Innate Immunity:
(I) Molecules & (II) Cells

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Part II: Cells (aka the Sentinels)

• Granulocytes
  – Neutrophil, Eosinophil, Basophil, Mast cell
• Monocytes/macrophages
• Dendritic cells
• Innate lymphoid cells
Myeloid Cells

- Recognize microbes
  - PRRs
  - Complement
  - Antibody
- Ingest & destroy microbes
- Kill infected/injured cells
- Regulate tissue homeostasis
- Antigen presentation
  - Help T cells

Two pathways for macrophage development

During inflammatory reactions

- Bone marrow
- Histiocytic stem cell
- Blood monocyte
- Activated macrophages in inflammation
  - Macrophages in skin, intestinal tract

Tissue-resident macrophages

- Liver
- Yolk sac
- Progenitor in yolk sac, fetal liver
- Resident tissue macrophages
  - (Kupffer cells, alveolar macrophages, microglia, etc.)

Further reading: Epelman et al. Immunity 2014
First responders recruit (Macrophages organize)

Activated macrophages secrete a range of cytokines

- IL-1β
- TNF-α
- IL-6
- CCL8
- IL-12

**Local effects**
- Activates vascular endothelium
- Activates lymphocytes
- Increases vascular permeability, which leads to increased entry of IgG, complement, and cells to tissues and increased fluid drainage to lymph nodes
- Lympohocyte activation
- Increased antibody production
- Chemotactic factor recruits neutrophils, basophils, and T cells to site of infection
- Activates NK cells

**Systemic effects**
- Fever
- Production of IL-6
- Fever: Mobilization of metabolites
- Shock
- Fever: Induces acute-phase protein production

**Figure 2.21** Janeway’s Immunobiology, Ed. 7© Garland Science 2013

First responders clear pathogens and dead cells
**Chronic Granulomatous Disease (CGD)**

- Recurrent bacterial infection (catalase positive organisms)
- Granulomas of skin, liver, lungs, lymph nodes observed
- Gene defect:
  - gp91 phox (X-Linked)
  - p22 phox (Autosomal Recessive)
  - p47 phox (Autosomal Recessive)
  - p67 phox (Autosomal Recessive)
- Phagocytic cells ingest but do not kill bacteria due to failure to form oxygen radicals

**IFNγ and macrophage activation**

- Mendelian susceptibility to mycobacterial disease (MSMD) – Ifnγ-mediated protection (IL-12, Ifnγ, Stat1 defects)
  - Failure of CD4+ T cells to activate macrophage killing of intracellular bacteria

TNF blockers might interfere with this process...

Bustamante et al Semin. Immuno. 2014
Endothelium activated by cytokines
Leukocytes activated by chemokines

**Endothelium activated by cytokines**

**Leukocytes activated by chemokines**

**Rolling adhesion**

**Tight binding**

**Diapedesis**

**Migration**

Integrins seal the deal

Chemokines direct

**Chemokines direct**

**Leukocyte migration during inflammation**

*Neutrophil NETs*

- Neutrophil extracellular traps
- NETosis with cell death traps microbes
  - Extrusion of chromatin decorated with antimicrobial molecules (e.g., elastase, MPO)
- Role in driving autoimmunity?

Kaplan et al, JI 2012
DCs & the next phase of immunity

DCs survey for pathogens or host damage (via PRRs) and respond by processing antigens and providing "second signals"

T cell priming requires 2 signals to avoid anergy: antigen (constant) + co-stimulation (activated DC)

The innate immune system provides second signals required for lymphocyte activation

2nd signals for T cells:
- CD28: B7 family members (CD80/B7.1, CD86/B7.2)
- [opposite for PDL1,2]
- ICOS: ICOSL
- OX40: OX40L
- CD137: 4-1BBL

2nd signals for B cells:
- CR3: Activated complement components
- TLRs: PAMPs
Dendritic Cell Subsets (Spleen)

- **Plasmacytoid**
  - MDP
  - FLT3L
  - HSC
  - Embryonic Precursor

- **Conventional**
  - MDC
  - MCSF

- **Monocyte-derived**
  - TipDC
  - Patrolling Mo
  - Macrophages

**Type I IFN**
- T cell priming
- Inflammation

**Cellular Markers**
- pDC
  - PDCA-1
  - B220
  - Siglec H
  - Gr-1
  - CD8α+ DNGR1+ XCR1+
  - CD4+ CD11b+
  - TipDC
  - CD11c+ Ly6C+ Ly6G+
  - Patrolling Mo
  - CX3CR1+ Ly6G+ CCR2+

**Monocyte**
-FLT3L
- MCSF
DC Migration is a Critical Step in T Cell Priming

DCs migrate from peripheral tissues to lymphoid organs via lymphatic vessels, guided by chemokines such as CCL19/21.

PRR activation leads to:
- Ag processing/presentation
- Co-stimulatory molecule expression
- CCR7 expression

Innate instruction of adaptive immunity: implications

- Autoimmunity
- Allergy
- Resistance to re-infection
- Vaccination

Once this principle was understood, the role of adjuvants could be explained:
- HBV vaccine: subunit and adjuvant
- *Adjuvare* = to help
- Hundreds of different adjuvants
  - CFA, Aluminum hydroxide, MF-59 (Squalene), TLR agonists, AS04 (Alum+MPL)

Medzhitov, 2001
Questions?

• Thanks
  – A. Abbas
  – K. Rock

• Further reading
  – Janeway’s Immunobiology, 8th edition
  – Abbas, Lichtman & Pillai Cellular & Molecular Immunology, 8th edition

NK Cells (ILC1)

• Different from NKT cells

• Germline encoded receptors

• Kill cells that are missing “stop” signals
  – Inhibitory receptors
    • KIRs

• Kill cells that express foreign or stress signals
  – Activating receptors
    • CLRs
    • NKG2D
    • FcgRIII (CD16)

• Infections
• Tumors
Innate lymphoid cells

ILCs make many of the same cytokines as T cells but lack TCRs

May contribute to early cytokine responses in host defense and inflammatory diseases

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<table>
<thead>
<tr>
<th>Receptor characteristic</th>
<th>Innate immunity</th>
<th>Adaptive immunity</th>
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<tbody>
<tr>
<td>Specificity inherited in the genome</td>
<td>Yes</td>
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<td>Expressed by all cells of a particular type (e.g. macrophages)</td>
<td>Yes</td>
<td>No</td>
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<td>Triggers immediate response</td>
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<td>No</td>
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<td>Recognizes broad classes of pathogens</td>
<td>Yes</td>
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<td>Interacts with a range of molecular structures of a given type</td>
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<td>Encoded in multiple gene segments</td>
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<td>Requires gene rearrangement</td>
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<td>Clonal distribution</td>
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<td>Able to discriminate between even closely related molecular structures</td>
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Principles of TLRs

Akira et al, Nat. Rev. Imm. 2004

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<tr>
<th>Receptor</th>
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<td>TLR1</td>
<td>Triacyl lipoprotein</td>
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*Proposed that TLRs recognize, in addition to endogenous ligands and/or other conserved modular components, a variety of other host defense molecules.

Akira et al, Nat. Rev. Imm. 2004
**Timepoint: minutes-hours**

1. **Block microbial invasion**
2. **Remove targeted microbes, dead cells & foreign bodies**
3. **Tissue homeostasis**

Plasma proteins $\rightarrow$ target & kill
   - Complement
   - Pentraxins (CRP, SAA, etc.)
   - Collectins & Ficolins

Phagocytes $\rightarrow$ eat & recruit
   - Pattern recognition receptors

Innate lymphoid cells $\rightarrow$ kill & coordinate
   - NK cells kill things that are non-self

*Increased hydrostatic pressure/permeability*

*Leak of protein-rich fluid into site = EDEMA*

*Structure of TLRs*

- An extracellular domain with LRRs (Leucine Rich Repeats)
- A transmembrane domain
- A cytosolic domain with a conserved TIR (Toll-interleukin 1 Receptor) domain
  - Shared with IL-1R family