Basic Human Pathology Lecture #5
Acute Inflammation / Wound Healing & Repair I

2007
Michael A. Kahn, DDS, Professor and Chairman
Lynn W. Solomon, DDS, MS, Assistant Professor
Department of Oral and Maxillofacial Pathology
Tufts University School of Dental Medicine

Overview: Tissue Responses to Damage

- Outcomes
  - Acute inflammation
    - Initial response to tissue damage
    - Relatively nonspecific response – eliminate dead tissue, protect against local infection, allow immune system access THEN . . .
  - Restitution - ideal outcome
    - Damaged area replaced by organized tissue identical in structure/function as original tissue
    - Damaging agent removed; destroyed cells regenerate
  - Fibrous repair – scar tissue
    - Cells cannot regrow and/or tissue architecture completely destroyed
    - Non-specialized; most frequent outcome of substantial tissue damage
  - Chronic inflammation
    - Damaging agent persists AND continuing tissue destruction AND attempts to heal by fibrous repair AND immune responses

(c) 2007. Michael A. Kahn, DDS
3. Acute Inflammatory Response

**Acute Inflammatory Response**

- **Causes**
  - Mechanical trauma
  - Thermal injury
  - Electrical injury
  - Chemical burn
  - Irradiation injury
  - Biological
    - Viral, bacterial, fungal infections

4. Acute Inflammatory Response

**Acute Inflammatory Response**

- **Functions**
  - Affected area occupied by transient acute inflammatory exudate
    - Exudate carries proteins, fluid, and cells from local blood vessels into the damaged area to mediate local defenses
  - If infective causative agent (e.g., bacteria) present, it is destroyed and eliminated by components of the exudate
  - Damaged tissue broken down, partly liquified with removal of debris from site of damage
5. Acute Inflammatory Response

Acute Inflammatory Response

- Controlled by production and diffusion of chemical messengers derived from damaged tissue and from acute inflammatory exudate
- Acute inflammatory exudate composition
  - Fluid
    - Contains salts, high conc. of protein (incl. immunoglobulins)
  - Fibrin
    - High MW, filamentous, insoluble protein
  - Neutrophils
    - From WBCs population
  - Macrophages
    - Phagocytes; derived from monocytes
  - Lymphocytes
    - Few

(c) 2007, Michael A. Kahn, DDS

6. Acute Inflammatory Response

Acute Inflammatory Response

- Vascular and cellular responses of acute inflammation steps
  - Small b.v. adjacent to area of tissue damage become dilated with increased blood flow, then decreased flow
  - Endothelial cells swell and partially retract (lose intact internal lining)
  - Exudation
    - Vessels become leaky and permit passage of water, salts, and some small plasma proteins (e.g., fibrinogen)
  - Margination and Emigration
    - Circulating PMNs initially adhere to swollen endo cells - - - ->
    - PMNs actively migrate through the vessel basement membrane - - > tissue damage area
  - Small numbers of monocytes and lymphocyte migrate in a similar manner

(c) 2007, Michael A. Kahn, DDS
7. Formation of Acute Inflammatory Exudate

Formation of Acute Inflammatory Exudate

- Death of tissue \( \rightarrow \) release of chemical mediators which act on nearby blood vessels
- Mediators produce
  - Persistent vasodilatation and loss of axial flow
  - Endothelial cell swelling and separation
  - Increased permeability with exudation of water, salts and small proteins including fibrinogen \( \rightarrow \) fibrin
- Mediators cause PMNs to adhere to endothelium (margination) and move through blood vessel walls into damaged tissue (emigration)
- Blood monocytes/macrophages also emigrate slightly later by similar mechanism
- Damaged area is progressively replaced by components of the exudate

(c) 2007, Michael A. Kahn, DDS

8. Formation of an Acute Inflammatory Exudate

Formation of an Acute Inflammatory Exudate

Images not available due to copyright restrictions.

(c) 2007, Michael A. Kahn, DDS
9. Clinical Effects of Acute Inflammation

Clinical Effects of Acute Inflammation

- Four cardinal effects/signs (Celsius, circa 6 A.D.)
  - Rubor (redness)
    - Due to vessel dilatation and increased blood flow
  - Calor (heat)
    - Due to vessel dilatation and increased blood flow
  - Dolor (pain)
    - Due to combination of pressure on nerve endings from swelling and direct effect of chemical mediators released due to the inflammatory response
  - Tumor (swelling)
    - Due to accumulation of exudate, particularly the fluid part

10. “4 + 1” Cardinal Signs of Inflammation

“4 + 1” Cardinal Signs of Inflammation

1. Rubor (redness)
2. Calsor (heat)
3. Fumor (swelling)
4. Dolor (pain)
5. Functio laesa (loss of function)
11. Acute Inflammatory Response

Acute Inflammatory Response

- Clinical indications
  - Generalize malaise
  - Fever
  - Pain often localized to the inflamed area
  - Rapid pulse rate

- Lab values
  - Raised neutrophil count in peripheral blood
  - Increased erythrocyte sedimentation rate
  - Increased acute phase proteins in the blood
    - Increase greatly in acute inflammation
    - Induced by IL-1 and produced by the liver
    - C-reactive protein (liver) is the most common
      - Used to monitor patients with acute myocardial infarction

12. Acute Inflammatory Response

Acute Inflammatory Response

- Fibrin
  - Long, insoluble, filamentous protein formed by polymerization of numerous molecules of smaller, soluble precursor plasma protein, fibrinogen
    - Fibrinogen emigrates from the vessels with the fluid and salts and then polymerizes via blood coagulation cascade
  - Network of fibrin threads prevents migration of microorganisms and produces a scaffold that may assist migration of PMNs and macrophages through the damaged area
    - Theory only, no proof yet

(c) 2007, Michael A. Kahn, DDS
13. Acute Inflammatory Response

Acute Inflammatory Response

- Fluids and salts
  - Dilute and buffer locally produced toxins in the tissue damaged area
  - Fluids also allow diffusion of mediators, esp. plasma-derived precursors
  - Not static; circulates from local vessels to extracellular space of damaged tissue to reabsorption in the lymphatics - increase of lymph flow takes antigens to the local nodes and assists development of specific immune response
- Glucose and oxygen diffuse into inflammatory area to support macrophages
- If there is an invading organism with a prior immunity then immunoglobulins of the exudate act as opsonins for PMN phagocytosis

14. Acute Inflammatory Response

Acute Inflammatory Response

- Main cellular events (caused by chemical mediators)
  - Inactive endothelium activated to allow adhesion of PMNs
  - Inactive PMNs activated to enhance phagocytosis, bacterial killing, and generation of inflammatory mediators
  - PMNs develop ability to move actively (e.g., vessel to tissue damage)
15. Acute Inflammatory Response

Acute Inflammatory Response

• Types of inflammatory cells
  ❖ Neutrophils (a.k.a. polymorphonuclear leukocytes or PMN's)
    ❖ Main effector cell to mediate effects of acute inflammation
    ❖ Most prominent inflammatory cells in foci of acute inflammation during the first 24 hours – diagnostic hallmark
    ❖ Main cell accumulating in the extracellular space
    ❖ Important causes of neutrophilia (increased neutrophils in the peripheral blood)
      – Bacterial infections
      – Infarctions

(c) 2007, Michael A. Kahn, DDS

16. Acute Inflammatory Response

Acute Inflammatory Response

❖ Neutrophils (cont’d)
  • Early release into peripheral blood is from bone marrow postmitotic reserve pool
    – Activated for phagocytosis, bacterial killing and release of mediators
  • Short life span so needs to be replaced constantly
  • Often an increased proportion of less mature cells
    – Band neutrophils

(c) 2007, Michael A. Kahn, DDS
17. Acute Inflammatory Response

Acute Inflammatory Response

- Neutrophils (cont’d)
  - Injury
    - Slight - normal numbers in blood are adequate
    - Severe - growth factors from the injured area cause more
to be released from bone marrow with immature forms
  (band cells)
    » Maintain this extra supply by growth factor derived from
the inflammatory process stimulating division of
myeloid precursors in the bone marrow
  - Most die locally in the inflammatory area
    - Others leave by lymphatics

18. Acute Inflammatory Response

Acute Inflammatory Response

- Neutrophils (cont’d)
  - Adhesion to endothelium - - - - -> aggregation along vessel
    walls (margination)
  - Margination 3 stages – cell adhesion mechanism
  - [pavement]
    - Rolling – PMNs roll along endothelium in close contact
    - Adhesion – PMNs firmly adhere to endothelium
    - Aggregation – adjacent PMNs adhere to each other and undergo
      shape change
  - When emigration starts, the PMNs actively move from
    vessels into tissues down a concentration gradient of
    chemotactic factors
19. Acute Inflammatory Response

Acute Inflammatory Response

- **Neutrophils (cont’d)**
  - Disadvantage – short lived; survive only a few hours in tissue so need to be constantly replenished to damaged area
    - Active phagocytic neutrophils of tissue mixed with dead neutrophil remnants
  - Neutrophils die --> lysosomal enzymes into tissue --> structural protein breakdown --> liquification of tissue --> thick, pus
    - Necrotic cell debris, live and dead neutrophils, and sometimes microorganisms
  - Greatest stimulation occurs with bacterial infections (have potent chemotactants, i.e., large scale emigration)
    - Breakdown and eradication of of damaged tissue AND phagocytize and kill causative bacteria

(c) 2007, Michael A. Kahn, DDS

20. Key Facts - Neutrophils

Key Facts - Neutrophils

- Produced by maturation of precursor cells in bone marrow
- Most numerous WBC, increase in numbers in acute inflammation
- Short lifespan once activated in tissues
- Ameboid and thus able to move from vessels to tissues
- Movement can be directional, attracted by chemotaxins
- Actively phagocytic
- Contain granules rich in a variety of proteases
- Generated free radicals kill phagocytized bacteria
- Source of arachidonic acid to facilitate prostaglandin production
- Increased production in bone marrow caused by cytokines generated in the inflammatory response

(c) 2007, Michael A. Kahn, DDS
21. Acute Inflammatory Response

**Acute Inflammatory Response**

- Activation of endothelium is a key process
  - Activated by both products of tissue damage and cytokines -> expression of surface cell adhesion molecules -> interact with complimentary molecules in the PMN cell membrane
  - Endothelium modified
    - Sticky for neutrophils
    - Secrete factors mediating vasodilatation
    - Promote platelet adhesion and aggregation

22. Acute Inflammatory Response

**Acute Inflammatory Response**

- **Endothelium**
  - Vital role as physical barrier against diffusion of plasma outside vessels + source of many regulatory molecules
  - Some refer to it as the largest endocrine organ of the body

- **Main factors secreted**
  - Nitric oxide and prostacyclin
    - **Vascular relaxation and inhibit platelet aggregation**
  - Endothelin, thromboxane A2 and angiotensin II
    - **Vascular constriction**
  - Growth factor PDGF
    - **Promote inhibitors**
  - Chemokines
23. Acute Inflammatory Response

**Acute Inflammatory Response**

- Normal state of endothelium
  - Surface prevents platelet aggregation and degranulation by balance of secreted factors
- In acute inflammation, endothelial surface properties are altered
  - Adhesion molecules and integrins are expressed
- In acute inflammation, balance of secreted factors is changed
  - Increased synthesis / secretion of platelet activating factor (PAF)
    - Increases vascular permeability
    - Increases synthesis of nitric oxide - - vascular dilatation
    - Increases expression of cell adhesion molecules - - allows neutrophil adhesion

24. Acute Inflammatory Response

**Acute Inflammatory Response**

- Neutrophil movement
  - Mediated by chemotactic factors which diffuse from areas of tissue damage
    - Bind to receptors on the surface of neutrophils and activate secondary messenger systems - - - - increased cytosolic calcium - - - assembly of cytoskeletal specializations involved in motility
25. Acute Inflammatory Response

Acute Inflammatory Response

- Neutrophils kill microorganisms and break down damaged tissue
- Packed with lysosomal cytoplasmic granules rich in proteolytic enzymes capable of breaking down both cells and extracellular matrix materials
- Great phagocytic potential and actively ingest pathogens - - -> destroyed by lysosomal enzymes and by mechanisms that generate toxic free radicals

26. Neutrophil Granules and Their Contents

Neutrophil Granules and Their Contents

- **Azurophil (primary)**
  - Large, dense
    - Lysosomal enzymes
    - Peroxidase ("myeloperoxidase")
    - Lysozyme (33%)
    - Cationic proteins

- **Specific (secondary)**
  - Smaller, less dense
    - Alkaline phosphatase
    - Lysozyme (67%)
    - Lactoferrin

(c) 2007, Michael A. Kahn, DDS
27. Acute Inflammatory Response

**Acute Inflammatory Response**

- **Neutrophilic phagocytosis**
  - Membrane receptors bind to
    - Fc portion of antibodies
    - complement factors bound to foreign particles
    - bacterial polysaccharides
  - Material must be bound to a membrane receptor on the surface of the neutrophil to be phagocytized

(c) 2007, Michael A. Kahn, DDS

28. Neutrophilic phagocytosis - cont’d

- PMN binds to abnormal particle via specific receptor
- pushes out pseudopodia to surround particle (via actin filaments)
- pseudopodia fuse to completely enclose particle
- endocytic vesicle with phagosome
- phagosome fuses with neutrophil granules (esp. primary)
- contents of granules discharged
- lysosomal enzyme exposure (if particle is bacteria then killing enhanced by hydrogen peroxide and superoxide)
- residual body formation with degraded material

(c) 2007, Michael A. Kahn, DDS
29. Acute Inflammatory Response

Acute Inflammatory Response

- Macrophages
  - Minor component of AIIC (more imp. role in chronic inflammation)
  - Derived from monocytes in circulating blood which migrate into damage tissue area after neutrophils
  - Numbers slowly increase to facilitate elimination of dead material after 2-3 days of neutrophils
  - Actively phagocytic and powerful systems to kill bacteria
  - Survive much longer than neutrophils since they have oxidative metabolism
  - Also secrete growth factors and cytokines
    - Mediate some events of inflammatory response
  - Also assist in repair of damaged tissue

(c) 2007. Michael A. Kahn, DDS

30. Acute Inflammatory Response

Acute Inflammatory Response

- Types of inflammatory cells
  - Lymphocytes
    - Most prominent inflammatory cells in many viral infections
    - Combine with monocytes-macrophages and plasma cells to be the most prominent cells in chronic inflammation
    - Lymphohcytosis
      - Increased number of lymphocytes in the peripheral blood
      - Most often caused by viral infections
        - Influenza, mumps, rubella, infectious mononucleosis
      - Certain bacterial infections
        - Whooping cough, tuberculosis

(c) 2007. Michael A. Kahn, DDS
31. Acute Inflammatory Response

Acute Inflammatory Response

- Types of inflammatory cells
  - Eosinophils
    - Predominant inflammatory cells in allergic reactions and parasitic infections
    - Important eosinophilia causes
      - Allergies
        - Hay fever, asthma, hives
      - Parasitic infections
      - Polyarteritis nodosa
      - Hodgkin lymphoma

(c) 2007. Michael A. Kahn, DDS

32. Acute Inflammatory Response

Acute Inflammatory Response

- Types of inflammatory cells
  - Mast cells and basophils
    - Sources of histamine
    - Important basophilia causes
      - Chronic myelogenous leukemia
      - Other myeloproliferative diseases

(c) 2007. Michael A. Kahn, DDS
33. White Blood Cells (a.k.a. leukocytes or WBC’s)

White Blood Cells (a.k.a. leukocytes or WBC’s)

Image not available due to copyright restrictions.

(c) 2007. Michael A. Kahn, DDS

34. Acute Inflammatory Response

Acute Inflammatory Response

• Acute inflammatory exudate
  – Varies in its composition depending on site and cause
    • Purulent exudate – when neutrophils abundant
      – Material liquified to pus; thick, creamy at times
    • Fibrinous exudate – when fibrin abundant
      – Ex. – serosal surfaces of pericardium, lung, peritoneum
      – Shaggy gross (macroscopic) appearance
    • Serous exudate – when fluid is abundant
      – Significant when occur in a confined space (e.g., pericardial cavity) creates increased pressure

(c) 2007. Michael A. Kahn, DDS
35. Parulis (gum boil; abscess on the gingiva) = localized accum...

Parulis (gum boil; abscess on the gingiva) = localized accumulation of neutrophils

36. Pus draining from a fistula of an abscessed tooth

Pus draining from a fistula of an abscessed tooth

(c) 2007, Michael A. Kahn, DDS
37. Fibrinous Exudate – Pericardium

Fibrinous Exudate – Pericardium

Images not available due to copyright restrictions.

38. Purulent Exudate of the Brain

Purulent Exudate of the Brain

Image not available due to copyright restrictions.

Multiple Lung Abscesses

Image not available due to copyright restrictions.
39. Abscess in the Skin = Localized Accumulation of Neutrophils...

Abscess in the Skin = Localized Accumulation of Neutrophils

Image not available due to copyright restrictions.

(c) 2007. Michael A. Kahn, DDS

40. Acute Inflammatory Response

Acute Inflammatory Response

- **Acute inflammatory exudate – key facts**
  - Derived from local blood vessels
  - Contains fluid and electrolytes
  - Contains protein
    - Esp. fibrinogen/fibrin and immunoglobulins
  - Brings chemical mediators of inflammation into site of damage
  - Contains neutrophils
    - Main cells involved in acute inflammation

(c) 2007. Michael A. Kahn, DDS
41. Acute Inflammatory Response

Acute Inflammatory Response

- **Abscess**
  - Mass of necrotic tissue with dead and viable neutrophils suspended in the fluid products of tissue breakdown by neutrophil enzymes
  - Results from local tissue breakdown
  - Extensive tissue necrosis caused by pyogenic (pus-forming) bacterium
  - **Acute abscess**
    - Early stages surrounded by layer of acute inflammatory exudate
    - May continue to enlarge if the bacteria survives
  - Acute abscess enlarges slowly or not at all \(\rightarrow\) acute inflammatory exudate replaced by scar tissue
    - \(\rightarrow\) central area of damaged tissue not eradicated and bacteria there proliferate \(\rightarrow\) more tissue damage \(\rightarrow\) chronic abscess

42. Acute Inflammatory Response

Acute Inflammatory Response

- **Chemical mediators**
  - Many mediate and orchestrate events
  - Can be modified by drug therapy
  - Cell mediators group
    - Stored
      - Histamine
    - **Active synthesis**
      - Prostaglandins
      - Leukotrienes
      - Plasma activating factor
      - Cytokines
      - Nitric oxide
      - Chemokines
Acute Inflammatory Response

- Chemical mediators
  - Plasma-derived group – gain entry to damaged area via inflammatory exudate; activated by proteolytic enzymes; short half-lives; in tissues rapidly inactivated
    - Kinin system
      - Bradykinin
    - Clotting pathway
      - Activated Hageman factor
    - Thrombolytic system
      - Plasmin
    - Complement pathway
      - C3a
      - C3b
      - C5a

(c) 2007. Michael A. Kahn, DDS

Acute Inflammatory Response

- Histamine
  - Main preformed mediator
  - Released from mast cells, basophils, and platelets
  - Causes intransient dilatation of arterioles
  - Increases permeability in venules
  - Primary cause of increased vascular permeability in first hour after injury

- Prostaglandins and leukotrienes
  - Derived by local synthesis from arachidonic acid (liberated from cell membrane by activation of phospholipase A₂)
45. Acute Inflammatory Response

Acute Inflammatory Response

- Two main pathways of arachidonic acid metabolism
  - (1) Cyclo-oxygenase – (2 forms – COX-1 [normally in cells] and COX-2 [specially induced in cells for inflammation]; produces
    - Thromboxane
      - Aggregates platelets and causes vasoconstriction
    - Prostacyclin
      - Inhibits platelet aggregation and dilates vessels
    - Prostaglandins (cause vasodilatation and increase vascular permeability)
      - Another also causes pain

(c) 2007, Michael A. Kahn, DDS

46. Acute Inflammatory Response

Acute Inflammatory Response

- Two main pathways of arachidonic acid metabolism (cont’d)
  - (2) Lipoxygenase - produces
    - Leukotrienes
      - Cause vasoconstriction and increase permeability in venules
      - Another stimulates leukocyte adhesion to endothelium
47. **Cell Membrane Phospholipids**

![Diagram of Cell Membrane Phospholipids]

(c) 2007, Michael A. Kahn, DDS

48. **Endogenous Mediators:**

![Diagram of Endogenous Mediators]

(c) 2007, Michael A. Kahn, DDS
49. Acute Inflammatory Response

Acute Inflammatory Response

- **Drug therapy of acute inflammation**
  - Phospholipase A₂ activity inhibited by steroids so less arachidonic acid produced and thus less of its metabolites
  - Aspirin and indomethacin
    - Inhibit cyclo-oxygenase pathway
    - Prevent production of prostaglandin and thromboxane A₂

50. Biosynthesis of Leukotrienes and Lipoxins

Biosynthesis of Leukotrienes and Lipoxins

Image not available due to copyright restrictions.

(c) 2007, Michael A. Kahn, DDS
51. Acute Inflammation Mechanisms

Acute Inflammation Mechanisms

❖ Lipoxins
  – Produced via the lipoxygenase pathway and a mechanism induced by aspirin
    • Modulate leukotriene responses and inhibit neutrophil chemotaxis and adhesion
    • Regulate the production of prostaglandins including prostacyclin synthesis
    • May be involved in other immune responses

52. Acute Inflammation Mechanisms

Acute Inflammation Mechanisms

• Cellular response of leukocytes
  ❖ Oxygen-dependent microbial killing - Myeloperoxidase-halide system of bacterial killing
    • Most important intracellular microbicidal process
    • Trapping of oxygen by leukocyte generation of active peroxide and hydrogen peroxide radicals and singlet oxygen
    • Phagocytosis → hexose monophosphate shunt activated → oxidative burst and electrons to NADPH oxidase (phagosomal membrane) → superoxide anion \( \text{O}_2^- \) → hydrogen peroxide \( \text{H}_2\text{O}_2 \) by dismutation → activated hydroxyl radical \( \text{OH}^- \)
    • \( \text{H}_2\text{O}_2 \) + myeloperoxidase (leukocyte enzyme) + Chloride or Iodine ion (halides) → oxidation of microbial proteins and cell wall disruption

(c) 2007. Michael A. Kahn, DDS
Acute Inflammation Mechanisms

- Cellular response of leukocytes – cont’d
  - Oxygen-independent microbial killing
    - Much less effective than oxygen dependent
  - Mediation
    - Proteins
      - Lysozyme (muramidase), lactoferrin – lyse cell walls
      - Major basic protein of eosinophils
      - Acid hydrolases and H⁺ ion
      - Cationic proteins
        - Bactericidal permeability-increasing protein
        - Defensins

(c) 2007, Michael A. Kahn, DDS

Acute Inflammation Mechanisms

- Exogenous and endogenous mediators of acute inflammation
  - Influence chemotaxis, vasomotor phenomena, vascular permeability, pain, and other aspects of the inflammatory process
  - Vasoactive mediators
    - Vasoconstriction
      - Thromboxane \( \text{TxA}_2 \); Leukotrienes \( \text{LTC}_4, \text{LTD}_4, \text{LTE}_4 \)
    - Vasodilation
      - Prostaglandins \( \text{PGI}_1, \text{PGD}_2 \); \( \text{PGE}_2, \text{PGF}_2\alpha\alpha \); Bradykinin, PAF
  - Increased vascular permeability
    - Histamine
    - Serotonin
    - Prostaglandins \( \text{PGD}_2 \); \( \text{PGE}_2 \); \( \text{PGF}_2\alpha\alpha \)
    - Leukotrienes \( \text{LTC}_4, \text{LTD}_4, \text{LTE}_4 \)
    - Bradykinin
    - PAF (platelet activating factor)
    - Nitric oxide

(c) 2007, Michael A. Kahn, DDS
Acute Inflammation Mechanisms

• Exogenous mediators
  ❖ Most often of microbial origin
  ❖ Exemplified by formylated peptides of *Escherichia coli*
    • Chemotactic for neutrophils
• Endogenous mediators
  – Host origin
  ❖ Vasoactive amines
    ❖ Histamine
      – Mediates the increase in capillary permeability associated with contraction of endothelial cells in postcapillary venules that occurs with mild injuries – first 30 minutes
      – Liberated from basophils, mast cells, and platelets

(c) 2007, Michael A. Kahn, DDS

Acute Inflammation Mechanisms

• Endogenous mediators – cont’d
  – Vasoactive amines – cont’d
    ❖ Histamine
      – Basophils and mast cells
        » Histamine is liberated by degranulation triggered by the following stimuli - - binding of specific antigen to basophil and mast cell membrane-bound IgE; binding of anaphylatoxins (C3a and C5a) to specific cell-surface receptors
      – Platelets
        » Histamine is liberated by platelet aggregation and the release reaction triggered by endothelial injury and thrombosis or by PAF
        » PAF derived from granules of basophils and mast cells and from endothelial cells, macrophages, neutrophils, and eosinophils
        » PAF activates and aggregates platelets with the release of histamine and serotonin - - > vasoactive and bronchospastic effects and activates arachidonic acid metabolism

(c) 2007, Michael A. Kahn, DDS
57. Acute Inflammation Mechanisms

Acute Inflammation Mechanisms

• **Endogenous mediators (cont’d)**
  – Platelet activating factor
  • Synthesized by mast cells/basophils; also by platelets, neutrophils, monocytes, and endothelium
  • Can be stimulated by IgE-mediated release
  • Specialized phospholipid compound
  • Causes vasoconstriction, increased vascular permeability, platelet aggregation
  • Also stimulates the synthesis of arachidonic acid metabolites

(c) 2007, Michael A. Kahn, DDS

58. Acute Inflammation Mechanisms

Acute Inflammation Mechanisms

• **Endogenous mediators – cont’d**
  – Vasoactive amines – cont’d
    ✤ Serotonin
      – Acts similarly to histamine
      – Derived from platelets
      – Liberated from platelets along with histamine during the release reaction – first 30 minutes
    ✤ Arachidonic acid metabolites
      ✤ Eicosanoids
        – Derivatives of arachidonic acid, polyunsaturated long chain fatty acids in cell membranes including leukocytes and endothelial cells
        » Thromboxanes, prostaglandins, and leukotrienes
          – Have cellular activity
        • Phospholipase A2 stimulates release of arachidonic acid from membrane phospholipids
        • Metabolism of arachidonic acid proceeds along two pathways
          ✤ Cyclooxygenase and lipoxygenase pathways

(c) 2007, Michael A. Kahn, DDS
Acute Inflammation Mechanisms

Endogenous mediators – cont’d

Arachidonic acid metabolites – cont’d

- Cyclooxygenase pathway
  - Catalyzed by two enzyme isoforms
    - Cyclooxygenase – 1 (COX-1)
    - Cyclooxygenase – 2 (COX-2)
  - Inhibited by aspirin and other anti-inflammatory drugs
  - Yields thromboxanes (vasoconstrictors) and prostaglandins (powerful vasodilators and pain producers)
    - Take time to produce and in effect after the histamine response
    - TXA₂ in platelets – powerful vasoconstrictor and platelet aggregant
    - PGI₂ in endothelial cells – powerful vasodilator and inhibitor of platelet aggregation

(c) 2007, Michael A. Kahn, DDS

Acute Inflammation Mechanisms

Endogenous mediators – cont’d

Arachidonic acid metabolites – cont’d

- Lipoxygenase pathway
  - Gives rise to leukotrienes
  - Yields HPETE and derivatives 12-HPETE (platelets) and 5-HPETE (leukocytes) and 15-HPETE (leukocytes)
  - 5-HPETE → HETE (chemotactic for neutrophils)
  - 5-HPETE → leukotrienes
    - LTB₄ – chemotactic factor for neutrophils
    - LTC₄, LTD₄, LTE₄ – potent vasoconstrictors, bronchoconstrictors and mediators of increased capillary permeability (slow-reacting substance of anaphylaxis)

(c) 2007, Michael A. Kahn, DDS
Acute Inflammation Mechanisms

- **Endogenous mediators – cont’d**
  - **Cytokines**
    - Polypeptide products of activated lymphocytes and monocytes
    - Main ones in acute inflammation are:
      - Interleukin-1
      - Interleukin-8
      - Tumor necrosis factor alpha
    - Responsible for:
      - Induction of cell adhesion molecules on endothelium
      - Induction of prostacyclin synthesis
      - Induction of platelet activating factor
      - Fever, anorexia, and stimulation of acute phase protein synthesis by the liver
      - Stimulation of fibroblast proliferation and secretory activity
      - Attraction of neutrophils into damaged area

(c) 2007, Michael A. Kahn, DDS

---

Acute Inflammation Mechanisms

- **Endogenous mediators – cont’d**
  - **Cytokines**
   - Soluble proteins
   - Act as effector molecules influencing the behavior of other cells
   - Mediators of immunologic response
     - *E.g.*, interferon-gamma activates monocytes
   - Important mediators of inflammation
   - Cytokines IL-1 and TNF are secreted by monocytes-macrophages

(c) 2007, Michael A. Kahn, DDS
63. Acute Inflammation Mechanisms

Acute Inflammation Mechanisms

- Endogenous mediators – cont’d
  - Cytokines – cont’d
    - Induce acute phase responses
      - Systemic effects of inflammation – fever, leukocytosis
      - Hepatic synthesis
        - Acute phase proteins such as C-reactive protein, serum amyloid-associated proteins, complement components, fibrinogen, prothrombin, α₁-antitrypsin, α₂-macroglobulin, ferritin, and ceruloplasmin
      - Synthesis of adhesion molecules
      - Neutrophil degranulation
    - Reduce the thromboreistant properties of endothelium thus promoting thrombosis

(c) 2007. Michael A. Kahn, DDS

64. Acute Inflammation Mechanisms

Acute Inflammation Mechanisms

- Chemokines
  - Family of factors secreted by leukocytes and endothelial cells in response to tissue damage and in response to other inflammatory mediators
  - Locally bound to extracellular matrix and heparin sulfate proteoglycans of cells
  - Establish a concentration gradient away from the focus of inflammation
  - Neutrophils encounter them on endothelial cells when they roll
    - Specific chemokine receptors activated - - - > leukocyte integrin activation - - - > mediation of adhesion and emigration
  - Removed from circulation via Duffy antigen receptor expressed on RBCs

(c) 2007. Michael A. Kahn, DDS
Acute Inflammation Mechanisms

**Nitric oxide**
- Small molecule locally synthesized by endothelium and macrophages via nitric oxide synthase
- Powerful cause of vascular dilation and increases vascular permeability
  - Stimulates relaxation of smooth muscle
- Can also mediate cell and bacterial killing
- Inhibits platelet aggregation, contributing to endothelial thromboresistance

Endogenous mediators – cont’d

**Complement system**
- Consists of group of plasma proteins that participate in immune lysis of cells
- Plays a significant role in inflammation
  - **C3a** and **C5a** mediated degranulation of basophils and mast cells with the release of histamine
  - **C5a**
    - Chemotactic mediates release of histamine from platelet dense granules
    - Induces expression leukocyte adhesion molecules
  - **C3b** - opsonin
  - **C2-kinin** causes vasodilation
    - It takes time to generate but lasts longer
67. Overview of the Complement System

Image not available due to copyright restrictions.

68. Acute Inflammation Mechanisms

- Endogenous mediators – cont’d
  - The kinin system
    - Small peptides derived from plasma precursors by proteolytic cleavage
    - Initiated by activated Hageman factor (XIIa)
    - Early, short-acting vasodilators that can cause pain
      - Peptides of amino acids
    - Also activates intrinsic pathway of coagulation and the plasminogen system
    - Activation of this activates the complement campaign
    - Factor XIIa links the kinin, coagulation, plasminogen, and complement systems
    - Converts prekallikrein to kallikrein → cleavage of HMWK to bradykinin
69. **Acute Inflammation Mechanisms**

**Acute Inflammation Mechanisms**

- **Endogenous mediators – cont’d**
  - The kinin system – cont’d
    - Bradykinin
      - Principal kinin
      - 9 amino acids long
      - Mediates vascular permeability
      - Derived from factor XIIa activating kallikrein that acts on kininogen to produce bradykinin
    - Results in cleavage by kallikrein

(c) 2007, Michael A. Kahn, DDS

70. **Acute Inflammatory Response**

**Acute Inflammatory Response**

- **Clotting pathway**
  - Responsible for coagulation of blood by formation of fibrin from fibrinogen
    - Fibrinopeptides are formed - - --> increased vascular permeability and chemotactic for neutrophils
  - Factor XII activated in the inflam. exudate when it comes in contact with collagen outside the vessel - - - > deposition of fibrin, activates kinin system, stimulates thrombolytic system

(c) 2007, Michael A. Kahn, DDS
71. Acute Inflammatory Response

Acute Inflammatory Response

Key facts

- Vasodilatation
  - Histamine, prostaglandin, nitric oxide, bradykinin, PAF

- Increased permeability
  - Histamine, C3a, C5a, bradykinin, leukotrienes, PAF, nitric oxide

- Neutrophil adhesion
  - IL-1, TNFalpha, PAF, LTB4, C5a, chemokines

- Neutrophil chemotaxis
  - C5a, LTB4, bacterial components, chemokines

- Fever
  - IL-1, TNF, prostaglandin

- Pain
  - Prostaglandin; bradykinin

- Tissue necrosis
  - Neutrophil lysosomal granules; free radicals from neutrophils

(c) 2007, Michael A. Kahn, DDS