

CD8+ T Cell–Mediated Cytotoxicity

Antigen recognition • granule and death-receptor pathways • tissue injury

Pathology lecture

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Learning objectives

- Identify the target-recognition rule for CD8+ cytotoxic T lymphocytes (CTLs).
- Trace granule-mediated and Fas-dependent apoptosis.
- Connect CTL protection with immune-mediated tissue damage.
- Apply the mechanism to infection, autoimmunity, transplantation and tumors.

CTLs: One effector, two possible outcomes

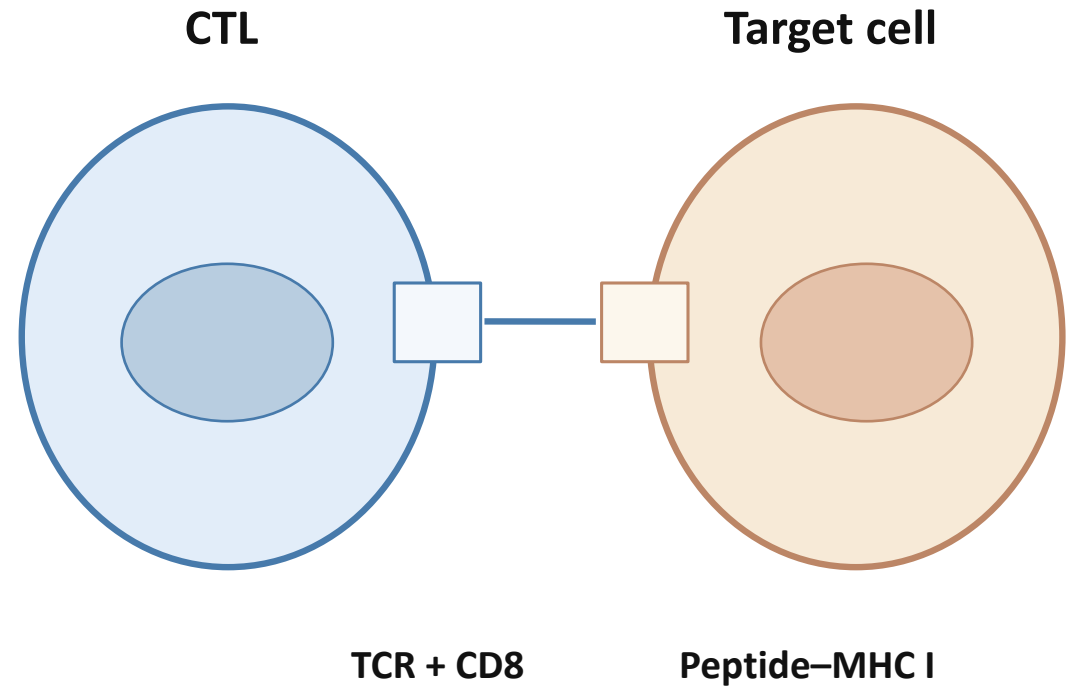
- A CD8+ CTL recognizes a target displaying cognate antigen.
- The same antigen-specific response may remove a dangerous cell or injure tissue.
- Outcome depends on the target and biological context.

Host protection

Host tissue injury

The defining event is target-cell killing

- The effector cell is a differentiated CD8+ T lymphocyte.
- Its target is an antigen-expressing host cell.
- The lethal event is directed at the recognized target rather than a free microbe.



Schematic

Why cytotoxicity is classified as type IV

- Type IV hypersensitivity is mediated by T cells.
- CD8+ CTLs cause injury through direct target-cell death.

Effector	Major action	Typical result
CD8+ CTL	Direct antigen-specific killing	Target-cell apoptosis
CD4+ effector T cell	Cytokine secretion	Leukocyte recruitment / activation

CTL injury is not the whole of type IV disease

- Many T-cell diseases combine cellular killing and inflammation.
- A CTL contribution does not exclude CD4+ cytokine responses.
- Identify the dominant mechanism, not just the infiltrating cell type.

Direct killing

CTL-mediated target-cell loss

Inflammation

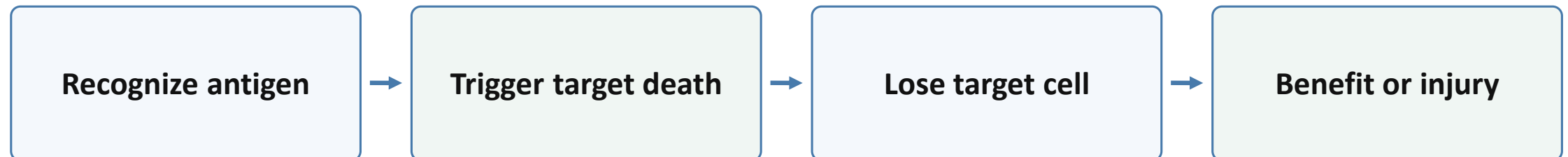
T-cell cytokine response

Overlap

Mechanisms may coexist

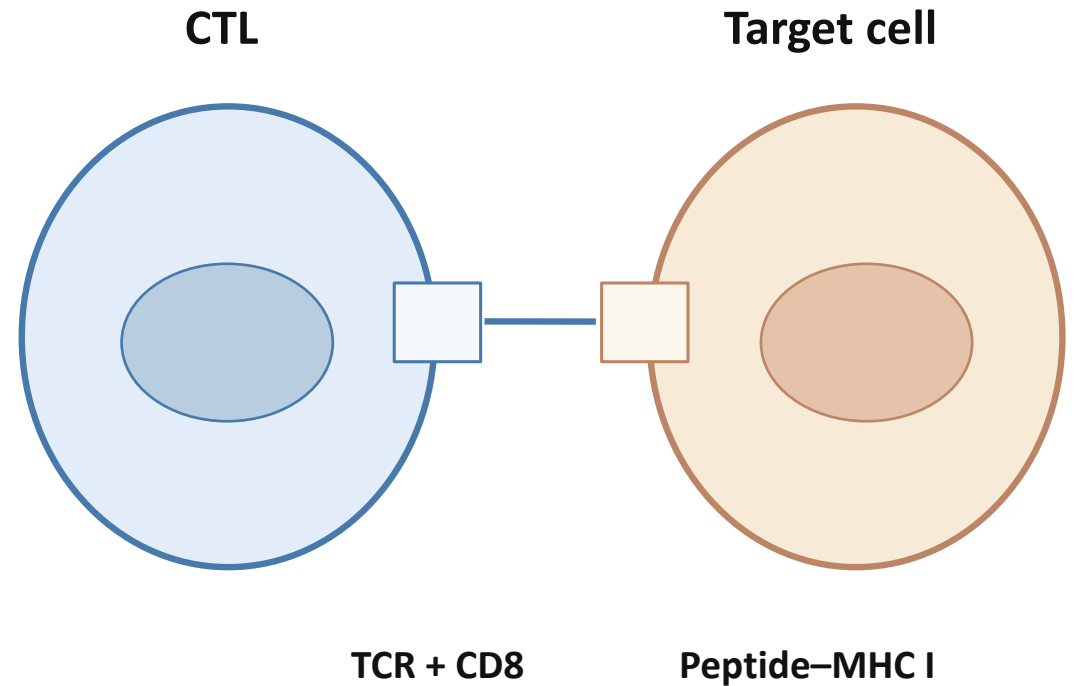
Protective and pathologic cytotoxicity share machinery

- Removal of a virus-infected cell may limit the infection.
- The same killing process may destroy functional parenchyma.
- Type 1 diabetes, hepatitis and graft rejection illustrate different target settings.



CD8+ T cells are MHC class I–restricted

- The T-cell receptor (TCR) recognizes peptide in an MHC class I complex.
- CD8 binds the class I molecule as a coreceptor.
- Peptide alone is not the physiologic recognition signal for a conventional CTL.



Schematic

Where MHC class I is expressed

- MHC class I is present on nucleated cells and platelets.
- Broad expression permits surveillance of infected or transformed host cells.
- Erythrocytes are not included among nucleated target cells.

Wide distribution

Nucleated tissues

Immune purpose

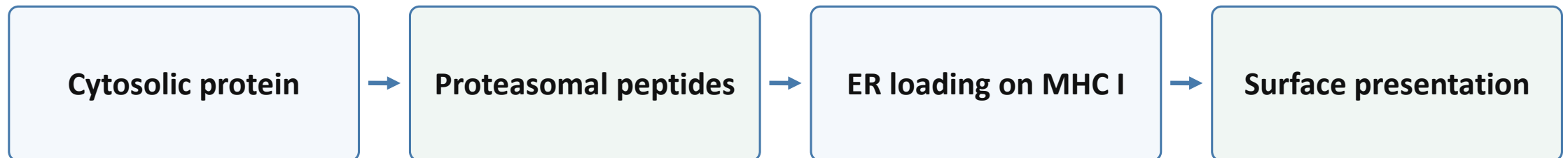
Antigen surveillance

Recognition gate

Peptide–MHC class I

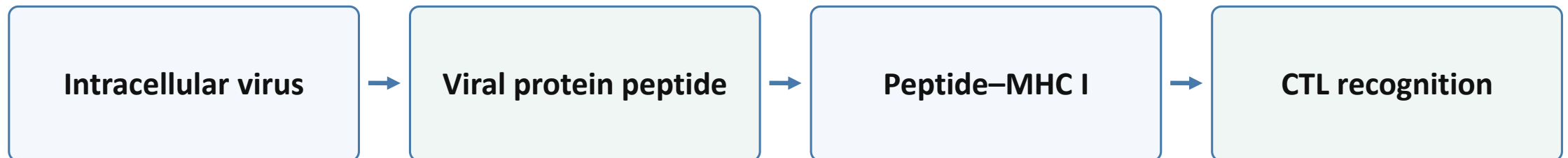
Class I presents cytosolic protein peptides

- Cytosolic proteins are broken down by proteasomes.
- Peptides enter the endoplasmic reticulum and associate with class I molecules.
- Stable peptide–MHC class I complexes travel to the cell surface.



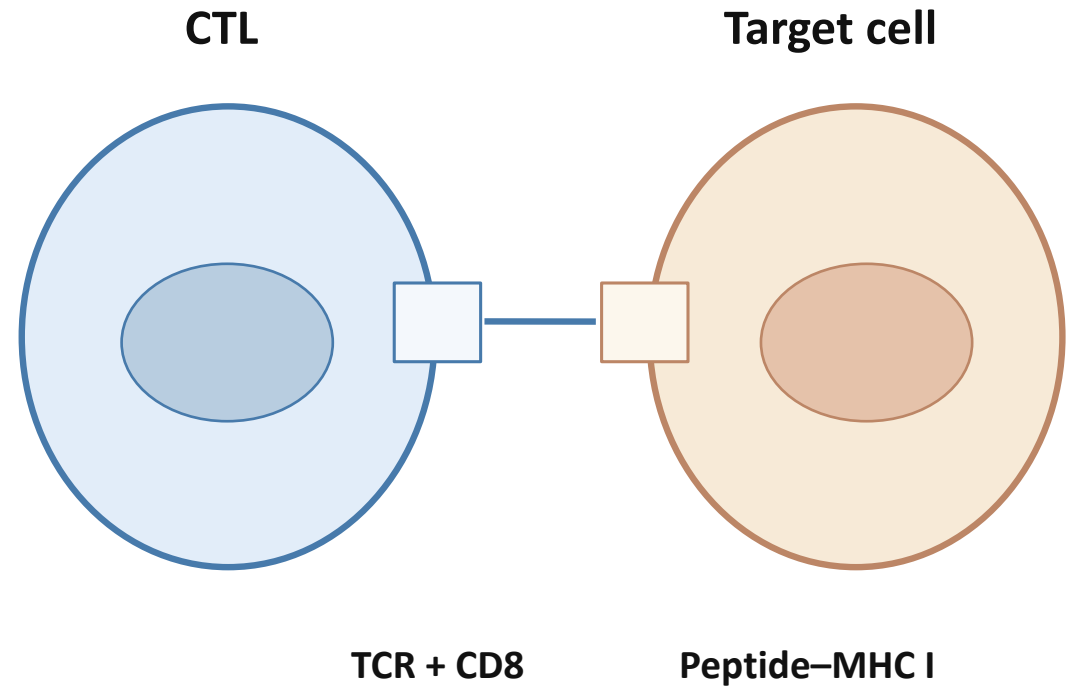
A viral antigen becomes a cell-surface signal

- The viral protein is produced inside an infected host cell.
- Its peptides can appear on cell-surface MHC class I.
- A CTL recognizing that complex can initiate cytotoxicity.



TCR and CD8 play distinct roles

- TCR supplies specificity for the presented peptide–MHC complex.
- CD8 binds the MHC class I heavy chain.
- Together they support recognition and triggering of the cytotoxic response.



Schematic

Peptide specificity constrains killing

- CTL recognition depends on the antigen shown by the target cell.
- A nearby cell lacking that recognized complex is not an equivalent target.
- Antigen display links the immune response to the cellular source of antigen.

Cognate peptide–MHC I

No cognate complex

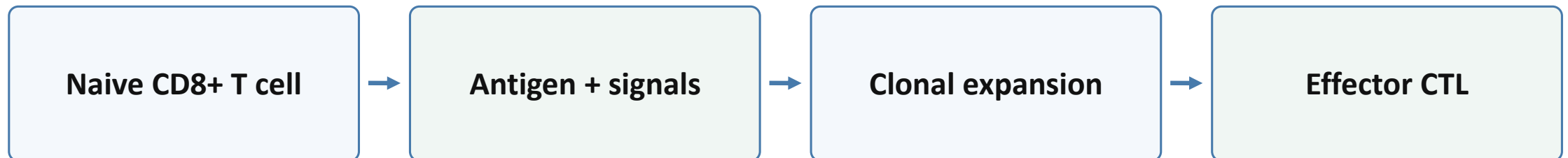
Class I versus class II: A useful contrast

- MHC class I displays mainly cytosolic peptides to CD8+ T cells.
- MHC class II displays mainly internalized extracellular antigens to CD4+ T cells.

Feature	MHC class I	MHC class II
Peptide source	Mainly cytosolic proteins	Mainly internalized proteins
Recognizing subset	CD8+ T cells	CD4+ T cells
Typical consequence	Cytotoxic killing	Helper / inflammatory response

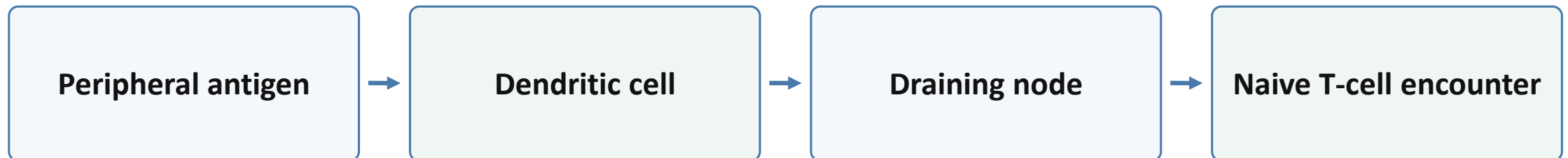
Naive CD8+ cells must first become effectors

- Naive T cells encounter antigen in secondary lymphoid organs.
- Antigen recognition with costimulation initiates activation.
- Proliferation and differentiation produce effector CTLs.



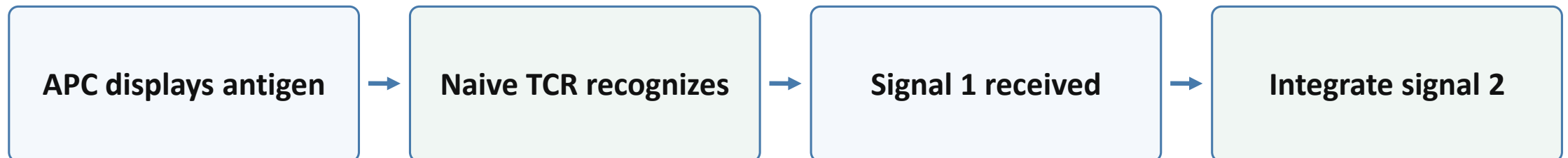
Dendritic cells link tissues to lymph nodes

- Dendritic cells capture antigens in peripheral tissues.
- They carry antigen to draining lymph nodes.
- Concentrating antigens helps rare naive antigen-specific T cells encounter them.



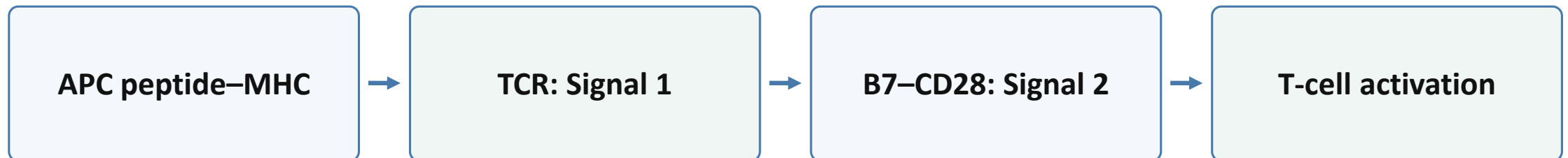
Antigen recognition is signal 1

- TCR engagement with peptide–MHC generates antigen-specific input.
- Signal 1 selects T cells with appropriate receptor specificity.
- Signal 1 is integrated with costimulatory signals during naive-cell activation.



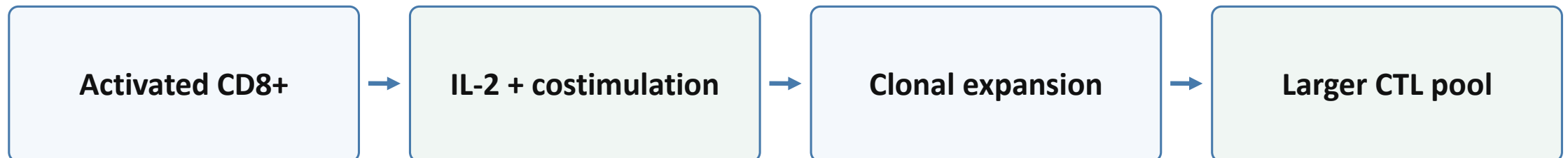
B7–CD28 supplies costimulation

- B7 molecules (CD80/CD86) are expressed by activated APCs.
- CD28 is a receptor for B7 on naive T cells.
- Signal 1 and signal 2 cooperate to drive activation.



IL-2 and costimulation drive expansion

- Activated CD8+ cells undergo extensive proliferation.
- Costimulators and IL-2 promote clonal expansion.
- The resulting effectors increase the capacity to clear antigen-bearing cells.



Differentiation creates a killing-capable cell

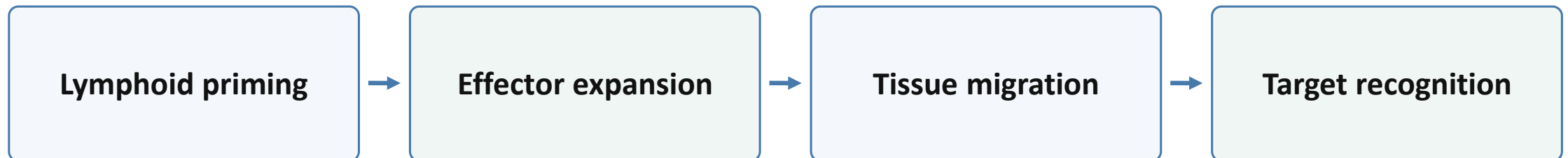
- The naive CD8+ T cell is the precursor, not the final killer.
- Activation generates effector CTLs.
- Effector CTLs eliminate cells harboring microbes in their cytosol.

Naive CD8+ cell

Differentiated CTL

Effector cells move to peripheral targets

- Naive cells circulate through secondary lymphoid organs.
- Effector T cells migrate to sites containing microbial antigens.
- Recognition and killing occur at the antigen-expressing tissue target.



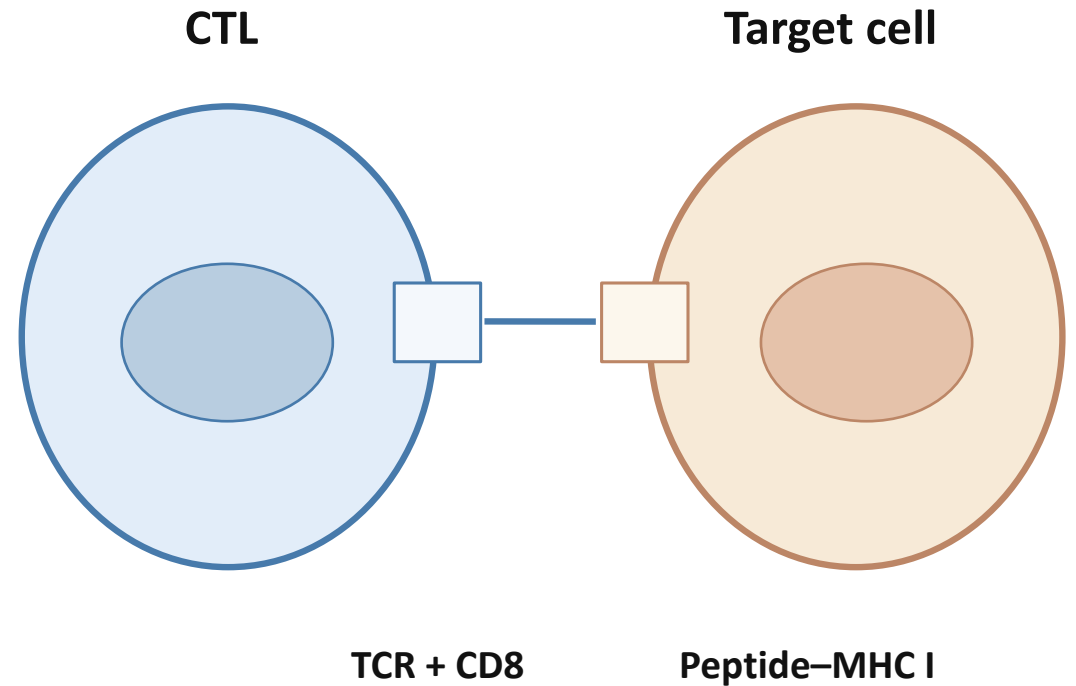
CTL activity must be distinguished from priming

- Dendritic cell interactions generate and expand the response.
- Tissue target cells are then recognized by differentiated CTLs.

Phase	Principal location	Core function
Priming	Secondary lymphoid tissue	Activate naive CD8+ cells
Execution	Antigen-bearing tissue	Kill recognized target cells

The CTL–target interface determines specificity

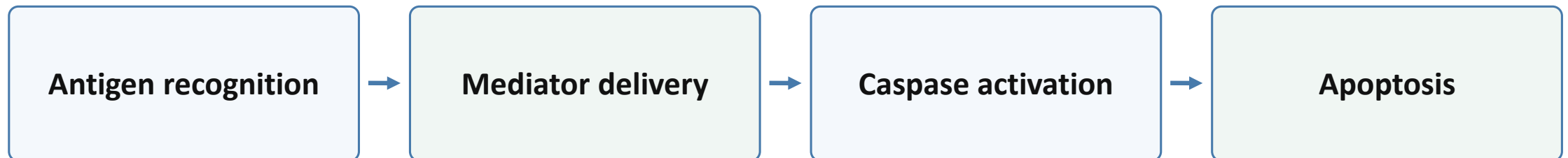
- A CTL contacts a target presenting the cognate peptide–MHC I.
- Recognition precedes discharge of cytotoxic mediators.
- The targeted cell is then driven toward apoptosis.



Schematic

Killing is a sequence, not a single molecule

- The recognition event identifies the cellular target.
- The CTL delivers apoptotic effectors through a cytotoxic pathway.
- Caspase activation executes the target-cell death program.



Why apoptosis is an effective cytotoxic endpoint

- Apoptosis dismantles a damaged or dangerous cell.
- Cellular contents remain membrane-contained during early fragmentation.
- Rapid clearance usually limits leakage and secondary inflammation.

Programmable

Protease-driven dismantling

Contained

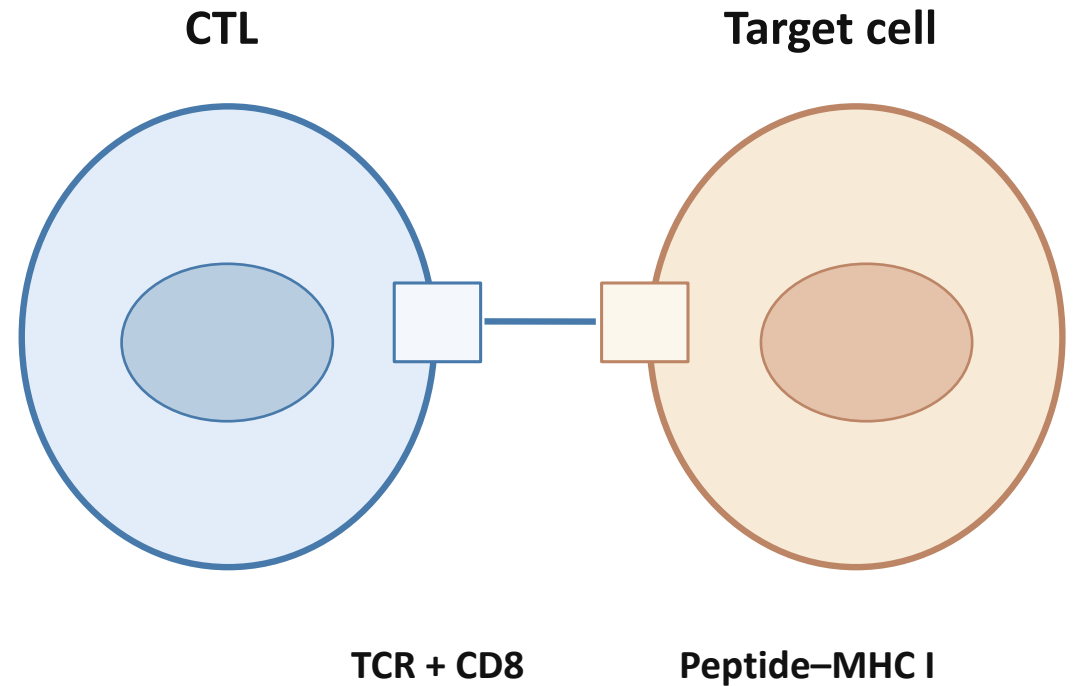
Apoptotic bodies

Cleared

Phagocytic disposal

CTL target cells may be otherwise viable

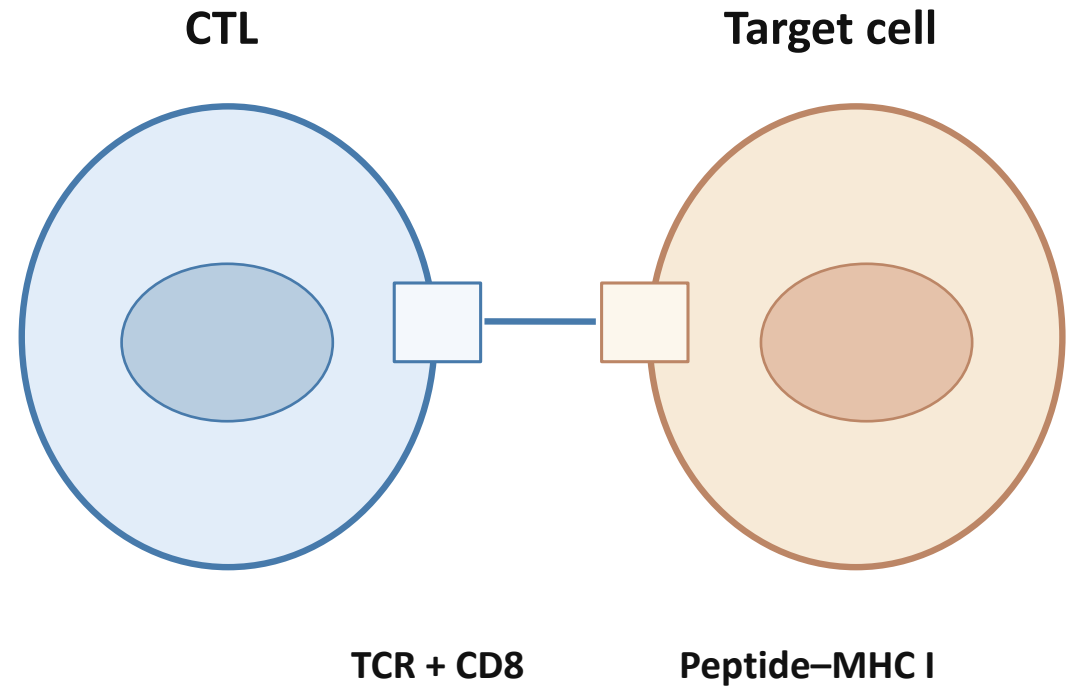
- A target need not be mechanically injured before recognition.
- The decisive feature is display of the recognized antigen.
- Immune specificity, not spontaneous cell failure, starts the lethal signal.



Schematic

Perforin and granzymes are the major pathway

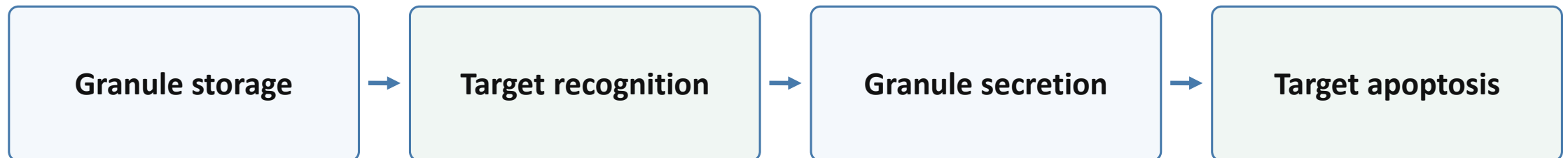
- CTLs contain lysosome-like cytotoxic granules.
- These granules contain preformed perforin, granzymes and other proteins.
- Upon recognizing the target, CTLs secrete the cytotoxic complex.



Schematic

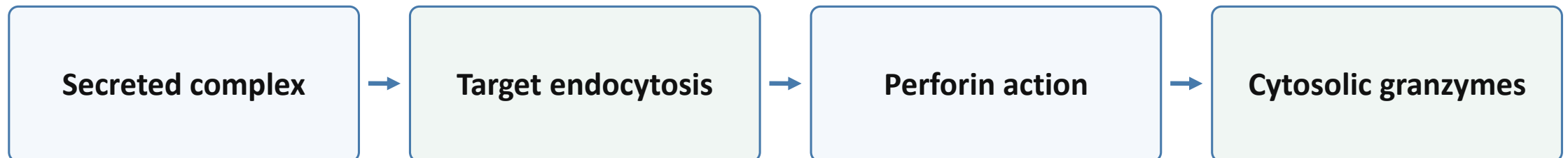
Preformed granules permit a rapid effector response

- The mediators are packaged in the differentiated CTL before target contact.
- Recognition is followed by release of the granule contents.
- The target cell subsequently activates its apoptotic machinery.



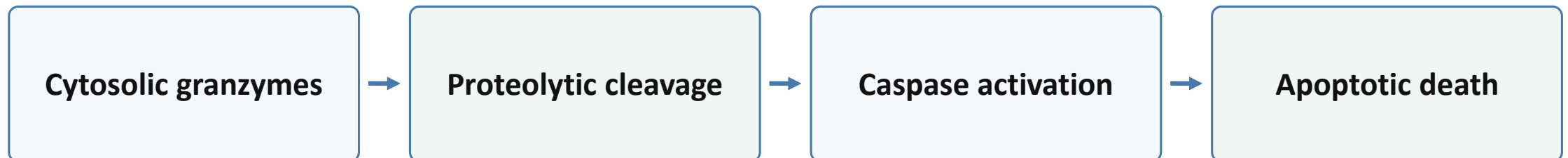
Perforin is a delivery facilitator

- The CTL releases a complex containing perforin and granzymes.
- The complex enters the target cell through endocytosis.
- Perforin facilitates granzyme release into the target-cell cytoplasm.



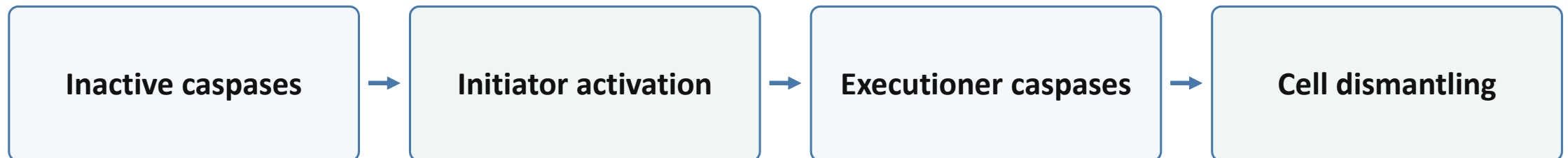
Granzymes are proteolytic death effectors

- Granzymes are proteases.
- They cleave and activate caspases within target cells.
- Activated caspases drive the execution of apoptosis.



Caspase activation is the decisive intracellular switch

- Caspases are produced initially as inactive enzymes.
- Activation initiates a proteolytic cascade.
- Execution-phase enzymes cause cellular fragmentation and death.



The target supplies its own apoptotic machinery

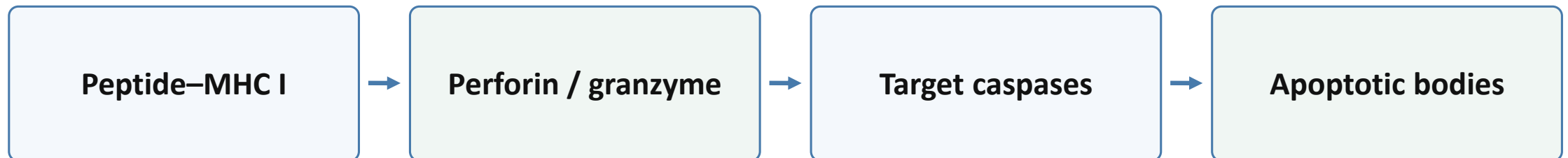
- The CTL delivers the trigger; The target executes the death program.
- Caspases degrade essential proteins and promote DNA fragmentation.
- Recognizing this division clarifies cell-mediated cytotoxicity.

CTL: Lethal trigger

Target: Apoptosis machinery

Granule pathway: Explain the causal chain

- A specific peptide–MHC interaction identifies the target.
- CTL granules provide perforin and granzymes.
- Cytosolic granzymes activate caspases, producing apoptosis.



Do not equate perforin with target-cell necrosis

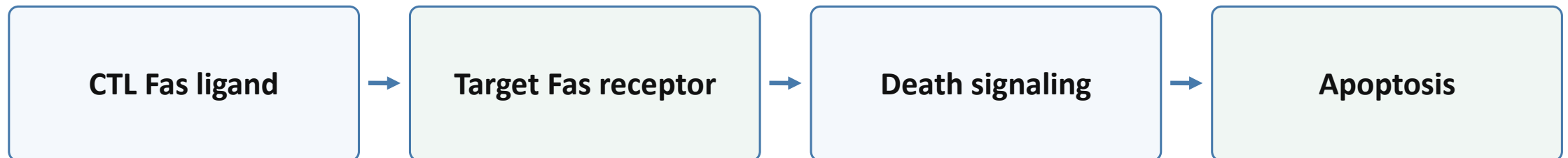
- The principal downstream effect is apoptosis.
- Perforin enables access of granzymes to the target cytosol.
- Caspase activation is central to the ensuing target-cell death.

Perforin: Granzyme access

Caspases: Apoptosis

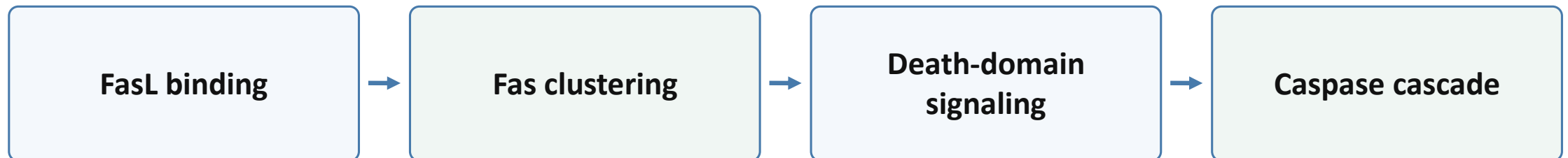
Fas ligand provides a second CTL route

- Activated CTLs may express Fas ligand (FasL).
- FasL binds the Fas death receptor on susceptible target cells.
- The signal triggers the extrinsic apoptotic pathway.



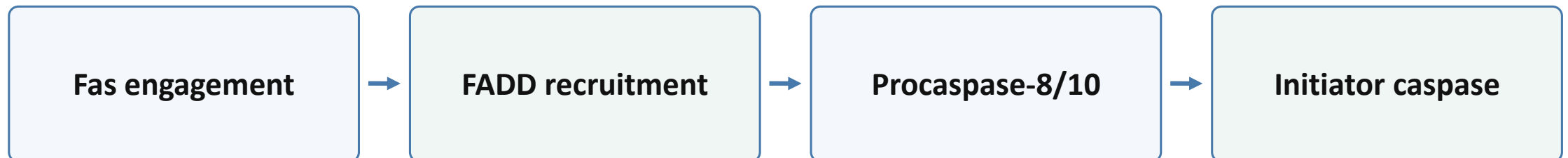
Fas is a death receptor of the TNF family

- Fas is also called CD95.
- Engagement by FasL clusters death receptors.
- The intracellular death domain recruits apoptotic signaling proteins.



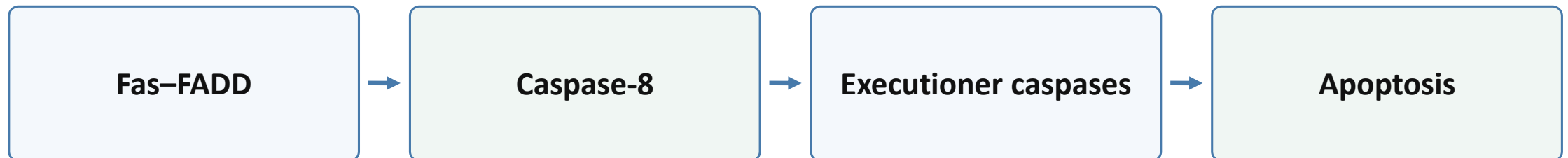
FADD links Fas to initiator caspases

- Engaged Fas recruits the adapter protein FADD.
- FADD recruits procaspase-8 (or procaspase-10).
- Proximity and cleavage generate active initiator caspase.



Extrinsic signaling converges on executioners

- Initiator caspase-8 activates downstream executioner caspases.
- The death program produces proteolysis and fragmentation.
- This mechanism is distinct at initiation but shares the apoptotic endpoint.



Granule and Fas pathways: Same endpoint

- Granule route delivers perforin and granzymes to the target.
- Fas route uses receptor-mediated initiation of apoptosis.

Property	Granule pathway	Fas pathway
CTL effector	Perforin, granzymes	Fas ligand
Target entry point	Endocytosis / cytosol	Fas death receptor
Convergence	Caspase activation	Caspase activation
Outcome	Apoptosis	Apoptosis

The granule mechanism is emphasized

- Perforin–granzyme release is described as the principal route.
- FasL–Fas is presented as a less important CTL killing mechanism.
- Importance is context-dependent; Neither route is a form of antibody cytotoxicity.

Major: Granules

Additional: FasL–Fas

Apoptosis begins with cell shrinkage

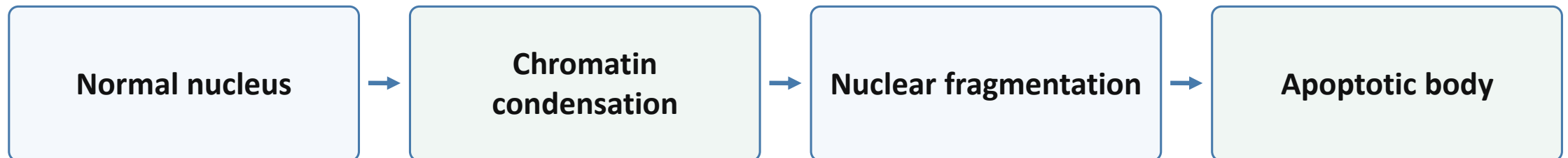
- The dying cell becomes smaller with denser cytoplasm.
- The cytoplasm may become brightly eosinophilic on H&E.
- This contrasts with the early swelling typical of necrosis.

Apoptosis: Shrinkage

Necrosis: Swelling

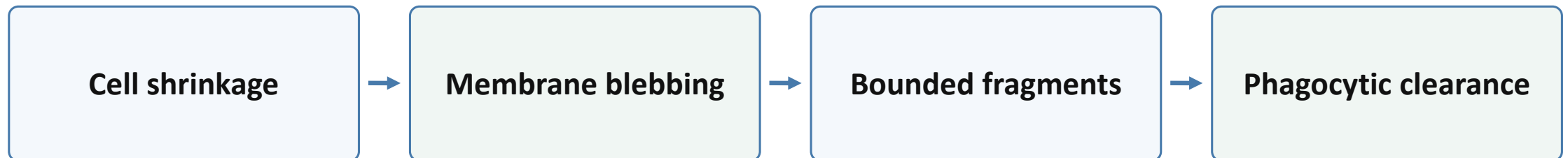
Chromatin condensation is characteristic

- Nuclear chromatin becomes dense and often peripheral.
- The nucleus may subsequently fragment.
- These changes are structural consequences of the apoptotic program.



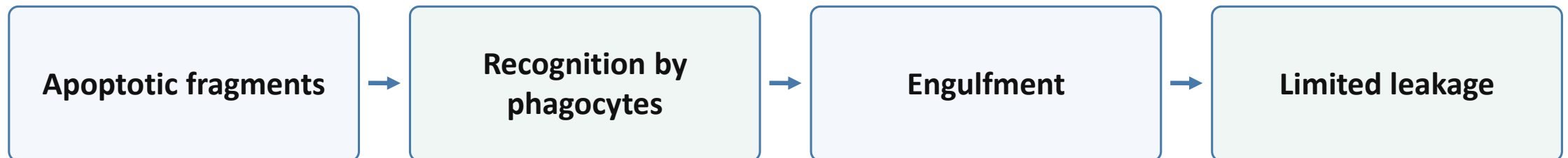
Membrane blebs produce apoptotic bodies

- The cell surface develops blebs.
- Fragments remain surrounded by plasma membrane.
- Apoptotic bodies can contain nuclear or cytoplasmic material.



Phagocytic clearance limits tissue reaction

- Apoptotic bodies expose signals recognized by phagocytes.
- Fragments are engulfed before cell contents are widely released.
- Individual apoptotic events may evoke little surrounding inflammation.



Why a biopsy may underestimate apoptosis

- Cell shrinkage and fragmentation occur quickly.
- Phagocytes remove the apoptotic remnants efficiently.
- A single H&E section may underrepresent the amount of prior cell death.

Rapid changes

Brief morphologic window

Clearance

Short tissue residence

Sampling

Limited snapshot

Apoptosis versus necrosis in tissue sections

- Apoptosis yields cell shrinkage, dense chromatin and discrete bodies.
- Necrosis more often includes swelling and plasma-membrane disruption.

Feature	Apoptosis	Necrosis
Cell size	Shrinkage	Swelling
Nuclear change	Condensation / fragmentation	Pyknosis, karyorrhexis, karyolysis
Cell boundary	Contained fragments	Membrane damage
Host response	Often minimal initially	Frequently inflammatory

CD8+ T cells can also produce IFN- γ

- CD8+ cells have activities beyond direct killing.
- Interferon- γ (IFN- γ) is a prominent secreted cytokine.
- This can contribute to tissue inflammatory reactions.

Direct cytolysis

IFN- γ –linked inflammation

CTL inflammation can resemble delayed hypersensitivity

- CD8+ cytokine responses resembling DTH.
- Such reactions are noted after some viral infections.
- Some contact-sensitizing exposures may also involve these responses.

CTL secretion

IFN- γ

Pattern

DTH-like inflammation

Settings

Virus / contact sensitizer

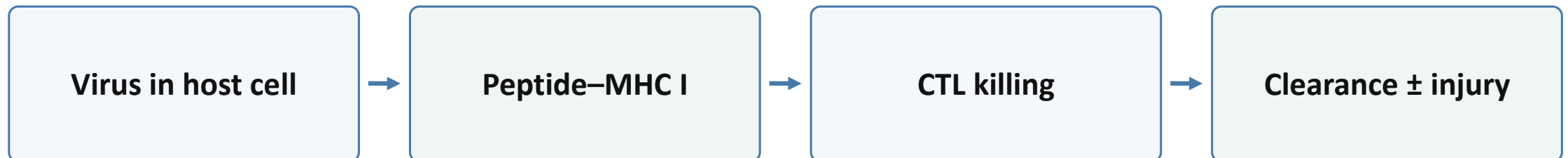
Differentiate primary killing from collateral inflammation

- Direct cytotoxicity removes specific antigen-bearing cells.
- Cytokine effects recruit or activate other inflammatory participants.

Feature	Cytotoxic effect	Inflammatory effect
Primary mediator	Perforin–granzyme / FasL	IFN- γ and other cytokines
Immediate target	Antigen-presenting cell	Inflammatory network
Main consequence	Cell death	Tissue inflammation

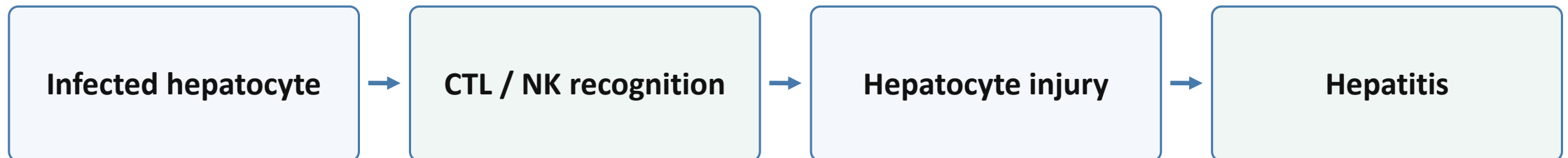
Viral infection: Protection has a tissue cost

- Virally infected cells display peptide on MHC class I.
- CTL killing helps eliminate the viral cellular reservoir.
- The resulting loss of infected tissue cells can cause disease manifestations.



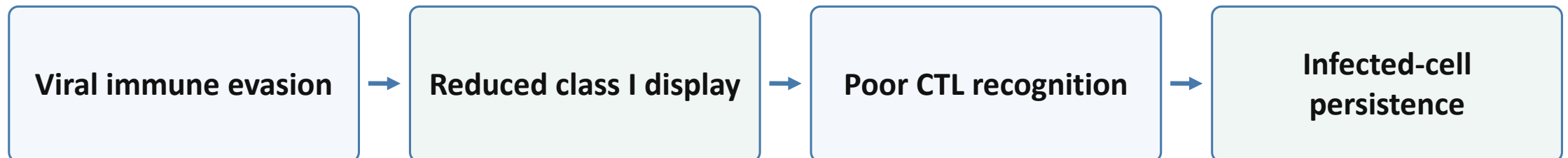
Viral hepatitis illustrates immunopathology

- Infected hepatocytes can be destroyed by cytotoxic lymphocytes.
- For hepatitis A, CTLs and NK cells as mediators of injury.
- Hepatocyte damage reflects the host response, not only viral presence.



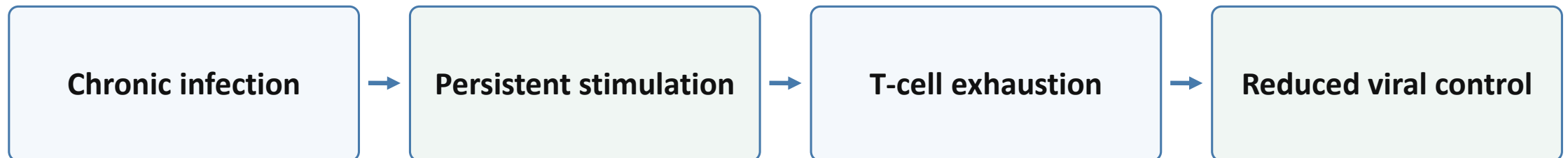
A virus can avoid CTL recognition

- Some DNA viruses interfere with MHC class I protein localization.
- Impaired peptide display reduces recognition by CD8+ CTLs.
- Antigen presentation is therefore a vulnerability in antiviral surveillance.



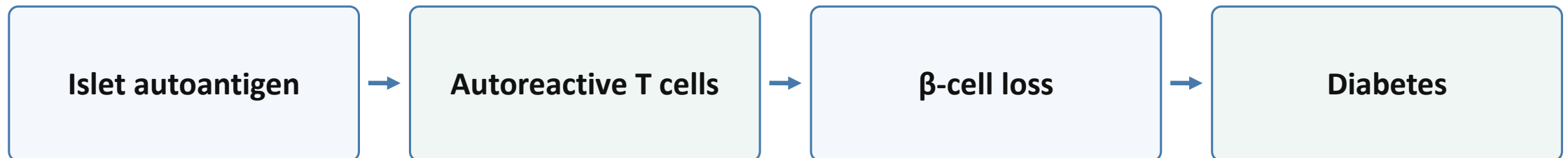
Chronic infection may attenuate CTL potency

- T-cell exhaustion in chronic HIV, HBV and HCV infections.
- The PD-1 pathway contributes to the exhausted phenotype.
- Persistent antigen can coexist with inadequate cellular control.



Type 1 diabetes: CTLs attack endocrine cells

- Pancreatic β -cell antigens become immune targets.
- T-cell inflammation and CTL-mediated β -cell destruction can coexist.
- Loss of β -cell mass compromises insulin production.



Insulitis reflects the immune injury setting

- Chronic inflammation in pancreatic islets.
- The lesion coexists with destruction of insulin-producing β cells.
- The tissue context matters beyond counting CD8+ cells.

Site

Pancreatic islet

Response

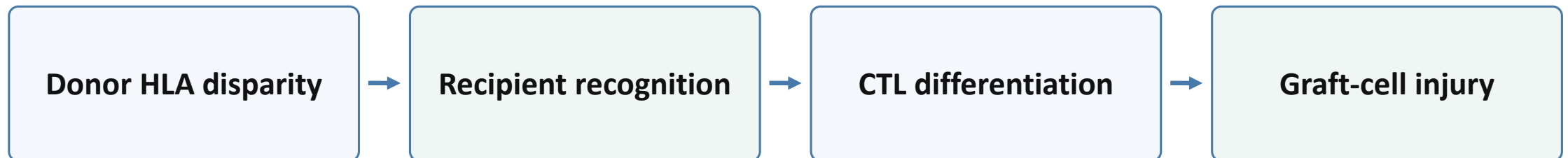
Inflammatory infiltrate

Result

β -cell destruction

Transplant rejection: Alloantigens are targets

- HLA molecules vary substantially between individuals.
- Recipient T cells may recognize donor alloantigens.
- Activated CD8+ effectors can damage the graft directly.



Acute cellular rejection has two T-cell arms

- CD8+ CTLs directly destroy graft cells.
- CD4+ T cells contribute cytokine-mediated inflammation.

Contributor	Mechanism	Tissue consequence
CD8+ CTL	Direct cellular cytotoxicity	Parenchymal cell death
CD4+ T cell	Cytokine-driven inflammation	Inflammatory tissue injury

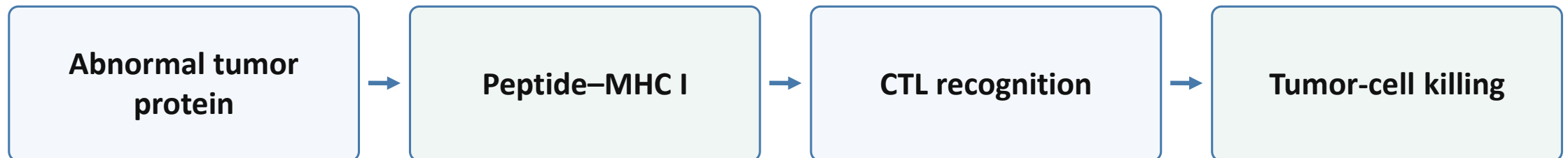
Cellular and antibody-mediated rejection differ

- Cellular rejection includes CTLs and CD4+ inflammatory responses.
- Antibody-mediated rejection targets graft endothelium via antibodies and complement.

Acute rejection arm	Immune effector	Core injury route
Cellular	T lymphocytes	Cytolysis / inflammation
Antibody-mediated	Donor-reactive antibodies	Complement / vascular injury

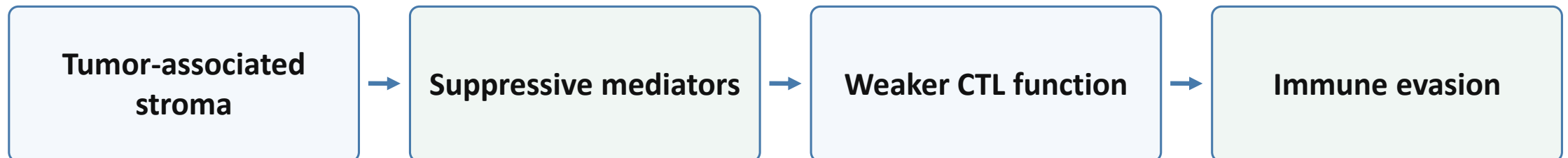
Tumor cells can present abnormal peptides

- Mutated or abnormal cytosolic proteins generate potential tumor peptides.
- MHC class I presents these peptides to antigen-specific CD8+ T cells.
- CTLs participate in host immune surveillance of transformed cells.



A tumor microenvironment may weaken CTLs

- Immunosuppressive stromal interactions.
- TGF- β and related factors may favor Tregs or suppress CD8+ function.
- Presence of tumor-specific CTLs does not guarantee effective tumor elimination.



CD8 positivity alone does not prove cytotoxicity

- CD8 is a T-cell lineage/coreceptor marker, not direct evidence of killing.
- Interpretation requires antigen context and evidence of target-cell injury.
- A mixed inflammatory lesion may reflect several simultaneous mechanisms.

Phenotype

CD8+ population

Target

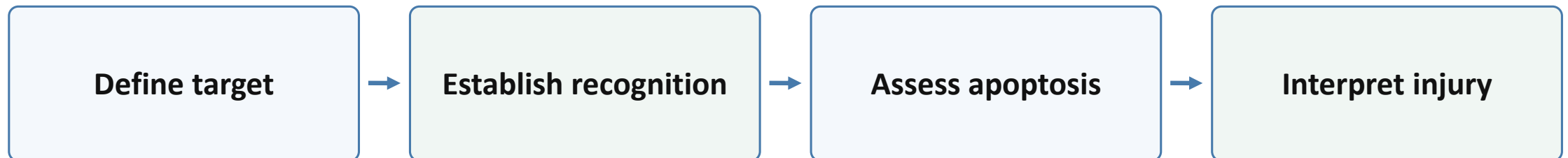
Relevant antigen display

Effect

Cell death / injury

A causal reading of a CTL-rich lesion

- Identify which tissue cells display the implicated antigen.
- Ask whether apoptotic injury affects those targets.
- Separate direct killing from cytokine-mediated secondary damage.



Why inflammation does not negate apoptosis

- The individual apoptotic event may provoke little acute inflammation.
- The immune disease itself can include continuing T-cell cytokine secretion.
- Tissue-level inflammation and cell-level apoptosis can therefore coexist.

Apoptotic target

Inflamed tissue

Case: Infected hepatocytes and cell injury

Clinical scenario

- A patient has acute viral hepatitis with hepatocyte death.
- The infected hepatocyte displays a viral peptide on MHC class I.
- Question: What immune effector and pathway can explain the injury?

Reason through the pathway

Identify target

Identify CTL signal

Predict tissue effect

Case reasoning: The hepatitis paradox

- The same CTL response helps limit infected-cell reservoirs.
- In an essential parenchymal organ, killing creates clinically important tissue damage.
- Protection and immunopathology are two consequences of the same interaction.

Viral control

Hepatocyte loss

Case: Selective loss of pancreatic β cells

Clinical scenario

- An autoimmune islet lesion contains lymphocytic inflammation.
- Insulin-producing β cells are progressively lost.
- Question: Why can CD8+ cytotoxicity contribute to endocrine failure?

Reason through the pathway

Identify target

Identify CTL signal

Predict tissue effect

Case: Acute graft dysfunction

Clinical scenario

- A transplanted organ develops acute cellular rejection.
- The lesion includes recipient T-cell responses to donor HLA.
- Question: Distinguish the cytotoxic and cytokine-mediated components.

Reason through the pathway

Identify target

Identify CTL signal

Predict tissue effect

Case: Impaired tumor immune surveillance

Clinical scenario

- A tumor bears abnormal protein-derived epitopes.
- Its microenvironment suppresses CD8+ T-cell activity.
- Question: Can tumor antigen presentation alone ensure destruction?

Reason through the pathway

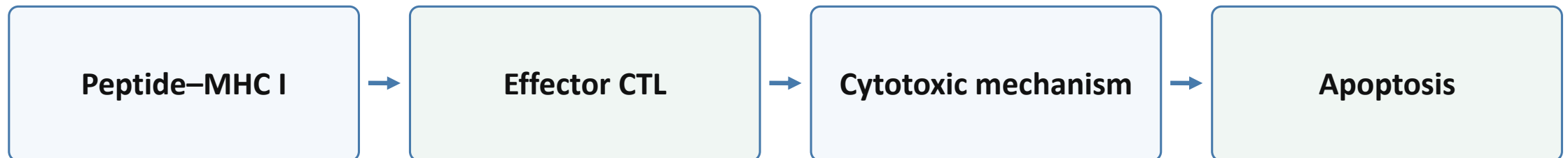
Identify target

Identify CTL signal

Predict tissue effect

From peptide presentation to cellular apoptosis

- Cytosolic antigen enters the class I peptide-display pathway.
- Activated CTL recognizes cognate peptide–MHC I on the target.
- Granules or Fas signaling initiate a caspase-driven apoptotic program.



One mechanism, four clinicopathologic settings

- Viruses: Infected-cell removal may injure parenchyma.
- Autoimmunity: Self-tissue cells become antigenic targets.

Context	CTL target	Consequence
Viral disease	Infected host cell	Control ± tissue injury
Type 1 diabetes	Pancreatic β cell	Endocrine cell loss
Allograft rejection	Donor tissue cell	Graft dysfunction
Tumor immunity	Transformed cell	Immune surveillance

What a pathology trainee should retain

- Recognition is antigen-specific and MHC class I-restricted.
- Perforin–granzymes dominate; FasL–Fas adds an extrinsic route.
- Caspases generate apoptotic morphology and cellular loss.
- IFN- γ adds an inflammatory dimension to CD8+ immune responses.

Selected primary textbook sources

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition.
- Immune-system disease: CTL cytotoxicity, antigen presentation and type IV injury.
- Cell injury and death: apoptosis and death-receptor pathways.
- Clinical examples: viral hepatitis, transplantation and neoplastic immunity.