

## ACUTE AND CHRONIC INFLAMMATION

Reading: Basic Pathology, Chapter 2, pp 33-43.

Introduction: Inflammation is the local response to injury involving alterations in blood flow, extravasation of plasma constituents, and white cell exudation. The latter and the cells involved are described, as are several important examples of the inflammatory reaction.

- I. DEFINITION - The local, circulatory and exudative reaction bringing fluid and white blood cells to a site of injury in vascularized tissues.
  - A. A primitive response usually helpful in providing the basis for repair and combating infection, but can be harmful such as in immunological diseases.
  - B. Relationship to immune response - inflammation is a component of the non-specific immune response. The inflammatory and immune responses have many mechanisms in common. Also, chronic inflammation has an immune component. We must survive the first encounter. Immunity gives the system specificity.
  
- II. GENERALITIES. Celsus. 1st Cent. A.D.
  - A. Signs - heat, redness, swelling, pain, and loss of function.
    1. Heat and redness - vasodilation.
    2. Swelling - fluid exudation.
    3. Pain and loss of function - chemical mediators.
  - B. Phases
    1. Acute - short duration.
      - a. Fluid and plasma protein exudation. Edema.
      - b. Emigration of polymorphonuclear leukocytes (PMNs).
    2. Chronic - longer duration.
      - a. Lymphocytes and macrophages. Proliferation of small blood vessels and fibroblasts.
      - b. A mixed event - inflammation, immune response, healing, and repair all go on at once.
  - C. Causes - Whatever the cause, the character of the immediate reaction is the same; this implies a common genesis.
    1. Infectious agents
    2. Noxious chemicals and physical agents causing direct injury.
    3. Endogenous substances in excess, or in the wrong place. Examples: HCl and enzymes; metabolic breakdown products like uric acid; immune complexes
  
- III. PRINCIPAL EVENTS - Alteration in blood flow due to dilation of precapillary arterioles; Starling's law; permeability changes usually in venules causing exudation; release and activation of chemical mediators; and, white cell "events".
  - A. Blood flow - local vascular response. Changes in permeability induce exit into tissues of proteins, salts, etc.
    1. Arteriolar dilation with increased blood flow, but slow rate of flow (heat, redness). Precapillary sphincters.
    2. Increased permeability of venules due to open junctions allows passage of proteins into tissues(see Fig. 2-4 in Robbins for other possible mechanisms).
    3. Result - local edema (swelling).
    4. Types of extravasation. Under control of mediators:
      - a. Transudate - low protein. Sp. gravity $\leq$  1.02
      - b. Exudate - inflammatory fluid with proteins; sp. gravity  $>1.02$ ; quality and quantity of exudate depends on nature of response.
      - c. Purulent exudate - rich in protein and lysed+intact WBC.
  - B. Exudation of WBC - this is not the same as the mechanism for fluid exudation.
    1. Slowing and stasis of blood; loss of normal zonation (axial flow);

2. Margination of WBC, then migration through vascular wall leads to emigration into tissues.
  - a. Stickiness of WBC especially PMNs. Due to adhesion proteins on tissue and WBC.
  - b. Open junctions to allow passage of WBC from venules into tissue. Chemotactic activity.
  
3. Adhesion proteins - receptor & ligand pairs on leukocytes & endothelial cells that are induced or upregulated during inflammation (Fig. 1).

Adhesion proteins also play an important role in immune cell interactions.

- a. integrins, Ig superfamily, & selectins: selectins E, P, & L on leukocytes or endothelium provide first, loose adhesion; firmer bond by induction and activation of  $\beta_2$  integrins CD11 & CD18 on leukocytes and Ig family members on endothelium. Regulation by mediators.

Table 1. Common Leukocyte-Endothelial Cell Adhesion Molecules in Inflammation

Leukocyte Molecule	CD <sup>a</sup> and Integrin Nomenclature	Leukocytes Expressing <sup>b</sup>	Actions	Endothelial Cell Counter-Ligand	CD Nomenclature of Counter-Ligand
L-selectin	CD6i2L	PMN, Mo, T, B, NK	Tethering, rolling	Sialyl-Lewis <sup>x</sup> on appropriate ligand	CD34 others
PSGL-1	CD162	PMN, Mo, T, B, NK	Tethering, rolling	P-selectin	CD62P
ESL-1 and CLA <sup>c</sup> bearing sialyl Lewis <sup>x</sup>	CD15s	PMN, Mo, T, B, NK	Tethering, rolling	E-selectin	CD62E
VLA-4	CD49d/CD29 ( $\alpha_4\beta_1$ )	Mo, B, Eo > NK, T, (PMN) <sup>d</sup>	Tethering, rolling Tight adhesion	VCA ICAM-1M-1	CD CD1 CD54
LFA-1	CD11a/CD18 ( $\alpha_L\beta_2$ )	PMN, Mo, T, B, NK	Tight adhesion	ICAM-2	02106
Mac-1, CR3	CD11b/CD18 ( $\alpha_M\beta_2$ )	PMN, Mo, NK	Tight adhesion	ICAM-1	CD54
PECAM-1	CD31	PMN, Mo, NK, subsets of T cells	Diapedesis	PECAM-1	CD31
CD99	CD99	Mo, PMN, T, B, NK		CD99	CD99

PSGL-1, P-selectin glycoprotein 1; VLA-4, very late antigen 4; VCAM-1, vascular cell adhesion molecule 1; LFA-1, leukocyte function antigen-1; ICAM-1, -2, intercellular adhesion molecule-1, -2; CR3, complement receptor 3; PECAM-1, platelet/endothelial cell adhesion molecule-1. Adapted from (Hajjar et al, 2001) with permission from the publisher.

<sup>a</sup>CD, Cluster of differentiation, the number assigned to the antigen by the International Workshops on Leukocyte Typing, as defined by monoclonal antibody recognition.

<sup>b</sup> PMN, neutrophils; Mo, monocytes; T, T lymphocytes; B, B lymphocytes; NK, natural killer cells; Eo, eosinophils

<sup>c</sup> ESL-1, E-selectin ligand, a protein with homology to fibroblast growth factor, has been identified in mice. CLA, cutaneous lymphocyte antigen, a molecule on the surface of skin-homing T cells related to PSGL-1, directs them to skin venules via interactions with E-selectin. The CD number refers to the sialyl Lewis<sup>x</sup> carbohydrate moiety no matter what protein backbone it is expressed on.

<sup>d</sup> (PMN) Although PMN were not believed to express VLA-4, recent evidence suggests that this integrin may be expressed on or be induced on PMN under certain conditions.

4. Extravasation mechanisms depend on Ig proteins ICAM-1 & PECAM-1: signals; capture/rolling of cells; cell activation; cell flattening, then extravasation. These are regulated by chemokines and their receptors (CCR). Chemokines are specific for the various cells involved in inflammation; produced by WBC, endothelial, & tissues cells; they activate WBC integrins → firm adhesion to endothelium and extravasation. Note: Two CCRs (CXCR4 & CCR5) are HIV receptors.

C. Tissue damage (pain, loss of function).

1. From original stimulus
2. From host response

D. Repair - Capillaries, fibroblasts, and macrophages.

IV. INFLAMMATORY CELLS & OTHER IMPORTANT ELEMENTS. Activation by mediators resulting in proliferation and differentiation.

- A. PMNs: granules and multilobate nuclei; first cell to site in acute inflammation. Role of G-CSF, GM-CSF, IL-8, & chemokines in mobilizing polys.
1. Functions of PMNs:
    - a. Chemotaxis - due to ligand binding on surface G-protein coupled receptors, serpentine, that regulate adhesion, migration, degranulation, and the oxidative response of polys; ligand binding followed by PLC activation leading intracellular release of DAG & IP<sub>3</sub> and then calcium release. Latter responsible for actin contraction and unidirectional motion. Need activity of matrix metalloproteinases (MMPs) from polys to degrade matrix and allow motion.
    - b. Phagocytosis - recognition requires opsonins - complement factors C4b, C3b, & C5b plus IgG. These attach to receptors C3bi (on PMNs) or Mac-1 (macrophages). Engulfment of particles into phagocytic vesicles follows with subsequent fusion with lysosomes (phagolysosome formation). H<sub>2</sub>O<sub>2</sub> produced and pH drops in the phagolysosome facilitating antimicrobial activity.
    - c. Antimicrobial activity. Degranulation by exocytoses; lysis of infectious agents & cells. MPO, HOCl, ozone & hydrogen peroxidase play important roles. NADPH-derived oxidants give rise to superoxides and peroxides. These factors and matrix metalloproteinases (MMPs) may also cause tissue damage that often accompanies inflammation.
  2. Important factors in PMN:
    - a. Acid hydrolases - in azurophilic granules; degrade bacteria in phagolysosome; include MPO & proteases
    - b. Neutral proteases - help in cleaning up; may damage host; antiproteases.
    - c. Cationic proteins -- vascular permeability
- B. Monocytes and macrophages. Major role in chronic inflammation.
1. Primitive scavenger cells of body - engulf and digest foreign particles, proteins, etc. This involves receptors for carbohydrates not present on surface of vertebrate cells such as mannose.
  2. Part of mononuclear - phagocytic system. GM-CSF, M-CSF, IFN- $\gamma$ , & chemokines important in proliferation and activation of monocytes.
    - a. Specialize in phagocytosis and regulation of lymphocyte responses.
    - b. Activation - enlargement and increase in hydrolytic and lysosomal enzyme activity giving rise to increased antimicrobial and antitumor cell activity.
    - c. Consists of monocytes (blood), alveolar macrophages (lungs), epidermal Langerhans' cells, dermal dendritic cells, microglial cells (CNS), Kupffer cell (liver), lymphoid macrophages, etc
    - d. Can be activated by cytokines, especially interferons or by microbial products.
    - e. Macrophages themselves make monokines such as IL-1 and TNF that can that can modify the inflammatory and immune responses.
    - f. Phagocytosis - release of lysosomal enzymes, chemotactic and permeability factors, pyrogens, healing factors, antibacterial, and antiviral factors.
    - g. Fusion gives rise to multinucleated Langerhans or foreign body giant cells.
- C. Lymphocytes and plasma cells.
1. B lymphocytes and plasma cells - antibody formation.
  2. T lymphocytes - cellular immunity. Lymphokine production. Key cells in cell-mediated immunity - regulatory and effector cells.
  3. Late appearance in inflammation means onset of immune response. Role of interleukins.
  4. Lymphatics and lymph nodes - act as filters to clean and police body.
    - a. Enlarge with inflammation - lymphangitis, lymphadenitis.
    - b. Act as secondary line of defense in infections.

- D. Platelets - lack nucleus. Contain three types of granules rich in histamine, calcium, ADP, coagulation factors, platelet derived growth factor (PDGF) and thromboxane. Platelet adherence, aggregation, and degranulation are critical in inflammation, coagulation, & wound healing.
- E. Eosinophils. Coarse red (eosinophilic) granules rich in peroxidase.
  - 1. Most in tissue (400:1) - esp. resp. & GI tract.
  - 2. Motile and phagocytic.
  - 3. Appear late in allergic and IgE-mediated immune hypersensitivity responses and characteristic of parasitic diseases. Mobilized by IL-5, eotaxin (a chemokine), IL-3 & GM-CSF.
  - 4. Produce major basic protein (MBP) toxic to parasites and contributing to damage in allergic reactions. Also make cytokines, eosinophil-specific, and lipid inflammatory mediators.
- F. Basophiles (circulating) and mast cells (tissue). In lung (submucosal) and skin (dermal). Sentinel function. Mobilized by chemokines, IL-3, & IL-4.
  - 1. Large blue (basophilic) granules with histamine, PAF, and other chemical mediators.
  - 2. Receptors for IgE, a class of immunoglobulins
  - 3. Trauma, inflammation, antigens, or mediators of inflammation give rise to degranulation and release of histamine, PAF, eosinophil chemotactic factors, and leukotrienes (see next lecture).

V. TYPES OF INFLAMMATION (THESE ARE OFTEN MIXED).

- A. Acute Inflammation
  - 1. Serous and fibrinous - seen in a blister or an abrasion, or on visceral or parietal surfaces.
    - a. Pleuritis, pericarditis, peritonitis. Edema; protein and cells in exudate.
    - b. Often few cells, much fibrin giving rise to shaggy look friction rubs.
    - c. Organization. Fibrinous adhesions.
  - 2. Suppurative or purulent exudate - often seen in bacterial infections.
    - a. PMNs early; later, mononuclear cells.
      - i. Pneumonia - hyperemia, red consolidation, gray consolidation, resolution - complete or incomplete.
      - ii. Appendicitis - pain, nausea, fever. Collection of WBC in closed space or pus - abscess; perforation and purulent peritonitis. Diverticulitis.
      - iii. Furuncle (a zit) - abscess in skin behind blocked duct; importance of drainage.
      - iv. Meningitis - inflammation and edema of meninges; exudate in spinal fluid; increased pressure in a closed system; results are relief or death.
      - v. Abscess formation (examples: prostate, liver)
      - vi. Others - otitis media (middle ear), cholecystitis (gall bladder), diverticulitis (GI tract), salpingitis(oviduct), catarrh (snotty nose). Importance of obstruction.
  - 3. Some possible results of acute inflammation
    - a. complete resolution
    - b. abscess formation
    - c. healing with fibrous tissue replacement (scar)
    - d. chronic inflammation
- B. Chronic non-granulomatous inflammation - some acute inflammations shade off into chronic inflammations due to persistent infections or exposure to toxic agents, or to autoimmune reactions.
  - 1. Exudate - lymphocytes, plasma cells, macrophages, activated fibroblasts.
  - 2. Examples -
    - a. Bacterial endocarditis - infection on damaged heart surface. Chronic pyelonephritis
    - b. Vasculitis - chronic inflammation of vessels. Graft rejection.
  - c. Peptic ulcers - stomach & duodenum. Mixed response.

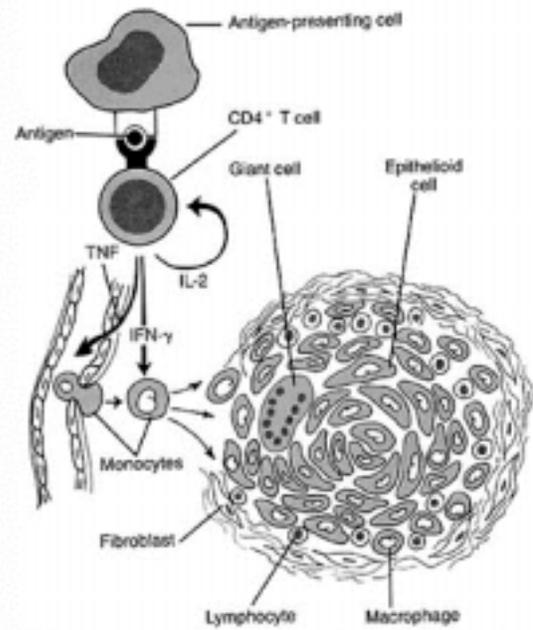
d. It is thought that atherosclerosis and even some forms of cancer may involve a chronic inflammatory process.

C. Chronic granulomatous inflammation or granulomas - can be diffuse or local (Fig. 2).

1. Distinct pattern of chronic inflammation evoked by certain agents or disease states. Strong immunological elements involving  $\text{TNF-}\alpha$ , IL-1, IL-2, &  $\text{IFN}\gamma$

2. They are 1-2 mm nodules with collections of activated macrophages or epithelioid cells and lymphocytes; may have central necrosis surrounded by epithelioid cells, lymphocytes, and giant cells, but necrosis and giant cells are not always present.

3. Example of diseases featuring granulomatous inflammation: tuberculosis, leprosy, syphilis, mycotic (fungal) and parasitic infections. Also sarcoidosis (cause unknown), foreign body granulomas such as silicosis or reaction to sutures, and some autoimmune diseases such as Crohn's disease.



D. Nature of response determined by character of causative agent, the tissue involved, and the immune response to it.

Summary: Inflammation is the major response involved in infectious, immunological, and other diseases, including arteriosclerosis and cancer. Many of the treatments you will employ regulate the inflammatory process.

<b><u>SOME IMPORTANT CYTOKINES</u></b>	
Interferons $\alpha, \beta, \gamma$	Antiviral and growth inhibitory substances; immunoregulators
Tumor necrosis factor (TNF- $\alpha$ ) and lymphotoxin(TNF- $\beta$ )	Growth regulation; cytotoxic for some cells; acute-phase response modifier; activates macrophages
IL-1 $\alpha$ and IL-1 $\beta$	Acute phase response modifiers; activates lymphocytes.
IL-2/IL-15	T-cell growth; B-cell growth & differentiation. IL-2 & 15 receptors on different cells
IL-3	Multipotential cell stimulation; mast cell growth.
IL-4/IL-13	B-, T-, mast & hematopoietic cell growth; stimul. of IgE production; inhib. macrophage cytotoxicity. Protective role in nematode infections.
IL-5	B-cell, T-cell and eosinophil differentiation; B-cell growth.
IL-6	B-cell immunoglobulin production and hepatocyte stimulation; acute phase response modifier; growth and differentiation of T-cells.
IL-7	Stimulate growth of bone marrow B-cell precursors; thymocytes, and mature T-cells; enhance generation of cytotoxic T-cells and lymphokine-activated killer cells (LAK).
IL-8	Neutrophil chemotaxis and activation; T-cell chemotaxis.
IL-9	Support growth of T helper cells, thymocytes, and mast cells; enhance generation of erythroid cells.
IL-10	Inhibition of IFN $\gamma$ production; stimulate mast cell growth; enhance B-cell survival; upregulate MHC II molecules; & inhib. macrophage cytotoxicity. B cell differentiation and class switching.
IL-11	Similar to IL-6, stimulate hematopoiesis and liver production of acute phase proteins; inhibit tissue injury.
IL-12	Stimulate IFN $\gamma$ production; drive TH-1 differentiation.
IL-16	Interacts with CD4 on T cells, chemotactic factor for CD4 and T cells, monocytes, and eosinophils; activation of CD4 + T cells.
IL-17	Produced by T cells, induces pro-inflammatory cytokines.
IL-18	IFN- $\gamma$ induction; role in TH-1 differentiation. Synergy with IL-12.
GM-CSF	Promotes poly, eosinophil and macrophage bone marrow colonies and maturation of mature polys.
G-CSF	Promotes poly growth.
M-CSF	Promotes macrophage growth.
Epidermal Growth Factor (EGF)	Epithelial growth
Fibroblast Growth Factor (FGF)	Fibroblast growth; angiogenic substances
Insulin-like Growth Factors (IGF)	Cell growth regulation
Nerve Growth Factors (NGF)	Nerve cell growth.
Platelet Derived Growth Factor (PDGF)	Similar to oncogene <i>sis</i> .
Transforming Growth Factors $\alpha$ & $\beta$ (TGF $\alpha$ & $\beta$ )	Cell growth regulation; wound healing; TGF- $\beta$ stimulates IgA production.

