

Chromosomal Changes

Chromosomal alterations in cancer: mechanisms, examples, and clinical significance

Translocations · Deletions · Amplification · Chromothripsis

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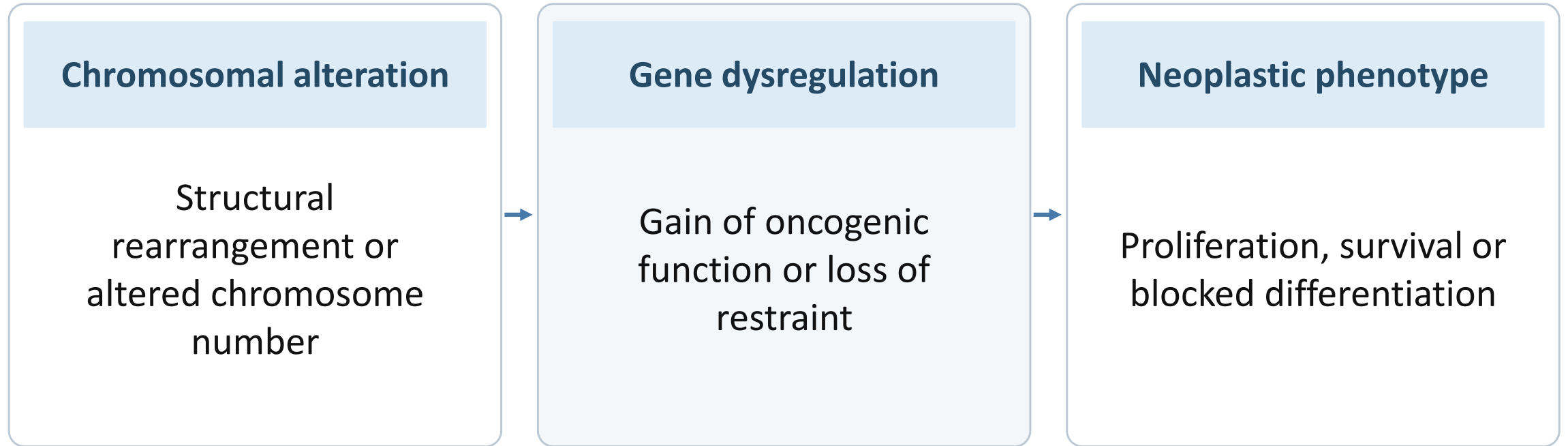
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Learning outcomes

- Classify numerical and structural chromosomal changes in tumor cells.
- Explain enhancer substitution, fusion oncogenes, deletion and amplification.
- Relate recurrent abnormalities to selected neoplasms and targeted therapy.
- Interpret chromothripsis and the limits of the source evidence.

The central biological consequence



Different chromosome lesions converge on changed activity of cancer-associated genes.

Chromosome number versus structure

Numerical change

- Whole chromosomes gained or lost
- Aneuploidy is common in tumor genomes
- May appear during progression or early in some contexts

Structural change

- DNA segments moved, deleted, inserted or amplified
- Can create recurrent tumor-specific lesions
- May directly alter proto-oncogenes or tumor suppressors

Recurrent changes are not random trivia

- Characteristic lesions have been identified in most leukemias and lymphomas.
- Many sarcomas and an increasing number of carcinomas also have recurrent changes.
- A recurrent breakpoint is a clue to a gene important in the tumor.
- Chromosome-level changes provide biological and clinical information.

When do chromosome alterations arise?

Often later

Changes accompany progression



Sometimes early

Telomere loss can precede transformation



Key interpretation

Timing depends on the underlying tumor pathway

Chromosome damage can sometimes be an initiating lesion, not merely a late event.

Genomic instability enables additional lesions

- Normal p53-dependent checkpoints limit persistence of grossly damaged genomes.
- Loss of p53 function permits survival of cells with structural chromosome damage.
- Error-prone end joining can preserve rearranged chromosomes.
- Genomic instability can accelerate acquisition of cancer-promoting changes.

Two complementary ways to study the cancer karyotype

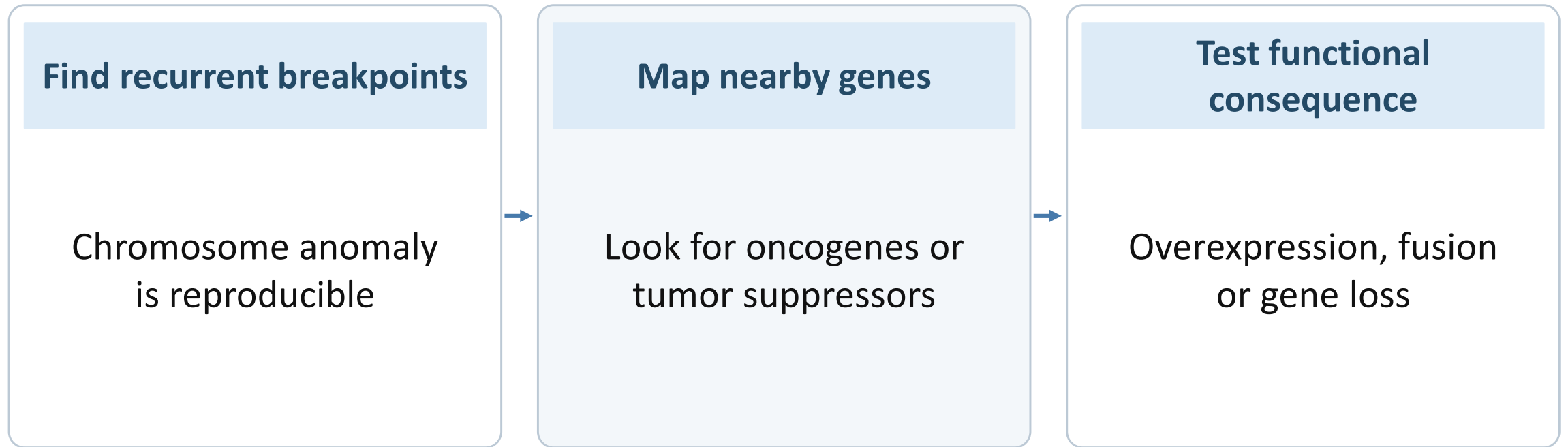
Metaphase karyotyping

- Morphologic identification of metaphase chromosomes
- Historically the foundational approach
- Provides chromosome-scale patterns

Genome-sequence reconstruction

- Chromosomes reconstructed from deeply sequenced cancer DNA
- Recognizes simple and complex rearrangements
- Increasingly used in research; Future clinical replacement is uncertain

From a breakpoint to a candidate cancer gene



Recurrent breakpoints can identify cancer-associated genes such as MYC, BCL2, ABL, APC and RB.

Why chromosomal changes matter clinically

Diagnosis

Some lesions help define a tumor type.

Prognosis

Selected abnormalities correlate with disease course.

Therapy and monitoring

Fusion proteins can be drug targets; Molecular products can track treatment response.

Structural lesions: The core mechanisms

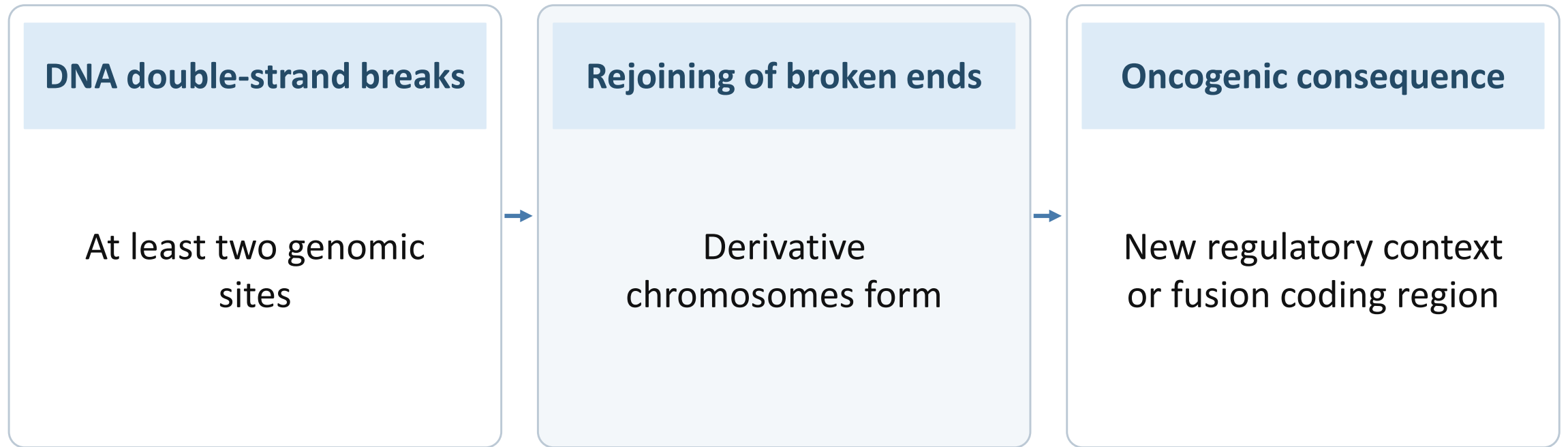
Alteration

- Translocation
- Regulatory element substitution or fusion gene

Typical consequence

- Deletion
- Tumor suppressor loss; Sometimes promoter juxtaposition or fusion

How translocation can activate an oncogene



Breakage and rejoining alone do not guarantee malignancy; The affected genes determine biological significance.

The two fundamental translocation outcomes

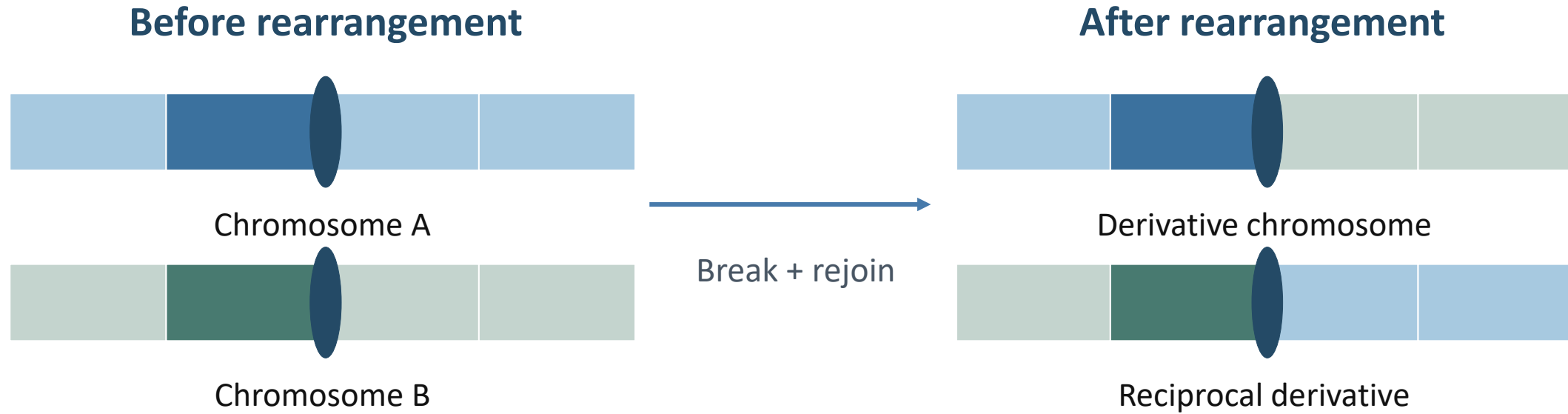
Enhancer/promoter substitution

- Proto-oncogene coding region stays intact
- New, highly active regulation raises protein abundance
- Prototype: MYC–IGH in Burkitt lymphoma

Fusion gene

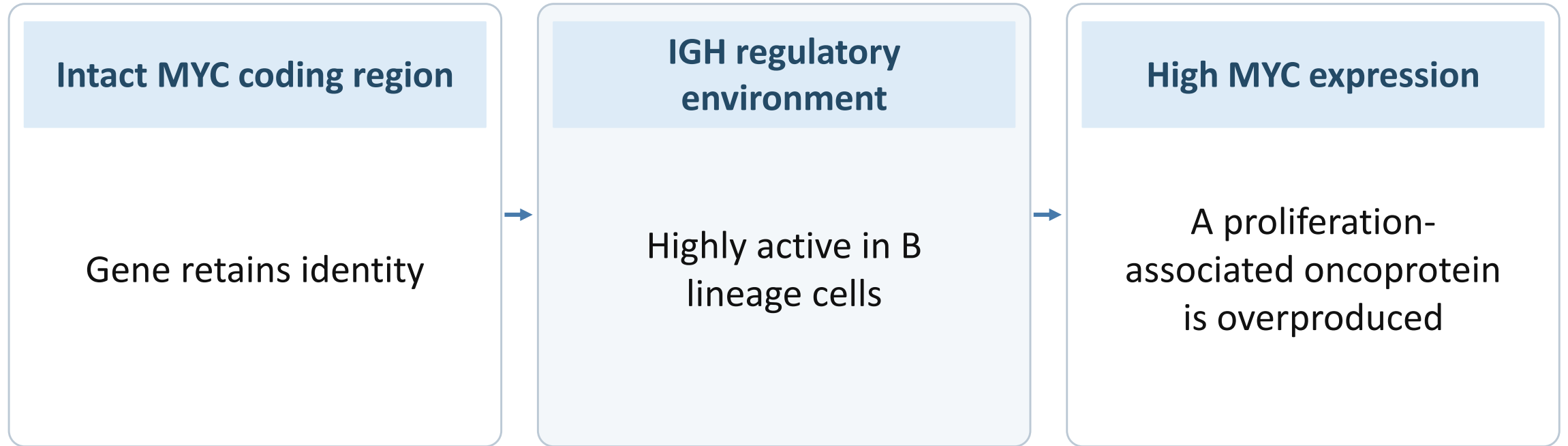
- Parts of two coding regions become joined
- Novel chimeric protein with altered function
- Prototype: BCR::ABL in CML

Schematic reciprocal translocation



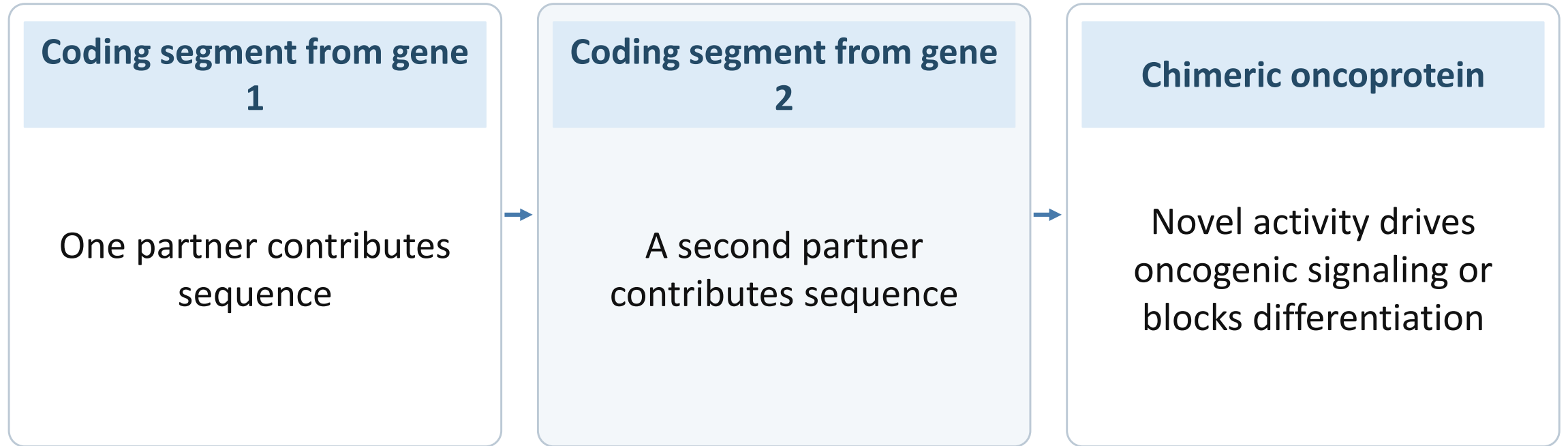
1. Two original chromosomes
2. Breakpoints and rejoined segments
3. Two derivative chromosomes

Regulatory substitution changes expression—not sequence



The position of the breakpoint governs the precise mechanism.

Fusion changes the protein itself



The consequence depends on the functional domains assembled.

Double-strand breaks are prerequisite events

- Translocations require breakage at two or more genomic locations.
- Broken ends are joined into derivative chromosomes.
- The source identifies nonhomologous end joining in BCR::ABL formation.
- The oncogenic product is the causal focus—not merely the abnormal karyotype.

Why lymphoid cells are vulnerable to translocations

- Antigen receptor gene recombination normally involves regulated DNA breaks.
- Both B- and T-cell progenitors rearrange antigen receptor genes.
- Class switching occurs in antigen-stimulated mature B cells.
- Mistargeted breakage or joining can juxtapose powerful receptor-locus regulation with oncogenes.

Antigen receptor locus predicts lineage

Immunoglobulin locus involved

- The associated tumor is of B-cell origin.
- Regulatory regions of active immunoglobulin genes may drive an oncogene.
- Examples: MYC, CCND1 or BCL2 with IGH.

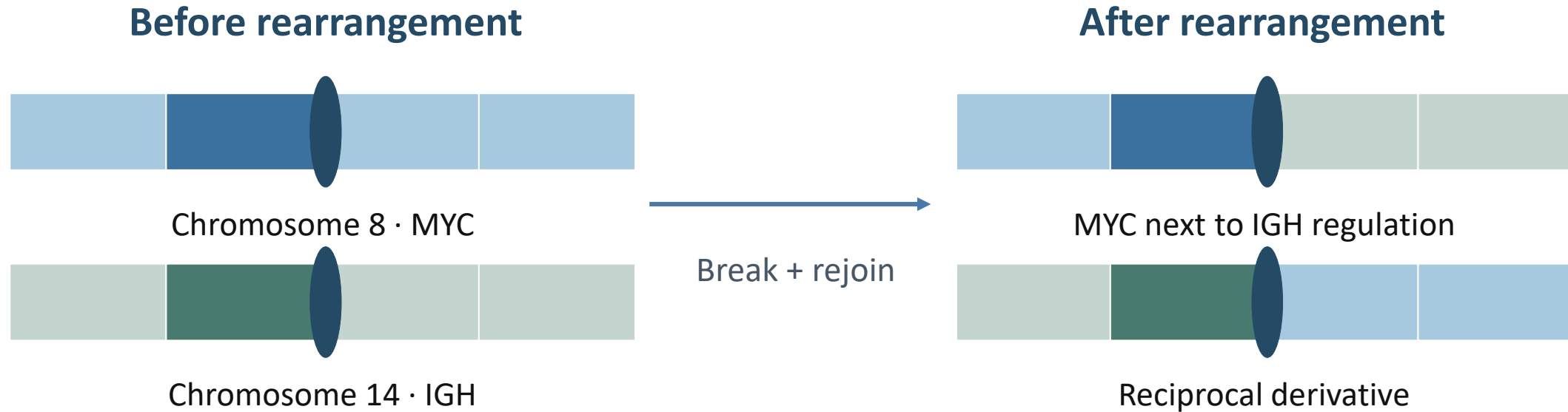
T-cell receptor locus involved

- The associated tumor is of T-cell origin.
- Antigen receptor rearrangement offers a route to oncogenic juxtaposition.
- The oncogenic partner varies across lymphoid tumors.

MYC in normal proliferating cells

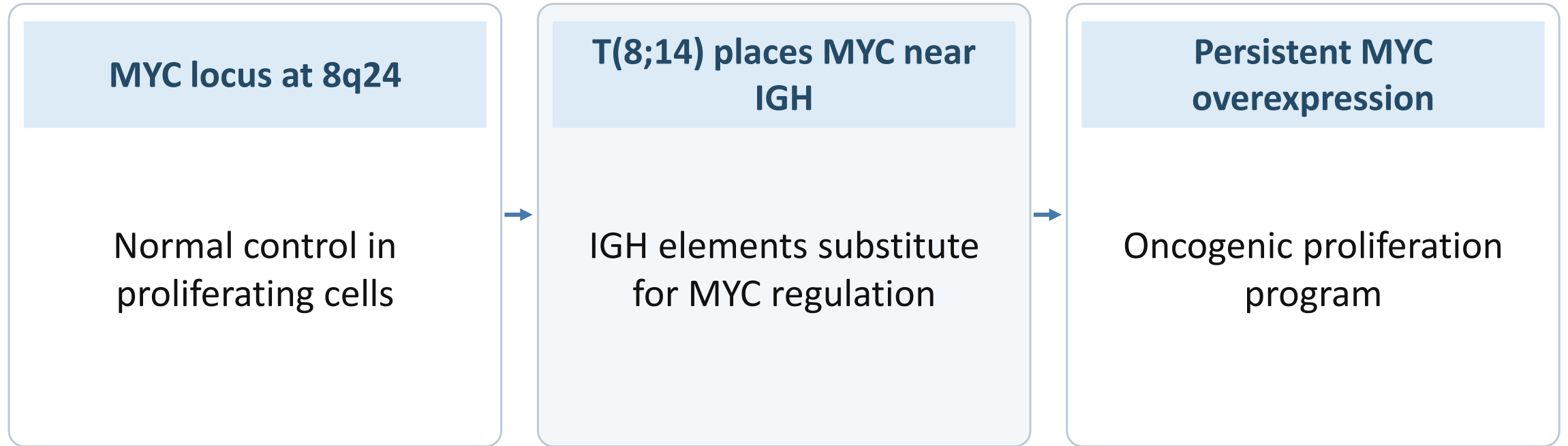
- MYC is a proto-oncogene whose expression is normally tightly controlled.
- High MYC expression is physiologic chiefly in actively dividing cells.
- The tumor-promoting lesion in Burkitt lymphoma primarily changes regulation.
- The coding region can remain intact despite strong oncogenic consequences.

Burkitt lymphoma: T(8;14)(q24;q32)



1. MYC resides at 8q24
2. IGH locus lies at 14q32
3. MYC becomes controlled by an active B-cell regulatory environment

Burkitt: Regulatory relocation to excessive MYC



The MYC–immunoglobulin rearrangement is central to Burkitt lymphoma pathogenesis.

Burkitt: Read the notation accurately

- T denotes a chromosomal translocation.
- (8;14) identifies the chromosomes involved.
- (q24;q32) identifies the chromosomal arm/band positions.
- In this example, MYC is at 8q24 and IGH is at 14q32.

MYC activation is not a MYC fusion protein

What changes in Burkitt lymphoma

- Regulatory context of MYC
- Abundance and timing of MYC expression
- Relationship to an immunoglobulin locus

What does not need to change

- MYC coding sequence may remain unaltered
- No MYC–IGH hybrid protein is required
- Chromosomal juxtaposition is the pathogenic mechanism

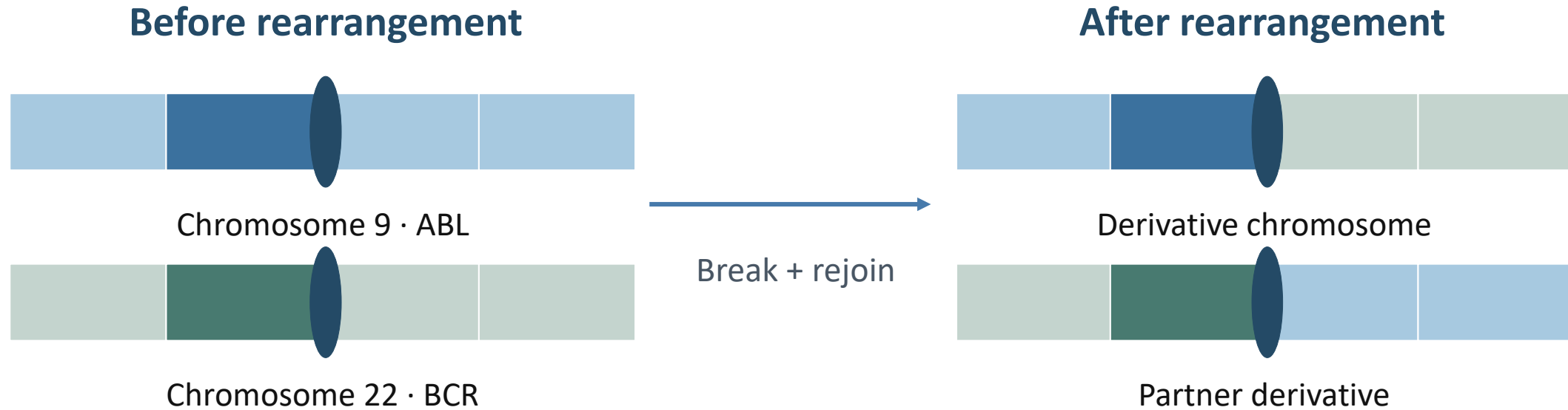
Selected translocations in lymphoid tumors

Tumor	Rearrangement	Key genes
Burkitt lymphoma	T(8;14)(q24;q32)	MYC / IGH
Mantle cell lymphoma	T(11;14)(q13;q32)	CCND1 / IGH
Follicular lymphoma	T(14;18)(q32;q21)	IGH / BCL2

BCR::ABL: The Philadelphia chromosome

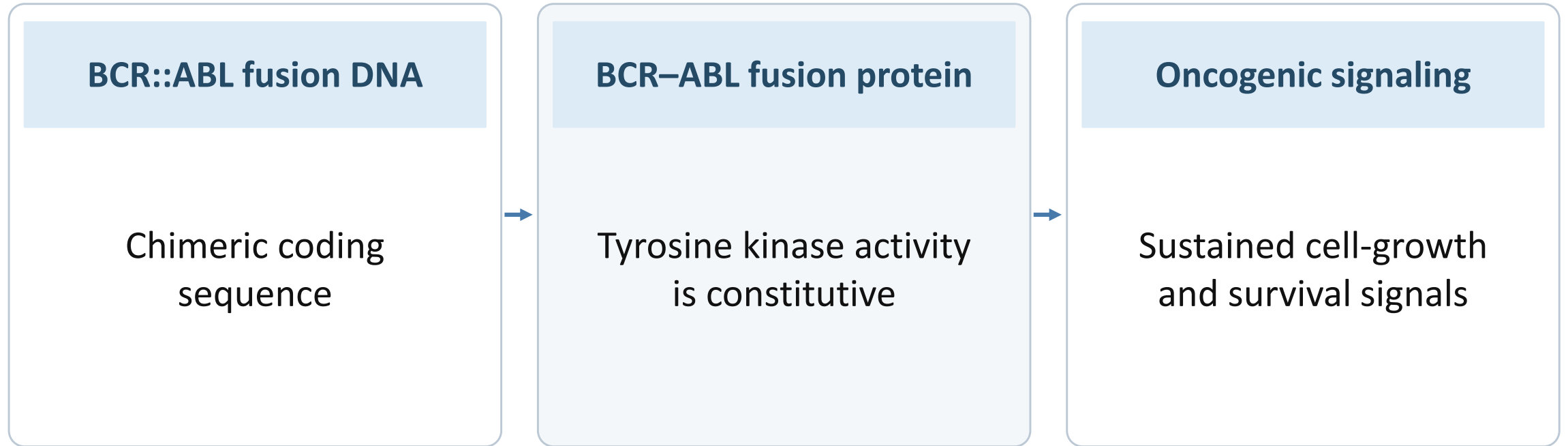
- CML is the prototypic malignancy associated with the Philadelphia chromosome.
- The translocation joins sequences from ABL on chromosome 9 and BCR on chromosome 22.
- BCR::ABL is formed on derivative chromosome 22.
- The rearrangement also occurs in a subset of B-cell acute lymphoblastic leukemias.

T(9;22) creates a fusion gene



1. ABL breakpoint: Chromosome 9
2. BCR breakpoint: Chromosome 22
3. Derivative chromosome 22 carries BCR::ABL

BCR–ABL: Constitutive kinase signaling



Gene/fusion transcript notation BCR::ABL; Protein written BCR–ABL.

Why CML molecular tests are clinically useful

At initial evaluation

- Detect the BCR::ABL fusion or its RNA product.
- The source identifies fusion detection as essential for diagnosis of CML.
- Links malignancy to a specific driver.

During kinase inhibitor therapy

- Quantify the fusion gene product or transcript.
- Molecular measurements follow treatment response.
- Converts genomic mechanism into a longitudinal marker.

Why BCR–ABL is a therapeutic target

- The abnormal kinase has constitutive enzymatic activity.
- An oncogenic enzyme can be inhibited pharmacologically.
- BCR–ABL kinase inhibitors are an established example in the source.
- A genomic abnormality can predict sensitivity to mechanism-directed treatment.

Fusion oncogenes: Two principal output classes

Kinase fusion

- Creates an overactive signaling enzyme.
- Primary effect: Persistent downstream oncogenic signals.
- Example: BCR–ABL.

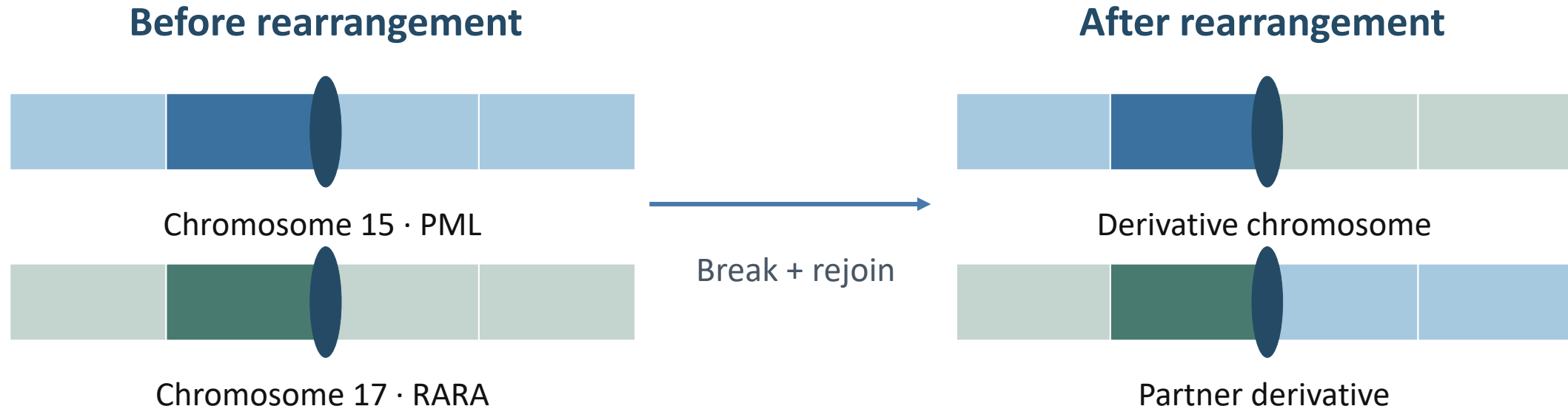
Nuclear regulatory fusion

- Alters transcription or chromatin regulation.
- Primary effect can be failure of differentiation.
- Example: PML–RARA.

Acute promyelocytic leukemia: Central genetic event

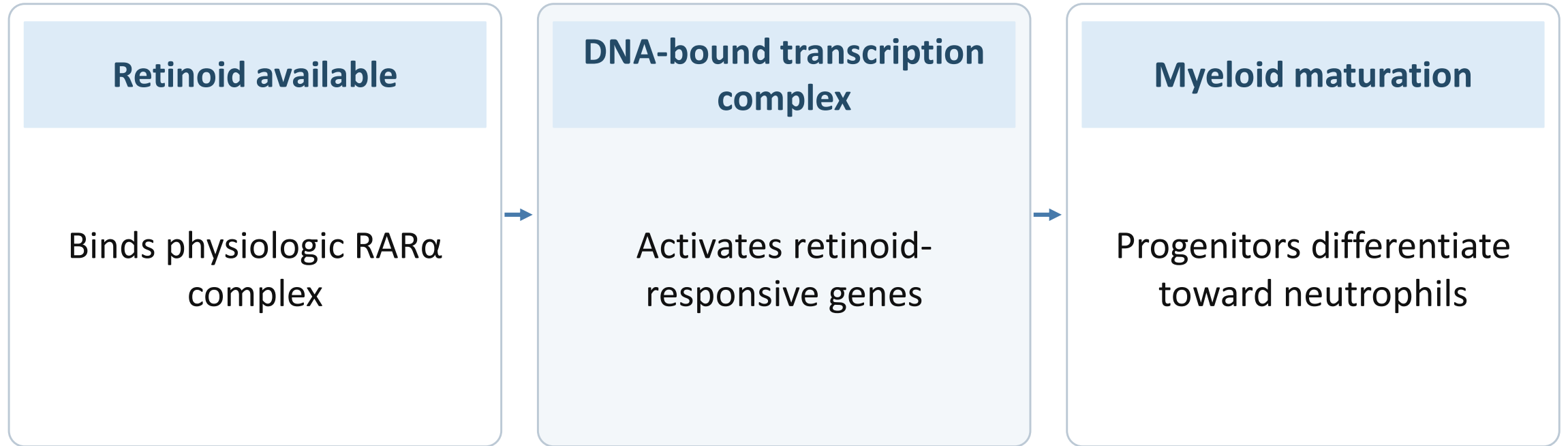
- APL is virtually always associated with t(15;17) in the supplied chapter.
- The reciprocal rearrangement generates PML::RARA.
- The fusion protein incorporates portions of PML and retinoic acid receptor α (RAR α).
- Unlike a constitutive kinase, the central abnormality is transcriptional regulation.

PML::RARA derives from t(15;17)



1. PML is a nuclear regulatory partner
2. RARA encodes retinoic acid receptor α
3. PML::RARA joins coding sequences from both genes

Normal RAR α supports myeloid differentiation



Normal RAR α is part of a DNA-binding transcription factor complex.

Unliganded PML–RARA blocks maturation

**PML–RARA has reduced
retinoid affinity**

Physiologic retinoid is
insufficient



**Repressor complexes
remain recruited**

Differentiation genes
stay inhibited



Promyelocytes accumulate

Normal hematopoietic
elements are displaced

Failure of maturation causes abnormal accumulation of myeloid progenitors.

Normal RAR α versus PML–RARA

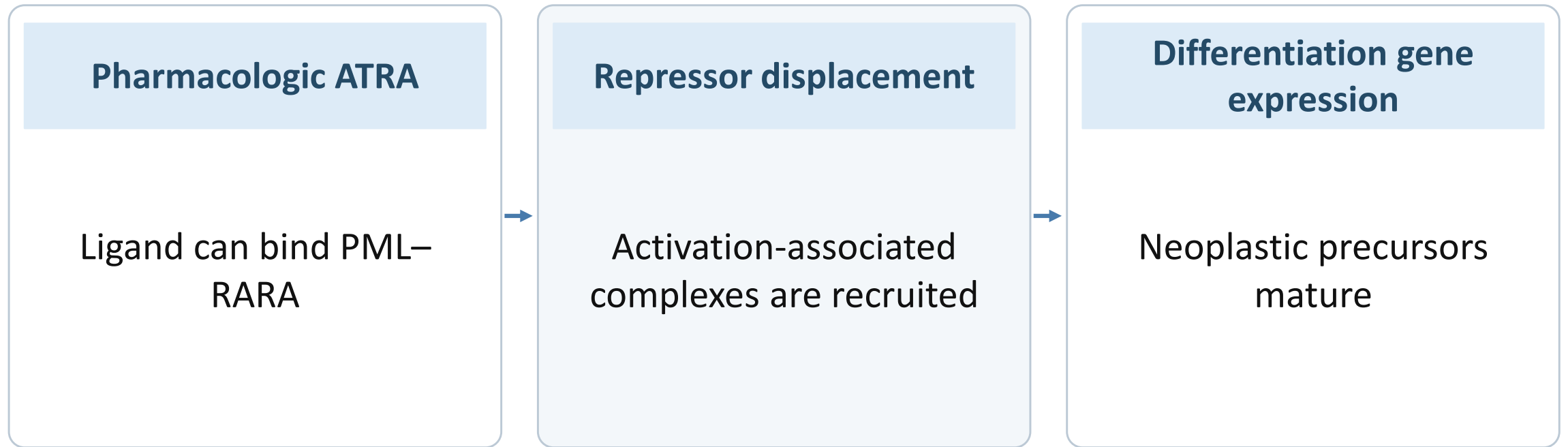
Normal retinoid response

- Retinoids bind the receptor complex.
- Activating transcriptional cofactors support gene expression.
- Neutrophil differentiation proceeds.

Pathologic fusion response

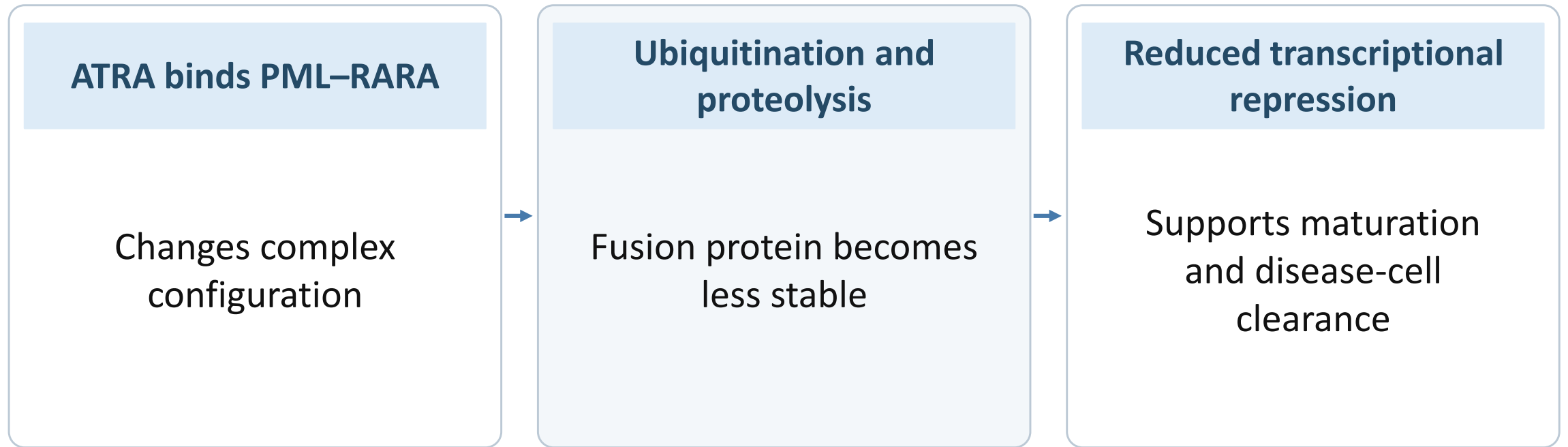
- Reduced affinity at physiologic retinoid levels.
- Repressor recruitment inhibits the target genes.
- Differentiation is arrested.

ATRA reverses the transcriptional block



ATRA changes the fusion-protein complex from a repressive to a differentiation-permitting state.

ATRA also promotes fusion-protein clearance



Proteasomal removal reduces persistence of the differentiation-blocking complex.

Differentiation therapy: A mechanistic success

- APLM illustrates treatment of a malignant phenotype by inducing maturation.
- Differentiated neutrophils have a limited lifespan rather than indefinite self-renewal.
- The source describes marrow clearance over several days and recovery of hematopoiesis.
- The paradigm motivated efforts against other nuclear fusion oncoproteins.

Three prototypes of oncogenic chromosome rearrangement

Tumor	Molecular lesion	Functional result
Burkitt lymphoma	MYC near IGH regulatory region	MYC overexpression
CML	BCR::ABL fusion	Constitutive tyrosine kinase
APML	PML::RARA fusion	Transcriptional repression; Maturation arrest

Selected myeloid leukemia translocations

Tumor in source	Translocation	Affected genes
CML	T(9;22)(q34;q11)	ABL / BCR
AML	T(8;21)(q22;q22)	RUNX1T1 / RUNX1
APML	T(15;17)(q22;q21)	PML / RARA

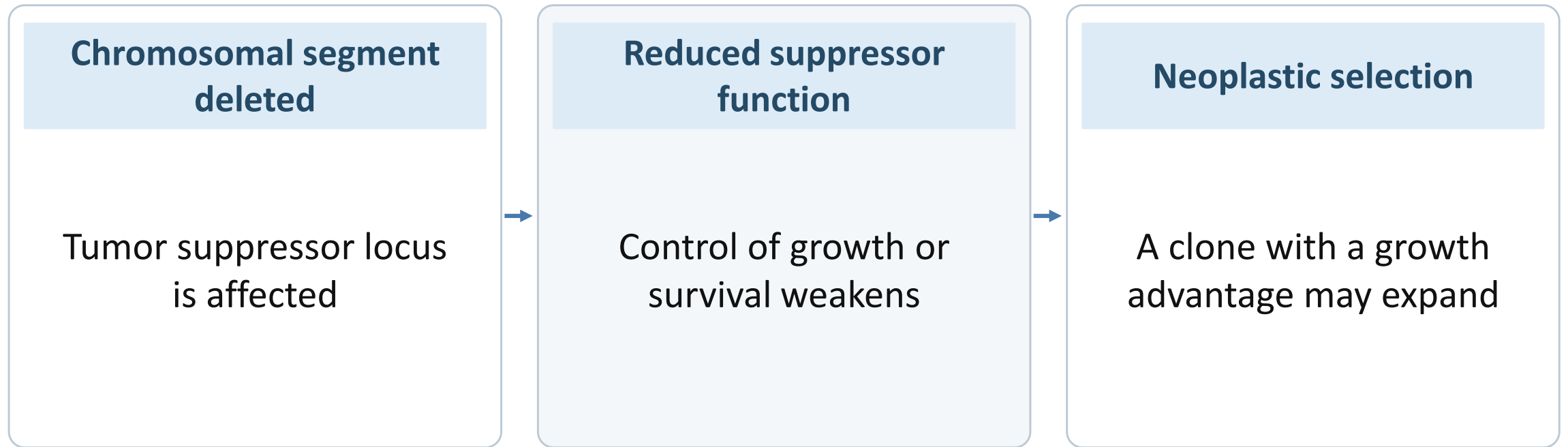
Examples beyond lymphoid and myeloid neoplasia

Setting	Translocation	Affected genes
Ewing sarcoma	T(11;22)(q24;q12)	FLI1 / EWSR1
Prostatic adenocarcinoma	T(7;21)(p22;q22)	ETV1 / TMPRSS2
Prostatic adenocarcinoma	T(17;21)(p21;q22)	ETV4 / TMPRSS2

Deletion is not synonymous with oncogene loss

- Deletions are frequent chromosomal structural abnormalities in cancer.
- Most familiar consequence: Loss of a tumor suppressor gene.
- But some deletions activate oncogenes through regulatory juxtaposition.
- Others create a fusion gene by bringing two coding segments together.

Tumor suppressor deletion: Loss of restraint



The consequence depends on which growth-restraining gene is removed.

Examples of tumor suppressor loss

RB locus in retinoblastoma

- Chromosome 13q14 deletion can involve RB.
- RB is a tumor suppressor linked to cell-cycle restraint.
- An example of chromosomal loss in cancer.

VHL locus in renal carcinoma

- Chromosome 3p deletion can involve VHL.
- Loss of VHL function is common in renal cell carcinoma.
- Different locus, same general deletion principle.

Small deletion can activate an intact oncogene

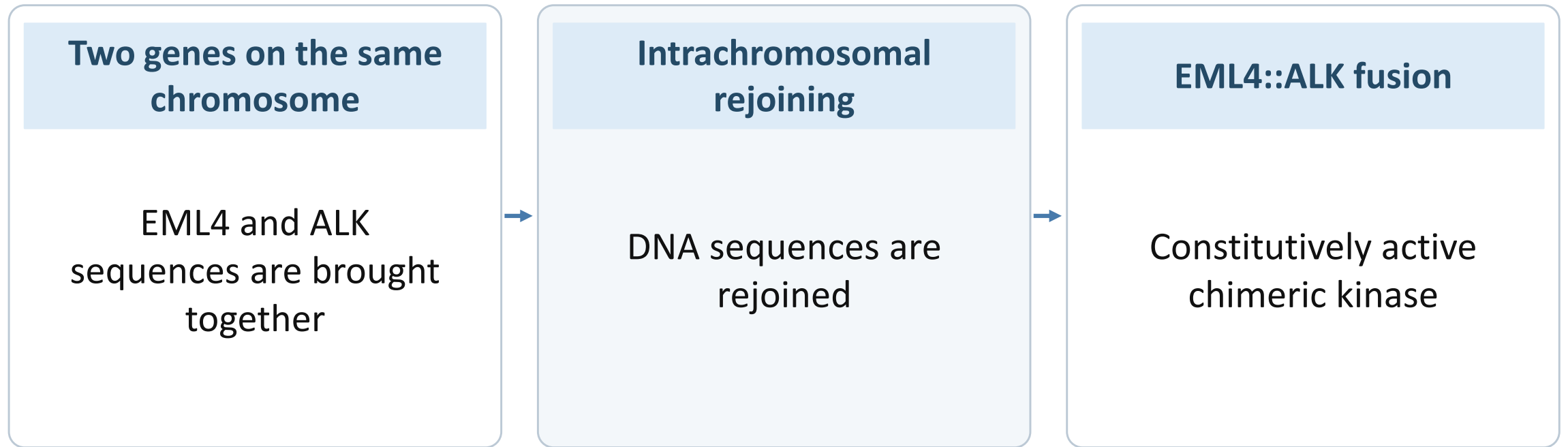


Deletion can activate a nearby proto-oncogene without altering its coding sequence.

TAL1 deletion: A T-ALL example

- The source reports small chromosome 1 deletions in about 25% of T-cell ALL.
- These deletions juxtapose TAL1 with a nearby active promoter.
- The result is increased TAL1 transcription-factor expression.
- This is a regulatory mechanism rather than tumor suppressor deletion.

An intrachromosomal rearrangement can produce a fusion



Fusion of partner sequences creates a new kinase-driving oncogene.

EML4::ALK in lung adenocarcinoma

- The supplied chapter reports the fusion in about 5% of lung adenocarcinomas.
- The intrachromosomal rearrangement joins EML4 and ALK sequences.
- The encoded EML4–ALK protein has constitutive tyrosine kinase activity.
- The kinase is an important therapeutic target.

Deletions have distinct functional outcomes

Deletion pattern

- RB / VHL deleted
- Loss of tumor suppressor function

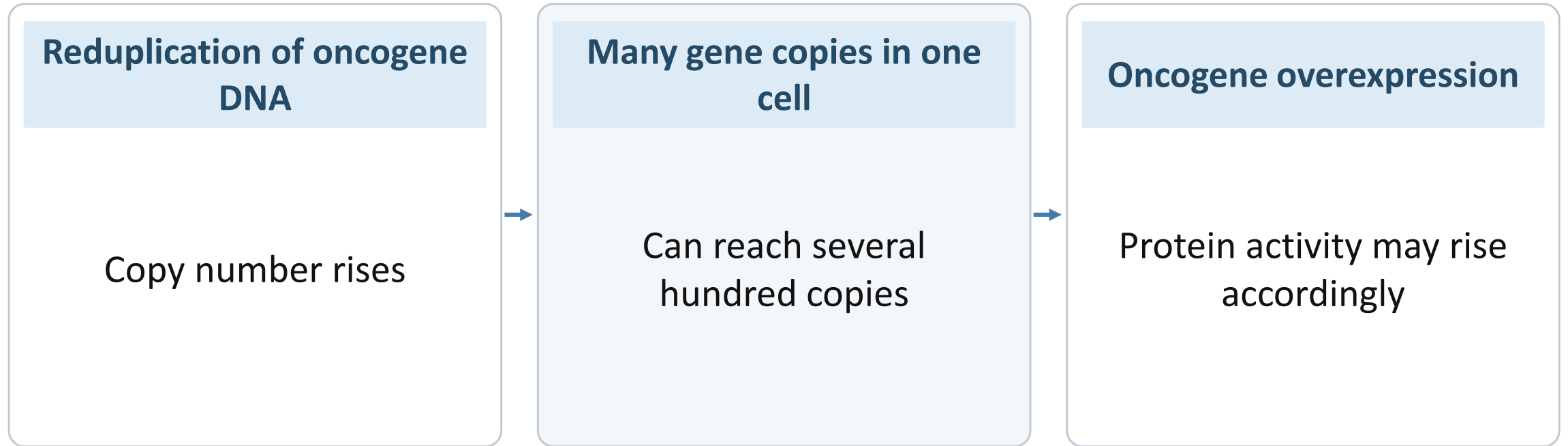
Biological consequence

- Regulatory intervening DNA removed near TAL1
- Active promoter drives TAL1 overexpression

Insertions and microsatellite expansion

- DNA insertions can also alter the function of cancer-associated genes.
- The text emphasizes expansions of DNA microsatellite sequences.
- Such insertions are a feature of cancers with defective mismatch repair.
- This distinguishes small sequence changes from large karyotypic rearrangements.

Gene amplification increases oncogene dosage



Some amplifications create recognizable structural cytogenetic patterns.

Two cytogenetic manifestations of amplification

Double minutes

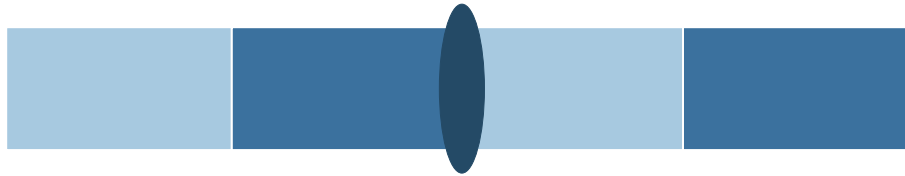
- Many small extrachromosomal DNA structures.
- Often circular DNA, capable of high copy number.
- Appear as separate elements in karyotypes.

Homogeneous staining region

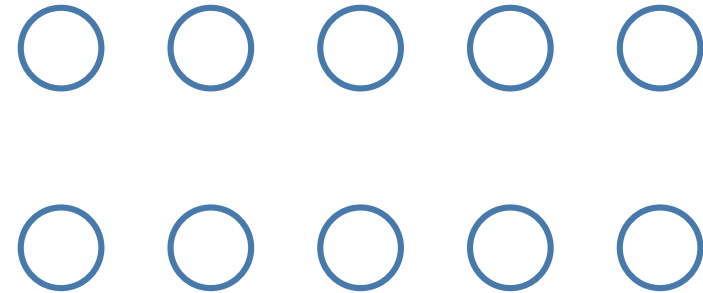
- Amplified sequences inserted into a chromosome.
- Region lacks normal light/dark band pattern.
- Appears uniformly stained on the chromosome.

Double minutes: Extrachromosomal DNA

Main chromosomal DNA



Amplified extrachromosomal units

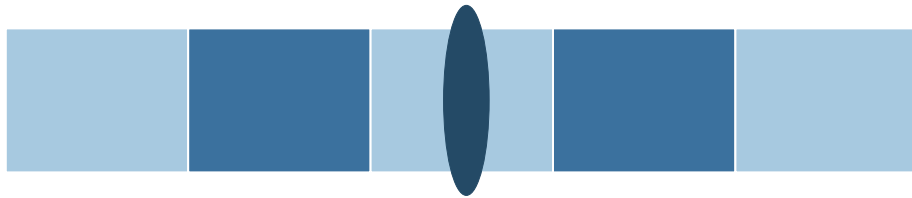


1. Multiple small DNA elements
2. Amplified oncogene sequence
3. Extrachromosomal, often circular DNA

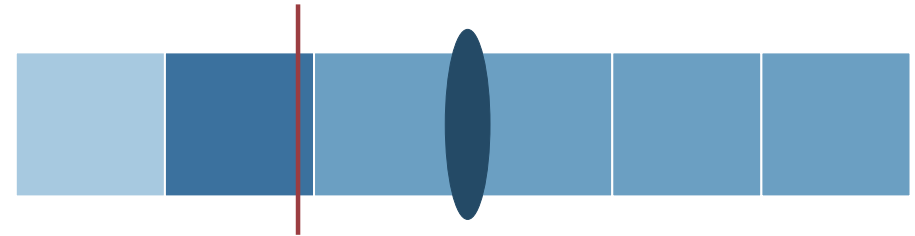
Schematic—not a stained metaphase spread

Homogeneous staining regions

Banding pattern retained



Broad uniform amplified region



1. Amplified segment inserted in a chromosome
2. Banding pattern becomes homogeneous
3. The oncogene may be relocated from its usual locus

Schematic—not a stained metaphase spread

MYCN amplification in neuroblastoma

Mechanism

- Amplification raises copies of the MYCN oncogene (termed NMYC in source).
- The chapter reports amplification in 25–30% of neuroblastomas.
- This is gene-dosage dysregulation.

Clinical implication

- MYCN amplification is associated with poor prognosis.
- The abnormality is a prognostic marker in this example.
- Do not interpret this association as a drug-response test.

ERBB2 amplification in breast carcinoma

Mechanism

- ERBB2 gene amplification increases HER2 receptor abundance.
- The supplied chapter reports amplification in about 20% of breast cancers.
- This is a molecularly defined subset.

Clinical implication

- Therapy directed against HER2 is effective in this subset.
- Here the marker has predictive treatment relevance.
- The slide does not specify current testing criteria.

Different roles of chromosome biomarkers

Biomarker	Example	Clinical role in source
Diagnostic	BCR::ABL in CML	Establishes a defining fusion
Monitoring	Quantified BCR::ABL product	Tracks response to kinase inhibition
Prognostic	MYCN amplification in neuroblastoma	Associated with poor prognosis
Predictive	ERBB2 amplification in breast cancer	Identifies HER2-directed treatment context

Genome sequencing exposes hidden complexity

- Whole-genome reconstruction detects many simple rearrangements.
- Small deletions, duplications and inversions can evade classic cytogenetics.
- Some tumor genomes also contain clustered, highly complex rearrangements.
- Chromothripsis is the source's example of catastrophic structural change.

Chromothripsis: Break and reassemble



The initiating cause of catastrophic chromosomal breakage remains uncertain.

Chromothripsis: Shattered chromosome schematic



1. One or several chromosomes may fragment
2. DNA repair rejoins numerous pieces
3. Reassembled material carries complex structural changes

Chromothripsis: Observed versus hypothesized

Reported

- Observed in roughly 1–2% of cancers overall.
- Described as particularly common in osteosarcoma and glioma.
- Can create multiple rearrangements simultaneously.

Proposed explanation

- Origin of the breaks is uncertain.
- A single catastrophe might change several cancer genes at once.
- Accelerated carcinogenesis remains presented as a hypothesis.

Not every rearrangement has the same evidentiary status

- A recurrent lesion may be closely associated with a tumor type.
- A fusion can be a validated tumor driver or actionable enzyme.
- A complex genome may contain passenger alterations as well as drivers.
- Chromothripsis as an accelerator of cancer is a proposed mechanism in this source.

Mechanism-to-consequence synthesis

Lesion	Molecular effect	Representative example
Regulatory translocation	Increased oncogene expression	MYC / IGH
Fusion translocation	Chimeric kinase	BCR::ABL
Transcriptional fusion	Blocked maturation	PML::RARA
Deletion	Suppressor loss or oncogene activation	RB; TAL1; EML4::ALK
Amplification	Increased oncogene dosage	MYCN; ERBB2

Application: Recognize regulatory translocation

QUESTION

A lymphoma has t(8;14)(q24;q32) and high MYC expression. Is a MYC–IGH chimeric protein required?

ANSWER

No. The usual mechanism is relocation of largely intact MYC into an active immunoglobulin regulatory environment.

- Gene-expression dysregulation need not require fusion of coding regions.
- The hallmark molecular output is MYC overexpression.

Application: Interpret a kinase fusion

QUESTION

A leukemia harbors BCR::ABL on derivative chromosome 22. What functional abnormality follows?

ANSWER

The fusion encodes a constitutively active BCR–ABL tyrosine kinase.

- Fusion proteins can be pharmacologic targets.
- Fusion transcript quantification can monitor response in CML.

Application: Explain a differentiation therapy

QUESTION

Why can pharmacologic ATRA counter the maturation arrest of PML::RARA-positive APML?

ANSWER

It binds the fusion complex, relieves transcriptional repression and promotes fusion-protein degradation.

- This enables transcription of maturation-associated genes.
- The treatment mechanism differs from kinase inhibition.

Application: Infer an effect of small deletion

QUESTION

A short deletion juxtaposes TAL1 with an active promoter. Which category of molecular lesion is most relevant?

ANSWER

Oncogene activation by regulatory juxtaposition, not obligatory loss of a tumor suppressor.

- Deletion can increase transcription of an intact gene.
- The chromosomal size alone does not determine biological effect.

Application: Distinguish prognostic from predictive

QUESTION

Compare MYCN amplification in neuroblastoma with ERBB2 amplification in breast cancer. What differs clinically?

ANSWER

The source emphasizes adverse prognosis for MYCN and effective HER2-directed therapy for ERBB2.

- Do not equate a prognostic association with prediction of drug response.
- Molecular consequence and clinical use should be specified separately.

Five principles to retain

- Structural changes can alter expression or create novel oncogenic proteins.
- A tumor-defining translocation may be a regulatory swap or a coding fusion.
- Deletions may remove suppressors or unexpectedly activate oncogenes.
- Amplification changes gene dosage; Double minutes and HSRs are distinct patterns.
- Chromothripsis represents exceptional rearrangement complexity with unresolved causation.

A practical interpretation checklist

- Classify the alteration: chromosome number, DNA rearrangement, segment loss, or copy-number gain.
- Determine the gene-level effect: dysregulated expression, fusion protein, or tumor suppressor loss.
- Specify its clinical use: diagnosis, prognosis, treatment selection, or response monitoring.
- Distinguish demonstrated molecular drivers from proposed effects of catastrophic rearrangement.