A Day in the Life of a Phagocytic Leukocyte

Selectin-mediated Adhesion is Weak and Promotes "Rolling" of Leukocyte Along Endothelia

Firm Adhesion is Triggered by Chemokine Activation of Leukocyte Integrins

Diapedesis: Crawling Through Endothelial Junctions and Into the Tissue

Leukocyte Migration, Start to Finish

The Innate Immune Response to Bacterial and Fungal Infections
Relative Risk of Death Associated With Death of a Biological Parent Before the Age of 50

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>1.7</td>
</tr>
<tr>
<td>&quot;Natural causes&quot;</td>
<td>2.0</td>
</tr>
<tr>
<td>Infectious</td>
<td>5.8</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>4.5</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Conclusion: Genes that determine responses to infectious agents have a disproportionate effect on mortality


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Distinctions Between Innate and Adaptive Immunity

<table>
<thead>
<tr>
<th>Innate immune system</th>
<th>Adaptive immune system</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Receptors</strong></td>
<td>Germline-encoded</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Non-clonal</td>
</tr>
<tr>
<td><strong>Kinetics</strong></td>
<td>Rapid</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>Recognizes non-self &quot;pattern recognition&quot;</td>
</tr>
<tr>
<td><strong>Effector Cells</strong></td>
<td>All</td>
</tr>
<tr>
<td>Somatics engineered</td>
<td>Clonal Clonal (requires clonal expansion)</td>
</tr>
<tr>
<td>Recognizes &quot;altered self&quot;</td>
<td>Primary structure (TCR)</td>
</tr>
<tr>
<td>Higher order structure (Immunoglobulin; BCR)</td>
<td>Primarily lymphocytes, DCs, Mφ</td>
</tr>
</tbody>
</table>

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Soluble "Defense Collagens" Participate in Innate Immunity

**Domain Structure of Surfactant Protein A (SP-A), a Lung Soluble Defense Collagen (Collectin)**

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What Really Happens During the Lag Period Before the Acquired Immune Response?
The Complement System is Critical for Innate Immunity and is Triggered by Multiple Ligands

Complement is a Group of Proteins that Deposit On Microbial Pathogens and Help Kill Them

Mast Cells Can Phagocytose Too!

Phagocytosis of IgG-coated Targets by Macrophages

Extension of an F-actin-rich "Phagocytic Cup" Around Phagocytic Targets
Examples of “Pattern Recognition Receptors” that Participate in Phagocytosis

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Expression</th>
<th>Target</th>
<th>Ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrins (CD11b/CD18, αMβ2)</td>
<td>PMN, Mo, Mφ</td>
<td>Yeast</td>
<td>β-glucan</td>
</tr>
<tr>
<td></td>
<td>Luek</td>
<td>Yeast (β-glucan)</td>
<td>C3bi, fibrinogen, LPS, ICAM (Yeast)</td>
</tr>
<tr>
<td>Scavenger Receptors</td>
<td>Gram-positive bacteria</td>
<td>Gram-negative bacteria</td>
<td>Lipopolysaccharide (LPS), Gram-positive bacteria</td>
</tr>
<tr>
<td>MARCO</td>
<td>Mφ</td>
<td>E. coli, S. aureus</td>
<td></td>
</tr>
<tr>
<td>Lectins</td>
<td>Mφ, DC</td>
<td>Yeast</td>
<td>β-glucan</td>
</tr>
</tbody>
</table>

The Scavenger Receptor Superfamily

Elie Metchnikoff, 1845-1916

Phagosome-Lysosome Fusion?
Post-phagocytic Events: Phagosome-Lysosome Fusion

Phagocytosis of Bacteria is Followed by Phagosome-Lysosome Fusion


Granulomatous inflammation consists of epithelioid macrophages, giant cells, lymphocytes, plasma cells, and fibroblasts.

Epithelioid cells accumulate around the center of a granuloma. They get their name from the fact that they have pink cytoplasm similar to squamous epithelium.

Chronic Granulomatous Disease, an Inherited Defect of the NADPH Oxidase Complex


Granulomas

Langhans-type Giant Cells

Epithelioid Cells

Oxidant-dependent Killing of Bacteria and Fungi

QuickTime™ and a Cinepak decompressor are needed to see this picture.
Post-phagocytic Events: "Phagosome-Oxidase Fusion"

NADPH oxidase
Pathogen
Macrophage

$2O_2 \rightarrow 2O_2^\cdot + H^+$

Post-phagocytic Events: Generation of $H_2O_2$

NADPH oxidase
Pathogen
Macrophage

$2O_2 \rightarrow 2O_2^\cdot + H^+$

Superoxide dismutase

$O_2^\cdot + O_2^\cdot + 2H^+ \rightarrow H_2O_2 + O_2$

Post-phagocytic Events: Myeloperoxidase Activity

NADPH oxidase
Pathogen
Macrophage

$2O_2 \rightarrow 2O_2^\cdot + H^+$

Superoxide dismutase

$H_2O_2 + Cl^- \rightarrow HOCl + OH^-$

Peroxynitrite Production

NADPH oxidase
Pathogen
Macrophage

$2O_2 \rightarrow 2O_2^\cdot + H^+$

Superoxide dismutase

$H_2O_2 + Cl^- \rightarrow HOCl + OH^-$

$2O_2^\cdot + NO \rightarrow ONOO^-$

Bacterial Virulence Factors Subvert Host Defenses

Phagosome maturation stalled (M. tuberculosis; Legionella)
Ingestion phase impaired (Yersinia)
Resistance to lysosomal degradation (Salmonella)
Modification of phagocytic receptors (P. aeruginosa)
Escape from phagosome into cytosol (Listeria, Shigella)

Note: QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.
Epithelial Cells Express Defensins, Too

HD-5  \( \rightarrow \)  HBD-2  \( \rightarrow \)  H. pylori, untreated

HBD-1

HBD-2  \( \rightarrow \)  H. pylori, treated

HBD-2


The Relationship Between the Innate Immune Response and Acquired Immunity

Structural Similarity of a Chemokine and a Defensin

Chemokine CCL20  \( \rightarrow \)  β-Defensin BD2

β-pleated sheets are represented by green arrows; arginine and lysine residues are shown in blue

From: Perez-Canadillas et al., J. Biol. Chem. 2001 276:28372

The (Primary) Acquired Immune Response is Initiated by Innate Immune Recognition

The Role of Defensins in Orchestrating the Immune Response

Infected defenders. A model of defensins activity in an infected epithelium. Epithelial cells synthesize antimicrobial defensins both constitutively and in response to infectious and inflammatory stimuli. Other defensins are introduced by the influx of phagocytic cells that use them to kill ingested microbes. Released defensins attract dendritic cells and memory T cells, setting the stage for the adaptive phase of the immune response. From Ganz, Science 288:420, 1999.

Phagocytosis: Not Just for Bugs
Phagocytosis is the Principal Mechanism of Disposal of Apoptotic Corpses

Implications: Disposal of apoptotic corpses occurs continuously during the lifetime of an individual. In this setting, phagocytosis is not accompanied by inflammation, but rather by an anti-inflammatory signal (the production of TGF-β). As apoptotic corpses contain many potential self antigens, the lack of an appropriate anti-inflammatory signal has the potential to trigger autoimmunity.

Immunological Consequences of Phagocytosis

<table>
<thead>
<tr>
<th>Clearance of pathogens</th>
<th>Death of pathogenic microbe</th>
<th>Persistence of pathogenic microbe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution of infection</td>
<td>Failure of resolution of infection</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clearance of apoptotic corpses</th>
<th>Suppression of inflammation</th>
<th>Inappropriate inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolerance</td>
<td>Break in tolerance</td>
<td></td>
</tr>
</tbody>
</table>

Summary

1. Innate immunity represents the first-line of host defense. Its receptors are germline-encoded and recognize pathogen-associated “molecular patterns.”

2. Phagocytosis is a component of innate and acquired immunity. It is the principal means of destroying pathogenic bacteria and fungi. Phagocytosis initiates the process of antigen presentation.

3. Many phagocytic receptors recognize a diverse array of microbial pathogens. Some pathogens (e.g., S. pneumoniae) require opsonization for their clearance. However, bugs fight back.

4. Phagocytic leukocytes employ oxidative and non-oxidative means of killing. The NADPH oxidase generates reactive oxidants, such as superoxide anion and hypochlorous acid (bleach).

5. Innate immunity ushers in acquired immunity: innate immune activation of APCs results in up-regulation of co-stimulatory molecules and enhances the effectiveness of antigen presentation.

6. Phagocytosis is an essential component of development and tissue remodelling. Ingestion of apoptotic bodies is immunologically “silent” and is normally accompanied by a suppression of inflammation. Failure of this mechanism may result in autoimmunity.