Tissue Repair, Fibrosis, and Healing

HST.035

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Tissue Repair (Healing)

- Regeneration of injured tissue (replacement by normal cells of the same kind)
- Replacement by fibrous tissue (fibrosis, scarring)
Normal Cell Proliferation

Proliferating cells progress through a series of defined phases and checkpoint, collectively call the *cell cycle*.
Control of Cell Cycle

- Progression through the cell cycle is controlled at specific **checkpoints** (*restriction point in G₁, mitosis entry and mitosis exit*)

- Transition between stages of mitosis is triggered by increased activity of **cyclin-dependent kinases (CDK)**

- Each CDK modulates the activity of a subset of cellular targets specific for progression through individual transitions with the cell cycle
Control of Cell Cycle
Control of Cell Cycle

CDK activity is controlled by constant synthesis and cyclic breakdown of specific *cyclins*.
Control of Cell Cycle

- Cyclin-CDK complexes are also regulated by the binding of **CDK-inhibitors**

- CDK-inhibitors are particularly critical at cell cycle checkpoints, such as G₁ → S and G₂ → M, where adequacy and fidelity of DNA synthesis and replication are monitored.

- When DNA is found to be damaged, TP53 (p53) is stabilized and induces transcription of CDKN1A (p21), an inhibitor which arrests cells in G₁ or G₂.

- If DNA damage is too extensive, TP53 will initiate apoptosis.
Cell growth and differentiation are dependent on extracellular signals from soluble polypeptide growth factors and the ECM.
Polypeptide Growth Factors

- Soluble growth factors are transported either via the Gap junctions, or by autocrine, paracrine, endocrine, or synaptic transmission.

- For intracellular receptors, ligand binding leads to formation of complexes that directly associate with nuclear DNA and activate transcription.

- For cell surface receptors, ligands bind to a variety of receptor types that ultimately lead to activation of nuclear transcription factors.
Major Types of Cell Surface Receptors

Diagram showing various types of cell surface receptors, including ligands, receptors, ion channels, and pathways such as PI3 Kinase, MAP Kinase Pathway, IP₃ Pathway, cAMP Pathway, and JAK/STAT Pathway. The diagram also illustrates the involvement of transcription factors and DNA transcription.
ECM: *Interstitial Matrix and Basement Membrane*

Biological Roles of the ECM

- Mechanical support
- Determination of cell polarity
- Control of cell growth
- Control/maintenance of cell differentiation
- Scaffolding for tissue renewal
- Establishment of tissue microenvironment
- Storage and presentation of regulatory proteins
Major Components of the ECM

- Collagen
- Elastic fibers
- Proteoglycans and hyaluronan
- Fibronectin
- Laminin
- Integrins
Fibrillar Collagen: Tensile Strength

Collagen Fibrills
Elastic Fibers: Stretch and Recoil

- Stretch
- Relax
- Cross-link
- Single elastin molecule
Proteoglycans and Hyaluronan: Hydrated Gels

Proteoglycans have a core of protein to which glycosaminoglycans are attached.

Glycoproteins are globular proteins with branched monosaccharide chains.

Proteoglycans such as syndecan can be transmembrane proteins with ligand binding capacity.
Fibronectin and Laminin

- Fibronectin bind to a wide spectrum of ECM components and can attach to cell surface integrins
- Laminin is a key glycoprotein in the basement membrane that binds underlying ECM components such as type IV collagen
- Laminin also modulates cell survival, proliferation and differentiation
Integrins link the ECM to Actin Cytoskeleton through Focal Adhesion Complexes.
ECM and Growth Control
Repair by Connective Tissue (Fibrosis/Scarring)

- Occurs when severe cell injury and damage to ECM framework precludes regeneration of native tissue
- Fibrosis progresses through four main stages:
  - Angiogenesis
  - Migration and proliferation of fibroblasts
  - Deposition of ECM
  - Remodeling of ECM
Fibrosis/Scarring

Overview of Tissue Response to Injury

VASCULAR AND CELLULAR RESPONSE

ACUTE INFLAMMATORY EXUDATION

Stimulus promptly destroyed

No or minimal necrosis of cells
Exudate resolved
Restitution of normal structure
Example: Mild heat injury

Exudate organized
Scarring
Example: Fibrinopurulent pericarditis, peritonitis

Stimulus not promptly destroyed

Necrosis of cells
Tissue of stable or labile cells
Framework intact
Regeneration
Restitution of normal structure
Example: Lobar pneumonia

Framework destroyed
Scarring
Example: Bacterial abscess

Tissue of permanent cells
Scarring
Example: Myocardial infarction