Inflammation, Inflammatory Disorders, and Wound Healing

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INTRODUCTION

I. **INFLAMMATION**
   A. Allows inflammatory cells, plasma proteins (e.g., complement), and fluid to exit blood vessels and enter the interstitial space
   B. Divided into acute and chronic inflammation

ACUTE INFLAMMATION

I. **BASIC PRINCIPLES**
   A. Characterized by the presence of edema and neutrophils in tissue (Fig. 2.1A)
   B. Arises in response to infection (to eliminate pathogen) or tissue necrosis (to clear necrotic debris)
   C. Immediate response with limited specificity (innate immunity)

II. **MEDIATORS OF ACUTE INFLAMMATION**
   A. Toll-like receptors (TLRs)
      1. Present on cells of the innate immune system (e.g., macrophages and dendritic cells)
      2. Activated by pathogen-associated molecular patterns (PAMPs) that are commonly shared by microbes
         i. CD14 (a TLR) on macrophages recognizes lipopolysaccharide (a PAMP) on the outer membrane of gram-negative bacteria.
      3. TLR activation results in upregulation of NF-κB, a nuclear transcription factor that activates immune response genes leading to production of multiple immune mediators.
      4. TLRs are also present on cells of adaptive immunity (e.g., lymphocytes) and, hence, play an important role in mediating chronic inflammation.
   B. Arachidonic acid (AA) metabolites
      1. AA is released from the phospholipid cell membrane by phospholipase A_2 and then acted upon by cyclooxygenase or 5-lipoxygenase.
         i. Cyclooxygenase produces prostaglandins (PG).
            a. PGI_2, PGD_2, and PGE_2 mediate vasodilation and increased vascular permeability.
            b. PGE_2 also mediates pain.
         ii. 5-lipoxygenase produces leukotrienes (LT).
            a. LTB_4 attracts and activates neutrophils.
            b. LTC_4, LTD_4, and LTE_4 (slow reacting substances of anaphylaxis) mediate vasoconstriction, bronchospasm, and increased vascular permeability.
   C. Mast cells
      1. Widely distributed throughout connective tissue
      2. Activated by (1) tissue trauma, (2) complement proteins C3a and C5a, or (3) cross-linking of cell-surface IgE by antigen

i. Immediate response involves release of preformed histamine granules, which mediate vasodilation of arterioles and increased vascular permeability.
ii. Delayed response involves production of arachidonic acid metabolites, particularly leukotrienes.

D. Complement
1. Proinflammatory serum proteins that "complement" inflammation
2. Circulate as inactive precursors; activation occurs via
i. Classical pathway—C1 binds IgG or IgM that is bound to antigen.
ii. Alternative pathway—Microbial products directly activate complement.
iii. Mannose-binding lectin (MBL) pathway—MBL binds to mannose on microorganisms and activates complement.
3. All pathways result in production of C3 convertase (mediates C3 → C3a and C3b), which, in turn, produces C5 convertase (mediates C5 → C5a and C5b). C5b complexes with C6-C9 to form the membrane attack complex (MAC).
i. C3a and C5a (anaphylatoxins)—trigger mast cell degranulation, resulting in histamine-mediated vasodilation and increased vascular permeability
ii. C5a—chemotactic for neutrophils
iii. C3b—opsonin for phagocytosis
iv. MAC—lyses microbes by creating a hole in the cell membrane

E. Hageman factor (Factor XII)
1. Inactive proinflammatory protein produced in liver
2. Activated upon exposure to subendothelial or tissue collagen; in turn, activates
i. Coagulation and fibrinolytic systems
ii. Complement
iii. Kinin system—Kinin cleaves high-molecular-weight kininogen (HMWK) to bradykinin, which mediates vasodilation and increased vascular permeability (similar to histamine), as well as pain.

III. CARDINAL SIGNS OF INFLAMMATION

A. Redness (rubor) and warmth (calor)
1. Due to vasodilation, which results in increased blood flow
2. Occurs via relaxation of arteriolar smooth muscle; key mediators are histamine, prostaglandins, and bradykinin.

B. Swelling (tumor)
1. Due to leakage of fluid from postcapillary venules into the interstitial space (exudate)
2. Key mediators are (1) histamine, which causes endothelial cell contraction and (2) tissue damage, resulting in endothelial cell disruption.

C. Pain (dolor)
1. Bradykinin and PGE_2 sensitize sensory nerve endings.

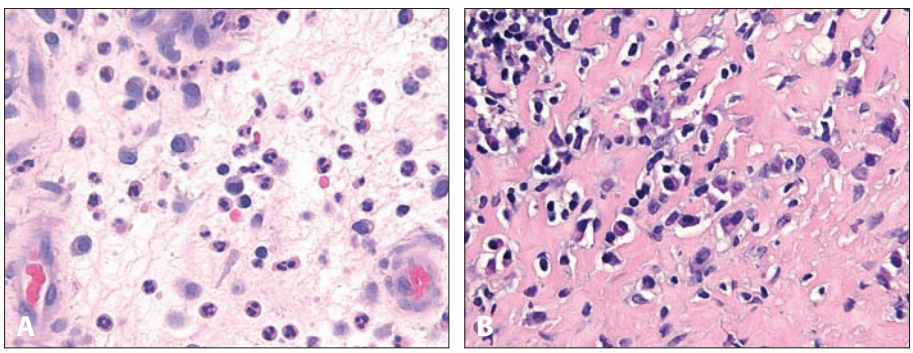

Fig. 2.1 Inflammation. **A**, Acute inflammation with neutrophils. **B**, Chronic inflammation with lymphocytes and plasma cells.

D. Fever
   1. Pyrogens (e.g., LPS from bacteria) cause macrophages to release IL-1 and TNF, which increase cyclooxygenase activity in perivascular cells of the hypothalamus.
   2. Increased PGE_2 raises temperature set point.

IV. NEUTROPHIL ARRIVAL AND FUNCTION

A. Step 1—Margination
   1. Vasodilation slows blood flow in postcapillary venules.
   2. Cells marginate from center of flow to the periphery.

B. Step 2—Rolling
   1. Selectin "speed bumps" are upregulated on endothelial cells.
      i. P-selectin release from Weibel-Palade bodies is mediated by histamine.
      ii. E-selectin is induced by TNF and IL-1.
   2. Selectins bind sialyl Lewis X on leukocytes.
   3. Interaction results in rolling of leukocytes along vessel wall.

C. Step 3—Adhesion
   1. Cellular adhesion molecules (ICAM and VCAM) are upregulated on endothelium by TNF and IL-1.
   2. Integrins are upregulated on leukocytes by C5a and LTB_4.
   3. Interaction between CAMs and integrins results in firm adhesion of leukocytes to the vessel wall.
   4. Leukocyte adhesion deficiency is most commonly due to an autosomal recessive defect of integrins (CD18 subunit).
      i. Clinical features include delayed separation of the umbilical cord, increased circulating neutrophils (due to impaired adhesion of marginated pool of leukocytes), and recurrent bacterial infections that lack pus formation.

D. Step 4—Transmigration and Chemotaxis
   1. Leukocytes transmigrate across the endothelium of postcapillary venules and move toward chemical attractants (chemotaxis).
   2. Neutrophils are attracted by bacterial products, IL-8, C5a, and LTB_4.

E. Step 5—Phagocytosis
   1. Consumption of pathogens or necrotic tissue; phagocytosis is enhanced by opsonins (IgG and C3a).
   2. Pseudopods extend from leukocytes to form phagosomes, which are internalized and merge with lysosomes to produce phagolysosomes.
   3. Chediak-Higashi syndrome is a protein trafficking defect (autosomal recessive) characterized by impaired phagolysosome formation. Clinical features include
      i. Increased risk of pyogenic infections
      ii. Neutropenia (due to intramedullary death of neutrophils)
      iii. Giant granules in leukocytes (due to fusion of granules arising from the Golgi apparatus)
      iv. Defective primary hemostasis (due to abnormal dense granules in platelets)
      v. Albinism
      vi. Peripheral neuropathy

F. Step 6—Destruction of phagocytosed material
   1. O_2-dependent killing is the most effective mechanism.
   2. $HOCl^{\cdot}$ generated by oxidative burst in phagolysosomes destroys phagocytosed microbes.
      i. O_2 is converted to $O_2^{-\cdot}$ by NADPH oxidase (oxidative burst).
      ii. $O_2^{-\cdot}$ is converted to H_2O_2 by superoxide dismutase (SOD).
      iii. H_2O_2 is converted to $HOCl^{\cdot}$ (bleach) by myeloperoxidase (MPO).

3. Chronic granulomatous disease (CGD) is characterized by poor O_2-dependent killing.
   i. Due to NADPH oxidase defect (X-linked or autosomal recessive)
   ii. Leads to recurrent infection and granuloma formation with catalase-positive organisms, particularly *Staphylococcus aureus, Pseudomonas cepacia, Serratia marcescens, Nocardia,* and *Aspergillus*
   iii. Nitroblue tetrazolium test is used to screen for CGD. Leukocytes are incubated with NBT dye, which turns blue if NADPH oxidase can convert O_2 to O_2^-, but remains colorless if NADPH oxidase is defective.
4. MPO deficiency results in defective conversion of H_2O_2 to $HOCl^\cdot$.
   i. Increased risk for Candida infections; however, most patients are asymptomatic.
   ii. NBT is normal; respiratory burst (O_2 to H_2O_2) is intact.
5. O_2-independent killing is less effective than O_2-dependent killing and occurs via enzymes present in leukocyte secondary granules (e.g., lysozyme in macrophages and major basic protein in eosinophils).

G. Step 7—Resolution
1. Neutrophils undergo apoptosis and disappear within 24 hours after resolution of the inflammatory stimulus.

V. MACROPHAGES

A. Macrophages predominate after neutrophils and peak 2–3 days after inflammation begins.
1. Derived from monocytes in blood

B. Arrive in tissue via the margination, rolling, adhesion, and transmigration sequence

C. Ingest organisms via phagocytosis (augmented by opsonins) and destroy phagocytosed material using enzymes (e.g., lysozyme) in secondary granules (O_2-independent killing)

D. Manage the next step of the inflammatory process. Outcomes include
1. Resolution and healing—Anti-inflammatory cytokines (e.g., IL-10 and TGF-β) are produced by macrophages.
2. Continued acute inflammation—marked by persistent pus formation; IL-8 from macrophages recruits additional neutrophils.
3. Abscess—acute inflammation surrounded by fibrosis; macrophages mediate fibrosis via fibrogenic growth factors and cytokines.
4. Chronic inflammation—Macrophages present antigen to activate $CD4^+$ helper T cells, which secrete cytokines that promote chronic inflammation.

CHRONIC INFLAMMATION

I. BASIC PRINCIPLES

A. Characterized by the presence of lymphocytes and plasma cells in tissue (Fig. 2.1B)

B. Delayed response, but more specific (adaptive immunity) than acute inflammation

C. Stimuli include (1) persistent infection (most common cause); (2) infection with viruses, mycobacteria, parasites, and fungi; (3) autoimmune disease; (4) foreign material; and (5) some cancers.

II. T LYMPHOCYTES

A. Produced in bone marrow as progenitor T cells

B. Further develop in the thymus where the T-cell receptor (TCR) undergoes rearrangement and progenitor cells become $CD4^+$ helper T cells or $CD8^+$ cytotoxic T cells
1. T cells use TCR complex (TCR and CD3) for antigen surveillance.

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