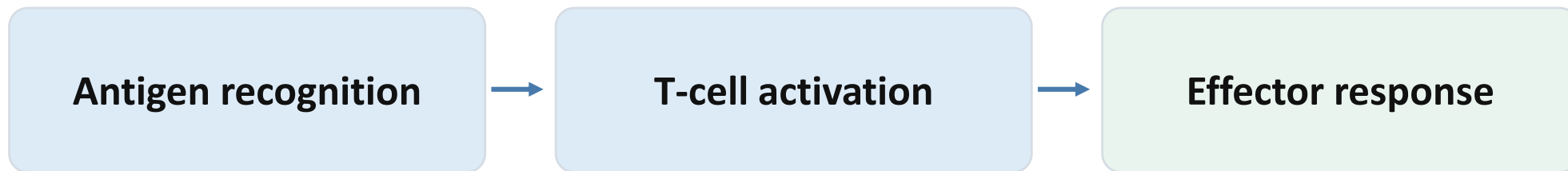


Cell-Mediated Immunity

Activation of T lymphocytes and elimination of intracellular microbes



Antigen-bearing cells → activated T cells → infected-tissue defense

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning outcomes

- Trace antigen capture, lymphoid activation, and effector-cell deployment.
- Explain how peptide–MHC recognition and costimulation activate naive T cells.
- Contrast Th1 macrophage activation with CD8⁺ cytotoxic killing.
- Relate helper-T-cell subsets to their cytokines and dominant functions.

Why cell-mediated immunity is required

Intracellular problem

- Microbes can survive within phagocytes or infected host cells.
- A cell may conceal microbial antigens from circulating antibodies.

T-cell solution

- CD4⁺ T cells activate microbe-containing phagocytes.
- CD8⁺ CTLs destroy infected cells harboring cytosolic microbes.

Antigen location selects the effector route

Microbial antigen inside cells

Engulfed by phagocyte

CD4⁺ Th1 response

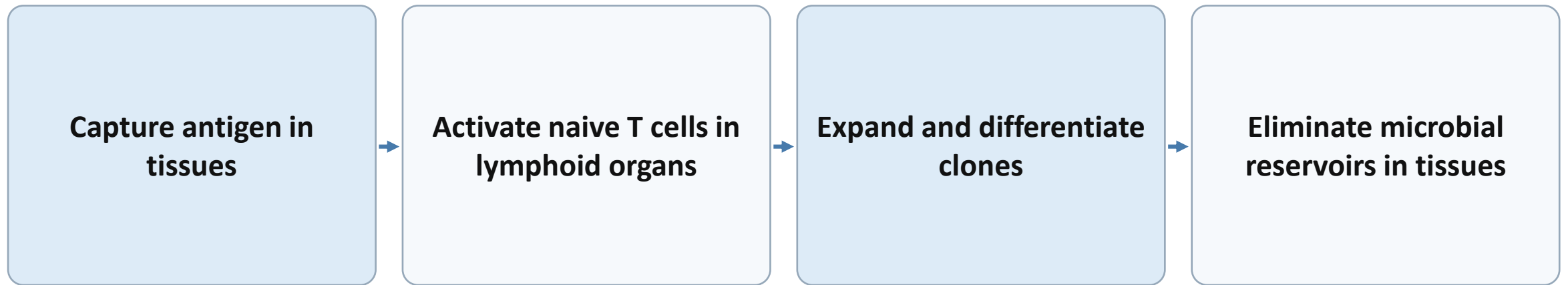
Activate the macrophage

Present in cell cytosol

CD8⁺ CTL response

Kill the infected cell

Cell-mediated immunity has four linked phases



Location and timing separate T-cell priming from tissue-level effector function.

Naive T cells cannot inspect every tissue

A rare antigen-specific naive T cell is unlikely to meet its antigen by random tissue patrol.

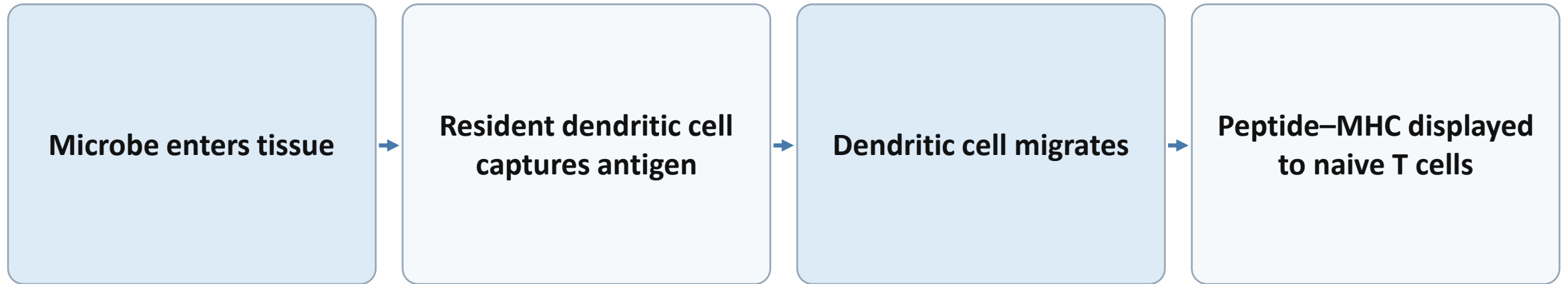
Antigens are concentrated

Naive cells recirculate through nodes

Encounter becomes probable

Secondary lymphoid organs solve the encounter problem.

Dendritic cells bring antigen to lymph nodes



This is the bridge from a peripheral infection to adaptive T-cell activation.

Dendritic-cell maturation links innate and adaptive immunity

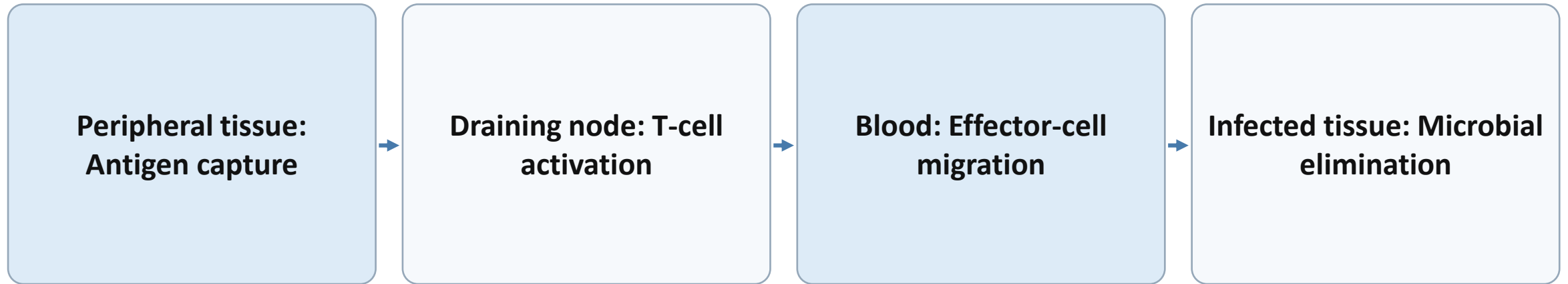
In tissue

- DC captures microbial antigen.
- Innate stimuli activate the presenting cell.

In lymph node

- DC displays peptide–MHC complexes.
- MHC and costimulatory expression is enhanced.

Priming and defense occur in different places



Effector cells are generated in lymphoid organs and then move to antigen-bearing tissues.

T cells recognize processed protein antigens

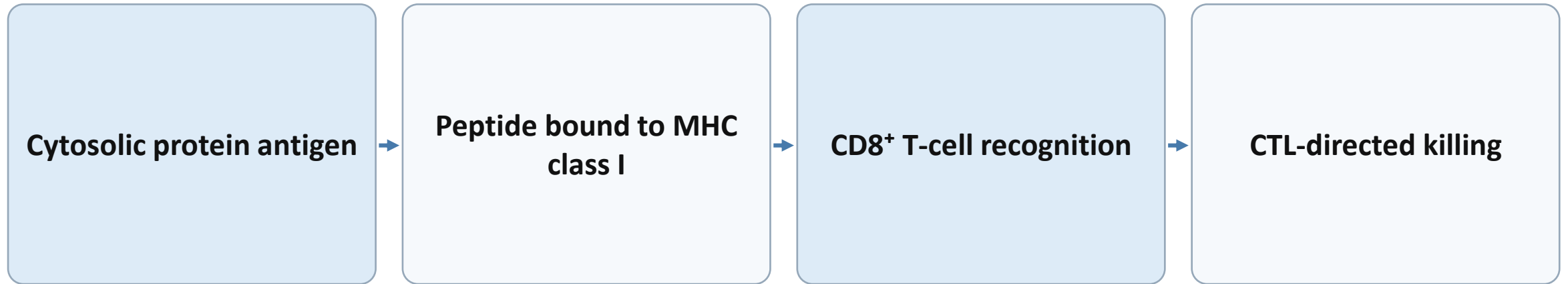
T-cell receptor recognition

- T-cell receptor binds a peptide displayed by an MHC molecule.
- T cells do not recognize intact soluble proteins as B cells do.

Consequence

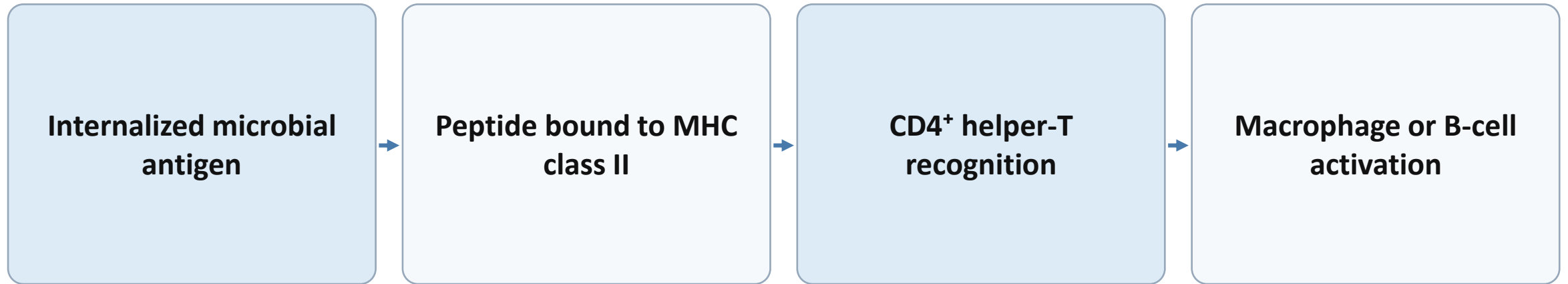
- Antigen recognition is restricted by self MHC.
- The presenting route determines which T-cell class responds.

MHC class I guides CD8⁺ responses



Class I presentation provides immune surveillance for cytosolic infection and tumor-derived abnormal proteins.

MHC class II guides CD4⁺ responses



Professional antigen-presenting cells, including DCs, macrophages and B cells, express class II MHC.

MHC class I and II have different tasks

Feature	MHC class I / CD8 ⁺	MHC class II / CD4 ⁺
Typical source	Cytosolic proteins	Internalized proteins
Responding T cell	Cytotoxic T cell	Helper T cell
Effector outcome	Kill infected cell	Activate phagocyte / aid B cell
Immune problem	Cytosolic microbes	Ingested microbes

Innate stimuli license antigen presentation

Antigen display alone is not the full activation signal for naive T lymphocytes.

**Microbe stimulates innate
sensors**



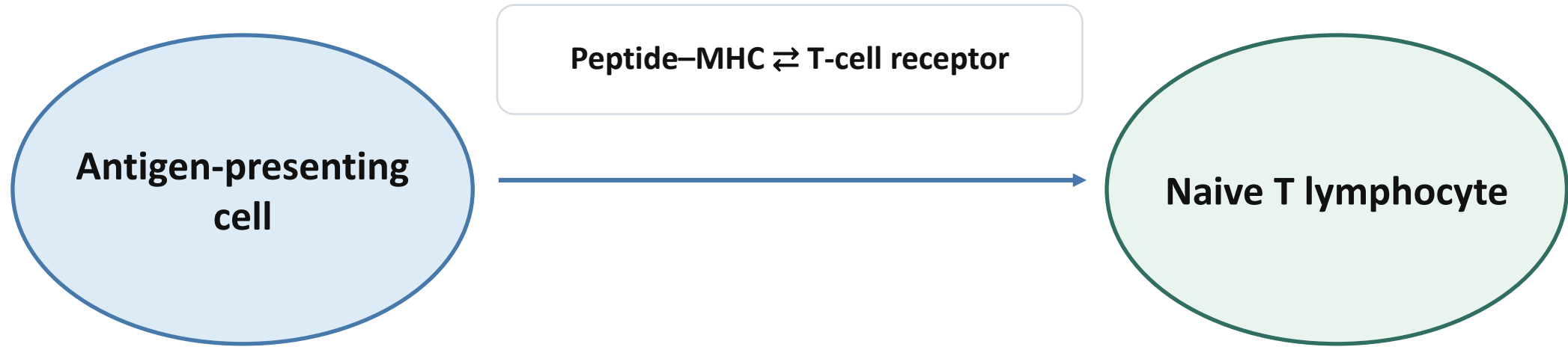
APC increases costimulators



**T cell receives coordinated
signals**

Adaptive activation is coupled to signs of microbial encounter.

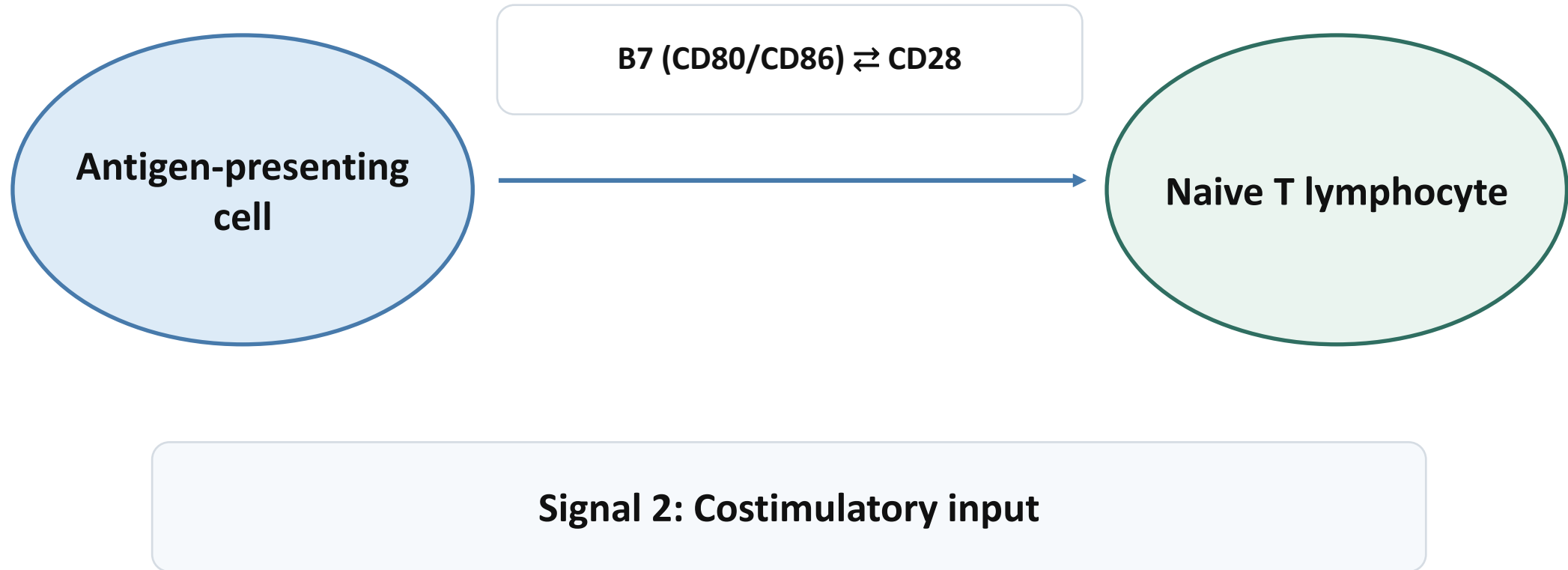
Signal 1 confers antigen specificity



Signal 1: Antigen-specific recognition

Signal 1 selects the responding T-cell clone.

Signal 2 provides costimulation



B7 expression increases on APCs during innate immune activation.

Both signals cooperate during T-cell priming

Naive T-cell activation

```
graph TD; A[Naive T-cell activation] --> B[Signal 1]; A --> C[Signal 2];
```

Signal 1

Specific peptide–MHC

Which clone responds?

Signal 2

B7–CD28 costimulation

Is APC activated?

Costimulation limits indiscriminate responses

- The innate response induces APC costimulators after microbial recognition.
- Naive T cells require antigen recognition together with costimulation.
- This requirement helps prevent vigorous responses to innocuous antigens.
- Other control mechanisms also restrain anti-self responses despite APC activation.

Lymphoid compartments organize encounters

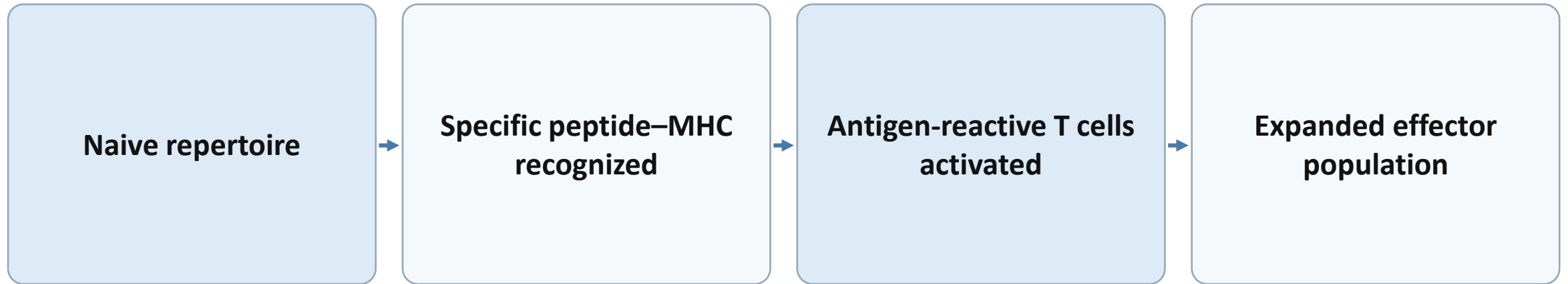
T-cell zone

- Naive T cells encounter antigen-presenting dendritic cells.
- Peptide–MHC and costimulators initiate T-cell activation.

B-cell follicle

- B lymphocytes and Tfh interactions support antibody responses.
- Distinct localization allows specialized helper functions.

Activation selects rare antigen-specific clones



Proliferation increases the number of T cells specific for the encountered antigen.

IL-2 is produced early by activated helper T cells

- Activated CD4⁺ helper T lymphocytes secrete IL-2.
- They also increase expression of high-affinity IL-2 receptors.
- The same activated clone can respond to the IL-2 it produces.
- The resulting growth signal drives T-cell proliferation.

High-affinity IL-2 receptors amplify responsiveness

Receptor upregulation makes activated T cells highly responsive to IL-2.

Antigen-driven activation



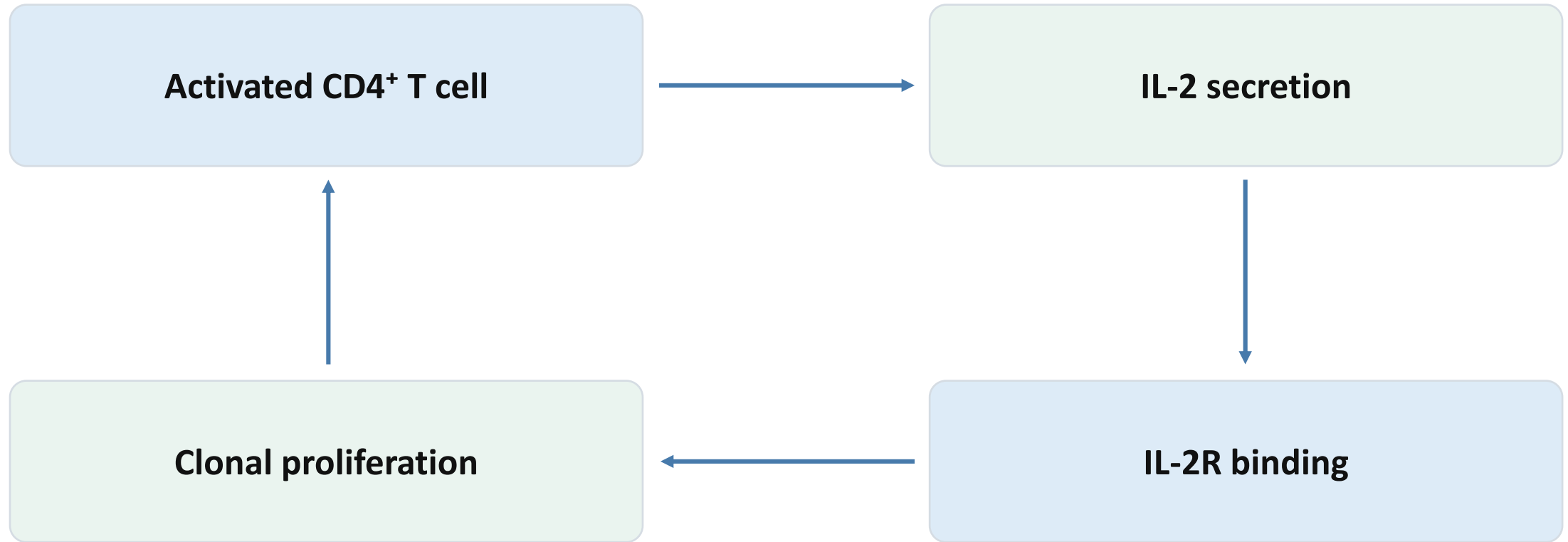
High-affinity IL-2R expression



IL-2-dependent proliferation

The growth-factor receptor is part of the activation program.

IL-2 creates an autocrine proliferation loop



Clonal expansion increases effector capacity

Before activation

- Few naive cells are specific for any one microbial antigen.
- The clone has not yet acquired its tissue-defense program.

After activation

- Antigen-specific cell numbers rise.
- Proliferating cells acquire helper or cytotoxic effector functions.

Differentiation produces distinct T-cell fates

Activated naive T lymphocyte

```
graph TD; A[Activated naive T lymphocyte] --> B[Effector cells]; A --> C[Memory cells];
```

Effector cells

Act during current infection

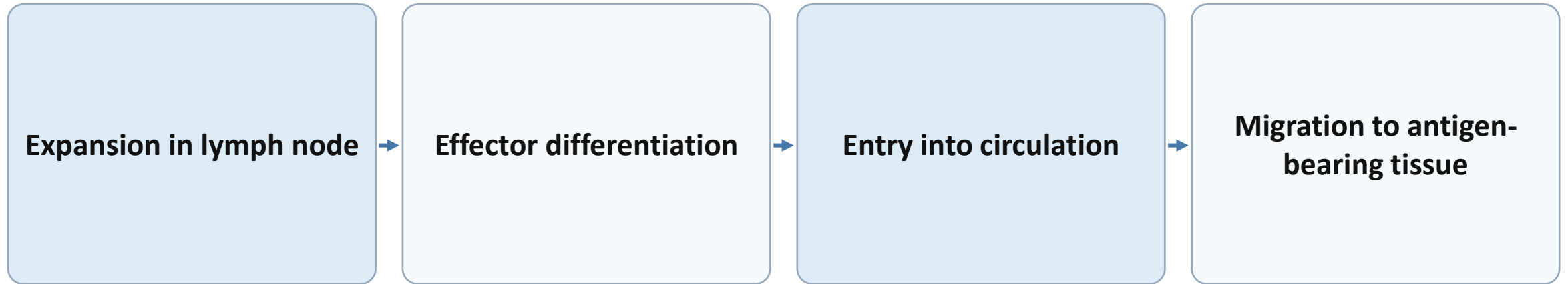
Migrate to infected tissues

Memory cells

Persist after response

Enable faster secondary responses

Effector T cells leave lymphoid organs



Local tissue defense is performed by differentiated cells generated during priming.

CD4⁺ helper cells act through two mechanisms

Antigen-recognizing CD4⁺ T cell

Membrane-bound CD40 ligand

CD40 on target cells

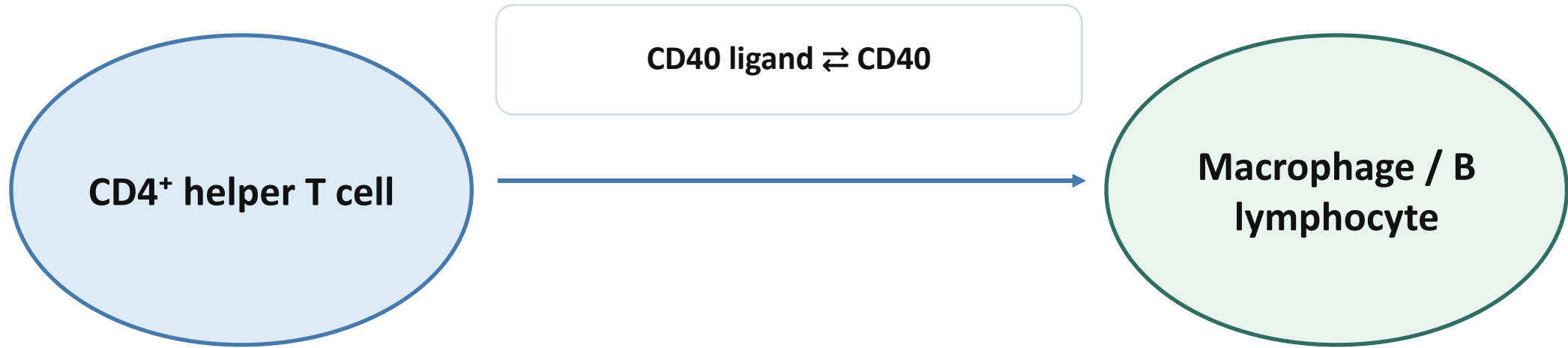
Direct cell-contact activation

Secreted cytokines

Signal through cytokine receptors

Functional programming of target cells

CD40L–CD40 is a contact-dependent signal



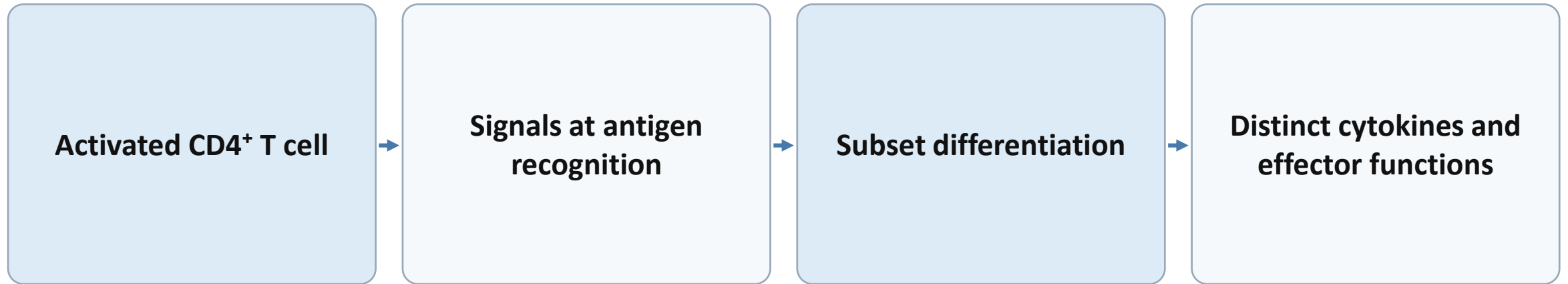
Cell contact activates the antigen-presenting target

Helper T cells express CD40L when recognizing antigen displayed by the target.

Helper-T-cell cytokines program target cells

- Cytokines are secreted proteins that mediate immune-cell communication.
- Their effects may be autocrine or paracrine; Endocrine actions are less common.
- Distinct helper subsets secrete different cytokine combinations.
- Cytokines collaborate with cell-contact signals such as CD40L.

CD4⁺ helper T cells diversify into subsets

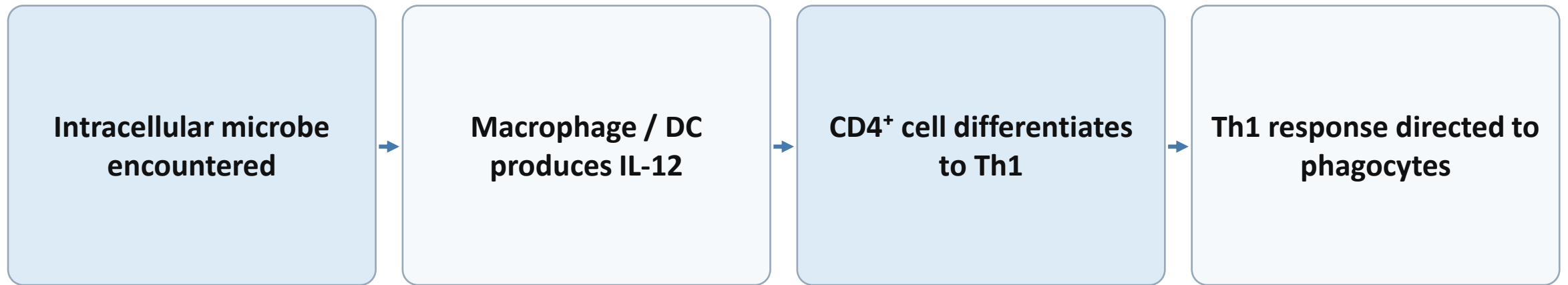


Functional differentiation is matched to the microbial challenge.

Major helper-T-cell programs are distinct

Subset	Key cytokine / induction	Principal function
Th1	IFN- γ ; Induced by IL-12	Classical macrophage activation
Th2	IL-5; IL-4; IL-13	Eosinophils; Alternative macrophage activation
Th17	IL-17	Neutrophil / monocyte recruitment
Tfh	CD40L and cytokine help	High-affinity B-cell antibody responses

IL-12 favors Th1 differentiation

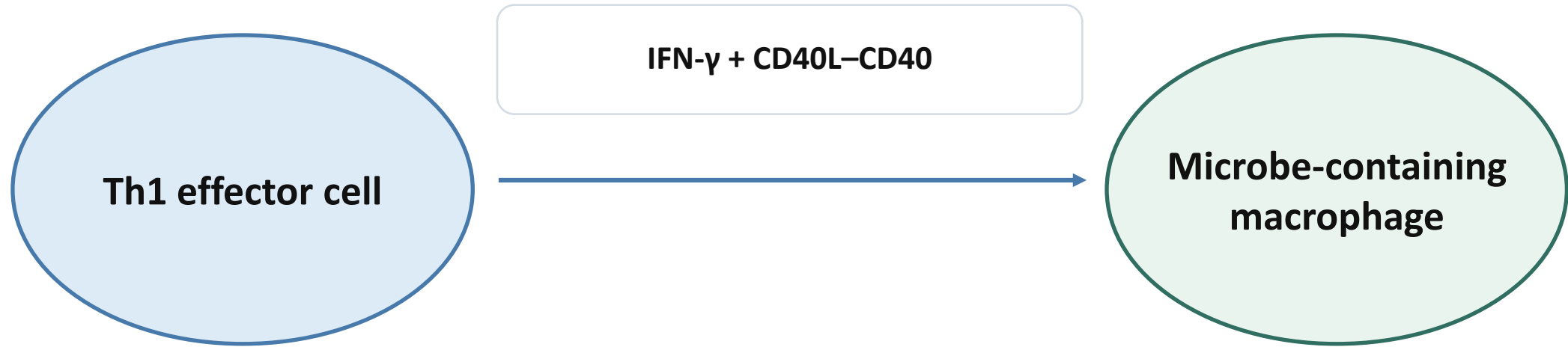


Microbial context shapes the responding helper-cell population.

Th1 cells produce interferon- γ

- Th1 is the principal helper subset for activation of microbe-containing macrophages.
- Its characteristic cytokine is interferon- γ (IFN- γ).
- IFN- γ delivers a potent activating signal to macrophages.
- Contact signals reinforce the cytokine-driven response.

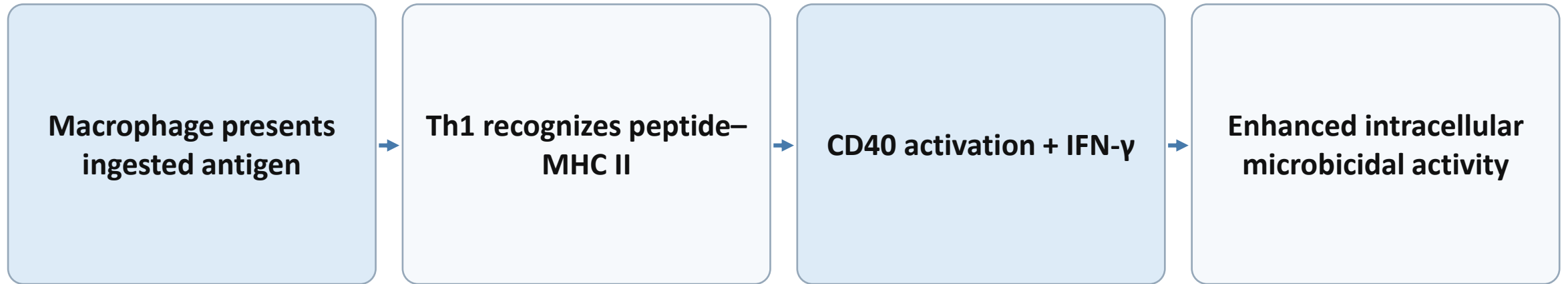
Th1 cells and macrophages form a functional pair



Classical macrophage activation

The macrophage presents antigen from its ingested microbes to the helper cell.

Classical macrophage activation requires cooperation



Cooperative contact and cytokine signals induce the classical activation program.

Why activate the macrophage rather than kill it?

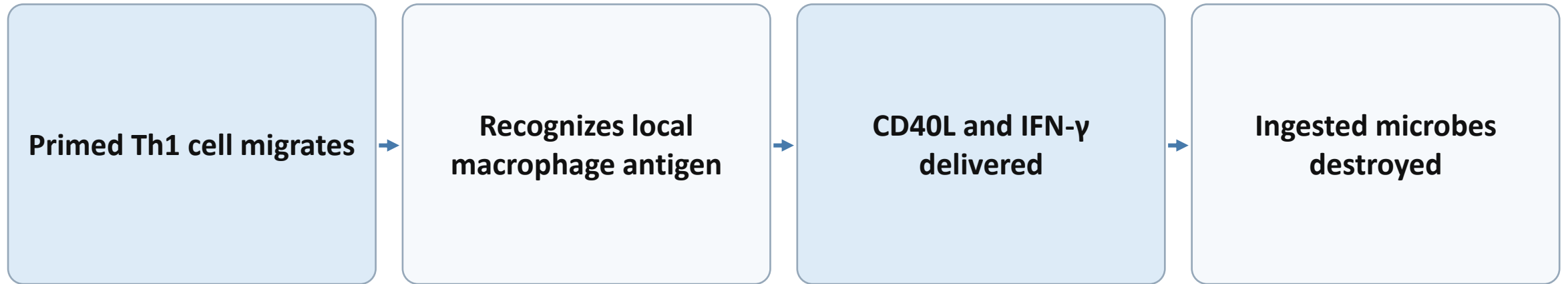
Macrophage harbors ingested microbes

- Microbes may be contained within phagocytic compartments.
- The infected phagocyte can remain an antimicrobial effector.

Th1 response enhances killing

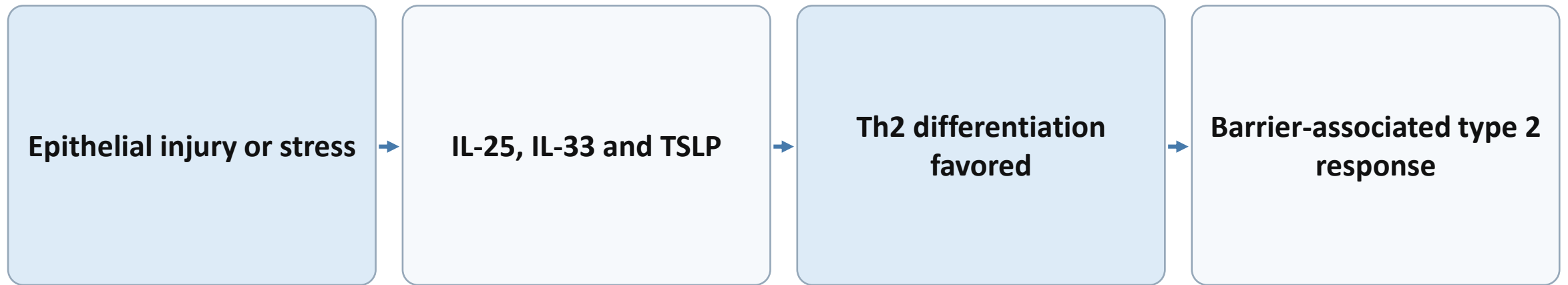
- IFN- γ and CD40 signals increase microbicidal function.
- The macrophage eliminates microbes it has ingested.

The Th1 response operates at the infection site



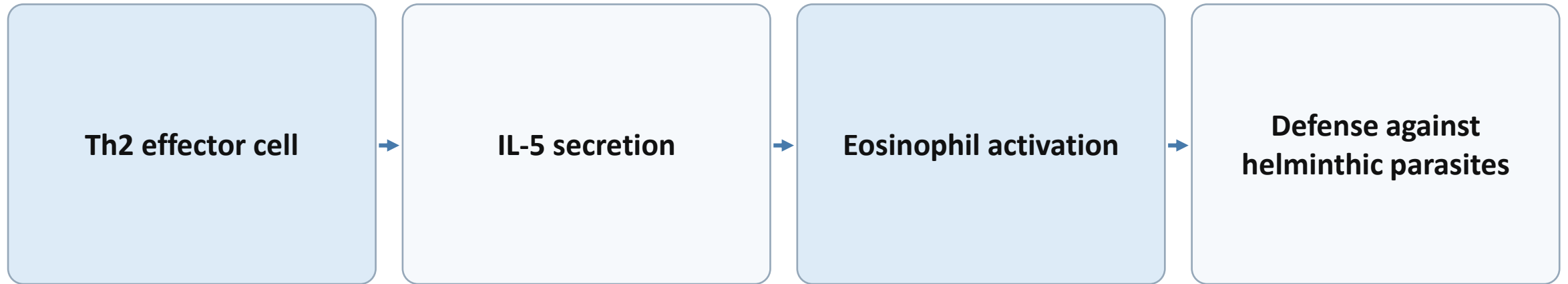
Antigen recognition and effector activation are linked in the infected tissue.

Th2 differentiation reflects epithelial danger signals



The source links this subset to epithelial interfaces and their characteristic stimuli.

Th2 IL-5 promotes eosinophil responses



Helminth defense is a distinct helper-cell function, not the principal Th1 route.

Th2 IL-4 and IL-13 alter macrophage programs

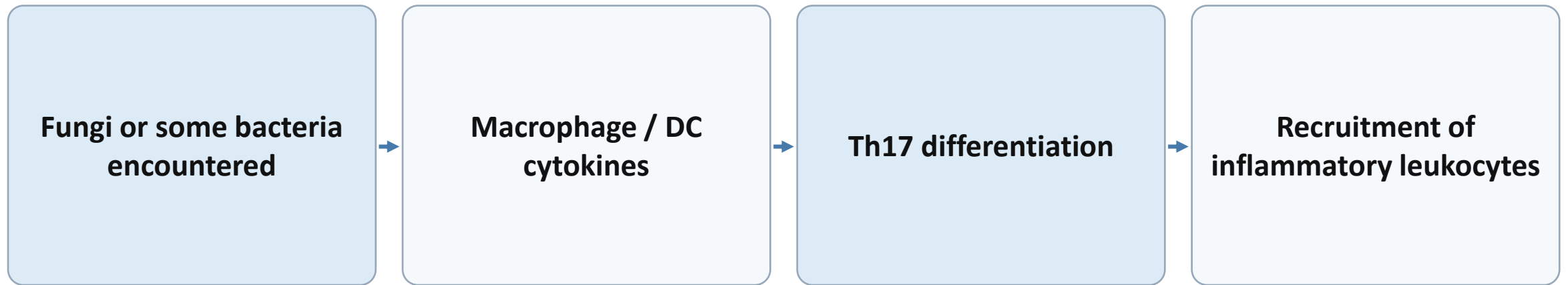


Alternative and classical activation represent different functional responses.

Classical versus alternative macrophage activation

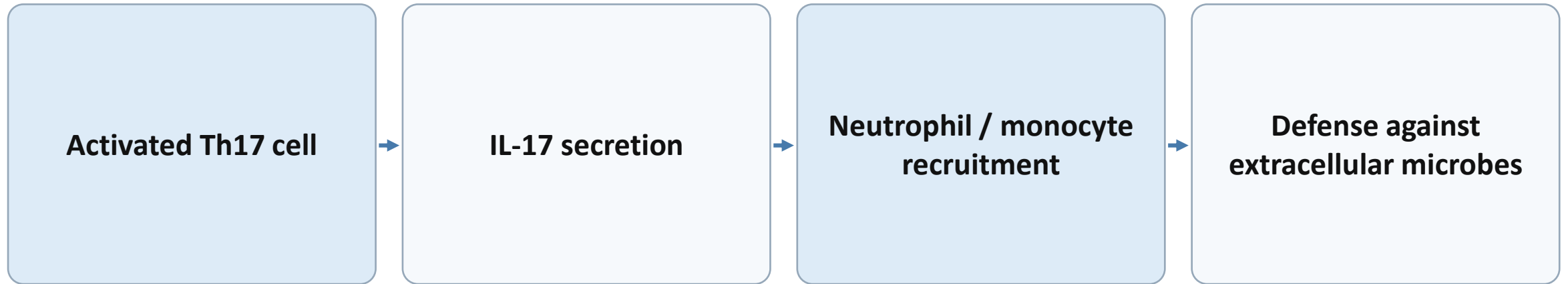
Feature	Classical activation	Alternative activation
Associated helper cell	Th1	Th2
Signals	IFN- γ + CD40	IL-4 / IL-13
Principal function	Kill ingested microbes	Tissue repair / fibrosis
Teaching distinction	Host defense inside phagocyte	Remodeling and repair

Th17 cells arise during fungal and bacterial responses



The extracted section does not list specific Th17-inducing cytokines; None are inserted.

IL-17 recruits neutrophils and monocytes



Th17 functions differ from Th1 macrophage activation and Th2 eosinophil recruitment.

Helper subsets align with pathogen biology

Challenge	Preferred helper activity	Effector outcome
Ingested intracellular microbes	Th1 → macrophage activation	Microbicidal killing
Helminthic parasites	Th2 → IL-5 / eosinophils	Parasite defense
Extracellular bacteria / fungi	Th17 → leukocyte recruitment	Neutrophil-rich defense
Protein antigens in follicles	Tfh → B-cell help	Higher-affinity antibody

Helper-cell identities are not absolute

- Th1, Th2, and Th17 describe characteristic cytokine and functional programs.
- Some activated T cells produce multiple cytokines.
- Other activated cells do not fit perfectly into a single canonical subset.
- Use the subsets as mechanistic patterns, not mutually exclusive boxes.

T follicular helper cells remain near B cells

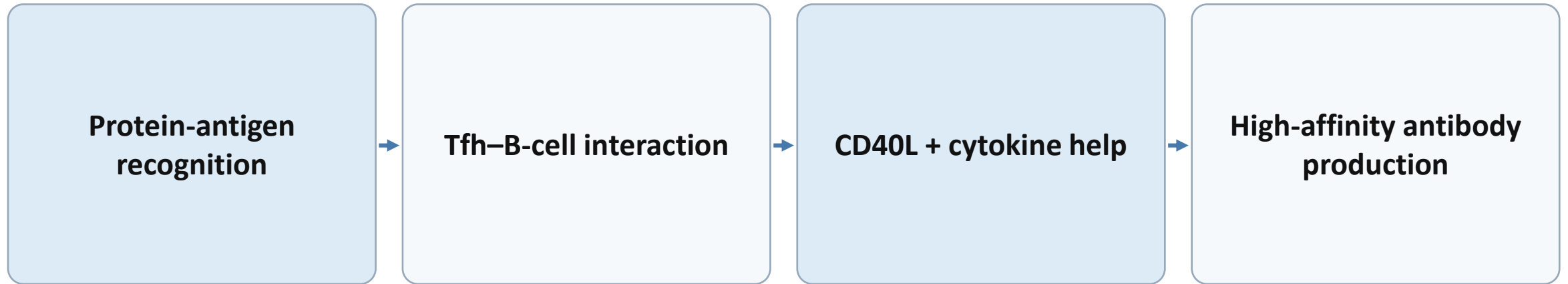
Migrating helper cells

- Th1, Th2, and Th17 effectors move toward peripheral sites.
- They activate leukocytes in infected or inflamed tissues.

T follicular helper cells

- Concentrate in lymphoid follicles with B cells.
- Provide signals for high-affinity antibody responses.

Tfh cells connect T-cell help to antibodies



This is a lymphoid-organ function of CD4⁺ cells rather than direct intracellular killing.

Helper effector location reflects function

Subset	Typical site of action	Immediate target
Th1	Infected tissues	Antigen-bearing macrophage
Th2	Barrier / infected tissues	Eosinophil; Macrophage
Th17	Inflamed infected tissues	Recruitable leukocytes
Tfh	Lymphoid follicle	B lymphocyte

CD8⁺ T cells undergo antigen-driven activation

- The early activation steps resemble those of CD4⁺ T cells.
- Peptide–MHC class I recognition provides antigen specificity.
- Costimulation and IL-2 support their proliferative response.
- Activated CD8⁺ cells differentiate into cytotoxic T lymphocytes (CTLs).

CD8⁺ clones expand extensively

Activated CD8⁺ lymphocytes proliferate especially strongly.

**Peptide–MHC I and
costimulation**



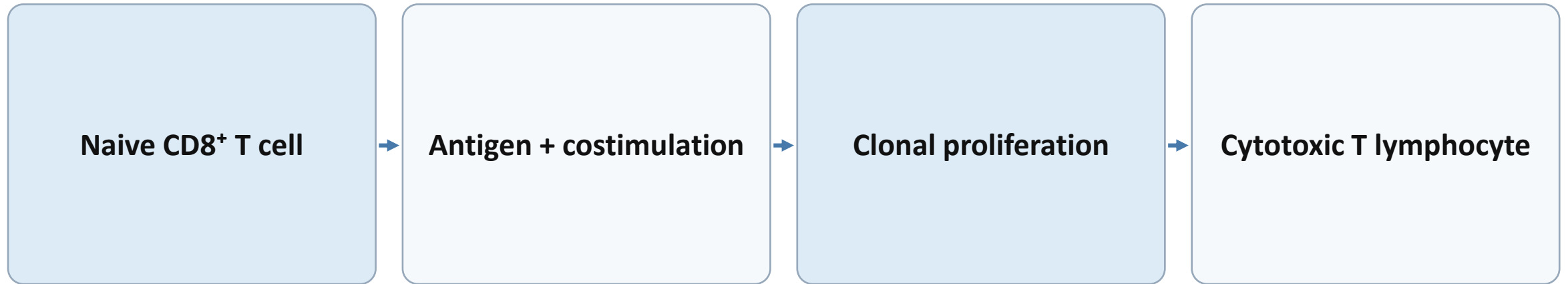
IL-2-supported expansion



**Large antigen-specific CTL
population**

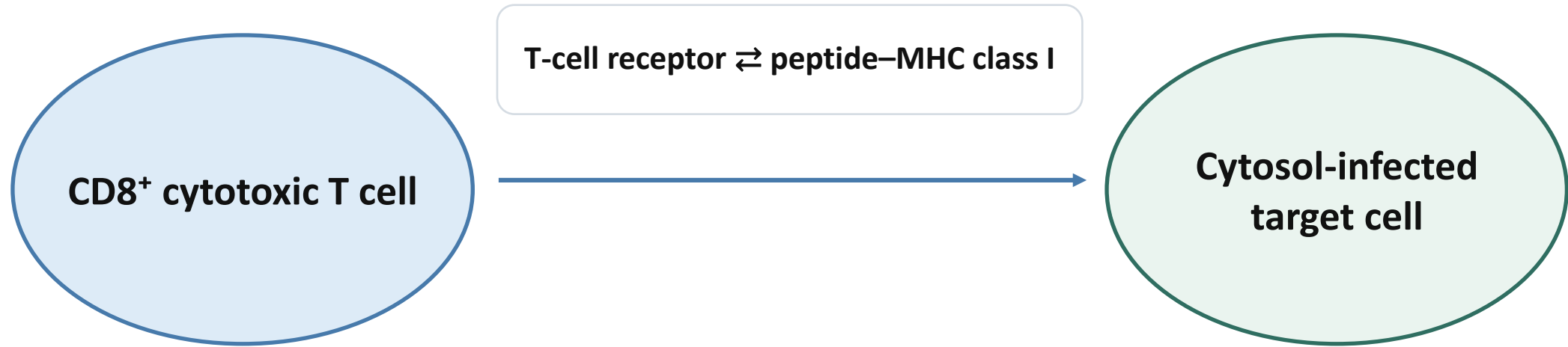
The Robbins source describes more extensive CD8⁺ than CD4⁺ proliferation.

CTL differentiation creates a killing effector



The central new function is selective destruction of cells expressing the target antigen.

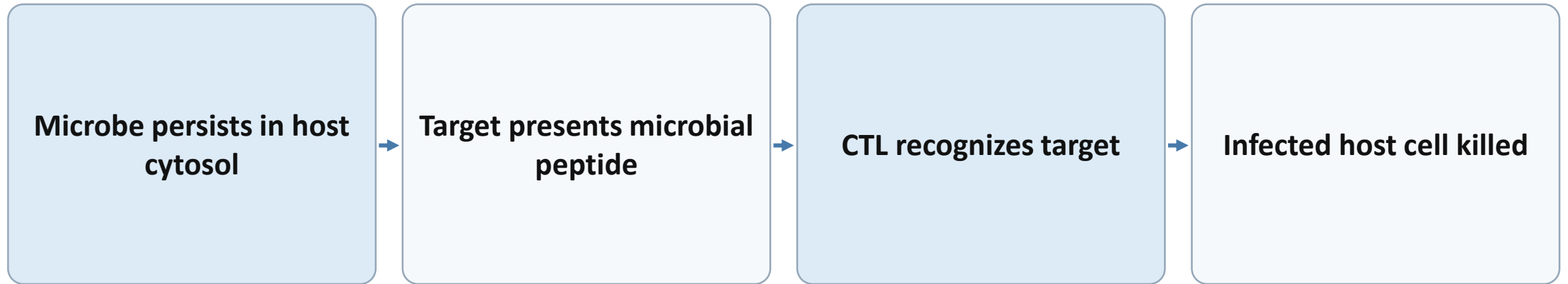
CD8⁺ CTLs detect cytosolic infection



Recognition of infected cell → directed killing

The infected cell displays peptides derived from its intracellular proteins.

CTLs eliminate infected host cells



Eliminating the host cell also eliminates a cellular reservoir of infection.

Killing the reservoir is the CTL strategy

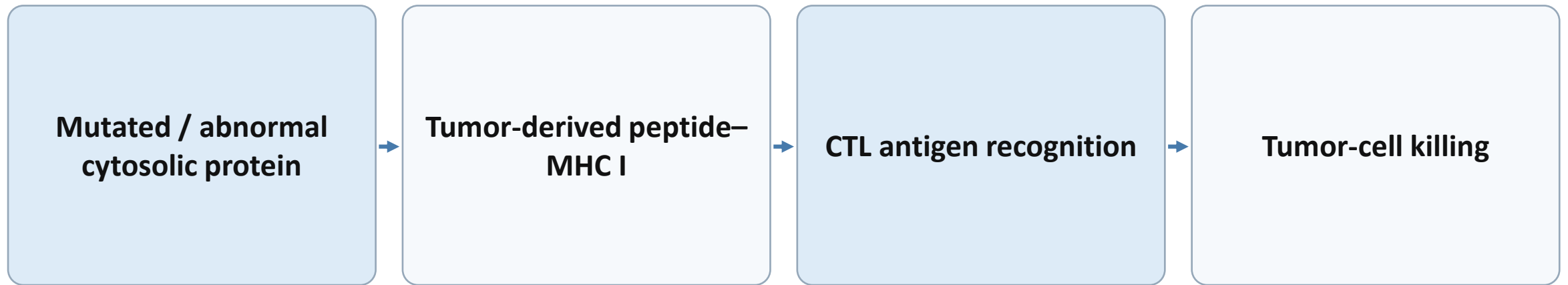
If infection is cytosolic

- The pathogen occupies a host-cell compartment.
- Macrophage activation alone may not remove the infected reservoir.

CTL effect

- The antigen-bearing host cell is destroyed.
- The intracellular reservoir is removed from the tissue.

Tumor cells can also be CTL targets



This is a second biological application of class I-restricted cytotoxicity described in the source.

CD4⁺ and CD8⁺ T cells solve different problems

Dimension	CD4 ⁺ helper T cell	CD8 ⁺ CTL
Antigen display	Peptide–MHC class II	Peptide–MHC class I
Effector mechanism	CD40L + cytokines	Kill target cell
Principal target	Macrophage / B cell	Infected or tumor cell
Microbial focus	Ingested microbes	Cytosolic microbes

Two intracellular niches, two effector strategies

Where is the microbial reservoir?

Within a phagocyte

Th1 sees MHC II–peptide

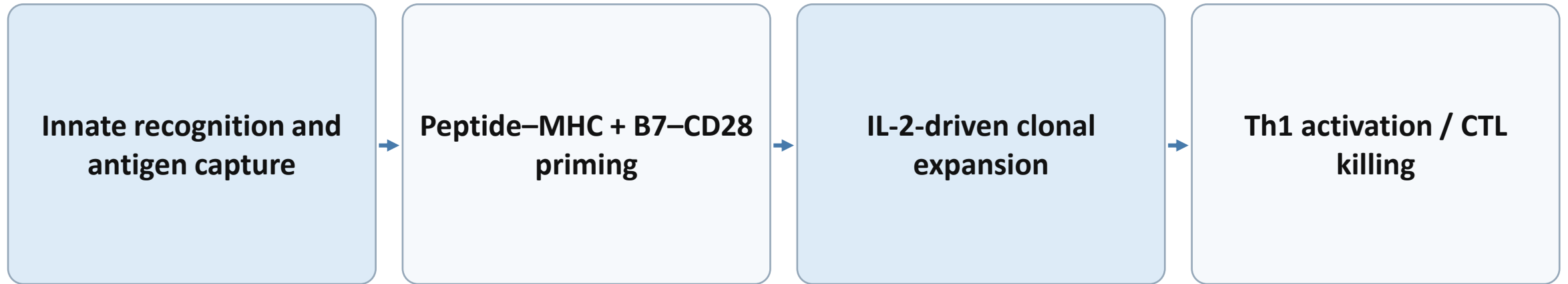
Amplify phagocyte killing

Within a cytosol-infected cell

CTL sees MHC I–peptide

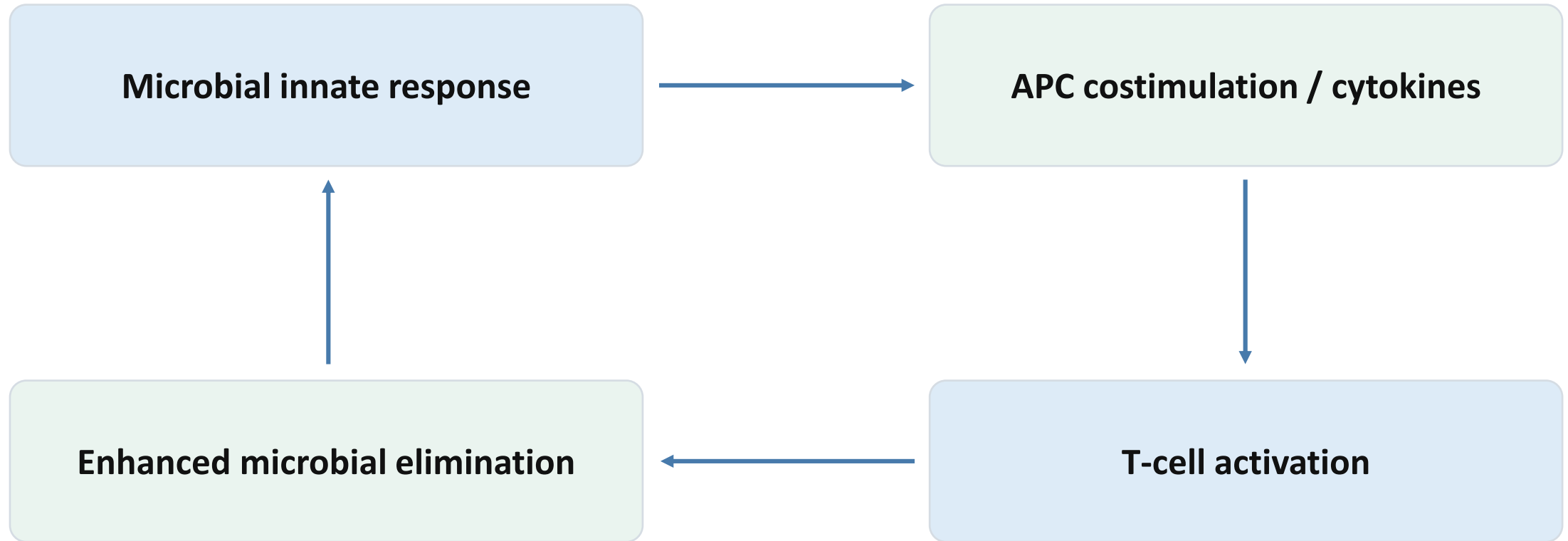
Destroy infected cell

An integrated timeline links priming and defense



The early events are shared; The later effector paths diverge by antigen location.

Innate and adaptive immunity reinforce one another



Effector cytokines can also drive immunopathology

Protective function

- Helper subsets coordinate inflammation appropriate to the pathogen.
- IFN- γ , IL-5 and IL-17 mobilize different effectors.

Clinical implication

- The same cytokine programs may participate in inflammatory disease.
- Biologics can block selected inducing or effector cytokines.

Therapeutic cytokine blockade is subset-specific

- Helper subsets differ in inducing stimuli and secreted effector cytokines.
- Antibodies that block these pathways are used in diseases driven by the respective subset.
- Blocking a cytokine targets an immune program, not a universal inflammatory switch.
- The selected Robbins passage does not specify particular drugs or indications.

Case: Ingested intracellular microbe

A macrophage has phagocytosed a microbe but needs enhanced intracellular killing. Which T-cell subset provides the characteristic activating signals?

A. Th2: IL-5-driven eosinophil response

B. Th1: IFN- γ plus CD40L–CD40

C. Th17: IL-17-driven leukocyte recruitment

Case: Virus in the cytosol

A host cell is producing microbial proteins in its cytosol. Which antigen-display and effector combination directly eliminates this infected cell?

A. MHC II → Th1-dependent macrophage activation

B. Th2 → eosinophil activation

C. MHC I → CD8⁺ cytotoxic T lymphocyte

Case: Inflammatory leukocyte recruitment

A T-cell response is characterized by IL-17 and recruitment of neutrophils and monocytes. Which helper lineage best explains the pattern?

A. Th1

B. Th17

C. Tfh

Three causal relationships to retain

**B7–CD28 + peptide–MHC →
activation**



IL-2 / IL-2R → clonal expansion



**Th1 / CTL → intracellular
microbial control**

Differentiate signals that activate T cells from effector mechanisms that eliminate infection.

Primary source and figure context

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026). Chapter 6, pp. 175–179.
- “Display and Recognition of Antigens” and “Cell-Mediated Immunity: Activation of T Lymphocytes and Elimination of Intracellular Microbes.”
- Conceptual sequences grounded in the explanatory text and captions of Figures 6.10 and 6.11.