

Etiologic and Pathogenetic Factors in White Cell Neoplasia

Acquired drivers • Inherited susceptibility • Immunologic and environmental factors

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Learning outcomes

By the end of this session, learners should be able to:

Explain how driver mutations alter differentiation, self-renewal, proliferation, and survival.

Distinguish AID-associated errors from V(D)J recombinase errors.

Identify inherited predisposition and viral, inflammatory, iatrogenic, and smoking-related associations.

Integrate an etiologic exposure with a molecular event and tumor phenotype.

Three major families of white cell neoplasia

The biological lineage helps define the neoplasm and the genetic events that matter.

Lymphoid tumors derive from B, T, or natural killer cells.

Myeloid tumors arise from hematopoietic progenitors.

Histiocytoses involve macrophage or dendritic-cell lineages.

Lymphoid

Myeloid

Histiocytic

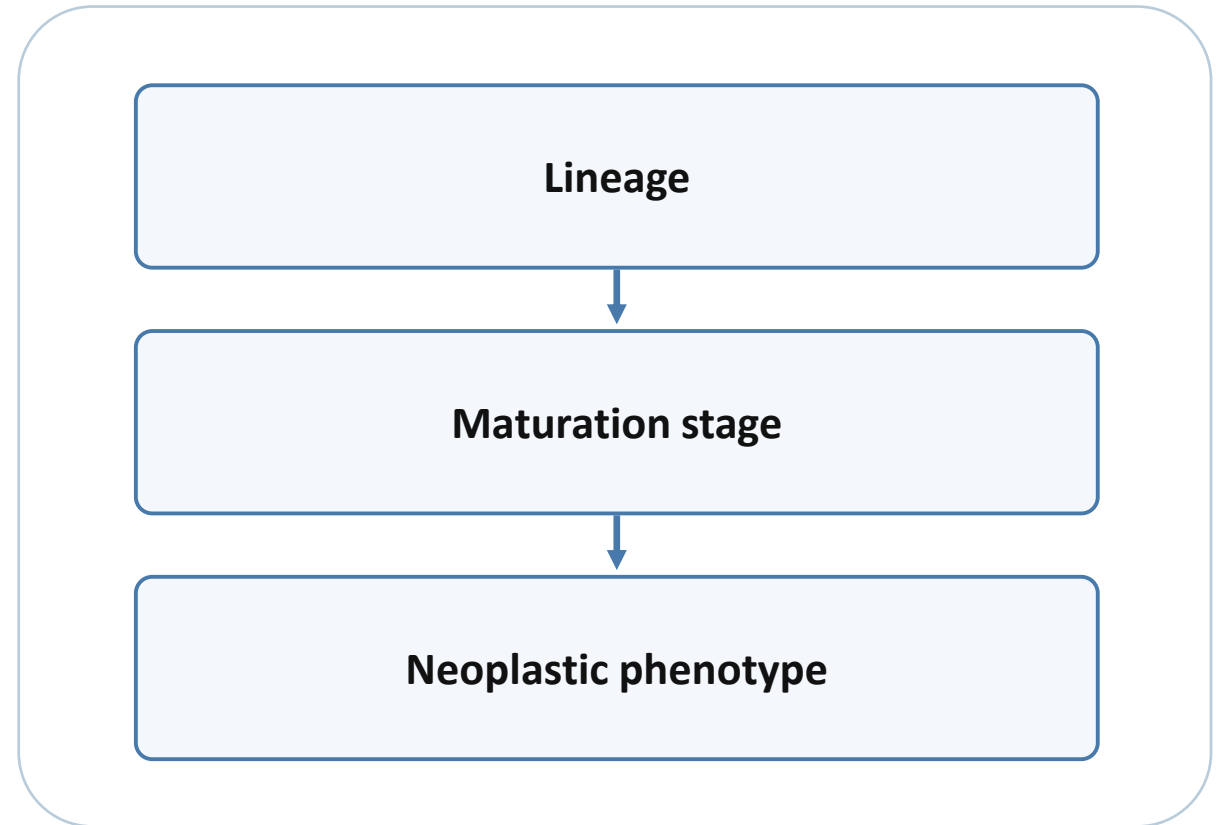
Lymphoid neoplasia spans maturation states

The phenotype of a malignant lymphoid cell often resembles its normal developmental counterpart.

B-cell, T-cell and NK-cell origin remain central to interpretation.

Immature and mature lymphocyte stages have different opportunities for DNA rearrangement.

Cellular phenotype is integrated with genetic abnormalities.



Myeloid neoplasia reflects distinct output failures

Different abnormalities of myeloid progenitors produce contrasting hematopoietic phenotypes.

Acute myeloid leukemia: Accumulation of immature precursors.

Myelodysplastic neoplasia: Ineffective hematopoiesis with cytopenias.

Myeloproliferative neoplasia: Excess production of mature myeloid elements.

Immature-cell accumulation

Ineffective production

Excess mature output

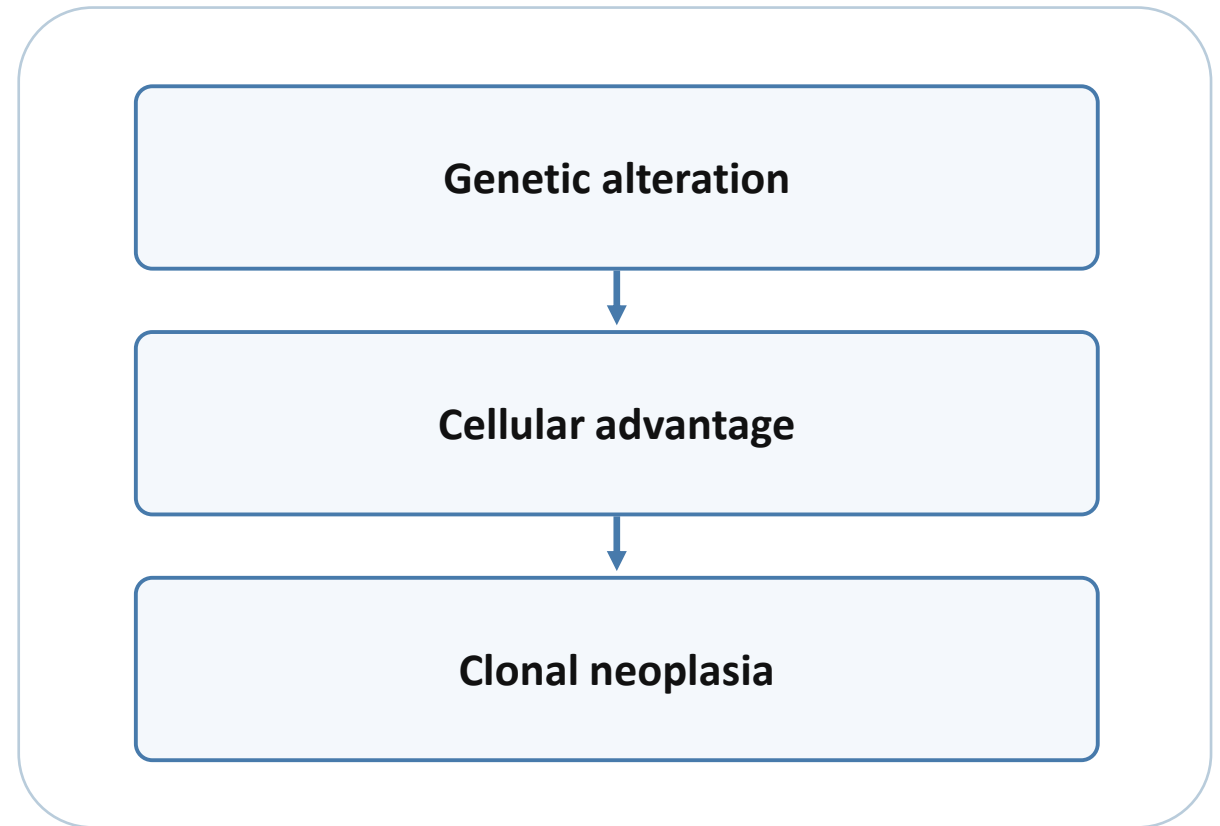
Cancer genes are the common etiologic denominator

Inherited or acquired alterations in cancer genes underlie hematolymphoid malignancy.

Driver events change key cellular activities,
rather than merely changing morphology.

Altered maturation, growth, self-renewal, or
survival create selective advantages.

The resulting disease phenotype depends on
the lineage and maturation stage.



Germline susceptibility and somatic drivers are distinct

Inherited predisposition and mutations acquired in hematopoietic cells operate at different levels.

Inherited factors can increase the probability that malignancy develops.

Acquired drivers directly alter the behavior of individual neoplastic clones.

Environmental exposures may promote acquisition of additional abnormalities.

**Germline
susceptibility**

**Somatic oncogenic
alteration**

Different mechanisms or causal contexts

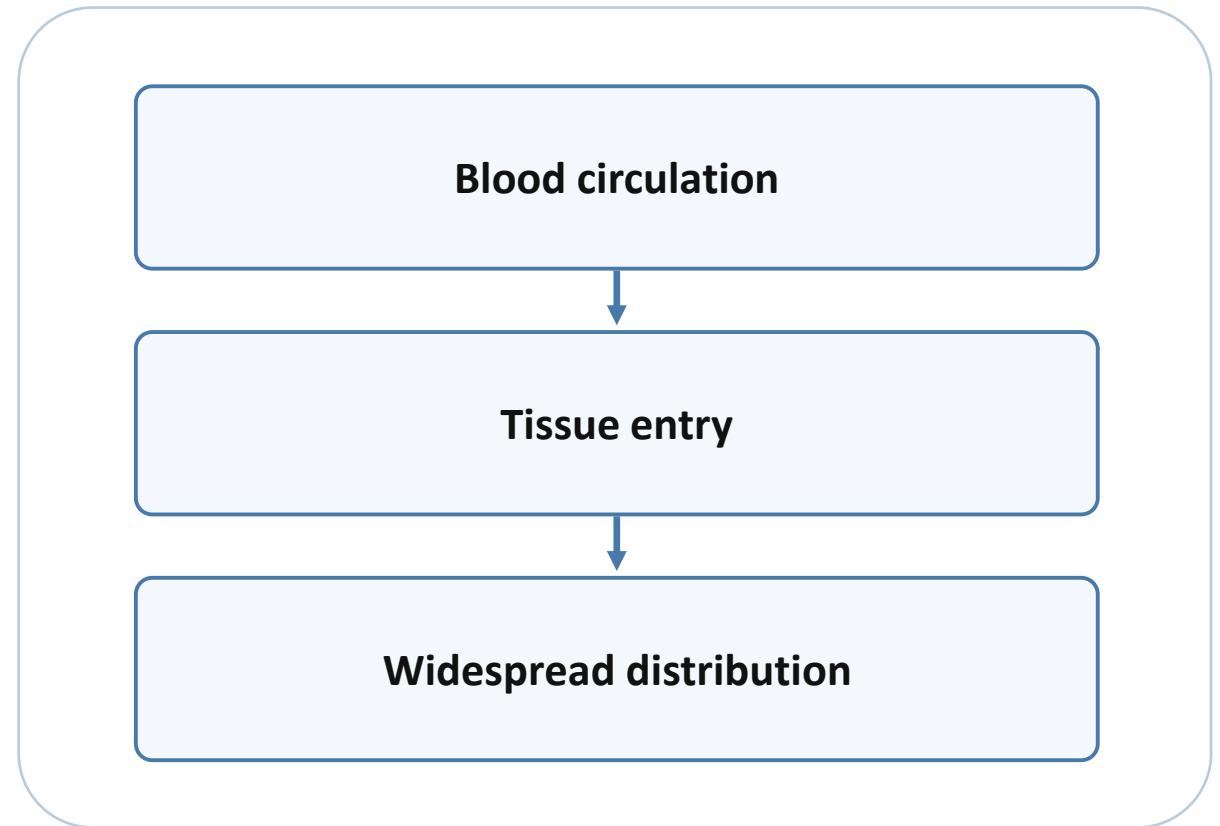
Hematopoietic cells already migrate and circulate

Normal white-cell biology explains why hematologic tumors can disseminate readily.

White cells travel through blood and enter tissues as part of normal physiology.

Some properties considered cancer hallmarks in solid tumors are native to these cells.

Dissemination alone does not identify a specific oncogenic driver.



Genetic complexity: A qualified textbook observation

Hematologic malignancies as generally less genetically complex than many solid tumors.

This is a broad comparison—not a rule for every tumor.

The text suggests that lower complexity may contribute to greater curability.

Individual disease behavior still depends on its specific molecular lesions.

Comparative observation

Proposed implication

Important limitation

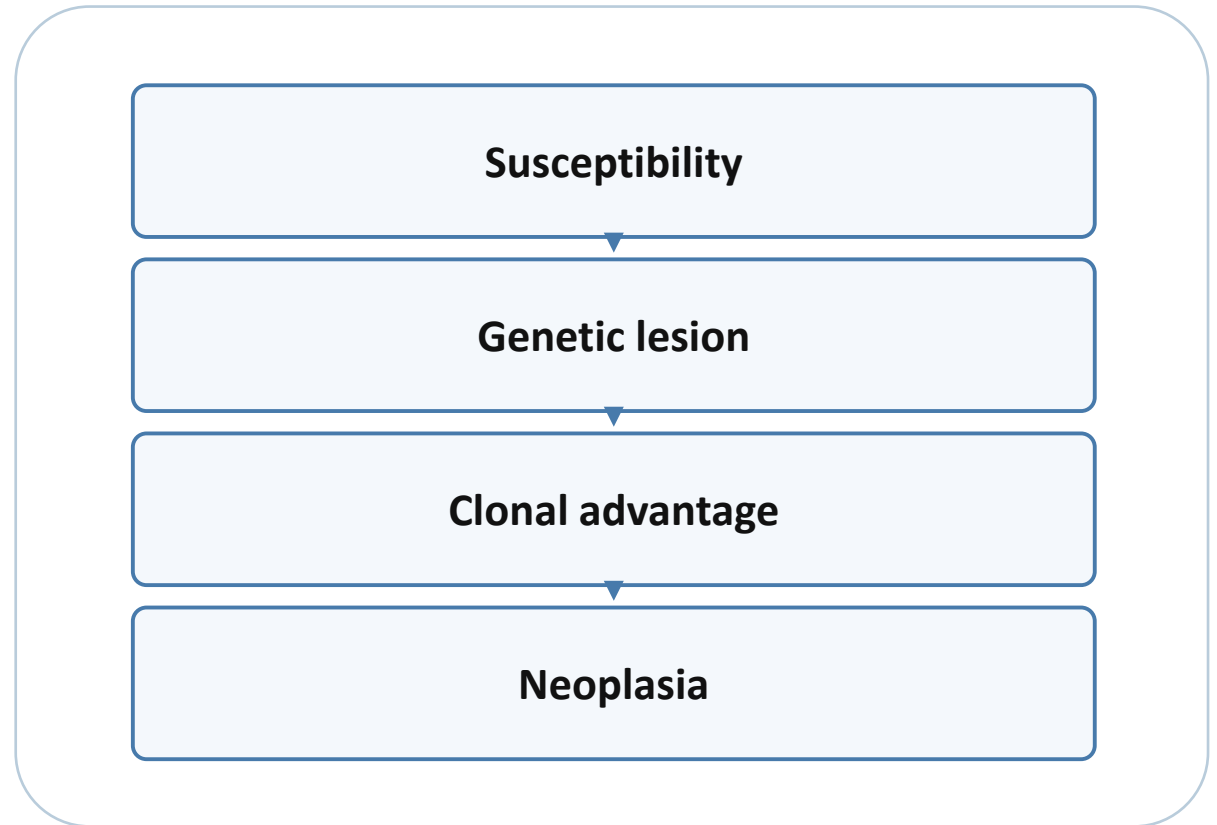
Four complementary levels of causation

A coherent causal account links predisposition, lesion formation, selection, and tumor phenotype.

Predisposition can be inherited or related to the environment.

DNA lesions may be acquired during normal physiologic processes.

Driver mutations confer growth, survival, or maturation advantages.



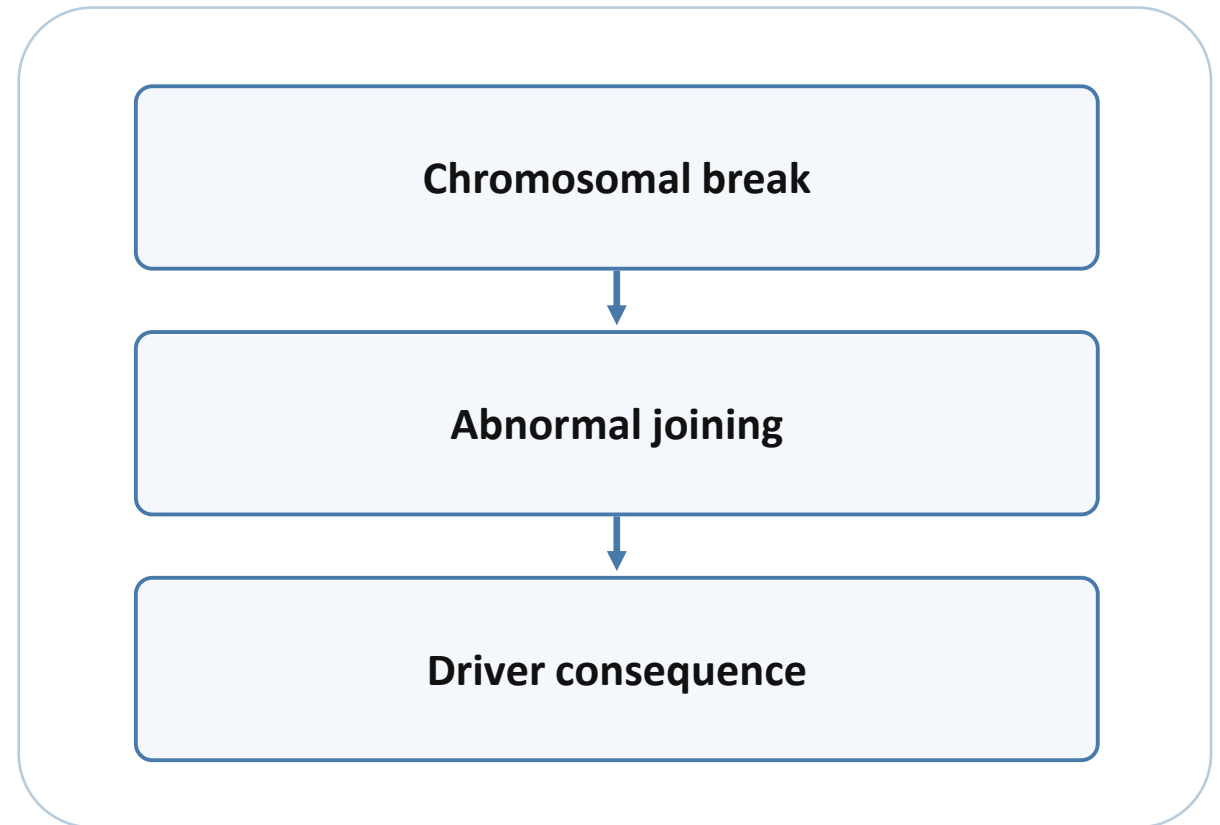
Nonrandom chromosomal rearrangements are recurrent

Many white cell neoplasms harbor characteristic structural chromosome abnormalities.

Translocations are particularly common among recurrent changes.

Some rearrangements are associated closely with specific neoplasms.

Recurrent lesions can contribute directly to oncogenesis.



Recurrently altered genes mirror normal cell needs

Cancer drivers frequently affect genes governing the normal counterpart's biology.

Developmental regulators control maturation and cell identity.

Growth pathways determine how a cell responds to proliferative inputs.

Survival machinery controls whether an abnormal cell undergoes apoptosis.

Differentiation

Growth

Survival

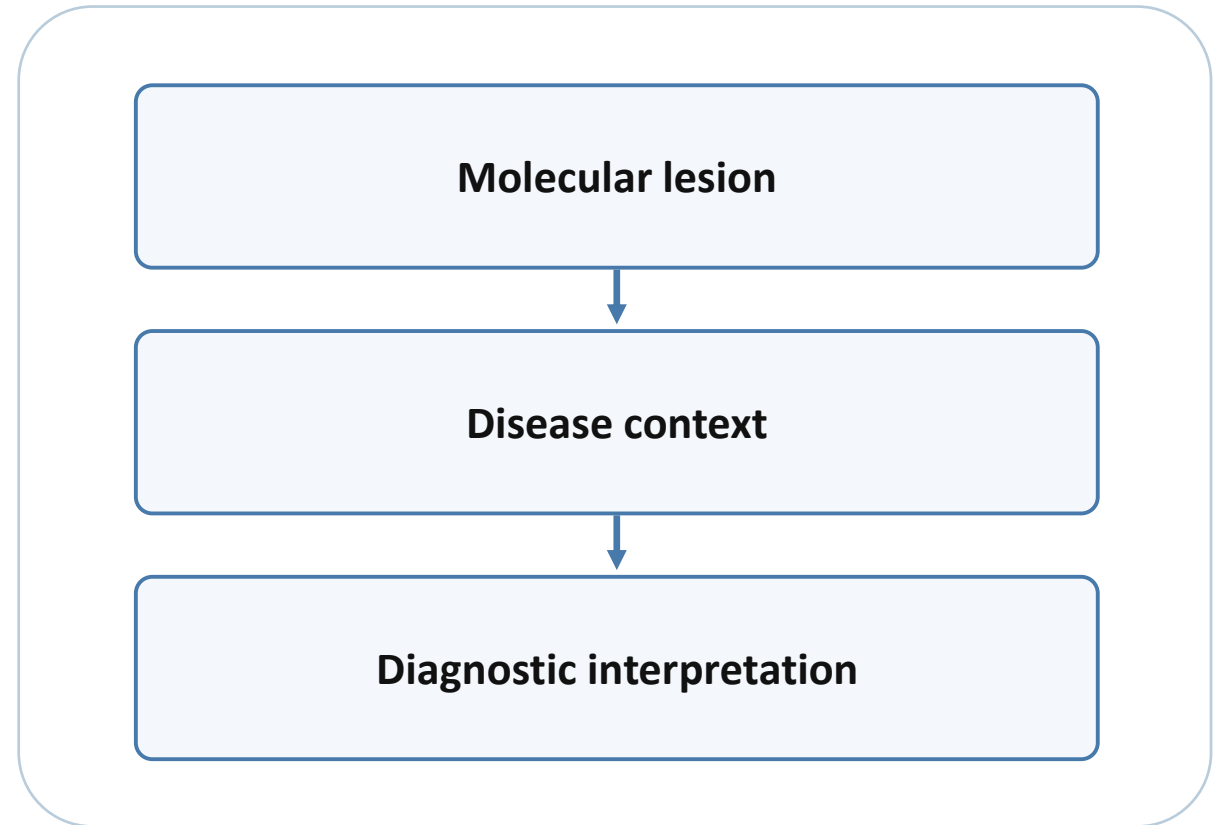
A molecular alteration may define tumor identity

Some mutations are associated so strongly with a neoplasm that diagnosis requires them.

Genetic findings are not merely incidental laboratory observations.

The meaning of a driver must be interpreted within cellular lineage and phenotype.

A translocation is not interchangeable with all other genomic alterations.



Gain of function and loss of function differ

Oncogenic mutations can either raise abnormal activity or impair normal regulation.

Gain of function: Inappropriate activity of a normal cellular function.

Loss of function: Disruption of a normally required activity.

Dominant-negative oncoproteins can inhibit another protein's normal function.

**Inappropriately active
function**

**Interference with
normal function**

Different mechanisms or causal contexts

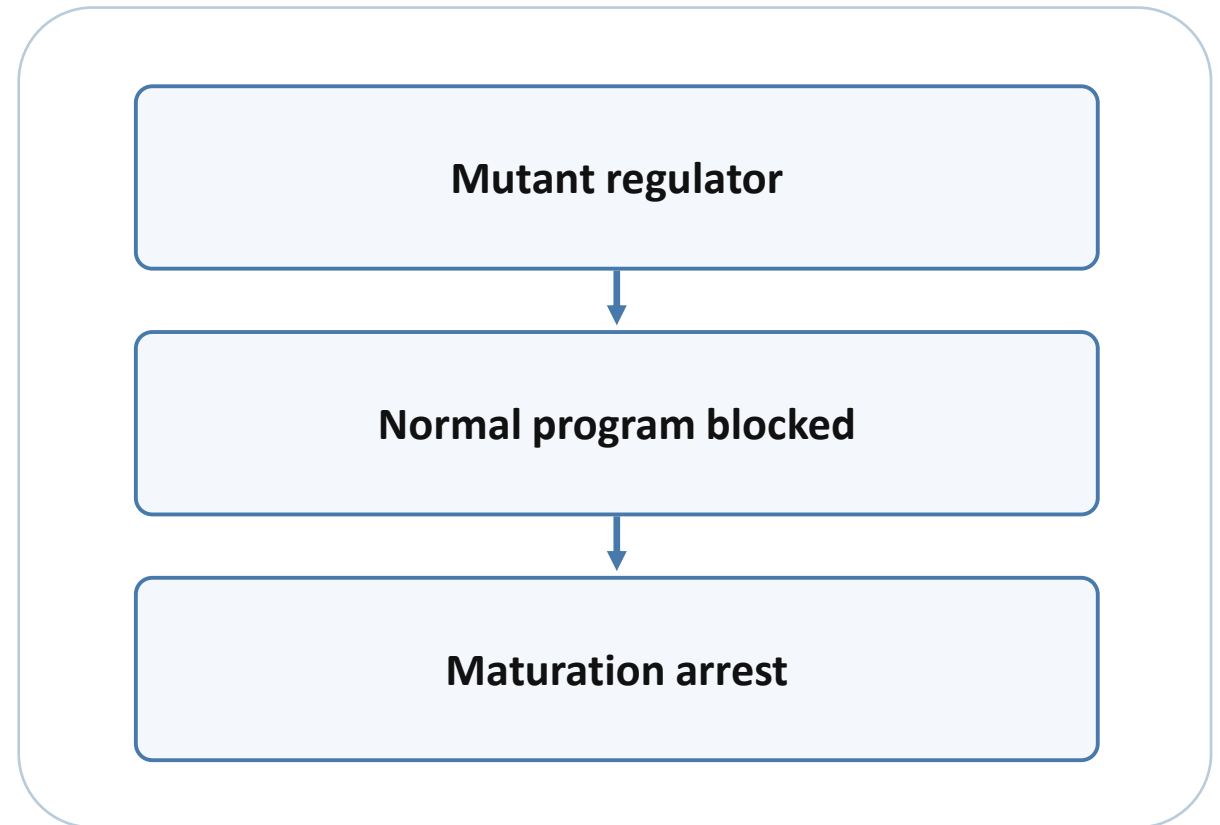
Dominant-negative proteins impede cellular programs

An altered protein may obstruct a differentiation function normally performed by its counterpart.

The molecular defect need not eliminate the normal gene entirely.

Interference with transcription-factor functions can prevent maturation.

The biological result may be accumulation of immature precursors.



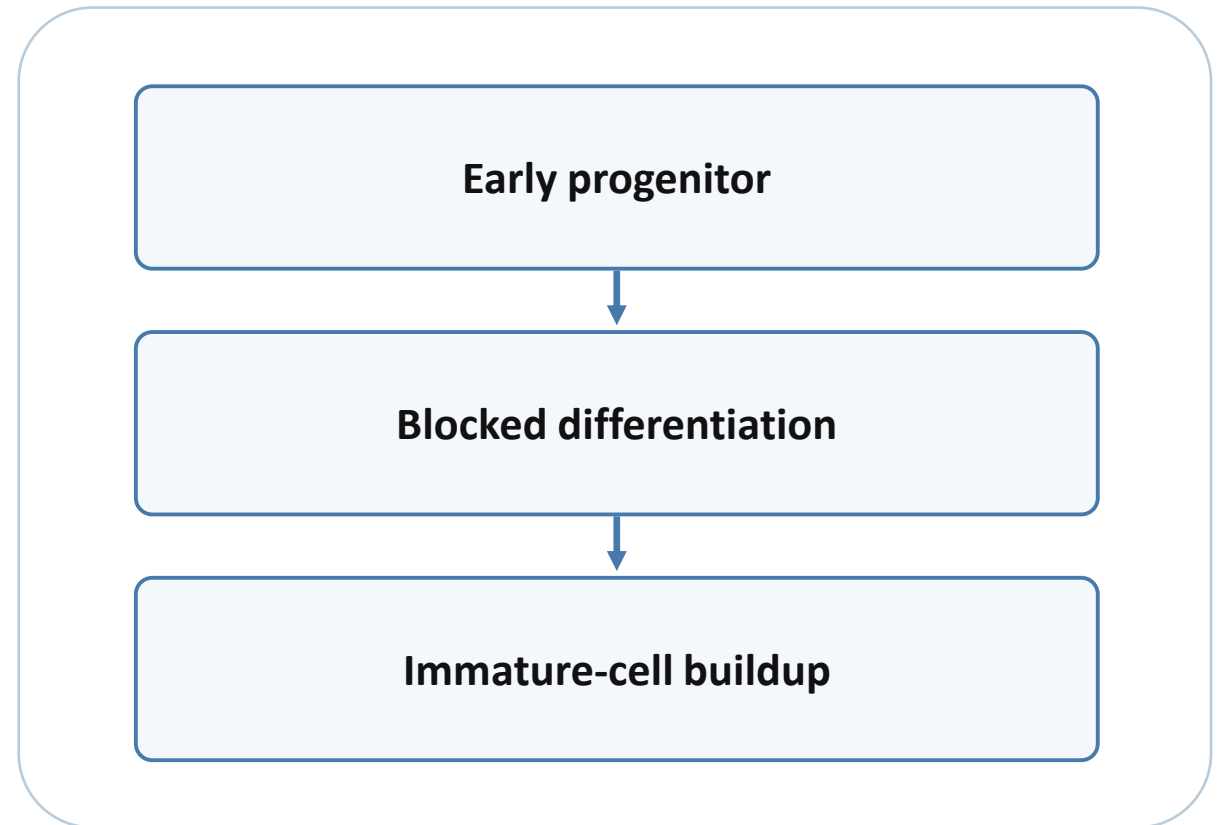
Failure of maturation is a leukemic mechanism

Acute leukemia provides a clear example of differentiation arrest.

Oncogenic changes can block early lymphoid or myeloid differentiation.

Arrest may occur while the affected cells remain capable of rapid proliferation.

Immature cells then accumulate rather than completing normal development.



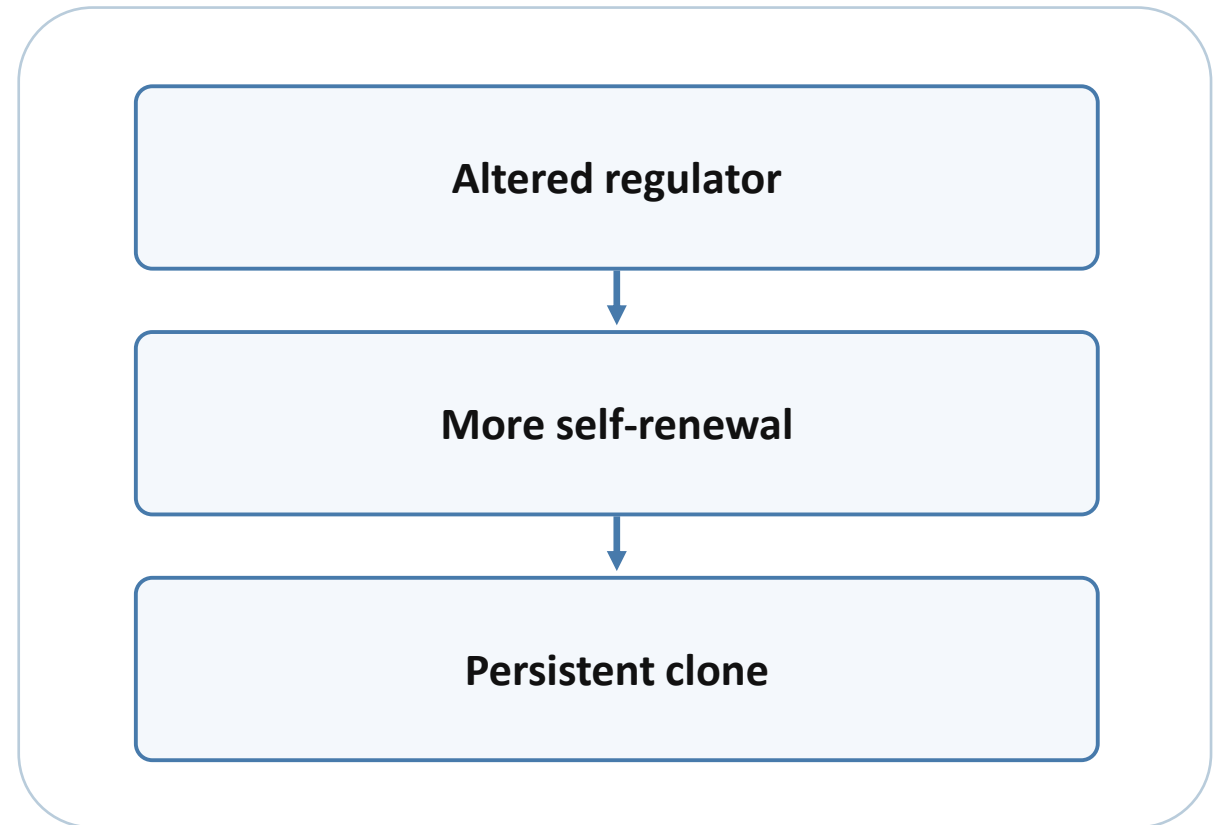
Self-renewal confers stem-cell–like behavior

Mutations in transcriptional regulators can increase the persistence of a malignant clone.

Self-renewal maintains progeny capable of additional cell divisions.

Pathologic self-renewal is distinct from merely accelerating one cell cycle.

These alterations can cooperate with growth-promoting drivers.



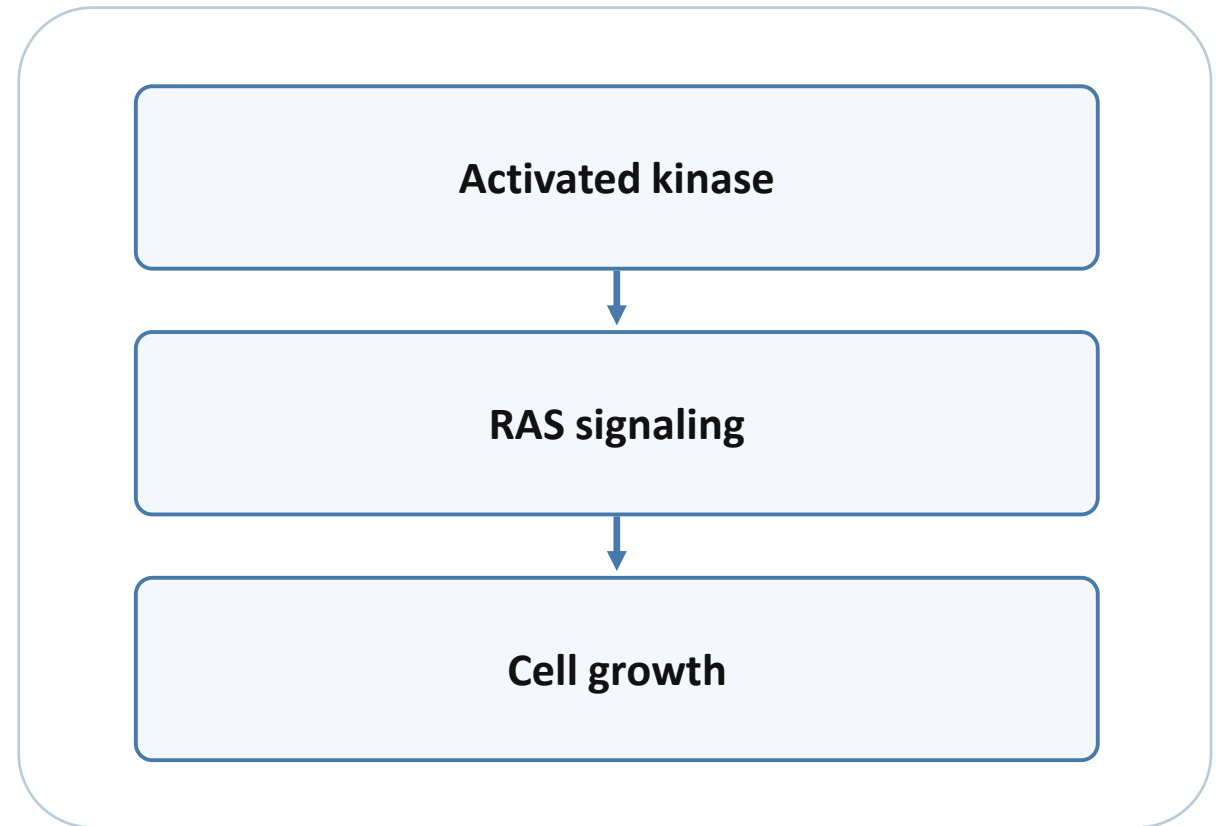
Constitutive kinases uncouple growth from control

Some driver lesions activate tyrosine kinase signaling independent of normal regulation.

Kinase activation transmits downstream proliferative signals.

The RAS signaling node links activated kinases to effector pathways.

Constitutive stimulation produces sustained growth pressure.



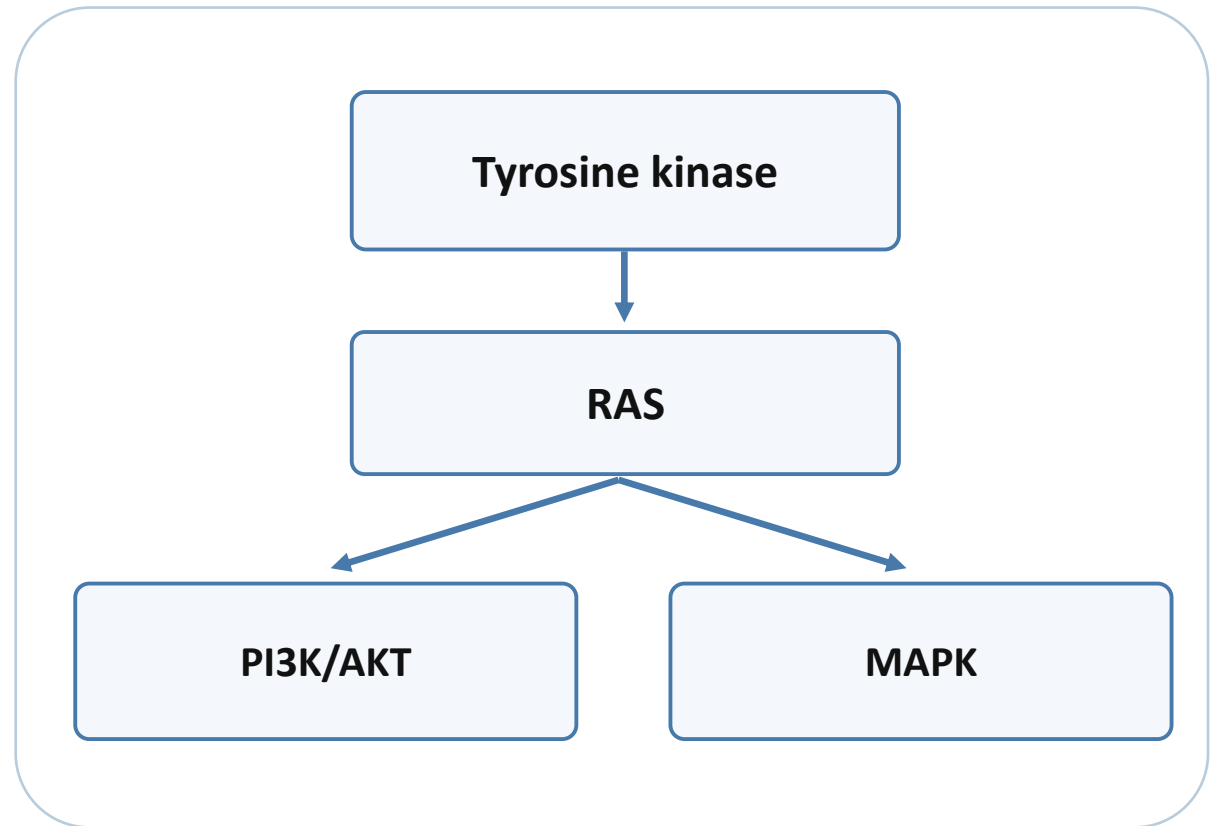
RAS connects signaling to two effector arms

PI3K/AKT and MAPK pathways downstream of RAS.

The two arms are pathways through which growth signals act.

They are part of the same broad growth-promoting process.

The diagram depicts the relationship, not a complete biochemical network.



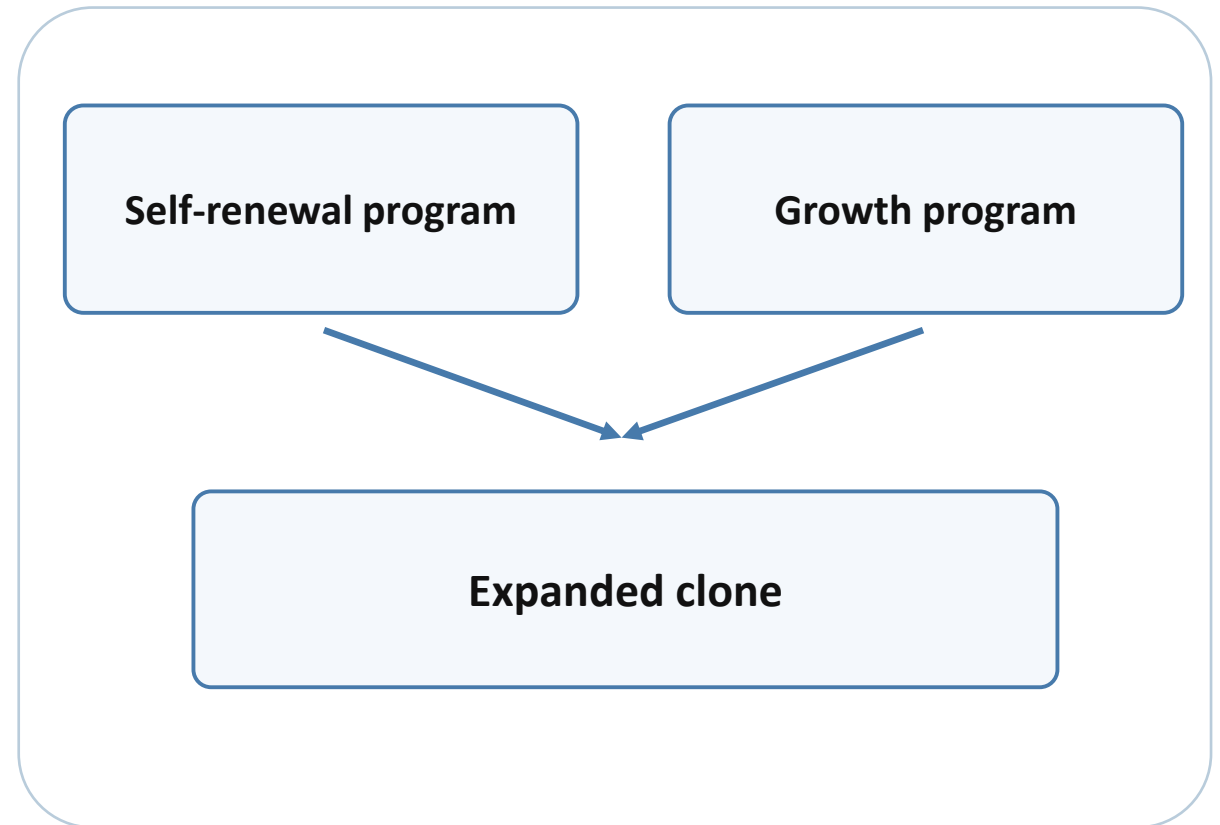
Cooperation between driver classes

A tumor clone may benefit from both self-renewal and constitutive growth signaling.

Transcriptional-regulator alterations can increase self-renewal.

Tyrosine-kinase alterations stimulate pathways for cell growth.

Their collaboration yields a stronger proliferative phenotype.



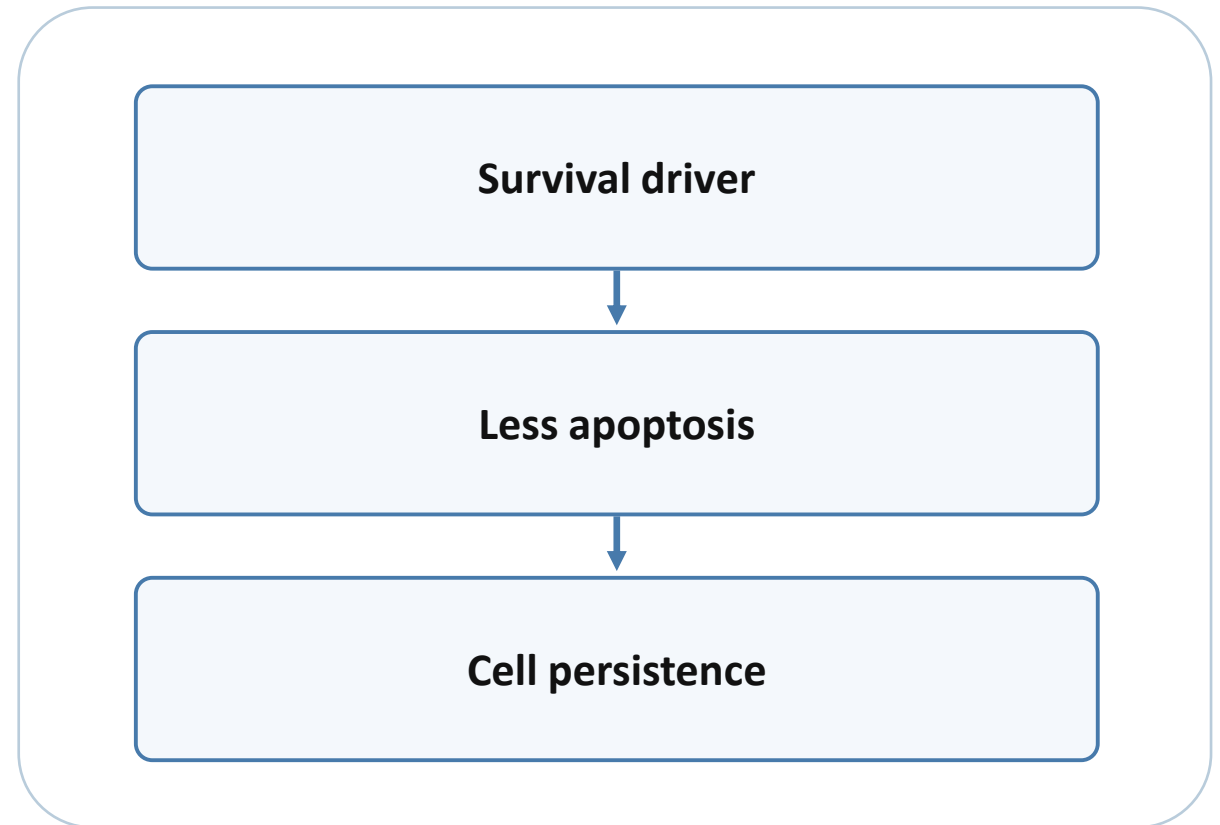
Impaired apoptosis supports clone survival

A cell population can expand by losing cells more slowly—not only by dividing faster.

Mutations that inhibit programmed cell death are common in some neoplasms.

Survival advantage allows abnormal cells to persist.

This mechanism complements growth activation and differentiation arrest.



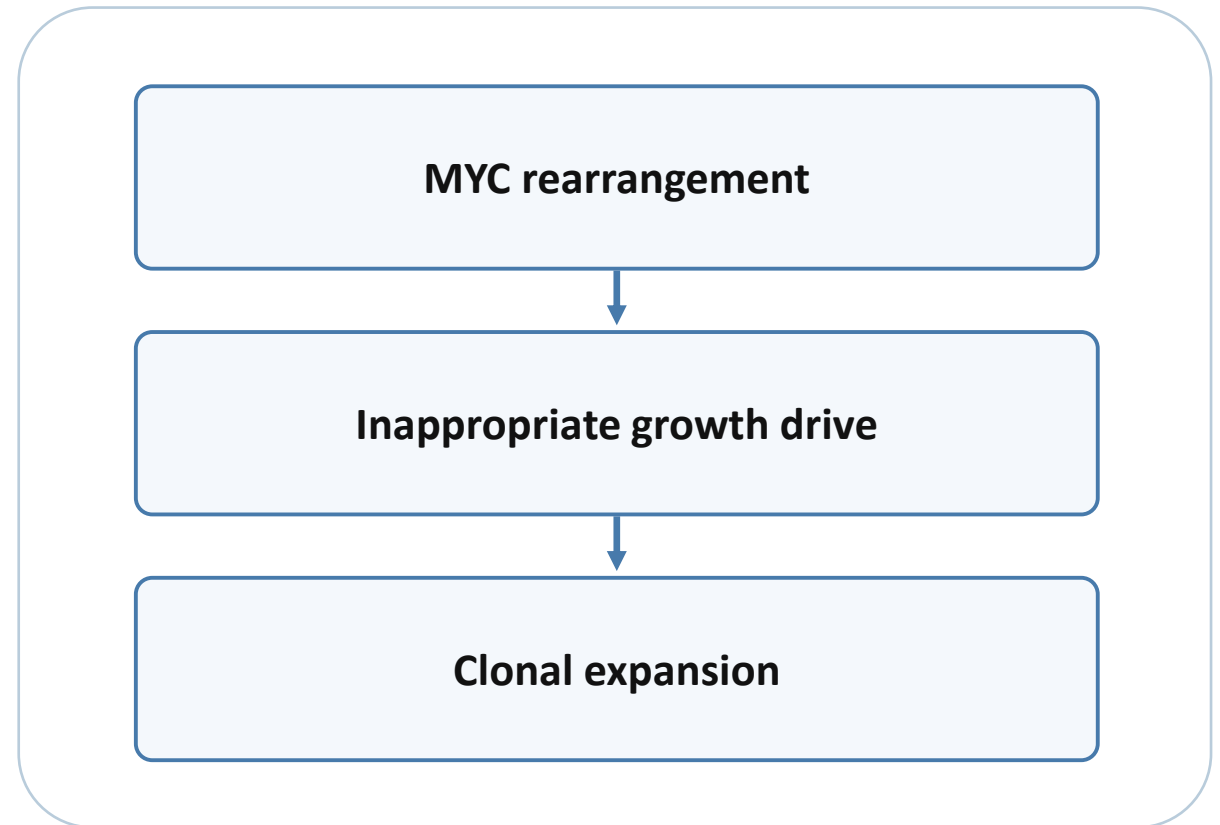
MYC illustrates a pro-growth abnormality

Translocation involving MYC is an example of a growth-promoting lesion.

MYC appears in the pro-growth category' pathogenesis framework.

Antigen-receptor regulatory loci can aberrantly activate proto-oncogenes.

MYC::IGH is a specific example discussed for B-cell neoplasia.



BCL2 illustrates a pro-survival abnormality

A BCL2 translocation represents an alteration that helps cells evade apoptosis.

A survival lesion changes the balance between cell production and loss.

Reduced apoptosis permits persistence of abnormal lymphocytes.

This is mechanistically distinct from a MYC-driven growth advantage.

MYC: Pro-growth

BCL2: Pro-survival

Different mechanisms or causal contexts

KMT2A and PML::RARA exemplify regulatory lesions

Oncogenic fusions involving transcriptional programs can alter cell fate.

The Robbins figure includes KMT2A rearrangements and PML::RARA.

These illustrate the contribution of transcriptional regulators.

The exact pathogenic action must be interpreted for each disease entity.

KMT2A rearrangement

PML::RARA fusion

Altered cell-state control

Three cellular effects converge on tumor burden

Robbins organizes the major genetic effects into complementary mechanisms.

More growth increases cellular production.

More self-renewal sustains the abnormal population.

Less apoptosis decreases cellular loss.

Increased proliferation

Increased self-renewal

Decreased apoptosis

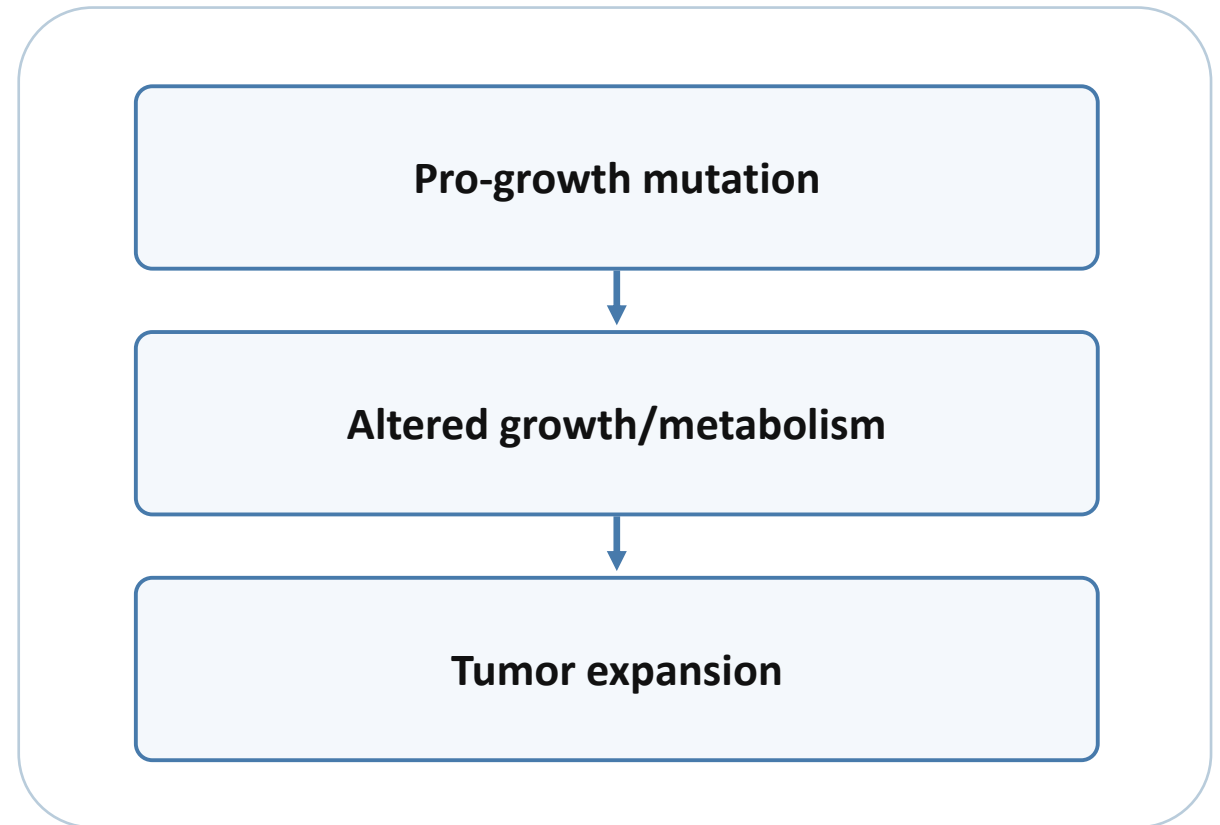
Metabolic reprogramming accompanies proliferation

The Robbins schematic includes Warburg metabolism in the pro-growth arm.

Metabolism is part of the transformed growth phenotype.

It is shown as a biological consequence rather than a measured clinical test.

No quantitative metabolic rate is specified in the source section.



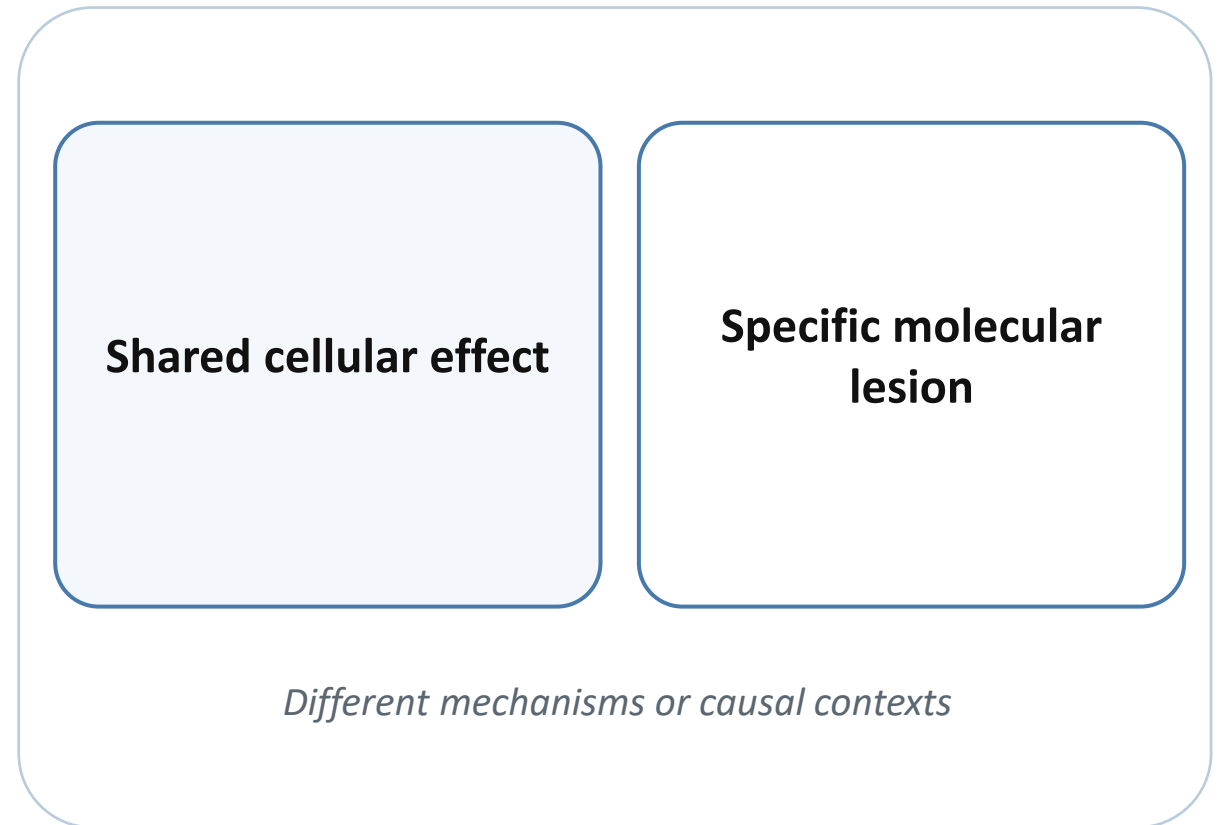
The same phenotype can arise by different lesions

Cellular behavior and molecular mechanism are related but nonidentical classifications.

Several mutations can enhance growth or alter cell-state programs.

A lesion's molecular identity may be diagnostically specific.

A pathogenesis diagram summarizes classes—it cannot replace entity-specific genetics.



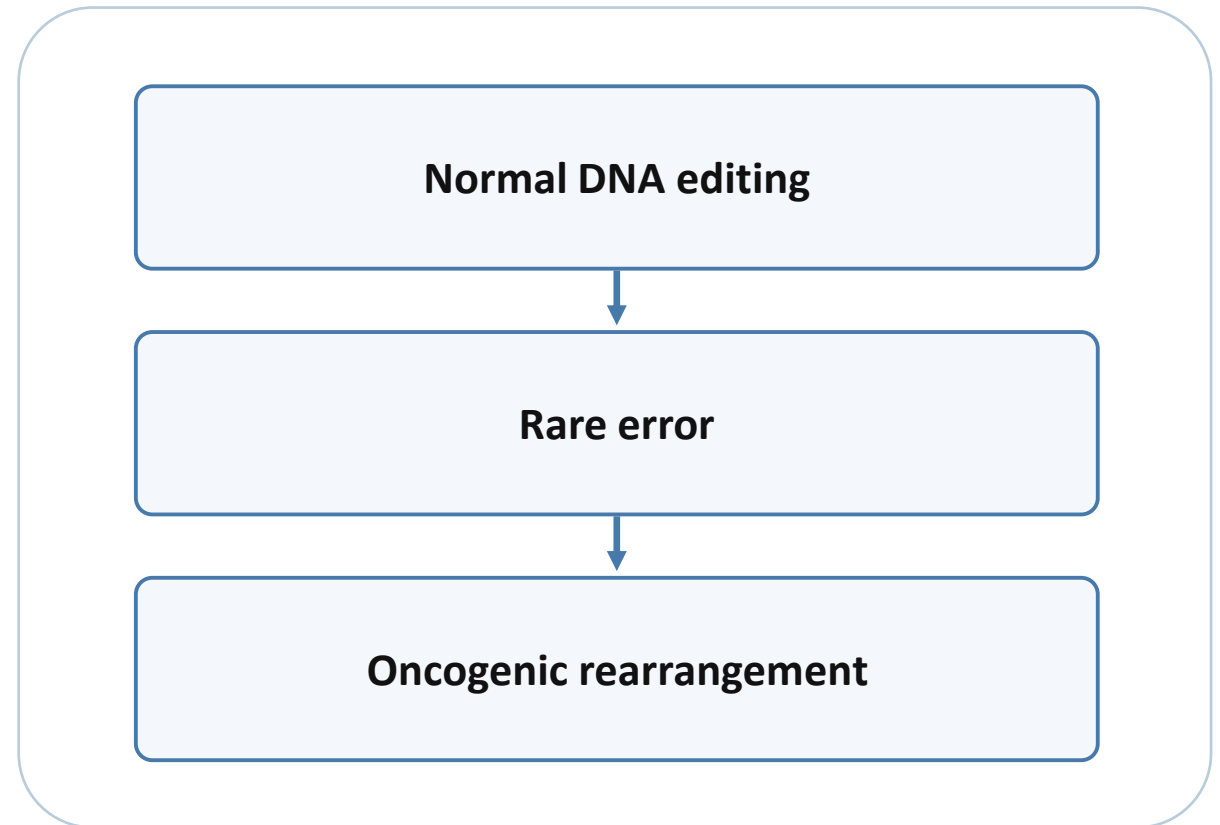
Lymphocytes deliberately modify their DNA

Normal lymphocyte development and activation require controlled genomic alteration.

These processes generate a diverse antigen receptor repertoire.

The same DNA-handling steps can occasionally create oncogenic mistakes.

Risk depends on whether the cell is a precursor or an activated B cell.



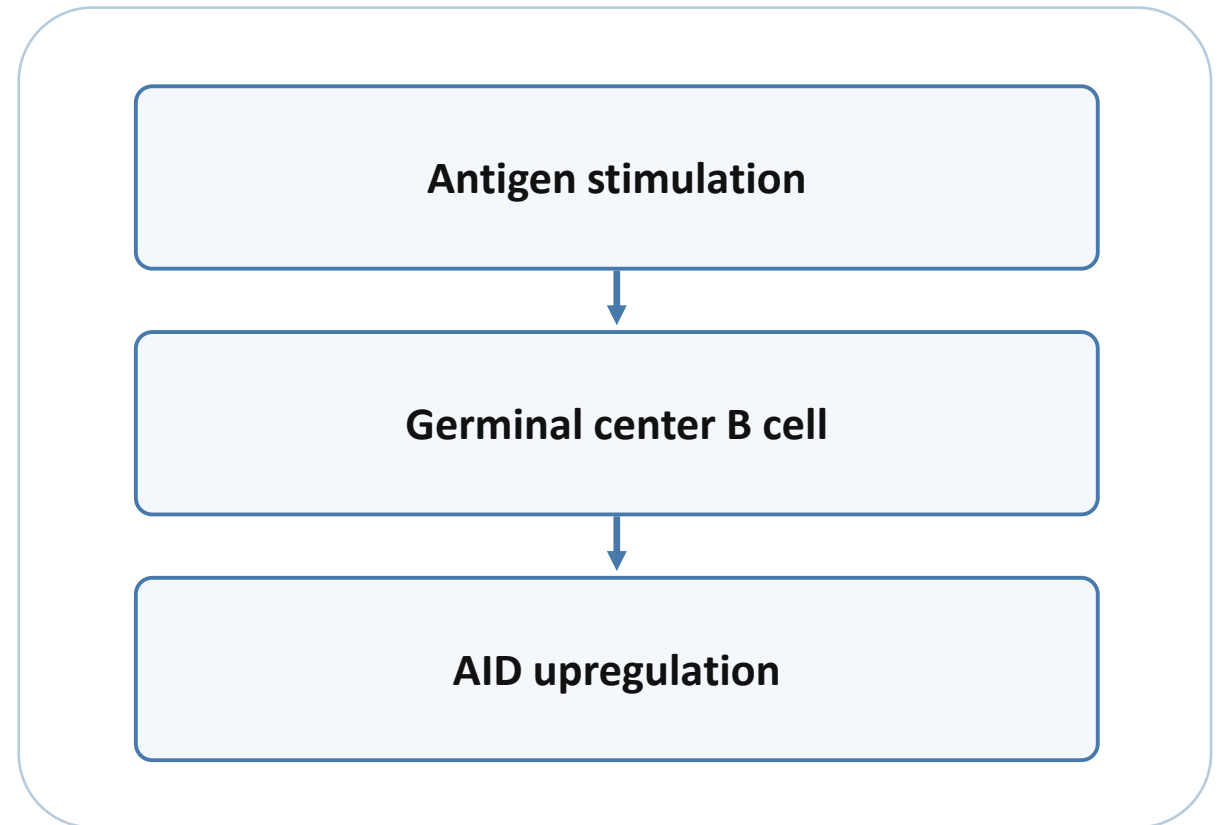
Germinal centers are sites of potent DNA editing

Antigen-stimulated B cells enter germinal centers and express activation-induced cytidine deaminase.

AID enables immunoglobulin class switching.

AID also supports somatic hypermutation.

These processes create genomic lesions that must be correctly resolved.



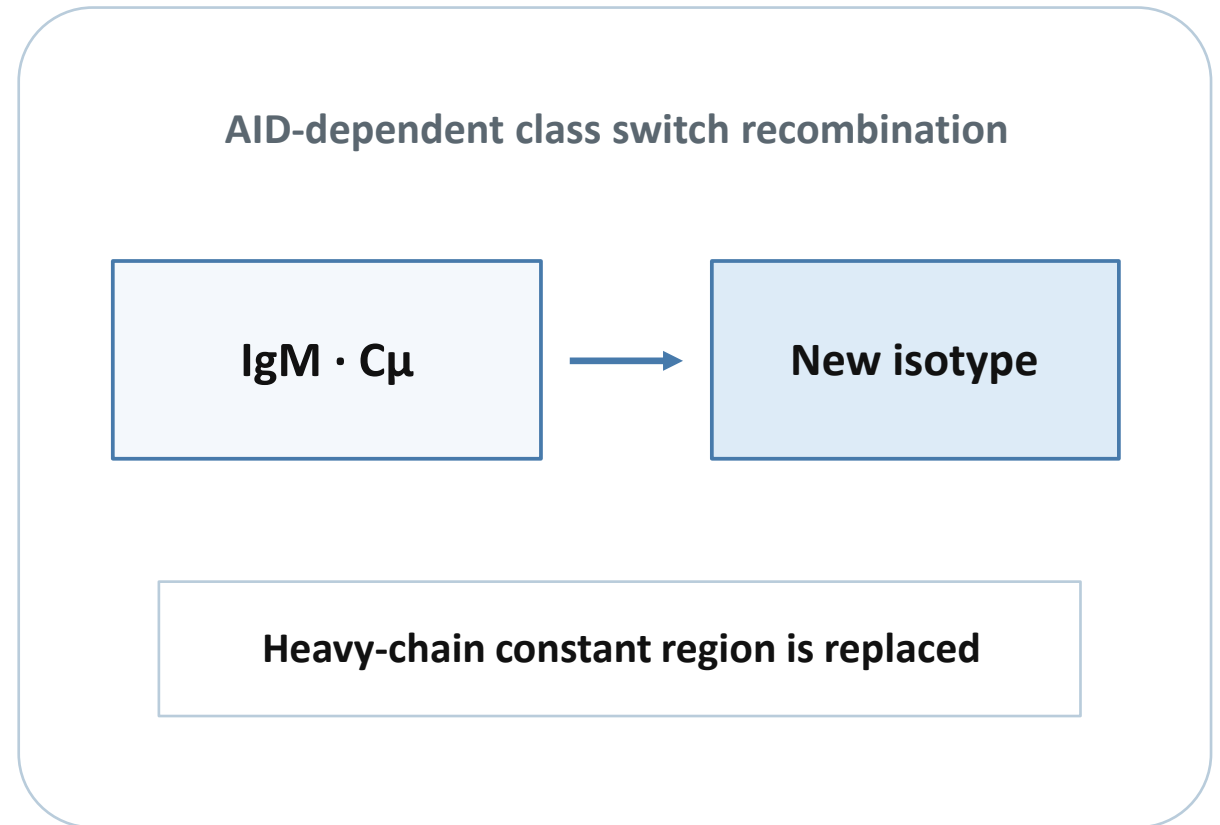
Class switching changes antibody isotype

The immunoglobulin heavy-chain constant region can be replaced during B-cell activation.

Class switch recombination is an intragenic recombination event.

The constant-region segment changes while antibody specificity can be retained.

This physiologic event is AID dependent.



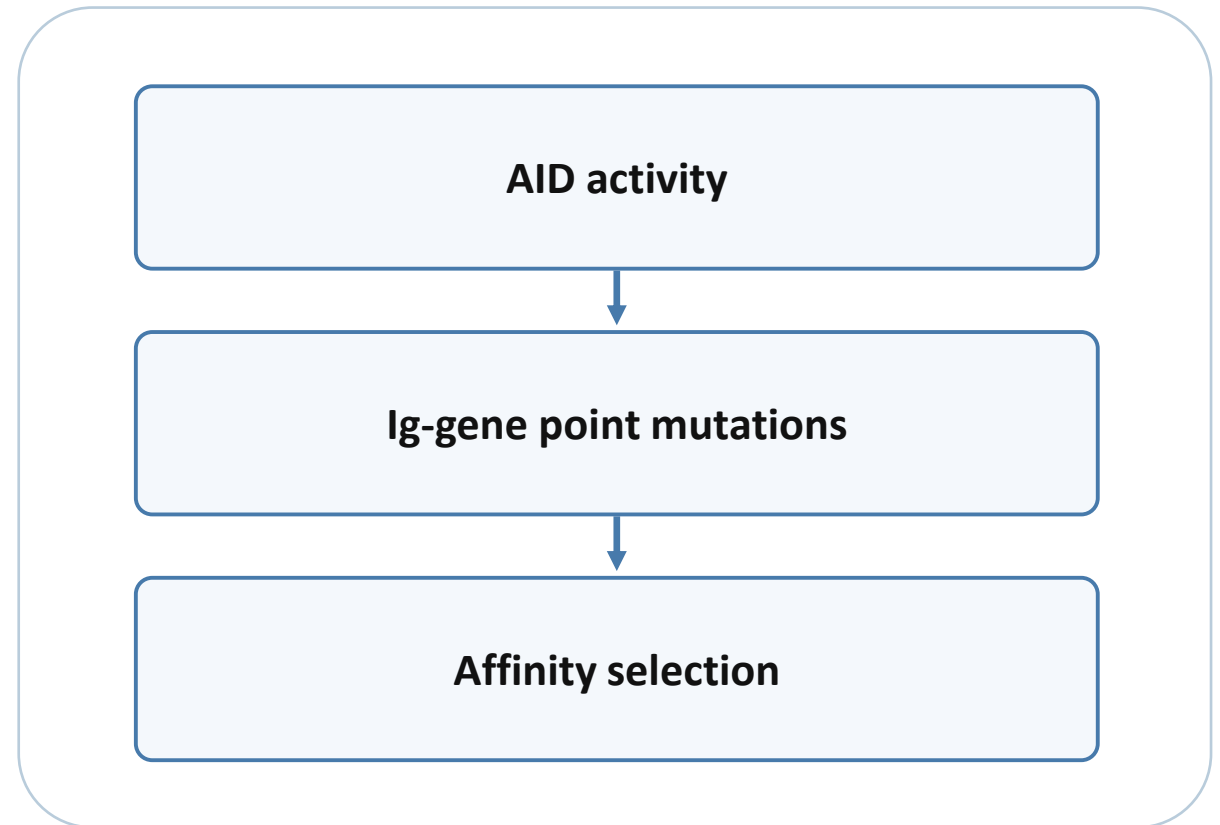
Somatic hypermutation changes antibody genes

Antigen-stimulated B cells acquire point mutations in immunoglobulin loci.

Mutations introduce sequence diversity in antibody genes.

Some changes can increase binding affinity for antigen.

The process relies on AID and creates potential off-target risk.



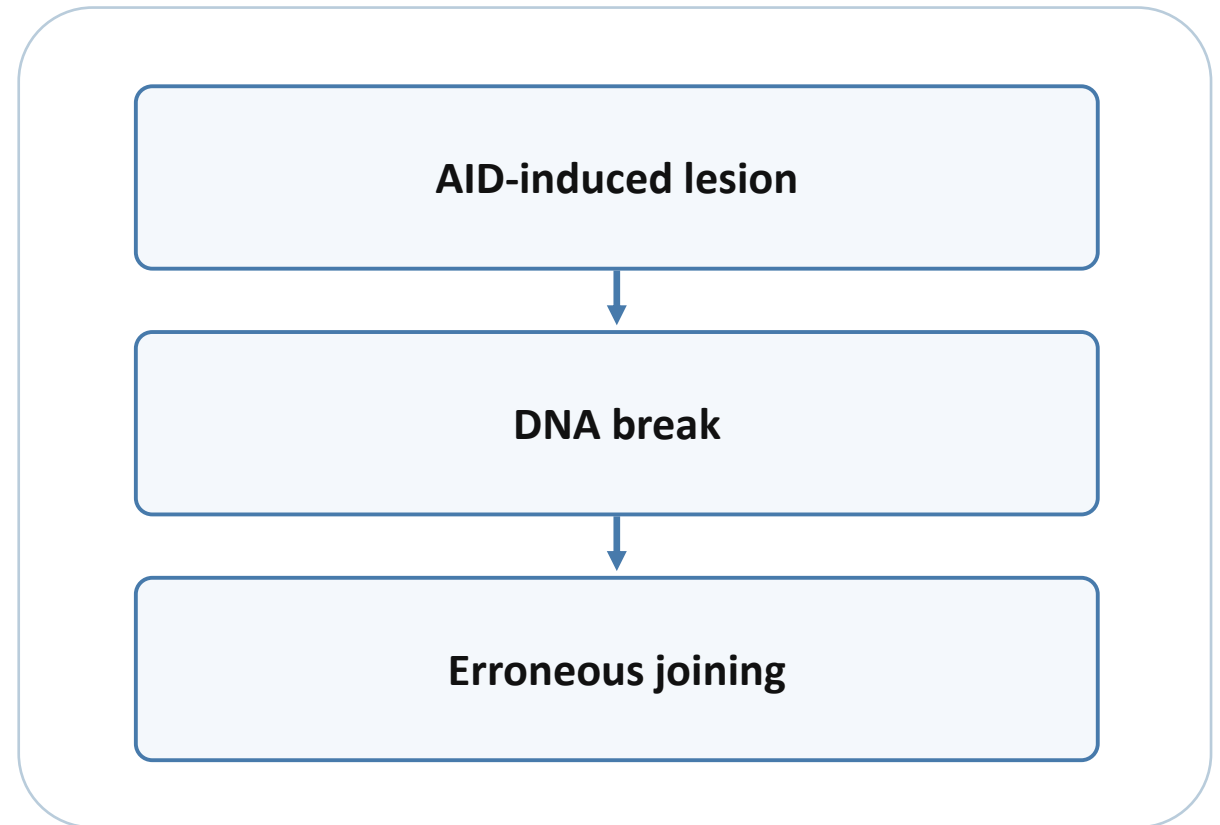
AID is useful because it can damage DNA

The normal genomic-editing function carries an intrinsic oncogenic hazard.

AID creates lesions that can result in chromosomal breaks.

Normal germinal center B cells can rarely contain MYC::IGH translocations.

Physiologic DNA editing therefore provides an origin for some driver rearrangements.



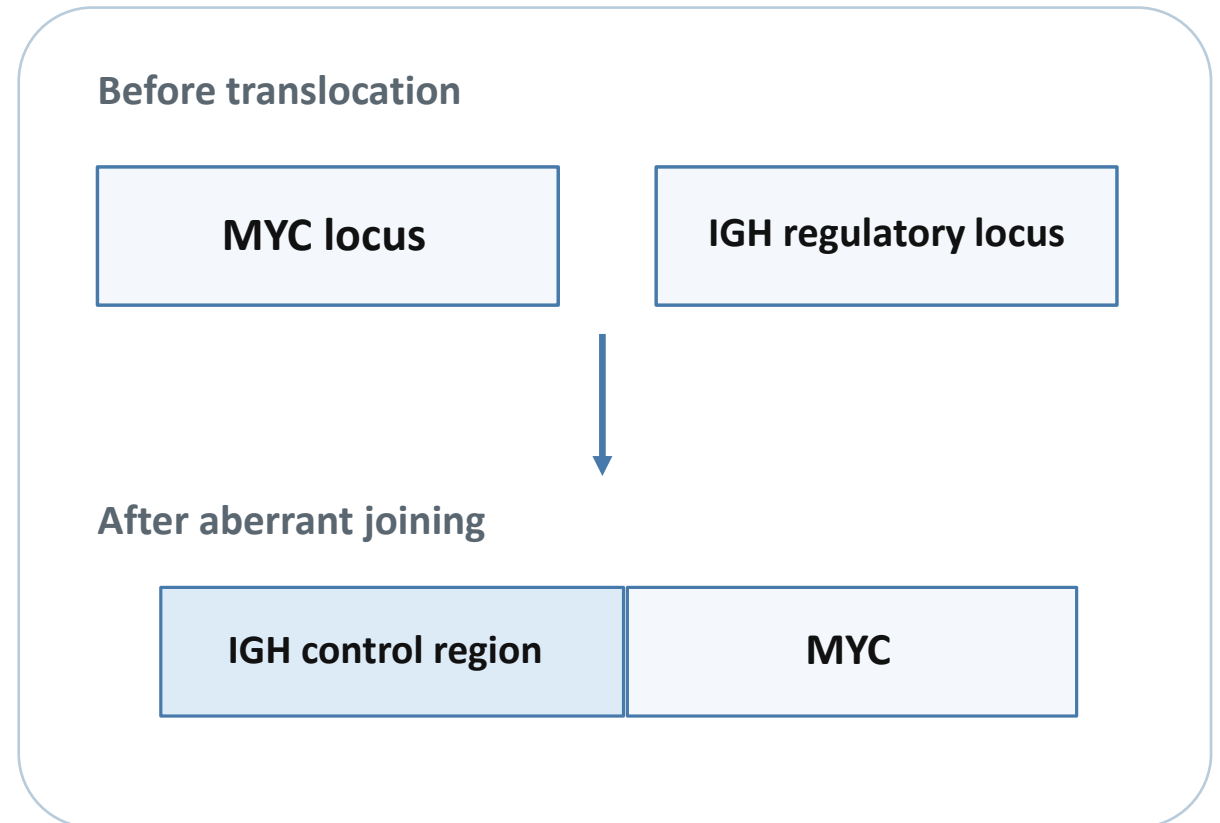
The immunoglobulin locus can misregulate MYC

A rearrangement may juxtapose MYC with a transcriptionally active immunoglobulin locus.

Immunoglobulin regulatory elements are active in B cells.

Chromosomal translocation can place MYC in an abnormal regulatory context.

The resulting proto-oncogene activation promotes neoplasia.



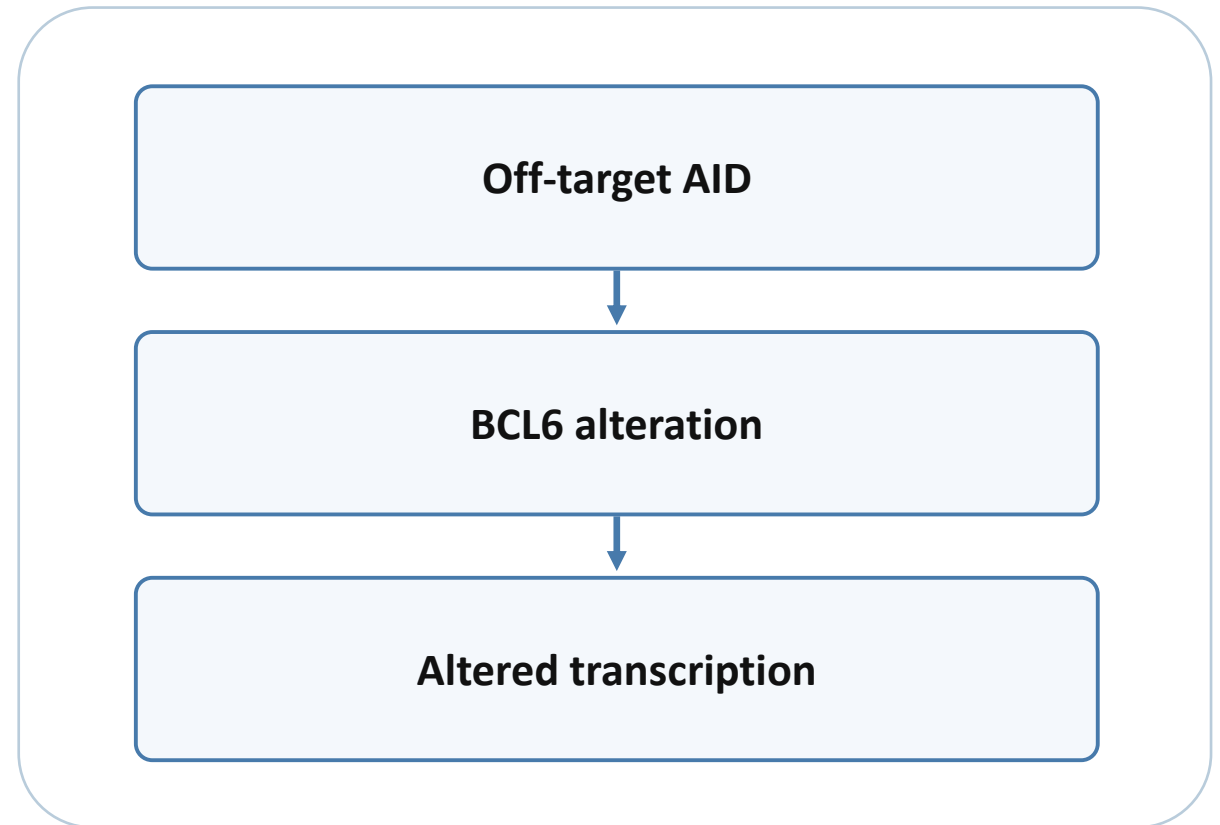
AID mistargeting can activate BCL6

The cancer risk of AID extends beyond canonical immunoglobulin targets.

Mistargeted AID can create point mutations in proto-oncogenes.

Upregulation of BCL6 as one consequence.

BCL6 is an oncogenic transcription factor in several B-cell malignancies.



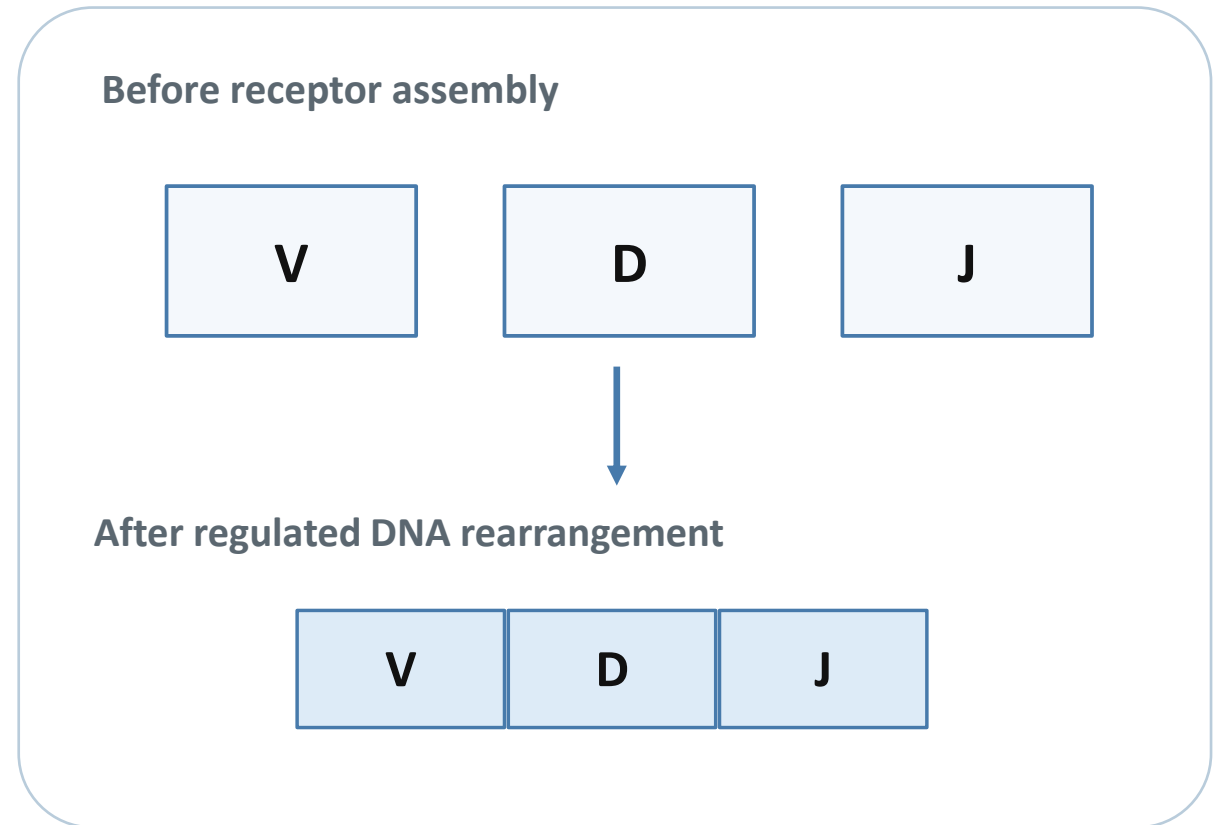
V(D)J recombination assembles antigen receptors

B- and T-cell precursors use recombinase-mediated DNA cutting during development.

Immunoglobulin loci are rearranged in precursor B cells.

T-cell receptor loci are rearranged in precursor T cells.

This is essential for generating receptor diversity.



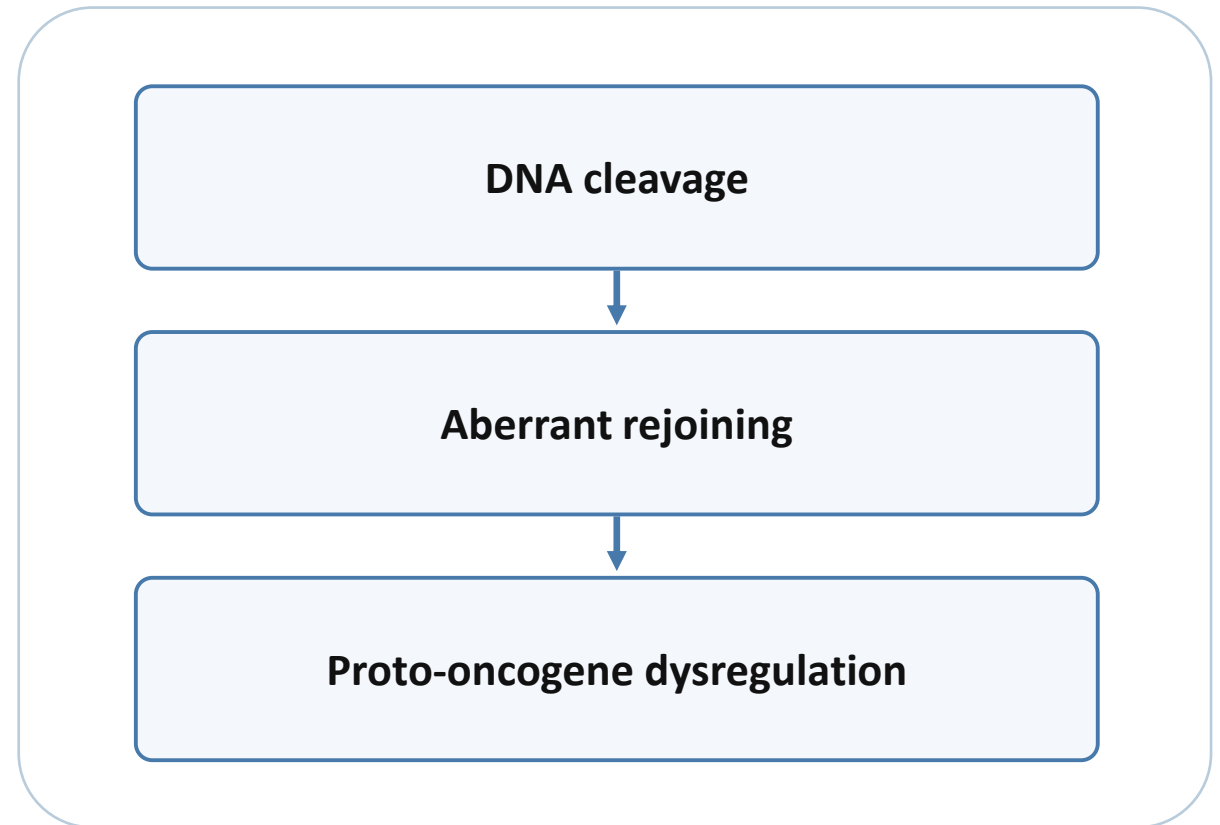
V(D)J repair errors can activate proto-oncogenes

Misrepair of physiologic chromosome breaks can produce oncogenic joins.

Normal recombinase activity targets antigen receptor loci.

Errant joining may connect a proto-oncogene with receptor-gene regulatory elements.

The resulting rearrangement can initiate a B- or T-cell neoplasm.



Precursor cells and germinal center cells differ

The developmental context predicts which physiologic DNA process creates genomic risk.

Precursor B/T cells: V(D)J recombination during receptor assembly.

Germinal center B cells: AID-dependent class switching and hypermutation.

Both processes can cause inappropriate oncogenic rearrangements.

**Precursors: V(D)J
recombination**

**Germinal center B
cells: AID**

Different mechanisms or causal contexts

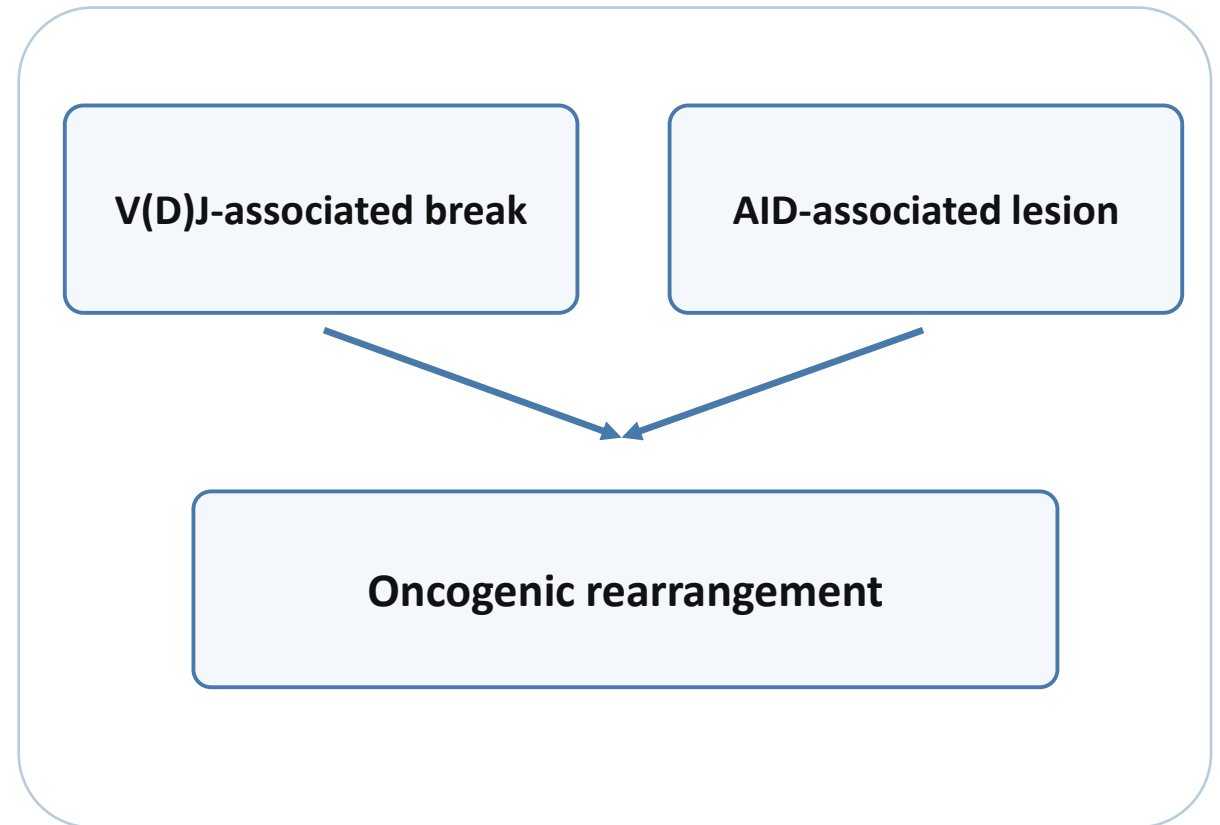
Two routes to proto-oncogene activation

Antigen receptor gene regulation can be misused at distinct differentiation stages.

V(D)J errors arise during precursor receptor assembly.

AID errors arise during activated germinal center B-cell diversification.

Both can juxtapose proto-oncogenes with strong regulatory elements.



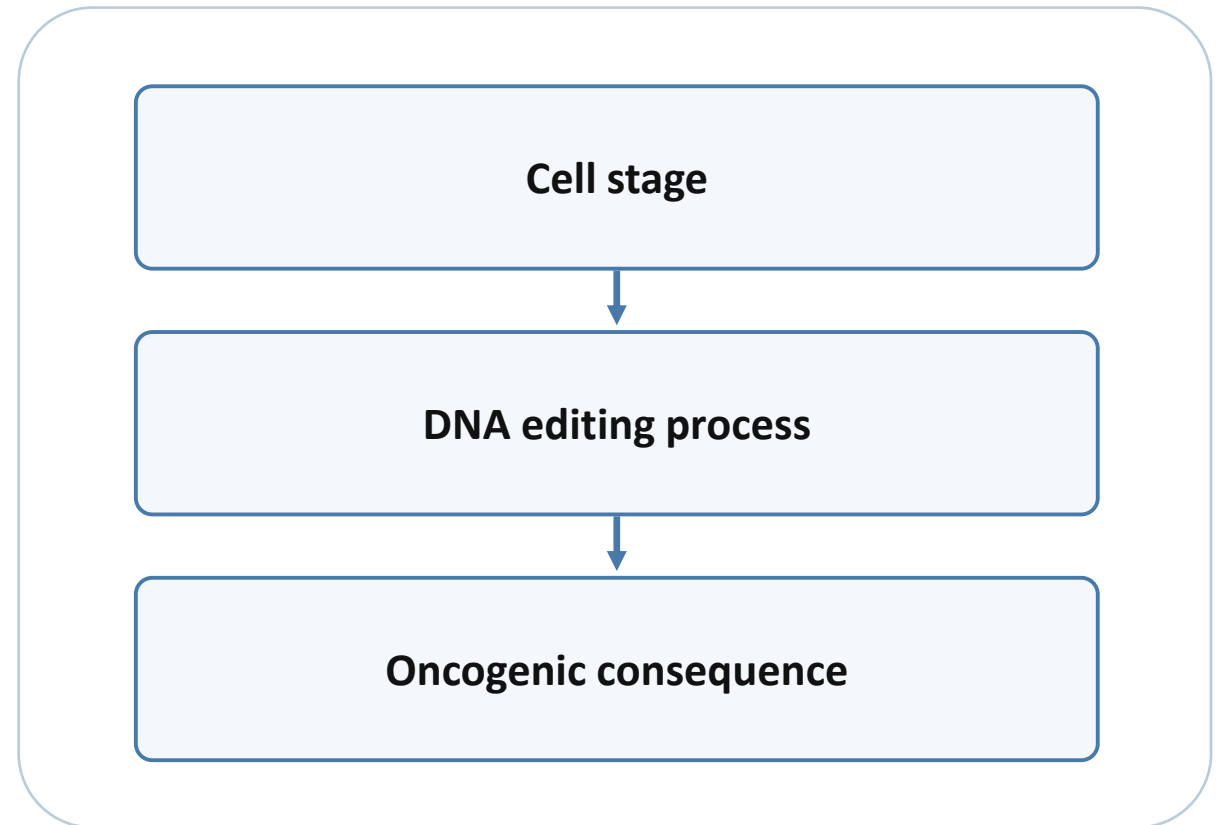
Mechanistic questions to ask of a rearrangement

Interpreting the driver requires locating the event in normal lymphocyte development.

Which cell stage normally expresses the DNA-editing machinery?

Which antigen-receptor locus was involved?

Does the rearrangement alter transcriptional regulation or protein function?



Genomic instability syndromes increase risk

Constitutional defects that destabilize the genome predispose to acute leukemia.

Bloom syndrome, Fanconi anemia, and ataxia telangiectasia.

These conditions are risk factors; They do not imply inevitable malignancy.

A later somatic malignant clone still requires interpretation.

Bloom syndrome

Fanconi anemia

Ataxia telangiectasia

Developmental syndromes also modify leukemia risk

Not all inherited susceptibility is presented as a generic DNA-instability syndrome.

Down syndrome (trisomy 21) is associated with childhood leukemia.

Type I neurofibromatosis is also associated with childhood leukemia.

The source reports associations without quantitative risks in this section.

**Down syndrome
(trisomy 21)**

**Type I
neurofibromatosis**

Different mechanisms or causal contexts

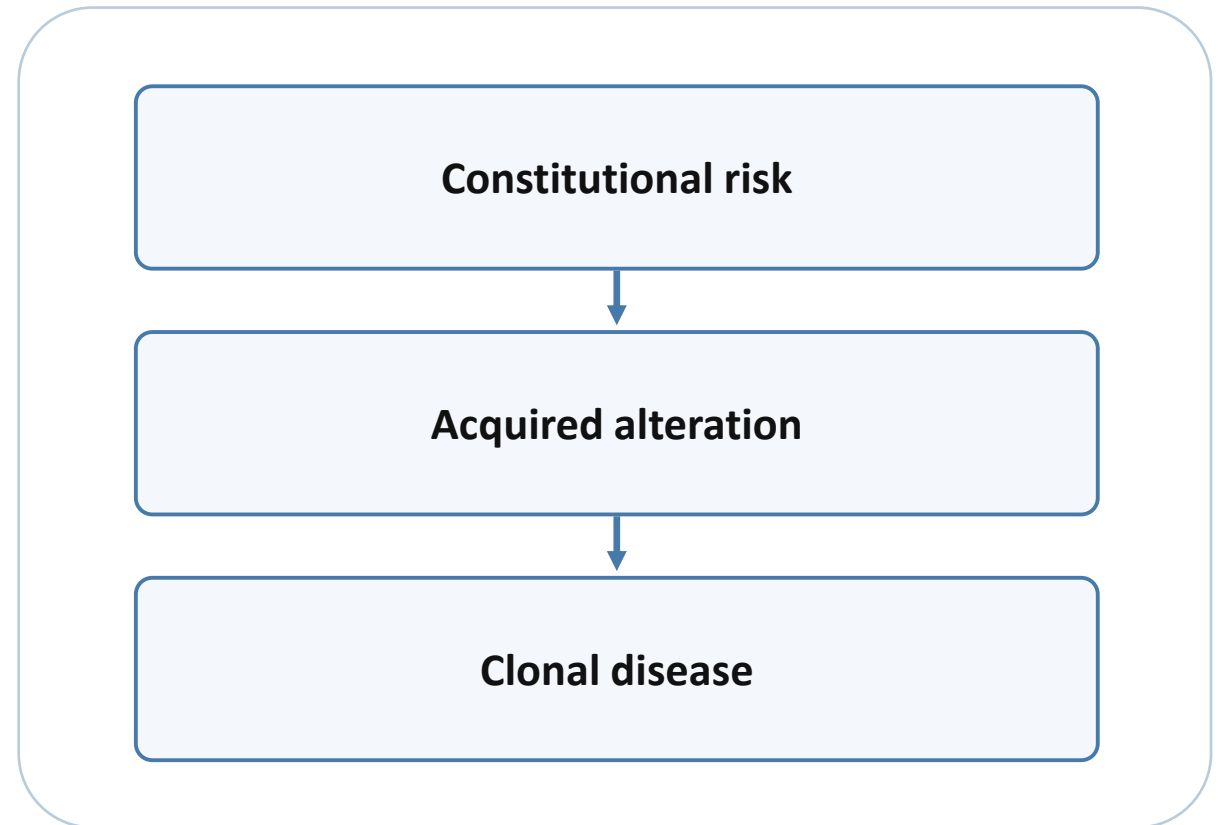
Predisposition is not equivalent to a tumor genotype

A constitutional risk condition and an acquired driver answer different questions.

Predisposition concerns the chance of developing malignancy.

A driver mutation explains a neoplastic clone's molecular behavior.

Both can contribute to one patient's causal history.



Three implicated lymphotropic viruses

Specific viral agents linked to selected lymphoid tumors.

HTLV-1 is associated with adult T-cell leukemia/lymphoma.

EBV is implicated in several B-cell and rare NK-cell neoplasms.

HHV8/KSHV is associated with an effusion-based B-cell lymphoma.

HTLV-1

EBV

HHV8 / KSHV

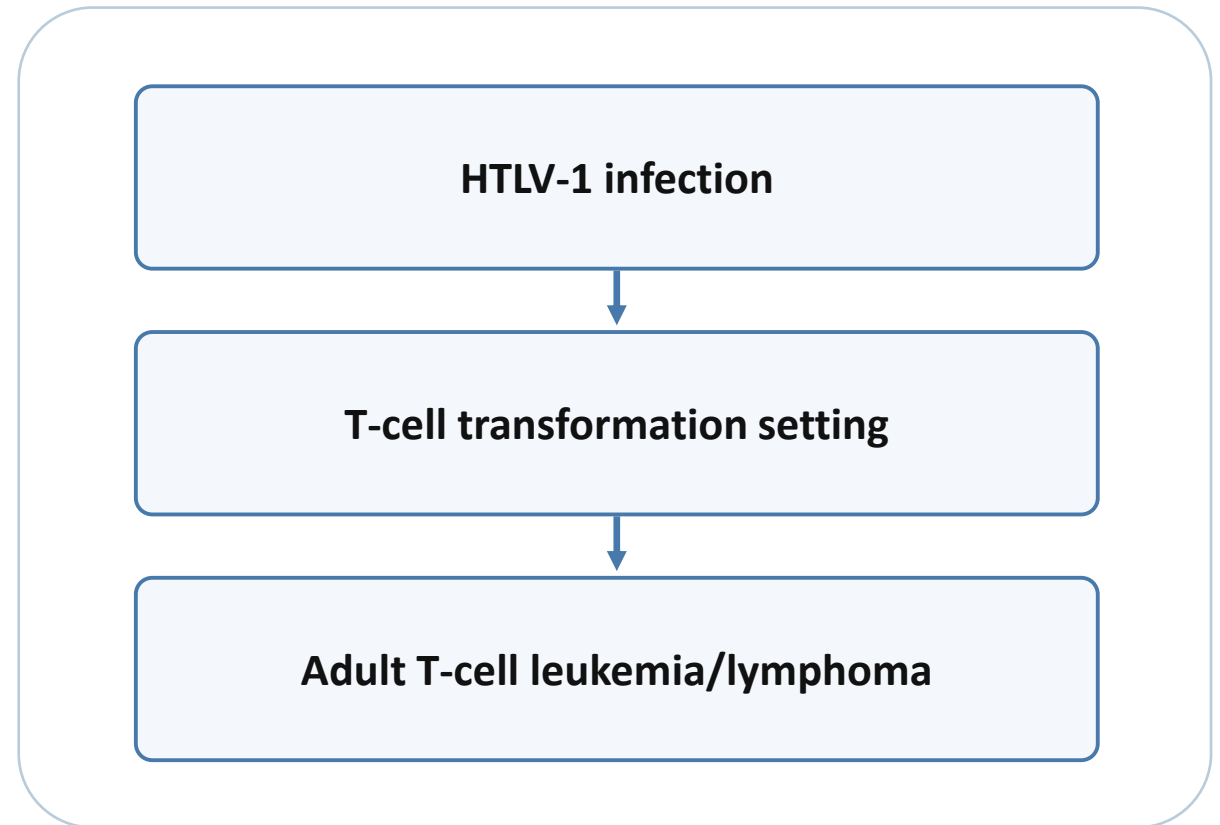
HTLV-1 and adult T-cell leukemia/lymphoma

A viral etiologic association can be particularly linked to a named lymphoid disease.

HTLV-1 is a human T-cell leukemia virus.

Its recognized tumor association is adult T-cell leukemia/lymphoma.

The present source section does not specify viral prevalence or clinical staging.



EBV is associated with heterogeneous tumors

The same oncogenic virus can be linked with more than one tumor class.

EBV occurs in a subset of Burkitt lymphomas.

EBV in 30%–40% of Hodgkin lymphomas.

It also occurs in many B-cell lymphomas with T-cell immunodeficiency and rare NK-cell lymphomas.

Burkitt lymphoma: Subset

Hodgkin lymphoma: 30%–40%

Immunodeficiency-linked / rare NK tumors

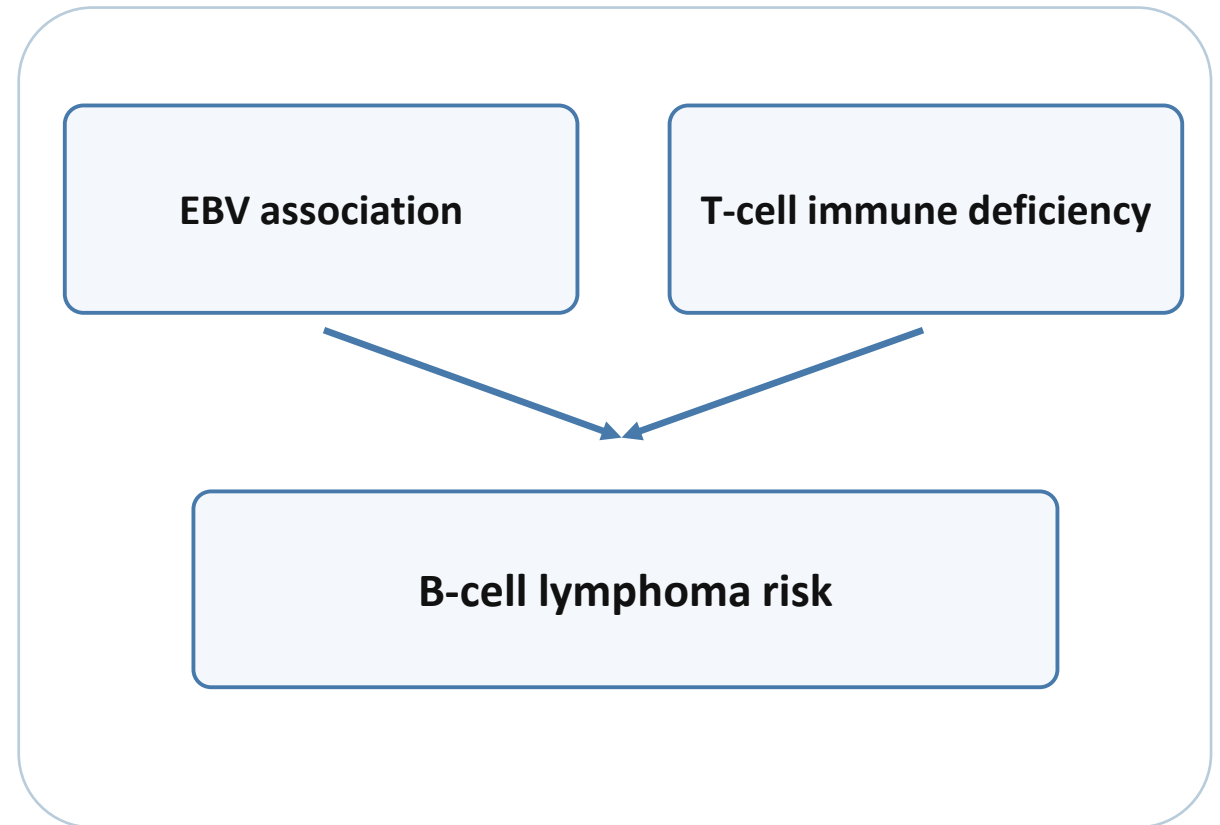
EBV lymphoma risk interacts with immune status

T-cell immune competence influences which EBV-associated neoplasms appear.

Some EBV-associated B-cell lymphomas arise in T-cell immunodeficiency.

Immune dysregulation and viral association are distinct but interacting risk factors.

Pathogenic inference should consider the immune context.



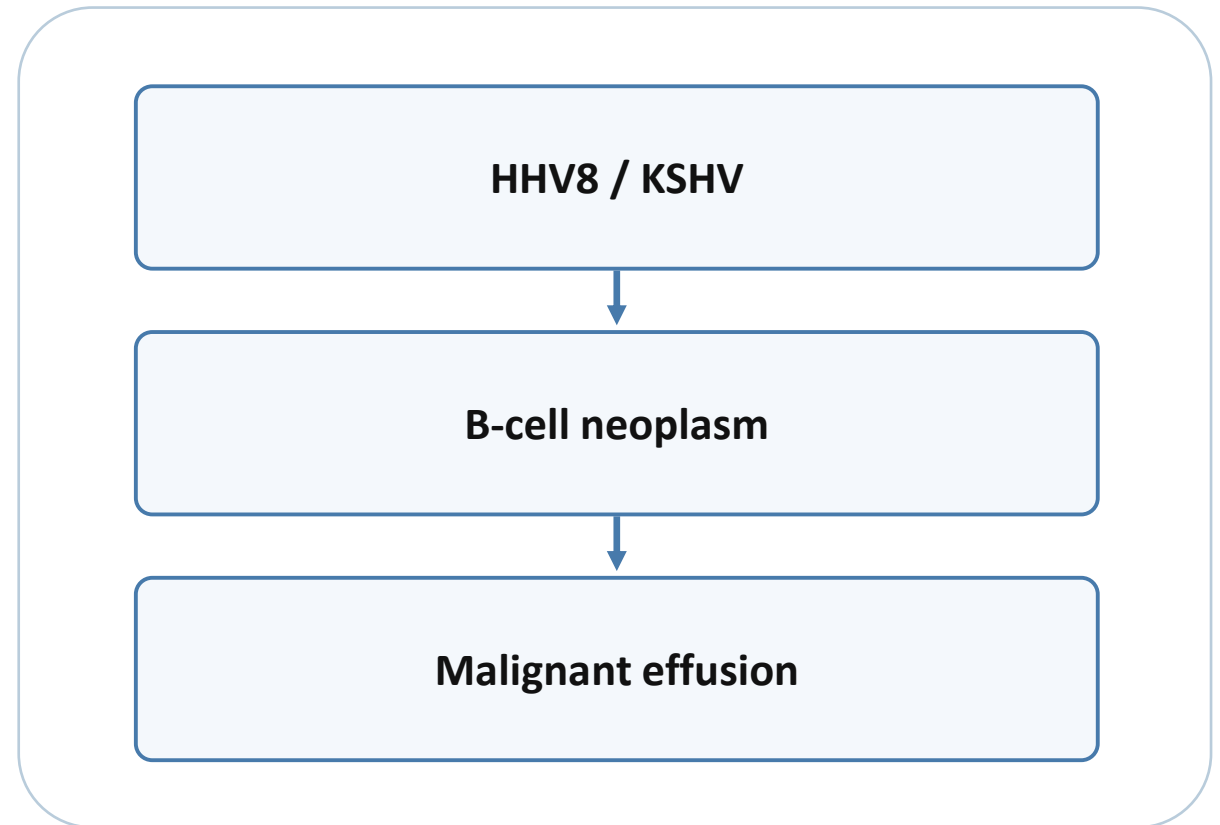
HHV8/KSHV and malignant effusions

HHV8 is linked with a B-cell lymphoma that may present as an effusion.

HHV8 is also called Kaposi sarcoma herpesvirus (KSHV).

The source describes an unusual B-cell lymphoma involving body-cavity fluid.

Pleural presentation is a characteristic example, not the only possible cavity.



Viral association must be interpreted precisely

Different viruses have different characteristic hematolymphoid associations.

A viral association does not mean that every case of the tumor contains that virus.

EBV is explicitly present only in subsets of some named malignancies.

Etiologic attribution should not be replaced by nonspecific “viral lymphoma” labeling.

Etiologic association

Universal presence in every case

Different mechanisms or causal contexts

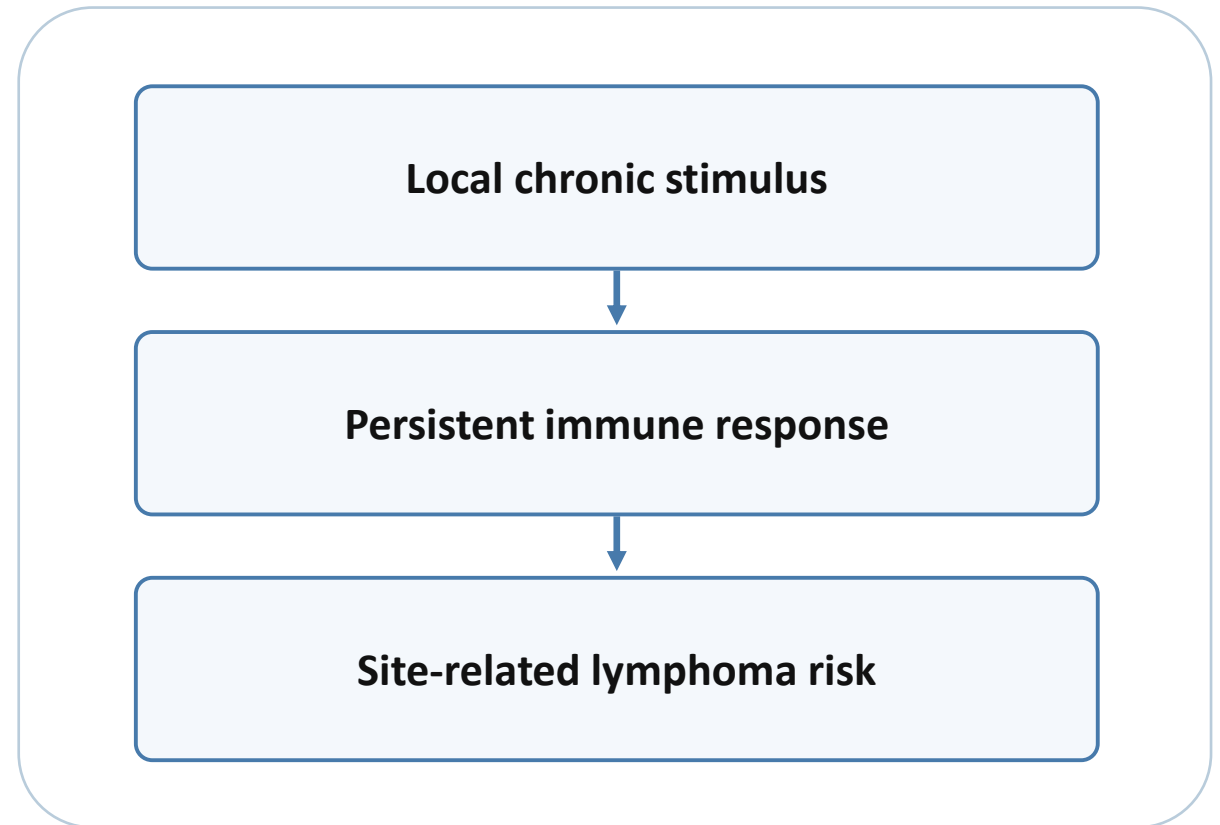
Local chronic inflammation predisposes locally

Some lymphoid tumors develop in tissues exposed to sustained antigenic or inflammatory stimuli.

The neoplasm often arises within the chronically inflamed tissue.

Risk is tied to a particular organ-specific setting.

This pattern with the systemic risk accompanying HIV.



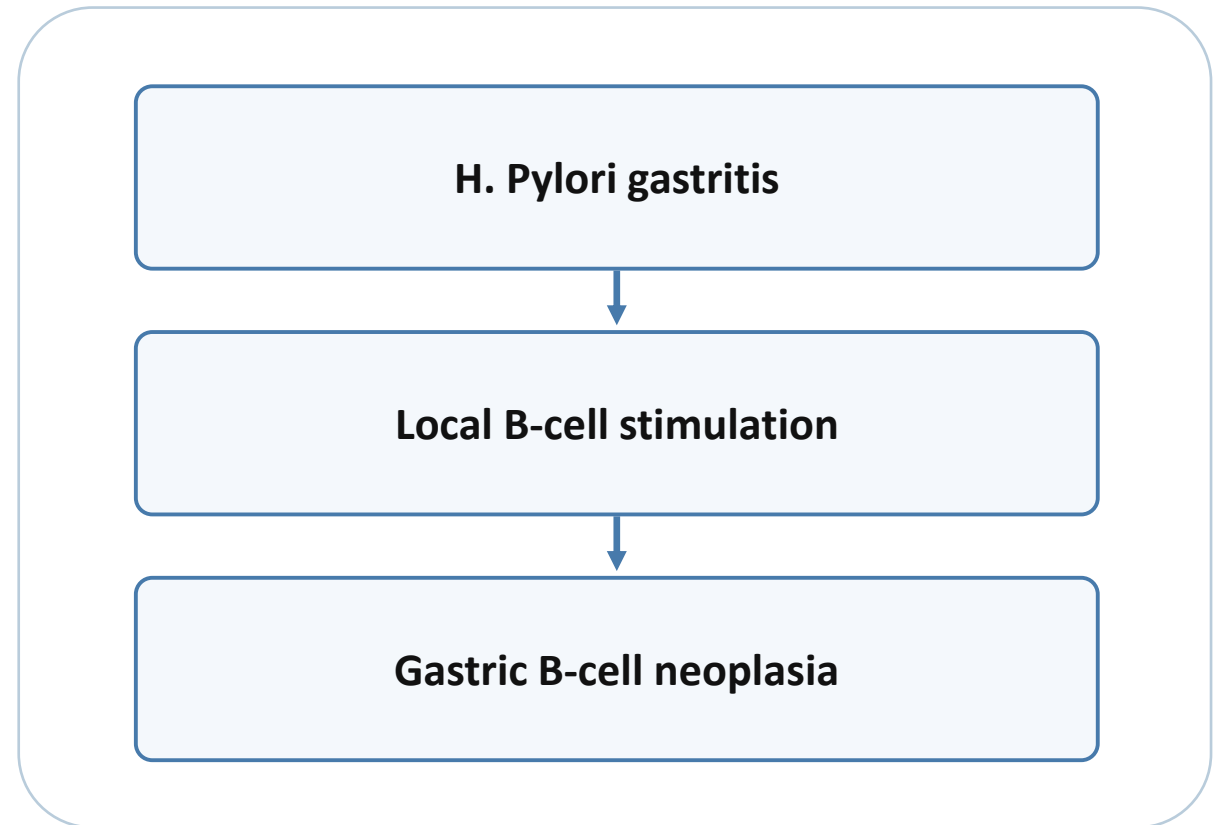
H. Pylori provides a gastric example

Chronic Helicobacter pylori infection is associated with gastric B-cell lymphoma.

The etiologic exposure occurs in gastric mucosa.

The associated tumor is of B-cell lineage.

The example illustrates localized inflammation-associated neoplasia.



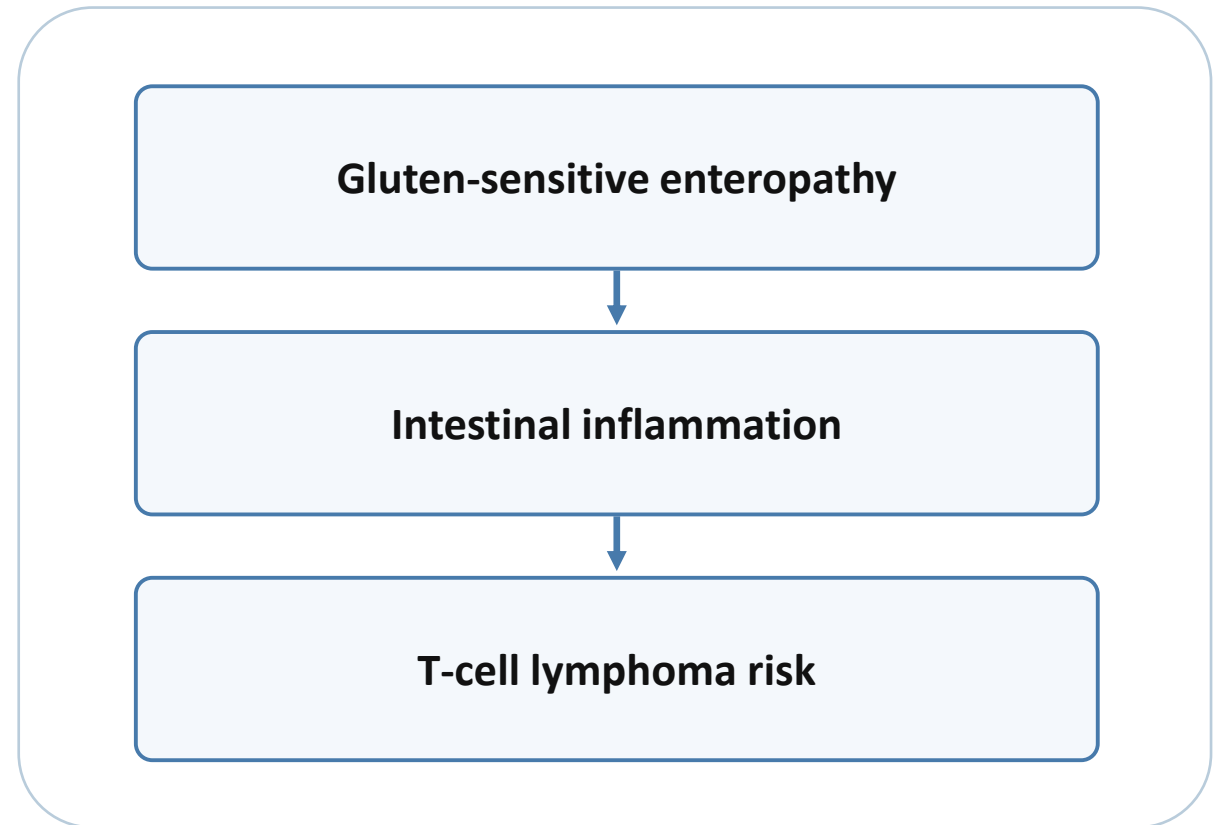
Gluten-sensitive enteropathy provides a T-cell example

Chronic immune-mediated intestinal injury is associated with intestinal T-cell lymphoma.

The initiating disease is gluten-sensitive enteropathy.

The associated neoplasm arises in the intestinal setting.

This demonstrates that inflammatory predisposition is not restricted to B cells.



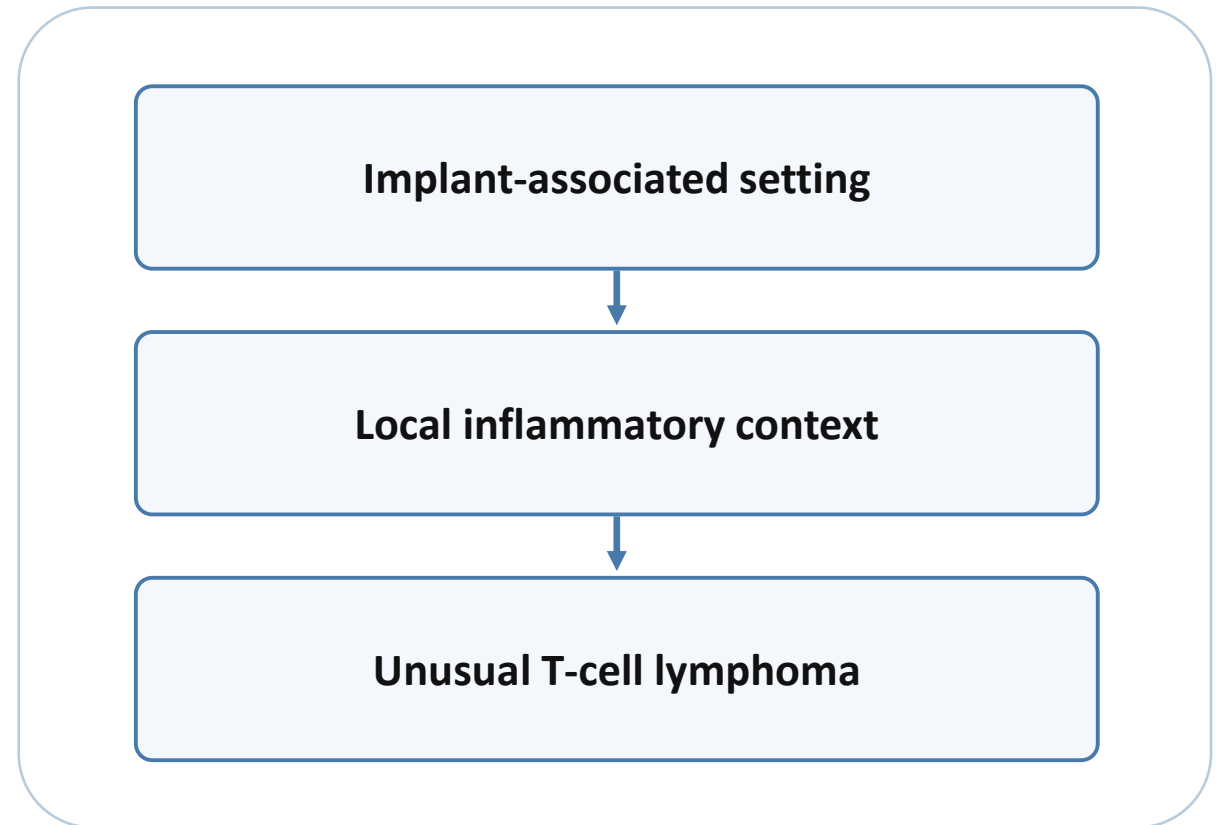
Breast implants are a distinct local association

The source identifies an unusual T-cell lymphoma associated with breast implants.

This is not presented as a general cause of all lymphomas.

Its anatomic association is clinically distinctive.

The relevant causal context differs from gastric infection or enteropathy.



Three local associations: A comparative view

Location and lymphoid lineage distinguish the examples.

Etiologic setting	Typical site	Associated lineage
H. pylori	Stomach	B cell
Gluten-sensitive enteropathy	Intestine	T cell
Breast implant	Implant-associated site	T cell

HIV is not simply another localized stimulus

HIV-related B-cell lymphomas can arise in many different organs.

Unlike localized inflammatory associations,
the risk is systemic.

Early infection is accompanied by B-cell
germinal center hyperplasia.

Advanced infection adds marked T-cell
immunodeficiency.

**Localized chronic
inflammation**

**Systemic HIV-
associated
dysregulation**

Different mechanisms or causal contexts

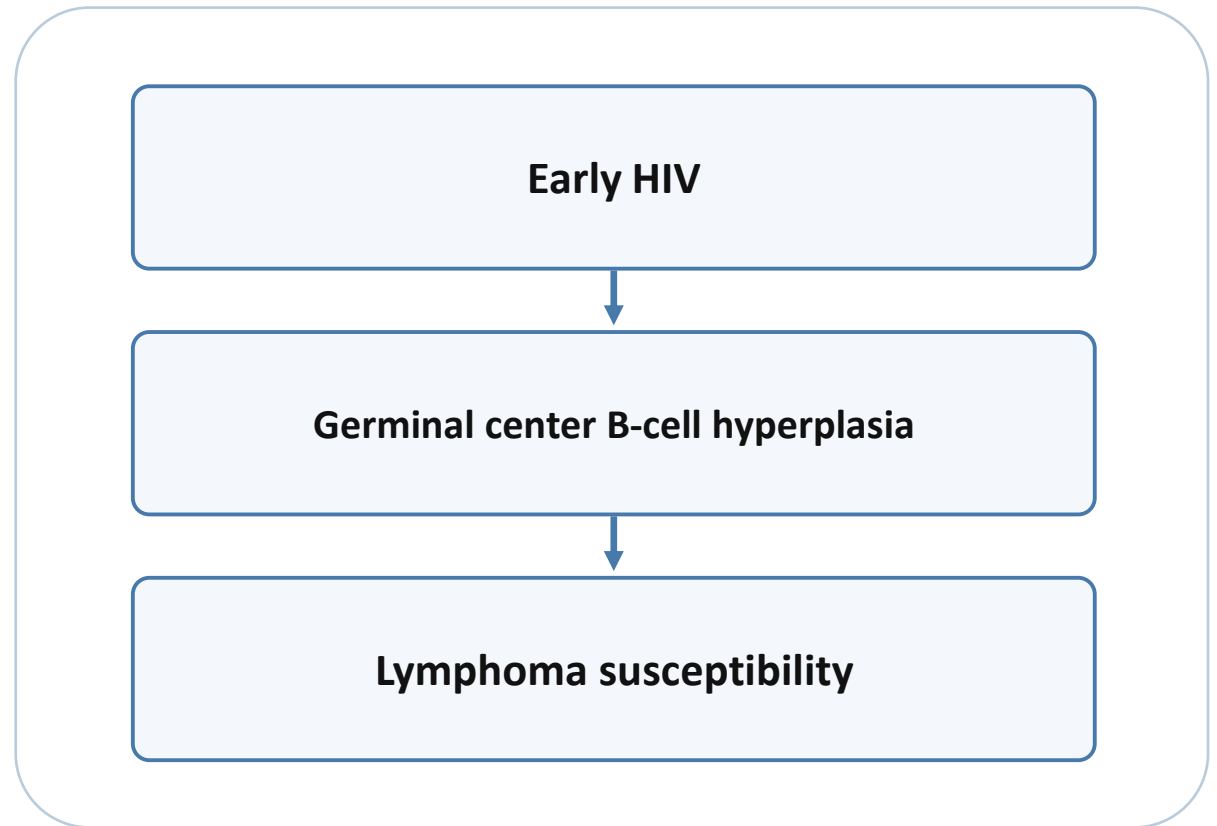
Early HIV: Germinal center hyperplasia

T-cell dysregulation can drive a broad B-cell germinal center response.

Systemic germinal center B-cell hyperplasia early in HIV.

This is linked to more germinal center B-cell lymphomas.

The association connects immune stimulation with malignant risk.



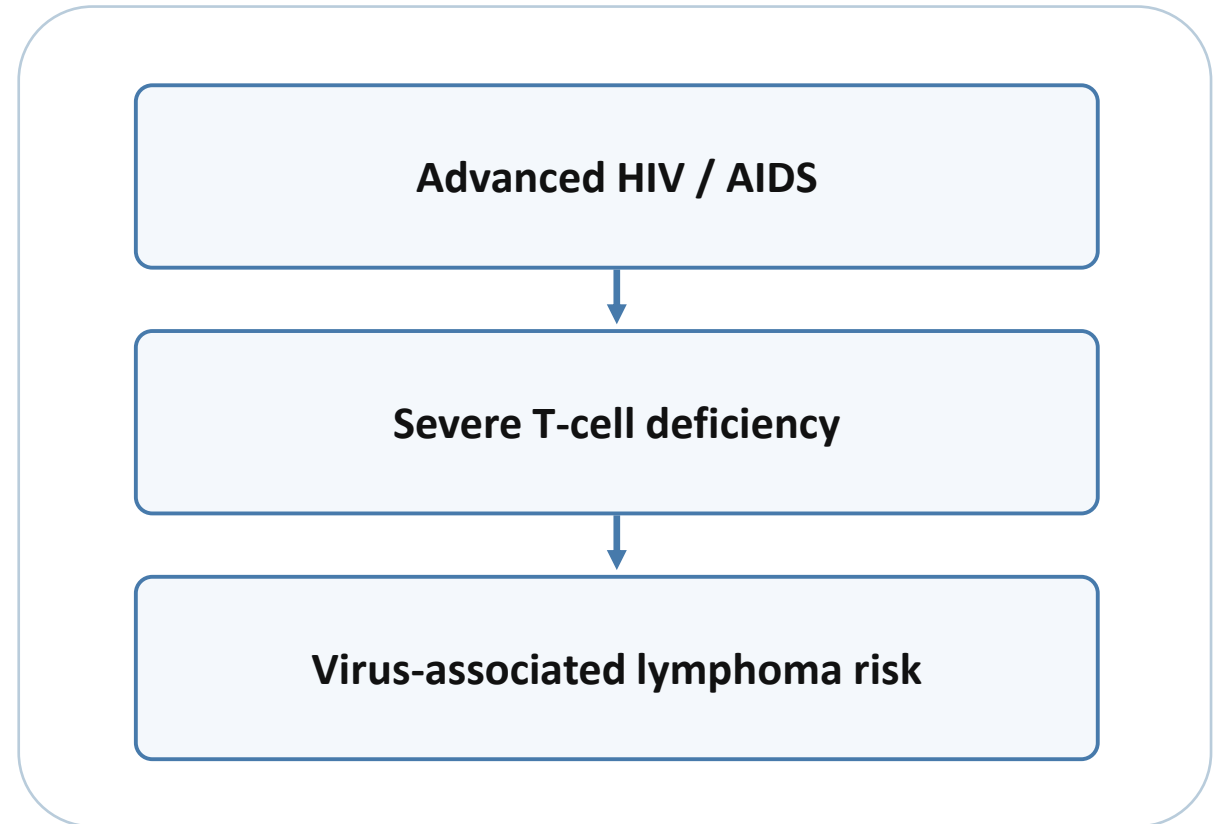
Advanced HIV: Loss of immune surveillance

Severe T-cell immunodeficiency further increases B-cell lymphoma risk.

The risk rises in advanced HIV infection (AIDS).

EBV-associated lymphomas become particularly important.

KSHV/HHV8-associated lymphomas are also emphasized.



HIV creates two sequential risk contexts

Dysregulated stimulation and immune deficiency both contribute to a changing risk environment.

Early: Systemic germinal center stimulation of B cells.

Late: Profound T-cell deficiency and increased viral-associated tumors.

These mechanisms differ despite belonging to one infection history.

Early: GC hyperplasia

**Advanced: T-cell
immunodeficiency**

Different mechanisms or causal contexts

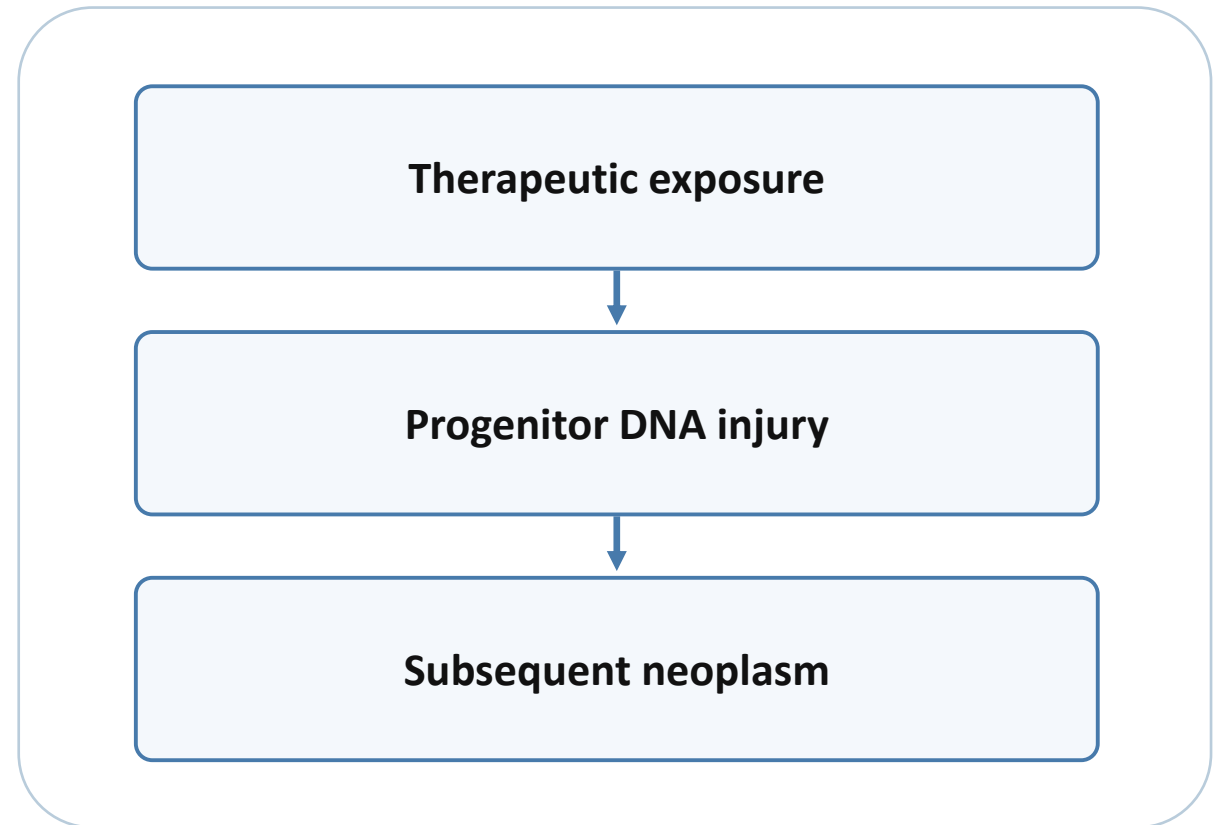
Cancer therapy can cause secondary neoplasia

Radiotherapy and some cytotoxic drugs can damage hematolymphoid progenitors.

Ionizing radiation is mutagenic.

Certain cancer chemotherapies also have mutagenic effects.

Subsequent myeloid or lymphoid malignancies may develop.



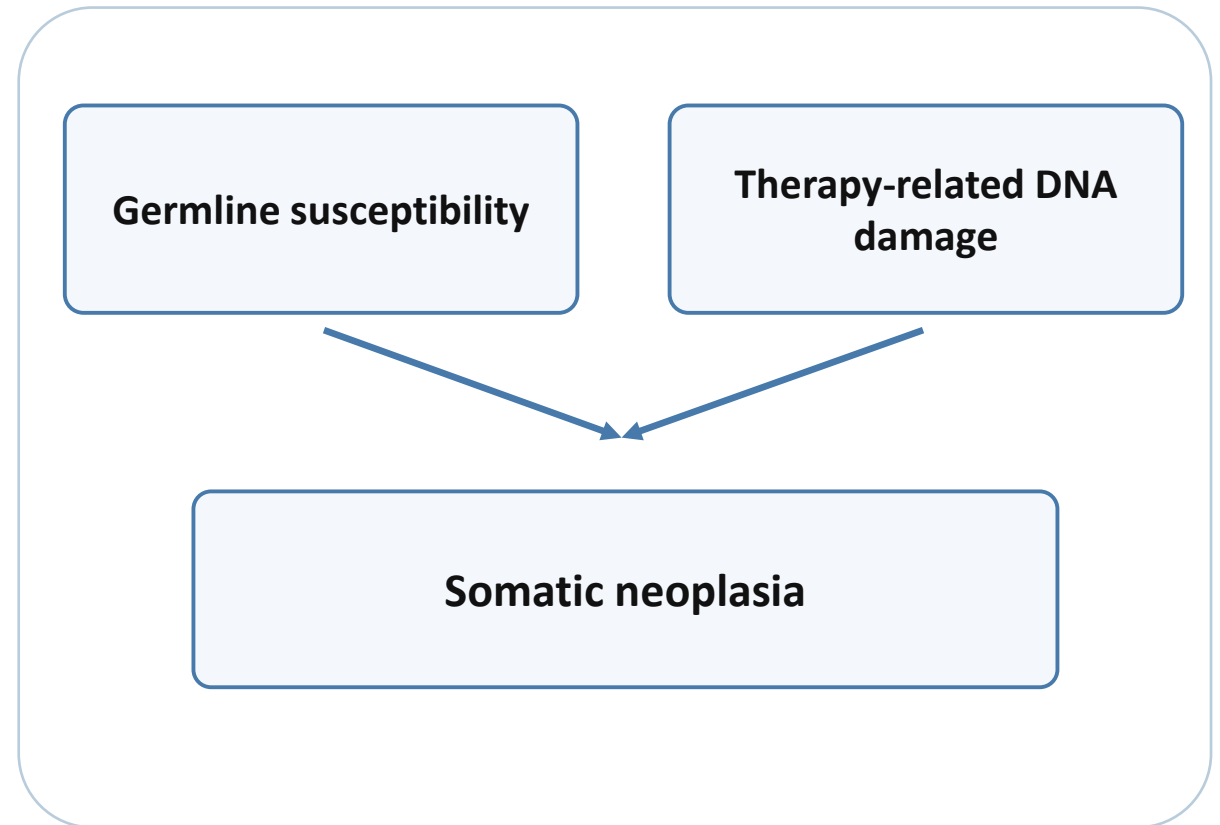
Therapy-related risk differs from inherited risk

The causal point of entry differs, although both can facilitate malignant evolution.

Therapy-related: An acquired exposure can induce mutations in progenitors.

Inherited: Constitutional factors increase susceptibility.

Both pathways ultimately intersect with oncogenic genetic change.



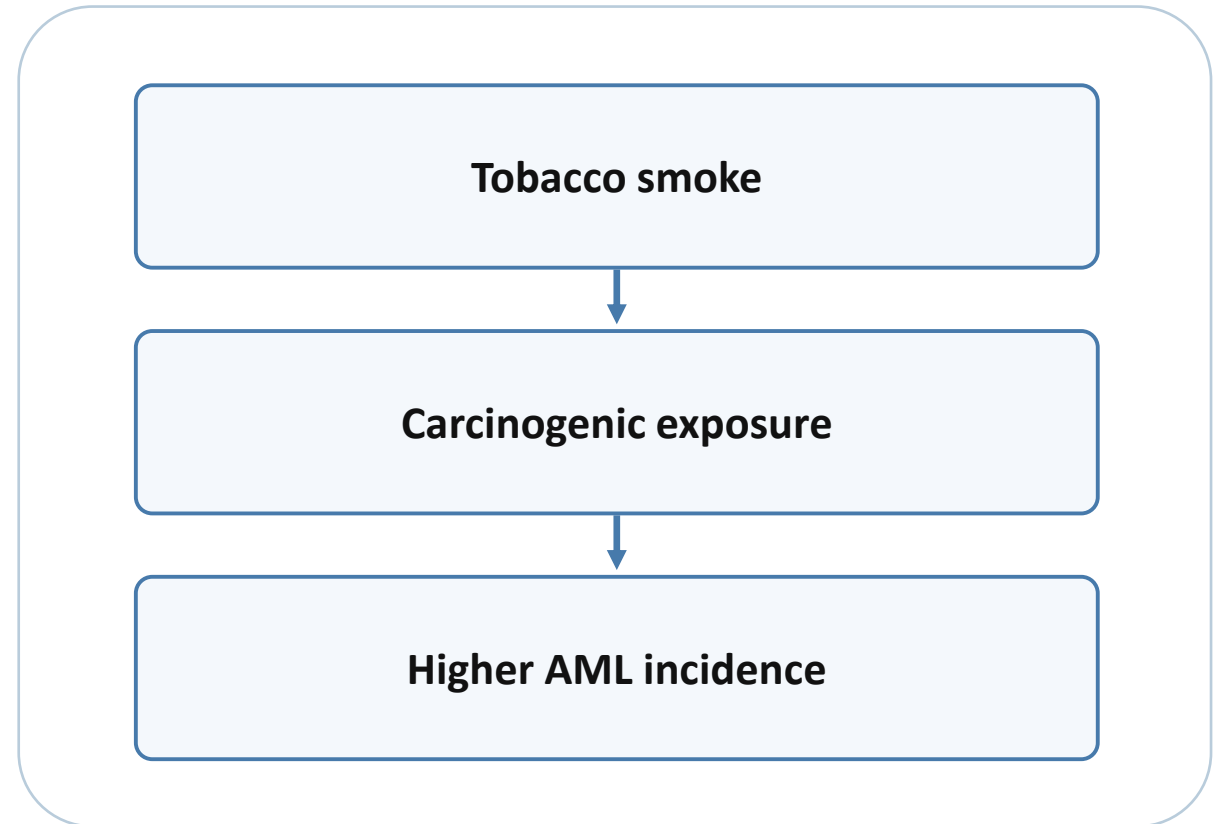
Smoking is associated with higher AML incidence

A relative increase in AML among smokers.

The reported elevation is 1.3- to 2-fold.

Exposure to carcinogens such as benzene in tobacco smoke is proposed.

This is an association and plausible mechanism—not an individual risk prediction.



Etiologies can be grouped by their causal entry point

The risk factor may act at the DNA, immune-system, or tissue-microenvironment level.

Inherited instability affects baseline susceptibility.

Recombination errors and mutagens create acquired lesions.

Viruses and inflammation modify the biologic context in which clones arise.

Inherited susceptibility

Acquired genome change

Immune / inflammatory milieu

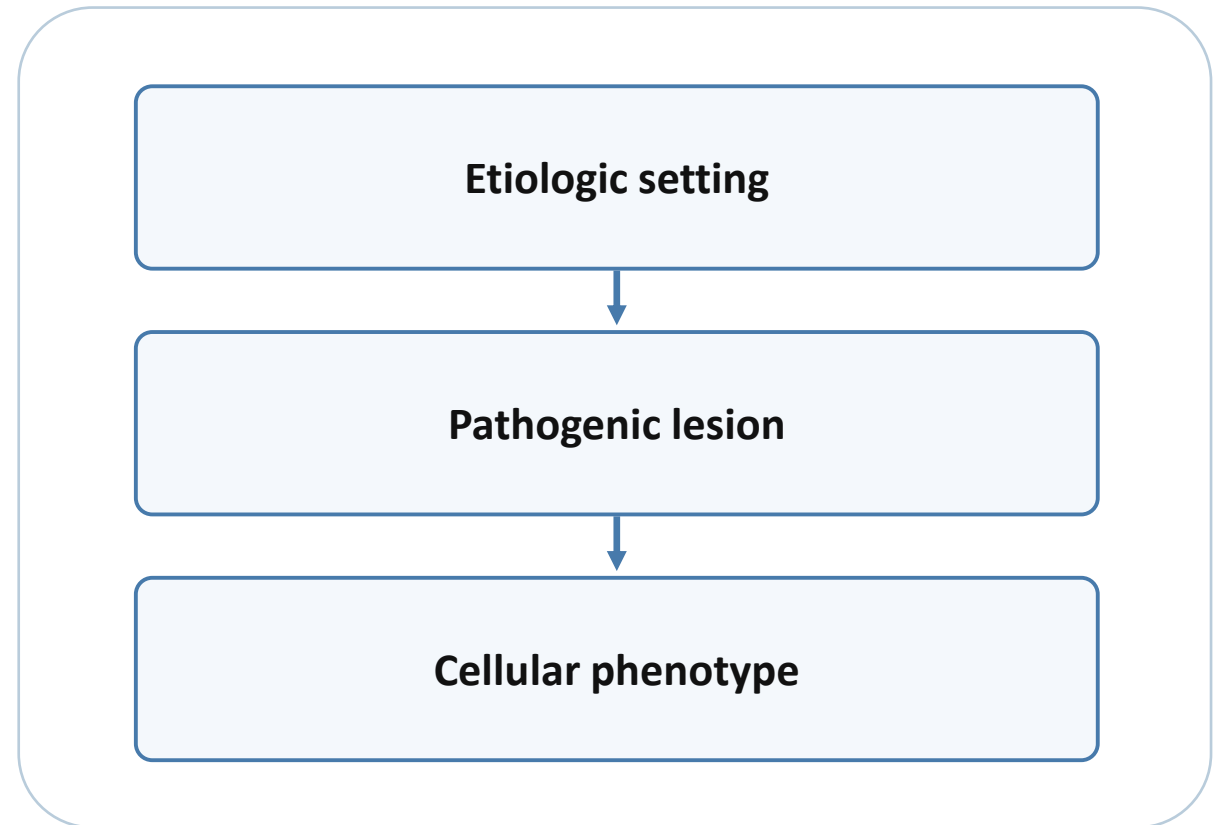
Risk factor, driver, and phenotype answer different questions

Clear reasoning separates causes of susceptibility from mechanisms of tumor behavior.

Risk factor: Why is malignancy more likely in this patient or tissue?

Driver lesion: What cellular activity does the mutation change?

Phenotype: How does the resulting malignant population behave?



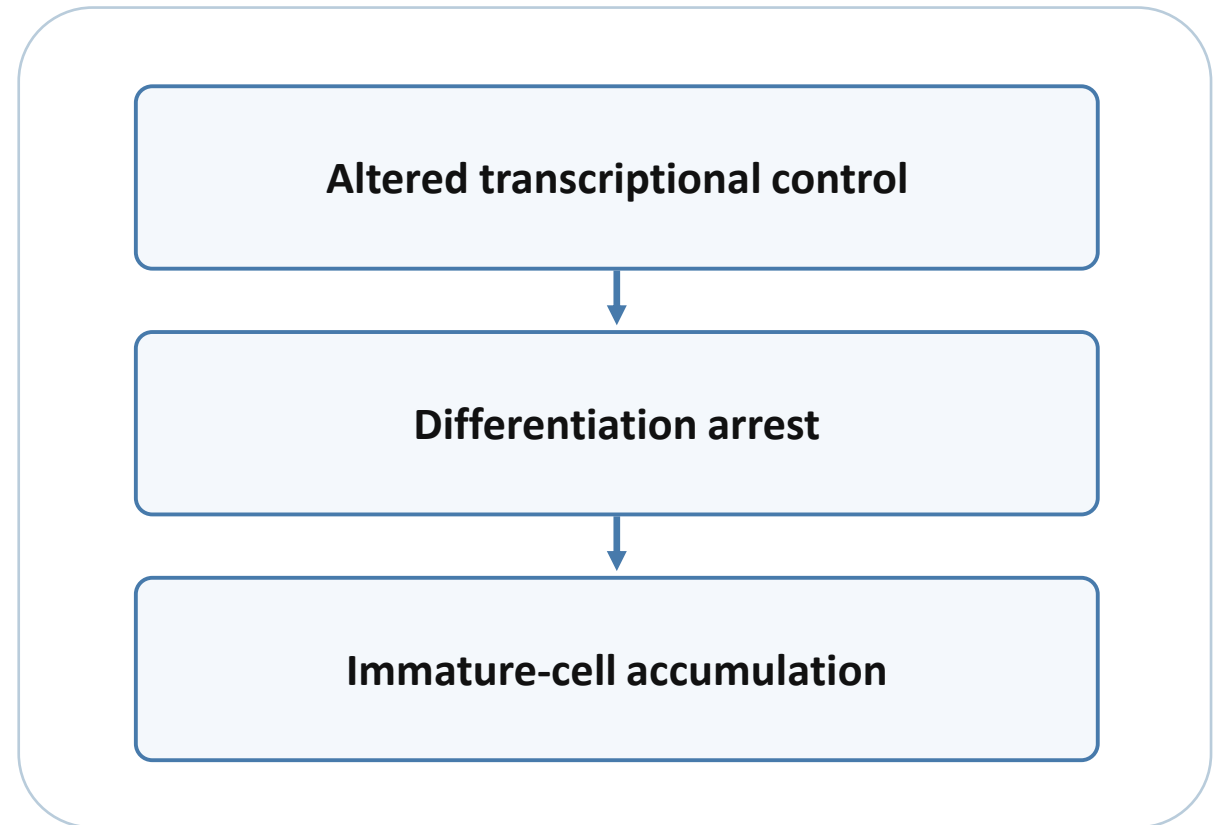
Case reasoning: A blocked myeloid maturation program

An acute leukemia contains a regulatory fusion and an accumulation of immature precursors.

Pathogenic question: Which cellular program is disabled?

Expected effect: Differentiation arrest at a proliferative stage.

Growth-enhancing cooperating events may contribute to clone expansion.



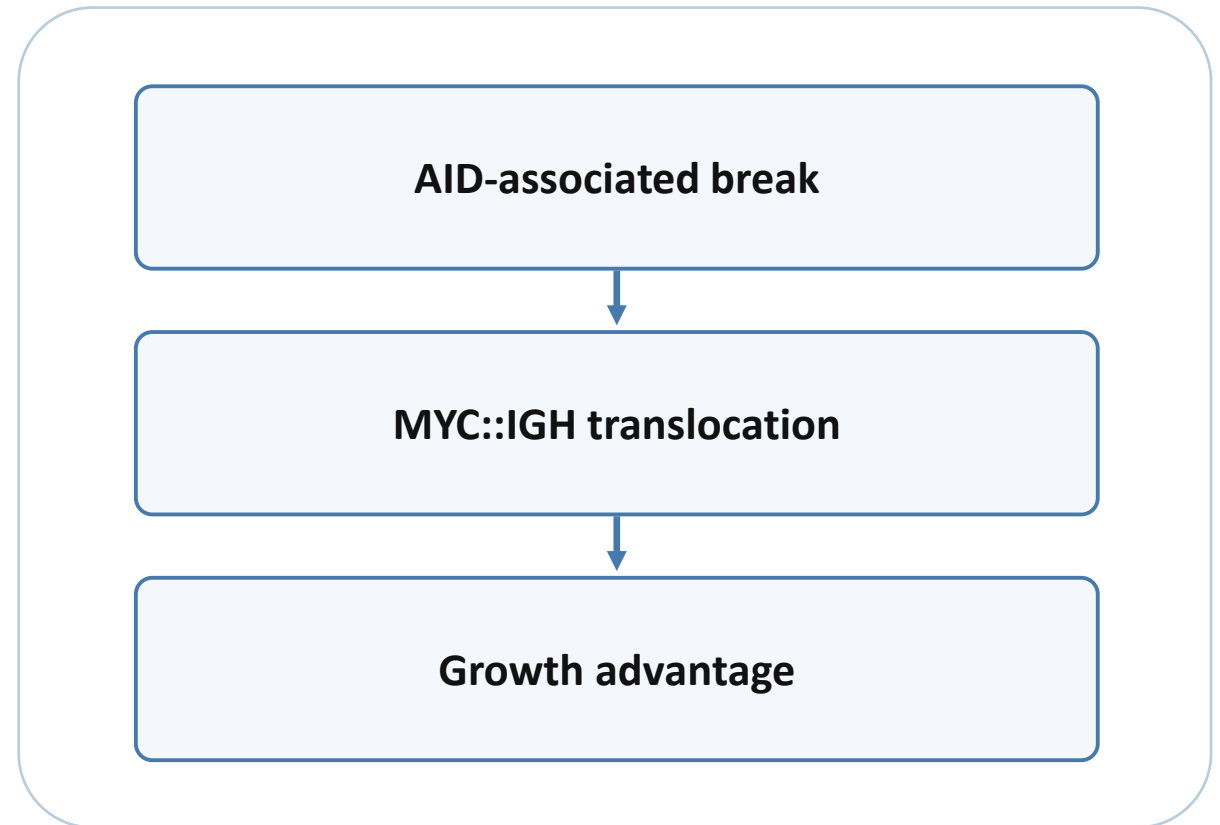
Case reasoning: MYC rearrangement in a B-cell tumor

A B-cell neoplasm contains a MYC::IGH translocation.

Mechanistic clue: An active immunoglobulin regulatory locus.

Potential origin: An AID-associated DNA break and abnormal joining.

Biologic consequence: Inappropriate proto-oncogene activation.



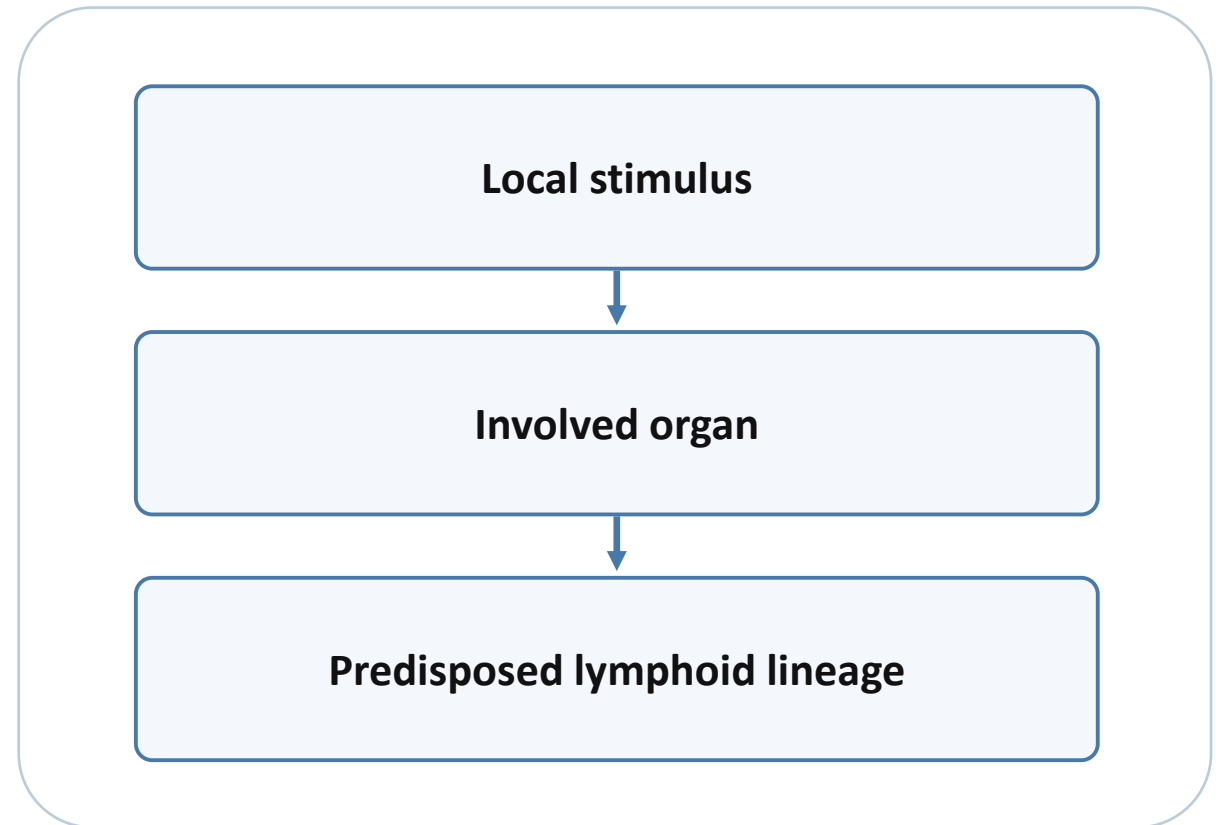
Case reasoning: Organ-specific lymphoma risk

A patient with longstanding localized immune stimulation develops lymphoma at that site.

Consider the local etiologic stimulus and the organ involved.

Identify whether the associated lineage is B cell or T cell.

Contrast this localized causal setting with systemic HIV-related risk.



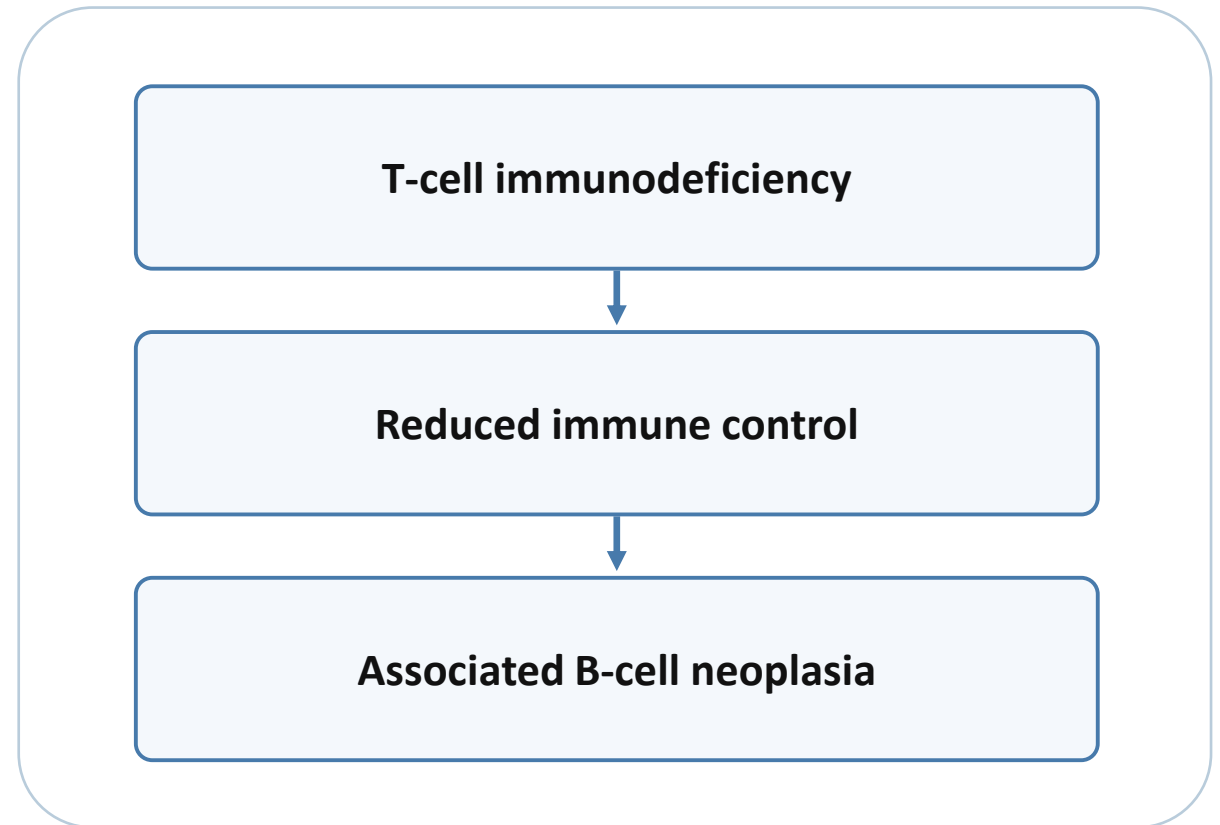
Case reasoning: Immune status changes viral risk

A person with advanced HIV develops a B-cell lymphoma.

Severe T-cell immunodeficiency is a major pathogenic context.

EBV and HHV8/KSHV associations should be considered where relevant.

A viral association alone does not establish a complete tumor classification.



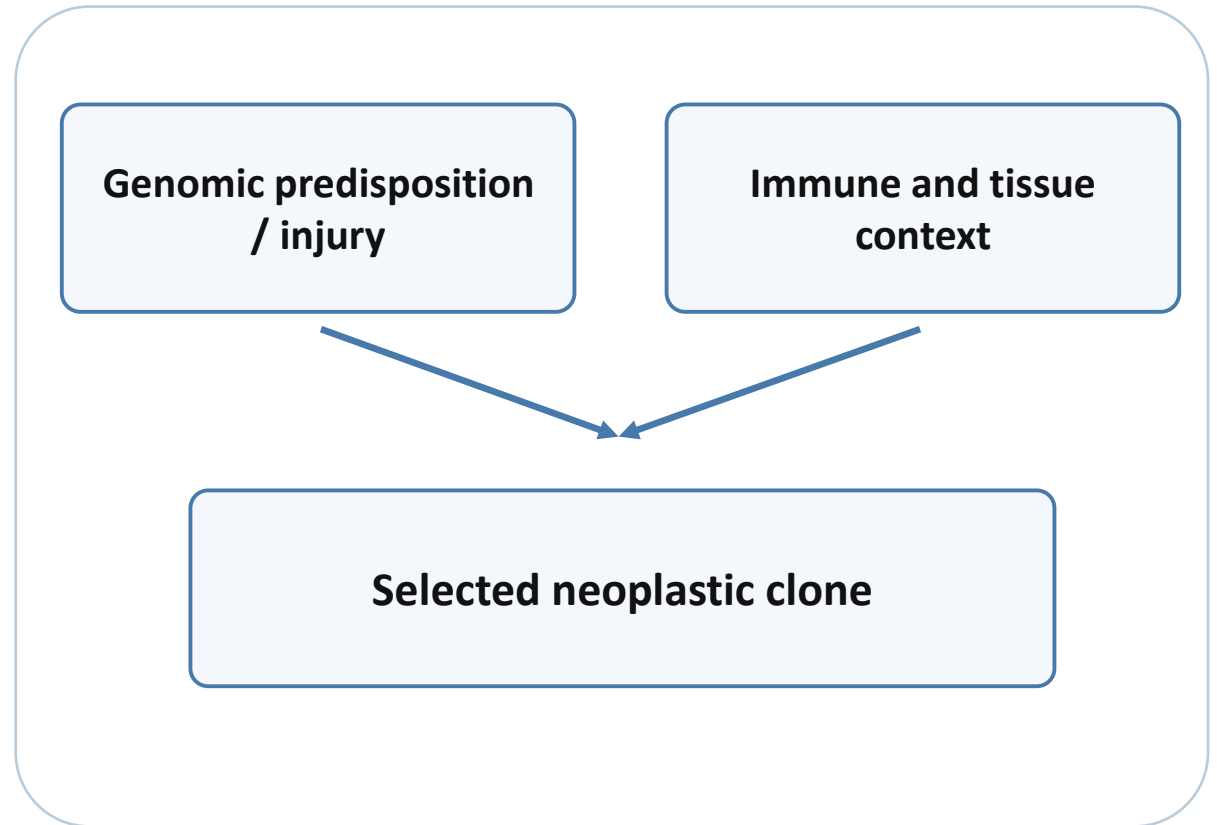
Integrated map of white-cell oncogenesis

Different etiologic factors converge on selected clones with altered growth, cell fate, or survival.

Inherited factors and external exposures
modify probability of mutations.

Physiologic immune-receptor editing supplies
lymphocyte-specific risks.

The molecular lesion and tissue context
together shape the disease phenotype.



Core distinctions to retain

A useful explanation of any hematolymphoid neoplasm specifies both the lesion and its context.

Differentiate growth, self-renewal, maturation arrest, and apoptosis resistance.

Distinguish AID-based errors from V(D)J recombination errors.

Separate localized inflammation from systemic HIV-related immune dysregulation.

Recognize inherited, viral, treatment-related, and smoking-associated contributions.

What changed?

Where / when did it change?

What advantage resulted?

Primary reading and source boundaries

Primary text

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026). Chapter 13, “Diseases of White Blood Cells, Lymph Nodes, Spleen, and Thymus,” pp. 536–538.

Scope

General etiologic and pathogenetic mechanisms. Disease-specific diagnostic criteria, molecular subtypes, treatment algorithms, and original histology figures are not reproduced here.