

Cell and Tissue Regeneration

How injured tissue restores its cells, structure, and function

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Learning objectives

- Distinguish regeneration from replacement by scar tissue.
- Classify tissues as labile, stable, or permanent on the basis of proliferative capacity.
- Explain growth-factor, extracellular matrix, and stem-cell contributions to regeneration.
- Predict tissue responses to selected patterns of injury.

Repair restores tissue after injury



Repair may restore normal architecture or create fibrous replacement.

Two mechanisms of tissue repair

Tissue injury

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graph TD; A[Tissue injury] --> B[Regeneration]; A --> C[Scar formation]; B --> D[Restitution of normal cells]; C --> E[Connective tissue replaces lost tissue]
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Regeneration

Restitution of normal cells

Scar formation

Connective tissue replaces lost tissue

Regeneration aims at structural restitution

- Lost components are replaced with cells of the original tissue.
- Surviving differentiated cells may re-enter the cell cycle.
- Tissue stem cells and progenitors can provide new mature cells.
- Restoration is most complete when a supporting tissue scaffold survives.

Scarring preserves continuity without restitution

- Fibrous connective tissue fills a defect that cannot be fully regenerated.
- It is favored by limited cell proliferative capacity or disruption of support structures.
- A scar may preserve mechanical stability despite altered tissue architecture.
- Regeneration and scarring often coexist after a single injury.

The fate of an injury depends on two variables

Cellular proliferative reserve

Can surviving cells divide?

Are functional stem cells retained?

ECM scaffold integrity

Is basement membrane intact?

Is stromal architecture preserved?

Multiple cell populations participate in repair

Residual tissue cells

Replace injured parenchyma
when capable of proliferation

Endothelial cells

Form vessels delivering nutrients
to injured tissue

Fibroblasts

Deposit connective tissue in
defects not repaired by
regeneration

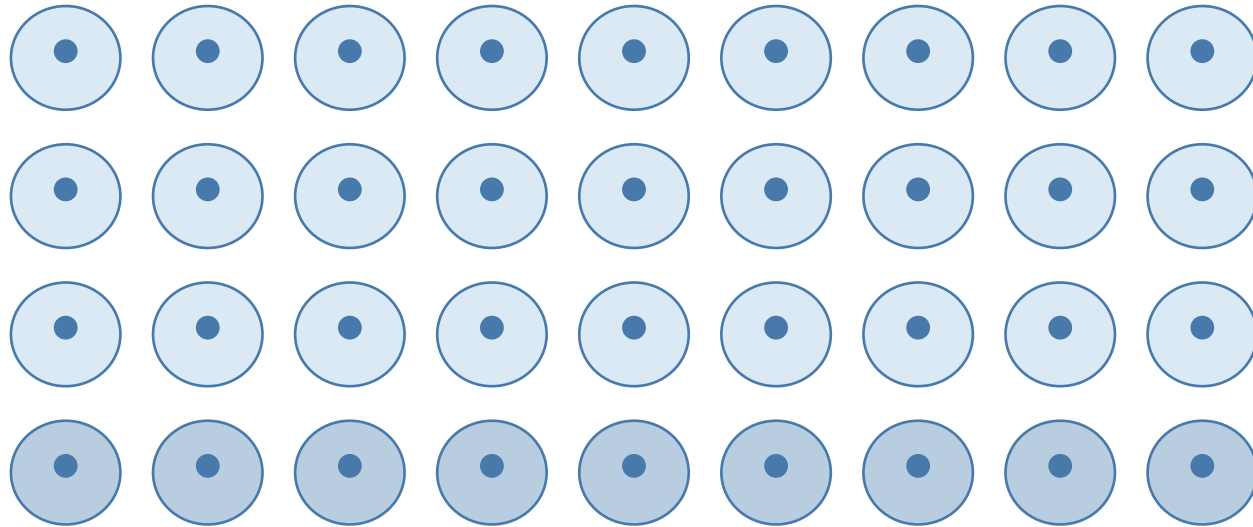
Three classes of tissues by proliferative capacity

Class	Resting state	Response to injury
Labile	Continuous renewal	Robust if stem cells persist
Stable	Predominantly G ₀	Inducible but often limited
Permanent	Nonproliferative mature cells	Scar-dominant response

Labile tissues renew cells continuously

- Cells are normally lost and replaced during physiologic life.
- Replacement reflects stem-cell maturation and proliferation of mature cells.
- Rapid renewal supports regeneration after superficial injury.
- Preservation of the tissue stem-cell population is essential.

Epidermis is a labile epithelium



Basement membrane

Stratified squamous epithelium is continuously renewed.

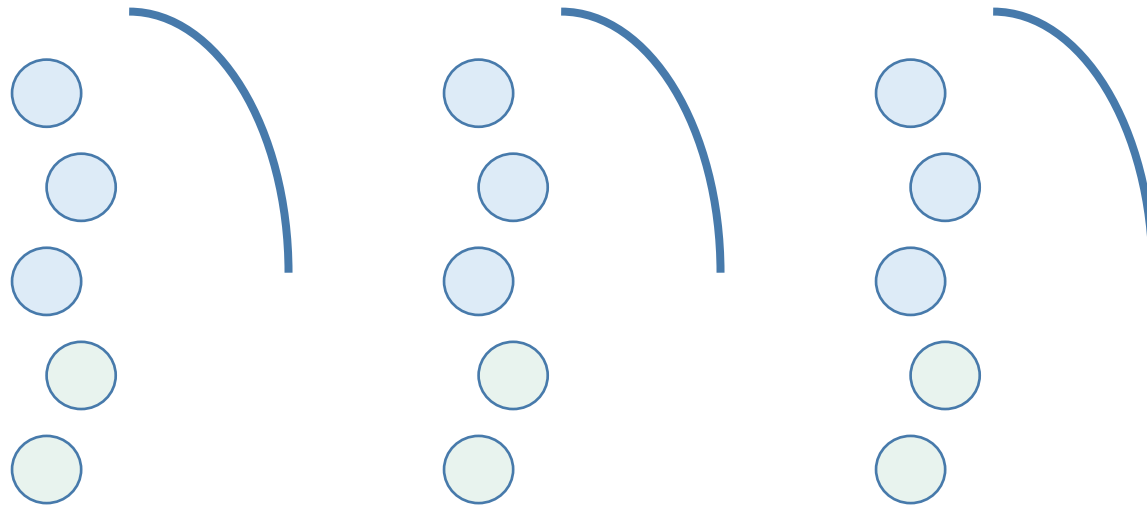
Superficial cell loss can be replaced if regenerative compartments survive.

Schematic: Renewal from basal cells toward the surface

Labile stratified mucosae

- Examples: Oral cavity and esophagus.
- Also includes vagina and cervix.
- These stratified epithelia replenish cells continually.
- An injury sparing renewing cell populations allows epithelial restitution.

Gastrointestinal epithelium: Renewal in crypts



Crypt niches → differentiated epithelium

Columnar gastrointestinal epithelium is labile.

Intestinal stem cells occupy crypt niches (Chapter 1).

Schematic: Crypt-to-surface epithelial renewal

Ductal epithelia also retain regenerative capacity

- Cuboidal cells lining ducts of exocrine organs are labile.
- Examples include salivary ducts, pancreatic ducts, and biliary passages.
- Ductal repair differs from recovery of specialized glandular parenchyma.
- Cell type—not only organ name—determines proliferative behavior.

Urothelium and reproductive tract epithelia

Transitional epithelium

Urinary tract

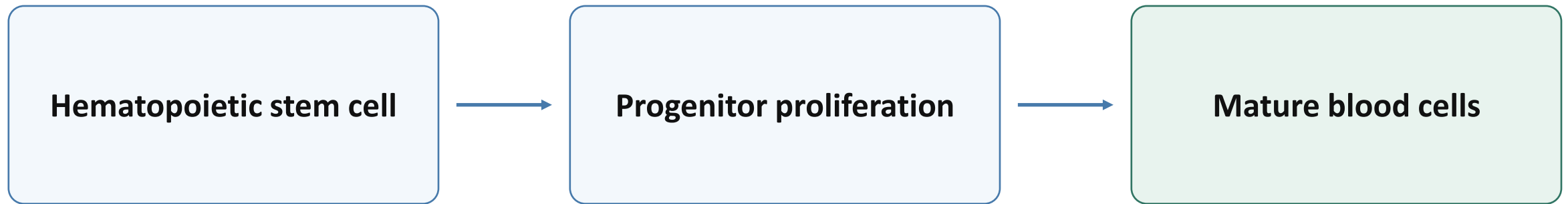
Labile cell population

Columnar epithelium

Uterus and fallopian tubes

Included among labile epithelia

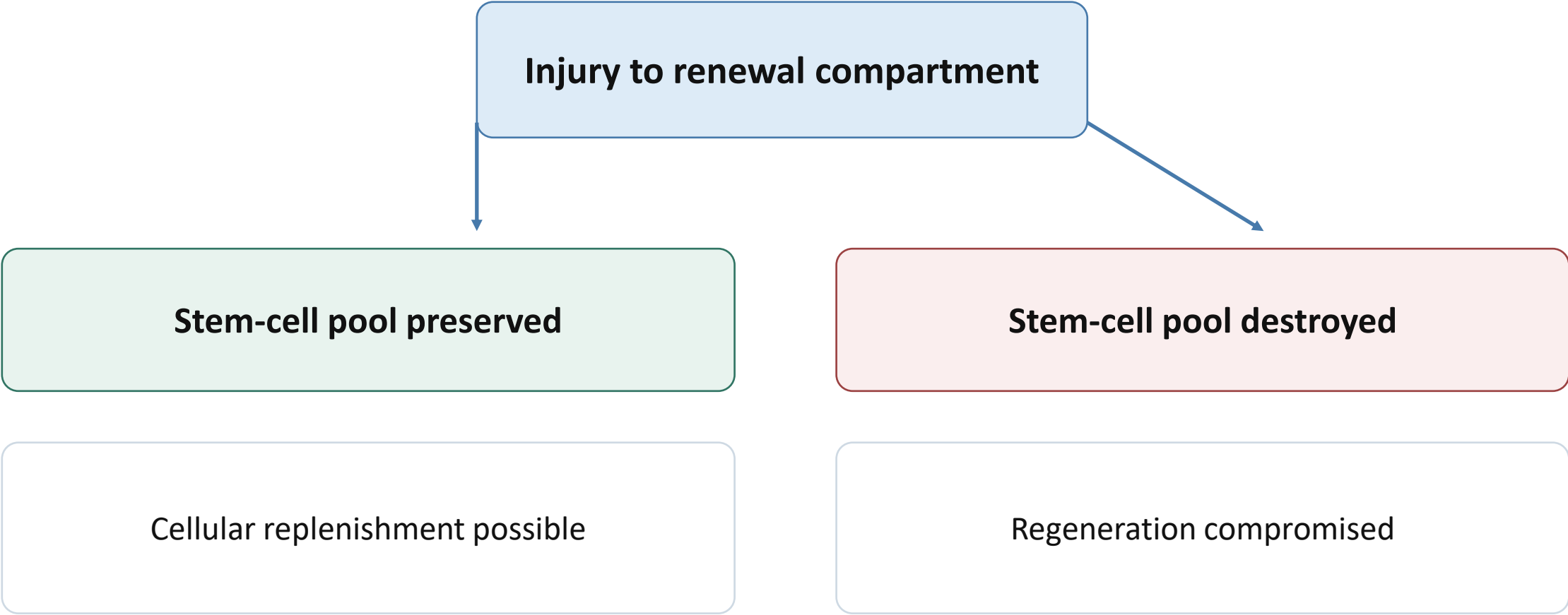
Bone marrow is a labile cellular compartment



Continual replacement accommodates loss and consumption of blood cells.

When labile tissues fail to regenerate

Injury to renewal compartment



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graph TD; A[Injury to renewal compartment] --> B[Stem-cell pool preserved]; A --> C[Stem-cell pool destroyed]; B --> D[Cellular replenishment possible]; C --> E[Regeneration compromised];
```

Stem-cell pool preserved

Cellular replenishment possible

Stem-cell pool destroyed

Regeneration compromised

Stable tissues are quiescent, not inert

- Most cells reside outside the active cycle, in G_0 .
- Baseline proliferative activity is low.
- Injury or reduction of tissue mass can induce cell division.
- Inducible proliferation does not ensure complete organ regeneration.

G_0 and cell-cycle re-entry



Division requires regulated entry into the cell cycle.

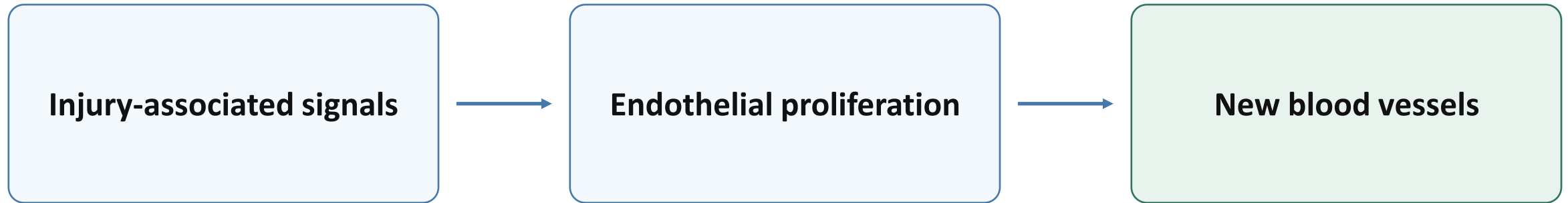
The liver is a major exception among stable organs

- Hepatocytes can proliferate after loss of liver mass.
- Regeneration may occur through division of surviving hepatocytes.
- A separate topic addresses detailed pathways of liver regeneration.
- The example shows why resting mitotic rate is not equal to regenerative potential.

Kidney and pancreas: Stable but limited

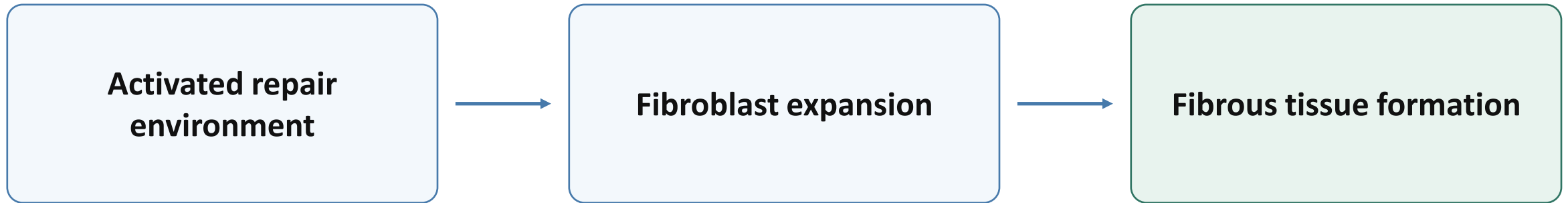
- Renal and pancreatic parenchyma belong to the stable-tissue class.
- Cells may divide in response to injury.
- Their capacity to reconstruct extensive damage is limited compared with liver.
- Destruction of the framework further biases repair toward scarring.

Endothelial proliferation supports tissue repair



Vascular growth supplies nutrients to the repairing site.

Fibroblasts proliferate during repair



Fibroblast activity becomes particularly important when regeneration is incomplete.

Smooth muscle cells have inducible proliferation

- Smooth muscle belongs to the stable cell compartment.
- Its basal turnover is low relative to labile epithelia.
- Proliferative activity can increase during injury responses.
- This contrasts with terminally differentiated cardiac myocytes.

Stable cell does not mean fully restorable organ

Cell-level capability

Some viable cells re-enter the cycle.

Proliferation can replace limited cell loss.

Organ-level outcome

Complex architecture may not be rebuilt.

Scar formation can still dominate extensive injury.

Permanent tissues: Terminal differentiation

- Most mature cells do not proliferate appreciably after birth.
- Loss of cells may therefore be persistent.
- Repair commonly replaces the damaged region with a scar.
- Restricted stem-cell activity does not necessarily restore tissue function.

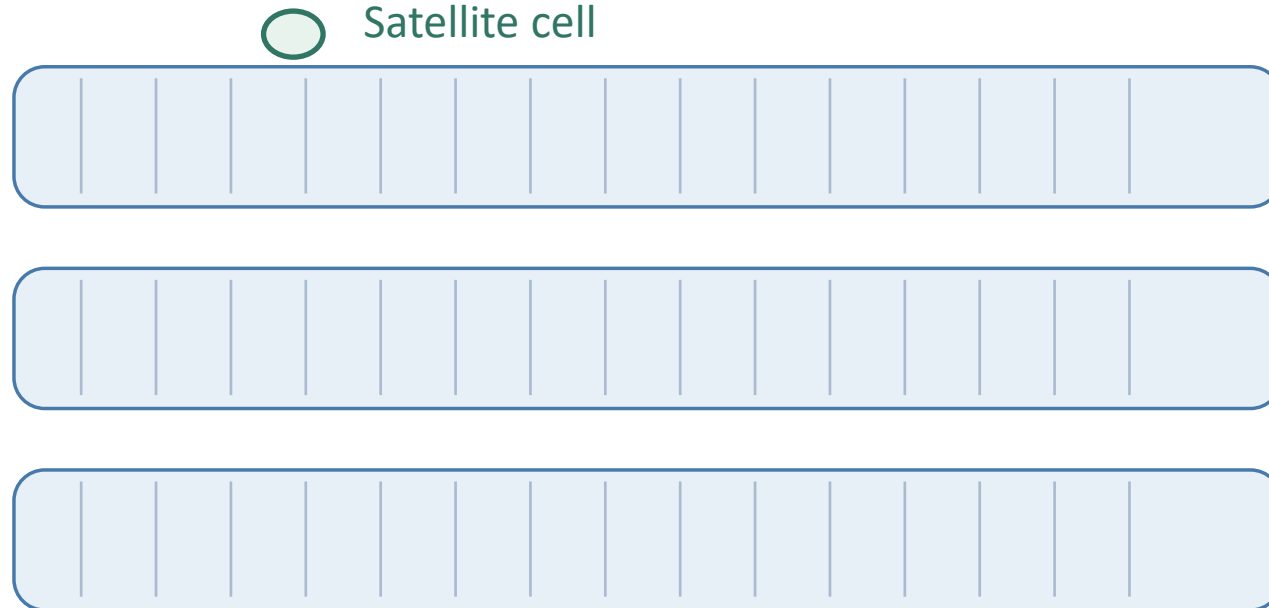
Neurons have insufficient regenerative capacity

- Most neurons are classified as permanent cells.
- Limited stem-cell replication occurs in some adult brain regions.
- This does not restore major neuronal tissue loss after injury.
- Structural repair in damaged brain remains unlike routine epithelial renewal.

Cardiac myocytes are functionally permanent

- Cardiac muscle cells have very little effective regenerative capacity.
- Evidence of limited proliferation does not imply meaningful replacement after infarction.
- Extensive ischemic necrosis leads to fibrous replacement.
- This illustrates the difference between detectable division and functional regeneration.

Skeletal muscle has an important exception



Skeletal muscle is usually classified as permanent.

Satellite cells provide a reservoir for regenerative responses.

Schematic: Satellite cells permit limited muscle regeneration

Adult brain versus skeletal muscle

Feature	Adult brain	Skeletal muscle
Dominant mature cell	Neuron	Skeletal myofiber
Regenerative compartment	Limited, localized niches	Satellite cells
After substantial injury	Insufficient restitution	Some regeneration possible

A small proliferative signal is not recovery

Proliferation detected

Cell-cycle activity may be measurable.

Stem cells may be present in a niche.

Regeneration achieved

Enough correct cells are restored.

Architecture and useful tissue function return.

Tissue-classification synthesis

Cell class	Representative sites	Characteristic limitation
Labile	Skin, gut, marrow, ducts	Needs functioning stem-cell pool
Stable	Liver, kidney, pancreas, endothelium	Variable extent of restoration
Permanent	Neurons, cardiac myocytes	Mature cells largely nondividing

Proliferation requires more than cell loss



The extracellular context controls whether viable cells divide.

Macrophages coordinate proliferative signaling

- Activated macrophages are prominent local sources of growth factors.
- Tissue damage recruits and activates macrophage responses.
- Secreted mediators influence multiple cells needed for repair.
- Macrophages link the inflammatory phase with the proliferative response.

Epithelial and stromal cells also signal

- Growth factors arise from cells adjacent to injury.
- Epithelial cells are one local source.
- Stromal cells contribute to the same paracrine environment.
- No single growth factor has to act on every responding cell type.

Some growth factors have broad targets

Broad-acting factors

Affect more than one cell lineage.

Coordinate multiple tissue-repair populations.

Restricted factors

Act preferentially on particular cells.

Help generate lineage-appropriate responses.

Growth factors can be stored by the matrix



The ECM is a signaling reservoir, not merely a structural filler.

Growth-factor effects on cells

Cycle progression

Promote entry and progression through cell-cycle stages

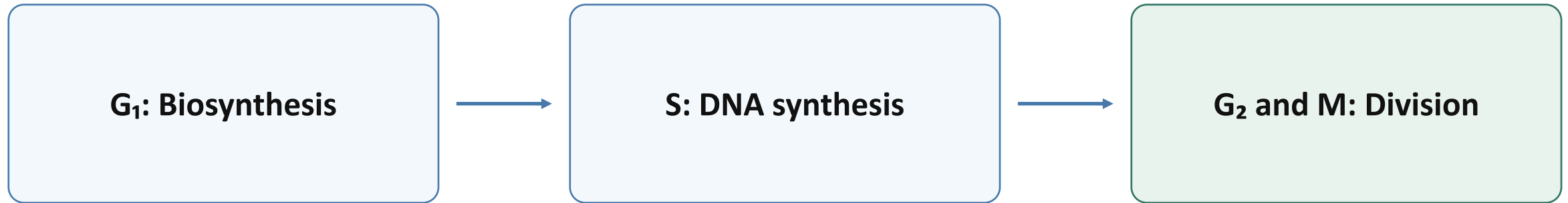
Cell survival

Can prevent apoptosis during repair

Cell biosynthesis

Increase macromolecules needed for daughter cells

The cell cycle produces two daughter cells



DNA and cellular components must be duplicated and partitioned.

Cyclins and CDKs gate the cell cycle

- Cyclins associate with cyclin-dependent kinases (CDKs).
- Changing cyclin abundance changes CDK activity over the cycle.
- Regulated progression coordinates replication and mitosis.
- This explains how a mitogenic signal becomes an orderly division response.

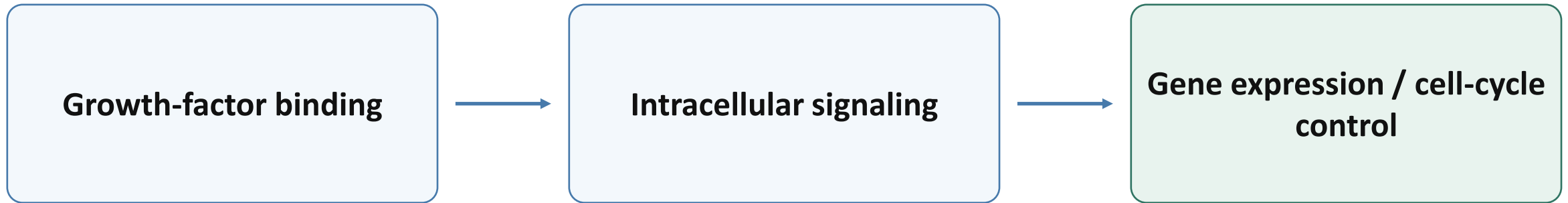
Checkpoints protect proliferating cells

- The G_1 –S checkpoint assesses DNA integrity before replication.
- The G_2 –M checkpoint assesses completion and fidelity of DNA replication.
- Cell-cycle arrest can prevent propagation of genomic damage.
- Regeneration requires proliferation that maintains genetic integrity.

A new cell requires extensive biosynthesis

- DNA duplication alone cannot produce a functional daughter cell.
- Membranes, organelles, and proteins must also increase.
- Growth-factor pathways promote metabolic and synthetic activity.
- The biosynthetic program supports regeneration of tissue mass.

Proliferation is regulated, not autonomous



A proliferative response depends on extracellular inputs and internal checkpoints.

Growth-factor examples relevant to repair

Factor	Principal action in repair	Example target
EGF / TGF-α	Mitogenic signaling	Epithelia, hepatocytes
HGF	Survival, migration, proliferation	Hepatocytes, epithelia
PDGF	Chemotaxis and proliferation	Fibroblasts, smooth muscle
VEGF-A	Endothelial proliferation/migration	Endothelial cells

ECM supports regeneration through structure and signaling

Scaffold

Supports tissue polarity,
anchorage and cell migration

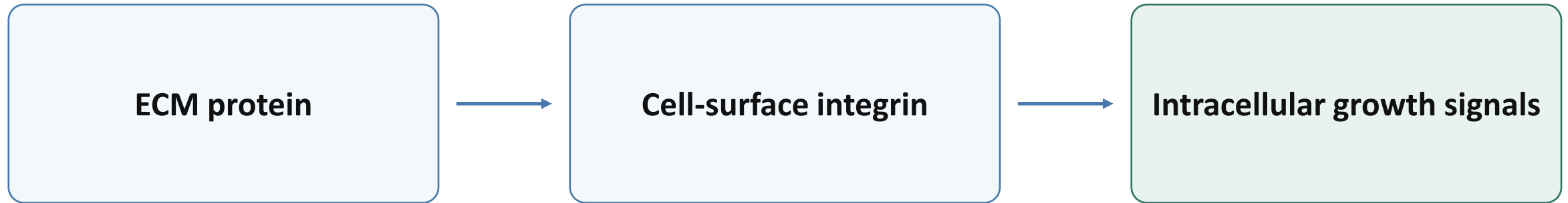
Signaling

Displays growth factors and
interacts with integrins

Microenvironment

Provides specialized basement-
membrane boundaries

ECM directs proliferation through integrins



Integrin engagement provides a second route to proliferative signaling.

Integrin and growth-factor signals cooperate

Growth-factor receptors

Detect soluble or matrix-bound mediators.

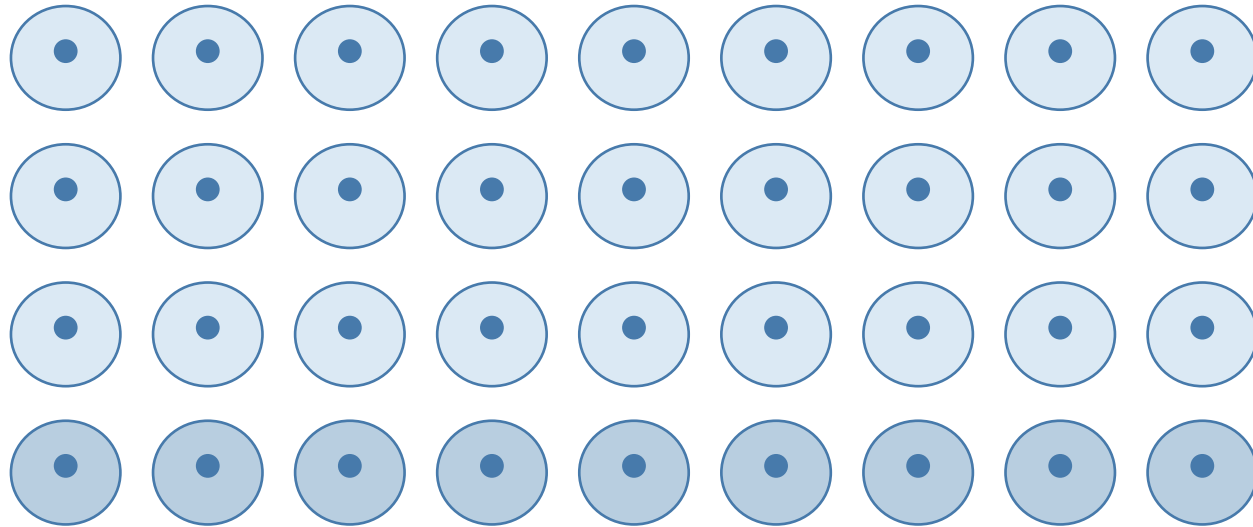
Drive survival, biosynthesis and division.

Integrin receptors

Detect attachment to ECM proteins.

Influence proliferation and cell behavior.

Basement membrane organizes epithelial repair



Basement membrane

Basement membrane supports the orientation of the epithelial layer.

Loss of the foundation can prevent organized restitution.

Schematic: Epithelium anchored to a basement membrane

Interstitial matrix supports connective tissue

- The interstitial matrix occupies connective tissue spaces.
- Its macromolecules include collagen, fibronectin, elastin, and proteoglycans.
- It provides cell anchorage and paths for migration.
- Intact matrix helps retain organized tissue architecture.

Why matrix destruction favors a scar

Viable cells after injury

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graph TD; A[Viable cells after injury] --> B[Scaffold retained]; A --> C[Scaffold disrupted]; B --> D[Organized regeneration more likely]; C --> E[Fibrous replacement more likely];
```

The diagram is a flowchart starting with a blue box 'Viable cells after injury'. It branches into two paths. The left path, indicated by a vertical arrow, leads to a green box 'Scaffold retained', which then leads to a light blue box 'Organized regeneration more likely'. The right path, indicated by a diagonal arrow, leads to a red box 'Scaffold disrupted', which then leads to a light blue box 'Fibrous replacement more likely'.

Scaffold retained

Organized regeneration more likely

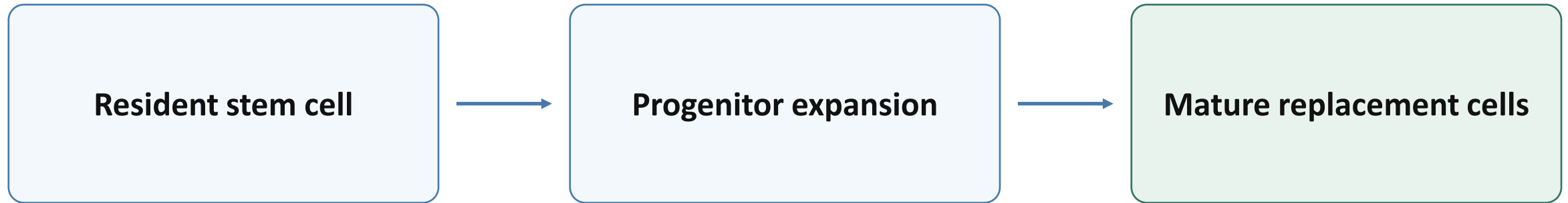
Scaffold disrupted

Fibrous replacement more likely

ECM is simultaneously structure and signal

ECM contribution	Effect on regeneration
Mechanical anchorage	Supports cell polarity and migration
Growth-factor reservoir	Localizes proliferative signals
Integrin engagement	Transmits signals to cells
Stromal / basement membrane scaffold	Guides tissue architecture

Tissue stem cells supplement surviving cells



Stem-cell input is most important when surviving mature cells divide poorly.

Stem-cell niches are specialized environments

- Tissue stem cells are maintained within local microenvironments.
- Neighboring cells and soluble factors regulate their activity.
- Niche signals balance quiescence, expansion and differentiation.
- An injured tissue can activate resident stem cells to replenish cell loss.

Examples of anatomical stem-cell niches

Tissue	Niche
Bone marrow	Perivascular niches
Intestine	Epithelial crypts
Skin	Hair-follicle bulge
Cornea	Limbus
Brain	Subventricular zone

Self-renewal and differentiation are distinct

Stem-cell division

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graph TD; A[Stem-cell division] --> B[Self-renewal]; A --> C[Differentiation]; B --> D[Maintains renewing-cell pool]; C --> E[Produces functional tissue cells];
```

Self-renewal

Maintains renewing-cell pool

Differentiation

Produces functional tissue cells

Asymmetric versus symmetric division

Asymmetric division

One daughter maintains stem identity.

The other enters a differentiation pathway.

Symmetric self-renewal

Both daughters retain stem-cell identity.

The stem-cell pool can expand when needed.

Adult stem cells have restricted lineages

- Tissue stem cells ordinarily produce cells characteristic of their resident tissue.
- High-turnover tissues depend on continual stem-cell output.
- Low-turnover tissues may use stem cells when mature cells divide poorly.
- The presence of a stem cell does not guarantee restoration of complex injury.

Two cellular sources of regenerated tissue

Surviving differentiated cells

Direct re-entry into the proliferative program.

Prominent example: Hepatocytes.

Tissue stem cells

Proliferation plus maturation of progeny.

Prominent examples: Epidermal and intestinal renewal.

Case: Superficial epithelial abrasion

An abrasion removes superficial epithelium but preserves the underlying basement membrane and renewing cells.

Clinical reasoning

Which repair mechanism should predominate?

Explanation

Regeneration: Preserved renewing cells and scaffold favor restitution.

Case: Deep epithelial wound

A deep wound destroys epithelial cells and disrupts the supporting connective-tissue framework.

Clinical reasoning

Why will full restitution be difficult?

Explanation

The loss of scaffold favors connective-tissue replacement alongside any epithelial regeneration.

Case: Myocardial infarction

Ischemic necrosis destroys a region of cardiac muscle in an adult.

Clinical reasoning

Why does fibrous repair predominate?

Explanation

Cardiac myocytes have insufficient effective regenerative proliferation after major injury.

Case: Limited skeletal-muscle injury

A focal skeletal-muscle injury occurs while a population of satellite cells survives.

Clinical reasoning

What distinguishes the response from cardiac muscle?

Explanation

Satellite cells confer some regenerative capacity on otherwise permanent skeletal muscle.

Predict the repair pattern

Injury context	Mechanistic expectation
Labile lining; Stem cells + matrix preserved	Relatively favorable regeneration
Stable organ; Surviving cells + scaffold intact	Variable, limited restitution
Permanent parenchyma lost	Scar likely to dominate
Severe disruption of ECM support	Scar contribution increases

Four errors to avoid

- “Quiescent” is not synonymous with “unable to divide.”
- Stem-cell presence is not proof of clinically effective regeneration.
- Repair by scarring is not equivalent to restoration of normal architecture.
- Cellular proliferation cannot substitute for a destroyed tissue scaffold.

Mechanism of regeneration: Integrated model



Successful regeneration additionally requires preservation of appropriate tissue architecture.

Consolidated conclusions

- Intrinsic proliferative capacity sets an important ceiling on regeneration.
- Labile, stable and permanent tissues respond differently to injury.
- Growth factors, cell-cycle machinery and ECM signals enable repair proliferation.
- Stem cells help repopulate tissues; Matrix integrity determines organized restoration.

Knowledge check

A previously quiescent parenchymal cell enters G_1 after injury; Nearby ECM remains intact.

Clinical reasoning

Name the tissue class and two signaling systems that can support proliferation.

Explanation

Stable tissue; Growth-factor receptors and integrin–ECM signaling.

Primary reading

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 3, “Tissue Repair” and “Cell and Tissue Regeneration,” pp. 92–94.

Supporting context: Chapter 1, “Growth Factors and Receptors,” “Extracellular Matrix,” and “Maintaining Cell Populations,” pp. 18–27.

Original schematic diagrams and comparisons in this lecture were prepared as editable teaching graphics.