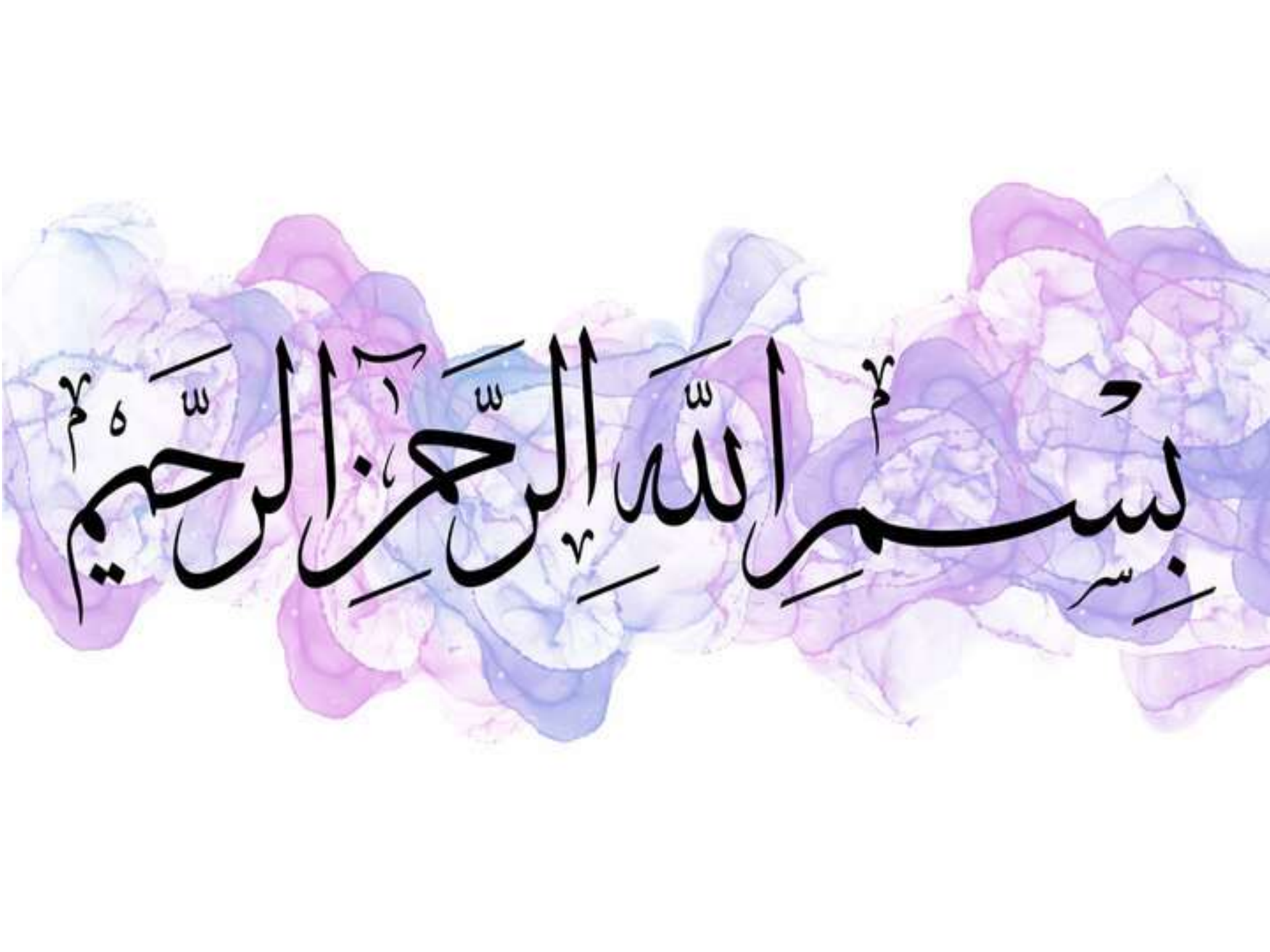
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Foundation Module II

Cellular Events In Acute Inflammation

LGIS

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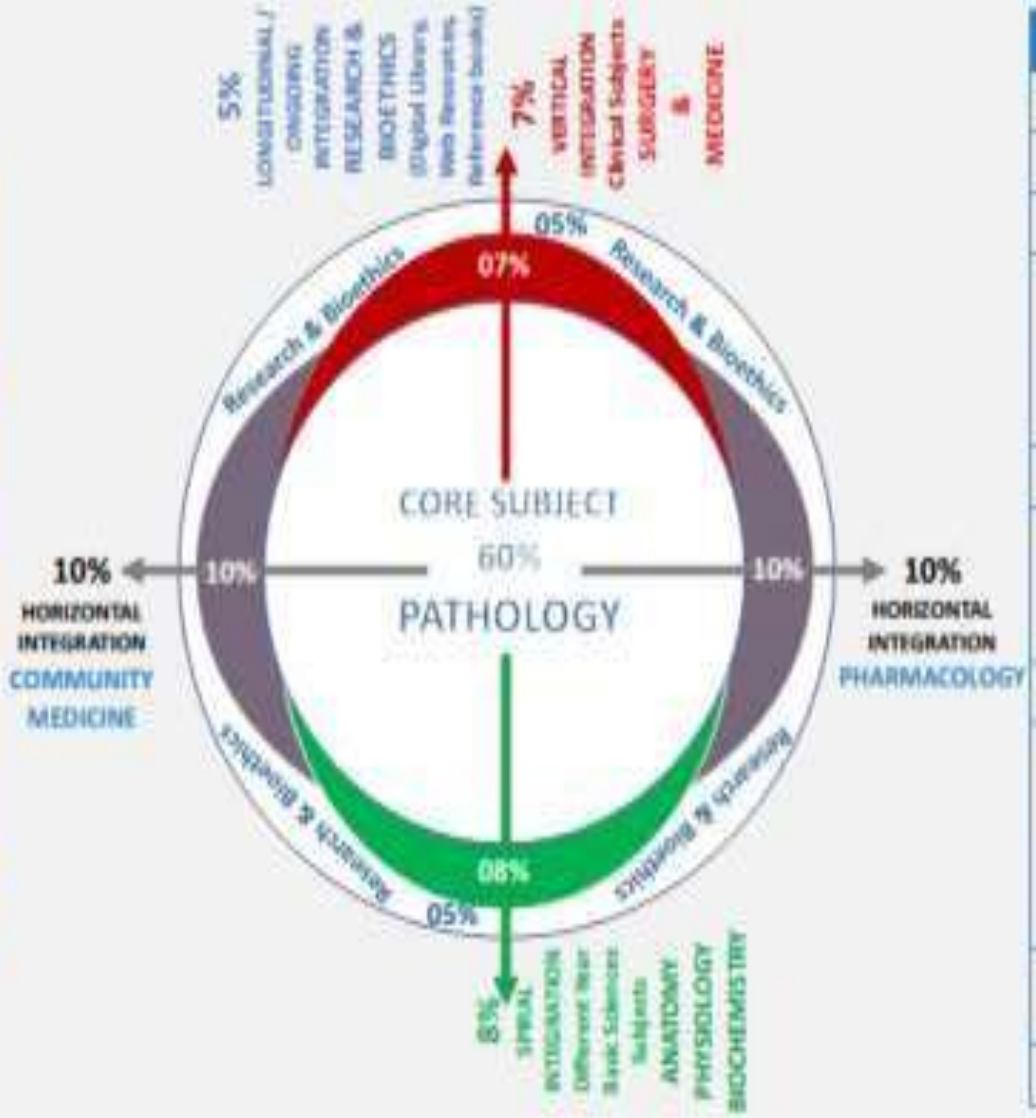
Motto

Vision; The Dream/Tomorrow

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures

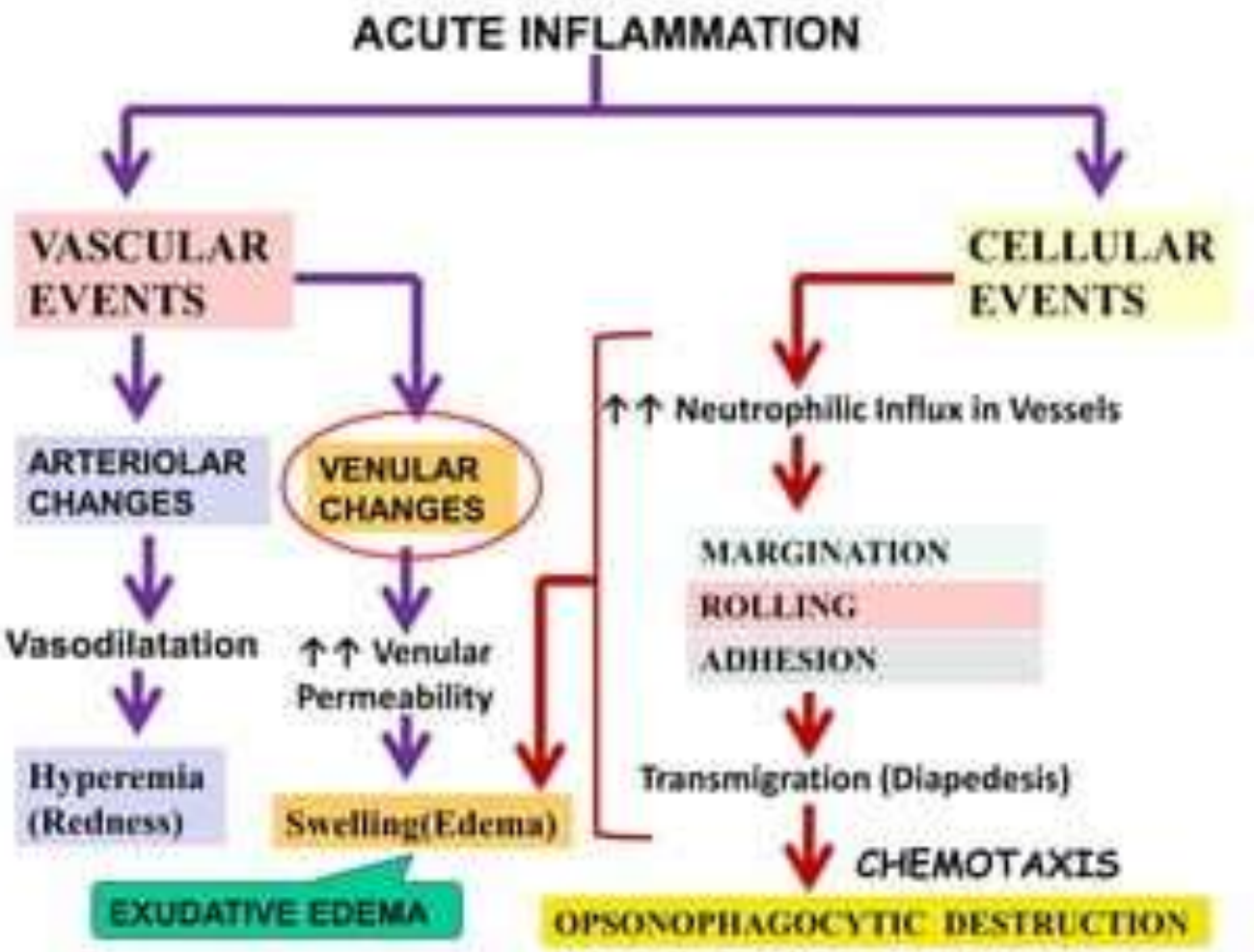


Model 3rd Year Pathology LGIS (≈30 slides)	
Core Subject – 60% (≈ 18-20 slides)	
Pathology (≈ 18-20 slides)	
Horizontal Integration – 20% (≈ 5-6 slides)	
Same Year Subjects	• Pharmacology (10%) (≈ 2-3 slides) • Community Medicine (10%) (≈ 2-3 slides)
Vertical Integration – 07% (≈ 2-3 slides)	
Clinical Subjects	• Medicine (3-5%) (≈ 1-2 slides) • Surgery (3-5%) (≈ 1-2 slides)
Spiral Integration – 08% (≈ 2-3 slides)	
Different Year Basic Sciences Subjects	• Anatomy (1-3%) (≈ 1-2 slides) • Physiology (1-3%) (≈ 1-2 slides) • Biochemistry (1-3%) (≈ 1-2 slides)
Longitudinal / Ongoing Integration – 05% (≈ 1-2 slides)	
Research & Bioethics (≈ 1-2 slides)	

Learning Objectives

- By the end of this session, you should be able to:
- Describe the steps of leukocyte transmigration, a key process in inflammation.
- Explain the role of adhesion molecules in inflammation, including selectins and integrins.
- Understand the process of chemotaxis and phagocytosis, essential for immune defense.
- Discuss leukocyte activation and its consequences, including tissue damage.
- Correlate cellular events with clinical conditions, such as acute and chronic inflammation.
- Explore pharmacological agents targeting inflammation, including anti-histamines and biologics.

Learning Resources : Robbins & Cotran Pathologic Basis Of Disease 10th Edition


ACUTE INFLAMMATION
VASCULAR EVENTS
CELLULAR EVENTS
ARTERIOLAR CHANGES
VENULAR CHANGES
↑↑ Neutrophilic Influx in Vessels
Vasodilatation
↑↑ Venular Permeability
MARGINATION
ROLLING
ADHESION
Hyperemia (Redness)
Swelling(Edema)
Transmigration (Diapedesis)
CHEMOTAXIS
EXUDATIVE EDEMA
OPSONOPHAGOCYTIC DESTRUCTION

Overview of Cellular Events

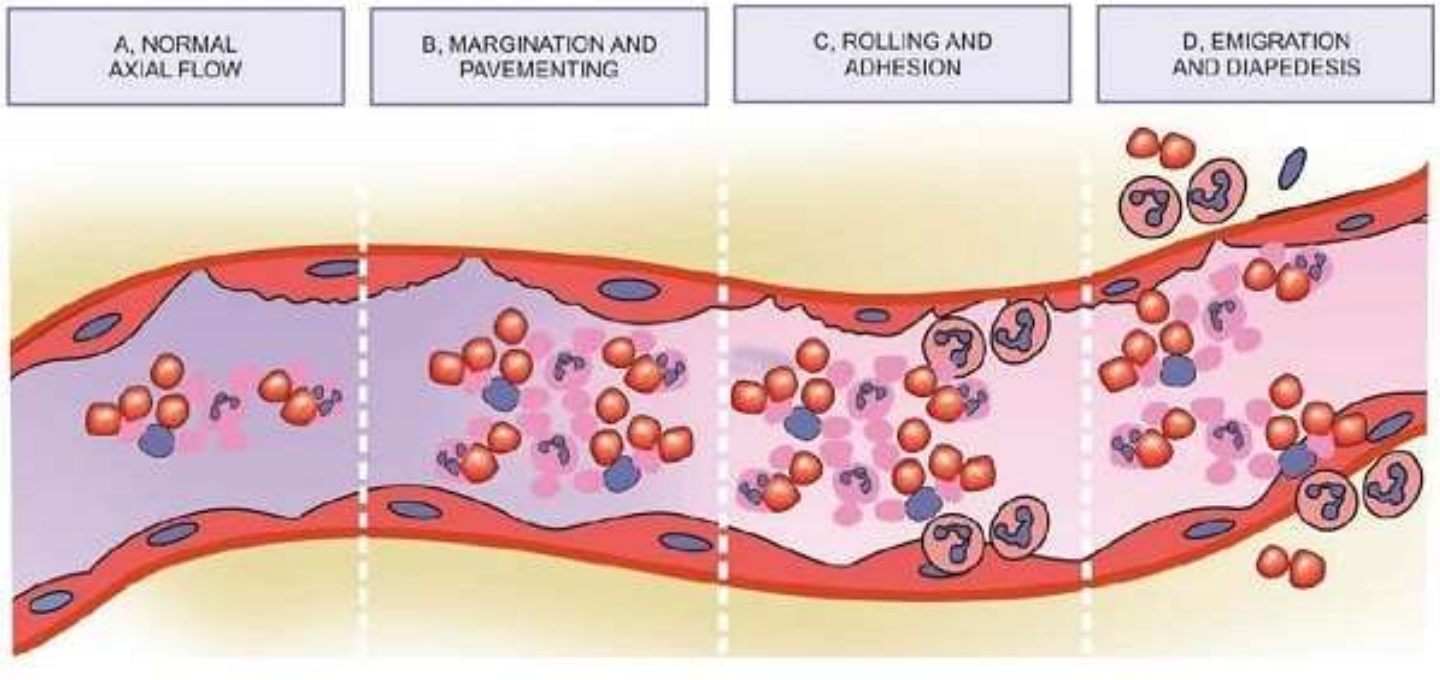
- **Leukocyte Recruitment**: Key step in inflammation, involving the movement of immune cells.
- **Margination**: Leukocytes move to vessel walls due to slowed blood flow.
- **Rolling**: Mediated by selectins, allowing leukocytes to interact with the endothelium.
- **Adhesion**: Firm attachment via integrins, enabling leukocytes to stop rolling.
- **Transmigration**: Migration through endothelium, a process called diapedesis.
- **Chemotaxis**: Movement toward inflammatory site, guided by chemoattractant

Leukocyte Margination

Definition: Leukocytes move to vessel periphery, a process driven by hemodynamics.

- **Causes**: Slowed blood flow in inflammation, allowing leukocytes to interact with the endothelium.
- **Mechanism**: Driven by hemodynamic changes, such as increased vascular permeability.
- **Importance**: Prepares leukocytes for adhesion, the next step in recruitment.
- **Outcome**: Leukocytes interact with endothelium, setting the stage for rolling.

Events in Leukocyte Migration



Leukocyte Rolling

- **Mediators**: Selectins (E-selectin, P-selectin), which bind to ligands on leukocytes.
- **Ligands**: Sialyl-Lewis X on leukocytes, which interact with selectins on the endothelium.
- **Cytokines**: TNF-α and IL-1 increase selectin expression, promoting rolling.
- **Transient Bonds**: Form between leukocytes and endothelium, allowing slow movement.
- **Outcome**: Leukocytes roll along endothelium, preparing for firm adhesion.

Leukocyte Adhesion

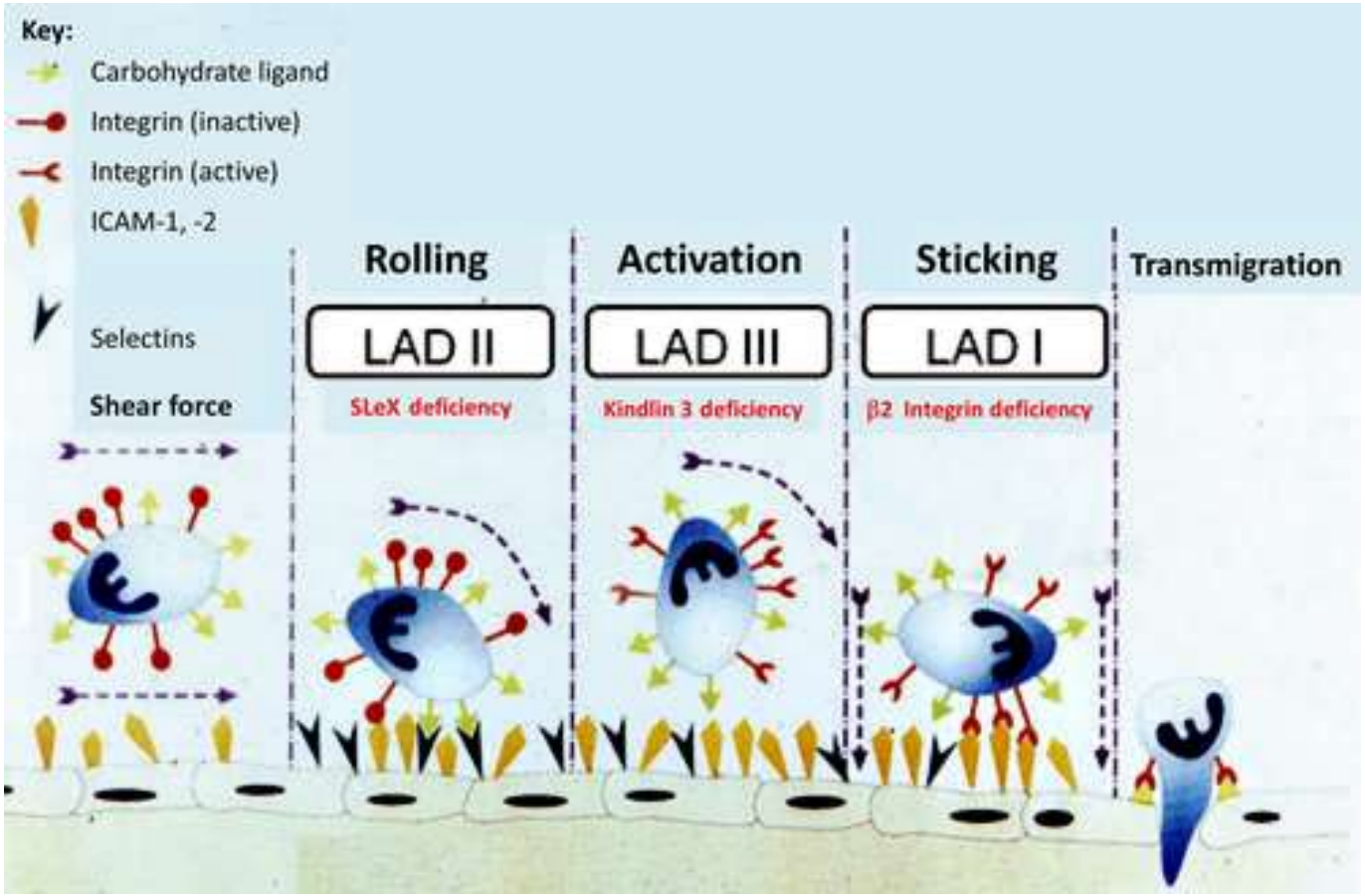
- **Mediators**: Integrins (e.g., LFA-1, Mac-1), which bind to endothelial receptors.
- **Ligands**: ICAM-1, VCAM-1 on endothelium, which interact with integrins.
- **Activation**: Chemokines trigger integrin activation, strengthening adhesion.
- **Strong Bonds**: Form between leukocytes and endothelium, stopping rolling.
- **Outcome**: Leukocytes stop rolling and adhere firmly, ready for transmigration.
- **Diagram**: Leukocyte adhesion, showing integrin-ICAM-1 interactions.

Adhesion Molecules

- **Selectins**: E-selectin, P-selectin, L-selectin, which mediate rolling.
- **Integrins**: LFA-1, Mac-1, VLA-4, which mediate firm adhesion.
- **Immunoglobulin Superfamily**: ICAM-1, VCAM-1, which bind to integrins.
- **Function**: Mediate rolling, adhesion, and transmigration, essential for inflammation.
- **Clinical Relevance**: Targeted in anti-inflammatory drugs, such as biologics.
- **Diagram**: Adhesion molecules and their roles, showing their interactions.

Vertical integration

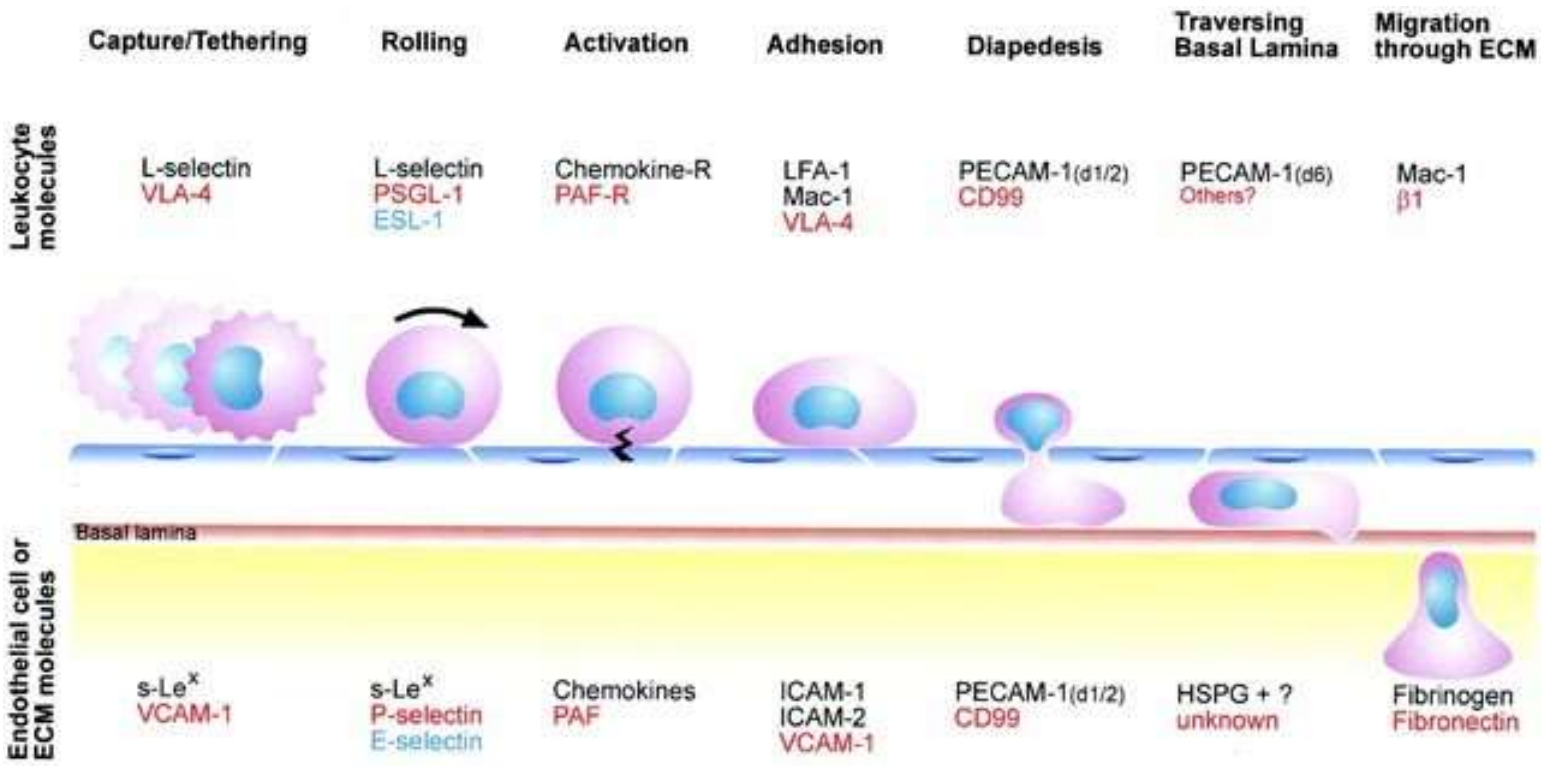
Defects in Adhesion



Transmigration (Diapedesis)

- **Definition**: Leukocytes migrate through vessel walls, a process called diapedesis.
- **Mediators**: PECAM-1 (CD31), which facilitates transmigration.
- **Process**: Leukocytes squeeze between endothelial cells, entering tissues.
- **Chemotaxis**: Directed movement toward chemokines, guiding leukocytes to the site of injury.
- **Outcome**: Leukocytes enter tissue spaces, where they combat infection.
- **Diagram**: Transmigration process, showing leukocytes crossing the endothelium.

Transmigration (Diapedesis)



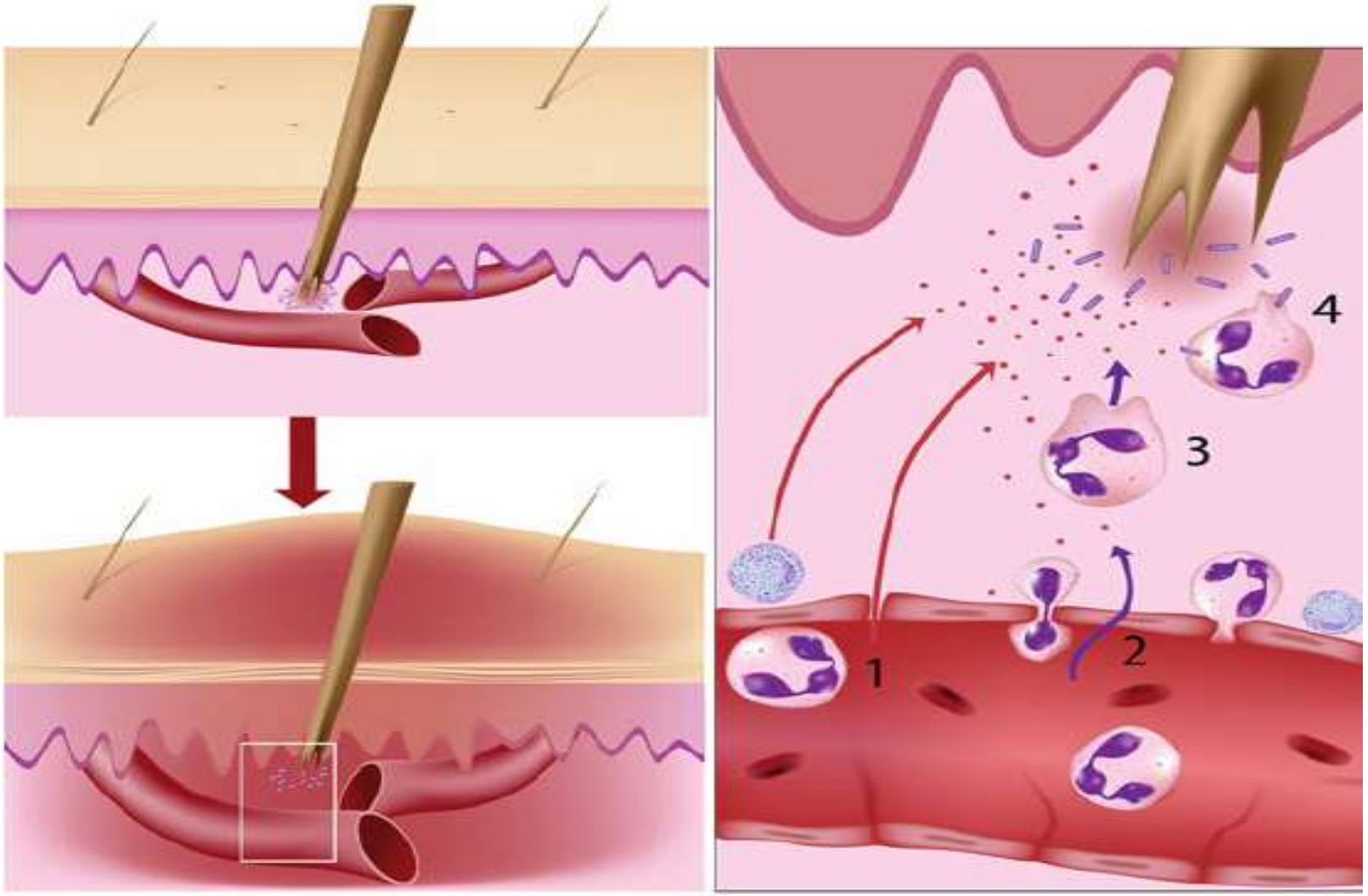
Chemotaxis

Definition: Directed movement toward chemotactic agents, such as C5a and IL-8.

- **Chemoattractants**: C5a, LTB4, IL-8, bacterial products, which guide leukocytes.
- **Receptors**: G-protein-coupled receptors on leukocytes, which detect chemoattractants.
- **Mechanism**: Actin polymerization drives cell movement, allowing directional migration.
- **Outcome**: Leukocytes reach the site of inflammation, where they perform their functions.
- **Diagram**: Chemotaxis process, showing leukocytes moving toward a chemoattractant.

Vertical integration

Chemotaxis

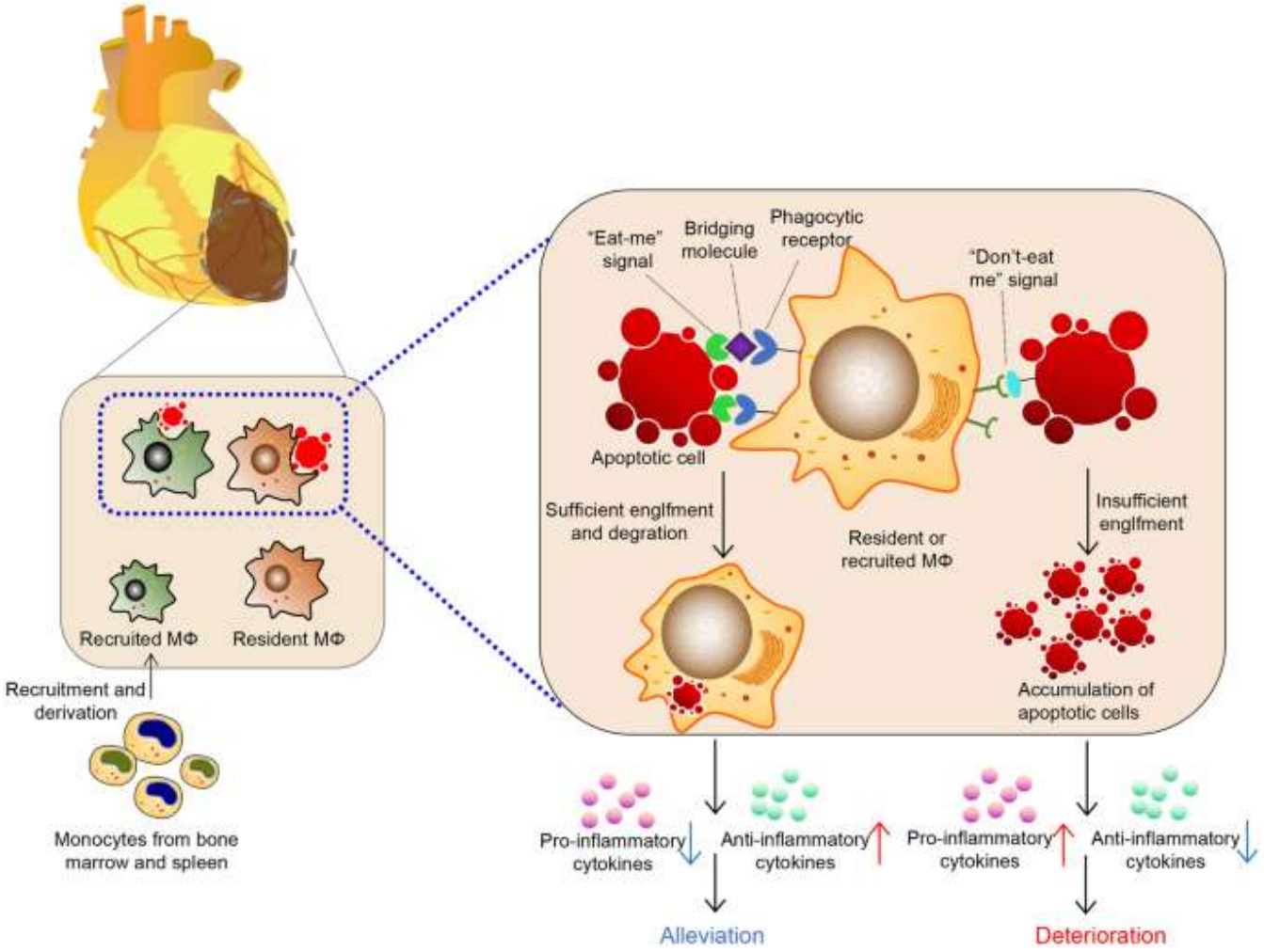


Phagocytosis

- **Definition**: Engulfment and destruction of pathogens, a key immune defense mechanism.
- **Steps**: Recognition, engulfment, phagosome formation, which trap pathogens.
- **Opsonins**: IgG, C3b enhance phagocytosis, marking pathogens for destruction.
- **Phagolysosome**: Fusion of phagosome with lysosome, where pathogens are degraded.
- **Destruction**: Enzymes and ROS kill the pathogen, clearing the infection.

Vertical integration

Phagocytosis Of Necrotic cells Post MI



Leukocyte Activation

- **Triggers**: Pathogens, cytokines, immune complexes, which activate leukocytes.
- **Respiratory Burst**: Production of ROS, which kill microbes but can damage tissues.
- **Degranulation**: Release of enzymes (e.g., MPO), which degrade pathogens.
- **Cytokine Secretion**: Amplifies inflammation, recruiting more immune cells.
- **Outcome**: Enhanced phagocytosis and tissue damage, a double-edged sword.
- **Diagram**: Leukocyte activation, showing ROS production and degranulation.

Respiratory Burst

- **Definition**: Rapid release of reactive oxygen species (ROS), a key defense mechanism.
- NADPH oxidase generates superoxide, the first step in ROS production.
- **Products**: Superoxide, hydrogen peroxide, hypochlorous acid, which kill microbes.
- **Function**: Microbial killing, essential for clearing infections.
- **Side Effect**: Tissue damage, a consequence of excessive ROS production.
- **Diagram**: Respiratory burst mechanism, showing ROS generation.

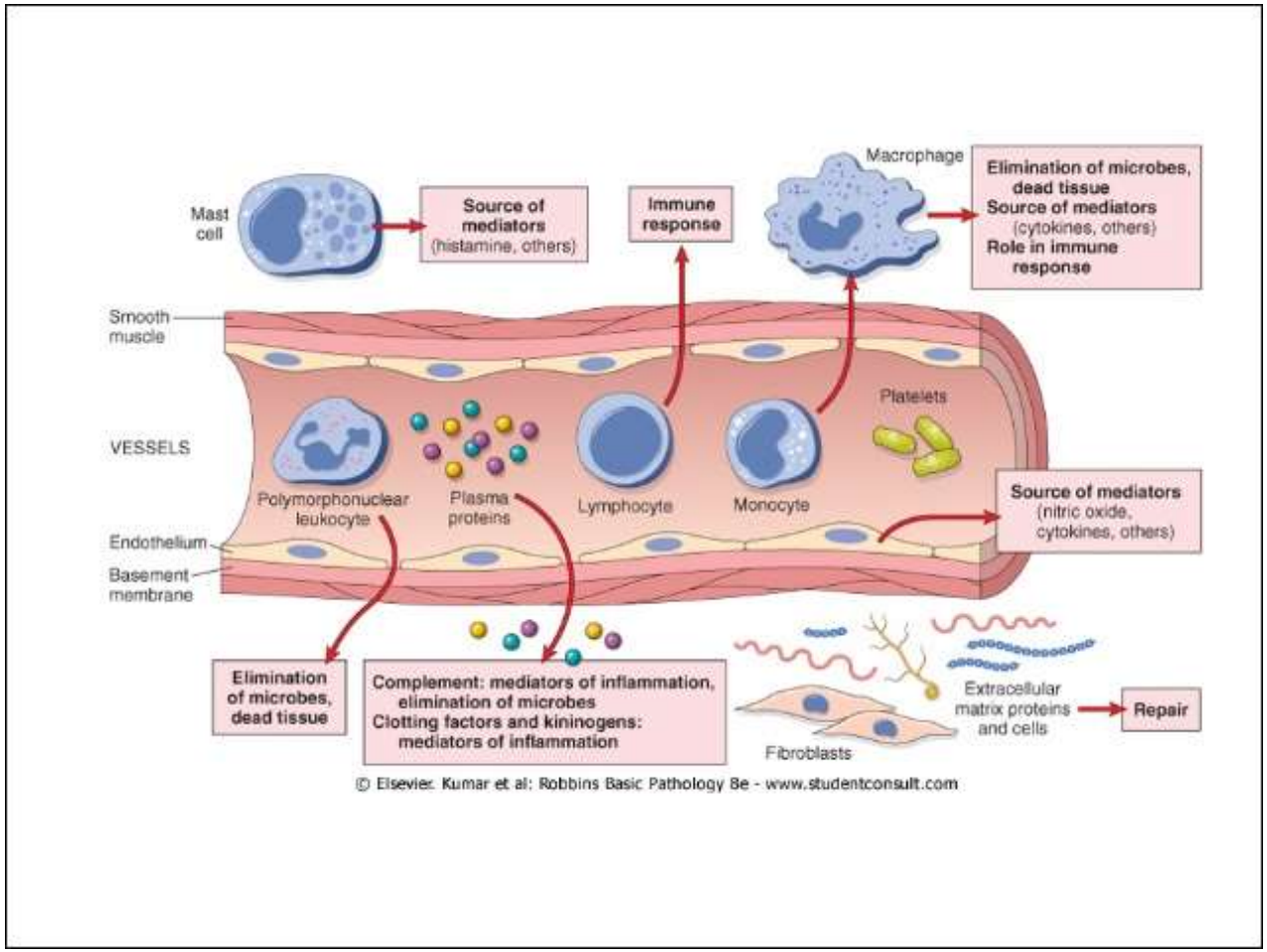
Degranulation

- **Definition**: Release of granules from leukocytes, containing enzymes and mediators.
- **Granules**: Contain enzymes (e.g., MPO, elastase), which degrade pathogens.
- **Function**: Microbial killing and tissue remodeling, essential for inflammation.
- **Regulation**: Controlled by calcium signaling, ensuring timely release.
- **Outcome**: Enhanced inflammation and tissue damage, a necessary trade-off.
- **Diagram**: Degranulation process, showing granule release.

Cytokine Secretion

- **Pro-inflammatory Cytokines**: TNF-α, IL-1, IL-6, which amplify inflammation.
- **Chemokines**: IL-8, MCP-1 attract leukocytes, guiding them to the site of injury.
- **Anti-inflammatory Cytokines**: IL-10, TGF-β, which resolve inflammation.
- **Function**: Amplify or resolve inflammation, maintaining immune balance.
- **Outcome**: Systemic effects (e.g., fever), reflecting widespread inflammation.
- **Diagram**: Cytokine network, showing pro- and anti-inflammatory cytokines

Release of Mediators



Types of Leukocytes

- **Neutrophils**: First responders, short-lived, essential for acute inflammation.
- **Macrophages**: Long-lived, phagocytic, key players in chronic inflammation.
- **Eosinophils**: Parasitic infections, allergies, involved in hypersensitivity reactions.
- **Basophils/Mast Cells**: Release histamine, driving allergic responses.
- **Lymphocytes**: Adaptive immunity, providing long-term immune memory.
- **Diagram**: Types of leukocytes, showing their roles in inflammation.

Clinical Correlation: Acute Inflammation

- **Neutrophil Predominance**: Pus formation, a hallmark of acute inflammation.
- **Symptoms**: Redness, swelling, heat, pain, reflecting increased blood flow and permeability.
- **Examples**: Bacterial infections, abscesses, common causes of acute inflammation.
- **Outcome**: Resolution or progression to chronic inflammation, depending on the cause.
- **Complications**: Tissue damage, fibrosis, if inflammation is not resolved.
- **Diagram**: Acute inflammation, showing neutrophil infiltration.

Vertical integration

Clinical Correlation: Chronic Inflammation

- **Macrophage/Lymphocyte Predominance**: Granulomas, a feature of chronic inflammation.
- **Causes**: Persistent infections, autoimmune diseases, driving long-term inflammation.
- **Examples**: Tuberculosis, rheumatoid arthritis, common chronic inflammatory diseases.
- **Outcome**: Tissue remodeling, fibrosis, leading to organ dysfunction.
- **Complications**: Organ dysfunction, a consequence of prolonged inflammation.
- **Diagram**: Chronic inflammation, showing granuloma formation.

Horizontal integration

Pharmacological Agents

- **Anti-histamines**: Block histamine receptors, reducing allergic symptoms.
- **Corticosteroids**: Suppress cytokine production, reducing inflammation.
- **NSAIDs**: Inhibit cyclooxygenase pathway, reducing pain and swelling.
- **Biologics**: Target TNF-α, IL-1, IL-6, used in autoimmune diseases.
- **Antibiotics**: Treat bacterial infections, addressing the root cause of inflammation.
- **Diagram**: Pharmacological targets in inflammation, showing drug mechanisms.

Longitudinal integration

Novel Anti-inflammatory Agents

- **Lipoxins**: Promote resolution of inflammation, reducing tissue damage.
- **Resolvins**: Derived from omega-3 fatty acids, enhancing inflammation resolution.
- **Protectins**: Protect tissues from inflammatory damage, promoting healing.
- **Clinical Trials**: Testing new biologics and small molecules, improving treatment options.
- **Future Directions**: Personalized anti-inflammatory therapy, tailored to individual patients.
- **Diagram**: Novel anti-inflammatory pathways, showing lipoxins and resolvins.

Longitudinal integration

Bioethics in Inflammation Research

- **Informed Consent**: Essential for clinical trials, ensuring patient understanding.
- **Animal Models**: Ethical use in research, balancing scientific progress and animal welfare.
- **Patient Autonomy**: Respecting treatment choices, a cornerstone of medical ethics.
- **Equitable Access**: Ensuring fair distribution of therapies, addressing health disparities.
- **Transparency**: Reporting research findings accurately, maintaining public trust.
- **Diagram**: Bioethics principles, showing key ethical considerations.

Summary of Cellular Events

- **Margination, Rolling, Adhesion**: Mediated by selectins and integrins, essential for leukocyte recruitment.
- **Transmigration**: PECAM-1 mediates diapedesis, allowing leukocytes to enter tissues.
- **Chemotaxis**: Directed by chemoattractants, guiding leukocytes to the site of injury.
- **Phagocytosis**: Engulfment and destruction of pathogens, a key immune defense.
- **Leukocyte Activation**: ROS, degranulation, cytokine secretion, amplifying inflammation

Summary of Adhesion Molecules

- **Selectins**: Mediate rolling, allowing leukocytes to interact with the endothelium.
- **Integrins**: Mediate firm adhesion, stopping leukocyte rolling.
- **Immunoglobulin Superfamily**: ICAM-1, VCAM-1, which bind to integrins.
- **Clinical Relevance**: Targeted in anti-inflammatory drugs, such as biologics.
- **Outcome**: Leukocyte recruitment and tissue infiltration, driving inflammation.

Therapeutic Agents

- **Anti-histamines**: Block histamine receptors, reducing allergic symptoms.
- **Corticosteroids**: Suppress cytokine production, reducing inflammation.
- **NSAIDs**: Inhibit prostaglandin synthesis, reducing pain and swelling.
- **Biologics**: Target specific cytokines, used in autoimmune diseases.
- **Antibiotics**: Treat infections causing inflammation, addressing the root cause.

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Nitric oxide in cellular adaptation and disease

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ARTICLE INFO

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Adaptation
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ABSTRACT

Nitric oxide synthases are the major sources of nitric oxide, a critical signaling molecule involved in a wide range of cellular and physiological processes. These enzymes comprise a family of genes that are highly conserved across all eukaryotes. The three family members found in mammals are important for inter- and intra-cellular signaling in tissues that include the nervous system, the vasculature, the gut, skeletal muscle, and the immune system, among others. We summarize major advances in the understanding of biochemical and tissue-specific roles of nitric oxide synthases, with a focus on how these mechanisms enable tissue adaptation and health or dysfunction and disease. We highlight the unique mechanisms and processes of neuronal nitric oxide synthase, or NOS1. This was the first of these enzymes discovered in mammals, and yet much remains to be understood about this highly conserved and complex gene. We provide examples of two areas that will likely be of increasing

EOLA

- A 4-year boy is brought to the pediatric clinic by his parents due to recurrent bacterial infections, including frequent episodes of otitis media, sinusitis, and pneumonia. The parents report that the child has had multiple courses of antibiotics over the past two years. On further questioning, they mention that the child has also had several skin abscesses caused by *Staphylococcus aureus*.
- Based on the clinical presentation and laboratory findings, which of the following is the most likely underlying defect in this patient?

- A. Defect in NADPH oxidase complex
- B. Defect in adhesion molecules (e.g., LFA-1)
- C. Defect in chemokine receptors (e.g., CXCR1/CXCR2)
- D. Defect in myeloperoxidase (MPO)
- E. Defect in complement component C3

Thank You