

Mechanisms of Hyperplasia

From mitogenic signals to increased cell number

Cell proliferation • tissue stem cells • regeneration • pathologic growth

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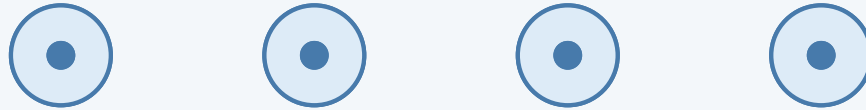
Learning objectives

- Explain the two cellular sources of increased cell number: Mature-cell division and stem-cell output.
- Trace growth-factor signaling to cell-cycle entry and proliferation.
- Apply these mechanisms to liver, bone marrow and hormone-responsive tissues.
- Distinguish regulated hyperplasia from neoplastic proliferation.

Emphasis: Stimulus → cellular response → tissue consequence.

Hyperplasia changes cell number, not merely cell size

Baseline



Hyperplasia



An increase in the number of constituent cells expands tissue mass in response to a stimulus.

Hyperplasia and hypertrophy are distinct adaptations

Feature	Hyperplasia	Hypertrophy
Primary change	More cells	Larger individual cells
Requirement	Cells capable of division	Cell enlargement without cell division
Relationship	May coexist with hypertrophy	May coexist with hyperplasia

A proliferative cell pool is essential

- Hyperplasia requires mature cells able to enter the cell cycle or a stem/progenitor pool.
- Nonproliferative cell populations have limited ability to expand by cell division.
- Tissue-specific proliferative potential helps predict the response to a growth stimulus.

Cell number cannot increase through hypertrophy alone.

Two complementary cellular sources of hyperplasia

Growth-factor or hormonal stimulation

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graph TD; A[Growth-factor or hormonal stimulation] --> B[Mature-cell route]; A --> C[Stem-cell route]; B --> D[Division of surviving differentiated cells]; C --> E[Expansion and maturation of tissue stem-cell progeny];
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Mature-cell route

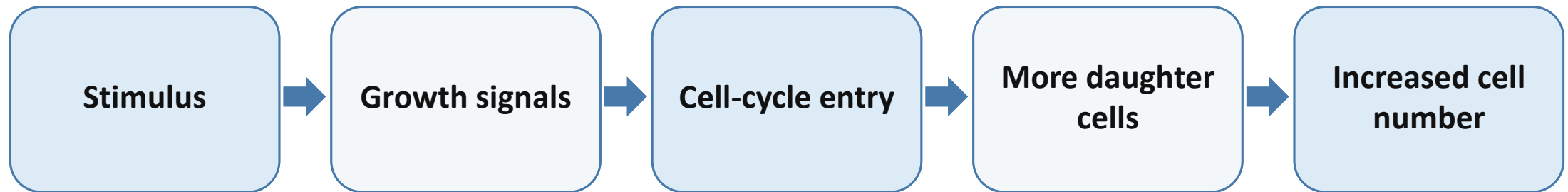
Division of surviving differentiated cells

Stem-cell route

Expansion and maturation of tissue
stem-cell progeny

Relative contribution depends on tissue and injury context.

From initiating stimulus to tissue enlargement

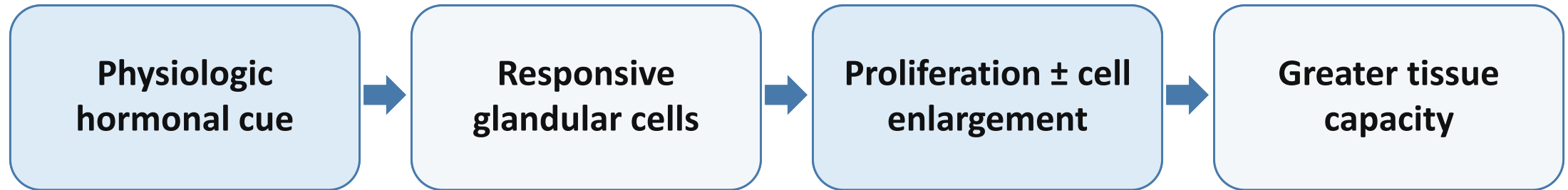


A regulated response links extracellular cues to intracellular proliferation.

Physiologic versus pathologic stimulation

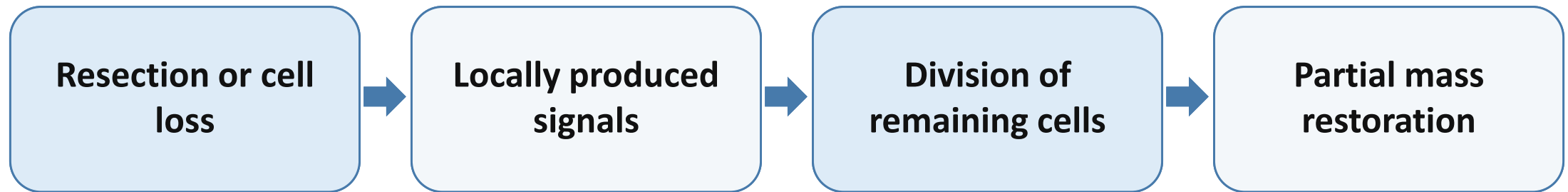
Dimension	Physiologic	Pathologic
Typical purpose	Meet functional demand or replace lost cells	Response to excessive/inappropriate signals
Illustration	Pregnancy breast; Liver after resection	Endometrial or prostatic hyperplasia
Control	Feedback-limited	Often remains stimulus-dependent

Hormonal hyperplasia increases functional capacity



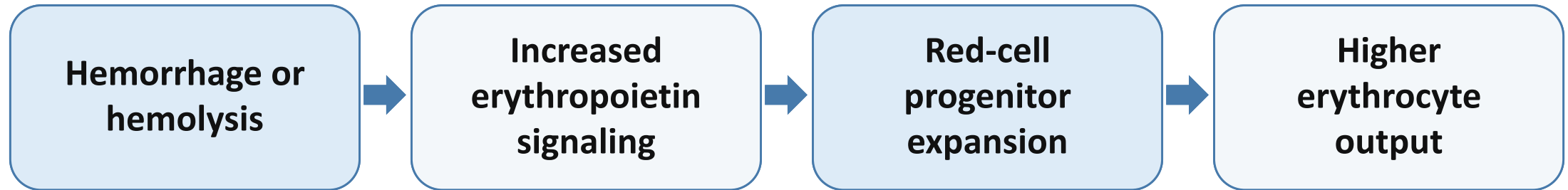
Mammary glandular epithelium expands during puberty and pregnancy.

Compensatory hyperplasia replaces lost tissue mass



Liver regeneration is the classic illustration.

Marrow compensates for erythrocyte deficit



Feedback couples a circulating deficit to marrow proliferation.

Abnormal growth signals can remain regulated

- Excess hormones or growth factors can produce pathologic hyperplasia.
- The target cells still respond to extracellular cues and regulatory pathways.
- Regression or stabilization may follow removal of the driving hormonal signal.

Stimulus dependence helps separate hyperplasia from autonomous neoplasia.

The endometrium illustrates hormonal balance

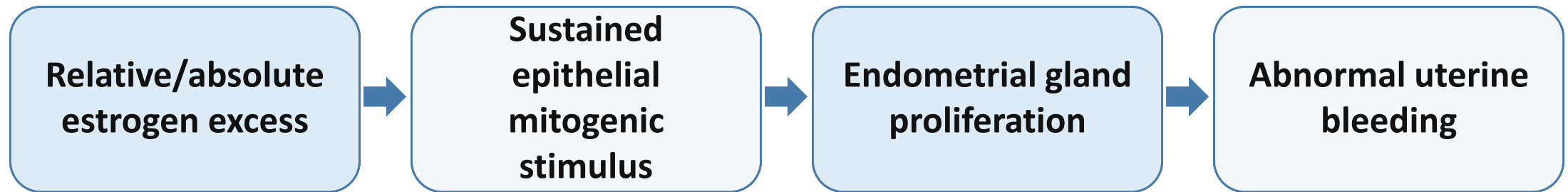
Estrogen-dominant interval

- Estrogen promotes endometrial proliferative activity.
- Glandular cellularity increases during the proliferative phase.

Progesterone influence

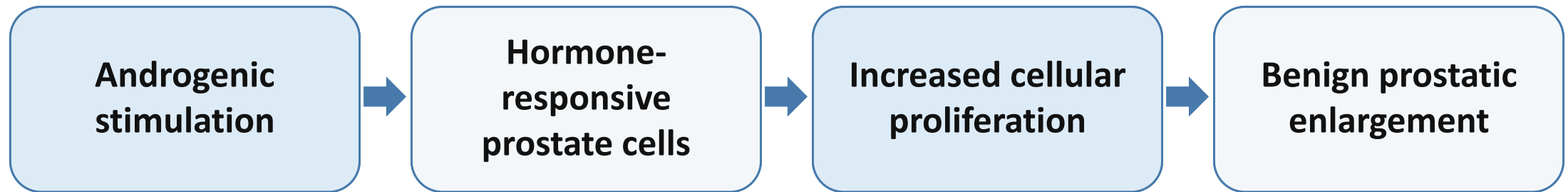
- Progesterone counterbalances proliferative stimulation.
- Normal cycling prevents sustained unopposed gland proliferation.

Unopposed estrogen favors glandular expansion



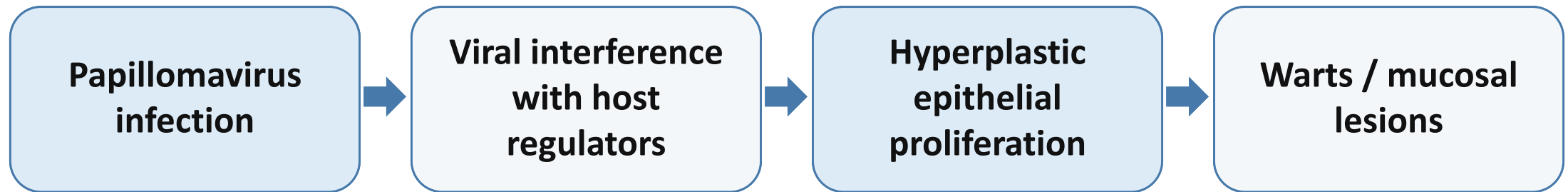
The clinical symptom follows from abnormal endometrial growth and cycling.

Androgen signaling drives prostatic hyperplasia



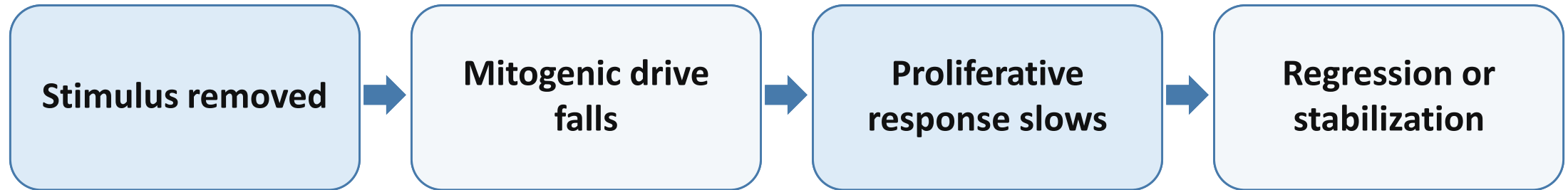
An endocrine input can provoke a non-neoplastic mass increase.

Viral proteins can dysregulate proliferation



Viral hyperplasia highlights a mechanism other than hormonal excess.

Reversibility reflects stimulus dependence

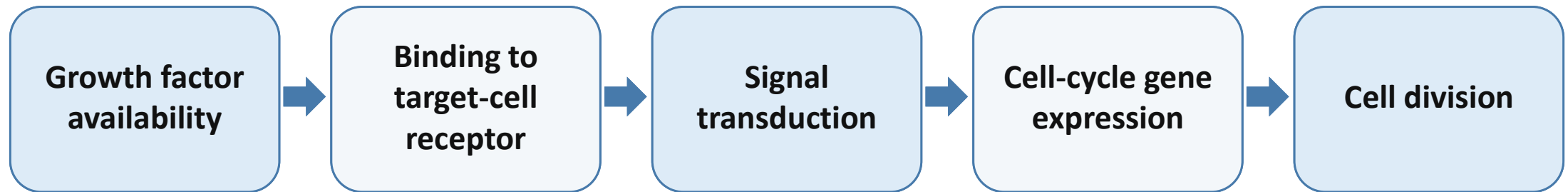


The source describes hormone-dependent hyperplasia as remaining controlled.

Regulated proliferation differs from neoplasia

Question	Hyperplasia	Neoplasia
Primary driver	An external growth signal	Acquired autonomous growth advantage
Response to cue withdrawal	Can regress or stabilize	May persist independently
Relationship	May create a risk context	Represents a distinct clonal disease process

Growth factors are the proximate mitogenic signal



Both homeostatic proliferation and injury responses use these steps.

Growth factors act through tissue-specific contexts

Source or factor	Representative source	Relevant effect
HGF	Liver stromal / nonhepatocyte cells	Hepatocyte mitogenesis
TGF- α	Macrophages, keratinocytes and others	Epithelial / hepatocyte proliferation
EGF	Macrophages and epithelia	Many epithelial proliferative responses

Activated macrophages supply local repair signals

- Macrophages become activated at sites of tissue damage.
- They provide growth factors that stimulate reparative proliferation.
- The same tissue response also recruits stromal, vascular and epithelial contributions.

The injury microenvironment helps determine which cells expand.

Growth signals come from more than one cell type

Parenchymal and epithelial cells

- Surviving local cells may secrete mitogenic factors.
- Their receptors may also respond to neighboring factors.

Stromal and inflammatory cells

- Macrophages and fibroblasts contribute growth-factor signals.
- Extracellular matrix can hold factors near responding cells.

Receptor recognition links ligand to response



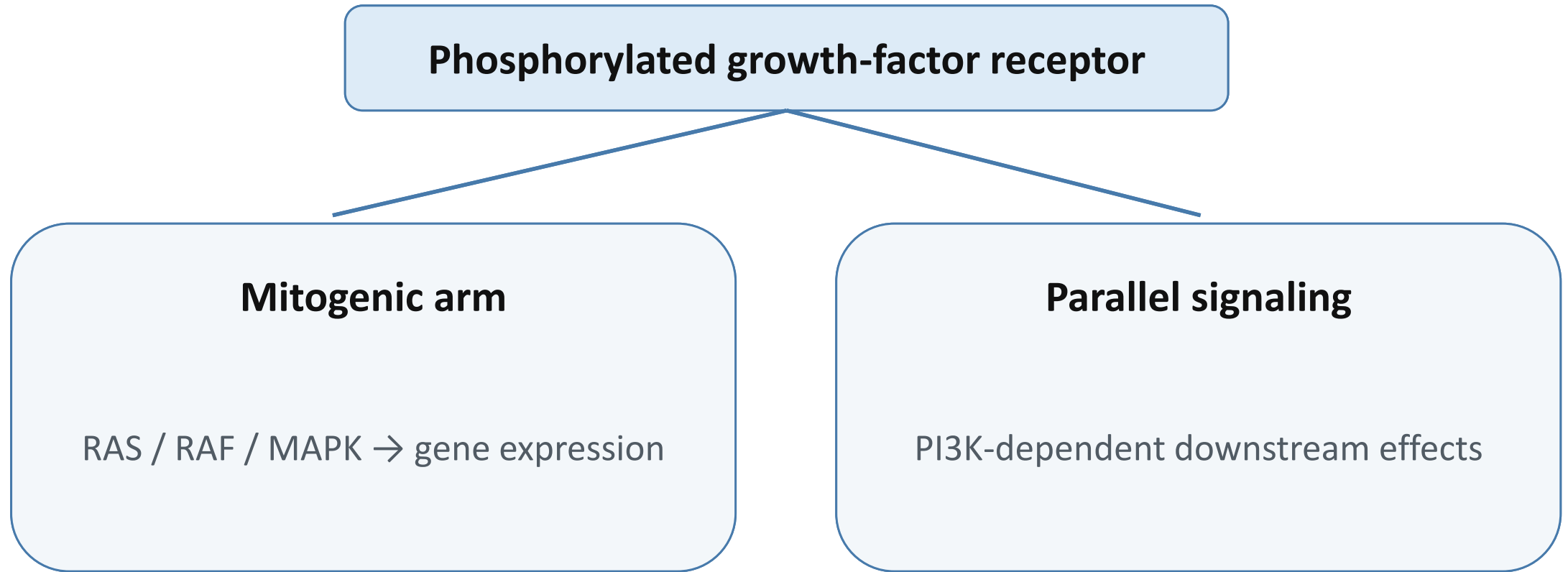
A cell must be competent to recognize and transduce the signal.

RAS–RAF–MAPK transduces a mitogenic signal



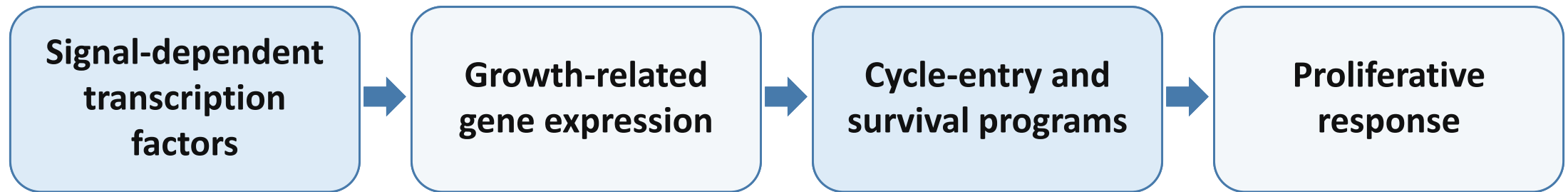
A representative pathway; Not every growth signal uses this exact sequence.

Activated receptors engage multiple outputs



Signaling networks branch; Avoid equating one receptor with one linear pathway.

Transcription converts a transient cue into a cellular program

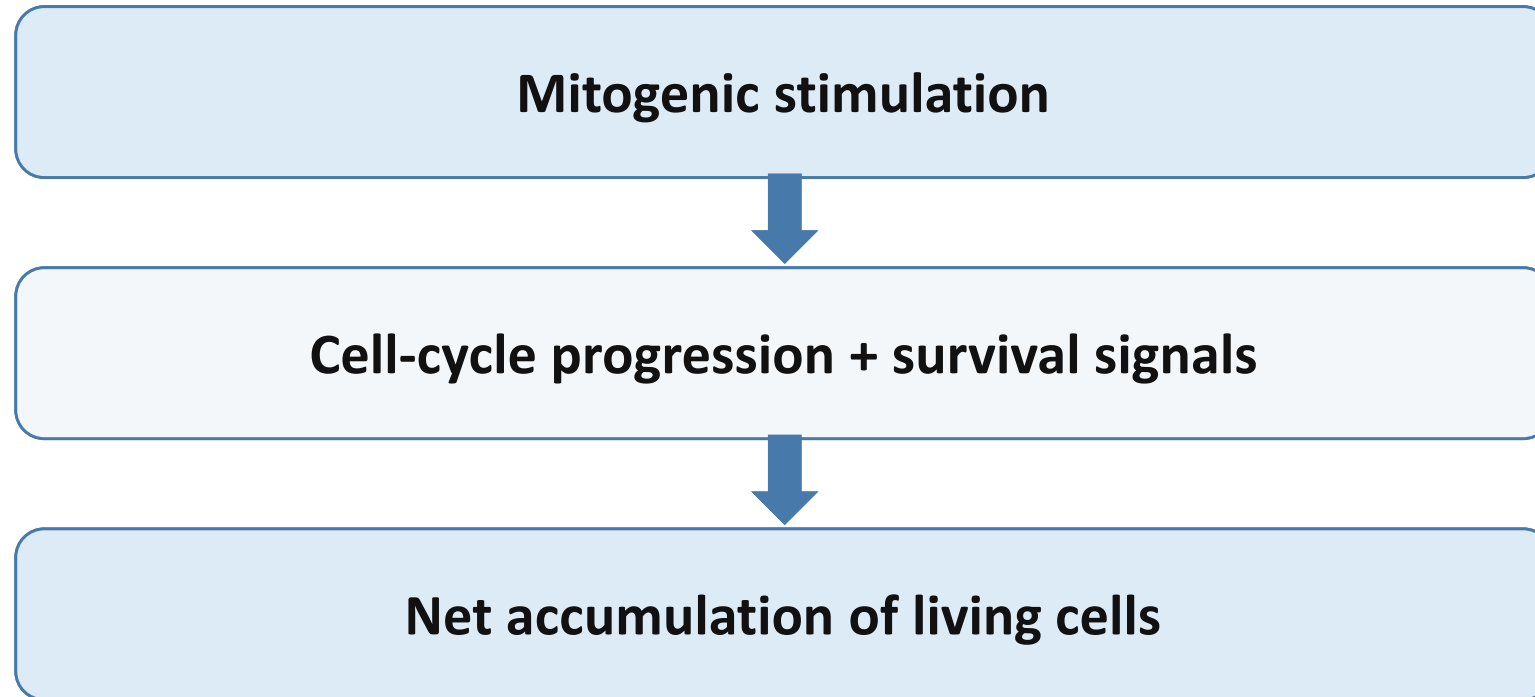


The source discusses MYC and JUN among growth-promoting transcriptional regulators.

Growth-factor signaling coordinates four major outputs

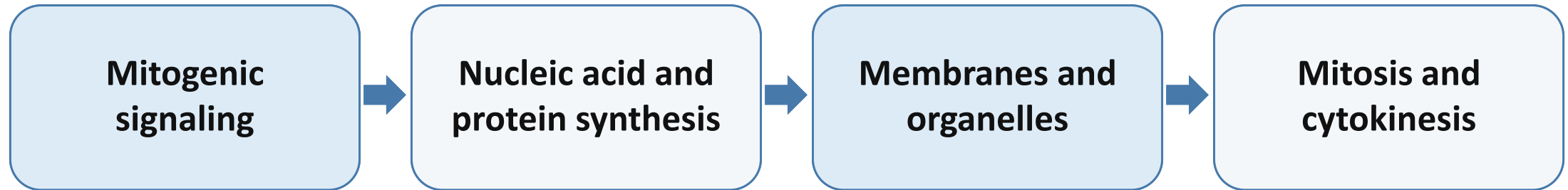
Output	Mechanistic consequence
Cell-cycle entry	Quiescent cells acquire proliferative competence
Checkpoint progression	Inhibitory barriers may be appropriately relieved
Cell survival	Apoptotic loss is reduced
Macromolecule synthesis	DNA, protein, membrane and organelle production increases

Hyperplasia requires survival as well as division



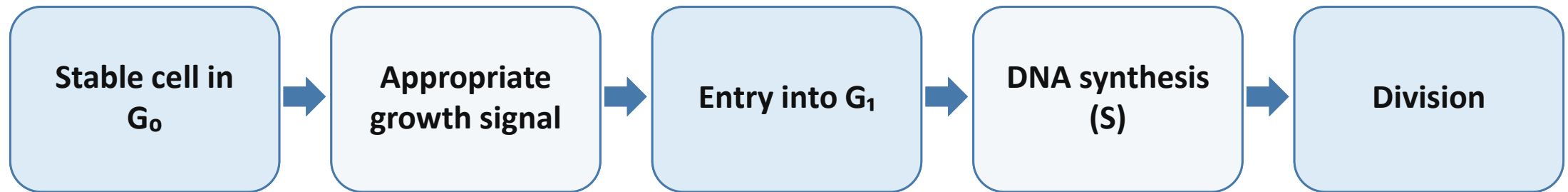
Net cell number reflects production balanced against cellular loss.

Daughter cells require new biomass



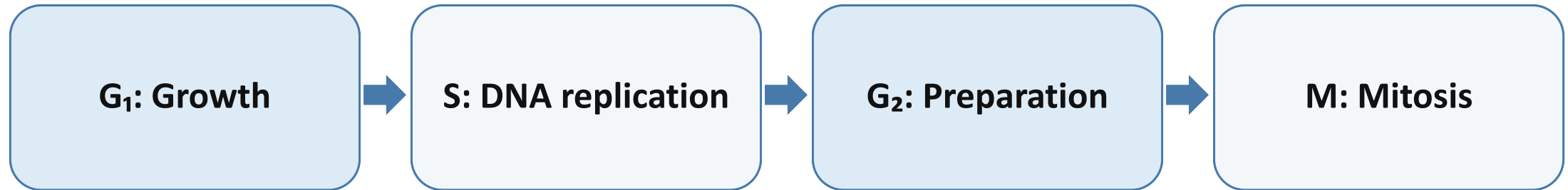
DNA replication alone is insufficient for successful proliferation.

Quiescent cells can re-enter the cycle



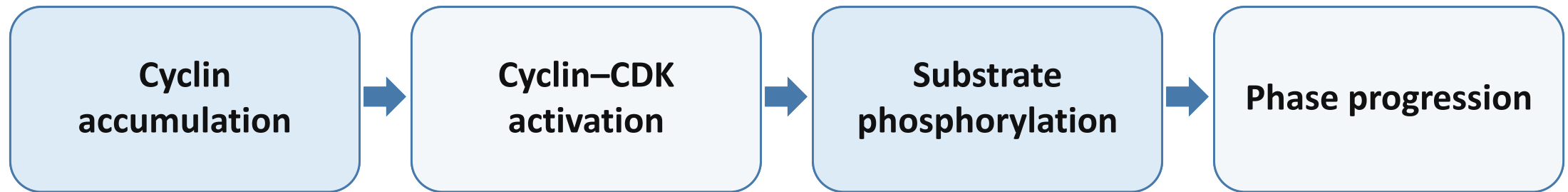
Residual hepatocytes are an important example of a quiescent proliferative pool.

Cell-cycle phases are ordered, not interchangeable



Quiescence (G_0) is a separate state that can precede G_1 entry.

Cyclins and CDKs govern cycle transitions



Sequential cyclins D, E, A and B participate in coordinated transitions.

DNA surveillance accompanies proliferation

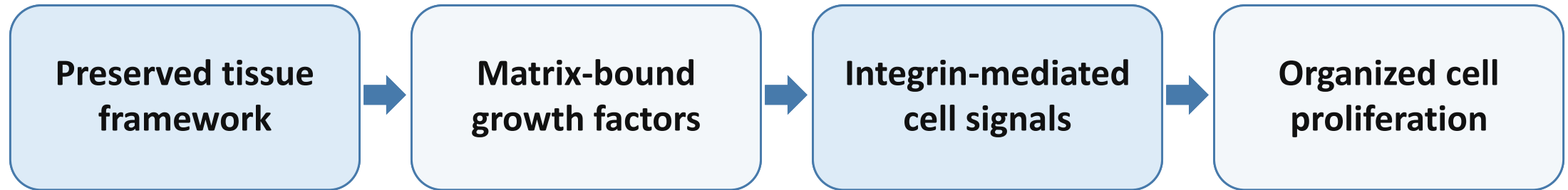
Checkpoint	Question assessed	Protective response
G ₁ /S	Is DNA suitable for replication?	Delay cycle to permit repair
G ₂ /M	Was genome replication accurate?	Delay division if abnormalities persist
Irreparable injury	Can safe division resume?	Apoptosis or senescence

Normal mitogenesis is constrained by inhibitors

- Cyclin-dependent kinase inhibitors counterbalance growth-promoting complexes.
- Checkpoint activation can pause proliferation while DNA damage is repaired.
- Cellular senescence or apoptosis prevents propagation of irreparable injury.

Hyperplasia engages proliferative machinery; It does not require its complete deregulation.

Extracellular matrix provides a permissive context



An intact extracellular matrix supports effective regeneration.

Matrix and soluble signals converge

Tissue cell

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graph TD; A[Tissue cell] --> B[Soluble route]; A --> C[Adhesion route]; B --> D["Growth factors → receptors"]; C --> E["ECM → integrins"]
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Soluble route

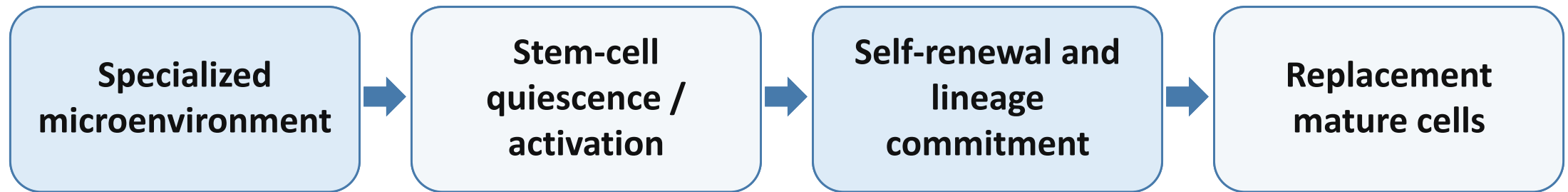
Growth factors → receptors

Adhesion route

ECM → integrins

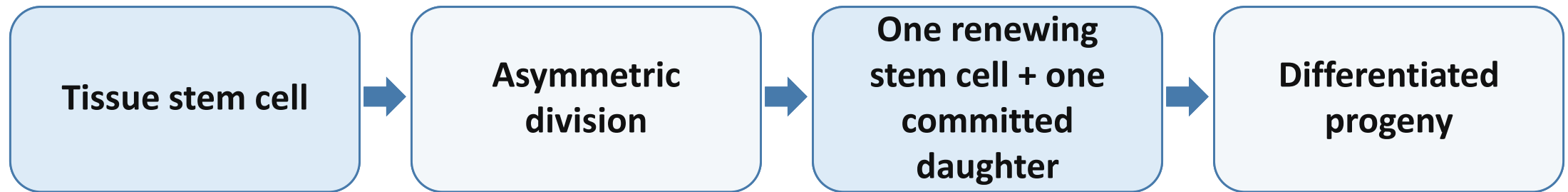
These inputs can jointly facilitate cell proliferation and survival.

Stem-cell niches regulate the reserve pool



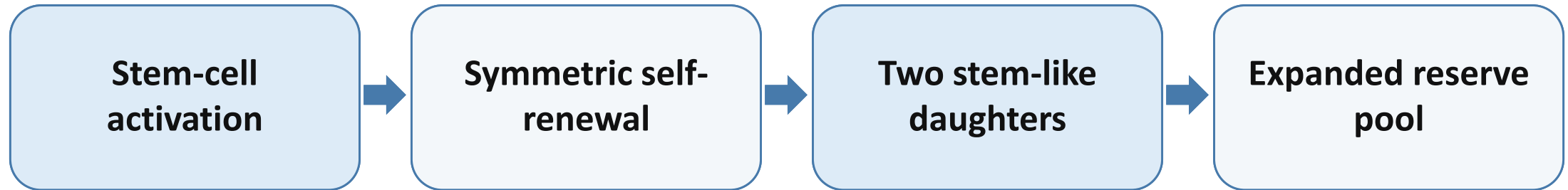
Niches maintain local progenitors until homeostasis or injury calls on them.

Asymmetric division preserves a stem-cell pool



Balanced renewal supports ongoing replacement without exhausting the pool.

Symmetric division expands stem-cell numbers



Symmetric expansion under strong demands, such as marrow recovery.

Mature-cell and stem-cell routes are complementary

Feature	Residual mature cell	Tissue stem cell
Starting point	Differentiated surviving cell	Relatively undifferentiated niche cell
Required step	Re-entry into cell cycle	Expansion and differentiation
Contribution	Direct increase of functional cells	Replenishes mature population

Proliferative potential predicts adaptive capacity

Tissue class	Baseline state	Examples
Labile	Continuous cell replacement	Surface epithelia, marrow
Stable	Mostly quiescent; Recrutable	Liver, kidney; Fibroblasts
Permanent	Very limited cell replication	Most neurons, cardiac myocytes

Labile tissues routinely depend on renewal

Surface epithelium

- Cells are continuously lost and replaced.
- Preserved stem cells make regeneration feasible.

Bone marrow

- Hematopoietic progenitors continually produce mature cells.
- Growth signals can rapidly expand lineage output.

Stable hepatocytes are recruitable from G₀



Quiescence is not equivalent to terminal differentiation.

Permanent tissues exemplify the limit

Neurons and cardiomyocytes

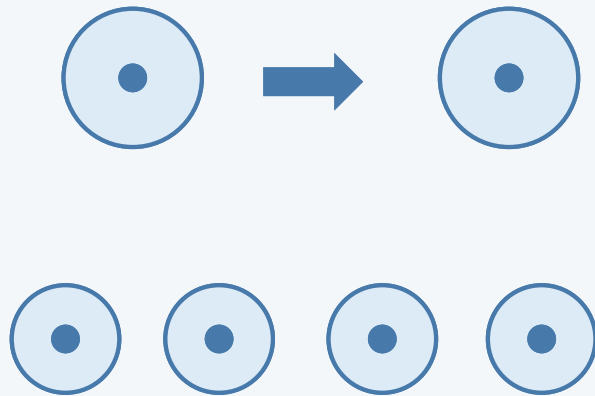
- Most cells have little useful adult proliferative capacity.
- Severe losses are not compensated by bulk hyperplasia.

Regenerative exceptions

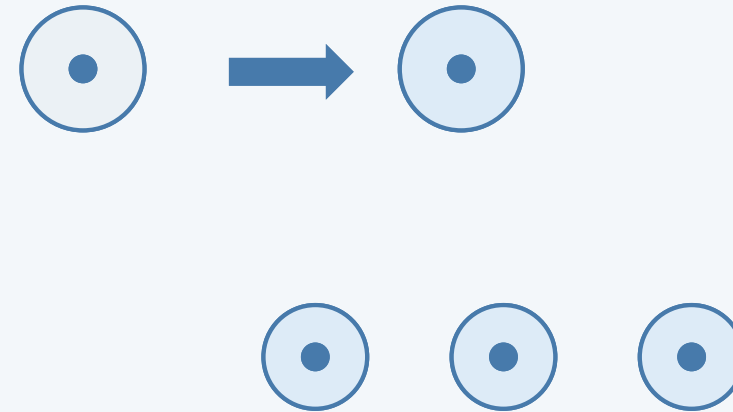
- Skeletal muscle satellite cells can supply some repair.
- Restricted replication in brain/heart is insufficient for full restoration.

Cell source determines the route of tissue reconstitution

Mature-cell division



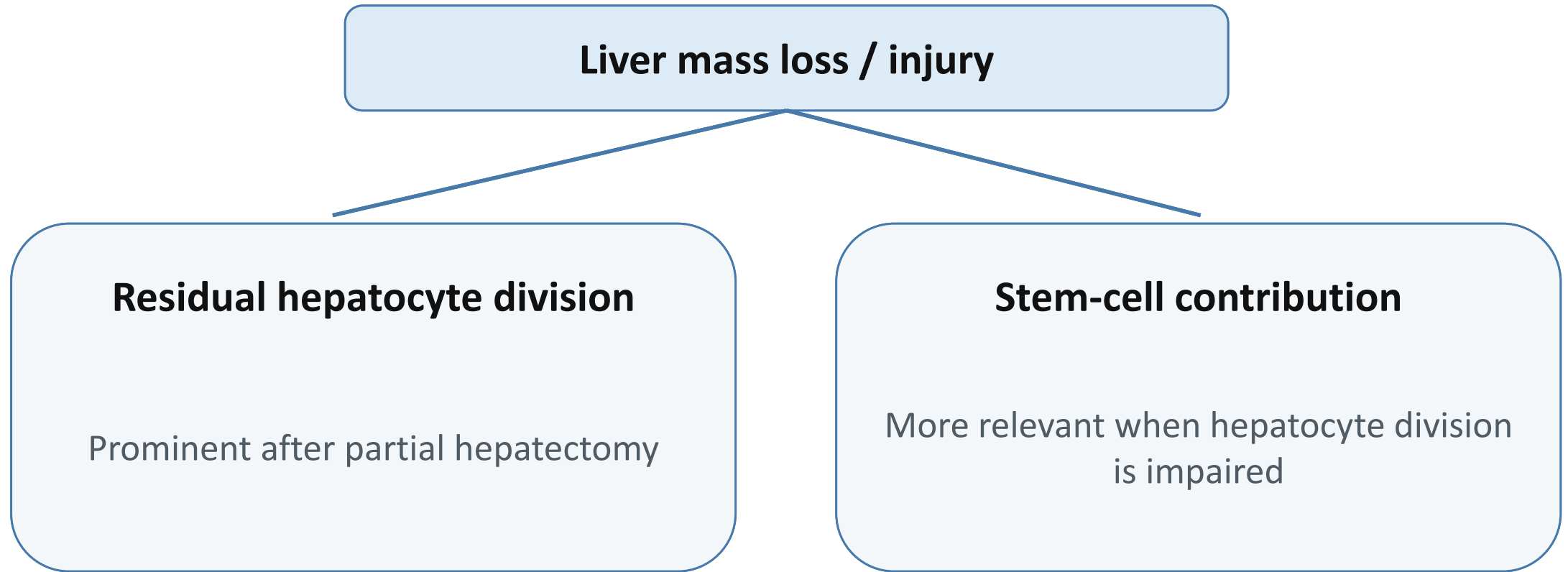
Stem-cell output



Stem → progenitor → mature cells

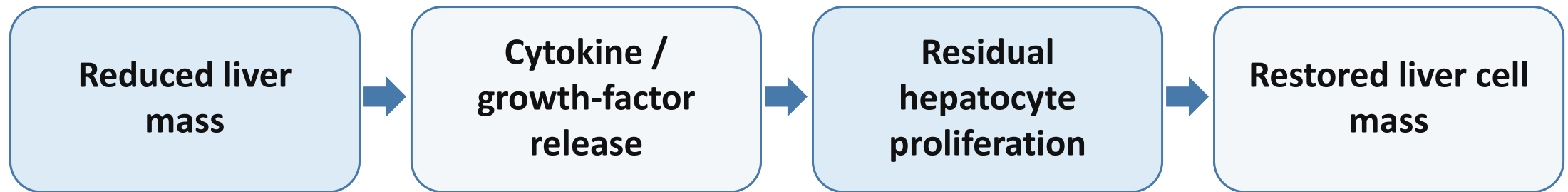
The same net increase in cell number may arise from division of residual cells or stem-cell maturation.

Liver regeneration is a two-route model



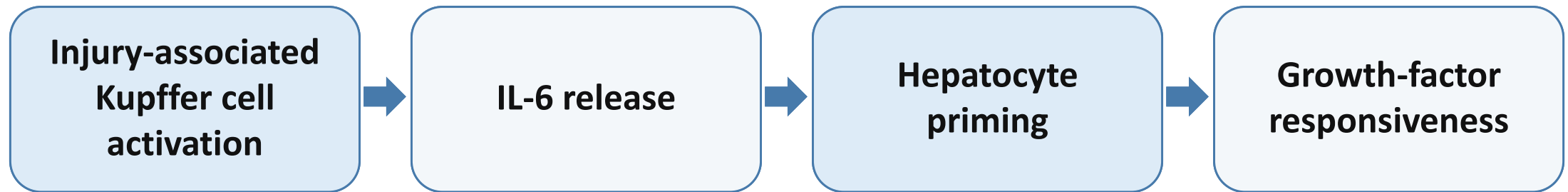
The dominant route depends on the type and persistence of injury.

Partial hepatectomy initiates compensatory growth



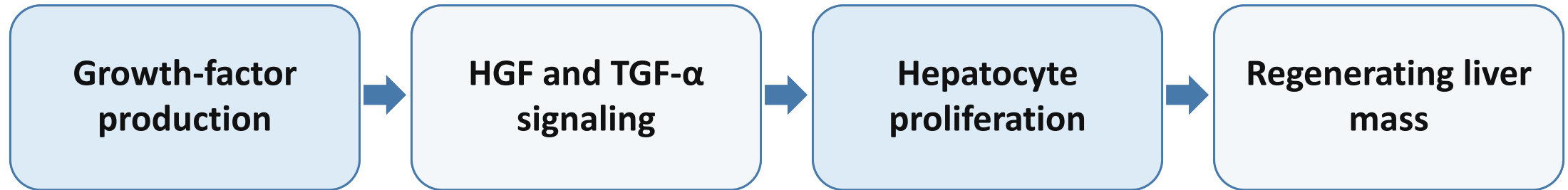
This is compensatory hyperplasia rather than enlargement of hepatocytes alone.

IL-6 primes surviving hepatocytes



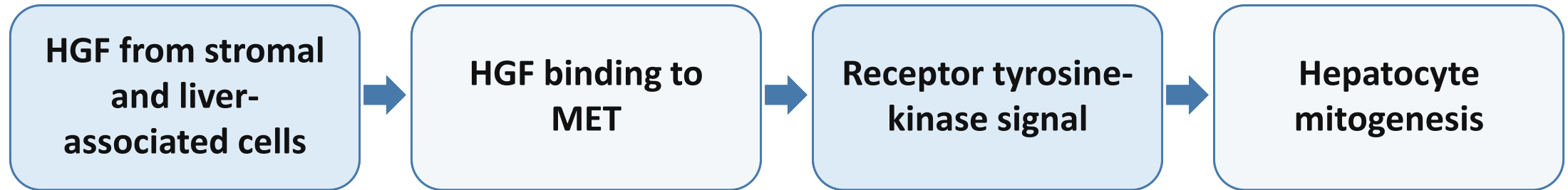
Cytokine priming before strong mitogenic signaling.

HGF and TGF- α stimulate the primed liver



Priming and growth-factor drive are complementary stages.

HGF signals through the MET receptor



HGF–MET is a named receptor-ligand pair Chapter 1.

Residual hepatocytes drive much hepatic regrowth

- After partial hepatectomy, surviving hepatocytes retain replicative competence.
- Cytokines make them responsive to growth factors, followed by mitotic expansion.
- Extensive human liver regeneration can follow proliferation of residual hepatocytes.

Do not equate restored organ mass with exact restoration of resected architecture.

Chronic damage changes the dominant cell source

Hepatocyte proliferative capacity

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graph TD; A[Hepatocyte proliferative capacity] --> B[Preserved]; A --> C[Compromised]; B --> D[Residual mature hepatocyte division predominates]; C --> E[Intrahepatic stem-cell contribution becomes important];
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Preserved

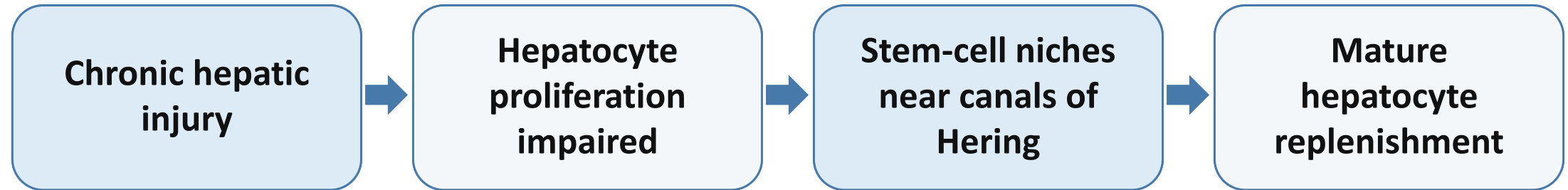
Residual mature hepatocyte division
predominates

Compromised

Intrahepatic stem-cell contribution
becomes important

Mechanistic emphasis changes with the condition of the surviving cells.

Canals of Hering are a hepatic stem-cell niche

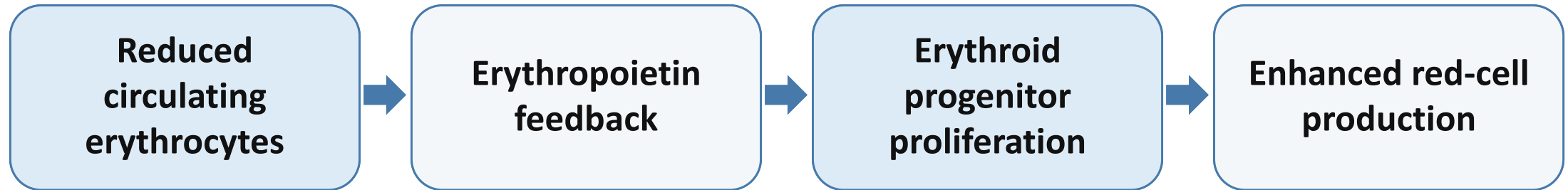


The source locates some hepatic stem cells near bile canaliculi–duct connections.

Regeneration competes with scar formation

Outcome	Regeneration	Fibrous repair
Biologic basis	Replacement of functional cells	Collagen-rich connective tissue deposition
Requirements	Proliferative capacity + preserved ECM	More important when structural injury is severe
Tissue result	Restoration toward normal	Mechanical continuity; Altered architecture

Erythropoietin couples demand to marrow output

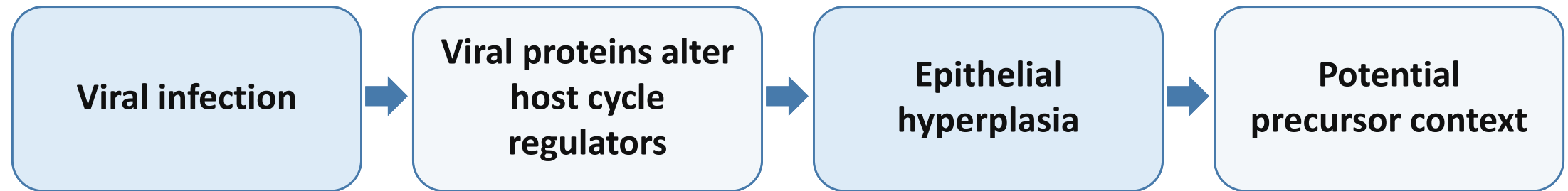


Hemorrhage and hemolysis to illustrate compensatory marrow hyperplasia.

Pathologic and physiologic signals differ by context

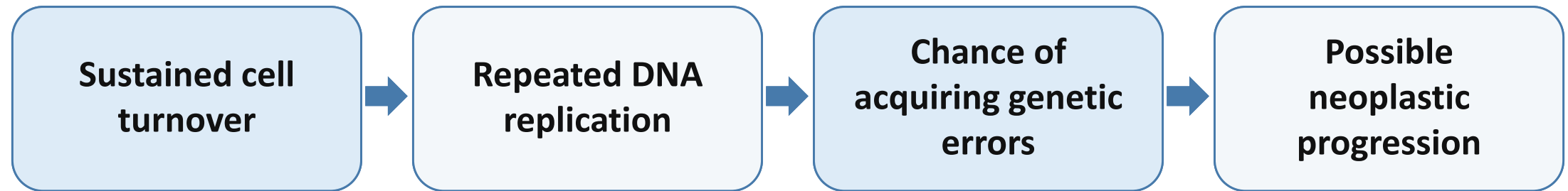
Feature	Compensatory growth	Excess hormonal growth
Initiating problem	Functional cell or tissue deficit	Inappropriately sustained stimulus
Illustration	Liver resection / anemia	Endometrial estrogen excess
Response principle	Growth-factor-driven proliferation	Growth-factor or hormone-driven proliferation

Papillomavirus adds a distinct proliferative mechanism



This is not identical to ordinary growth-factor-stimulated liver regeneration.

More mitoses can increase mutation opportunities



Risk does not imply that every hyperplastic lesion is precancerous.

Cancer risk depends on the hyperplastic context

Context	Proliferative stimulus	Clinical interpretation
Compensatory liver growth	Demand after loss of tissue mass	Adaptive replacement of hepatocytes
Endometrial hyperplasia	Sustained relative / absolute estrogen excess	Some patients face increased cancer risk
Papillomavirus lesions	Viral interference with cell-cycle regulators	Some lesions are cancer precursors

Clinical reasoning: Abnormal uterine bleeding

Teaching vignette (hypothetical)

A patient has persistent bleeding with a sustained estrogenic effect relative to progesterone.

Which proliferative mechanism could expand the endometrium?

Mechanistic interpretation: Hormone-driven epithelial proliferation increases endometrial glandular cellularity; Evaluate histology clinically.

Clinical reasoning: Living liver donation

Teaching vignette (hypothetical)

A healthy donor undergoes partial hepatectomy with viable residual hepatocytes.

**Which cell source
should supply most
early compensatory
proliferation?**

Mechanistic interpretation: Residual differentiated hepatocytes respond to cytokine priming and growth factors, then re-enter the cell cycle.

Clinical reasoning: Hemolysis

Teaching vignette (hypothetical)

Accelerated erythrocyte destruction produces a sustained demand for replacement.

Which signal links the deficit to expansion of the marrow cell pool?

Mechanistic interpretation: Feedback involving erythropoietin expands erythroid precursors, increasing new erythrocyte output.

Clinical reasoning: Chronically injured liver

Teaching vignette (hypothetical)

Chronic hepatic inflammation has impaired the ability of surviving hepatocytes to proliferate.

Which additional source of mature hepatocytes becomes relevant?

Mechanistic interpretation: Intrahepatic stem-cell contributions, including niches in the canals of Hering.

Integrated model of adaptive cell-number increase

A signal-responsive tissue

```
graph TD; A[A signal-responsive tissue] --> B[Mature-cell proliferation]; A --> C[Stem/progenitor output]; B --> B1[Growth factor -> receptor -> cell cycle -> daughter cells]; C --> C1[Niche activation -> expansion -> differentiated progeny]
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Mature-cell proliferation

Growth factor → receptor → cell cycle
→ daughter cells

Stem/progenitor output

Niche activation → expansion →
differentiated progeny

The extent and success of expansion depend on signals, cell competence and ECM.

Mechanistic synthesis

- Hyperplasia is growth-stimulus–dependent expansion of cell number.
- In most settings, competent mature cells proliferate in response to growth factors.
- Tissue stem cells replenish populations, particularly when mature-cell division is limited.
- Physiologic and pathologic hyperplasia share machinery but differ in stimulus and consequences.

Clinical interpretation begins by identifying the stimulus, cell source and tissue context.

Principal textbook sections

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 2: Hyperplasia; Mechanisms of Hyperplasia.
- Chapter 3: Cell and Tissue Regeneration; Liver Regeneration.
- Chapter 1: Growth Factors and Receptors; Proliferation and the Cell Cycle; Stem Cells.

References and source locators are detailed in the speaker notes.