

TP53: Guardian of the Genome

Stress sensing • genome integrity • tumor suppression

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Learning objectives

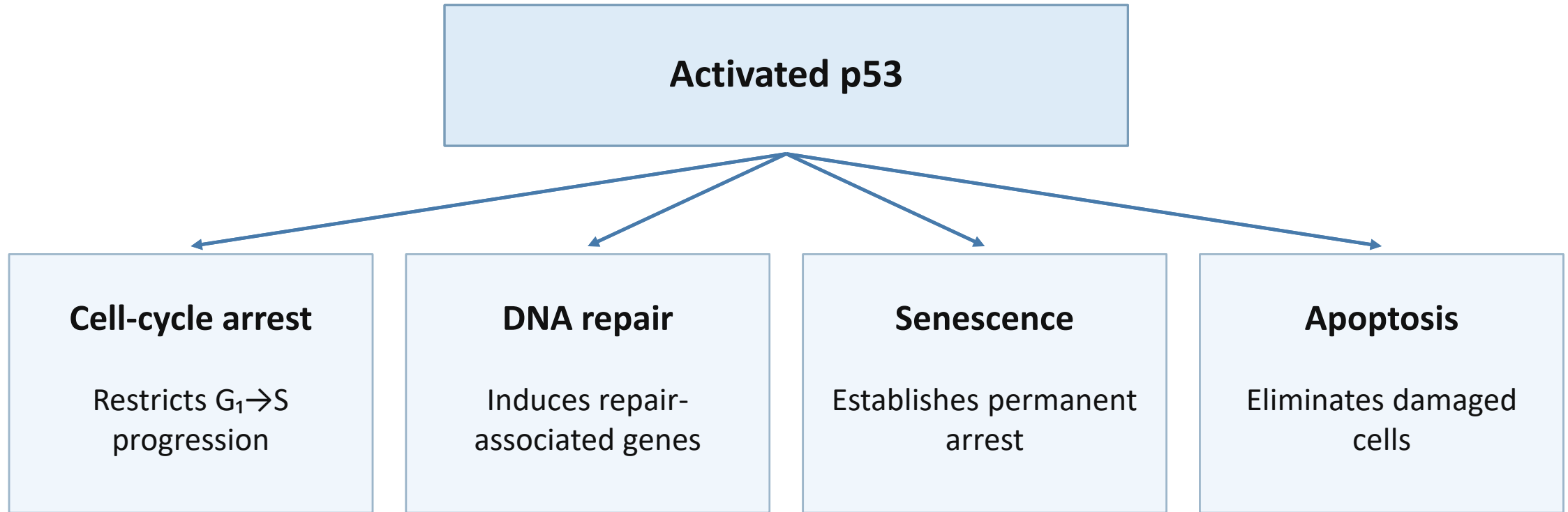
- Explain how p53 integrates DNA damage and oncogenic stress signals.
- Trace p53-mediated G₁ arrest, repair, senescence, and apoptosis.
- Distinguish genetic TP53 loss from functional inactivation of p53.
- Interpret inherited TP53 predisposition and therapy-response implications.

Why “guardian of the genome”?

P53 prevents propagation of cells with potentially oncogenic genomic damage.

- A temporary pause creates an opportunity for repair.
- Persistent or irreversible damage may trigger permanent arrest or cell death.
- Loss of this restraint allows genetically abnormal clones to expand.

Four protective activities of p53



These responses together constrain malignant transformation.

TP53 gene and p53 protein

- TP53 is a tumor suppressor gene located at chromosome 17p13.1.
- TP53 encodes the p53 transcription factor.
- The gene is distinguished from its protein product in mechanistic discussions.
- The central function is cellular stress-responsive control of gene expression.

TP53 is a frequent cancer target

The source describes TP53 as the most frequently mutated gene in human cancer.

- Loss-of-function mutations are reported in more than 50% of cancers.
- The statement refers to the textbook's overall cancer estimate—not a uniform rate across tumor types.

Cancer types with TP53 abnormalities

- TP53 mutations occur across a very broad spectrum of malignancies.
- The Robbins examples include carcinomas of lung, colon, and breast.
- Tumor type alone does not establish a specific TP53 genotype.
- Different cancers can also impair p53 through regulators rather than the TP53 gene itself.

Somatic and inherited TP53 mutations

Somatic setting

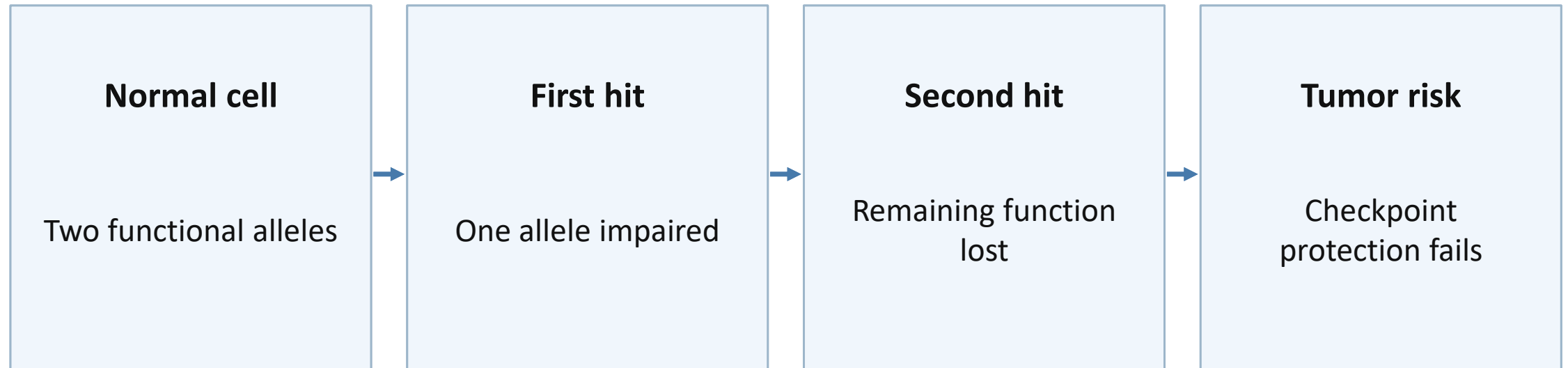
- Alteration acquired in tumor-lineage cells
- Most cancers have somatic TP53 abnormalities
- Loss of both functional alleles is typical model

Inherited setting

- One mutated allele is present in the germline
- Remaining normal allele is susceptible to an additional hit
- Creates predisposition rather than a tumor at birth

Both settings converge on loss of a protective p53 response.

The two-hit tumor suppressor model



Schematic of biallelic inactivation; Inherited carriers begin with the first hit.

Genetic loss is not the only route

TP53 mutation

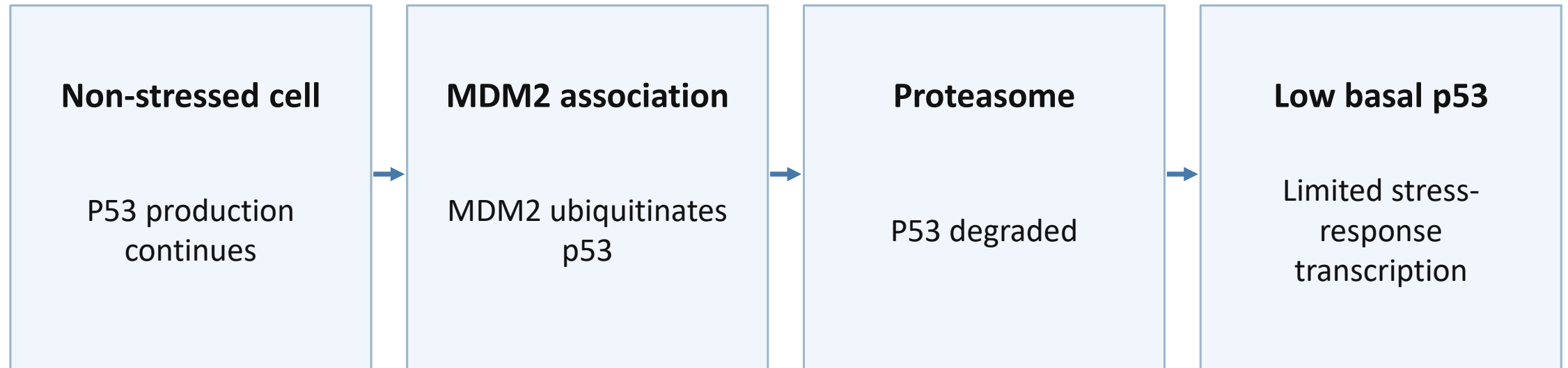
- Coding gene itself is altered
- P53 response may be absent or defective
- Common route in many carcinomas

P53 pathway suppression

- TP53 sequence may remain normal
- Regulatory proteins suppress p53 abundance/activity
- Illustrated by MDM2 excess or viral E6

A normal TP53 coding sequence does not guarantee normal p53 function.

Constitutive p53 turnover in healthy cells



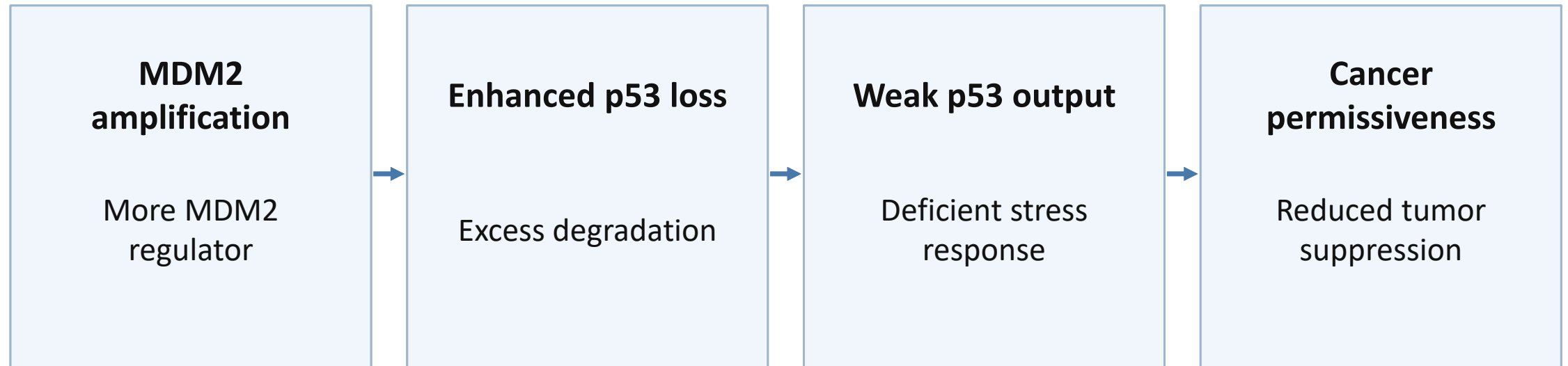
Rapid degradation keeps p53 protein at very low levels during ordinary growth.

MDM2 is a key negative regulator

MDM2 is an enzyme that ubiquitinates p53 and promotes proteasomal degradation.

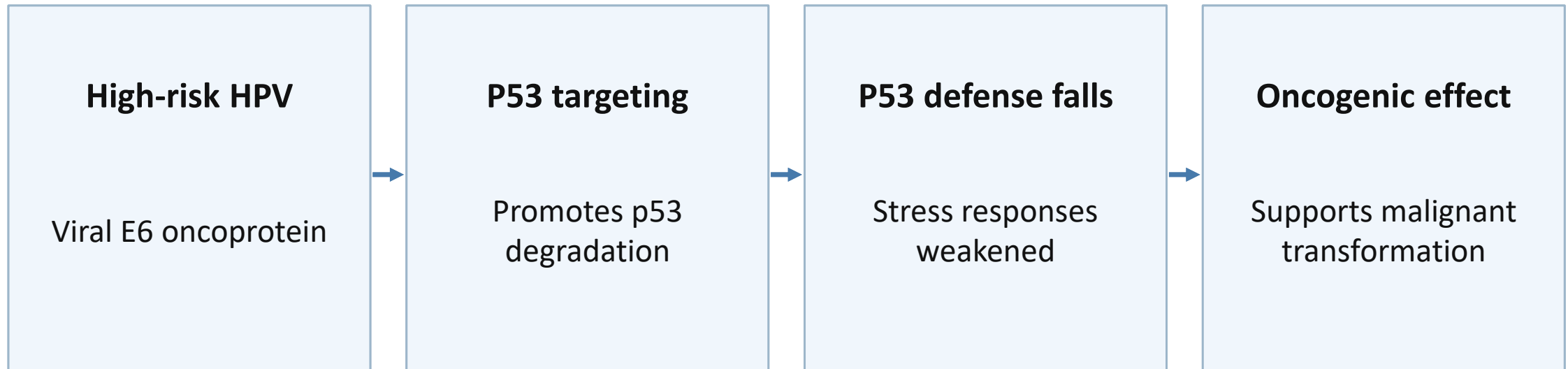
- The p53–MDM2 interaction restrains p53 in the absence of stress.
- To activate p53, a stressed cell must relieve this inhibitory interaction.

MDM2 gene amplification and p53 dysfunction



MDM2 amplification in 33% of human sarcomas; This is a source-specific figure.

High-risk HPV E6 inactivates p53



Examples in the source: Cervical carcinoma and head-and-neck squamous carcinoma.

Mechanisms that lower p53 function

Route	Primary alteration	Functional consequence
TP53 loss	Gene mutation/inactivation	Defective p53-dependent transcription
MDM2 excess	Regulator overexpression/amplification	Enhanced p53 degradation
Viral E6	High-risk HPV oncoprotein	Targeted p53 degradation

Distinct upstream causes can converge on defective p53-mediated tumor suppression.

Cellular stresses detected by the p53 network

- DNA damage is a major activating stimulus.
- Other stresses include hypoxia and shortened telomeres.
- Excessive signaling from oncogenes such as RAS and MYC can also activate p53.
- Different inputs converge on stabilization of the p53 protein.

Two routes to p53 stabilization

Cellular stress

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graph TD; A[Cellular stress] --> B[DNA damage]; A --> C[Hypoxia]; A --> D[Oncogenic signaling]; B --> E[ATM/ATR kinase pathway]; C --> F[ATM/ATR-associated response]; D --> G[P14/ARF-MDM2 pathway];
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DNA damage

ATM/ATR kinase pathway

Hypoxia

ATM/ATR-associated response

Oncogenic signaling

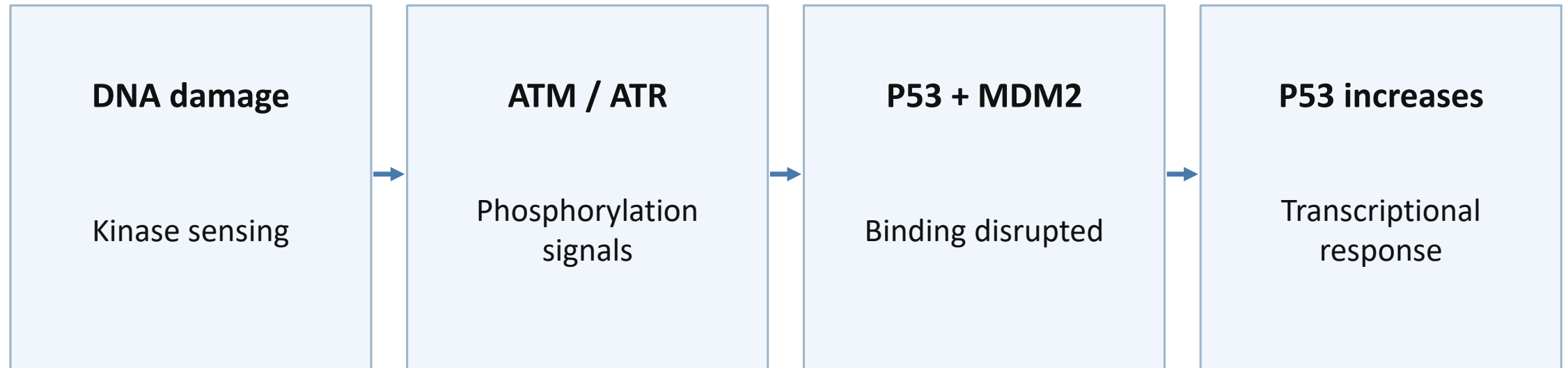
P14/ARF-MDM2 pathway

Different sensors converge on greater availability of p53.

ATM and ATR: Stress-response kinases

- ATM denotes ataxia-telangiectasia mutated.
- ATR denotes ataxia-telangiectasia and Rad3-related.
- They detect differing DNA lesion/stress contexts, but both can stabilize p53.
- Their activation leads to phosphorylation of p53 and MDM2.

DNA damage activates p53



Phosphorylation disrupts p53 degradation and increases its cellular abundance.

Why phosphorylation matters

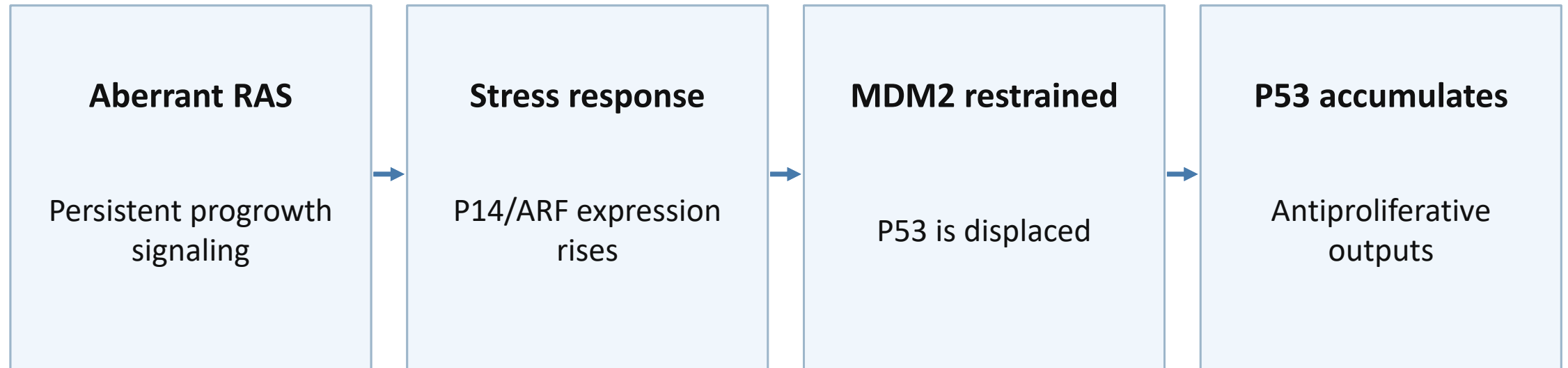
Stabilization precedes effective p53-driven transcription.

- Stress-induced phosphorylation interferes with the p53–MDM2 degradation axis.
- The resulting increase in p53 abundance enables induction of downstream targets.

ATM and inherited cancer predisposition

- ATM was first identified in patients with ataxia-telangiectasia.
- The textbook associates germline ATM mutations with defects in repair of some DNA lesions.
- These individuals have an increased incidence of cancer.
- This illustrates why upstream DNA damage sensing also protects against neoplasia.

Oncogenic RAS signaling evokes p53



The intermediate mechanisms as incompletely understood.

P14/ARF links oncogenic stress to p53

- The CDKN2A tumor suppressor locus encodes p14/ARF.
- Oncogenic growth signals can increase p14/ARF expression.
- P14/ARF associates with MDM2 and displaces p53 from inhibitory regulation.
- This is a different route to p53 stabilization from ATM/ATR signaling.

DNA-damage versus oncogenic-stress inputs

DNA damage / hypoxia

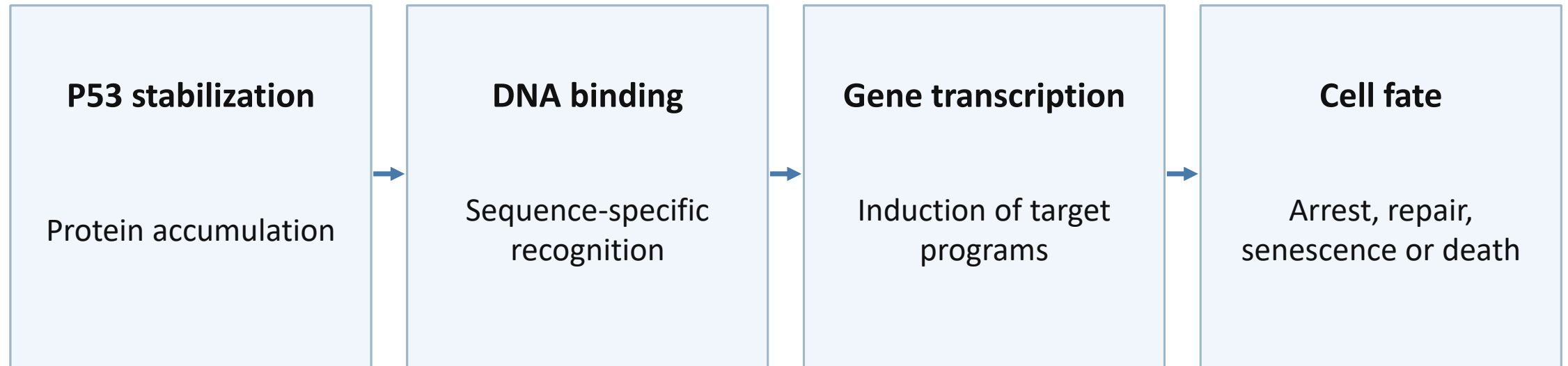
- Input: Lesion or oxygen-related stress
- Mediator: ATM and ATR kinases
- Effect: P53 and MDM2 phosphorylation

Aberrant growth signals

- Input: Excessive RAS or MYC signaling
- Mediator: P14/ARF from CDKN2A
- Effect: P53 released from MDM2 restraint

Both pathways release p53 from its basal inhibitory state.

Activation converts p53 into a gene regulator

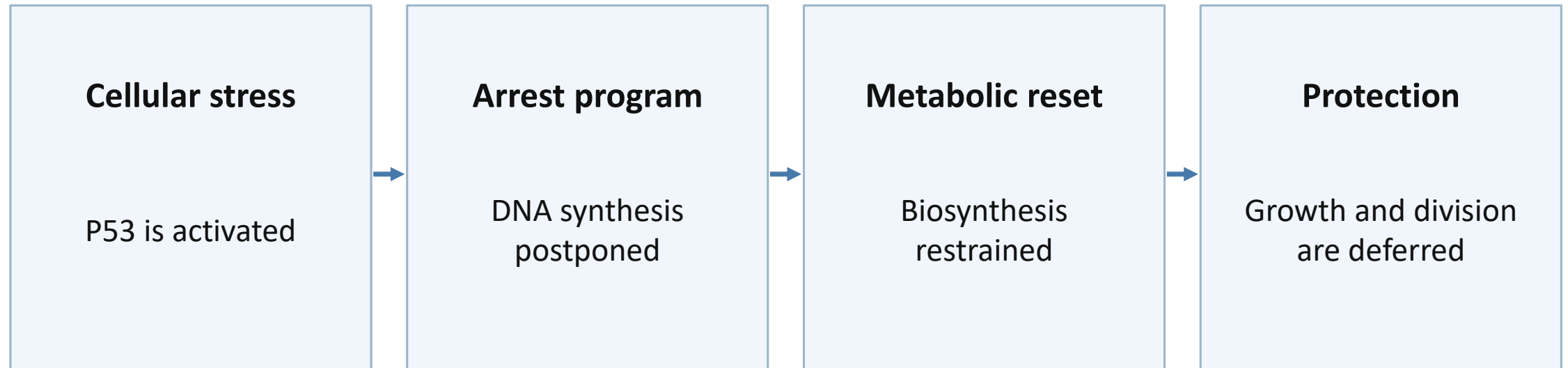


The source states that p53 controls hundreds of target genes.

Three broad classes of p53 target genes

- One group induces cell-cycle arrest.
- Another promotes apoptosis.
- A third reduces anabolic metabolism or enhances catabolic functions.
- DNA-repair programs are also induced as part of the protective stress response.

P53 coordinates proliferation and metabolism



The source links reduced macromolecule synthesis to cessation of proliferation.

Three major cell-fate routes

Sustained p53 response

Transient arrest

Allows lesion repair

Senescence

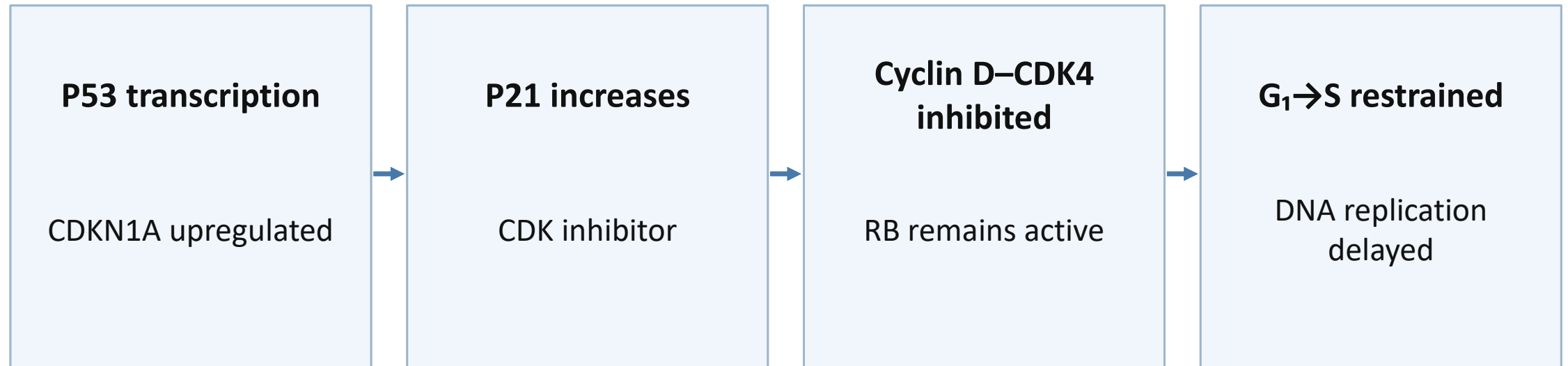
Permanent arrest

Apoptosis

Removes damaged cells

The selected outcome depends on context; The mechanism is not a rigid universal switch.

P53 initiates the G₁ checkpoint



A causal link between p53 and RB-mediated inhibition of cell-cycle progression.

CDKN1A encodes p21

P21 is a cyclin-dependent kinase inhibitor induced by p53.

- It inhibits cyclin D–CDK4 complexes in the Robbins model.
- Its action keeps RB in the active, hypophosphorylated state.

Active RB versus inactive RB

Active, hypophosphorylated RB

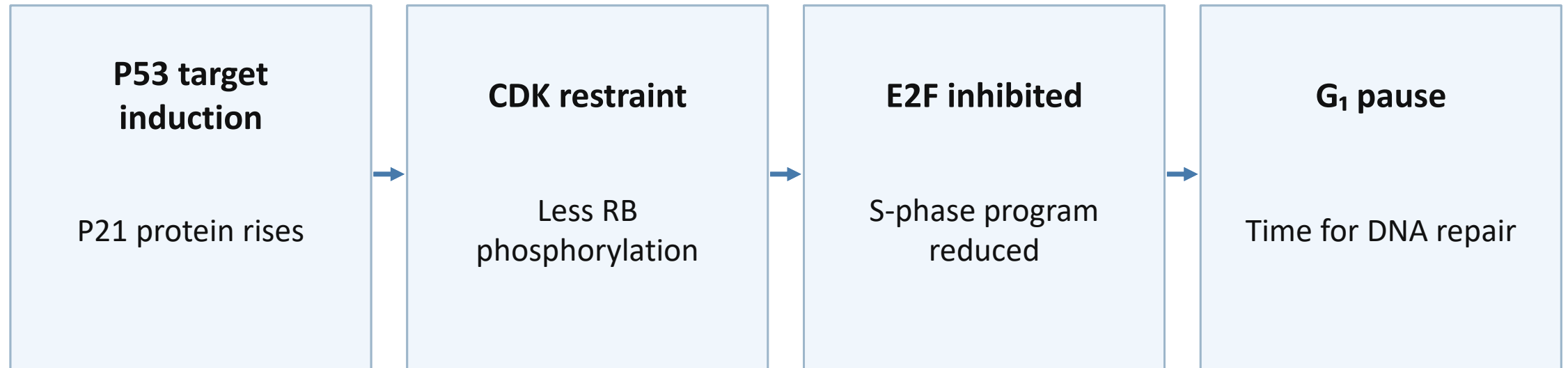
- Sequesters E2F transcription factors
- Restricts transcription needed for S phase
- Supports the p53-induced checkpoint

Inactive, hyperphosphorylated RB

- Releases E2F-driven transcription
- Supports G₁-to-S transition
- Can bypass checkpoint restraint

P53 and RB connect two major tumor suppressor pathways.

How p21 enforces the cell-cycle pause



The signal restricts entry into S phase while damage is assessed.

The pause preserves genomic integrity

A damaged cell should not replicate an unrepaired DNA template.

- Transient arrest makes repair possible before the next S phase.
- When the lesion is resolved, the checkpoint can be released.

P53 supports DNA repair



GADD45 is explicitly named as a repair-enhancing p53 target.

Successful repair terminates the p53 response

- Repair reduces the stimuli responsible for p53 stabilization.
- The inhibitory MDM2-regulated turnover can again limit p53 abundance.
- P21-dependent arrest subsides and cell cycling may resume.
- Successful repair restores growth without transmitting the original damage.

Transient arrest and senescence

Transient arrest

- Occurs promptly after p53 activation
- Potentially reversible after repair
- Preserves the possibility of normal cycling

Senescence

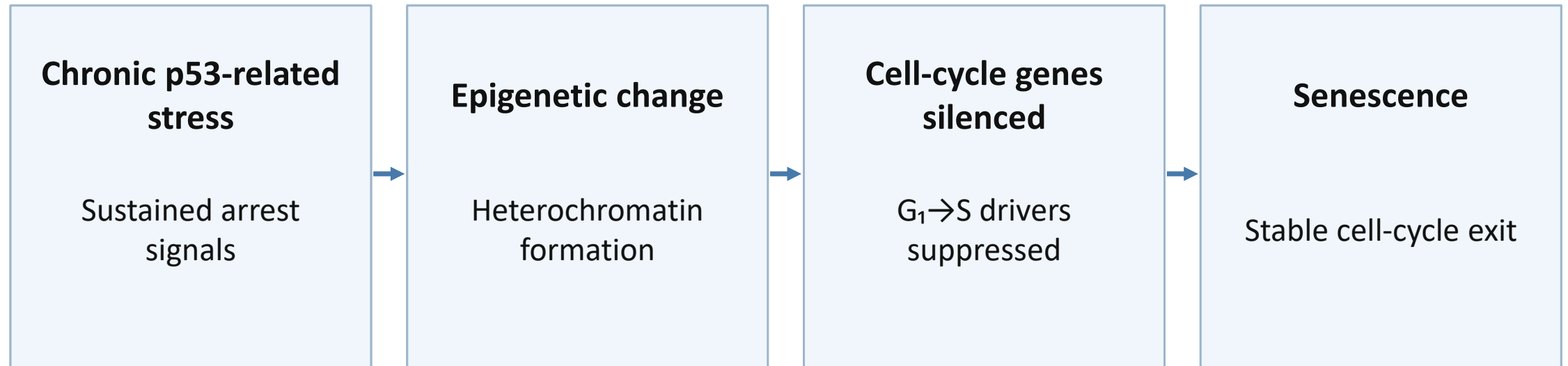
- Persistent or permanent cell-cycle block
- Associated with changed morphology and gene expression
- Prevents future clonal proliferation

The decisive contrast is reversibility, not whether the cell remains alive.

P53-induced senescence

- Senescence represents permanent cell-cycle arrest.
- It is accompanied by characteristic morphology and gene-expression changes.
- The source distinguishes it from the transient damage-induced pause.
- Although senescent cells persist, they cannot continue proliferating.

One proposed mechanism of senescence



Robbins explicitly describes the precise fixation mechanism as incompletely understood.

Stresses that can promote senescence

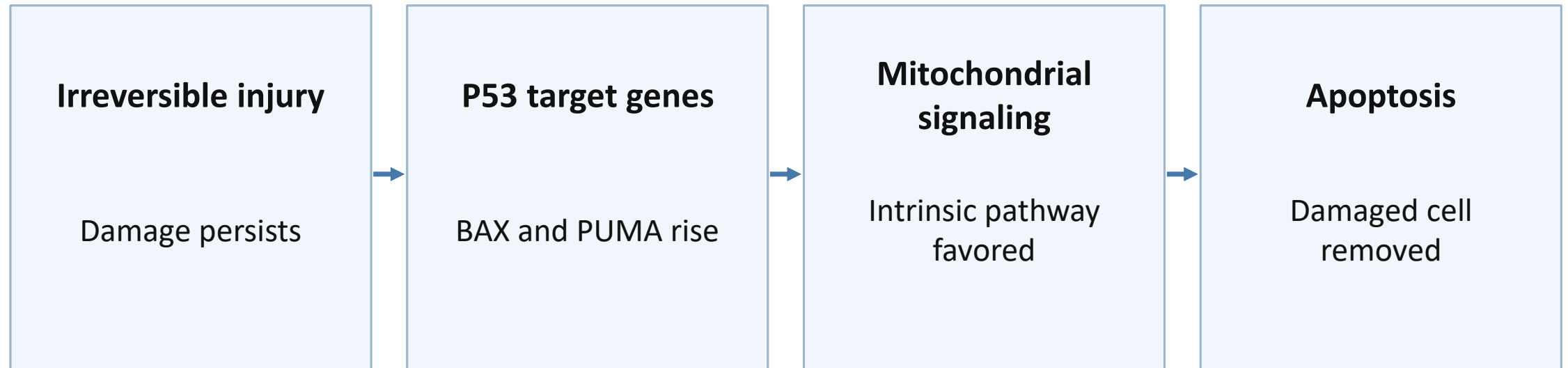
- Unopposed oncogene signaling creates persistent proliferative stress.
- Hypoxia can activate the senescence-associated stress response.
- Shortened telomeres are another recognized signal.
- The ability to remain nonproliferative is an antineoplastic safeguard.

Why senescence blocks tumor formation

A cell unable to divide cannot itself generate an expanding malignant clone.

- Permanent arrest contains cells whose normal growth program cannot be restored.
- This is a protective fate distinct from elimination by apoptosis.

P53 activation can trigger apoptosis



Apoptosis is a definitive route to eliminate a cell with severe DNA injury.

BAX and PUMA: Proapoptotic effectors

- BAX and PUMA among p53-induced proapoptotic genes.
- Their transcription shifts the balance toward the intrinsic apoptosis pathway.
- The mitochondrial route is important when damage cannot safely be repaired.
- This response removes a potential source of future driver mutations.

Senescence versus apoptosis

Senescence

- Cell persists but is nondividing
- Permanent arrest is the major outcome
- Prevents clonal expansion of damaged cell

Apoptosis

- Cell undergoes programmed death
- Intrinsic mitochondrial pathway is activated
- Eliminates the damaged cell

Both are tumor suppressive, but they achieve protection differently.

How p53 may select a cell fate

Degree / duration of p53 activation

Early / limited

Repair-focused response

Persistent

Senescence may emerge

Strong induction

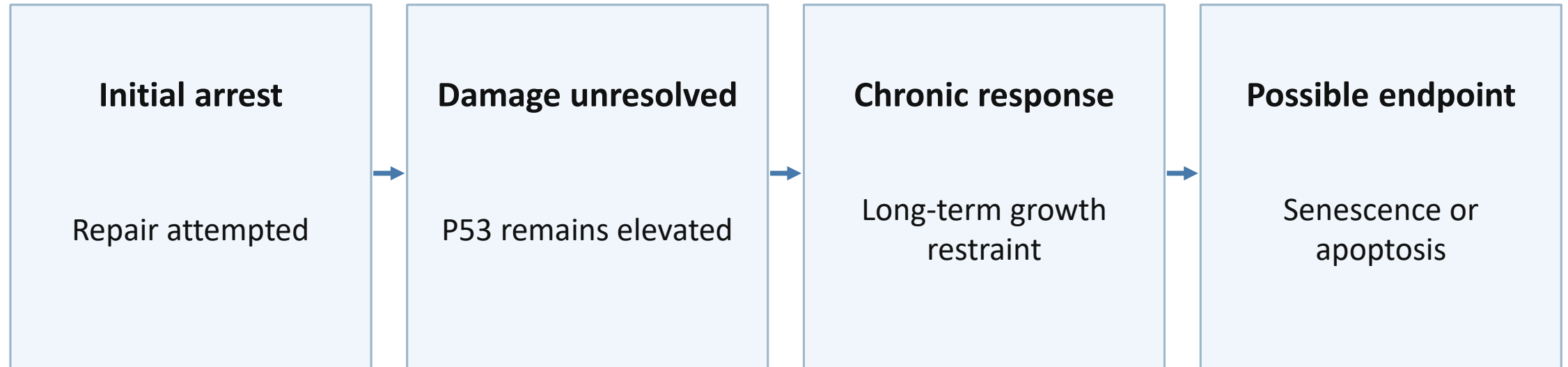
Apoptotic program may
dominate

This is a proposed conceptual model, not a quantitative threshold rule.

Different p53 targets have different sensitivities

- Robbins suggests p53 binds certain repair-gene regulatory sites more avidly.
- Promoters/enhancers of proapoptotic genes may require greater p53 accumulation.
- This provides a plausible ordering: Repair before elimination.
- The explanation does not fully account for all cell-type-specific responses.

When p53 activation persists



Persistent signaling changes the response from reversible containment to stronger protection.

Cell type influences the p53 response

Identical stresses need not yield identical p53-mediated fates in every tissue.

- Some cell types tend toward rapid apoptosis; Others favor senescence.
- This variability as not yet fully explained.
- Avoid depicting repair–senescence–death as an inflexible deterministic sequence.

Intact versus defective p53 after injury

Intact p53

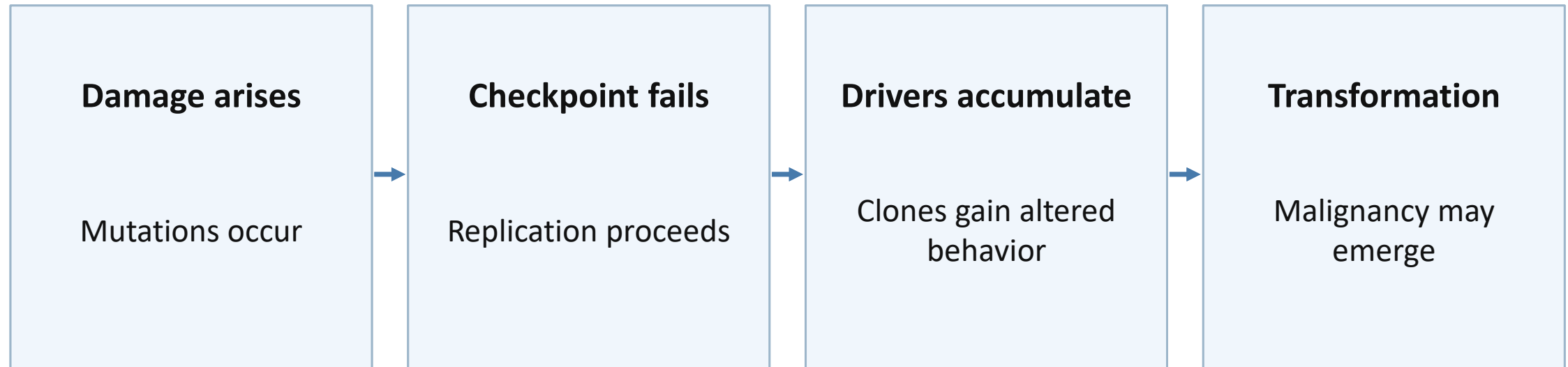
- Damage sensed and p53 stabilized
- G₁ pause and repair program induced
- Unresolved damage may cause senescence or apoptosis

Defective p53

- Protective transcription is impaired
- Damaged cells may continue cycling
- Progressive accumulation of alterations is possible

The essential distinction is the fate of genetically injured cells.

Loss of p53 supports tumor evolution



Schematic causal model; Cancer requires additional alterations.

Genomic damage is not equivalent to cancer

Loss of p53 permits survival and division despite potentially harmful lesions.

- Additional driver mutations in oncogenes and other cancer genes can then accumulate.
- Tumor formation is a multistep process—not an automatic consequence of one TP53 hit.

Mechanism–effector–outcome map

Upstream event	Key effector	Protective result
DNA damage	ATM/ATR → p53	Checkpoint activation
G ₁ checkpoint	CDKN1A / p21 / RB	Replication delay
Repair attempt	GADD45-associated program	Lesion correction
Irreparable damage	BAX / PUMA	Apoptosis
Persistent stress	Sustained arrest program	Senescence

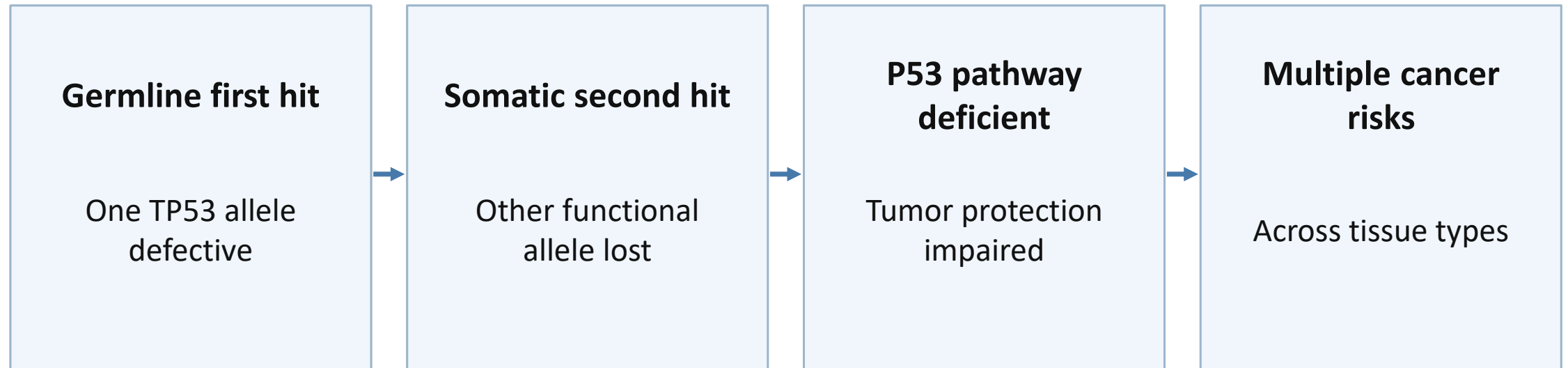
All arrows and associations summarize the supplied Robbins text; Each box is editable.

Li-Fraumeni syndrome: Inherited predisposition

A germline pathogenic TP53 allele predisposes to diverse malignant tumors.

- Loss of the remaining protective allele can eliminate p53 tumor suppression.
- The syndrome differs from sporadic acquisition of two somatic alterations.

Inherited TP53 loss and the second hit



Conceptual inheritance pathway; Individuals are predisposed, not born with a tumor.

Li-Fraumeni: Spectrum of malignancy

- The Robbins examples include sarcomas and breast cancers.
- Leukemias and brain tumors are also common examples.
- Adrenocortical carcinomas form another characteristic category.
- The breadth reflects the widespread tumor-suppressive role of p53.

Li-Fraumeni: Age and multiplicity

- Affected individuals commonly develop malignant tumors at younger ages.
- Multiple primary tumors of differing histologic types may occur.
- The family history can be clinically informative when hereditary predisposition is considered.
- These are syndrome-level features, not sufficient alone for a molecular diagnosis.

Textbook risk estimate for Li-Fraumeni

A 25-fold higher likelihood of malignancy by age 50 than the general population.

- This is a source-specific comparison, not a population-specific lifetime-risk estimate.
- No separate contemporary clinical risk figure is introduced in this source-only lecture.

Inherited RB and TP53 syndromes

Inherited RB alteration

- Strong classically characteristic retinoblastoma association
- One inherited defective tumor suppressor allele
- Second hit can permit tumor formation

Inherited TP53 alteration

- Broad spectrum of malignant tumors
- One inherited defective tumor suppressor allele
- Second hit can disable p53 protection

The two-hit logic is shared; The tissue distribution differs.

Clinical application: Multiple primary tumors

A young adult has a history of sarcoma and a second, histologically unrelated primary malignancy. A close relative developed cancer unusually early.

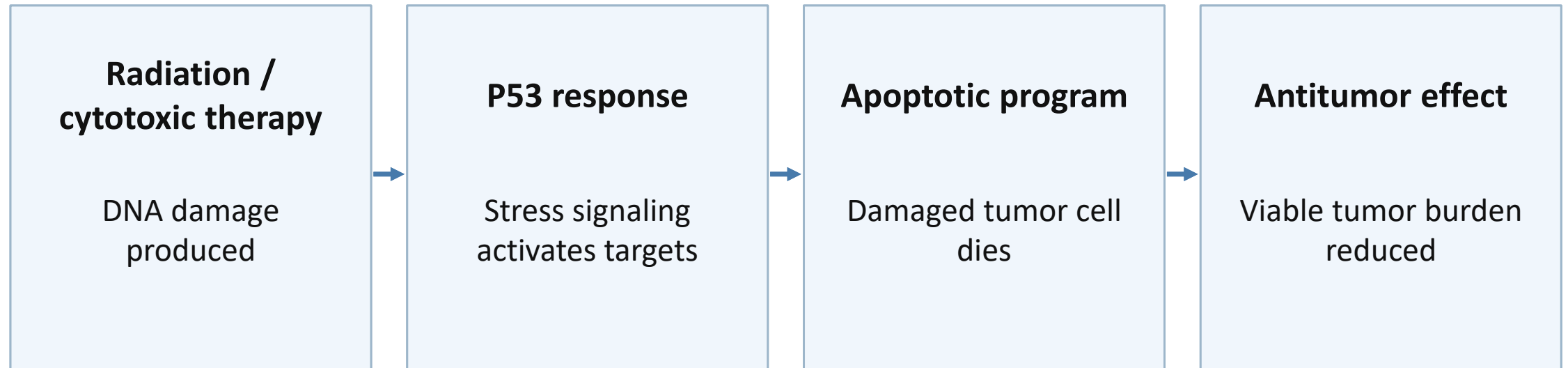
- Which hereditary tumor suppressor syndrome should enter the differential?
- What explains susceptibility to different tumor types?

Application: Hereditary TP53 dysfunction

Consider Li-Fraumeni syndrome as a possible explanation for the vignette.

- Germline TP53 impairment weakens a broadly used genomic stress checkpoint.
- A confirmed diagnosis requires appropriate clinical and molecular evaluation; The vignette is not diagnostic.

DNA-damaging therapy engages p53



A mechanistic rationale; Individual clinical responses have multiple determinants.

Wild-type versus mutant TP53 and therapy

Wild-type TP53 pathway

- Damage can trigger p53-mediated apoptosis
- This with greater sensitivity
- Effect remains tumor- and context-dependent

Mutated TP53 pathway

- DNA damage may fail to induce apoptosis
- This with relative resistance
- Not a universal resistance rule or stand-alone test

Therapeutic response is an association in the source, not an absolute predictor.

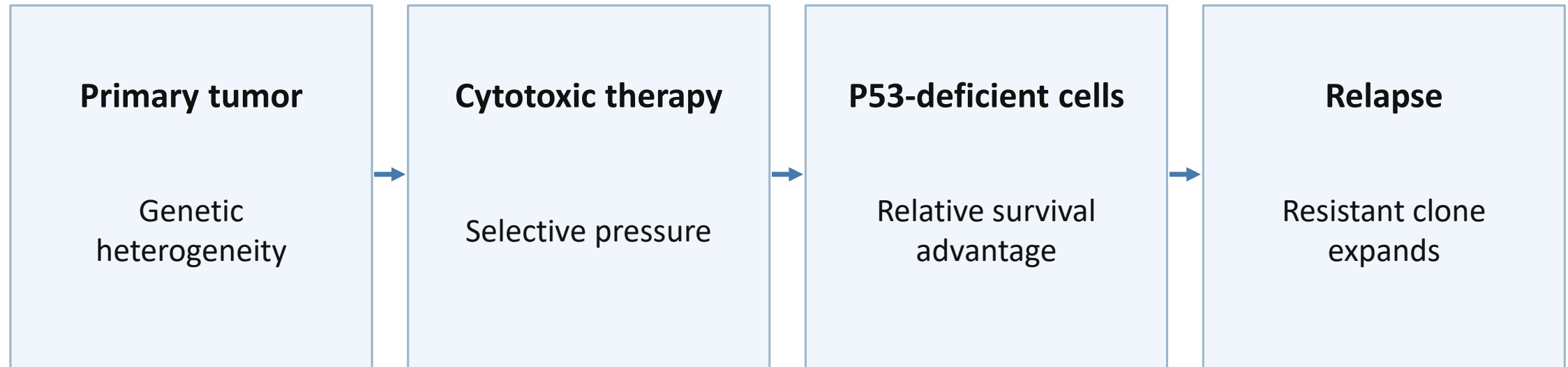
Examples of p53-associated chemosensitivity

- Testicular germ cell tumors often retain wild-type TP53 in the source discussion.
- Childhood acute lymphoblastic leukemia is another example given.
- Both illustrate contexts with excellent clinical outcomes and generally intact p53.
- The treatment response cannot be attributed to TP53 status alone.

Examples of relative treatment resistance

- Lung cancers frequently harbor TP53 mutations at presentation.
- Colorectal cancers are also cited as commonly mutated.
- Relative resistance to DNA-damaging therapy in these groups.
- Mutation status is one mechanistic contributor rather than a complete clinical forecast.

Therapy can select resistant subclones



The source associates relapsed disease with enrichment for TP53-mutant subclones.

Relapse is a population-level evolutionary event

A treatment-sensitive majority may be eliminated while rare resistant clones survive.

- Subclones with TP53 dysfunction may gain a survival advantage under DNA-damaging therapy.
- The relapsed lesion may therefore be genetically different from the original mass.

Clinical application: Wild-type TP53 sarcoma

A sarcoma retains a nonmutated TP53 coding sequence, yet its p53-dependent damage response is suppressed. Molecular analysis reveals MDM2 amplification.

- Why can p53 function be impaired without a TP53 sequence mutation?
- Which level of the pathway is affected?

Application: Functional p53 inactivation

Excess MDM2 can increase p53 ubiquitination and degradation.

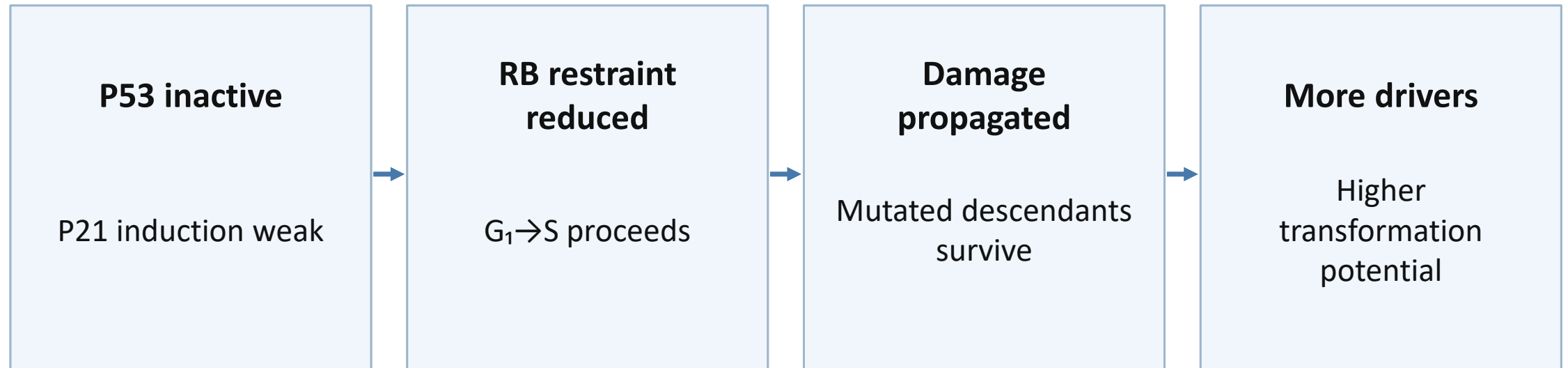
- The p53-dependent program may therefore be reduced despite wild-type TP53.
- Gene sequence and pathway function are related but not interchangeable.

Clinical application: Damage without G₁ arrest

A neoplastic clone with defective p53 continues proliferating after DNA injury. Over subsequent divisions, additional driver lesions appear.

- What checkpoint mechanism has been lost?
- Why does continued cell division increase oncogenic potential?

Application: The checkpoint failure chain



This teaching schematic joins p53 regulation with the RB cell-cycle gate.

P53 review: Input → mediator → fate

Stimulus	Principal mediators	Outcome
Routine growth	MDM2-mediated turnover	Low basal p53
DNA damage	ATM/ATR phosphorylation	Stabilized p53
Aberrant RAS signal	p14/ARF–MDM2	Stabilized p53
Potentially reparable damage	p21 / RB; GADD45	Arrest and repair
Persistent/irreparable damage	Senescence and BAX/PUMA pathways	Permanent arrest or apoptosis

Compact pathway summary; Distinctions reflect the supplied Robbins discussion.

Five conclusions about the genome guardian

TP53 is a commonly inactivated tumor suppressor.

- MDM2, stress sensors, and oncogenic signaling determine p53 availability.
- P21–RB arrest, repair, senescence, and apoptosis provide complementary defenses.
- Inherited TP53 defects confer broad cancer predisposition.
- Loss of p53 may contribute to tumor evolution and cytotoxic resistance.

Reference and further reading

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Neoplasia: tumor suppressor genes and the p53 stress-response pathway.
- For further study: regulation of p53, the p21–RB checkpoint, DNA repair, senescence, and intrinsic apoptosis.
- Mechanism illustrations in this lecture are explanatory schematics, not histologic specimens or quantitative data.