Inflammation and Chemokines

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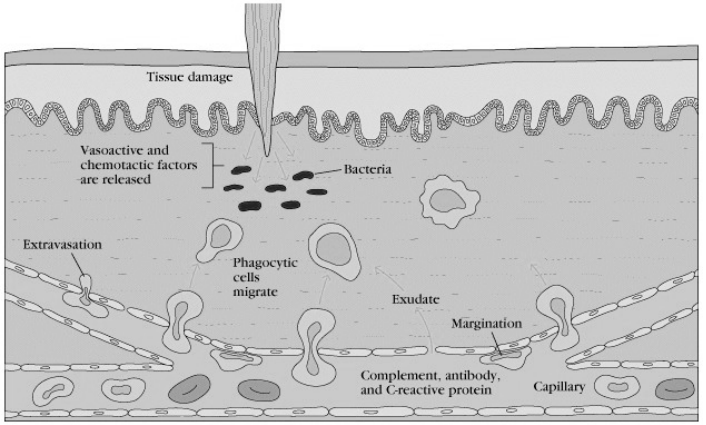
MCB150

Acute Inflammation

Redness Pain Swelling Heat

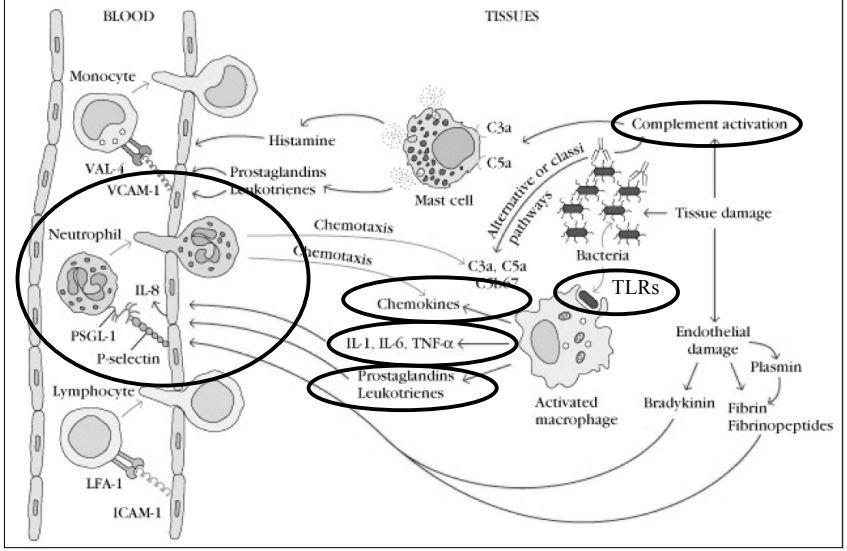


Triggered by tissue damage or presence of pathogens.

Initiation of Acute Inflammation

- Vasodilation
  - Increase in the diameter of blood vessels.
- Increased capillary permeability
  - Allows influx of fluid and cells into tissue.
- Influx of inflammatory cells
  - Increased permeability and more CAMs are induced by CKs to allow for neutrophil/ monocyte/ lymphocyte extravasation.

Inflammation



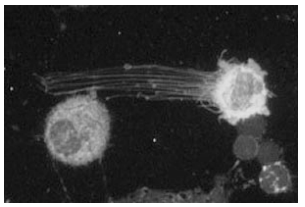
How do Pathogens directly initiate inflammation?

- Activation through recognition of invariant parts of pathogens (LPS, peptidoglycan, mannans, flagellin).
- Pathogen Associated Molecular Patterns (PAMPs) are invariant parts of pathogens.
- PAMPs (especially on bacteria) bind to pattern recognition receptors (PRRs) on macrophages and dendritic cells.

Activation of TLRs

Innate Differentiation of Self vs Nonself

- Produces cytokines/chemokines---> inflammation.
- Activation of APCs produces cytokines, increased MHC, and costimulatory molecules.



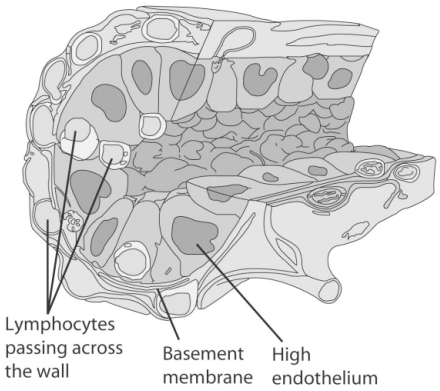
- Part of the "DANGER SIGNAL"

How do we get the immune cells to the lymph nodes or a site of infection?

High endothelial venules (HEVs) in LNs and spleen

Lymphocyte circulation is controlled by chemokines and

cell adhesion molecules (CAMs).



Schematic picture of HEV

Inflammed endothelial =high expression of CAMs

- "Inflammed" endothelial tissue is found in the blood vessels near the site of inflammation in tissue.
- CAM expression is different at site of inflammation than in HEV of lymph node.

Trafficking of Different T cell Populations

- Naive cells some CAMs primarily travel through to LNs.
- Activated Effector T cells have more CAMs and leave bloodstream for LNs and tissues.
- Memory T cells express specific adhesion molecules.

Cell Adhesion Molecules (CAMs)

4 families of CAMs

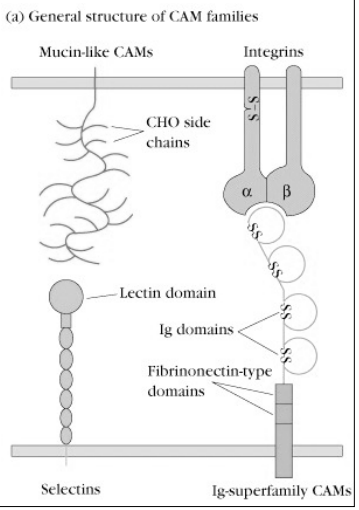
(b) Selected CAMs belonging to each family

Mucin-like CAMs:
- GlyCAM-1
- CD34
- PSGL-1
- MAdCAM-1

Selectins:
- L-selectin
- P-selectin
- E-selectin

Ig-superfamily CAMs:
- ICAM-1, -2, -3
- VCAM-1
- LFA-2 (CD2)
- LFA-3 (CD58)
- MAdCAM-1

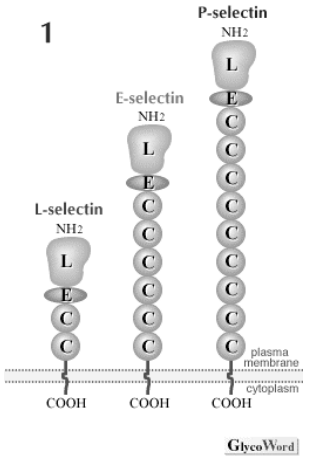
Integrins:
- α4β1 (VLA-4, LPAM-2)
- α4β7 (LPAM-1)
- α6β1 (VLA-6)
- αLβ2 (LFA-1)
- αMβ2 (Mac-1)
- αXβ2 (CR4, p150/95)



Selectins

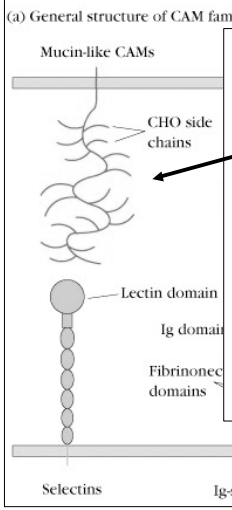
Bind to Mucin-like CAMs

- Have lectin domain which binds to CHO.
- Only 3 in family.
  - P-selectin found on endothelium.
  - E-selectin found on endothelium.
  - L-selectin expressed on neutrophils and lymphocytes.



Mucin-Like CAMs

Bind to Selectins

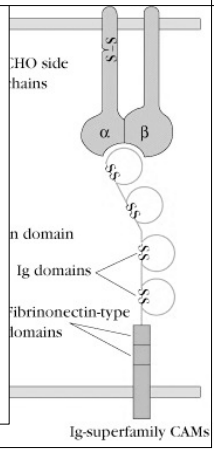


- CHO structures to bind lectins.
- Expressed on endothelium as signal for cells to exit bloodstream.
- EXAMPLES
  - GlyCAM-1 found on HEV.
  - MadCAM-1 mucosal endothelium.

Ig-superfamily binds Integrins

- Expressed on endothelium and APCs
- EXAMPLES
  ICAM-1, ICAM-2, ICAM-3
  LFA-2, LFA-3

- αβ chain heterodimers.
- ubiquitously expressed and provide tight binding.
- EXAMPLES
  LFA-1, α4β7



Chemokines

Chemokine = chemoattractant cytokine

- Four sub-types distinguished by positions of N-terminal cysteines: C, CC, CXC and CXXXC.
- Net positive charge leads to association with proteoglycans in tissues.
- Receptors are seven transmembrane domain G-protein coupled molecules.

Chemokines

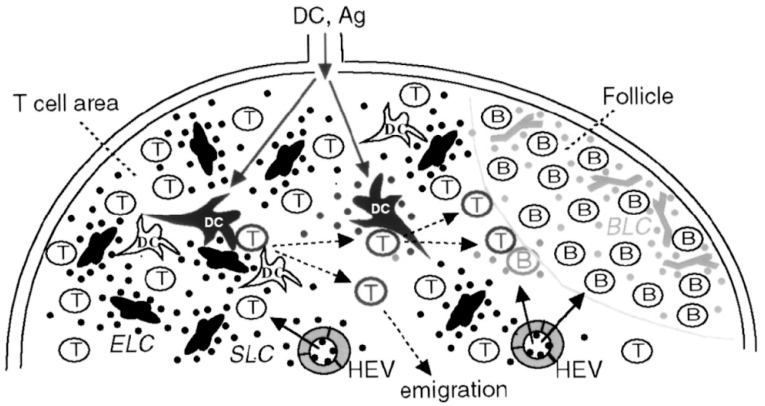
CXC SUBGROUP	
CXCR1	IL-8, GCP-2
CXCR2	IL-8, Gro-α, Gro-β, Gro-γ, NAP-2, ENA-78
CXCR3	IP-10, Mig, I-TAC
CXCR4	SDF-1, PBSF
CXCR5	BCA-1
CC SUBGROUP	
CCR1	MIP-1, RANTES, MCP-2, MIP-5
CCR2	MCP-1, MCP-2, MCP-3
CCR3	Eotaxin, RANTES, MCP-2, MCP-3, MCP-4, Eotaxin-2, MIP-5
CCR4	TARC, RANTES
CCR5	MIP-1α RANTES, MIP-1β
CCR6	Exodus-1
CCR7	ELC
CCR8	1-309
CCR10	MCP-1, MCP-2, MCP-3, RANTES

SOURCE: Adapted from Nelson and Krensky, 1998, *Curr. Opin. Immunol.* **10:**265, and Baggiolini, 1998, *Nature* **392:**565.

Chemokines and their receptors are very pleiotropic and redundant.

Important co-receptor for HIV infection.

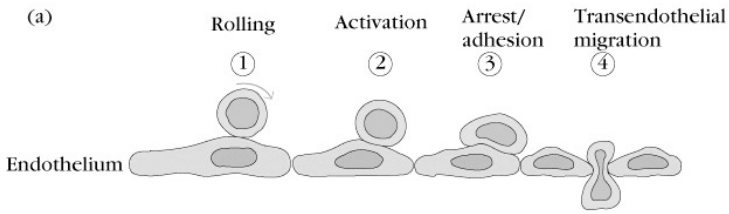
Selective expression of chemokines establish the architecture of the lymph node



Extravsation
Cells leaving the bloodstream

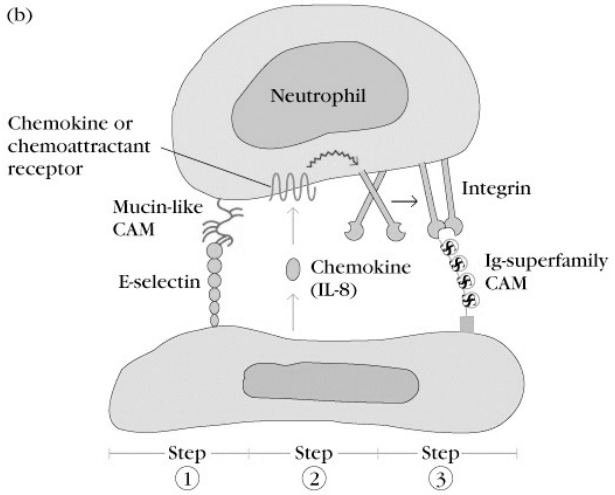
- Inflammatory mediators act on the endothelium to increase the expression of CAMs.
  - The cells must adhere strongly enough not to be swept away.
- HEV or inflamed endothelium express the right combination of **vascular addressins**
  - e.g. E, P, selectin. GlyCAM-1, ICAM 1,2,3. MadCAM1.

Neutrophil Extravasation

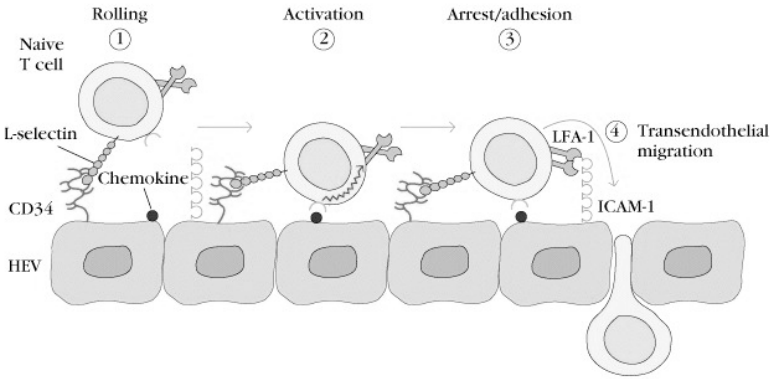


1. **Rolling and Tethering.** E-P selectin on endothelium bind to mucin-like on Neutrophils.
2. **Activation** of Neutrophils by chemokine (IL-8).
3. **Arrest/adhesion** from ICAMs on endothelium bind to integrins on neutrophils.
4. **Trans-endothelial migration** of Neutrophil from bloodstream to tissue.

Neutrophil Extravasation



T Cell Extravasation



Mediators of acute inflammation

Inflammatory cells

Neutrophils and macrophages

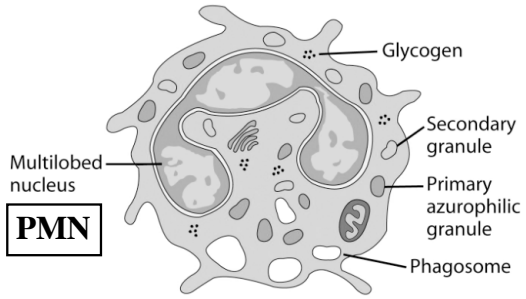
- These phagocytic cells scavenge and clean up area.
- Release mediators which kill pathogens.
- Activate immune system.

Mediators of acute inflammation

Role of Neutrophils

Short lived cells.
Chemoattractants : IL-8, C3a, C5a, lipid mediators.

Phagocytosis mostly opsonization with Fc Receptors.



(a) Neutrophil

Mediators of acute inflammation

Role of Neutrophils

Mediators released from Neutrophils

- Oxygen radicals.
- Enzymes: proteases, phospholipases, collagenases.
- Lysozyme splits the proteoglycan cell wall of bacteria.

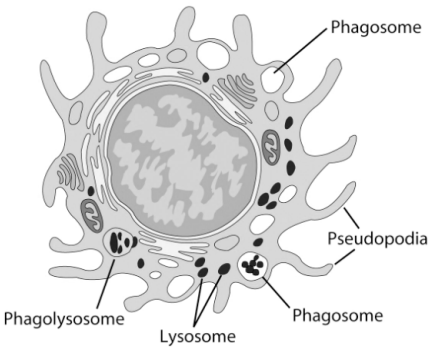
- These anti-microbial enzymes and reactive molecules are used inside in phagolysosomes. but can be released from granules to kill extracellular microorganisms and cause tissue damage.

Mediators of acute inflammation

Activated Macrophages

activated by antigen or cytokines
phagocytosis OR opsonization (binding through CRs and FcRs).

(b) Macrophage



- Produce oxygen radicals and enzymes for killing.
- Have increased antigen presentation and costimulation for T cell activation.

Activated macrophages

Secrete pro-inflammatory cytokines.

TABLE 2-7 Some factors secreted by activated macrophages

Factor	Function
Interleukin 1 (IL-1)	Promotes inflammatory responses and fever
Interleukin 6 (IL-6)	Promote innate immunity and elimination of pathogens
TNF-α	
Complement proteins	Promote inflammatory response and elimination of pathogens
Hydrolytic enzymes	Promote inflammatory response
Interferon alpha (IFN-α)	Activates cellular genes, resulting in the production of proteins that confer an antiviral state on the cell
Tumor necrosis factor (TNF-α)	Kills tumor cells
GM-CSF	Promote inducible hematopoiesis
G-CSF	
M-CSF	

Mediators of acute inflammation

Cytokines

Pro-inflammatory cytokines

- **IL-1, TNF-α, IL-6**. Primarily produced by activated macrophages.

Chemokines

- Responsible for chemotaxis and leukocyte localization.

Mediators of acute inflammation

Complement

By-products of complement activation.

C3a, C4a, and C5a activate inflammation.

C3a, C4a, and C5a are called anaphylatoxins for their ability to induce "anaphylaxis".

Mediators of acute inflammation

Plasma Enzyme Activators

Produced in response to blood vessel injury.

Kinin System

- Bradykinin causes vasodilation, C5--> C5a, C5b.

Clotting Factors

- Thrombin and Fibrin are part of clotting cascade but also activate inflammation.

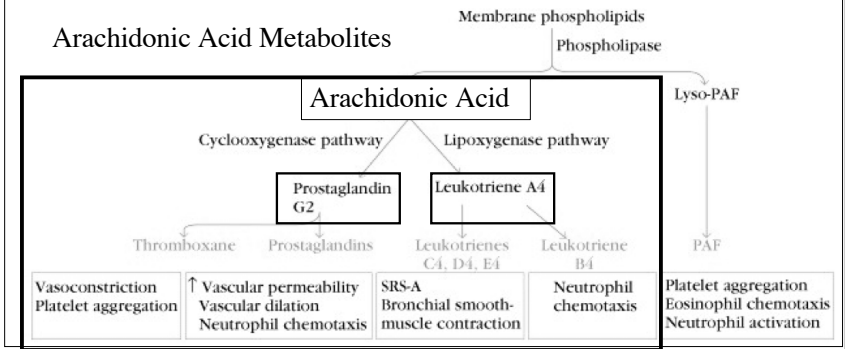
Mediators of acute inflammation

Lipid Inflammatory Mediators Produced

by inflammatory cells --macrophages and polymorphonuclear cells (PMNs).

Membrane phospholipids are cleaved into Platelet-Activating Factor (PAF) and Arachidonic Acid Metabolites
Prostaglandins and Leukotrienes

Arachidonic Acid Metabolites



Mediators of acute inflammation

Prostaglandins and Leukotrienes

Prostaglandins are products of Cyclooxygenase pathway

EXAMPLE Prostaglandin E2 (PGE2) activate neutrophils and cause increased vascular permeability

Leukotrienes are products of Lipoxygenase pathway

- LTA4 and LTB4 ---> Neutrophil chemotaxis.
- LTC4, D4, E4 --> bronchial smooth muscle contraction.

Anti-Inflammatory Agents

Steroids

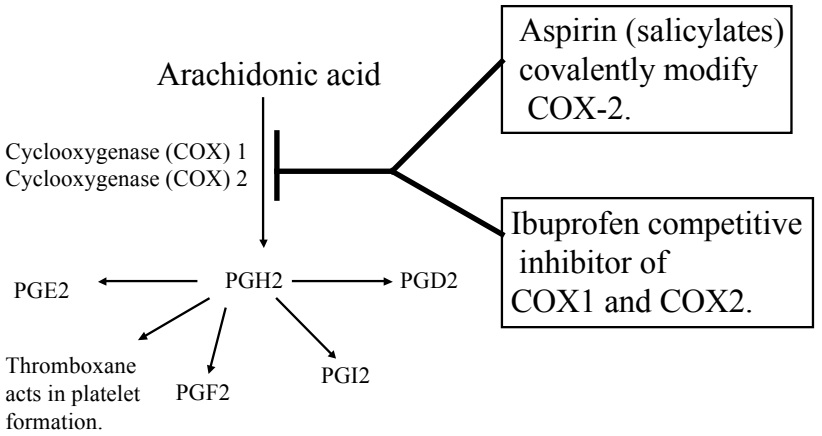
- Corticosteroids (e.g. Prednisone) mimic hormones with immunosuppressive effects.
- Prednisone increases production of IκB and inhibits NF-κB signaling.

Non-steroidal

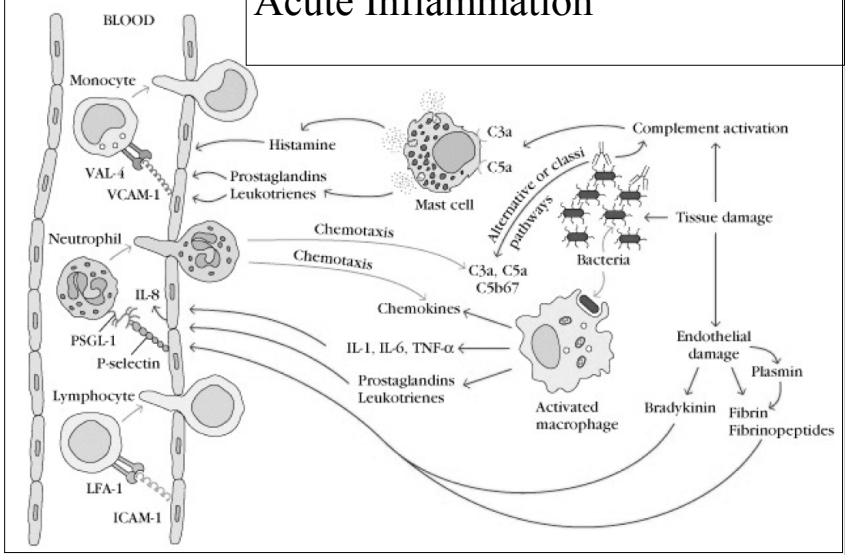
- Non-steroidal anti-inflammatory drugs (NSAIDS) block cyclooxygenase pathway and therefore production of prostaglandins.

Anti-inflammatories NSAIDS

Cyclooxygenase inhibitors



Many Different Mechanisms to Initiate Acute Inflammation



Class Details

- New article posted on website for section
- Problem set coming on Complement/Inflammation
- Beatty OH Thursdays 1-2

Outcome of Acute Inflammation

- Short term and local acute inflammation is beneficial to attract immune response, activate clotting mechanisms, and trigger tissue repair.
- Clearance of antigen by neutrophils and macrophages will limit inflammation.
- However, prolonged local activation or systemic inflammation will result in disease.

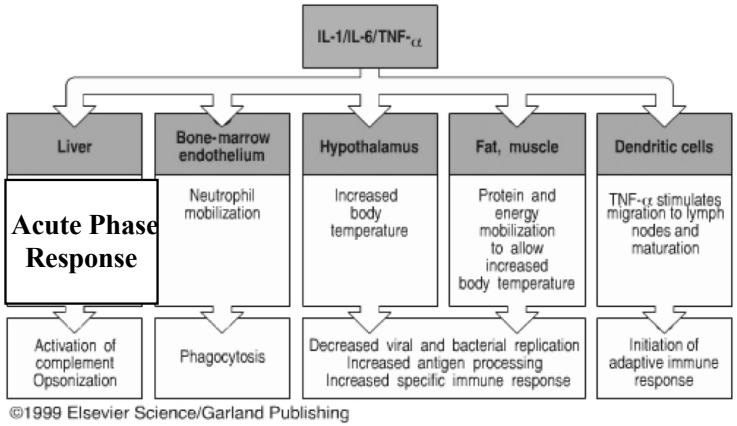
Systemic Acute Inflammation IL-1 IL-6, TNF-α

Large amounts of IL-1 IL-6, TNF-α can cause many disseminated effects.

Some good such as fever, increased metabolism.

Some bad such as in massive fluid loss and shock.

Systemic Acute Inflammation
IL-1 IL-6, TNF-α



Systemic Acute Inflammation
Acute Phase Response (APR)

APR is activated by IL-1 IL-6, TNF-α if:

- ◆localized inflammatory responses do not contain the injury or infection.
- ◆systemic activation of inflammation (through systemic infection or toxins).

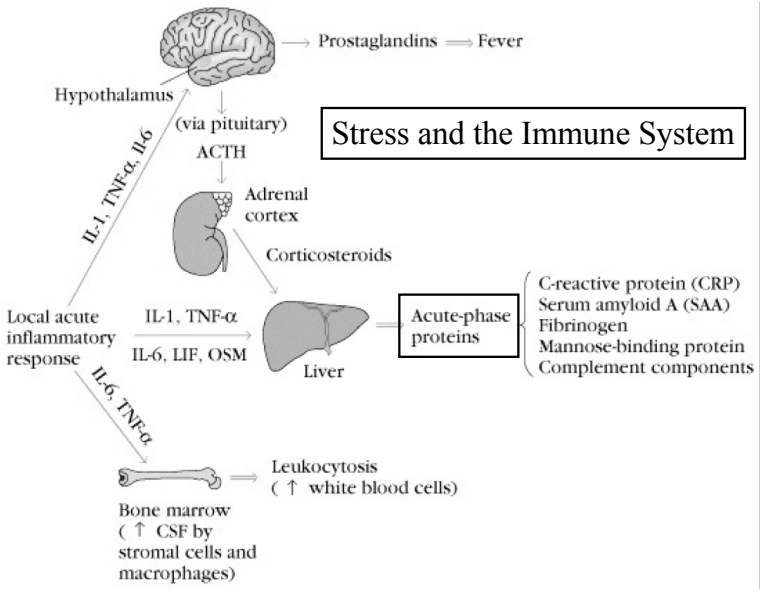
Acute Phase Response (APR)
Activation of Innate Immune Responses

Liver produces

Acute Phase Proteins

C-reactive protein, AP Complement proteins, fibrinogen, and others.

- ◆These proteins trigger increased complement activation, increased production of ACTH, steroids, fever etc.
- ◆Part of "stress response".



Stress and the Immune Response

Immune ⇄ Central Nervous System

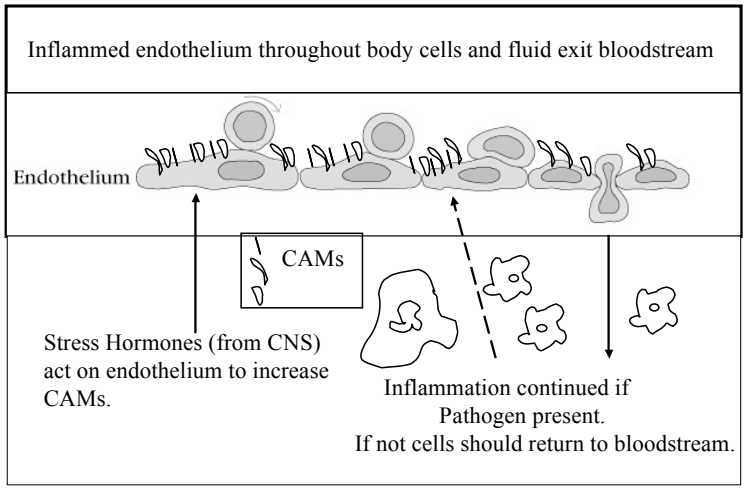
- CNS can activate APR in the liver.
  - IL-1, IL-6, TNF-α, Oncostatin-M, Leukemia inhibitory factor, produced by CNS can ALL activate production of acute phase proteins.
- Acute phase proteins and cytokines can activate hormonal pathways and CNS.

Effects of "Stress" on Immune Response

- Stress hormones (e.g. glucocorticoids) can be made by the CNS and have immunosuppressive effects (inhibit Th1).
- Stress hormones and cytokines made by CNS can act on endothelium to initiate inflammatory cascade.

Effects of "Stress" on Immune Response

"Systemic Inflammation"



Chronic Stress vs Chronic Inflammation

- Acute stress can activate acute inflammation.

"Chronic stress" = chronic acute inflammation
(can lead to activation of innate and suppression of adaptive).

- "Chronic inflammation" usually a result of adaptive immune response.
  - characterized by Th1 cells and macrophages making IFN-γ and TNF-α.

Adaptive Immune Responses Leading to Chronic Inflammation

- Infectious agent persisting.
- Autoimmunity.
- Cancer. Tissue damage or an adaptive immune response to tumor can result in chronic inflammation in area surrounding tumor.
- Delayed type hypersensitivity (DTH).