

Major Histocompatibility Complex Molecules

The peptide display system of adaptive immunity

MHC class I · CD8⁺

MHC class II · CD4⁺

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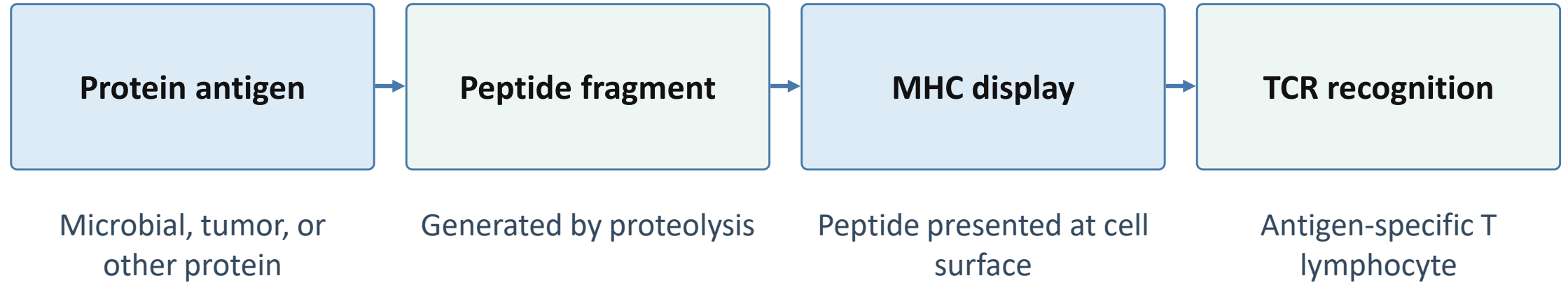
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Learning objectives

- Relate HLA gene architecture and polymorphism to antigen display.
- Distinguish class I and class II structure, distribution, and peptide sources.
- Trace antigen processing to CD8⁺ and CD4⁺ T-cell recognition.
- Explain HLA-dependent immune responses and transplantation compatibility.

T cells recognize processed protein antigens



The T-cell receptor recognizes a peptide in the context of its displaying MHC molecule.

Peptide display makes intracellular events visible

Inside a host cell

Microbial or abnormal proteins are processed

Peptides enter the class I presentation route

CD8⁺ cells survey the presented peptides

After cellular uptake

Ingested proteins are digested in vesicles

Peptides enter the class II presentation route

CD4⁺ cells respond to the presented peptides

T cells and B cells recognize different antigen forms

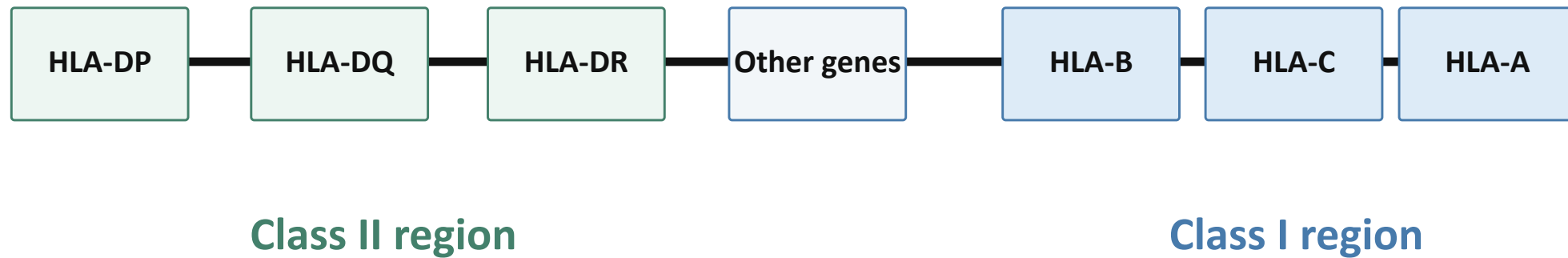
Feature	T lymphocyte	B lymphocyte
Recognized target	Peptide–MHC complex	Native antigen via membrane Ig
Main receptor	T-cell receptor (TCR)	B-cell receptor (BCR)
Functional connection	Cell-mediated response or helper function	Antibody production after activation

Why “major histocompatibility complex”?

- MHC molecules were identified through their role in graft rejection.
- Differences between individuals influence tissue compatibility.
- In humans these molecules are called human leukocyte antigens (HLA).
- They became central to understanding antigen recognition and immune disease.

The HLA system is encoded on chromosome 6

Chromosome 6 · HLA gene complex



Two molecular classes divide peptide-display tasks

MHC class I

Displays peptides derived from cytosolic proteins

Recognized by CD8⁺ T cells

Supports elimination of infected or tumor cells

MHC class II

Displays peptides derived from internalized proteins

Recognized by CD4⁺ helper T cells

Supports macrophage activation and antibody responses

HLA alleles are exceptionally polymorphic

- Human populations contain thousands of HLA gene alleles.
- Sequence variation changes the peptides that individual molecules can bind.
- Most unrelated individuals express different HLA combinations.
- This diversity contributes to immune breadth and graft incompatibility.

The HLA locus contains distinct class I and II regions

Class I

HLA-A, HLA-B, and HLA-C
encode class I heavy
chains.

Class II

HLA-DP, HLA-DQ, and
HLA-DR encode class II
molecules.

Additional genes

The complex also includes
genes for antigen-
processing proteins.

HLA-A, HLA-B, and HLA-C encode class I heavy chains

- Three closely linked genes encode the polymorphic α chain of class I MHC.
- Their protein products bind diverse peptides through variable groove residues.
- Each expresses a form of class I molecular display at the cell surface.

Class I display is broadly distributed

**Nucleated host
cell**

CLASS I

Virus-infected cell

CLASS I

**Potential tumor
cell**

CLASS I

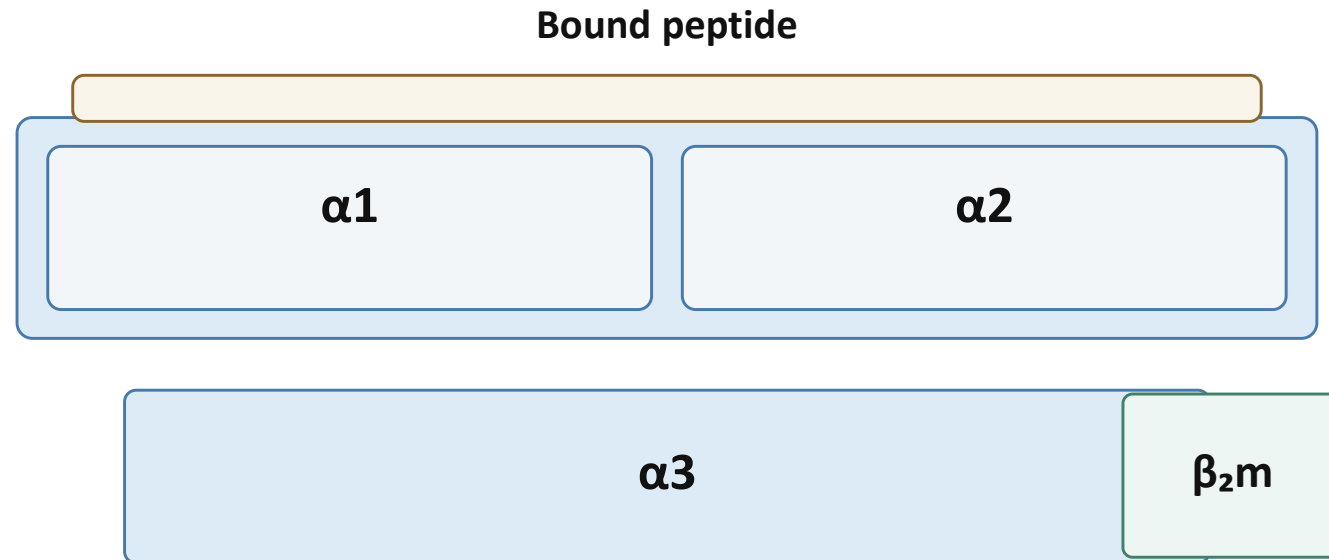
Platelet

CLASS I

Broad host-cell surveillance for cytosolic antigens

MHC class I consists of two associated proteins

- Polymorphic α heavy chain
- Nonpolymorphic β_2 -microglobulin
- $\alpha 1$ / $\alpha 2$ create groove
- $\alpha 3$ contacts CD8



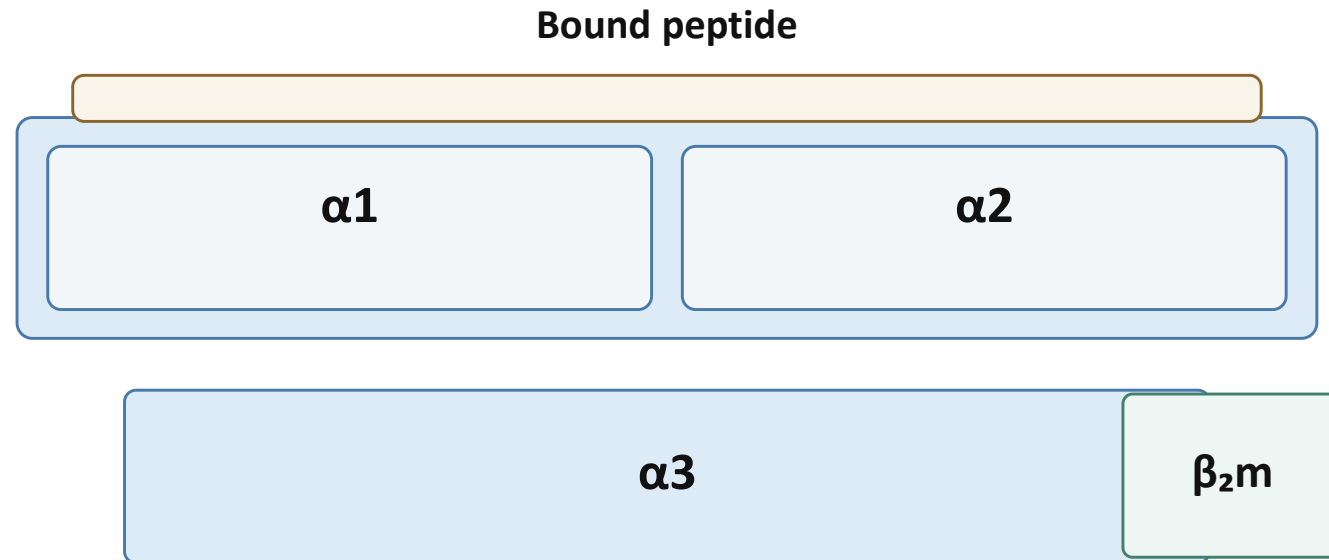
Schematic: Peptide groove formed by $\alpha 1$ and $\alpha 2$

Class I heavy chain contains three external domains

- The heavy α chain has $\alpha 1$, $\alpha 2$, and $\alpha 3$ extracellular domains.
- The $\alpha 1$ and $\alpha 2$ domains construct the peptide-binding cleft.
- The $\alpha 3$ domain provides a contact site for the CD8 coreceptor.
- The nonpolymorphic β_2 -microglobulin associates noncovalently with the heavy chain.

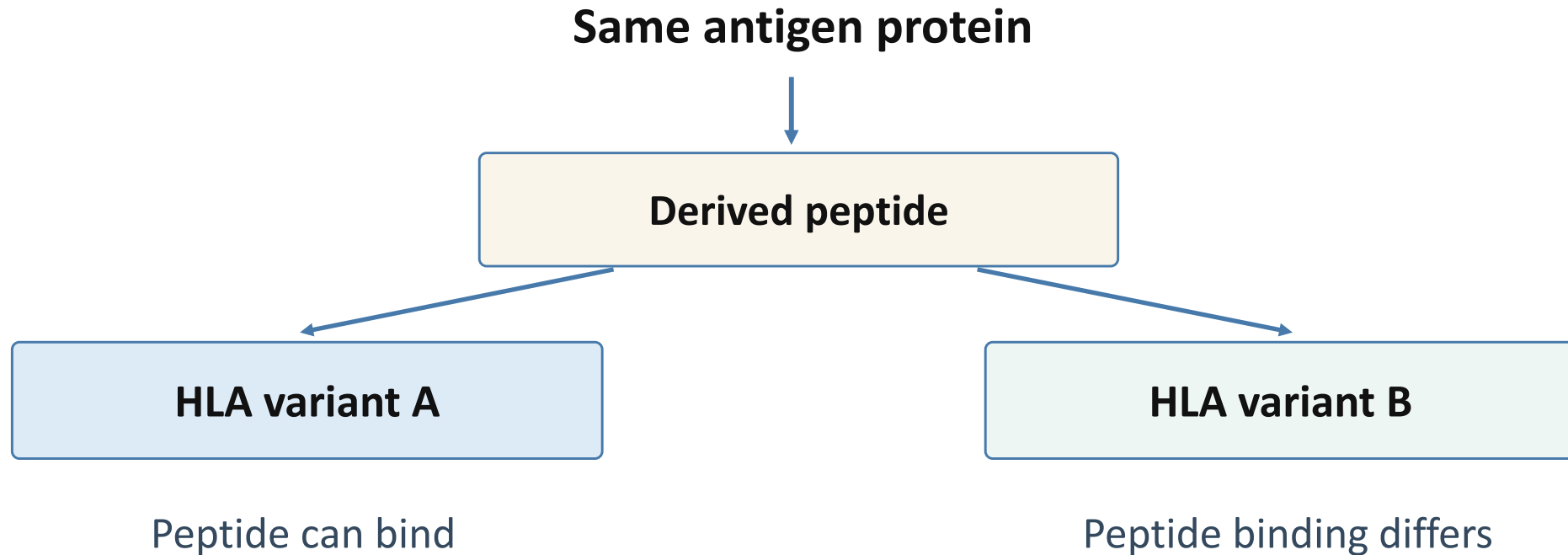
The class I peptide groove is formed by $\alpha 1$ and $\alpha 2$

- Polymorphic α heavy chain
- Nonpolymorphic β_2 -microglobulin
- $\alpha 1$ / $\alpha 2$ create groove
- $\alpha 3$ contacts CD8



Schematic: Peptide groove formed by $\alpha 1$ and $\alpha 2$

Class I allele variation changes the peptide repertoire



Illustrates allele-dependent peptide presentation, not an absolute binding prediction

Class I samples proteins originating in the cytosol

Cellular source

Cytosolic proteins are a major source of class I peptide antigens.

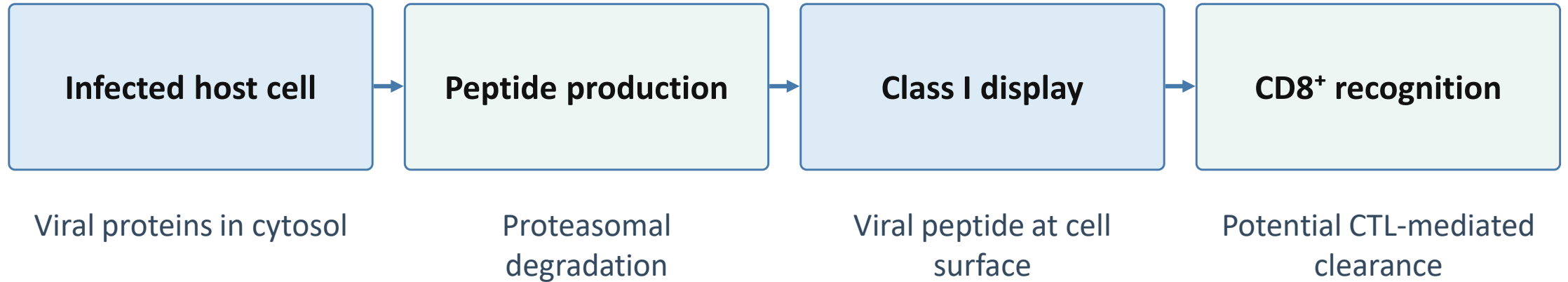
Infection

Viral proteins can enter this processing pathway.

Neoplasia

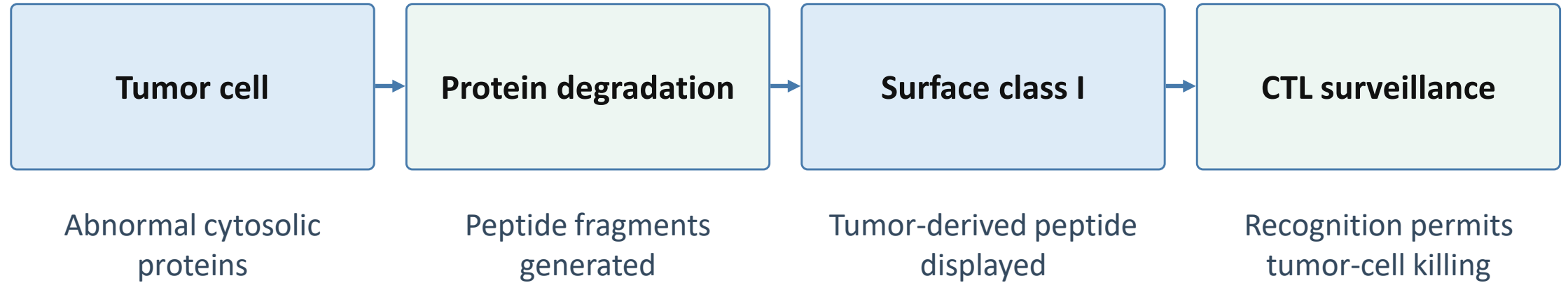
Abnormal tumor proteins can generate displayed peptides.

Viral infection creates class I antigen targets



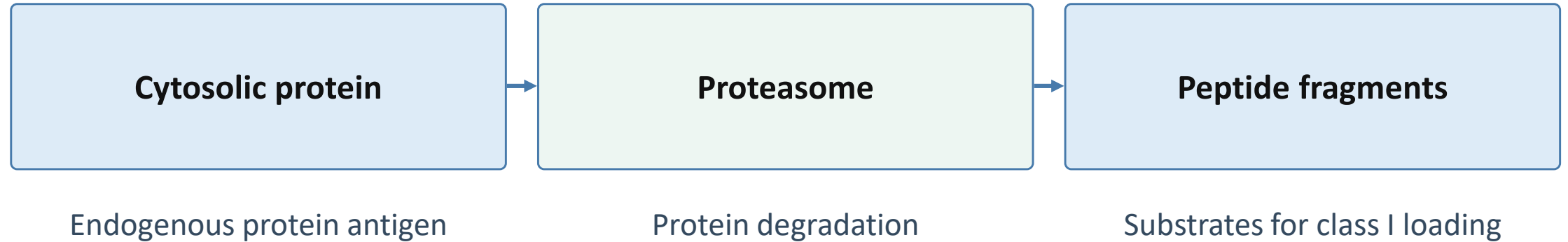
The target is the infected cell displaying a viral peptide–MHC class I complex.

Tumor proteins may enter the class I pathway



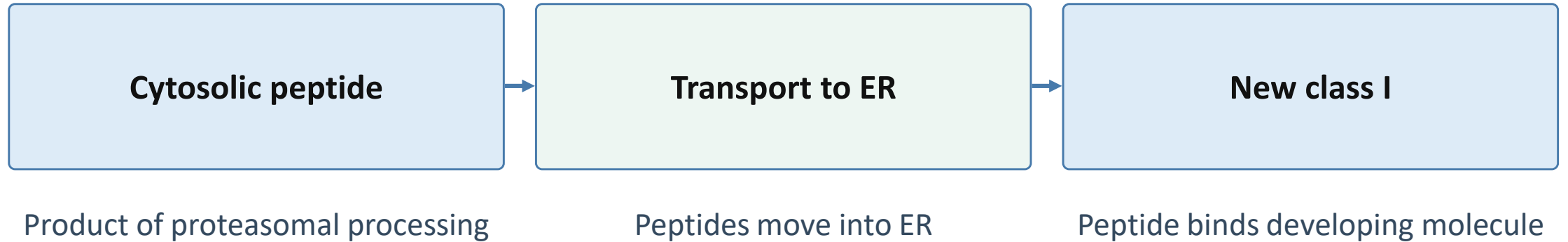
Class I displays intracellular tumor-derived antigens to CD8⁺ cytotoxic T cells.

Proteasomes generate cytosolic peptide fragments



Class I antigen processing begins with degradation of cytosolic proteins.

Class I peptides enter the endoplasmic reticulum

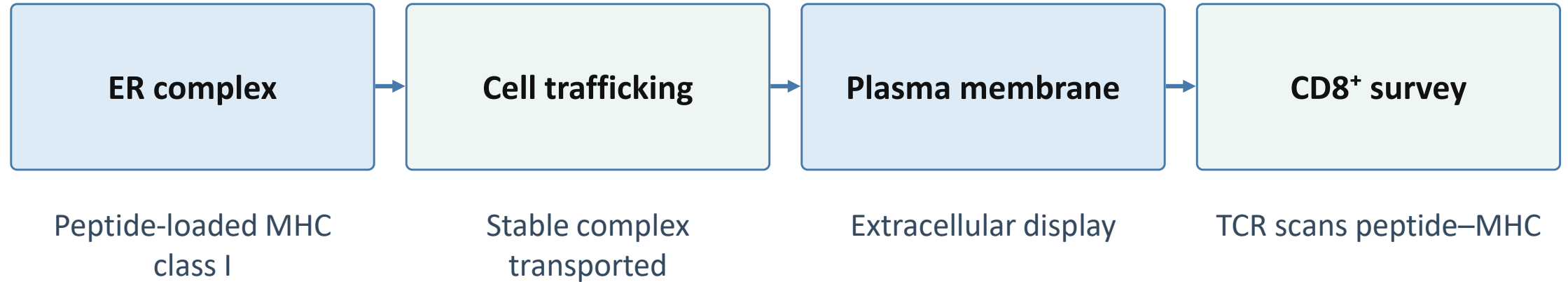


Antigen processing and class I assembly converge within the endoplasmic reticulum.

Peptide binding stabilizes the class I complex

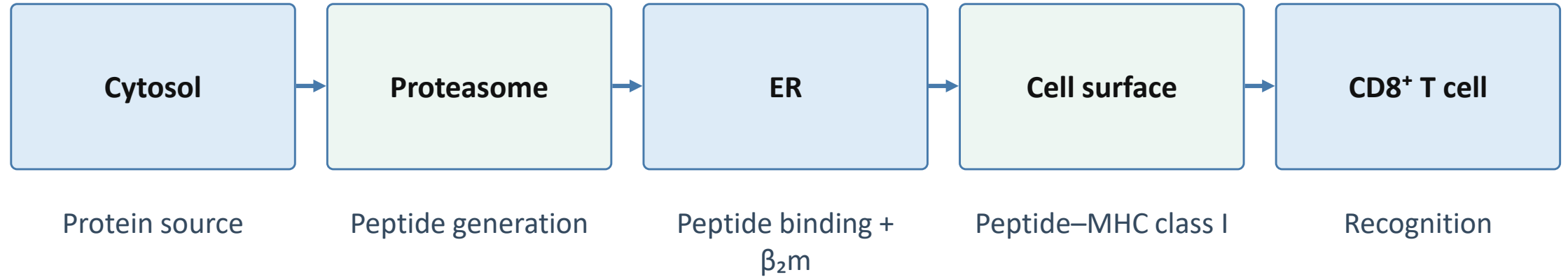
- Newly synthesized class I molecules bind suitable peptides in the ER.
- Association with β_2 -microglobulin supports a stable peptide–MHC complex.
- The assembled complex is subsequently transported to the plasma membrane.

Surface trafficking completes class I presentation



A cytosolic antigen becomes accessible to lymphocytes outside the cell.

Class I antigen processing: Integrated pathway



CD8 binds the class I $\alpha 3$ domain

CD8⁺ T lymphocyte

T-cell receptor (TCR)

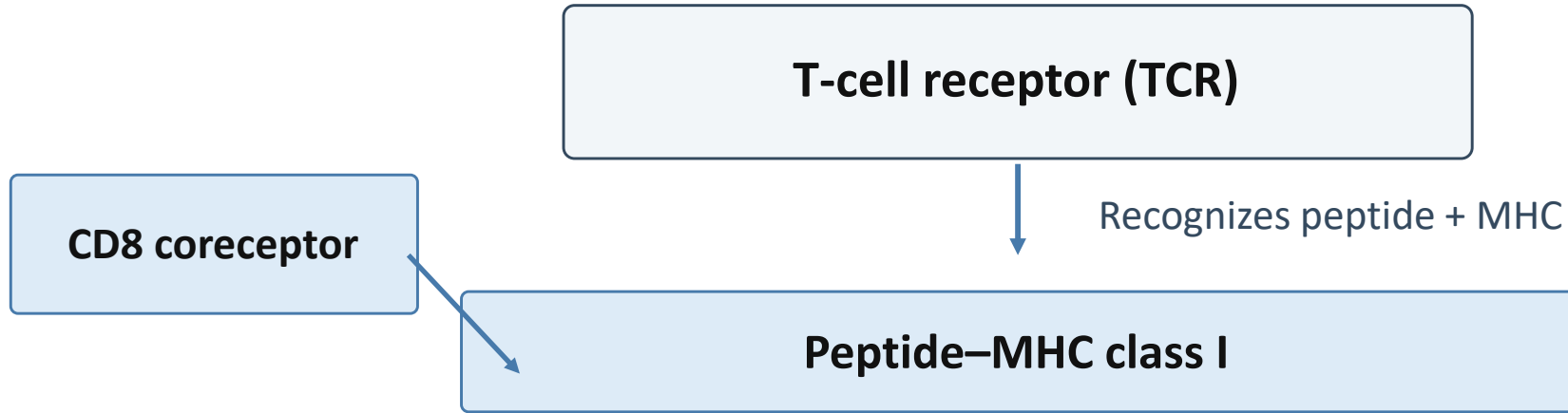
Recognizes peptide + MHC

CD8 coreceptor

Peptide–MHC class I

Binds the $\alpha 3$ domain of class I

Schematic: TCR and coreceptor have distinct contacts



The TCR and CD8 make distinct molecular contacts

- The TCR recognizes the composite peptide–MHC class I complex.
- CD8 binds a nonpolymorphic region of the class I heavy chain.
- CD8 acts as a coreceptor during antigen recognition and T-cell activation.
- The antigenic peptide determines specificity; The MHC class determines coreceptor pairing.

MHC class I restriction defines CD8⁺ recognition

Compatible recognition

Antigen peptide is displayed by class I

TCR engages peptide–class I

CD8 associates with class I $\alpha 3$

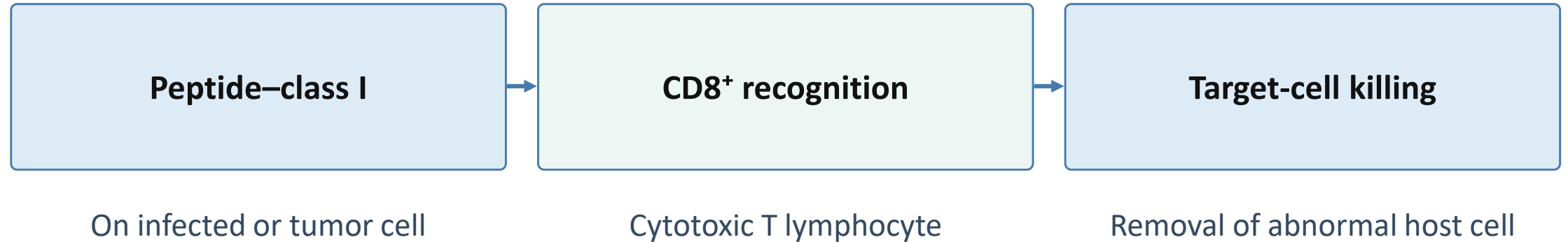
Incompatible context

Peptide by itself is not the normal target

Class II does not substitute for class I

The class I restriction requirement is not met

Recognition by CD8⁺ cells supports cytotoxic defense



Class I connects intracellular antigens with CTL-mediated elimination.

Why class I is expressed on virtually all nucleated cells

- Viruses may infect many different nucleated cell types.
- Tumors can arise from many kinds of nucleated host cells.
- Broad class I display allows cytotoxic T cells to survey such cells.
- Platelets also express class I MHC, as stated in the source.

HLA-DP, HLA-DQ, and HLA-DR form class II loci

HLA-DP

Class II genes encoding α and β components.

HLA-DQ

Another class II gene subregion within HLA-D.

HLA-DR

A third principal class II gene subregion.

Unlike class I, the two chains of class II are both polymorphic.

Class II expression is concentrated in antigen presenters

Dendritic cell

CLASS II

Macrophage

CLASS II

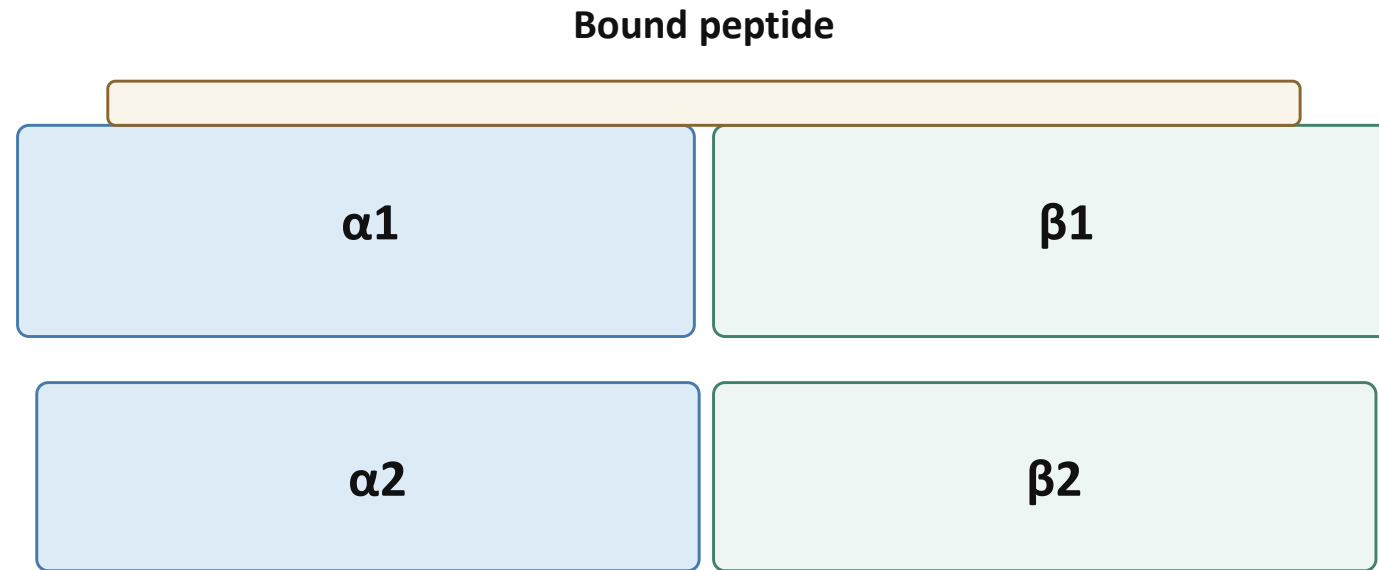
B lymphocyte

CLASS II

Professional antigen presentation of ingested proteins

MHC class II contains an α chain and a β chain

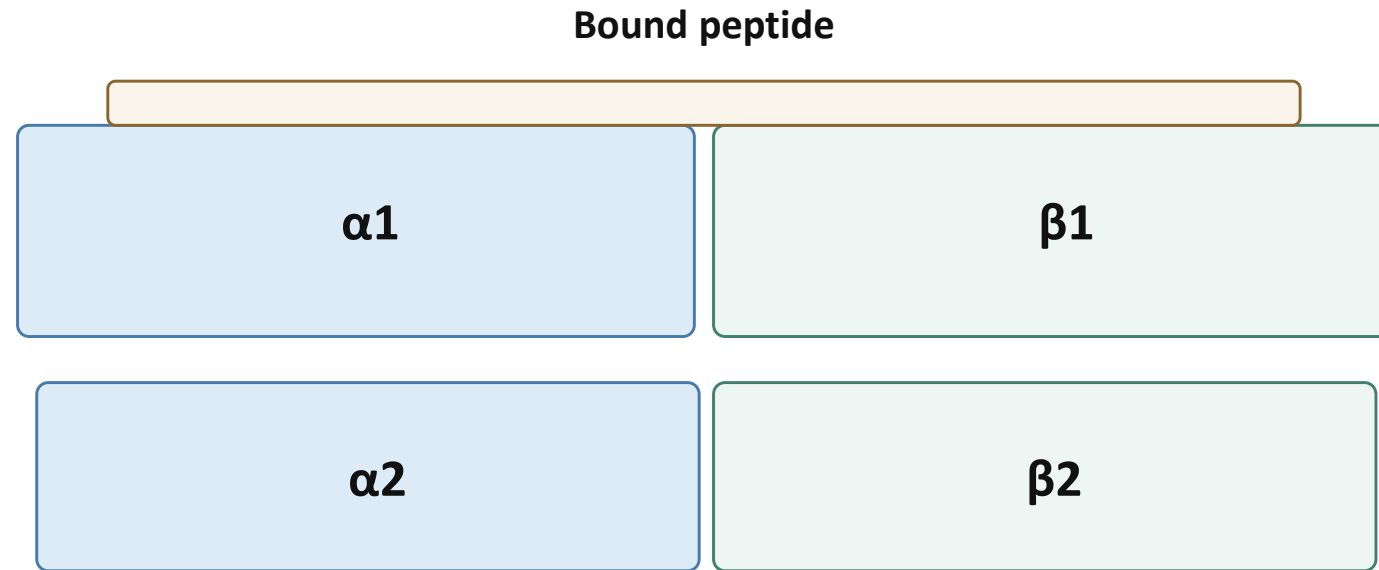
- Both α and β chains vary
- $\alpha 1$ / $\beta 1$ create groove
- $\alpha 2$ / $\beta 2$ form lower domains
- $\beta 2$ contacts CD4



Schematic: Peptide groove formed by $\alpha 1$ and $\beta 1$

Class II forms its peptide groove from $\alpha 1$ and $\beta 1$

- Both α and β chains vary
- $\alpha 1$ / $\beta 1$ create groove
- $\alpha 2$ / $\beta 2$ form lower domains
- $\beta 2$ contacts CD4

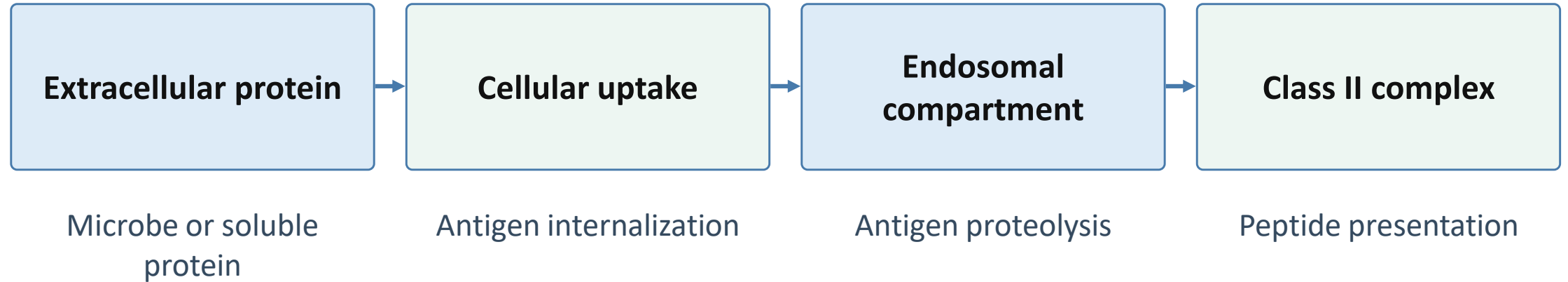


Schematic: Peptide groove formed by $\alpha 1$ and $\beta 1$

Both class II chains contribute to polymorphism

- The noncovalently associated class II α and β chains are both polymorphic.
- The antigen-binding cleft depends on the $\alpha 1$ and $\beta 1$ domains.
- Most allelic differences described in the text occur in this peptide-binding region.
- Variation therefore changes which extracellular-derived peptides can be presented.

Class II antigens originate from internalized proteins

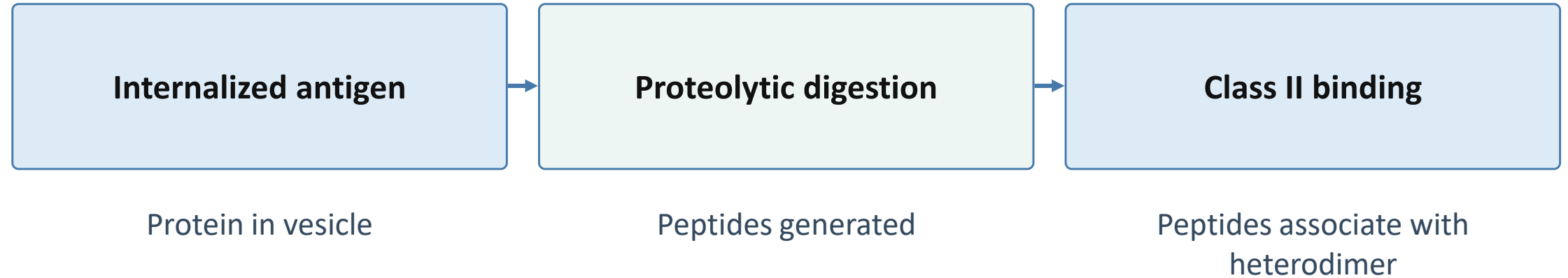


The uptake route distinguishes class II presentation from class I processing.

Endosomes and lysosomes digest internalized antigens

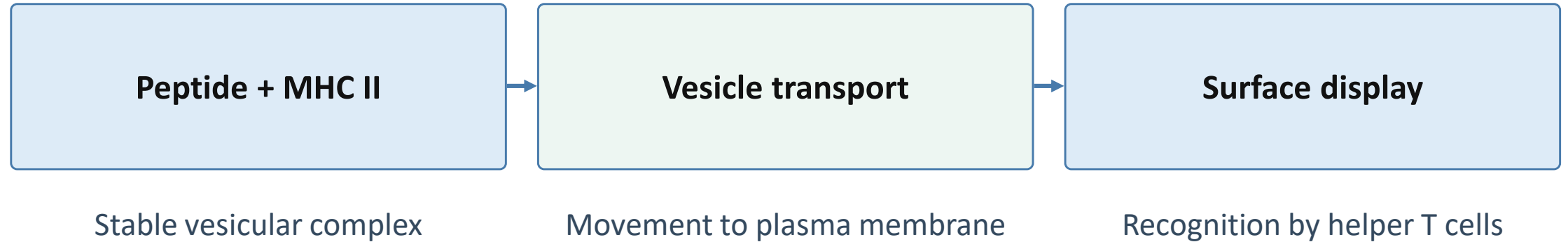
- After uptake, proteins enter intracellular vesicular compartments.
- Proteolysis in endosomes or lysosomes generates peptide fragments.
- These peptides become available for loading onto class II molecules.

Class II loading occurs in intracellular vesicles



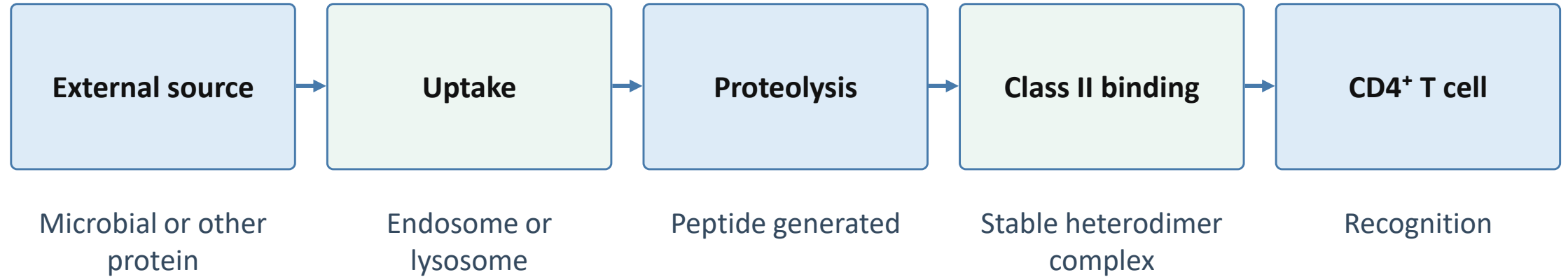
Peptide–class II complexes are assembled within vesicular compartments.

Class II complexes travel to the cell surface



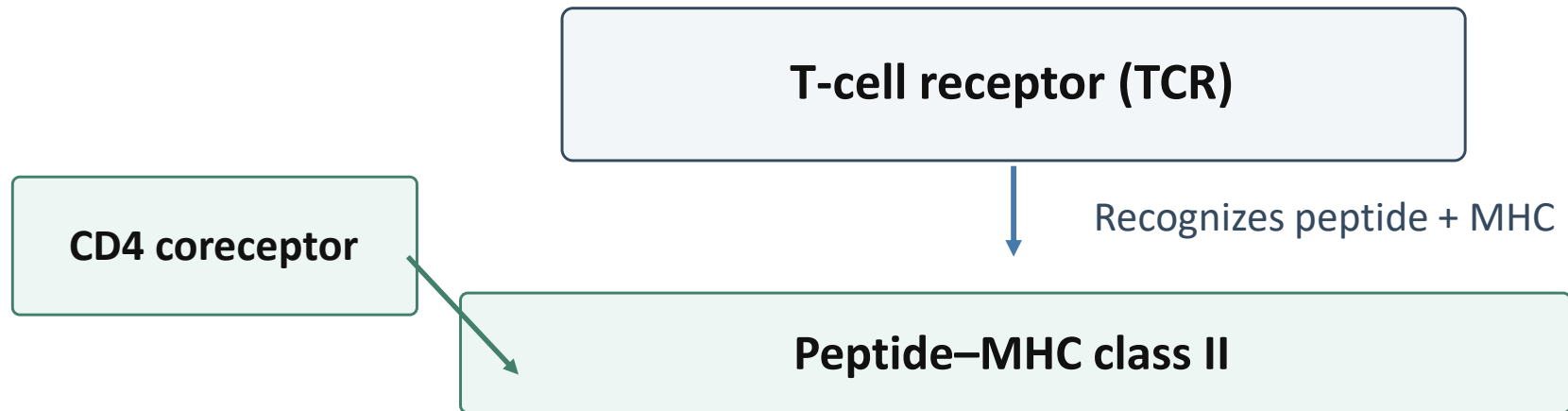
The same physical logic applies: Peptide becomes visible only when displayed by MHC.

Class II processing: Integrated pathway



CD4 binds the class II $\beta 2$ domain

CD4⁺ helper T lymphocyte



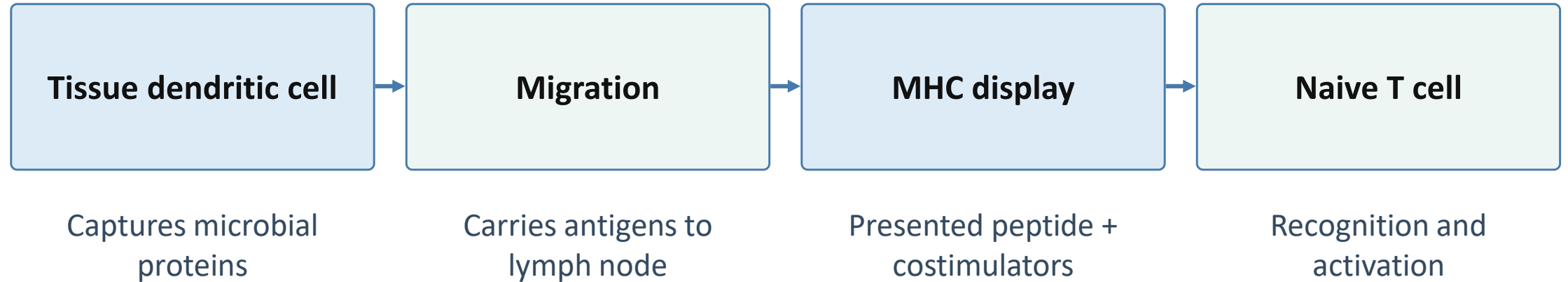
Binds the $\beta 2$ domain of class II

Schematic: TCR and coreceptor have distinct contacts

MHC class II restriction defines helper recognition

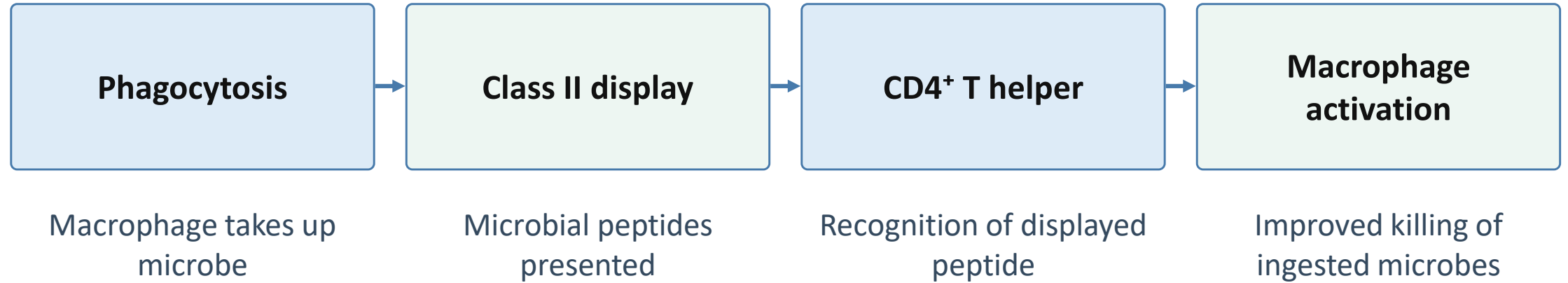
- CD4⁺ cells recognize antigen in association with MHC class II.
- The TCR engages the peptide–class II complex.
- CD4 acts as a coreceptor by binding the class II β 2 domain.
- Helper function is therefore coupled to the class II presentation pathway.

Dendritic cells link antigen capture to T-cell priming



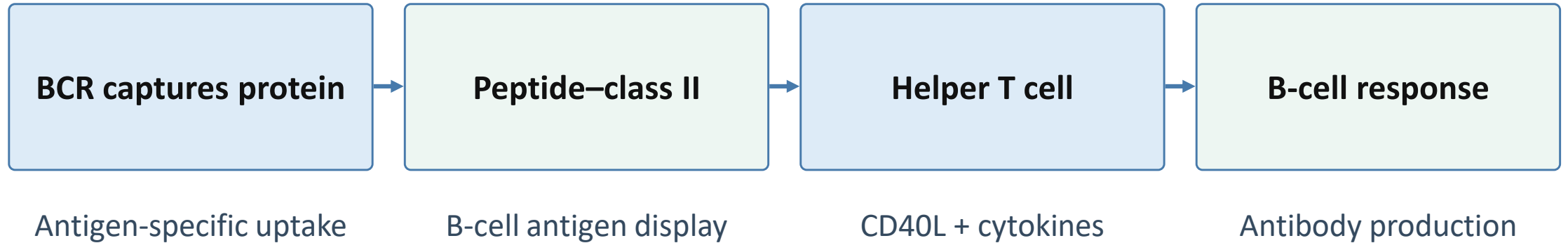
Antigen capture and lymphoid-organ presentation concentrate encounters with rare naive T cells.

Macrophages present ingested microbial antigens



Class II display enables helper cells to act on the same phagocyte containing the microbe.

B lymphocytes present protein antigens to helper T cells



B cells require linked peptide presentation to receive cognate help for many protein antigens.

CD4⁺ helper cells coordinate distinct effector arms

Macrophage help

Helper T cells activate phagocytes that have ingested microbes.

B-cell help

Helper cells drive antibody responses to protein antigens.

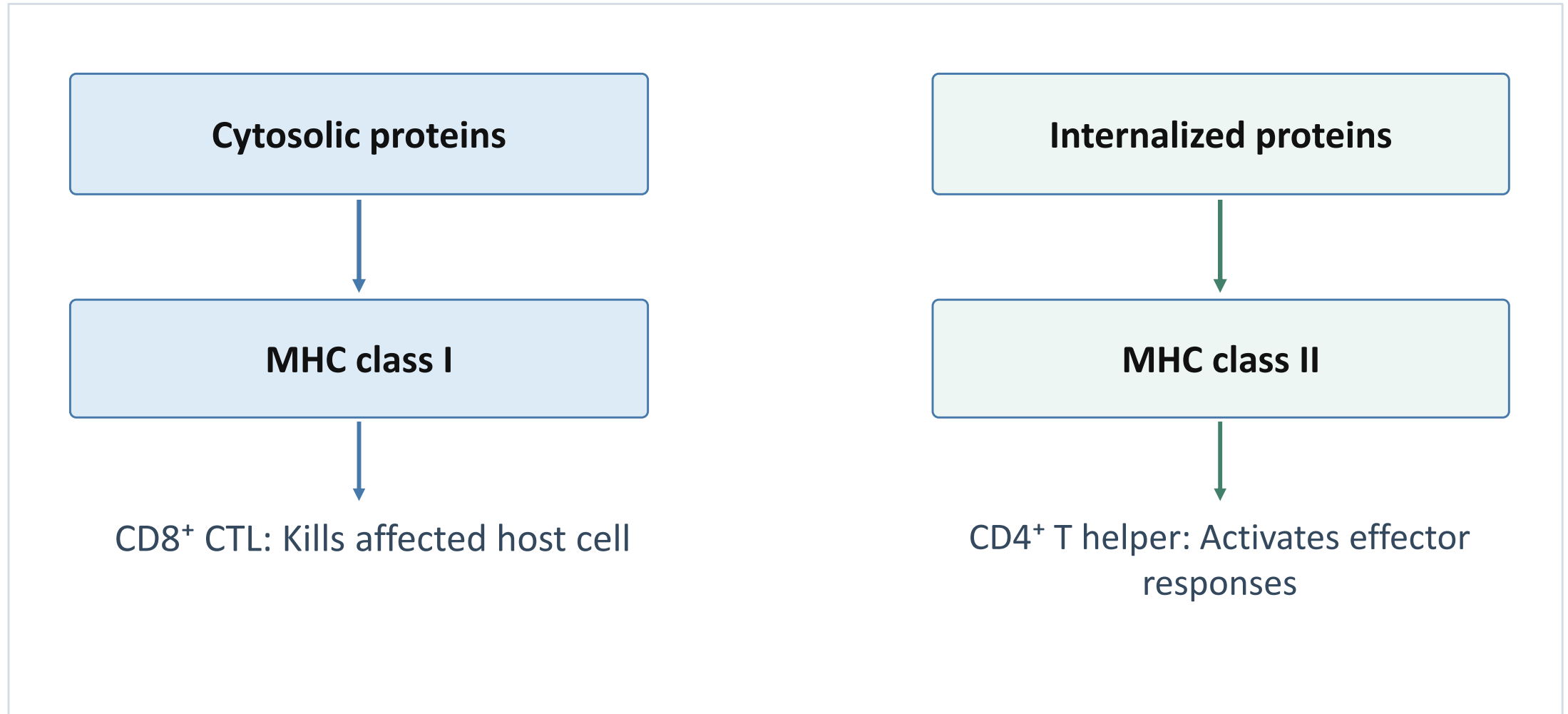
Immune direction

Class II links internalized antigens to protective effector programs.

Class I and class II differ at every functional level

Property	MHC class I	MHC class II
Principal gene region	HLA-A, -B, -C	HLA-DP, -DQ, -DR
Protein chains	α heavy chain + β_2m	Polymorphic α + β chains
Main peptide origin	Cytosolic proteins	Internalized proteins
Coreceptor	CD8	CD4
T-cell program	Cytotoxic killing	Helper responses

Different intracellular compartments determine peptide origin



T-cell identity predicts the presenting MHC class

T cell	Coreceptor target	MHC-restricted recognition	Typical function
CD8⁺	Class I $\alpha 3$	Peptide–MHC I	CTL killing
CD4⁺	Class II $\beta 2$	Peptide–MHC II	Macrophage and B-cell help

Peptide display alone does not complete naive T-cell activation

Signal 1

TCR recognizes peptide displayed by MHC

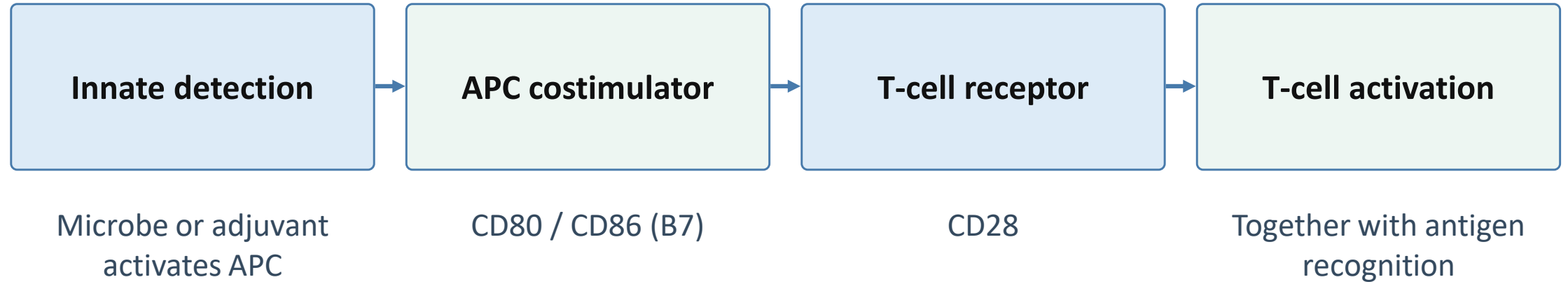
Specifies the antigen recognized by the T cell

Signal 2

APC provides costimulatory molecules

Supports naive T-cell activation in response to danger

CD80/CD86–CD28 is a principal costimulatory interaction



Costimulation is mechanistically separate from the peptide–MHC–TCR interaction.

HLA haplotypes are inherited gene combinations

- An HLA haplotype is the set of HLA alleles on one chromosome.
- Each individual inherits one HLA haplotype from each parent.
- The inherited set is usually transmitted as a block.
- Together the two haplotypes determine an individual's HLA profile.

HLA haplotypes pass from each parent to offspring

Parent 1

H1

H2

Parent 2

H3

H4

Possible offspring combinations (one haplotype from each parent)

H1 + H3

H1 + H4

H2 + H3

H2 + H4

If two siblings inherit the same pair: 1 of 4 possible pairings under standard assumptions

Both parental HLA sets are generally expressed

Maternal chromosome

Contains one inherited HLA haplotype

Contributes HLA molecules to cell surface

Paternal chromosome

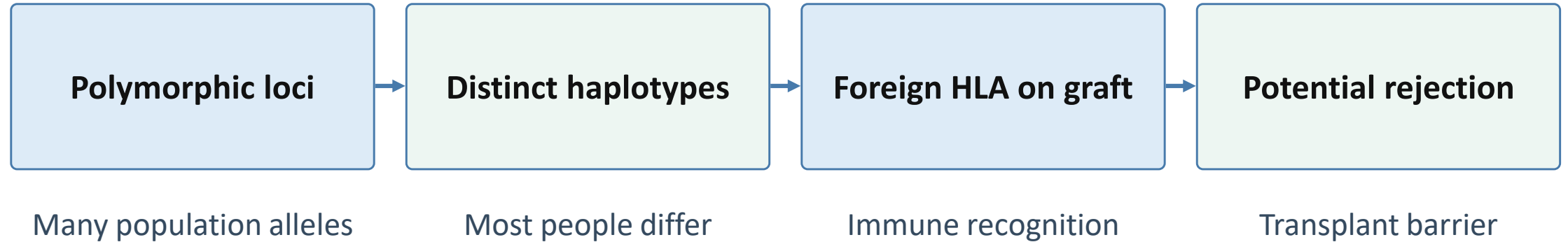
Contains the second inherited HLA haplotype

Also contributes HLA molecules to surface

HLA-identical siblings: The one-in-four principle

- Each sibling inherits one of two parental haplotypes from each parent.
- With usual inheritance assumptions, four parental combinations are equally likely.
- The probability that two siblings share both inherited haplotypes is 1 in 4.
- This probability is for a specified sibling pair, not a guarantee in a family.

Extreme HLA diversity complicates organ matching



The original discovery of MHC molecules came from transplant compatibility.

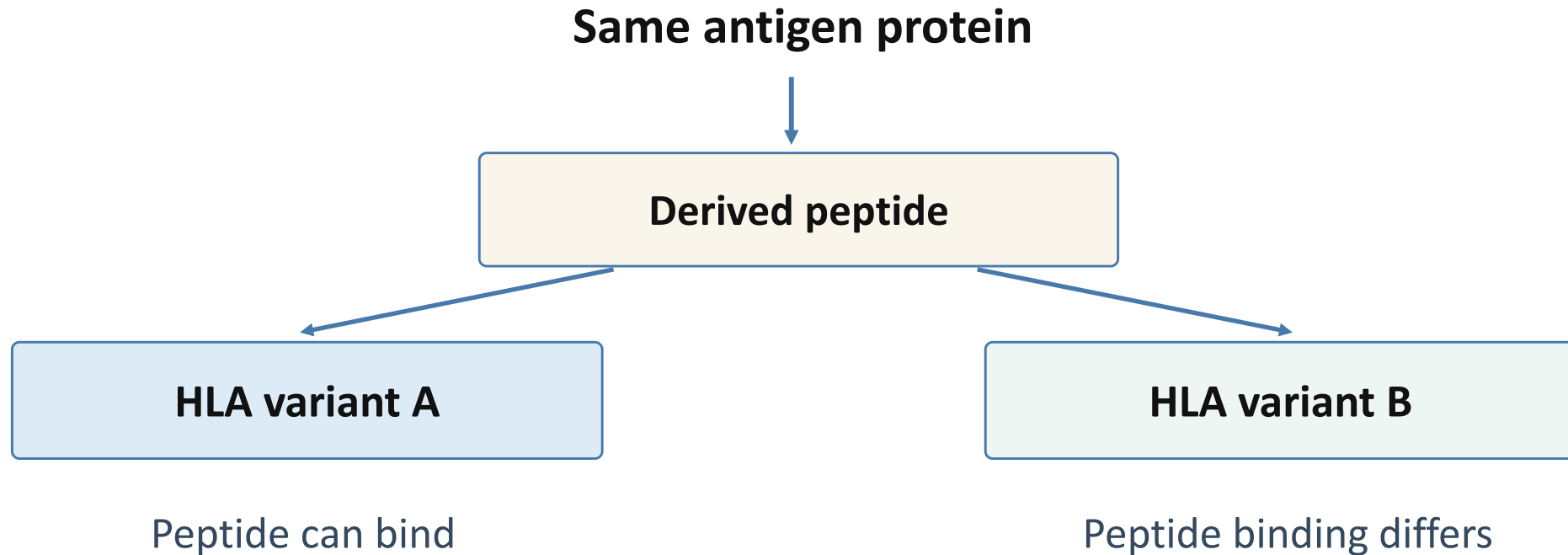
Sibling HLA matching has practical transplant importance

- Close relatives may share complete HLA haplotypes.
- Siblings are often evaluated as potential donors when clinically appropriate.
- The text specifically cites kidney and hematopoietic stem cell transplantation.
- The HLA profile is one part of donor–recipient compatibility assessment.

Polymorphism broadens species-level immune recognition

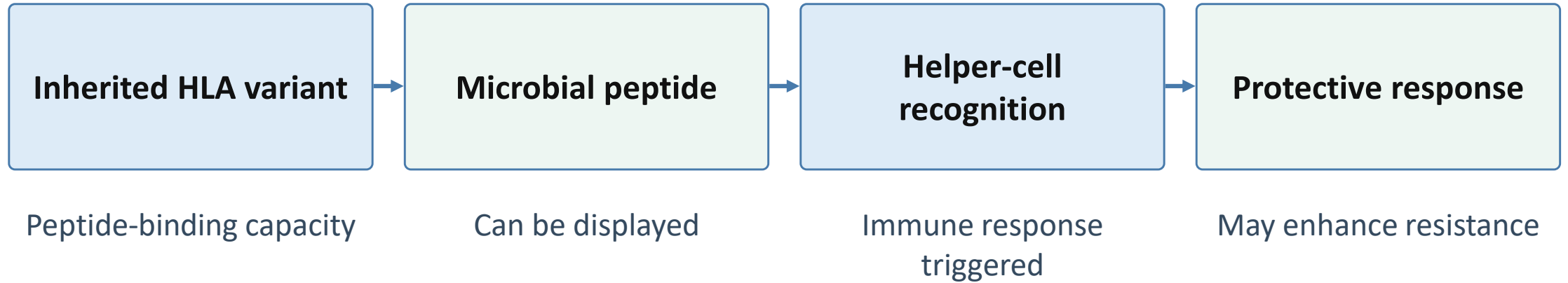
- An HLA molecule binds only a subset of possible antigenic peptides.
- Different alleles broaden the peptide repertoire across a population.
- The text proposes that this diversity offers protection against diverse infections.
- The advantage occurs at population level even when individuals differ in responsiveness.

Peptide binding constrains each individual's T-cell response



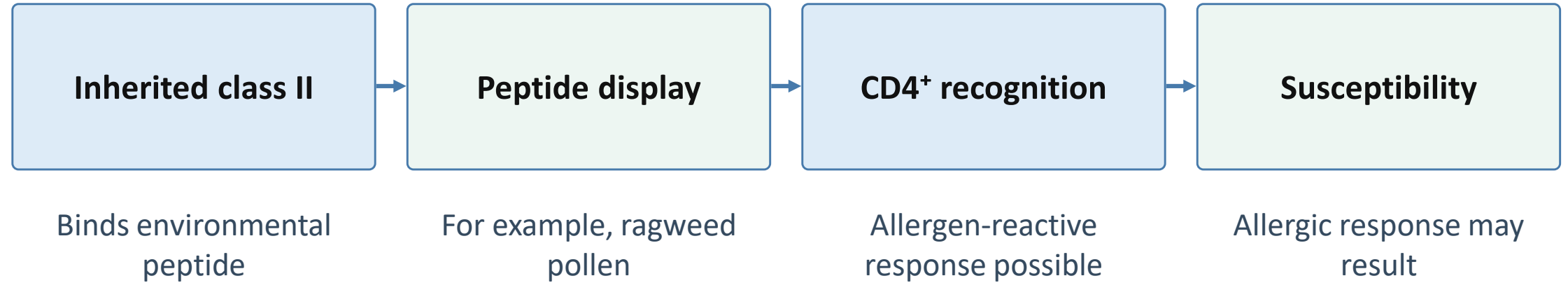
Illustrates allele-dependent peptide presentation, not an absolute binding prediction

HLA variation may determine protection from a microbe



The text presents this as a plausible consequence of antigen binding, not a universal guarantee.

HLA variation can also predispose to allergic responses



Antigen presentation is a susceptibility factor, not sufficient proof of clinical allergy.

HLA–autoimmunity associations require causal caution

- Several autoimmune and other diseases associate with particular HLA alleles.
- Peptide-binding differences provide a biologically plausible connection.
- An association does not imply that an allele alone produces disease.
- Additional mechanisms under autoimmunity later in the chapter.

Case: A cell containing replicating virus

A nucleated epithelial cell contains viral proteins in its cytosol. The immune system must identify this infected cell.

Which MHC class is expected to display viral peptides, and which T-cell subset recognizes them?

Predict the pathway and the responding T-cell subset

Case interpretation: Cytosolic viral peptides

MHC class I → CD8⁺ cytotoxic T lymphocyte

- Viral proteins enter the cytosolic processing pathway.
- Peptide display on class I permits TCR recognition with CD8 coreceptor binding.
- A CTL response can eliminate the infected host cell.

Case: A macrophage has ingested bacteria

A tissue macrophage has engulfed microbes and is displaying peptides derived from the ingested organisms.

Which MHC class presents these peptides, and what type of T-cell assistance follows?

Predict the pathway and the responding T-cell subset

Case interpretation: Internalized microbial proteins

MHC class II → CD4⁺ helper T cell

- Internalized proteins are processed in endosomal or lysosomal vesicles.
- The class II $\beta 2$ domain engages the CD4 coreceptor.
- Helper T-cell responses can activate the macrophage to destroy ingested microbes.

Follow antigen location to the appropriate immune response

Cytosolic proteins



MHC class I



CD8⁺ CTL: Kills affected host cell

Internalized proteins



MHC class II



CD4⁺ T helper: Activates effector responses

Core principles of HLA-mediated antigen display

MHC molecules display antigen-derived peptides rather than intact protein.

Class I: Cytosolic peptides → CD8⁺ cytotoxic T-cell recognition.

Class II: Internalized proteins → CD4⁺ helper T-cell recognition.

HLA polymorphism changes peptide repertoire and transplant compatibility.

HLA haplotypes are inherited from both parents and shape immune variation.

Primary reference and source boundaries

Robbins, Cotran & Kumar

Pathologic Basis of Disease · 11th edition (2026)

Chapter 6 · Diseases of the Immune System

MHC antigen-presentation section, pp. 174–176

Supporting context: lymphocyte receptors and activation, pp. 171–178