

RB: Governor of Proliferation

Tumor suppression, G₁/S control and retinoblastoma genetics

Molecular basis of cancer

Pathology lecture

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraisakhri.com

Learning objectives: From cell-cycle brake to cancer

- Explain how phosphorylation switches RB from an E2F repressor to a permissive cell-cycle state.
- Distinguish inherited predisposition from biallelic loss in the developing tumor.
- Connect cyclin D, CDK4/6, p16 and viral oncoproteins to RB dysfunction.

Schematic

Describe the G₁/S RB–E2F checkpoint



Contrast two routes to RB inactivation



Apply the two-hit model to retinoblastoma



Identify upstream and viral mechanisms

RB is a central negative regulator of proliferation

- RB regulates the critical G₁/S transition.
- The normal pathway responds to both mitogenic and growth-inhibitory signals.
- Direct RB mutation is only one way to disable its antiproliferative function.

Schematic

Functional RB restrains G₁ → S



Loss of the brake permits inappropriate cell-cycle entry

Many cancers inactivate RB directly or indirectly

RB1 and RB protein are related but distinct entities

- The RB locus is mapped to chromosome 13q14 in the retinoblastoma model.
- A functioning RB gene supplies the RB protein that represses E2F-dependent transcription.
- A retained RB allele or detectable protein does not, by itself, prove normal pathway activity.

Schematic

RB1 gene: Chromosome 13q14



RB protein: Tumor-suppressive pocket protein



Binding E2F limits S-phase gene expression



Loss of function permits neoplastic growth

RB belongs to the tumor suppressor class

- Tumor suppressors normally oppose one or more hallmarks of cancer.
- Loss of tumor suppressor function can permit excessive cell proliferation.
- RB illustrates how a growth-regulatory checkpoint becomes a cancer vulnerability.

Schematic

Proto-oncogene activation

Gain of growth-promoting activity

Examples: Cyclin D, CDK4

Pushes cell-cycle progression

Tumor suppressor loss

Loss of growth-restraint activity

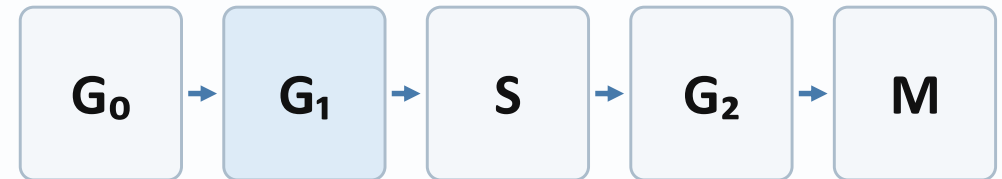
Example: RB loss

Releases cell-cycle restraint

The mammalian cell cycle provides the setting

- Quiescent cells are in G_0 and may re-enter the cycle after appropriate stimuli.
- G_1 precedes DNA synthesis; S is the DNA-replication phase.
- The G_1/S and G_2/M checkpoints provide distinct safeguards.

Schematic



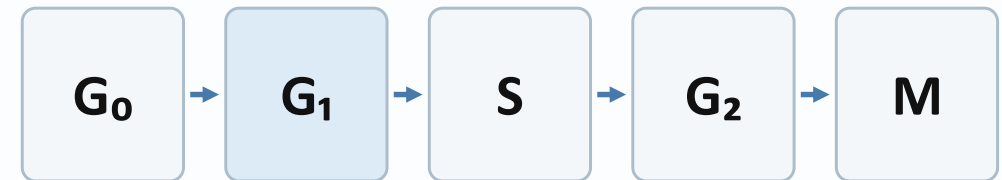
G_1 is the major RB-regulated decision interval

S phase involves DNA synthesis

The G₁ restriction point is a commitment decision

- The G₁ restriction point marks commitment to continued cycle progression.
- Before this decision, growth-factor availability helps determine whether the cell proceeds.
- RB integrates the opposing inputs that shape the G₁/S decision.

Schematic



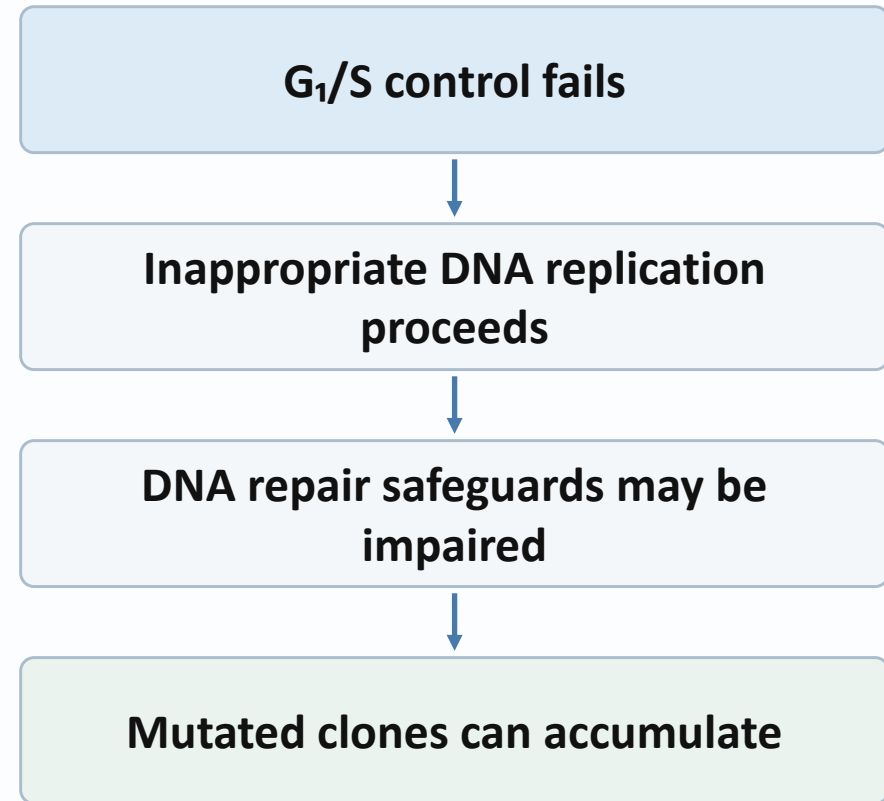
Restriction point: Cell can proceed without further initiating signal

Decision is regulated by growth-promoting versus inhibitory cues

Why the G₁/S checkpoint matters in cancer

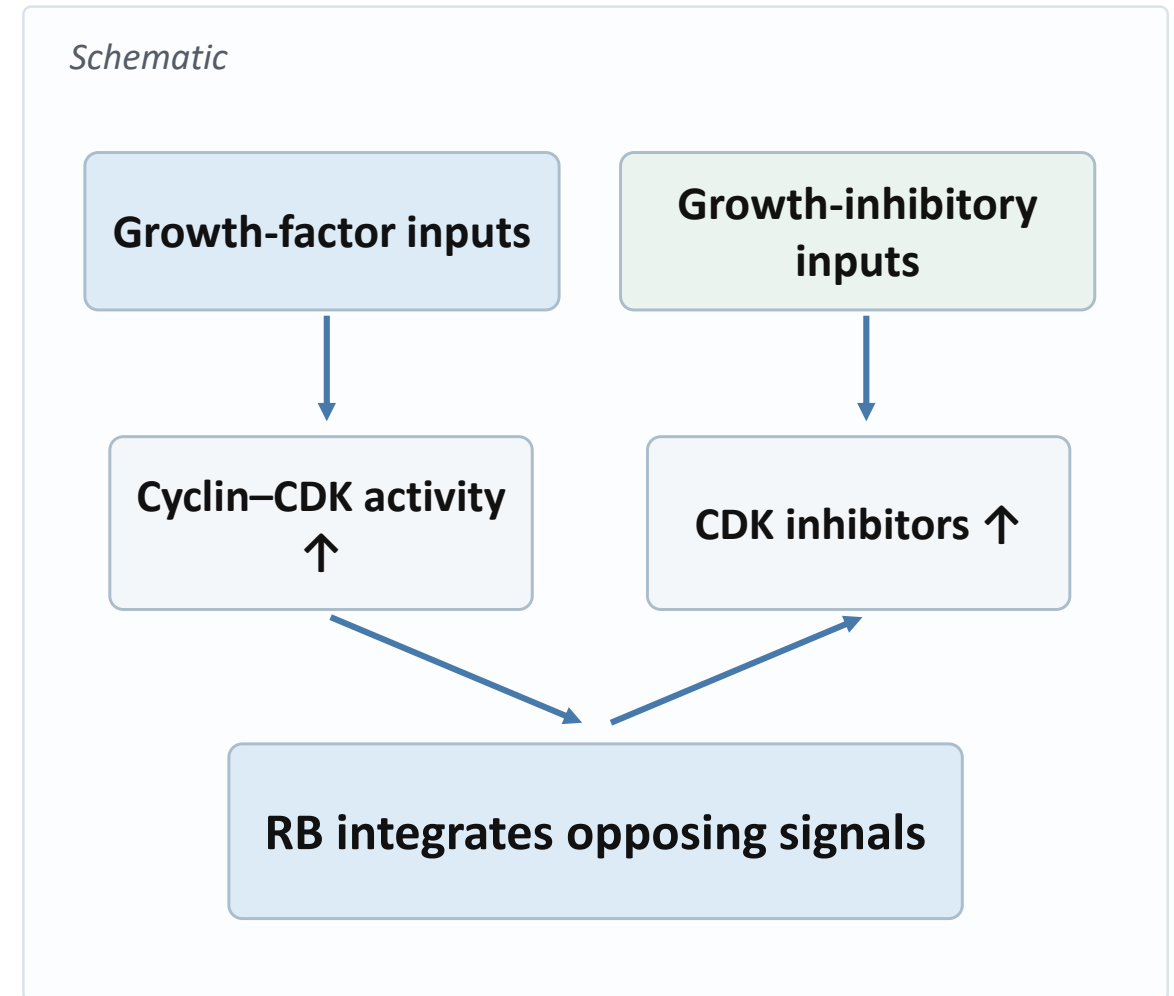
- Defects at G₁/S release proliferative restraint.
- Checkpoint defects can also favor genomic instability.
- Dysregulated growth and a mutator phenotype reinforce neoplastic progression.

Schematic



Mitogenic drive and cell-cycle restraint are opposed

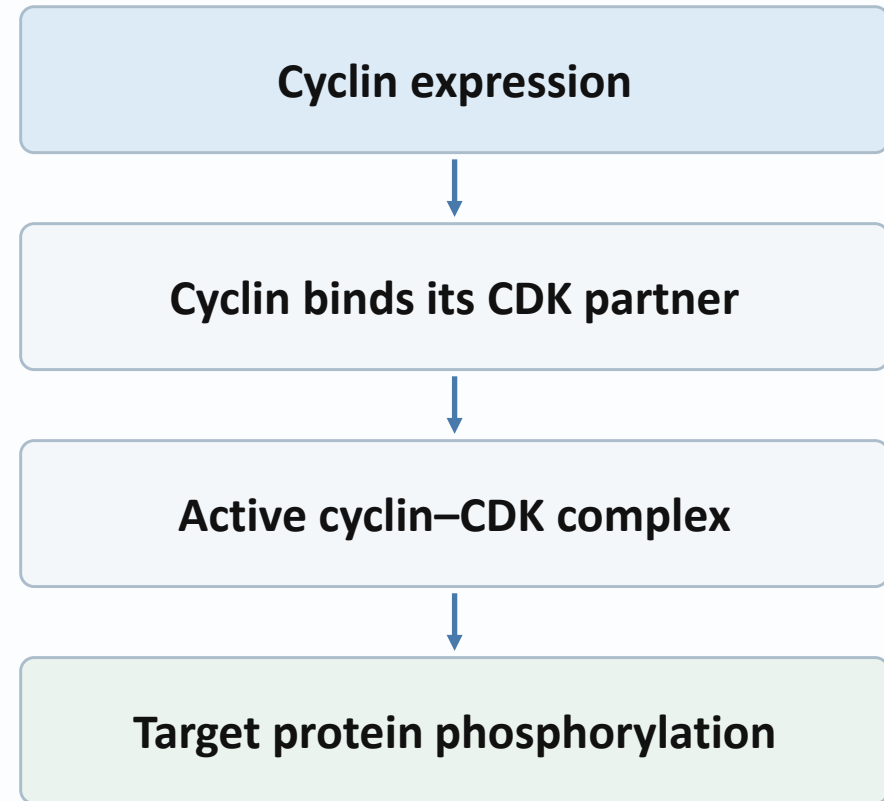
- Mitogens generally activate cyclin–CDK complexes.
- Antiproliferative inputs induce CDK inhibitors.
- The phosphorylation state of RB reflects the net effect of these pathways.



Cyclins activate cyclin-dependent kinases

- Cyclin levels vary over the cell cycle through regulated synthesis and degradation.
- Cyclin binding activates the associated CDK.
- The resulting kinase activity drives stage-specific transitions by phosphorylating target proteins.

Schematic



RB restrains E2F by physical sequestration

- RB is a pocket protein that binds E2F transcription factors.
- When bound by functional RB, E2F cannot freely induce its target genes.
- This interaction is an immediate molecular basis for RB-mediated growth inhibition.

Schematic

Active, hypophosphorylated RB



RB binds E2F



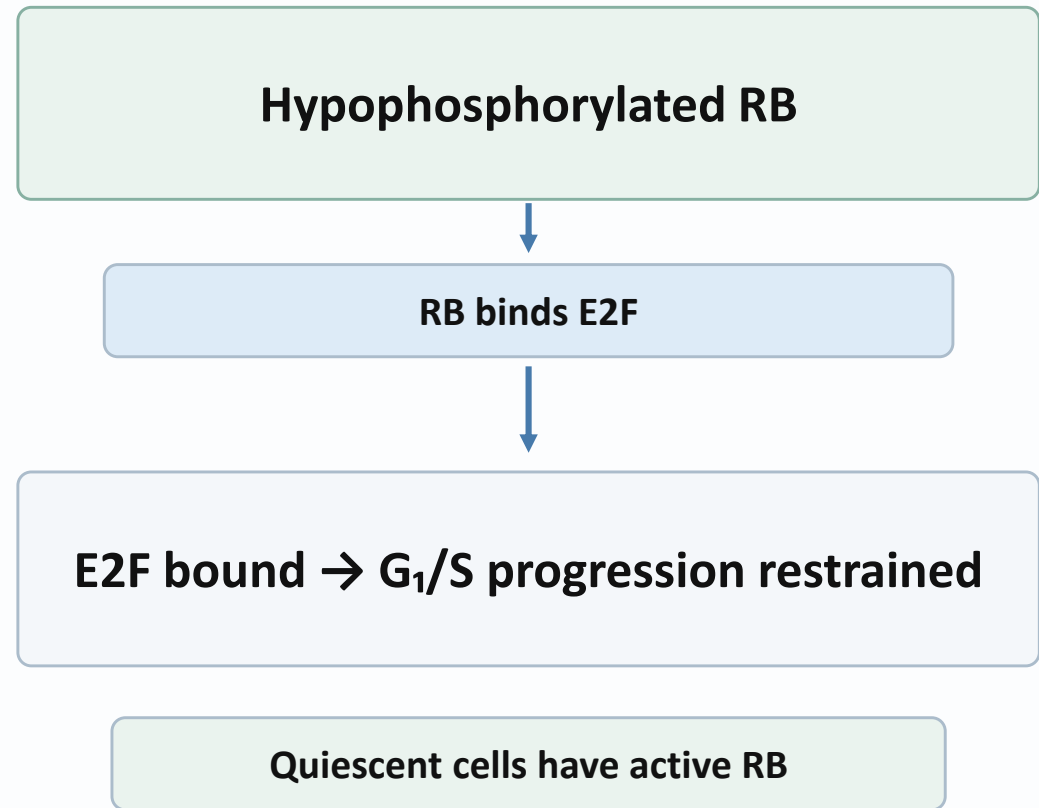
E2F-driven S-phase transcription restrained

RB acts upstream of the G₁/S gene-expression program

Hypophosphorylated RB is the active brake

- RB is active in its hypophosphorylated state.
- Quiescent cells are characterized by this growth-restraining RB state.
- The central effect is inhibition of E2F-regulated transcription.

Schematic



Hyperphosphorylation functionally inhibits RB

- Cell-cycle entry is accompanied by RB hyperphosphorylation.
- Hyperphosphorylated RB no longer effectively sequesters E2F.
- E2F transcription factors can then stimulate genes required for S phase.

Schematic

Cyclin–CDK-mediated phosphorylation



RB becomes hyperphosphorylated



E2F release → S-phase gene expression

A state change can mimic genetic RB deletion

- RB1 loss-of-function is one route to failed growth control.
- Persistent upstream kinase activation can inhibit intact RB protein.
- Function must not be inferred from DNA sequence alone.

Schematic

Genetic pathway loss

Both RB copies
inactivated

RB tumor suppressor
function lost

E2F restriction
abolished

Functional pathway loss

RB gene may remain
normal

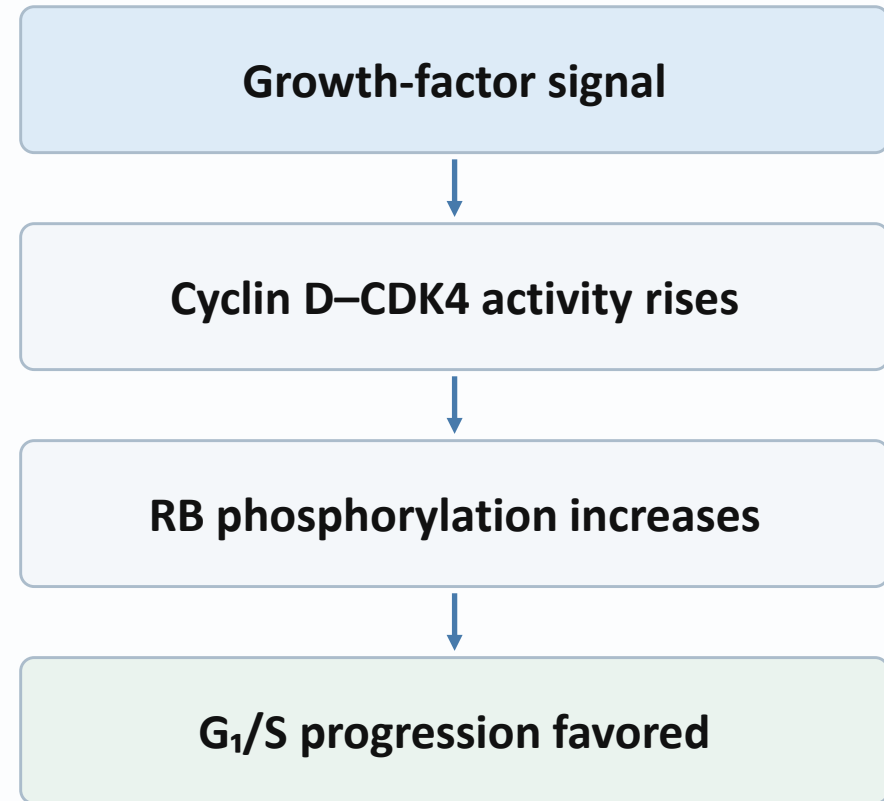
RB phosphorylation
increased

E2F restriction
weakened

Cyclin D–CDK4 is an RB-directed kinase complex

- Cyclin D–CDK4 phosphorylates RB.
- Excessive activity can tip RB toward its inhibited state.
- Gain-of-function alterations affecting this complex can drive oncogenic proliferation.

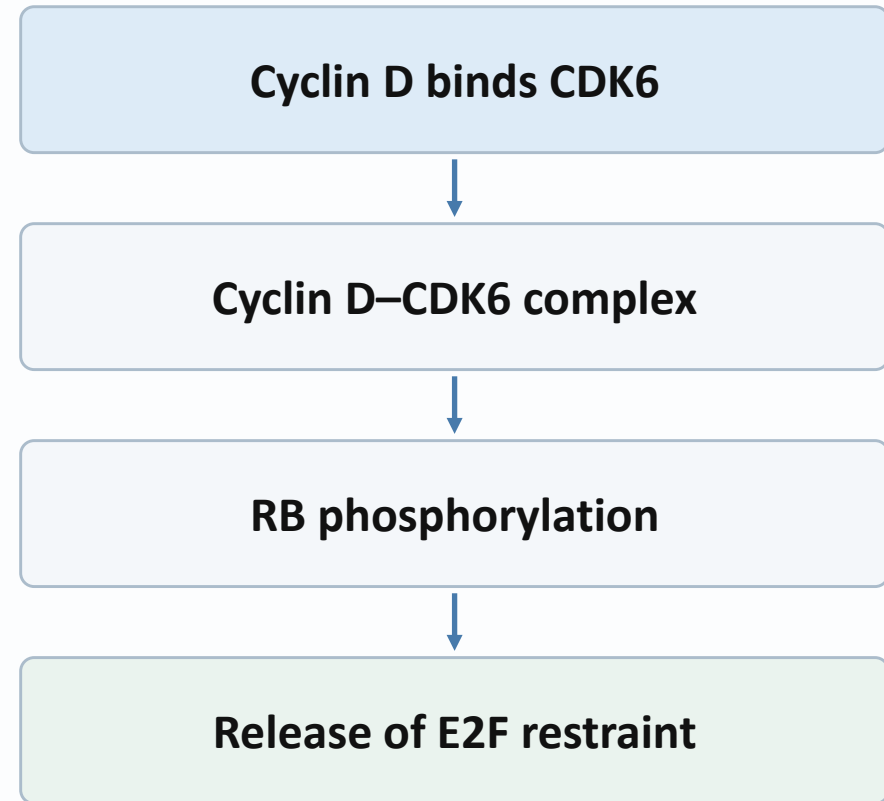
Schematic



Cyclin D–CDK6 acts alongside CDK4

- Cyclin D can form active complexes with CDK6 as well as CDK4.
- Both cyclin D–CDK4 and cyclin D–CDK6 participate in controlling G₁ progression.
- CDK inhibition can preserve a growth-inhibitory RB state.

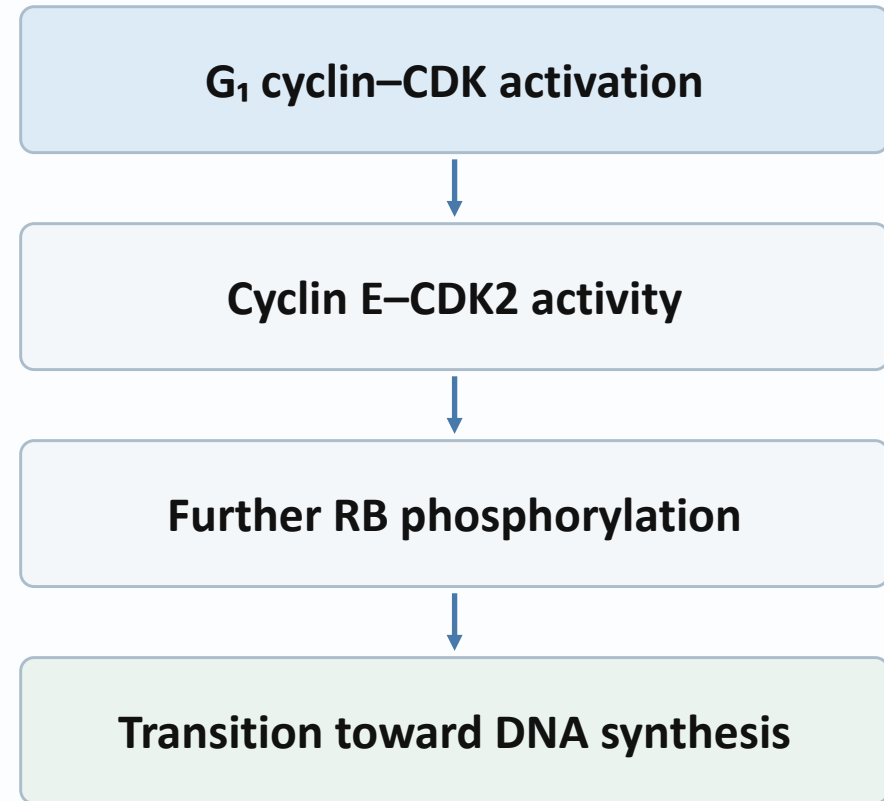
Schematic



Cyclin E–CDK2 supports passage into S phase

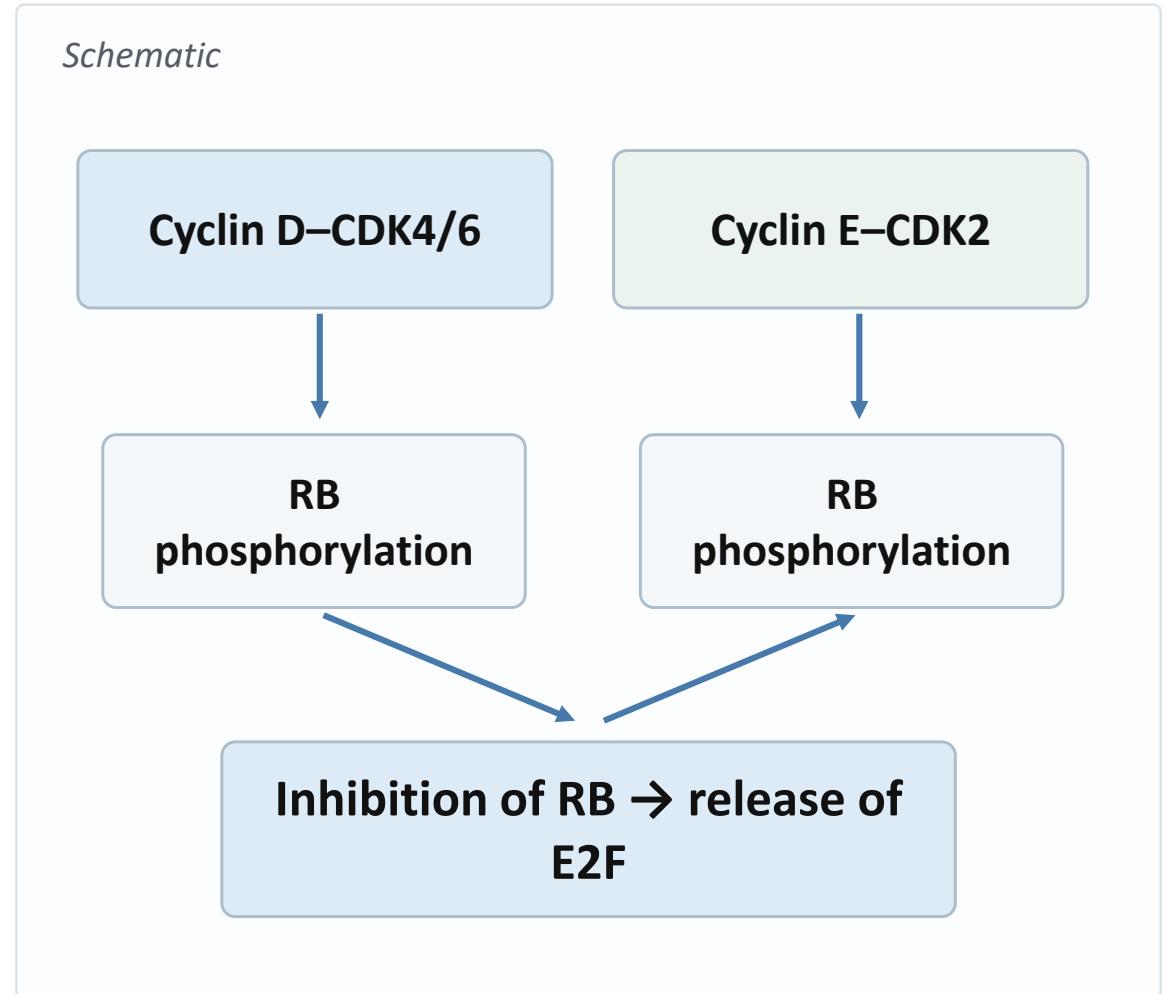
- Cyclin E–CDK2 is another complex contributing to G₁/S progression.
- High activities of the G₁-associated complexes promote RB hyperphosphorylation.
- The effect converges on E2F-dependent S-phase gene expression.

Schematic



Multiple kinase complexes converge on RB

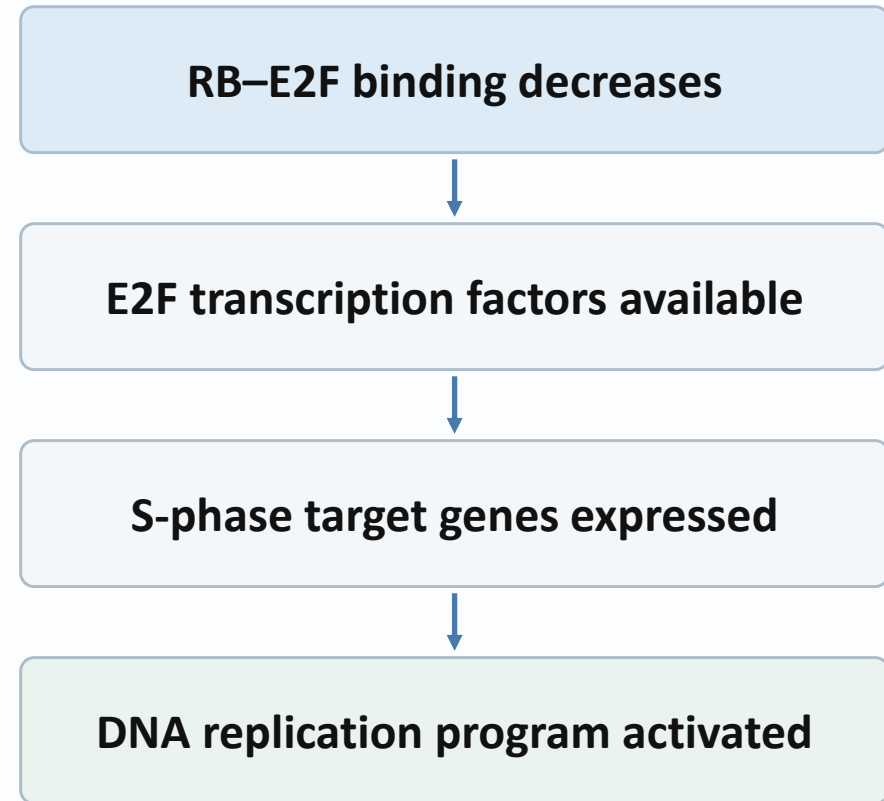
- CDK4–cyclin D, CDK6–cyclin D and CDK2–cyclin E all contribute.
- The biochemical endpoint is increased RB phosphorylation.
- Inhibited RB permits the transcriptional program needed for G₁/S transit.



E2F links RB activity to S-phase genes

- E2F is the key transcription-factor output of the RB pathway.
- Available E2F stimulates genes required for cell-cycle progression.
- This explains how an RB phosphorylation event becomes a proliferative phenotype.

Schematic



Growth-factor signaling pushes the RB gate open

- Mitogenic signals normally stimulate cyclin–CDK activity.
- The activated complexes promote RB hyperphosphorylation.
- This is a regulated physiological route through G₁/S in a responding cell.

Schematic

Growth factor engages receptor



Pro-growth signaling increases



Cyclin–CDK activity rises



RB inactivated → E2F release

Growth-inhibitory signals preserve RB activity

- Growth-inhibitory inputs can induce CDK inhibitors.
- Reduced kinase activity helps keep RB in its active form.
- Active RB maintains repression of E2F-dependent proliferation.

Schematic

Growth-inhibitory signaling



CDK inhibitor expression ↑



Cyclin-CDK activity restrained



Hypophosphorylated RB persists

TGF- β signals can oppose G₁/S passage

- TGF- β as a growth-inhibitory input in the RB checkpoint diagram.
- CDK inhibitors are part of the response to these inhibitory cues.
- The pathway protects the active RB state rather than directly replacing RB.

Schematic

TGF- β growth-inhibitory input



CDK inhibitor response



Less phosphorylation of RB

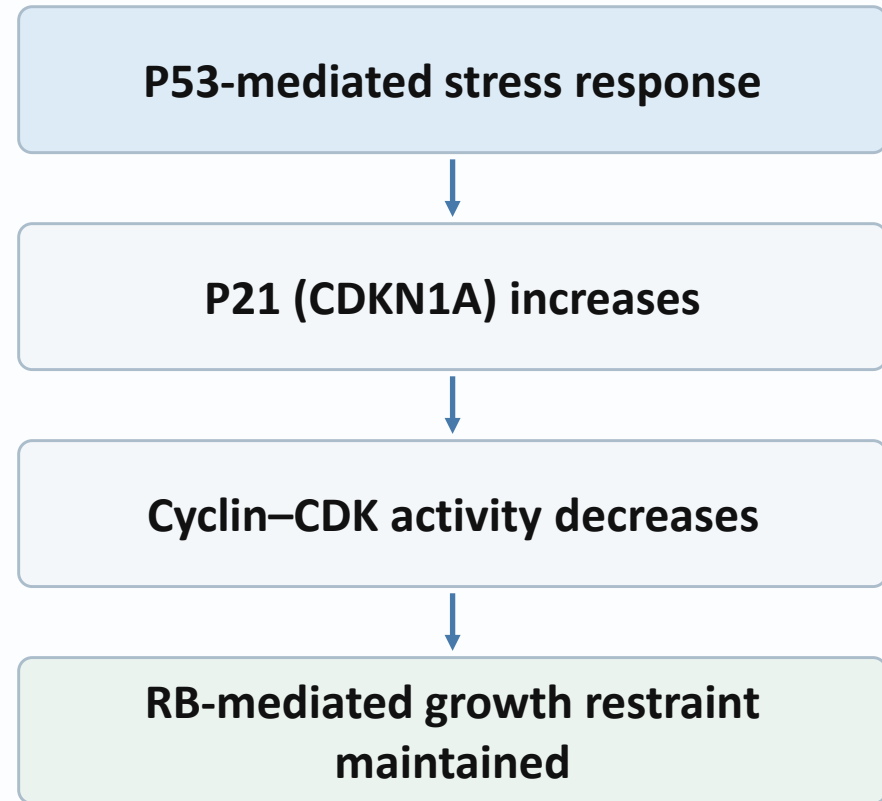


Cell-cycle entry restrained

P53 can restrain the RB gate through p21

- P53 can induce the CDK inhibitor p21.
- P21 inhibits cyclin–CDK complexes and favors RB-dependent arrest.
- This is a point of functional interaction, not identity, between RB and p53.

Schematic



INK4 inhibitors selectively target CDK4/6

- The INK4 family comprises p15, p16, p18 and p19.
- These proteins selectively restrain CDK4 and CDK6 complexes.
- The downstream consequence is preservation of functional RB.

Schematic

INK4 proteins: P15, p16, p18, p19



Cyclin D–CDK4/6 inhibited



RB phosphorylation is limited

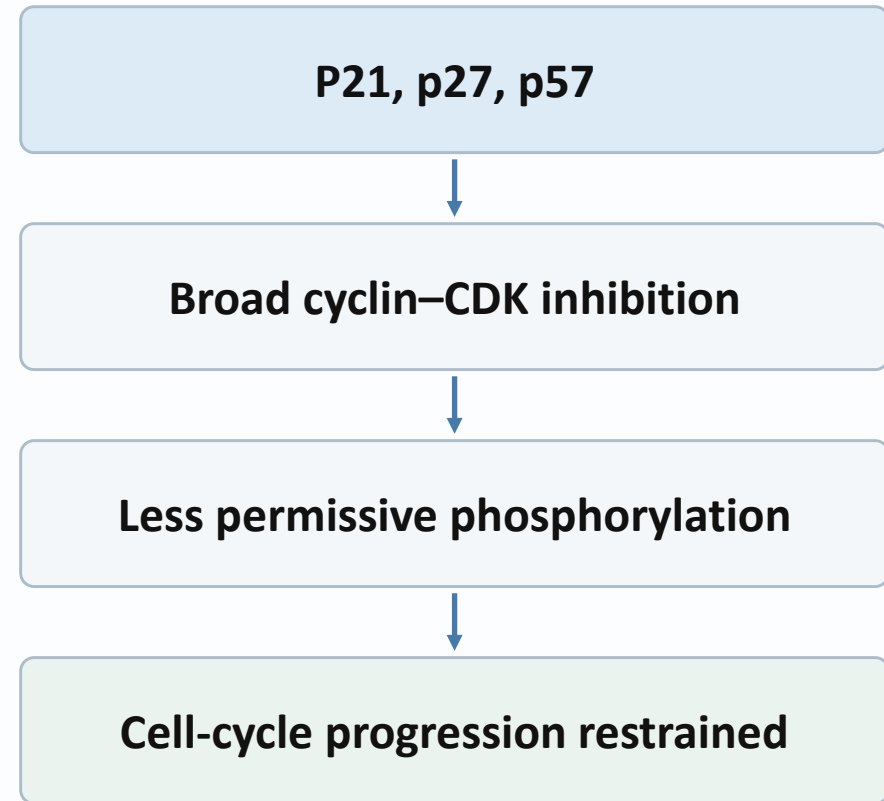


E2F repression maintained

The CIP/KIP family inhibits broader CDK activity

- P21, p27 and p57 belong to the CIP/KIP CDK-inhibitor family.
- They have broader activity than INK4 inhibitors.
- Loss of CDK inhibitor function can compromise checkpoints despite an intact RB gene.

Schematic



P16 and p21 restrain the same gate differently

- Both proteins suppress kinase activity upstream of RB.
- P16 is an INK4 family inhibitor; P21 belongs to CIP/KIP.
- They arise from distinct regulatory programs and must not be conflated.

Schematic

P16/INK4a

Encoded by CDKN2A

Targets cyclin D–
CDK4/6

Promotes active RB

P21/CIP1

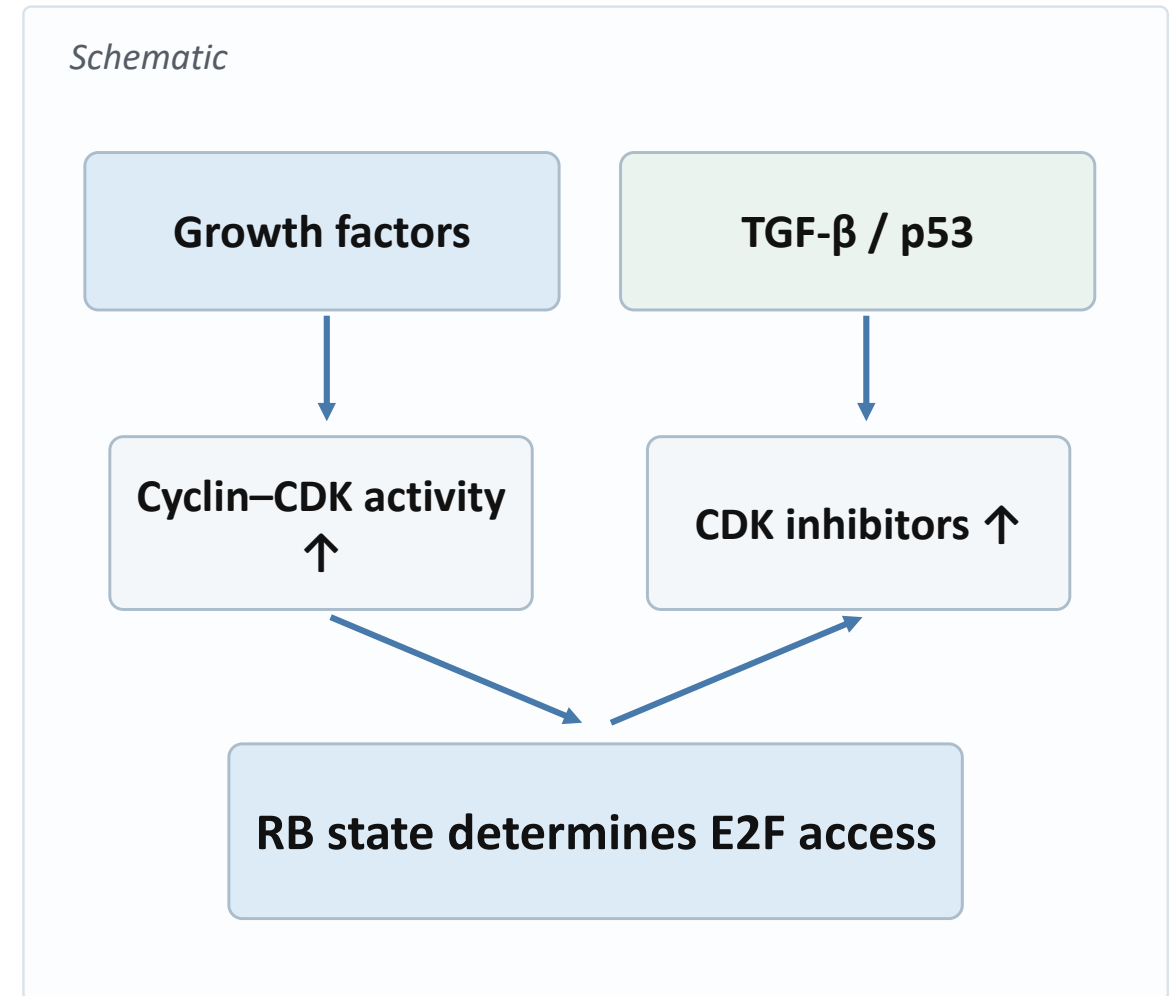
Encoded by CDKN1A

Induced by p53

Broad CDK inhibitor

Growth and inhibitory inputs meet at RB

- Extracellular growth cues promote kinase activity.
- Growth-inhibitory and stress pathways oppose those kinases.
- RB converts these competing signals into control of the E2F program.



Normal cell-cycle entry is conditional, not autonomous

- Normal progression requires a balance favoring cell-cycle advance.
- Checkpoint signaling can prevent inappropriate entry into S phase.
- Oncogenic lesions undermine this conditionality.

Schematic

**Adequate growth
signal**

**Strong inhibitory
signal**

Cyclin–CDK drive ↑

CDK inhibitors ↑

RB becomes inactive

RB remains active

E2F genes turn on

E2F remains
constrained

Two major classes of RB pathway failure

- Both RB alleles can acquire loss-of-function alterations.
- Alternatively, upstream regulatory lesions can drive excessive RB phosphorylation.
- The shared downstream consequence is loss of E2F restraint.

Schematic

Direct RB loss

Biallelic loss of RB

No effective RB brake

Retinoblastoma
prototype

Indirect RB inactivation

Cyclin/CDK gain

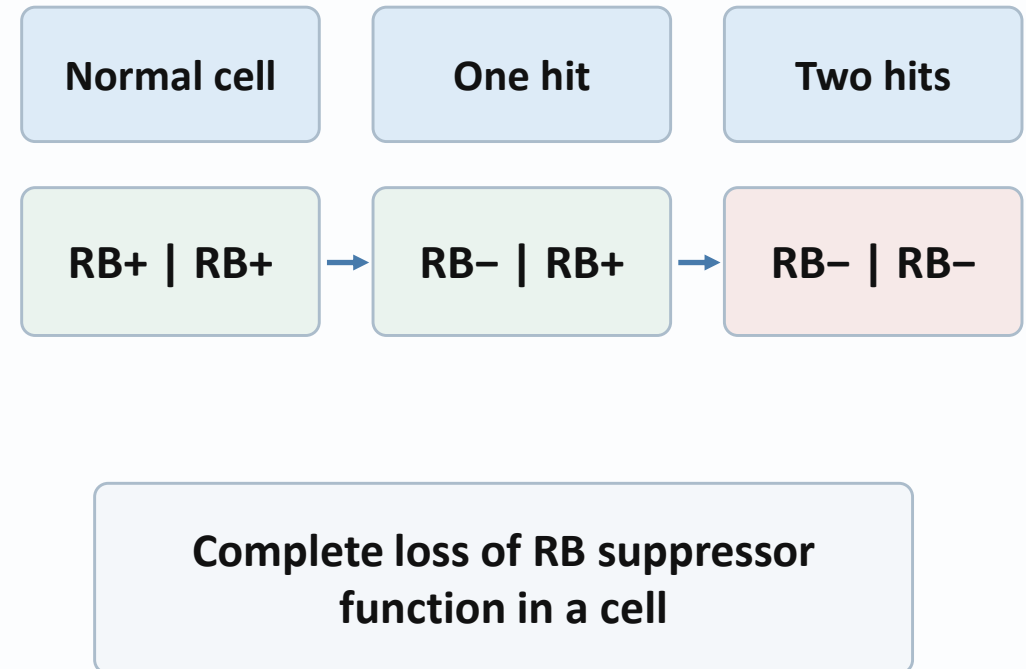
CDK inhibitor loss

Hyperphosphorylated
RB

Biallelic RB loss is a cellular genetic event

- Two loss-of-function hits must affect the RB alleles in the retinoblastoma model.
- One altered allele alone does not normally abolish cellular growth control.
- Loss of the remaining functional allele removes the suppressive brake.

Schematic



Knudson's model explains retinoblastoma initiation

- The two-hit hypothesis arose from inherited and sporadic retinoblastoma patterns.
- Both RB copies must lose function within a tumor-founding retinal cell.
- The model distinguishes inherited cancer predisposition from tumor-cell genotype.

Schematic

Two hits in the same retinal lineage

At least one RB allele functions initially



Separate loss-of-function events disable both alleles



Retinal cell escapes RB-mediated suppression

Familial retinoblastoma starts with a germline hit

- A germline pathogenic RB allele is inherited from a carrier parent.
- Every somatic cell begins with one defective and one functional copy.
- A later somatic alteration of the remaining allele can initiate retinal tumorigenesis.

Schematic

Inherited predisposition

Conception: One RB allele is already defective



All somatic cells carry that first RB alteration



A retinal second hit creates biallelic loss

Sporadic retinoblastoma requires two somatic hits

- Neither RB hit is inherited in the classical sporadic model.
- Two independent somatic events must accumulate in the same retinal lineage.
- This lower-probability sequence helps explain sporadic disease frequency.

Schematic

Sporadic pathway

Conception: Both RB alleles functional



First somatic hit in one retinal cell



Second somatic hit in its lineage → RB loss

The pathways converge on an identical cell state

- The origin of the first mutation differs between the two routes.
- Both result in tumor-founding cells with biallelic RB inactivation.
- The affected cell, not the family history alone, determines the tumor phenotype.

Schematic

Familial predisposition

First hit: Germline

Second hit: Retinal cell

Both RB copies lost

Sporadic initiation

First hit: Retinal cell

Second hit: Retinal cell

Both RB copies lost

Dominant inheritance coexists with recessive cellular loss

- An inherited RB defect produces an autosomal dominant predisposition to cancer.
- At the level of an individual cell, a second loss-of-function hit is needed.
- This resolves the apparent contradiction between family transmission and the two-hit mechanism.

Schematic

Patient/family level

Predisposition is inherited

Autosomal dominant pattern

One inherited abnormal allele

Individual cell level

Growth suppression often retained

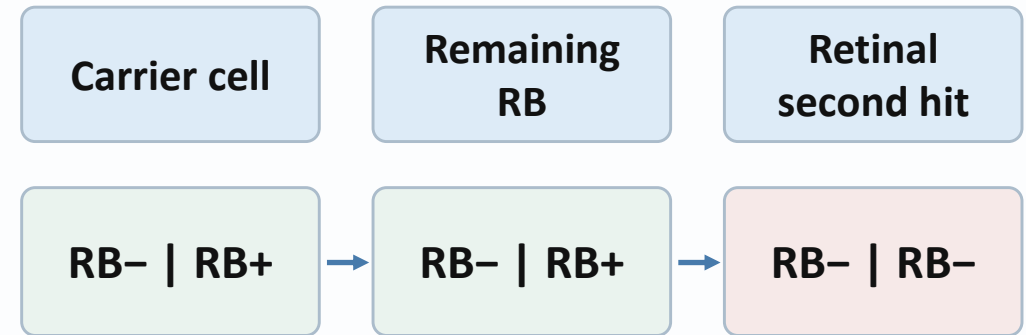
Both RB copies must fail

Cellular loss is recessive

Why a heterozygous carrier can have normal cells

- Most carrier cells retain one functional RB allele.
- This remaining copy usually maintains adequate cellular RB activity.
- Tumor formation follows additional loss in a susceptible retinal cell.

Schematic



Normal growth persists until the remaining allele is lost

Inherited RB defects increase opportunities for a second hit

- Every retinal cell in a germline carrier begins with a first RB hit.
- A second hit can occur independently in separate retinal cells.
- This helps explain the tendency toward bilateral or multiple retinal lesions.

Schematic

First mutation present from conception



Large number of retinal cells at risk



Second hits arise in individual cells



One or multiple retinal tumors may develop

Retinoblastoma patterns differ between clinical groups

- Approximately 40% of retinoblastomas as familial and 60% as sporadic.
- Bilateral involvement strongly fits a germline-predisposition mechanism.
- Laterality is a pattern, not a definitive molecular test.

Schematic

Familial/heritable

Sporadic

≈40% text

≈60% text

Often affects both eyes

Virtually always one
eye

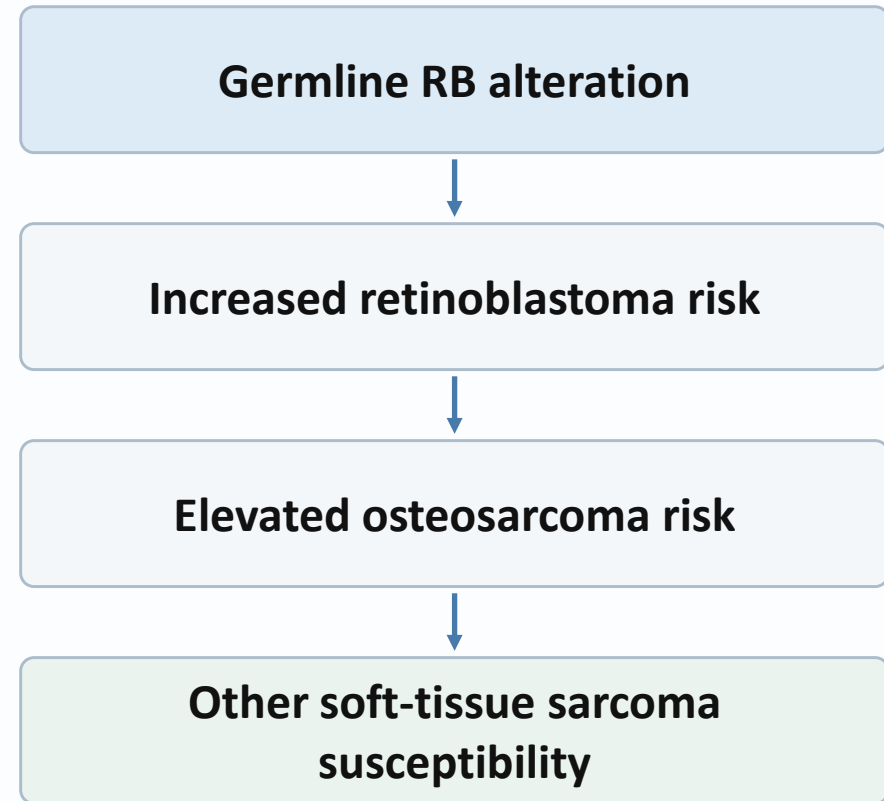
Germline
predisposition

Two somatic RB hits

A germline RB defect expands cancer susceptibility

- Carriers are at greatly increased risk of retinoblastoma.
- Robbins also associates germline RB alterations with osteosarcoma.
- Other soft-tissue sarcomas are part of the described hereditary risk spectrum.

Schematic



The two-hit model predicts somatic counterparts

- Study of familial retinoblastoma established a general tumor-suppressor paradigm.
- The same tumor suppressor can also be altered in sporadic malignancies.
- Inherited susceptibility and somatic oncogenesis share a molecular endpoint.

Schematic

Heritable RB-predisposition syndrome



RB loss in tumor cells



Somatic RB lesions also found in cancers



A common tumor-suppressor principle

Somatic RB mutations occur beyond the retina

- Somatic RB alterations are reported in several tumor types.
- The textbook specifically cites subsets of glioblastoma and lung, breast and bladder carcinomas.
- Direct RB mutation frequencies vary; A normal RB gene does not exclude pathway dysregulation.

Schematic

Retinoblastoma and osteosarcoma



Subsets of glioblastoma



Subsets of lung and breast carcinoma



Subsets of bladder carcinoma

Why retina-predominant susceptibility is unresolved

- The retinal predilection is not simply explained by RB expression.
- This tissue specificity remains incompletely understood.
- Proposed compensation by related proteins is a plausible contributor, not a complete proof.

Schematic

RB is expressed in many cell types

Germline RB defects preferentially lead to retinoblastoma

The complete tissue-selectivity mechanism is not established

RB family proteins may provide partial compensation

- Related RB-family proteins may substitute for RB in certain tissues.
- This is one hypothesis explaining the tumor spectrum in germline carriers.
- The source does not establish a complete mechanistic explanation.

Schematic

RB is part of a protein family



Related members may replace some functions



Functional redundancy varies by cell type



Retinoblasts may be especially vulnerable

The four key regulators of the RB axis

- P16/INK4a, cyclin D, CDK4 and RB.
- Lesions in these functionally connected regulators converge on cell-cycle escape.
- The broader network includes CDK6, cyclin E–CDK2 and upstream growth signals.

Schematic

P16/INK4a

Cyclin D

CDK4

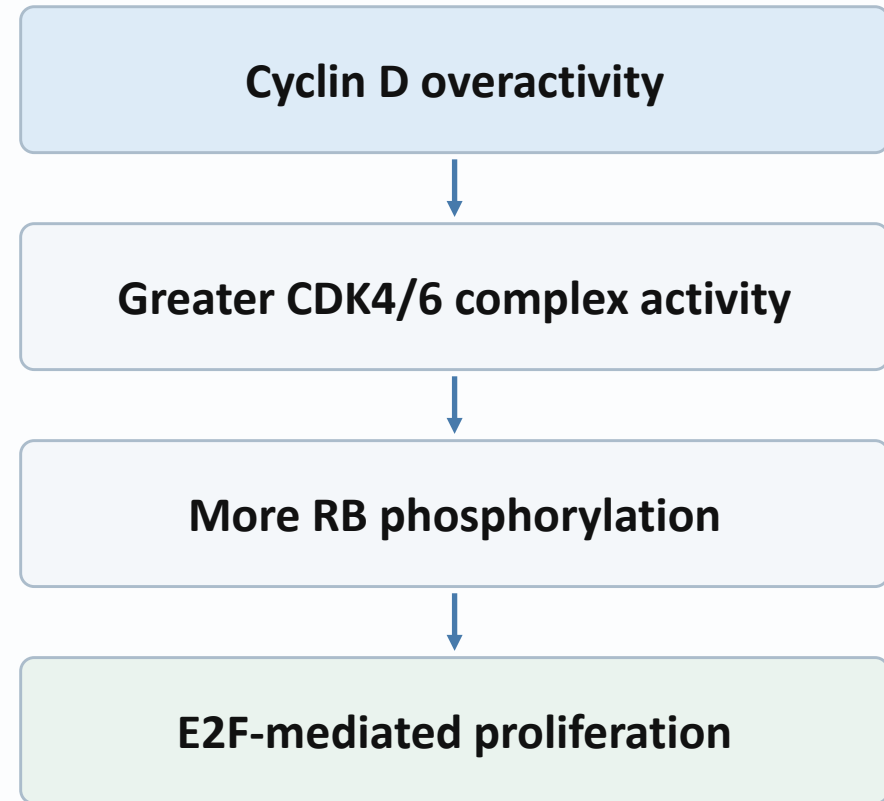
RB

Dysregulation of at least one node is common
in cancers

Cyclin D gain enhances RB phosphorylation

- D-cyclin genes can undergo gain-of-function changes in cancer.
- Increased cyclin D activity promotes the inhibitory RB phosphorylation state.
- This is oncogenic drive operating through a tumor-suppressor checkpoint.

Schematic



CDK4 gain can disable functional RB

- CDK4 gene amplification or activating alteration enhances kinase signaling.
- An intact RB gene may therefore fail to restrain proliferation.
- The causal route is aberrant phosphorylation, not necessarily RB1 mutation.

Schematic

CDK4 activation / amplification



Excess cyclin D–CDK4 activity



Hypophosphorylated RB depleted



E2F-driven G₁/S passage

P16/INK4a loss removes an upstream inhibitor

- P16 normally inhibits cyclin D-associated CDK4/6 activity.
- Loss of p16 permits increased phosphorylation and inactivation of RB.
- This is a tumor-suppressor defect upstream of the RB protein.

Schematic

CDKN2A / p16 function lost



CDK4/6 inhibition weakened



RB hyperphosphorylation favored



G₁/S entry facilitated

Upstream oncogenic signals also converge on RB

- RB function can be compromised without mutation of any of the four core regulators.
- The source cites receptor tyrosine kinases and RAS as upstream examples.
- Pathway analysis must therefore extend beyond sequencing RB1 alone.

Schematic

Activated RTK or RAS signaling



Cyclin/CDK expression or activity ↑



RB phosphorylation ↑



E2F-dependent cycle advance

Distinct mutations can produce an RB-loss phenotype

- Mutations in multiple genes can converge on the same endpoint.
- Functionally similar tumors need not share the same mutated gene.
- This is why the RB pathway is more broadly dysregulated than the RB1 locus alone.

Schematic

Direct loss

RB1 biallelic mutation

Functional RB absent

E2F liberated

Indirect mimic

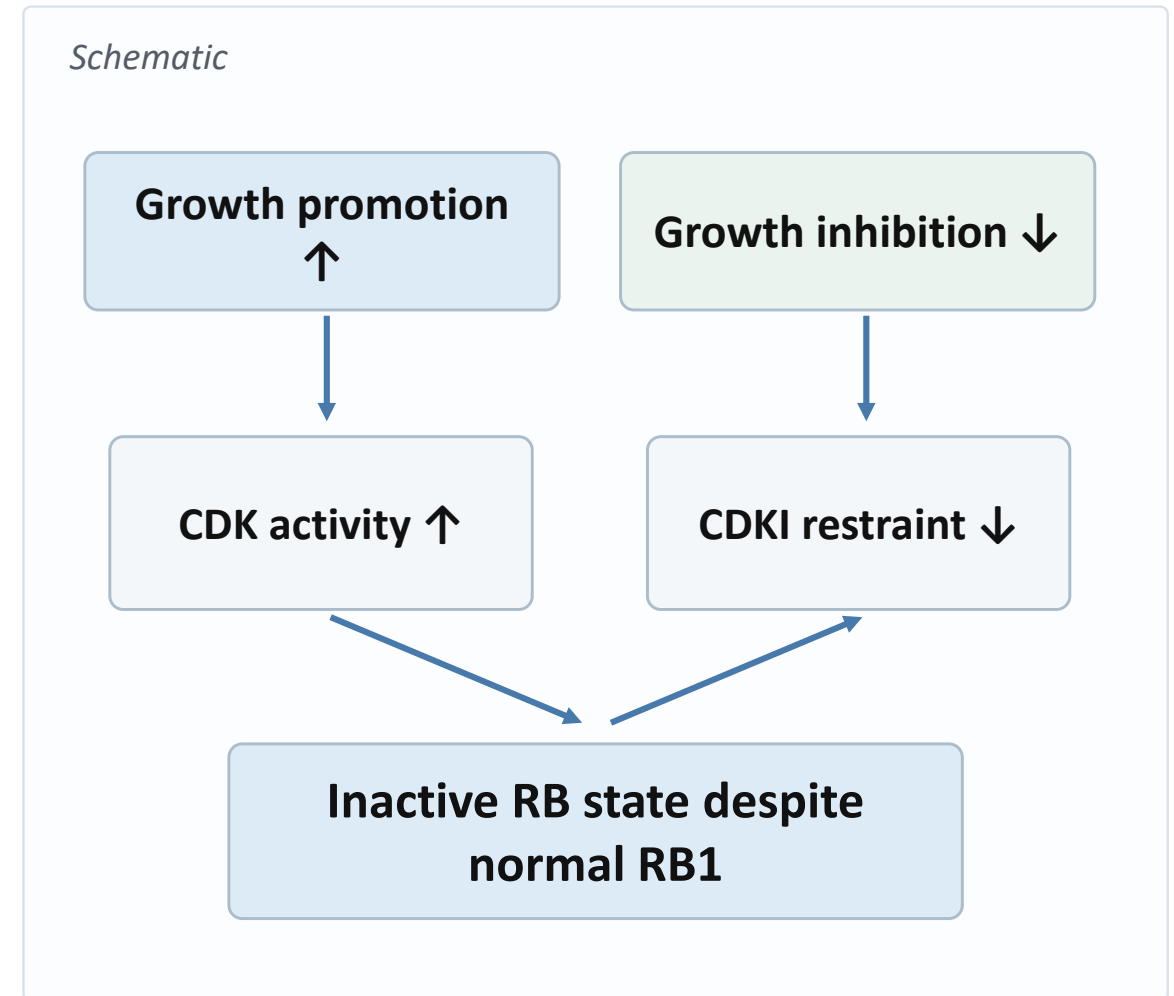
Cyclin D / CDK4 gain

P16 loss

E2F liberated

Pathway-level reasoning changes tumor interpretation

- Both increased pro-growth drive and diminished inhibition favor RB phosphorylation.
- The phosphorylated protein can be present but functionally inactive.
- A functional pathway readout may differ from a simple mutation inventory.



Oncogenic DNA viruses can bind RB directly

- Several DNA viruses encode RB-binding oncoproteins.
- Binding disrupts a protein–protein checkpoint rather than necessarily altering RB DNA.
- Released E2F favors cell-cycle progression.

Schematic

Viral oncoprotein expressed



RB pocket domain bound



RB–E2F sequestration lost

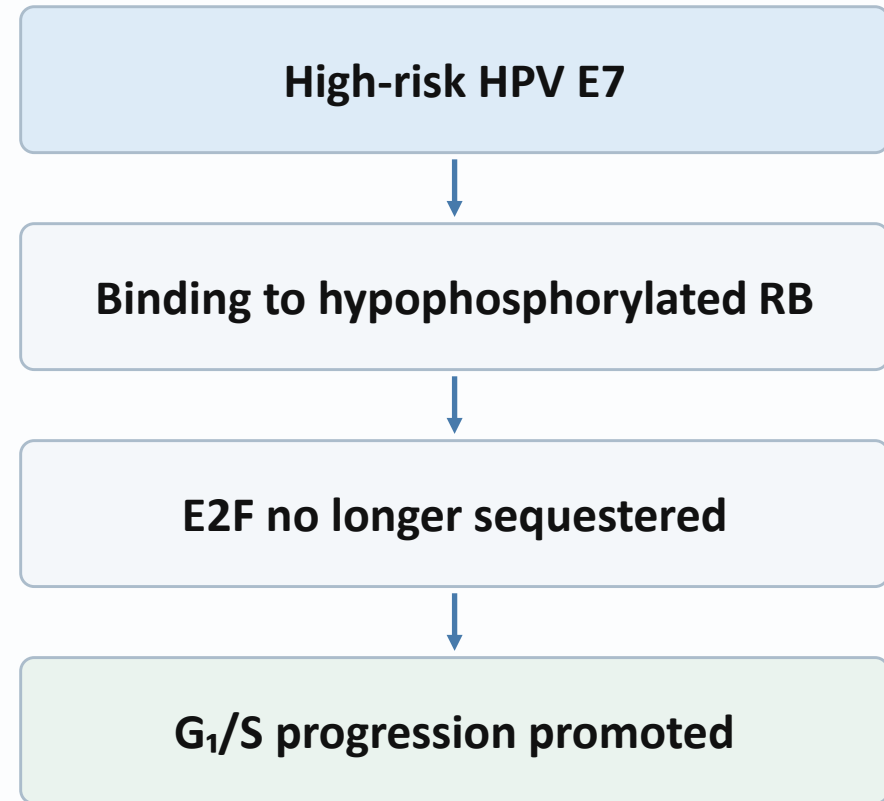


E2F-driven proliferation enabled

High-risk HPV E7 targets the RB pocket

- E7 proteins of high-risk HPV types such as HPV16.
- E7 binds the RB pocket used to associate with E2F.
- This is a direct nonmutational route to RB inactivation.

Schematic



Polyomavirus large T antigen also inhibits RB

- Polyomavirus large T antigen is another viral RB-binding protein.
- Its biochemical mechanism illustrates the conserved importance of the RB pocket.
- The slide depicts a molecular mechanism, not clinical prevalence or causation for a specific tumor.

Schematic

Polyomavirus large T antigen



Interaction with RB pocket



Loss of RB-mediated E2F restraint



Proliferative transcription allowed

Viral RB binding and CDK action share an endpoint

- Cyclin–CDK signaling and viral oncoproteins disable RB differently.
- Both mechanisms weaken RB sequestration of E2F.
- This is biochemical convergence, not equivalence of genetic events.

Schematic

Kinase-mediated

RB
hyperphosphorylation

E2F released

Cell-cycle entry favored

Viral-protein-mediated

RB pocket bound by E7
/ T

E2F released

Cell-cycle entry favored

RB inactivation is not always an RB1 mutation

- RB status must be interpreted on both genetic and protein-functional levels.
- Upstream activation and viral binding can alter RB output while RB1 remains intact.
- A mutation-negative RB1 result does not demonstrate a normal RB signaling axis.

Schematic

Pathway mechanism

Does RB1 have to mutate?

Biallelic RB loss

Yes, for direct RB loss

Cyclin/CDK activation

No

CDK inhibitor loss

No

CDK4/6 inhibitors illustrate translational relevance

- Clinical effectiveness of CDK4/6 inhibitors in certain forms of breast cancer.
- Their pathway target lies upstream of RB phosphorylation.
- Do not derive unprovided eligibility criteria or predictive performance from this excerpt.

Schematic

Cyclin D–CDK4/6 phosphorylates RB

CDK4/6 inhibitors are used in certain breast cancers

The supplied source provides no patient-selection algorithm

Mechanistic diagrams do not establish clinical biomarkers

- A mechanistic dependency is not automatically a validated predictive biomarker.
- The excerpt does not define a testing assay, threshold or treatment-selection rule.
- Clinical decision criteria need independent current verification beyond this source.

Schematic

RB is a key G₁/S regulator

CDK4/6 is a plausible therapeutic target in some contexts

Predictive testing thresholds are not given in this source

Case: A germline RB alteration precedes retinal tumor

- A child carries one pathogenic RB allele in all somatic cells.
- Which additional event is necessary for the classic retinoblastoma mechanism?
- A second somatic RB loss must remove the remaining functional allele.

Schematic

Explain the second-hit requirement

Child inherits RB- / RB+



A susceptible retinal cell loses RB+



RB- / RB- cell can proliferate abnormally

Case: Unilateral tumor without inherited predisposition

- A child has sporadic retinoblastoma in one eye.
- The classical molecular model requires two acquired RB inactivation events.
- A single tumor does not itself prove the absence of germline susceptibility.

Schematic

Apply the sporadic pathway

Retinal cell begins RB+ / RB+



Two somatic hits occur in one lineage



Biallelic RB loss permits tumor formation

Case: RB1 intact but cyclin D–CDK4 overactive

- A cancer has no identified RB1 mutation but increased CDK4 activity.
- Its RB protein can still be functionally disabled by phosphorylation.
- This is indirect checkpoint loss rather than biallelic RB1 loss.

Schematic

Cyclin D–CDK4 overactivity



RB becomes hyperphosphorylated

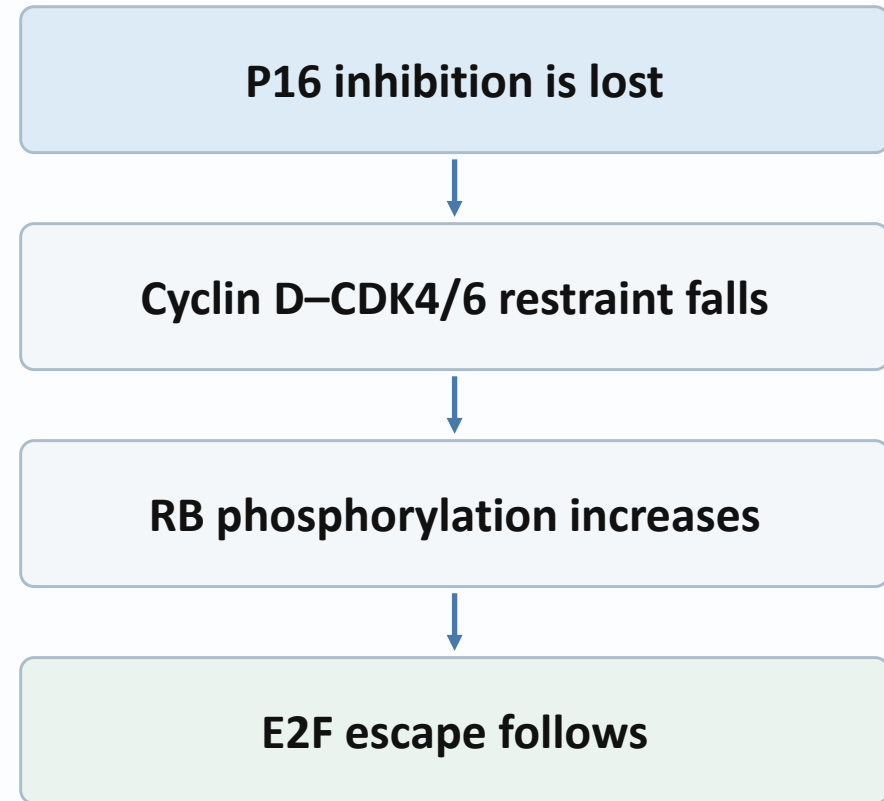


E2F transcription increases

Case: P16 loss and a preserved RB1 locus

- Loss of p16 can compromise the checkpoint while RB1 DNA remains normal.
- The immediate disinhibited enzymes are CDK4 and CDK6.
- The final molecular effect is a shift toward inactive RB.

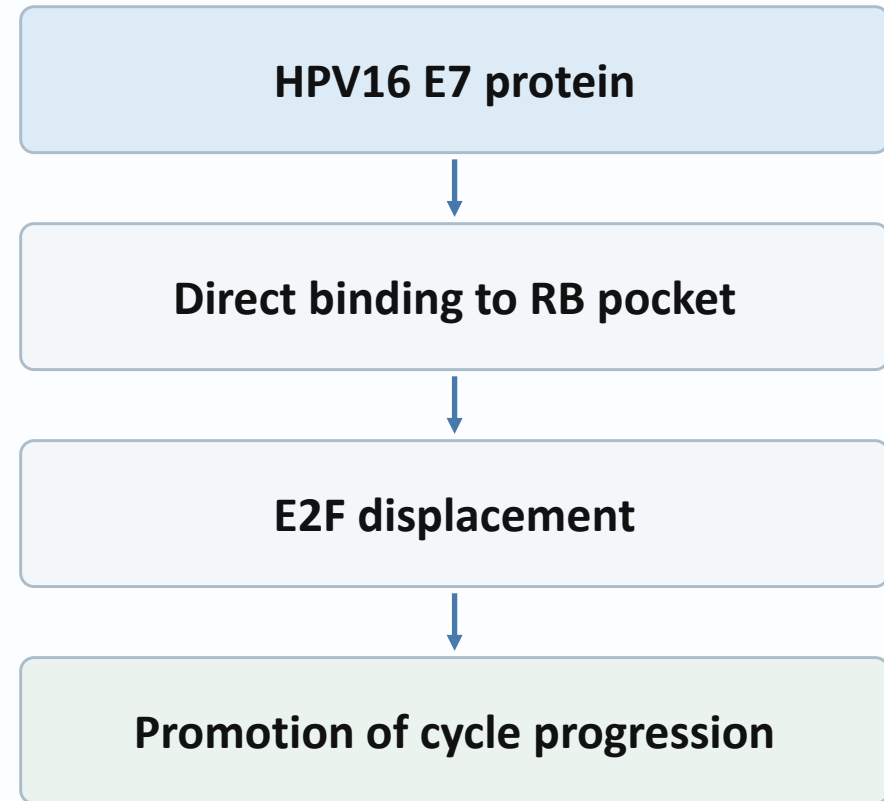
Schematic



Case: HPV16 E7 with no RB1 sequence alteration

- The viral protein occupies the RB pocket used to bind E2F.
- Consequent RB inhibition does not require an RB1 gene mutation.
- This shows why pathway-level and gene-level descriptions must be distinguished.

Schematic



Case: DNA stress engages the p53–p21–RB route

- P53 can impose cell-cycle arrest through induction of p21.
- CDK inhibition protects hypophosphorylated, active RB.
- Disturbance at several levels can undermine this restraint.

Schematic

Stress response activates p53



P21 CDK inhibitor increases



RB phosphorylation is restrained



G₁/S arrest becomes possible

Diagnose the checkpoint lesion, not just the gene name

- The same G₁/S escape phenotype can arise through genetically diverse alterations.
- Mechanistic classification separates upstream kinase changes from RB protein loss.
- Viral RB binding is an additional nonmutational mechanism.

Schematic

RB1 loss

Cyclin D gain

CDK4 activation

P16 loss

Different lesions converge on functional E2F
release

Common interpretive errors in the RB pathway

- An intact RB1 coding sequence is not proof of a competent RB checkpoint.
- Autosomal dominant transmission does not contradict recessive tumor-cell loss.
- A molecular mechanism should not be promoted to an unverified clinical test criterion.

Schematic

RB1 genotype and RB activity are different readouts

Phosphorylation, kinase inputs and viral binding all matter

Do not equate unilateral disease with guaranteed sporadic genotype

Synthesis: Normal RB limits entry into S phase

- RB exerts its brake through E2F binding.
- Cyclin–CDK hyperphosphorylation weakens this inhibition.
- Normal mitogenic and inhibitory signals tune this molecular switch.

Schematic

Active hypophosphorylated RB



E2F remains bound



S-phase genes repressed



G₁/S progression restrained

Synthesis: Four routes converge on failed restraint

- Direct loss removes the RB protein's function.
- Excess CDK activity or deficient CDK inhibition promotes RB inactivation.
- DNA viral oncoproteins directly disrupt RB–E2F sequestration.

Schematic

Biallelic RB loss

Cyclin D gain

CDK4 activation

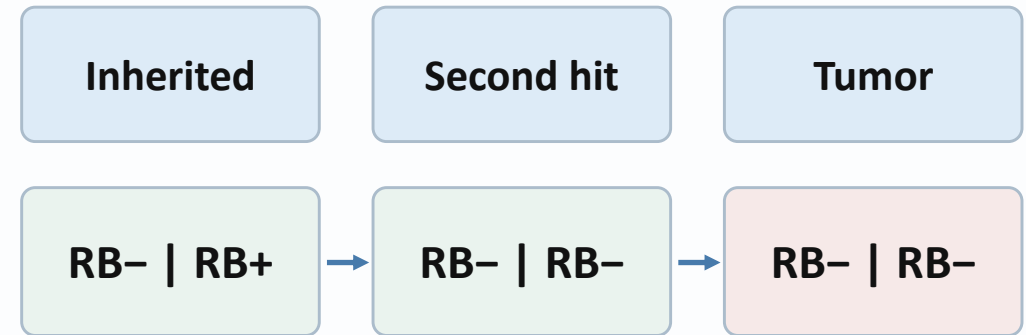
CDK inhibitor loss

Plus viral E7 / large T binding of RB

Synthesis: Inherited predisposition versus tumor initiation

- An inherited first hit increases opportunities for somatic second hits.
- Sporadic retinoblastoma acquires both hits within the same retinal lineage.
- In both settings, biallelic loss is the classical cell-level initiating event.

Schematic



Dominant inherited risk; Recessive loss in the tumor cell

Source material and interpretation boundaries

Primary source

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026), Chapter 7, pp. 256–262; Chapter 1, pp. 24–25.

Source excerpts used

RB: Governor of Proliferation; Insensitivity to Growth Inhibition; Cyclins and Cyclin-Dependent Kinases; cell-cycle checkpoint overview.

The diagrams are original, simplified, editable schematics—not reproduced textbook figures or clinical specimens.