Basic Human Pathology Lecture #6
Acute Inflammation / Wound Healing & Repair II

2007
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Acute Inflammatory Response

Vascular permeability factors
- Two main mechanisms for increased permeability of small vessels following tissue damage
  - Toxins and physical agents
    - Cause necrosis of vascular endothelium with abnormal leakage
  - Chemical mediators
    - Cause retraction of endothelial cells with resultant intermediate gaps

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3. Acute Inflammatory Response

**Acute Inflammatory Response**

- **Vascular permeability factors**
  - Three patterns of increased leakage from vessels
    - **Immediate transient response** for 30-60 minutes mediated by histamine acting on endothelium
    - **Delayed response** that starts 2-3 hours after injury and lasts for up to 8 hours mediated by bradykinin, factors derived from complement and factors released from dead neutrophils in the exudate
    - **Immediate response** prolonged for over 24 hours if there has been direct necrosis of endothelium (e.g., burn, chemical toxin)

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4. Biphasic Permeability Response

**Biphasic Permeability Response**

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5. Acute Inflammation Mechanisms

Acute Inflammation Mechanisms

❖ Vasoactive changes
❖ Begin with brief period of vasoconstriction
   • Most likely under neural reflex of the autonomic system sympathetic fibers around small vessels
❖ Followed by dilation of arterioles, capillaries, and postcapillary venules \( \rightarrow \) marked increase in blood flow to the affected area, sluggish flow, aids in extravasation of cells
   • Clinical appearance - redness and increased warmth
     – Vasoconstriction causes a blanching at the scratch line and then quickly disappears
     – Followed by vasodilation and a reddened line
     – Erythrocytes aggregate or line up (rouleaux)

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6. Demonstration of Transient Vasoconstriction

Demonstration of Transient Vasoconstriction

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7. Circulatory Changes in Inflammation

Circulatory Changes in Inflammation

Precapillary Sphincters in Arterioles Relax Resulting in More Flow and Dilation of Capillaries and Postcapillary Venules

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8. Dilation of Capillaries and Postcapillary Venules in Inflammation

Dilation of Capillaries and Postcapillary Venules in Inflammation

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9. Acute Inflammation Mechanisms

Acute Inflammation Mechanisms

- Post-capillary venules are primarily affected after the tissue is damaged by either:
  - Non-mediated mechanism
    - Toxins and physical agents can cause necrosis of endothelial cells resulting in abnormal leakage
  - Mediated (chemical) mechanism
    - Many mediators of various origins cause vasodilation and increased permeability; Ex. - histamine
    - Most are short-lived

10. Acute Inflammation Mechanisms

Acute Inflammation Mechanisms

- Increased capillary permeability
  - Results in leakage of proteinaceous fluid - - -> edema
  - Caused by wide spectrum of endothelial changes
    - Contraction of endothelial cells in postcapillary venules with widening of interendothelial gaps
    - Major endothelial damage involving arterioles, capillaries, and venules
11. Morphologic Reaction of Endothelial Cells to Injury

Morphologic Reaction of Endothelial Cells to Injury

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12. Increased Permeability of Vessels Due to Various Indicated F...

Increased Permeability of Vessels Due to Various Indicated Factors

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13. Patterns of Permeability Response

Patterns of Permeability Response

- **Bi-phasic response**
  - **Immediate**
    - Very short acting; caused mainly by histamine
  - **Delayed**
    - Longer acting
    - Develops and peaks 2-4 hours after injury and lasts up to 8 hours
    - Mediators
      - Local cells - dead neutrophils
      - Plasma - bradykinin and complement
      - Cause a widened gap junction and endothelial cell contraction

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14. Patterns of Permeability Response

Patterns of Permeability Response

- **Other possibilities**
  - Immediate-sustained or prolonged
    - Occurs with severe damage or injury as in a burn or toxin
    - Can last up to 24 hours
  - Delayed-sustained or prolonged
    - Seen in sunburns
    - Widened endothelial gaps

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15. Various Mechanisms Underlying Increased Vascular Permeability in Inflammation

Various Mechanisms Underlying Increased Vascular Permeability in Inflammation

- Gaps due to endothelial contraction
- Direct injury
- Leukocyte-dependent injury
- Increased transcytosis
- New blood vessel formation

16. Acute Inflammation Mechanisms

Acute Inflammation Mechanisms

- Cellular response of leukocytes
  - Emigration
  - Adhesion molecules
  - Chemotaxis
  - Phagocytosis
  - Opsonization
17. Acute Inflammation Mechanisms

**Acute Inflammation Mechanisms**

- **Cellular response of leukocytes**
  - **Emigration**
    - Passage of inflammatory leukocytes between the endothelial cells into the adjacent interstitial tissue
    - Before emigration, circulating leukocytes from the central blood flow move toward the endothelial surface
  - **Margination**
    - Leukocytes localize at outer margin of the blood flow adjacent to the vascular endothelium
  - **Pavementing**
    - Leukocytes line the endothelial surface
  - **Rolling (tumbling)**
    - Mediated by the action of endothelial E- and P-selectins loosely binding to leukocytes and producing a characteristic "rolling" movement of the leukocytes along the endothelial surface

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18. Biochemical Events in Leukocyte Activation

**Biochemical Events in Leukocyte Activation**

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19. Cellular Changes in Inflammation

Cellular Changes in Inflammation

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20. Acute Inflammation Mechanisms

Acute Inflammation Mechanisms

- Adhesion molecules
  - Play important role in acute inflammation
  - Divided into 3 families
    - Selectins
    - Immunoglobulin-family adhesion proteins
    - Integrins
21. Acute Inflammation Mechanisms

Acute Inflammation Mechanisms

❖ Adhesion molecules - cont’d
❖ Selectins
  • Induced by cytokines interleukin-1 (IL-1) and tumor necrosis factor (TNF) acting on the endothelial cells
  • E- and P-selectins
    – Expressed on endothelial cells and bind to oligosaccharides (e.g., Sialyl-Lewis X) on the surface of leukocytes
    – P-selectins are stored in Weibel-Palade bodies and platelet alpha granules
      » Relocate to the plasma membrane after stimulation by histamine and thrombin
  • L-selectins
    – Expressed on neutrophils and bind to endothelial mucin-like molecules (e.g., GlyCam-1)

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22. Acute Inflammation Mechanisms

Acute Inflammation Mechanisms

❖ Adhesion molecules – cont’d
❖ Immunoglobulin-family adhesion proteins
  • Intercellular adhesion molecules 1 and 2 (ICAM-1 and ICAM-2) expressed on endothelial cells and bind to integrin molecules on leukocytes
  • Vascular adhesion molecules (VCAMs) similarly are expressed on endothelial cells and bind to integrin molecules on leukocytes
❖ Integrins
  • Ex. – leukocyte LFA-1, MAC-1, and VLA-4
  • Bind to immunoglobulin-family adhesion proteins

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23. Acute Inflammation Mechanisms

Acute Inflammation Mechanisms

• Cellular response of leukocytes – cont’d
  ❖ Emigration – cont’d
  ❖ Adhesion/Aggregation
    » Leukocytes adhere to endothelial surface and aggregate to each other
    » Mediated by interaction of integrins on leukocytes binding to immunoglobulin-family adhesion protein on endothelium (activated)
    » IL-1 and TNF activate endothelial receptors of the smallest vessels
  ❖ Transmigration
    » Movement of leukocytes across the endothelium
    » Mediated by platelet endothelial cell adhesion molecule-1 (PECAM-1) on both leukocytes and endothelium

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24. Emigration

Emigration

Molecules mediating endothelial-neutrophil interaction

(1) Initial adhesion
(2) Activation of leukocytes

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25. Emigration

Molecules mediating endothelial-neutrophil interaction

(3) **Firm adhesion** via integrin-endothelial cell receptor interactions [ICAMs, VCAMs]

(4) **Homotypic (like-like) interaction** of platelet endothelial cell adhesion molecule 1 (PECAM-1) (CD31) on leukocytes and endothelial cells mediates transmigration between cells

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26. Adhesion of Neutrophils to Endothelial Cells by Surface Mole...

Adhesion of Neutrophils to Endothelial Cells by Surface Molecule Binding

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27. Three General Mechanisms

Three General Mechanisms

Mediating increased leukocyte-endothelial adhesion in the setting of inflammatory stimuli

A. Redistribution of P-selectin

B. Cytokine activation of endothelium, resulting in increased de novo synthesis of adhesion molecules

C. Increased binding affinity of integrins with ICAM-1, intercellular adhesion molecule 1; IL-1, interleukin 1; TNF, tumor necrosis factor

28. Sequence of Events in Inflammatory Leukocyte Emigration

Sequence of Events in Inflammatory Leukocyte Emigration

The leukocytes:

(1) Roll

(2) Adhere to endothelium

(3) Transmigrate through an intercellular junction and pierce the basement membrane

(4) Migrate toward chemoattractants released from a source of injury
29. Emigration of Neutrophils

Emigration of Neutrophils

Emigration by margination, pavementing, rolling, achesion, transmigration, ameboid movement and phagocytosis

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30. A Vascular and Cellular Response

A Vascular and Cellular Response

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31. Acute Inflammation Mechanisms

Acute Inflammation Mechanisms

- Cellular response of leukocytes – cont’d
  - Chemotaxis
    - Process by which leukocytes are attracted to and move toward injury (unidirectional locomotion)
      - Neutrophils, macrophages and lymphocytes
    - Mediated by diffusible chemical agents (factors)
    - Movement of leukocytes occurs along a chemical gradient of factors
      - Receptors detect the chemical concentration gradient
  - Measured in an in vitro system - Boyden chamber
    - Assesses migration of cells from an upper chamber through a microporous membrane to a lower chamber filled with a chemoattractant

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32. Acute Inflammation Mechanisms

Acute Inflammation Mechanisms

- Cellular response of leukocytes – cont’d
  - Chemotaxis – cont’d
    - Chemotactic factors for neutrophils produced at the site of injury
      - Products from bacteria
      - Complement components, especially C5a
      - Arachidonic acid metabolites, especially
        - Leukotriene B₄ (LTB₄)
        - Hydroxyeicosatetraenoic acid (HETE)
        - Kallikrein

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33. Chemotactic Factors or Mediators

Chemotactic Factors or Mediators

- **Products of bacteria, viruses, cells**
- **Activated or released products of inflammation**
  - Complement components - C3, C5, C6, C7
  - Fibrin and plasmin systems
  - Collagen
  - Leukotrienes

34. Chemotaxis

Chemotaxis

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35. Chemotactic Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
<th>Chemotactic for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formylated peptides</td>
<td>E. Coli products</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>C5a</td>
<td>Activated complement component</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>HETE, LTB4</td>
<td>Leukotrienes</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Kallikrein</td>
<td>Product of Factor Xll-mediated conversion of prekallikrein</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Plasma protein</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>PAF</td>
<td>AGEPC – basophils, mast cells</td>
<td>Eosinophils</td>
</tr>
<tr>
<td>PDGF</td>
<td>Platelets, monocytes-macros, smooth muscle cells, endothelial</td>
<td>Neutrophils and macrophages</td>
</tr>
<tr>
<td>TGF-Beta</td>
<td>Platelets, neutrophils, macrocytes, lymphocytes, fibroblasts</td>
<td>Macrophages and fibroblasts</td>
</tr>
<tr>
<td>Fibronectin</td>
<td>Extracellular matrix protein</td>
<td>Fibroblast and Endothelial cells</td>
</tr>
</tbody>
</table>

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36. Acute Inflammation Mechanisms

**Acute Inflammation Mechanisms**

- **Cellular response of leukocytes – cont’d**
  - **Phagocytosis**
    - Ingestion and processing of particulate material by phagocytic cells
      - Tissue debris, living or dead bacteria, other foreign cells
      - Neutrophils and monocytes-macrophages are the most important phagocytic cells

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37. Acute Inflammation Mechanisms

**Acute Inflammation Mechanisms**

- Cellular response of leukocytes – cont’d
  - Phagocytosis - cont’d
    - Process
      - Adherence/Binding
        - Matter to cell surface
        - Aided by opsonization
      - Ingestion
        - Matter to form phagocytic vacuole or phagosome
      - Fusion
        - Phagosome with lysosome to form phagolysosome (pH=4)
        - Killing occurs inside the phagolysosome
      - Degradation
        - Results in residual body or extrusion

38. Phagocytosis of a Particle

**Phagocytosis of a Particle**

*Attachment (adherence) and binding of opsonins* (e.g., collectins, or C3b and the Fc portion of immunoglobulin) to receptors on the leukocyte surface

- *Engulfment (ingestion)*
- *Fusion* of the phagocytic vacuole with granules (lysosomes), and *Degranulation (degradation)*

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Acute Inflammation Mechanisms

- Cellular response of leukocytes – cont’d
  - Opsonization
    - “to prepare the table”
    - Coating of particulate material by opsonins
      - Immunoglobulin (Ig)
        or
      - Complement (C)
  - Facilitates phagocytosis – “adherence/binding” step

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Acute Inflammation Mechanisms

- Cellular response of leukocytes – cont’d
  - Opsonization - cont’d
    - IgG and C3b cellular receptors on membranes of neutrophils and macrophages bind firmly to IgG and C3b molecules which are attached to particles or cells
      - Binding immobilizes the particles on the surface of the phagocyte (i.e., neutrophils and macrophages)
    » Fragment opsonized by IgG is bound to phagocytic cells by cell surface receptors for the Fc portion of the IgG molecule
    » Fragments opsonized by C3b are bound to cellular receptors for C3b

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41. Steps in Phagocytosis

Steps in Phagocytosis

• Adherence/Binding
• Ingestion to form Phagosome
• Fusion of Lysosome forming Phagolysosome
• Degradation with release of contents and killing - - - > Residual Body

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42. Acute Inflammation Mechanisms

Acute Inflammation Mechanisms

• Cellular response of leukocytes – cont’d
  – Phagocytosis – cont’d
    ◆ Anatomic changes
      – Internalization of attached opsonized particle by pseudopodial extensions from the surface of the leukocyte
      – Enclose the foreign particle - - - > phagosome (internalized vesicle)
        » Phagosomes fuse with cytoplasmic lysosomes - - - > phagolysosomes
        » Phagolysosome formation associated with leukocytic degranulation

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43. Chemical Mediators of Inflammation

![Image](image-url)

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44. Chemical Mediators, Sources and Possible Actions

<table>
<thead>
<tr>
<th>Mediator Cellular Preformed</th>
<th>Source</th>
<th>Vascular Leakage</th>
<th>Chemotaxis</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>Mast Cells, Basophils, Platelets</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Serotonin</td>
<td>Platelets</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Lysosomal Enzymes</td>
<td>Neutrophils, Macrophages</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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45. Chemical Mediators, Sources, and Possible Actions

### Chemical Mediators, Sources, and Possible Actions

<table>
<thead>
<tr>
<th>Cellular (Newly synthesized)</th>
<th>Source</th>
<th>Vascular Leakage</th>
<th>Chemotaxis</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandins</td>
<td>Leukocytes; platelets, endothelial cells</td>
<td>Potentiate</td>
<td>No</td>
<td>Vasodilation, pain, fever</td>
</tr>
<tr>
<td>Leukotrienes</td>
<td>Leukocytes, mast cells</td>
<td>Yes</td>
<td>Yes (LTB4)</td>
<td>Vasooconstriction and bronchoconstriction</td>
</tr>
<tr>
<td>Platelet activating factors</td>
<td>Leukocytes, endothelial cells</td>
<td>Yes</td>
<td>Yes</td>
<td>Bronchoconstriction</td>
</tr>
<tr>
<td>Activated oxygen species</td>
<td>Leukocytes</td>
<td>Yes</td>
<td>No</td>
<td>Endothelial, tissue damage</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Macrophage, endothelial cell</td>
<td>No</td>
<td>No</td>
<td>Vasodilation, cytotoxicity</td>
</tr>
<tr>
<td>Cytokines IL-1, IL-8, TNF</td>
<td>Lymphocytes, macrophages, endothelial cells</td>
<td>No</td>
<td>Yes</td>
<td>Leukocyte activation, endothelial activation, fever</td>
</tr>
</tbody>
</table>

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46. Chemical Mediators, Sources, and Possible Actions

### Chemical Mediators, Sources, and Possible Actions

<table>
<thead>
<tr>
<th>Source</th>
<th>Vascular Leakage</th>
<th>Chemotaxis</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma derived (from liver to plasma) Factor XII (Hageman factor) activation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinin system</td>
<td>Blood</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Blood</td>
<td>No</td>
<td>Stabilize platelet plug, Lyse fibrin plug</td>
</tr>
<tr>
<td>Coagulation/ Fibrinolysis system</td>
<td>Blood</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Complement activation</td>
<td>Blood</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>C3a</td>
<td>Blood</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>C5a</td>
<td>Blood</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>C5b-9</td>
<td>Blood</td>
<td></td>
<td>Membrane attack</td>
</tr>
</tbody>
</table>

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47. The Lymphatics in Acute Inflammation

The Lymphatics in Acute Inflammation

- Lymphatic channels become dilated and drain the edema fluid or exudate with its large proteins from the inflammatory site
  - Drainage limits the swelling
    - If blocked, severe edema results = lymphedema
  - Early in the inflammatory process
    - Lymphatics are blocked by fibrin
  - Later in the inflammatory process
    - Plasmin system breaks down the fibrin and opens up the lymphatic drainage.

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48. Hereditary Defects that Impair the Acute Inflammatory Response...

Hereditary Defects that Impair the Acute Inflammatory Response

- Deficiency of complement components
  - Increased susceptibility to infection
  - Particularly complement components
    - C2
    - C3
    - C5

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49. Hereditary Defects that Impair the Acute Inflammatory Response

Hereditary Defects that Impair the Acute Inflammatory Response

• Defects in neutrophils
  ❖ Chronic granulomatous disease of childhood
    • Usually X-linked with deficient activity of NADPH oxidase
    • Phagocytic cells ingest but do not kill certain microorganisms
      ❖ Catalase-positive organisms
        • Ingested but not killed e.g., Staph aureus, can destroy \( \text{H}_2\text{O}_2 \) generated by bacterial metabolism and so \( \text{H}_2\text{O}_2 \) not available for myeloperoxidase-halide system of killing bacteria
      ❖ Catalase-negative organisms
        • Ingested and killed e.g., Strep, that produce sufficient \( \text{H}_2\text{O}_2 \) to permit oxygen-dependent microicide so the bacteria in a sense kill themselves.

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50. Neutropenia Resulting in Periodontal Disease and Mucosal Ulc...

Neutropenia Resulting in Periodontal Disease and Mucosal Ulceration

Source: TUSDM

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51. Oral Inflammation, Infections, Ulcerations

Oral Inflammation, Infections, Ulcerations

Source: TUSDM

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52. Hereditary Defects that Impair the Acute Inflammatory Response...

Hereditary Defects that Impair the Acute Inflammatory Response

• Defects in neutrophils – cont’d
  – Myeloperoxidase deficiency
    • Sometimes recurrent infections but often no clinical consequence

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53. Hereditary Defects that Impair the Acute Inflammatory Response...

Hereditary Defects that Impair the Acute Inflammatory Response

• Defects in neutrophils – cont’d
  ▶ Chediak-Higashi syndrome
    • Autosomal recessive
    • Neutropenia, albinism, cranial and peripheral neuropathy, repeated infections
    • Abnormal WBC
      – Functionally have abnormal microtubule formation affecting movement so impaired chemotaxis and migration
      – Morphologically have large cytoplasmic granules (abnormal lysosomes) in granulocytes, lymphocytes, and monocytes and large melanosomes in melanocytes

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54. Leukocyte Function Defects

Leukocyte Function Defects

▶ Causes of deficient phagocytosis
  – Opsonization defects
    • Hypogammaglobulinemia
  – Engulfment defects
    • Drugs: morphine
  – Degranulation defects
    • Drugs, steroids
    • Lack of NADPH-oxidase and failure to kill organisms
  – Severe glucose-6-phosphate dehydrogenase deficiency
    • No peroxide is generated

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55. **Outcome of the Acute Inflammatory Reaction**

**Outcome of the Acute Inflammatory Reaction**

- Depends upon the removal of the inflammatory exudate and its replacement either by regenerated cells of the original type (restitution) or by scar tissue (fibrous repair)
  - End results are
    - Resolution
    - Healing by repair
    - Chronic inflammation

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56. **Tissue Damage of Necrosis**

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57. Outcome of the Acute Inflammatory Reaction

**Outcome of the Acute Inflammatory Reaction**

- **Resolution**
  - The best possible outcome not common and usually supporting stroma damage and healing is by scar formation
  - Occurs when even though extensive destruction damage to the supporting tissues is minimal
  - Acute inflammatory exudate resolves and only the epithelial cells are deficient
    - Exudate removed by liquefaction by neutrophil enzymes and phagocytosis of particulate debris by macrophages
    - Damaged cells regenerate leaving the structure virtually as before and normal function regained
    - Example – lobar pneumonia

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58. Outcome of the Acute Inflammatory Reaction

**Outcome of the Acute Inflammatory Reaction**

- **Factors favoring resolution**
  - Minimal cell death
  - Tissue has regenerative capacity
  - Fast destruction of agent
  - Fast removal of debris
  - Good drainage

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Resolution Occurring in Pneumonia

Outcome of the Acute Inflammatory Reaction

- **Resolution key facts**
  - End result is restoration of normal structure and function without scarring
  - Acute inflammatory exudates removed by liquefaction and phagocytosis
  - Support stroma must be intact
  - Damaged cells must be able to regenerate
    - Only certain cells can regenerate
      - Surface epithelia constantly dividing
      - Liver and kidney can divide if to replace after damage
      - Nerve and cardiac cells cannot divide so loss is permanent
61. Outcome of the Acute Inflammatory Reaction

Outcome of the Acute Inflammatory Reaction

- **Labile cells**
  - High turnover rate
  - Have high capacity for regeneration
  - Ex. - squamous, glandular, and GI epithelium; bone marrow
- **Stable cells**
  - Low turnover rate
  - Can proliferate rapidly when called upon
  - Ex. - liver, kidney, fibroblasts, osteoblasts and endothelial cells
- **Permanent cells**
  - Cannot divide
  - Cannot regenerate
  - Heal with scar tissue
  - Ex. - neurons and cardiac cells

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62. Outcome of the Acute Inflammatory Reaction

Outcome of the Acute Inflammatory Reaction

- **Organization and repair**
  - Type of healing that occurs when substantial structural damage to the tissue stroma
  - Eventually leads to formation of a scar
  - Sequence of changes
    - Pre-existing capillaries in undamaged tissue form new capillaries by budding into the damaged area which is also infiltrated by macrophages, fibroblasts, and myofibroblasts
    - Macrophages phagocytize inflammatory exudate and dead tissue
    - Vascular granulation tissue (fragile complex of interconnecting capillaries, macrophages, and support cells) replaces the area of tissue damage

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63. Outcome of the Acute Inflammatory Reaction

**Outcome of the Acute Inflammatory Reaction**

- **Organization and repair**
  - Sequence of changes (cont’d)
    - Progressive growth of fibroblasts and myofibroblasts and tissue defect filled with complex capillary network and a few residual macrophages (fibrovascular granulation tissue)
      - Many of the newly formed capillaries regress until only a relative few vascular channels remain
    - Intervening spaces between vessels come progressively filled with fibrous granulation tissue
      - Fibroblasts align themselves so collagen deposited in a uniform pattern that follows a direction best adapted to physical stresses
      - Contraction of the granulation occurs (myofibroblasts) and thus the size of the damaged area is reduced
    - Production of dense collagen by fibroblasts forms a collagenous scar

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64. Outcome of the Acute Inflammatory Reaction

**Outcome of the Acute Inflammatory Reaction**

- **Organization and repair**
  - Sequence of changes (cont’d)
    - Fibroblasts that have synthesized sufficient collagen to fill the defect change to a resting state with scanty cytoplasm and elongated spindle-shaped nucleus (aka fibrocytes)
    - Process of inflammatory exudate replaced by granulation tissue is called organization of the exudate
    - Process by which granulation tissue replaced by fibrous scar is called fibrous repair

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65. Removal of Debris by Macrophages

**Removal of Debris by Macrophages**

**Vascular granulation tissue**

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66. Vascular Granulation Tissue

**Vascular Granulation Tissue**

**Fibrovascular granulation tissue**

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67. Fibrovascular Granulation Tissue

Fibrovascular Granulation Tissue

Collagenous scar formation

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68. Early Collagenous Scar

Early Collagenous Scar

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69. Outcome of the Acute Inflammatory Reaction

Outcome of the Acute Inflammatory Reaction

- **Healing of wounds**
  - Occurs through the processes of organization and formation of granulation and scar tissue
  - Ideal is when adjacent surfaces are closely apposed and held together by suture material
    - Only a narrow space between adjacent tissue with minimal amount of dead tissue limited to the very edges of the wound

70. Outcome of the Acute Inflammatory Reaction

Outcome of the Acute Inflammatory Reaction

- **Healing of wounds - cont’d**
  - If extensive loss of cells then large tissue defect which has to be filled by granulation tissue
    - Inflammatory response at edges of wound is intense and large amount of granulation tissue needed so healing takes a long time
    - Ultimate size of collagenous scar is reduced by shrinkage of the healing wound
      - Wound contraction – myofibroblasts contract at granulation tissue formation; 90% of original wound surface lost!

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71. Outcome of the Acute Inflammatory Reaction

**Outcome of the Acute Inflammatory Reaction**

- **Healing of wounds**
  - Primary intention
    - Healing of closely apposed surfaces
    - E.g. sutured skin wound
  - Secondary intention
    - Greater amount of in-fill required to bridge the tissue defect

72. Outcome of the Acute Inflammatory Reaction –

**Outcome of the Acute Inflammatory Reaction –**

**Stages in the healing of a sutured skin wound**

- **Day 1**
  - Neutrophils at margin of incision
  - Acute inflammatory response on each side of the narrow incisional space → swelling, redness, and pain
  - Epithelial cells at edge of wound undergo mitosis and begin to migrate across wound

- **Day 2**
  - Macrophages begin to infiltrate the incisional space and to demolish fibrin
  - Surface epithelia continuity is re-established in the form of a thin surface layer

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73. Outcome of the Acute Inflammatory Reaction –

**Outcome of the Acute Inflammatory Reaction –**

**Stages in the healing of a sutured skin wound**

- **Day 3**
  - Granulation tissue begins to invade tissue space
  - Surface epithelial continuity is reinforced by thickening of epithelial layer
- **Day 5**
  - Incisional space filled with vascular granulation tissue - collagen is progressively deposited
  - Surface epithelium achieves normal thickness
  - Acute inflammatory response at wound margin begins to subside; swelling and redness of adjacent tissues reduced

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74. Outcome of the Acute Inflammatory Reaction –

**Outcome of the Acute Inflammatory Reaction –**

**Stages in the healing of a sutured skin wound**

- **Day 7**
  - Sutures commonly removed from skin wounds
  - Wound has ~ 10% of tensile strength of normal skin
- **Day 10**
  - Further fibroblast proliferation and collagen deposition occur in granulation tissue in the incisional space, adding to strength of wound

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Outcome of the Acute Inflammatory Reaction –

Stages in the healing of a sutured skin wound

- **Day 15**
  - Collagen deposition follows the lines of stress
  - Granulation tissue loses some vascularity but still appears pinker than adjacent tissues
- **Day 30**
  - Wound now has 50% of tensile strength of normal skin
- **3 months**
  - Wound now has 80% of tensile strength of normal skin
  - Only marginally more vascular than adjacent skin
  - Complete blanching of scar takes several more months

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Outcome of the Acute Inflammatory Reaction –

Local and Systemic Factors of Wound Healing

- **Impairment of organization and wound healing**
  - Inadequate nutrition – protein, vitamin C, zinc needed
  - Ischemia to tissues – markedly impairs repair
  - Infection of tissues – continued tissue damage
  - Foreign material – nidus for infection, promote inflammation
  - Steroids – hinder granulation tissue formation; predispose to infection
  - Radiation exposure – reduced capacity to repair
  - Diabetes mellitus - increased susceptibility to infection, vascular disease and ischemia
  - Denervation – impairs healing

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77. Outcome of the Acute Inflammatory Reaction –

Outcome of the Acute Inflammatory Reaction –

Local and Systemic Factors of Wound Healing

• Healing Promoters
  – Removal of dead tissues to allow apposition of healthy tissues
  – Administration of appropriate antibiotics in cases of infection

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78. Outcome of the Acute Inflammatory Reaction

Outcome of the Acute Inflammatory Reaction

• Brain damage
  – Not repaired through proliferation of fibroblasts but through proliferation of the support cells of the brain (astrocytes)
  – Necrotic tissue removed - - -> replaced by fluid - - - >cystic lesion surrounded by compacted glial fibers produced by astrocytes = glial scar (astrocyte gliosis)

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Outcome of the Acute Inflammatory Reaction

- **Bone damage**
  - Collagenous scarring insufficiently strong to repair bone (e.g., post fracture)
  - Bone fracture undergoes organization, granulation tissue formation, and fibroblasts in-growth but also proliferation of osteoblasts
  - → highly specialized collagen extracellular matrix (osteoid) → mineralized to bone
  - Callus = mixture of fibrous granulation tissue and developing new bone
    - Bridges between the broken bone ends
    - Later, refashioned to re-establish the normal structure of the bone