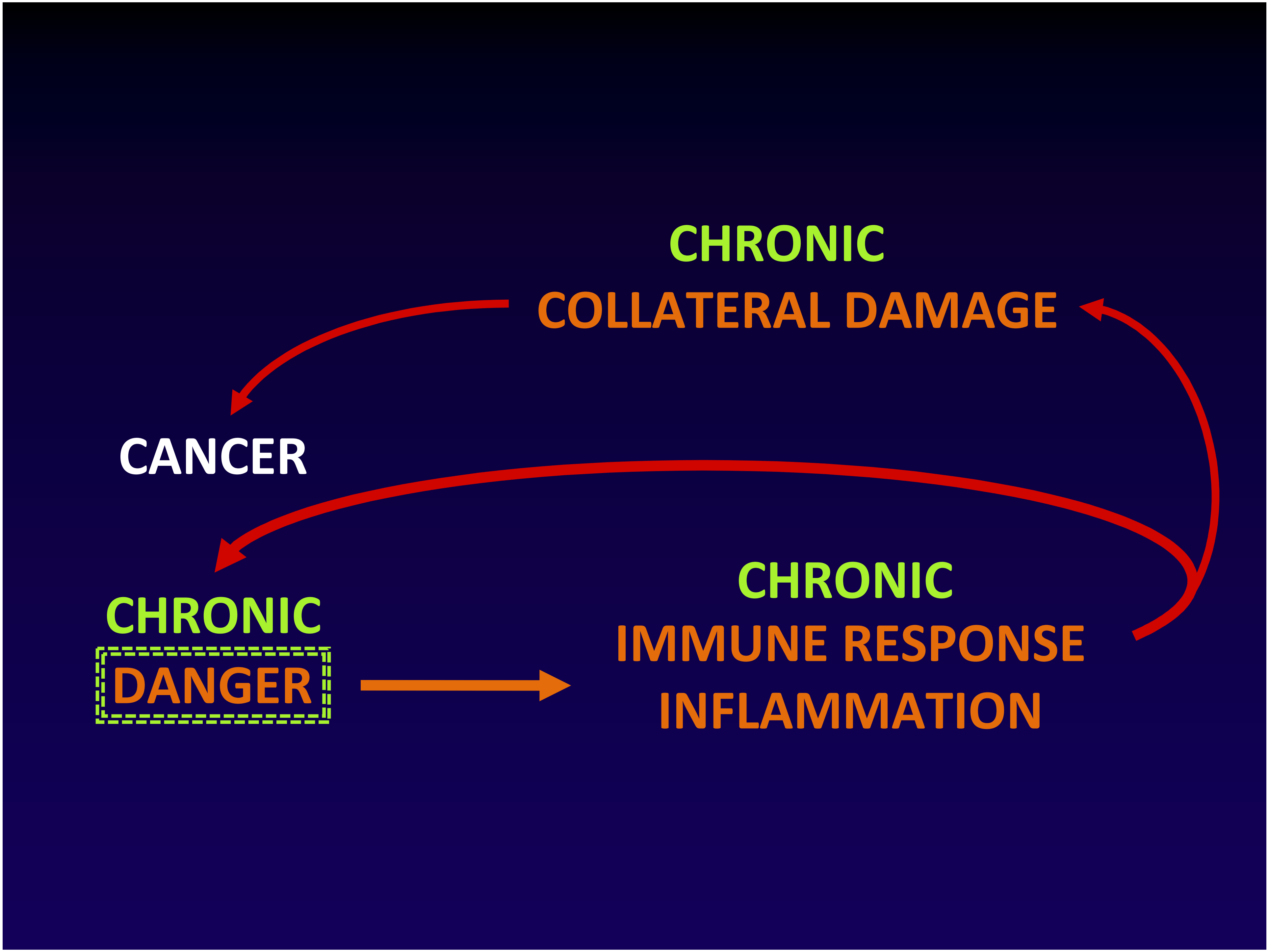
CHRONIC
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CANCER
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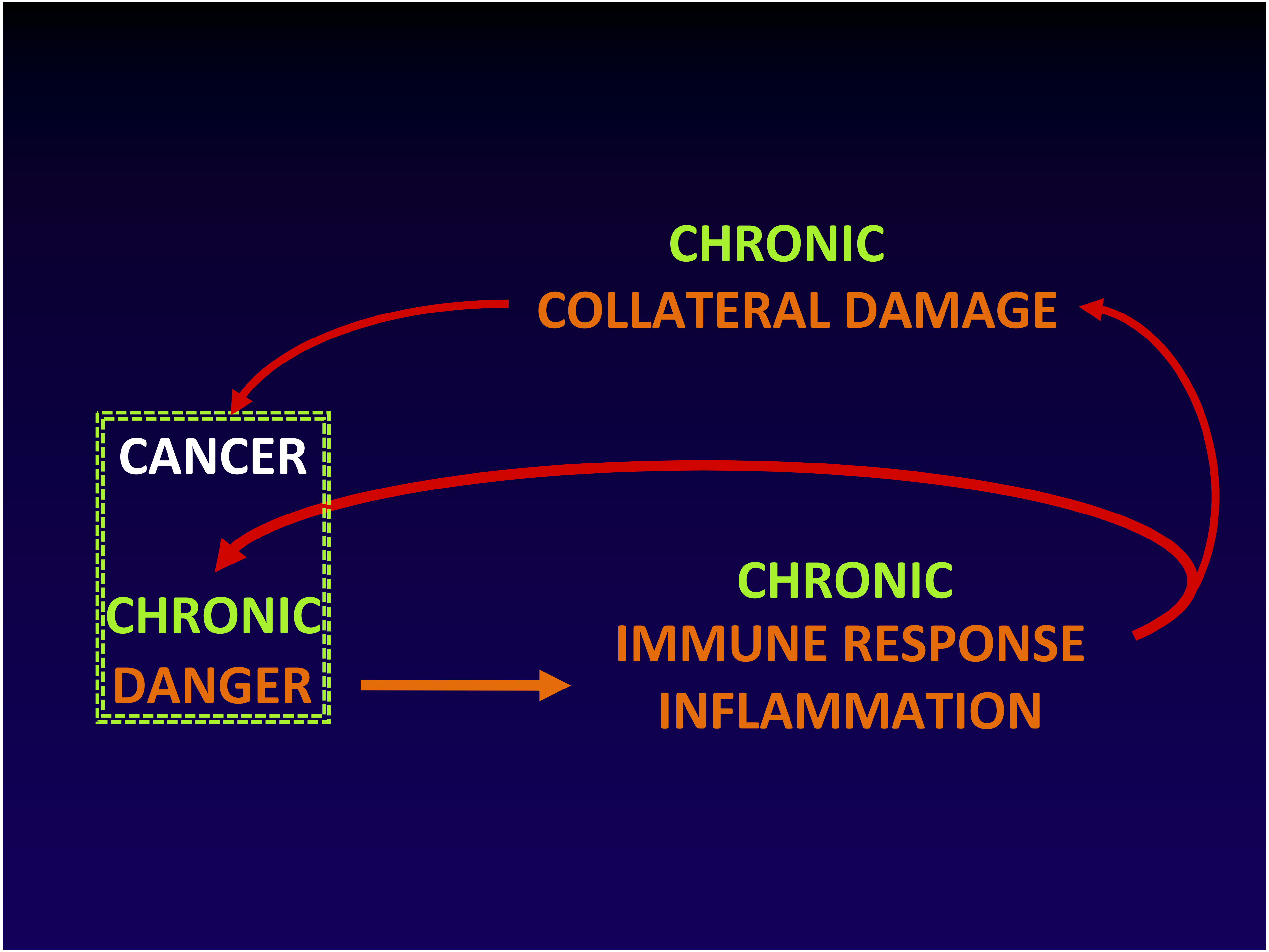
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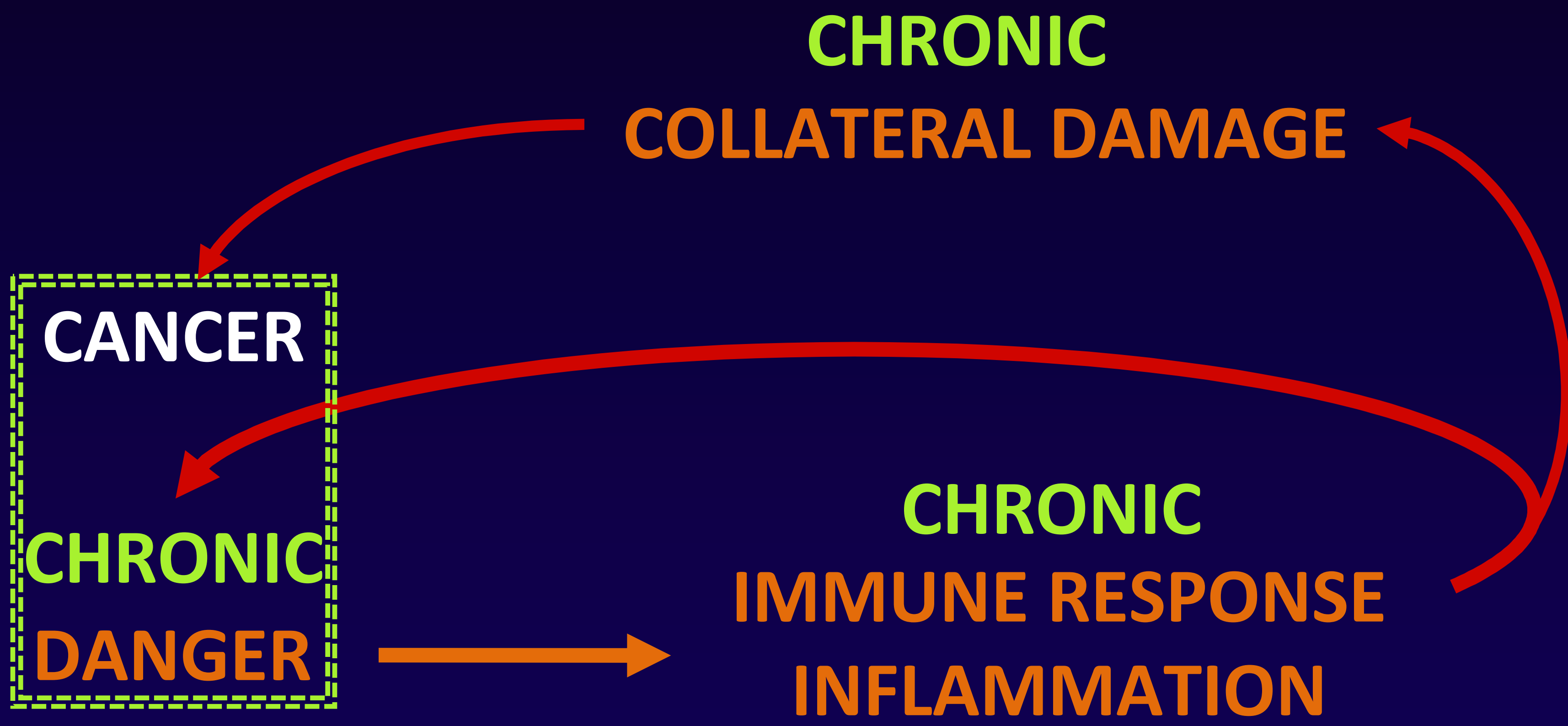


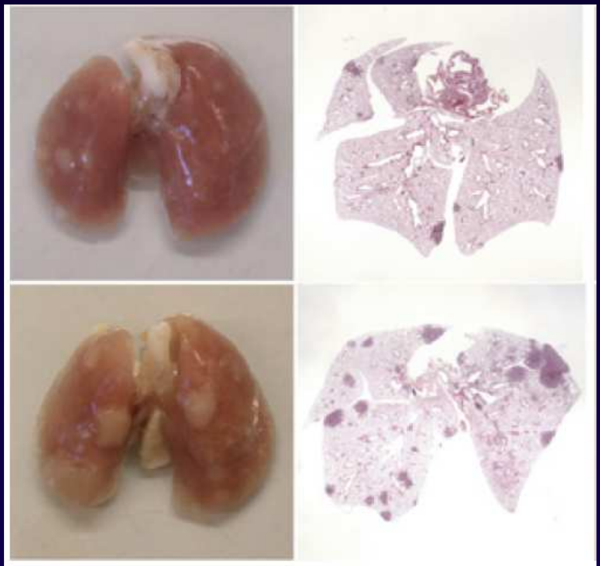
cancer: a “never-healing wound”

Dvorak , *NEJM* 1986

Inflammation can Promote Cancer: collaboration with K-ras mutation

no smoking

4 cigarettes per day



K-ras mutation
&
normal myeloid cells

Takahashi et al. , *Cancer Cell* 2010

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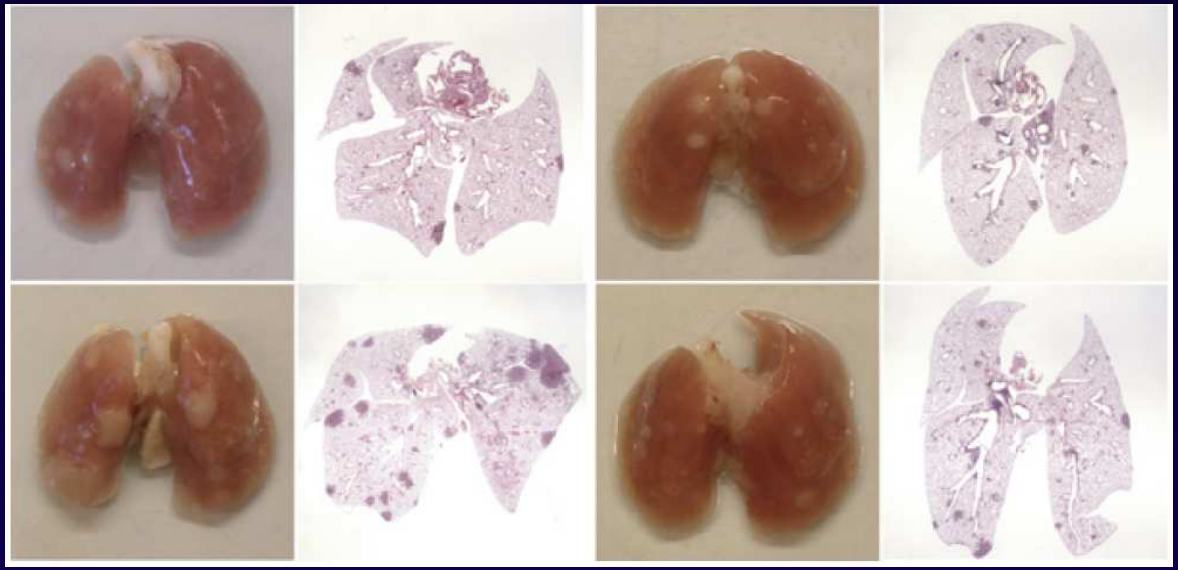

K-ras mutation & normal myeloid cells

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

Takahashi et al. , *Cancer Cell* 2010

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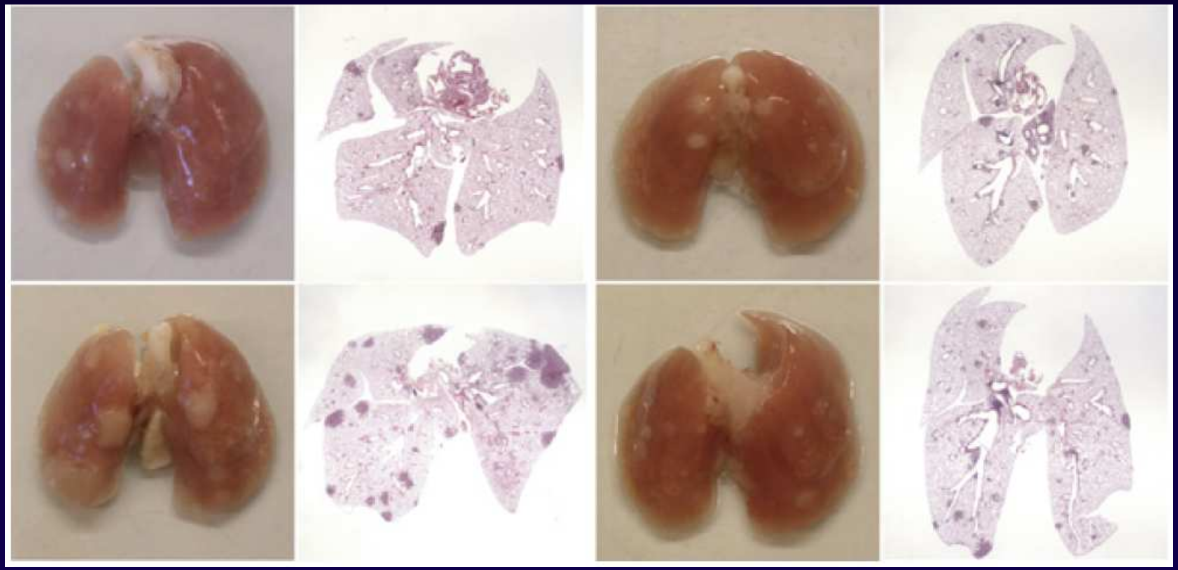


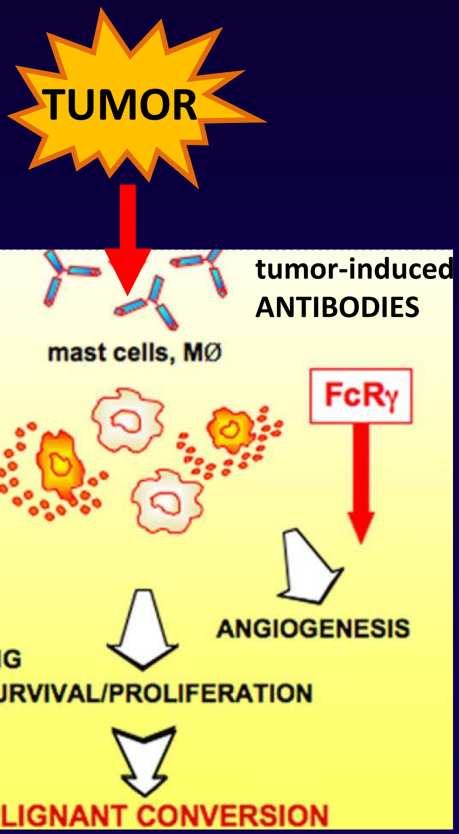
K-ras mutation & normal myeloid cells

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

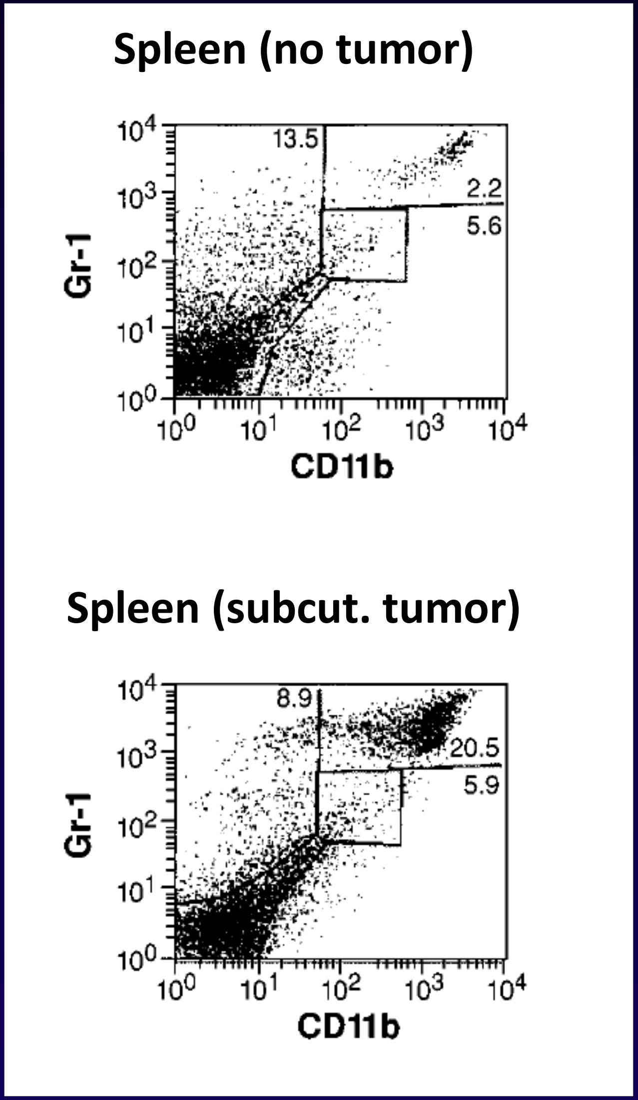
Tumors can induce bad inflammation

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]*

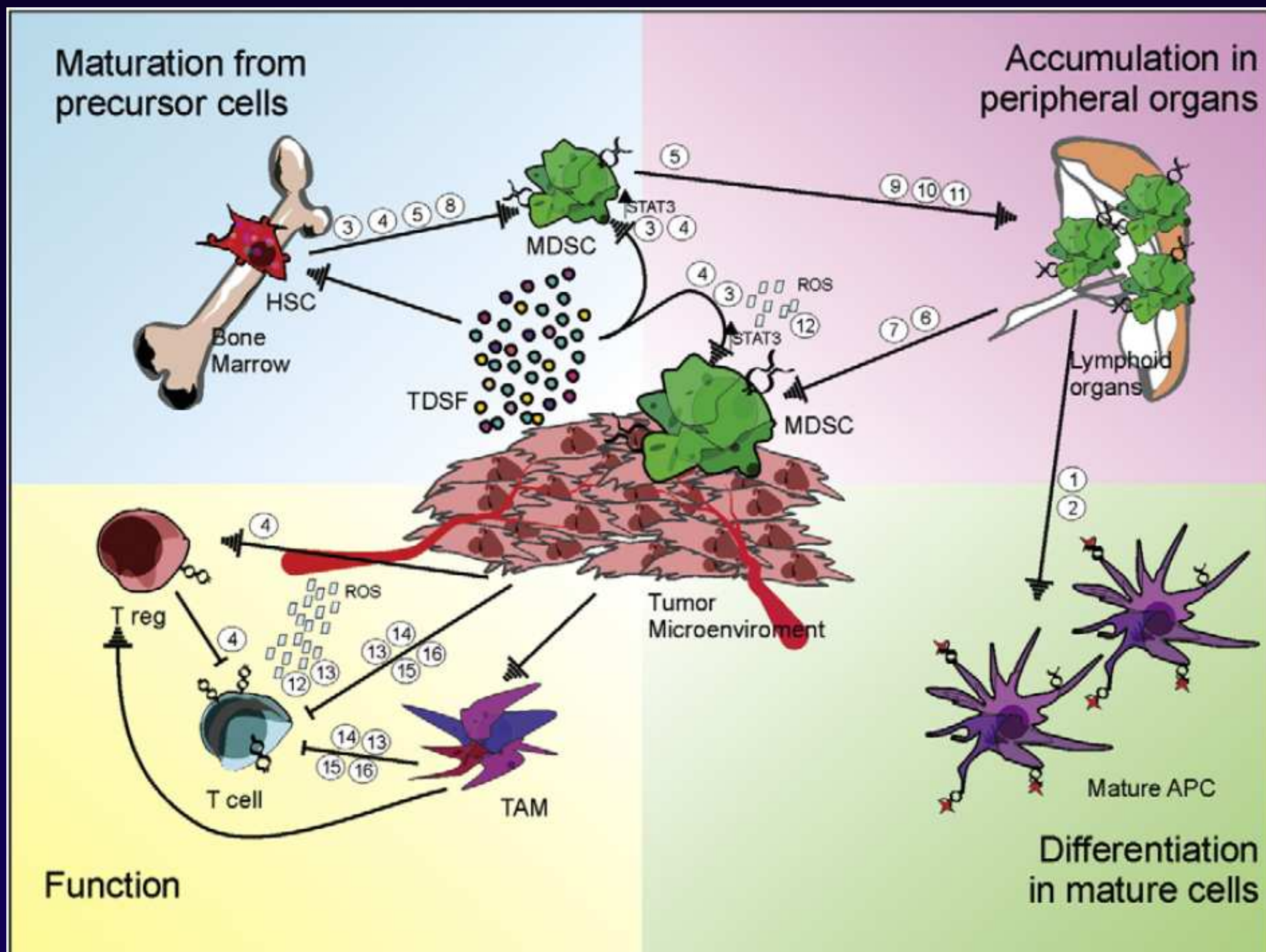
The Journal of Immunology, 1998, 161: 5313–5320.

Tumors can induce bad inflammation



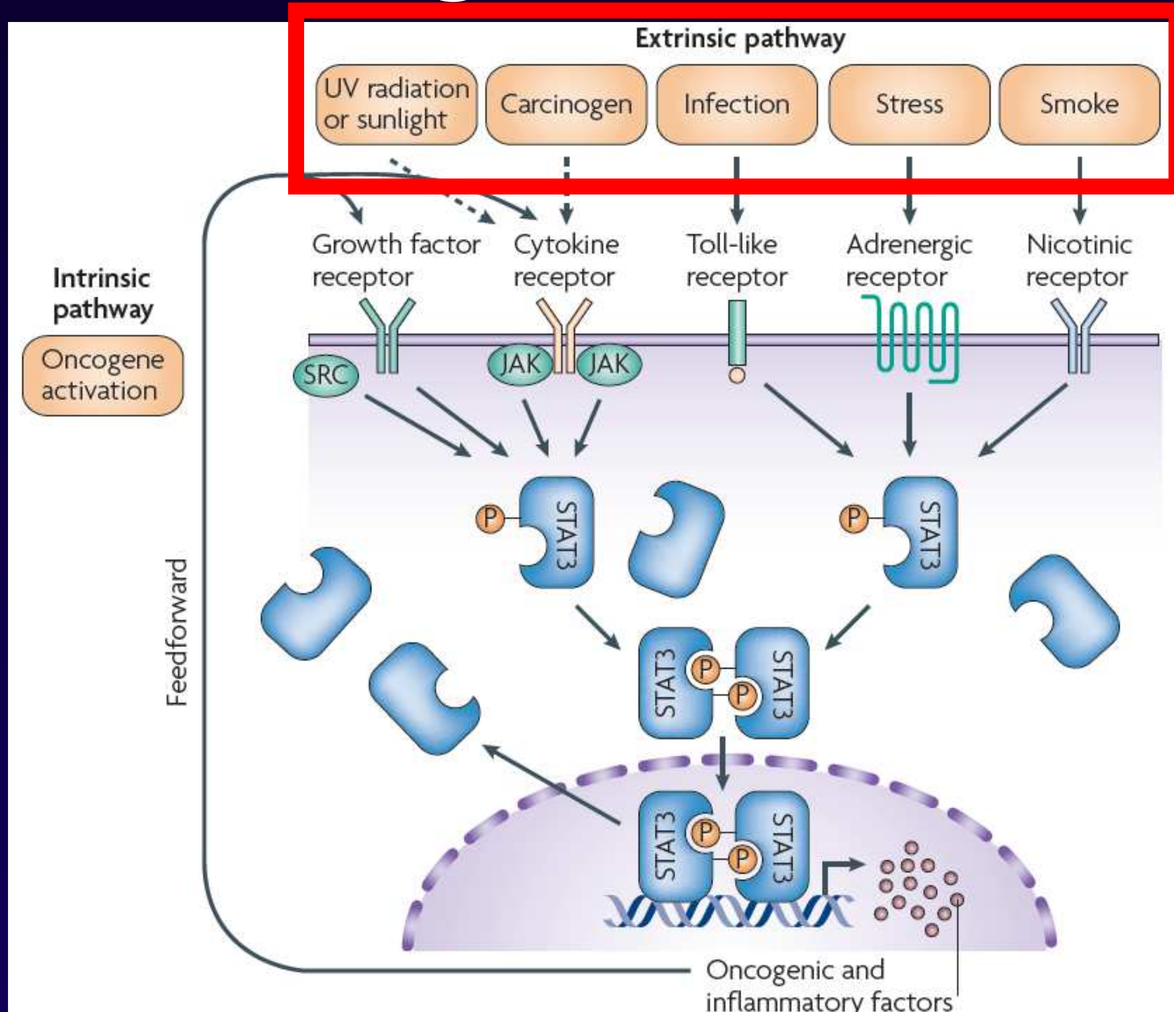
Bronte et al., *J. Immunol.* 1999

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

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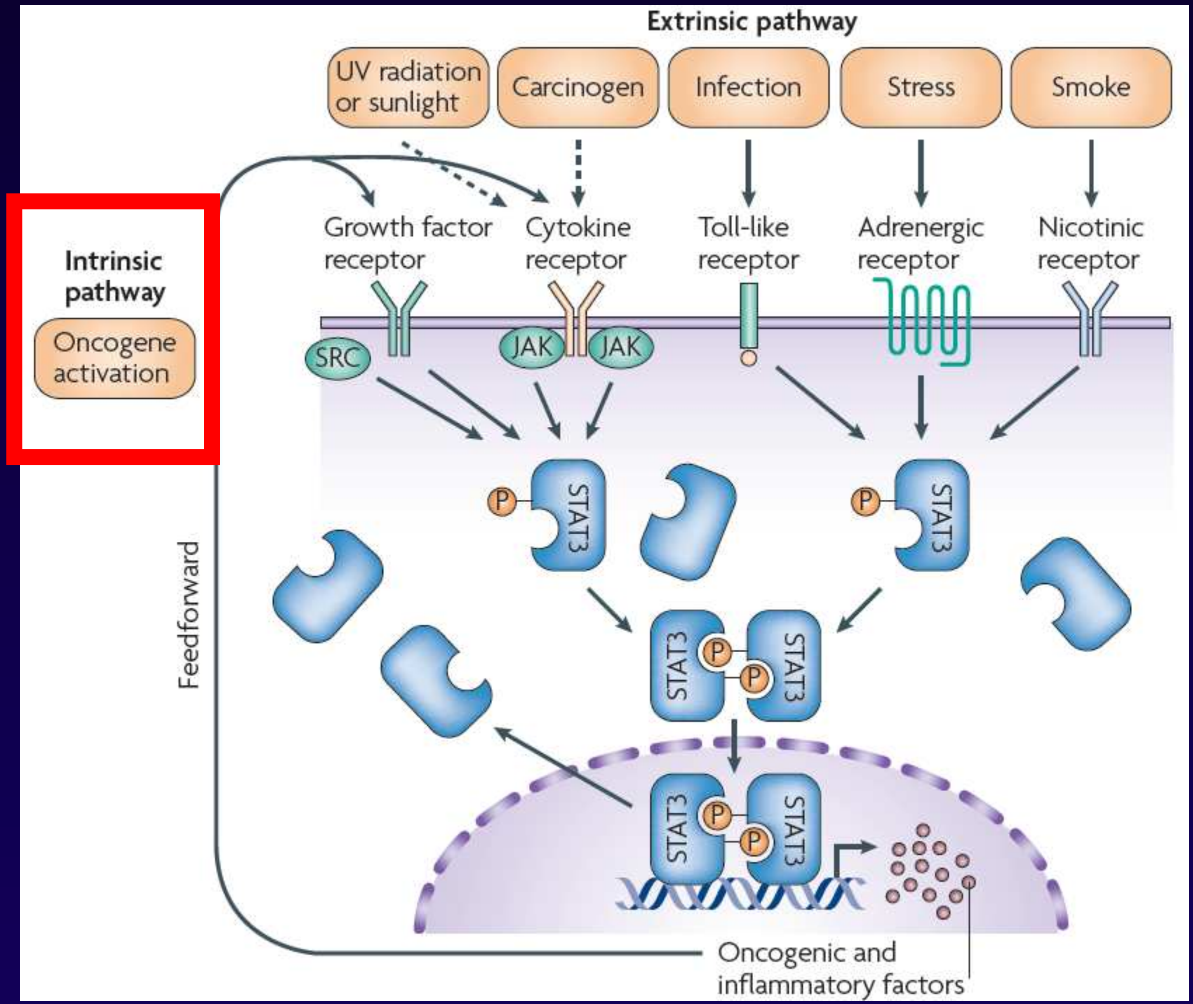
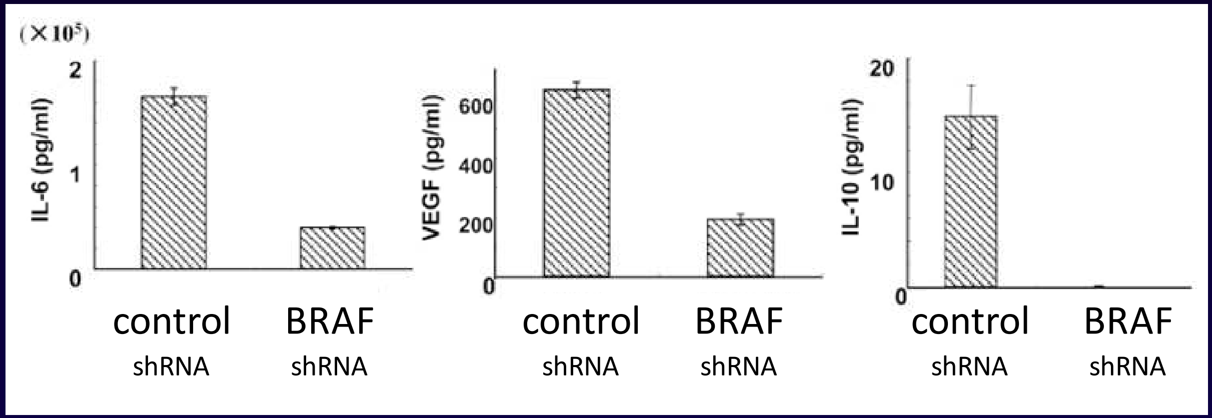


Yu et al., *Nat. Rev. Cancer* 2009

Mutations can Drive Bad Inflammation

Mutated BRAF → tumor cells produce bad, imunosuppressive cytokines



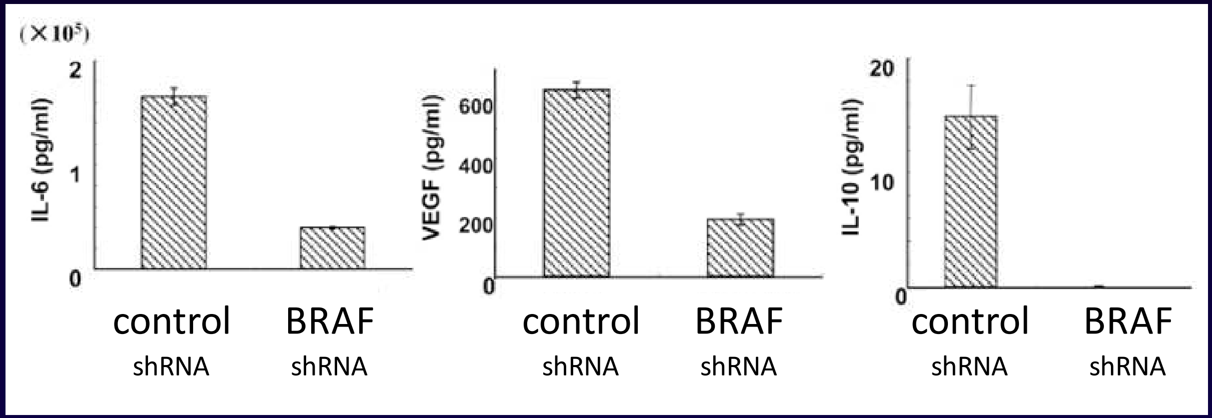
Sumimoto et al., *J. Exp. Med.* 2006

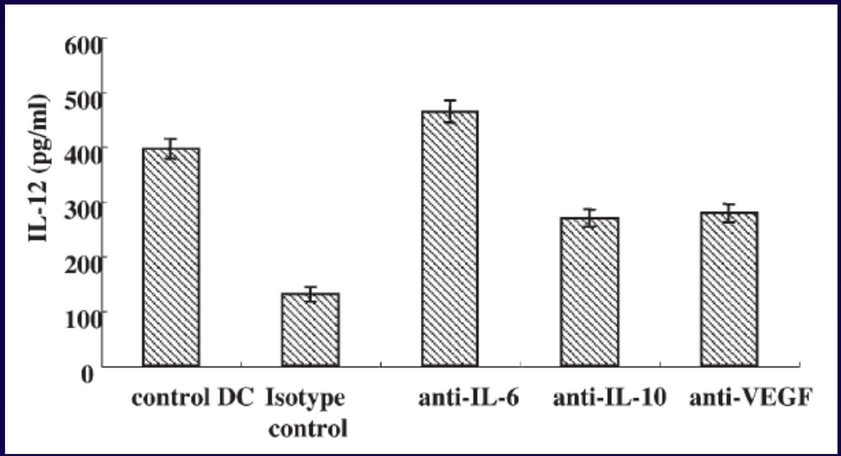
Mutations can Drive Bad Inflammation

Mutated BRAF → tumor cells produce <u>bad, imunosuppressive cytokines</u>

↓

block production of good cytokines in DCs





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

Mutations can Drive Bad Inflammation

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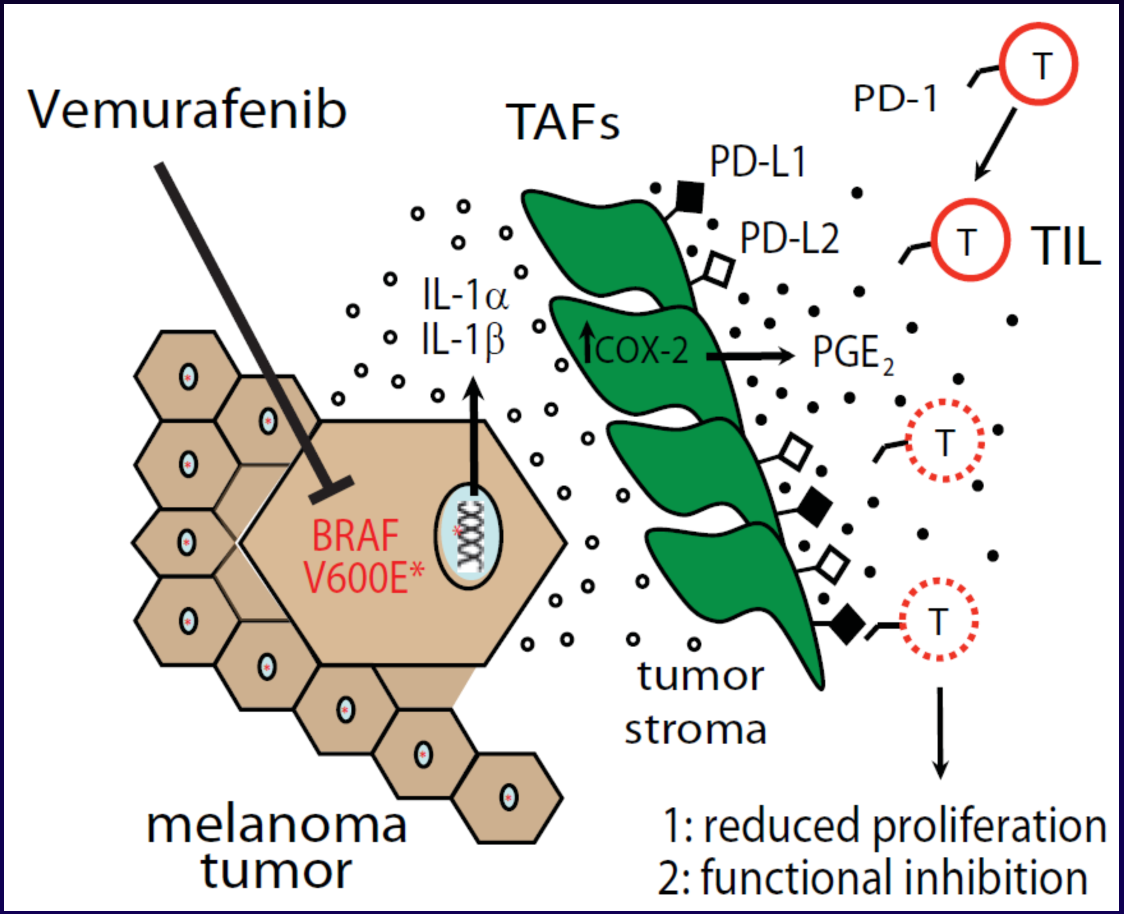
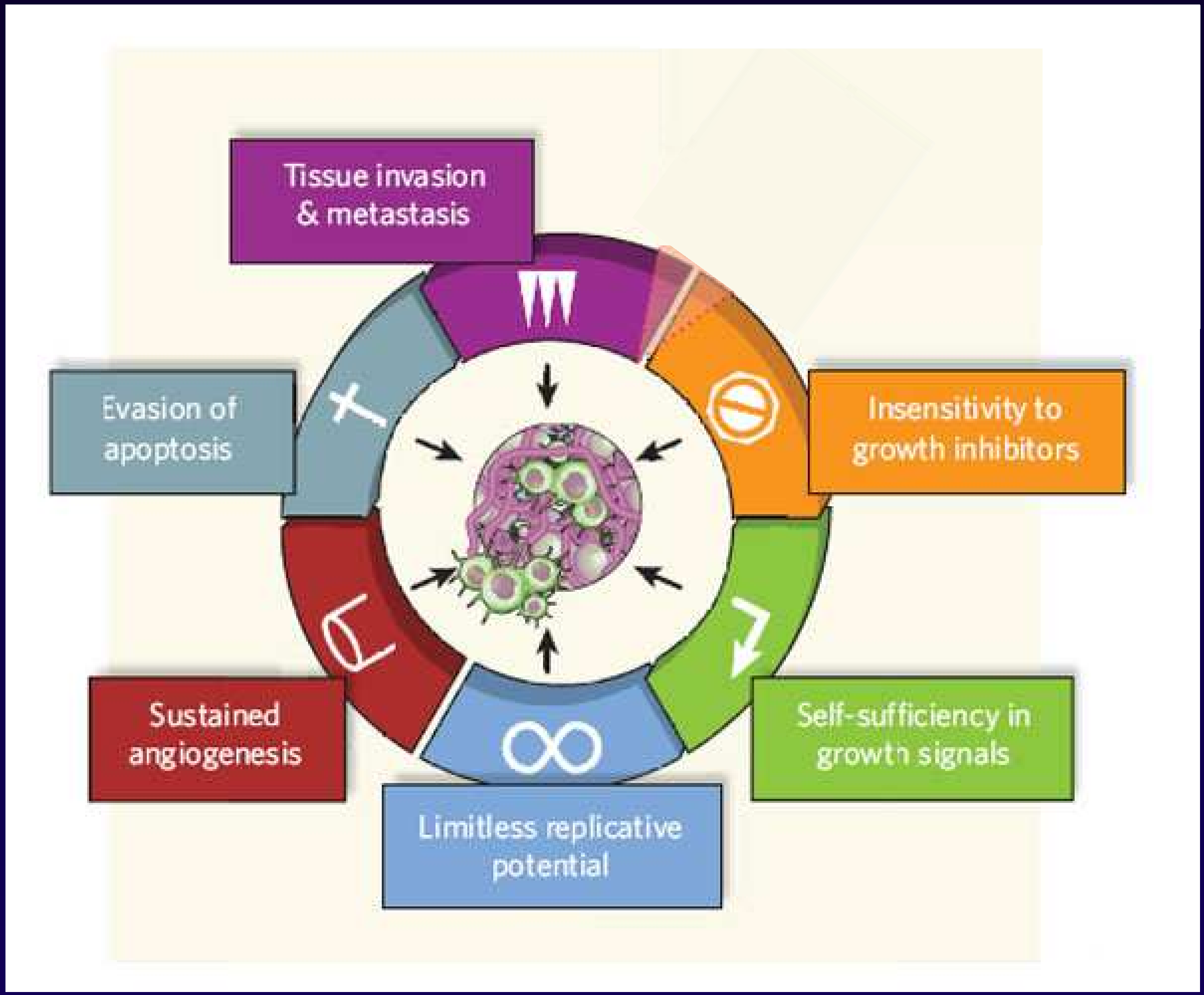
↓

promote expression of immunosuppressive molecules



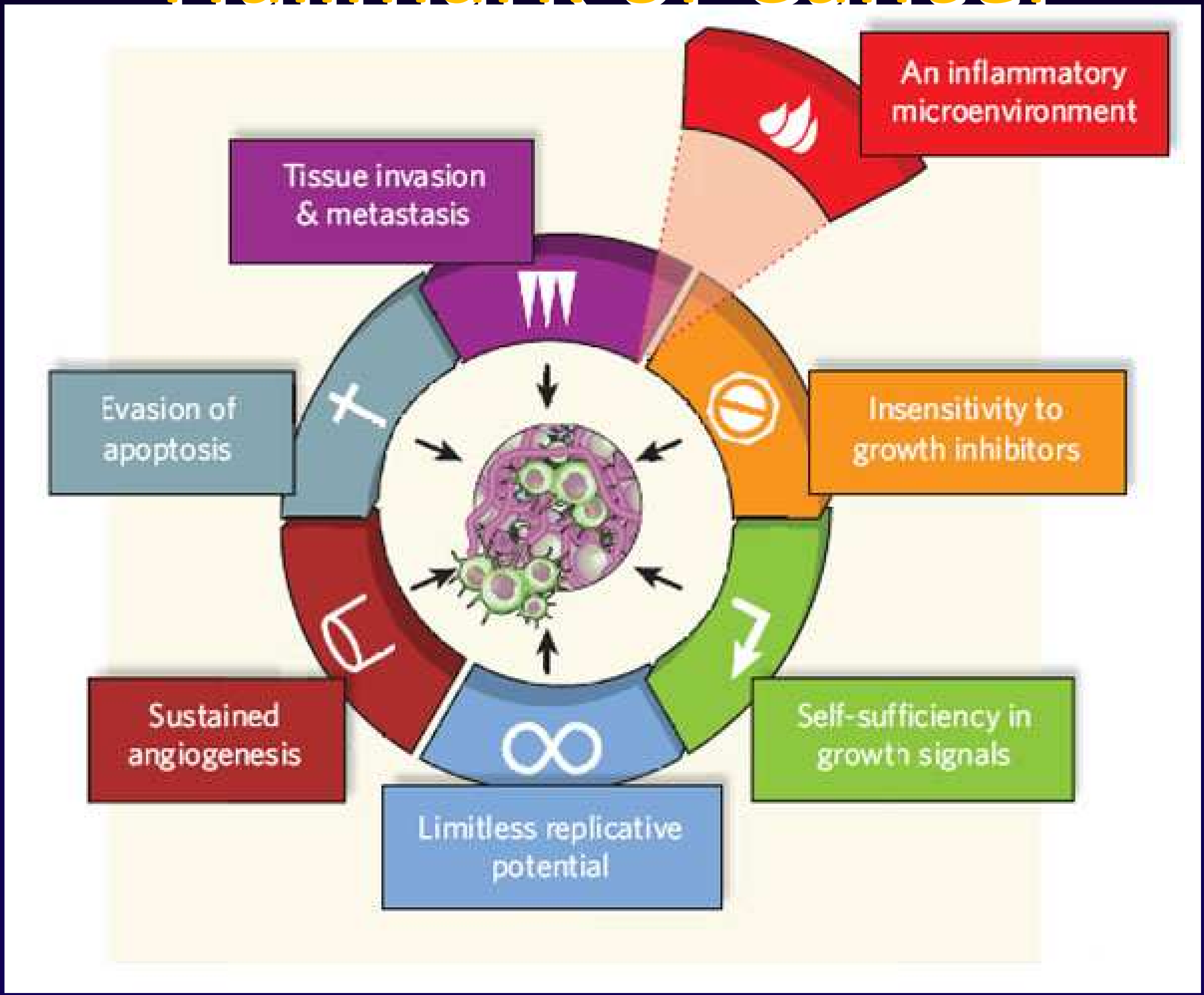
Khalili et al., *Clin. Cancer Res.* 2012

Classic Hallmarks of Cancer



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

Inflammation is (now) a Classic Hallmark of Cancer



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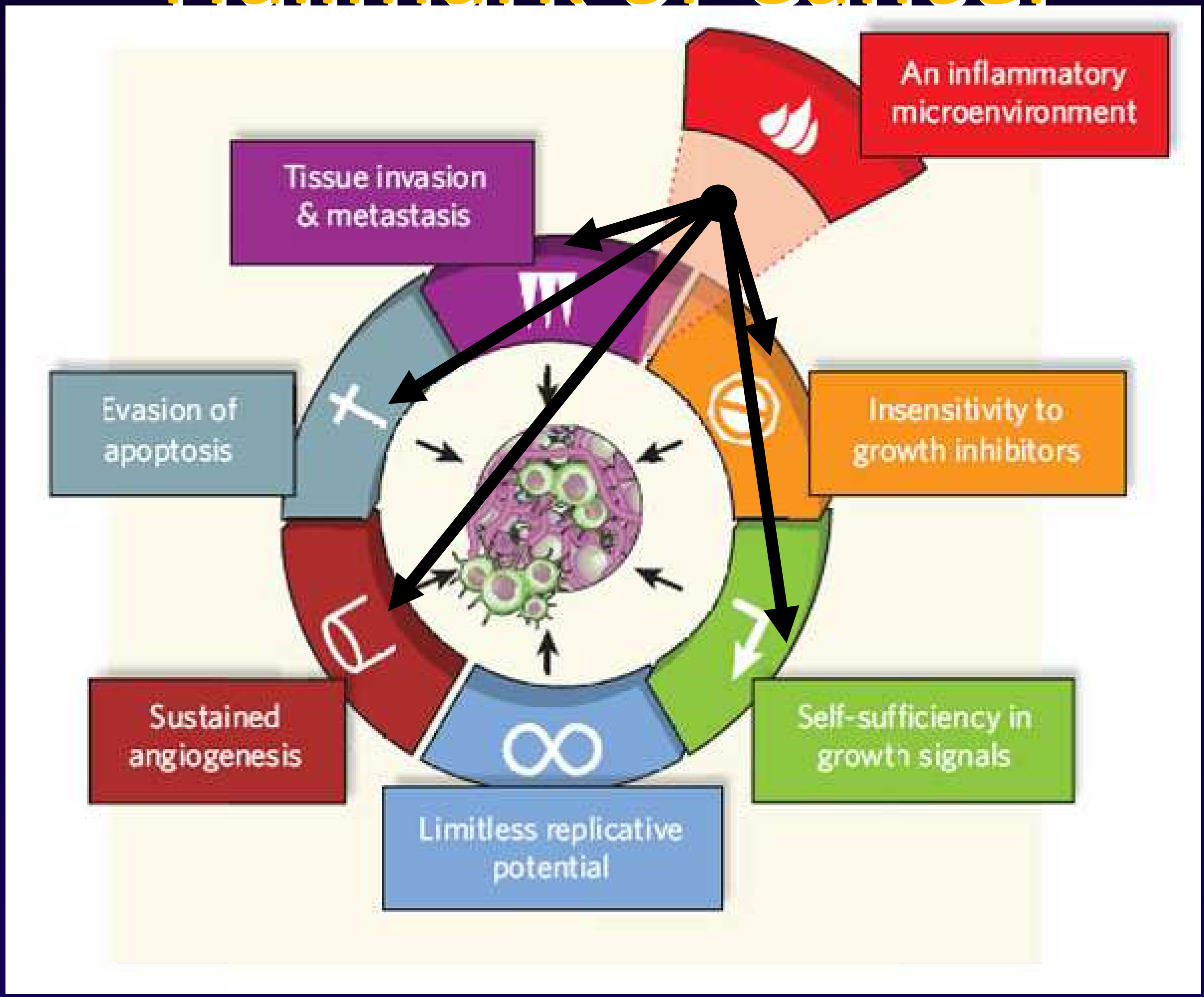

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Good *vs.* Bad Inflammation in Cancer

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

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

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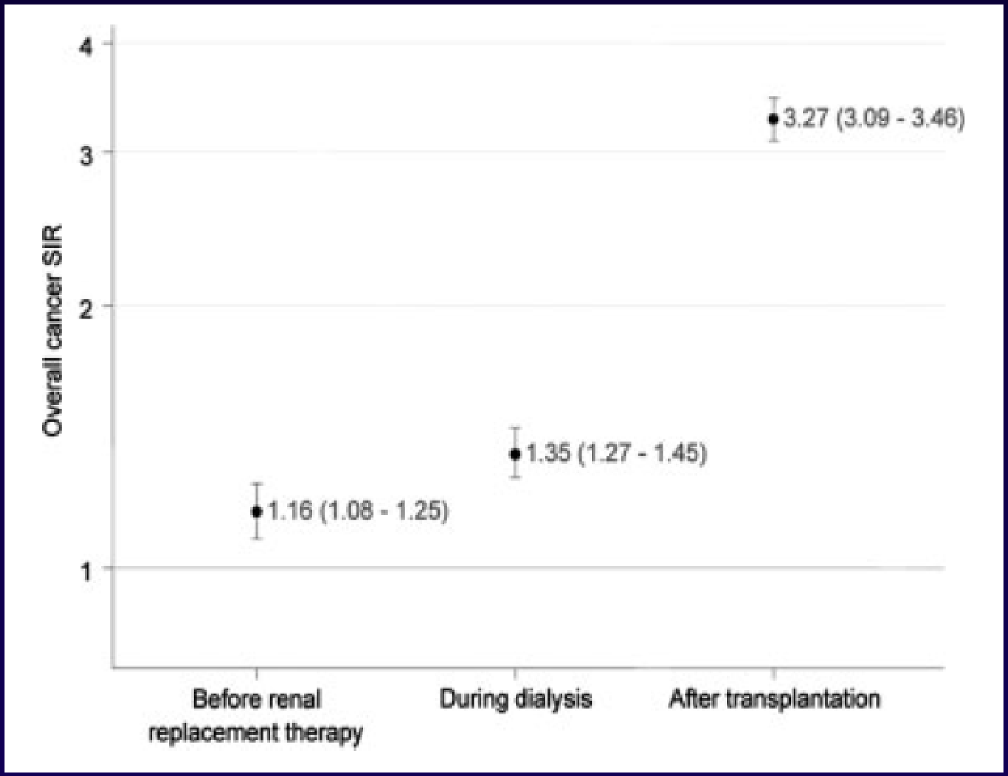
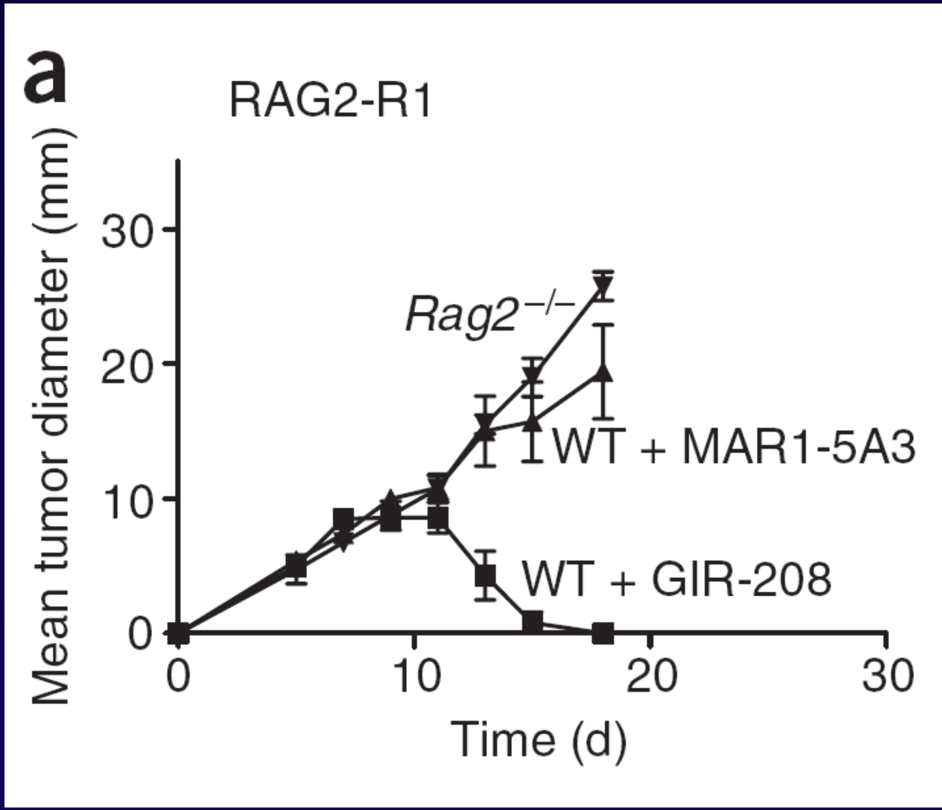
MacKie et al., *NEJM* 2003

Post-transplant Immunosuppression Increases Cancer Incidence



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

Type I IFNs Suppress Growth of Transplanted Tumors

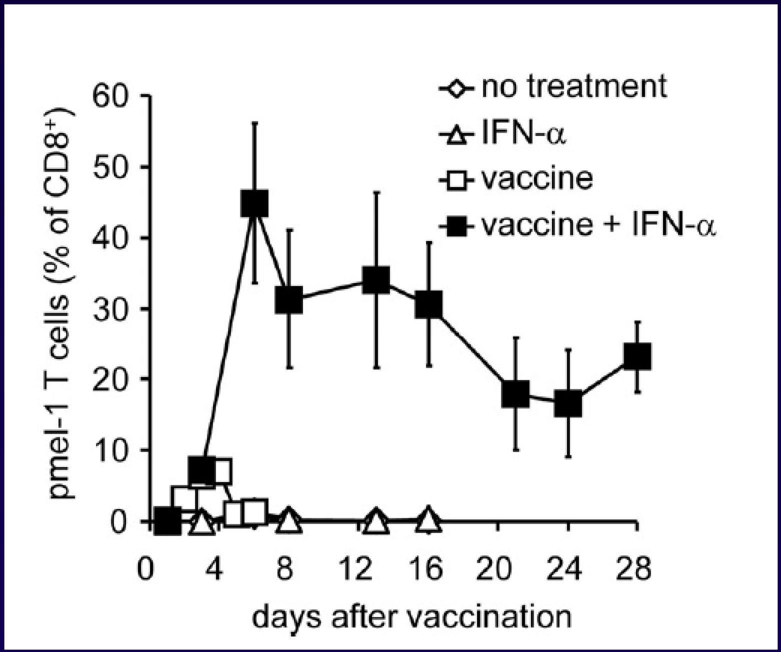


IFN-α receptor blocking mAb

control mAb

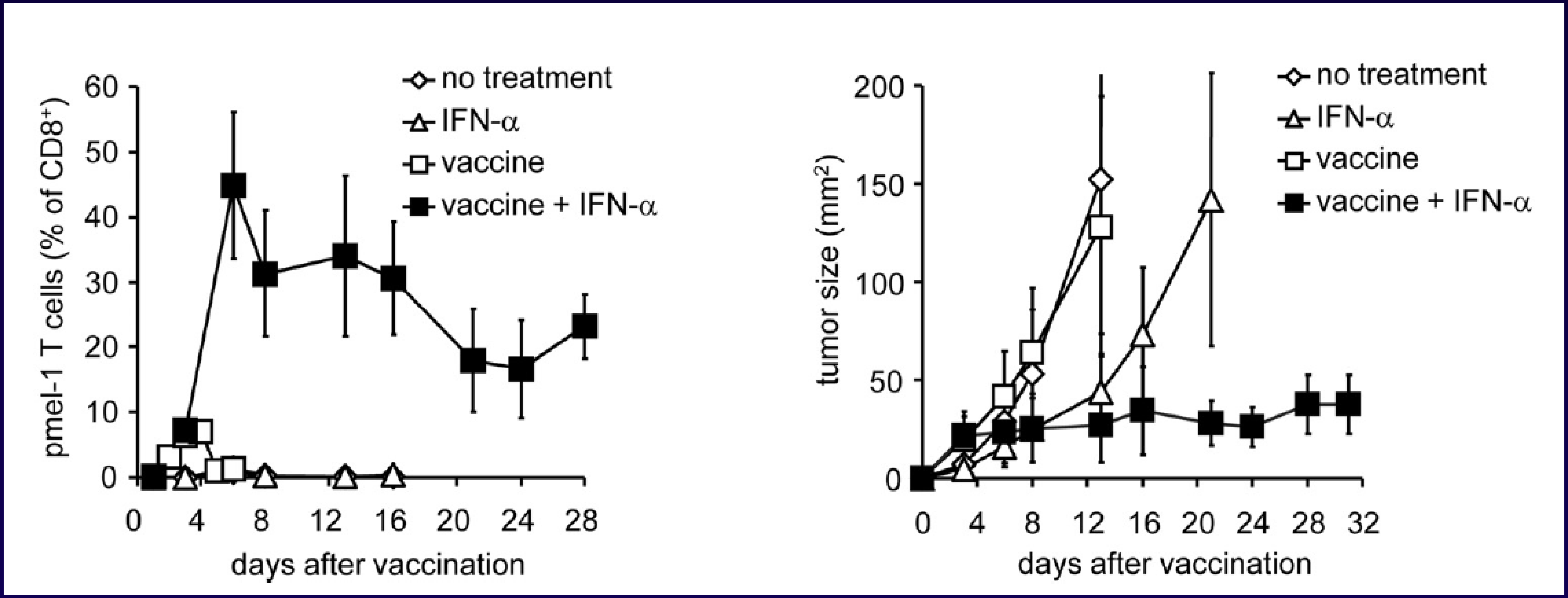
Dunn et al. *Nat. Immunol.* 2005

IFN-α treatment enhances anti-cancer vaccination



Sikora et al. *J. Immunol.* 2009

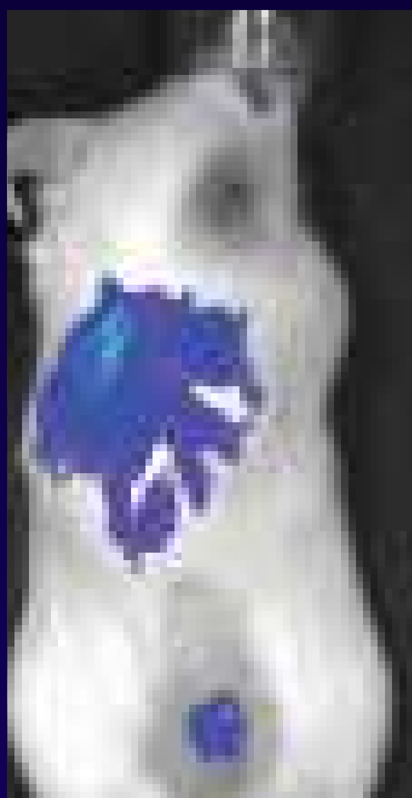
IFN-α treatment enhances anti-cancer vaccination



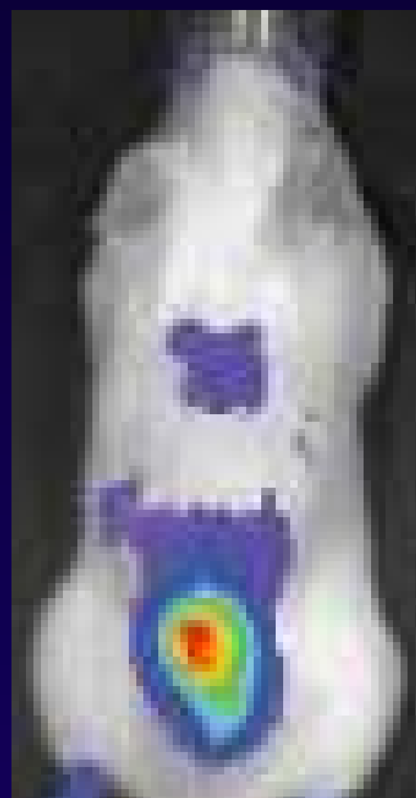
Sikora et al. *J. Immunol.* 2009

CpG Causes Tumor Inflammation and Intratumoral T cell Accumulation

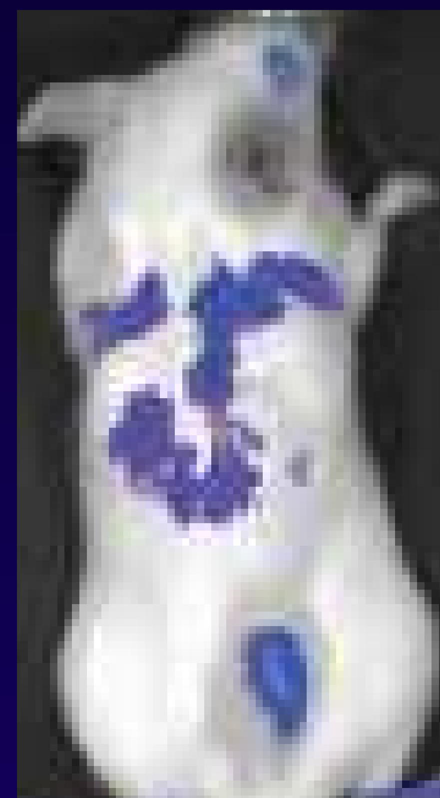
Intratumoral PBS



Intratumoral CpG

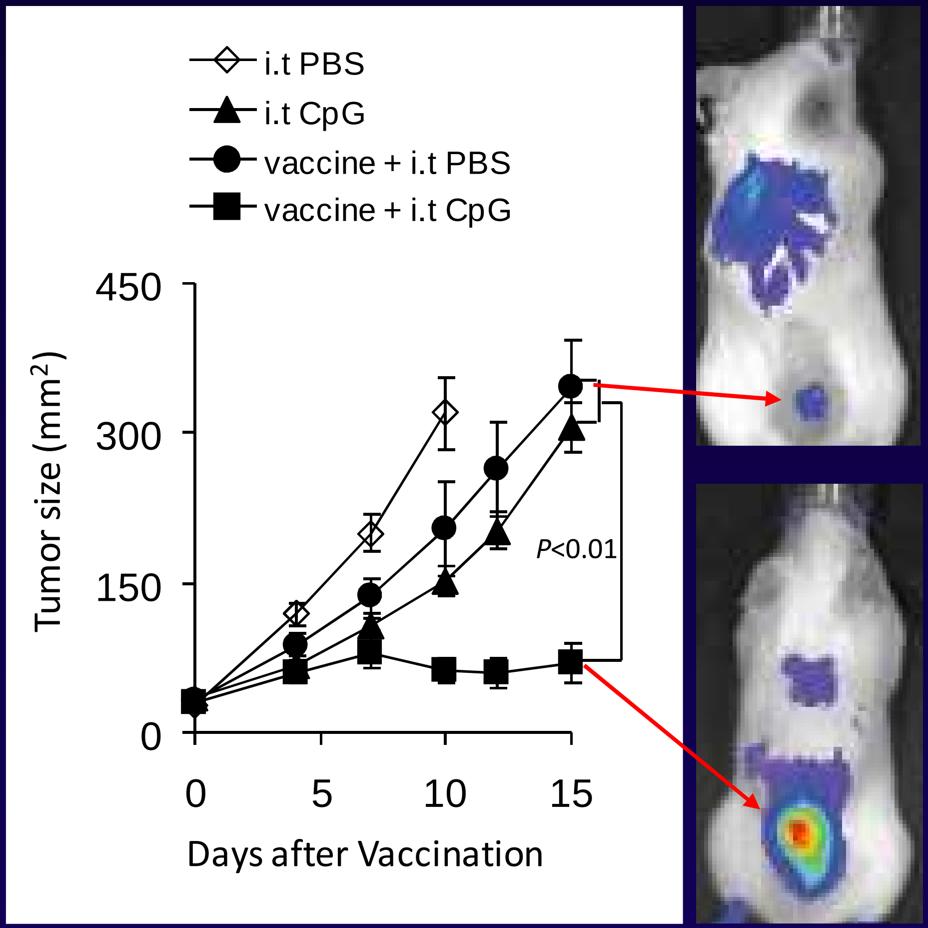


Intravenous CpG



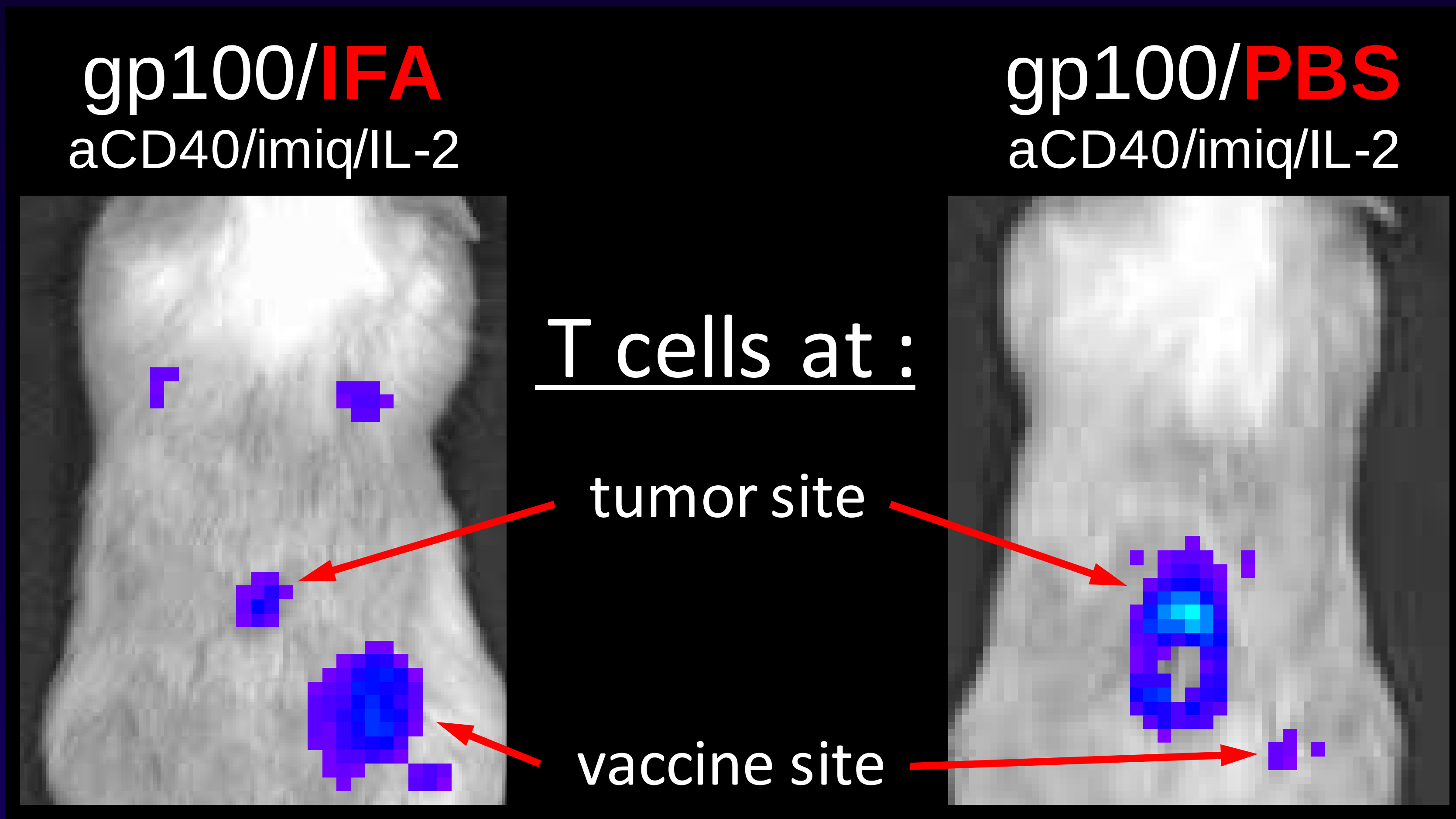
Lou et al. , *J. Immunother*. 2011

CpG Causes Tumor Inflammation and Intratumoral T cell Accumulation



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

Choice of vaccine adjuvant controlsT cell trafficking to tumor



Hailemichael et al. , *Nat. Med.* 2013

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

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- Targeted Therapy? — TKI inhibitors (many cancers)

In the Clinic: Cancer Therapies that Induce Good Inflammation

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- Bacteria BCG (bladder)

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	CpG (B cell lymphoma)

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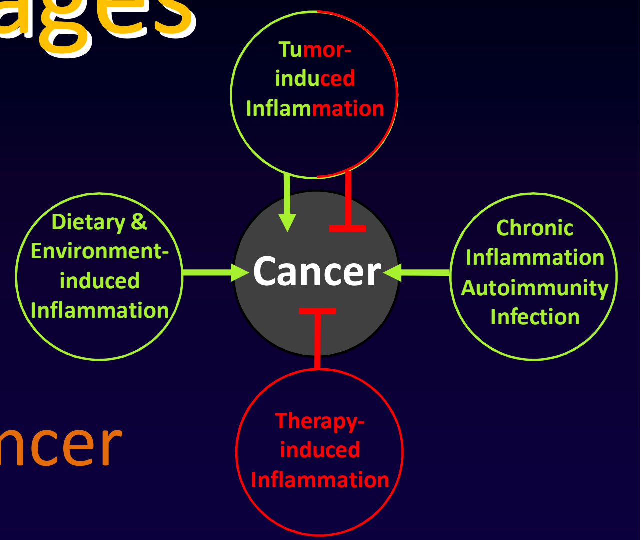
•	Vaccine	PAP-loaded DCs (prostate)

How therapeutics may promote cancer

- induce mutation (chemotherapy)
- induce inflammation (cytokines, TLR agonists, agonistic antibodies)
- change the microbiome (antibiotics, foods)?
- **block cells/factors that suppress cancer**
  $CD8^+$ T cells/NK cells
  type I IFN, IFN-γ
  TNF-α - lymphoma?
  IL-15?
  IL-12/IL-23
  IL-17A?

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

1. What is the importance of Innate immunity and Inflammation (I&I) in cancer?

a)I&I can **prevent** the development and/or progression of cancer

b)I&I can **promote** the development and/or progression of cancer

c)I&I plays an important role in the induction of therapeutic anti-cancer immune responses

d)All of the above.

2. Inducing inflammation is effective to treat cancer

a) Yes

b) No

c) Yes, especially inflammation that increases VEGF, IL-10, and MDSCs and Tregs

d) Sometimes, for example inflammation that increases IFN-gamma, cytotoxic T cells, and Type I macrophages

3. The immune system can sometimes suppress tumor growth

a) Yes, because transplant patients on immunosuppressive drugs get more of certain types of cancer

b) No, because the immune system did not evolve to fight cancer

4. Smoking can cause cancer by:

a) Damaging DNA

b) Causing tissue inflammation

c) Damaging DNA and causing tissue inflammation

d) Smoking doesn’t cause cancer, it’s a conspiracy theory funded by the political party I’m not voting for.

5. Causing systemic inflammation is an effective way to treat cancer

a) Yes, because the systemic inflammation systemically activates the immune system

b) No, because systemic inflammation causes aberrant migration of immune cells

c) Yes, because systemic inflammation is usually completely non-toxic