

Mechanisms of Immune Evasion by Cancers

Tumor recognition • inhibitory pathways • suppressive microenvironment

Antigen display

Immune checkpoints

Tumor microenvironment

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Learning objectives

- Trace the normal CD8+ cytotoxic T-cell response to tumor antigens.
- Distinguish antigen-presentation failure, checkpoint inhibition, and microenvironmental suppression.
- Explain the rationale, response patterns, and adverse effects of checkpoint blockade.

Immune evasion enables growth in competent hosts

- Many malignant tumors arise without an overt systemic immunodeficiency.
- A growing tumor can avoid recognition or resist antitumor effector mechanisms.
- Evasion mechanisms are multiple and are not mutually exclusive.

Potential T-cell response

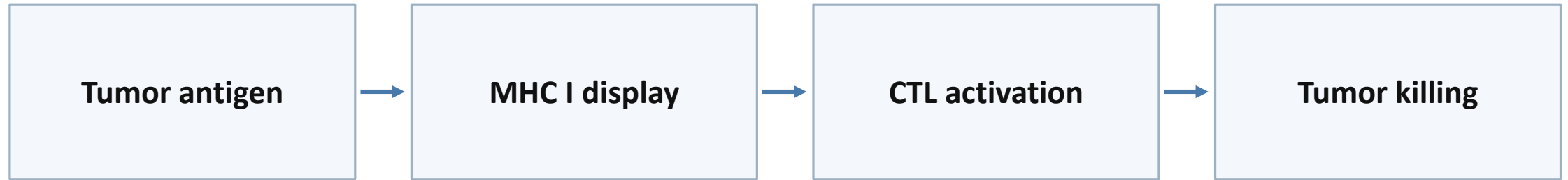


Tumor-acquired escape



Continued tumor growth

Effective surveillance requires a complete recognition chain



- Antigen production, MHC class I display, T-cell priming, and effector activity are all required.
- Disruption at any stage may permit a tumor clone to survive.

Recognizable tumor antigens have several origins

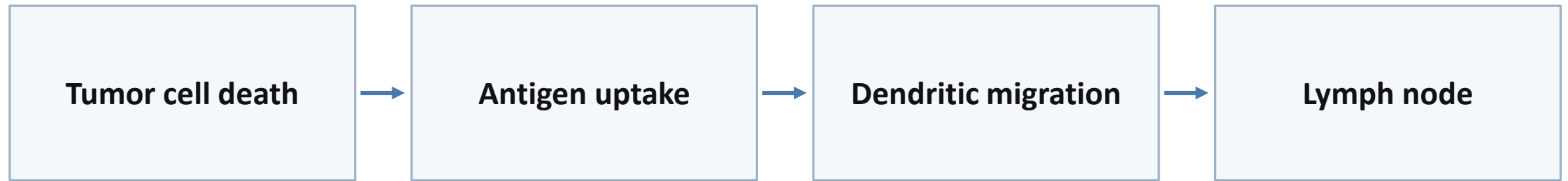
Mutated proteins

Aberrant cellular proteins

Viral proteins

- Mutated driver or passenger gene products can create neoantigens.
- Overexpressed or aberrantly expressed proteins can become targets.
- Oncogenic viral proteins provide foreign antigens in some cancers.

Dendritic cells link tumor death to adaptive immunity



- Dendritic cells ingest tumor material released during tumor cell death.
- They migrate to draining lymph nodes and present antigens to T cells.

CD8+ T cells require antigen recognition and costimulation

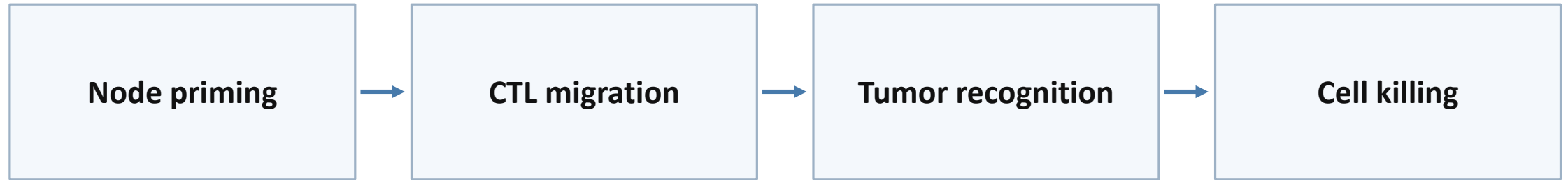
Antigen-specific signal

- Signal 1: T-cell receptor recognition of peptide–MHC class I.
- Tumor-derived danger signals may promote APC costimulatory function.

Costimulatory signal

- Costimulatory molecules on antigen-presenting cells support activation.

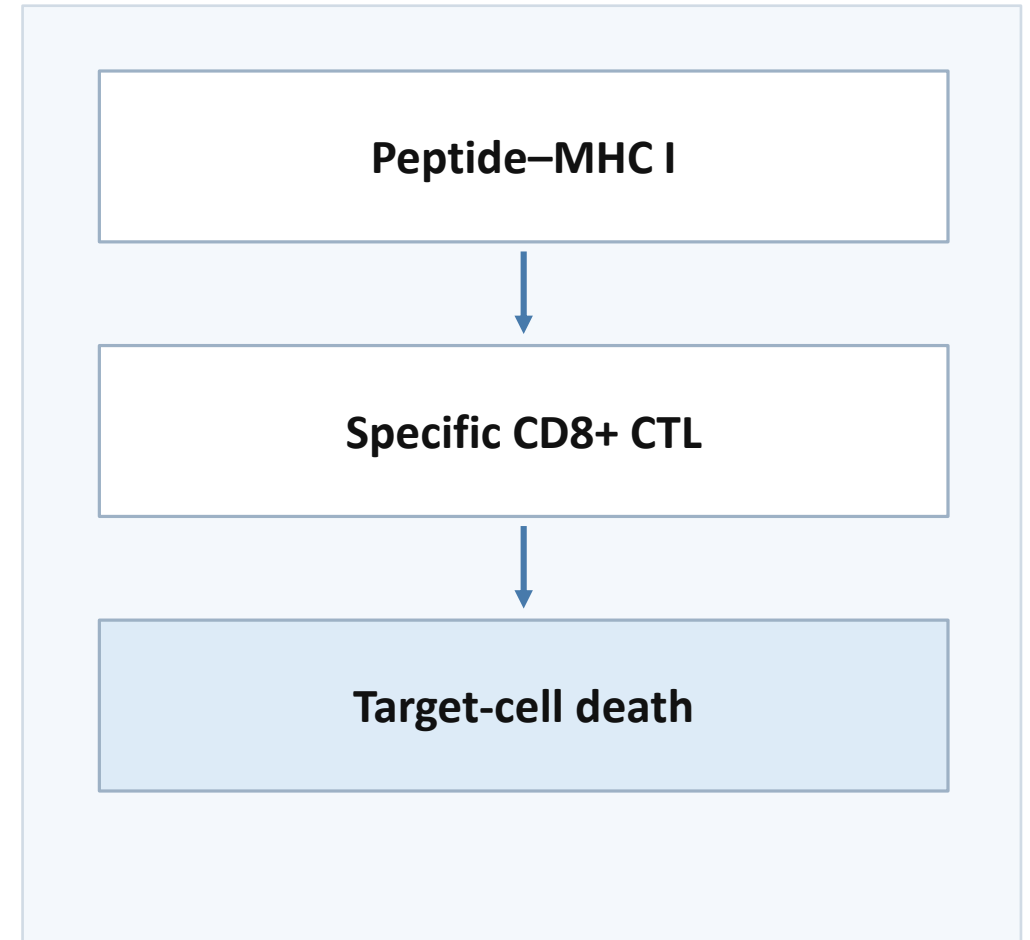
Activated CTLs travel back to the tumor



- Primed tumor-specific CTLs leave lymph nodes and enter tumor tissue.
- Antigen recognition at the tumor permits direct cytotoxic killing.

CD8+ CTLs are the dominant antitumor effectors

- Most relevant tumor antigens are displayed by class I MHC molecules.
- CTLs can directly and serially kill antigen-bearing tumor cells.
- Evasion may interrupt either recognition or effector-cell activity.



NK activity highlights a limitation of MHC loss

CD8+ CTL / needs peptide–MHC I

- Loss of MHC I impairs conventional CD8+ CTL recognition.
- The importance of NK cells against spontaneous human tumors remains less firmly established.

NK cell / may kill MHC I-low target

- Activated NK cells can kill some MHC I-low tumor targets without prior sensitization.

Five complementary routes to immune escape

Antigen or MHC loss

Checkpoint engagement

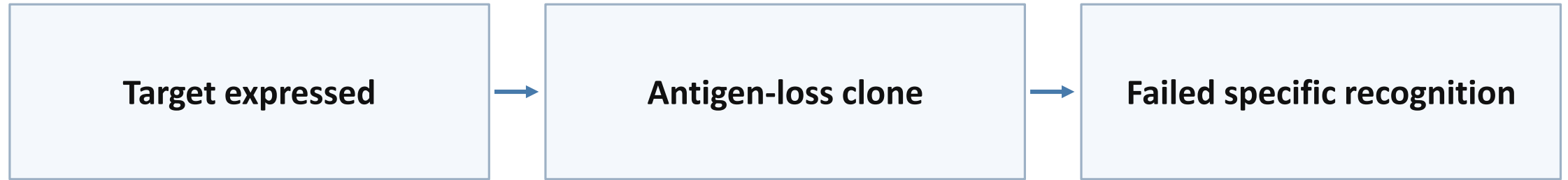
Soluble inhibitors

Tregs and MDSCs

Suppressive stroma

- Antigen loss and defective class I presentation prevent recognition.
- Inhibitory receptors restrain activation of tumor-reactive T cells.
- Soluble mediators, regulatory cells, and suppressive stroma limit immunity.

Antigen-loss variants become invisible to specific CTLs



- A CTL targeting one tumor epitope cannot recognize a clone lacking that antigen.
- Loss of the target does not imply that the entire tumor lacks other antigens.

Escape can occur through failure to produce the antigen

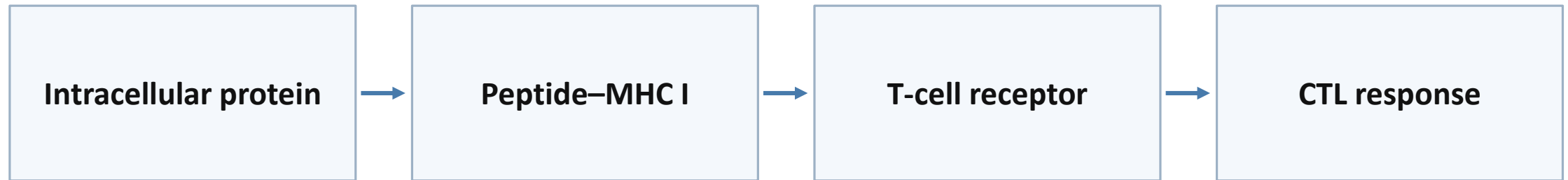
Antigen retained

- Antigen-positive cells remain candidates for cognate T-cell attack.
- The explanatory figure distinguishes antigen loss from MHC loss.

Antigen absent

- Antigen-negative variants cannot engage CTLs specific for that missing epitope.

MHC class I makes cytosolic tumor antigens visible



- Endogenously synthesized tumor proteins furnish peptides for MHC class I display.
- Peptide-MHC I complexes can be recognized by antigen-specific CD8+ CTLs.

Reduced HLA class I expression blocks CD8+ recognition

- Some tumor cells express abnormally low HLA class I levels.
- Failure of cytosolic antigen display allows escape from CTLs even if antigens remain.
- Reduced staining or expression is mechanistically different from absence of antigen.

Tumor antigen present

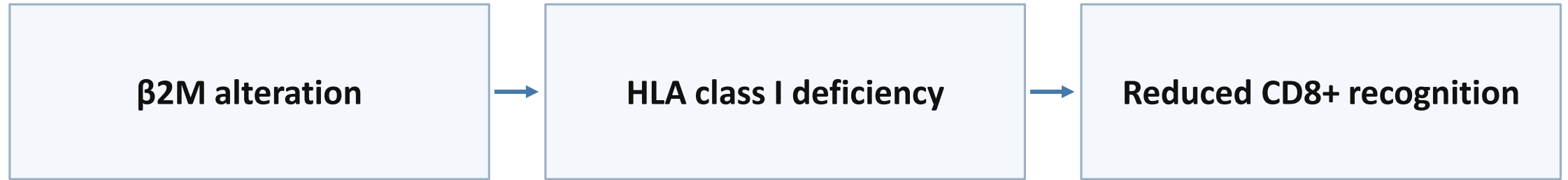


HLA I display reduced



CTL recognition reduced

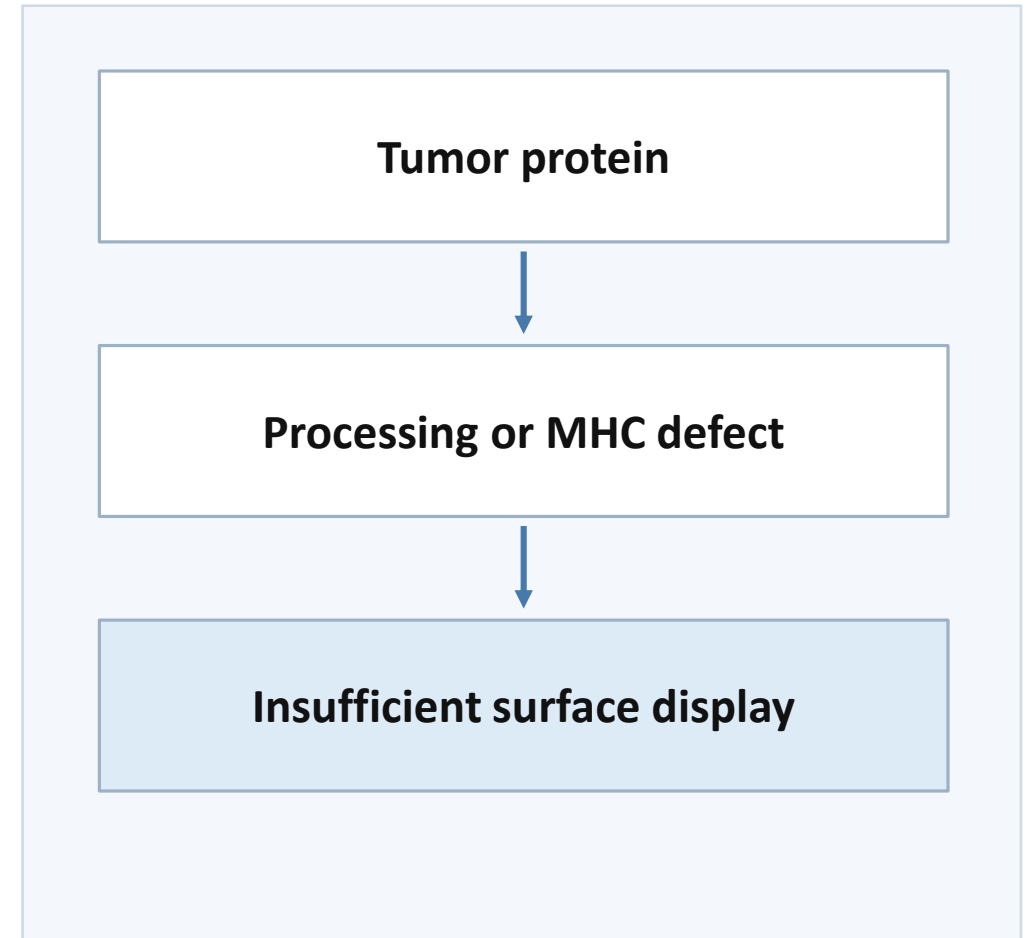
β 2-microglobulin is essential for stable HLA class I



- β 2-microglobulin is the invariant subunit of the HLA class I heterodimer.
- Mutation or silencing of its gene is a prominent mechanism of reduced HLA I expression.
- The result is deficient display of tumor peptides to conventional CTLs.

Antigen-processing defects can mimic MHC loss

- The textbook immune-evasion figure includes altered genes required for antigen processing.
- A tumor may possess antigenic proteins yet fail to present the relevant peptide.
- Separate the antigen source from the class I presentation apparatus.



MHC escape creates a CTL–NK distinction

Property	CD8+ CTL	NK cell
Principal recognition	Peptide–MHC I	Can react to selected MHC I-low targets
Need for priming	Antigen-specific activation	May act without prior sensitization
Source caveat	Major antitumor effector	Spontaneous-tumor role less established

Recognition failure is not identical to T-cell paralysis

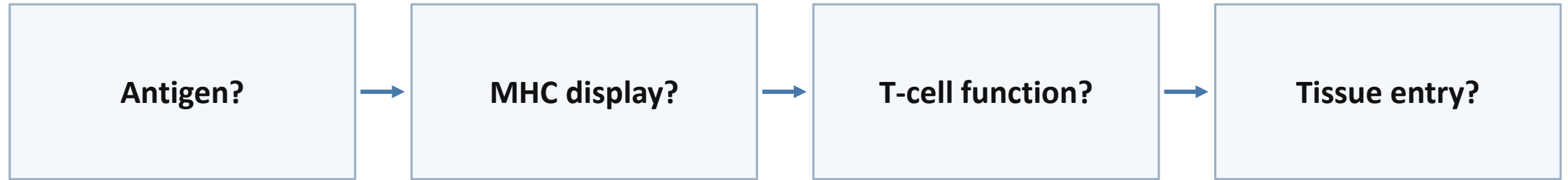
Target not visible

- Recognition failure: Absent antigen or defective peptide–MHC display.
- The mechanism matters when reasoning about checkpoint treatment.

T cell inhibited despite target

- Functional inhibition: Tumor-reactive T cells exist but are suppressed.

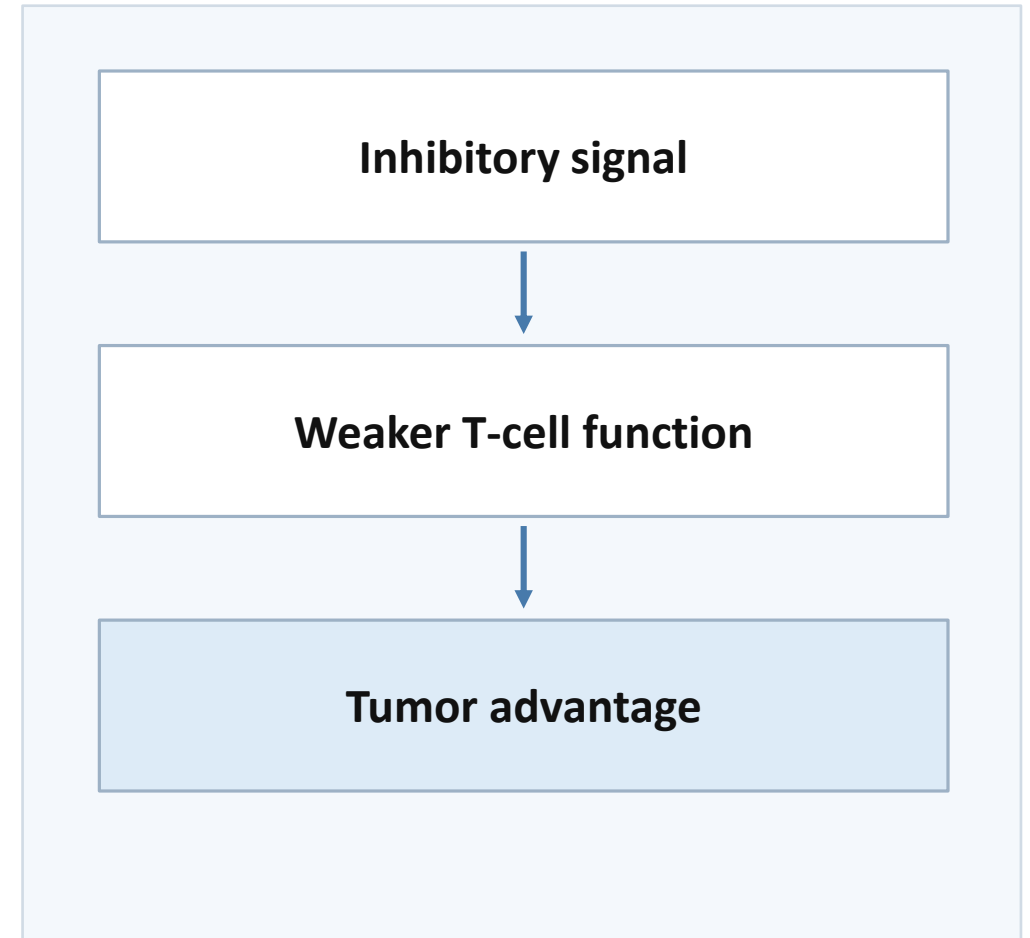
Analyze immune escape at four checkpoints



- A conceptual diagnostic sequence asks whether antigen, presentation, priming, and effector access are intact.
- The stages identify possible failure points; They are not a validated clinical testing algorithm.

Immune checkpoints physiologically restrain responses

- Inhibitory receptor systems help maintain self-tolerance.
- Tumors can exploit these brakes to reduce antitumor T-cell activity.
- Therapeutic blockade can restore function at the cost of inflammatory toxicity.



T-cell activation depends on two distinct signals

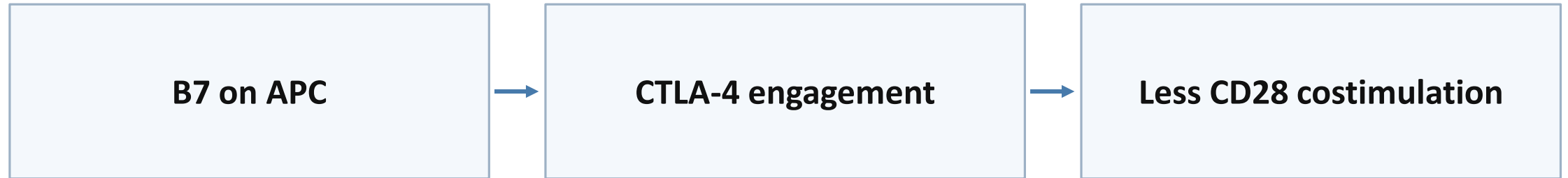
TCR + peptide–MHC

- TCR recognition of peptide–MHC alone does not guarantee full activation.
- Inhibitory checkpoints can counter these activating interactions.

CD28 + B7

- CD28 costimulation via B7 molecules on APCs promotes priming.

CTLA-4 inhibits the priming phase of T-cell responses



- CTLA-4 is an inhibitory receptor on T cells.
- Its engagement with B7 limits use of B7 by activating CD28.
- The source places this regulatory interaction at antigen-presenting cells.

B7 competition explains the CTLA-4 brake

B7 → CD28: Activation

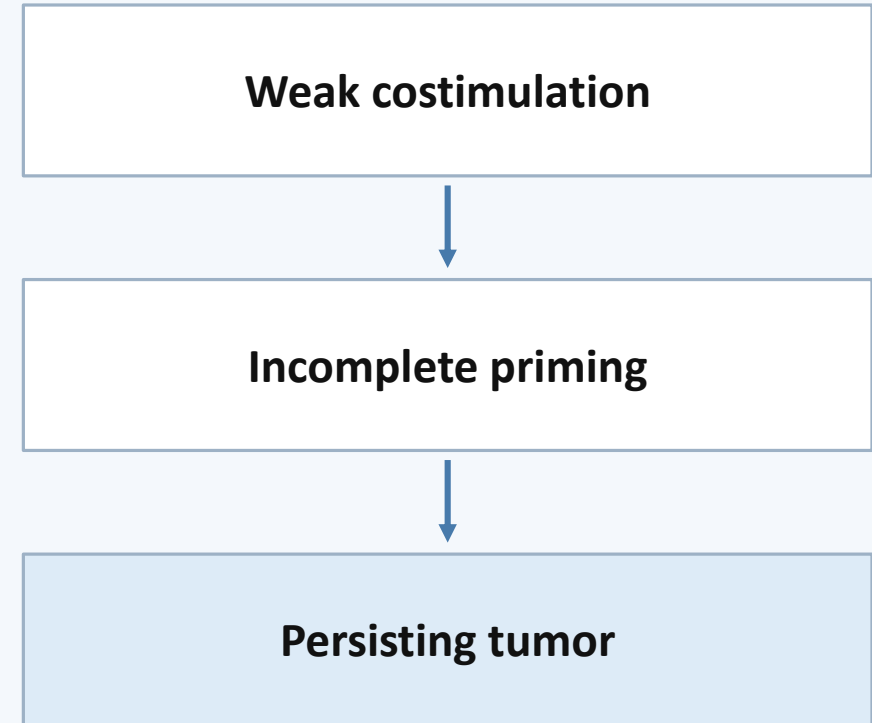
- With CD28 engagement, APC B7 molecules support T-cell activation.
- Both receptor pathways influence the same priming interaction.

B7 → CTLA-4: Inhibition

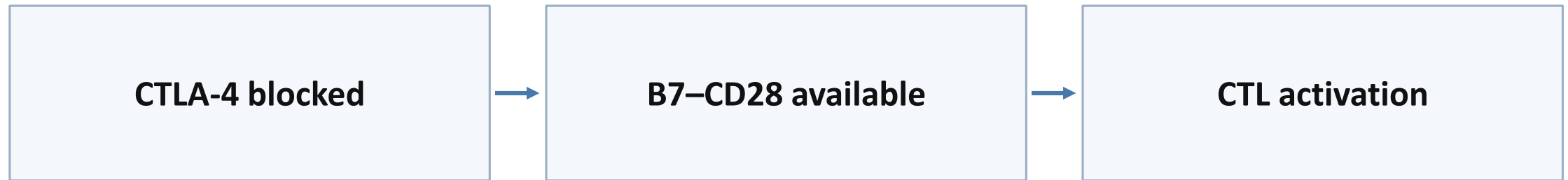
- When CTLA-4 engages B7, effective costimulation is reduced.

Inadequate costimulation can cause unresponsiveness

- Reduced B7–CD28 engagement may prevent sensitization to tumor antigen.
- Inhibitory signaling may also favor prolonged T-cell unresponsiveness.
- A priming defect may precede an effective tumor-specific CTL response.

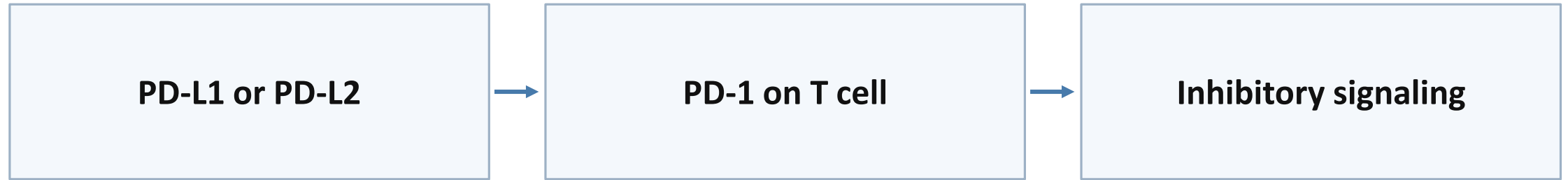


Anti-CTLA-4 releases a brake on T-cell priming



- Blocking CTLA-4 permits greater access of CD28 to B7 on APCs.
- The resulting costimulation can promote tumor-specific T-cell activation.
- This acts on a different inhibitory step from PD-1 blockade.

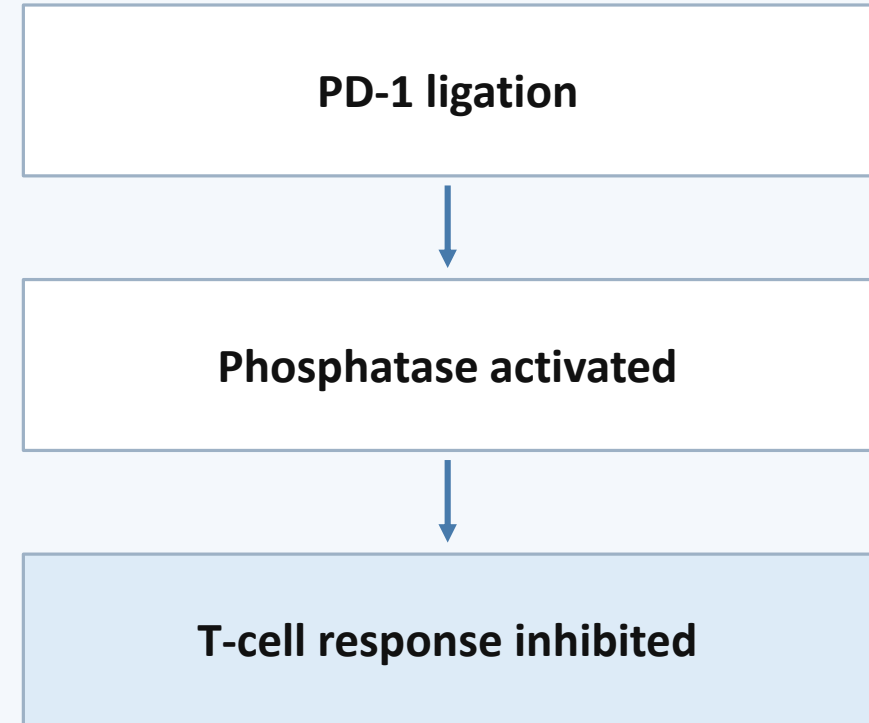
PD-1 suppresses responses of effector T cells



- PD-1 is an inhibitory receptor on tumor-reactive effector T cells.
- Ligand binding suppresses signaling needed for T-cell activation and function.

PD-1 signaling recruits a cellular phosphatase

- Engagement of PD-1 activates inhibitory phosphatase-mediated signaling.
- T-cell activation falls despite recognition of a tumor antigen.
- This represents functional suppression rather than loss of antigen display.



PD-L1 and PD-L2 serve as inhibitory ligands

Ligand on tumor cell

- Tumor cells may upregulate PD-L1 and PD-L2 on their surface.
- Upregulation provides an active means of suppressing effector responses.

PD-1 on effector T cell

- Either ligand can engage the PD-1 receptor on T cells.

Checkpoint-ligand genes can be genomically altered

- The source describes amplification or translocation affecting PD-L1 or PD-L2 genes.
- Such alterations can drive excessive inhibitory-ligand expression.
- Do not assume that all tumors with PD-L1 expression share the same genomic mechanism.

Gene amplification or translocation



Ligand overexpression



PD-1 inhibition

Blocking PD-1 or its ligand can restore CTL function



- Antibodies against PD-1 or PD-L1 interrupt inhibitory receptor engagement.
- Relief of PD-1 signaling can re-enable tumor-specific T-cell activity.
- The source illustrates restored CTL killing after checkpoint blockade.

CTLA-4 and PD-1 constrain different phases

Feature	CTLA-4	PD-1
Dominant teaching site	APC–T-cell priming	Effector response in tumor tissue
Core interaction	CTLA-4 with B7	PD-1 with PD-L1/PD-L2
Effect of blockade	Restores costimulation	Removes inhibitory effector signal

Checkpoint blockade acts on host immunity

Direct cytotoxic agent

- Checkpoint antibodies do not themselves replace tumor-specific antigen recognition.
- A tumor lacking necessary immune targets may remain resistant.

Checkpoint inhibitor

- They remove inhibitory signaling imposed on existing or newly primed immune responses.

Immunosuppressive secretions form a second escape axis

TGF- β

IL-10

PGE₂

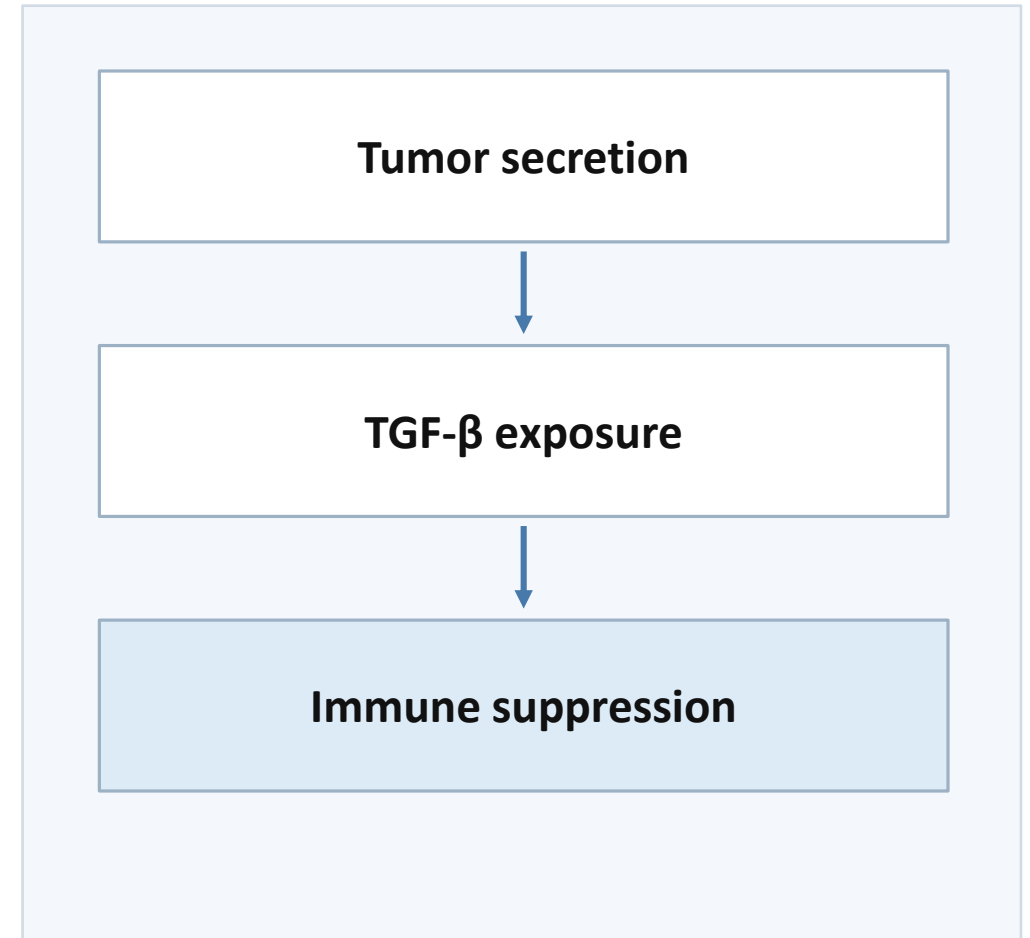
Tryptophan metabolites

VEGF

- Tumors can release molecules that restrain immune responses.
- TGF- β , IL-10, PGE₂, tryptophan-derived metabolites, and VEGF.
- Some specific mechanisms are established; Others are presented as suspected.

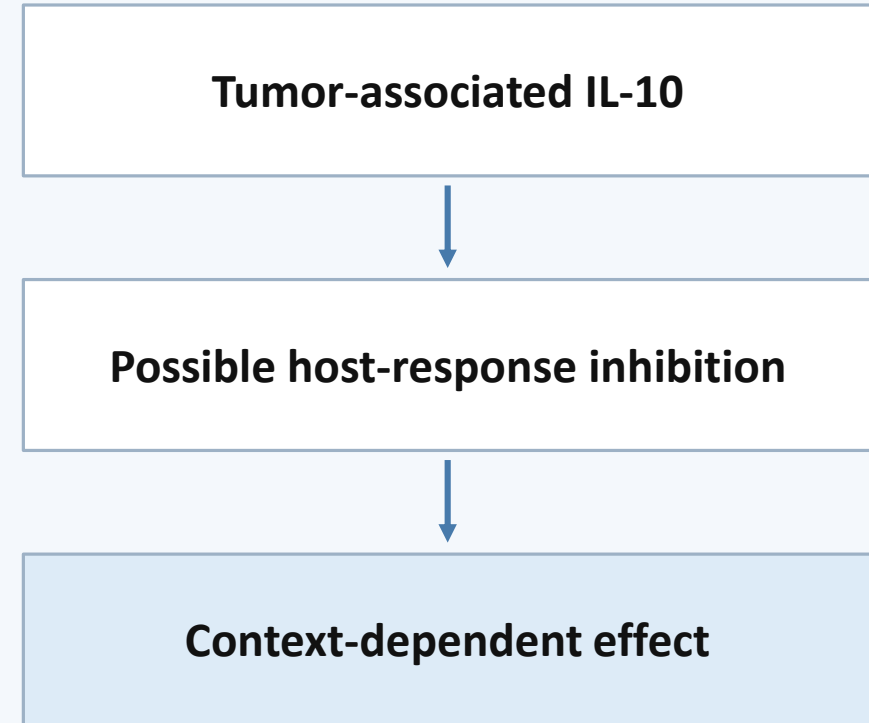
TGF- β is a potent tumor-associated immunosuppressant

- Many tumors secrete TGF- β in substantial amounts.
- TGF- β suppresses host immune responses and may promote tumor persistence.
- The source identifies this as a comparatively well-supported soluble mechanism.



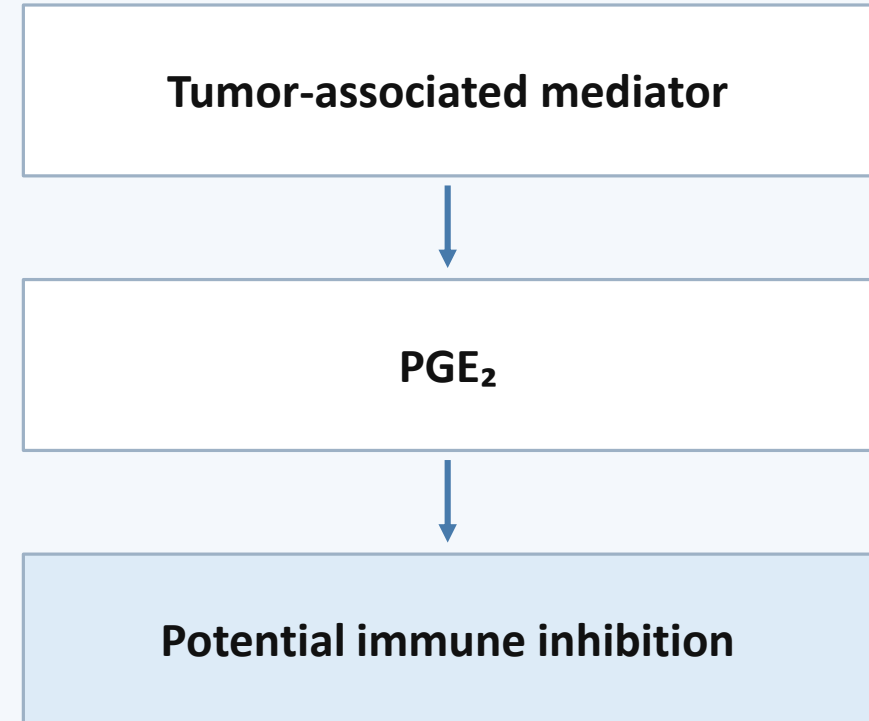
IL-10 is a candidate soluble suppressive mediator

- IL-10 is listed among factors produced by tumors that may inhibit immunity.
- Several such mediators with varying degrees of certainty.
- Do not infer a defined contribution for every tumor type from this general list.

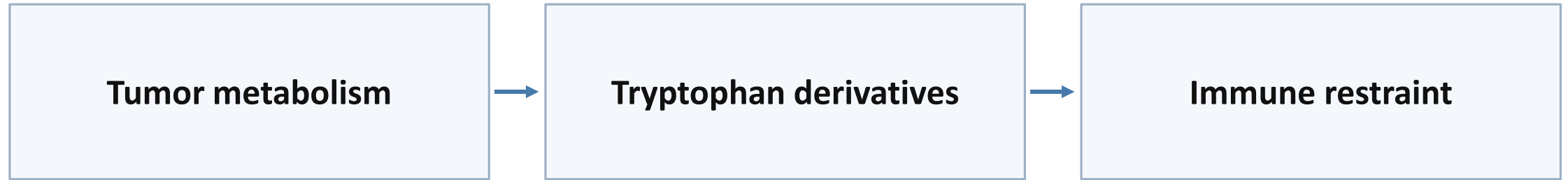


Prostaglandin E₂ is implicated in immune suppression

- Prostaglandin E₂ is identified among soluble products suspected of inhibitory activity.
- Its presence illustrates that immune evasion is not restricted to protein checkpoints.
- The supplied section does not provide a tumor-specific quantitative effect.

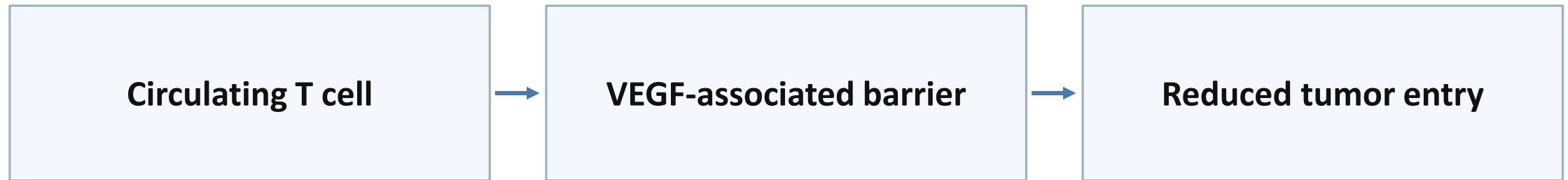


Tryptophan metabolites provide a metabolic route



- Certain tryptophan-derived metabolites are implicated in suppression of host immunity.
- The text does not attribute the effect to a specific enzyme or quantitative threshold.
- Conceptually, metabolic products may inhibit immunity without loss of antigen.

VEGF may impair T-cell entry into the tumor bed



- The supplied chapter notes that VEGF can inhibit migration of T cells from vessels into tumors.
- Thus antigen-specific CTLs may be present systemically yet poorly represented within tumor tissue.
- This is an access problem, not necessarily a priming problem.

Soluble factors target different stages of immunity

Factor / group	Source-described connection	Interpretive caution
TGF- β	Potent immunosuppression	Magnitude varies by tumor
IL-10, PGE ₂ , metabolites	Suspected host-response inhibition	Mechanisms not specified in excerpt
VEGF	May impede T-cell movement into tumor	Immune exclusion is multifactorial

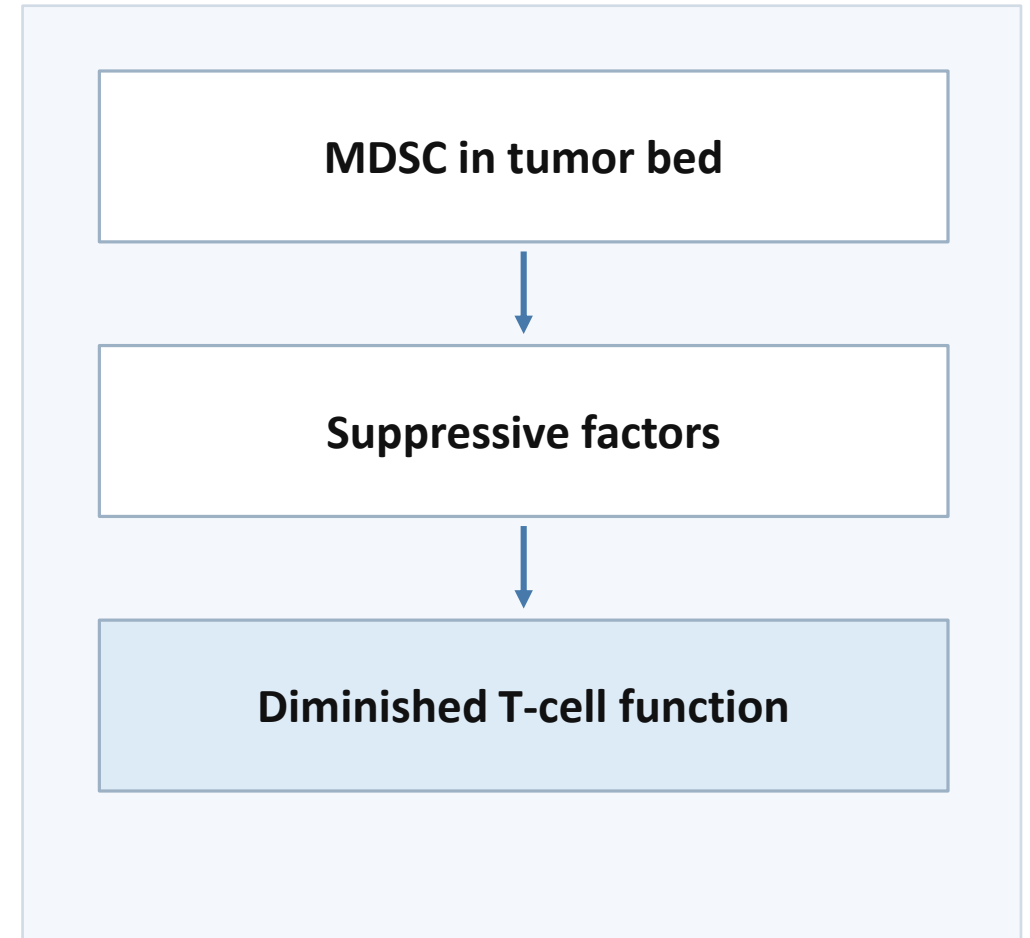
Some tumors recruit regulatory T cells



- Tumor products may favor development of immunosuppressive regulatory T cells (Tregs).
- Tregs can contribute to suppression of antitumor T-cell responses.
- The source uses cautious language: “some studies suggest” this mechanism.

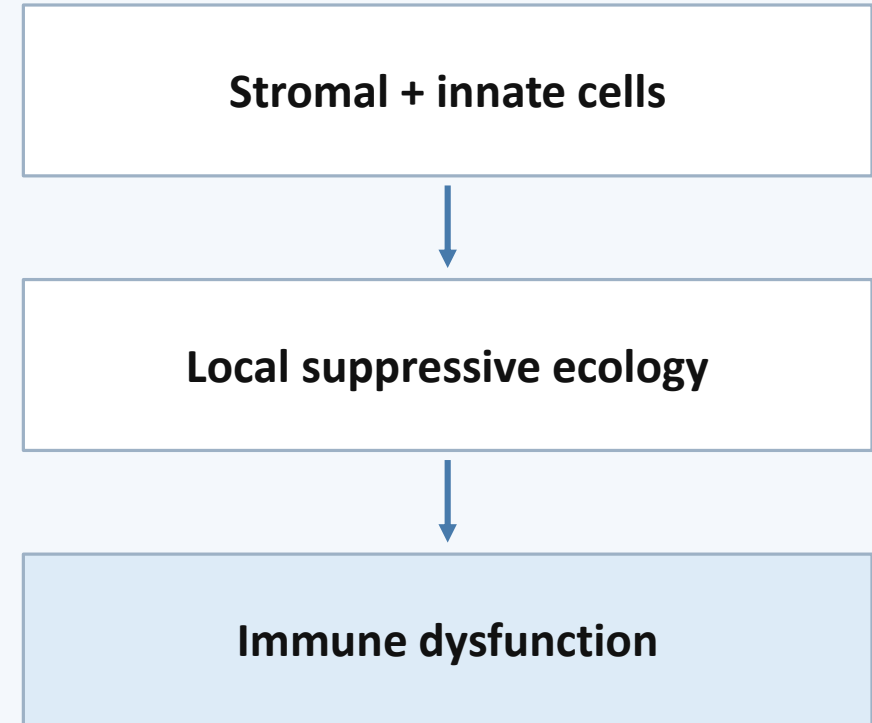
Myeloid-derived suppressor cells appear in the escape model

- The caption to Figure 7.40 includes myeloid-derived suppressor cells (MDSCs).
- Such cells are represented as producing factors that suppress T-cell function.
- The extracted text does not define MDSC subsets or subtype-specific mechanisms.



Stromal and innate cells can reinforce tumor escape

- Tumors frequently contain innate immune populations and nonmalignant stromal cells.
- These cells can participate in local suppression of host responses.
- Some underlying mechanisms remain undefined.



The microenvironment integrates cellular and soluble brakes

Inhibitory ligands

Soluble suppressors

Treg / MDSC

Stromal cells

- Suppressive ligands may act at the tumor–T-cell interface.
- Secreted factors can act beyond direct cell contact.
- Tregs, MDSCs, and stroma may amplify a hostile immune environment.

Immune exclusion differs from dysfunctional infiltration

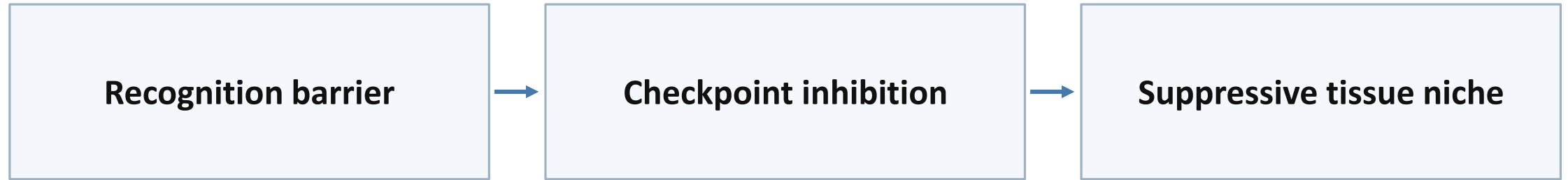
Limited T-cell entry

- Excluded or “cold” tumors have few associated immune effector cells.
- Checkpoint blockade presumes a biologically restorable antitumor response.

T cells present but restrained

- Inflamed tumors contain T cells but may still suppress their function.

Immune evasion is a layered, nonexclusive process



- One tumor may lose antigen display and express inhibitory ligands.
- Regulatory cells and soluble mediators can simultaneously reinforce suppression.
- No single mechanism should be presumed to explain every resistant tumor.

Hot and cold describe the tumor immune context

Hot: T-cell infiltrated

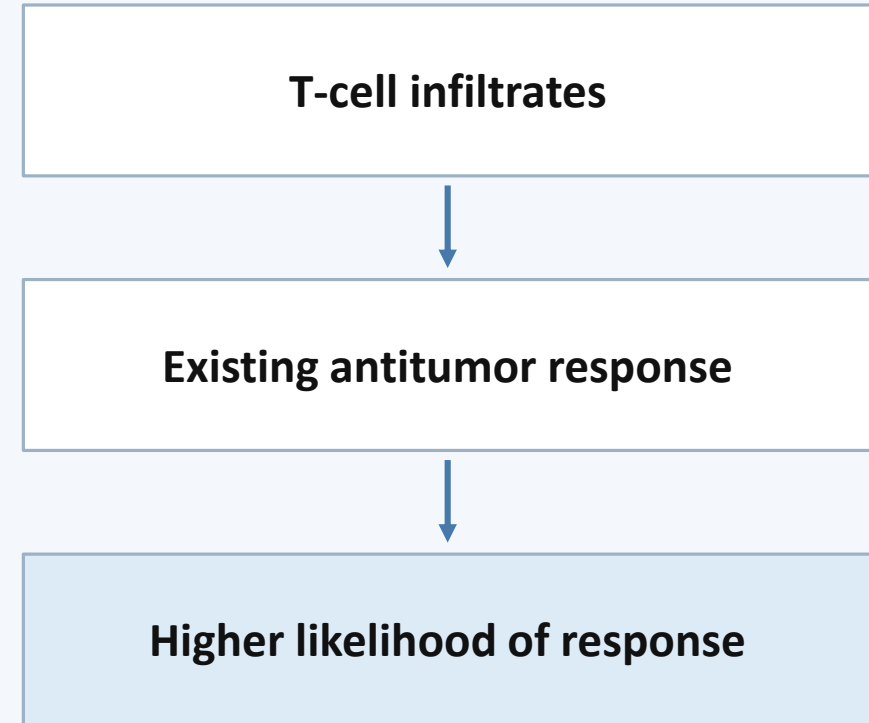
- “Hot” tumors exhibit histologic evidence of a host T-cell response.
- These broad descriptors summarize tissue context, not a standalone validated diagnostic assay.

Cold: Immune-cell poor

- “Cold” tumors lack substantial associated immune-cell infiltrates.

Intra-tumoral T cells correlate with favorable response

- The source notes that T-cell infiltrates often correlate with better prognosis.
- Immune-infiltrated tumors are more likely to respond to checkpoint blockade.
- Association does not mean that every infiltrated tumor will respond.

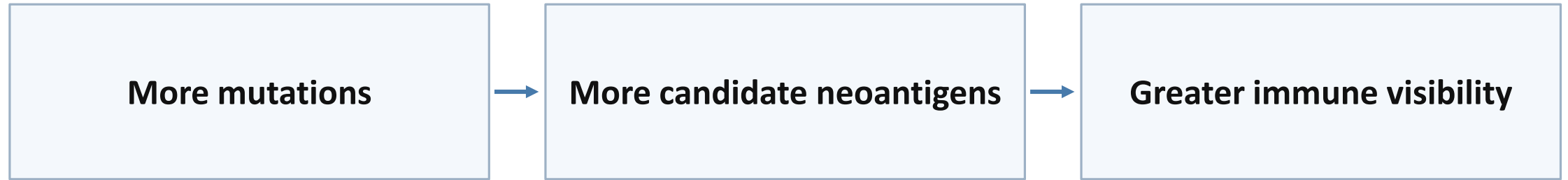


Cold tumors may resist checkpoint blockade



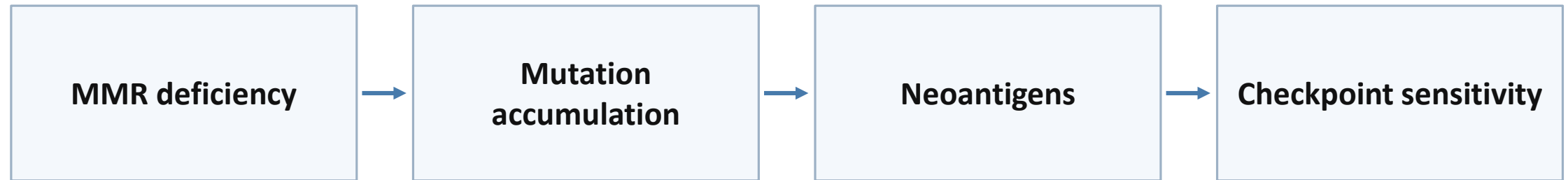
- In immune-cell-poor tumors there may be little antitumor T-cell activity to reactivate.
- Gliomas are offered as an example of a relatively cold and poorly responsive setting.
- Strategies to convert cold tumors into hot tumors are under investigation.

Neoantigen burden is a treatment-response correlate



- More somatic mutations can produce additional non-self peptide targets.
- Tumor neoantigen burden correlates with the effectiveness of immunomodulatory therapy.
- The association is not an individual-patient response guarantee.

Mismatch repair deficiency is a mechanistic exemplar



- Defective mismatch repair permits accumulation of DNA replication errors.
- These tumors frequently carry particularly high mutation burdens.
- This biology to increased sensitivity to PD-1–axis blockade.

High mutational burden is predictive, not sufficient

High neoantigens + intact immunity

- Neoantigens help only if they are generated, presented, and recognized.
- Multiple escape mechanisms can coexist in a highly mutated tumor.

High neoantigens + escape mechanism

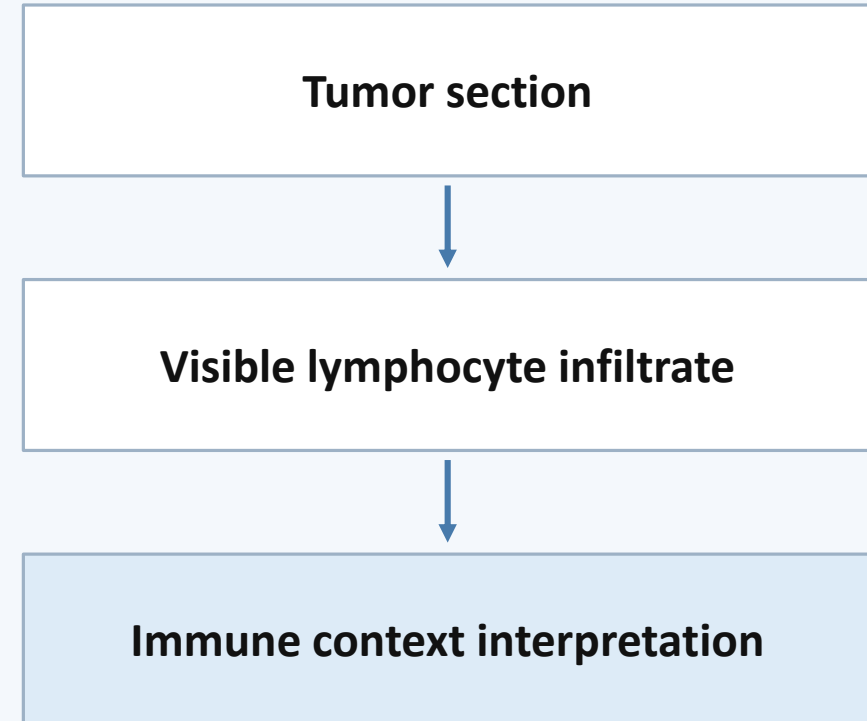
- MHC I loss or profound immune exclusion may undermine checkpoint response.

Clinical sensitivity varies widely between cancers

Textbook examples	Relative responsiveness	Interpretation
Melanoma; Hodgkin lymphoma; NSCLC	Often responsive	Responses remain heterogeneous
Glioma; pancreatic cancer	Generally poorly responsive	Other escape routes may dominate
Any histology	Response not assured	Mechanism and tissue context matter

Histologic immune context is biologically informative

- T-cell infiltrates are evidence of a host response to tumor tissue.
- Their distribution and abundance may inform why checkpoint therapy could work.
- The supplied excerpt does not define a numeric T-cell threshold or scoring system.



Checkpoint resistance can occur at multiple levels

Antigen absent

MHC I reduced

Cold tumor

Other suppressors

- Antigen-negative or MHC-deficient cells evade recognition.
- Poor T-cell entry leaves few effectors in tumor tissue.
- Suppressive cells or soluble factors may act despite checkpoint inhibition.

Checkpoint blockade benefits only a subset of tumors

- Clinical responses differ markedly across histologic tumor types.
- Tumors that rely less on CTLA-4 or PD-1 inhibition may fail to respond.
- Restoring one checkpoint pathway need not reverse all immune-escape mechanisms.

Checkpoint target blocked



Other escape persists



Incomplete response

Durable remissions may involve immune memory



- Checkpoint blockade can produce prolonged tumor control in some patients.
- The source proposes development of tumor-specific memory T cells as a possible explanation.
- This mechanism is plausible but is presented as an interpretation, not proven for every responder.

Distinct checkpoints provide a combination rationale

CTLA-4 / priming

- CTLA-4 regulates the balance of costimulation during priming.
- Targeting both may address separable immune suppressive stages.

PD-1 / effector

- PD-1 acts on inhibitory signaling in effector responses.

Combined CTLA-4 and PD-1 blockade is source-supported

- The source describes combined checkpoint blockade as more effective than anti-CTLA-4 alone in selected settings.
- Melanoma and lung cancer are its examples.
- This is a mechanistic teaching point, not a claim of universal treatment superiority.

Priming restraint relieved

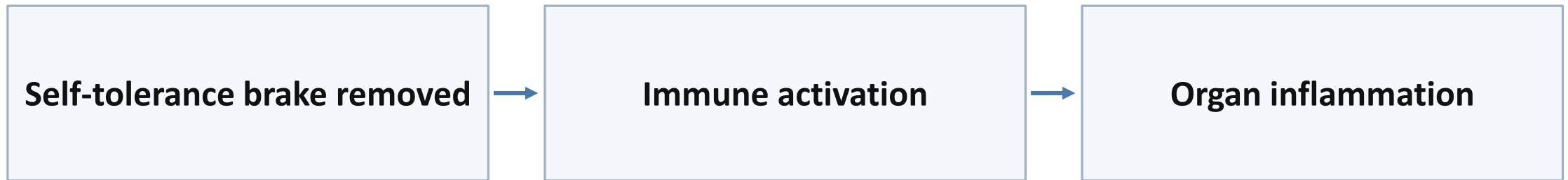


Effector brake relieved



Potential added activity

Checkpoint toxicities follow directly from their biology



- Physiologic inhibitory checkpoints limit excessive immune activation.
- Their blockade can weaken peripheral tolerance to self antigens.
- The resulting adverse effects include inflammatory or autoimmune tissue injury.

Immune-related injury can affect several organs

Colon

Lungs

Endocrine organs

Heart

Skin

- Colon, lungs, endocrine organs, heart, and skin.
- The involved organ determines clinical surveillance and intervention.
- Severe toxicity may necessitate stopping otherwise effective treatment.

Application: A tumor loses β 2-microglobulin

CLINICAL–MECHANISTIC PROBLEM

Scenario: Tumor cells retain mutated proteins but show loss of functional HLA class I display.

Question: Which immune effector is most directly disadvantaged?

Mechanistic answer: Antigen-specific CD8+ CTLs cannot efficiently recognize tumor peptide–MHC I.

Application: An MMR-deficient cancer

CLINICAL–MECHANISTIC PROBLEM

Scenario: A tumor accumulates many mutations due to mismatch-repair deficiency.

Question: Why could PD-1 blockade be effective?

Mechanistic answer: Mutation-derived neoantigens may provide targets for restored T-cell responses.

Application: An immune-cell-poor tumor

CLINICAL–MECHANISTIC PROBLEM

Scenario: A tumor biopsy shows few infiltrating T cells despite expression of an inhibitory ligand.

Question: Why may checkpoint blockade alone underperform?

Mechanistic answer: Too few active tumor-reactive T cells may be present to release from inhibition.

Choose the mechanism from the observed failure

Observed failure	Mechanistic category	Immediate consequence
Absent tumor epitope	Antigen-loss escape	Specific CTL cannot recognize
Reduced HLA class I	Presentation escape	Peptide display to CTL impaired
PD-L1 engagement of PD-1	Checkpoint suppression	Effector T-cell activation inhibited
Few intratumoral T cells	Poor immune access / cold state	Little local response to restore

The organizing model: Visibility, activation, access



- **Visibility:** Tumor antigens must be displayed by a functional presentation pathway.
- **Activation:** Inhibitory receptors and regulatory signals must not dominate.
- **Access:** Tumor-reactive T cells must reach and function within tumor tissue.

Key concepts

Recognition

Loss of tumor antigens or class I MHC prevents cognate CTL recognition.

Regulation

CTLA-4 and PD-1 pathways inhibit different stages of T-cell responses.

Microenvironment

Suppressive secretions, Tregs, myeloid cells, and stroma reinforce immune escape.

Treatment

Checkpoint response depends on antigenic potential and immune context; Toxicity reflects loss of immune restraint.

Questions to consolidate the mechanisms

- Why might an HLA class I-deficient tumor resist checkpoint therapy despite retaining many mutations?
- Why can CTLA-4 and PD-1 blockade be mechanistically complementary?
- Why are inflammatory and autoimmune adverse effects predictable consequences of checkpoint inhibition?