

Causes of Apoptosis

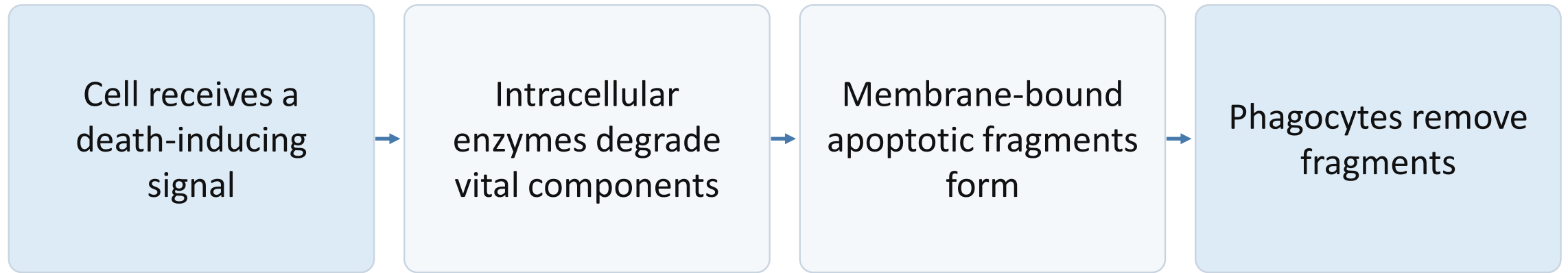
Physiologic cell removal and pathologic cell loss

Learning objectives

- Classify the major physiologic and pathologic triggers of apoptosis.
- Explain why survival-signal withdrawal and injurious stimuli produce selective cell loss.
- Link representative diseases and normal processes to their apoptotic causes.
- Distinguish apoptosis from necrotic cell death in clinicopathologic interpretation.

Aetiology → cellular decision → tissue consequence

Apoptosis is regulated cellular self-destruction



Cell contents are contained during clearance, minimizing inflammation.

Apoptosis and necrosis differ in their consequences

Apoptosis

- Regulated intracellular degradation
- Membrane-bound cellular fragments
- Rapid phagocytic clearance
- Typically little or no inflammation

Necrosis

- Loss of membrane integrity
- Leakage of cellular constituents
- Inflammatory reaction
- Often prominent after severe tissue injury

Two broad contexts initiate apoptosis

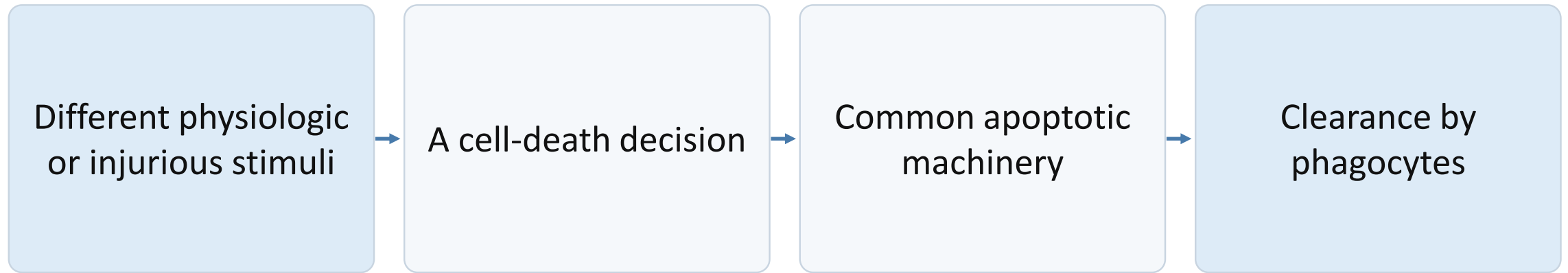
Physiologic

- Removes unnecessary cells
- Sculpts developing tissues
- Balances cell production
- Terminates selected immune responses

Pathologic

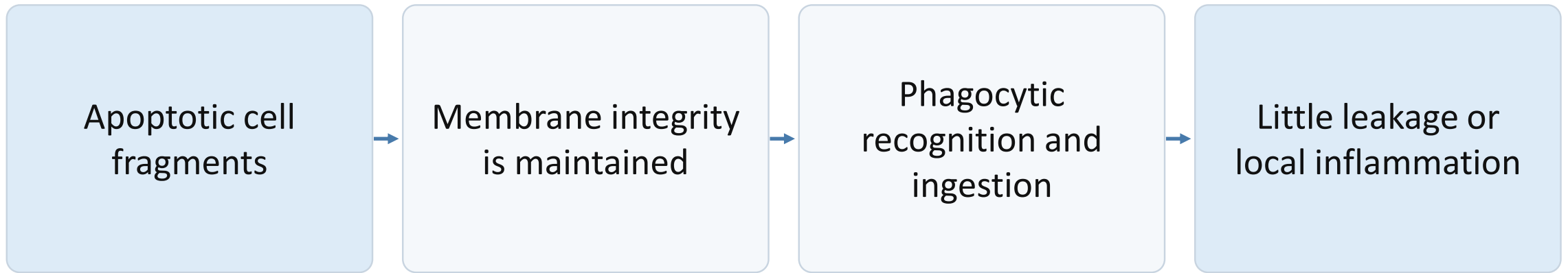
- Eliminates irreparably injured cells
- Limits persistence of DNA-damaged cells
- Can remove infected cells
- May cause loss of parenchymal cells

The trigger matters more than cell appearance



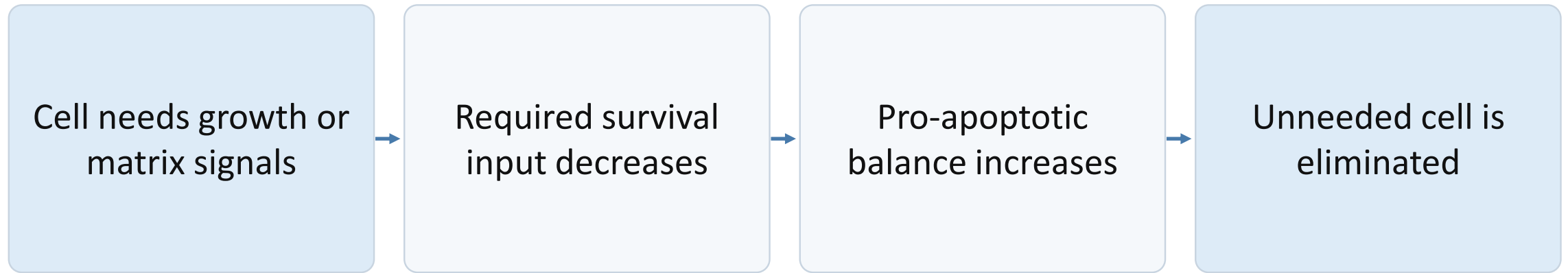
The same cellular outcome can support development, tissue homeostasis, or disease.

Efficient clearance limits bystander injury



This contrasts with the inflammatory response that follows necrotic membrane disruption.

A common physiologic mechanism: Survival-signal withdrawal



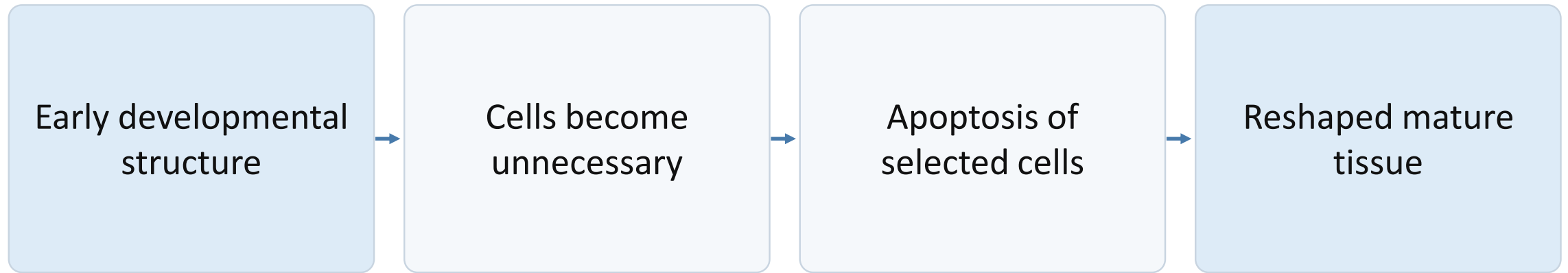
External signals determine whether a cell remains viable in its tissue niche.

Physiologic apoptosis removes surplus cells

- During development, more cells or structures may form than the mature organ requires.
- Cells in excess of the needed number are eliminated selectively.
- The result is controlled tissue remodeling rather than accidental injury.

Development → selective elimination → mature architecture

Developmental remodeling is a selective process



Apoptosis is a mechanism of developmental involution and remodeling.

Involution of primordial structures

- Some early developmental structures are temporary.
- Their removal requires targeted loss of cells rather than generalized tissue destruction.
- Apoptotic clearance permits neighboring tissue to remain relatively undisturbed.

Temporary structure → apoptosis → involution

Tissue maturation requires removal as well as growth

Addition

- Cell proliferation increases cell numbers.
- Differentiation establishes specialized properties.

Removal

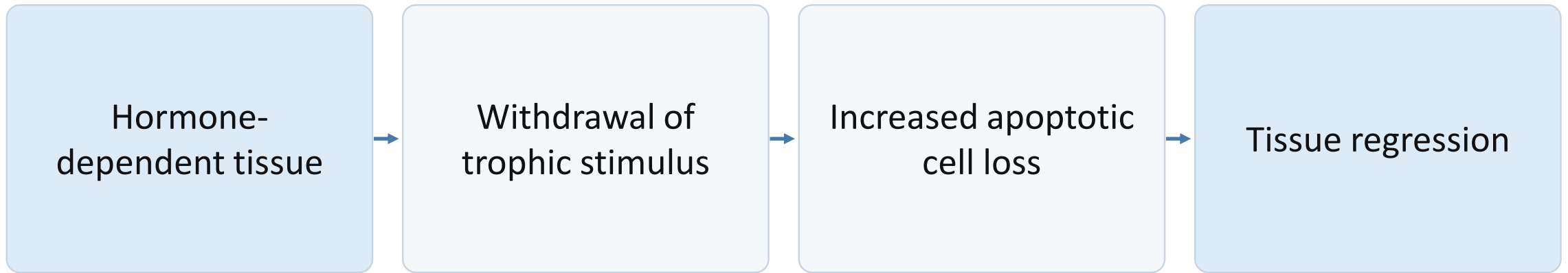
- Apoptosis eliminates surplus cells.
- Selective loss refines tissue form and cellular composition.

“Programmed cell death” terminology

- Apoptosis describes the characteristic pattern of cell death across many settings.
- “programmed cell death” specifically for developmentally regulated apoptosis.
- The terms should not be treated as identical in every source or research field.

Textbook terminology is explicitly contextual.

Hormone withdrawal can initiate involution



Physiologic regression follows a change in hormonal support.

Endometrial breakdown during the menstrual cycle

- The endometrium responds to cyclic hormonal cues.
- Loss of hormonal support contributes to programmed removal of endometrial cells.
- Apoptosis is one cellular component of menstrual endometrial breakdown.

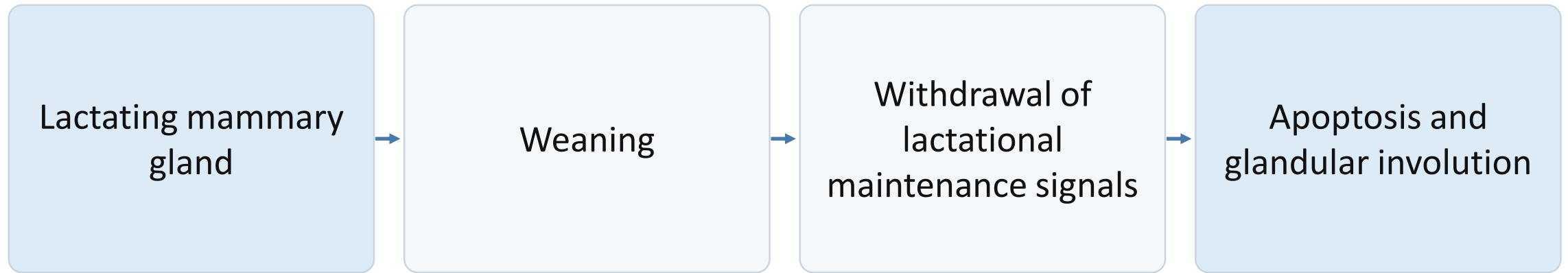
Hormonal withdrawal → endometrial cell loss

Ovarian follicular atresia

- Ovarian follicles require appropriate hormonal and local survival support.
- Follicles that do not persist can undergo atresia with apoptotic cell loss.
- Follicular atresia, including in menopause, among physiologic examples.

Loss of support → follicular cell apoptosis

Breast regression after weaning

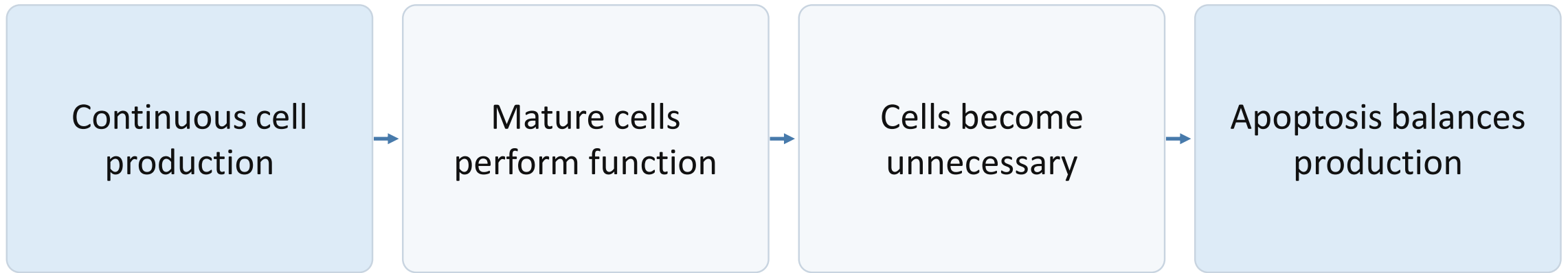


Regression of the lactating breast is a classic physiologic setting.

Three hormone-dependent examples

Tissue	Physiologic transition	Apoptotic context
Endometrium	Menstrual hormonal changes	Endometrial cell breakdown
Ovarian follicle	Loss or alteration of follicular support	Follicular atresia
Lactating breast	Weaning	Regression of the gland

Apoptosis maintains cell-number homeostasis



A stable tissue population requires both cell generation and cell removal.

The intestinal crypt is a turnover example

- Intestinal epithelium is a proliferating cell population.
- Homeostatic replacement requires coordinated production and loss.
- Intestinal crypt epithelium as a setting in which apoptosis maintains cell numbers.

Cell renewal and cell elimination are linked.

Cell number reflects opposing rates

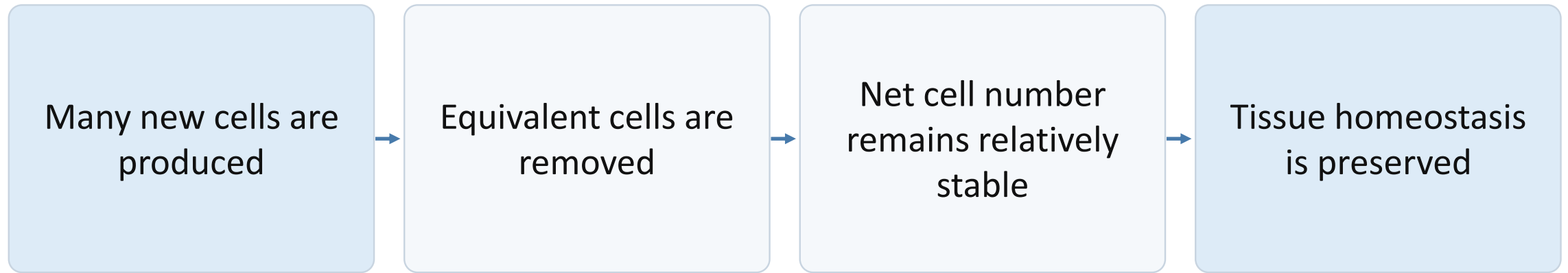
Cell addition

- Proliferation introduces new cells.
- Supports epithelial replacement and renewal.

Cell removal

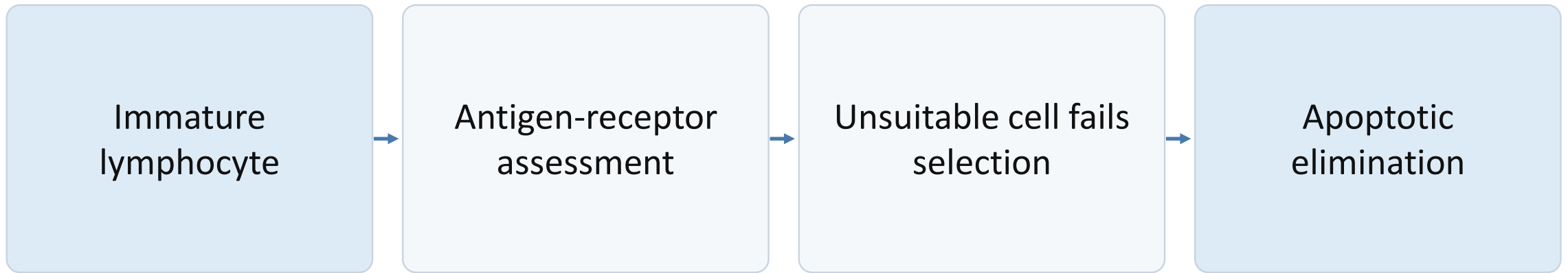
- Apoptosis disposes of unwanted cells.
- Prevents unchecked accumulation in normal tissues.

Why high turnover does not imply tissue enlargement



This is a conceptual balance, not a claim that all tissues turn over at identical rates.

Immune-cell development includes quality control



Lymphocytes lacking useful receptors need not persist.

Bone marrow removes unsuitable immature lymphocytes

- Immature lymphocytes develop and are selected in primary lymphoid tissues.
- Cells that fail to generate useful antigen-receptor functions can be eliminated.
- The outcome is a better-selected lymphocyte population.

Receptor inadequacy → apoptosis

Thymic selection involves apoptotic cell loss

- Developing T lymphocytes pass through selection checkpoints.
- Cells that fail selection do not need to survive indefinitely.
- Apoptotic removal contributes to the composition of the mature T-cell pool.

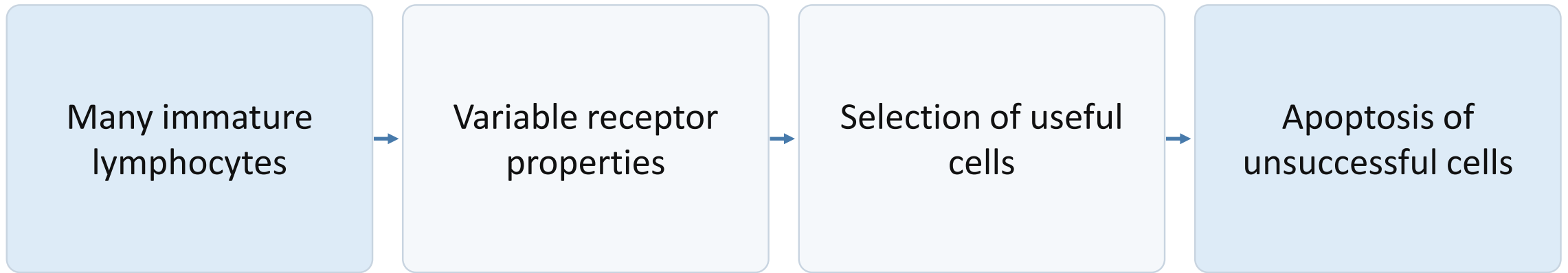
Selection failure → cellular deletion

Germinal-center B-cell selection

- B cells in germinal centers undergo functional selection.
- Cells failing to produce suitable antigen-receptor function may be eliminated.
- Apoptosis removes B cells that do not meet survival-selection requirements.

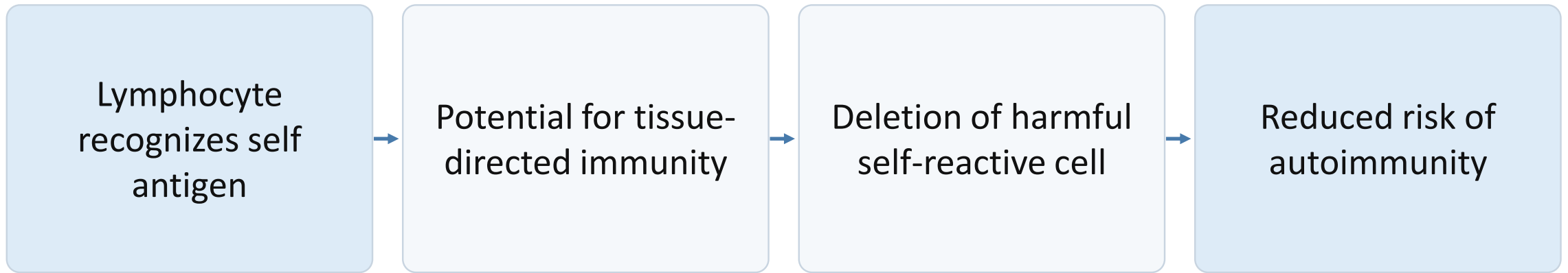
Functional B-cell selection → apoptosis

Selection converts diversity into a functional pool



The final repertoire reflects both successful survival and selective death.

Self-reactive lymphocytes must be controlled



Apoptosis is an important route to immunologic tolerance.

Deletion of autoreactive cells preserves tolerance

- Recognition of the body's own antigens can make certain lymphocytes dangerous.
- Apoptotic elimination reduces survival of potentially self-reactive clones.
- Loss of this regulatory function can permit unwanted immune responses.

Self-reactivity → deletion → tolerance

Lymphocyte selection has two distinct purposes

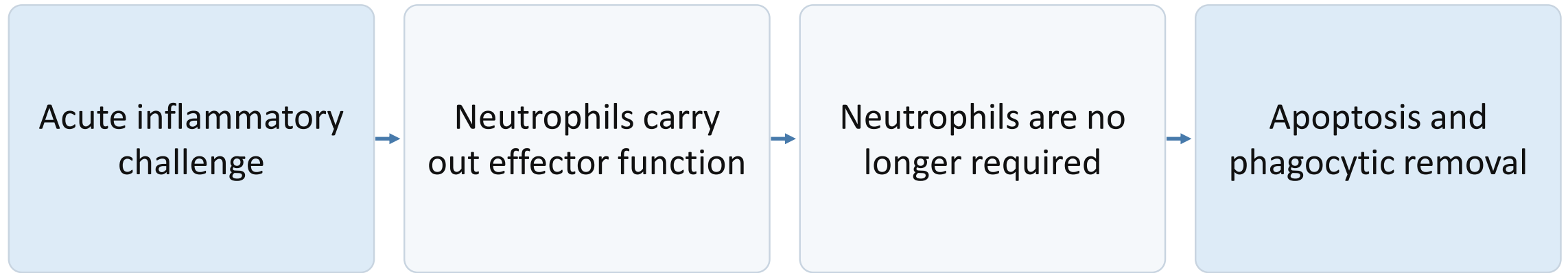
Functional competence

- Eliminate cells with nonfunctional receptors.
- Improve the quality of the mature repertoire.

Self-tolerance

- Eliminate potentially harmful autoreactive cells.
- Limit immune reactions against host tissues.

Apoptosis contributes to inflammation resolution



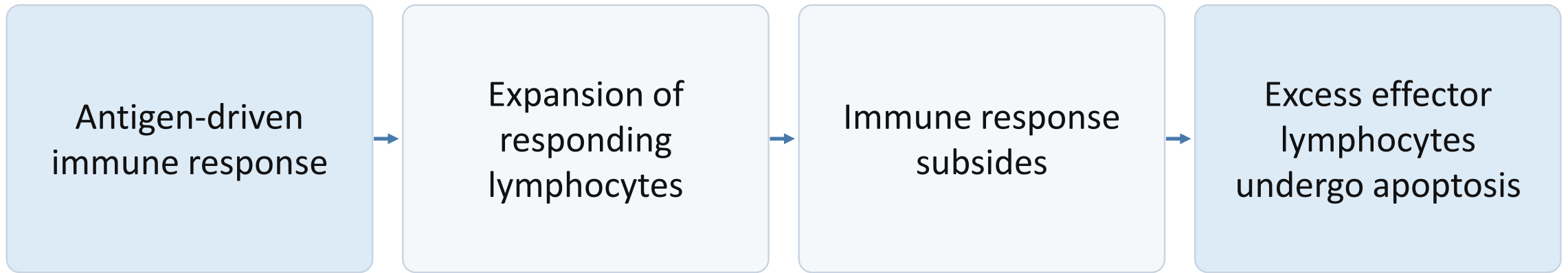
Removal of spent neutrophils helps end an acute inflammatory response.

Neutrophils are removed after useful service

- Neutrophils are short-lived participants in acute inflammation.
- Persisting effector cells are unnecessary after the initiating threat subsides.
- Apoptotic death helps clear these cells without releasing their contents.

Resolution of acute inflammation

Expanded lymphocyte populations contract



Cell death restores a smaller post-response lymphocyte population.

The end of an immune response requires cell loss

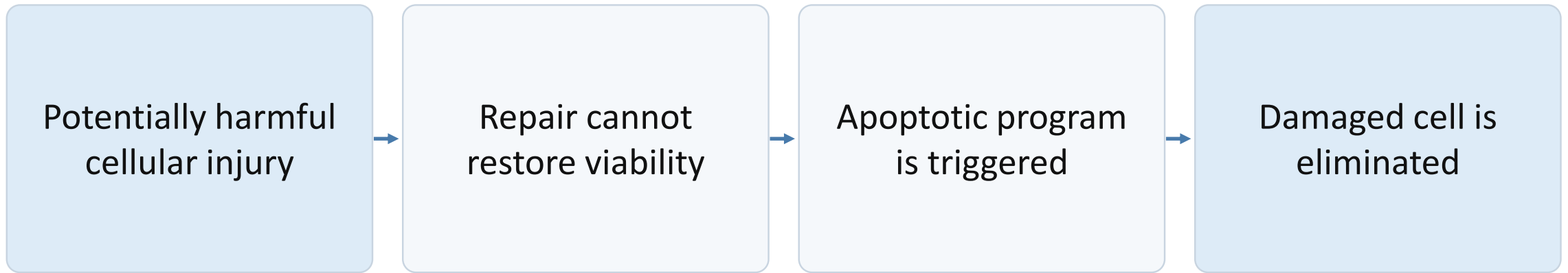
- Immune activation increases the number of responding cells.
- After the response, much of that expanded population is no longer needed.
- Apoptosis contributes to termination and population contraction.

Response → expansion → contraction

Physiologic triggers can be grouped by function

Function	Example	Reason for apoptosis
Development	Surplus cells	Refine organ architecture
Endocrine adaptation	Breast after weaning	Tissue involution
Homeostasis	Intestinal epithelium	Balance renewal
Immune selection	Unsuitable lymphocytes	Quality control
Immune tolerance	Self-reactive lymphocytes	Avoid self-injury
Immune resolution	Neutrophils, lymphocytes	End effector activity

Pathologic apoptosis removes irreparably injured cells



Apoptosis can protect surrounding tissue by preventing persistence of injured cells.

Apoptotic death has a protective boundary

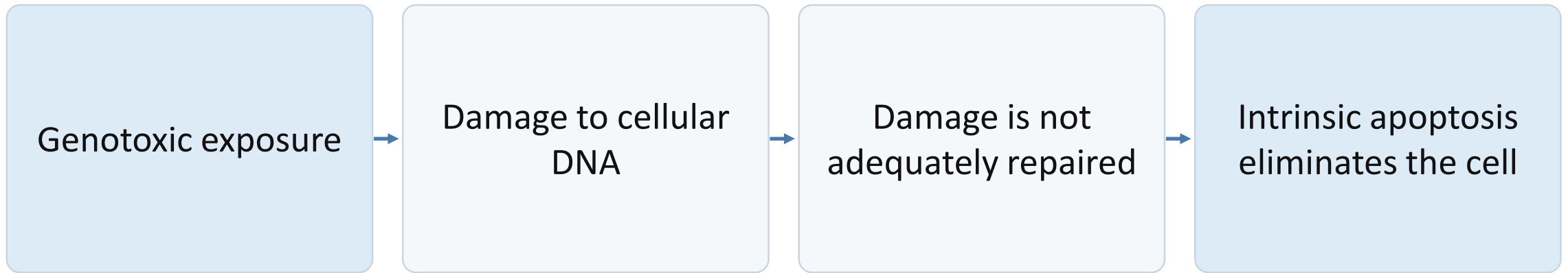
Protective role

- Remove cells with unrepaired damage.
- Reduce persistence of mutant or infected cells.
- Limit leakage of inflammatory contents.

Pathologic cost

- Loss of functional parenchymal cells.
- Infection-related or immune-mediated tissue damage.
- Organ atrophy in selected settings.

DNA damage is a major pathologic trigger



Robbins specifically lists radiation and cytotoxic anticancer drugs.

Radiation can produce apoptotic DNA injury

- Radiation may damage DNA directly.
- Radiation-associated free radicals may also damage nucleic acids.
- When the injury cannot be repaired, apoptosis prevents continued survival of the damaged cell.

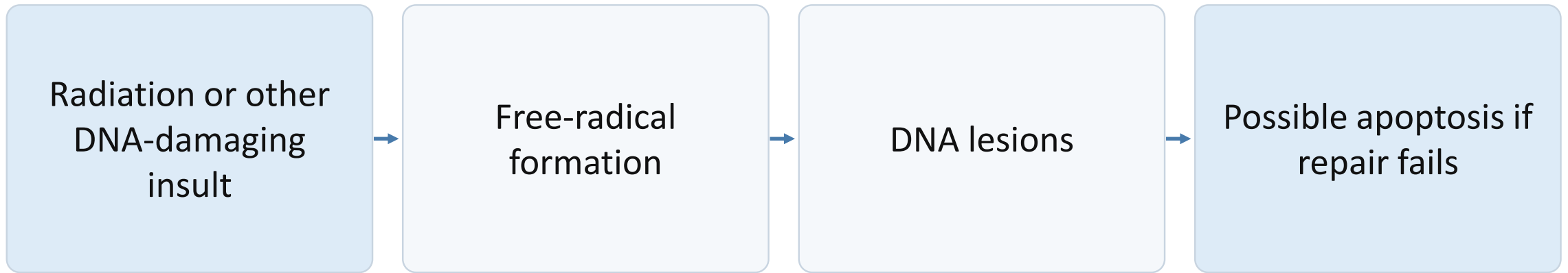
Radiation → irreparable DNA damage → apoptosis

Cytotoxic anticancer drugs can trigger apoptosis

- Many cytotoxic anticancer treatments injure DNA.
- Persistent injury activates the cell's death response.
- Apoptosis is one mechanism by which susceptible tumor cells are eliminated.

Drug-induced DNA injury → cellular elimination

Free radicals amplify DNA injury



Free radicals are a route to damage, not a separate universal requirement for apoptosis.

Repair capacity determines the response to DNA injury

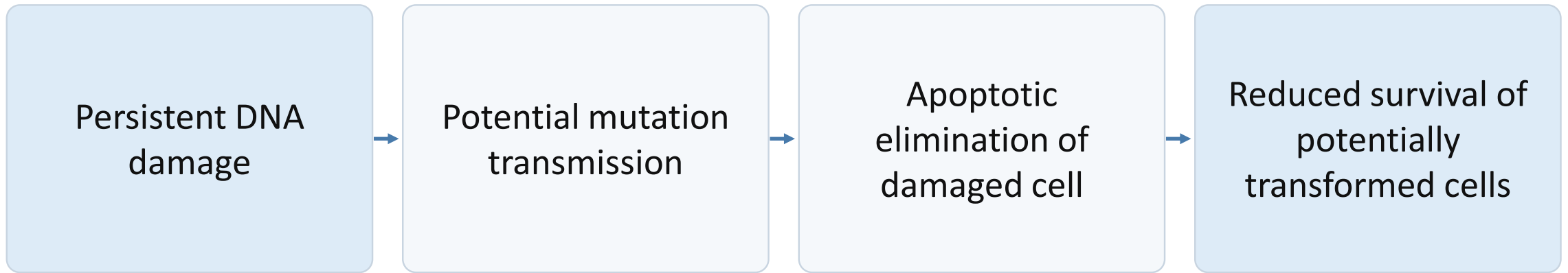
Damage can be repaired

- Cellular damage-response mechanisms act.
- Survival remains possible.

Damage cannot be repaired

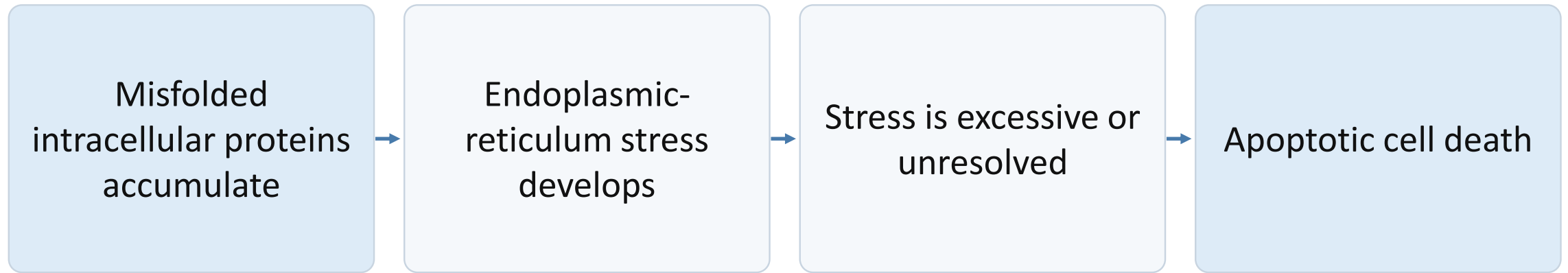
- Pro-apoptotic mechanisms predominate.
- The cell is removed before mutations persist.

Removing DNA-damaged cells reduces cancer risk



Apoptosis as a protection against malignant transformation.

Misfolded proteins can elicit apoptosis



Protein quality-control failure can become a pathologic cell-death signal.

Unresolved ER stress links protein injury to death

- The endoplasmic reticulum normally handles protein folding.
- Accumulation of improperly folded proteins produces ER stress.
- When adaptive responses are insufficient, apoptotic cell loss may follow.

Protein misfolding → ER stress → apoptosis

Infections may initiate apoptosis by two routes

Virus-associated injury

- Some viral infections can directly induce apoptosis.
- Adenovirus and HIV as examples.

Host immune response

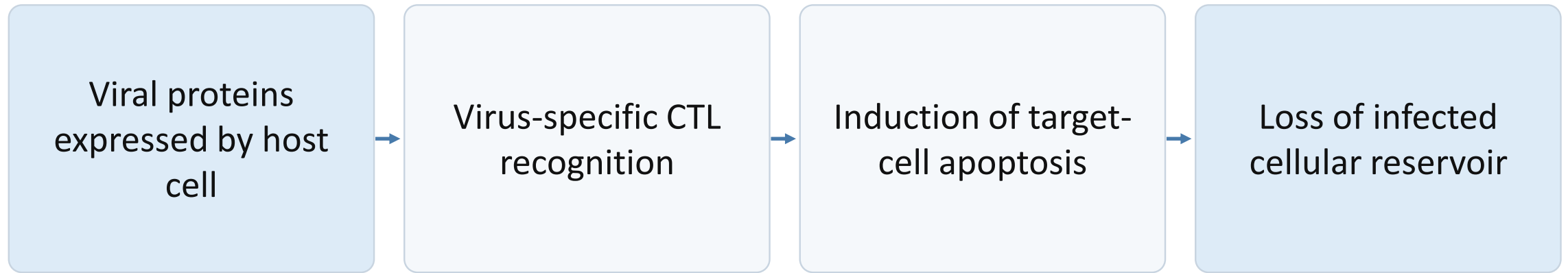
- Cytotoxic T lymphocytes recognize infected cells.
- Killing the infected cell can damage tissue.

Certain viruses can directly induce cell apoptosis

- Viral infection may provide the initiating injury or death signal.
- Adenovirus and HIV infection are examples listed.
- Direct virus-associated injury is distinct from cytotoxic lymphocyte killing.

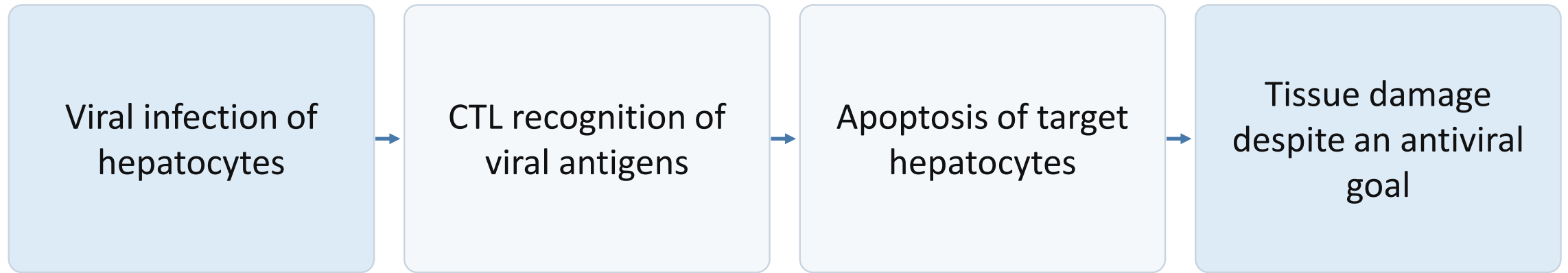
Infected host cell → apoptotic response

Cytotoxic T cells eliminate virus-infected cells



Immune cytotoxicity protects the host by removing infected cells.

Viral hepatitis illustrates immune-related tissue injury



The immune response can be protective and injurious simultaneously.

Antiviral killing has two competing consequences

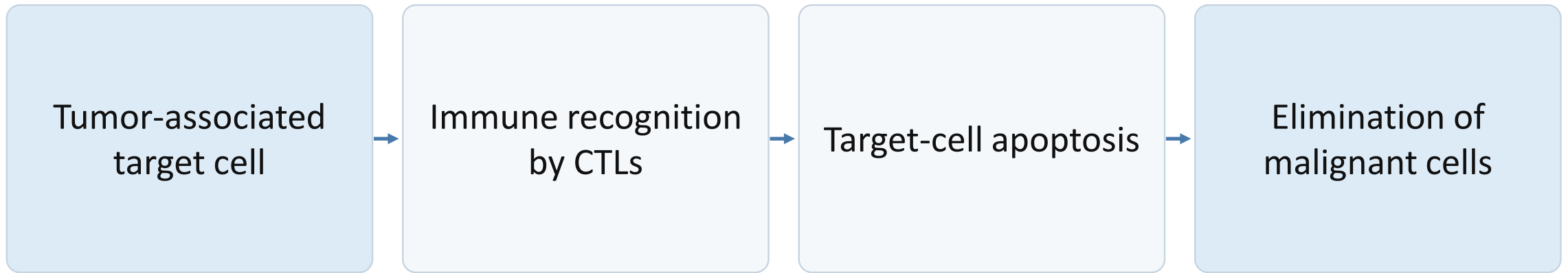
Benefit

- Eliminates infected cells.
- Limits reservoirs of infection.

Cost

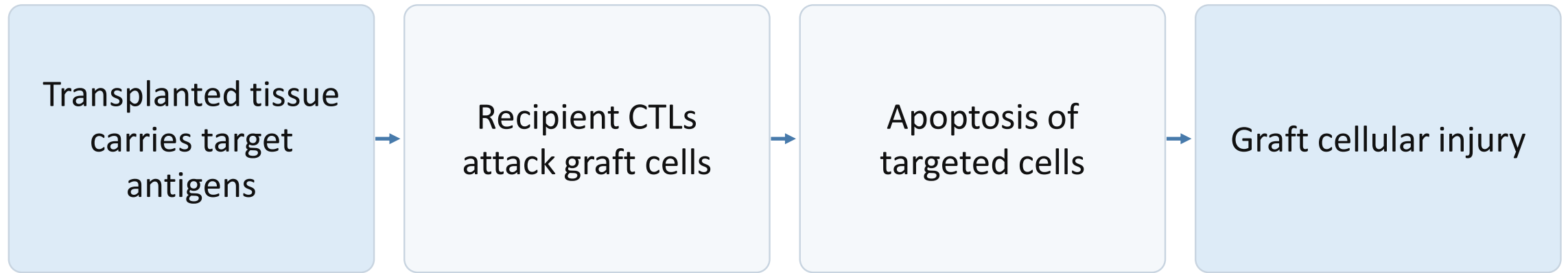
- Destroys host cells.
- May cause clinically significant tissue injury.

CTL cytotoxicity also removes tumor cells



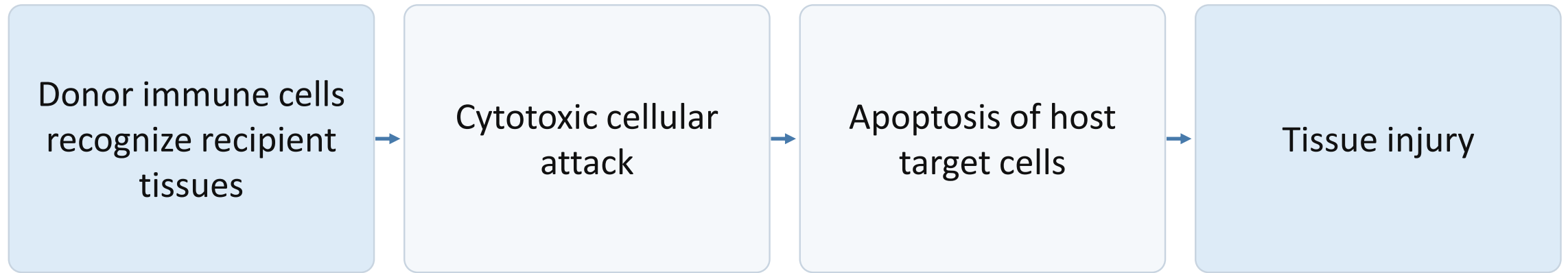
CTL-mediated apoptosis with anti-tumor cytotoxicity.

Cellular transplant rejection involves apoptosis



The same effector mechanism that defends against viruses can injure allografts.

Graft-versus-host disease involves target-cell loss

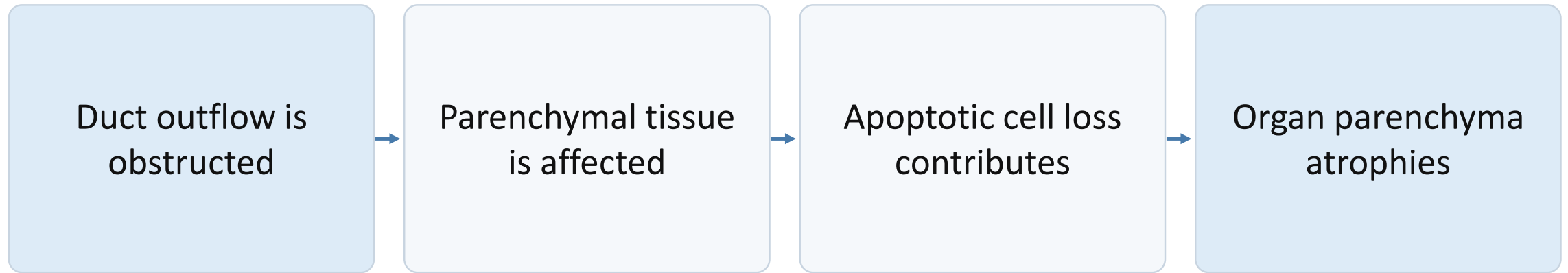


Apoptotic killing is a mechanism contributing to graft-versus-host disease.

A shared CTL effector mechanism spans diseases

Setting	Cell targeted	Functional consequence
Viral infection	Infected host cell	Helps clear infection
Tumor immunity	Tumor cell	Eliminates neoplastic targets
Transplant rejection	Allograft cell	Graft injury
Graft-versus-host disease	Recipient tissue cell	Host tissue injury

Duct obstruction can lead to pathologic atrophy



Pancreas, parotid gland, and kidney.

Pancreatic duct obstruction and cell loss

- Duct obstruction may affect pancreatic parenchyma.
- Loss of parenchymal cells contributes to atrophy.
- Apoptosis is one mechanism implicated in this form of pathologic regression.

Obstruction → parenchymal apoptosis → atrophy

Parotid gland atrophy after obstruction

- The parotid gland is a second example of obstructive parenchymal atrophy.
- Sustained obstruction can be associated with apoptotic cell loss.
- The tissue consequence is loss of glandular substance.

Obstruction-associated loss of salivary parenchyma

Renal parenchymal atrophy and obstruction

- The kidney among organs that can atrophy after duct obstruction.
- Cellular loss can include apoptosis.
- The initiating problem is obstructed drainage, not a normal physiologic need for involution.

Obstruction-associated renal parenchymal loss

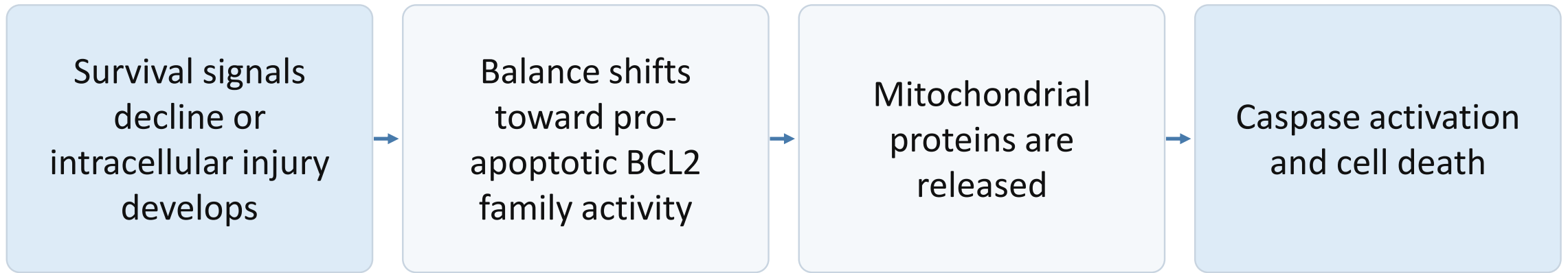
One trigger can have several organ outcomes

Organ	Pathologic context	Result
Pancreas	Duct obstruction	Parenchymal atrophy
Parotid gland	Duct obstruction	Parenchymal atrophy
Kidney	Urinary outflow obstruction	Parenchymal atrophy

Physiologic and pathologic causes converge

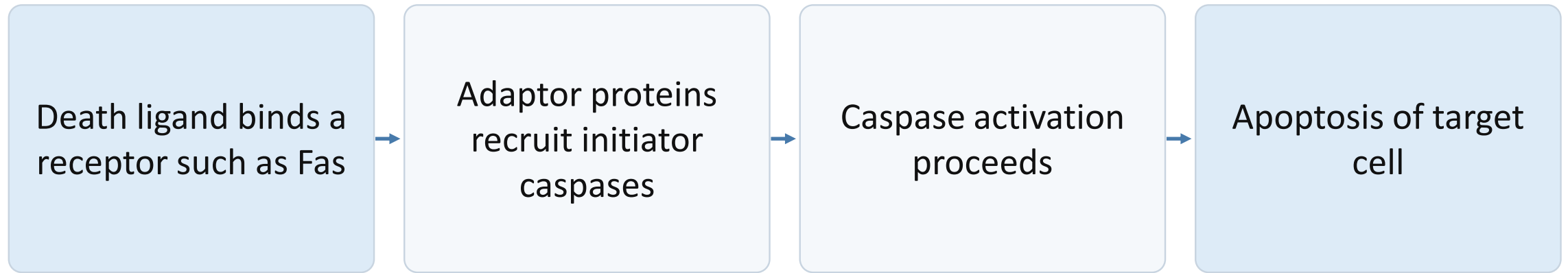
Initiating condition	Representative setting	Biologic purpose or consequence
Survival-signal withdrawal	Tissue involution	Remove unneeded cells
Failed lymphocyte selection	Immune development	Improve repertoire
DNA damage	Radiation, cytotoxic therapy	Remove severely damaged cells
ER stress	Misfolded protein accumulation	Eliminate injured cell
CTL-mediated recognition	Infection, transplant	Target-cell killing
Obstruction	Pancreas, parotid, kidney	Parenchymal atrophy

Most triggers engage intrinsic death machinery



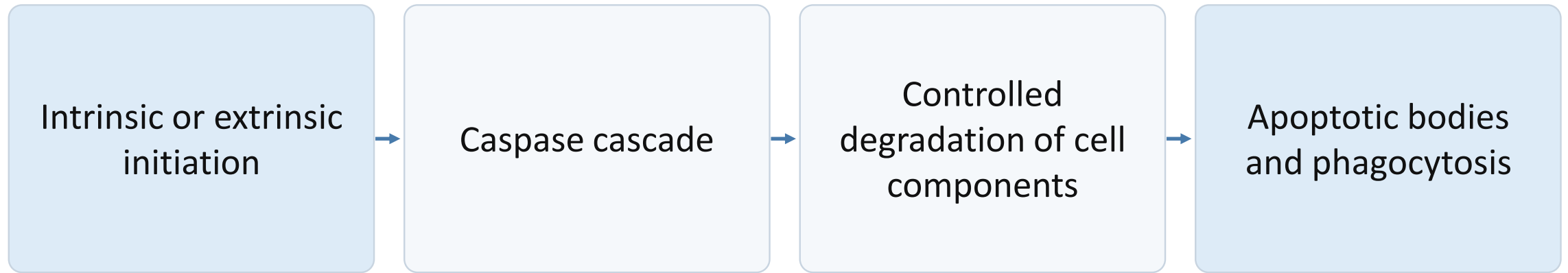
Mechanistic bridge from the adjacent Robbins section; Not an exhaustive pathway map.

Death-receptor signals provide another entry



Death-receptor initiation is another route described in the adjacent section.

Different triggers share common apoptotic execution



The common endpoint explains similar morphology despite different causes.

Morphology confirms the process—not its cause

Morphologic recognition

- Cell shrinkage
- Chromatin condensation
- Membrane-bound apoptotic bodies
- Rapid phagocytosis

Etiologic attribution

- Requires knowledge of tissue context.
- Physiologic turnover and disease can look similar.
- Cell death alone does not identify the initiator.

Apoptosis can be sparse in a tissue section

- Individual cells shrink and fragment.
- Apoptotic bodies are rapidly removed by phagocytes.
- A substantial rate of apoptosis may be difficult to appreciate in a single H&E section.

A single static section is a limited temporal sample.

Application: The breast after weaning

After cessation of breastfeeding, a previously lactating mammary gland decreases in functional glandular mass.

What apoptotic trigger best explains this change?

Discuss the initiating condition and its biological purpose or consequence.

Application: Interpreting breast involution

Why is this not necessarily pathologic atrophy?

- The initiating event is a normal physiologic transition—cessation of lactation.
- Selective cell loss helps return the tissue from a lactational state.
- The cellular mode of death is apoptosis, but the context is physiologic.

Application: Hepatocyte apoptosis in viral hepatitis

Liver tissue from a patient with viral hepatitis contains scattered apoptotic hepatocytes in a background of an antiviral cellular immune response.

Which mechanism is most directly implicated?

Discuss the initiating condition and its biological purpose or consequence.

Application: Antiviral defense versus injury

Why can effective immunity damage an organ?

- CTL-mediated killing removes infected target cells.
- The target cell is also a functional component of host tissue.
- Cumulative apoptotic death can contribute to organ injury.

Application: Apoptosis during anticancer therapy

Tumor cells exposed to a DNA-damaging cytotoxic agent accumulate injury that cannot be adequately repaired.

Why might these cells undergo apoptosis?

Discuss the initiating condition and its biological purpose or consequence.

Application: DNA damage and cell-fate selection

What is the protective significance?

- Persistently damaged DNA creates a risk of mutation.
- Apoptotic clearance removes cells with irreparable injury.
- In a tumor, the same mechanism contributes to the intended cytotoxic effect.

Discriminate causes, mechanisms, and consequences

Cause	Proximal cellular signal	Contextual consequence
Weaning	Withdrawal of tissue-maintenance signals	Physiologic involution
Unsuccessful immune selection	Inadequate receptor/survival cues	Repertoire quality control
Radiation	DNA injury that cannot be repaired	Elimination of damaged cells
Viral hepatitis	CTL-mediated attack	Infected-cell loss and tissue injury
Duct obstruction	Stress and loss of parenchymal cells	Pathologic atrophy

Core synthesis: The biologic context defines the cause

- Physiologic apoptosis removes surplus, obsolete, or potentially harmful cells.
- Pathologic apoptosis follows irreparable injury, infection-related killing, or selected obstructive disease.
- Both are regulated processes with rapid clearance and relatively little inflammatory leakage.
- Identify the initiating condition before assigning the significance of apoptotic morphology.

Same cell-death process; Different biological meanings.

Reference and scope

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 2, “Causes of Apoptosis,” printed pp. 39–41.

Adjacent textbook context: “Apoptosis,” pp. 39; “Morphologic and Biochemical Changes in Apoptosis,” pp. 41–42; “Mechanisms of Apoptosis,” pp. 42–43.

The source supplied for this deck is a Markdown extraction. Original chapter PDF pages were not available for comparison. No textbook figures are reproduced.