

Other Tumor Suppressor Genes

How loss of growth restraints drives neoplasia

APC • CDH1 • CDKN2A • TGF- β /SMAD • PTEN • VHL • STK11

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

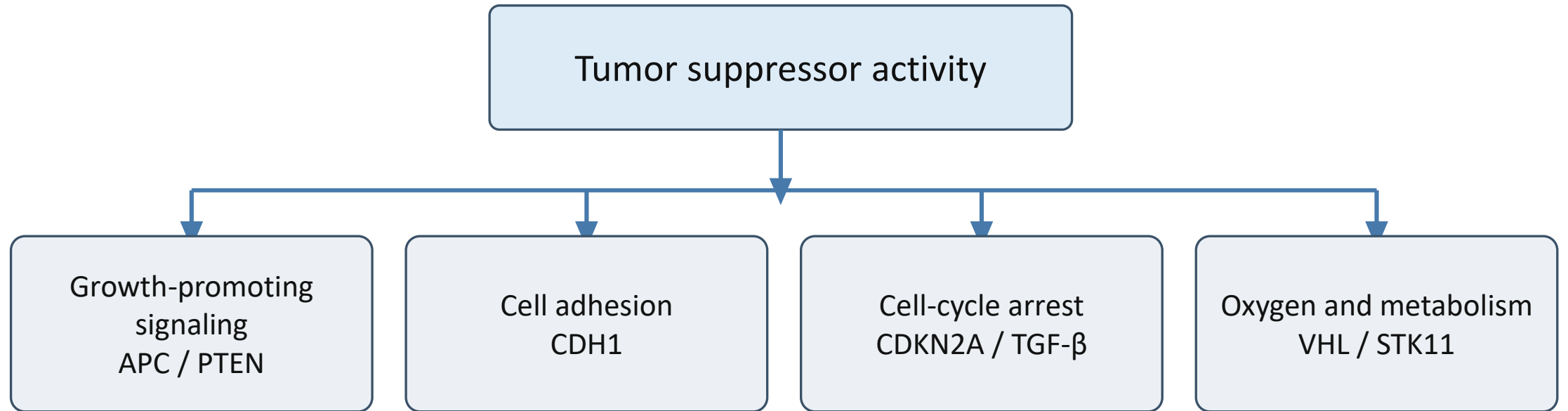
www.abusuraihsakhri.com

Learning outcomes

By the end of the lecture, explain:

- How APC regulates β -catenin stability and colonic epithelial proliferation.
- How CDH1, CDKN2A and TGF- β signaling restrain growth or invasion.
- How PTEN, VHL and STK11 control intracellular signaling and metabolism.
- How inherited defects differ from additional somatic events in tumor evolution.

Seven suppressors, several cellular brakes



Each mechanism restrains an aspect of the neoplastic phenotype.

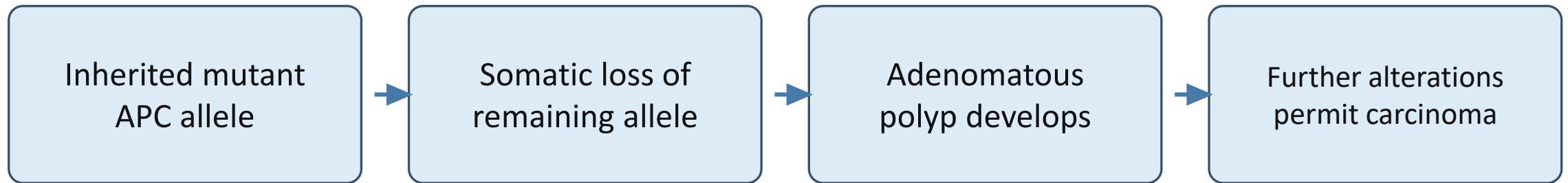
Tumor suppressors are functional restraints

The affected pathway matters as much as the gene.

- Tumor suppressors influence one or more hallmarks of cancer.
- Recurrent chromosomal deletions can disable suppressor loci.
- Cancer genome sequencing continues to define the full set of suppressors.
- The examples in this section illustrate distinct suppressive mechanisms.

A hereditary allele predisposes; Additional loss initiates

APC illustrates the need to inactivate both copies.



Familial predisposition and subsequent tumor progression are not the same genetic event.

Map each suppressor to its primary brake

Gene / pathway	Physiologic restraint	Loss-of-function consequence
APC	β -catenin turnover	Constitutive Wnt-like transcription
CDH1	Intercellular adhesion	Reduced cohesion; altered β -catenin
CDKN2A	RB and p53 checkpoint support	Easier cell-cycle progression
TGF- β / SMAD	Antiproliferative gene program	Escape from growth inhibition
PTEN	PI3K–AKT pathway brake	Excess progrowth signaling
VHL	Oxygen-dependent HIF α disposal	Persistent hypoxia-response signaling
STK11	Metabolic regulation	Altered metabolic control

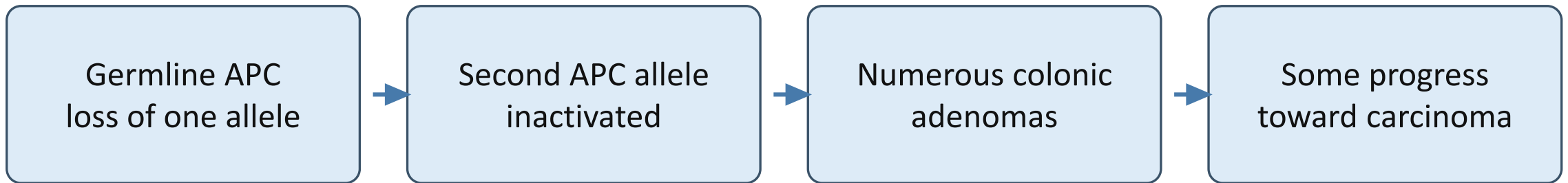
APC: The gatekeeper of colonic neoplasia

Loss of a growth-signal brake is an early lesion.

- APC is a tumor suppressor on chromosome 5q21.
- Germline loss-of-function variants underlie familial adenomatous polyposis (FAP).
- Both APC copies must be lost for an adenoma to arise.
- Further acquired alterations are needed for carcinoma progression.

Familial adenomatous polyposis follows a two-hit pattern

FAP is autosomal dominant at the family level.



The inherited phenotype is dominant, but an individual adenoma requires loss of both functional APC copies.

The clinical phenotype of FAP

The colon develops an extensive adenoma burden.

- Affected individuals often develop thousands of adenomas.
- Polyps commonly appear during adolescence or early adulthood.
- One or more adenomas almost invariably undergo malignant transformation without effective intervention.
- The mechanism connects inherited susceptibility to sequential somatic changes.

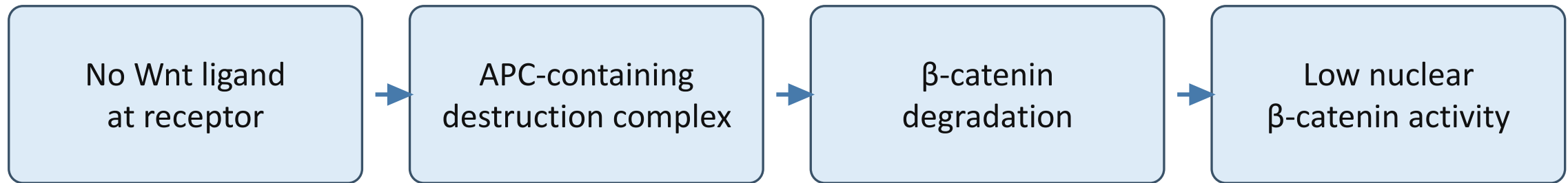
APC loss is common in sporadic colorectal tumors

Hereditary and sporadic tumors can converge mechanistically.

- APC defects in 70%–80% of nonfamilial colorectal carcinomas and sporadic adenomas.
- Acquired abnormalities may affect both APC alleles.
- Convergence on a common growth-control pathway supports a central causal role for APC.
- Inherited and acquired APC lesions differ in origin, not in the pathway disrupted.

Wnt absent: The APC destruction complex is active

The resting colonic epithelium keeps β -catenin low.



Proteasomal removal of β -catenin limits the transcription of progrowth genes.

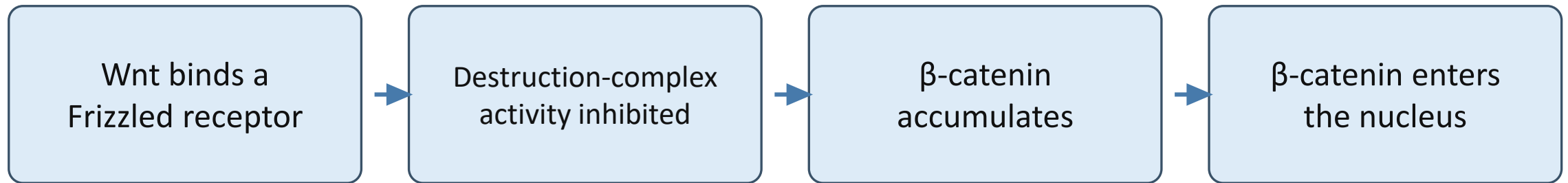
Why β -catenin must be regulated

Its abundance changes a transcriptional program.

- β -catenin is both a signaling effector and a component of adhesion complexes.
- A stabilized signaling pool can enter the nucleus.
- With TCF, nuclear β -catenin increases expression of genes that drive epithelial cell growth.
- The APC complex normally prevents inappropriate accumulation.

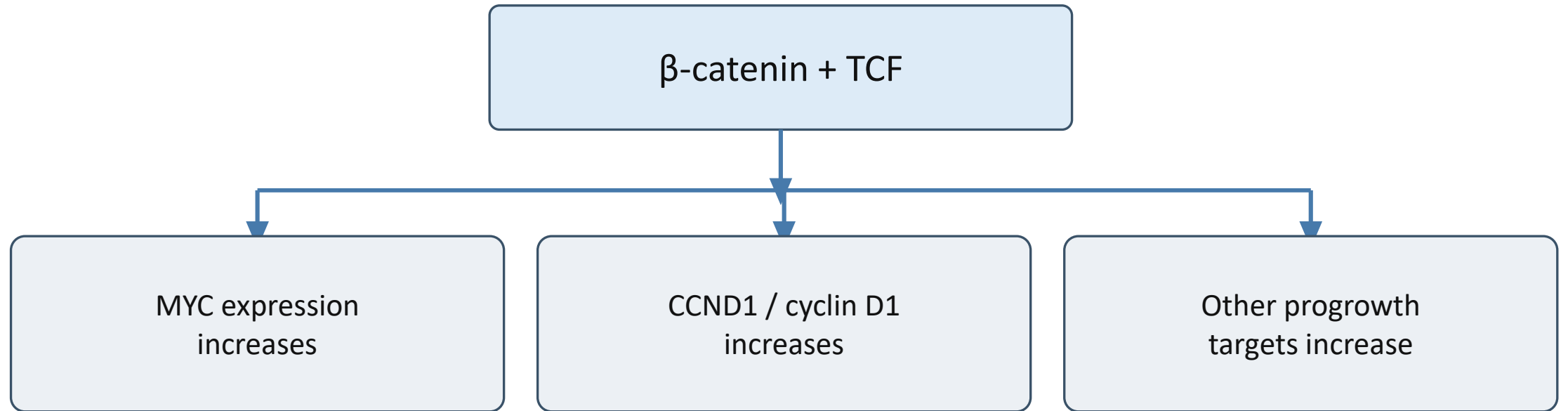
Wnt present: The destruction complex is suppressed

Extracellular Wnt changes β -catenin fate.



Physiologic Wnt signaling permits controlled activation of growth and differentiation programs.

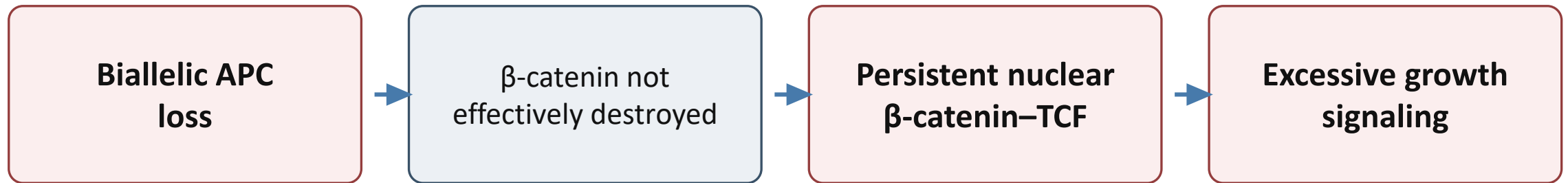
Nuclear β -catenin is a transcriptional activator



These transcriptional targets provide a mechanistic link to colonic epithelial proliferation.

APC loss creates ligand-independent signaling

The cell behaves as though Wnt is continuously present.



The upstream ligand is no longer required to maintain the β-catenin program.

Normal Wnt response versus APC-deficient state

Intact APC

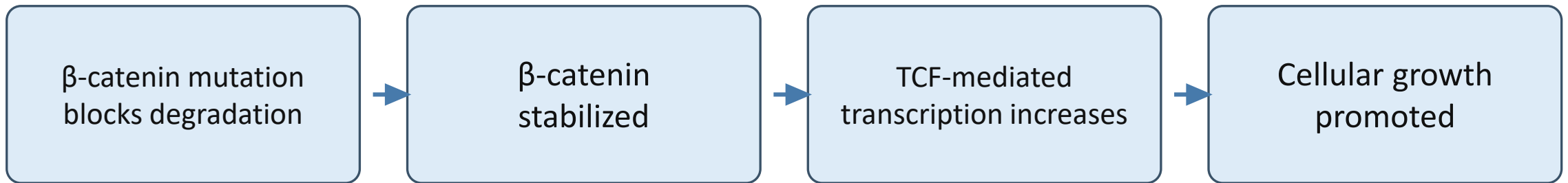
- β -catenin is degraded without Wnt.
- Signal increases transiently when Wnt activates the receptor.
- Proliferation is responsive to its regulatory environment.

APC loss

- Destruction complex cannot adequately dispose of β -catenin.
- Nuclear β -catenin activity persists.
- Growth appears Wnt-stimulated even in the absence of ligand.

Activating β -catenin mutations can mimic APC loss

Different genetic lesions reach the same signaling endpoint.



Some colon tumors with intact APC carry β -catenin mutations that prevent its destruction.

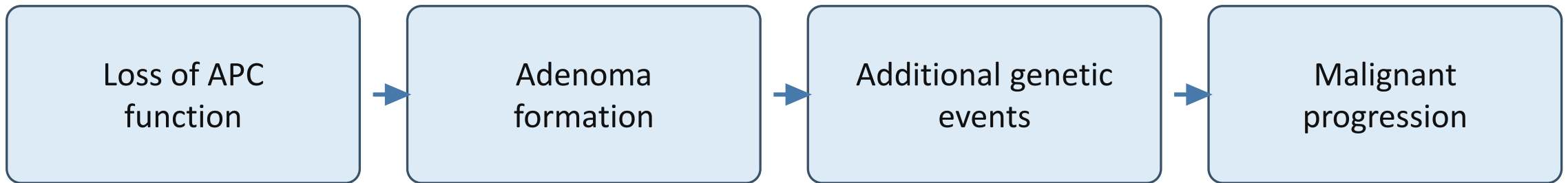
β -catenin dysregulation is not colon-specific

The pathway has relevance beyond colorectal cancer.

- β -catenin is a proto-oncoprotein regulated by tumor suppressor APC.
- Activating β -catenin mutations in approximately 20% of hepatocellular carcinomas.
- The same transcriptional mechanism can operate in different tissues.
- A pathway should not be equated with a single tumor site.

An adenoma is not yet a carcinoma

APC loss is an initiating event, not a complete malignant genotype.



Separating initiation from progression prevents over-attributing malignancy to a single suppressor defect.

Applied mechanism: Numerous colonic adenomas

A young adult has an extensive colonic adenoma burden and relatives with colorectal neoplasia.

Which suppressor is the leading candidate, and why do adenomas still require a second event?

Pause and explain the molecular mechanism.

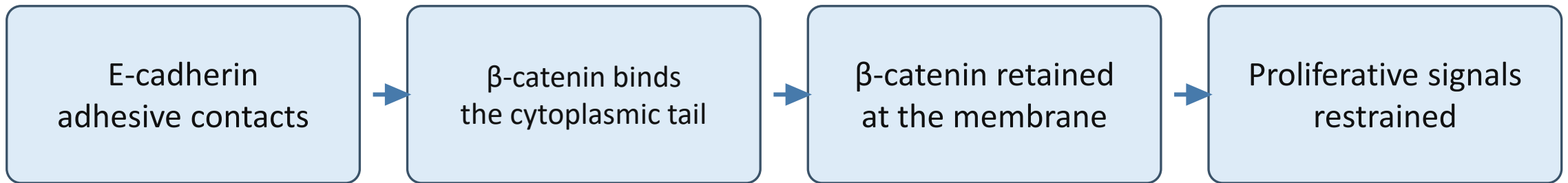
E-cadherin: The epithelial adhesion restraint

Adhesion regulates both cohesion and growth signaling.

- E-cadherin is a cell-surface adhesion protein encoded by CDH1.
- Its cytoplasmic tail binds β -catenin.
- Intact contacts help sequester β -catenin at the membrane.
- Cell–cell contact therefore contributes to contact inhibition.

Intact epithelial junctions sequester β -catenin

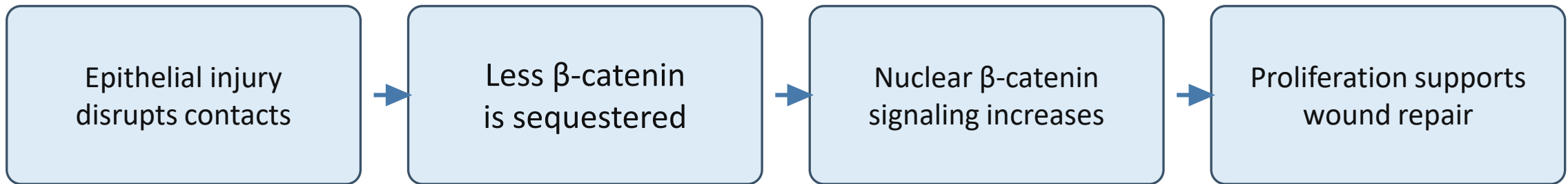
Physical contact limits the signaling pool.



The adhesion complex establishes a link between tissue architecture and transcriptional regulation.

Wounding releases a transient proliferative signal

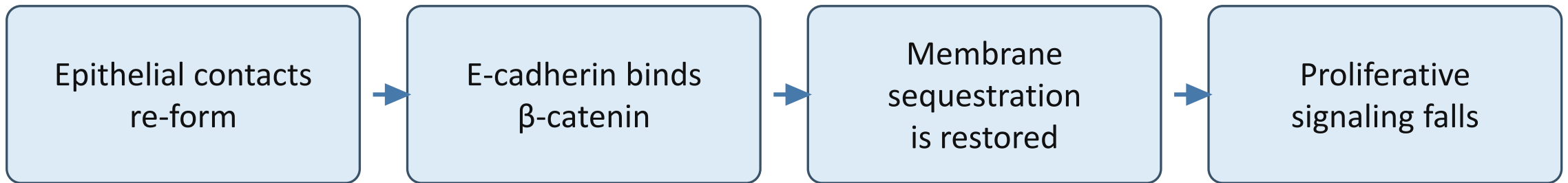
Loss of contact can be appropriate during repair.



This reversible response is physiologic when followed by re-formation of intercellular junctions.

Healing restores contact inhibition

Re-establishing junctions ends the transient response.



The same molecular circuit can support repair or drive dysregulated growth, depending on its control.

CDH1 dysfunction has two consequences

Loss of functional E-cadherin

```
graph TD; A[Loss of functional E-cadherin] --> B[Less cell-cell cohesion  
→ invasion potential]; A --> C[Altered β-catenin control  
→ growth signals];
```

Less cell-cell cohesion
→ invasion potential

Altered β -catenin control
→ growth signals

Both effects can contribute to malignancy, although their relative importance varies by tumor.

Why weaker adhesion favors dissemination

Cohesion is a physical barrier to invasion.

- Reduced E-cadherin weakens epithelial cell–cell interactions.
- Looser interactions may facilitate local invasion.
- The same loss of cohesion can contribute to subsequent metastatic spread.
- A loss of adhesion is not synonymous with metastasis by itself.

CDH1 is a hereditary gastric-cancer susceptibility gene

An inherited adhesion defect can predispose to cancer.

- Germline CDH1 loss-of-function variants are associated with familial gastric carcinoma.
- Some sporadic gastric carcinomas also show loss of E-cadherin expression.
- In sporadic cancers, reduced expression may follow mutation or indirect mechanisms.
- An observed loss of protein expression does not alone specify the molecular cause.

E-cadherin reduction spans multiple carcinomas

This is a recurring malignant epithelial phenotype.

- Reduced cell-surface expression is common in several carcinomas.
- Examples in the source include esophageal, colorectal, breast, ovarian and prostatic tumors.
- The alteration may affect local tumor cell cohesion and β -catenin regulation.
- Its presence is not unique to gastric carcinoma.

APC and CDH1 converge on β -catenin

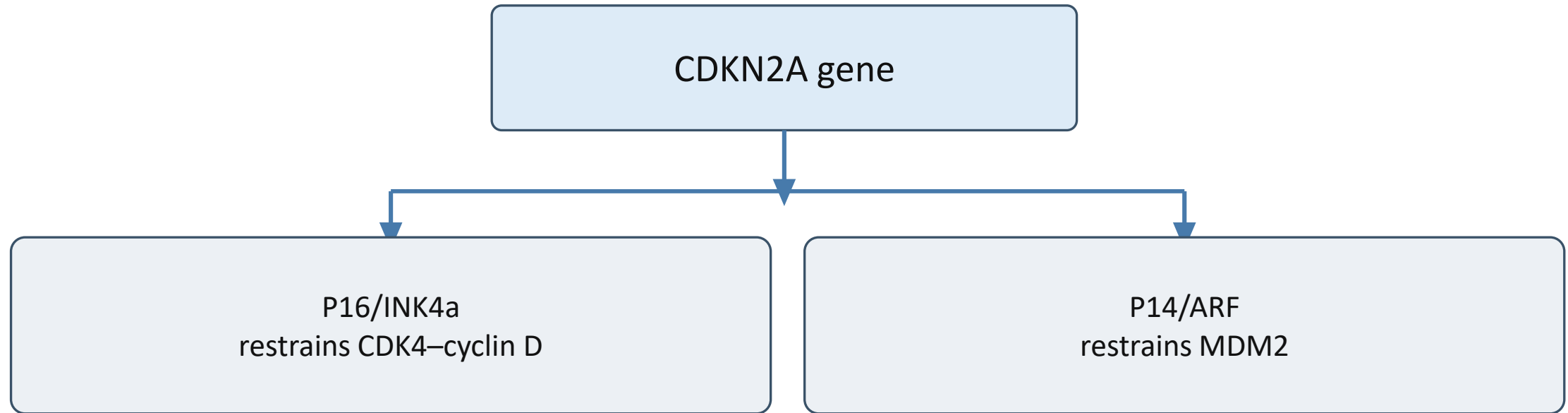
APC defect

- Primary lesion: β -catenin destruction is impaired.
- β -catenin–TCF transcription becomes persistently active.
- Strong association with colorectal adenoma formation.

CDH1 defect

- Primary lesion: Epithelial adhesion is reduced.
- β -catenin sequestration at contacts may be weakened.
- Both growth-control and invasion-related effects may occur.

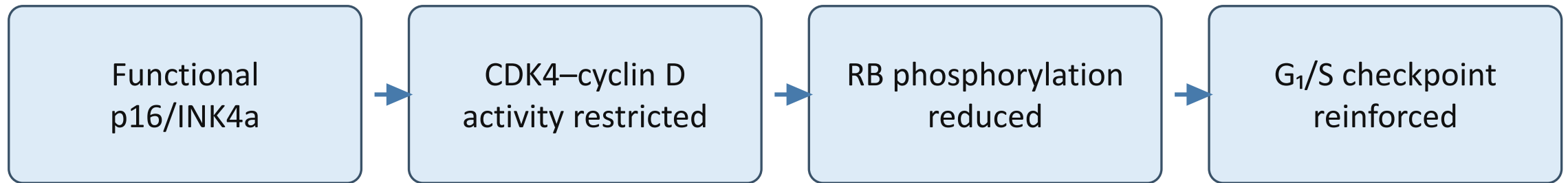
One CDKN2A locus encodes two suppressive proteins



These two products protect different checkpoint pathways: RB and p53.

P16 maintains the RB restriction point

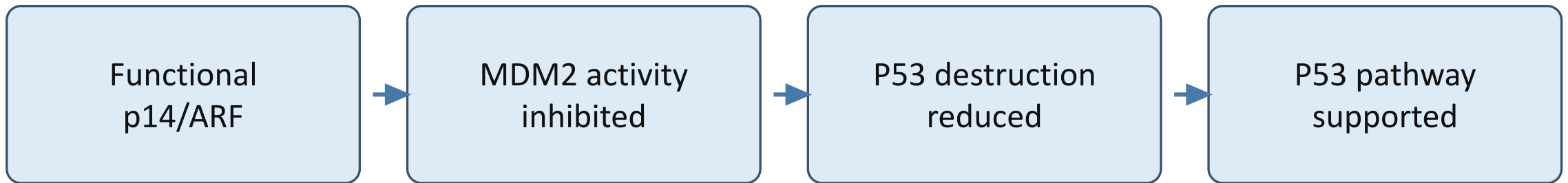
Cyclin-dependent kinase inhibition protects G₁/S control.



Loss of p16 weakens RB-mediated suppression of cell-cycle progression.

P14/ARF supports the p53 pathway

MDM2 negatively regulates p53.



Both products of CDKN2A act as restraints, but by distinct molecular routes.

P16 contributes to cellular senescence

The checkpoint function extends beyond transient arrest.

- P16-mediated suppression of cyclin-dependent kinase activity reinforces growth arrest.
- The source also links p16 to induction of cellular senescence.
- A lesion at CDKN2A can therefore disrupt multiple restraints on proliferation.
- Do not assume that every CDKN2A alteration affects both products identically.

Inherited CDKN2A defects predispose to melanoma

A hereditary checkpoint defect can define a cancer family.

- Germline mutations are associated with familial forms of melanoma.
- CDKN2A encodes two mechanistically distinct suppressors.
- Loss of cell-cycle control increases the opportunity for clonal expansion.
- Clinical association alone does not specify the effect of an individual variant.

Sporadic CDKN2A alterations occur in diverse tumors

Examples cited in Robbins	Tumor type / context
Bladder	Carcinoma
Head and neck	Tumors of the region
Acute lymphoblastic leukemia	Hematolymphoid malignancy
Cholangiocarcinoma	Biliary epithelial carcinoma

Loss of a suppressor is not always a deletion

Genetic mechanisms

- Chromosomal deletion may remove a locus.
- Inactivating sequence mutations may affect a protein.
- These changes can abolish a functional brake.

Epigenetic mechanisms

- Promoter hypermethylation may silence expression.
- The DNA coding sequence need not be changed.
- The text notes this mechanism for CDKN2A in some tumors.

Two checkpoint arms meet at CDKN2A

P16/INK4a → RB

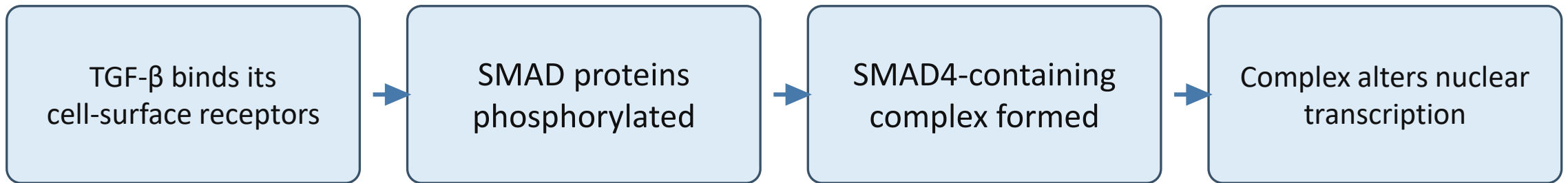
- Restrains CDK4–cyclin D.
- Limits RB phosphorylation.
- Reinforces G₁/S arrest.

P14/ARF → p53

- Inhibits MDM2.
- Protects p53 from destruction.
- Supports the p53 stress response.

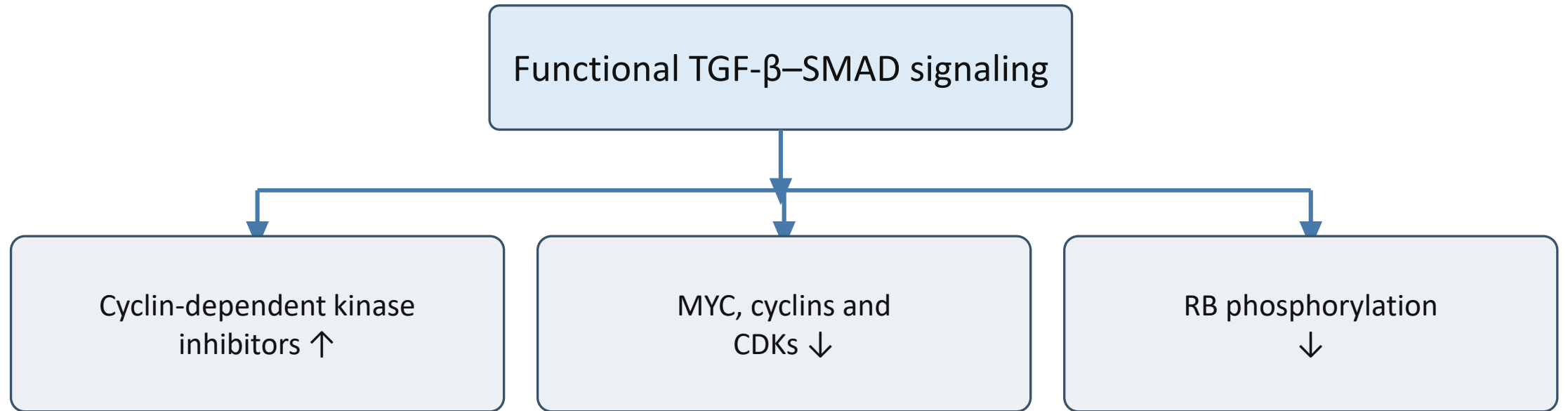
TGF- β receptors signal through SMAD proteins

Ligand-receptor engagement creates a transcriptional response.



The normal program is antiproliferative in many epithelial, endothelial and hematopoietic cells.

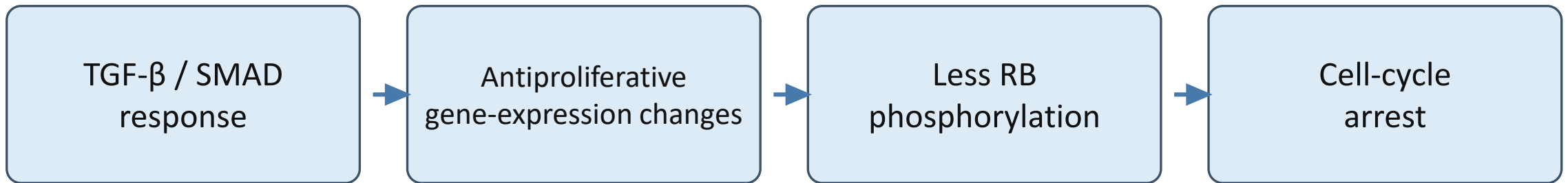
TGF- β signaling activates a growth-arrest program



The shared functional endpoint is suppression of cell-cycle progression.

Reduced RB phosphorylation enforces arrest

TGF- β ultimately converges on the G₁/S restriction point.



Multiple growth-suppressive circuits converge on RB, even when their initiating receptors differ.

TGF- β receptor lesions disable growth inhibition

Defects can occur at the receptor level.

- Loss-of-function changes impair transmission of TGF- β signals.
- The source notes receptor mutations in colon, stomach and endometrial cancers.
- The resulting cell may resist a normally potent extracellular growth inhibitor.
- Mutations in different pathway components can produce similar escape.

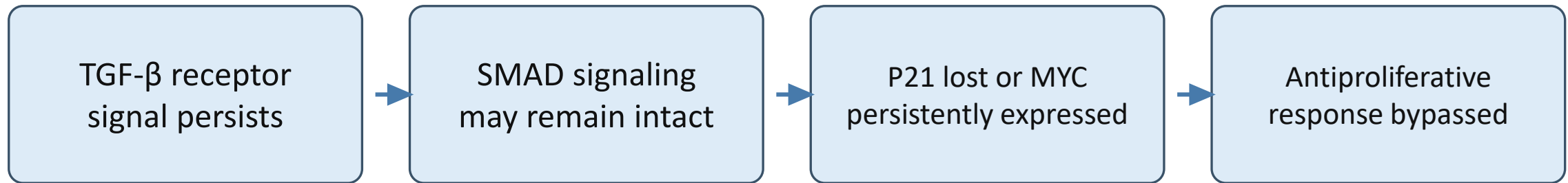
SMAD4 loss is important in pancreatic carcinoma

The transcriptional response may fail despite ligand binding.

- SMAD4 partners with phosphorylated SMAD proteins.
- SMAD4-containing complexes regulate nuclear transcription.
- Mutational inactivation of SMAD4 is common in pancreatic cancers.
- The site of pathway interruption can be downstream of intact receptors.

Tumors can escape downstream of intact SMADs

Target-gene defects can cancel the growth-arrest output.



An apparently intact upstream pathway does not guarantee a functional growth-inhibitory response.

TGF- β can suppress or favor tumor progression

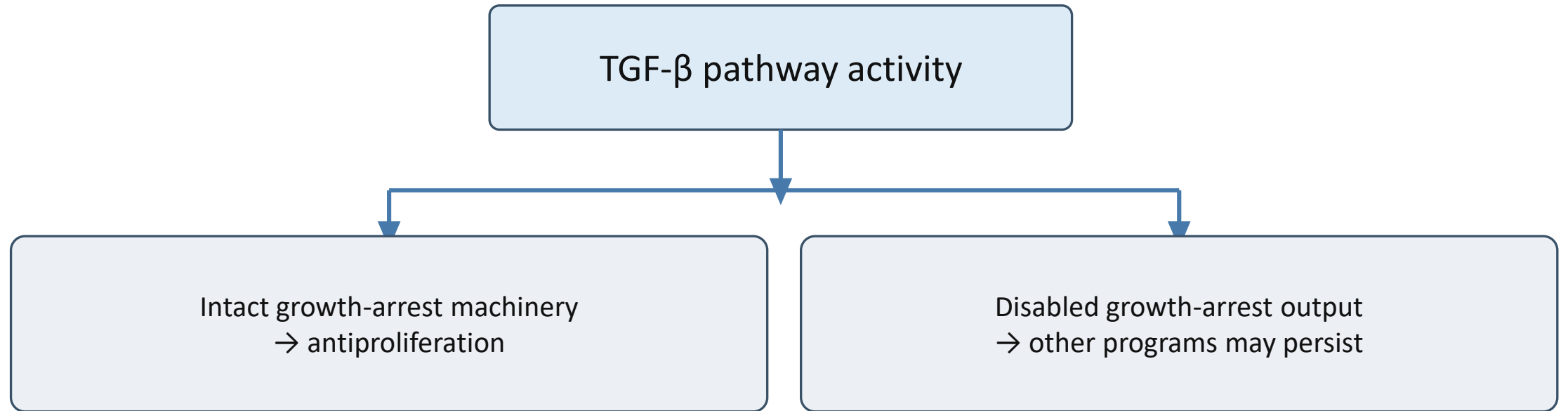
Growth suppression

- CDK inhibitors are upregulated.
- Proliferation-driving genes are restrained.
- RB-dependent cell-cycle arrest follows.

Context-dependent promotion

- Growth suppression can be lost downstream.
- Other TGF- β responses may persist.
- These responses may support immune evasion or angiogenesis.

The TGF- β paradox depends on genetic context



TGF- β cannot be classified as uniformly inhibitory or promotional in all tumor cells.

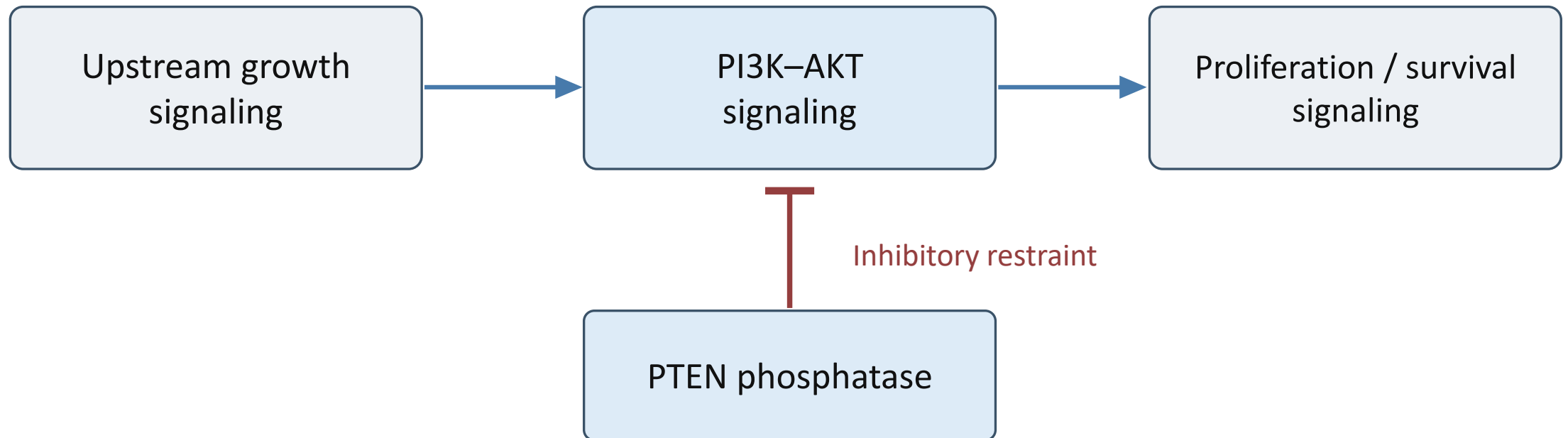
PTEN antagonizes the PI3K–AKT growth pathway

A phosphatase acts as a molecular brake.

- PTEN is a membrane-associated phosphatase.
- Its gene lies on chromosome 10q23.
- PTEN restrains signaling through the PI3K–AKT pathway.
- Loss of function removes a negative regulator of cell growth and survival signaling.

PTEN limits PI3K–AKT signaling

PTEN inhibits a pathway rather than acting as a downstream activator.



PTEN loss removes an inhibitory influence on PI3K–AKT signaling.

PTEN inactivation has several molecular routes

A functional suppressor can be lost without one unique lesion.

- Deletion may remove all or part of the gene.
- Deleterious point mutations can disrupt function.
- Epigenetic silencing may reduce expression.
- These routes converge on reduced PTEN-mediated pathway restraint.

Cowden syndrome links PTEN to hereditary neoplasia

A germline defect creates multiorgan susceptibility.

- Germline PTEN mutations are associated with autosomal dominant Cowden syndrome.
- The source describes benign skin appendage tumors.
- Epithelial cancer risk is increased, especially breast, endometrial and thyroid cancers.
- A syndromic phenotype may identify a particular pathway defect.

APC and PTEN both restrain growth signals

APC

- Suppresses β -catenin–TCF transcription.
- Acts within the Wnt pathway.
- Strongly linked to colorectal adenoma initiation.

PTEN

- Opposes PI3K–AKT signaling.
- Acts as a membrane-associated phosphatase.
- Associated with Cowden syndrome and diverse cancers.

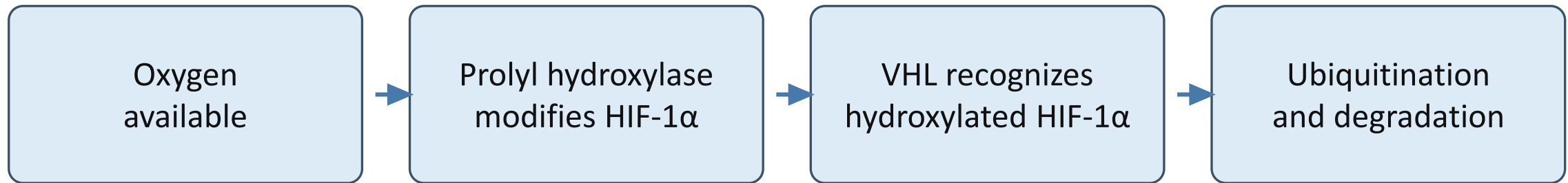
VHL coordinates responses to ambient oxygen

The suppressor participates in regulated protein disposal.

- VHL is located on chromosome 3p.
- It forms part of a ubiquitin-ligase complex.
- An essential target is hypoxia-inducible factor 1 α (HIF-1 α).
- Oxygen availability determines whether HIF-1 α can be recognized for degradation.

Normoxia: Hydroxylation marks HIF-1 α for removal

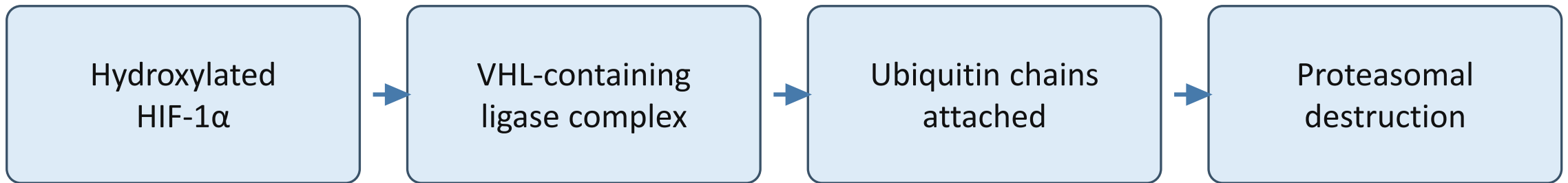
Oxygen-dependent recognition is the critical step.



When oxygen is present, VHL helps maintain low HIF-1 α protein abundance.

The VHL complex targets HIF-1 α to the proteasome

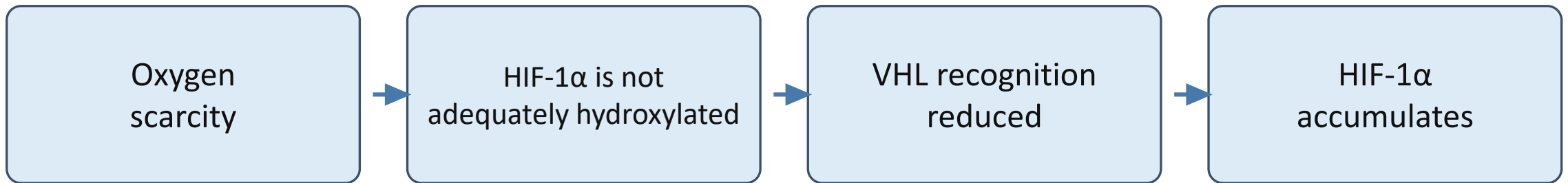
Ubiquitin tagging connects recognition to degradation.



The mechanism is post-translational: HIF-1 α is controlled by protein stability.

Hypoxia: HIF-1 α escapes VHL recognition

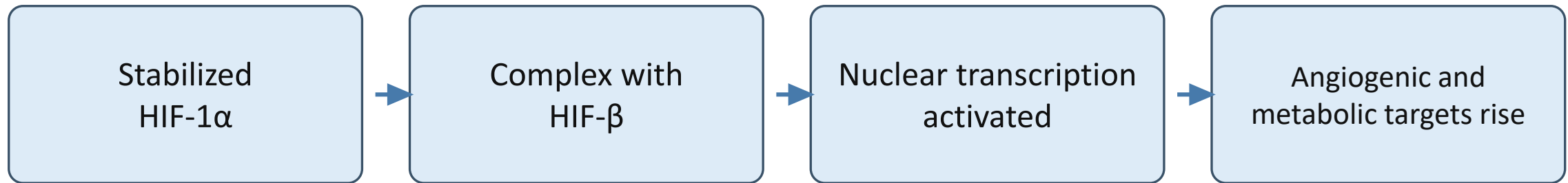
Low oxygen interrupts the hydroxylation step.



An intact VHL gene does not trigger degradation when the required oxygen-dependent modification fails.

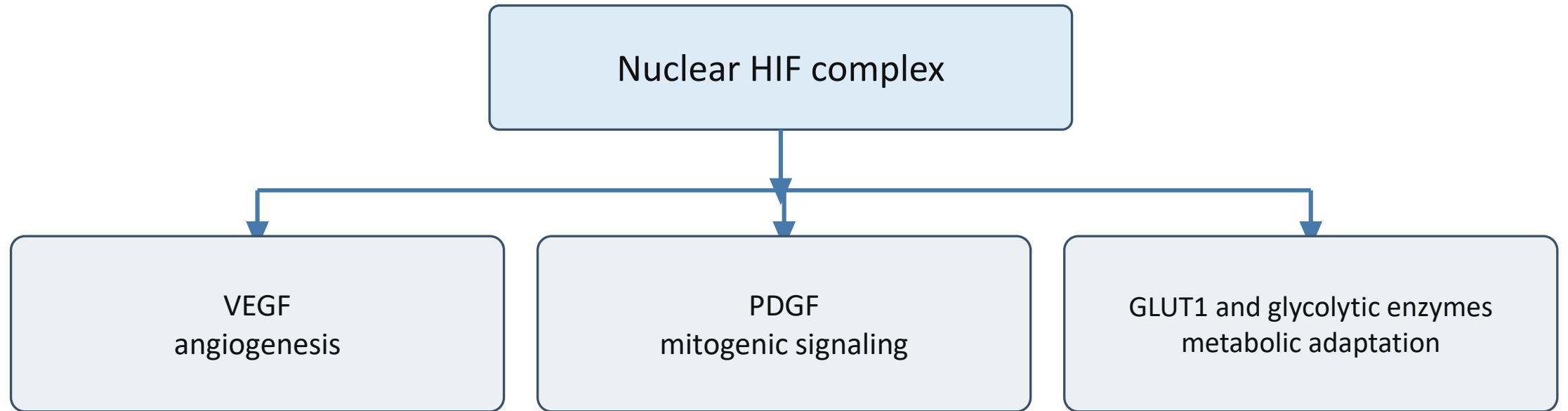
Accumulated HIF alters nuclear gene expression

The hypoxia response couples oxygen sensing to transcription.



This is the physiologic adaptive response to hypoxia; It also becomes oncogenic when deregulated.

HIF activates angiogenic and metabolic effectors



The downstream programs support blood-vessel formation and altered energy handling.

VHL loss produces a false hypoxia signal

HIF-1 α persists even when oxygen is available.

- Inactivating VHL mutations prevent normal HIF-1 α ubiquitination.
- HIF-1 α can accumulate under normoxic conditions.
- Angiogenic growth factors and metabolic programs are consequently elevated.
- This constitutes loss of an oxygen-dependent tumor-suppressive brake.

Three oxygen-sensing states

Intact VHL with normoxia

- HIF-1 α undergoes hydroxylation.
- VHL recognizes and targets it for degradation.
- Low HIF-mediated transcription.

Hypoxia or VHL inactivation

- Hypoxia prevents the recognition modification.
- VHL loss prevents degradation despite oxygen.
- Both can lead to HIF accumulation.

Different upstream causes can yield a similar HIF transcriptional state.

VHL-related tumors illustrate hereditary and somatic loss

Renal neoplasia is an important clinical association.

- Germline VHL loss-of-function mutations predispose to hereditary renal cell carcinoma and other lesions.
- Somatic VHL mutations also occur in a subset of sporadic renal cell carcinomas.
- The shared mechanism involves persistent hypoxia-response signaling.
- The exact lesion spectrum is developed in the organ-specific chapter.

Applied mechanism: HIF remains high in room air

Tumor cells accumulate nuclear HIF-1 α despite adequate oxygen delivery and express angiogenic factors.

Which tumor suppressor defect provides a direct explanation?

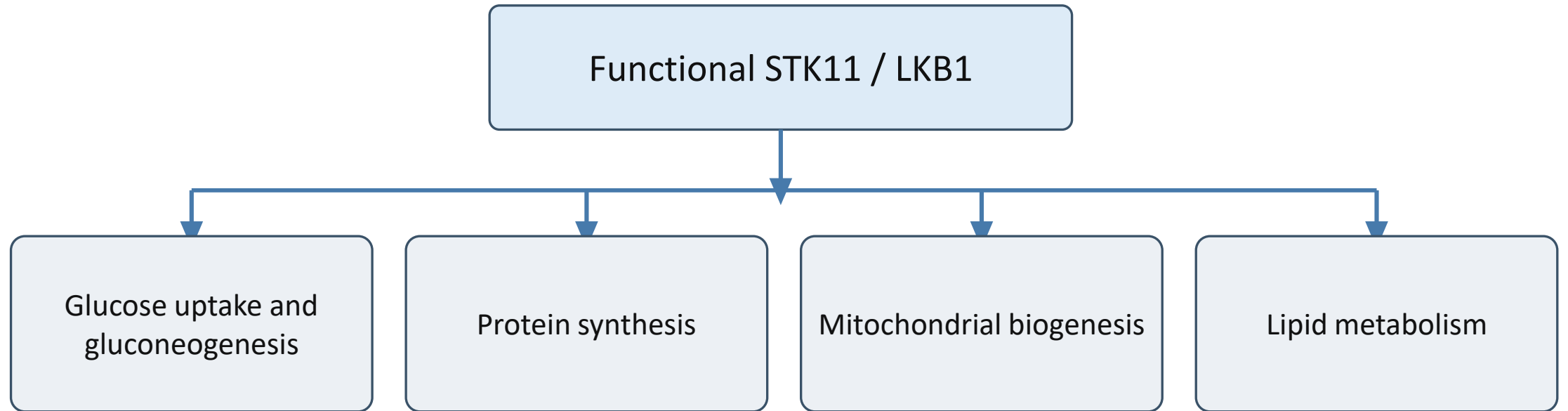
Pause and explain the molecular mechanism.

STK11/LKB1 links tumor suppression and metabolism

The suppressor is a serine/threonine kinase.

- STK11 is also known as LKB1.
- It regulates several aspects of cellular metabolism.
- The source emphasizes the breadth of its effects rather than one terminal effector.
- Its inactivation reveals that metabolic regulation contributes to suppression of transformation.

STK11 regulates multiple metabolic processes



A single metabolic regulator can coordinate several resources required for cell growth.

Peutz–Jeghers syndrome is associated with STK11

Inherited metabolic regulation defects predispose to tumors.

- Germline loss-of-function STK11 variants cause Peutz–Jeghers syndrome.
- The syndrome is autosomal dominant.
- Benign gastrointestinal polyps occur.
- Risk of multiple epithelial cancers is increased, particularly gastrointestinal and pancreatic carcinomas.

Sporadic STK11 loss broadens the mechanism

The pathway matters outside a hereditary syndrome.

- Sporadic inactivating STK11 mutations occur in diverse carcinomas.
- Metabolic adaptation is relevant to establishment and maintenance of the transformed state.
- The source does not reduce STK11 function to a single metabolic substrate.
- STK11 is one example of a metabolic tumor suppressor.

What is interrupted when each suppressor is lost?

Defect	Normal functional brake	Immediate pathway effect
APC	β -catenin destruction	Nuclear β -catenin–TCF rises
CDH1	Cell adhesion and β -catenin retention	Cohesion falls; signaling changes
CDKN2A	RB/p53 checkpoint reinforcement	Proliferative restraints weakened
TGF- β /SMAD	Antiproliferative transcription	Growth-inhibitory response impaired
PTEN	PI3K–AKT restraint	Growth signaling rises
VHL	HIF-1 α turnover	HIF targets rise in normoxia
STK11	Metabolic control	Multiple metabolic programs altered

Inherited syndromes point to suppressor pathways

Syndrome / clinical setting	Gene	Mechanistic theme
Familial adenomatous polyposis	APC	Wnt / β -catenin
Familial gastric carcinoma	CDH1	Adhesion and signaling
Familial melanoma	CDKN2A	RB and p53 checkpoint support
Cowden syndrome	PTEN	PI3K–AKT
Hereditary VHL-related renal tumors	VHL	HIF regulation
Peutz–Jeghers syndrome	STK11	Metabolic regulation

Not all suppressors are removed by the same mechanism

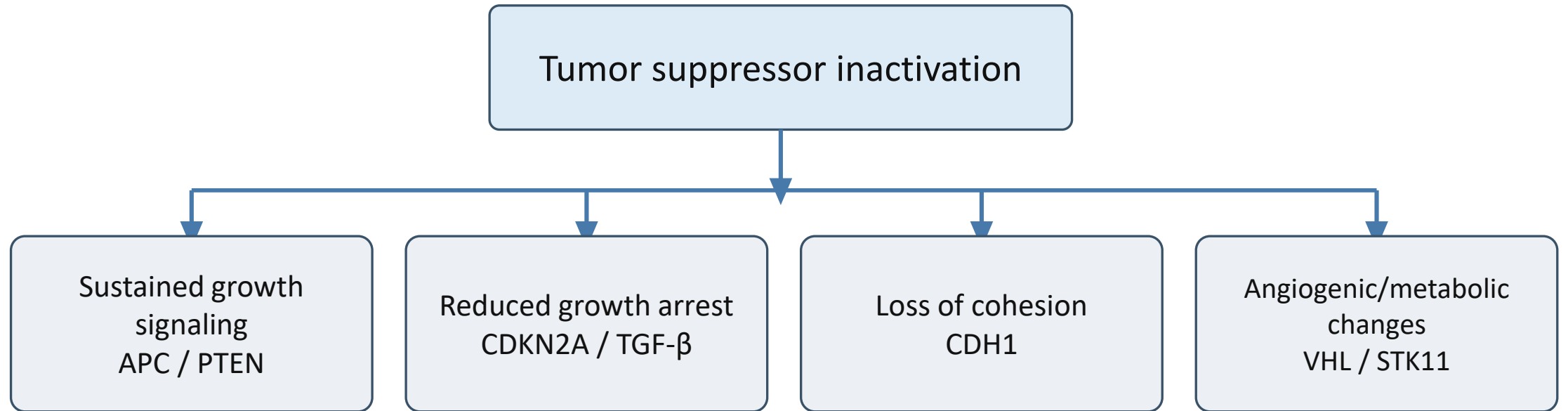
Loss of the gene or protein

- Deletion or inactivating point mutation.
- Can involve both alleles in a neoplastic cell.
- Common mechanisms for APC and PTEN, among others.

Loss of the functional response

- Epigenetic silencing can prevent expression.
- Downstream gene defects may bypass an intact pathway.
- Examples: CDKN2A silencing; TGF- β target-gene escape.

Distinct lesions converge on cancer hallmarks



The phenotype is determined by the pathway lesion and the additional genetic context.

Syndromic application: Skin lesions and epithelial cancers

A family shows benign skin appendage lesions and increased breast, thyroid and endometrial carcinomas.

Which suppressor and signaling pathway should be recalled?

Pause and explain the molecular mechanism.

Syndromic application: Gastrointestinal polyps

Several relatives have gastrointestinal polyps with an inherited predisposition to gastrointestinal and pancreatic cancers.

Which metabolic tumor suppressor fits this pattern?

Pause and explain the molecular mechanism.

Mechanism discrimination: Test the direct consequence

Finding	Most informative pathway
β -catenin escapes proteasomal destruction	APC / Wnt
Cells lose cohesion and β -catenin sequestration	CDH1 / E-cadherin
CDK4–cyclin D is insufficiently restrained	CDKN2A / p16
SMAD4-dependent antiproliferative output is lost	TGF- β / SMAD
PI3K–AKT growth signaling lacks its brake	PTEN
HIF-1 α persists in normoxia	VHL
Metabolic regulatory kinase inactivated	STK11 / LKB1

Integrated summary: The key distinctions

Tumor suppression is a family of mechanisms.

- APC restrains β -catenin; CDH1 anchors junctions and helps regulate β -catenin availability.
- CDKN2A protects RB and p53 checkpoints; TGF- β –SMAD induces growth arrest in susceptible cells.
- PTEN limits PI3K–AKT; VHL limits HIF-1 α ; STK11 coordinates metabolic pathways.
- Inherited predisposition requires additional cellular events; Tumors often converge on shared signaling outputs.

Primary reading and scope

Source-based lecture, without external guideline updates.

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Chapter 7, Neoplasia: “Other Tumor Suppressor Genes,” printed pages 264–267.
- Original figures 7.28–7.30 are described in the source; this lecture uses independent, native editable schematics.
- Tumor-specific diagnostic criteria, testing algorithms and management are outside this excerpt.