INNATE IMMUNE RESPONSE

Micro 451

Presented By Dr. Nagwa Aref
TEACHING OBJECTIVES

• Understand the mechanisms of combating infection/disease
  • How does the body kill pathogens?
• To know the humoral and cellular components of the innate immune response
  • What are the key features and timing?
  • What is the mechanism of action of the components of the innate immune response?
OVERVIEW OF THE IMMUNE SYSTEM

Immune system

Innate (nonspecific)
1st line of defense
- Cellular components
- Humoral components

Adaptive (specific)
2nd line of defense
- Cellular components
- Humoral components
INNATE HOST DEFENSES AGAINST INFECTION

• Anatomical barriers
  • Mechanical, chemical, biological

• Humoral components
  • Complement, coagulation system, cytokines
  • Cellular components
  • Neutrophils, monocytes & macrophages, NK cells, eosinophils
# ANATOMICAL BARRIERS - MECHANICAL

<table>
<thead>
<tr>
<th>System/Organ</th>
<th>Cell type</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Squamous epithelium</td>
<td>Physical barrier Desquamation</td>
</tr>
<tr>
<td>Mucous membranes</td>
<td>Non-ciliated epithelium (e.g. GI tract)</td>
<td>Peristalsis</td>
</tr>
<tr>
<td></td>
<td>Ciliated epithelium (e.g. respiratory tract)</td>
<td>Mucociliary elevator</td>
</tr>
<tr>
<td></td>
<td>Epithelium (e.g. nasopharynx)</td>
<td>Flushing action of tears, saliva, mucus, urine</td>
</tr>
<tr>
<td>System/Organ</td>
<td>Component</td>
<td>Mechanism</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Skin</td>
<td>Sweat</td>
<td>Antimicrobial fatty acids</td>
</tr>
<tr>
<td>Mucous membranes</td>
<td>HCl (parietal cells), tears &amp; saliva</td>
<td>Low pH</td>
</tr>
<tr>
<td></td>
<td>Defensins (respiratory &amp; GI tract)</td>
<td>Lysozyme &amp; phospholipase A</td>
</tr>
<tr>
<td></td>
<td>Surfactants (lung)</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Opsonin</td>
</tr>
</tbody>
</table>
# Anatomical Barriers - Biological

<table>
<thead>
<tr>
<th>System/Organ</th>
<th>Component</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and mucous membranes</td>
<td>Normal flora</td>
<td>Antimicrobial substances</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Competition for nutrients and colonization</td>
</tr>
</tbody>
</table>
## HUMORAL COMPONENTS

<table>
<thead>
<tr>
<th>Component</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complement</td>
<td>Lysis of bacteria and some viruses</td>
</tr>
<tr>
<td></td>
<td>Opsonin</td>
</tr>
<tr>
<td></td>
<td>Increase in vascular permeability</td>
</tr>
<tr>
<td></td>
<td>Recruitment and activation of phagocytic cells</td>
</tr>
<tr>
<td>Coagulation system</td>
<td>Increase vascular permeability</td>
</tr>
<tr>
<td></td>
<td>Recruitment of phagocytic cells</td>
</tr>
<tr>
<td></td>
<td>B-lysin from platelets – a cationic detergent</td>
</tr>
<tr>
<td>Lactoferrin and transferrin</td>
<td>Compete with bacteria for iron</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Breaks down bacterial cells walls</td>
</tr>
<tr>
<td>Cytokines</td>
<td>Various effects</td>
</tr>
</tbody>
</table>
CELLS OF THE IMMUNE SYSTEM

Immune system

Myeloid cells
- Granulocytic
  - Neutrophils
  - Basophils
  - Eosinophils
- Monocytic
  - Macrophages
  - Kupffer cells
  - Dendritic cells

Lymphoid cells
- T cells
  - Helper cells
  - Suppressor cells
  - Cytotoxic cells
- B cells
  - Plasma cells
- NK cells
<table>
<thead>
<tr>
<th>Cell</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>Phagocytosis and intracellular killing</td>
</tr>
<tr>
<td></td>
<td>Inflammation and tissue damage</td>
</tr>
<tr>
<td>Macrophages</td>
<td>Phagocytosis and intracellular killing</td>
</tr>
<tr>
<td></td>
<td>Extracellular killing of infected or altered self targets</td>
</tr>
<tr>
<td></td>
<td>Tissue repair</td>
</tr>
<tr>
<td></td>
<td>Antigen presentation for specific immune response</td>
</tr>
<tr>
<td>NK and LAK cells</td>
<td>Killing of virus-infected and altered self targets</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>Killing of certain parasites</td>
</tr>
</tbody>
</table>
PHAGOCYTOSIS AND INTRACELLULAR KILLING

Neutrophils and Macrophages
PHAGOCYTE RESPONSE TO INFECTION

• The SOS signals
  – N-formyl methionine-containing peptides
  – Clotting system peptides
  – Complement products
  – Cytokines released by tissue macrophages

• Phagocyte response
  – Vascular adherence
  – Diapedesis
  – Chemotaxis
  – Activation
  – Phagocytosis and killing

Source: SOM PathMicro online textbook
PHAGOCYTOSIS

A. Attachment via receptors
   - FcR, complement R, scavenger R, Toll-like R

B. Pseudopod extension

C. Phagosome formation

D. Granule fusion and Phagolysosome formation
# Respiratory Burst

**O₂-dependent MPO-independent reactions**

<table>
<thead>
<tr>
<th>Glucose + NADP⁺</th>
<th>G-6-P-dehydrogenase</th>
<th>Pentose-P + NADPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>NADPH + O₂</td>
<td>NADPH oxidase</td>
<td>NADP⁺ + O₂</td>
</tr>
<tr>
<td>2O₂⁻ + 2H⁺</td>
<td>Superoxide dismutase</td>
<td>H₂O₂ + ¹⁰₂</td>
</tr>
<tr>
<td>2O₂⁻ + H₂O₂</td>
<td></td>
<td>OH⁺ + OH⁻ + ¹⁰₂</td>
</tr>
</tbody>
</table>

Toxic compounds: superoxide anion O₂⁻, hydrogen peroxide H₂O₂, singlet oxygen ¹⁰₂, hydroxyl radical OH⁺
RESPIRATORY BURST

O$_2$-dependent MPO-dependent reactions

\[
\begin{align*}
\text{H}_2\text{O}_2 + \text{Cl}^- & \xrightarrow{\text{myeloperoxidase}} \text{OCl}^- + \text{H}_2\text{O} \\
2\text{OCl}^- + \text{H}_2\text{O} & \xrightarrow{} \text{O}_2^1 + \text{Cl}^- + \text{H}_2\text{O}
\end{align*}
\]

Toxic compounds: hypochlorous acid OCl$^-$, singlet oxygen O$_2^1$
### RESPIRATORY BURST

Detoxification reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Catalyst</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>$O_2^- + 2H^+$</td>
<td>Superoxide dismutase</td>
<td>$H_2O_2 + O_2$</td>
</tr>
<tr>
<td>$2H_2O_2$</td>
<td>Catalase</td>
<td>$H_2O + O_2$</td>
</tr>
</tbody>
</table>
# O$_2$-INDEPENDENT KILLING

<table>
<thead>
<tr>
<th>Effector molecule</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cationic proteins (cathepsin)</td>
<td>Damage to microbial membranes</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Hydrolyses mucopeptides in the cell wall</td>
</tr>
<tr>
<td>Lactoferrin</td>
<td>Deprives pathogens of iron</td>
</tr>
<tr>
<td>Hydrolytic enzymes (proteases)</td>
<td>Digests killed organisms</td>
</tr>
</tbody>
</table>
SUMMARY OF INTRACELLULAR KILLING PATHWAYS

- Intracellular killing
  - \( O_2 \) dependent
  - \( O_2 \) independent
    - Myleoperoxidase dependent
    - Myleoperoxidase independent
NITRIC OXIDE-DEPENDENT KILLING

- Bacteria binds to macrophage
- Production of TNF-alpha
- Upregulates iNOS
- Release of NO
- NO is toxic to infected cells in vicinity of macrophage

$\text{IFN-\gamma} \rightarrow \text{TNF} \rightarrow \text{NO synthetase}$  

$\text{O}_2 + \text{L-arginine} \rightarrow \text{NO} + \text{citrulline}$  

Macrophage
NON-SPECIFIC KILLER CELLS

NK cells
Eosinophils
Mast cells
INNATE RESPONSE TO VIRUS INFECTION AND ALTERED SELF

- Infected or altered self (transformed) cell down regulated MHC
- NK does not receive inhibitory signal
- Signals kill infected cell
INNATE RESPONSE TO EXTRACELLULAR MICROORGANISMS (PARASITES)

- Activated eosinophils release granule components
  - Major basic protein
    - Major component of granules
  - Eosinophil peroxidase
    - Cationic hemoprotein
  - Eosinophil cationic protein
    - Ribonuclease
DETERMINANTS RECOGNIZED BY THE INNATE IMMUNE RESPONSE

- PAMPs- pathogen associated molecular patterns
- PRRs- pattern recognition receptors
PATHOGEN-ASSOCIATED MOLECULAR PATTERNS (PAMPS)

- Non-specific (not antigen specific) receptor recognition
- Part of innate antimicrobial defense
- Toll-like receptors on macrophages bind pathogen and cause activation
DETERMINANTS RECOGNIZED BY THE INNATE IMMUNE SYSTEM

Opsonization: complement activation
- PAMP = microbial cell wall
  - PRR = complement
- PAMP = mannose-containing carbs
  - PRR = mannose-binding protein

Production of IFN (antiviral)
- PAMP = dsRNA
  - PRR = TLR3
- PAMP = U-rich ssRNA (viral)
  - PRR = TLR7

Macrophage activation; secretion of inflammatory cytokines
- PAMP = LPS
  - PRR = TLR4
- PAMP = flagellin
  - PRR = TLR5
- PAMP = CpG containing DNA
  - PRR = TLR9

Phagocytosis
- PAMP = polyanions
  - PRR = scavenger receptors
IMMUNE RESPONSE TO DAMAGE

- Dependent on what, where and how bad
- Phased response with critical timing
  - Requires chemokine signaling, receptor binding, etc

Days: 0 4 7
Weeks: 2 4 6