

Proliferation and the Cell Cycle

Cell-cycle progression • Quality-control checkpoints • Tissue homeostasis

From coordinated cell division to control of tissue cell populations

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Learning objectives

- Distinguish G_0 , G_1 , S, G_2 and M phases and identify their essential events.
- Explain the sequential actions of cyclins, CDKs and CDK inhibitors.
- Relate checkpoint integrity to DNA repair, senescence, apoptosis and cancer risk.
- Connect proliferative control with stem-cell renewal and tissue maintenance.

Why controlled proliferation matters

Proliferation is an organized biological process, not simply an increase in cell number.

- Generates cells during development and organ growth.
- Replaces cells lost through normal turnover or injury.
- Preserves organ function by coordinating cellular gain and loss.
- Requires complete duplication and accurate allocation of cellular contents.

A dividing cell must reproduce both its genome and its cellular machinery.

Three tasks underlying one successful division



Distinct coordinated events—not synonyms

- DNA must be replicated accurately.
- Proteins, membranes and organelles must be synthesized.
- Mitosis segregates chromosomes; Cytokinesis separates daughter cells.

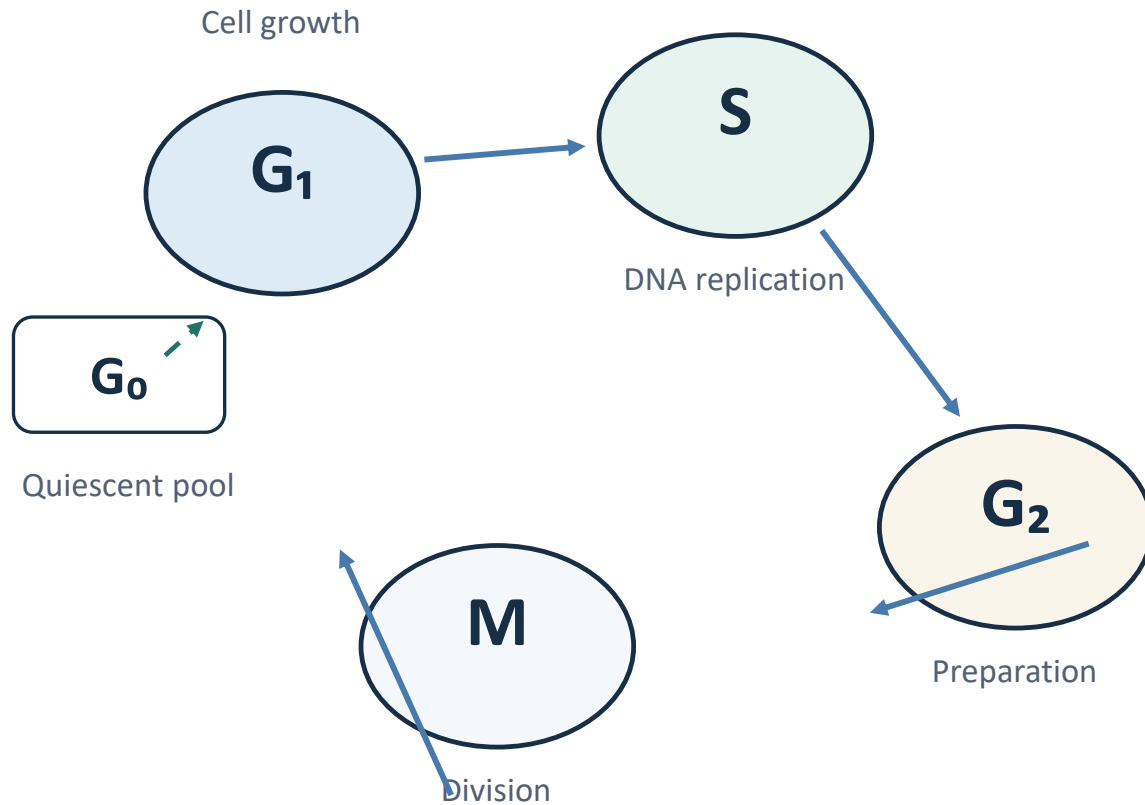
A failure in any task can compromise the next cell generation.

Related processes with distinct meanings

- Cell growth: Increase in biosynthetic mass and components.
- DNA synthesis: Duplication of genetic information.
- Mitosis: Ordered separation of duplicated chromosomes.
- Cytokinesis: Physical partitioning into daughter cells.

Growth, genome replication and cell division are coordinated but nonidentical.

The cell-cycle map



- G₁, S, G₂ and M form the active cycle.
- G₀ is a noncycling quiescent state.
- G₁ can follow mitosis or re-entry from G₀.
- Each phase depends on successful completion of the preceding steps.

Cell-cycle order safeguards inherited information.

G_0 versus the proliferative cycle

Quiescence $\neq$ permanent inability to divide

G_0 : Not actively cycling



G_1 : Re-entry possible

Loss of proliferative capacity

- G_0 cells are not actively replicating.
- Some quiescent cells can be recruited back into G_1 .
- Cells with permanently lost proliferative capacity are distinct from reversibly quiescent cells.

G₁ phase: Biosynthesis before DNA replication

- Cell mass increases and cellular components accumulate.
- Growth signals can influence entry and continued progression.
- The G₁ restriction point marks commitment beyond a requirement for the initiating mitogenic signal.
- The G₁/S surveillance gate assesses DNA integrity before synthesis.

Commitment to cycle progression and DNA-damage checking are conceptually distinct.

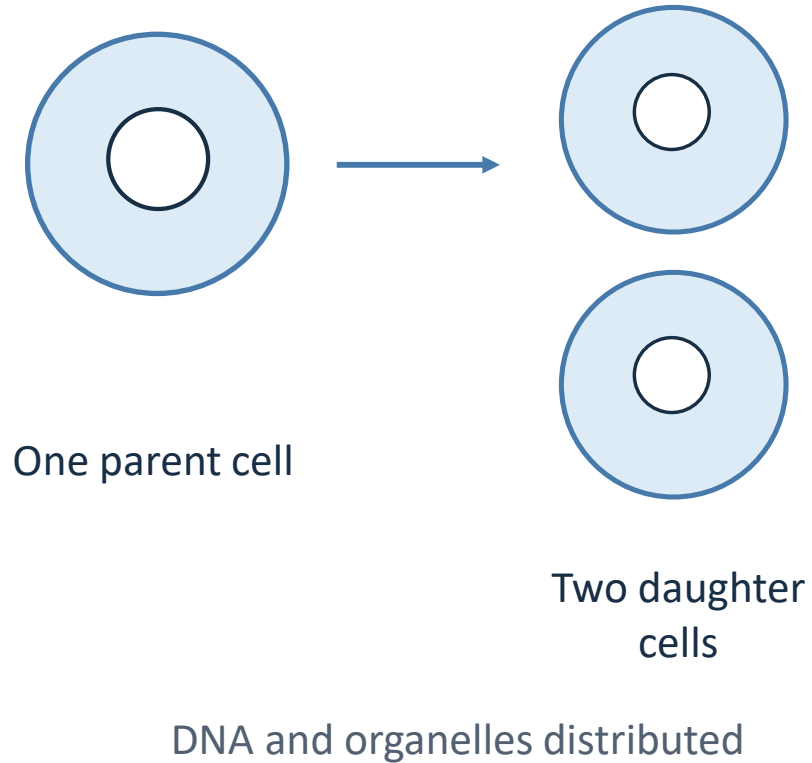
S phase: Duplication of the genome

- The defining event is DNA synthesis.
- Chromosome duplication must preserve sequence and completeness.
- Replication errors can activate cycle-control mechanisms.
- Cyclin A–associated kinase complexes act during this phase.

G₂ phase: Preparing for chromosome segregation

- Occurs after DNA synthesis and before mitosis.
- The cell prepares its organelles and machinery for division.
- The G₂/M checkpoint detects incompletely duplicated or damaged DNA.
- Progression into M phase depends on cyclin B–CDK1.

M phase: Segregation and physical division



- Mitosis separates duplicated chromosomes.
- Cytokinesis divides cytoplasm and other cellular components.
- Two daughter cells enter G_1 after completion of division.
- Successful partitioning maintains genomic continuity.

Directionality is fundamental

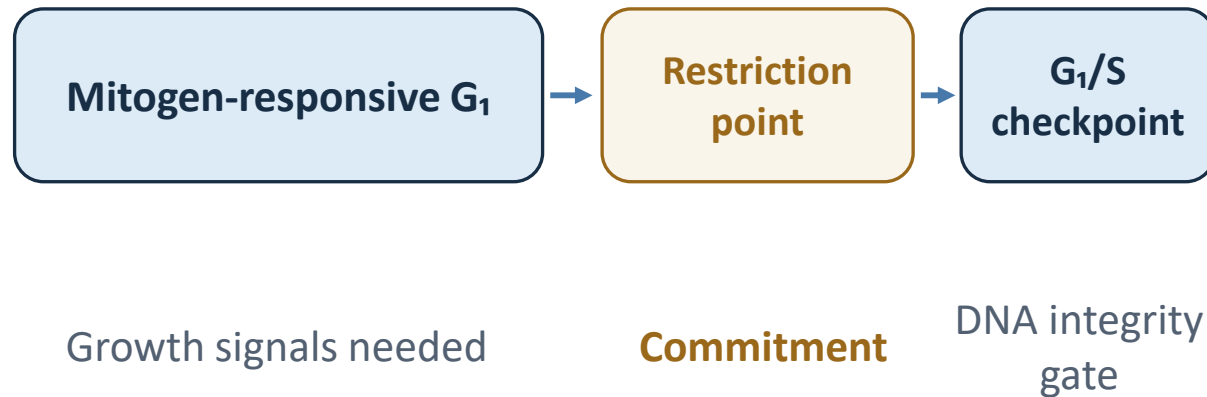


Quiescence Growth DNA synthesis Preparation Cell division

Entry into G₁ from quiescence or after mitosis

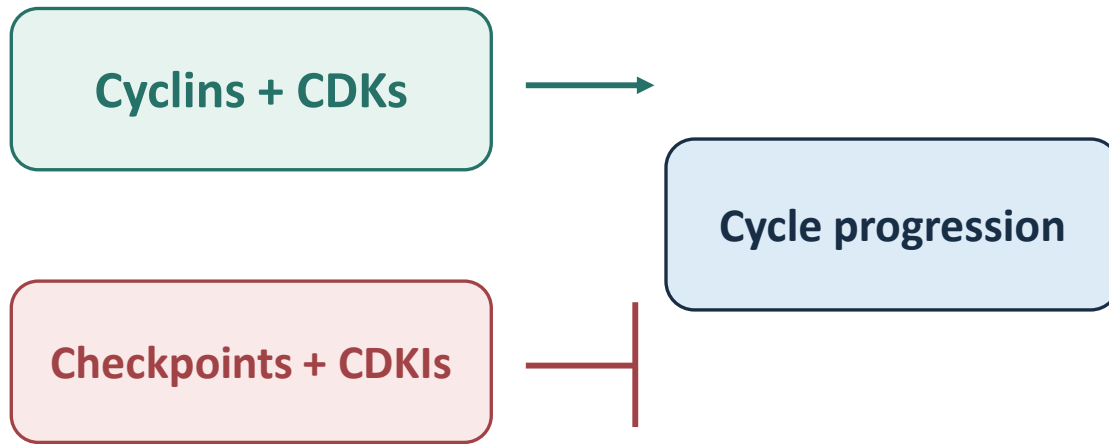
- Progression follows $G_1 \rightarrow S \rightarrow G_2 \rightarrow M$.
- G₀ lies outside active cycling.
- Quality-control events delay progression when prerequisites are unmet.

Restriction point versus G₁/S checkpoint



- Restriction point: Commitment to continue through the cycle without additional initiating growth signal.
- G₁/S checkpoint: DNA-integrity surveillance before replication.
- These controls occur in related but nonidentical functional contexts.

Cell-cycle control has opposing forces



- Cyclin–CDK complexes promote phase transitions.
- CDK inhibitors restrain activity of these complexes.
- Damage-responsive checkpoints prevent inappropriate progression.

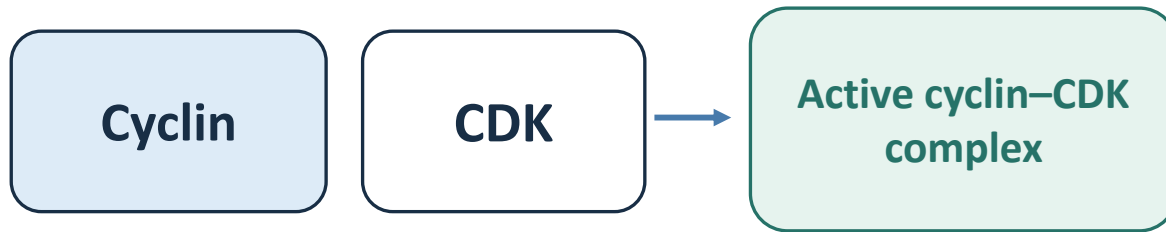
Progression requires both activating signals and permissive surveillance

Two-part logic of cyclin-dependent kinases

- Cyclins are dynamically produced and degraded.
- CDKs are synthesized more constitutively.
- Binding of a relevant cyclin confers CDK kinase activity.
- Active complexes phosphorylate protein substrates to advance cell-cycle events.

CDK activity depends on the presence of its phase-appropriate cyclin.

How a cyclin activates a CDK



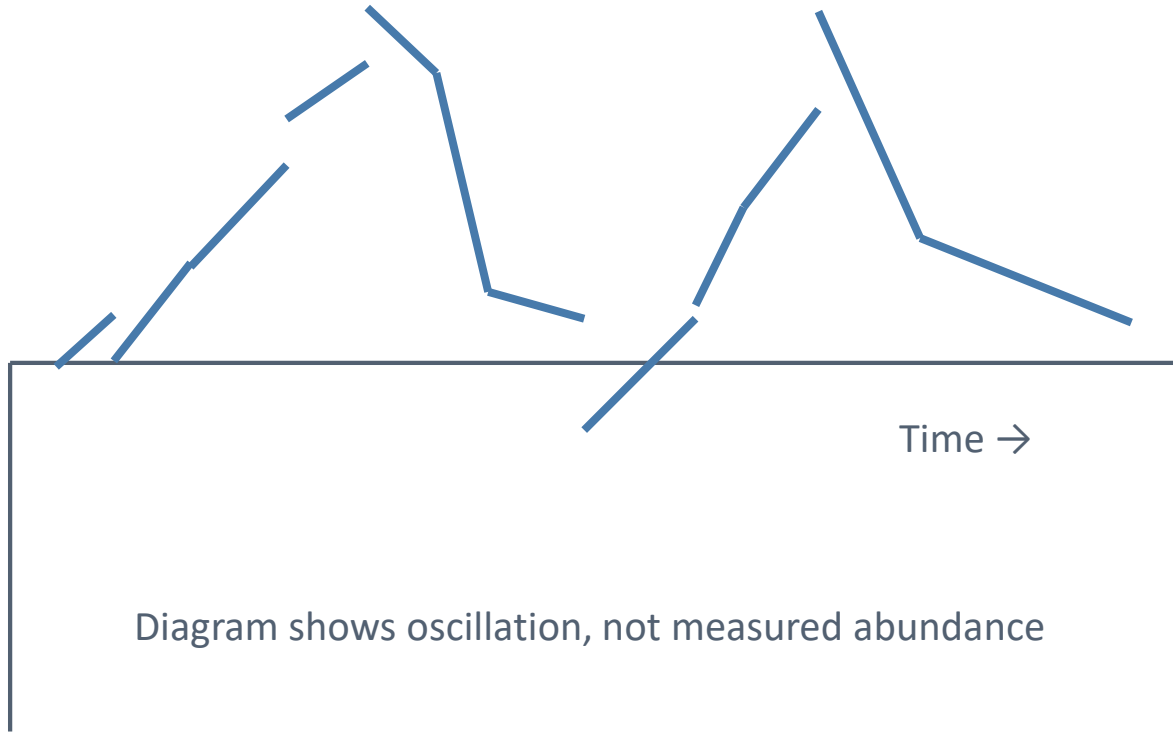
CDK alone has little relevant kinase activity

Cyclin binding enables substrate phosphorylation

- Cyclin binding enables the CDK to phosphorylate substrates.
- A temporary cyclin increase raises activity of the cognate kinase.
- Cyclin degradation terminates a wave of CDK activity.

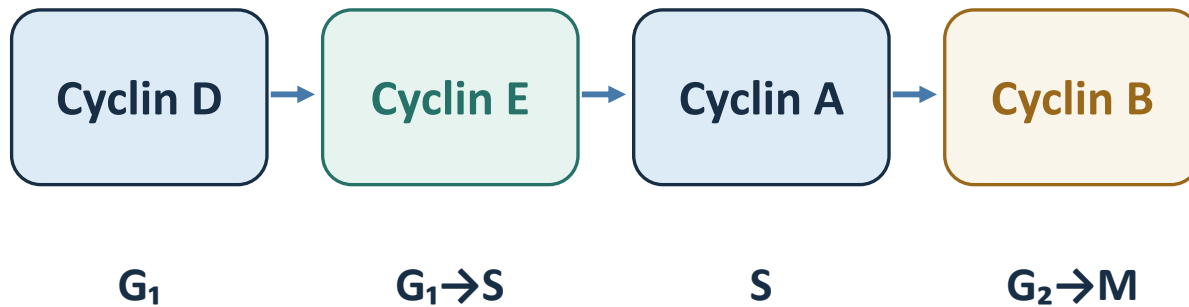
Cyclin abundance is dynamic

Cyclin availability (qualitative)



- Cyclin production rises in a phase-associated sequence.
- Regulated degradation lowers associated kinase activity.
- The resulting oscillation coordinates ordered transitions.

The cyclin relay: $D \rightarrow E \rightarrow A \rightarrow B$



Sequential activation; Cyclins subsequently degrade

- Cyclin D participates in G₁ progression.
- Cyclin E regulates the G₁-to-S transition.
- Cyclin A functions during S phase.
- Cyclin B is essential for G₂-to-M progression.

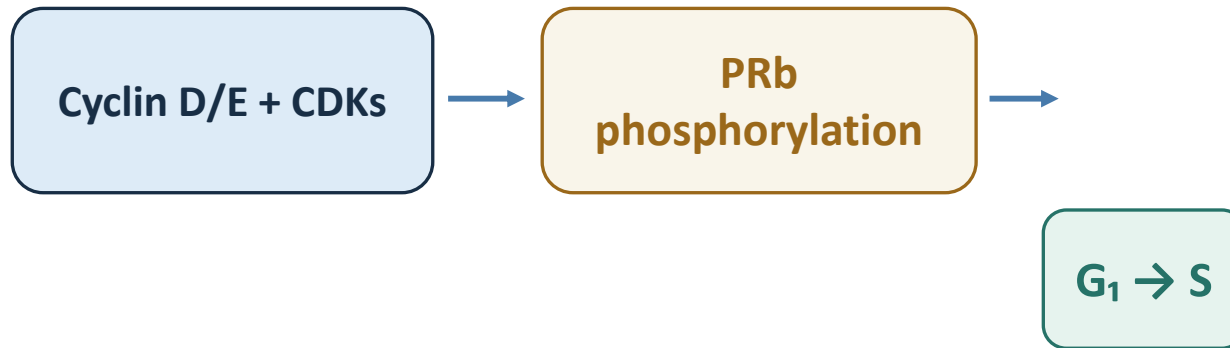
Cyclin D and CDK4/6 at early progression

- Cyclin D forms active complexes with CDK4 and CDK6.
- These complexes help regulate the G₁-to-S transition.
- Phosphorylation of retinoblastoma protein (pRb) is an important target event.
- INK4-family inhibitors preferentially restrain this module.

Cyclin E and CDK2 approaching S phase

- Cyclin E associates with CDK2.
- The complex participates in control of the G₁/S transition.
- It contributes to phosphorylation of pRb pathway.
- Unchecked activation can undermine orderly cycle regulation.

PRb links G₁ kinase activity to S-phase entry



- Cyclin D–CDK4/6 and cyclin E–CDK2 phosphorylate pRb.
- The source figure locates these actions at the G₁-to-S transition.
- Interpret the diagram as a simplified mechanistic relationship.

Simplified textbook relationship: CDK-mediated pRb phosphorylation accompanies G₁/S progression

Cyclin A: Coordination of S-phase activity

- Cyclin A associates with CDK2 during S phase.
- Cyclin A can also associate with CDK1 in the S-phase regulatory program.
- Different CDK partners contribute to phase-specific activity.
- The subsequent cyclin relay prepares the transition toward mitosis.

Cyclin B and CDK1: G₂-to-M control

- Cyclin B partners with CDK1.
- This complex is required for transition from G₂ into mitosis.
- The kinase program is active only when the appropriate stage is reached.
- Checkpoint restraint protects mitotic entry when DNA is incomplete or damaged.

Cyclin–CDK complexes by cell-cycle stage

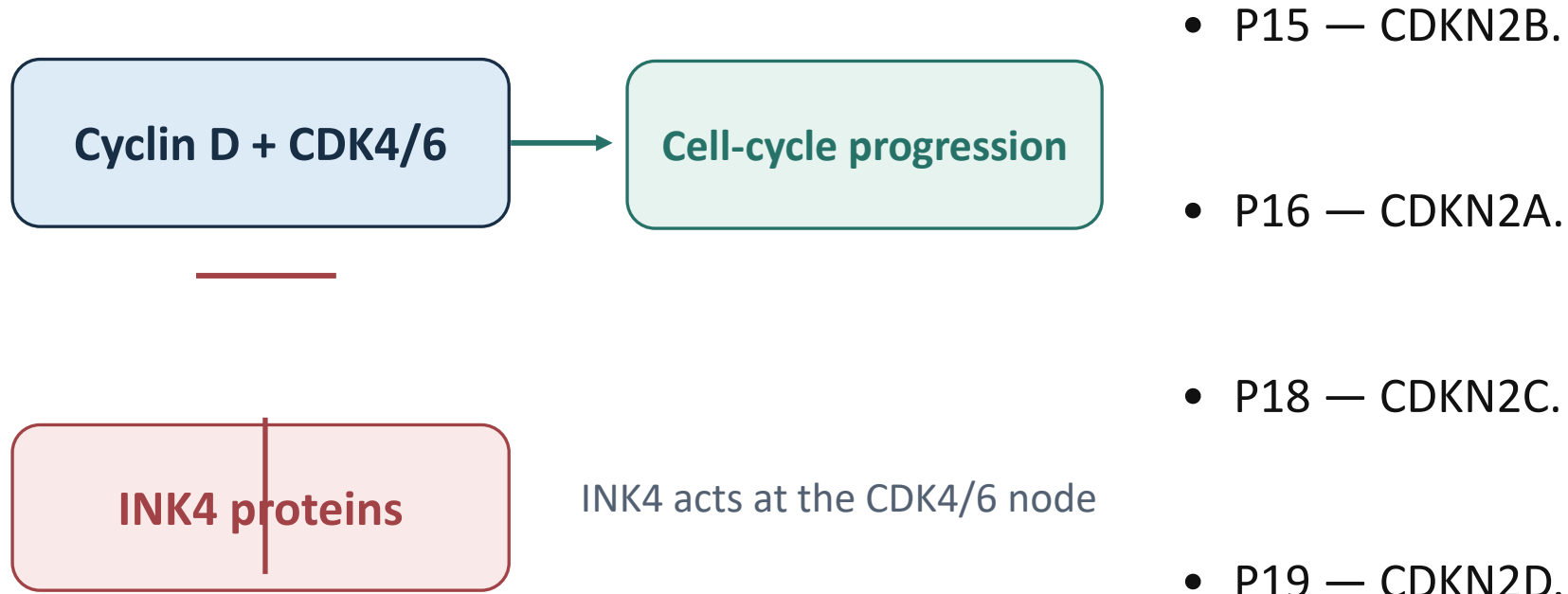
Complex	Principal stage / transition	Source-described role
Cyclin D–CDK4/6	$G_1 \rightarrow S$	PRb phosphorylation; G_1 progression
Cyclin E–CDK2	$G_1 \rightarrow S$	PRb phosphorylation; G_1/S control
Cyclin A–CDK2	S phase	S-phase kinase activity
Cyclin A–CDK1	S phase	S-phase kinase activity
Cyclin B–CDK1	$G_2 \rightarrow M$	M-phase entry

Why cyclical cyclin degradation matters

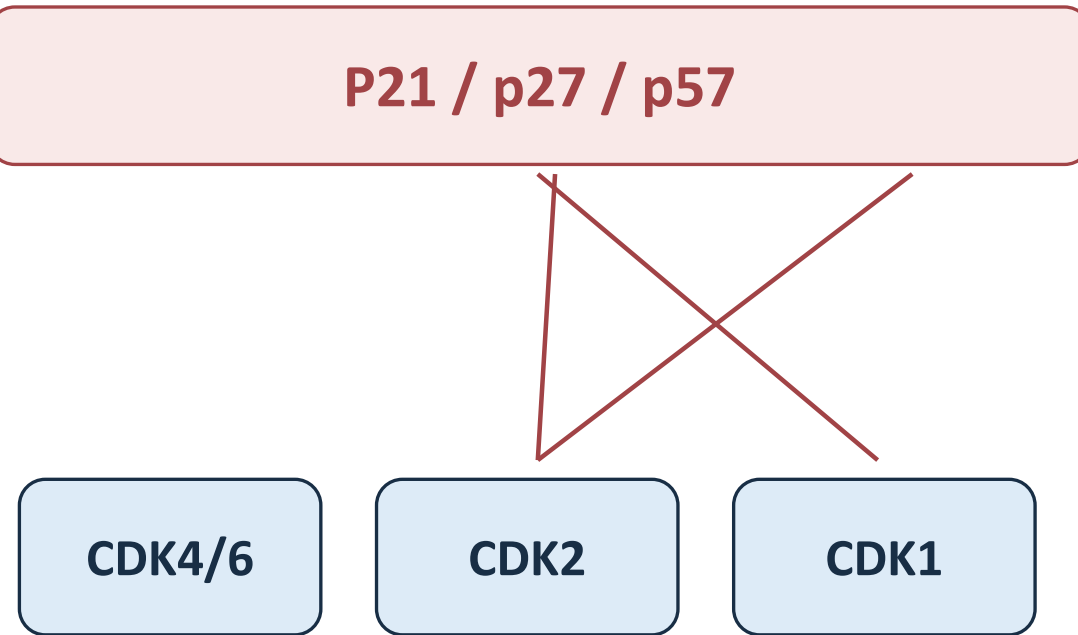
- A cyclin pulse turns on its corresponding CDK function.
- Proteolytic removal limits that kinase activity once its task is completed.
- Subsequent cyclins introduce the next regulatory program.
- Sequential activation prevents sustained use of a single phase program.

Oscillatory regulator abundance gives the cell cycle its temporal order.

INK4-family CDK inhibitors target CDK4/6



The p21-family inhibitors have broader targets



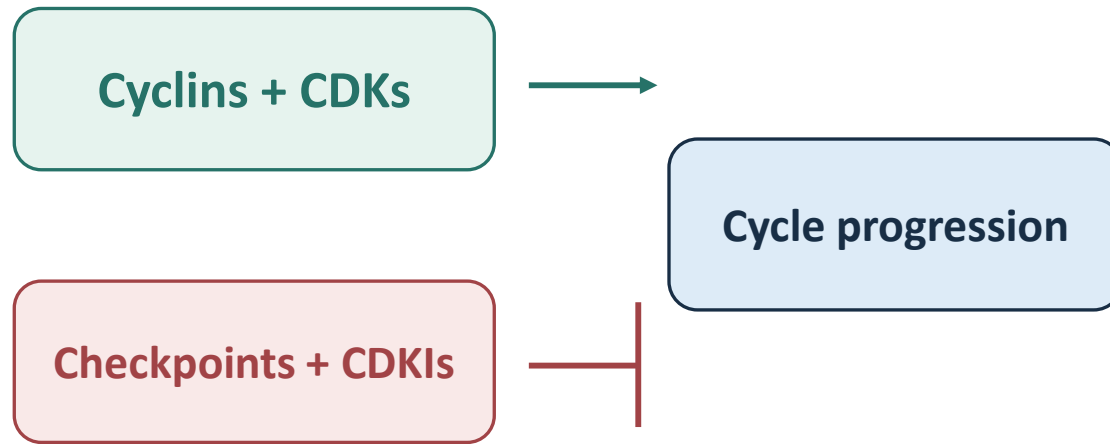
Broad suppression of cyclin–CDK activity

- P21 — CDKN1A.
- P27 — CDKN1B.
- P57 — CDKN1C.
- Collectively inhibit multiple cyclin–CDK complexes.

Two CDK-inhibitor families: Compare and recall

Feature	INK4 family	Cip/Kip family
Members	P15, p16, p18, p19	P21, p27, p57
Gene symbols	CDKN2B, CDKN2A, CDKN2C, CDKN2D	CDKN1A, CDKN1B, CDKN1C
Main activity	Selective CDK4/6 inhibition	Broad CDK inhibition
Physiologic meaning	Restraint at G ₁ control	Control across multiple phases

Activation and inhibition form a control network



Progression requires both activating signals and permissive surveillance

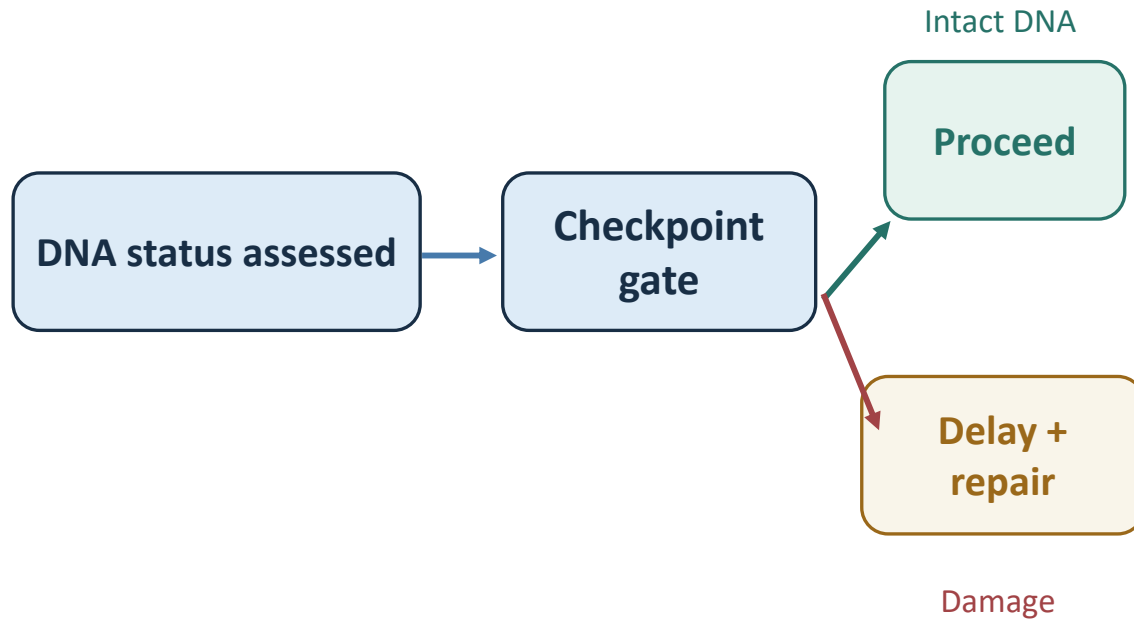
- An activator alone does not make progression safe.
- CDKI activity can arrest otherwise activated cyclin–CDK machinery.
- Checkpoint signals depend on this inhibitory capacity.

Both positive and negative regulators are physiologically necessary.

Checkpoints are quality-control mechanisms

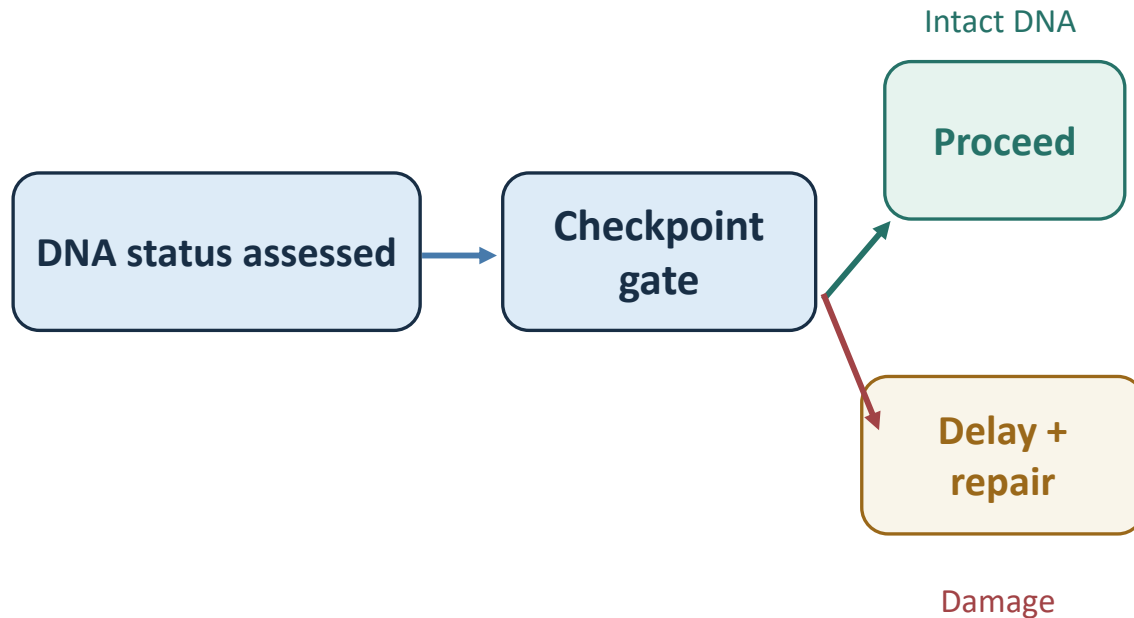
- Detect DNA injury or problems with genetic replication.
- Delay progression until required conditions are met.
- Create time for corrective processes, including DNA repair.
- Help prevent inheritance of defective chromosomes.

The G₁/S checkpoint checks DNA integrity



- Operates before irreversible commitment of resources to DNA replication.
- A detected genetic lesion delays cycle progression.
- Repair responses may allow subsequent cycling.

The G₂/M checkpoint tests replication completion

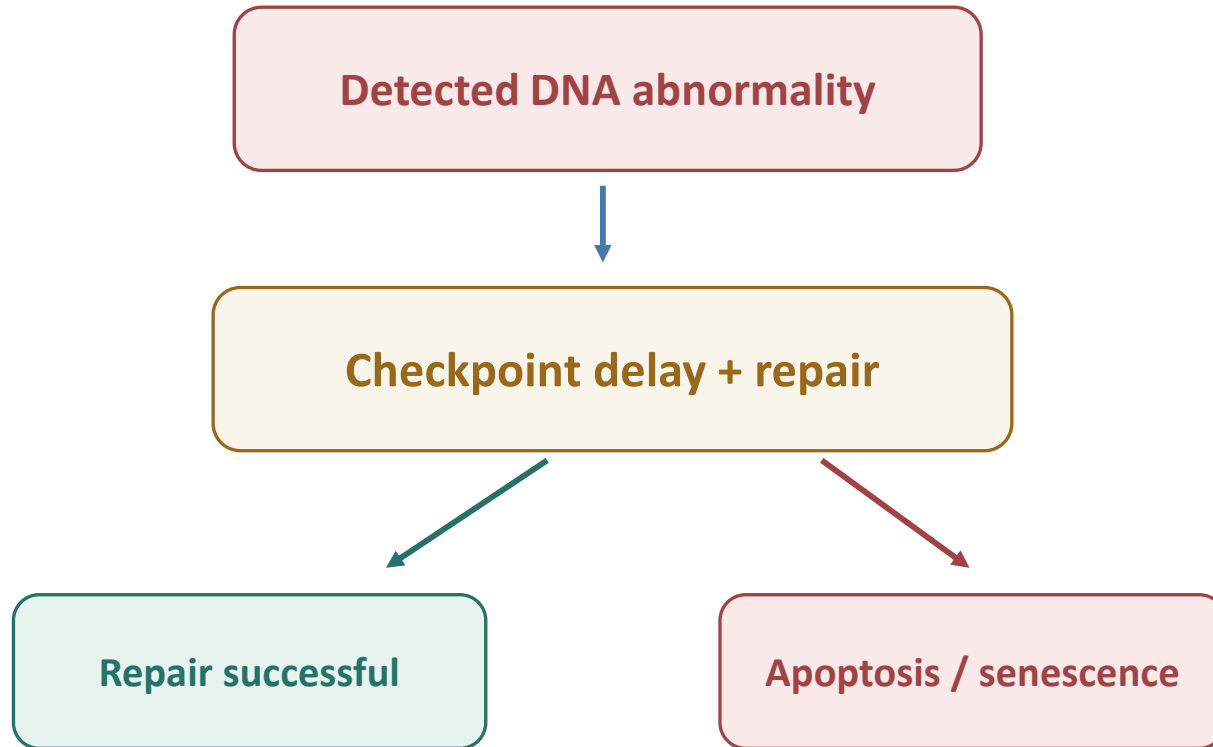


- Assesses whether the genome has been duplicated accurately.
- DNA injury or incomplete replication delays mitotic entry.
- This reduces the likelihood of transmitting defective chromosomes.

G₁/S versus G₂/M: Distinct surveillance tasks

Control	When it operates	Primary question
G₁/S checkpoint	Before DNA synthesis	Is DNA sufficiently intact to replicate?
G₂/M checkpoint	After synthesis, before mitosis	Has DNA been duplicated accurately and completely?
Restriction point	During G ₁ , before later cycle entry	Is continued cycling committed despite withdrawal of initiating mitogen?

DNA damage: Cell-cycle delay gives time for repair



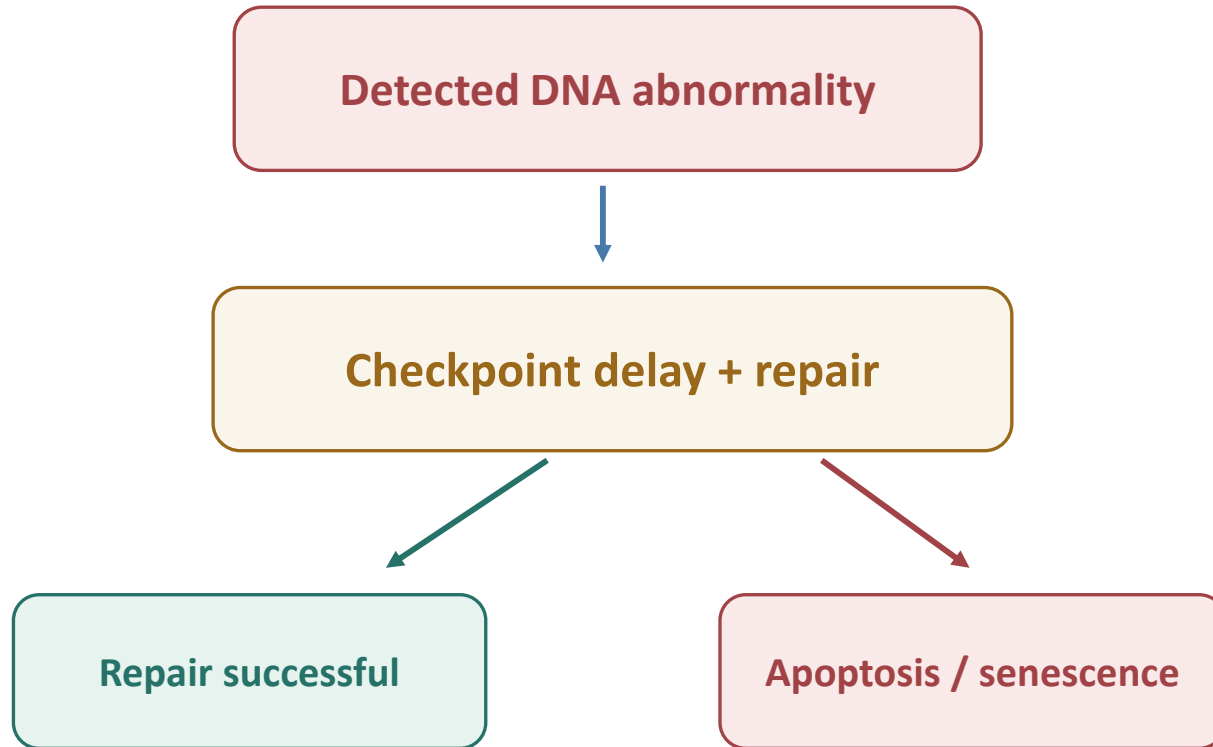
- Damage sensors activate control pathways.
- Checkpoint enforcement delays an unsafe transition.
- Successful repair can restore normal progression.
- Severe injury can instead trigger senescence or apoptosis.

The p53 axis links damage to cell fate

- When DNA irregularities are severe, p53-dependent mechanisms are especially important.
- Responses include durable growth arrest (senescence).
- Alternatively, cells may be eliminated through apoptosis.
- The source describes these as safeguards after damage is detected.

The goal is to prevent replication of seriously compromised genomes.

Severe damage creates diverging cell fates

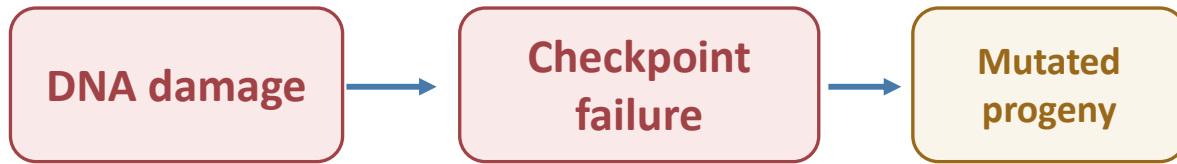


- Repairable disturbance → temporary arrest and repair.
- Unrepairable disturbance → apoptosis or nonreplicative senescence.
- The source emphasizes p53 dependence for these terminal responses.

Senescence is not identical to transient G₀

- G₀ designates the noncycling state; Some cells can be reactivated.
- Senescence denotes a nonreplicative state after an enduring arrest.
- Both may lack active DNA synthesis, but their biologic contexts differ.
- Here, senescence is one protective outcome of severe DNA injury.

What follows loss of checkpoint enforcement?



Faulty surveillance permits propagation of genetic defects

- CDKI defects can permit divisions despite DNA damage.
- Daughter cells may acquire and propagate mutations.
- This process as a risk for malignant transformation.

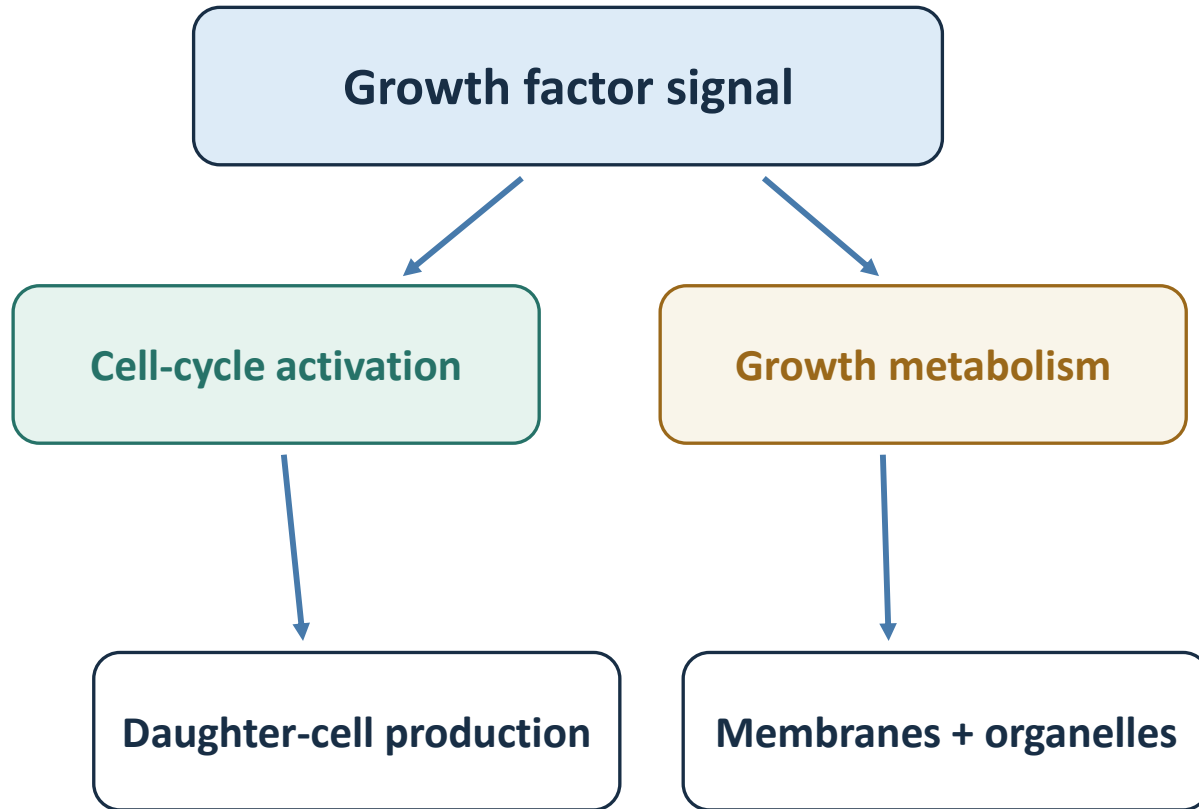
Cell-cycle dysregulation and oncogenic potential

- Normal progression depends on both mitogenic drive and genomic surveillance.
- Excessive kinase activity or inadequate inhibitory control weakens this balance.
- Checkpoint failure allows faulty replication or segregation products to persist.
- Mutation propagation creates conditions for malignant evolution.

Four different outcomes of a cell-cycle signal

Finding	Cellular response	Meaning
Adequate growth signals	Progression	Replication program can proceed
No mitogenic drive	G ₀ / quiescence	Reversible noncycling state in competent cells
Repairable DNA lesion	Checkpoint delay	Protection while damage is corrected
Severe DNA derangement	Senescence / apoptosis	Prevention of defective daughter cells

Division requires biomass, not DNA alone

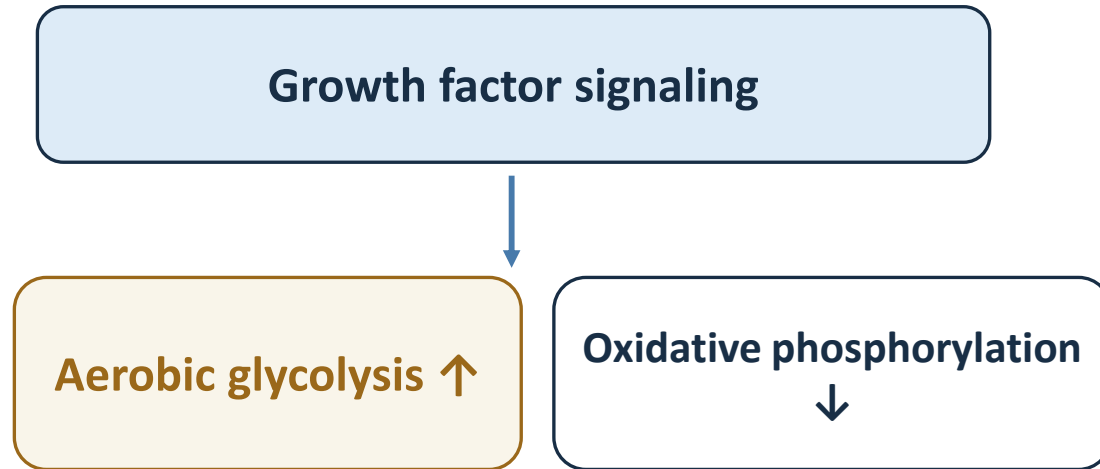


- Two daughter cells need membranes, cytoplasmic proteins and organelles.
- Growth signals coordinate both cell-cycle progression and biosynthesis.
- Metabolic reprogramming supports an increased synthetic workload.

Growth signaling also promotes metabolism

- Mitogenic signaling does not merely activate cyclin–CDK complexes.
- It concurrently promotes the metabolism needed to build cellular components.
- The target is successful generation of two functional daughter cells.
- This couples biochemical growth capacity to cycle progression.

Aerobic glycolysis: The Warburg effect



Relative metabolic shift

- Increased aerobic glycolysis in growing cells.
- It occurs despite oxygen availability.
- A relative reduction in oxidative phosphorylation is highlighted.
- The same metabolic program is important in cancer biology.

The Warburg effect in its correct context

- A metabolic shift supports the cell-growth program.
- Aerobic glycolysis does not mean that oxygen is absent.
- The source explicitly links this program to cancer-cell growth.
- Detailed neoplastic metabolism is deferred by Robbins to Chapter 7.

Avoid equating aerobic glycolysis with obligatory mitochondrial inactivity.

Different tissues have different division capacities

Labile

Continuous cycling

Epidermis; Intestinal epithelium

- Labile: Normally cycling cells, such as skin and gastrointestinal epithelium.

Stable

Quiescent; Re-enter cycle

Hepatocytes

- Stable: Quiescent cells that may re-enter cycle, such as hepatocytes.

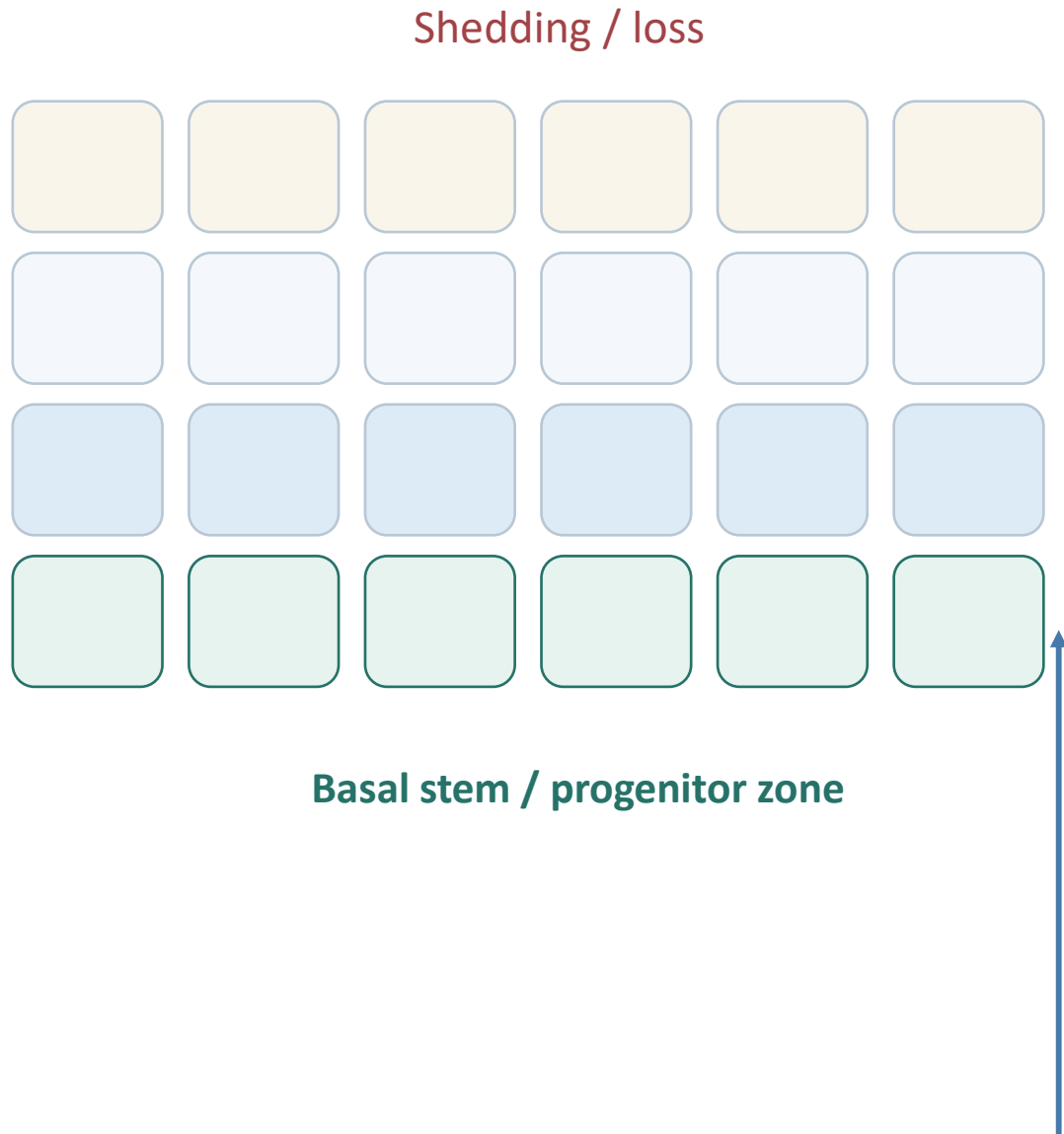
Permanent

Proliferative capacity lost

Neurons; Cardiac myocytes

- Permanent: Cells that have lost proliferative capacity, such as neurons and cardiac myocytes.

Labile epithelia maintain continuous replacement



- Basal stem/progenitor populations produce new epithelial cells.
- Their daughters mature as they move away from the proliferative zone.
- Differentiated surface cells are ultimately lost by shedding.

Stable cells: Quiescence permits regenerative entry



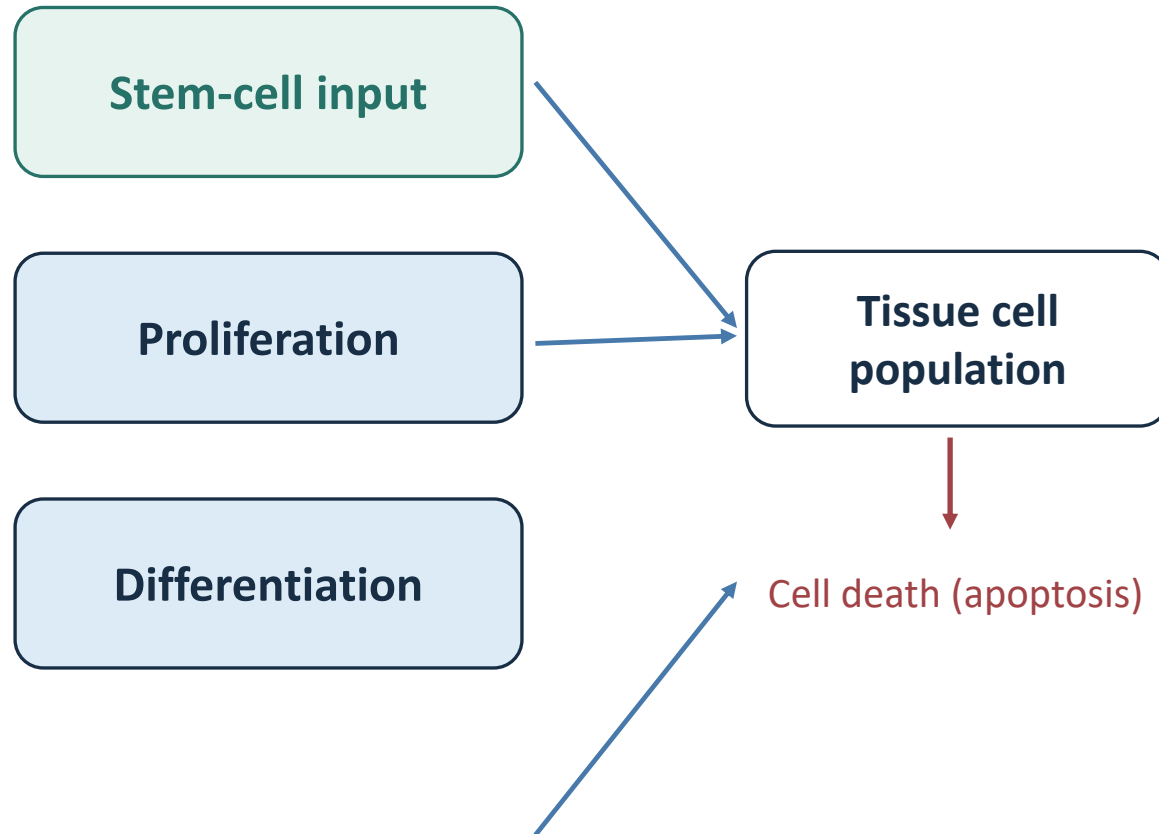
Stable populations can proliferate in response to demand

- Hepatocytes exemplify cells that can remain outside active cycle.
- Under appropriate demand, these cells can re-enter proliferative phases.
- This differs from continuous division in labile tissues.

Permanent cells have limited division capacity

- The cited examples are neurons and cardiac myocytes.
- Their inability to readily re-enter the cycle constrains cellular replacement.
- Injury-related recovery therefore differs from high-turnover epithelia.
- This is a tissue-level consequence of cell-cycle competence.

Tissue homeostasis is a population balance

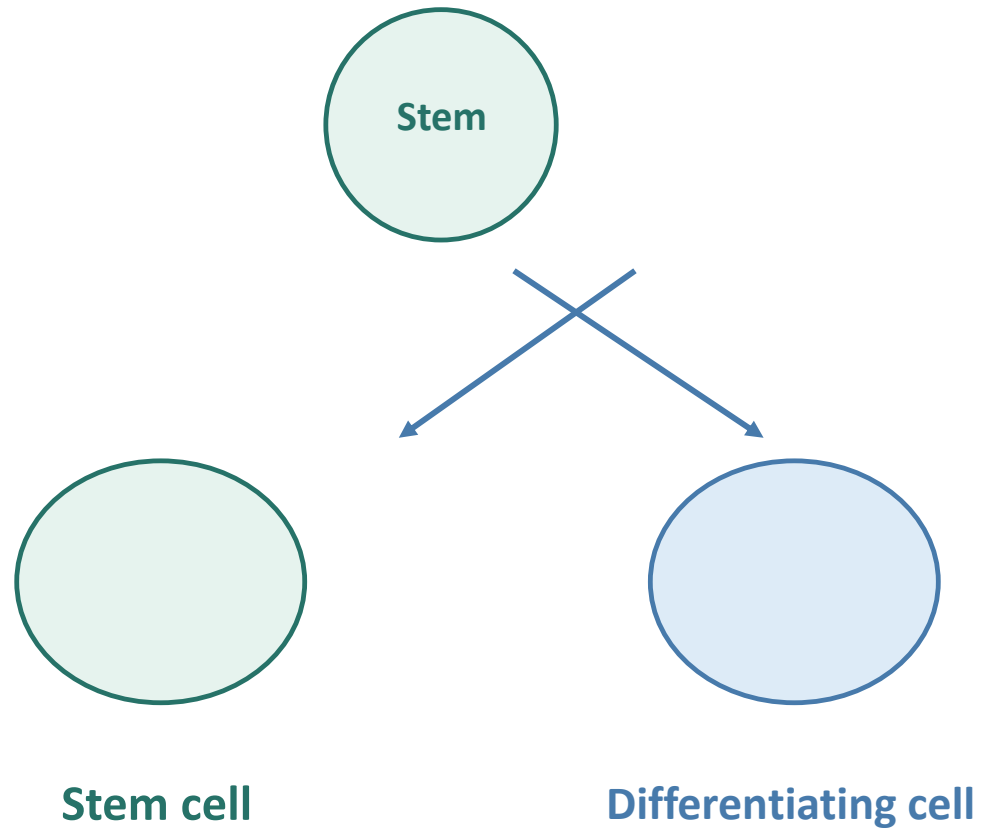


- Stem-cell input and proliferation expand the population.
- Differentiation changes the distribution of cellular states.
- Apoptotic removal decreases mature cell number.
- These rates jointly determine steady-state cellular composition.

Stem cells have two defining capabilities

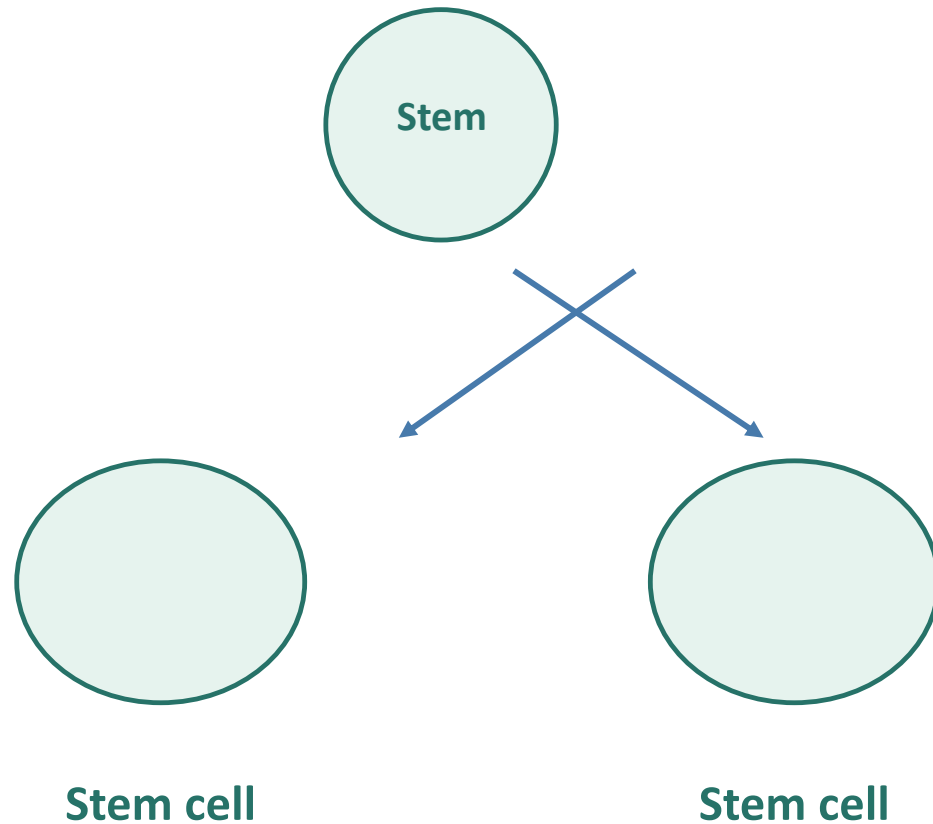
- Self-renewal: Preserve an undifferentiated stem-cell pool.
- Differentiation: Produce more specialized daughter cells.
- Both properties sustain long-term tissue replacement.
- Homeostasis depends on balancing output with maintenance of the pool.

Asymmetric stem-cell division



- One daughter preserves stem-cell identity.
- The other begins a differentiation pathway.
- The stem-cell pool is maintained while mature-cell output continues.

Symmetric self-renewing division



- Both daughter cells retain self-renewal capacity.
- This expands the available stem-cell population.
- Expansion during embryogenesis and repopulation after stress.

Symmetric and asymmetric renewal compared

Feature	Asymmetric division	Symmetric self-renewal
Daughter-cell identities	One stem + one differentiating	Two stem daughters
Net stem-cell pool	Maintenance	Expansion
Source example	Normal tissue homeostasis	Embryogenesis; Marrow recovery after stress
Biologic purpose	Sustain output without depleting pool	Rebuild or enlarge stem-cell reserves

Stem-cell potency narrows during differentiation

Zygote • Totipotent

Inner cell mass / ES • Pluripotent

**Adult tissue stem • Lineage
limited**

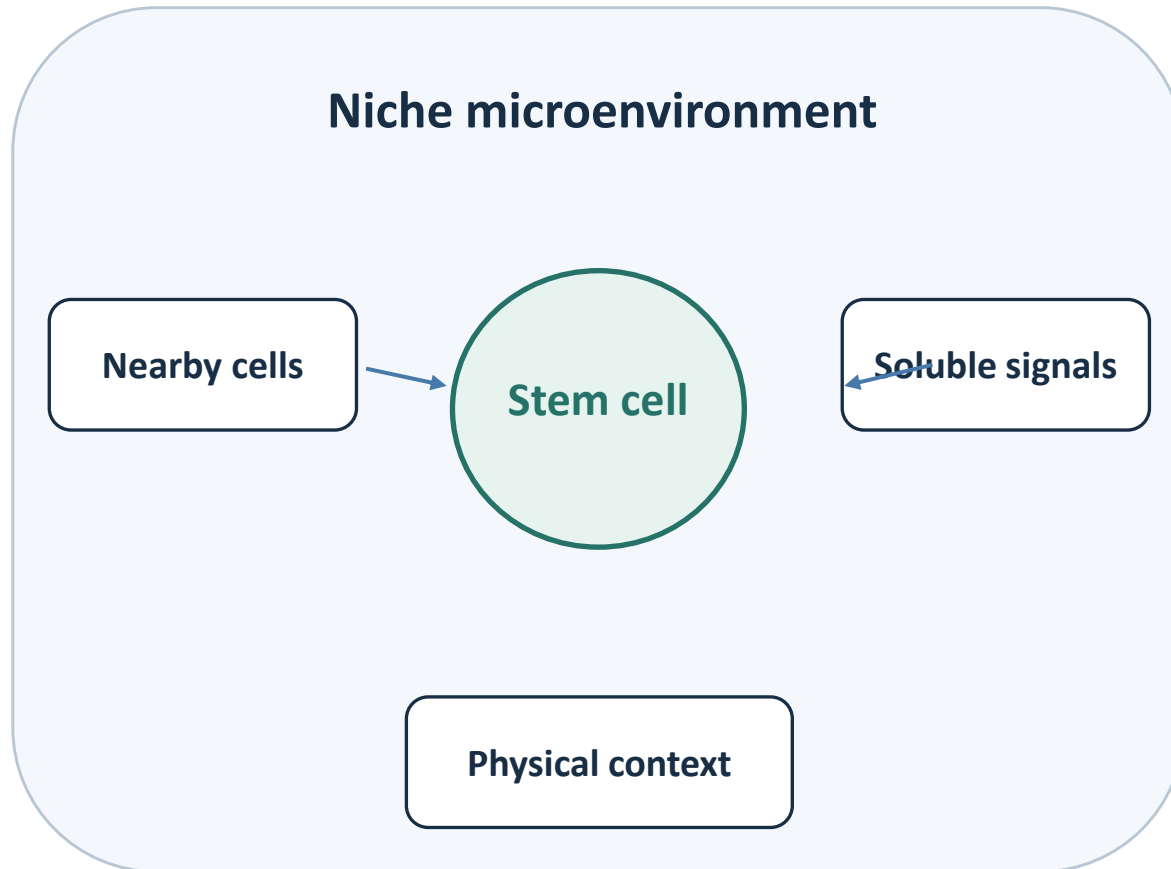
**Mature cells •
Differentiated**

- Totipotency characterizes the earliest developmental cells.
- Embryonic stem cells of the inner cell mass are pluripotent.
- Adult stem cells generally have tissue-restricted lineage potential.
- Fully differentiated cells typically have specialized function.

Embryonic versus adult tissue stem cells

Dimension	Embryonic stem cells	Adult tissue stem cells
Location	Inner cell mass of blastocyst	Niches within mature tissues
Differentiation range	Pluripotent: Derivatives of three germ layers	Normally tissue / lineage restricted
Renewal	Extended self-renewal under suitable conditions	Local maintenance and repair
Typical function	Broad developmental potential	Replace cells normally present in their tissue

Stem-cell niches regulate cell fate



- A niche is a specialized tissue microenvironment.
- Signals from neighboring cells and soluble factors regulate behavior.
- A niche governs quiescence, expansion and differentiation.

Where tissue stem cells reside

Tissue	Niche location	Relevance
Bone marrow	Perivascular regions	Hematopoietic cell maintenance
Intestinal epithelium	Crypts	Continual epithelial renewal
Hair follicle	Bulge region	Epithelial stem-cell residence
Cornea	Limbus	Surface-cell renewal
Brain	Subventricular zone	Resident neural stem-cell niche

Hematopoietic stem cells maintain blood production

Hematopoietic stem cell

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graph TD; A[Hematopoietic stem cell] --> B[Blood-cell renewal]; A --> C[Marrow reconstitution];
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Blood-cell renewal

Marrow reconstitution

- Hematopoietic stem cells replace diverse circulating blood-cell lineages.
- They are found in marrow and can be mobilized into peripheral blood.
- Their transplantation can reconstitute marrow after intensive therapy.

Bone marrow and mobilized peripheral blood are clinical cell sources

Clinical implication: Marrow reconstitution

- Hematopoietic stem cells can be collected from marrow.
- Selected colony-stimulating factors can mobilize them into peripheral blood.
- Transplantation is used to repopulate marrow after cytotoxic treatment.
- Robbins also notes use for selected inherited blood-cell disorders.

Mesenchymal stromal / stem-cell potential

- Marrow and adipose tissue contain populations with mesenchymal differentiation potential.
- Source-listed stromal derivatives include cartilage, bone, fat and muscle lineages.
- Their expansion and immunomodulatory properties motivate regenerative applications.
- Such potential should not be confused with unrestricted embryonic pluripotency.

Application 1: A DNA-integrity decision

A cell has received sufficient mitogenic stimulation to advance through G₁. Molecular surveillance then detects significant DNA damage.

Which control should delay entry into S phase, and why?

Discussion prompt — answer follows

Application 1: Reasoning

- The G₁/S checkpoint monitors integrity before DNA replication.
- Damage triggers delay and an opportunity for repair.
- Severe unresolved lesions may result in apoptosis or senescence.
- Advancing with damaged DNA risks transmitting mutations.

Application 2: Expanded stem-cell production

A patient needs marrow repopulation after intensive cytotoxic therapy. A surviving stem-cell population must increase the number of undifferentiated precursors.

Which stem-cell division mode directly expands that precursor pool?

Discussion prompt — answer follows

Application 2: Reasoning

- Symmetric self-renewal produces two stem-cell daughters.
- The stem-cell pool expands rather than merely being maintained.
- Asymmetric division generates one differentiating cell while retaining one stem cell.
- The balance of these modes supports tissue restoration.

Application 3: A proliferative defect

A hypothetical tumor clone loses an inhibitory regulator of the cyclin D–CDK4/6 module.

Which CDKI family directly restrains that kinase pair, and what is the potential consequence?

Discussion prompt — answer follows

Application 3: Reasoning

- The INK4 family preferentially inhibits cyclin D–CDK4/6.
- P15, p16, p18 and p19 belong to this family.
- Reduced CDKI restraint can permit propagation of DNA-damaged daughter cells.
- The source links defective checkpoint proteins to malignant-transformation risk.

Integrated summary: Mechanism to tissue outcome

- Cyclin–CDK oscillations drive the ordered $G_1 \rightarrow S \rightarrow G_2 \rightarrow M$ sequence.
- Checkpoints and CDKIs restrain unsafe transitions and genomic instability.
- Metabolic growth and organelle synthesis accompany genome duplication.
- Stem-cell self-renewal, differentiation and cell death jointly maintain tissue populations.

Loss of proliferative control links basic cell biology to neoplastic risk.

Principal source and interpretation notes

Primary source

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026). Chapter 1, “Proliferation and the Cell Cycle” and “Stem Cells,” pp. 23–27.

Interpretive points

- All scientific schematics are original editable PowerPoint drawings; no microscopy or data plots were fabricated.
- The source text’s “totipotent” description of ES cells conflicts with its own Fig. 1.22; the presentation correctly calls inner-cell-mass ES cells pluripotent.
- Stem-cell material is included because it is explicitly grouped with this topic in the supplied Robbins teaching unit.