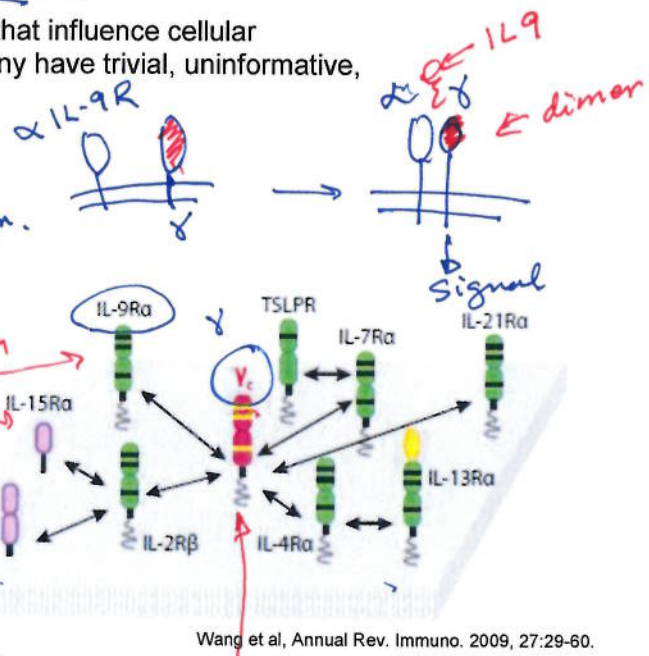
# Lecture 3: Cytokines & Inflammation

Suggested Reading: Chapter 2, 12.

## Cytokines (chemokines, lymphokines, interleukins [IL]):

Small glycoproteins secreted by immune and other cells that influence cellular behavior by facilitating communication between cells: Many have trivial, uninformative, names, e.g. TNFα – tissue necrosis factor α, IL-8, etc.
**Chemokines** – principle activity is chemotaxis.

**Key Cell Types:** $T_H$ cells, dendritic cells, macrophages



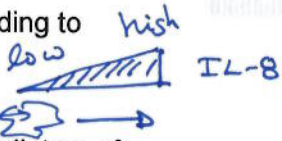

Wang et al, Annual Rev. Immuno. 2009, 27:29-60.

**Nomenclature of Cytokine Families:**

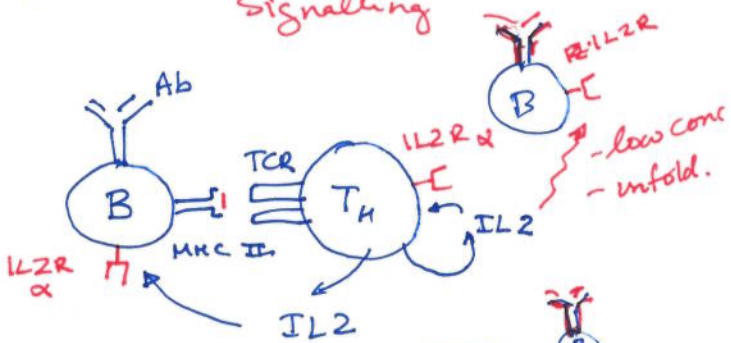

**Receptors**: Most cytokine receptors contain multiple chains:
1. one specific for the cytokine
2. one involved in signaling, often shared.

**Effects:**

1. Form concentration gradients leading to chemotaxis of cells (chemokines).

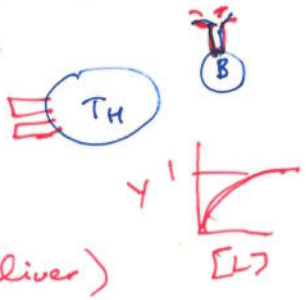



2. These are often very powerful mediators of cell function. Yet they are specific and avoid affecting cells (*innocent bystanders*) they shouldn't.

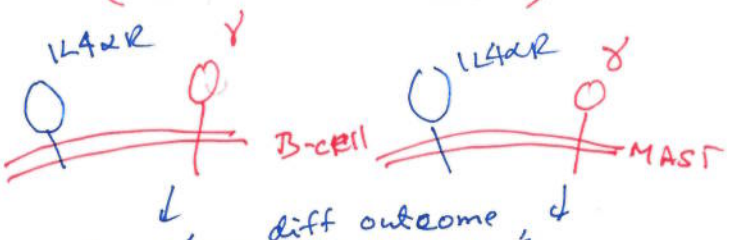



- induce production of receptor.
- low conc. away from the secreating cell
- cytokines are unstable

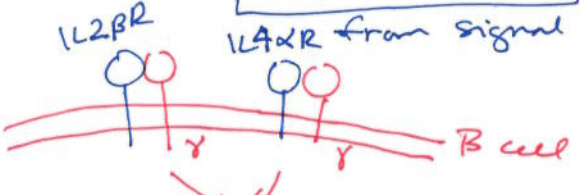
3. Show a wide range of action at a distance.
   1. autocrine — IL2 — $T_H$ → self stimulate
   2. paracrine — IL2 — $T_H$ → B
   3. endocrine — IL6 acts at distance. (infected site → liver)




4. Exhibit pleiotropy, one cytokine can have many different effects.
   IL-4 activates both B cells & Mast cells.

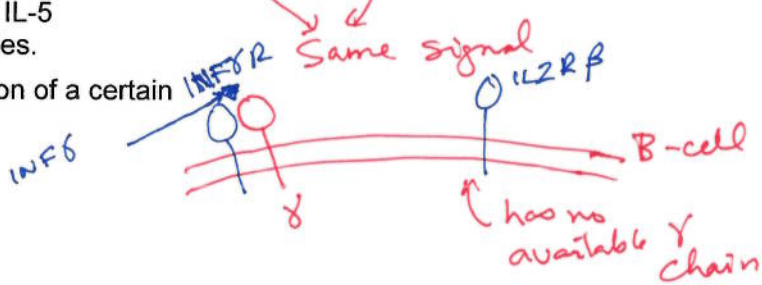



5. Redundant- different cytokines have same effect. IL-2 and IL-4 all activate B-cells.



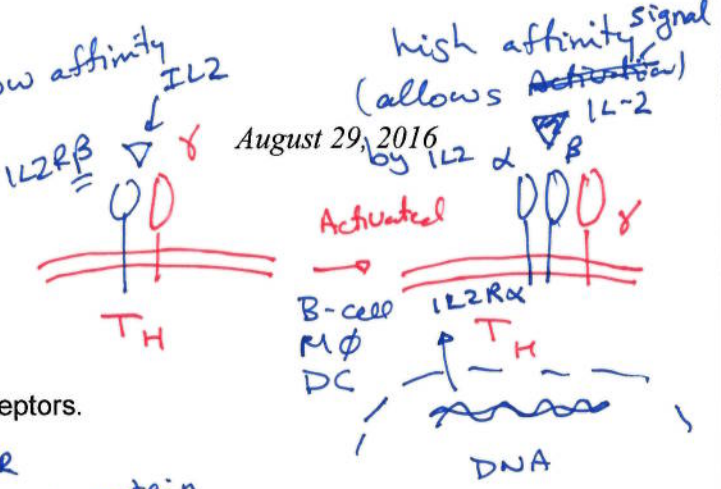

6. Synergistic – combination of IL-4 & IL-5 induce production of certain antibodies.

7. Antagonistic: INF-γ blocks production of a certain antibody type by B cells.



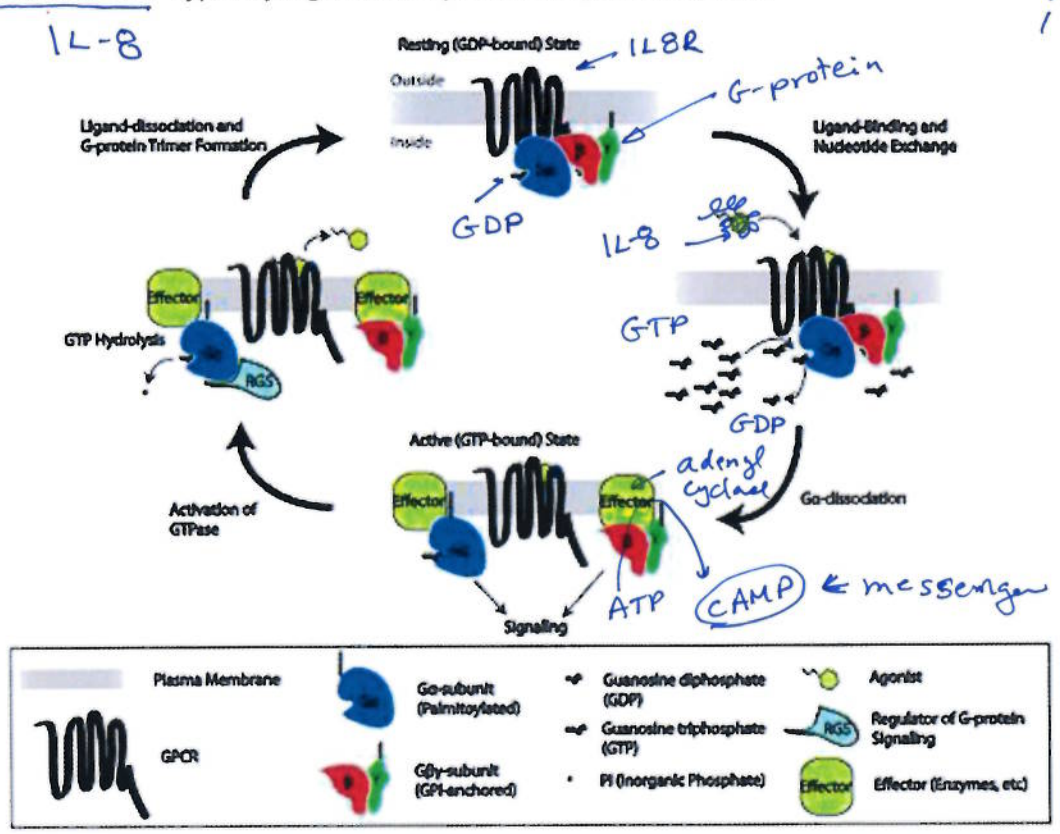
IL2

8. Receptors may contain different numbers of chains (IL2Rβγ, IL2Rαβγ), with different affinities that change due to cell activation or other signals.



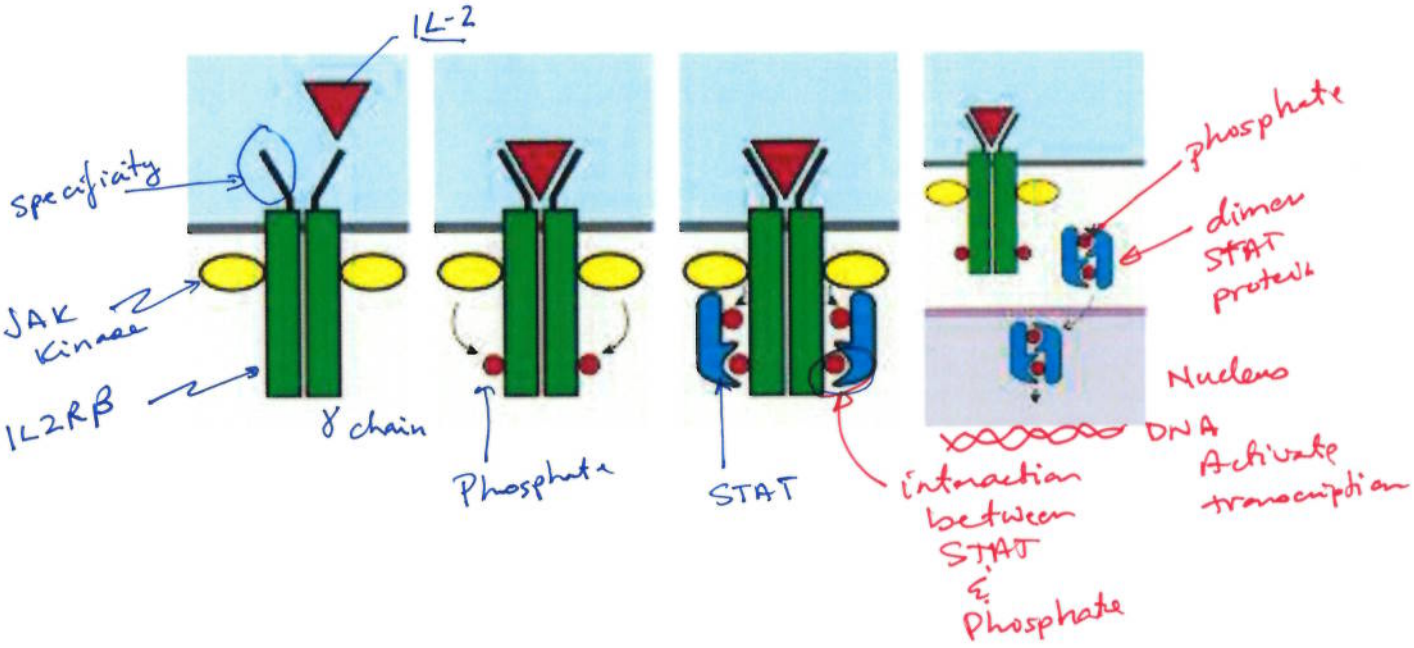

**Cytokine Signal Pathways:**

**Chemokines:** Typically signal via G-protein coupled receptors.



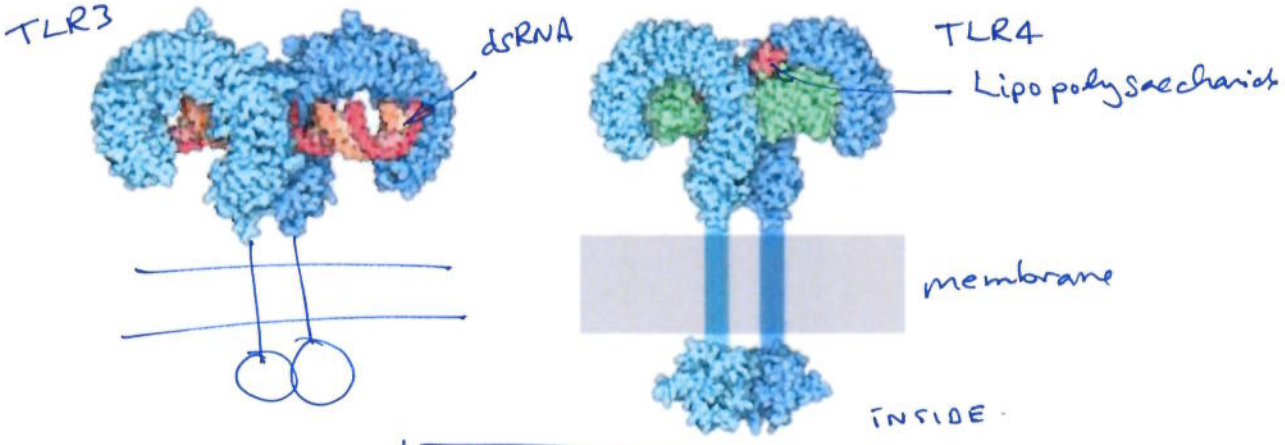

**Cytokines: Dimerization and activation of kinases (JAK/STAT)** IL-2

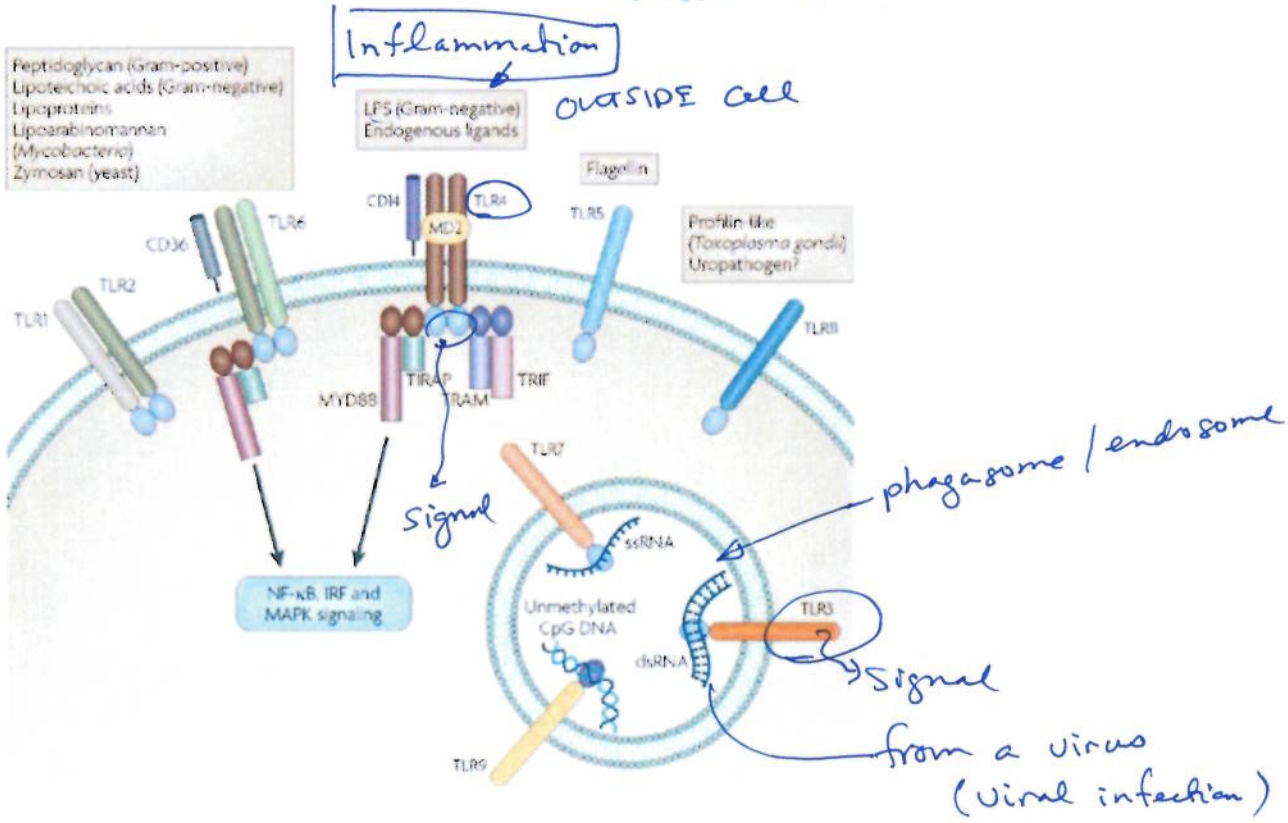
- JAK- Janus (two faced) kinase.
- STAT-signal transduction and activation of transcription (STAT 1-6)



**Toll-like receptors** (TLR) have specificity for components of pathogens. These components are additional examples of PAMPs (pathogen associated molecular patterns)

| Receptor | Ligand | Path. | Cell types | Location of receptor | Cytokines produced |
|---|---|---|---|---|---|
| **TLR3** | dsRNA | viruses | NK & others | Endosome | IFN-α, IFN-β |
| **TLR4** | Lipopoly-saccharide | bacteria | Macro-phage | Surface | TNFα + inflammatory cytokines. |

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# 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 local activation of the alternative complement pathway.

**Stage 2 – Inflammation** (local)

**Induction:**

a. Detection of pathogen via receptors on **macrophage** cytokines (IL-1, TNFα, IL-6, IL-8) released.
b. Activation of complement.
c. Tissue **mast cells** bind C3a, C5a, degranulate, releasing **histamine**.
d. Tissue damage activates several protein factors, including **bradykinin**.

⇒ Start inflammation
- redness
- swelling
- pain
- heat

**Major Features of Cytokines released by macrophages.**

| | IL-6 | TNF-α | IL-1 | IL-8 |
|---|---|---|---|---|
| **Local effects** | | i) Activates vascular endothelium (produce adhesion molecules, ICAM)<br>ii) Increases vascular permeability | Activates vascular endothelium (IL-8 production) | i) Increases affinity of adhesion molecules on circulating neutrophils.<br>ii) Chemotactic recruitment of neutrophils in tissue. |
| **Long range** | Acute phase proteins | | Fever | |

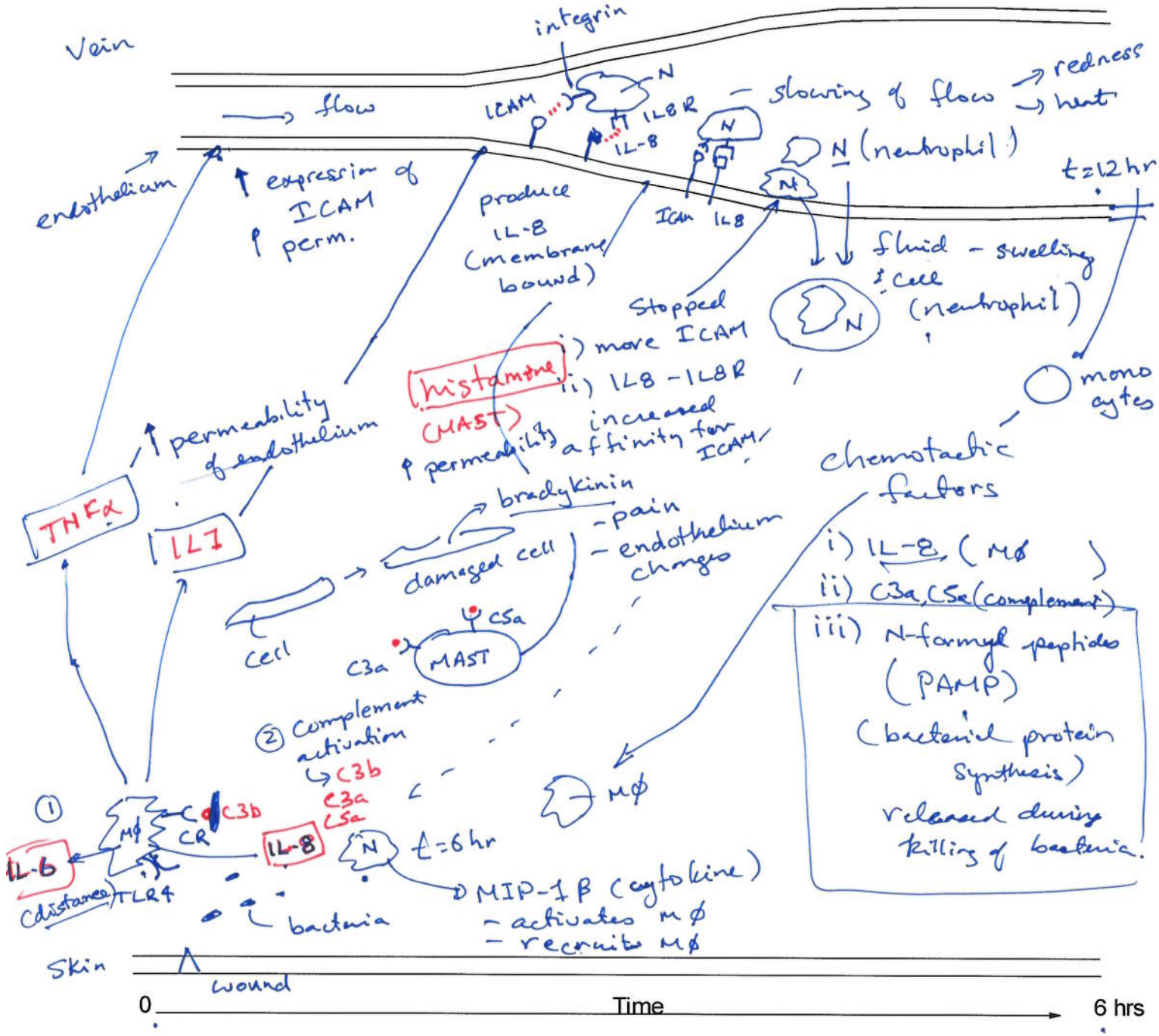
**Inflammatory Process:**

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**, 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.

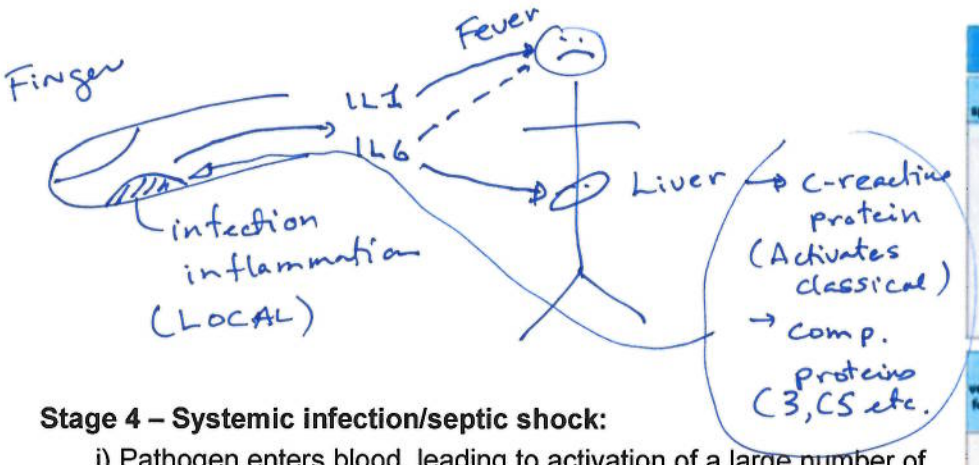
## Inflammation – Acute and Systemic:

### 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.

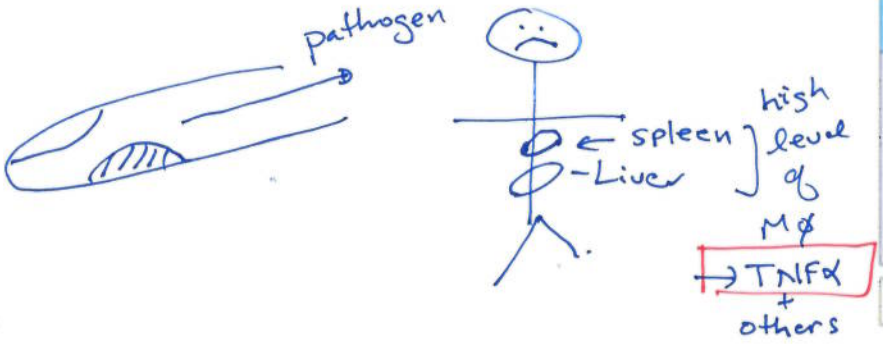
Induction of **Fever**, due to endocrine action of cytokines from activated macrophages (IL6).

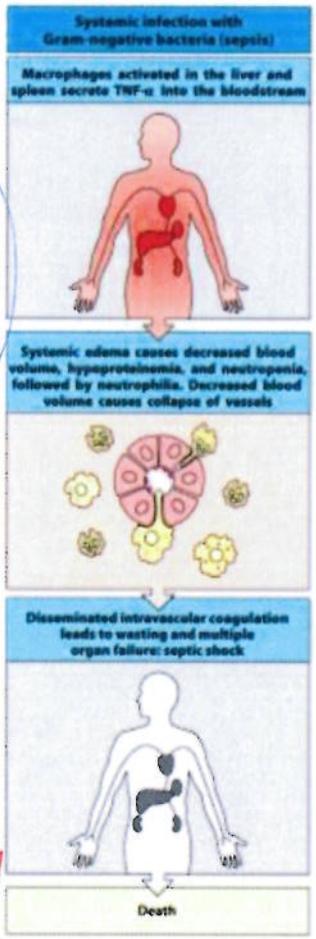



### Stage 4 – Systemic infection/septic shock:

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.

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### Summary of Cytokines and Histamine in the Inflammatory response

| Cytokine | ↑ vas. Permeab. | ↑ adhesion mol on endothel | IL-8 product. endothel | ↑ LFA affinity Neutroph. | Chemo-tractant - Neutroph. | Recruits macrophage | ↑ syn proteins liver | Fever |
|---|---|---|---|---|---|---|---|---|
| TNFα | ✓ | ✓ | | | | | | |
| IL-1 | | | ✓ | | | | | ✓✓ |
| IL-8 | | | | ✓ | ✓ | | | |
| MIP-1β | | | | | | ✓ | | |
| IL-6 | | | | | | | ✓ | ✓ |
| | | | | | | | | |
| Histamine | ✓ | | | | | | | |