Innate Immunity and Inflammation

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Center for Cancer Immunology Research
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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 $A \neq$ 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

Adherence to epithelium

Normal flora
Local chemical factors
Phagocytes (especially in lung)

Janeway, Immunobiology, 7th Ed.
Innate Immunity and Inflammation: A Paper Cut

- Adherence to epithelium
  - Tissue macrophage
  - Tissue dendritic cell

- Local infection, penetration of epithelium
  - Blood vessel

- Protection against:
  - Normal flora
  - Local chemical factors
  - Phagocytes (especially in lung)
  - Wound healing induced
  - Antimicrobial proteins and peptides, phagocytes, and complement destroy invading microorganisms
  - Activation of γδ T cells?
Innate Immunity and Inflammation: A Paper Cut

Adherence to epithelium
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Local infection, penetration of epithelium
- Wound healing induced
- Antimicrobial proteins and peptides, phagocytes, and complement destroy invading microorganisms
- Activation of γδ T cells?

Local infection of tissues
- Complement, cytokines, chemokines, Phagocytes, NK cells
- Activation of macrophages
- Dendritic cells migrate to lymph nodes to initiate adaptive immunity
- Blood clotting helps limit spread of infection

Protection against infection

Janeway, Immunobiology, 7th Ed.
Innate Immunity and Inflammation: A Paper Cut

- **Adherence to epithelium**
  - Normal flora
  - Local chemical factors
  - Phagocytes (especially in lung)

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- **Local infection of tissues**
  - Complement, cytokines, chemokines, Phagocytes, NK cells
  - Activation of macrophages
  - Dendritic cells migrate to lymph nodes to initiate adaptive immunity
  - Blood clotting helps limit spread of infection

- **Adaptive immunity**
  - Infection cleared by specific antibody, T-cell dependent macrophage activation and cytotoxic T cells

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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

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: granulocytes

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

Recognize
- pathogens
- antibodies

Cause
- pathogen clearance
- inflammation

Janeway, Immunobiology, 7th Ed.
Innate Immune Cells: phagocytes

<table>
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<tr>
<th>Cell</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Monocyte</strong></td>
<td>Blood precursor of tissue Macrophages and Dendritic Cells</td>
</tr>
<tr>
<td><strong>Macrophage</strong></td>
<td>Phagocytosis and activation of bactericidal mechanisms Antigen presentation</td>
</tr>
<tr>
<td><strong>Dendritic cell</strong></td>
<td>Antigen uptake in peripheral sites Antigen presentation</td>
</tr>
</tbody>
</table>

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

- **PAMPs**
  - Flagellin
  - LPS
  - Peptidoglycans
  - Glycolipids
  - Zymosan
  - ssRNA
  - Envelope

- **Bacteria**

- **Fungus**
  - Profilin
  - T. Gondi

- **Virus**

**DAMAGE**

- **DAMPs**
  - Necrosis
  - HMGB1
  - IL-18
  - IL-1α
  - Heparan sulphate
  - Uric acid
  - Hyaluronan
  - Extracellular matrix

- **Tumour cells**
  - ATP
  - DNA

- **Injury**

**Normal tissue**

**PRRs**

- **NK cells**
- **Basophils**
- **Eosinophils**
- **Neutrophils**
- **Monocytes**
- **IDCs**

**Adaptive immune response**

**Innate immune response**

Rubartelli & Lotze, *Trends in Immunology* 2007
Danger signals start inflammation

PATHOGENS

DAMAGE

PRRs (TLRs, NLRs, RLRs)

Rubartelli & Lotze, Trends in Immunology 2007
Receptors sense Danger: Pathogens
Receptors sense Danger: Damage

Kawai & Akira, Nat. Immunol. 2010
Innate Immunity and Inflammation

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Innate Immunity and Inflammation in Cancer

• Outcomes vary:
  - Promote cancer (Bad inflammation)
  - Suppress cancer (Good inflammation)
Innate Immunity and 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
IMMUNE RESPONSE

INFLAMMATION

COLLATERAL DAMAGE

DANGER
IMMUNE RESPONSE

INFLAMMATION

COLLATERAL DAMAGE
IMMUNE RESPONSE

DANGER

COLLATERAL DAMAGE

INFLAMMATION
IMMUNE RESPONSE

CHRONIC DANGER

INFLAMMATION

COLLATERAL DAMAGE
CHRONIC IMMUNE RESPONSE
INFLAMMATION

CHRONIC DANGER

CHRONIC COLLATERAL DAMAGE
CHRONIC IMMUNE RESPONSE INFLAMMATION

CHRONIC COLLATERAL DAMAGE

CANCER

CHRONIC DANGER
IMMUNE RESPONSE

COLLATERAL DAMAGE

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

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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

- K-ras mutation & normal myeloid cells
- K-ras mutation & IKK\(^{-/-}\) myeloid cells

- \(\downarrow\) NF-\(\kappa\)B
- \(\downarrow\) pSTAT3
- \(\downarrow\) IL-6
- \(\downarrow\) neutrophils
- \(\downarrow\) angiogenesis

Takahashi et al., *Cancer Cell* 2010

no smoking
4 cigarettes per day
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

A apoptotic Death of CD8⁺ T Lymphocytes After Immunization: Induction of a Suppressive Population of Mac-1⁺/Gr-1⁺ Cells

Vincenzo Bronte, Michael Wang, Willem W. Overwijk, Deborah R. Surman, Federica Pericle, Steven A. Rosenberg, and Nicholas P. Restifo

Tumors can induce bad inflammation

Bronte et al., J. Immunol. 1999
Tumors can induce bad inflammation
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, immunosuppressive cytokines

Sumimoto et al., J. Exp. Med. 2006
Mutations can Drive Bad Inflammation

Mutated BRAF → tumor cells produce bad, immunosuppressive 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

- Tissue invasion & metastasis
- Evasion of apoptosis
- Sustained angiogenesis
- Limitless replicative potential
- Self-sufficiency in growth signals
- Insensitivity to growth inhibitors
- An inflammatory microenvironment
Inflammation is (now) a Classic Hallmark of Cancer

Mantovani et al., Nature 2009
Hanahan & Weinberg, Cell 2000
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Good vs. Bad Inflammation in Cancer

Immunity, Inflammation, and Cancer
Sergei I. Grivennikov, Florian R. Greten, and Michael Karin
Cell 140, 883–899, March 19, 2010

Cancer and Inflammation: Promise for Biologic Therapy
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 treatment enhances anti-cancer vaccination

IFN-\(\alpha\) treatment enhances anti-cancer vaccination

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
Tumor-induced Inflammation

Dietary & Environment-induced Inflammation

Chronic Inflammation Autoimmunity Infection

Therapy-induced Inflammation

Adapted from Grivennikov et al. Cell 2010
### Bottom Line: Inflammation can be Good or Bad: Pro or Anti-Tumor

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

Grivennikov et al. Cell 2010

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

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- Remove suppressors: Cycl/Fludar + T cells (melanoma)
- Cytotoxic Therapy?: Radiation/Chemother. (all cancers)
## In the Clinic: Cancer Therapies that Block Bad Inflammation

<table>
<thead>
<tr>
<th>Category</th>
<th>Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>COX-2 inhibitor</td>
<td>Aspirin, Celecoxib (colorectal)</td>
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<td>Kill Helicobacter Pylori</td>
<td>Clarithrom./Amoxicillin (gastric)</td>
</tr>
<tr>
<td>Remove suppressors</td>
<td>Cycl/Fludar + T cells (melanoma)</td>
</tr>
<tr>
<td>Cytotoxic Therapy?</td>
<td>Radiation/Chemother. (all cancers)</td>
</tr>
<tr>
<td>Targeted Therapy?</td>
<td>TKI inhibitors (many cancers)</td>
</tr>
</tbody>
</table>
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)
- **Cytokines**: IL-2 (melanoma, renal)
- **Cytokines**: IFN-α (melanoma, renal, CML)
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- **Antibodies**
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- **Surgery**
  - Danger/inflammation? (cervical)
In the Clinic: Cancer Therapies that Induce Good Inflammation

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- T cells: Adoptive T cell Transfer (melanoma)
In the Clinic: Cancer Therapies that Induce Good Inflammation

- **Bacteria**  
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  CpG (B cell lymphoma)

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  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