

Cyclins and Cyclin-Dependent Kinases

Cell-cycle control, checkpoints, and neoplastic deregulation

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Learning objectives

- Describe the sequential cyclin–CDK complexes that govern cell-cycle transitions.
- Explain how RB, E2F, CDK inhibitors, and DNA-damage checkpoints regulate G₁/S progression.
- Relate cyclin/CDK dysregulation to oncogenesis and selected clinicopathologic examples.

Why proliferating cells need a cell-cycle engine

- Division requires faithful duplication of DNA and coordinated synthesis of cellular constituents.
- Each stage depends on completion of the preceding stage.
- Cyclin–CDK complexes provide an ordered phosphorylation-based mechanism for progression.

Cycling versus quiescent cells

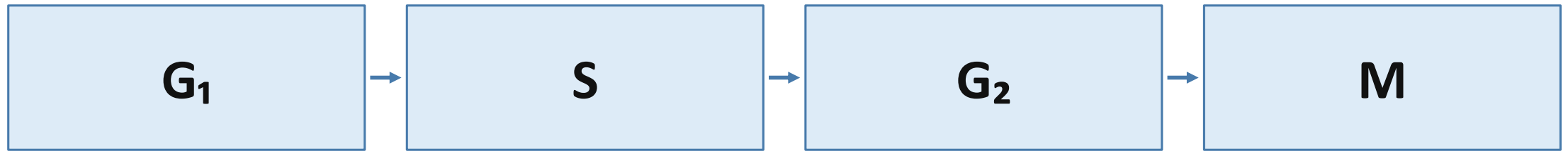
Actively cycling

- Traverse G_1 , S, G_2 , and M.
- Require phase-specific cyclin–CDK activity.
- Produce daughter cells after mitosis.

Quiescent (G_0)

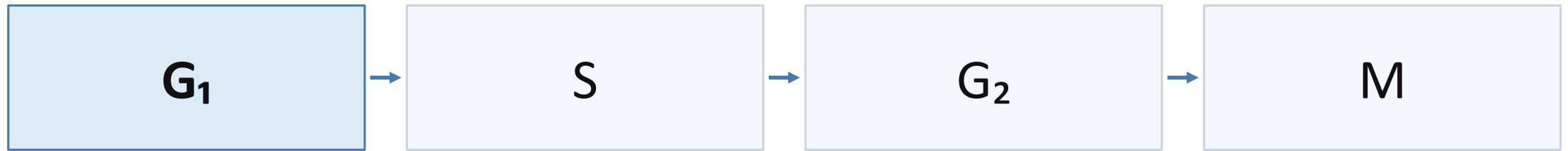
- Not actively traversing the cycle.
- Some cell populations can re-enter G_1 .
- Quiescence is distinct from an active DNA-synthesis phase.

The cell cycle has four main phases



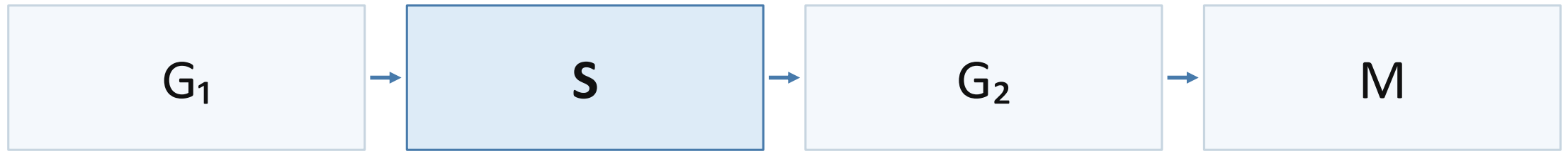
- **G₁**: Growth and preparation
- **S**: DNA synthesis
- **G₂**: Preparation for mitosis
- **M**: Chromosome segregation and division

G_1 prepares the cell for genome duplication



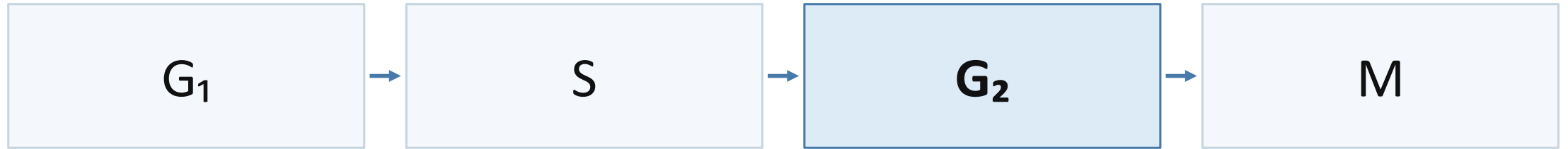
- Follows mitosis or exit from G_0
- Integrates extracellular growth cues
- Contains the restriction point and G_1/S surveillance

S phase replicates the DNA



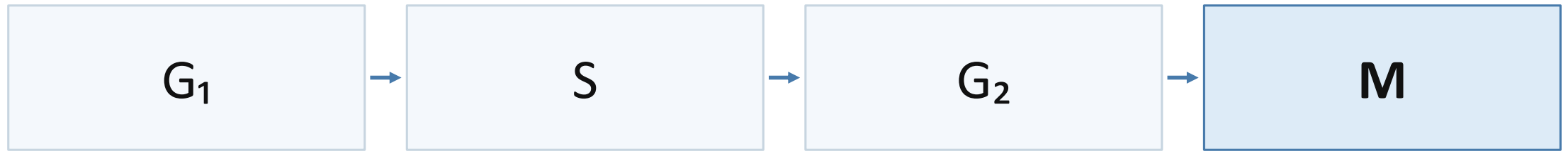
- Genome replication proceeds after G_1 commitment
- Cyclin A complexes support S-phase events
- Replication integrity is essential before division

G₂ checks readiness for mitosis



- Follows DNA replication
- G₂/M surveillance checks replication integrity
- Mitotic entry depends on cyclin B–CDK1

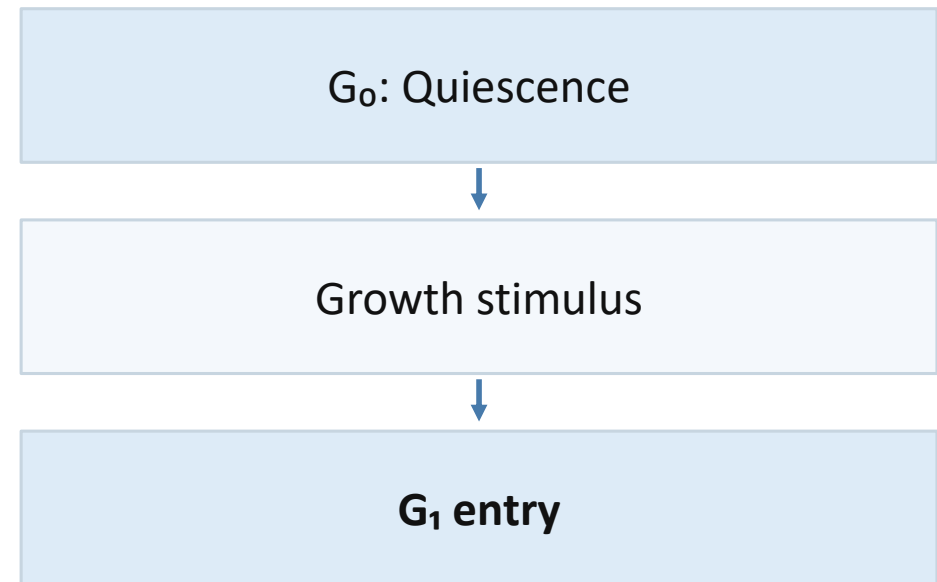
M phase partitions duplicated chromosomes



- Chromosomes are segregated
- Mitosis and cytokinesis yield daughter cells
- Cells may enter another G_1 or leave active cycling

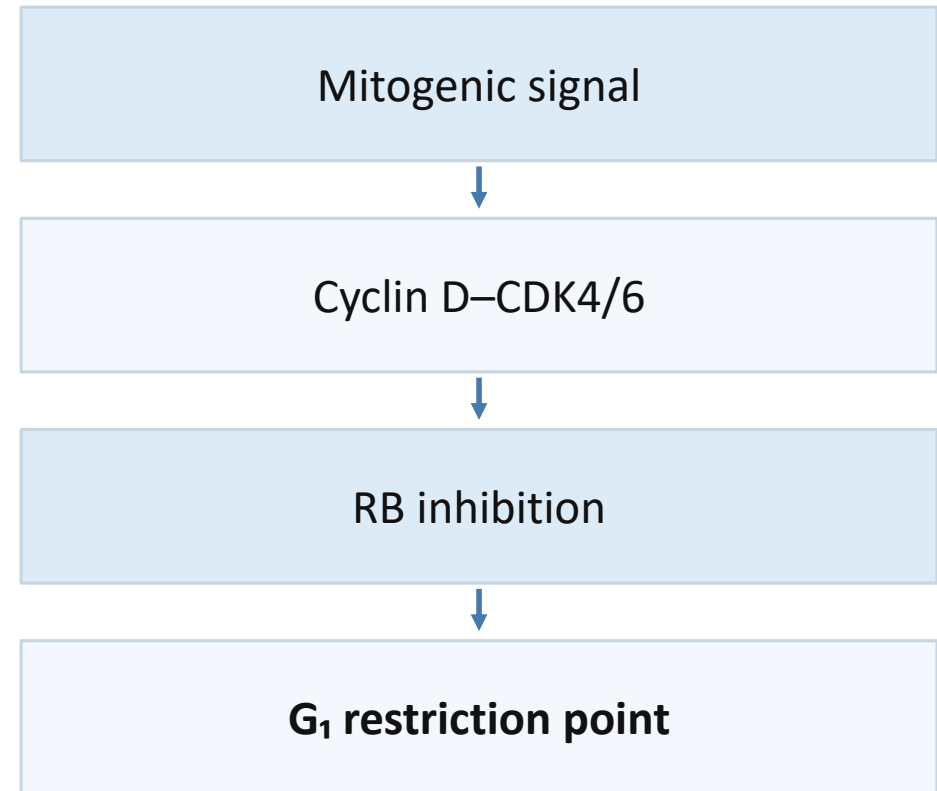
G_0 provides a quiescent starting pool

- G_0 denotes cells outside active cycling.
- Appropriate stimulation can recruit certain quiescent cells into G_1 .
- Other differentiated cells have limited or absent proliferative capacity.



The restriction point creates a commitment decision

- The restriction point occurs within G_1 .
- After passing it, progression no longer requires the initiating growth signal.
- Its principal molecular control involves cyclin D/CDKs, RB, and E2F.



The two major checkpoint transitions

G₁/S checkpoint

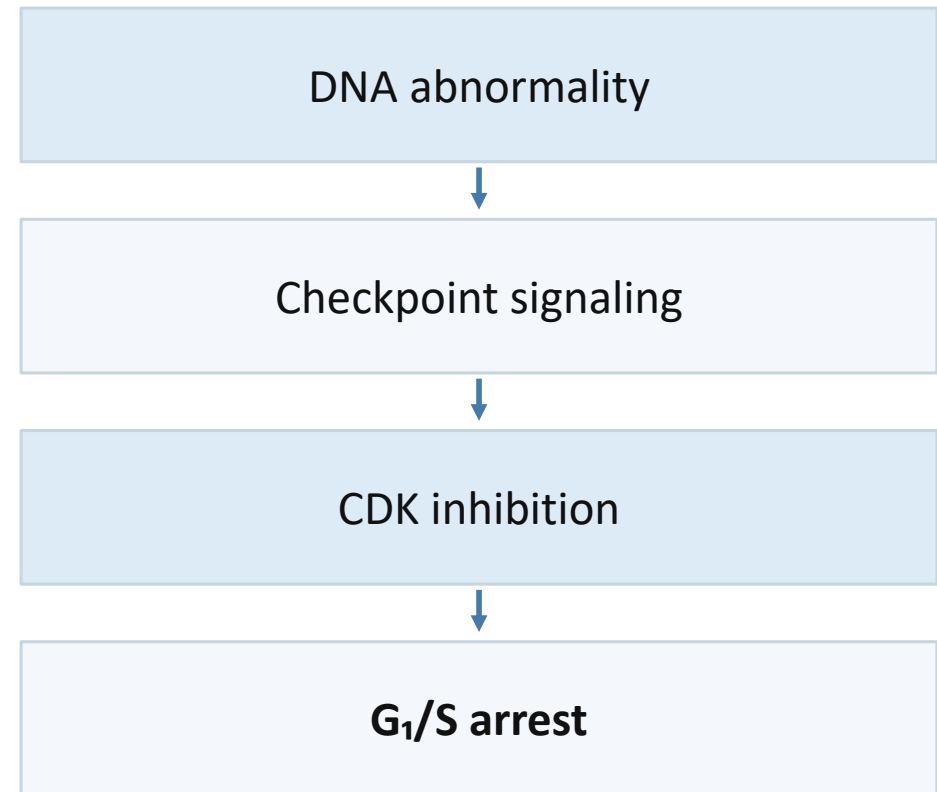
- Assesses DNA integrity before DNA synthesis.
- Prevents damaged templates from entering replication.
- Especially consequential in oncogenesis.

G₂/M checkpoint

- Assesses whether DNA replication is complete and accurate.
- Restrains entry into mitosis after damage.
- Defects may permit division with damaged DNA.

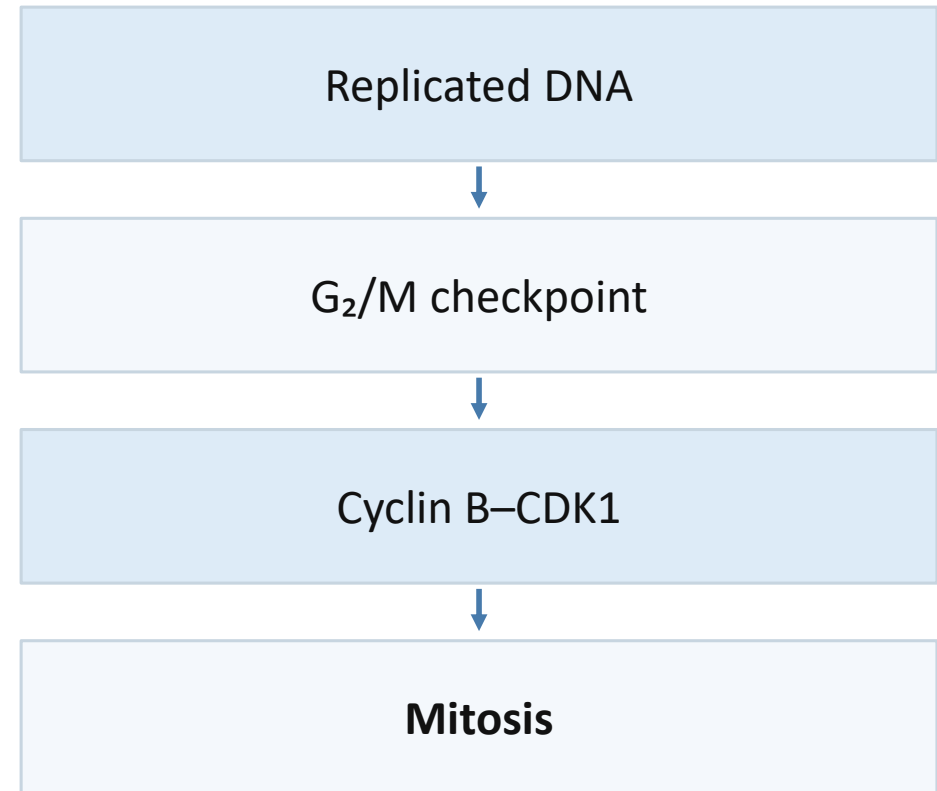
G₁/S surveillance protects DNA fidelity

- DNA damage can activate checkpoint signaling in late G₁.
- Checkpoint proteins reduce cyclin–CDK drive.
- The resulting delay permits DNA repair before synthesis.



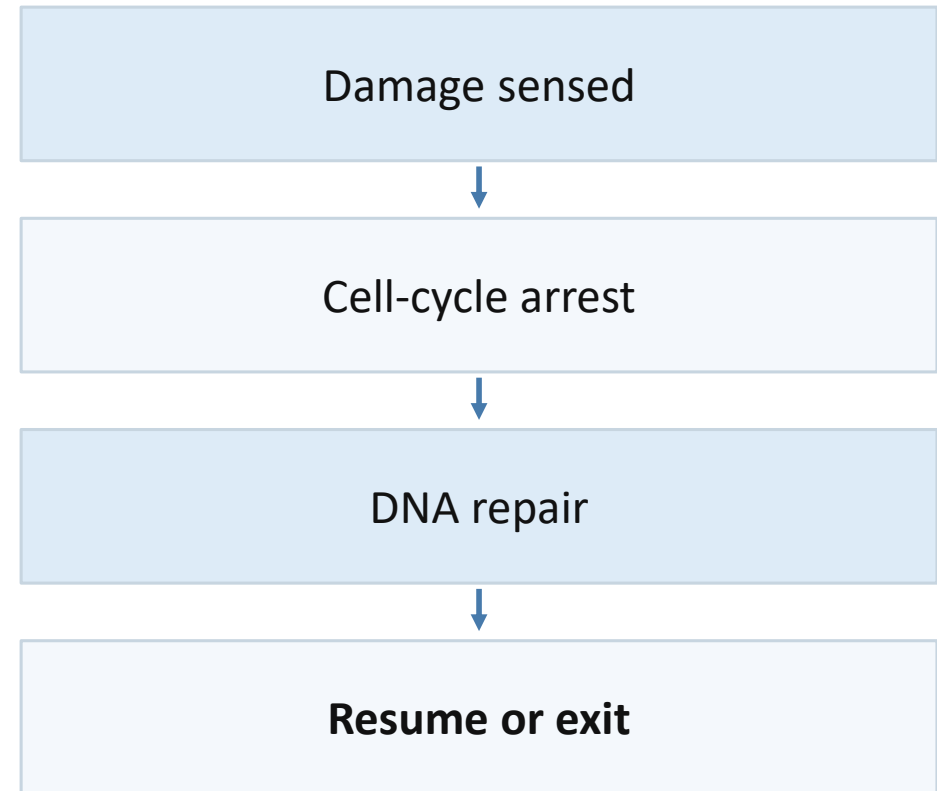
G₂/M surveillance protects chromosome segregation

- Cells should not enter mitosis with incompletely or inaccurately replicated DNA.
- A G₂/M checkpoint delays mitotic progression when replication integrity is impaired.
- Cyclin B–CDK1 normally drives the G₂-to-M transition.



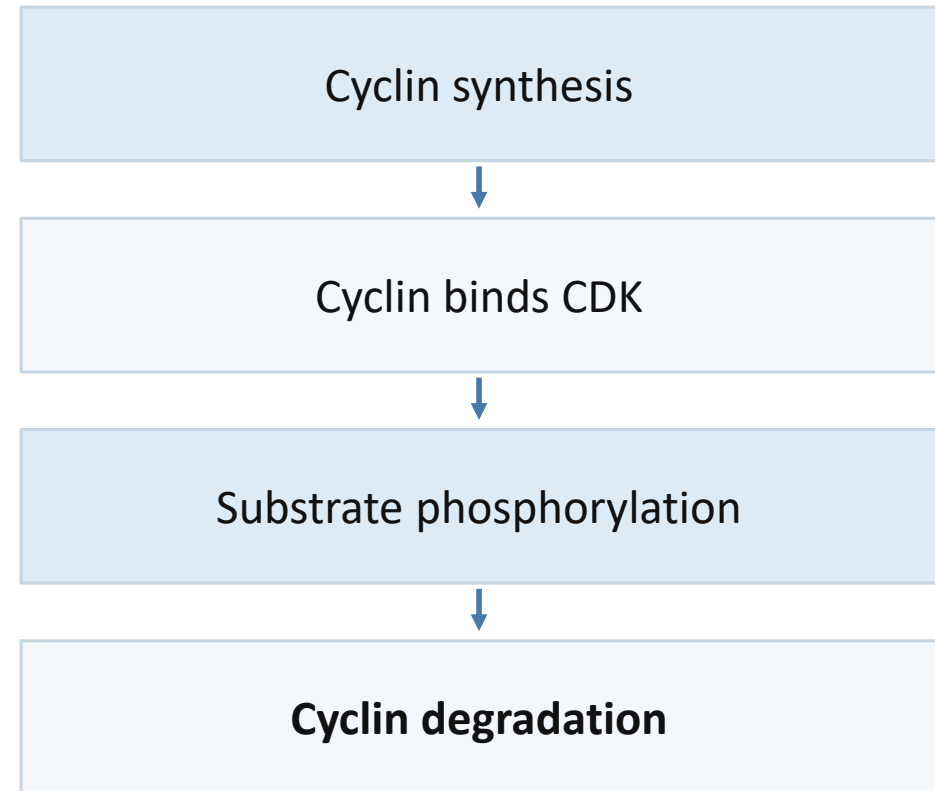
DNA damage can pause progression for repair

- Checkpoint activation transiently delays the cell cycle.
- Repair can restore conditions for controlled progression.
- Unreparable damage can culminate in apoptosis or senescence.



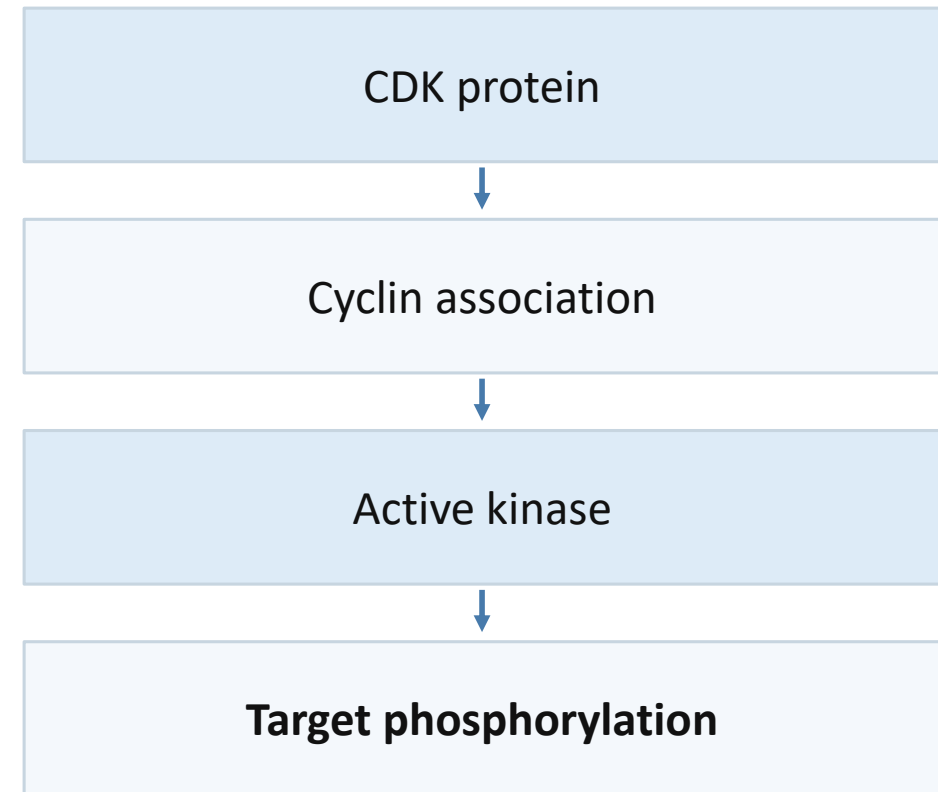
Cyclins are dynamic regulatory proteins

- Cyclin abundance rises and falls during successive phases.
- Synthesis of a cyclin permits activation of its partner CDK.
- Cyclin destruction terminates the corresponding burst of kinase activity.



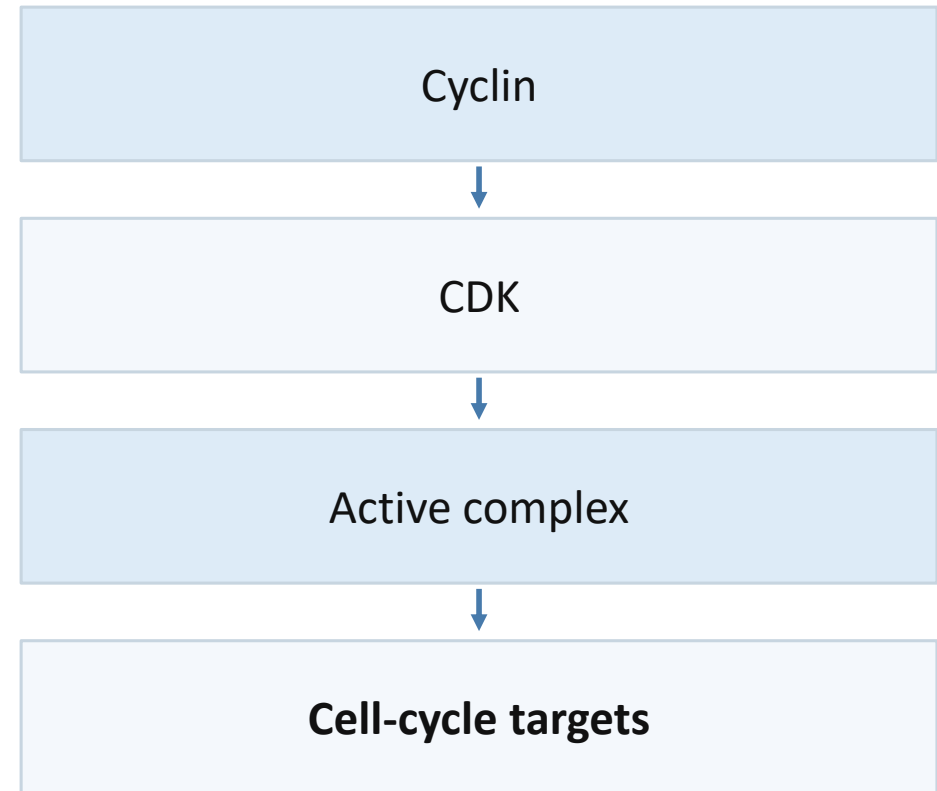
CDKs are the catalytic components

- CDKs phosphorylate target proteins when activated.
- CDKs are synthesized relatively constitutively, unlike their cycling partners.
- Their phase-specific activity is largely imposed by cyclin availability.



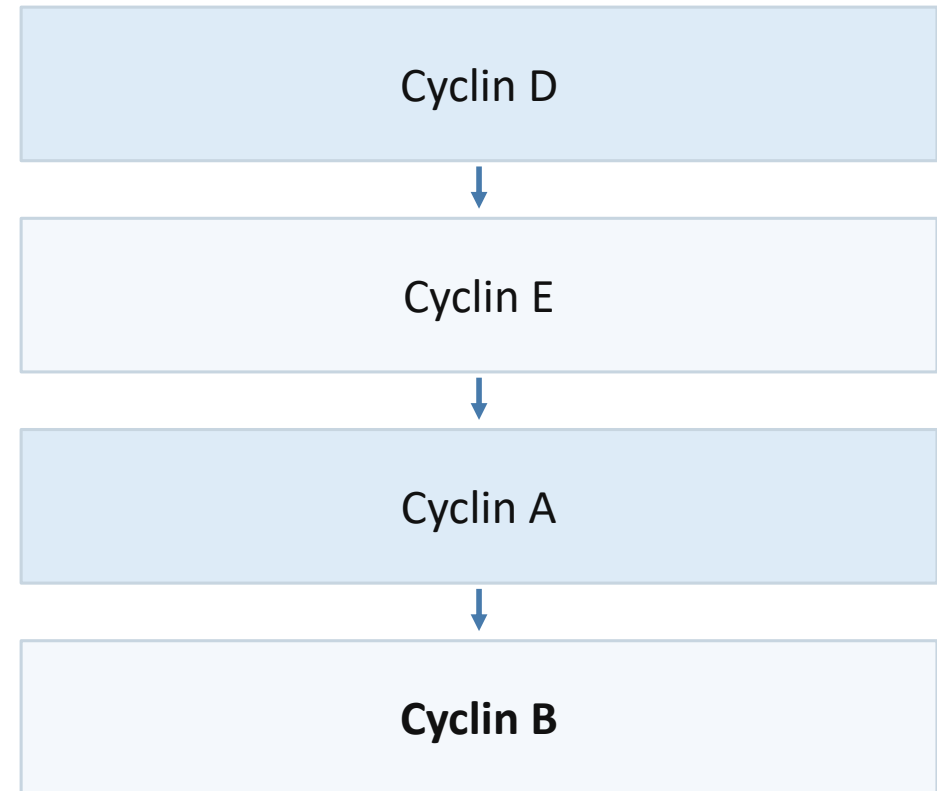
A cyclin–CDK complex is a functional unit

- Cyclin availability alone is insufficient without a partnering CDK.
- CDK abundance alone does not imply activity.
- The complex drives key transitions through phosphorylation of substrate proteins.



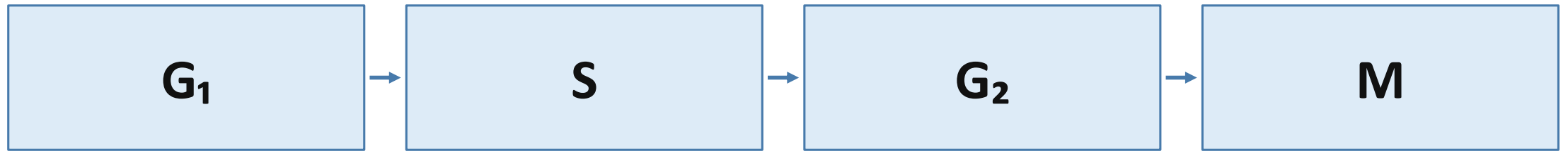
Oscillating cyclin levels generate sequential activity

- New cyclins appear as earlier cyclins disappear.
- Partnered CDK activity rises and declines with cyclin abundance.
- This ordered relay limits inappropriate activation of later phases.



Cyclin sequence is schematic; Exact timing overlaps.

Cyclin families form an ordered relay



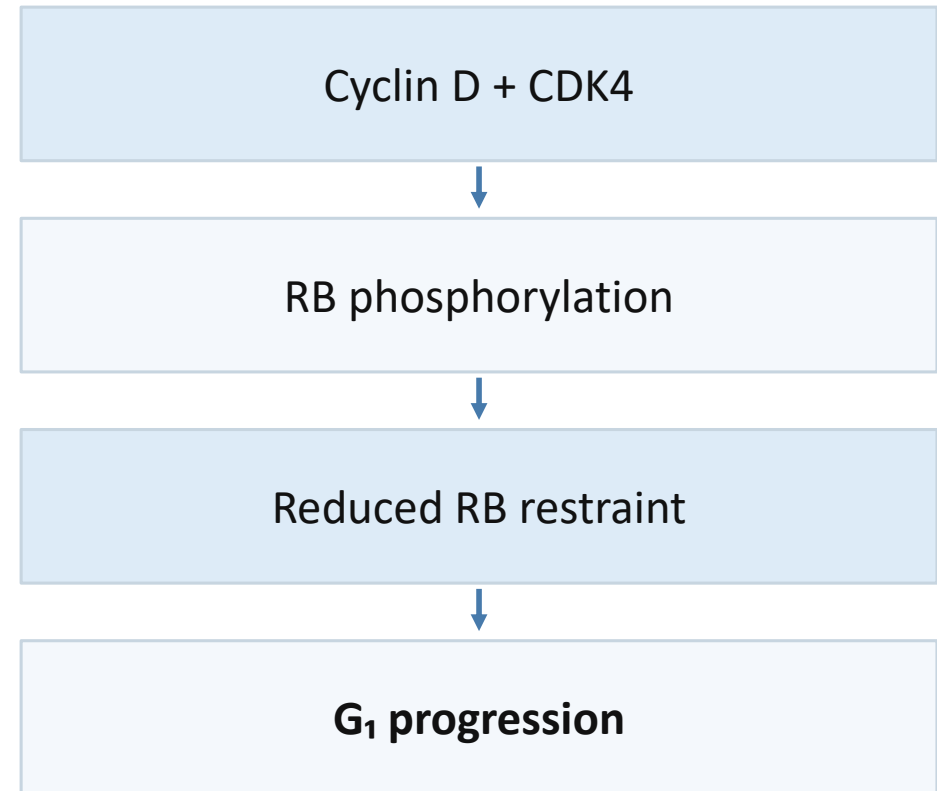
- Cyclin D predominates in G₁ control
- Cyclin E contributes at G₁/S
- Cyclin A acts through S phase
- Cyclin B drives G₂/M

Core cyclin–CDK partnerships

Cyclin	Partner CDK	Main interval / function
D	CDK4, CDK6	G ₁ progression; RB phosphorylation
E	CDK2	G ₁ /S progression; RB phosphorylation
A	CDK2, CDK1	S-phase events
B	CDK1	G ₂ -to-M transition

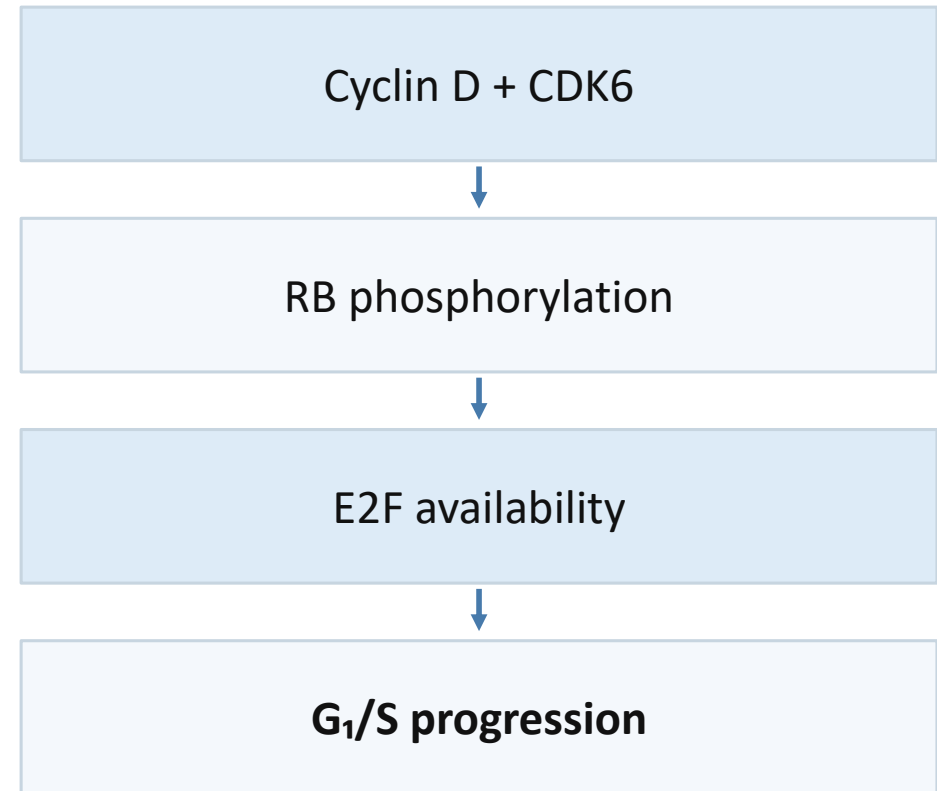
Cyclin D–CDK4 initiates a pivotal G₁ signal

- D-type cyclins form active complexes with CDK4.
- These complexes phosphorylate RB.
- The RB change supports passage through the G₁ restriction point.



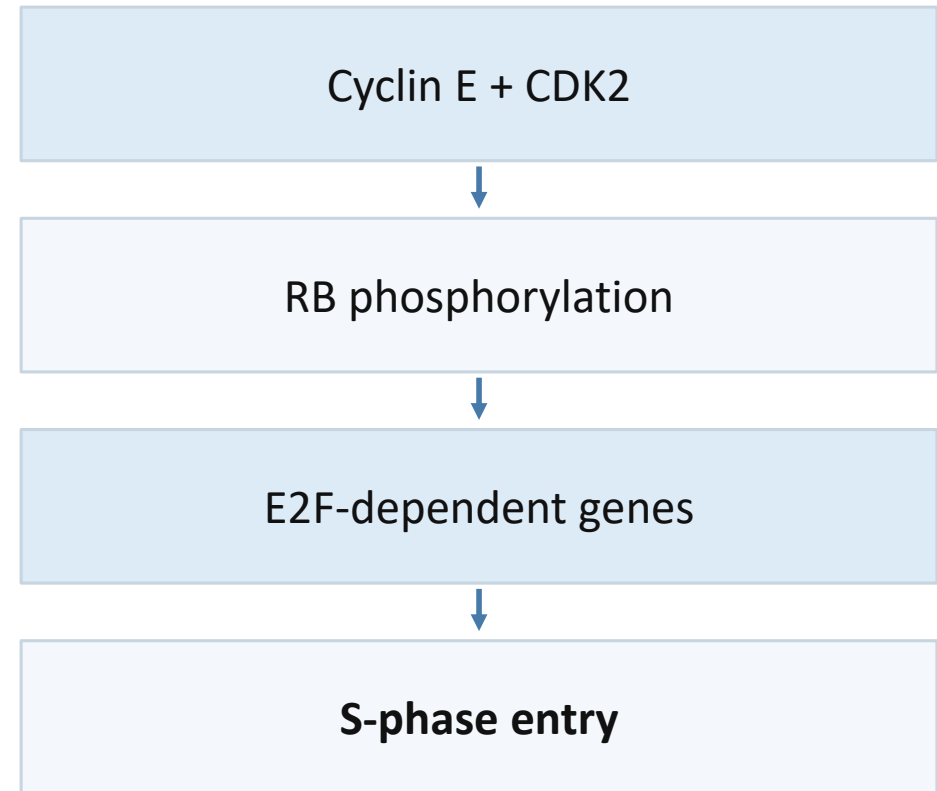
Cyclin D–CDK6 provides related G₁ activity

- Cyclin D also partners with CDK6.
- Cyclin D–CDK6 contributes to RB phosphorylation.
- CDK4 and CDK6 are therefore related targets of cell-cycle-directed therapy.

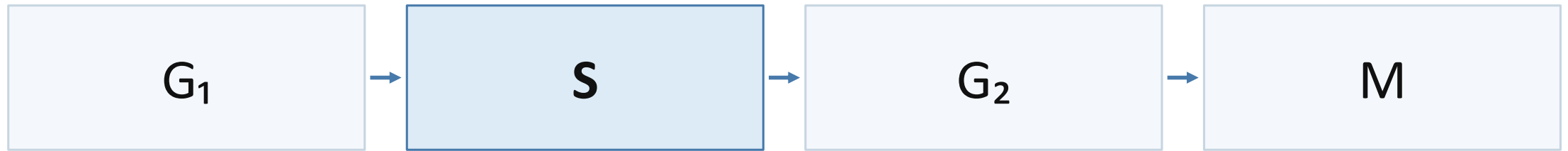


Cyclin E–CDK2 reinforces G₁/S progression

- Cyclin E–CDK2 contributes to RB phosphorylation.
- Together with cyclin D complexes, it promotes the G₁-to-S switch.
- Cyclin D/CDK4 as the major frequently altered oncogenic node.



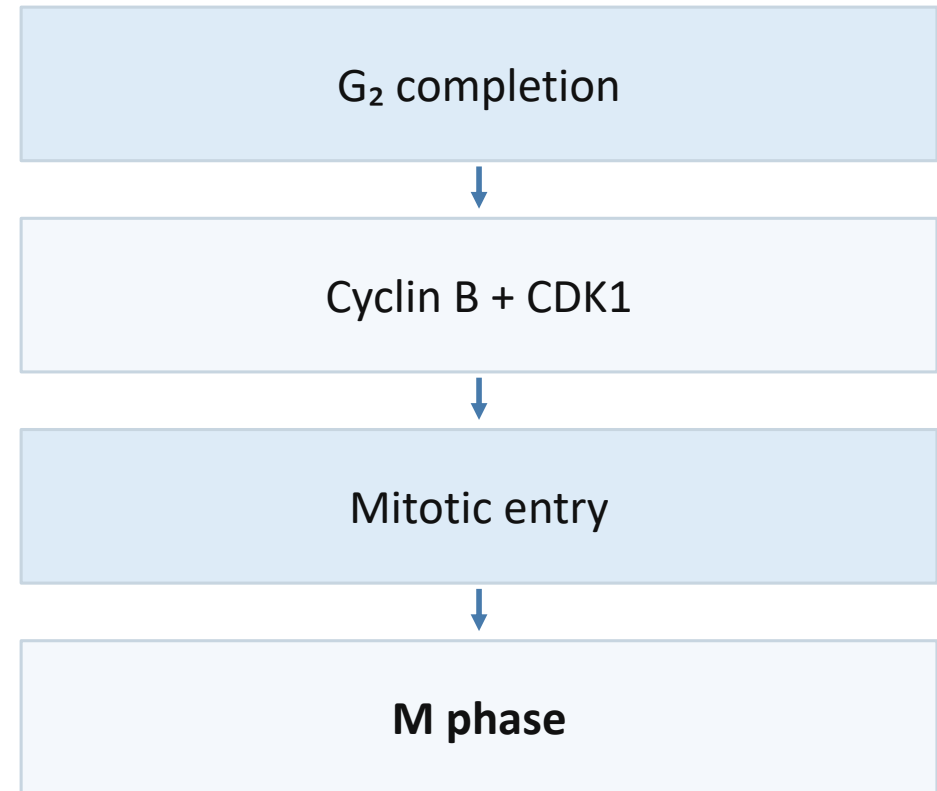
Cyclin A complexes act in S phase



- Cyclin A partners with CDK2 and CDK1
- Their activity is associated with DNA-synthesis phase
- This role differs from cyclin D–CDK4/6 control of G₁

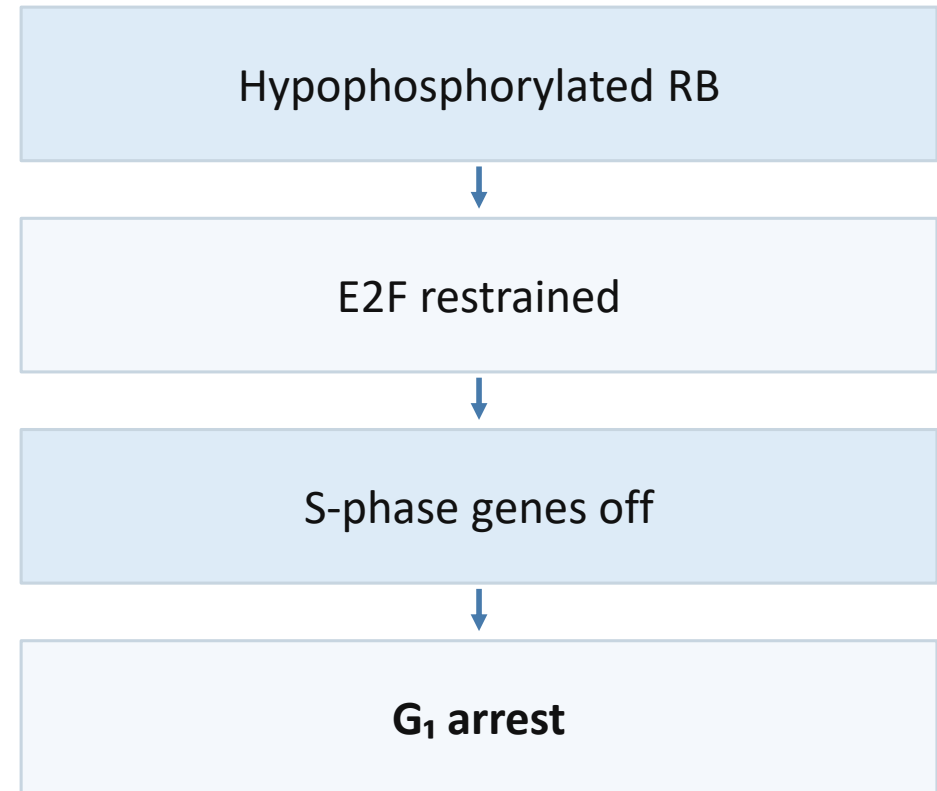
Cyclin B–CDK1 controls mitotic entry

- Cyclin B partners with CDK1.
- The complex is essential for the G₂-to-M transition.
- Its action represents a later checkpoint-controlled step than the G₁/S gate.



RB is the central G₁/S integrator

- Active, hypophosphorylated RB binds E2F transcription factors.
- E2F sequestration suppresses genes needed for S phase.
- Mitogenic cyclin–CDK activity inhibits RB by phosphorylation.



RB changes state across the G₁/S switch

Active RB

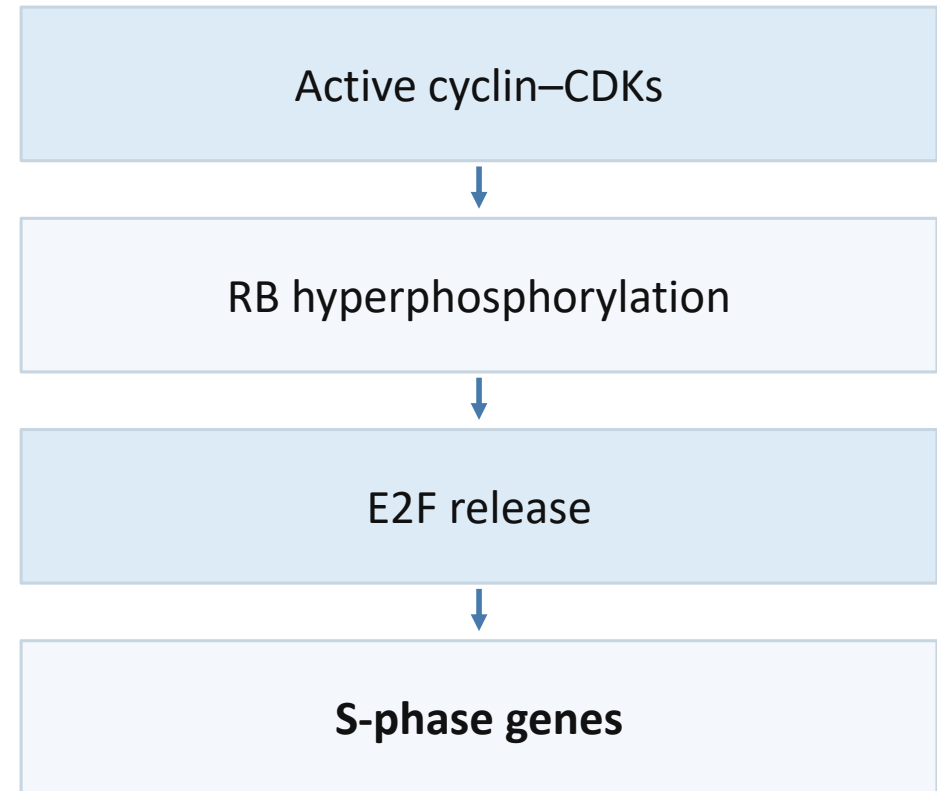
- Predominantly hypophosphorylated.
- Binds E2F transcription factors.
- Restrains G₁/S progression.

Inactive RB

- Hyperphosphorylated by cyclin–CDK drive.
- E2F factors are released.
- S-phase gene transcription increases.

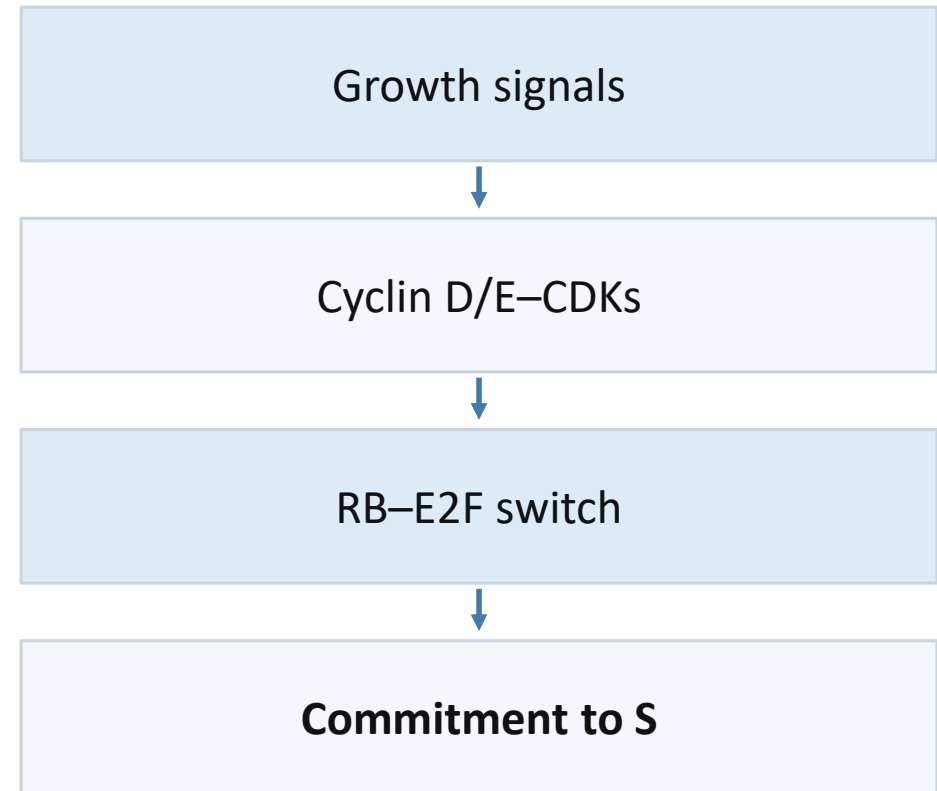
RB phosphorylation releases E2F

- Cyclin D–CDK4/6 and cyclin E–CDK2 phosphorylate RB.
- Hyperphosphorylated RB no longer restrains E2F effectively.
- E2F drives transcription of genes required for S-phase entry.



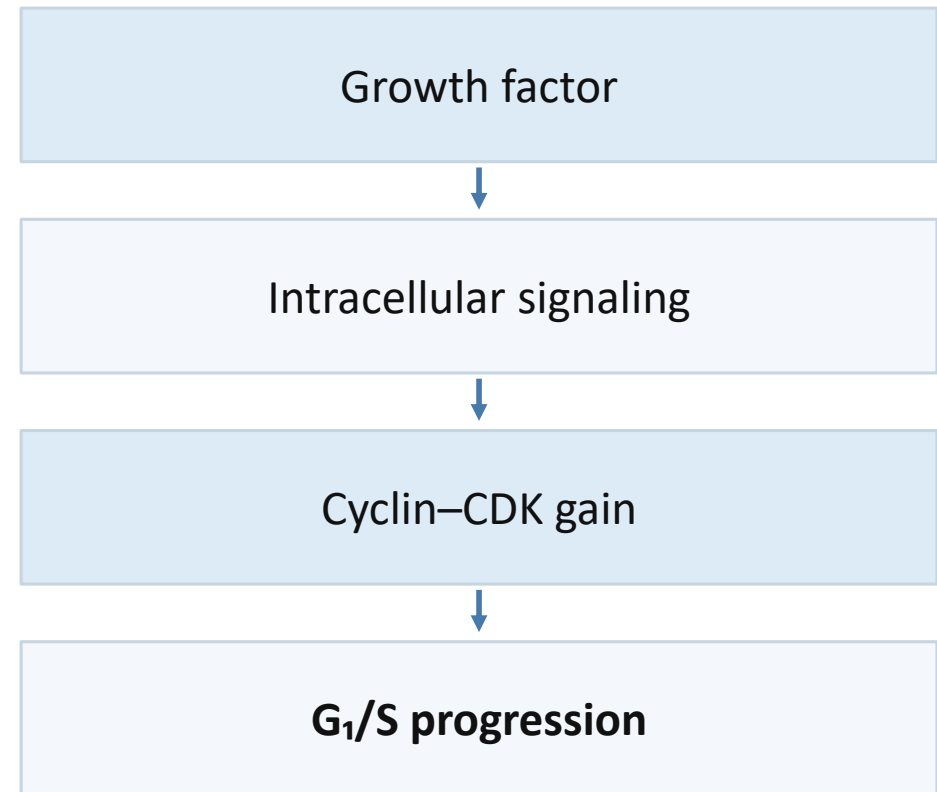
The restriction point converts signals into commitment

- Upstream growth signals increase cyclin–CDK activity.
- RB integrates these stimulatory and inhibitory influences.
- Release of E2F commits cells to a program supporting DNA synthesis.



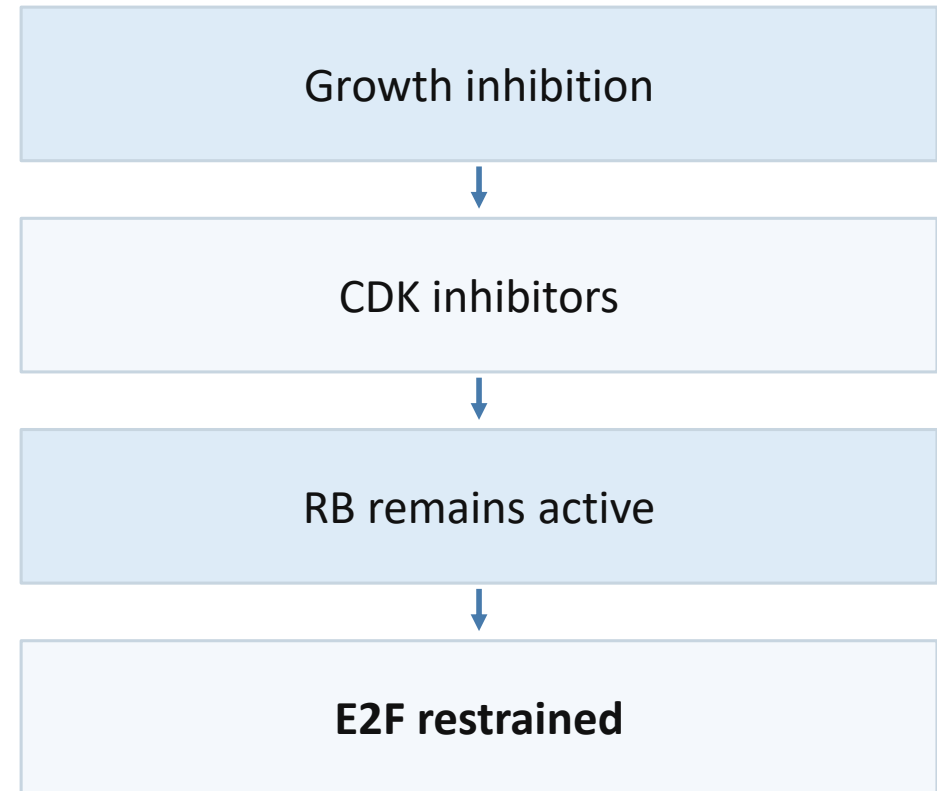
Mitogenic signaling pushes the RB switch forward

- Growth factor receptors activate intracellular signaling pathways.
- These signals increase activity of cyclin–CDK complexes.
- Mitogenic signaling can also downregulate CDK inhibitors.



Growth-suppressive signals reinforce the brake

- Negative growth cues promote CDK inhibitor expression.
- Reduced cyclin–CDK activity preserves hypophosphorylated RB.
- RB retains E2F and suppresses S-phase entry.



Proliferation reflects opposing molecular forces

Pro-proliferative arm

- Growth factors induce cyclin–CDK activity.
- RB becomes phosphorylated.
- E2F-dependent transcription promotes S phase.

Antiproliferative arm

- Growth-suppressive signals induce CDK inhibitors.
- RB remains hypophosphorylated.
- E2F-dependent transcription is restrained.

CDK inhibitors provide a molecular brake

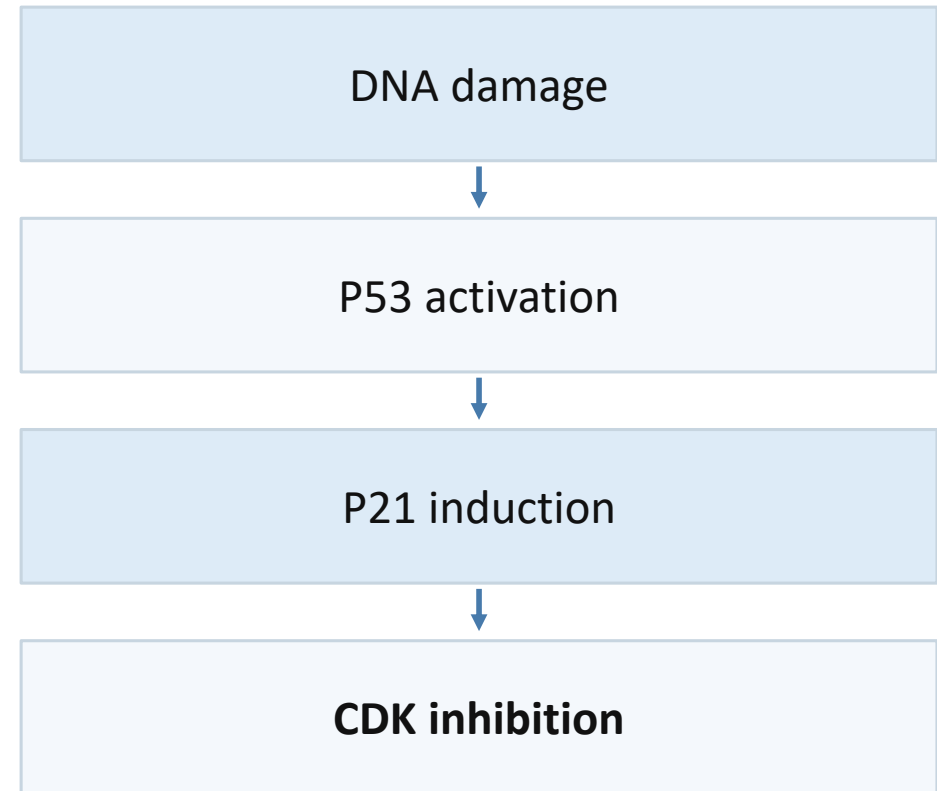
- CDK inhibitors (CKIs) reduce kinase activity of cyclin–CDK complexes.
- CKI expression is regulated by inhibitory signals and DNA-damage responses.
- Their dysfunction can remove checkpoint restraint on abnormal cells.

The CIP/KIP inhibitor family

Protein	Gene	Principal role
P21	CDKN1A	Broad inhibition of CDK complexes; P53-responsive
P27	CDKN1B	Broad CDK inhibition; Responsive to growth suppression
P57	CDKN1C	Broad inhibitory CDKI family member

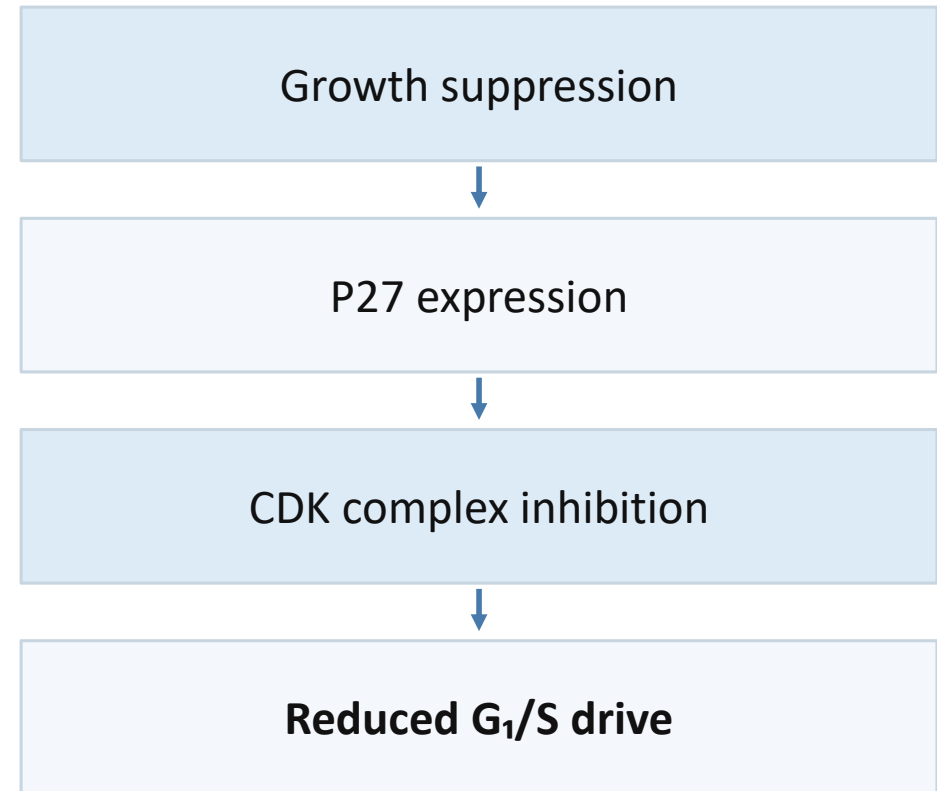
P21 links DNA damage to CDK inhibition

- Activation of p53 stimulates p21 expression.
- P21 binds and inhibits cyclin–CDK complexes.
- This produces G₁/S arrest and allows time for DNA repair.



P27 responds to growth-inhibitory cues

- P27 is a CIP/KIP-family CDK inhibitor.
- P27 regulation to signals such as TGF- β .
- Its inhibitory action counters excessive cyclin–CDK activity.



P57 completes the broad-inhibitor family

- P57 is encoded by CDKN1C.
- Alongside p21 and p27, it belongs to the CIP/KIP class.
- The class broadly restrains CDK complexes rather than selectively targeting only CDK4/6.

The INK4 inhibitor family

Protein	Gene	Principal target
P15	CDKN2B	Cyclin D–CDK4/6
P16	CDKN2A	Cyclin D–CDK4/6
P18	CDKN2C	Cyclin D–CDK4/6
P19	CDKN2D	Cyclin D–CDK4/6

P15 and p16 selectively oppose D cyclin complexes

P15 (CDKN2B)

- INK4-family CDK inhibitor.
- Restrains D cyclin–CDK4/6 activity.
- Contributes to negative G₁ regulation.

P16 (CDKN2A)

- INK4-family CDK inhibitor.
- Blocks CDK4/cyclin D–mediated RB phosphorylation.
- Acts as an important tumor suppressor.

P18 and p19 share the INK4 target preference

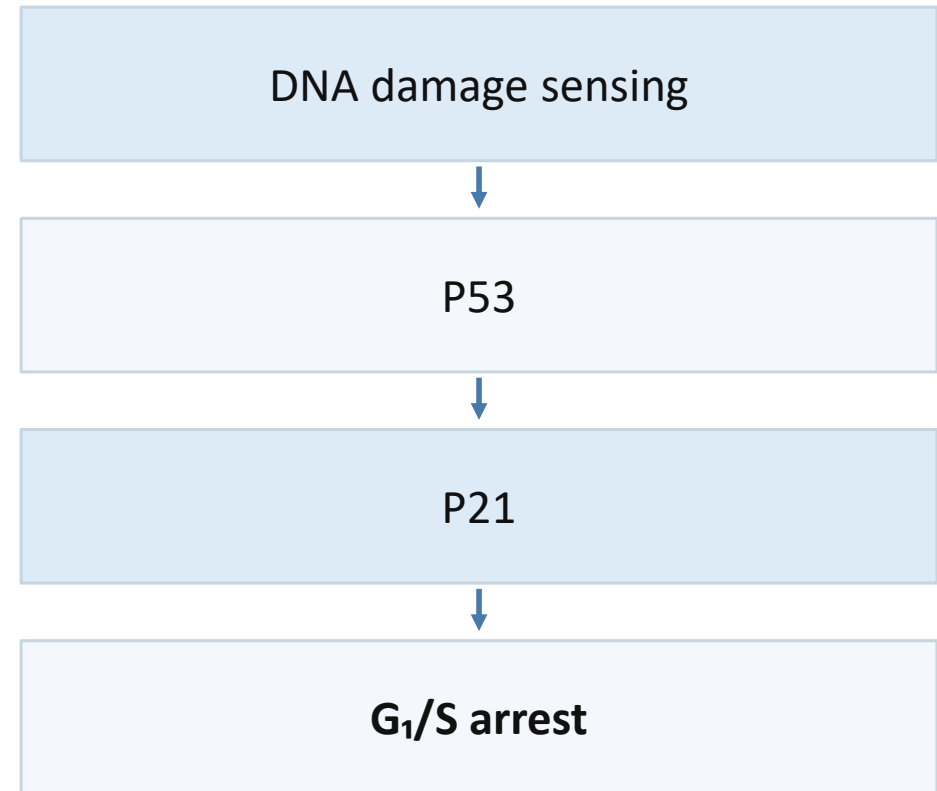
- P18 (CDKN2C) and p19 (CDKN2D) are members of the INK4 family.
- Both predominantly inhibit CDK4/6 complexes associated with cyclin D.
- The shared target distinguishes INK4 proteins from broad CIP/KIP inhibitors.

CIP/KIP and INK4 inhibitors are not interchangeable

Feature	CIP/KIP	INK4
Members	P21, p27, p57	P15, p16, p18, p19
CDK scope	Broad inhibition	Selective CDK4/6 inhibition
Link to cancer	Checkpoint loss	Loss of G ₁ restraint / p16 alteration
Representative input	P53 → p21	P16 → CDK4/6

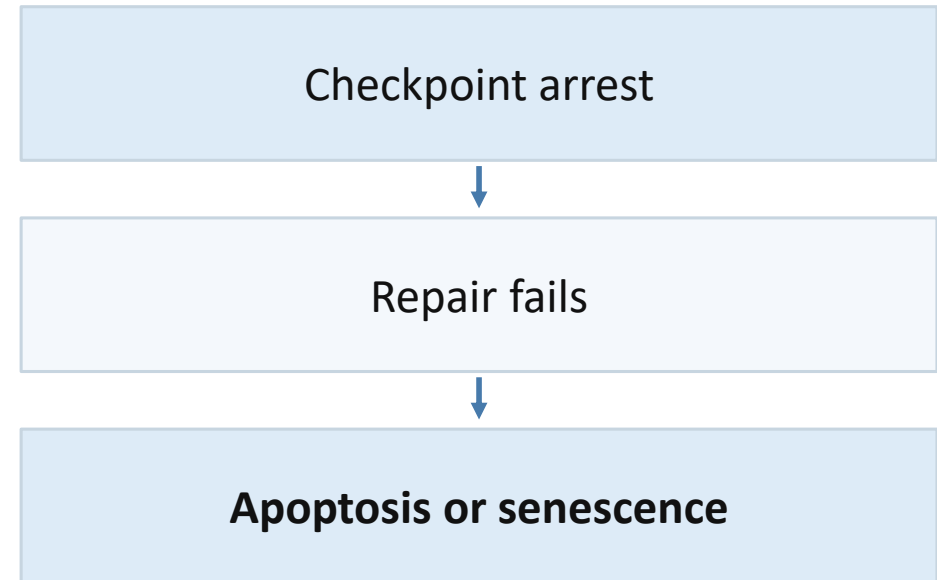
The p53–p21 arm stops damaged cells

- DNA damage sensors can activate p53.
- P53 raises the abundance of p21.
- P21 restrains cyclin–CDK activity and delays the G₁/S transition.



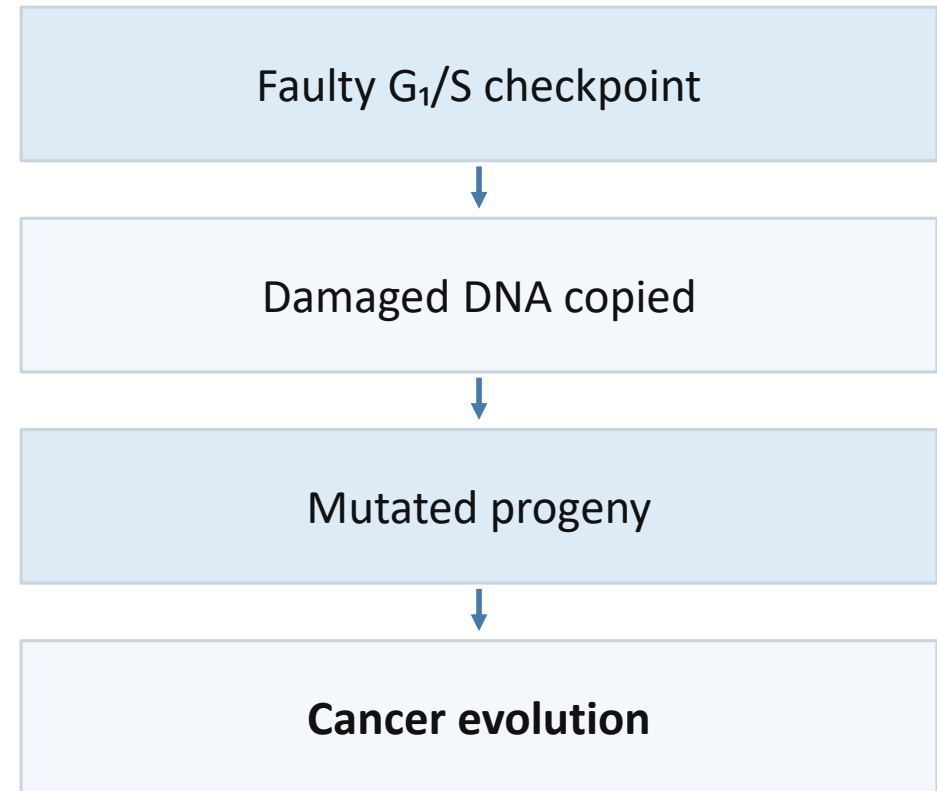
Severe damage can terminate proliferation

- Checkpoint arrest first gives time to correct DNA abnormalities.
- If damage cannot be repaired, cells may undergo apoptosis.
- Alternatively, cells may enter a stable nonreplicative senescent state.



Checkpoint failure can create a mutator phenotype

- Defective G_1/S control permits replication despite DNA damage.
- Resulting daughter cells may inherit mutations.
- This genomic instability can facilitate tumor development and progression.



Two broad routes to inappropriate G₁/S entry

Oncogene activation

- Gain of cyclin D or CDK4 function.
- Excessive phosphorylation of RB.
- Increased G₁/S passage.

Tumor-suppressor loss

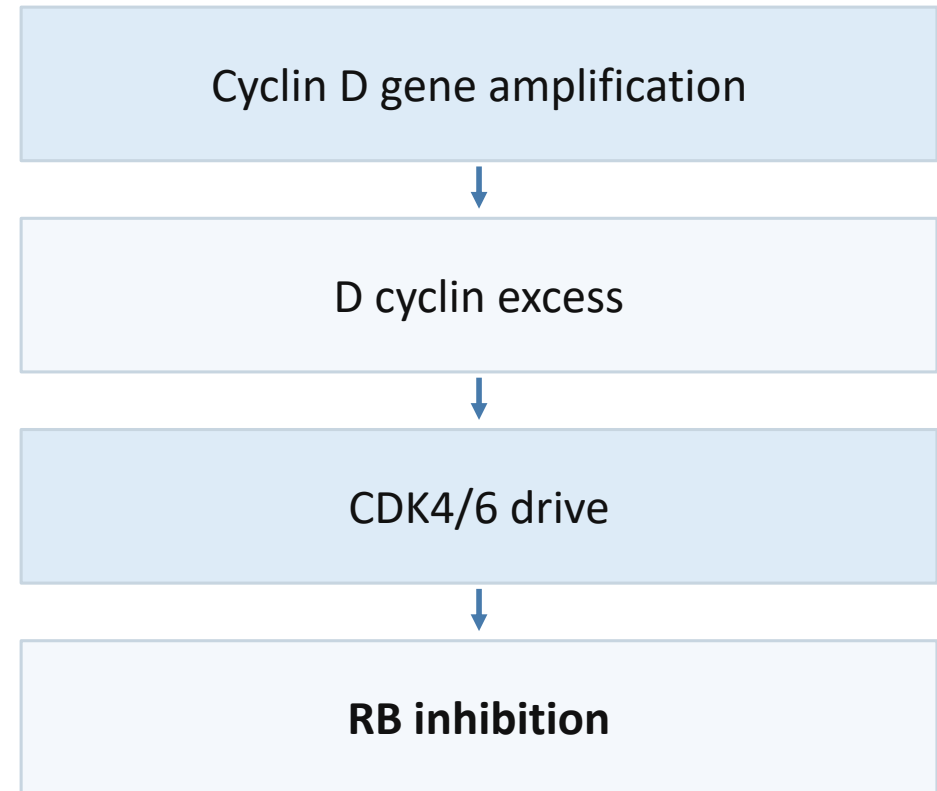
- Inactivation of CDK inhibitor genes.
- Insufficient restraint on cyclin–CDKs.
- Loss of checkpoint control.

The three D-type cyclins have overlapping functions

- Cyclin D1, D2, and D3 are the three D cyclin proteins.
- The three are functionally interchangeable in the G₁-control setting.
- Acquired changes can dysregulate these proteins in human malignancies.

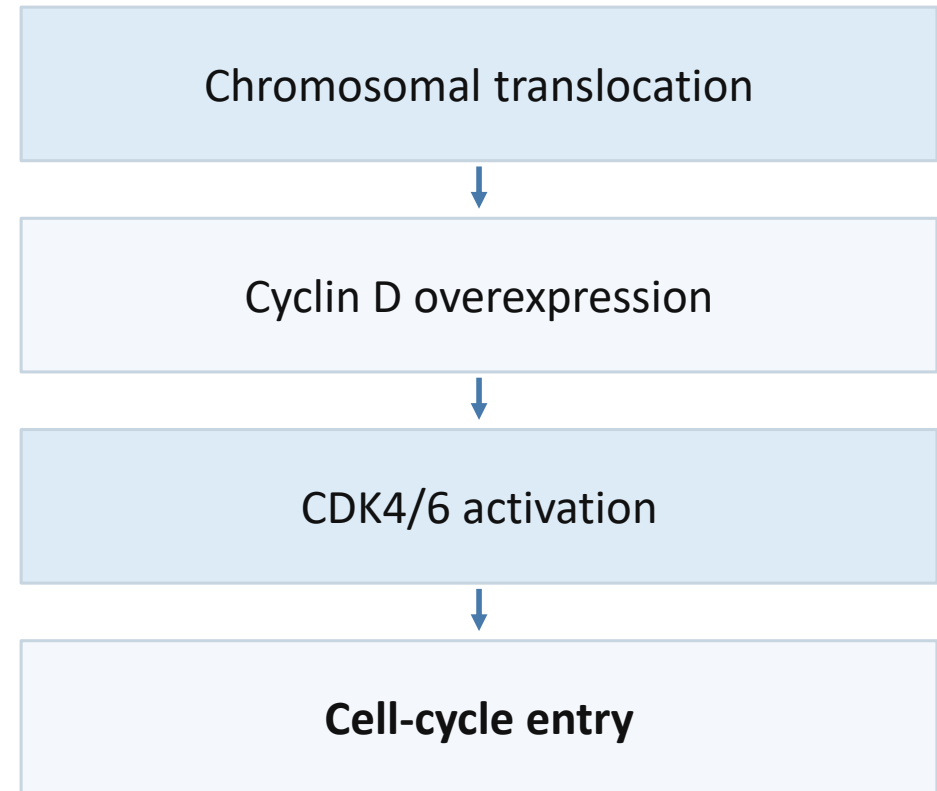
Cyclin D amplification produces excessive drive

- Gene amplification can increase D cyclin abundance.
- More D cyclin supports greater CDK4/6 complex activity.
- Excessive RB phosphorylation favors G₁/S progression.



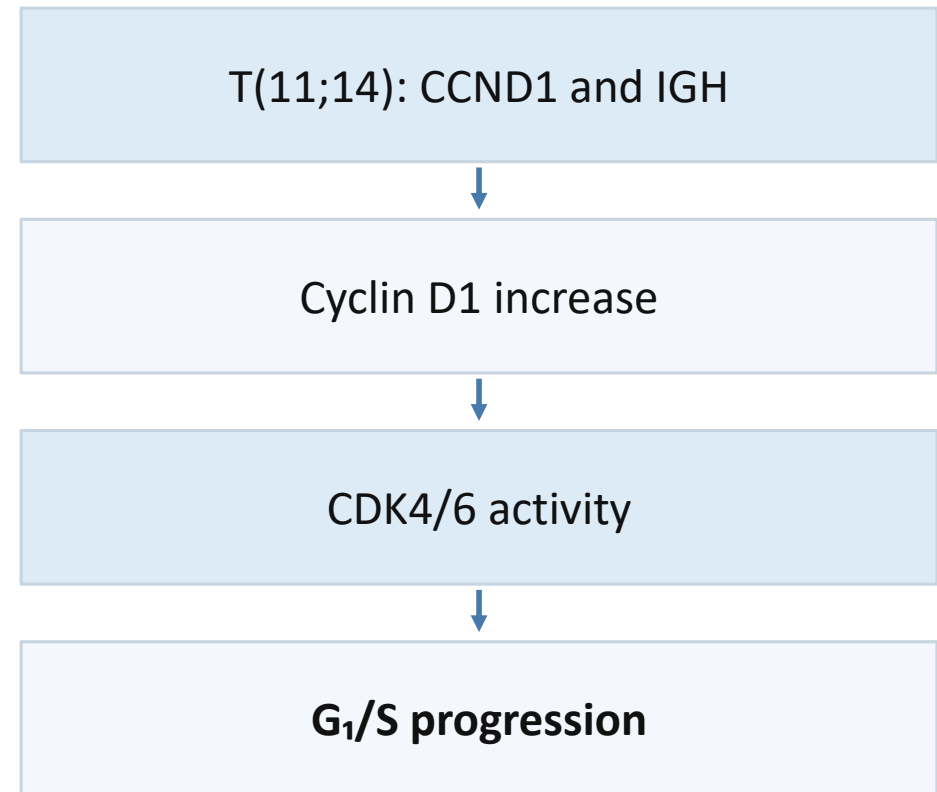
Cyclin D translocation can deregulate expression

- Chromosomal translocations can place D cyclin genes under abnormal regulatory control.
- This mechanism is particularly associated with some lymphoid tumors.
- The downstream effect is heightened G₁/S progression.



CCND1 rearrangement is central to mantle cell lymphoma

- Mantle cell lymphoma typically harbors t(11;14) involving CCND1 and IGH.
- The rearrangement elevates cyclin D1 expression.
- Excess cyclin D1 promotes progression from G₁ toward S phase.

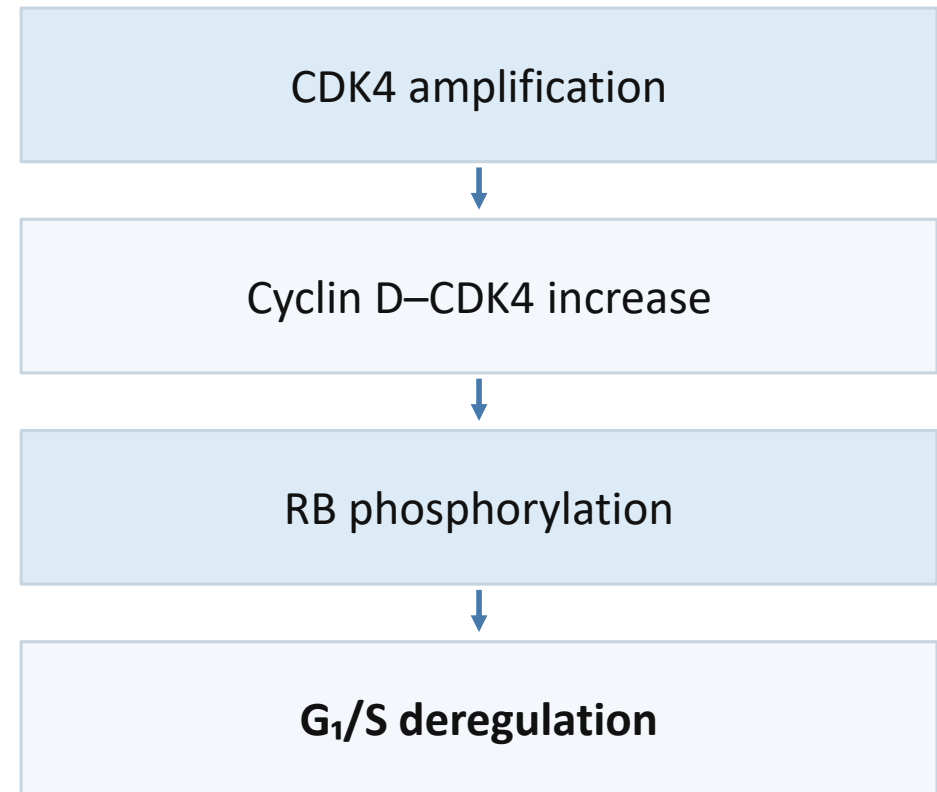


Cyclin D1 amplification also occurs in carcinomas

- CCND1 amplification in breast and esophageal cancers.
- Amplification and translocation are mechanistically distinct genetic alterations.
- Both can converge on elevated cyclin D1 activity and altered G₁ control.

CDK4 amplification increases catalytic capacity

- CDK4 itself may be amplified or otherwise activated.
- When partnered with D cyclins, excess CDK4 reinforces RB phosphorylation.
- This provides an oncogenic route separate from cyclin gene alteration.



CDK4 genetic alteration spans several cancers

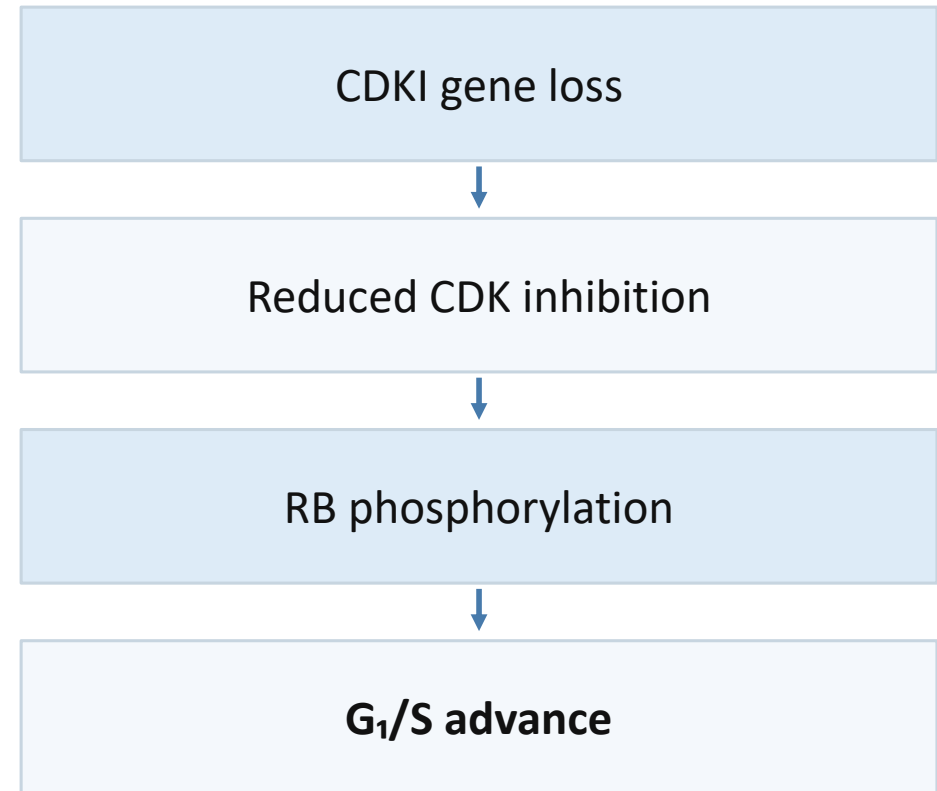
- CDK4 amplification in melanomas and sarcomas.
- Aggressive glial tumors are another associated setting.
- Tumor type alone does not establish CDK4 amplification; The finding is a molecular alteration.

Other CDK and cyclin E alterations are less frequent

- Alterations involving cyclin E and CDKs other than CDK4 are described in cancer.
- That these occur less frequently than major D cyclin/CDK4 events.
- This pattern highlights the dominant regulatory importance of the G₁/S gate.

Loss of inhibitors removes a negative regulator

- CDKI genes may undergo inactivating mutation or silencing.
- Loss of inhibitory proteins permits stronger cyclin–CDK activity.
- The consequence converges on inappropriate G₁/S progression.



CDKN2A produces two distinct tumor suppressors

P16 / INK4a — RB axis

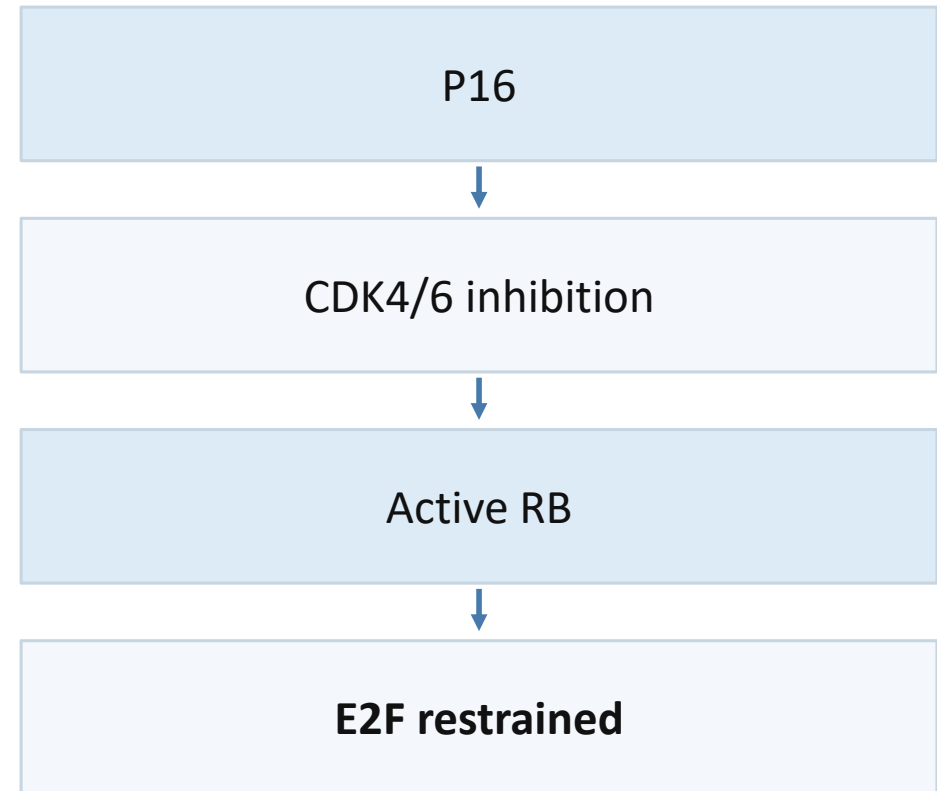
- Encoded by the CDKN2A locus.
- Inhibits cyclin D–CDK4/6 activity.
- Helps maintain active RB and E2F restraint.

P14 / ARF — p53 axis

- A separate product of CDKN2A.
- Inhibits MDM2 and raises p53 stability.
- Supports p53-linked checkpoint activity.

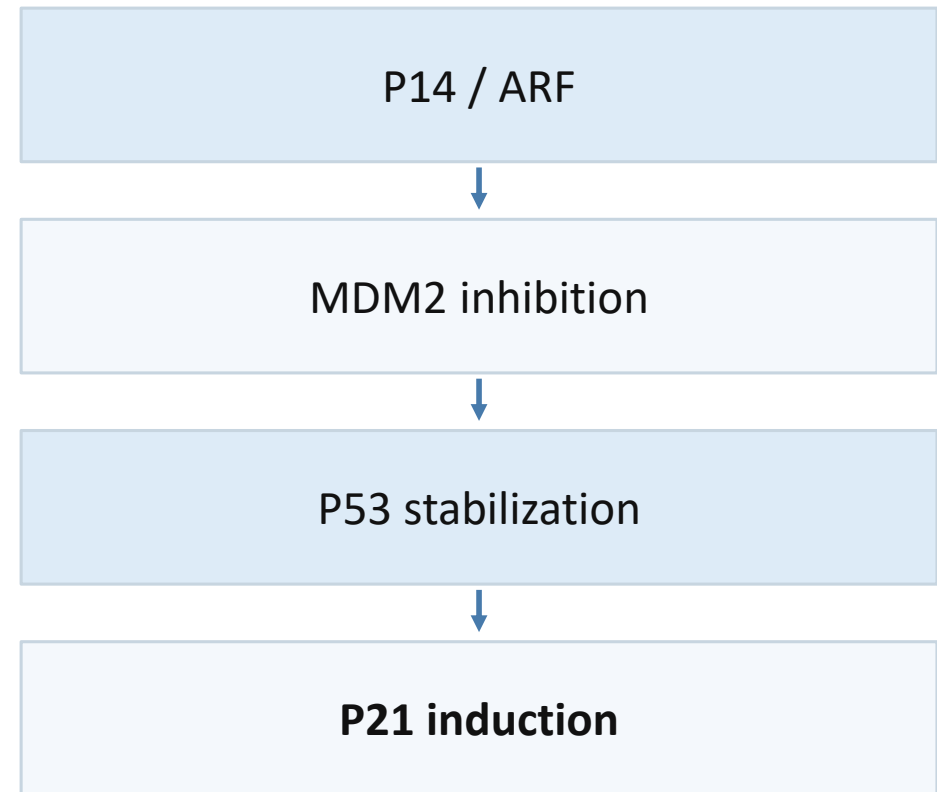
The p16 arm restrains RB phosphorylation

- P16 binds to and inhibits CDK4-associated cyclin D complexes.
- Reduced CDK activity helps RB remain hypophosphorylated.
- E2F repression is thereby preserved.



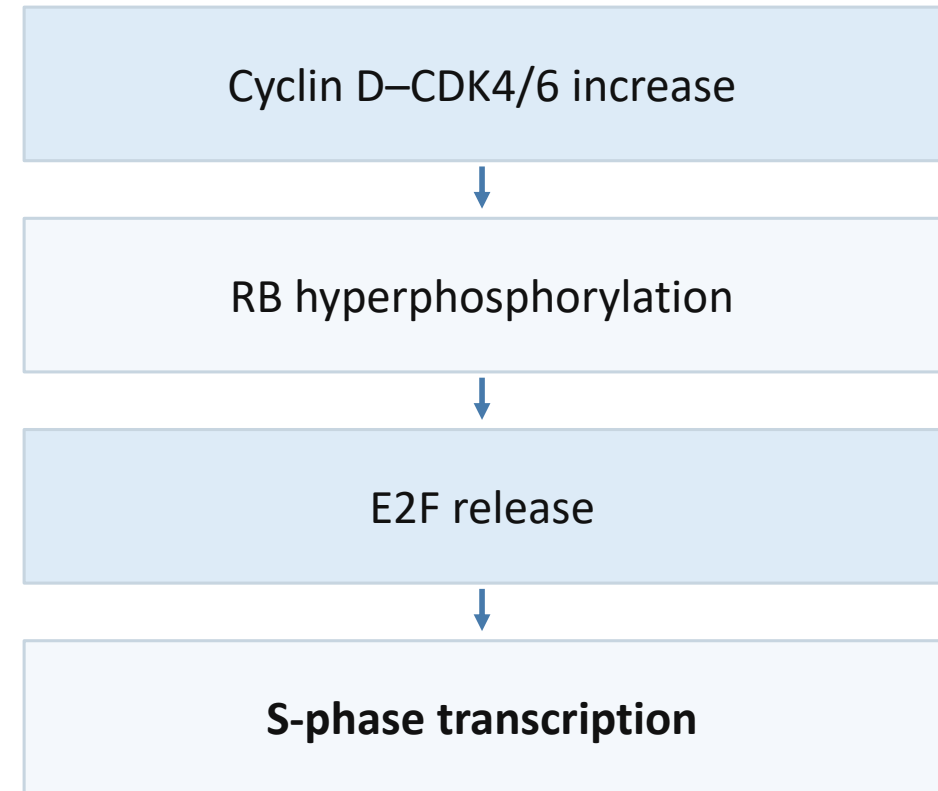
The p14/ARF arm supports the p53 checkpoint

- P14/ARF inhibits MDM2 activity.
- Lower MDM2-mediated inhibition permits higher p53 levels.
- The resulting p53 response can upregulate p21 and enforce arrest.



Four molecular nodes form one vulnerable circuit

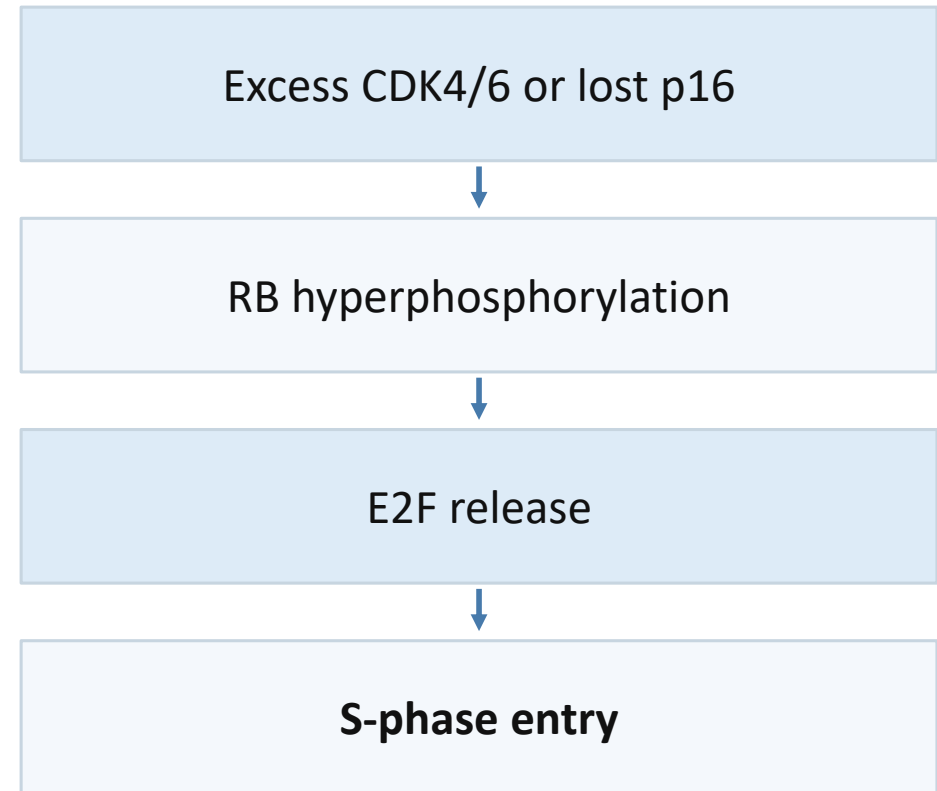
- Cyclin D and CDK4 promote RB phosphorylation.
- P16 normally inhibits the cyclin D–CDK4 axis.
- RB opposes E2F-driven S-phase gene expression.
- Alteration of any of these nodes can disrupt G₁/S control.



P16 inhibits the first step; Loss of p16 removes this brake.

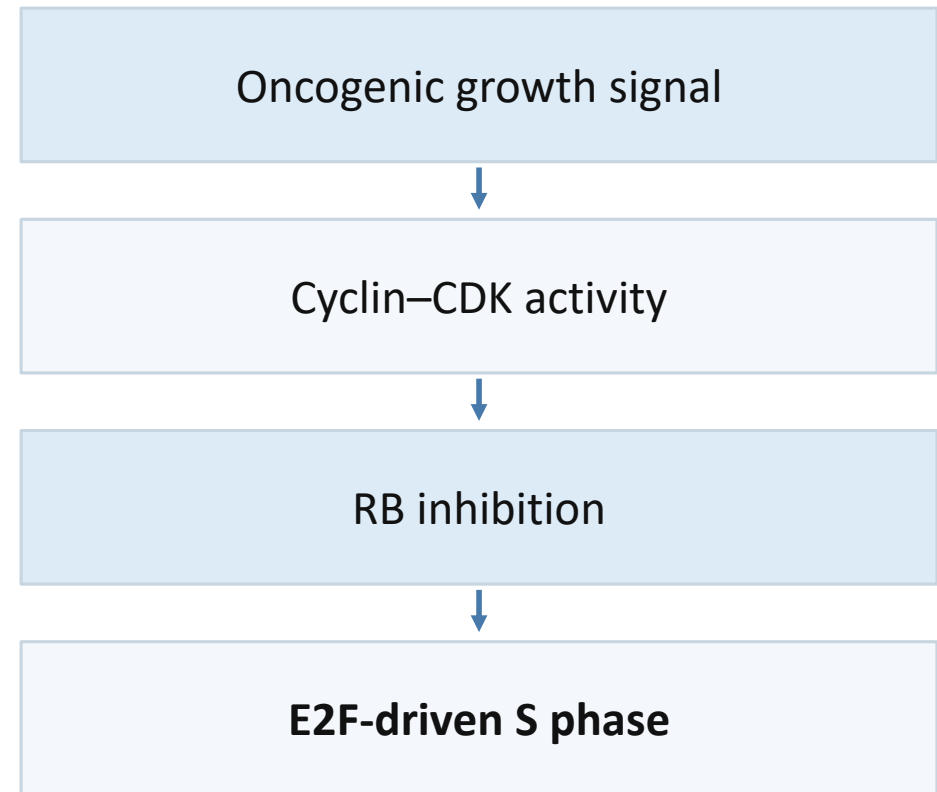
Wild-type RB can be functionally inactivated

- RB need not carry a mutation to become ineffective.
- Excessive D cyclin/CDK4 activity can hyperphosphorylate RB.
- Loss of p16 can likewise disable RB-mediated growth restraint.



Upstream oncogenic signals can feed the G₁ engine

- Growth factor–receptor pathways provide mitogenic input.
- Deregulated signaling enhances cyclin–CDK activity.
- The downstream result may resemble a direct cell-cycle-gene alteration.



Representative cell-cycle alterations in cancer

Molecular alteration	Cancer example	Pathogenic effect
CCND1 translocation	Mantle cell lymphoma	Cyclin D1 overexpression
CCND1 amplification	Breast, esophageal carcinomas	Increased cyclin D drive
CDK4 amplification	Melanoma, sarcoma, glial tumors	Greater CDK4 activity
CDKN2A inactivation	Melanoma and several carcinomas	Loss of p16 restraint

Application: Cyclin D1 in a B-cell lymphoma

Scenario

A lymphoid tumor is found to have an IGH-associated CCND1 rearrangement.

Question

How does this rearrangement promote proliferation?

Suggested interpretation is provided in presenter notes.

CDK4/6 inhibition is a therapeutic application

- CDK4/6 inhibitors target kinase activity in the cyclin D–CDK4/6 pathway.
- Clinical efficacy for certain forms of breast cancer.
- Pathway biology supplies the rationale; Individual drug indications require independent current guideline review.

Molecular mechanism and clinical prediction are different

Mechanistic statement

- CDK4/6 activity promotes RB phosphorylation.
- Targeting CDK4/6 can suppress this drive.
- This is a pathway-level explanation.

Clinical interpretation

- Not every tumor with pathway activation responds identically.
- Therapy choices depend on disease context.
- Do not infer treatment eligibility from a generic schematic.

Application: Loss of p16 in a carcinoma

Scenario

A carcinoma retains an apparently intact RB gene, but CDKN2A is inactivated.

Question

Why can G₁/S control nevertheless fail?

Suggested interpretation is provided in presenter notes.

Application: DNA damage before S phase

Scenario

A proliferating cell detects major DNA damage while still in G₁.

Question

Trace the protective response from p53 to the cell-cycle machinery.

Suggested interpretation is provided in presenter notes.

Normal control versus neoplastic deregulation

Physiologic cycling

- Mitogenic input is counterbalanced by inhibitors.
- RB restrains E2F until appropriate phosphorylation.
- Checkpoints halt damaged cells.

Neoplastic deregulation

- Cyclin/CDK activation or CDKI loss biases the switch.
- RB restraint can be overcome.
- Checkpoint failure favors mutation accumulation.

Integrated interpretation of the G₁/S pathway

- Cyclin abundance controls when partner CDKs can become active.
- RB/E2F converts CDK phosphorylation into gene-expression commitment.
- CDKI and damage responses oppose inappropriate progression.
- Cancer exploits both increased accelerator activity and weakened brakes.

Three distinctions to retain

- Cyclins regulate CDK activity; CDKs are the enzymes that phosphorylate targets.
- The restriction point and DNA-damage checkpoints are related but distinct concepts.
- RB can be genetically lost or functionally inhibited by upstream alterations.

Recommended reading

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition.
- Cell-cycle regulation in Chapter 1 and cell-cycle oncogenes in Chapter 7.
- Related mechanisms: RB, p53, and CDKN2A tumor-suppressor pathways.