

Tumor Antigens

Recognition, antigen presentation and antitumor immunity

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Learning objectives

- Classify tumor antigens as mutation-derived, altered self, or virus-derived.
- Explain why peptide–MHC class I display is required for antigen-specific CD8⁺ recognition.
- Trace dendritic-cell priming and cytotoxic T-cell engagement of tumors.
- Identify why antigen presence may not translate into an effective antitumor response.

Immunosurveillance creates an antigen-recognition problem

- The immune system can recognize some malignant cells as foreign.
- Yet clinically evident tumors often develop in immunocompetent hosts.
- Tumors that persist must avoid detection or suppress an effective response.

Tumor antigens explain what the immune system might recognize.

Independent observations support cancer immunosurveillance

- Tumor-specific T cells and tumor-reactive antibodies are detectable in patients.
- The character of immune infiltrates can correlate with tumor outcome.
- Certain cancers occur more often in immunodeficient individuals.
- Restoring latent T-cell activity can produce tumor regression.

The evidence is convergent, rather than a single definitive experiment.

What qualifies as a tumor antigen?

- A tumor antigen is a molecule in a neoplasm that can be recognized by the immune system.
- Some are truly altered or foreign proteins; Others are normal proteins in an unusual context.
- Expression of a molecule does not by itself prove that it elicits protective immunity.

Antigen expression and productive immune recognition are distinct.

Self recognition differs from tumor-directed recognition

Normal self display

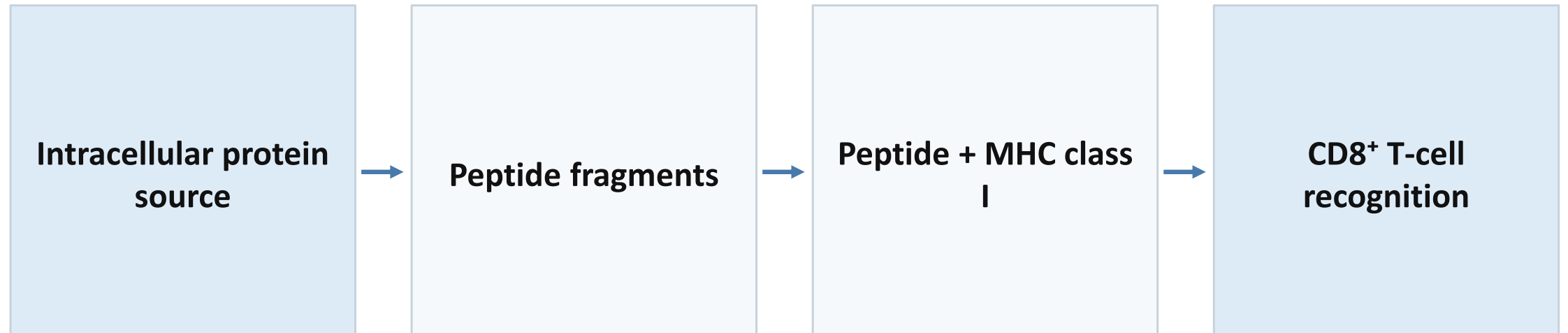
- Normal cells present their own peptides on MHC class I.
- Recognition of healthy self ordinarily does not elicit a destructive CTL response.

Tumor-associated display

- Cancer cells can present variant, excess, ectopic, or viral proteins.
- Some of these peptide–MHC complexes are targets for tumor-specific CTLs.

The biological context and specificity of a peptide matter.

Cytotoxic T cells see processed protein, not naked DNA



The antigenic target at the cell surface is a peptide–MHC complex.

Why CD8⁺ cytotoxic T cells dominate this section

- Many relevant tumor antigens derive from proteins synthesized within tumor cells.
- Endogenous peptides can be displayed by MHC class I.
- CD8⁺ cytotoxic T lymphocytes (CTLs) recognize suitable peptide–MHC-I targets.
- CTL killing is the principal antitumor effector mechanism emphasized by Robbins.

Antigen origin helps explain effector-cell selection.

Three broad molecular sources of tumor antigens

Mutated tumor proteins

**Overexpressed /
aberrantly expressed self**

Oncogenic viral proteins

Alternative sources; The categories are not sequential stages.

This is a classification by origin, not a ranking of clinical usefulness.

Tumor antigen classes: Compare the underlying changes

Source	What changed?	Robbins example
Mutant self	Protein sequence differs	Driver or passenger mutation
Altered self	Amount or tissue context differs	Tyrosinase; MAGE
Viral	Protein comes from a virus	HPV E6/E7; EBV EBNA

Mutated, deregulated, and viral expression produce different antigenic contexts.

Three constraints separate expression from an effective target

- The tumor must synthesize an antigenic protein or peptide source.
- A relevant peptide must be displayed in the context of the individual's MHC molecules.
- An antigen-specific T-cell response must be activated and reach the tumor.

Failure at any link can disconnect antigenicity from tumor killing.

Tumor neoantigens arise from altered protein sequences

- Somatic mutations can generate protein variants not encountered by the host immune system.
- Some mutant epitopes are perceived as non-self.
- Both oncogenic driver mutations and biologically neutral passenger mutations may contribute.

Immunogenicity depends on the altered epitope, not necessarily the mutation's growth effect.

Driver mutation to potential CTL target



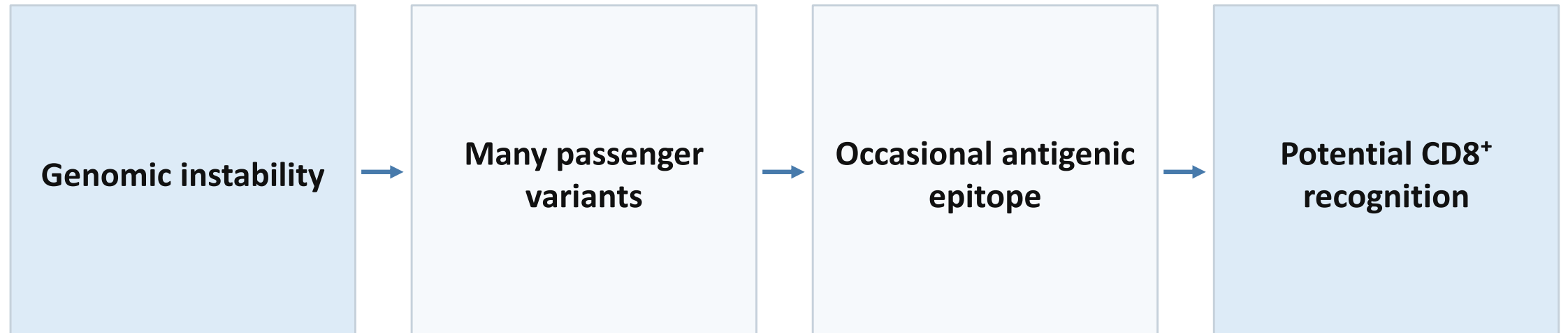
A growth-promoting mutation can also change the antigenic sequence.

Driver mutations and tumor antigens are different concepts

- A driver mutation contributes to malignant transformation or fitness.
- Its protein product may include a sequence recognized as foreign.
- Oncogenic function alone does not establish MHC binding or T-cell recognition.

Biological driver status does not equal antigenic potency.

Passenger mutations can become immunologically important



A neutral mutation for tumor fitness may still matter to the immune system.

Passenger mutations are not merely background noise

- Passenger alterations are not required for the transformed phenotype.
- They may change amino acid sequences without conferring a growth advantage.
- By chance, an altered peptide may be presented by host MHC and become antigenic.

“Passenger” describes cancer biology; It does not rule out immune relevance.

Driver versus passenger mutations

Driver

- Selected because they support malignant behavior.
- May produce a protein variant recognized as non-self.

Passenger

- Do not improve tumor fitness.
- May incidentally generate antigenic sequence variants.

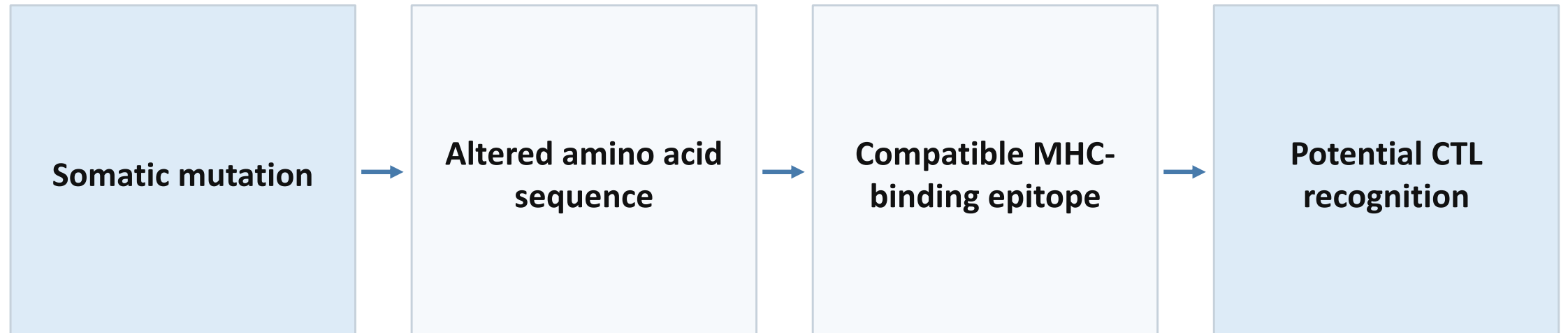
Either origin can yield a neoantigen if antigen-presentation conditions are met.

Genomic instability increases opportunities for novel epitopes

- Cancer genomes frequently accumulate multiple passenger mutations.
- More sequence variants create more opportunities for potentially novel peptides.
- Only a subset will satisfy the requirements for antigen display and T-cell recognition.

Mutation abundance expands possibilities; It does not certify targets.

MHC binding is a critical neoantigen filter



The source explicitly conditions immunogenicity on epitope–MHC compatibility.

HLA diversity makes neoantigens host-dependent

- Robbins specifies that a mutant epitope must bind the MHC molecules of the individual.
- A mutation present in a tumor is not automatically antigenic in every patient.
- The antigenic repertoire therefore depends partly on host antigen-presentation context.

Variant detection and peptide presentation are separate inferences.

Mutation found versus antigen actually presented

DNA sequencing identifies

- A somatic sequence change.
- The resulting candidate protein variant.

Immune recognition requires

- A peptide compatible with MHC display.
- A T-cell population able to recognize the complex.

Genomics is informative, but not equivalent to functional antigen validation.

Tumor mutation burden and CD8⁺ responses

- A positive association between total mutational load and CTL response strength.
- Mutational load is inferred from sequencing tumor DNA.
- The relationship is a population-level correlation, not a guarantee for any single tumor.

Use mutational burden as a probabilistic signal, not a direct T-cell assay.

Why higher mutational burden may favor immunotherapy

- A larger repertoire of variants may increase the chance of immunogenic epitopes.
- Higher mutation load with greater effectiveness of immune-modulating treatments.
- Actual tumor response also depends on presentation and immune-evasion mechanisms.

Antigen availability is necessary in many responses, but not sufficient.

Neoantigen inference: What each observation supports

Observation	Supports	Does not prove
Driver mutation	Variant protein is possible	Tumor-specific CTL response
Passenger mutation	Novel peptide is possible	Cancer-driving function
High mutation load	Broader candidate repertoire	Uniform treatment response

Avoid translating molecular observations into stronger conclusions than the data permit.

Case: Many mutations, no predicted immune response

HYPOTHETICAL TEACHING SCENARIO

A hypothetical tumor contains numerous coding mutations, but candidate mutant peptides are poorly compatible with the patient's MHC-I molecules.

Does a high mutation count alone ensure strong CD8⁺ recognition?

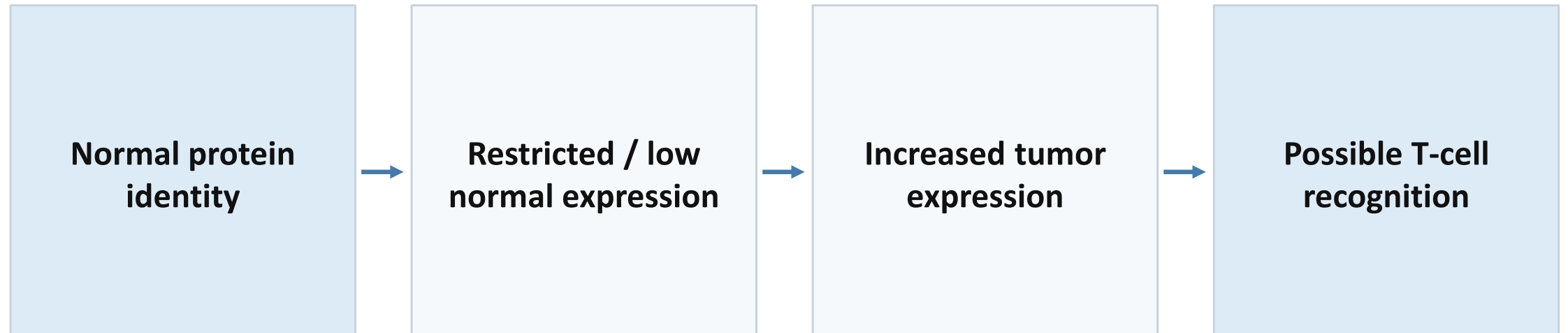
The MHC-binding step is a logical bottleneck.

Normal self proteins can become tumor antigens

- The amino acid sequence need not be mutated for a protein to be immunogenic.
- An abnormally high amount or expression in an unusual cellular setting may matter.
- Both overexpressed and aberrantly expressed self proteins.

Altered abundance and tissue distribution are distinct from neoantigen sequence change.

An overexpressed normal protein can be antigenic



The normal sequence can become more conspicuous in a malignant context.

Tyrosinase is the textbook example of overexpression

- Tyrosinase is an enzyme involved in melanin biosynthesis.
- Normal melanocytes and melanomas express this protein.
- The textbook uses tyrosinase to illustrate a normal self protein acting as a tumor antigen.

Tyrosinase is not a melanoma-specific mutation product.

Tyrosinase in normal melanocytes and melanoma

Normal melanocyte

- A restricted normal-cell population produces tyrosinase.
- Low or limited expression may fail to induce effective tolerance.

Melanoma cell

- Expresses the same lineage-associated protein.
- A tumor-directed immune response may recognize it.

Lineage restriction is different from absolute tumor specificity.

The tyrosinase tolerance explanation is provisional

- The textbook proposes that normally limited expression may not establish tolerance.
- Thus T-cell responsiveness to a normal self protein is biologically possible.
- This as a probable explanation, not a proven universal rule.

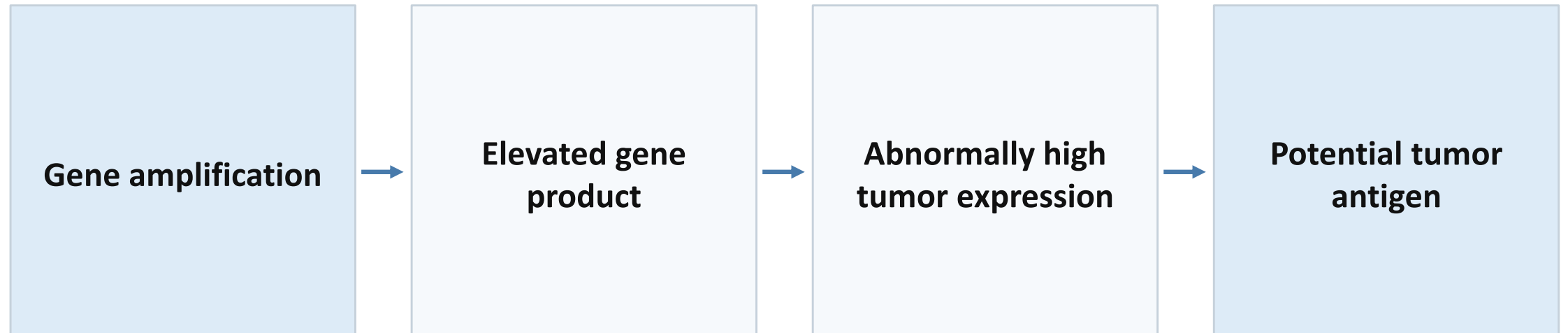
Distinguish mechanistic interpretation from established demonstration.

Aberrant expression creates another altered-self class

- Some cancer cells express proteins at levels far above those in most adult tissues.
- The genes may be normally silenced in adult somatic tissues.
- Tumors can reactivate their expression without changing the encoded sequence.

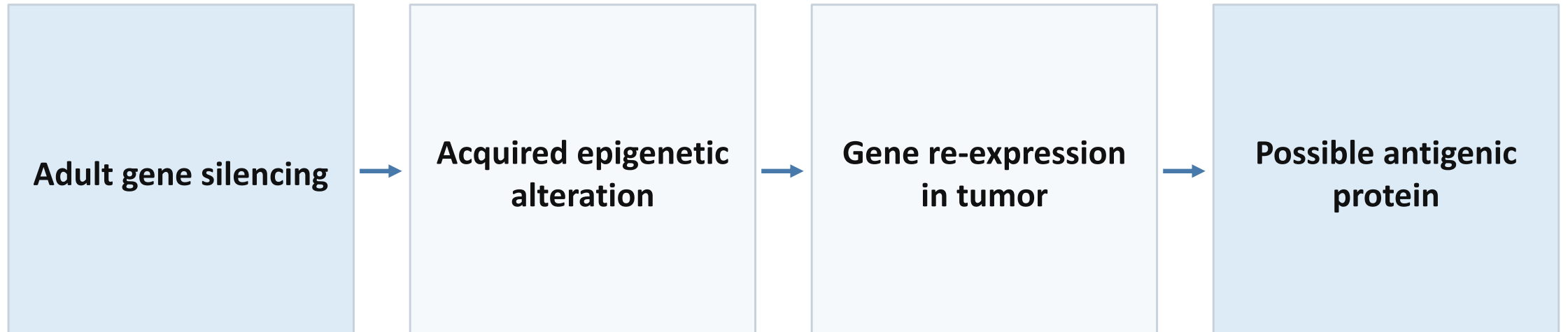
An epigenetically reactivated protein can be antigenic without mutation.

Gene amplification increases a protein's abundance



An increased amount is one route to aberrant antigen expression.

Epigenetic alteration unmask normally silent genes



The sequence can be normal while the expression program is abnormal.

Protein overexpression versus ectopic re-expression

Overexpression

- Normal protein is already produced in some healthy cells.
- Tumor production is conspicuously increased.

Aberrant re-expression

- Expression is usually limited or silenced in adult tissues.
- Malignant cells reactivate the gene.

Both alter antigenic context; Neither necessarily creates a mutant peptide.

Cancer–testis antigens are a distinctive altered-self group

- These proteins are normally associated with testicular germ cells.
- A subset of cancers aberrantly express them in other tissues.
- Their restricted normal distribution makes them unusually tumor-associated targets.

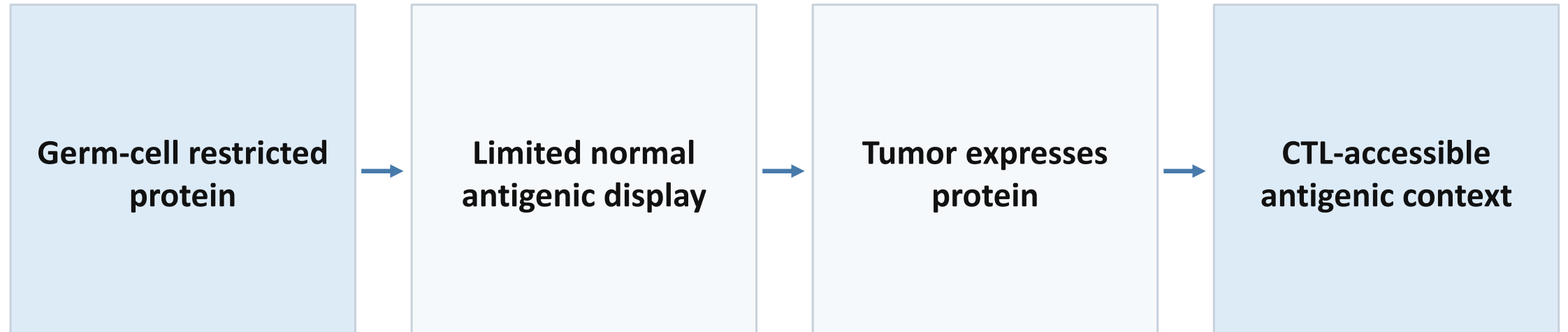
Cancer–testis antigens are defined by their pattern of expression.

Why the testis context limits immune presentation

- Sperm do not express MHC class I antigens.
- A germ-cell protein is therefore not displayed on sperm in an MHC-I antigenic form.
- The book describes cancer–testis proteins as functionally tumor-specific in this context.

This is a presentation-context argument, not a claim of absolutely unique expression.

Cancer–testis antigen recognition: A context switch



Tissue expression and MHC presentation together shape immune visibility.

MAGE is the prototype cancer–testis antigen family

- MAGE refers to the melanoma antigen gene family.
- It was first identified in the context of melanoma.
- The family exemplifies tumor expression of proteins normally limited to germ cells.

MAGE demonstrates the cancer–testis class—not a mutation-defined neoantigen.

MAGE expression extends beyond melanoma

- MAGE antigens occur in several different tumor types.
- Their name records their discovery context, not exclusive disease specificity.
- A positive MAGE-associated signal should not be interpreted as melanoma identification by itself.

The name of an antigen family does not define a cancer diagnosis.

Altered-self tumor antigens: Compare mechanisms

Subtype	Source mechanism	Example / implication
Overexpressed	Normal lineage-associated protein in tumor	Tyrosinase
Amplification-linked	Higher gene dosage and protein abundance	Aberrant expression mechanism
Epigenetically reactivated	Normally silent adult gene expressed	Cancer–testis proteins; MAGE

Different molecular processes can converge on abnormal protein display.

Case: Tyrosinase is present in melanoma

HYPOTHETICAL TEACHING SCENARIO

A hypothetical melanoma expresses tyrosinase. The same protein is also made by normal melanocytes.

Does this observation classify tyrosinase as a mutation-derived neoantigen?

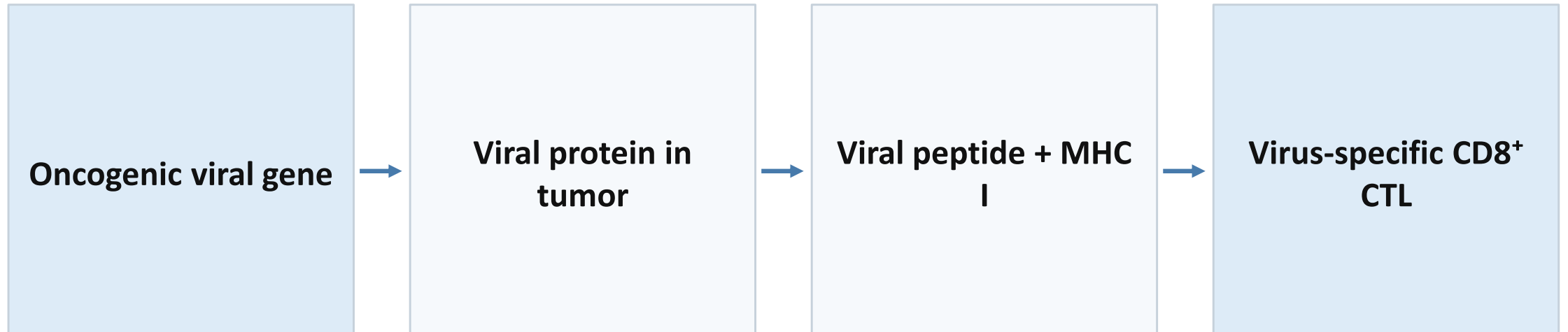
Classify tumor antigens according to origin and expression, not merely tumor association.

Oncogenic viruses supply genuinely foreign proteins

- Some malignancies arise in association with active or latent viral infection.
- Viral genomes encode proteins that are immunologically foreign to the host.
- These viral products can serve as tumor antigens recognized by CTLs.

The antigen is virus-derived, even though the target is a malignant host cell.

A virus-associated tumor can display foreign peptides



Intracellular viral antigen synthesis makes MHC-I recognition relevant.

Human papillomavirus antigens: E6 and E7

- The HPV E6 and E7 proteins as examples of viral tumor antigens.
- The figure associates them with cervical carcinoma.
- A virus-specific CTL can target tumor cells presenting viral protein fragments.

E6/E7 are foreign protein targets, not altered versions of host self proteins.

Epstein–Barr virus antigens: EBNA proteins

- Epstein–Barr virus produces nuclear antigens (EBNA proteins).
- The textbook figure associates EBNA expression with EBV-induced lymphoma.
- Viral antigen expression provides a route to CD8⁺ recognition of infected tumor cells.

Viral latency does not necessarily remove antigenic proteins from all tumors.

HPV and EBV: Two examples of viral tumor antigens

Human papillomavirus

- Example tumor: Cervical carcinoma.
- Example immune targets: E6 and E7 proteins.

Epstein–Barr virus

- Example tumor: EBV-induced lymphoma.
- Example immune targets: EBNA proteins.

The precise antigen depends on the virus and tumor context.

Active versus latent infection is relevant to tumor antigens

- The chapter includes cancers associated with either active or latent viral infection.
- Persistent viral gene expression can provide protein targets for immune surveillance.
- The presence of a viral genome alone does not specify which antigen is displayed.

Immune targeting must be linked to expressed viral proteins.

T-cell immunity constrains virus-associated neoplasia

- CTLs recognize viral antigens displayed by virus-infected tumor cells.
- The textbook assigns CTLs an important surveillance role in virus-induced tumors.
- Loss of effective T-cell immunity can permit tumors associated with oncogenic infection.

A clinical immunodeficiency pattern is consistent with cellular surveillance.

Immunodeficiency reinforces the viral surveillance model

- Certain virally induced cancers are more frequent with inherited or acquired T-cell deficiency.
- Robbins particularly highlights EBV- and HPV-associated tumors.
- The association illustrates the protective role of cellular immunity.

This is evidence of surveillance, not proof that every infected cell becomes cancerous.

Neoantigens versus altered self versus viral antigens

Class	Protein origin	Why potentially seen as foreign
Mutant	Host gene with altered sequence	Novel peptide sequence
Altered self	Normal host gene	Abnormal amount or tissue context
Virus-derived	Foreign viral gene	Foreign protein sequence

The identity of the protein source predicts how tumor antigenicity arises.

Case: A viral cancer in profound T-cell deficiency

HYPOTHETICAL TEACHING SCENARIO

In a hypothetical teaching scenario, an immunodeficient patient develops an EBV-associated tumor.

Which arm of immunity is central to detecting tumor cells displaying EBV antigens?

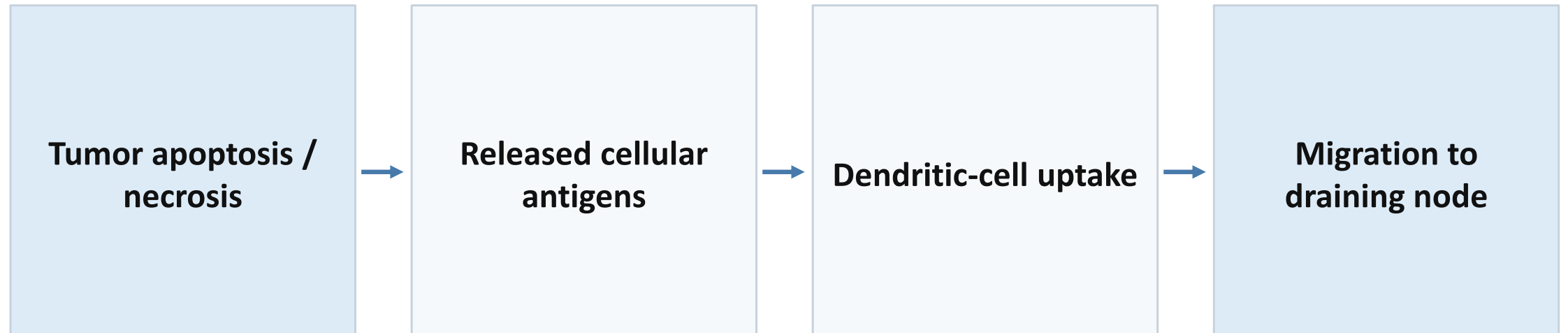
Recognize the biological implication without inventing patient-specific prognosis.

Antigen expression is upstream of CTL priming

- Tumor antigens must become accessible to host antigen-presenting cells for effective priming.
- Dendritic cells can acquire tumor cells or released tumor antigens.
- Recognition by a naïve or responding CD8⁺ T cell occurs in a host APC context.

The initiation site can differ from the tumor-cell killing site.

Cell death provides material for dendritic-cell capture



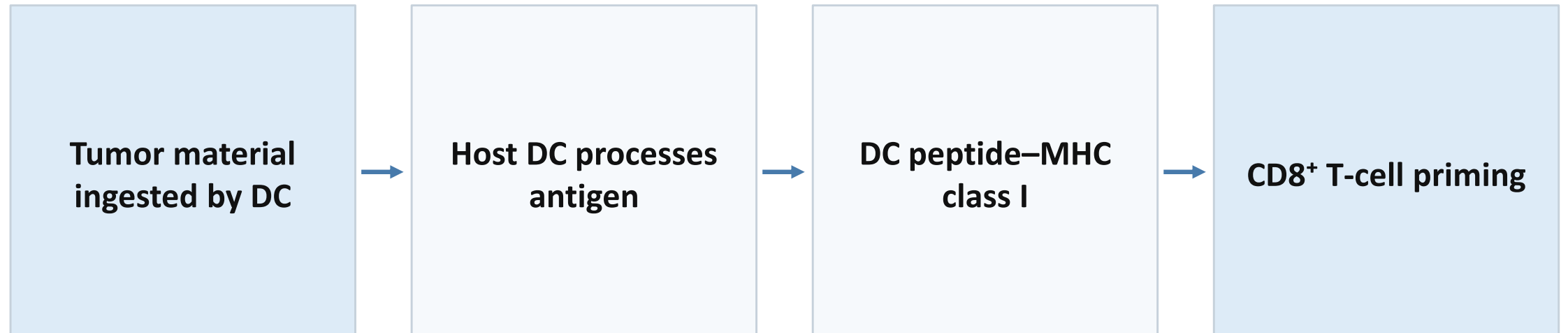
The antigen-processing pathway links tumor turnover to immune initiation.

Dendritic cells are the key initiating APCs

- Dendritic cells in the tumor environment ingest tumor cells or released antigens.
- They migrate from the tumor region to draining lymph nodes.
- There they present tumor-derived peptides to antigen-specific CD8⁺ cells.

Tumor-specific CTLs are initially activated by host APCs.

Cross-presentation primes antigen-specific CD8⁺ T cells



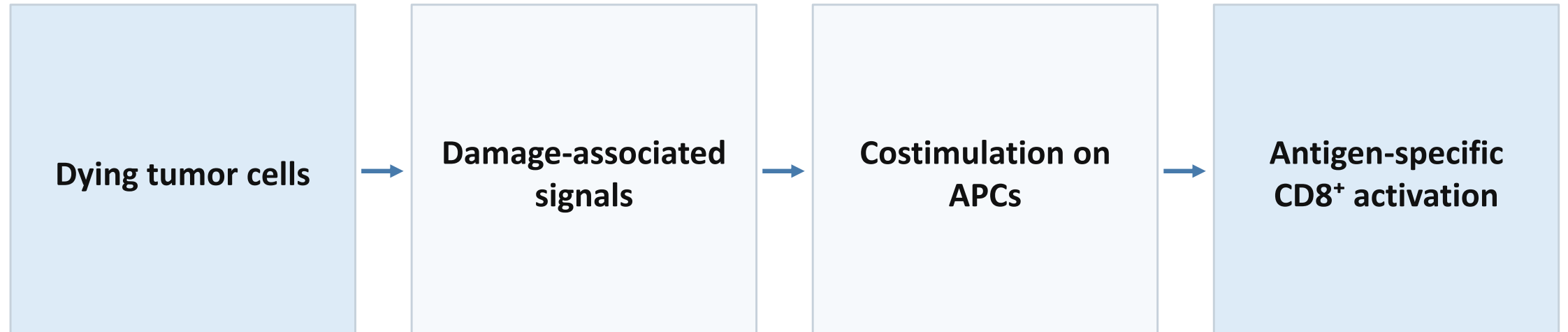
An APC can display acquired tumor antigen on class I MHC.

Costimulation turns recognition into T-cell activation

- Tumor peptide recognition is not the only requirement for priming.
- Host APCs upregulate costimulatory molecules during activation.
- Robbins suggests tumor cell damage-associated signals may drive this change.

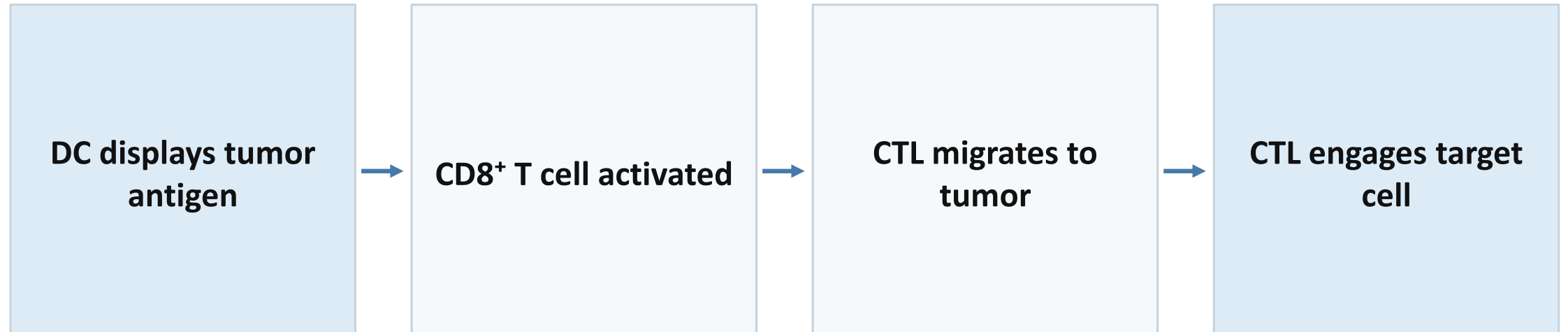
Antigen display and costimulation cooperate during CTL induction.

Tumor damage signals facilitate productive priming



“Danger signals” are a proposed route to APC maturation.

Primed CTLs return from lymph nodes to the tumor



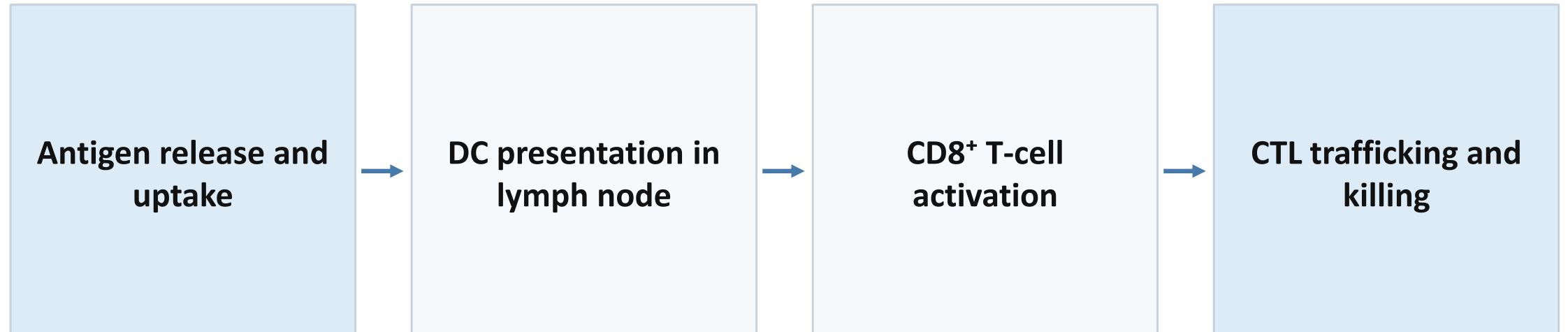
The lymph node is a priming site; The tumor is an effector site.

Activated CTLs can kill tumor cells directly

- Activated tumor-specific CTLs recognize matching antigen on tumor MHC I.
- They can directly kill antigen-bearing malignant cells.
- That a CTL can kill cells serially.

Once activated, cytotoxicity does not depend on an APC being present at each kill.

Full antitumor CTL sequence



An antigen becomes therapeutically relevant only within a functioning immune circuit.

Antibodies against tumor antigens are detectable

- Patients with cancer may have antibodies that bind their tumors.
- This demonstrates that some cancer antigens are recognized by humoral immunity.
- Robbins finds limited evidence for protective roles of these antibodies in ordinary physiology.

Detectable immune reactivity is not automatically effective tumor control.

CD4⁺ effector T cells provide additional context

- Antitumor CD4⁺ T-cell responses have been documented.
- In certain cancers, more intratumoral Th1-type cells correlate with better prognosis.
- Robbins gives colorectal carcinoma as an example.

CTL predominance does not imply that all other immune effectors are irrelevant.

CD8⁺ CTLs and NK cells respond differently to MHC class I

CD8⁺ CTLs

- Recognize peptides displayed in MHC-I context.
- Can lose recognition when tumor MHC-I expression falls.

NK cells

- May lyse tumor cells with reduced MHC class I.
- Do not require prior antigen-specific sensitization.

Changes that evade one effector pathway may alter susceptibility to another.

NK cells: Experimental capacity and remaining uncertainty

- After IL-2 and IL-15 activation, NK cells can kill many human tumor cells experimentally.
- They may target tumors that are poorly immunogenic for T cells after MHC-I loss.
- Their role against spontaneous human tumors is not fully established.

Do not overstate experimental lysis as proven natural protection.

Macrophages can acquire antitumor cytotoxicity

- Activated macrophages show tumor-cell killing in experimental systems.
- Interferon- γ from T cells and NK cells is a strong macrophage activator.
- Potential killing mechanisms include reactive oxygen species.

Macrophage antitumor function is presented as a possible ancillary mechanism.

Conventional CTLs versus CAR-T cells

Conventional CTL

- T-cell recognition requires suitable peptide–MHC I.
- Tumor-specificity can arise from mutated or viral peptide epitopes.

CAR-T cell

- Engineered receptor recognizes an accessible surface antigen.
- B-lineage targets can be present on malignant and normal B cells.

The receptor architecture determines which antigen form can be recognized.

CAR-T illustrates the risk of shared-lineage antigens

- Engineered CAR-T cells with potent activity against B-cell tumors.
- Because target antigens also occur on normal B cells, normal B cells may be eliminated.
- Inflammatory cytokine release can cause severe morbidity and occasional fatal toxicity.

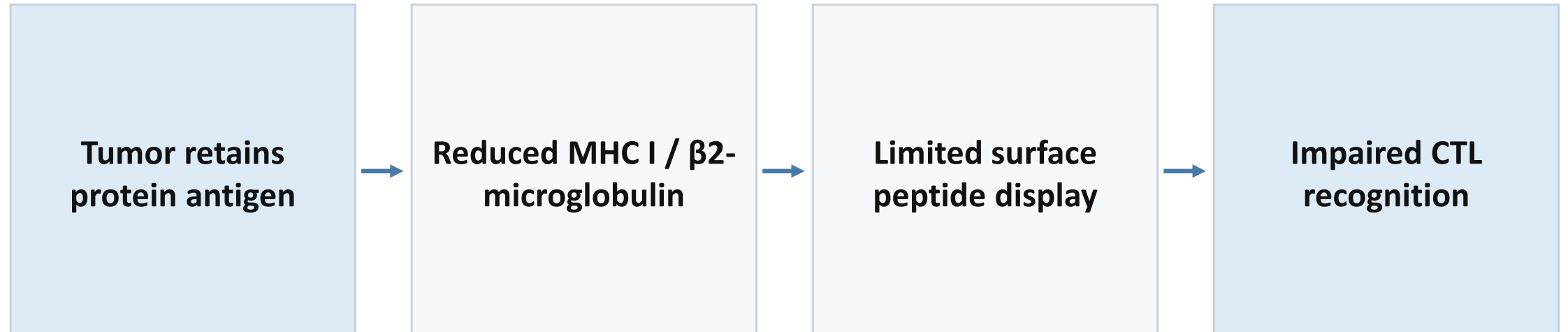
Tumor-associated does not necessarily mean tumor-exclusive.

Antigen display can be lost despite abundant tumor protein

- MHC-I reduction prevents effective display of intracellular antigenic peptides.
- Without peptide–MHC-I, a matched CTL may fail to recognize the tumor.
- The adjacent immune-evasion section names β 2-microglobulin defects as an important route.

An antigen can be genetically present but functionally invisible to CTLs.

A tumor can evade CTLs at the presentation step



Altered antigen presentation is distinct from loss of antigen expression.

Immune checkpoints can inhibit an antigen-specific response

- Tumors may upregulate pathways that negatively regulate T-cell activation.
- Inhibitory CTLA-4 and PD-1 pathways in the adjacent section.
- Thus antigen recognition may coexist with suppression of effector T-cell function.

Recognition alone is not equivalent to successful tumor eradication.

Antigenic visibility and immune permission are separate

Visibility

- The tumor expresses and presents a suitable antigen.
- A specific T cell can recognize the peptide–MHC complex.

Permission to respond

- Costimulatory signals permit initial activation.
- Inhibitory checkpoint pathways can restrain effector cells.

Presentation, priming and checkpoint inhibition are different control points.

Neoantigen load is associated with checkpoint response

- Greater neoantigen/mutation burden to responsiveness to checkpoint blockade.
- Mismatch repair–deficient cancers are noted as having high mutational loads.
- The chapter emphasizes that response still varies substantially between tumors.

A statistical predictor is not an absolute molecular determinant.

Immune infiltrates provide a readout of host engagement

- T-cell infiltration reflects that lymphocytes have reached the tumor environment.
- Better outcomes in some cancers with stronger immune infiltrates.
- An immunologically active tumor may be more responsive to certain immunomodulatory therapies.

Antigen expression and the observed tissue response provide complementary information.

Case: Antigen retained but MHC I lost

HYPOTHETICAL TEACHING SCENARIO

A hypothetical carcinoma continues to synthesize a known mutant protein but loses normal MHC class I expression.

Why might a previously reactive peptide-specific CD8⁺ CTL fail to kill it?

Do not equate persistence of a protein with persistence of CTL visibility.

Case: Shared lineage antigen on normal cells

HYPOTHETICAL TEACHING SCENARIO

An engineered CAR-T product recognizes a surface protein shared by malignant and normal B-lineage cells.

Which toxicity follows from target distribution, even if receptor recognition is specific?

Molecular specificity does not guarantee exclusive tumor-cell selectivity.

Choose the correct antigen classification

Finding	Correct class	Reason
Mutant passenger epitope	Neoantigen	Changed peptide sequence
Melanoma tyrosinase	Overexpressed self	Normal melanocyte protein
Tumor MAGE expression	Cancer–testis / altered self	Restricted normal expression
HPV E7 in carcinoma	Viral antigen	Foreign viral protein

Classify by molecular origin and expression context.

Integrated mechanism: Four conditions for CTL killing

- A potentially immunogenic tumor protein must be synthesized.
- A matching peptide must appear in MHC class I on tumor cells.
- Host APCs must initiate an effective antigen-specific CD8⁺ response.
- Activated CTLs must access the tumor and retain effector function.

The sequence explains both tumor immunity and principal routes of failure.

Final synthesis: What to remember about tumor antigens

- Mutant driver/passenger proteins, altered self proteins and viral proteins supply antigens.
- MHC-I display is central to CD8⁺ CTL recognition of intracellular tumor proteins.
- Dendritic-cell cross-presentation and costimulation support T-cell priming.
- Antigen burden can correlate with responses, while immune evasion limits predictability.

Use origin → display → priming → effector function as the reasoning framework.

Reference and further reading

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026). Chapter 7, Neoplasia.

Tumor Antigens and Antitumor Effector Mechanisms.

Conceptual diagrams are original, editable instructional schematics based on the supplied textbook excerpt.