M1 - Immunology, Winter 2008

Fantone, J.; Pietropaolo, M. T.

http://hdl.handle.net/2027.42/64939
Unless otherwise noted, the content of this course material is licensed under a Creative Commons Attribution - Non-Commercial - Share Alike 3.0 License.

Copyright 2008, Joseph Fantone.

The following information is intended to inform and educate and is not a tool for self-diagnosis or a replacement for medical evaluation, advice, diagnosis or treatment by a healthcare professional. You should speak to your physician or make an appointment to be seen if you have questions or concerns about this information or your medical condition. You assume all responsibility for use and potential liability associated with any use of the material.

Material contains copyrighted content, used in accordance with U.S. law. Copyright holders of content included in this material should contact open.michigan@umich.edu with any questions, corrections, or clarifications regarding the use of content. The Regents of the University of Michigan do not license the use of third party content posted to this site unless such a license is specifically granted in connection with particular content objects. Users of content are responsible for their compliance with applicable law. Mention of specific products in this recording solely represents the opinion of the speaker and does not represent an endorsement by the University of Michigan.

Viewer discretion advised: Material may contain medical images that may be disturbing to some viewers.
Phagocytic Cells: Mechanisms of Bacterial Killing and Tissue Injury

J. Fantone, M.D.
2/12/08
9:00-10:00am
Phagocytic Cells: Mechanisms of Bacterial Killing and Tissue Injury

• Learning Outcomes:
  – To understand the pathophysiologic role of phagocytic cells in host defense.
  – To understand the role of reactive oxygen metabolites and lysosomal granules in phagocytic cell function.
Phagocytic Cells

- Peripheral Blood Leukocytes (nrml. 4.5-11,000 cells/ul)
  - Lymphocytes (~ 30%)
  - Granulocytes (~ 70%)
- Granulocytes:
  - **Neutrophils** (~ 60% of total leukocytes in blood)
  - Eosinophils (~ 3%)
  - Basophils (<1%, rare)
  - **Monocytes** (~ 6%)
  - **Monocytes** → **Macrophages** (tissues)
- Kupffer cells (lining liver sinusoids)
Peripheral Blood Smear

Neutrophil

Lymphocyte

Source: Undetermined
Lymphocyte

Platelets

Source: Undetermined
Neutrophil

Source: Undetermined
Monocyte

Source: Undetermined
Neutrophils and Macrophages

• Function:
  – Ingest foreign material
  – Kill bacteria and other microbes
  – Degrade necrotic tissue and foreign antigens

• Tissue damage during prolonged inflammation
Neutrophil Recruitment

Selectins/Addressins → $\beta_2$-Integrin/ICAM-1

flow → rolling → adhesion → transmigration

Tissue Injury (e.g. Bacterial infection)

Endothelium

- inflammatory mediators
  - chemoattractant (e.g. IL-8, C5a)
  - phagocytosis
  - oxidant production
  - lysosomal granules

RAW TEXT_START
Neutrophil Recruitment

Selectins/Addressins → $\beta_2$-Integrin/ICAM-1

flow → rolling → adhesion → transmigration

Tissue Injury (e.g. Bacterial infection)

Endothelium

- inflammatory mediators
  - chemoattractant (e.g. IL-8, C5a)
  - phagocytosis
  - oxidant production
  - lysosomal granules

RAW TEXT_END
Phagocytic Cell Activation: Chemotactic Factors

Other receptors:
- Toll-like receptor
- Mannose receptor
Phagocytic Cell Functional Responses

- Adhesion (localization)
- Chemotaxis (migration)
- Phagocytosis
- NADPH oxidase activation
- Lysosomal granule fusion: degranulation
Opsonization and Phagocytosis

- Fc receptors for antibody
- Complement receptors: (e.g. C3b)
- Other
  - receptors for collectins (e.g. mannose-binding protein)
NEUTROPHIL PHAGOCYTOSIS OF OPSONIZED BACTERIA

Source: Undetermined
cell phagocytosis

Oxygen radicals

Elastase
Collagenase
Acid hydrolases

Source: Undetermined
Respiratory Burst: NADPH Oxidase

![Graph showing oxygen levels over time with a stimulus added. The graph compares normal and patient conditions.]
Reactive Oxygen Metabolites

Superoxide anion: $O_2^-$

$O_2 + e^- \rightarrow O_2^-$

Hydrogen peroxide: $H_2O_2$

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

Hydroxyl radical: $OH^.$

$H_2O_2 + Fe^{2+} \rightarrow OH^• + OH^- + Fe^{3+}$

Hypochlorous acid: $HOCl$

$H_2O_2 \xrightarrow{MPO} HOCl + OH^-$

myeloperoxidase = MPO

Chronic Granulomatous Disease of Childhood (CGD): deficiency of NADPH Oxidase
Nitric Oxide (NO •) Synthase

L-arginine → NO • → hydroxyl radical peroxynitrites

- Endothelial cell
- Macrophages (inducible): intracellular cytotoxic agent
- Nervous system
Oxidant Targets

a) unsaturated lipids: lipid peroxidation
   \[ \text{LOOH} = \text{lipid hydroperoxides} \]

c) proteins
   - sulfhydryl groups
   - methionine
   - tyrosine

d) nucleic acids
Degranulation

- **Bactericidal proteins** (e.g. defensins)
- **Proteases**
  - serine proteases (e.g. elastase)
  - metalloproteinases (e.g. collagenase, gelatinase)
- **Acid hydrolases**
Oxidants
Proteases

Anti-oxidants
Anti-proteases
Protective Mechanisms

Anti-oxidant: specific vs. non-specific

Specific enzymes:

Superoxide dismutase: \[ 2\text{O}_2^- + 2\text{H}^+ \rightarrow \text{H}_2\text{O}_2 + \text{O}_2 \]

Catalase: \[ 2\text{H}_2\text{O}_2 \rightarrow 2\text{H}_2\text{O} + \text{O}_2 \]

Glutathione peroxidase: \[ \text{H}_2\text{O}_2 + 2\text{GSH} \rightarrow 2\text{H}_2\text{O} + \text{GSSG} \]

\[ \text{LOOH} + 2\text{GSH} \rightarrow \text{H}_2\text{O} + \text{LOH} + \text{GSSG} \]

LOOH = lipid hydroperoxides
GSH = reduced glutathione
GSSG = oxidized glutathione
Non-specific scavengers:

- Vitamin E
- Vitamin C
- Beta-carotene
Anti-proteases

- $\alpha$-1- anti-protease (anti-trypsin):
  - plasma protein
  - binds proteases including elastase
  - inactivated by oxidants
- $\alpha$-2- macroglobulin
  - plasma protein
  - binds proteases
- TIMPs: tissue inhibitors of metalloproteinases
  - cell derived
Synergism: Inactivation of alpha-1-Anti-trypsin

1. HOCl Dependent

PMNs → HOCl → a-1-antitrypsin (active)

2. Metalloproteinase Dependent

PMNs → Metalloproteinase (collagenase) → a-1-antitrypsin (active) → a-1-antitrypsin (inactive)
Case: A 3 year old boy is brought to the emergency department

- **CC:** a productive cough, fever (temp 102.1 C), and headache.
- **PEx:** healthy boy with rales present on auscultation of the left lower chest.
- **CxR:** intra-alveolar infiltrate in the left lower lobe.
- **Hx:** mother reports multiple episodes (approx. 5 per year) of recurrent bacterial infections including otitis media, sinusitis, pneumonia, and purulent skin lesions. These infections usually responded to antibiotic treatment.
List three different mechanisms that could account for this patient's increased susceptibility to bacterial infection:

1. __________________________________________________________________________

2. __________________________________________________________________________

3. __________________________________________________________________________
Neutrophil Recruitment

Selectins/Addressins $\rightarrow \beta_2$-Integrin/ICAM-1

flow $\rightarrow$ rolling $\rightarrow$ adhesion $\rightarrow$ transmigration

Inflammatory mediators

Tissue Injury (e.g. Bacterial infection)

Endothelium

Chemoattractant (e.g. IL-8, C5a)

- Phagocytosis
- Oxidant production
- Lysosomal granules
Different mechanisms that could account for this patients increased susceptibility to bacterial infection:

1. Lack of neutrophils: leukopenia
2. Defective neutrophil function
   - Adhesion / migration
   - Phagocytosis
   - Bacterial killing
3. Lack of chemoattractants: deficiency
4. Lack of opsoninization of bacteria
   - antibody deficiency / complement def.
Additional References:

Phagocytic Cells:
Parham, The Immune System (2nd ed.): pgs. 15-17, 202-209.