MECHANISM OF TISSUE REGENRATION

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Learning Objectives

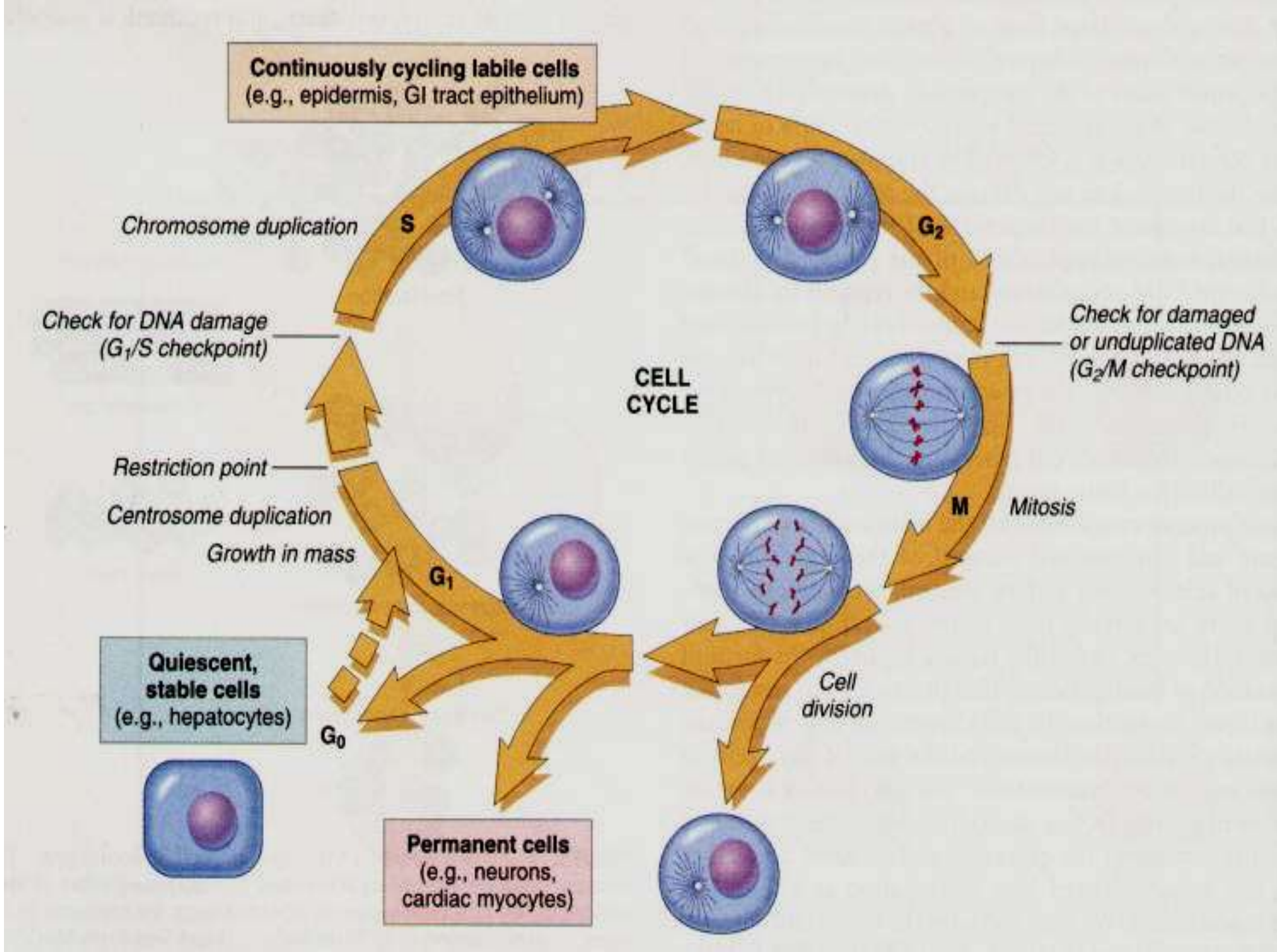
- Describe mechanism of tissue regeneration C2
- Define: Collagen, Elastin, Fibrillin,cell adhesion Proteins, Glycosaminoglycans, Proteoglycans C1
- Describe Extracellular Matrix and cell Matrix interaction
- Demonstrate collaborative team work and problem solving aptitude A3

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

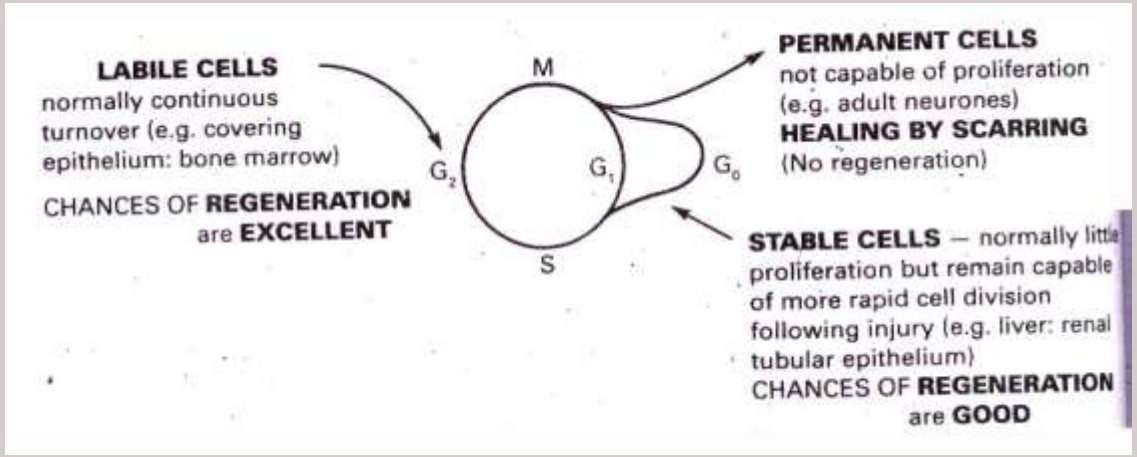
Topics of discussion

- What is the role of tissue regeneration in tissue repair. Core
- Describe proliferative capacities of different tissues.- Vertical Physiology
- Enlist and describe functions of growth factors and growth factor receptors involved in regeneration and repair. Core / vertical biochemistry
- How different paths of transduction of signals used by growth factors? Core
- Enlist and describe role of extracellular matrix components in tissue repair.- core
- What is therapeutic use of stem cells in regeneration Horizontal
- How is tissue regenerated in surgical incisions and in traumatic injuries – vertical surgery
- Research -

Article: Stem cells in regenerative medicine.(journal of clinical medicine, https://www.mdpi.com/2077-0383/11/18/5460/pdf


Continuously cycling labile cells
(e.g., epidermis, GI tract epithelium)
Chromosome duplication
S
G2
Check for damaged
or unduplicated DNA
(G2/M checkpoint)
Check for DNA damage
(G1/S checkpoint)
CELL
CYCLE
Restriction point
Centrosome duplication
Growth in mass
G1
M
Mitosis
Quiescent,
stable cells
(e.g., hepatocytes)
G0
Cell
division
Permanent cells
(e.g., neurons,
cardiac myocytes)

Types of cells on the Basis of their Regenerating Capabilities



1. Labile OR continuously Dividing Cells
2. Stable OR Quiescent Cells
3. No dividing OR Permanent Cells

1. Labile OR Continuously Dividing Cells

These cells proliferate through out life, replacing those cells that are continuously dying

Examples of Labile Cells:

a) Stratified squamous epithelium of skin, oral cavity, vagina and cervix

b) Cuboidal epithelium of the ducts draining exocrine organs e.g., salivary glands, pancreas and biliary tract.

c) Columnar epithelium of GIT , uterus, and fallopian tubes

d) Haemopoietic (blood forming) cells of bone marrow

.2. Quiescent OR Stable Cells

These cells have capacity to regenerate but in normal conditions do not actively replicate. However they can undergo rapid division in response to a variety of stimuli and are thus capable of reconstitution of the tissue of origin.

Examples:

a) Parenchymal cells of liver, kidney and pancreas

b) Mesenchymal cells e.g., smooth muscle cells, cartilage, connective tissue, fibroblast and vascular endothelial cells

3. No dividing OR Permanent Cells

These cells are incapable of division and regeneration If they are destroyed , the loss is permanent and repair occurs only by the connective tissue (i.e., by scar formation.

Examples:

a) Nerve cells (Neurons)

b) Cardiac Cells

c) Skeletal muscle cells

CORE CONCEPT

Control of Cell Growth

Cellular proliferation is controlled largely by biochemical factors produced in the local microenvironment that can either stimulate or inhibit cells growth. The factors that stimulate cell growth are called growth factors while those that inhibit growth are called inhibitory factors

CORE CONCEPT

- The important growth factors which have a broad target action or are specifically involved in directing healing at the site of injury are:

1. Epidermal Growth Factor (EGF)
2. Platelet Derived Growth Factor (PDGF)
3. Fibroblast Growth Factor (FGF)
4. Transforming Growth Factor β (TGF- β)
5. Vascular Endothelial Growth Factor (VEGF)
6. Insulin like Growth Factor (IGF)
7. Tumour Necrosis Factor (TNF)

CORE CONCEPT

Growth factors involved in Healing and Repair

Growth Factor	Abbreviation	Functions
Epidermal Growth Factor	EGF	Regeneration of epithelial cells
Transforming Growth Factor- β	TGF -β	-Stimulates fibroblasts proliferate and collagen synthesis -Controls epithelial regeneration
Platelets Derived Growth Factor	PDGF	Mitogenic and chemotactic for fibroblasts and smooth muscle cells
Fibroblasts Growth Factor	FGF	Stimulates fibroblasts proliferation ,angiogenesis and epithelial cell regeneration
Insulin like Growth Factor	IGF	Synergistic effect with other growth factors
Vascular Endothelial Growth Factor	VEGF	Promotes angiogenesis and is responsible for increase in vascular permeability
Tumour Necrosis Factor	TNF	Induce fibroblasts proliferation

CORE CONCEPT

Growth Factors involved in Healing and Repair: Summary of functions

- Stimulate fibroblasts proliferation and collagen synthesis
- Lead to epithelial cells regeneration
- Synergistic effect with other growth factors
- Promotes Angiogenesis
- Are responsible for increasing vascular permeability

CORE CONCEPT

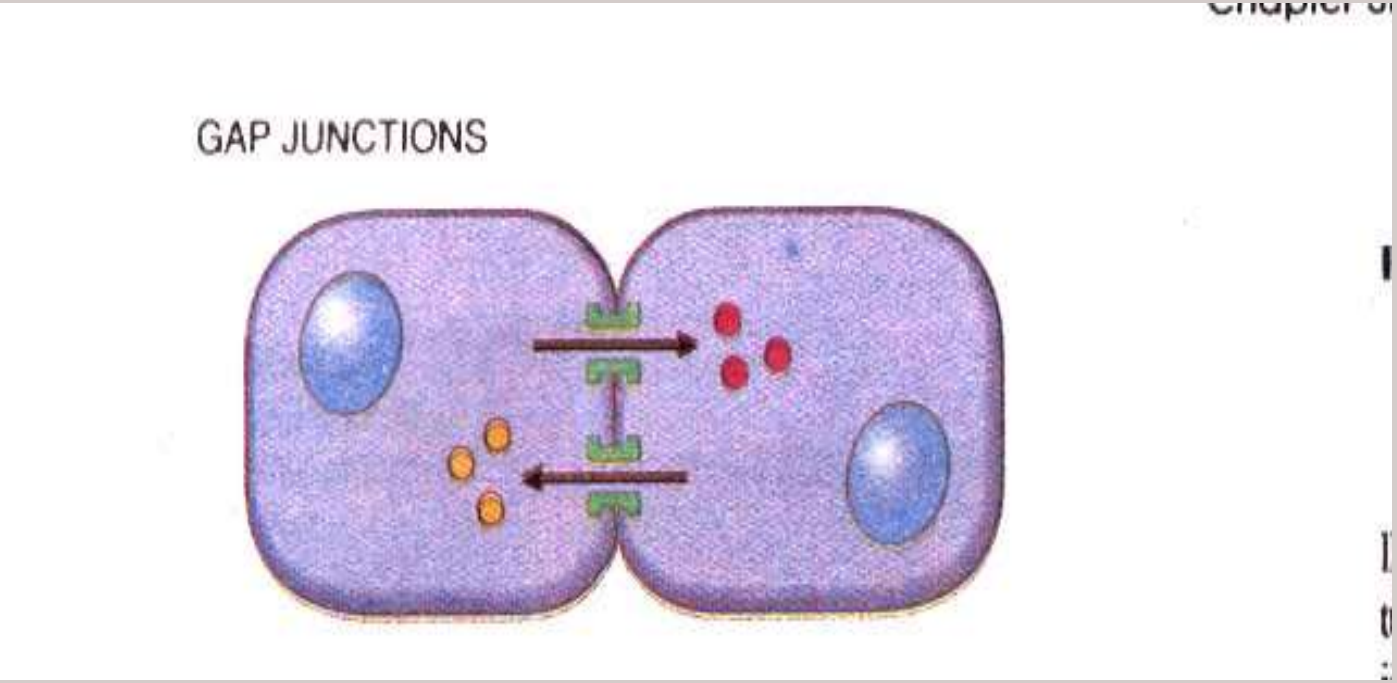
Signaling by Growth Factors in Healing and Repair

Signaling by growth factors take place in different ways:

1. Signaling through gap junctions
2. Autocrine signaling
3. Paracrine signaling
4. Synaptic Signaling
5. Endocrine signaling

CORE CONCEPT

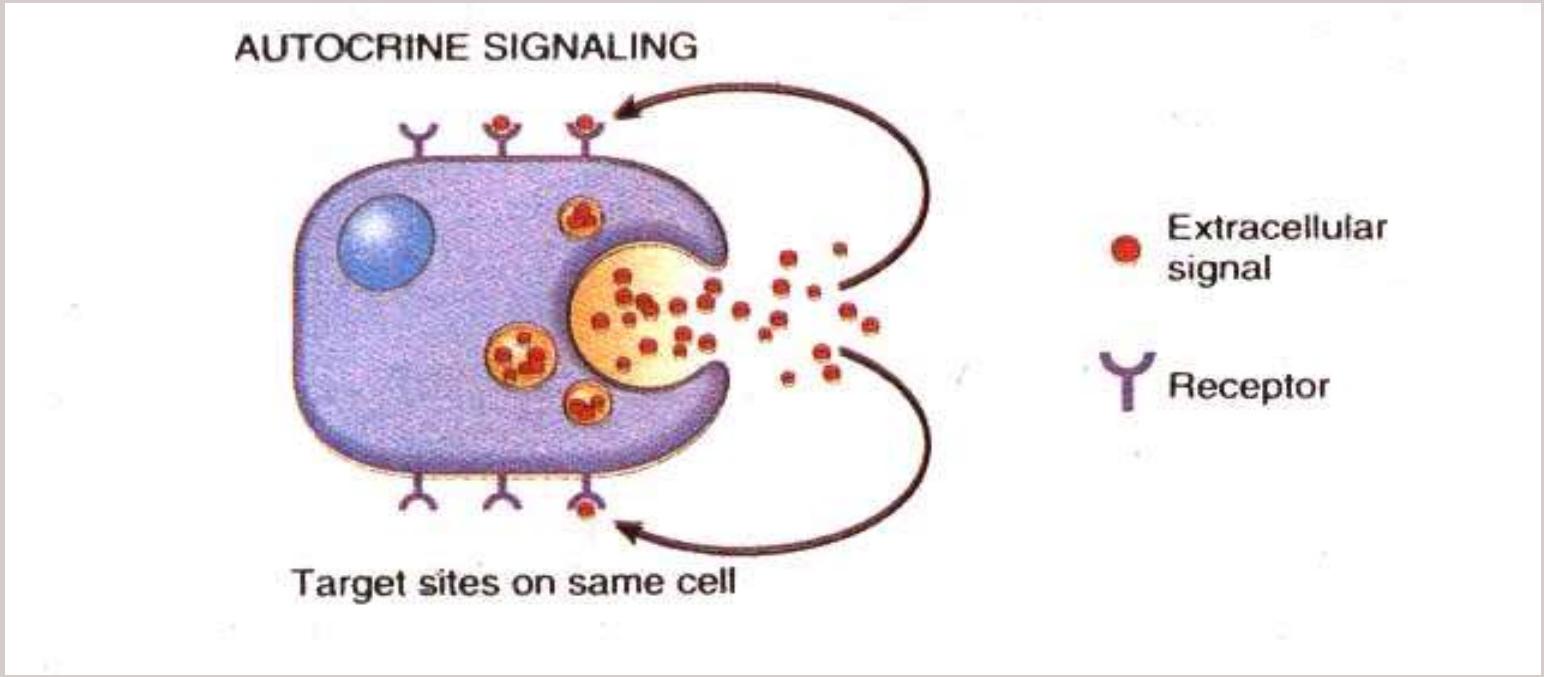
1. Signaling by Gap Junctions



Adjacent cells communicate via gap junctions, narrow hydrophilic channels that effectively connect two cells' cytoplasms. The channels permit movement of small ions, various metabolites and potential second messenger molecules.

CORE CONCEPT

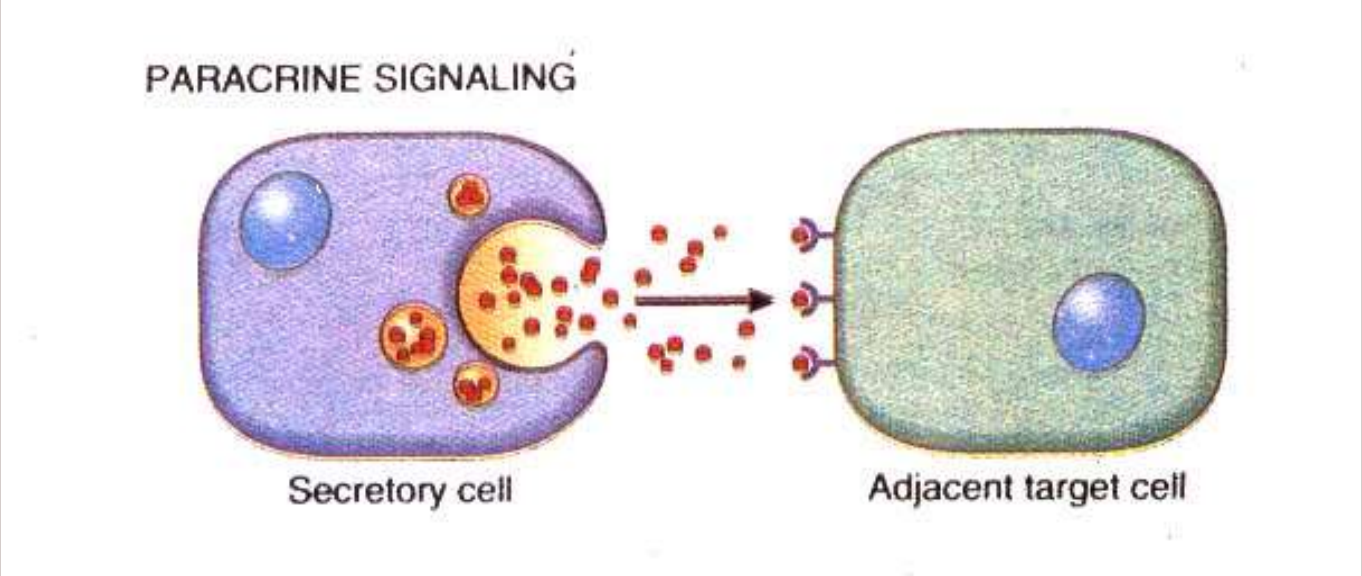
2. Autocrine Signaling



Soluble mediators acts predominantly (or even exclusively on the cell that secretes it. This pathway is important in immune response (cytokines) and in compensatory epithelial hyperplasia (i.e., liver regeneration)

CORE CONCEPT

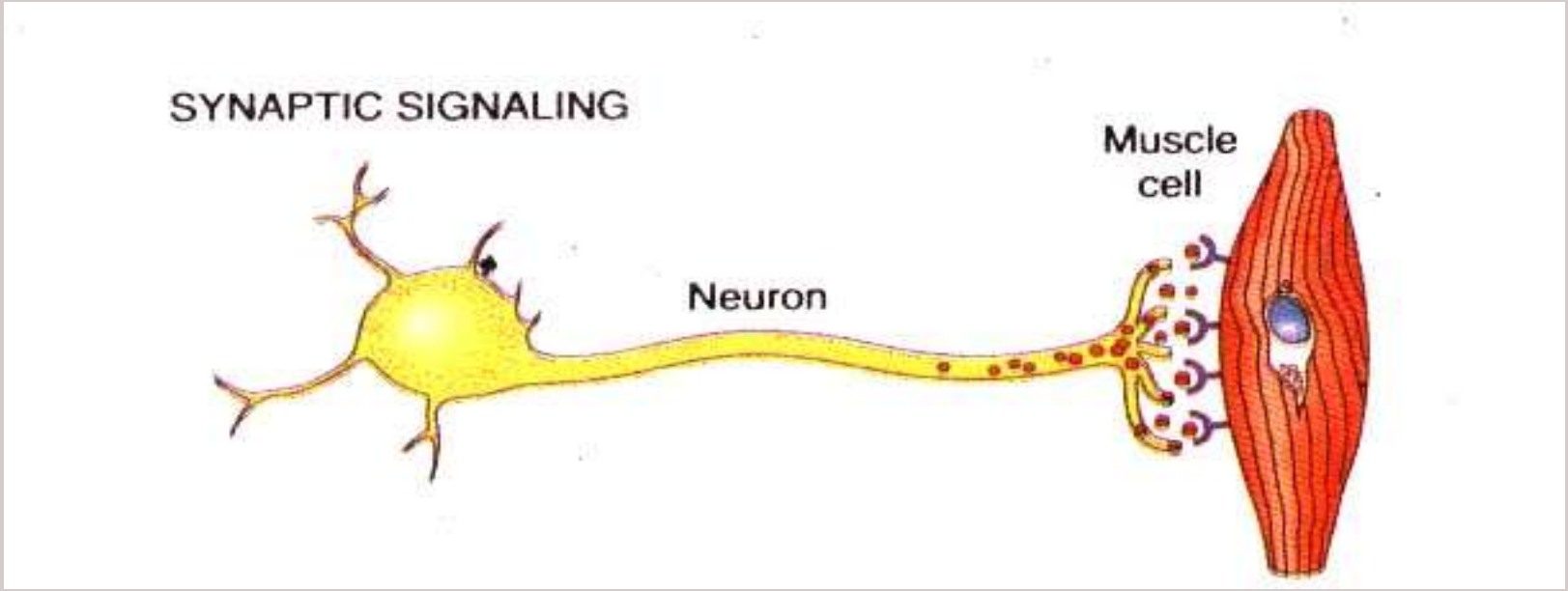
3. Paracrine Signaling



Mediators affect cells only in the immediate vicinity .This pathway is important for recruiting inflammatory cells to the site of infection an for controlled process of wound healing

CORE CONCEPT

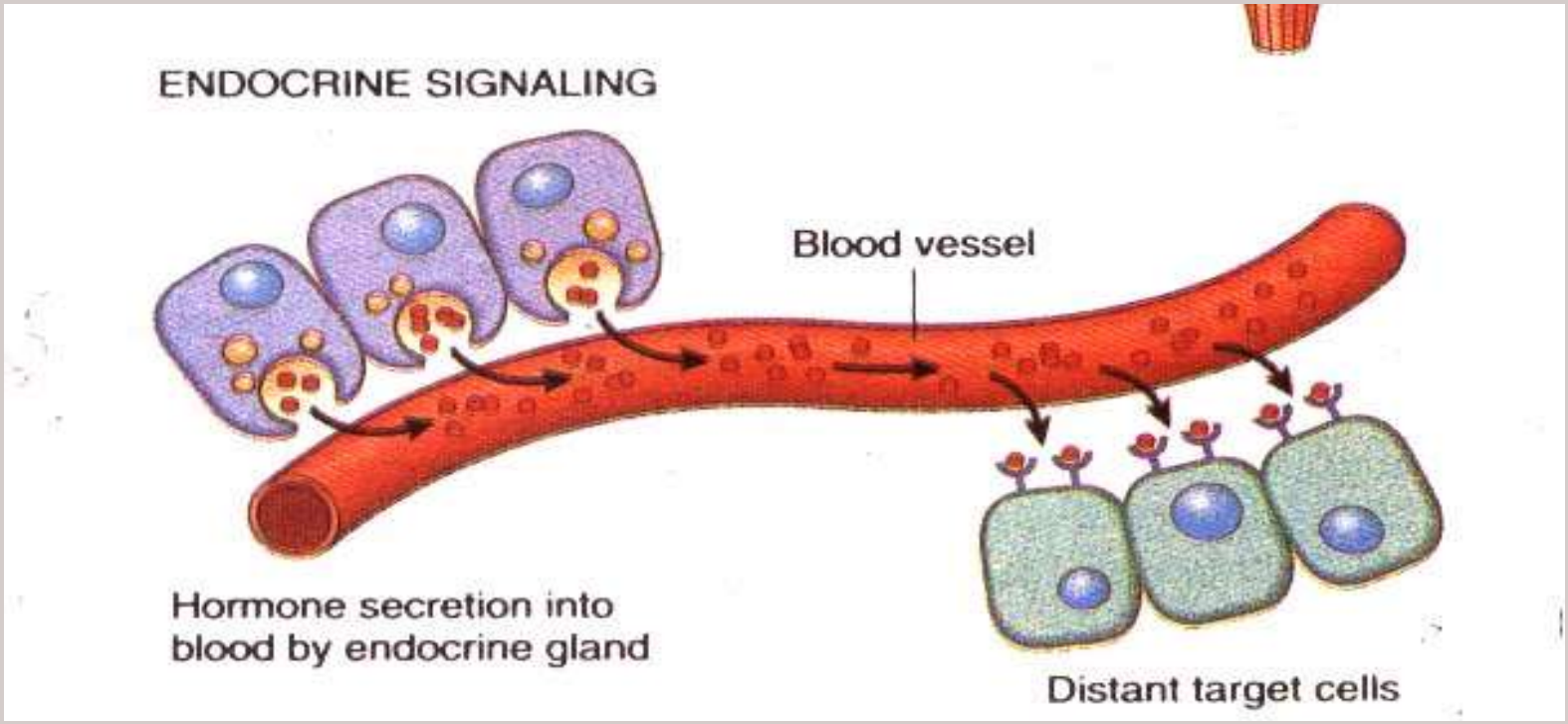
4. Synaptic Signaling



Activated neural tissues secretes neurotransmitters at a specialized cell junction (synapse) onto target cells such as other nerves or muscles.

CORE CONCEPT

5. Endocrine Signaling

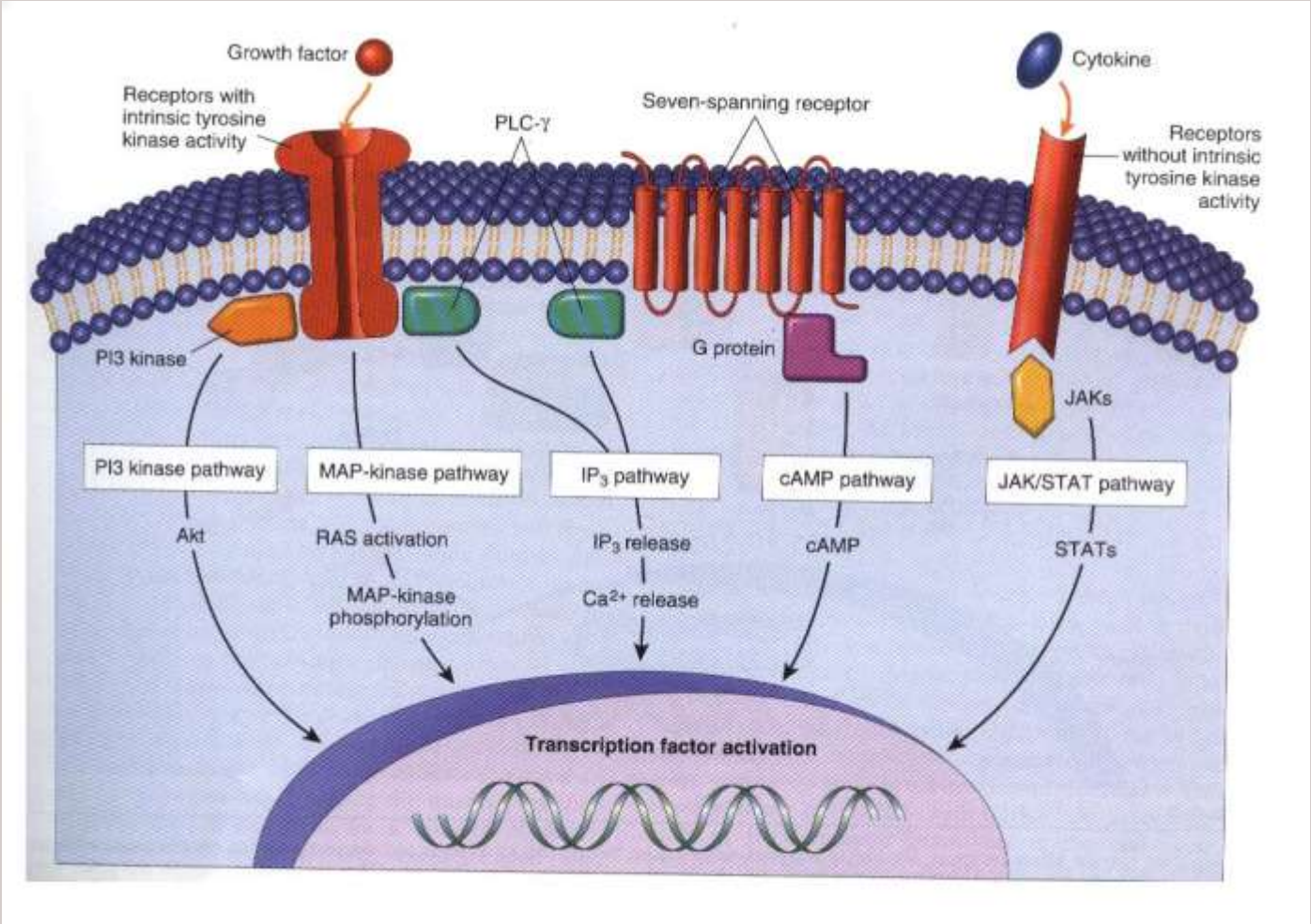


A regulatory substance such as a hormone is released into the blood stream and acts on target cell at a distance

Cell Surface Receptors for Growth Factors

Cell surface receptors for growth factors are of four types:

1. Ion channel receptors
2. Receptors with intrinsic kinase activity
3. G- protein – coupled receptors
4. Receptors with intrinsic enzymatic activity



Simplified overview of the major types of cell surface receptors and their principal signal transduction pathways leading to transcription factor activation and translocation into the nucleus

CORE CONCEPT

1. Ion channel receptors: Ligand binding alters the conformation of the receptor so that specific ions can flow through it.

Example: Acetylcholine receptor at the nerve muscle junction

2. Receptors with intrinsic kinase activity: These are transmembrane molecules with an extracellular ligand- binding domain. Ligand binding activates receptor which in turns then binds to intracellular proteins.

Example: Intracellular signaling of multiple growth factors

CORE CONCEPT

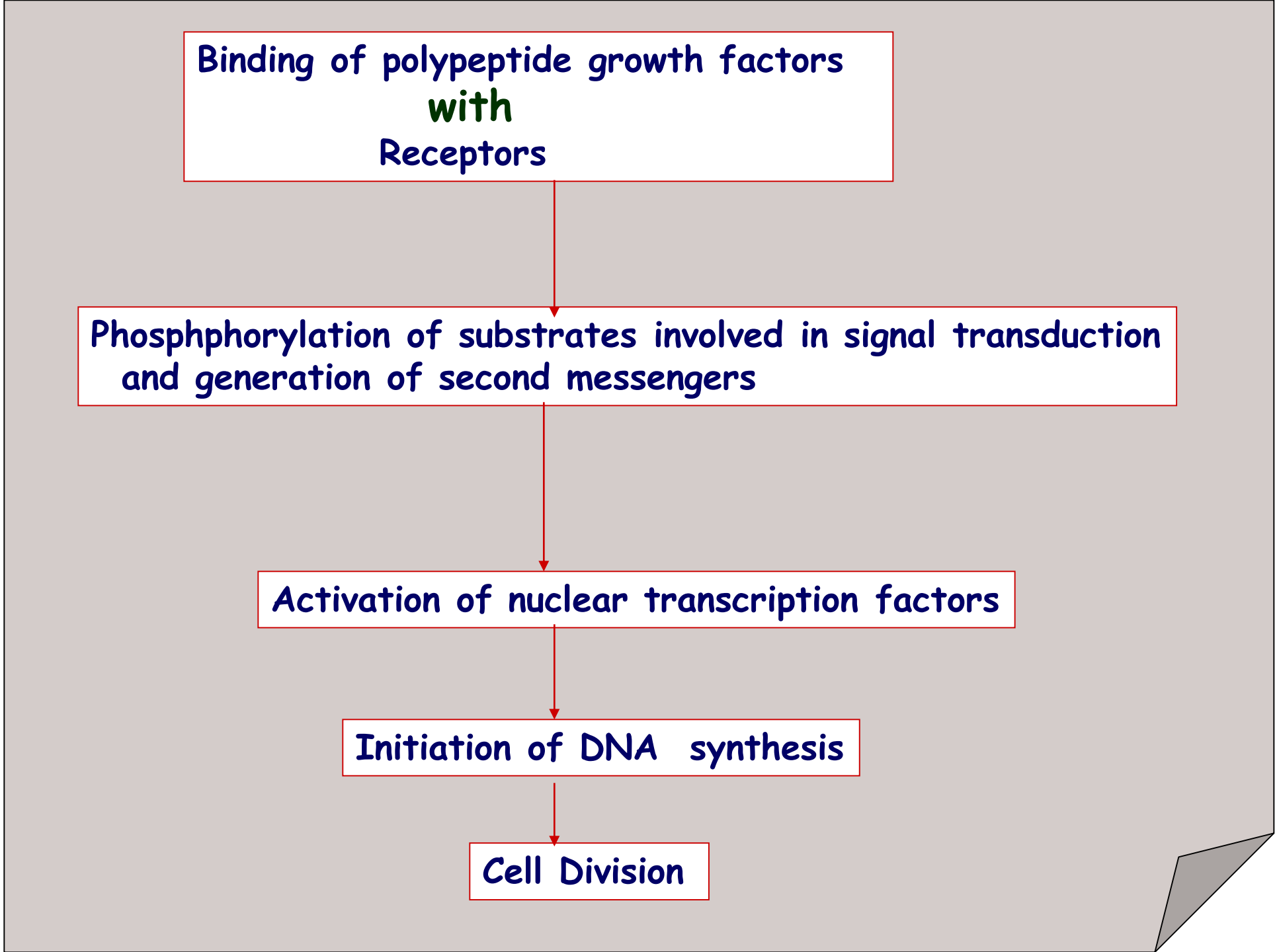
3. G- protein – coupled receptors: These are also transmembrane receptors. After binding to their specific ligand these receptors combine with intracellular GTP – hydrolyzing proteins

Examples: Epinephrine; Glucagon and Chemokines.

4. Receptors without intrinsic enzymatic activity: Transmembrane molecules with an extracellular ligand binding domain.Ligand interaction induces an intracellular conformational change that allows association with an activation of intracellular protein kinases.

Example: Rectors involved in cytokines activation in immune system and erythropoietin receptor .

CORE CONCEPT



CORE CONCEPT

- Extra Cellular matrix is a dynamic constantly remodeling macromolecular complex synthesized locally.

- It constitutes a significant proportion of any tissue.

- Besides providing turgor to soft tissues and rigidity to bones, Extracellular matrix supplies a substratum for cell adhesion and critically regulates the growth, movement and differentiation of the cells living within it.

- Extracellular matrix occurs in two forms:
  1. Interstitial Matrix
  2. Basement Membrane

CORE CONCEPT

.Components of Extracellular Matrix

1. Collagen
2. Elastin
3. Proteoglycans and Hyaluronan
4. Adhesive Glycoproteins
5. Fibronectin
6. Laminin
7. Integrins

CORE CONCEPT

Major Components of Extracellular Matrix

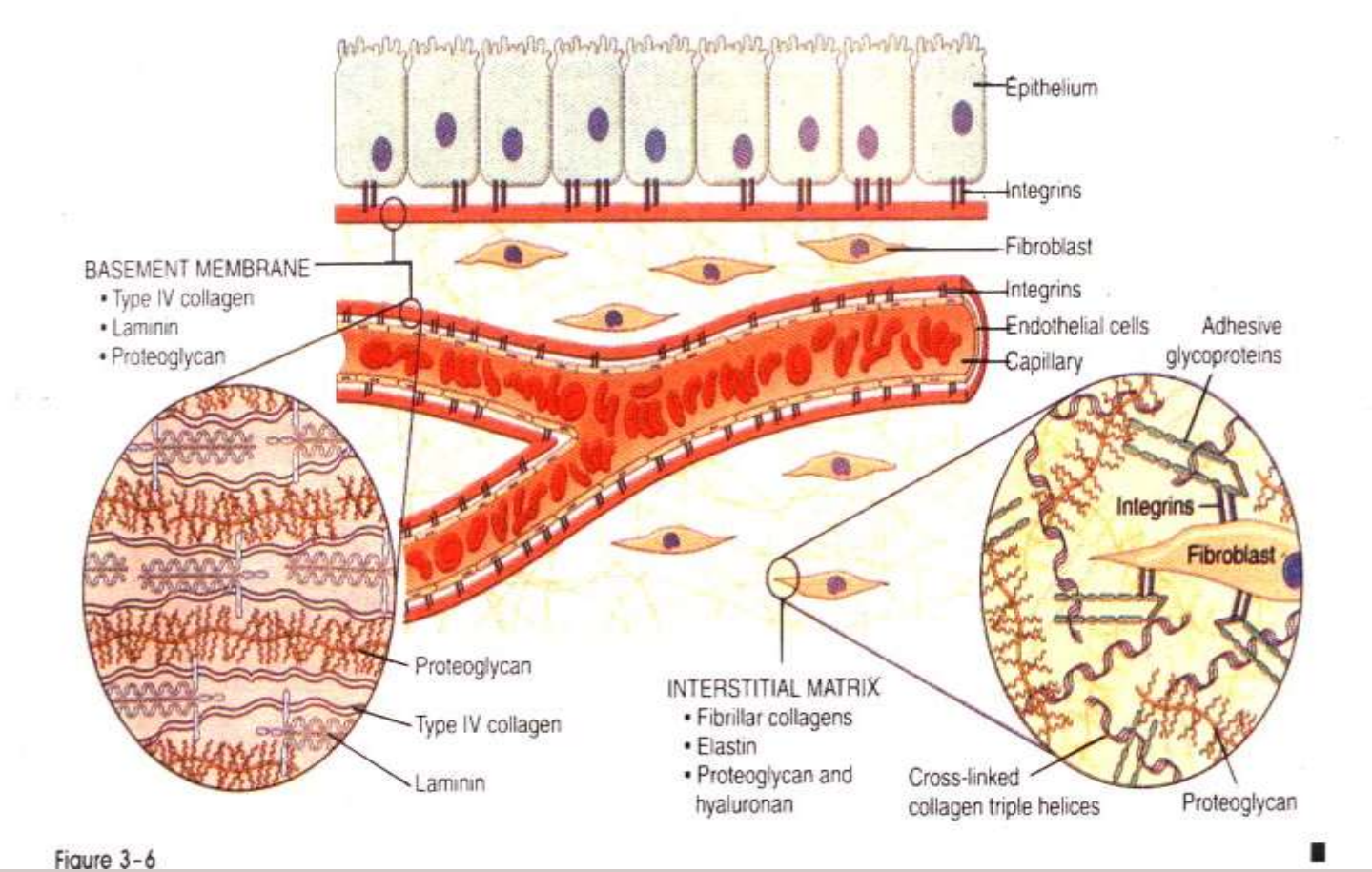
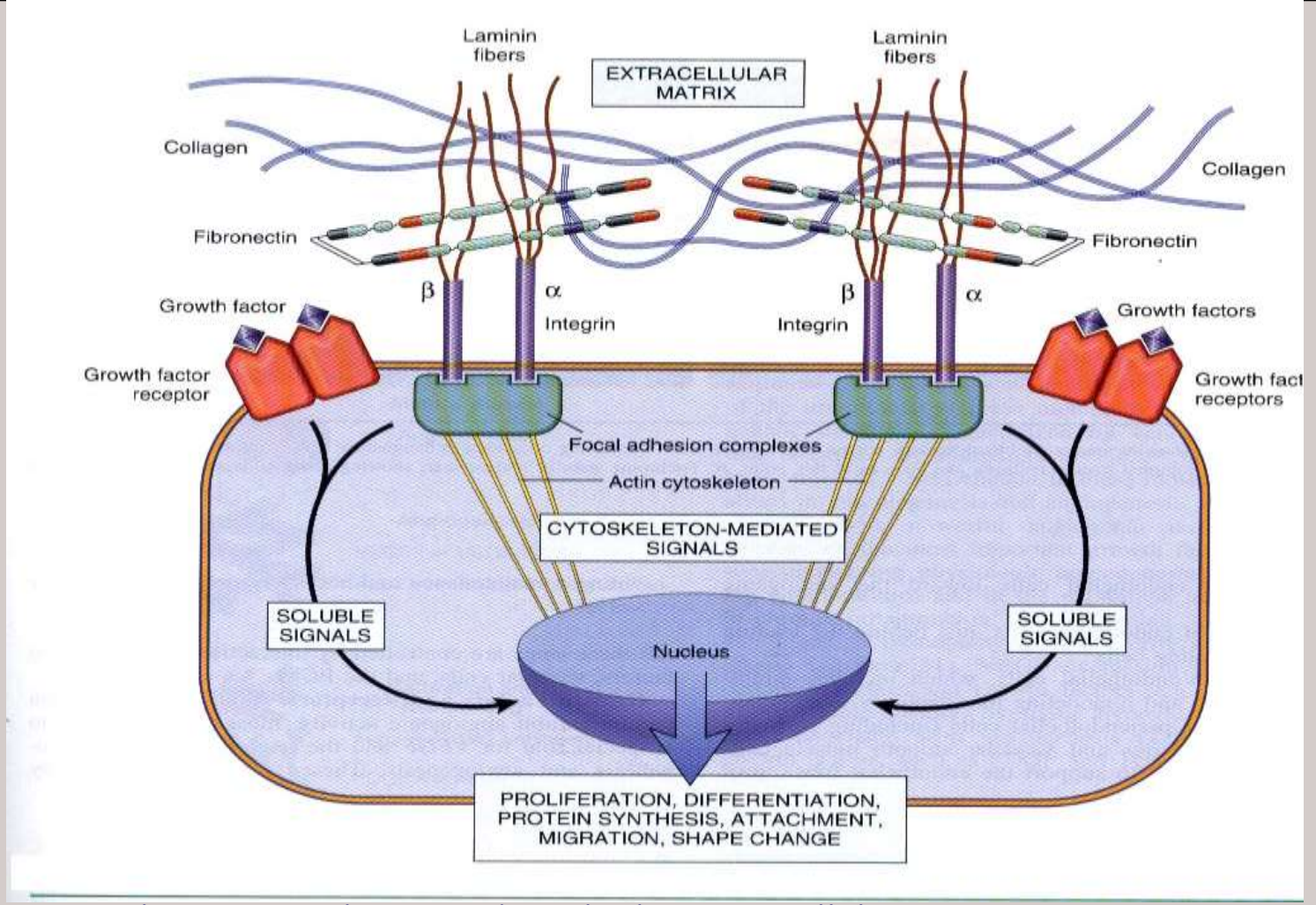


Figure 3-6

Role of Extracellular Matrix

1. Mechanical support for cell anchorage
2. Determination of cell orientation (Polarity)
3. Control of Cell Growth
4. Maintenance of Cell Differentiation
5. Scaffolding for tissue renewal .
6. Establishment of tissue microenvironments
7. Storage and presentation of regulatory molecules

CORE CONCEPT



Schematic mechanism showing mechanisms by which Extracellular matrix interactions and growth factors influence cell growth, motility differentiation & protein synthesis. Integrins bind ECM and interact with the cytoskeleton at focal adhesion complexes. This can initiate the production of intracellular second messengers or can directly mediate nuclear signals. Cell surface receptors for growth factors also initiate second signals. Together, these are integrated by the cell to yield various responses, including changes in cell growth , locomotion and differentiation.

- REGENERATIVE MEDICINE- THERAPEUTIC USE

There is evidence that aging and certain pathologies, such as diabetes, may decrease the capacity to mobilize progenitor cells.

Therefore, therapeutic strategies (granulocyte colony stimulant (G-CSF) and the CXCR4 antagonist, called plerixafor or AMD3100) can favor progenitor-cell mobilization,
facilitate regenerative processes, in healing of chronic ulcers in diabetics.

RESEARCH

- **Recent advances in molecular mechanisms of skin wound healing and its treatments**
- **Abdullah Al Mamun 1,†, Chuxiao Shao 1,†, Peiwu Geng 1,†, Shuanghu Wang 1,*, Jian Xiao 1,2,3,*,†**
- **PMCID: PMC111482**