BASIC MECHANISM INVOLVED IN THE PROCESS OF INFLAMMATION AND REPAIR-II

Abstract

The process of inflammation and repair is pivotal in maintaining tissue integrity and function following injury. A key component of inflammation is the migration of white blood cells (WBCs) to the injury site. This process, called chemotaxis, is driven by chemical signals that guide WBCs, particularly neutrophils and macrophages, to areas of damage. Mediators of inflammation, such as cytokines, chemokines, and prostaglandins, play critical roles in orchestrating this response. They regulate vascular changes, attract immune cells, and modulate the inflammatory process. Wound healing in the skin follows basic principles involving hemostasis, inflammation, proliferation, and remodeling. Initially, blood clotting occurs to prevent excessive bleeding, followed by an inflammatory phase where WBCs clear debris and pathogens. The proliferative phase involves the formation of new tissue and blood vessels, while the remodeling phase strengthens the tissue and restores normal function. In the pathophysiology of atherosclerosis, inflammation plays a central role. It begins with endothelial injury in blood vessels, leading to the accumulation of lipids and immune cells in the vessel wall. This results in the formation of atherosclerotic plaques, which can narrow arteries and reduce blood flow. Over time, these plaques may rupture, causing thrombosis and potentially leading to heart attacks or strokes. Understanding these mechanisms provides insight into therapeutic strategies to manage inflammation and promote tissue repair effectively.

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I. MIGRATION OF WBC'S

The migration of white blood cells (WBCs), also known as leukocytes, from the bloodstream to the site of tissue injury or infection is a critical step in the inflammatory response. This process involves several well-coordinated steps, including margination, rolling, adhesion, and transmigration. Here is a detailed overview:

Steps of Leukocyte Migration

1. **Margination**
   a. **Blood Flow Dynamics:** In normal conditions, leukocytes travel in the center of the bloodstream. During inflammation, blood flow slows down (due to vasodilation), and leukocytes move closer to the vessel wall (marginate).

2. **Rolling**
   a. **Selectins:** Endothelial cells express selectins (E-selectin and P-selectin) on their surface in response to inflammatory mediators like histamine and thrombin.
   b. **Leukocyte Interaction:** Selectins on the endothelial cells bind to carbohydrate ligands (e.g., sialyl Lewis X) on the leukocytes, causing the leukocytes to "roll" along the inner surface of the blood vessel.

3. **Adhesion**
   a. **Integrins:** Leukocytes express integrins (e.g., LFA-1, Mac-1) on their surface in a low-affinity state.
   b. **Activation of Integrins:** Chemokines presented on the endothelial surface activate these integrins, increasing their affinity for adhesion molecules.
   c. **Adhesion Molecules:** Endothelial cells express intercellular adhesion molecules (ICAM-1, VCAM-1). Activated integrins on leukocytes bind firmly to these adhesion molecules, causing the leukocytes to adhere strongly to the endothelium.

4. **Transmigration (Diapedesis)**
   a. **Transendothelial Migration:** After adhesion, leukocytes extend pseudopodia and migrate between endothelial cells through the basement membrane. This process involves the interaction of PECAM-1 (CD31) on both leukocytes and endothelial cells.
   b. **Basement Membrane Degradation:** Leukocytes secrete proteolytic enzymes (e.g., collagenases) to degrade the basement membrane, allowing them to pass through the vessel wall.

5. **Chemotaxis**
   a. **Migration to the Site of Injury:** Once in the tissue, leukocytes follow a gradient of chemotactic factors (e.g., bacterial products, complement components like C5a, chemokines like IL-8) that guide them to the site of infection or injury.

Molecular Mediators Involved in Leukocyte Migration

1. **Selectins**
   a. **E-Selectin:** Induced on endothelial cells by IL-1 and TNF.
   b. **P-Selectin:** Stored in Weibel-Palade bodies of endothelial cells and released in response to histamine and thrombin.

c. **L-Selectin:** Found on leukocytes and plays a role in their initial tethering and rolling.

2. **Integrins**
   a. **LFA-1 (CD11a/CD18):** Binds to ICAM-1.
   b. **Mac-1 (CD11b/CD18):** Binds to ICAM-1 and ICAM-2.
   c. **VLA-4 (CD49d/CD29):** Binds to VCAM-1.

3. **Adhesion Molecules**
   a. **ICAM-1 (Intercellular Adhesion Molecule-1):** Expressed on endothelial cells and binds to LFA-1 and Mac-1.
   b. **VCAM-1 (Vascular Cell Adhesion Molecule-1):** Expressed on endothelial cells and binds to VLA-4.

4. **Chemokines**
   a. **IL-8 (CXCL8):** Attracts neutrophils and promotes their adhesion.
   b. **MCP-1 (CCL2):** Attracts monocytes.
   c. **RANTES (CCL5):** Attracts T cells and monocytes.

Regulation and Resolution

1. **Anti-Inflammatory Signals:** To prevent excessive tissue damage, the migration of leukocytes is tightly regulated. Anti-inflammatory cytokines (e.g., IL-10, TGF-β) and specialized pro-resolving mediators (e.g., lipoxins, resolvins) help resolve the inflammation by inhibiting further leukocyte recruitment and promoting the clearance of apoptotic cells.
2. **Apoptosis of Neutrophils:** Neutrophils undergo apoptosis after fulfilling their role, and macrophages clear them to prevent prolonged inflammation and tissue damage.

II. MEDIATORS OF INFLAMMATION

Inflammation is regulated by a variety of chemical mediators, which are produced by both plasma proteins and cells. These mediators play critical roles in the initiation, amplification, and resolution of the inflammatory response.

1. **Vasoactive Amines**
   a. **Histamine**
      - **Source:** Mast cells, basophils, platelets.
      - **Function:** Causes vasodilation and increases vascular permeability by inducing endothelial cell contraction.
   b. **Serotonin**
      - **Source:** Platelets.
      - **Function:** Acts similarly to histamine in increasing vascular permeability and promoting vasodilation.

2. **Plasma Proteins**
   a. **Complement System**
      - **Components:** C3a, C5a (anaphylatoxins), C3b, C5b-9 (membrane attack complex).
      - **Function:** Enhance phagocytosis (opsonization), increase vascular permeability,

and attract leukocytes (chemotaxis).

b. Kinins
- **Example:** Bradykinin.
- **Function:** Causes vasodilation, increases vascular permeability, and induces pain.

c. Coagulation and Fibrinolysis Systems
- **Components:** Thrombin, fibrin degradation products.
- **Function:** Thrombin promotes inflammation by activating protease-activated receptors (PARs) on cells, leading to increased vascular permeability and leukocyte adhesion.

3. Eicosanoids

a. Prostaglandins
- **Source:** Arachidonic acid via cyclooxygenase (COX) pathway.
- **Examples:** PGE2, PGD2.
- **Function:** Cause vasodilation, increase vascular permeability, and induce fever and pain.

b. Leukotrienes
- **Source:** Arachidonic acid via lipoxygenase (LOX) pathway.
- **Examples:** LTB4, LTC4, LTD4, LTE4.
- **Function:** LTB4 is chemotactic for leukocytes; LTC4, LTD4, and LTE4 increase vascular permeability and cause bronchoconstriction.

c. Lipoxins
- **Source:** Arachidonic acid via alternative pathways.
- **Function:** Inhibit leukocyte recruitment and promote the resolution of inflammation.

4. Cytokines and Chemokines

a. Pro-inflammatory Cytokines
- **Examples:** Tumor necrosis factor (TNF-α), Interleukin-1 (IL-1), IL-6.
- **Function:** Induce endothelial activation, promote leukocyte recruitment, and stimulate the acute-phase response.

b. Anti-inflammatory Cytokines
- **Examples:** Interleukin-10 (IL-10), Transforming growth factor-beta (TGF-β).
- **Function:** Inhibit the inflammatory response and promote healing.

c. Chemokines
- **Examples:** IL-8 (CXCL8), MCP-1 (CCL2).
- **Function:** Direct the migration of leukocytes to the site of inflammation.

5. Reactive Oxygen Species (ROS)
- **Source:** Produced by activated leukocytes (neutrophils and macrophages).
- **Function:** Destroy pathogens and contribute to tissue damage if produced in excess.

6. Nitric Oxide (NO)

a. Source: Endothelial cells, macrophages, neurons.

b. Function: Causes vasodilation, reduces platelet aggregation and adhesion, and has antimicrobial properties.

7. **Neuropeptides**
   a. **Examples:** Substance P, neurokinin A.
   b. **Function:** Transmit pain signals, regulate vascular tone, and modulate immune responses.

Basic Mechanism Involved in the Process of Inflammation and Repair

1. **Recognition of the Injurious Agent**
   a. **Pathogen Recognition Receptors (PRRs)**
      - **Examples:** Toll-like receptors (TLRs), NOD-like receptors (NLRs).
      - **Function:** Recognize PAMPs and DAMPs to initiate the inflammatory response.

2. **Recruitment of Leukocytes**
   a. **Chemotaxis**
      - **Chemotactic Factors:** C5a, LTB4, IL-8.
      - **Function:** Attract leukocytes to the site of injury.
   b. **Leukocyte Adhesion and Migration**
      - **Selectins:** Mediate leukocyte rolling on the endothelium.
      - **Integrins:** Facilitate firm adhesion of leukocytes to endothelial cells.
      - **PECAM-1:** Assists in transmigration of leukocytes across the endothelium.

3. **Removal of the Injurious Agent**
   a. **Phagocytosis**
      - **Phagocytes:** Neutrophils, macrophages.
      - **Process:** Engulfment and digestion of pathogens and debris.
   b. **Degranulation**
      - **Cells:** Mast cells, basophils.
      - **Function:** Release granules containing histamine and other inflammatory mediators.

4. **Resolution of Inflammation**
   a. **Anti-inflammatory Signals**
      - **Mediators:** IL-10, TGF-β, lipoxins, resolvins.
      - **Function:** Suppress pro-inflammatory pathways and promote healing.
   b. **Apoptosis and Clearance of Neutrophils**
      - **Process:** Neutrophils undergo programmed cell death and are phagocytosed by macrophages.

5. **Tissue Repair**
   a. **Regeneration**
      - **Tissue:** Replacement of damaged cells with the same cell type.
   b. **Fibrosis**
      - **Formation:** Deposition of collagen and ECM components by fibroblasts.
      - **Result:** Scar tissue formation if regeneration is not possible.
   c. **Angiogenesis**
      - **Growth Factors:** VEGF, FGF.
      - **Function:** Formation of new blood vessels to supply nutrients and oxygen to the healing tissue.

d. Remodeling

- **Process:** Matrix metalloproteinases (MMPs) remodel the ECM to restore normal tissue architecture.

III. BASIC PRINCIPLES OF WOUND HEALING IN THE SKIN

Wound healing in the skin is a complex and dynamic process that involves multiple overlapping phases: hemostasis, inflammation, proliferation, and remodeling. Each phase is characterized by specific cellular and molecular events aimed at restoring the integrity and function of the injured skin.

Phases of Wound Healing

Wound healing in the skin is a well-coordinated process that can be divided into four overlapping phases: hemostasis, inflammation, proliferation, and remodeling. Each phase is characterized by specific cellular and molecular activities essential for effective tissue repair.

1. Hemostasis Phase

Immediate Response

a. **Vasoconstriction:** Blood vessels constrict immediately after injury to minimize blood loss.
b. **Platelet Activation:** Platelets adhere to the exposed extracellular matrix and aggregate to form a primary plug.
c. **Clot Formation:** The coagulation cascade is activated, leading to the conversion of fibrinogen to fibrin, which stabilizes the platelet plug, forming a stable clot that seals the wound and provides a provisional matrix for incoming cells.

Key Players

a. **Platelets:** Release clotting factors and growth factors (e.g., PDGF, TGF-β) that initiate and regulate healing.

2. Inflammation Phase

Vascular and Cellular Responses

a. **Vasodilation and Increased Permeability:** Histamine, bradykinin, and other inflammatory mediators cause vasodilation and increase vascular permeability, leading to the influx of plasma and immune cells into the wound site, resulting in edema.
b. **Leukocyte Recruitment:** Neutrophils arrive first to clear debris and pathogens through phagocytosis, followed by macrophages, which continue phagocytosis and secrete cytokines and growth factors.

Key Molecular Mediators

a. **Cytokines:** TNF-α, IL-1, IL-6.
b. **Chemokines:** IL-8 (CXCL8) that attract neutrophils.

Key Players

a. **Neutrophils:** Clear pathogens and debris.
b. **Macrophages:** Release cytokines and growth factors, regulate the transition to the proliferative phase.

3. Proliferation Phase

Tissue Formation

a. **Re-epithelialization:** Keratinocytes at the wound edges proliferate and migrate across the wound bed to cover the wound. EGF and KGF are crucial for this process.
b. **Angiogenesis:** New blood vessels form from existing ones to supply nutrients and oxygen to the healing tissue, driven by VEGF.
c. **Fibroplasia and Collagen Deposition:** Fibroblasts proliferate and synthesize extracellular matrix components, primarily collagen, which provides structural support.
d. **Formation of Granulation Tissue:** Granulation tissue, composed of new blood vessels, fibroblasts, and extracellular matrix, fills the wound bed and provides a scaffold for further tissue regeneration.

Key Molecular Mediators

a. **Growth Factors:** PDGF, TGF-β, VEGF.
b. **Cytokines:** IL-6, TNF-α.

Key Players

a. **Keratinocytes:** Proliferate and migrate to re-epithelialize the wound.
b. **Fibroblasts:** Synthesize and deposit collagen and other extracellular matrix components.
c. **Endothelial Cells:** Form new blood vessels through angiogenesis.

4. Remodeling Phase

Tissue Strengthening and Remodeling

a. **Collagen Maturation and Remodeling:** Initially deposited collagen type III is gradually replaced by collagen type I, which is stronger and more organized. This process involves matrix metalloproteinases (MMPs) and their inhibitors (TIMPs).
b. **Wound Contraction:** Myofibroblasts, which express contractile proteins, pull the edges of the wound together, reducing its size.
c. **Scar Formation:** As remodeling progresses, the vascularity of the granulation tissue decreases, leading to the formation of a less cellular and less vascular scar. The scar tissue continues to mature and gain tensile strength over time.

Key Molecular Mediators

a. **MMPs:** Degrade extracellular matrix components.
b. **TIMPs:** Inhibit MMP activity to regulate remodeling.

Cellular and Molecular Mediators

The wound healing process involves a variety of cells and molecular mediators that coordinate to restore tissue integrity and function. These mediators play specific roles in each phase of wound healing: hemostasis, inflammation, proliferation, and remodeling.

Hemostasis Phase

Cellular Mediators

a. **Platelets:** These are the first responders to vascular injury. They aggregate at the site of injury to form a primary plug and release granules containing clotting factors and growth factors.

Molecular Mediators

a. **Clotting Factors:** Proteins in the blood that are essential for coagulation. They include fibrinogen, which is converted to fibrin to form a stable clot.

b. **Growth Factors**
   - **Platelet-Derived Growth Factor (PDGF):** Released by platelets to recruit neutrophils, macrophages, and fibroblasts to the wound site.
   - **Transforming Growth Factor-Beta (TGF-β):** Released by platelets and other cells to promote fibrosis and regulate inflammation.

Inflammation Phase

Cellular Mediators

a. **Neutrophils:** The first leukocytes to arrive at the wound site, they clear debris and pathogens through phagocytosis.
b. **Macrophages:** These cells arrive later and continue phagocytosis. They release cytokines and growth factors to regulate the healing process and transition to the proliferative phase.
c. **Mast Cells:** Release histamine and other mediators that increase vascular permeability.

Molecular Mediators

a. **Cytokines**
   - **Tumor Necrosis Factor-Alpha (TNF-α):** Produced by macrophages, it promotes inflammation and the recruitment of additional immune cells.
   - **Interleukin-1 (IL-1):** Produced by macrophages and other cells, it induces fever, promotes inflammation, and recruits leukocytes.
   - **Interleukin-6 (IL-6):** Promotes the acute phase response and recruits leukocytes.
b. **Chemokines:**
   - **Interleukin-8 (IL-8 or CXCL8):** Attracts neutrophils to the wound site.
c. **Histamine:** Released by mast cells, it increases vascular permeability, allowing immune cells to enter the wound site.
d. **Bradykinin:** Increases vascular permeability and stimulates pain receptors.

Proliferation Phase

Cellular Mediators

a. **Keratinocytes:** Proliferate and migrate to cover the wound (re-epithelialization).
b. **Fibroblasts:** Proliferate and synthesize extracellular matrix components, particularly collagen.
c. **Endothelial Cells:** Form new blood vessels through angiogenesis.
d. **Myofibroblasts:** Differentiated fibroblasts that express contractile proteins to pull the wound edges together.

Molecular Mediators

a. **Growth Factors**
   - **Vascular Endothelial Growth Factor (VEGF):** Stimulates angiogenesis.
   - **Epidermal Growth Factor (EGF):** Promotes keratinocyte proliferation and migration.
   - **Keratinocyte Growth Factor (KGF):** Stimulates keratinocyte proliferation.
   - **Fibroblast Growth Factor (FGF):** Promotes fibroblast proliferation and angiogenesis.

b. **Cytokines**
   - **Transforming Growth Factor-Beta (TGF-β):** Promotes fibroblast activity and collagen synthesis.
   - **Interleukin-6 (IL-6):** Continued role in recruiting leukocytes and supporting fibroblast activity.
c. **Matrix Metalloproteinases (MMPs):** Enzymes that degrade the extracellular matrix, allowing for cell migration and remodeling.

Remodeling Phase

Cellular Mediators

a. **Myofibroblasts:** Mediate wound contraction by expressing contractile proteins.
b. **Fibroblasts:** Continue to produce and remodel collagen and other extracellular matrix components.

Molecular Mediators

a. **Matrix Metalloproteinases (MMPs):** Degrade extracellular matrix components to allow for remodeling.
b. **Tissue Inhibitors of Metalloproteinases (TIMPs):** Regulate the activity of MMPs to prevent excessive degradation.
c. **Collagen:** Type III collagen is initially deposited and later replaced by the stronger type I collagen.
d. **Cytokines and Growth Factors**
   - **TGF-β:** Continues to regulate collagen synthesis and fibroblast activity.
   - **PDGF:** Supports the remodeling process by stimulating fibroblast activity.

Key Growth Factors and Cytokines

Growth factors and cytokines are crucial for regulating the various phases of wound healing. They influence cell migration, proliferation, differentiation, and tissue remodeling. Here's a detailed look at the key growth factors and cytokines involved in the wound healing process:

1. Hemostasis and Inflammation Phases

Cytokines

a. Tumor Necrosis Factor-Alpha (TNF-α)
- **Source:** Macrophages, T cells, and other immune cells.
- **Function:** Promotes inflammation, fever, and the activation of endothelial cells. It also stimulates the production of other cytokines and growth factors.

b. Interleukin-1 (IL-1)
- **Source:** Macrophages, fibroblasts, and endothelial cells.
- **Function:** Induces fever, promotes inflammation, and enhances the recruitment of leukocytes. It also plays a role in the activation of other immune responses.

c. Interleukin-6 (IL-6)
- **Source:** Macrophages, fibroblasts, and endothelial cells.
- **Function:** Promotes the acute phase response, recruits leukocytes, and stimulates fibroblast proliferation.

Growth Factors

a. Platelet-Derived Growth Factor (PDGF)
- **Source:** Platelets, macrophages, and endothelial cells.
- **Function:** Attracts neutrophils, macrophages, and fibroblasts to the wound site. Stimulates fibroblast proliferation and collagen synthesis.

b. Transforming Growth Factor-Beta (TGF-β)
- **Source:** Platelets, macrophages, and fibroblasts.
- **Function:** Regulates inflammation, promotes fibroblast activity, collagen deposition, and tissue remodeling.

2. Proliferation Phase

Growth Factors

a. Vascular Endothelial Growth Factor (VEGF)
- **Source:** Macrophages, fibroblasts, and endothelial cells.
- **Function:** Stimulates angiogenesis by promoting the proliferation and migration of endothelial cells to form new blood vessels.

b. Epidermal Growth Factor (EGF)
- **Source:** Platelets, macrophages, and fibroblasts.
- **Function:** Promotes keratinocyte proliferation and migration, essential for re-epithelialization.

c. Keratinocyte Growth Factor (KGF)
- **Source:** Fibroblasts and other mesenchymal cells.
- **Function:** Stimulates keratinocyte proliferation and migration, supporting the restoration of the epithelial layer.

d. Fibroblast Growth Factor (FGF)
- **Source:** Platelets, macrophages, and fibroblasts.
- **Function:** Promotes fibroblast proliferation, angiogenesis, and extracellular matrix production.

Cytokines

a. **Interleukin-8 (IL-8)**
   - **Source:** Macrophages, fibroblasts, and endothelial cells.
   - **Function:** Attracts neutrophils to the wound site, facilitating inflammation and debris clearance.
b. **Transforming Growth Factor-Beta (TGF-β)**
   - **Continued Role:** Regulates fibroblast proliferation, collagen production, and modulates the inflammatory response.

3. Remodeling Phase

Growth Factors

a. **Matrix Metalloproteinases (MMPs)**
   - **Source:** Fibroblasts, macrophages, and endothelial cells.
   - **Function:** Enzymes that degrade extracellular matrix components, allowing for tissue remodeling and repair.
b. **Tissue Inhibitors of Metalloproteinases (TIMPs)**
   - **Source:** Fibroblasts and other cells.
   - **Function:** Regulate MMP activity to prevent excessive degradation of the extracellular matrix and control remodeling.

Cytokines

a. **Interleukin-10 (IL-10)**
   - **Source:** Macrophages and other immune cells.
   - **Function:** Anti-inflammatory cytokine that helps resolve inflammation and promote tissue repair.

IV. PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

Atherosclerosis is a chronic inflammatory disease of the arterial walls characterized by the formation of atherosclerotic plaques. These plaques consist of lipids, inflammatory cells, smooth muscle cells, and connective tissue. The disease progresses through several stages and involves complex interactions between various cellular and molecular mechanisms.

Stages of Atherosclerosis

1. **Endothelial Dysfunction**
   a. **Initiation:** The earliest step in atherosclerosis involves damage to the endothelial lining of arteries due to factors such as hypertension, smoking, diabetes, and high cholesterol levels.
   b. **Mechanism:** Endothelial cells lose their ability to produce nitric oxide (NO), a vasodilator and anti-inflammatory molecule, leading to increased vascular permeability and leukocyte adhesion.

2. **Lipoprotein Entry and Modification**
   a. **LDL Accumulation:** Low-density lipoprotein (LDL) particles penetrate the damaged endothelium and accumulate in the intima (inner layer) of the arterial wall.

b. Oxidation: LDL particles undergo oxidation to form oxidized LDL (oxLDL), which is highly atherogenic and promotes inflammation.

3. Leukocyte Recruitment and Foam Cell Formation

a. Leukocyte Adhesion: Endothelial cells express adhesion molecules (e.g., VCAM-1, ICAM-1) that facilitate the attachment of monocytes and T-cells to the endothelium.

b. Migration: Monocytes migrate into the intima and differentiate into macrophages.

c. Foam Cells: Macrophages engulf oxLDL via scavenger receptors, transforming into foam cells. These foam cells are a hallmark of early atherosclerotic lesions known as fatty streaks.

4. Plaque Progression

a. Smooth Muscle Cell Migration and Proliferation: Smooth muscle cells (SMCs) migrate from the media (middle layer) to the intima and proliferate in response to growth factors such as platelet-derived growth factor (PDGF).

b. Extracellular Matrix (ECM) Production: SMCs produce ECM components, including collagen and elastin, contributing to plaque stability.

c. Necrotic Core Formation: As foam cells die, they release their lipid content, forming a necrotic core surrounded by fibrous tissue.

5. Plaque Complications

a. Fibrous Cap Formation: A fibrous cap forms over the plaque, composed of SMCs and ECM. The stability of this cap determines the risk of plaque rupture.

b. Calcification: Calcium deposits accumulate within the plaque, contributing to its hardening.

c. Plaque Rupture and Thrombosis: If the fibrous cap ruptures, it exposes the necrotic core to the bloodstream, triggering platelet aggregation and thrombus (blood clot) formation. This can lead to partial or complete occlusion of the artery, resulting in ischemic events such as myocardial infarction (heart attack) or stroke.

Basic Mechanism Involved in the Process of Inflammation and Repair

1. Recognition of the Injurious Agent

a. Pathogen Recognition Receptors (PRRs)

- **Examples:** Toll-like receptors (TLRs), NOD-like receptors (NLRs).
- **Function:** Recognize PAMPs (pathogen-associated molecular patterns) and DAMPs (damage-associated molecular patterns) to initiate the inflammatory response.

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   c. **Lipoxins**
      - **Source:** Arachidonic acid via alternative pathways.
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4. **Cytokines and Chemokines**
   a. **Pro-inflammatory Cytokines**
      - **Examples:** Tumor necrosis factor (TNF-α), Interleukin-1 (IL-1), IL-6.
      - **Function:** Induce endothelial activation, promote leukocyte recruitment, and stimulate the acute-phase response.
   b. **Anti-inflammatory Cytokines**
      - **Examples:** Interleukin-10 (IL-10), Transforming growth factor-beta (TGF-β).
      - **Function:** Inhibit the inflammatory response and promote healing.
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      - **Examples:** IL-8 (CXCL8), MCP-1 (CCL2).
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   a. **Examples:** Substance P, neurokinin A.
   b. **Function:** Transmit pain signals, regulate vascular tone, and modulate immune responses.

Multiple-Choice Questions (Objective)

1. What is the primary goal of inflammation?
   a. To increase blood pressure
   b. To eliminate the initial cause of cell injury
   c. To decrease body temperature
   d. To reduce white blood cell count

2. Which of the following is NOT a key feature of acute inflammation?
   a. Rapid onset
   b. Short duration
   c. Tissue destruction and healing simultaneously
   d. Edema

3. What causes vasodilation during the acute inflammatory response?
   a. Decreased blood flow
   b. Vasoconstriction
   c. Increased blood flow
   d. Decreased vascular permeability

4. What type of leukocyte is primarily recruited during acute inflammation?
   a. Eosinophils
   b. Basophils
   c. Neutrophils
   d. Lymphocytes

5. Which of the following is a characteristic of chronic inflammation?
   a. Rapid onset
   b. Short-lived
   c. Persistent inflammation
   d. Immediate resolution

6. What is the definition of fibrosis in the context of tissue repair?
   a. Replacement of damaged tissue with the same type of cells
   b. Formation of new blood vessels
   c. Replacement of damaged tissue with fibrous connective tissue
   d. Cell division to replace lost cells

7. What factor influences the capacity of a tissue to regenerate?
   a. Age of the individual
   b. Nutritional status
   c. Type and extent of injury
   d. All of the above

8. Which chemical mediator is primarily responsible for increasing vascular permeability?
   a. Histamine
   b. Serotonin
   c. Interleukin-1
   d. Tumor necrosis factor-alpha

9. Which cells release histamine during an inflammatory response?
   a. Neutrophils
   b. Macrophages
   c. Mast cells
   d. Fibroblasts

10. What is the main function of cytokines such as TNF-α and IL-1 in inflammation?
    a. Promote anti-inflammatory effects
    b. Induce endothelial activation
    c. Decrease leukocyte recruitment
    d. Inhibit the acute-phase response

11. What triggers the recruitment of leukocytes to the site of injury?
    a. Blood clotting
    b. Chemotactic factors
    c. Platelet aggregation
    d. Reduced blood flow

12. Which phase of wound healing involves re-epithelialization?
    a. Hemostasis
    b. Inflammation
    c. Proliferation
    d. Remodeling

13. Which mediator is involved in the formation of new blood vessels during wound healing?
    a. TGF-β
    b. VEGF
    c. PDGF
    d. EGF

14. What role do macrophages play in the inflammatory response?
    a. Release histamine
    b. Produce cytokines and growth factors
    c. Form blood clots
    d. Increase vascular permeability

15. Which of the following is a symptom of acute inflammation?
    a. Increased heart rate
    b. Redness
    c. Muscle cramps
    d. Joint stiffness

16. What is the primary cause of endothelial dysfunction in atherosclerosis?
    a. Hypertension
    b. High cholesterol levels
    c. Smoking
    d. All of the above

17. Which cells transform into foam cells in the development of atherosclerosis?
    a. Lymphocytes
    b. Neutrophils
    c. Macrophages
    d. Platelets

18. What is the primary function of matrix metalloproteinases (MMPs) in wound healing?
    a. Promote fibrosis
    b. Degrade extracellular matrix components
    c. Increase vascular permeability
    d. Stimulate collagen production

19. Which cytokine is primarily anti-inflammatory and promotes healing?
    a. TNF-α
    b. IL-1
    c. IL-6
    d. IL-10

20. What is the function of selectins in the inflammatory response?
    a. Mediate leukocyte rolling
    b. Facilitate leukocyte firm adhesion
    c. Assist in transmigration of leukocytes
    d. Enhance phagocytosis

Short Answer Type Questions (Subjective)

1. What are the primary goals of inflammation?
2. Describe the key features of acute inflammation.
3. Explain the process of leukocyte recruitment during acute inflammation.
4. What are the main differences between acute and chronic inflammation?
5. How does the body achieve vasodilation during an inflammatory response?
6. What is fibrosis and how does it occur?
7. Describe the role of macrophages in the inflammatory response.
8. What are the clinical signs of inflammation and their underlying mechanisms?
9. Explain the process of phagocytosis during inflammation.
10. How does histamine contribute to the inflammatory response?
11. Describe the different phases of wound healing.

12. What factors influence tissue repair and regeneration?
13. Explain the role of cytokines in the inflammatory response.
14. What is the significance of VEGF in wound healing?
15. How does endothelial dysfunction contribute to the development of atherosclerosis?
16. Describe the formation and role of foam cells in atherosclerosis.
17. Explain the function of matrix metalloproteinases (MMPs) in tissue remodeling.
18. What is the role of chemokines in leukocyte migration?
19. How do anti-inflammatory cytokines contribute to the resolution of inflammation?
20. Describe the process of angiogenesis during wound healing.

Long Answer Type Questions (Subjective)

1. Discuss the basic mechanisms involved in the process of inflammation, including recognition, recruitment, and removal of the injurious agent.
2. Describe the differences between acute and chronic inflammation, including their mechanisms, key features, and clinical significance.
3. Explain the phases of wound healing in the skin, detailing the cellular and molecular mediators involved in each phase.
4. Discuss the pathophysiology of atherosclerosis, including the stages of plaque formation and the role of inflammation.
5. Explain the role of chemical mediators in the regulation of inflammation, including vasoactive amines, cytokines, and eicosanoids.
6. Describe the clinical signs of inflammation and the molecular mechanisms underlying these signs.
7. Discuss the process of leukocyte migration during inflammation, including the roles of selectins, integrins, and chemokines.
8. Explain the role of macrophages in both the initiation and resolution of inflammation.
9. Discuss the factors that influence tissue repair and regeneration, including the type and extent of injury and systemic factors.
10. Describe the molecular mediators of inflammation and repair, focusing on their sources, functions, and interactions.

Answer Key for MCQ Questions

1. b. To eliminate the initial cause of cell injure
2. c. Tissue destruction and healing simultaneously
3. c. Increased blood flow
4. c. Neutrophils
5. c. Persistent inflammation
6. c. Replacement of damaged tissue with fibrous connective tissue
7. d. All of the above
8. a. Histamine
9. c. Mast cells
10. b. Induce endothelial activation
11. b. Chemotactic factors
12. c. Proliferation
13. b. VEGF
14. b. Produce cytokines and growth factors

15. b. Redness
16. d. All of the above
17. c. Macrophages
18. b. Degrade extracellular matrix components
19. d. IL-10
20. a. Mediate leukocyte rolling