

TISSUE REPAIR PROCESSES

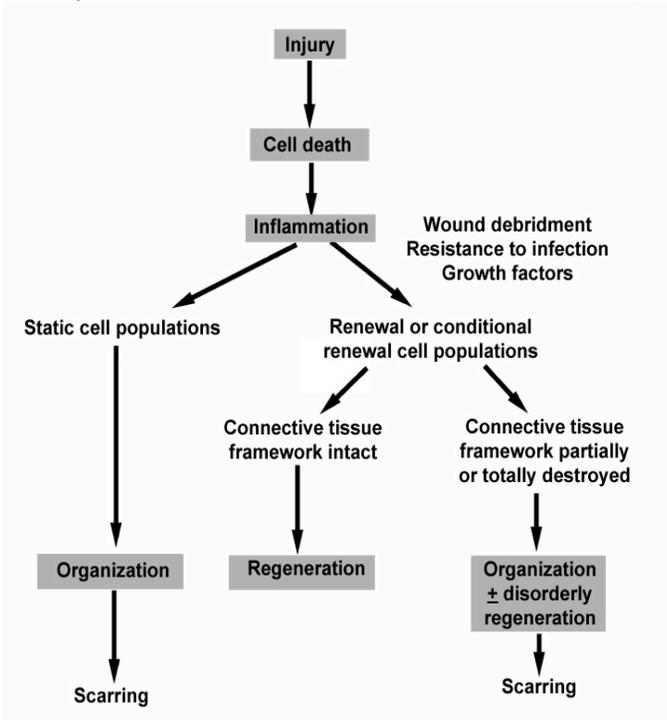
Reading: Basic Pathology, Chapter 3.

Summary: The mechanism for the resolution of the inflammatory response and cell necrosis is discussed followed by a survey of the important serum and tissue factors regulating this response. Circumstances that aid or hinder repair are listed.

I. REVIEW-INFLAMMATION YIELDS TO HEALING AND REPAIR.

- A. Resolution of inflammation due to cytokine inhibitors IL-10, IL-4, & IL-13, return of endothelium to pre-inflammatory state, inactivation of chemotactic agents, and apoptosis and phagocytosis of polys by macrophages. Dissolution of fibrin clot follows (Figure 1).

- B. Best resolution of all is regeneration or total replacement of tissue: often not possible in man. The solution to this problem may lie in the use of stem cells that are from the blastocystic stage of the embryo. The inner cell mass of the blastocyst contains cells that will become the fetus. Some of these cells are pluripotent stem cells that give rise to all types of somatic and germ cells. These at some stage give rise to



multipotent tissue-specific stem cells, that in turn generate both germ line and tissue-specific, multipotent stem cells.

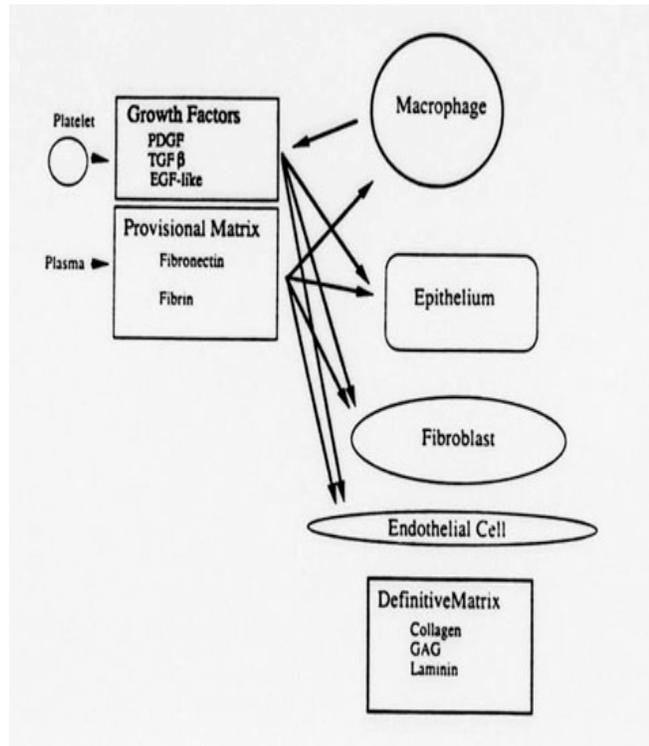
1. Compromise - replacement by connective tissue - scar formation.
2. Scar formation previously thought absolutely necessary in non-replicating, highly-differentiated tissues - heart, brain, etc.
3. Cell death by apoptosis does not induce inflammation, vascular proliferation, or collagen deposition. Necrosis results in tissue fibrosis.

II. REGENERATION POTENTIAL- 3 Cell Types.

- A. Labile - continuously proliferating - surface epithelium, hematopoietic, endometrium-can be replaced.
- B. Stable - discontinuous replication; arrest in G₀ in mitotic cycle; slow but definite replication; can replace necrotic tissue; normal supporting stroma must remain intact as an organizer if replacement is to be successful - liver, renal tubules, etc.
- C. Permanent cells - non-replicating, highly specialized such as neurons & cardiac muscle; same tissues that undergo hypertrophy; cell death here gives rise to scarring and loss of function; DNA synthesis goes on in these cells, but this is repair of DNA, not replication. Current challenge to this concept: with respect to the myocardium, mitosis of cardiac myocytes after infarct; to the CNS, proliferation of neuronal tissue after stroke.

- III. REPAIR - proliferation of tissue at the site of an injury to fill a gap.
- A. Simple removal of cells such as mild burn or an abrasion - cells grow in from sides to fill gap.
- B. Cleanly incised wound - healing without granulations or healing by first intention (Figure 2).

1. First response - inflammation, hemorrhage. Vascular injury causes release of endothelial cell granules containing P-selectin that adheres to endothelium, and von Willebrand factor, that is deposited on exposed extracellular matrix and causes platelet adhesion. Platelet degranulation releases an integrin promoting further platelet adhesion. Platelet factors recruit polys & monocytes. Release histamine, serotonin, & thromboxane.



2. Fibrin clot fills any gap and stabilizes platelet plug. Fibronectin - see section IVe2a
3. In first 24 hours - neutrophil migration.
4. Later - macrophages.
5. By 3 to 5 days - capillaries and fibroblasts enter clot-granulation tissue proliferation.
 - a. Fibroblasts make collagens, deposit other extracellular matrix elements including elastin, proteoglycans, and hyaluronic acid; they give rise to contracting myofibroblast cells. Collagen - the most abundant protein in nature. Triple-stranded structure. Final steps in synthesis of collagen from procollagen are extracellular. Wound strength proportional to collagen accumulation.
 - b. Capillaries - degradation of basement membrane of venules allowing formation of capillary sprouts followed by migration of endothelial cells into tissue; proliferation of endothelial cells, and maturation with organization into capillary loops, that grow as closed tubes from all directions, branch, unite, open up, and establish blood supply. Angiogenesis factors: bFGF, VEGFs, angiopoietins- Ang 1 & 2 & TIEs (TK receptors for Ang 1 & 2, see Fig 4-15, Robbins). Hypoxia-inducible factor (HIF-1) is a transcriptional activator of VEGFs made within 24h of an infarct; bFGFs are chemotactic & mitogenic for endothelium. Matrix proteolytic enzymes (MMPs) allow capillaries to penetrate tissues. Lymphatics form in the same general manner, using somewhat different mediators.
 - c. Phagocytes (mostly macrophages) clean up debris, fat, clot, proteins, etc.
 - d. By 7-14 days strength of tissue almost normal because collagen

- laid down by fibroblasts forms scar; so, can remove sutures in a week but strength not maximal for several weeks.
- C. Repair of an open wound or ulcer - healing by second intention or with granulations. Ulcer - break in any epithelial tissue (skin, mucous membrane) exposing underlying tissue.
 1. Sequence as described above, but gap filled with granulation tissue. Inflammation may be more intense.
 2. Epithelial regeneration - growth from edge, then mitosis and sliding
 3. When epithelium covers granulation tissue, it stops growing.
 4. Wound closure: primary; secondary by gradual granulation tissue formation & epithelialization with contraction and, delayed closure.
 5. May give rise to a scar which is collagen + some fibroblasts.
 6. Contraction of scar due to both myofibrils and collagen.
 7. Good end result - healing; bad-adhesions, loss of function.
 - D. Variations in different tissues, but the repair process is basically the same.
 1. Muscle - need intact sarcolemma and nuclei to get repair. Production of collagen can prevent healing.
 2. Nerves - axons sprout and Schwann cells proliferate along neurotubules.
 3. Bone - formation of callus.
- IV. REGULATION OF CELL PROLIFERATION AND WOUND HEALING. During wound healing this is a well-controlled process, but when regulators of growth go awry, we get uncontrolled growth (neoplasia).
- A. Cell surface growth receptors.
 1. Intrinsic kinases for growth factors. Following ligand binding, receptors dimerize, and self phosphorylate. Chains of intracellular phosphorylation result in activation of nuclear transcription factors.
 2. Receptors requiring extrinsic kinases. Important in cytokine actions.
 3. G-linked receptors. Ligand binding activates G protein to form cyclic AMP. Hormone action.
 - B. Signal transduction pathways. Transmit external signals to nucleus.
 1. Mitogen-activated protein (MAP) kinase - signals by growth factors. Activates RAS proteins that eventually induce growth.
 2. Janus kinase (JAK)- Signal transducers and activators of transcription (STAT). Important in cytokine biological activity.
 3. Other pathways are discussed in Robbins pp64-66.
 - C. Cell cycle regulatory & tissue growth factors. Signals may be autocrine (self response), paracrine (response by cells in close proximity), or endocrine (response at a distance)
 1. Cyclins, acting with cyclin-dependent kinases (CDKs) induce cascade of phosphorylations resulting in mitosis. Check points regulate cyclins - most important is p53 that increases expression of CDK inhibitor p21.
 2. Growth factors
 - a. Fibronectin - acts as a glue that binds fibrin, collagen, cells, etc. Exists in several forms in tissues. Receptor is an integrin. Synthesized locally in wounds mostly by fibroblasts. Chemotactic for fibroblasts, endothelial cells, and monocytes. Promotes wound contraction and epithelial migration.
 - b. Platelet - derived growth factor (PDGF) - synthesized in epithelial cells and macrophages, but stored in platelet granules that are growth factor for fibroblasts & are chemotactic for fibroblasts and macrophages. Stimulates synthesis of collagen. PDGF has structural homology to β chain of oncogene sis. PDGF has been

used for treatment of poorly healing skin ulcers.

- c. Transforming growth factor- β (TGF- β) actually inhibits cell growth (epithelial and T cells), but promotes differentiation of fibroblasts and epithelium; made in macrophages and stored in platelets. Promotes synthesis of collagen and fibronectin by fibroblasts, and is angiogenic. Synthesized by macrophages at wound site. Chemotactic for macrophages and fibroblasts
- d. Epidermal growth factor (EGF)/ transforming growth factor- α (TGF- α). Licking your wounds is good therapy, for male rodents. Made in platelets; keratinocyte mitogen; give rise to marked increase in connective tissue & endothelial growth.
- e. Other factors - cytokines. Nerve cell growth factor (NGF) promotes directional migration of axons; fibroblast growth factors (FGFs) - promote angiogenesis; and, insulin-like growth factors (IGF) also synergizes with PGDF in stimulating connective tissue growth.

II. COLLAGEN AND WOUND HEALING. PDGF, FGF, IL-1, and TNF induce collagen production

III. FACTORS IN WOUND HEALING.

- 1. To help - apposition, immobilization, and good blood supply.
- 2. Factors hindering healing - infections, diabetes, poor circulation; presence of devitalized tissue or foreign bodies - need for debridement
- 3. Paradox of the suture - apposition by a foreign body.
- 4. Other factors.
 - a. Presence of another wound - no effect.
 - b. Nutrition - especially vitamin C.
 - c. Hormones & drugs - steroids, non-steroidal anti-inflammatory drugs, anticoagulants, or immunosuppressives impair healing and scar formation.

IV. WHEN THINGS DON'T GO QUITE RIGHT.

- A. Excessive scarring- keloid formation. A keloid is a hard, projecting mass of scar tissue due to over production of collagen during the healing process.
- B. Impairment of function by scars -examples: surgical adhesions, cirrhosis of the liver, & rheumatic heart disease. In cirrhosis, ethanol gives rise to cetaldehyde, hydrogen peroxide, and free radicals in the liver thru oxidation by P450 enzymes. These induce TNF- α & TGF- β that result in collagen formation and fibrogenesis.