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# Downstream Components of the Receptor Tyrosine Kinase Signaling Pathway

**RAS • MAPK • PI3K/AKT • tumor suppressor brakes**

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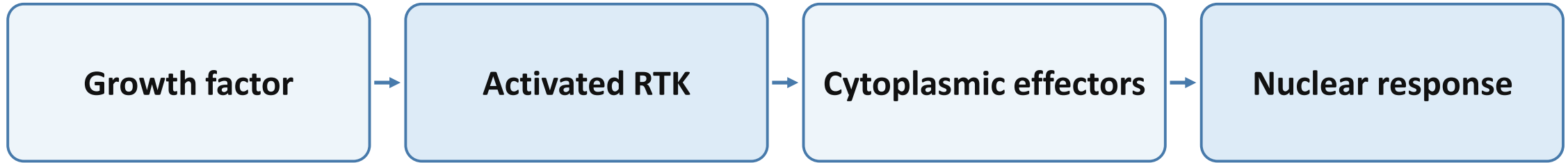
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## Learning outcomes

- Trace growth factor receptor signals through RAS, MAPK and PI3K/AKT.
- Explain normal RAS nucleotide cycling and the protective roles of GAPs, NF1 and PTEN.
- Interpret oncogenic alterations in RAS, BRAF and PI3K and their therapeutic implications.

## Growth signals must be transmitted inside the cell



- Ligand binding activates the receptor; The cytoplasmic tail undergoes tyrosine phosphorylation.
- Intracellular adaptors and signal-transducing proteins relay this extracellular instruction.

*Cancer can deregulate signaling at any point in this chain.*

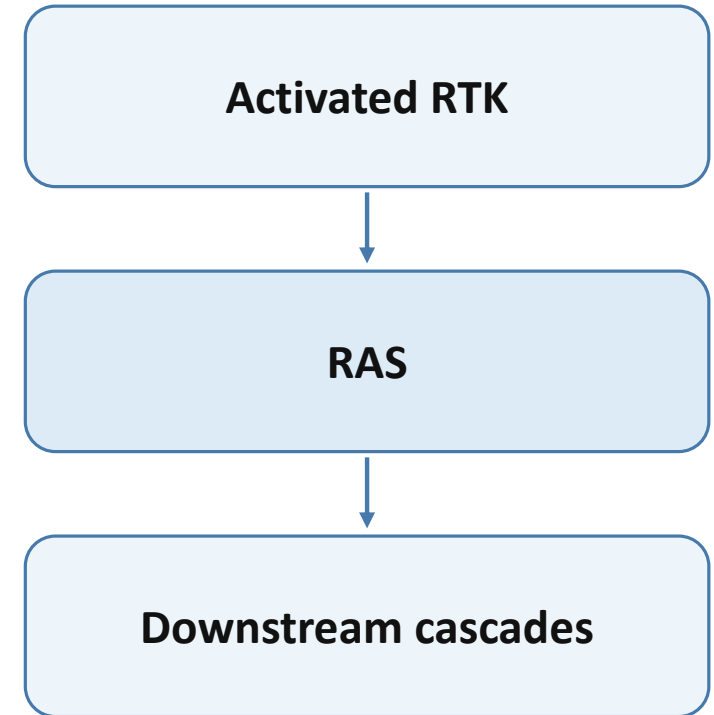
## An oncogenic lesion can uncouple growth from ligand

| Physiologic signaling             | Oncogenic signaling                          |
|-----------------------------------|----------------------------------------------|
| Requires a growth factor input    | A downstream mutant may signal without it    |
| Receptor activation is transient  | Growth-promoting activity becomes persistent |
| Controls restrain signal duration | Mutations may disable the restraints         |

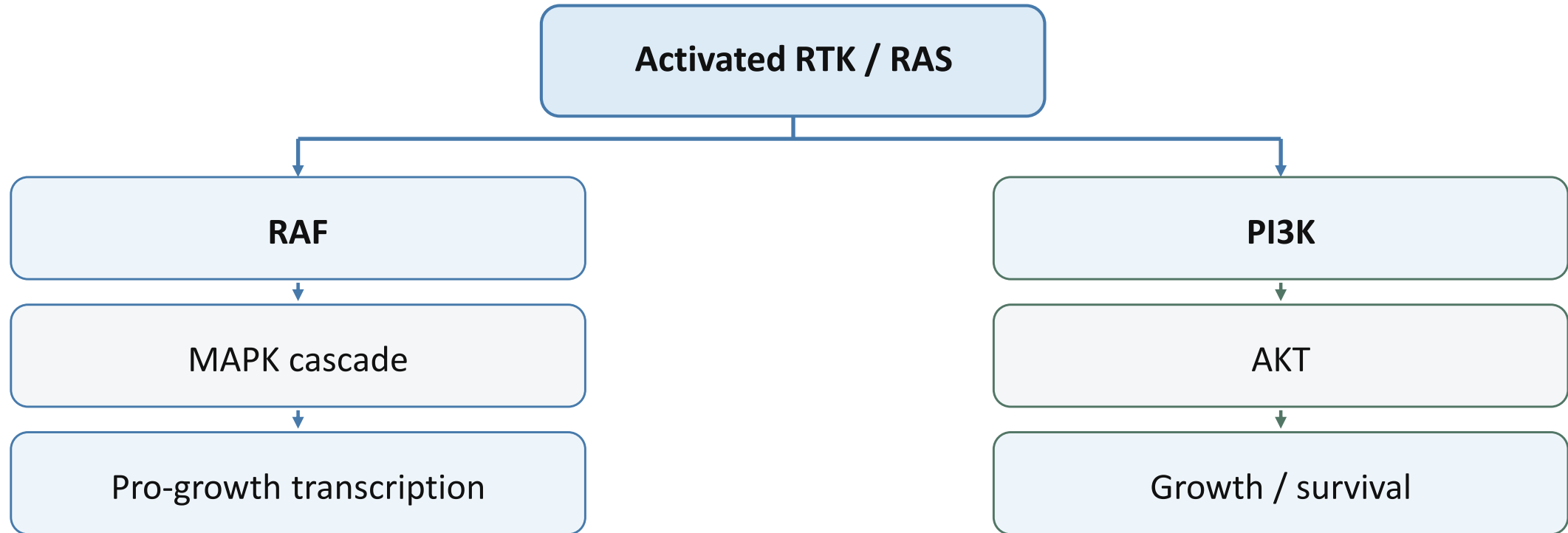
*A mutant signaling protein can bypass the need for an activated receptor.*

## RAS sits immediately downstream of many RTKs

- RTK phosphorylation creates docking sites for downstream signaling complexes.
- RAS converts receptor input into intracellular kinase-cascade activation.
- RAS is an intracellular signaling node rather than a growth factor receptor.



# RTK signaling divides into two major effector arms



The MAPK arm chiefly transmits mitogenic signals to nuclear transcription machinery. • The PI3K/AKT arm coordinates growth, metabolism, protein synthesis and survival.

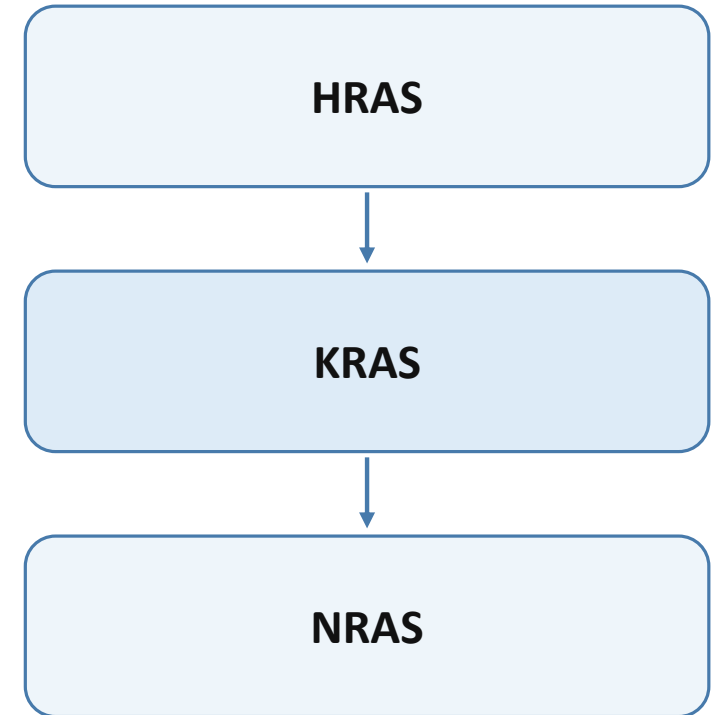
# Signals move through distinct biochemical switches

| Component  | Functional mechanism                    |
|------------|-----------------------------------------|
| RTK        | Receptor with tyrosine kinase activity  |
| RAS        | Small G protein, activated by bound GTP |
| RAF / AKT  | Intracellular serine/threonine kinases  |
| GAP / PTEN | Negative regulators of signaling        |

*The mechanisms differ; All may become targets of cancer-associated alterations.*

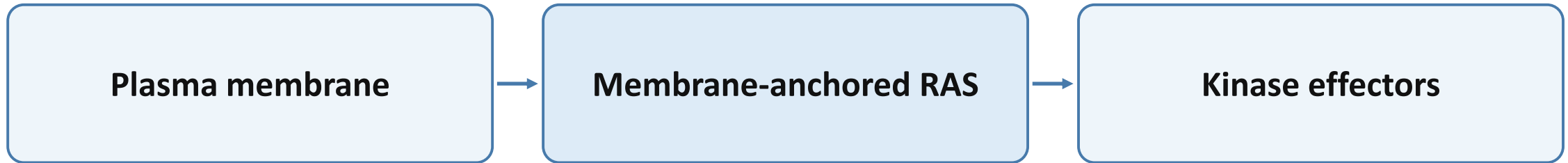
# Human RAS proteins are encoded by three genes

- HRAS, KRAS and NRAS encode closely related RAS proteins.
- All function as nucleotide-regulated signal-transducing G proteins.
- The shared GDP/GTP switch explains how multiple RAS genes can act as oncogenes.



*Three genes, one common signaling logic.*

## RAS is membrane-associated, not a transmembrane RTK



- RAS proteins are associated with the plasma membrane.
- A membrane anchor helps position RAS near signaling complexes activated by RTKs.

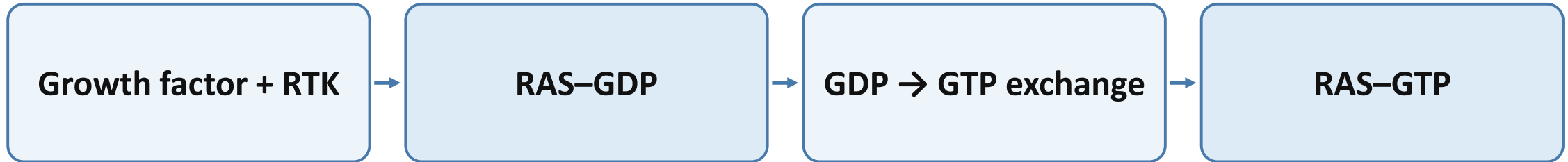
*Subcellular localization connects receptor activation to RAS function.*

## GDP-bound and GTP-bound RAS are different states



- RAS-GDP is the relatively inactive state.
- RAS-GTP is the active, signal-transmitting state.
- GDP/GTP exchange changes RAS conformation and downstream interactions.

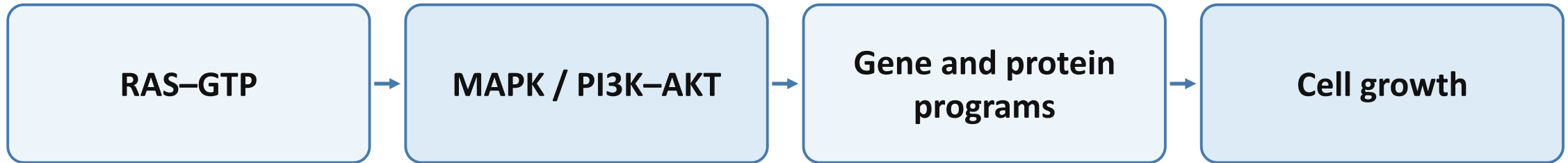
## Growth factor stimulation initiates the RAS switch



- Activated RTKs promote exchange of bound GDP for GTP on RAS.
- RAS undergoes a conformational change and becomes able to signal to effectors.

*A receptor input is translated into an active nucleotide state.*

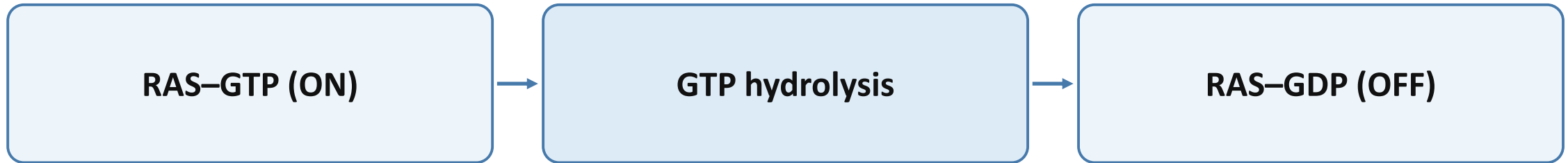
## Activated RAS propagates the growth signal



- GTP-bound RAS triggers downstream signaling pathways.
- Its activation is normally brief, linking responses to the period of upstream stimulation.

*Signal transduction integrates proliferation with metabolic support.*

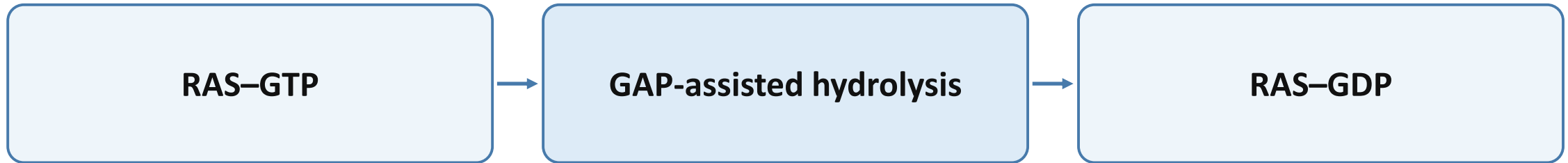
## Intrinsic GTPase activity turns RAS off



- RAS can hydrolyze bound GTP to GDP.
- Hydrolysis returns RAS toward the inactive state, terminating that cycle of signaling.

*GTP hydrolysis is a built-in timer for active RAS.*

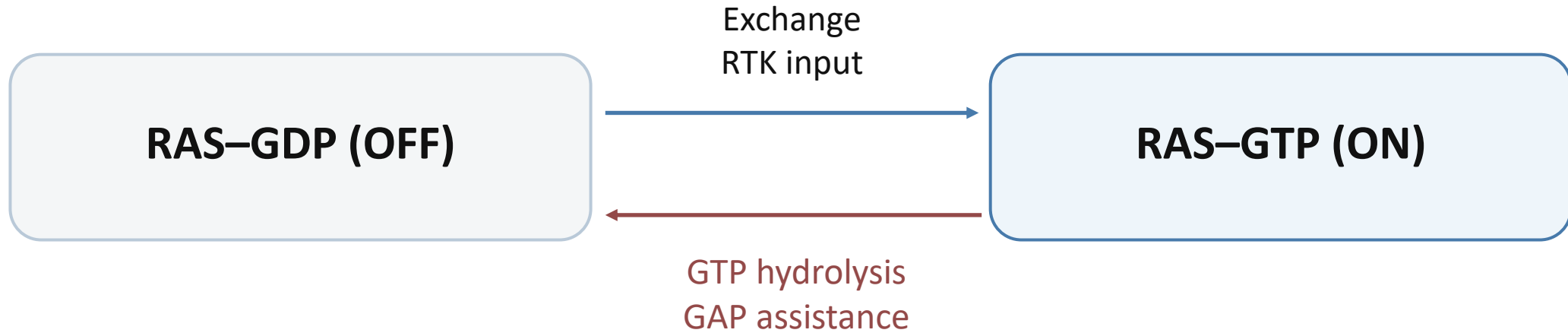
## GTPase-activating proteins accelerate signal termination



- GAPs bind activated RAS and markedly accelerate its GTPase activity.
- More than a 1000-fold enhancement of RAS GTP hydrolysis.

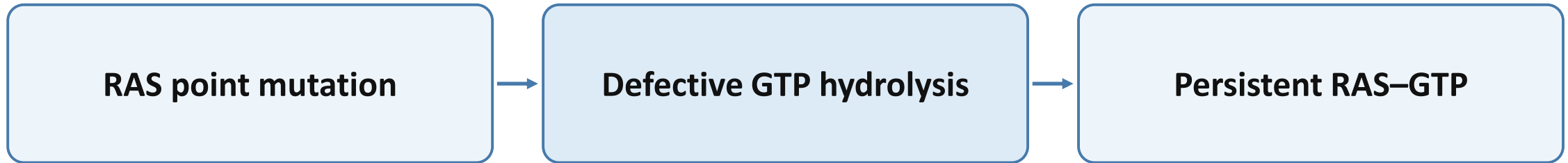
*GAPs are strong physiological brakes on RAS signaling.*

# The normal RAS cycle needs both ON and OFF reactions



- Growth factor signaling promotes GDP-to-GTP exchange.
- Intrinsic GTPase activity and GAP action return RAS to the GDP-bound state.

# Oncogenic RAS mutations impair GTP hydrolysis



- Cancer-associated point mutations can markedly reduce RAS GTPase activity.
- Mutant RAS remains predominantly in its signaling-competent GTP-bound form.

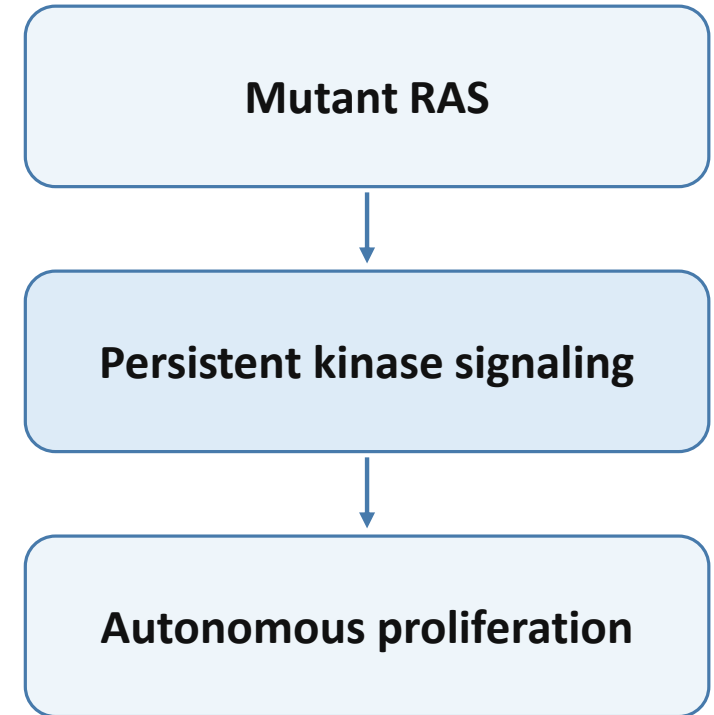
*The switch becomes functionally stuck in the ON state.*

## Normal and mutant RAS differ in signal duration

| Normal RAS                                            | Oncogenic RAS                                       |
|-------------------------------------------------------|-----------------------------------------------------|
| GDP/GTP cycling responds to receptor input            | GTP-bound signaling persists despite regulation     |
| GAP-assisted hydrolysis efficiently terminates signal | Mutation diminishes the normal GTPase OFF mechanism |
| Time-limited downstream signaling                     | Sustained pro-growth output                         |

# RAS is an oncogene through gain of function

- The altered protein acquires persistent signaling activity.
- An activating RAS allele can deliver pro-growth cues without continued RTK activation.
- This is a molecular mechanism of growth autonomy in cancer.



# RAS mutations are widespread, but not universal

**15–20%**

Of all human tumors (approx.)

- Approximately 15%–20% of all human tumors have activating mutations of a RAS gene.
- The overall figure conceals major variation between tumor types.
- A mutation frequency is descriptive—not a universal diagnostic test or treatment rule.

## RAS mutation prevalence varies across tumor types

| Tumor type                          | Approximate RAS mutation frequency |
|-------------------------------------|------------------------------------|
| Pancreatic adenocarcinoma           | 90%                                |
| Colon, endometrial, thyroid cancers | ~50% each                          |
| Lung adenocarcinoma                 | ~30%                               |
| Myeloid leukemias                   | ~30%                               |

*Figures are approximate Robbins textbook estimates, not assay-specific prevalence.*

## Pancreatic adenocarcinoma illustrates strong RAS selection

**~90%**

Pancreatic adenocarcinoma

- About 90% of pancreatic adenocarcinomas contain a RAS mutation in the supplied text.
- A recurrent growth-signal lesion can become common in a particular tumor lineage.
- The statistic concerns mutation prevalence—not drug sensitivity.

## Intermediate frequencies require tumor-specific context

| Group                                   | RAS alterations in Robbins                            |
|-----------------------------------------|-------------------------------------------------------|
| Colon / endometrial / thyroid cancers   | Approximately half have RAS mutations                 |
| Lung adenocarcinoma / myeloid leukemias | Approximately three in ten                            |
| Interpretive caution                    | Mutation distributions differ by histology and cohort |

*Do not extrapolate one tumor type's frequency to every malignancy.*

## An RAS lesion can substitute for an oncogenic RTK



- In dominant tumor clones with activating RAS mutations, activating RTK mutations are almost always absent.
- The source interprets this pattern as functional substitution by activated RAS.

*A downstream oncogenic switch may make upstream activation redundant.*

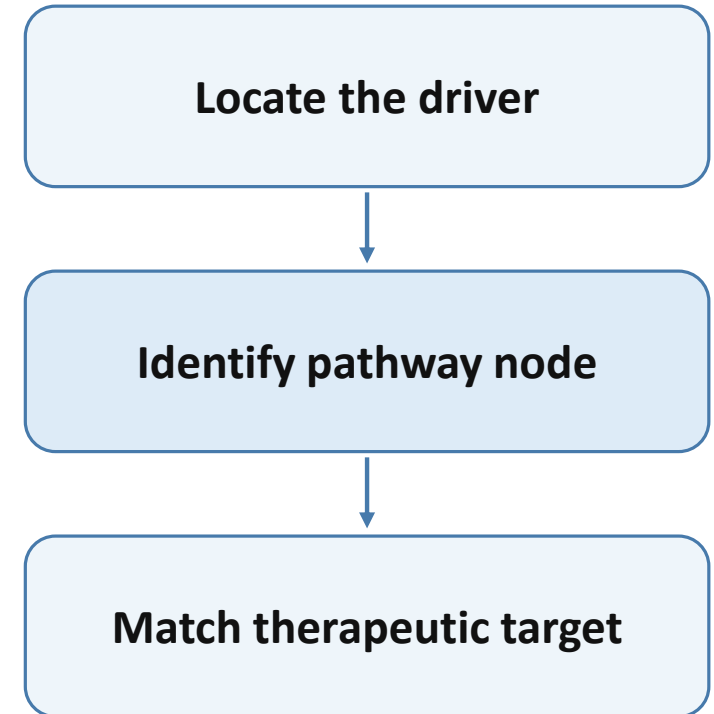
## Lung adenocarcinoma illustrates alternate driver routes

| RTK-driven molecular subtype                         | RAS-driven molecular subtype                         |
|------------------------------------------------------|------------------------------------------------------|
| Abnormal receptor kinase supplies signaling input    | RAS mutation supplies downstream activity            |
| RTK-targeted treatment may be relevant               | RAS genotype requires separate targeting strategy    |
| Dominant clone typically lacks activating RAS lesion | Dominant clone typically lacks activating RTK lesion |

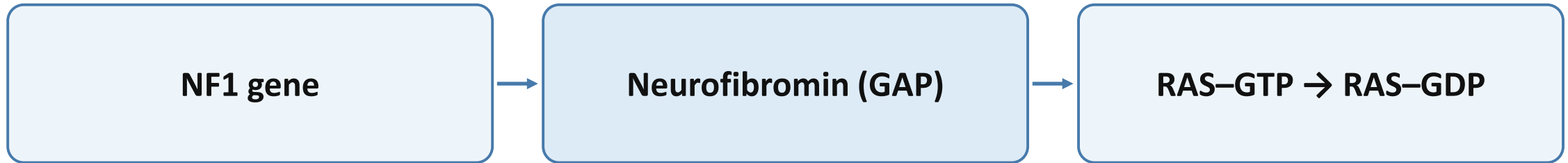
*“Almost always” does not mean absolute mutual exclusivity in every cell or tumor.*

# Molecular subtypes matter for drug selection

- The position of the oncogenic lesion affects the rationale for targeted therapy.
- Inhibition of an upstream receptor may not intercept signaling from autonomous downstream RAS.
- Tumor genotype therefore matters more than a generic label of “RTK pathway activation.”



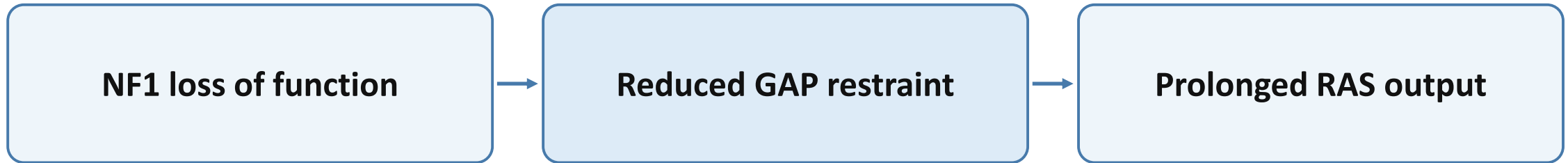
# NF1 encodes the RAS-regulating GAP neurofibromin



- Neurofibromin 1 is a GTPase-activating protein encoded by NF1.
- It promotes RAS inactivation by augmenting GTP hydrolysis.

*NF1 is a negative regulator, not another activating RAS family member.*

## NF1 loss removes a brake on wild-type RAS

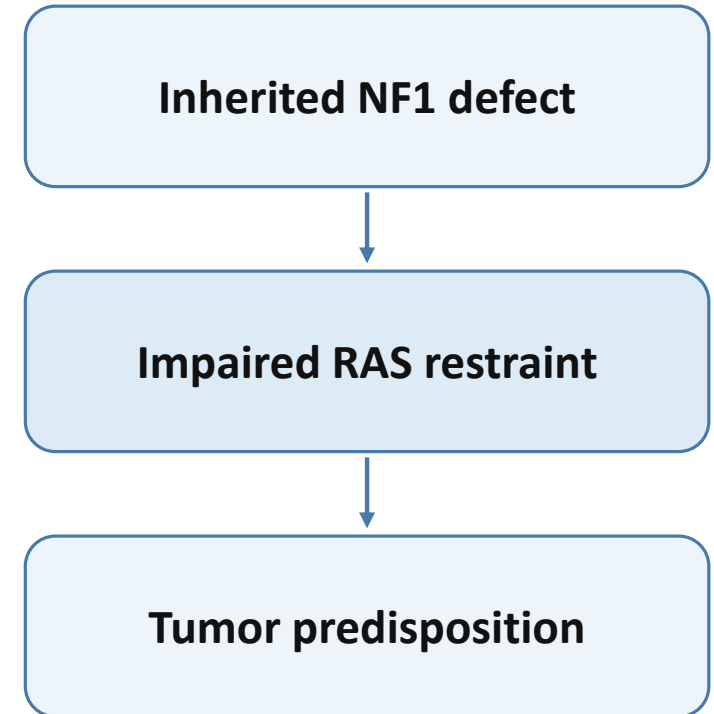


- Disabling NF1 mutations reduce the capacity to turn active RAS off.
- Elevated RAS pathway output can result even without an oncogenic RAS coding mutation.

*A lost brake can phenocopy an activated accelerator.*

## Neurofibromatosis type 1 links a syndrome to signaling

- Inherited NF1 loss is associated with familial neurofibromatosis type 1.
- The clinical syndrome exemplifies predisposition through defective RAS regulation.
- The pathogenic principle is loss of a tumor suppressor that normally restricts signaling.

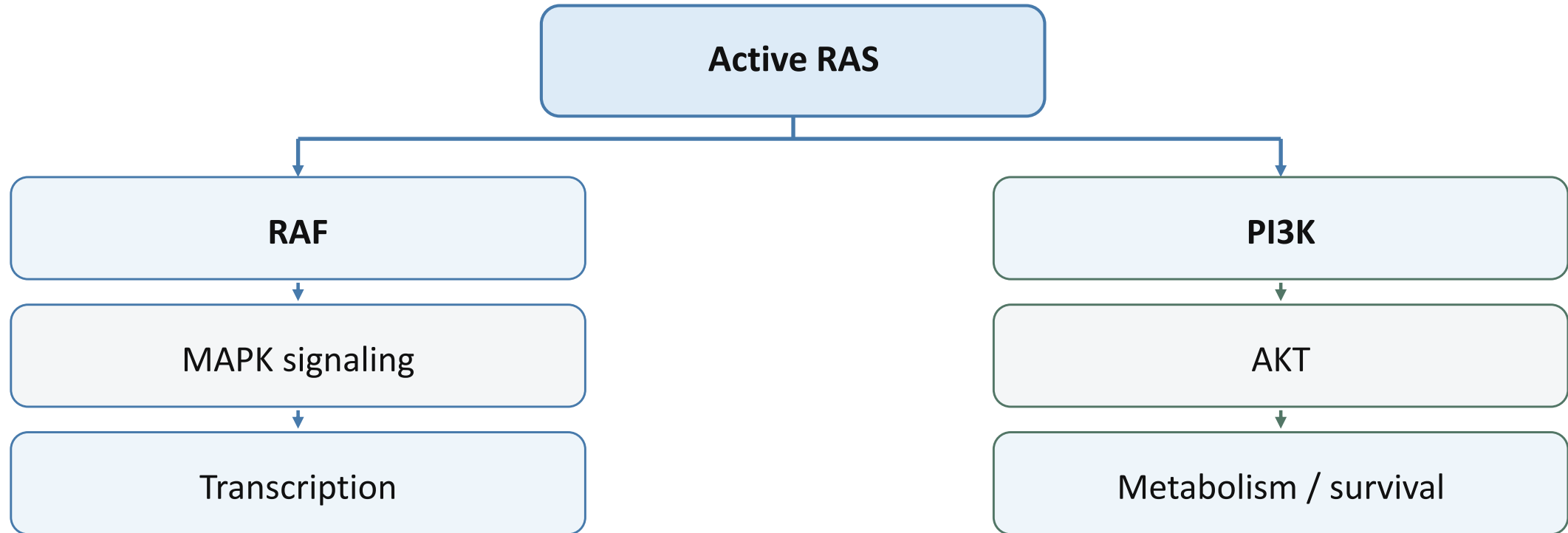


## RAS activation and NF1 loss have different genetics

| <b>RAS activating mutation</b>  | <b>NF1 disabling mutation</b>          |
|---------------------------------|----------------------------------------|
| Gain of proto-oncogene function | Loss of tumor-suppressor function      |
| RAS remains excessively active  | Normal RAS is inadequately inactivated |
| Pro-growth output rises         | Pro-growth output also rises           |

*The same signaling endpoint may arise from opposite classes of gene alteration.*

# Two major RAS-linked kinase cascades



The MAPK route and the PI3K/AKT route are major effectors of receptor signaling. • Both include kinase steps and generate pro-growth biological responses.

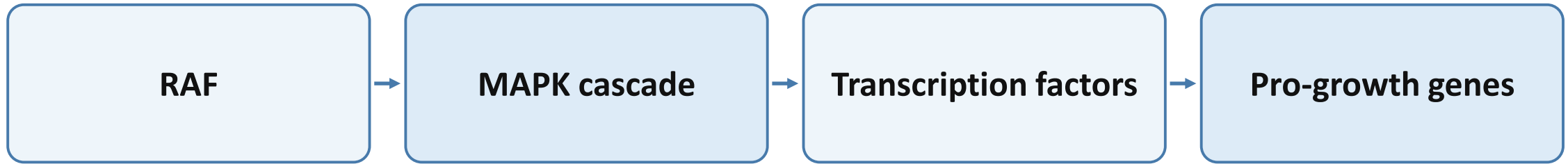
## RAF links RAS to the MAPK pathway



- RAF proteins are serine/threonine kinases positioned upstream in the MAPK cascade.
- RAS-mediated activation of RAF initiates a relay of additional kinases.

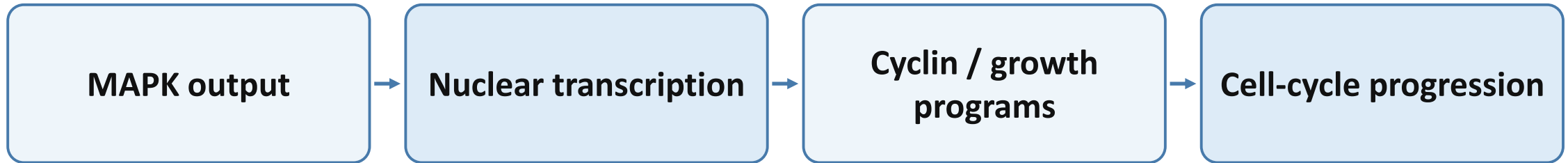
*An activated upstream kinase can influence multiple downstream targets.*

## The MAPK relay conveys signals toward the nucleus



- Sequential phosphorylation within the MAPK cascade propagates receptor-derived growth signals.
- Downstream activity ultimately regulates transcription factors and pro-growth genes.

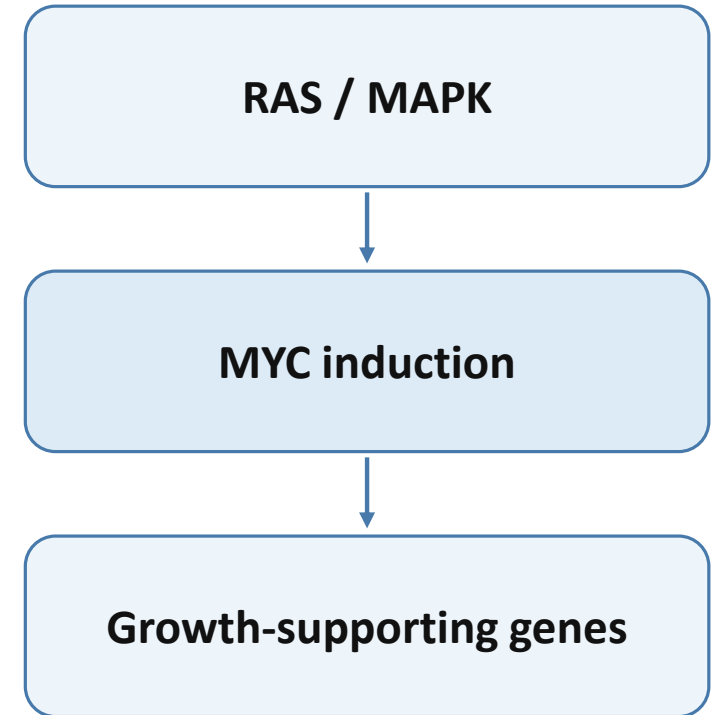
## Transcriptional output connects kinase activity to cycling



- The MAPK cascade acts upstream of gene expression changes that support proliferation.
- This supplies a mechanistic link between membrane signaling and cell-cycle entry.

## MYC is one downstream growth-response example

- The adjacent Robbins section identifies MYC as a rapid, transient response to RAS/MAPK signaling.
- MYC participates in transcriptional programs supporting growth and cell-cycle progression.
- Detailed MYC oncogenic mechanisms belong to the next topic rather than this pathway lecture.



## Activating BRAF alterations sustain MAPK signaling



- BRAF is a member of the RAF serine/threonine kinase family.
- Oncogenic activation stimulates kinases further downstream and increases transcription-factor activity.

*An oncogenic lesion below RAS can bypass the normal need for RAS stimulation.*

# BRAF is highly recurrent in hairy cell leukemia

**≈100%**

Hairy cell leukemia (close to)

- The Robbins extract reports BRAF mutation in close to 100% of hairy cell leukemias.
- This illustrates strong selection for a MAPK-pathway driver in a particular neoplasm.
- Mutation prevalence is a molecular observation, not a surrogate for microscopic diagnosis.

## BRAF is also prominent in melanoma

**~60%**

Melanoma

- The Robbins extract reports BRAF mutation in approximately 60% of melanomas.
- An altered MAPK signaling node provides a therapeutic target in selected advanced melanomas.
- Prevalence is not equivalent to a predicted individual treatment response.

## Oncogenic MAPK lesions cluster near the top



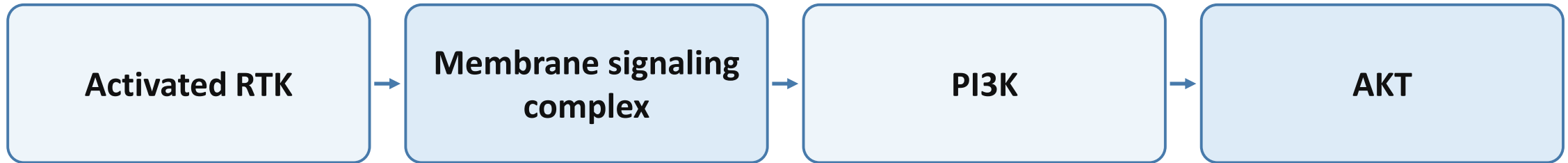
- The text observes that mutations downstream of BRAF are less common in cancer.
- Its interpretation: Lesions near the cascade origin can efficiently generate broad progrowth outputs.

*Pathway topology helps explain the prominence of upstream driver mutations.*

# MAPK is a cascade rather than a single protein

| Concept                       | Why the distinction matters                   |
|-------------------------------|-----------------------------------------------|
| RAS nucleotide switch         | Controls the initial signaling state          |
| RAF kinase activation         | Translates RAS input into a kinase relay      |
| MAPK signaling cascade        | Propagates signals through sequential enzymes |
| Transcription-factor response | Produces changed gene expression              |

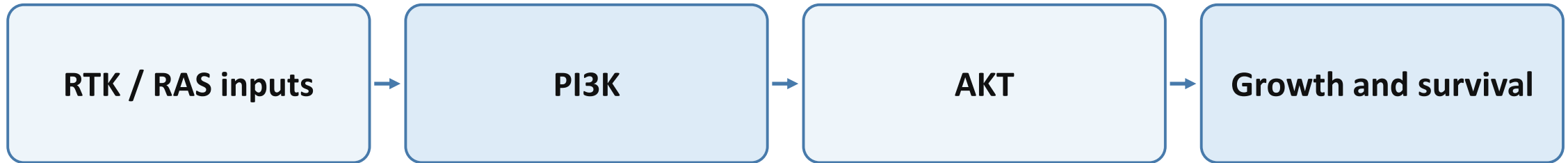
## PI3K is recruited to membrane-associated complexes



- After RTK activation, PI3K is recruited to signaling complexes near the plasma membrane.
- PI3K serves as an upstream node of a kinase network including AKT.

*Receptor recruitment helps localize the PI3K activation response.*

## PI3K/AKT forms a second major growth pathway



- PI3K activation leads to downstream serine/threonine kinase signaling.
- AKT is a principal effector linking receptor signaling to diverse cellular processes.

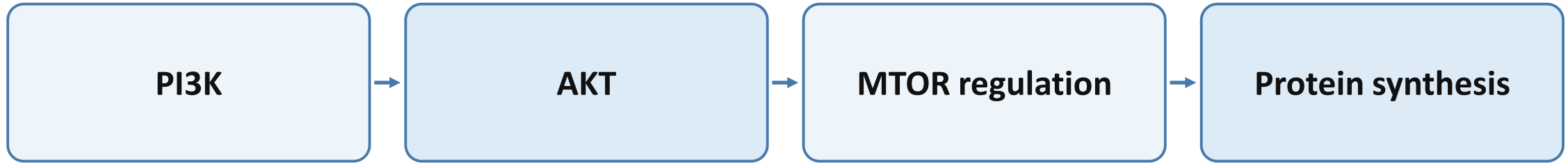
# AKT is a central signaling node

**>150**

AKT protein substrates

- AKT is described as phosphorylating more than 150 proteins.
- Its numerous substrates account for coordinated regulation of growth, metabolism and survival.
- A broad effector node can transmit one oncogenic signal to multiple downstream processes.

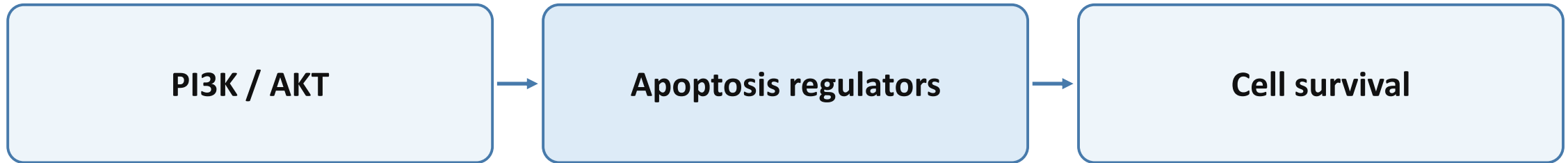
# AKT signaling supports protein biosynthesis



- MTOR is listed among key AKT-associated regulators of protein synthesis.
- Enhanced protein synthesis contributes to increased cellular mass during growth.

*Biomass accumulation complements cell-cycle entry.*

## AKT signaling also impinges on apoptosis



- The pathway engages regulators of programmed cell death, including BAD, FOXO, MDM2 and IAP.
- Altered survival regulation allows growth signaling to influence whether cells persist.

*Proliferation alone cannot explain expansion of a viable tumor population.*

## BAD and FOXO are AKT-regulated effectors

| Downstream target | Role in signaling interpretation                                 |
|-------------------|------------------------------------------------------------------|
| BAD               | Apoptosis-regulatory protein phosphorylated within AKT signaling |
| FOXO factors      | Transcription factors participating in apoptosis regulation      |
| Integrated effect | AKT integrates pro-growth signals with survival control          |

*The source groups these effectors as AKT targets; This lecture does not assign unverified phosphorylation sites.*

## MDM2 and IAP extend AKT's survival reach

| Downstream target         | Function emphasized by Robbins                            |
|---------------------------|-----------------------------------------------------------|
| MDM2                      | Apoptosis-associated regulatory component affected by AKT |
| IAP                       | Inhibitor-of-apoptosis protein family linked to AKT       |
| Biological interpretation | Multiple downstream effectors can alter cell survival     |

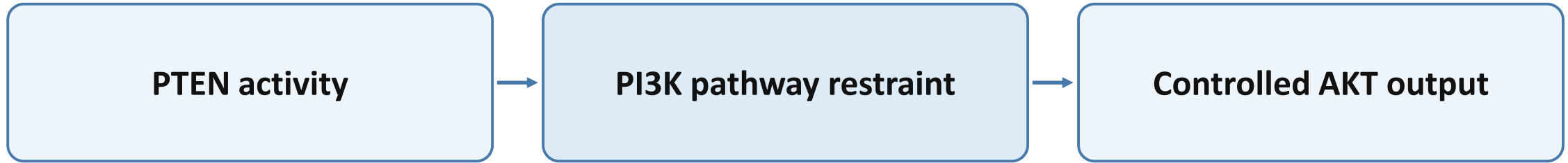
## PI3K gains of function occur in breast carcinoma

**~30%**

Breast carcinomas

- The text reports PI3K gain-of-function mutations in approximately 30% of breast carcinomas.
- These alterations affect an intracellular kinase node downstream of receptor input.
- Mutation status and therapeutic selection require tumor-specific molecular interpretation.

## PTEN is a negative regulator of PI3K signaling

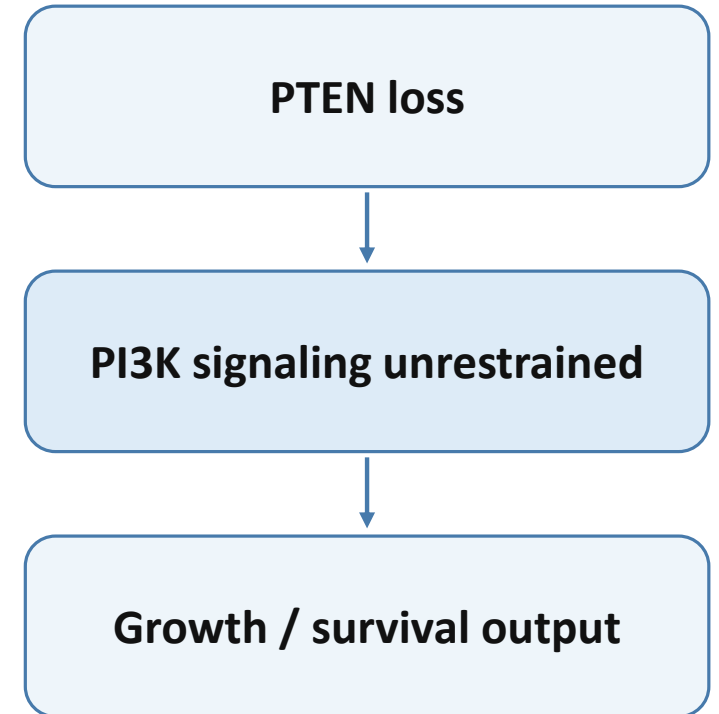


- PTEN is a tumor suppressor that restrains the PI3K pathway.
- Loss of PTEN permits excessive activity along the PI3K/AKT branch.

*Unlike PI3K oncogenic activation, PTEN-associated oncogenesis reflects lost inhibition.*

# PTEN loss is relevant in endometrial carcinoma

- Endometrial carcinoma as a common setting for PTEN mutations.
- Loss of this negative regulator can drive PI3K pathway activity.
- The mechanism is tumor-suppressor inactivation rather than receptor overexpression.



## PI3K activation and PTEN loss converge on AKT

| PI3K activating mutation                          | PTEN inactivating mutation           |
|---------------------------------------------------|--------------------------------------|
| Increases drive from a positive pathway component | Removes a negative pathway regulator |
| Gain of function                                  | Loss of function                     |
| Elevated PI3K/AKT pathway output                  | Elevated PI3K/AKT pathway output     |

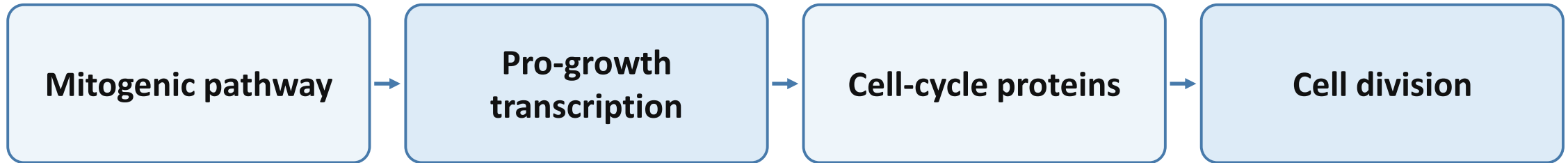
*Equivalent signaling consequences can arise from different mutation classes.*

# The MAPK and PI3K arms have overlapping outputs

| MAPK signaling                             | PI3K/AKT signaling                                |
|--------------------------------------------|---------------------------------------------------|
| Kinase relay to transcriptional activation | Kinase signaling to growth and survival effectors |
| Strong link to pro-growth gene expression  | Links protein synthesis, metabolism and apoptosis |
| BRAF a prominent oncogenic node            | PI3K activation or PTEN loss commonly implicated  |

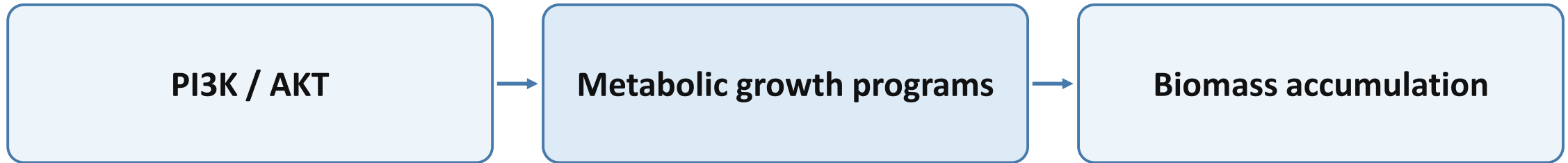
*These are emphases, not mutually exclusive functions.*

## Increased transcription promotes cell-cycle progression



- RTK–RAS–MAPK signaling leads to transcriptional induction of growth-promoting genes.
- The output helps advance the cell through controlled cell-cycle transitions.

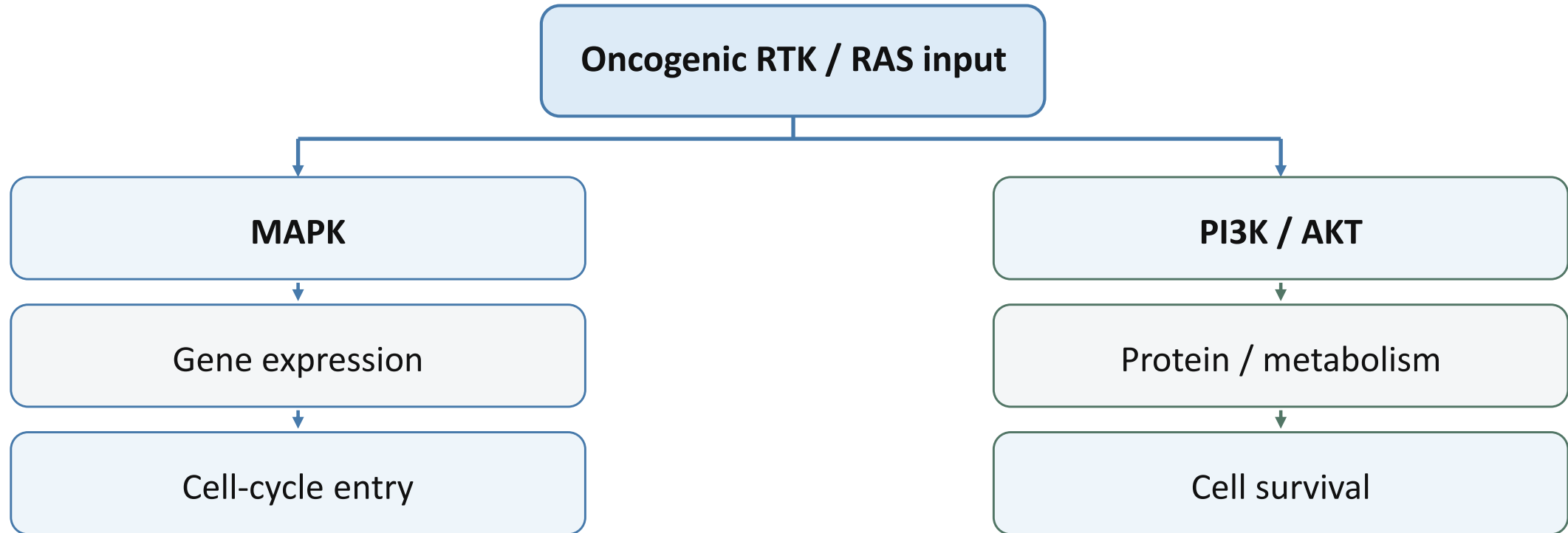
## Growth signaling must also supply metabolic capacity



- The PI3K/AKT branch supports metabolism needed for cell growth.
- Increased macromolecular synthesis accompanies proliferation rather than arising from cell division alone.

*A proliferating cell requires both a cell-cycle signal and material to build daughter cells.*

# Signaling coordinates proliferation with cell survival



MAPK-driven transcription and PI3K/AKT activity support complementary features of the growth program. • When cancer mutations make these signals persistent, growth autonomy emerges.

## Driver identity changes which pathway node to inhibit

| Genomic context | Pathway-level treatment rationale                            |
|-----------------|--------------------------------------------------------------|
| Mutant KRAS     | Block the appropriate mutant RAS protein when targetable     |
| Mutant BRAF     | Block the oncogenic RAF kinase in suitable tumors            |
| Mutant PI3K     | PI3K isoform inhibition may be relevant in selected cancers  |
| RTK mutation    | Targeting receptor activity addresses a more upstream lesion |

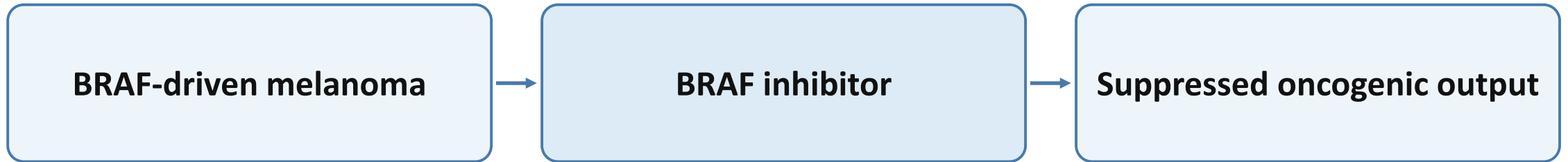
# KRAS G12C shows that RAS can be drugged



- Earlier efforts to inhibit RAS were largely unsuccessful.
- Approved drugs against KRAS with a glycine-to-cysteine change at residue 12.

*Allele specificity is central: This is not treatment for every RAS variant.*

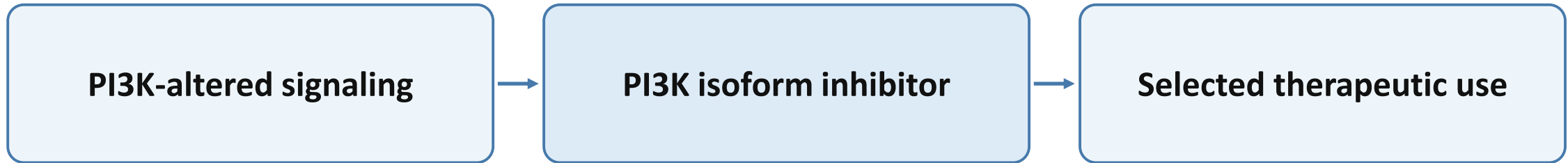
## BRAF inhibition provides pathway-directed therapy



- In advanced melanoma, BRAF-directed inhibitors can produce marked clinical responses.
- The therapeutic approach depends on an actionable lesion in the MAPK pathway.

*A pathway diagram becomes clinically useful when the disease-defining node is known.*

## Some PI3K isoform inhibitors have clinical approval

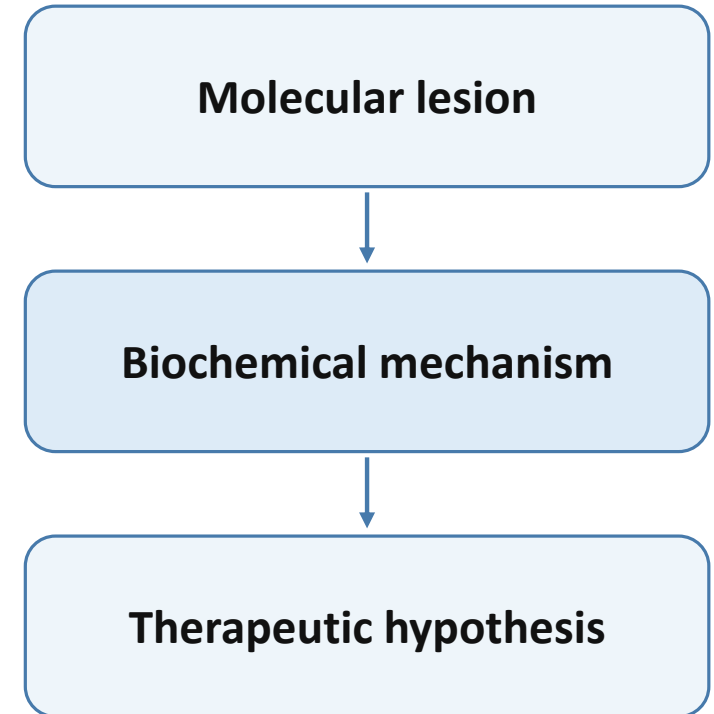


- The source reports development of drugs directed at PI3K isoforms.
- Some are approved for treatment of selected cancers; The text does not specify regimens or response rates.

*Do not infer universal effectiveness from the existence of an inhibitor.*

## Interpret treatment effects at the altered node

- Identify the alteration before predicting a logical inhibitor target.
- Determine whether the lesion affects a receptor, small G protein, kinase or inhibitor.
- Different alterations within one named pathway are not therapeutically interchangeable.



# Case exercise: An RTK-wild-type lung tumor

## Hypothetical application

- Hypothetical lung adenocarcinoma with an activating KRAS variant and no identified activating RTK variant.
- Which component is the most direct autonomous signaling driver?
- Why does an upstream receptor inhibitor not automatically suppress the downstream mutant?

## Reasoning target

Mutant KRAS can remain active without an oncogenic RTK; Treatment requires lesion-specific assessment.

# Case exercise: Inherited NF1 dysfunction

## Hypothetical application

- Hypothetical patient with a pathogenic inherited NF1 loss-of-function alteration.
- What is the normal biochemical action of neurofibromin?
- Why is NF1 classified as a tumor suppressor rather than an oncogene?

## Reasoning target

Neurofibromin acts as a RAS GAP; Its loss disables inhibitory signaling rather than activating a proto-oncogene directly.

# Case exercise: BRAF-mutant hairy cell leukemia

## Hypothetical application

- A molecular assay identifies BRAF mutation in a hypothetical hairy cell leukemia specimen.
- Which signaling branch is implicated?
- Why can a kinase lesion below RAS reproduce pro-growth effects?

## Reasoning target

The RAF–MAPK branch;  
Active BRAF can send signals to downstream kinases without normal upstream activation.

# Case exercise: PI3K versus PTEN

## Hypothetical application

- Two hypothetical tumors show increased PI3K/AKT pathway activity: One has PI3K gain of function; Another has PTEN loss.
- Which alteration involves an oncogene and which a tumor suppressor?
- Explain how both can produce excess AKT pathway output.

## Reasoning target

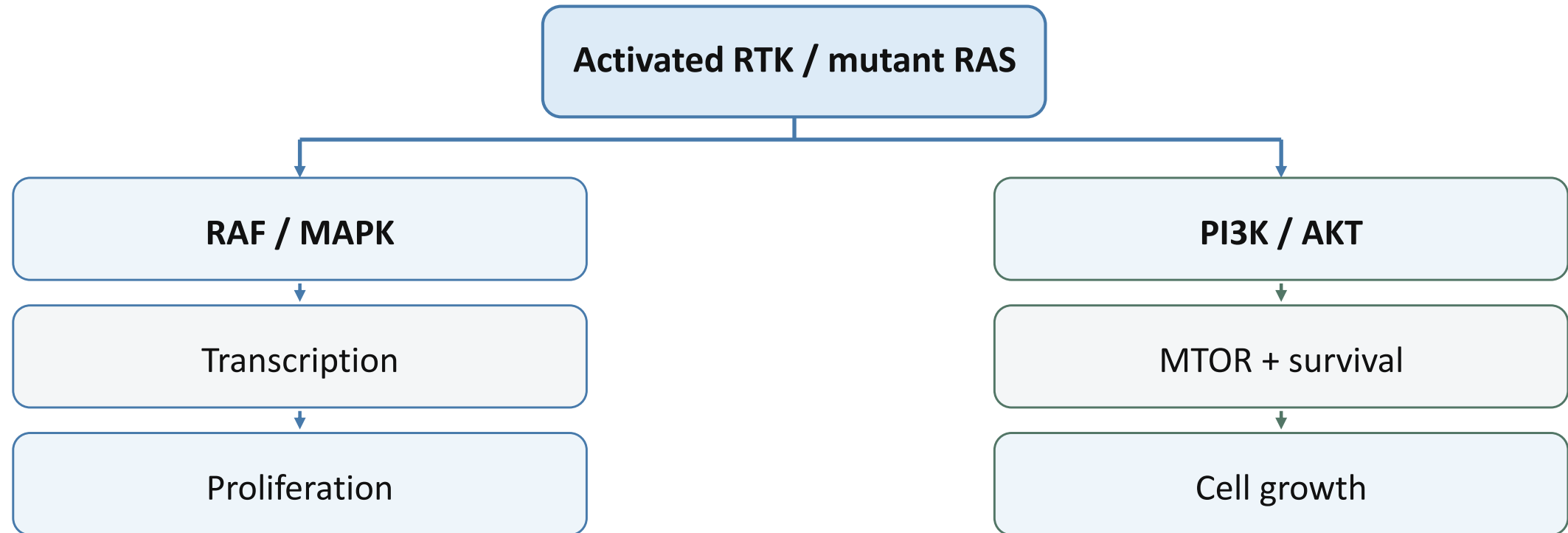
PI3K gain is oncogenic activation; PTEN loss removes negative regulation. Both can enhance AKT output.

## Map each molecular lesion to its mechanism

| Altered component | Mutation class   | Immediate pathway effect             |
|-------------------|------------------|--------------------------------------|
| RAS               | Gain of function | Persistent GTP-bound signaling       |
| NF1               | Loss of function | Reduced GAP-mediated RAS shutdown    |
| BRAF              | Gain of function | Persistent MAPK kinase-cascade input |
| PI3K              | Gain of function | Increased PI3K/AKT signaling         |
| PTEN              | Loss of function | Failure to restrain PI3K signaling   |

*A robust interpretation links gene → function → pathway output.*

# The integrated oncogenic signaling model



Normal growth factor dependence requires transient activation and effective negative regulators. • Cancer can bypass this control by gain-of-function drivers or loss-of-function restraints.

## Five mechanistic conclusions

- RAS is a GDP/GTP switch; GAPs terminate its activation.
- Mutant RAS and loss of NF1 can both produce excessive RAS activity.
- BRAF drives the MAPK transcriptional route; PI3K/AKT coordinates growth and survival.
- PTEN normally opposes PI3K signaling.
- Treatment selection depends on the specific altered molecule and genotype.

## Primary textbook source

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026).

Chapter 7, Neoplasia: “Downstream Components of the Receptor Tyrosine Kinase Signaling Pathway,” pp. 254–255.

Adjacent context: Growth Factor Receptors; Transcription Factors / MYC.