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
Innate Immunity and Inflammation

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• 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

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
- tissue macrophage
- tissue dendritic cell

Local infection, penetration of epithelium
- blood vessel

Local infection of tissues

Protection against infection
- 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?

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

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

Protection against infection

- 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?
- 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
- Infection cleared by specific antibody, T-cell dependent macrophage activation and cytotoxic T cells

Janeway, Immunobiology, 7th Ed.
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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.
Danger signals start inflammation

PATHOGENS

DAMAGE

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

**PATHOGENS**

- Bacteria: Peptidoglycans, LPS, Glycolipids, Flagellin, Zymosan
- Fungus: Profilin, T. Gondi
- Virus: ssRNA

**DAMAGE**

- DAMPs: Necrosis, Tumour cells, ATP, DNA, IL-1β, IL-1α, Heparan sulphate, Uric Acid
- Extracellular matrix: Hyaluronan

**PRRs** (TLRs, NLRs, RLRs)

**Adaptive immune response**

**Innate immune response**

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

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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
DANGER

IMMUNE RESPONSE

INFLAMMATION

COLLATERAL DAMAGE
DANGER → IMMUNE RESPONSE → INFLAMMATION → COLLATERAL DAMAGE
IMMUNE RESPONSE

COLLATERAL DAMAGE

CHRONIC DANGER

INFLAMMATION
CHRONIC IMMUNE RESPONSE

COLLATERAL DAMAGE

CHRONIC DANGER

CHRONIC INFLAMMATION
cancer: a “never-healing wound”

Dvorak, *NEJM* 1986
Inflammation can Promote Cancer: collaboration with K-ras mutation

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.

Takahashi et al., Cancer Cell 2010

- No smoking
- 4 cigarettes per day

K-ras mutation & normal myeloid cells vs. K-ras mutation & IKK-/- myeloid cells:
- ↓ NF-κB
- ↓ pSTAT3
- ↓ IL-6
- ↓ neutrophils
- ↓ angiogenesis
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

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
Mutations can Drive Bad Inflammation

Mutated BRAF \rightarrow\text{tumor cells produce bad, immunosuppressive cytokines}

\text{promote expression of immunosuppressive molecules}

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
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Good vs. Bad Inflammation in Cancer

Immunity, Inflammation, and Cancer
Sergei I. Grivennikov, Florian R. Greten, and Michael Karin

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
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

MacKie et al., *NEJM* 2003
Human Immune System can Suppress Existing Tumors for Years

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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

Sikora et al. *J. Immunol.* 2009
IFN-α 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., J. Immunother. 2011
Choice of vaccine adjuvant controls T cell trafficking to tumor

Hailemichael et al., Nat. Med. 2013
**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>
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<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</td>
<td>Production of cytokines?</td>
</tr>
<tr>
<td></td>
<td>cytotoxic cytokines</td>
<td></td>
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<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</td>
<td>Production of cytokines</td>
</tr>
<tr>
<td></td>
<td>tumor rejection; production of cytokines (IFN(\gamma))</td>
<td></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</td>
<td>Immunosuppression; production of cytokines</td>
</tr>
<tr>
<td></td>
<td>other suppressive mechanisms</td>
<td></td>
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<tr>
<td>Natural killer cells</td>
<td>Direct cytotoxicity toward cancer cells;</td>
<td></td>
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<td>production of cytotoxic cytokines</td>
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<tr>
<td>Neutrophils</td>
<td>Direct cytotoxicity; regulation of CTL</td>
<td>Production of cytokines, proteases, and ROS</td>
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<tr>
<td></td>
<td>responses</td>
<td></td>
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</tbody>
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Grivennikov et al. *Cell* 2010
In the Clinic: Cancer Therapies that Block Bad Inflammation
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• COX-2 inhibitor: Aspirin, Celecoxib (colorectal)
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• COX-2 inhibitor  Aspirin, Celecoxib (colorectal)
• VEGF blocker  Bevacizumab, Sorafenib (several)
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- Cytotoxic Therapy?: Radiation/Chemother. (all cancers)
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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

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  - IFN-α (melanoma, renal, CML)
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  - aCTLA4/aPD(L)-1 mAb (melanoma)
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5. **Surgery**
   - Danger/inflammation? (cervical)
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- **T cells**  Adoptive T cell Transfer  (melanoma)
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- 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)
- T cells: Adoptive T cell Transfer (melanoma)
- 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