

Chromosomal Translocations and Other Acquired Mutations

Genetic mechanisms of white cell neoplasia

Maturation arrest

Growth and self-renewal

Apoptosis resistance

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning outcomes

1

Distinguish oncogenic gene fusions from enhancer-mediated overexpression

2

Explain differentiation arrest, proliferative signaling and survival advantages

3

Trace AID- and V(D)J-associated rearrangements to B- and T-cell development

4

Connect recurrent lesions with selected leukemias and lymphomas

Acquired lesions are central to white cell neoplasia

Nonrandom genetic lesions alter programs that normally regulate leukocyte development, growth and survival.

- The affected genes often serve essential functions in the corresponding normal cell
- Different lesions can converge on the same malignant phenotype
- Some abnormalities are sufficiently characteristic to contribute to diagnosis

Recurrent chromosomal changes are not random

- Chromosomal abnormalities are demonstrable in most white cell neoplasms
- Translocations are especially common structural abnormalities
- Recurrent breakpoints implicate particular genes in pathogenesis
- Characteristic lesions connect molecular mechanism with tumor identity

Recurrence is biologic evidence—not merely a cytogenetic description.

Somatic mutations differ from inherited predisposition

Acquired / somatic

- Develop within a hematopoietic cell lineage
- Can be selected during clonal expansion
- Directly shape the neoplastic clone

Inherited predisposition

- Constitutional alteration or syndrome
- Raises risk of later neoplasia
- Additional acquired drivers are generally needed

This lecture focuses on the acquired alterations within tumor cells.

Cancer genes can be altered in several ways

Chromosomal rearrangement

Translocation or inversion
alters gene context

Sequence-level mutation

Substitution or small
variant changes protein or
regulation

Copy-number / structural loss

Deletion or gain changes
dosage or removes control

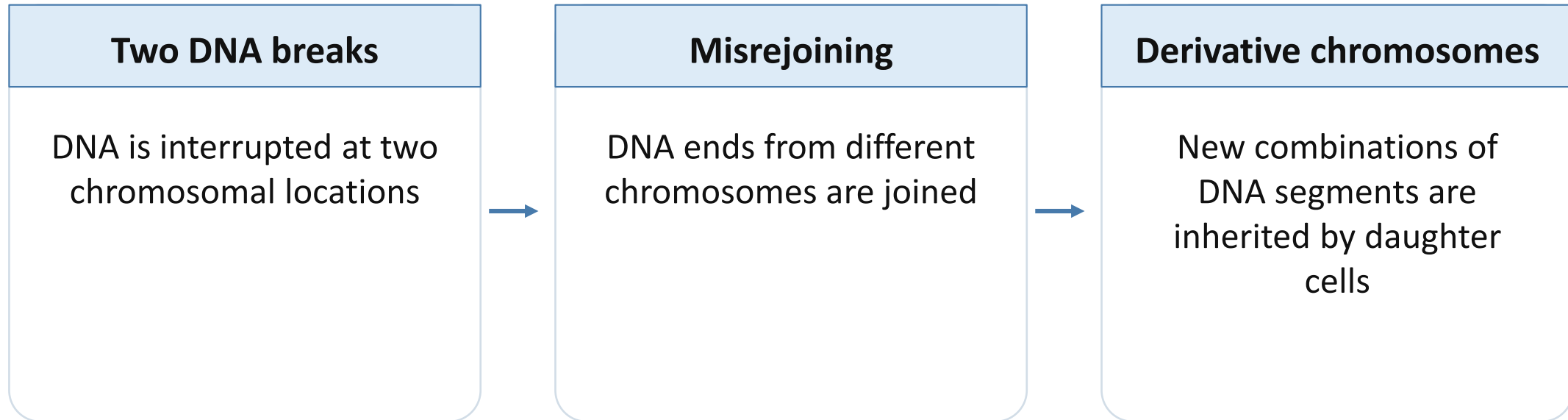
Different DNA lesion types may converge on increased growth, impaired differentiation or survival.

Recurrent genetic lesions can be diagnostic

- A molecular abnormality is sometimes tightly linked to one neoplasm
- Specific mutations may be required in an integrated disease definition
- Other lesions are shared across multiple neoplasms
- Molecular results must be interpreted with morphology and lineage

Association, pathogenesis and diagnostic specificity are different questions.

A translocation requires breakage and rejoining



Misrepair can change gene regulation or create an oncogenic fusion gene.

A structural change can have two molecular outcomes

Regulatory juxtaposition

- Coding sequence may remain intact
- Strong enhancer/promoter drives excess expression
- Example: MYC near IGH regulatory elements

Fusion oncoprotein

- Coding segments from two genes are joined
- A chimeric protein gains abnormal activity
- Example: BCR::ABL1 kinase

The location of the breakpoint determines the biochemical mechanism.

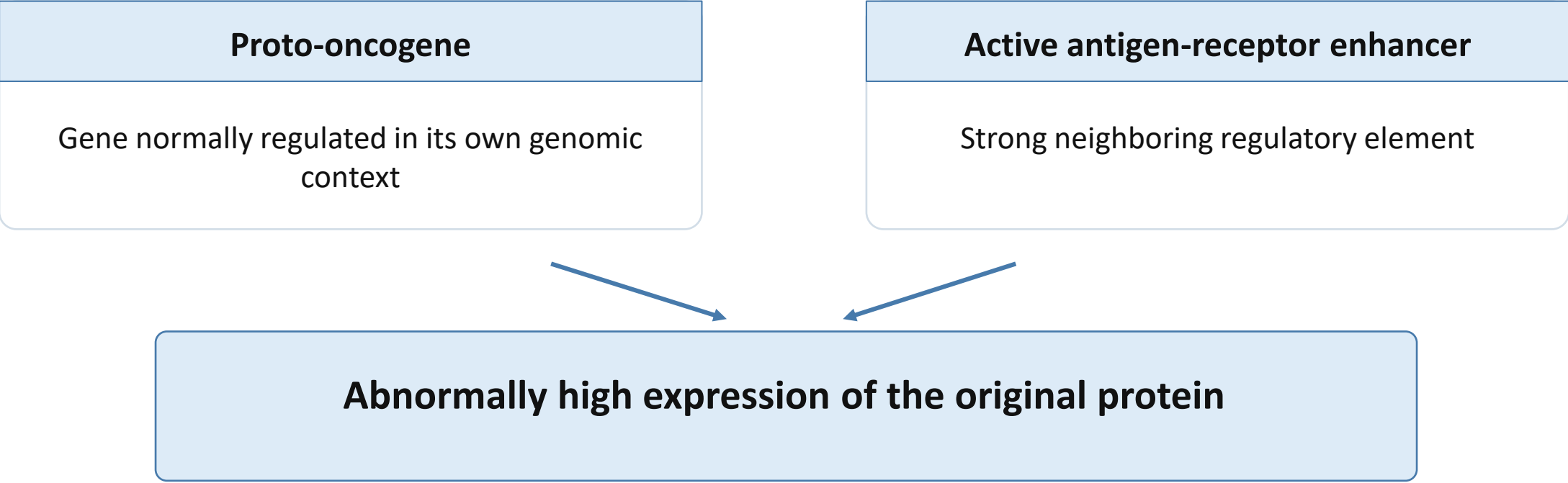
Enhancer juxtaposition overexpresses an intact gene

Proto-oncogene

Gene normally regulated in its own genomic context

Active antigen-receptor enhancer

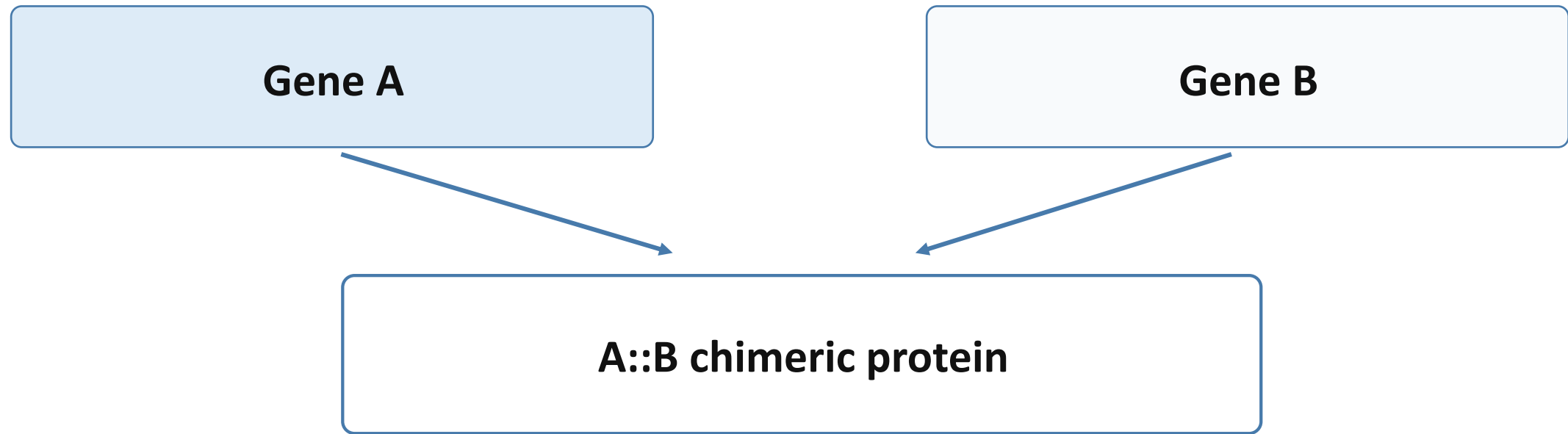
Strong neighboring regulatory element



Abnormally high expression of the original protein

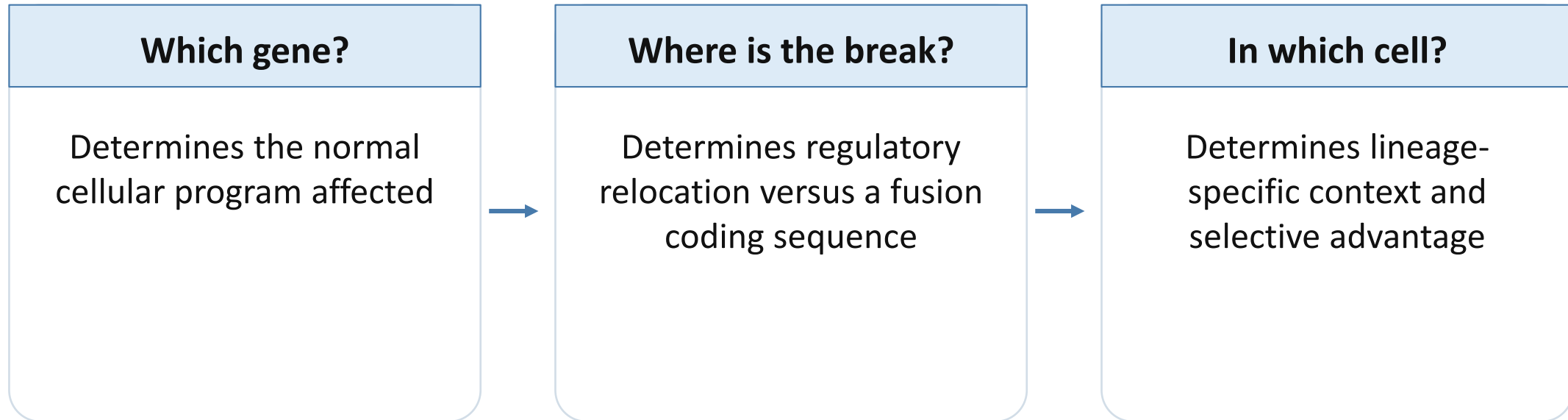
- Regulatory sequences are repositioned next to an oncogene
- No fusion coding sequence is necessary

Fusion genes generate new molecular activities



- Joining coding segments can change protein structure or localization
- Examples include constitutively active kinases and differentiation-blocking nuclear factors

Structural breakpoints explain molecular diversity



The same generic event—chromosome breakage—can produce distinct oncogenic outcomes.

The major acquired-mutation effects form a triad

More growth

Kinase lesions; MYC
activation

More self-renewal

Transcription-factor and
chromatin abnormalities

Less apoptosis

BCL2 overexpression

Maturation arrest often accompanies increased self-renewal, particularly in acute leukemia.

Differentiation arrest preserves immature progenitors

Lineage transcription program disrupted



Normal maturation becomes inefficient or blocked



Immature proliferative cells accumulate

This mechanism is especially prominent in acute leukemias.

Transcription factors control lineage commitment

- Hematopoietic maturation depends on ordered transcriptional programs
- Transcription-factor lesions can interrupt the next differentiation step
- Dominant-negative oncoproteins may suppress normal gene-regulatory functions
- Accumulation of blasts reflects impaired maturation plus clonal expansion

Loss of differentiation is mechanistically distinct from a simple increase in cell division.

Self-renewal gives progenitors a stem-like program

Acquired lesion in transcriptional regulator



Abnormal maintenance of self-renewal



Long-lived pool of malignant precursors

Additional growth signals can act on this persisting population.

Tyrosine-kinase activation creates growth autonomy

Activating kinase mutation or fusion



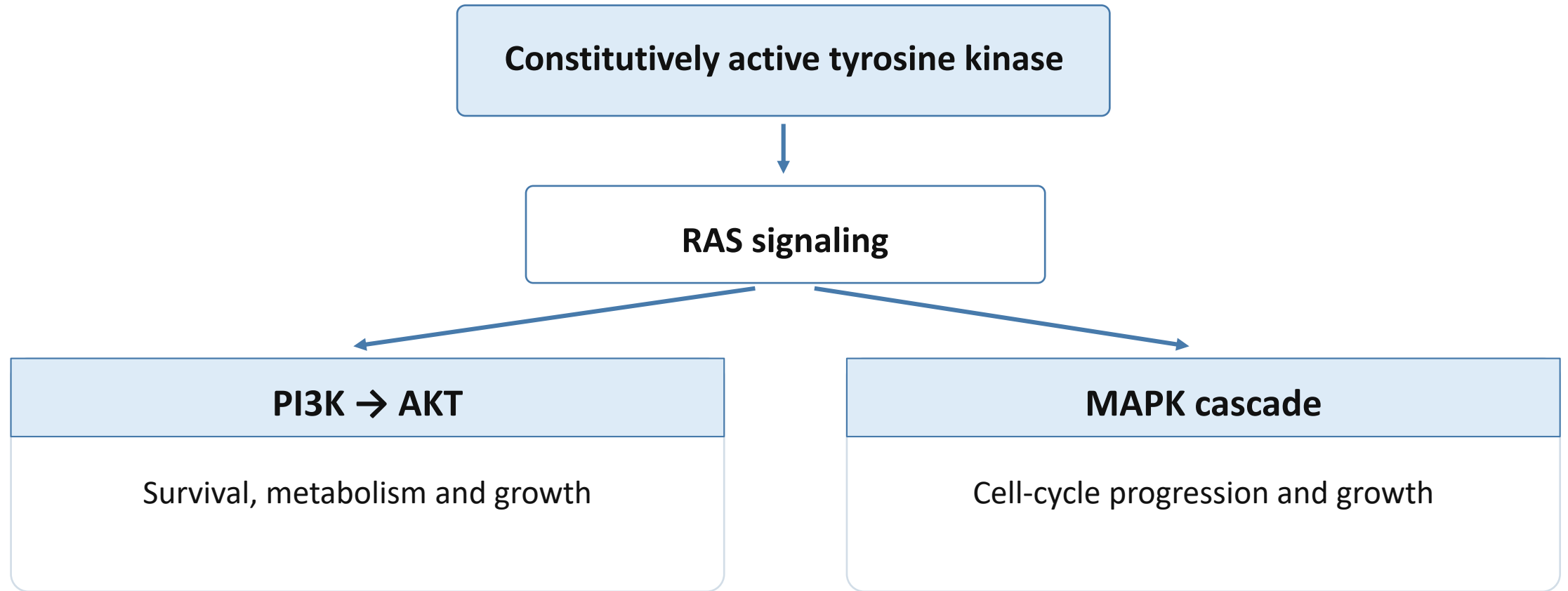
Persistent intracellular phosphorylation



Increased growth and survival signaling

A normal ligand-dependent signal becomes sustained or deregulated.

RAS pathways transmit oncogenic kinase signals



PI3K/AKT and MAPK as two downstream arms of RAS signaling.

Apoptosis resistance extends clone survival

Pro-survival mutation



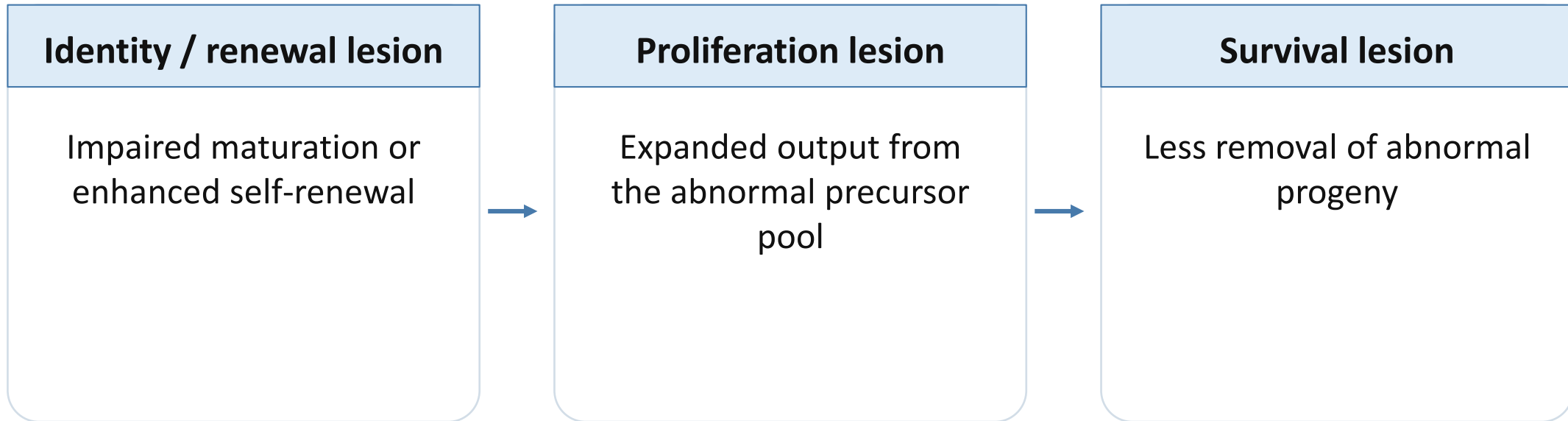
Reduced programmed cell death



Accumulation of cells that would otherwise be eliminated

BCL2 translocation exemplifies this acquired survival advantage.

Distinct mutation classes cooperate



Cooperating lesions explain why a single alteration is not always sufficient.

Gain of function and dominant-negative effects differ

Gain of function

- Creates excessive normal activity
- May activate a growth pathway
- May overexpress intact proto-oncogene

Dominant-negative effect

- Interferes with the normal protein complex
- Functionally suppresses differentiation machinery
- Produces loss of a normal regulatory program

Both may result from acquired genetic alterations.

Maturation state shapes the malignant phenotype

Early progenitor

- Differentiation arrest often prominent
- Blasts may fill marrow
- Loss of effective mature blood-cell production

More mature lineage

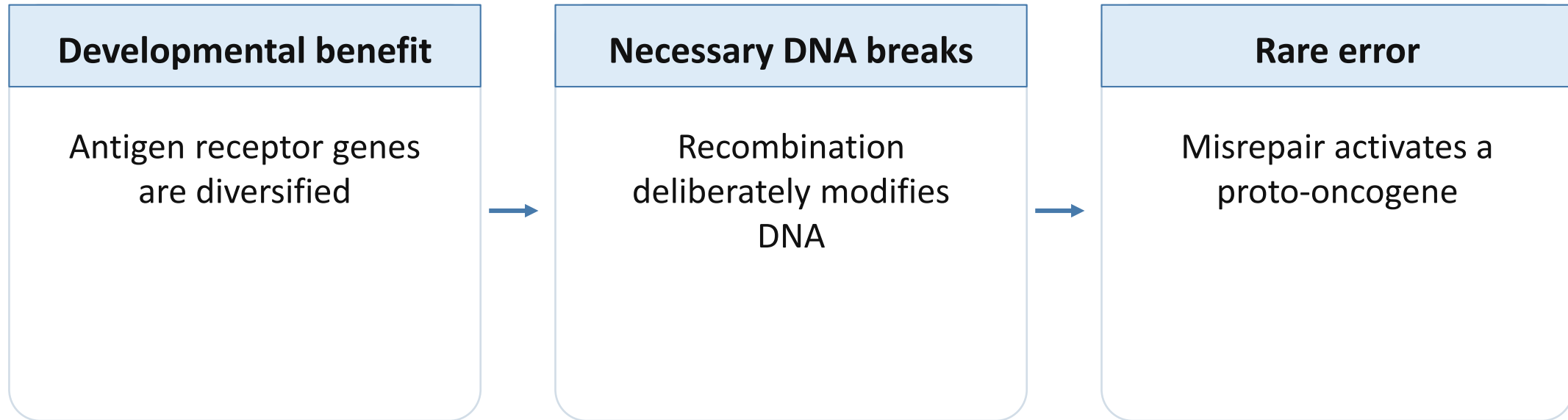
- Survival or signaling advantage may predominate
- Cells may retain lineage differentiation
- Distinct leukemia or lymphoma patterns arise

The phenotype depends on both the driver and the developmental stage at which it acts.

Driver lesions can be classified by functional output

Primary effect	Robbins examples	Core consequence
Proliferation	MYC translocation; kinase activation	More cell division / metabolism
Self-renewal or maturation	KMT2A rearrangement; PML::RARA	Persistence of immature cells
Survival	BCL2 translocation	Resistance to apoptosis

Antigen-receptor diversification creates a vulnerability



Physiologic genomic remodeling can inadvertently create oncogenic rearrangements.

V(D)J recombination belongs to precursor lymphocytes

- Precursor B cells rearrange immunoglobulin loci
- Precursor T cells rearrange T-cell receptor loci
- Site-specific DNA cleavage enables antigen-receptor diversity
- Erroneous joining may place a proto-oncogene near a receptor regulatory element

Developmental context determines the locus at risk.

V(D)J misrecombination can activate an oncogene

Proto-oncogene near a DNA break

Gene normally regulated in its own genomic context

Ig/TCR locus undergoing recombination

Strong neighboring regulatory element

Oncogene repositioned beside active regulatory DNA

- A DNA-diversification error becomes a heritable clonal lesion
- Can occur during B- or T-cell precursor development

Lymphoid lineage constrains the receptor partner

B-lineage precursor

- Immunoglobulin loci are being assembled
- Ig regulatory DNA may activate a proto-oncogene
- Translocation partner fits B-cell lineage

T-lineage precursor

- T-cell receptor loci are being assembled
- TCR regulatory DNA may activate a proto-oncogene
- Translocation partner fits T-cell lineage

Receptor-locus involvement is a clue to the cell of origin.

Germinal-center B cells remodel their Ig genes

Antigen-stimulated B cell enters germinal center



AID expression increases



Antibody genes undergo class switching and hypermutation

This normal maturation program creates a second window for DNA damage.

Activation-induced cytidine deaminase has two jobs

Somatic hypermutation

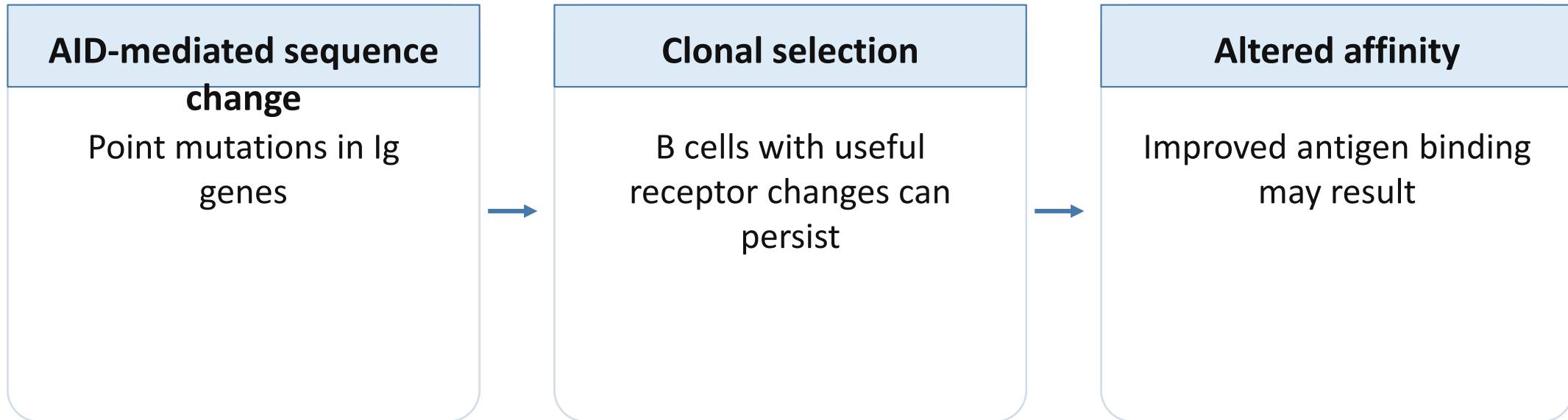
- Introduces point mutations in Ig variable-region genes
- Supports affinity maturation
- Can inadvertently affect other genes

Class-switch recombination

- Changes the Ig heavy-chain constant-region segment
- Alters antibody isotype
- Requires programmed recombination

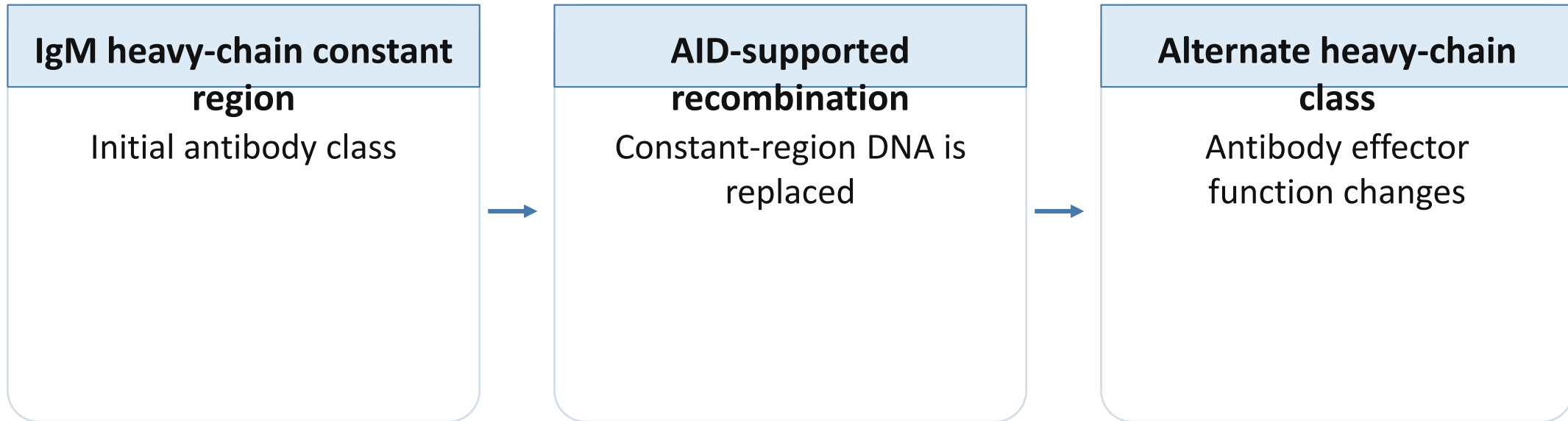
AID-associated DNA lesions are productive physiologically but hazardous if mistargeted.

Somatic hypermutation changes antibody affinity



Mutation of a normal Ig locus is not synonymous with malignant transformation.

Class switching changes isotype—not specificity



The variable-region antigen specificity can be retained during isotype switching.

AID mistargeting damages proto-oncogenes

AID acts outside the intended Ig region



Aberrant DNA lesions or point mutations occur



Oncogene dysregulation can follow

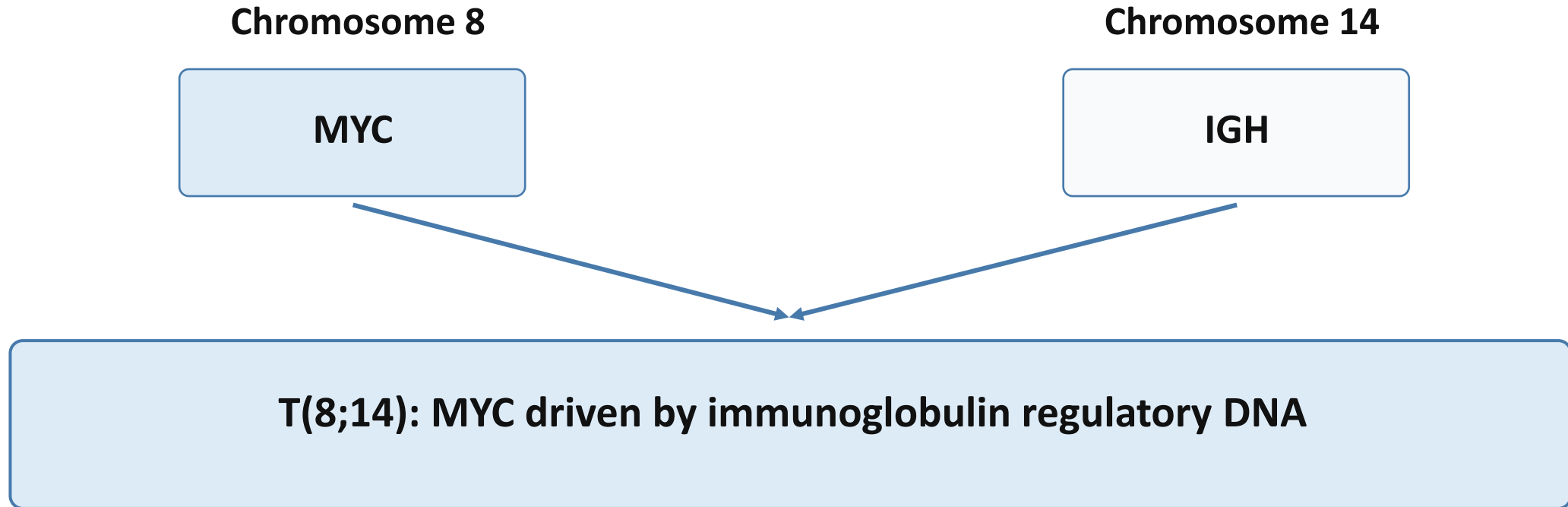
MYC rearrangements and BCL6 regulatory mutations.

MYC::IGH can arise in normal germinal centers

Formation of a translocation does not, by itself, establish that a cell is malignant.

- AID can induce MYC::IGH translocations in a small fraction of normal germinal-center B cells
- The lesion provides a potential driver but clonal evolution still matters
- Diagnostic interpretation depends on the entire cellular and tissue context

MYC activation uses a powerful Ig enhancer



Regulatory juxtaposition; High MYC expression, not a MYC–IGH chimeric protein

Simplified locus schematic; Not a karyogram

MYC couples proliferation to biosynthesis

MYC transcriptional activity rises



Biosynthesis / Warburg-type metabolism increases



Cell growth and proliferation accelerate

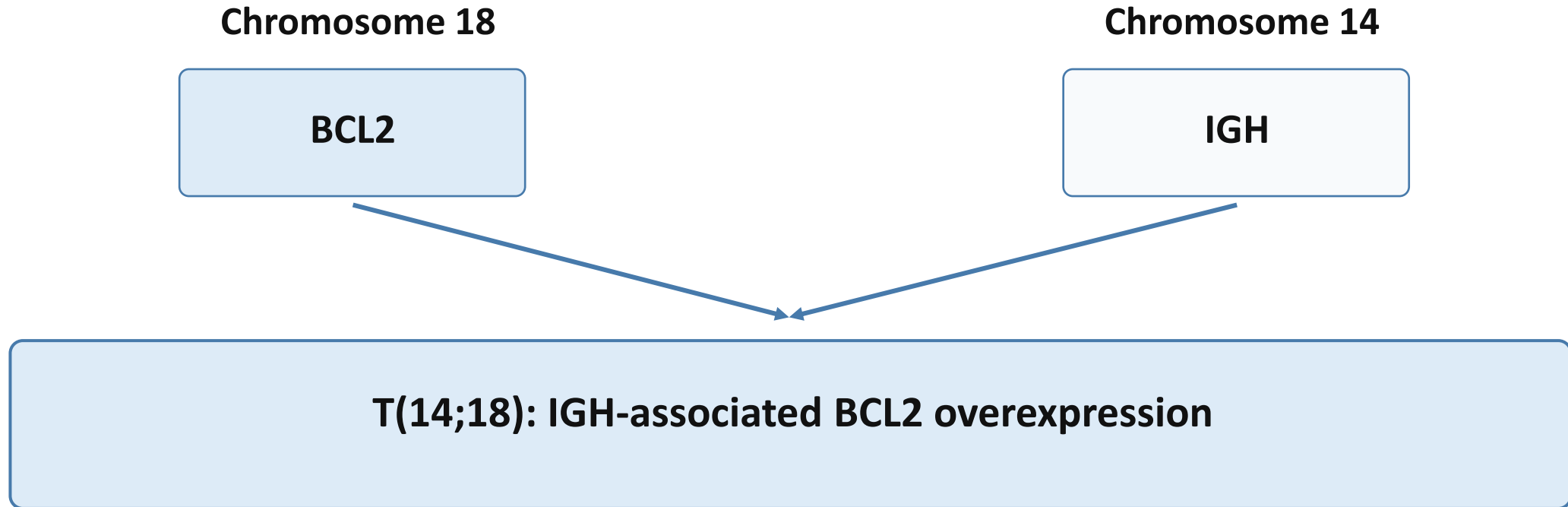
This mechanism helps explain the extreme proliferative activity of Burkitt lymphoma.

Burkitt lymphoma illustrates the pro-growth driver

- MYC rearrangements are central to the molecular pathogenesis
- IGH t(8;14) is the common partner; Ig light-chain partners also occur
- MYC enhances growth-related metabolic and transcriptional programs
- High proliferation coexists with abundant apoptotic cells

The molecular lesson is MYC overexpression—not blockade of apoptosis.

BCL2 becomes overexpressed after t(14;18)



Regulatory rearrangement that increases anti-apoptotic signaling

Simplified locus schematic; Not a karyogram

BCL2 helps abnormal B cells evade apoptosis

IGH-associated BCL2 expression rises



Programmed cell death is antagonized



Germinal-center-derived neoplastic B cells persist

This is a survival advantage rather than a direct acceleration of cell-cycle entry.

Follicular lymphoma exposes the survival phenotype

Normal germinal center

- Many B cells undergo apoptosis
- Selection eliminates unsuccessful cells
- Apoptotic debris is commonly observed

Follicular lymphoma

- BCL2 often overexpressed after t(14;18)
- Cell death is suppressed
- Apoptotic cells are characteristically sparse

The biologic signature is failure to delete cells that should die.

BCL6 mutations disrupt a physiologic regulator

Mutation affects BCL6 control sequences



Normal negative autoregulation is lost



Persistent BCL6 expression impedes differentiation and growth arrest

Mistargeted somatic hypermutation is implicated in some BCL6 promoter mutations.

BCL6 dysregulation has more than one route

BCL6 rearrangement

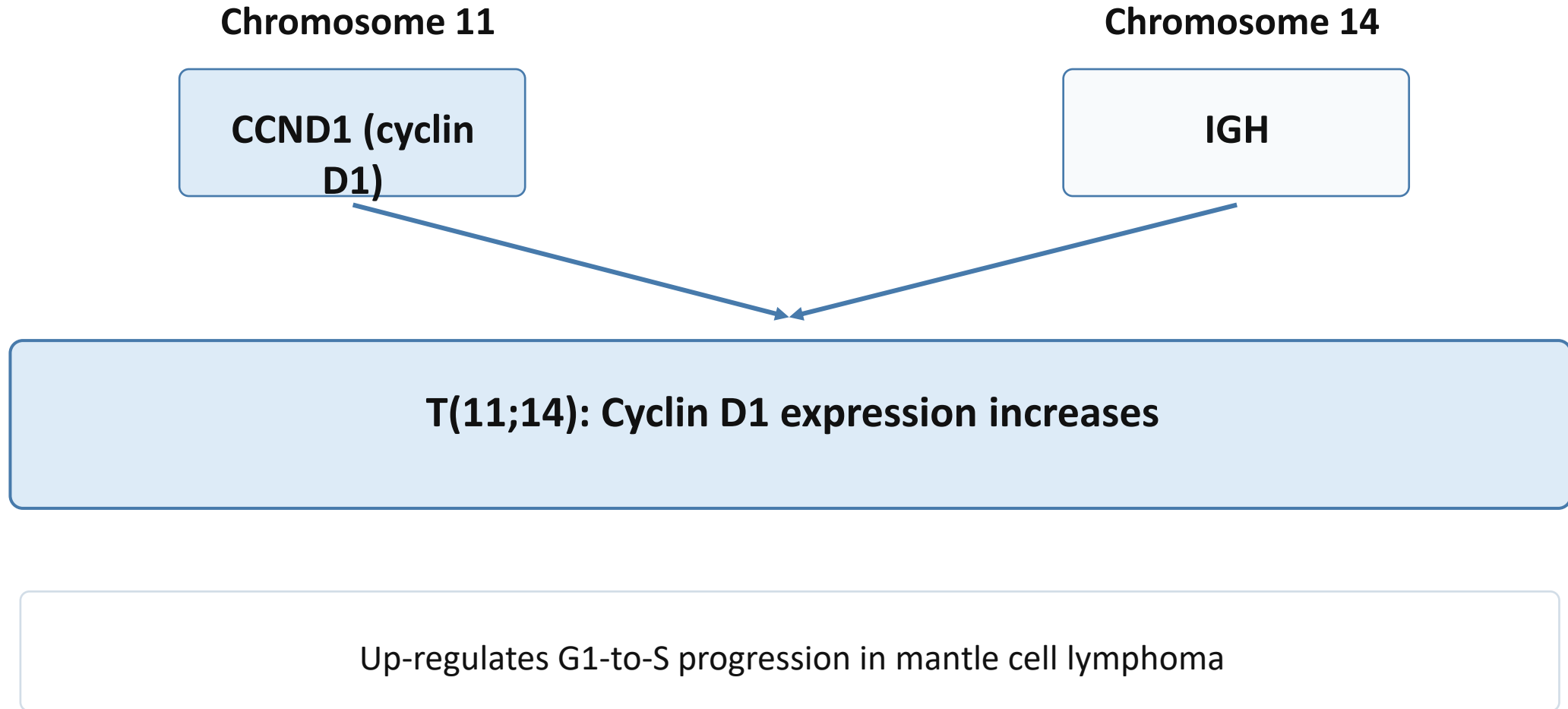
- Chromosome breakpoint involves BCL6
- Can alter gene regulation
- Observed in a subset of DLBCL

BCL6 promoter mutation

- Local acquired sequence change
- May escape normal autorepression
- Can likewise raise BCL6 activity

Chromosomal translocation is not the only acquired path to oncogene activation.

Cyclin D1 translocation advances the cell cycle



Simplified locus schematic; Not a karyogram

Ig-linked lesions differ in their downstream effect

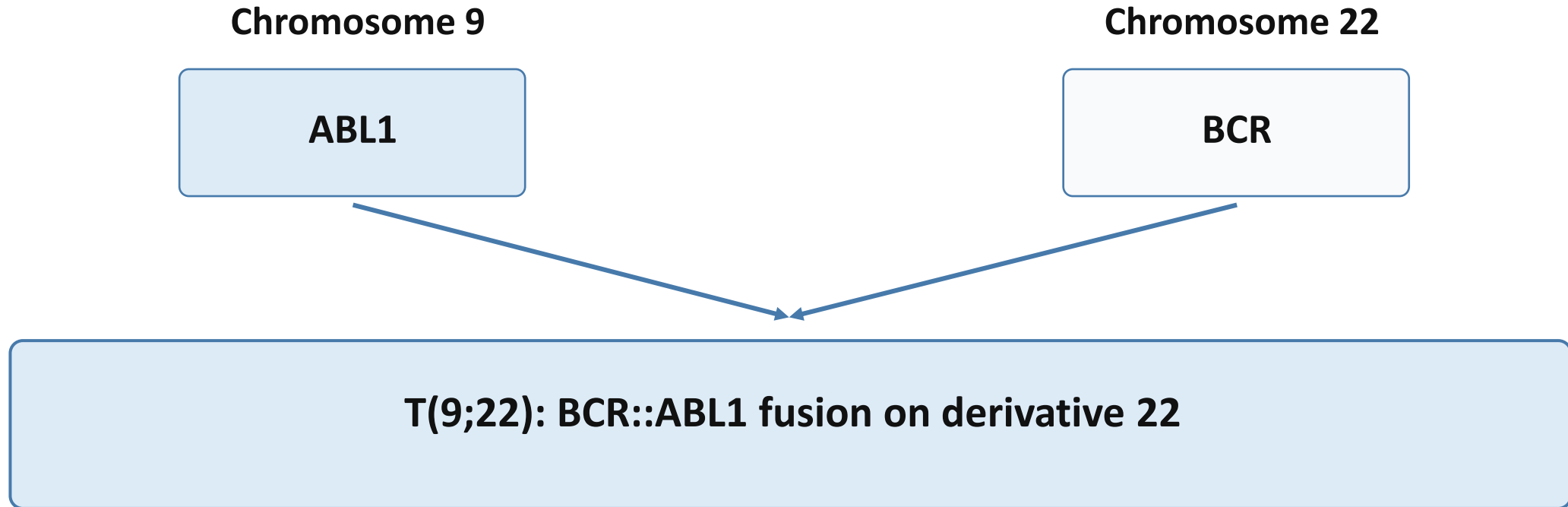
Rearrangement	Characteristic context	Main molecular output
MYC–IGH, t(8;14)	Burkitt lymphoma	Proliferation / metabolism
BCL2–IGH, t(14;18)	Follicular lymphoma	Anti-apoptotic survival
CCND1–IGH, t(11;14)	Mantle cell lymphoma	G1–S cell-cycle entry

A recurrent lesion is not an entire diagnosis

The same pathway can be perturbed by different mutations across distinct hematolymphoid malignancies.

- The partner gene, breakpoint and cellular lineage modify interpretation
- Genotype is integrated with morphology and immunophenotype
- An isolated abnormality does not reproduce a whole tumor classification

BCR::ABL1 creates an oncogenic fusion kinase



Constitutively active tyrosine kinase; Philadelphia chromosome

Simplified locus schematic; Not a karyogram

BCR::ABL1 signals without physiologic restraint

BCR supports kinase self-association



ABL kinase remains activated



RAS / JAK-STAT and related survival pathways are stimulated

Proliferation becomes less dependent on external hematopoietic growth signals.

CML illustrates proliferation with maturation

BCR::ABL1 output

- Growth-factor-independent expansion
- Prominent granulocytic and megakaryocytic production
- Differentiation remains relatively preserved

Acute leukemia pattern

- Lesions can block differentiation
- Immature blasts accumulate
- Normal marrow output is suppressed

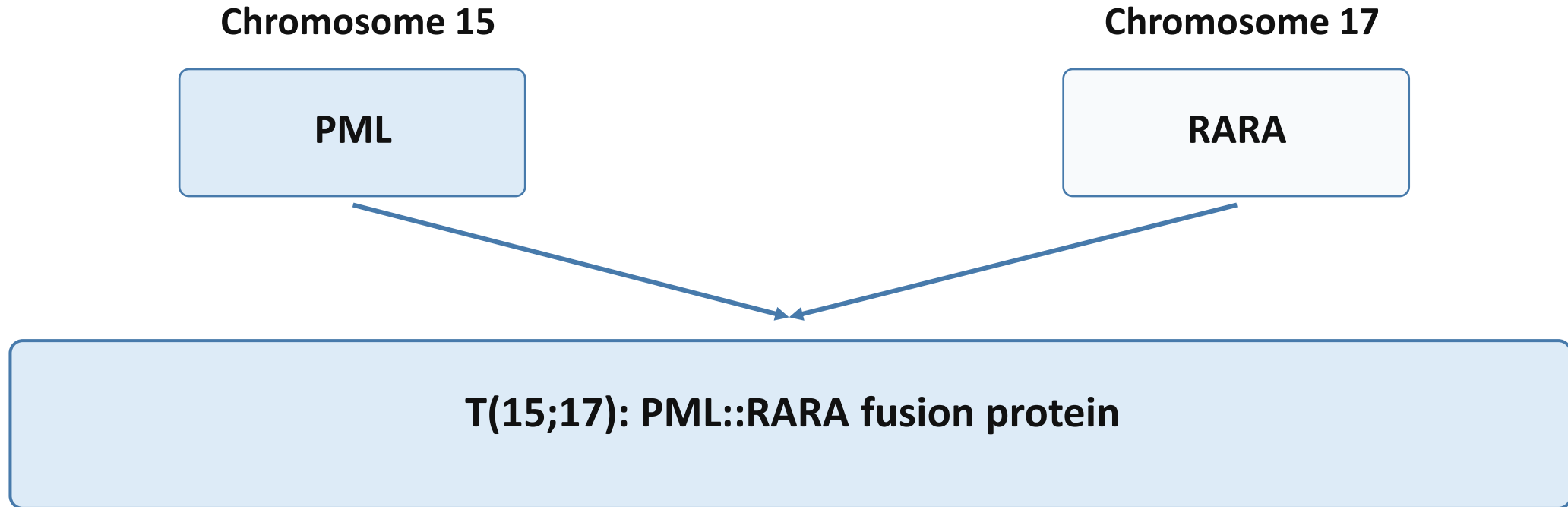
Kinase-driven proliferation does not necessarily imply a complete maturation block.

BCR::ABL1 is both a marker and a drug target

- Identification of the fusion gene is central to CML diagnosis
- Chromosome analysis or molecular tests can demonstrate BCR::ABL1
- Fusion-derived kinase activity provides a treatment target
- Quantitative assays of the fusion transcript enable disease monitoring

Diagnostic, predictive and monitoring roles should be distinguished.

PML::RARA is a nuclear fusion oncoprotein



Abnormal transcriptional repression blocks promyelocyte maturation

Simplified locus schematic; Not a karyogram

PML::RARA represses differentiation genes

Fusion receptor has altered retinoid response



Transcriptional repressors remain recruited



Myeloid progenitors fail to complete maturation

This is an archetypal transcription-factor-mediated differentiation block.

Retinoids can reverse the PML::RARA program

Pharmacologic all-trans retinoic acid binds fusion protein



Repressor complexes are displaced; Degradation is promoted



Differentiation resumes and malignant promyelocytes are cleared

A mechanistic demonstration of differentiation therapy.

Acute promyelocytic leukemia integrates mechanism and clinic

- PML::RARA results from recurrent t(15;17)
- The lesion blocks differentiation at the promyelocyte stage
- The disease is associated with characteristic abnormal promyelocytes
- Recognizing the molecular driver matters because differentiation therapy is effective

Molecular diagnosis can alter treatment directly.

KMT2A lesions alter transcriptional self-renewal

KMT2A chromosomal rearrangement



Abnormal regulation of differentiation and renewal genes



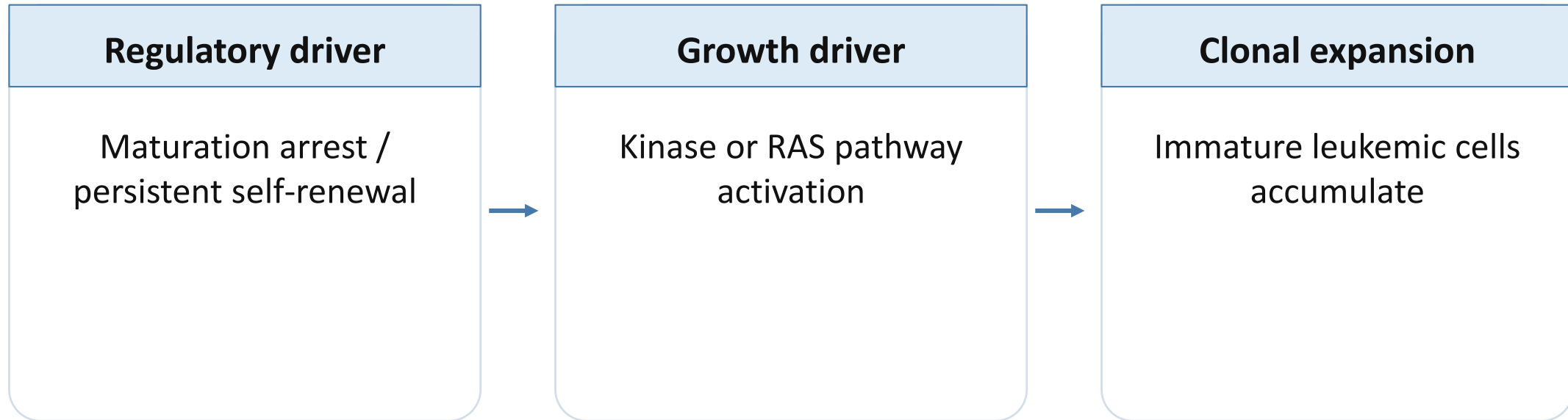
Persistence of leukemic progenitors

KMT2A rearrangement among lesions affecting self-renewal and maturation.

Fusion oncoproteins have different biochemical roles

Fusion	Biochemical category	Dominant pathogenic output
BCR::ABL1	Constitutively active kinase	Pro-growth and pro-survival signaling
PML::RARA	Abnormal nuclear regulator	Differentiation arrest
KMT2A rearrangement	Transcription/chromatin regulation	Abnormal renewal / maturation

Acute leukemias often require complementary lesions



Cooperation between transcription-factor and growth signaling lesions.

Acquired point mutations can also drive cancer

Coding-region change

- Alters activity of the encoded protein
- Can increase signaling or disable a regulator
- May create gain- or loss-of-function effects

Regulatory-region change

- Alters how much protein is produced
- Can disrupt normal negative feedback
- BCL6 promoter mutations are an example

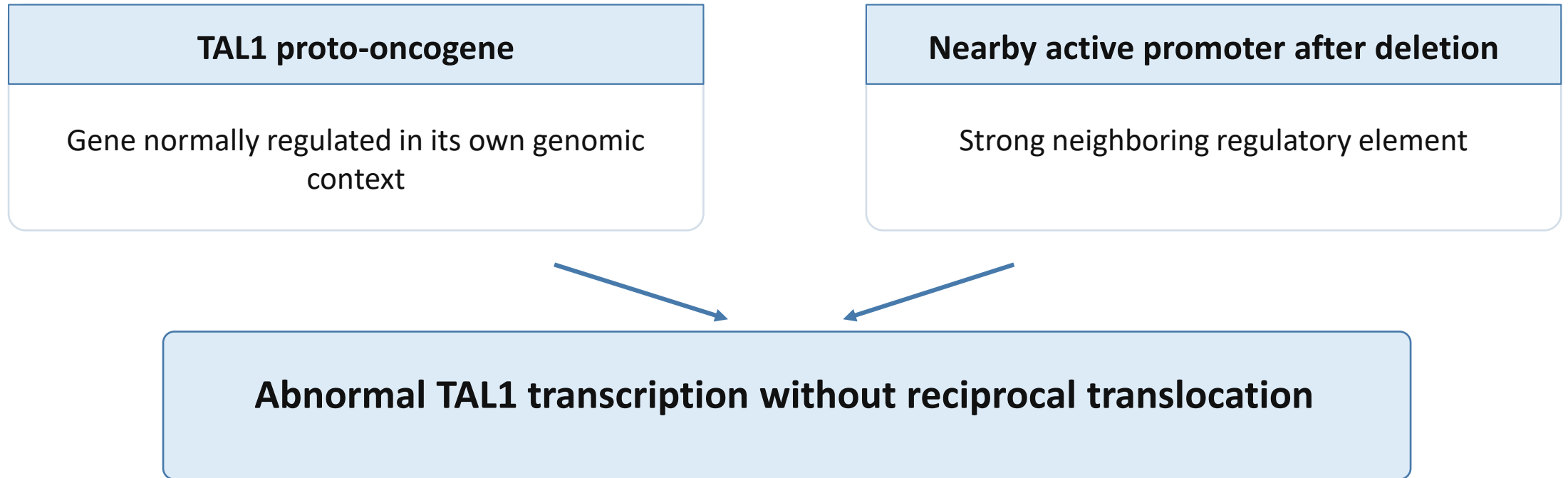
An abnormal gene sequence need not involve a visible chromosomal translocation.

Epigenetic regulators are acquired-mutation targets

- Mutated chromatin regulators alter DNA-accessibility and gene-expression programs
- DNMT3A influences DNA methylation in AML
- KMT2D and EZH2 mutations are described in follicular lymphoma
- Histone regulation provides an additional route to altered cell identity

Epigenetic changes can be caused by genetic mutations.

Small deletions can activate oncogenes

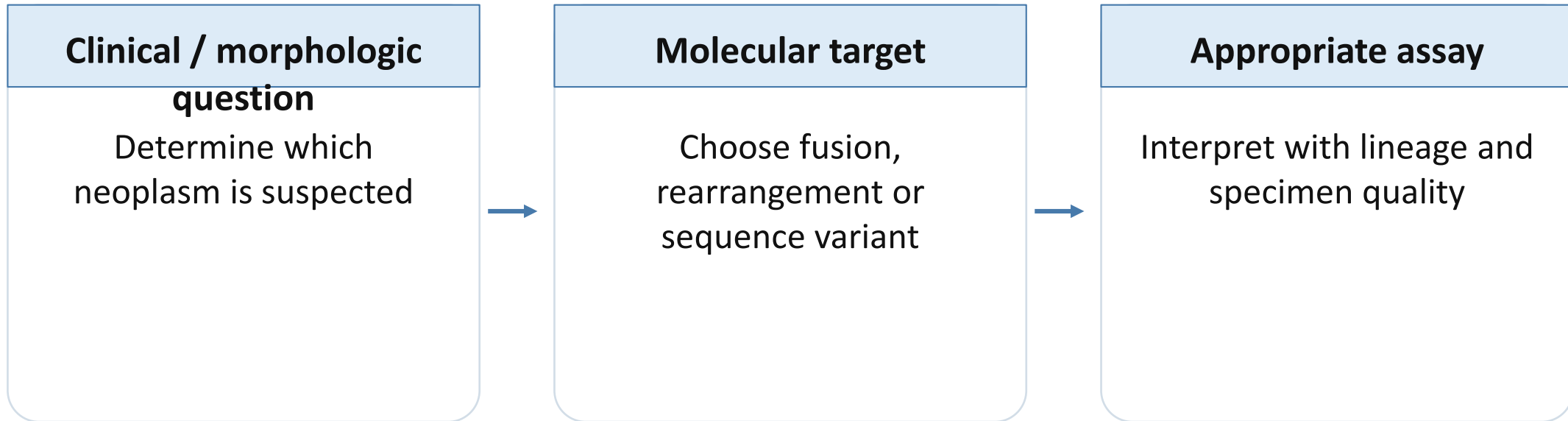


- A small chromosome 1 deletion can juxtapose a promoter and TAL1
- Reported by Robbins in a subset of T-cell ALL

Molecular assays interrogate different features

Method	Typical molecular feature	Practical role
Conventional karyotype	Larger structural and numerical changes	Global chromosomal overview
FISH	Specific rearrangement or copy change	Targeted localization / detection
RT-PCR / PCR	Fusion transcripts or defined sequence	Targeted sensitive detection
Sequencing	Acquired sequence variants; some fusions	Molecular characterization

The assay must match the suspected lesion



A negative targeted assay only excludes lesions within its validated detection scope.

Molecular findings need integrated interpretation

- The genetic lesion may be diagnostic, supportive or shared by entities
- Phenotype, histology, blood and marrow distribution remain relevant
- AID-associated rearrangements may occur in normal germinal centers
- The final diagnosis is not reducible to a single isolated sequence finding

Do not equate mutation detection with a malignant diagnosis in all circumstances.

Case 1 — A kinase-driven myeloproliferation

An adult has marked granulocytic leukocytosis. Molecular testing identifies a BCR::ABL1 fusion.

What does this fusion encode, and why can mature granulocytes still predominate?

T(9;22)

Constitutive tyrosine kinase

Relatively preserved maturation

Case 1 — CML mechanism resolved

BCR::ABL1 produces a constitutively active kinase.

- The fusion enhances growth-factor-independent signaling
- The proliferation of myeloid progenitors is increased
- Unlike strong differentiation-blocking lesions, maturation can continue

The Philadelphia chromosome is a mechanism-defining molecular finding.

Case 2 — An apoptosis-resistant B-cell clone

A follicular-pattern B-cell lymphoma harbors an IGH–BCL2 rearrangement.

Which malignant-cell advantage is most directly predicted?

T(14;18)

BCL2 overexpression

Reduced cell death

Case 2 — Survival rather than rapid cycling

IGH-associated BCL2 expression protects cells from apoptosis.

- BCL2 antagonizes programmed cell death
- Abnormal B cells persist when they would normally be eliminated
- This does not imply the MYC-like acceleration of biosynthesis

Tumor growth may reflect impaired removal as well as increased production.

Case 3 — A promyelocyte maturation block

Acute leukemia is associated with abnormal promyelocytes and a PML::RARA fusion.

Which transcriptional defect explains the maturation arrest?

T(15;17)

Retinoid-responsive transcription
factor

Repressor recruitment

Case 3 — A targetable differentiation program

PML::RARA enforces transcriptional repression at physiologic retinoid levels.

- Genes required for myeloid maturation are not activated
- Pharmacologic all-trans retinoic acid changes fusion-protein behavior
- Differentiation and elimination of abnormal cells become possible

A molecular lesion can determine a differentiation-based therapy.

Case 4 — A germinal-center translocation

A highly proliferative mature B-cell tumor has t(8;14), juxtaposing MYC with IGH.

Is the principal mechanism a chimeric protein or regulatory overexpression?

MYC gene remains intact

Ig heavy-chain regulatory DNA

Increased biosynthesis / cell
division

Case 4 — MYC is deregulated by enhancer context

This is regulatory juxtaposition, not production of an MYC–IGH fusion kinase.

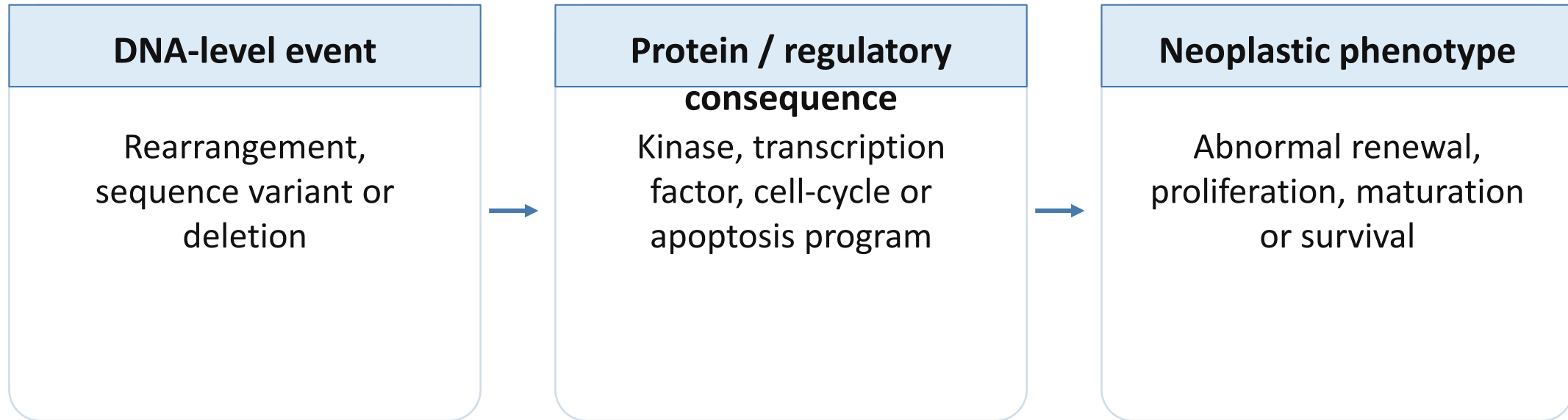
- IGH regulatory elements drive inappropriate MYC expression
- MYC raises cellular growth and metabolic programs
- The lesion is central to Burkitt lymphoma pathogenesis

Always distinguish a locus rearrangement from a chimeric coding fusion.

A comparative map of acquired lesions

Lesion	Tumor example	Molecular mechanism
MYC / IGH	Burkitt lymphoma	Proto-oncogene overexpression
BCL2 / IGH	Follicular lymphoma	Resistance to apoptosis
CCND1 / IGH	Mantle cell lymphoma	G1–S promotion
BCR::ABL1	CML	Constitutive kinase signaling
PML::RARA	Acute promyelocytic leukemia	Differentiation repression

Integration: A lesion must be translated to function



Mechanistic interpretation bridges cytogenetics, pathology and molecular diagnosis.

Core references

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Elsevier; 2026.

Related textbook material: oncogenic translocations, structural lesions and epigenetic changes.

Disease exemplars: B-ALL, Burkitt lymphoma, follicular lymphoma, mantle cell lymphoma, AML and CML.

Schematic diagrams in this deck are newly authored as editable PowerPoint elements.