
CHAPTER 5

Unit Cell Processes in the Tissue Environment

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5.1 DEFINITIONS

Healing

Process of restoration of injured tissue.

Healing by First Intention (also referred to as primary and direct healing):

Restoration of continuity of injured tissue without the intervention of granulation tissue. Examples are the healing of a scalpel incision in soft tissue or the healing in the very narrow gap (perhaps 2 cell diameters, 20 μm) between the fragments of a fractured bone that have been re-approximated.

Healing by Second Intention:

Healing involving granulation tissue filling the gap (defect) in the injured tissue.

Inflammation (Dorland's dictionary definition and Pathologic Basis of Disease)

A localized response elicited by injury or destruction of vascularized tissues, which serves to destroy, dilute, or wall off (sequester) both the injurious agent and the injured tissue. It is characterized in the acute form by the classical signs of pain (dolor), heat (calor), redness (rubor), swelling (tumor), and loss of function (functiоlaesa). It is caused by injurious agents: biological agents (bacteria), physical agents (heat and mechanical trauma), chemical agents (small toxic molecules and immunogenic macromolecules). The role of inflammation is to contain the injury and facilitate healing. Unresolved inflammation can be harmful.

Repair

The end result of healing is scar.

Regeneration

The end result of healing is tissue similar to the original tissue.

Clot

A semi-solid mass of blood platelets and blood cells in a fibrin matrix.

Coagulation

The process of clot formation.

Hematoma

A localized blood clot in a tissue or organ due to a ruptured blood vessel.

Thrombus

An aggregation of platelets and fibrin with entrapment of cellular elements within a blood vessel; frequently causing vascular obstruction.

Hemorrhage

Bleeding.

Hemostasis

Arrest of bleeding.

5.2 PROCESSES OF HEALING

5.2.1 Injurious Agents

- Biological Agents
 - Microbial infection
- Chemical Agents
- Physical Agents
 - Thermal
 - Electrical
 - Mechanical
 - Trauma
 - Surgery
 - Implant movement

5.2.2 Features Of Healing

End Result

- | | |
|----------------------------|--------------|
| Similar to original tissue | Regeneration |
| Scar | Repair |

Size of Wound

- | | |
|-------------------------------|---|
| No/minimal tissue destruction | Resolution |
| Small wound (e.g., incision) | Healing by first intention (primary or direct healing) |
| Large | Healing by second intention (healing with granulation tissue) |

Vascularity

- | | |
|-------------|---|
| Vascular | Inflammation precedes repair or regeneration |
| Nonvascular | No inflammation |
| | No healing (cornea, meniscus, articular cartilage), regeneration (epidermis), or repair (?) |

Time

- | | |
|--|----------------------|
| Early (e.g., due to surgery) | Acute inflammation |
| Late (e.g., due to persistence of "injury" associated with presence of an implant) | Chronic inflammation |

Predominant Cell Types

- | | |
|---------|--|
| Acute | PMN, Leukocytes, Macrophage, Endothelial, Fibroblast |
| Chronic | Macrophage, MFBGC, Fibroblast |

5.2.3 Repair vs. Regeneration

5.3 INFLAMMATION

5.3.1 Cell Involved in Inflammation

CELL TYPE	SOURCE	FUNCTION
Acute Inflammatory Cells		
Basophil	Circulation	Regulatory cell releases agents that mediate vascular leakage and inflammation (e.g., PAF, serotonin, and histamine)
Platelet	Circulation	Hemostasis of damaged blood vessels/clotting
Lymphocyte	Circulation	Involved in immune response
Plasma cell	Circulation	Antibody producing cell
PMN	Circulation (inflammation)	Phagocytosis/removal of necrotic tissue (acute)
Mast cell	Tissue	Regulatory cell releases heparin, serotonin, and histamine-containing granules (exocytosis-degranulation)
Endothelial cell	Severed vessel	Forms vessels/neovascularization
Macrophage	Circulation	Phagocytosis of necrotic tissue and lysed PMNs (acute and chronic); fuse to form multinucleated foreign body giant cells
Chronic Inflammatory Cells		
Macrophage		
Histiocyte	Tissue	Same as macrophage
Fibroblast	Tissue	Synthesis of collagen and other ECM components; production of degradative enzymes for remodeling (e.g., collagenase)

5.3.2 Acute Vs. Chronic Inflammation

5.3.2.1 Acute Inflammation

Comprises cellular processes, soluble mediators, and vascular changes occurring immediately following injury to vascular tissue and is of relatively short duration (from a few minutes to a few days). The classical clinical signs are: heat, redness, swelling, and pain. In many cases function of the tissue is compromised.

5.3.2.2 Chronic Inflammation

Cell types and activities associated with a persistent injury or permanent implant, that could continue for months or years.

5.3.2.2.1 Synovium

The chronic inflammatory tissue bordering an implant often has the cell composition (macrophages and fibroblasts) and arrangement (cells in mono- or multiple-layer) consistent with synovium, The tissue that lines joints and encapsulates fluid-filled sacs (bursae).

5.3.2.2.2 Granuloma

A focal accumulation of epithelioid cells (macrophages altered in appearance to resemble epithelial cells) and multinucleated giant cells. This term is also applied to collections of lymphocytes surrounded by fibrous tissue.

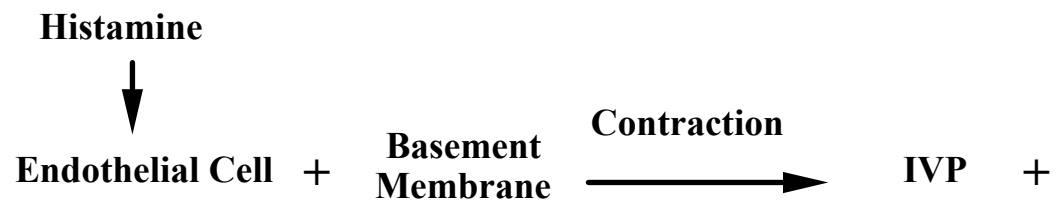
5.4 UNIT CELL PROCESSES OF WOUND HEALING

5.4.1 Blood Components and Vascular Response

5.4.1.1 Blood Components

5.4.1.2 Change in blood vessel diameter and permeability to fluid and cells due to the action of regulators on smooth muscle cells and endothelial cells, respectively.

5.4.1.3 **Increased vascular permeability** to fluid in vessels with intact endothelium is due to the action of regulators (*e.g.*, histamine) in causing co-contraction of endothelial cells, producing gaps in the junctions between the cells. This is normally the **immediate transient response**.



5.4.1.4 The combined effect of increased vascular permeability and dilation of the vessel is to slow the blood circulation resulting in **stasis** and **margination** of leukocytes that are normally confined to the center of the vessel.

5.4.1.5 Leukocyte migration through the vessel wall is controlled by the upregulation of certain cell adhesion molecules (CAMs) in the leukocyte membrane and the membrane of the endothelial cell.

5.4.1.5.1 **Adhesion** of the leukocyte to the endothelial cell is due to CAMs in the leukocyte (LFA1, MO1, and P150 upregulated by TNF and C5a) serving as ligands for the CAMs of the endothelial cell (ELAM-1 and ICAM-1 upregulated by IL-1 and TNF).

5.4.1.5.2 **Emigration** of leukocytes through separations in the junctions between endothelial cells.

5.4.1.5.3 **Migration** of the leukocyte through the extracellular matrix of tissue (chemotactic agents: bacterial products, eicosanoids such as LTB₄, and certain cytokines).

5.4.3 Phagocytosis

5.4.3.1 Primary* Phagocytic Cells

Polymorphonuclear neutrophils (PMN)

Macrophages

Multinucleated foreign body giant cells

*Other cells such as fibroblasts may be phagocytic under special circumstances

5.4.3.2 Stages of Phagocytosis

a) Contact

b) Binding

- membrane receptor binding

c) Formation of Phagosome

- infolding of the cell membrane engulfing the particle

- membrane-bound compartment containing the particle

d) Formation of Phagolysosome

- fusion of lysosome (membrane-bound packet of enzyme and other degradative agents) with the phagosome

5.4.3.3 Degradative and Inflammatory Regulators Released by the Macrophage During Phagocytosis

Degradative Agents

- Lysosomal enzymes

- Oxygen-derived free radicals

Regulators

Eicosanoids

- prostaglandins

- leukotrienes

Cytokines

- tumor necrosis factor

- interleukins

5.4.3.4 Mechanisms of Release of Products from the Macrophage

Cell death

Regurgitation

Perforation/Cell Wounding

Reverse endocytosis

5.4.3.5 Chemotactic Stimuli for Monocytes

Chemotactic peptides (bacteria)

Leukotriene B₄

Lymphokines (cytokines from lymphocytes)

Growth factors (*e.g.*, PDGF, TGF- β)

Collagen and fibronectin (fragments)

Fragments of complement molecules (*viz.*, C5a)

5.4.3.6 Macrophage Properties

Tissue Injury

Oxygen metabolites
Proteases
Eicosanoids
Cytokines

Fibrosis

Cytokines
– IL-1, TNF
– FGF, PDGF
– TGF- β
– angiogenesis factor

5.4.3.7 Increased Activities Associated with "Activated" Macrophages

Bacteriocidal activity
Tumoricidal activity
Chemotaxis
Endocytosis
Secretion of biologically active products

5.4.3.8 Life Spans of Phagocytes

PMNs: days

Macrophages: monocytes circulate in the peripheral blood 24-72 hours;
macrophages survive in tissue from months to years

Multinucleated Foreign Body Giant Cells: survive in tissue from months to ?

5.4.4 Neovascularization

- 1) Enzymatic degradation of the basement membrane of the parent vessel
- 2) Migration of endothelial cells
- 3) Proliferation of endothelial cells
- 4) Maturation of endothelial cells and organization into capillary tubes

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