Lecture 5: Inflammation – Part A

Cytokines:
- TNFα (macrophage & mast cells)
- IL1 (macrophage)
- IL6 (macrophage)
- IL8 (macrophage)
- MIP1-β

Others:
- C3a, C5a
- Histamine (mast cell)
- Bradykinin

Overview of Response to Pathogens (Bacterial):
Stage 0: physical, mechanical, chemical barriers.
Stage 1:
- Pathogens contained by activity of resident macrophages via phagocytosis/receptor mediated endocytosis & respiratory burst.
- Aided by activation of the alternative complement pathway.
Stage 2 – Inflammation (local)
Induction:
- Detection of pathogen via receptors on macrophage, cytokines (IL-1, TNFα, IL-6, IL-8) released.
- Activation of complement.
- Tissue mast cells bind C3a, C5a, degranulate, releasing histamine.
- Tissue damage activates several protein factors, including bradykinin.

Major Features of Cytokines released by macrophages.

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<th>IL-6</th>
<th>TNF-α</th>
<th>IL-1</th>
<th>IL-8</th>
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<tbody>
<tr>
<td><strong>Local effects</strong></td>
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<td>i) Activates vascular endothelium (produce adhesion molecules, ICAM)</td>
<td>Activates vascular endothelium (IL-8 production)</td>
<td>i) Increases affinity of adhesion molecules on circulating neutrophils. ii) Chemotactic recruitment of neutrophils in tissue.</td>
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<td>i) Increases vascular permeability</td>
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<td>Fever, acute phase proteins</td>
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<td>IL-8 production</td>
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<td><strong>Long range</strong></td>
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Inflammatory Process:
- i) increase in endothelial permeability due to cytokines (TNFα), and histamine:
  - neutrophils enter infected site
  - complement proteins enter – intense activation of alternative pathway
- ii) modification of blood flow to region by bradykinin.
- ↑ vascular diameter → ↑ blood volume → ↓ blood velocity

- iii) modification of endothelium by cytokines, increase in adhesion molecules, allowing neutrophils to bind and cross endothelium.
Details of Neutrophil Recruitment/Activation

1. Ligands for adhesion molecules up-regulated on endothelial wall by TNF-α and IL-1.
2. IL-8 produced from activated endothelial cells due to IL-1.
3. IL-8 binding to neutrophil increase affinity of LFA. Neutrophil begins to roll on surface of endothelium. Interaction between integrin (LFA, lymphocyte function associated antigen) on neutrophil and ICAM (intracellular adhesion molecule) on endothelium increases and neutrophil stops.
4. Neutrophil crosses endothelium (diapedesis), secreted proteases to digest basement membrane.
5. Attracted to infected site by gradient of IL-8, C3a, C5a, N-formyl peptides.
6. Activated neutrophils release MIP-1β, (MIP= macrophage inflammatory protein), recruits additional neutrophils, and monocytes, to tissue.