

Self-Sufficiency in Growth Signals: Oncogenes

Molecular mechanisms of autonomous cancer cell growth

Proto-oncogenes • signal transduction • cell-cycle entry

Normal growth control → oncogenic growth autonomy

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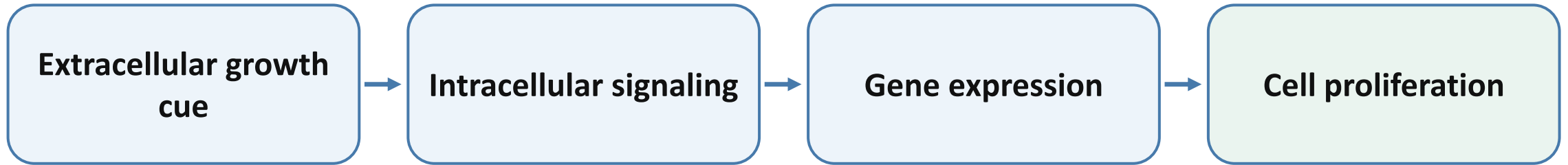
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Learning outcomes

- Define proto-oncogenes, oncogenes, and constitutively active oncoproteins.
- Map normal growth-factor signaling from receptor binding to cell division.
- Explain oncogenic activation at ligand, receptor, cytoplasmic, nuclear, and cell-cycle levels.
- Connect representative molecular lesions to tumor examples and therapeutic principles.

Growth autonomy is a hallmark of cancer



- Normal tissues regulate proliferation through transient, conditional signaling.
- Cancer cells can generate mitogenic drive despite absent external cues.
- Oncogenic autonomy does not imply independence from all nutrients or survival signals.

An oncogene is an activated progrowth gene

- An oncogene is an altered gene that drives excessive cell growth.
- It arises from a normal proto-oncogene through mutation or overexpression.
- Its oncoprotein often signals constitutively or resists normal feedback control.
- Cells consequently lose normal dependence on growth-promoting external stimuli.

Proto-oncogene and oncogene are functionally distinct

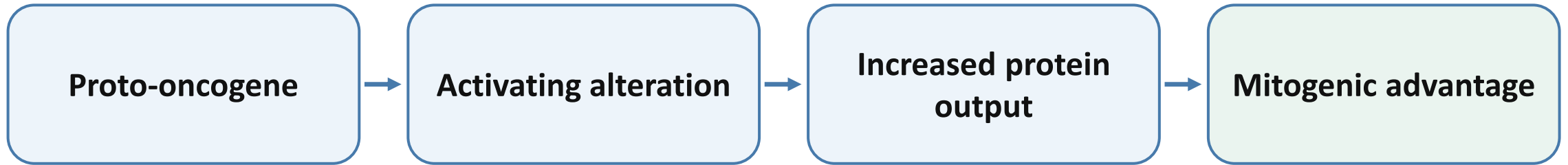
Normal proto-oncogene

- Physiologic protein supports regulated proliferation.
- Expression or activity responds to an appropriate signal.
- Activity is time-limited or restrained by negative regulators.

Oncogene

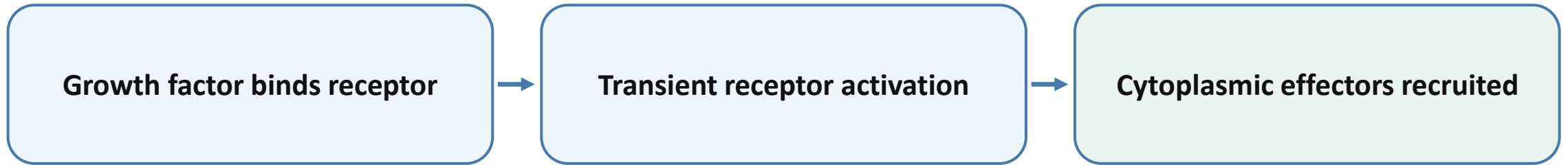
- Mutation or overexpression increases progrowth signaling.
- Protein may remain active in the absence of a ligand.
- Persistent output favors inappropriate cell-cycle progression.

Cancer-associated oncogenic change is typically gain of function



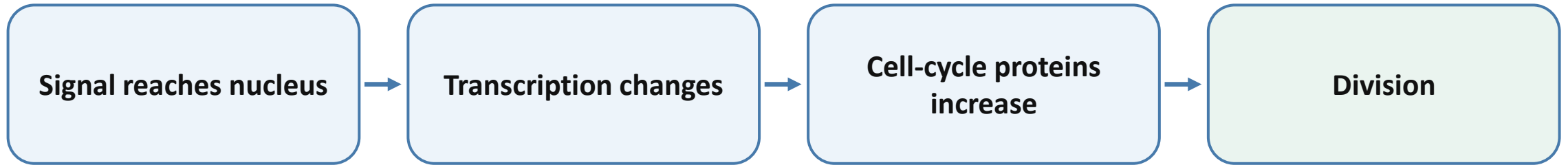
- Change may affect the protein sequence, abundance, or regulatory context.
- Constitutive activity is a common outcome, not the only biochemical mechanism.

Normal mitogenic signaling begins outside the cell



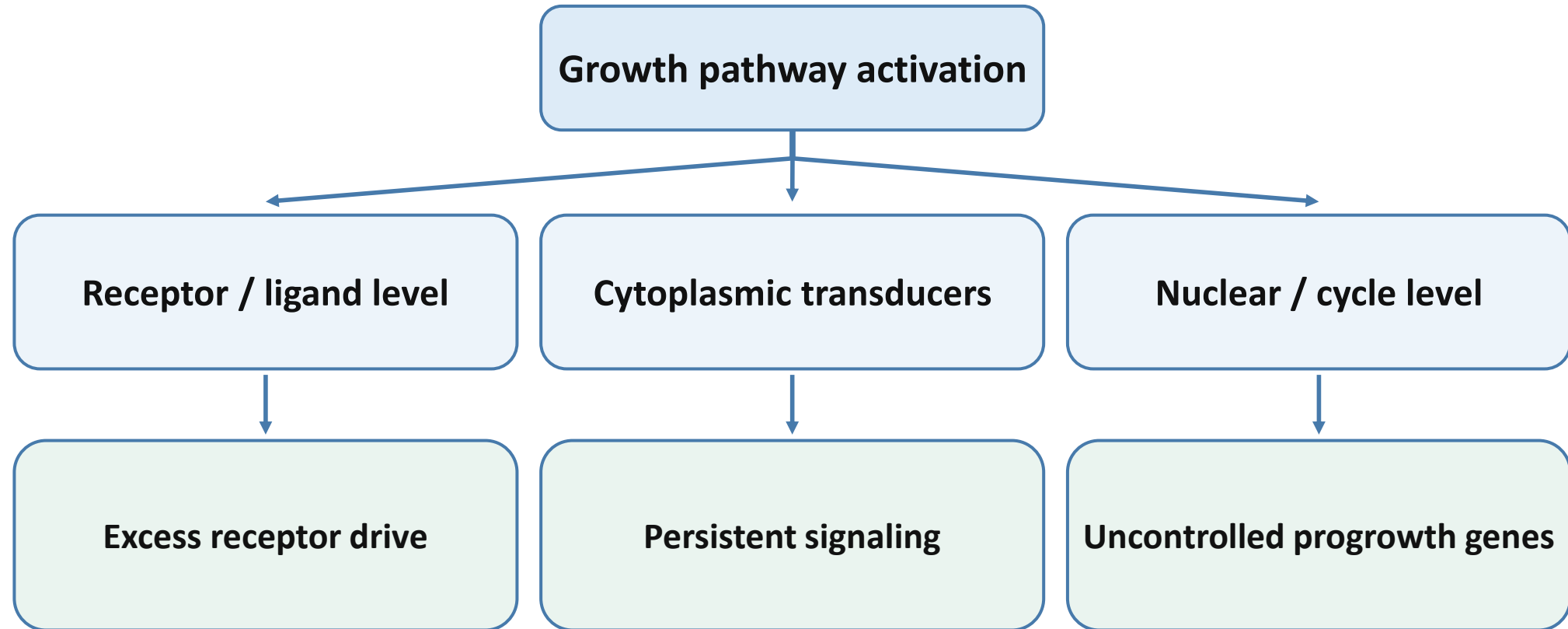
- Ligand recognition creates a regulated entry point for growth signals.
- Multiple cytoplasmic transducers relay or amplify the signal.
- Activation normally subsides after the appropriate response.

Normal mitogenic signaling culminates in division



- Transcription factors and epigenetic alterations support gene expression.
- Parallel signals promote survival and metabolic biosynthesis.

Oncogenic signaling can bypass normal checkpoints



Proto-oncogene products span five functional levels

Level	Normal activity	Cancer consequence
Growth factor	Paracrine signal	Autocrine stimulation
Receptor	Ligand-dependent activation	Constitutive kinase activity
Signal transducer	Reversible pathway relay	Persistent kinase or G-protein activity
Transcription factor	Timed growth-gene expression	Continuous gene activation
Cyclin / CDK	Regulated cycle progression	Excessive G ₁ /S entry

Several genetic mechanisms activate proto-oncogenes

Point mutation

Changes catalytic or regulatory behavior of a protein.

Gene amplification

Raises gene dosage and typically protein expression.

Chromosomal rearrangement

May create an active fusion or place a gene near strong enhancers.

Overexpression

Excess growth factor or signaling protein increases pathway output.

Oncogenes and tumor suppressors share signaling networks

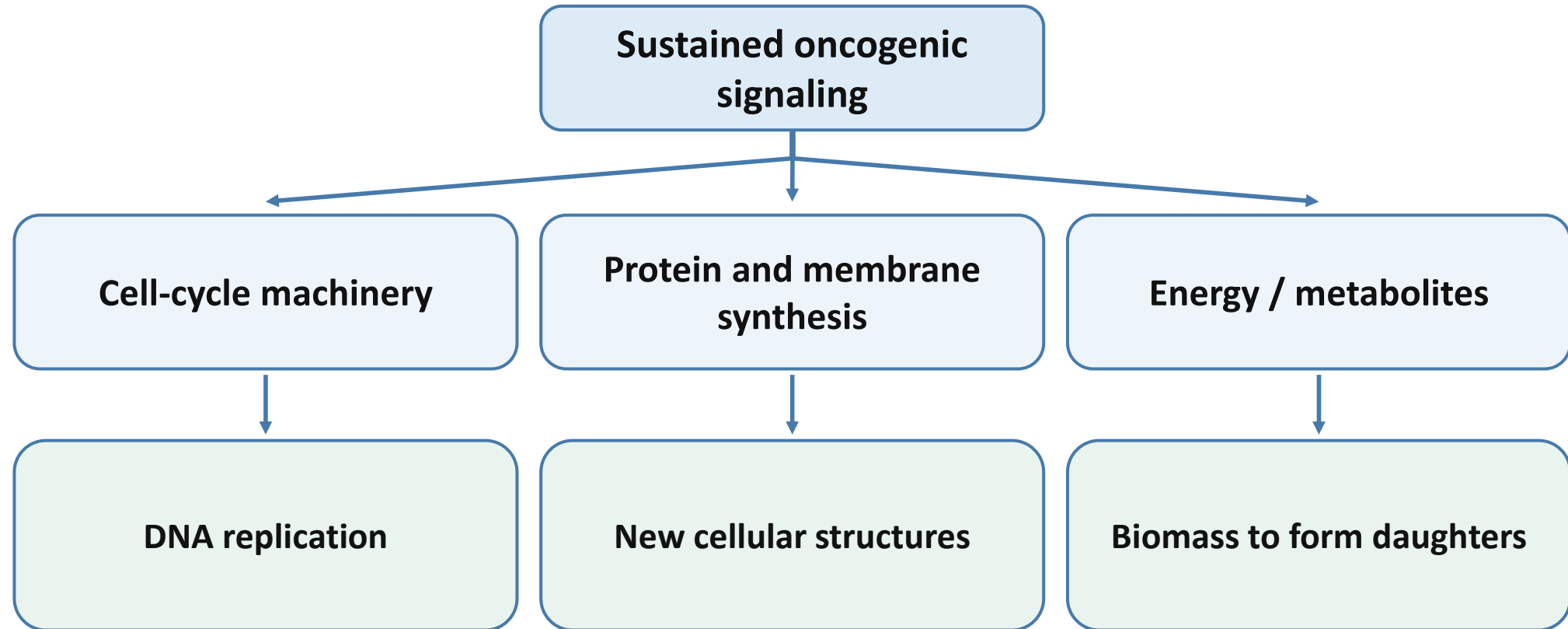
Oncogenic activation

- Gain of activity in a positive growth regulator.
- Example: Activated RAS stimulates downstream kinases.
- Excess positive signal accelerates proliferation.

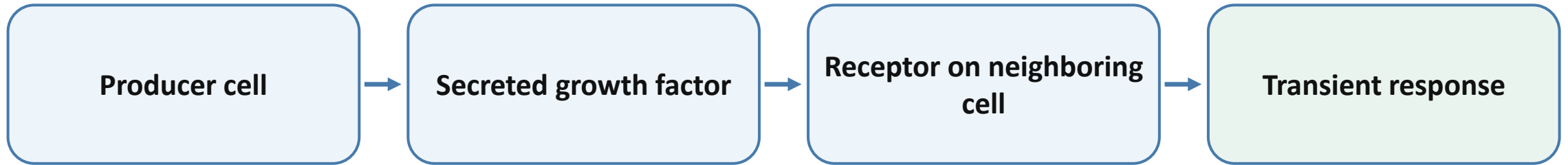
Tumor-suppressor loss

- Removes a negative regulator from the same pathway.
- Example: Loss of NF1 or PTEN releases signaling restraint.
- Loss of inhibition may phenocopy a progrowth mutation.

Proliferation requires more than DNA synthesis

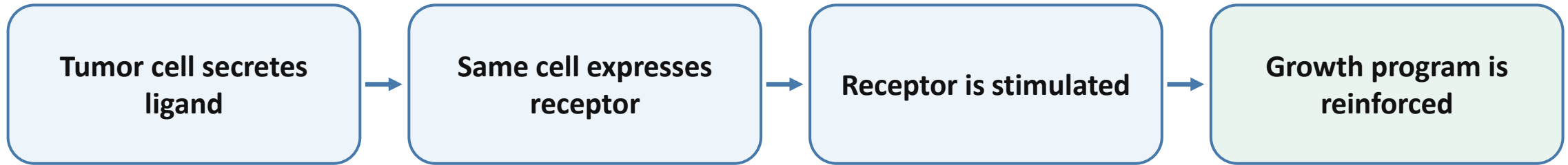


Growth factors usually act through paracrine circuits



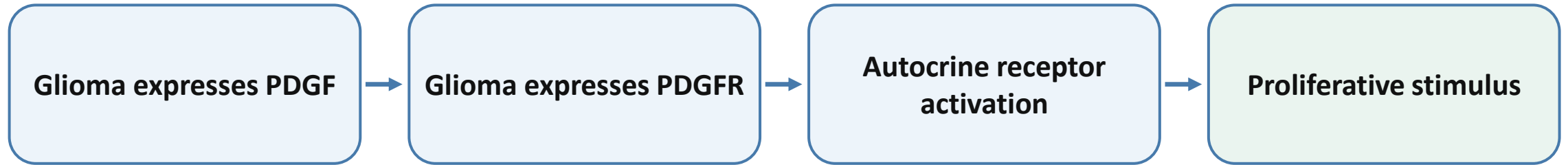
- Paracrine action separates ligand production from the responsive cell.
- Receptor expression helps determine which neighbors can respond.

Autocrine circuits create a self-stimulating loop



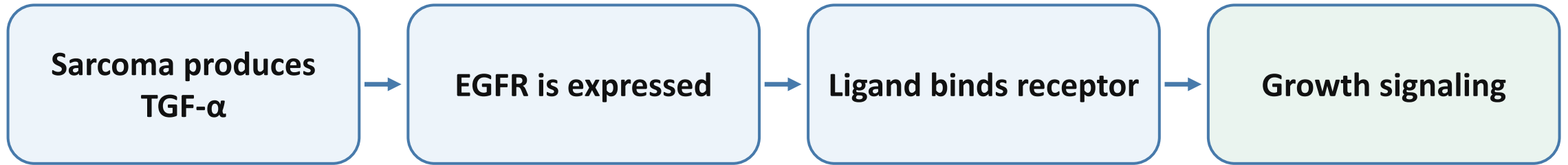
- Autocrine signaling reduces dependence on growth factor from nearby cells.
- Both ligand production and receptor expression are necessary for the loop.

PDGF–PDGFR illustrates autocrine growth in gliomas



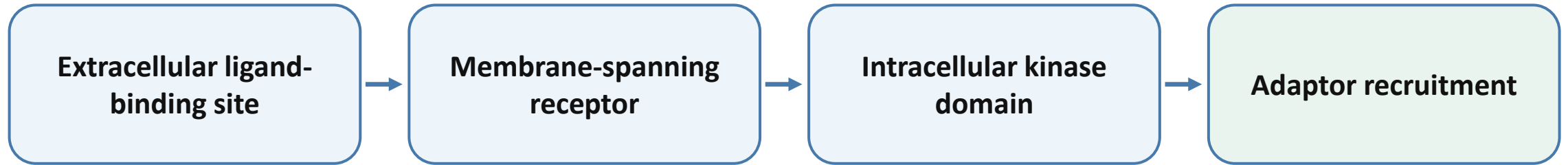
- Gliomas that express both platelet-derived growth factor and its receptor.
- This is a ligand-dependent form of growth autonomy, not necessarily a mutated receptor.

TGF- α –EGFR illustrates another autocrine circuit



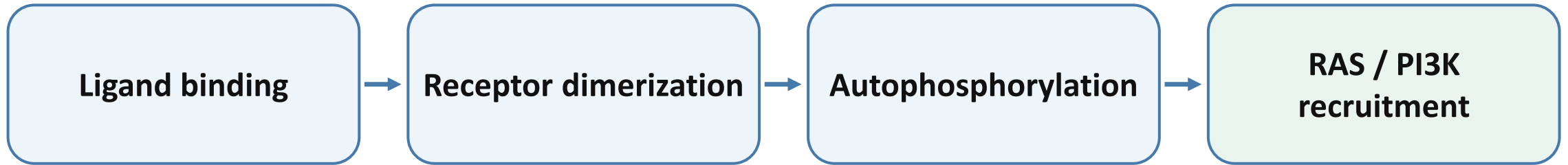
- Many sarcomas overexpressing transforming growth factor- α and EGFR.
- Ligand abundance and receptor presence together support the autocrine response.

Receptor tyrosine kinases connect ligand to cytoplasmic signals



- The receptor spans the membrane and contains a cytoplasmic tyrosine kinase.
- Tyrosine phosphorylation creates docking sites for signaling factors.

RTK activation is normally transient



- The active dimer initiates signaling through phosphorylation.
- Downstream activity is conditional on regulated receptor activation.

Receptor oncogenes evade ligand-dependent control

Activating point mutation

Catalytic activity persists despite absence of growth factor.

Gene amplification

Excess receptors increase signaling capacity and activity.

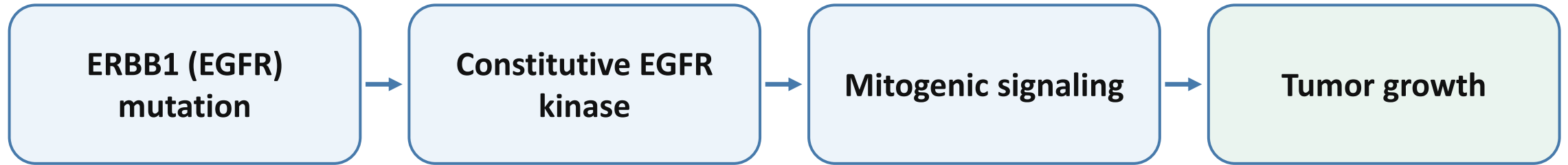
Gene rearrangement

A fusion may impose constitutive kinase activity.

Common endpoint

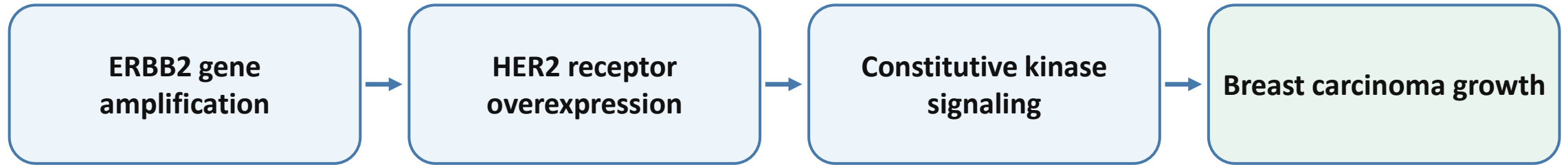
Continual mitogenic and survival signaling from receptor pathways.

EGFR activation can drive lung adenocarcinoma



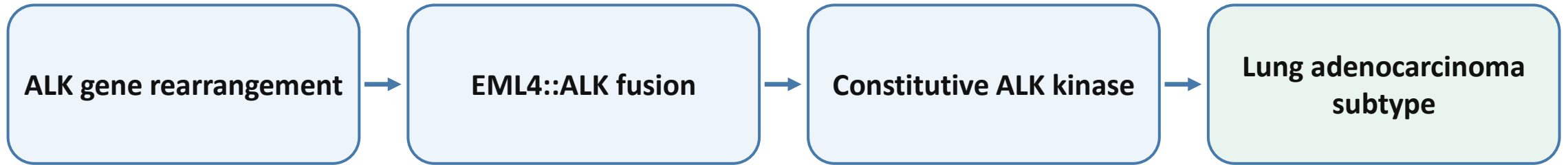
- Several ERBB1 point mutations in subsets of lung adenocarcinoma.
- The molecular lesion supplies a predictive rationale for EGFR kinase inhibition.

HER2 amplification is a receptor-dose mechanism



- HER2 is a member of the receptor tyrosine kinase family.
- Amplification rather than the example of point mutation drives this textbook association.

EML4::ALK is an oncogenic fusion kinase

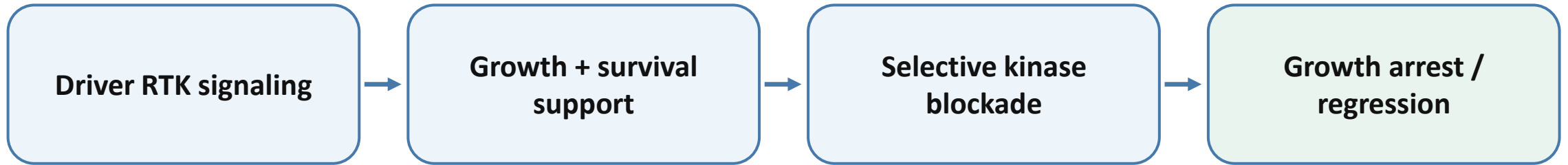


- A chromosome 5 rearrangement creates a chimeric EML4–ALK protein.
- ALK activating point mutations also occur in some neuroblastomas.

Three receptor oncogene patterns are not interchangeable

Gene / protein	Illustrative alteration	Tumor example
ERBB1 / EGFR	Activating point mutation	Lung adenocarcinoma
ERBB2 / HER2	Gene amplification	Breast carcinoma
ALK	Rearrangement → fusion	Lung adenocarcinoma
ALK	Activating point mutation	Subset of neuroblastomas

RTK addiction creates a therapeutic vulnerability



- In tumors bearing the target alteration, receptor inhibition can suppress growth.
- Tumor regression also reflects loss of prosurvival signaling.

Pathway inhibition can promote tumor-cell apoptosis

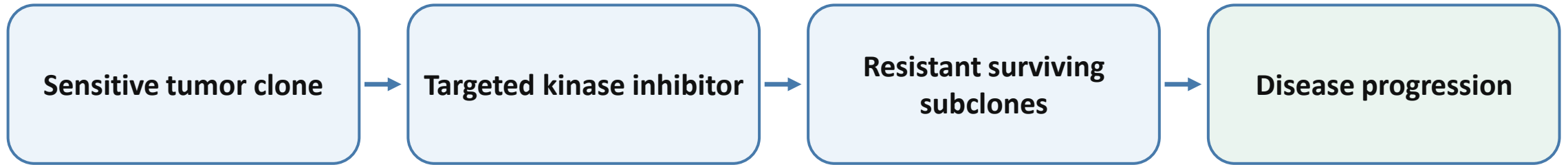
Before inhibitor

- Activated RTK supports cell proliferation.
- Parallel pathway activity contributes to survival.
- Cells remain dependent on oncogenic signaling.

After effective inhibitor

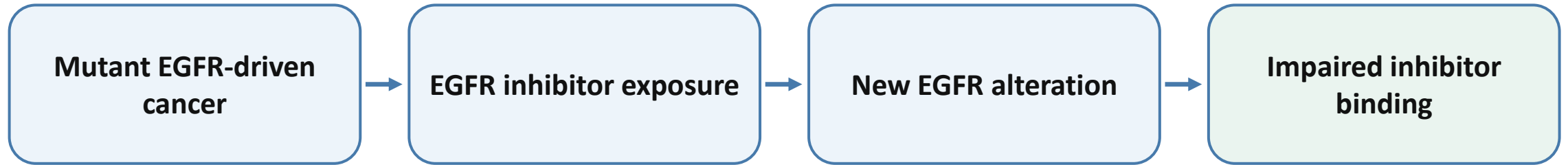
- Kinase activity is suppressed.
- Progrowth and survival signals decline.
- Growth inhibition and apoptosis may follow.

Acquired resistance limits advanced-cancer control



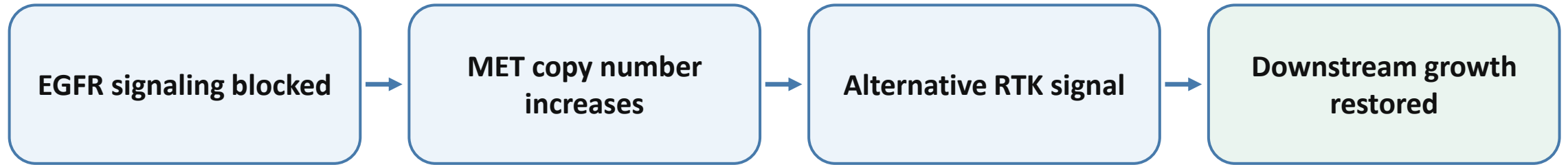
- Response to an inhibitor does not guarantee eradication of every tumor cell.
- Selection of genetically heterogeneous subclones provides a route to resistance.

EGFR inhibitor resistance can alter drug binding



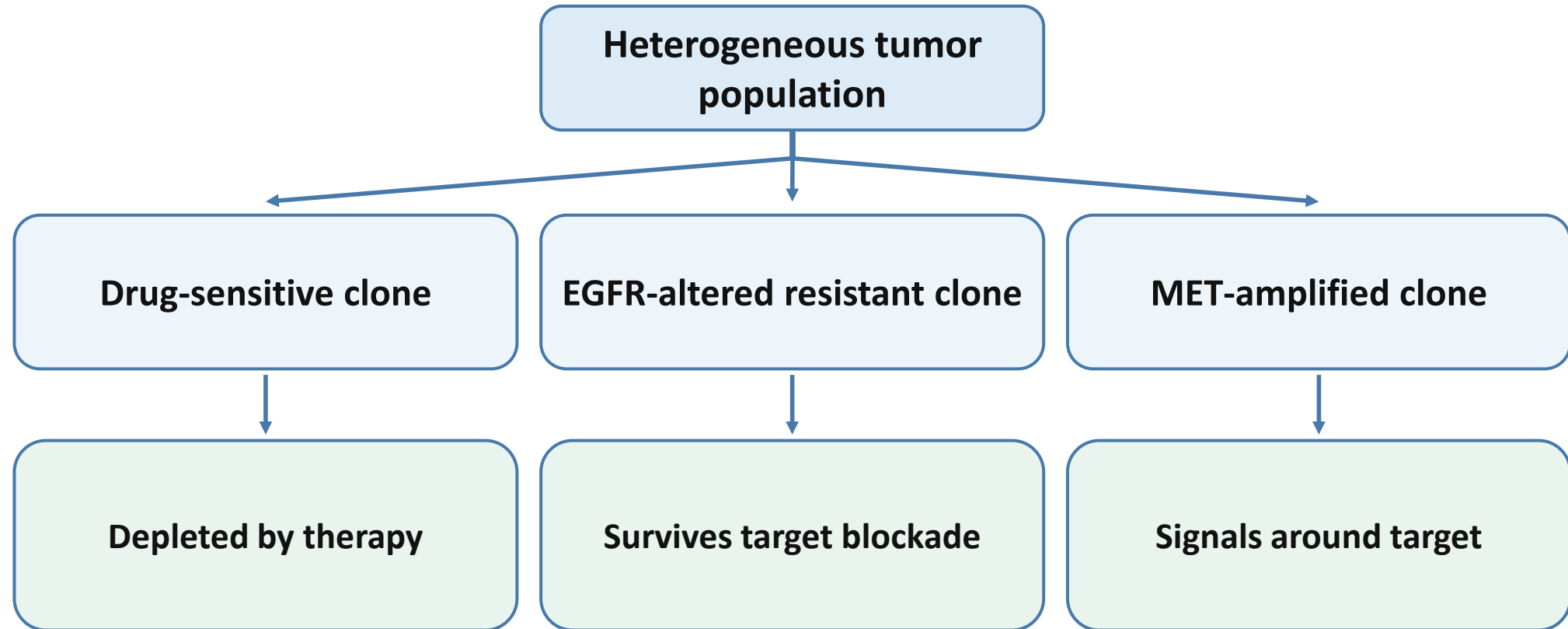
- Acquired EGFR mutations that interfere with inhibitor binding.
- The altered receptor can preserve signaling despite pharmacologic blockade.

MET amplification can bypass EGFR inhibition

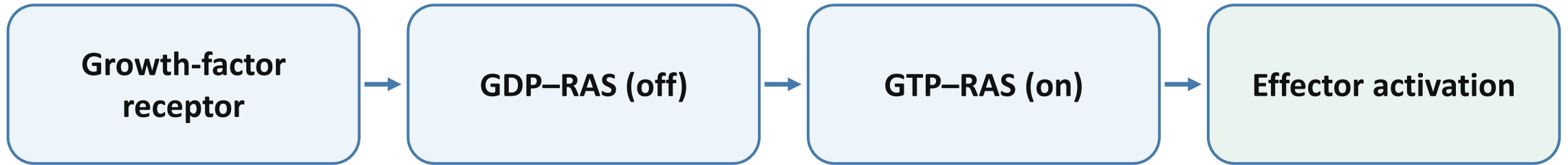


- MET encodes another receptor tyrosine kinase.
- Amplification creates a bypass pathway rather than restoring drug binding to EGFR.

Tumor heterogeneity supplies resistant subclones



RAS proteins are membrane-associated molecular switches



- Human RAS proto-oncogenes include HRAS, KRAS, and NRAS.
- Guanosine nucleotide exchange regulates the active signaling state.

RAS normally cycles between GDP and GTP states

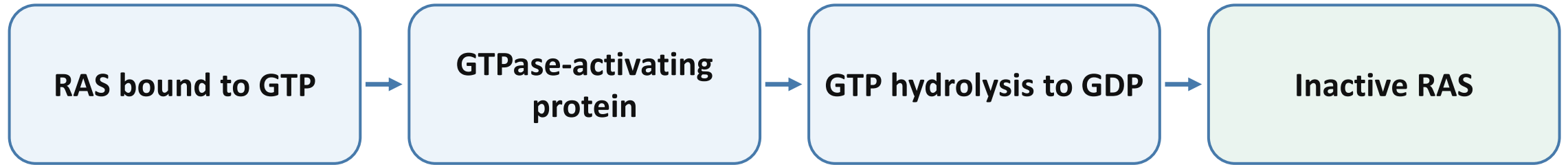
GDP-bound RAS

- Quiescent, signal-off state.
- Predominates after GTP hydrolysis.
- Does not relay the same active mitogenic output.

GTP-bound RAS

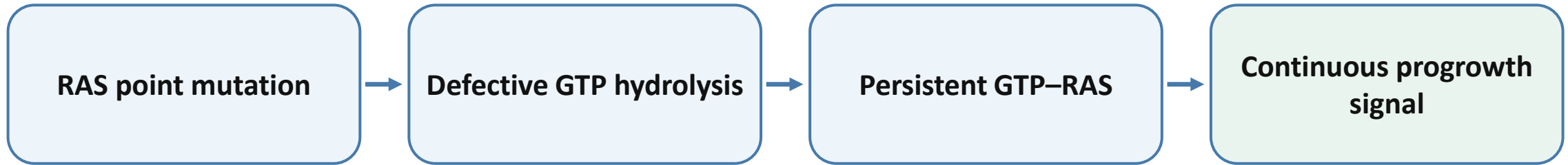
- Active, signal-transmitting state.
- Generated by receptor-coupled nucleotide exchange.
- Engages downstream growth-control effectors.

GAP proteins terminate active RAS signaling



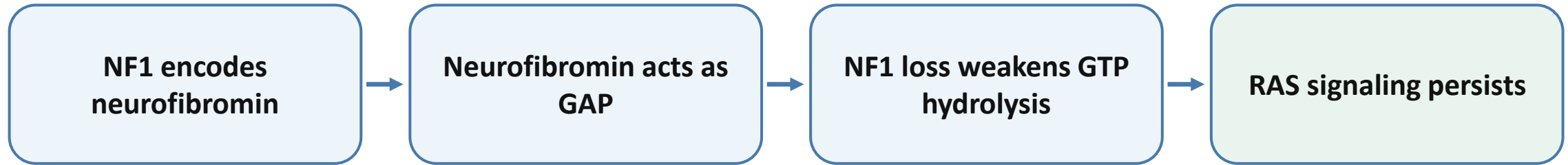
- RAS has intrinsic GTPase activity accelerated by GAPs.
- GAPs act as brakes that limit duration of RAS activation.

RAS point mutations can lock the switch on



- Mutant RAS resists return to the GDP-bound state.
- The resulting signal can remain active without repeated receptor stimulation.

NF1 loss demonstrates the role of a pathway brake



- NF1 is a tumor-suppressor gene, not a proto-oncogene.
- Germline loss predisposes to neurofibromatosis type 1.

Upstream RTK and RAS drivers are often alternative

RTK-driven clone

- Activating alteration at the receptor level.
- RAS and downstream signals follow receptor activation.
- An RTK-directed inhibitor may match the driver.

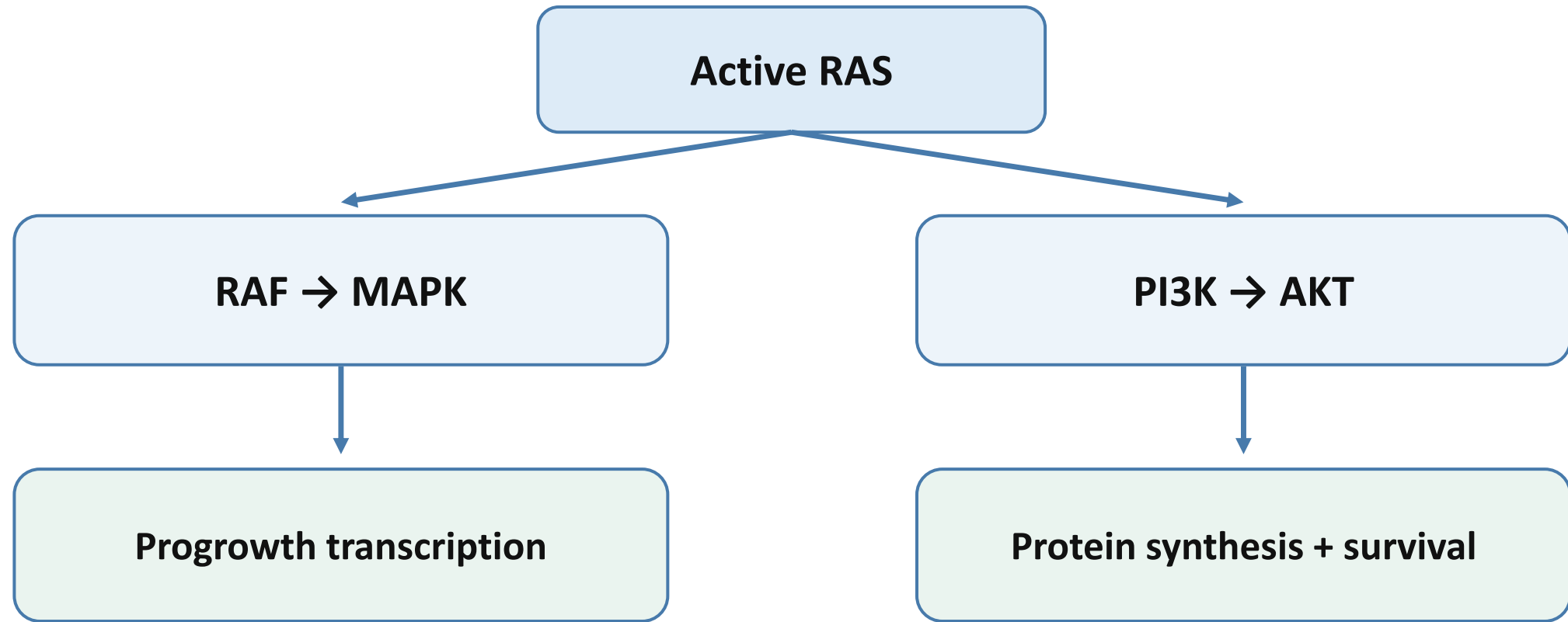
RAS-driven clone

- Oncogenic RAS provides a downstream input.
- RTK activating mutations are usually absent in the dominant clone.
- Blocking the receptor may not extinguish mutant RAS.

RAS mutations occur across multiple tumor lineages

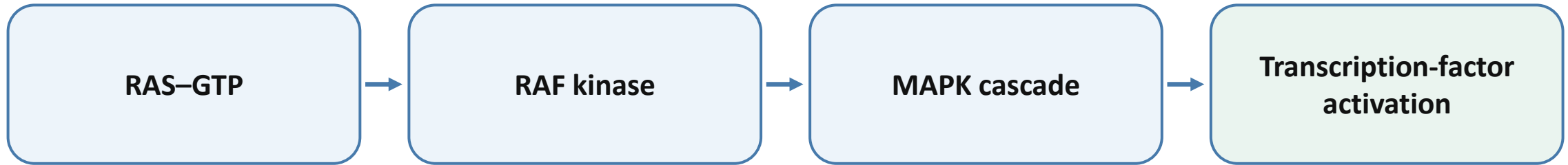
RAS family member	Illustrative tumor association	Mode
KRAS	Colorectal, lung, pancreatic tumors	Point mutation
HRAS	Bladder and kidney tumors	Point mutation
NRAS	Melanoma, hematologic malignancies	Point mutation

RAS feeds two major progrowth signaling arms



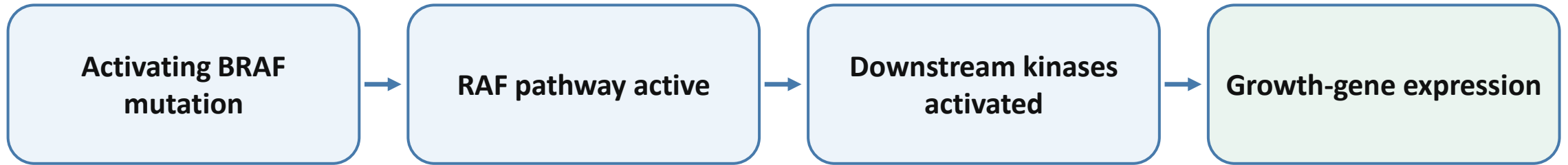
Integrated growth program supports cell division

RAF–MAPK transmits growth signals to the nucleus



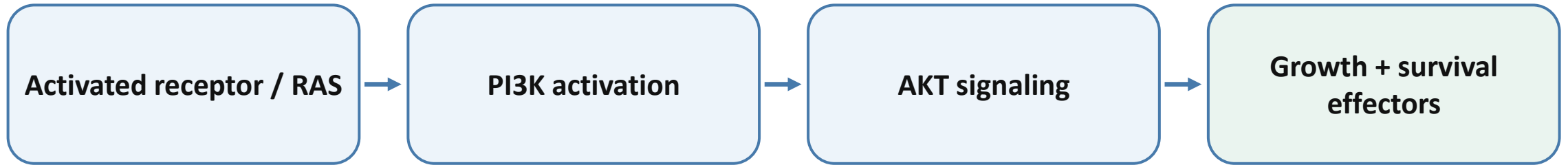
- RAF proteins are serine/threonine kinases.
- Activation of transcription factors increases expression of progrowth genes.

BRAF mutations activate the MAPK cascade



- BRAF activation with hairy cell leukemia and melanoma.
- Mutations near the top of signaling cascades can yield pronounced progrowth effects.

PI3K–AKT couples signals to biomass and survival



- PI3K operates near plasma membrane signaling complexes.
- AKT regulates protein synthesis, apoptosis-related factors, and other outputs.

PTEN imposes negative control on PI3K signaling

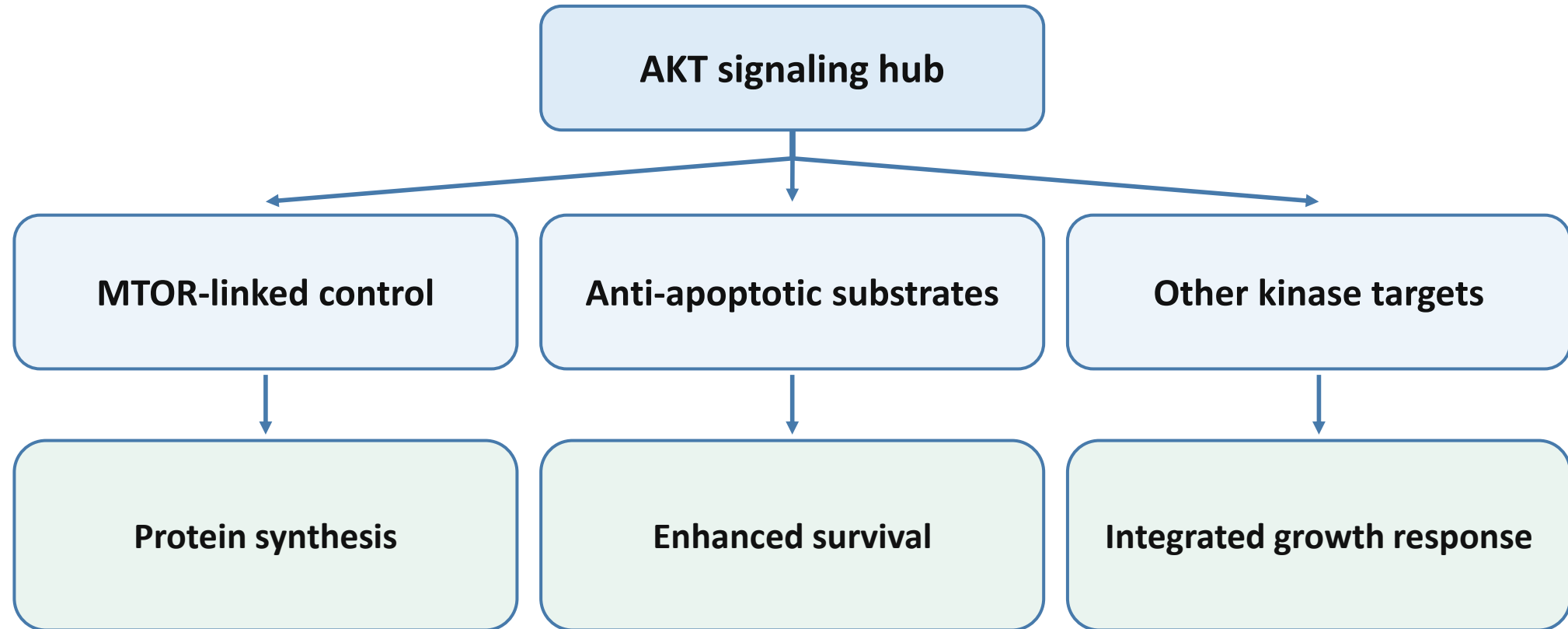
PTEN intact

- PTEN restrains the PI3K pathway.
- Negative regulation limits pathway activation.
- Growth and survival output remains regulated.

PTEN function lost

- PI3K signaling is less restrained.
- AKT pathway output can increase.
- Oncogenic pathway activation can arise without PI3K gain of function.

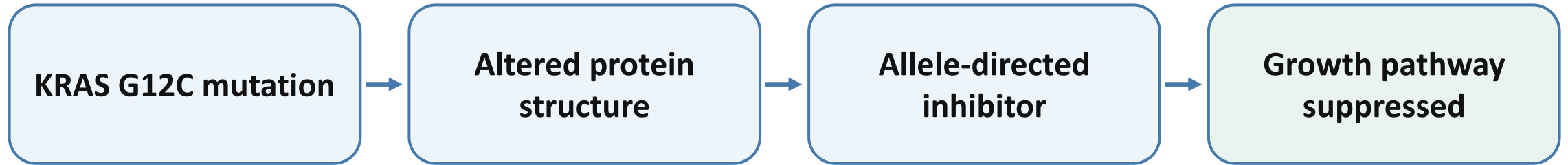
AKT signaling supports an anabolic phenotype



MAPK and PI3K/AKT have distinct emphases

Branch	Representative components	Major teaching emphasis
RAF / MAPK	RAS → RAF → MAPK	Transcriptional progrowth activation
PI3K / AKT	PI3K → AKT → mTOR	Biosynthesis and cell survival
Shared context	Both downstream of RTK/RAS	Coordinated cell growth

Mutant KRAS is targetable in selected settings



- The source describes approved agents targeting KRAS with glycine→cysteine substitution at codon 12.
- A specific molecular variant—not KRAS mutation in general—defines this therapeutic example.

Targeting RAF or PI3K is a pathway-level strategy

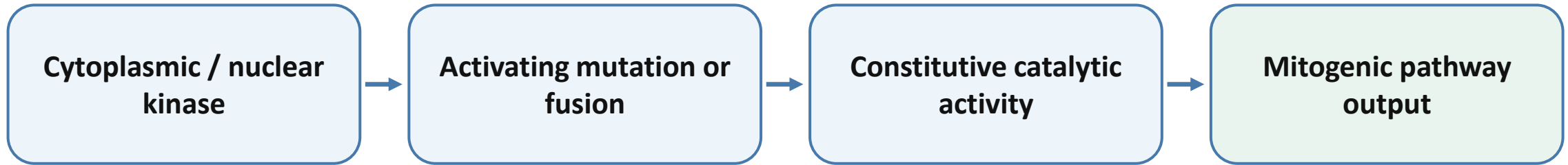
BRAF inhibitor strategy

- Targets an activated downstream kinase.
- Substantial responses in some advanced melanomas.
- Response depends on relevant tumor biology.

PI3K inhibitor strategy

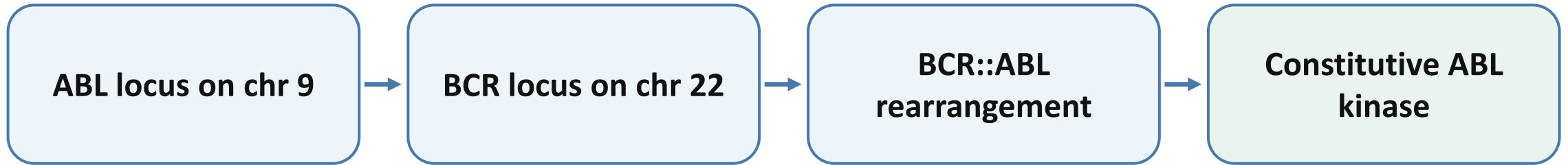
- Intervenes in a separate kinase cascade.
- Some PI3K isoform inhibitors are approved in selected malignancies.
- Pathway perturbation must be molecularly contextualized.

Nonreceptor kinases need no transmembrane domain



- Nonreceptor tyrosine kinases are normally located inside the cell.
- Oncogenic activation can stimulate pathways overlapping those of RTKs.

BCR::ABL is a fusion oncogene



- The fusion is characteristic of chronic myeloid leukemia.
- It also occurs in a subset of acute lymphoblastic leukemias.

The Philadelphia chromosome encodes BCR::ABL

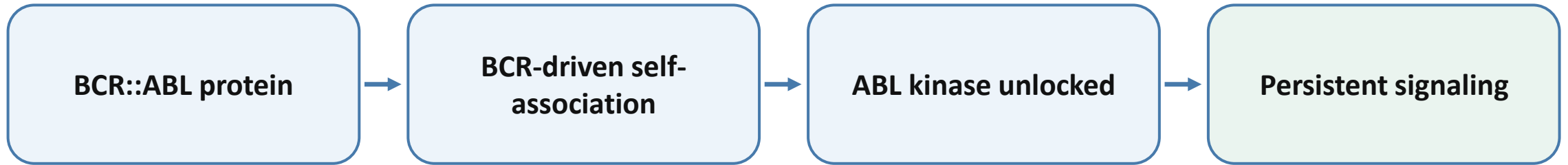
Rearrangement

- ABL is translocated from chromosome 9 to chromosome 22.
- ABL joins the BCR gene.
- The Philadelphia chromosome is derived from chromosome 22.

Functional consequence

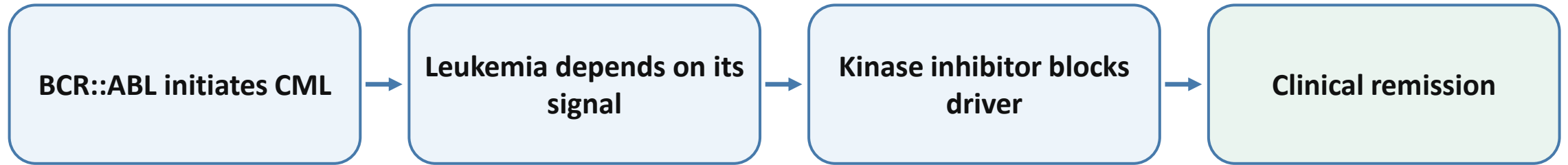
- BCR contributes self-association capacity.
- The chimeric ABL kinase becomes constitutively active.
- Excess signaling supports leukemic proliferation.

Fusion-partner self-association activates ABL



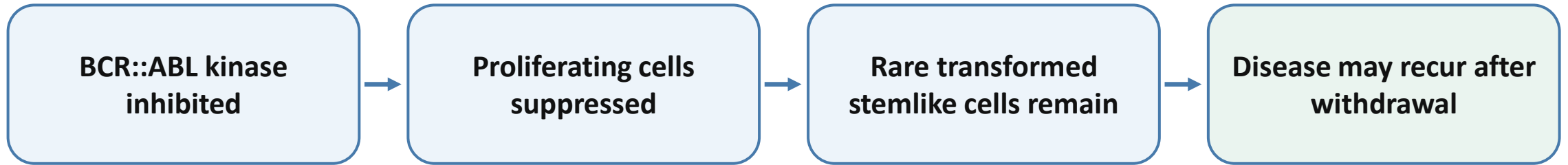
- Fusion protein formation removes normal control over ABL catalytic output.
- This mechanism recurs among multiple oncogenic kinase fusions.

CML exemplifies oncogene addiction



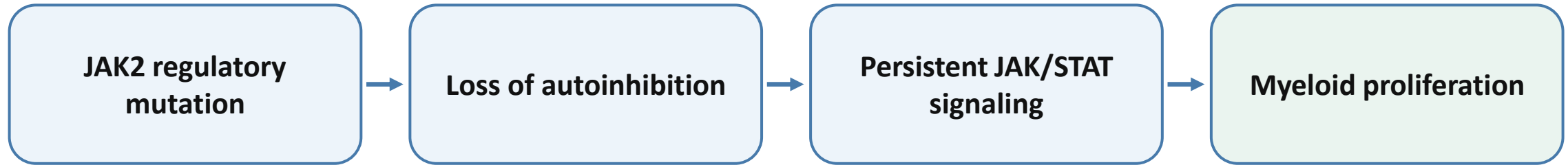
- A highly dominant oncogenic driver creates a therapeutic dependence.
- CML response to BCR–ABL inhibition as a central example.

Residual stemlike cells can outlast targeted therapy



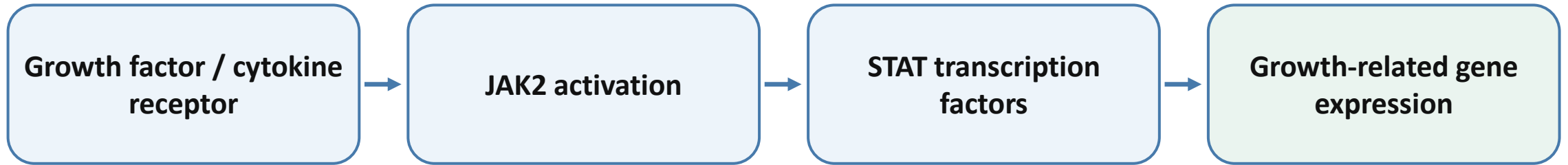
- A clinical remission need not equal eradication of all leukemia-initiating cells.
- Persistence of cells less dependent on BCR–ABL signaling for survival.

JAK2 mutations can activate nonreceptor signaling



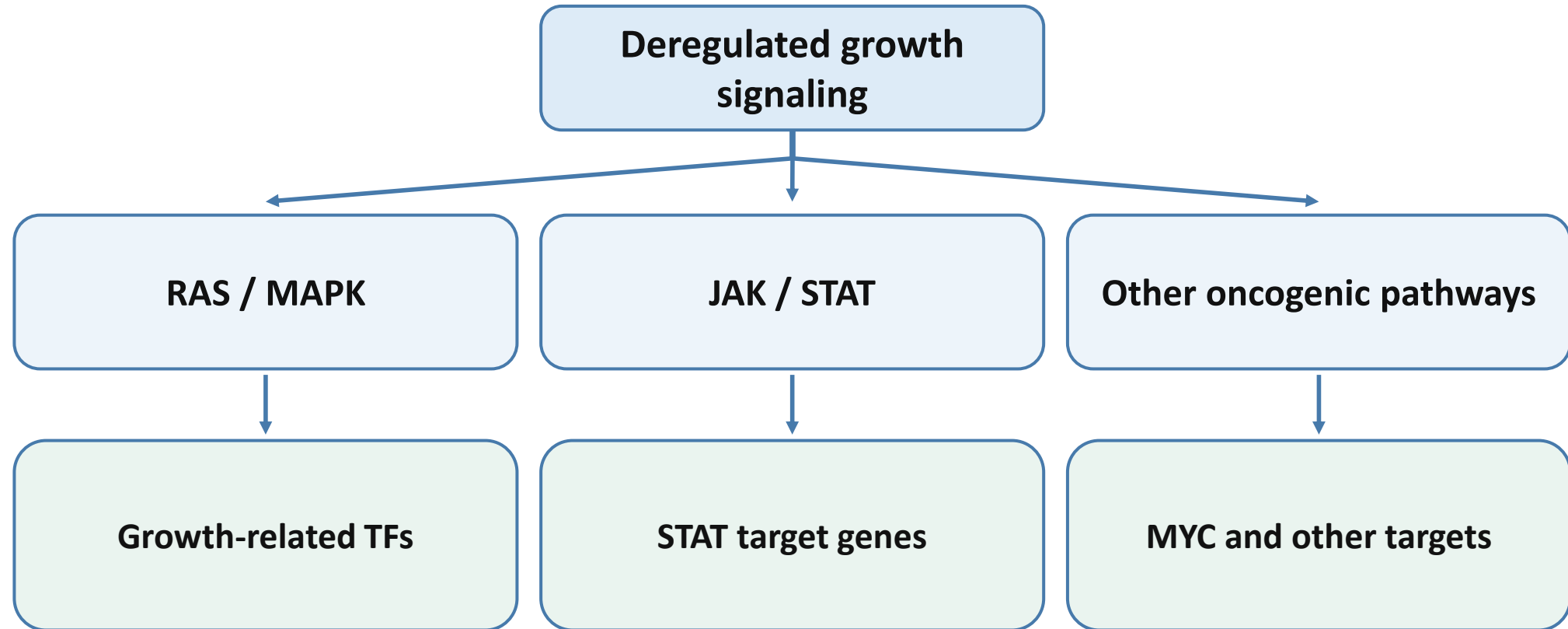
- JAK2 relays signals from cytokine receptors lacking intrinsic kinase domains.
- The source cites polycythemia vera and related myeloid neoplasms.

JAK/STAT links cytokine receptors to transcription

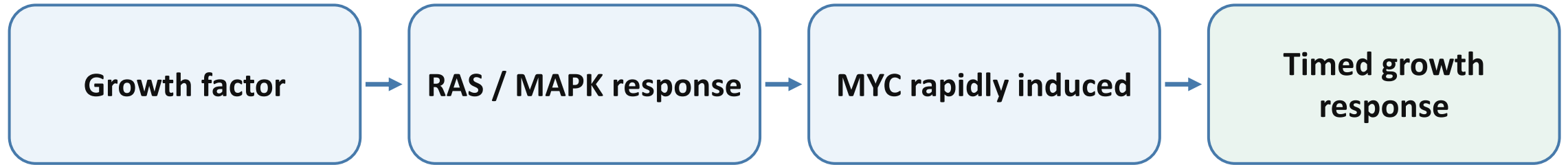


- Mutant JAK2 can reduce reliance on hematopoietic growth signals such as erythropoietin.
- The resulting transcriptional program promotes expansion of affected myeloid cells.

Mitogenic pathways converge on nuclear regulators

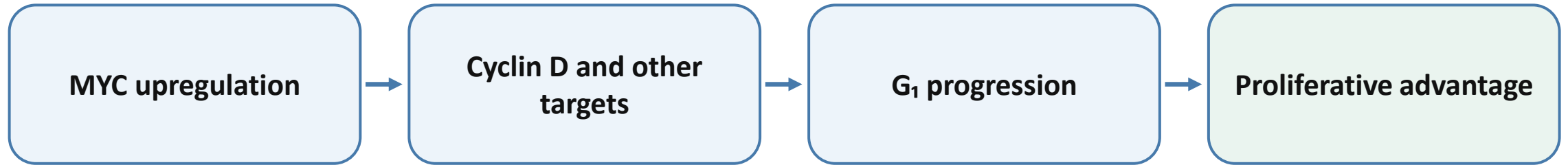


MYC is a rapid, normally transient response gene



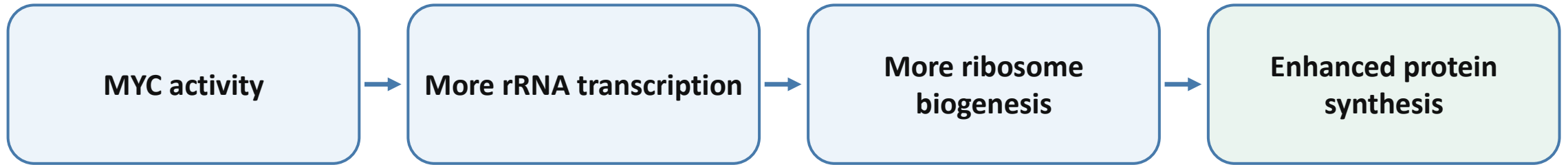
- MYC expression is normally controlled at transcription, translation, and protein stability levels.
- Persistent MYC expression drives a broad progrowth transcriptional program.

MYC stimulates cell-cycle and growth programs



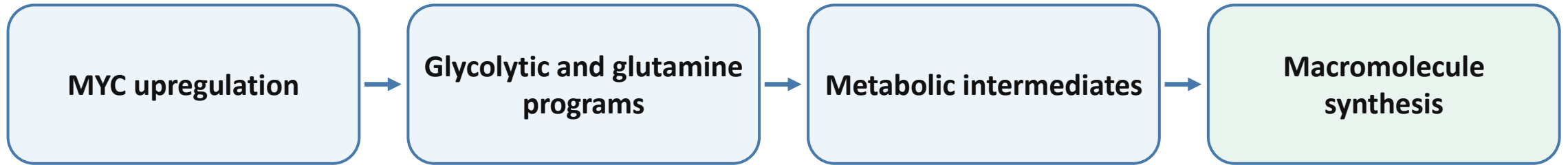
- MYC induces many genes involved in cell growth.
- Its output extends beyond simple acceleration of DNA replication.

MYC increases the cell's protein-making capacity



- Ribosomal RNA expression and processing are MYC-regulated programs.
- Biosynthetic capacity helps a dividing cell produce daughter-cell biomass.

MYC supports cancer-associated metabolic reprogramming



- MYC promotes production of precursors for proteins, lipids, and nucleic acids.
- This program with the Warburg effect.

MYC can contribute to immortalization and stemness

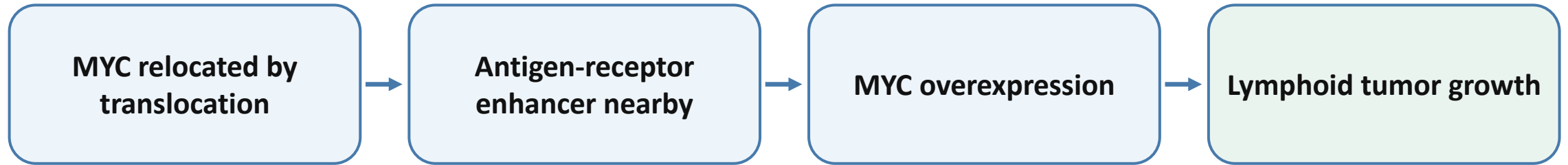
Telomerase connection

- MYC may increase telomerase expression in some contexts.
- Telomerase contributes to extended replicative capacity.

Cell-state connection

- MYC participates in somatic-cell reprogramming.
- The source discusses a possible contribution to cancer stemness.

MYC translocation alters enhancer control

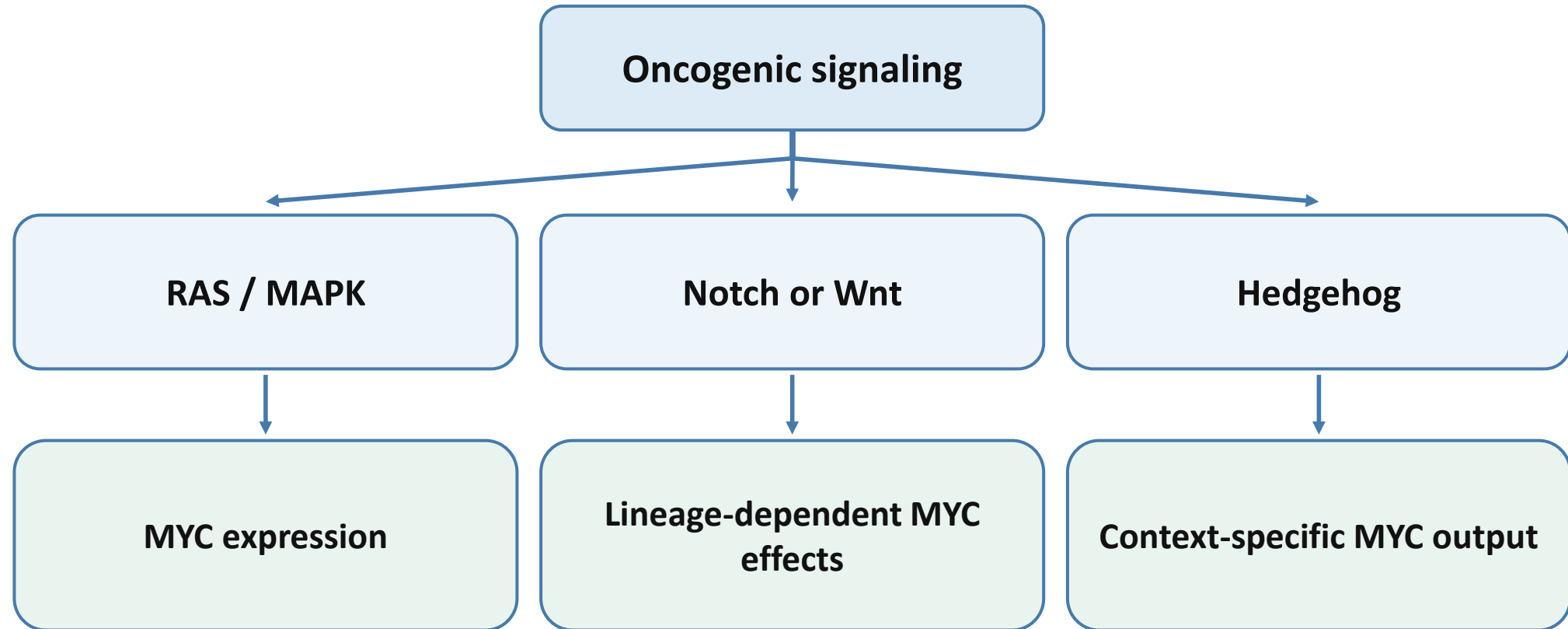


- Burkitt lymphoma characteristically involves an MYC translocation.
- Regulatory enhancers activate MYC expression inappropriately.

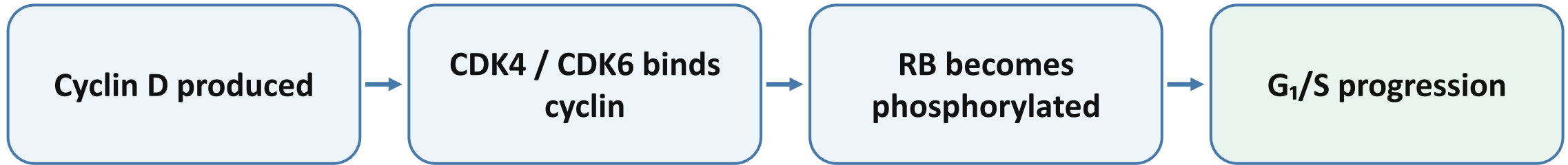
MYC family amplification increases gene dosage

Gene	Alteration	Illustrative tumor
MYC	Gene amplification	Breast, colon, and lung tumors
NMYC	Amplification	Neuroblastoma
LMYC	Amplification	Small-cell lung carcinoma

Several upstream pathways converge on MYC



Cyclin–CDK complexes drive cell-cycle progression



- Cyclins are regulated cyclically; CDKs are activated by cyclin binding.
- D cyclins and CDK4 act at the key G₁ restriction point.

G₁/S is an important oncogenic control point

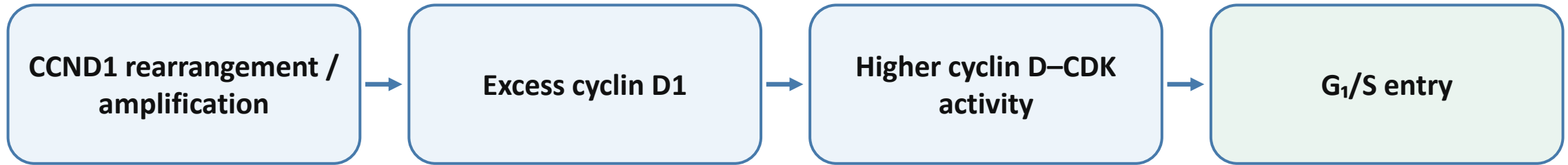
Properly controlled

- Growth cues regulate cyclin D–CDK activity.
- RB restrains E2F activity in its hypophosphorylated state.
- Checkpoint signals prevent inappropriate S-phase entry.

Oncogenic disturbance

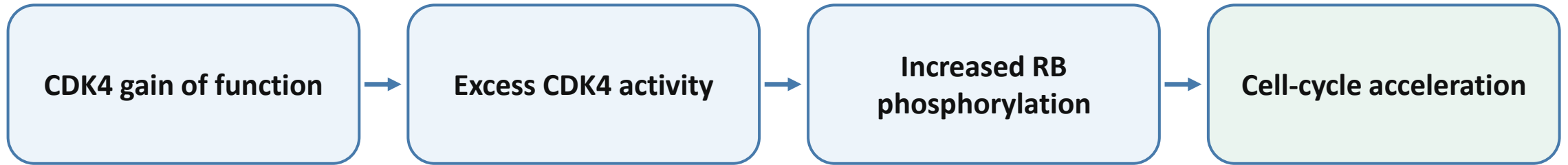
- Excess cyclin D or CDK4 increases kinase drive.
- RB phosphorylation releases E2F-dependent programs.
- G₁/S progression becomes less dependent on normal cues.

Cyclin D gene activation promotes unchecked G₁ progression



- CCND1 translocation is a textbook example in mantle cell lymphoma.
- Amplification also occurs in some breast and esophageal cancers.

CDK4 amplification is a cell-cycle oncogene mechanism



- CDK4 amplification with melanoma, sarcoma, and aggressive glial tumors.
- CDK4/6-targeted inhibitors illustrate a therapeutic consequence in selected breast cancers.

The same growth program can be deregulated at many levels

Signaling level	Representative lesion	Common output
Growth factor	PDGF autocrine loop	Persistent receptor stimulus
Receptor	EGFR mutant / ERBB2 gain	Constitutive kinase input
Cytoplasmic	KRAS / BRAF / PI3K	Progrowth signaling
Nuclear	MYC overexpression	Growth-gene transcription
Cell cycle	CCND1 / CDK4 activation	Unchecked G ₁ /S entry

Molecular alteration predicts where inhibition may act

Driver example	Major pathway position	Therapeutic logic
Mutant EGFR	Receptor kinase	Inhibit altered EGFR activity
EML4::ALK	Fusion receptor kinase	Block ALK kinase
BCR::ABL	Fusion nonreceptor kinase	Block ABL kinase
Mutant BRAF	MAPK arm	Inhibit activated RAF
KRAS G12C	RAS signaling node	Allele-specific RAS targeting

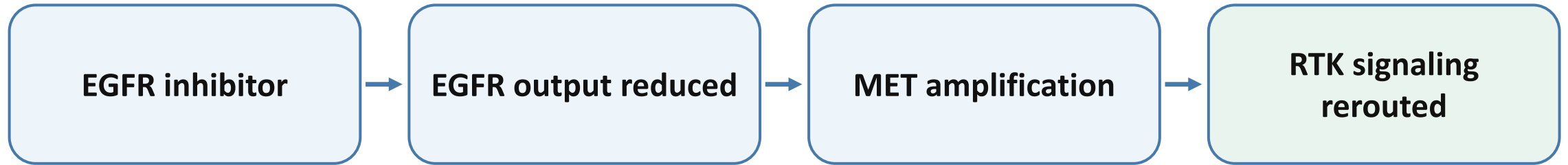
Application: EGFR mutation and progressive lung cancer

A lung adenocarcinoma harbors an activating ERBB1 mutation and initially regresses with an EGFR inhibitor. After a period of response, the tumor progresses, and MET amplification is identified.

Which pathway-level explanation best accounts for the progression?

- MET supplies alternative receptor signaling downstream.
- A new autocrine growth factor is necessarily present.
- The tumor has become biologically incapable of growth.

EGFR resistance: A bypass, not loss of growth autonomy



- MET-driven bypass can restore downstream progrowth signaling.
- Tumor evolution explains why the initial response does not guarantee cure.

Application: A constitutive fusion kinase in leukemia

A patient has chronic myeloid leukemia with a BCR::ABL fusion. A tyrosine kinase inhibitor markedly suppresses the proliferative population, but rare fusion-positive stemlike cells persist.

Which two Robbins concepts are illustrated?

- Oncogene addiction to BCR::ABL signaling.
- Incomplete eradication of a stemlike residual compartment.
- Mandatory loss of every tumor-suppressor gene.

CML response illustrates dependence and persistence

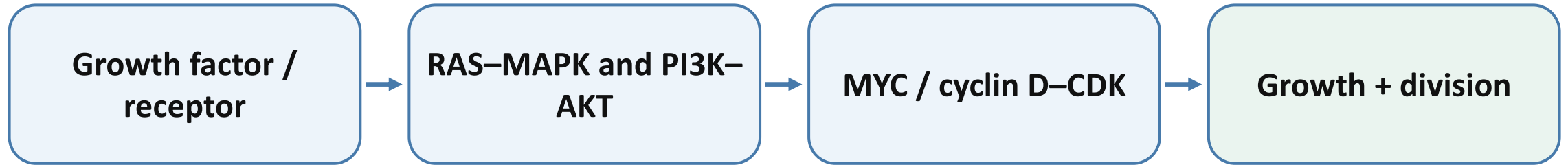
Strong clinical response

- BCR::ABL is a dominant driver.
- Kinase inhibition suppresses proliferating leukemia.
- Oncogene addiction creates high drug sensitivity.

Limits of molecular suppression

- Some rare stemlike cells remain.
- Residual cells may not require the same kinase signal to survive.
- Discontinuation can be followed by recurrent disease.

Integrative framework: Signals, circuitry, output



- Oncogenic alterations may act at any step of the normal signaling chain.
- Mutations in negative regulators can produce similar pathway activation.
- Therapeutic sensitivity depends on the operative molecular driver and tumor context.

Core principles to retain

- Oncogenes represent gain of progrowth function in normal cellular genes.
- Growth autonomy can be generated by ligands, receptors, switches, kinases, transcription factors, or cyclin–CDK components.
- MAPK transcriptional signals and PI3K–AKT biosynthetic/survival signals converge on sustained growth.
- Targeted inhibition exposes dependencies; Genetic heterogeneity and persistent cells can limit durability.

Primary reference and teaching scope

This lecture is grounded in the specified 2026 Robbins textbook chapter.

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026). Chapter 7, Neoplasia.
- Self-Sufficiency in Growth Signals: Oncogenes; Oncoproteins and Cell Growth; Growth Factors; Growth Factor Receptors.
- Downstream Components of the Receptor Tyrosine Kinase Signaling Pathway; Nonreceptor Tyrosine Kinases; Transcription Factors; MYC; Cyclins and Cyclin-Dependent Kinases.
- Mechanism schematics are original, editable PowerPoint constructions; no histologic or patient specimens are depicted.