Lecture 5: Inflammation – Part I

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>
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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.

↑ vessel 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, IL-8 is membrane bound.
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. Monocytes develop into macrophages.
Lecture 6 – Inflammation II, Innate Response to Viral Pathogens

Inflammation II – Acute and Systemic:

Stage 3 - Acute inflammatory response:
Liver releases a number of proteins, due to cytokines (IL6). These enter the infected site through the permeable endothelial wall:
- C-reactive protein, binds to phosphocholine on pathogens, activates classical complement pathway.
- Mannose binding lectin (MBL), binds to pathogens, activates lectin complement pathway.
- Blood clotting factors.
Induction of Fever, due to endocrine action of cytokines from activated macrophages (IL6).

Stage 4 – Systemic infection/septic shock: Mortality 30%

i) Pathogen enters blood, leading to activation of a large number of macrophages in liver and spleen.

ii) Release of large amounts of cytokines by macrophages causes rapid decrease in blood volume due to systemic increase in vascular permeability, leading to organ failure, death.

Summary of Cytokines and Histamine in the Inflammatory response

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