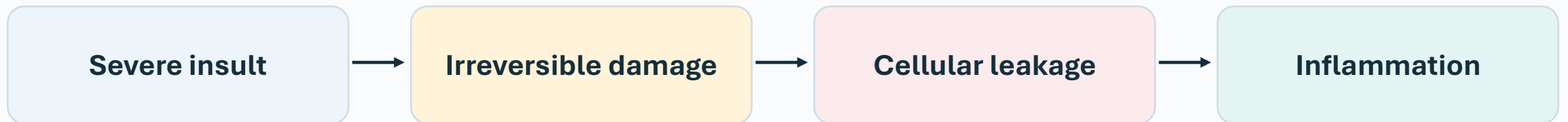


Necrosis

Irreversible injury, membrane breakdown, inflammation, and morphologic evidence



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Learning outcomes

- Define necrosis and identify the injuries that cause it.
- Connect irreversible mitochondrial and membrane dysfunction to cell lysis.
- Explain damage-associated molecular patterns and the inflammatory response.
- Recognize necrotic cytoplasmic, nuclear, and ultrastructural changes.
- Interpret leakage biomarkers in their tissue and clinical context.

Necrosis is a consequence of severe injury

Necrosis is a pathologic process resulting from lethal cellular injury.

- Severe damage becomes irreparable across multiple essential cell components.
- Loss of membrane integrity allows cellular constituents to escape.
- Enzymatic degradation and local inflammation accompany the process.

The four interlocking features

Protein denaturation

Cellular proteins lose their native structure and function.

Loss of membrane integrity

Intracellular components escape through damaged membranes.

Inflammatory reaction

Extracellular injury signals activate resident and recruited immune cells.

Enzymatic digestion

Lysosomal and leukocyte enzymes help dismantle dead cells.

Sources of severe injury

Loss of oxygen supply

Ischemia compromises mitochondrial energy generation and cellular homeostasis.

Microbial toxins

Infectious agents can produce severe cell damage by toxic mechanisms.

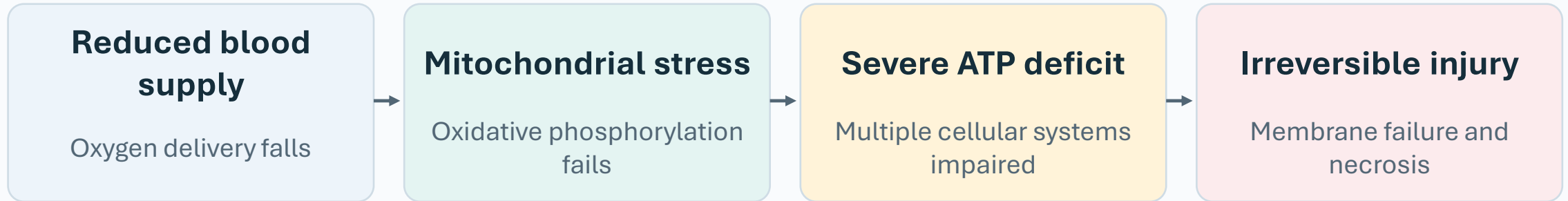
Physical / chemical injury

Burns and damaging chemicals can overwhelm cellular repair.

Protease-mediated injury

Active proteases escaping cells may damage surrounding tissue, as in pancreatitis.

Ischemia: Oxygen loss initiates injury



Microbial toxins can precipitate necrosis

Initial insult

- Toxic products from microorganisms injure susceptible cells.
- Multiple organelles or cell structures may be affected.
- Severity and persistence influence outcome.

Necrotic outcome

- Cell membrane barrier collapses.
- Cytoplasmic proteins and enzymes escape.
- Local inflammatory response develops.

Chemical and physical injury

Chemicals

Potential direct toxicity to cellular proteins, membranes, or organelles.

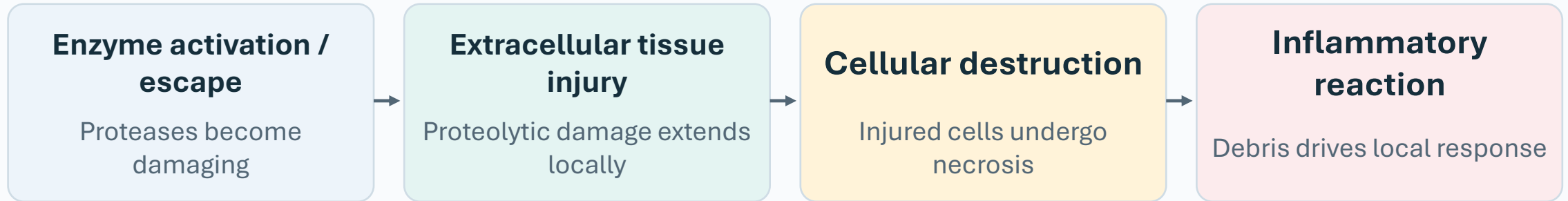
Burns

Severe physical damage causes irreversible cellular dysfunction.

Common endpoint

Multiple pathways can converge on membrane loss and tissue destruction.

Pancreatitis: A protease-centered example



Different triggers converge on one phenotype

Ischemia

Failure of oxygen supply and energy production.

Toxic stress

Irreparable disruption of key proteins or membranes.

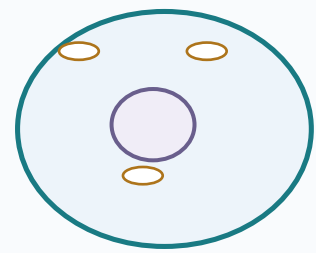
Physical injury

Severe destruction of cellular architecture.

Proteases

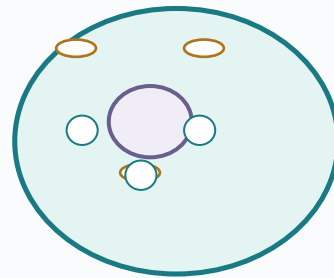
Enzymatic injury of cells and local tissue.

Progression from viable to dead cells



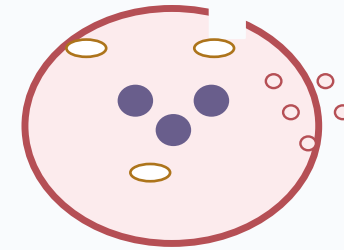
Viable

Integrity retained.



Potentially reversible

Early swelling and
dysfunction.



Necrotic

Membrane rupture and
digestion.

The boundary is not a universal fixed duration; Injury burden and cell type matter.

Severe injury is not merely severe swelling

Reversible cellular injury

- Cell and organelle swelling may occur.
- Plasma membrane can exhibit blebs.
- Recovery remains possible if stimulus abates.

Necrosis

- Critical membrane integrity is lost.
- Injury cannot be reversed by removing the stimulus alone.
- Digestion, leakage, and inflammation follow.

The “point of no return” is not sharply defined

The precise threshold for irreversibility is largely undefined.

- A single marker does not universally identify that transition.
- Severe dysfunction involves more than one linked cellular compartment.
- Persistent mitochondrial failure and major membrane derangement are consistent hallmarks.

Two consistent hallmarks of irreversibility

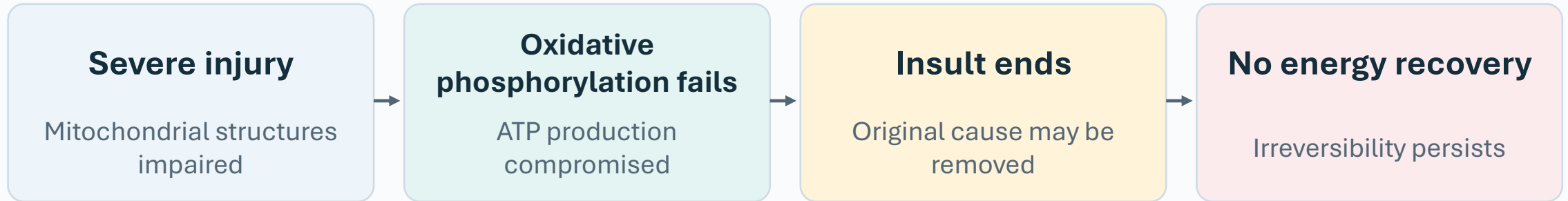
Nonrecovering mitochondria

Oxidative phosphorylation and ATP generation fail to recover even if the original injury is relieved.

Profound membrane disturbance

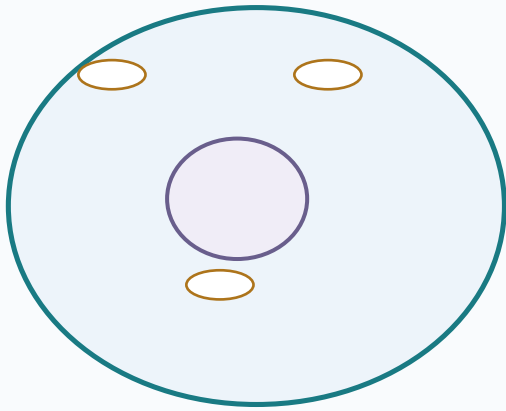
Loss of essential membrane functions allows gradients, contents, and enzymes to escape.

Mitochondrial failure cannot be rescued



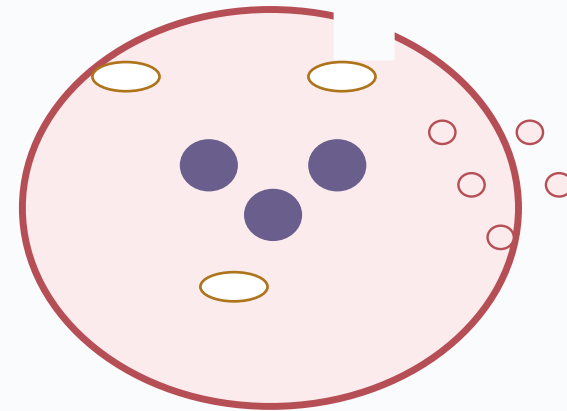
Plasma membrane breakdown

Schematic — not a photomicrograph



Intact cellular boundary

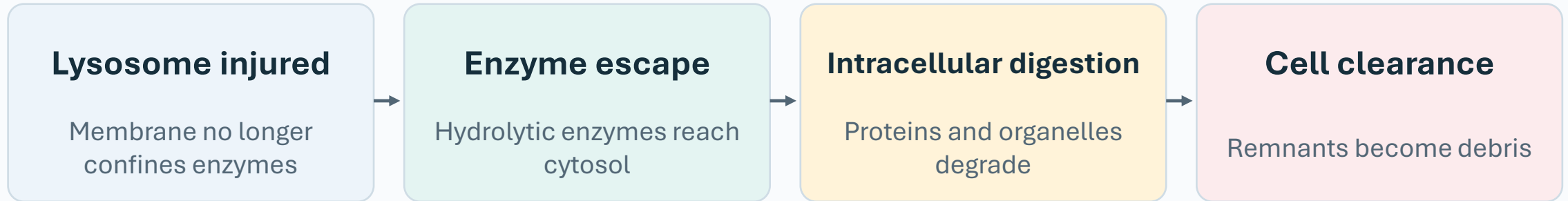
Nucleus and organelles retained



Irreversible membrane injury

Fragments leak; Debris is cleared

Lysosomal membranes: A destructive breach



Three cellular compartments in irreversible injury

Mitochondria

Persistent impairment of oxidative phosphorylation and ATP production

Plasma membrane

Loss of ion barrier and escape of cytosolic constituents

Lysosomal membrane

Enzyme escape and digestion of cellular structures

Protein denaturation is a defining feature

Necrotic injury disrupts the structure of numerous cellular proteins.

- Denaturation changes the native conformation of protein targets.
- Enzyme activity and structural integrity may be lost together.
- Morphologic consequences become apparent in the staining of necrotic cytoplasm.

Denaturation and digestion are distinct

Denaturation

- Native protein conformation is disturbed.
- Protein function becomes impaired.
- Cell structure may temporarily be recognizable.

Digestion

- Hydrolases cleave cellular constituents.
- Organelles and cells are dismantled.
- Debris is removed by phagocytes.

Lysosomal enzymes dismantle dead cells

Source inside the cell

Lysosomal leakage delivers enzymes to damaged cytoplasm.

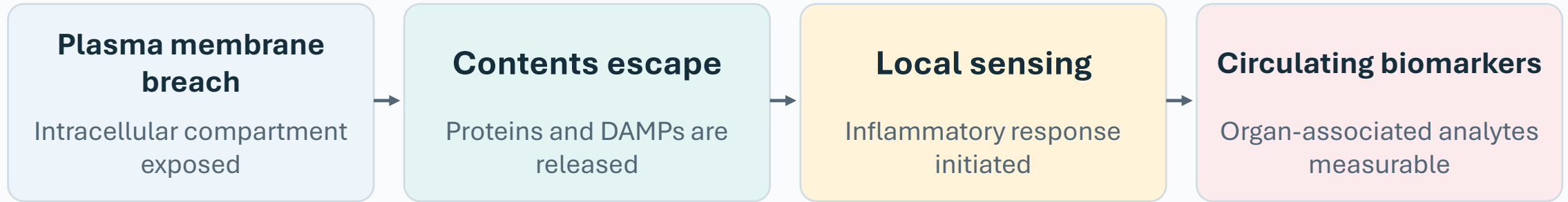
Extracellular response

Leukocytes can release additional degradative enzymes.

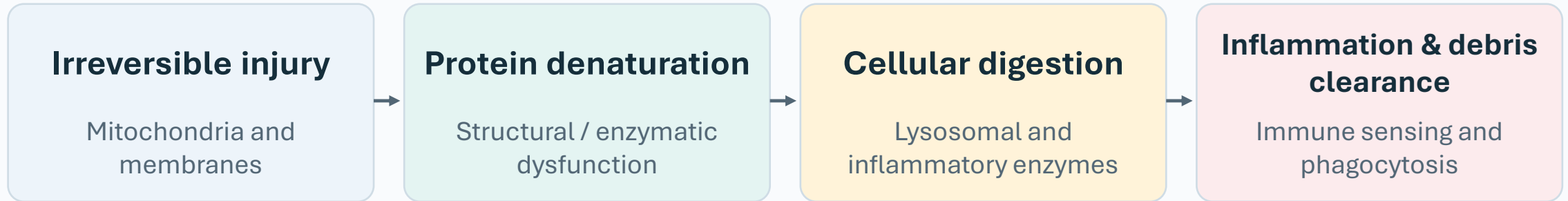
Fate of remnants

Enzymatic breakdown and phagocytosis remove necrotic debris.

Membrane failure enables two downstream effects

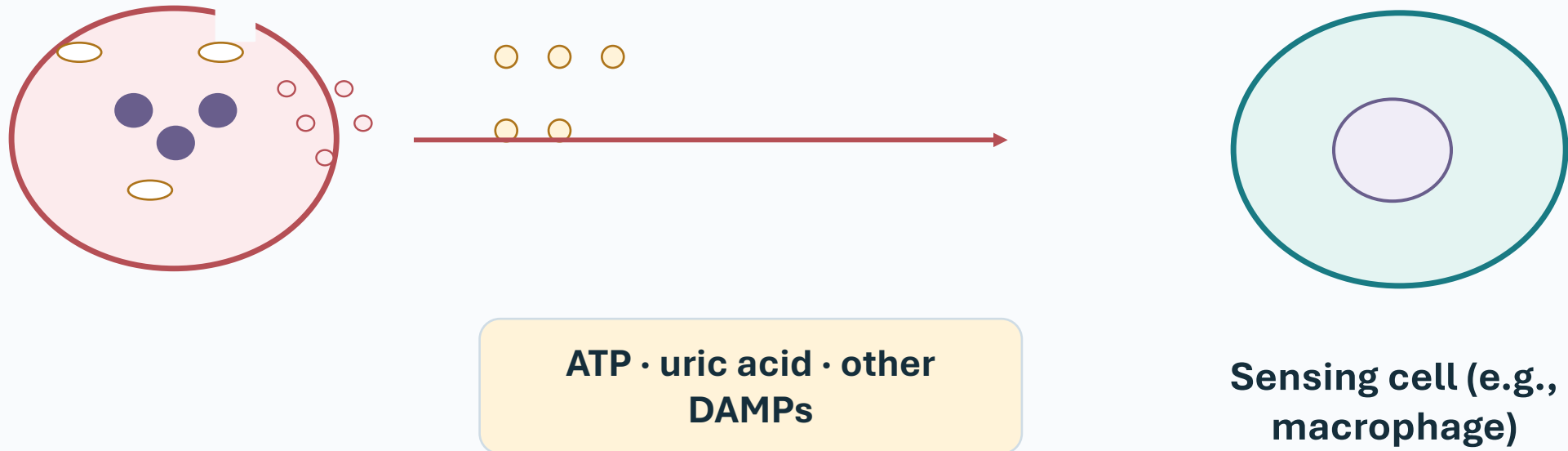


Necrosis is a coupled cascade



Why necrosis provokes inflammation

Schematic: Leakage leads to sterile inflammatory signaling



Recognition → cytokines → phagocytosis and leukocyte recruitment

Damage-associated molecular patterns (DAMPs)

DAMPs are endogenous molecules whose abnormal extracellular presence signals cell damage.

- Normally confined or regulated within healthy cells.
- Released in substantial injury when compartments lose integrity.
- Recognized by immune or tissue cells and can stimulate local inflammatory responses.

Two DAMP examples

ATP

Released in the context of damaged mitochondria and other injured cellular compartments.

Uric acid

A breakdown product of cellular DNA that can participate in danger signaling.

DAMPs are not microbial toxins

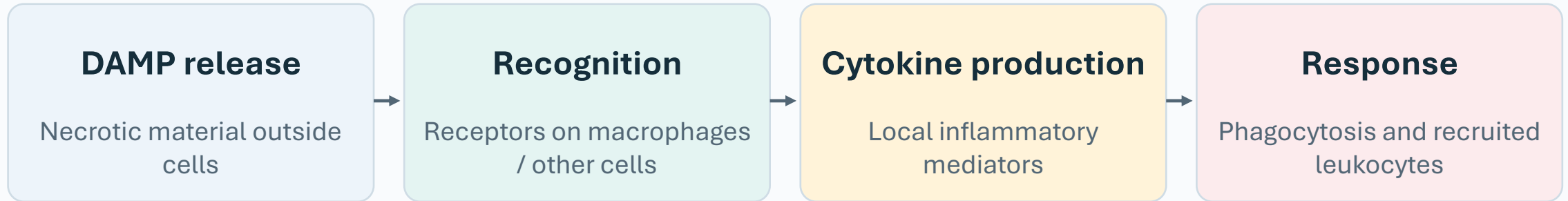
DAMPs

- Endogenous molecules associated with host-cell damage.
- May be exposed in sterile necrosis.
- Signal disrupted tissue homeostasis.

Microbial triggers

- Exogenous products associated with microorganisms.
- Can act as initiating injuries.
- Infection and tissue necrosis can coexist.

Cellular recognition of leaked injury signals



Macrophages: Sensing and removal

Recognition

Respond to molecules released from damaged cells.

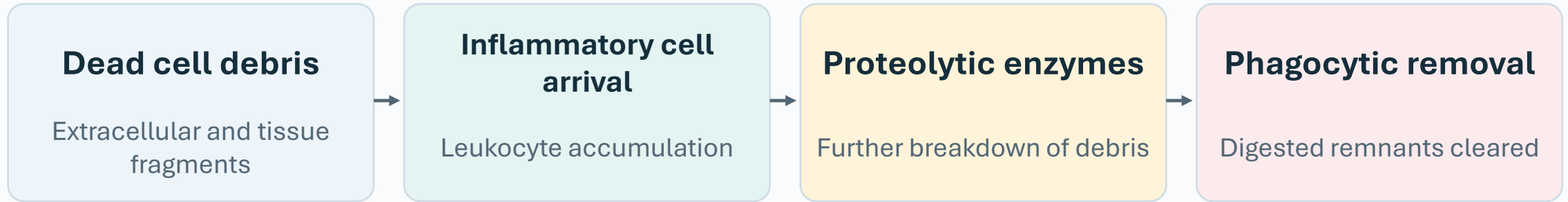
Mediator release

Produce cytokines that contribute to inflammatory recruitment.

Phagocytosis

Engulf cellular fragments and participate in cleanup.

Inflammation assists clearance



A reciprocal relationship: Injury and inflammation

Necrosis → inflammation

Leakage of DAMPs and cell proteins activates local innate responses.

Inflammation → clearance

Recruited inflammatory cells provide proteases and phagocytic activity.

Inflammation can amplify damage

Leukocyte enzymes can affect additional nearby constituents.

Not every inflammatory focus is infected

Necrotic sterile tissues can be inflammatory in the absence of microorganisms.

Sterile necrosis still triggers immunity

An infectious organism is not required for inflammation around necrotic cells.

- Injured host cells can release DAMPs without microbial invasion.
- Resident macrophages and other cells detect damage.
- The resulting response participates in the removal of necrotic material.

Inflammation is part of the tissue response

Trigger

Severe injury disrupts membranes and releases DAMPs.

Recognition

Macrophages and other receptor-bearing cells respond.

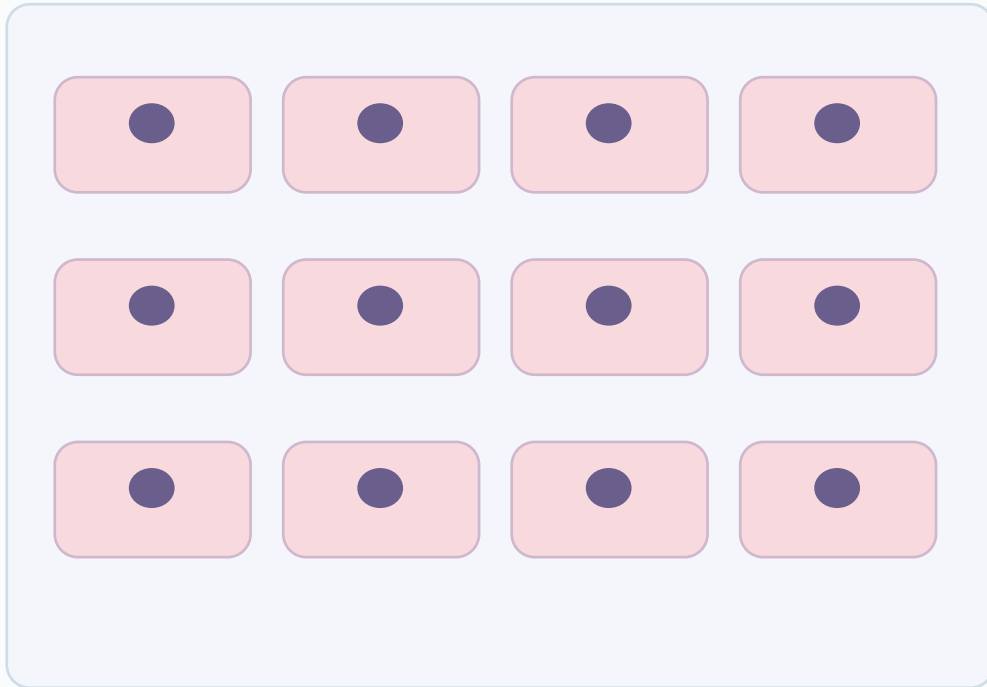
Effector phase

Cytokines and leukocytes support local inflammation.

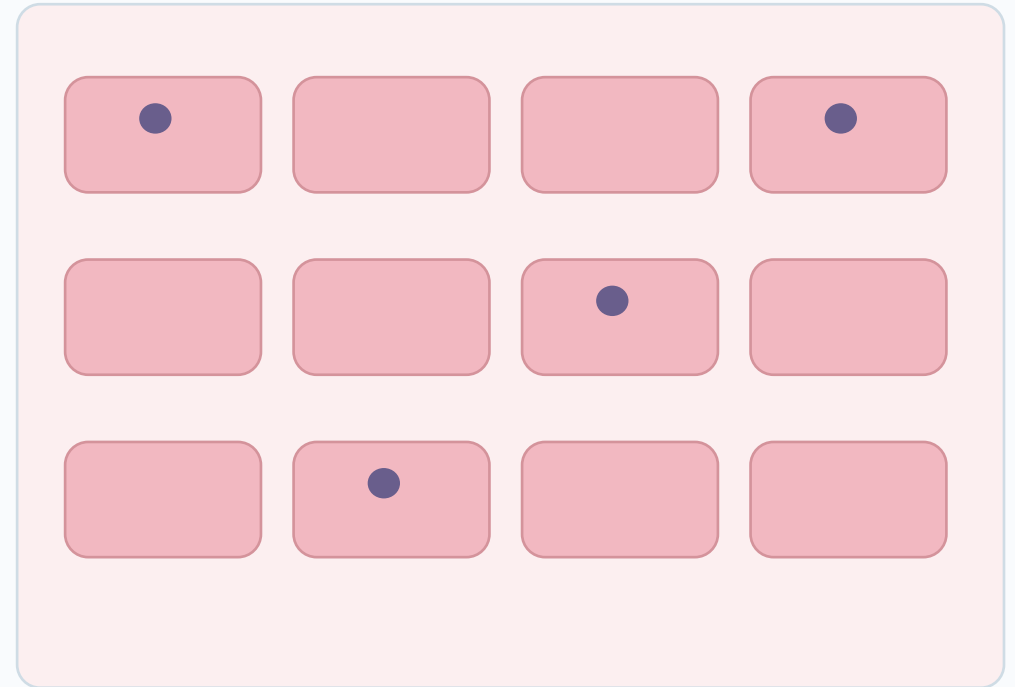
Resolution of debris

Proteolysis and phagocytosis clear dead cells.

Cytoplasmic eosinophilia in necrosis

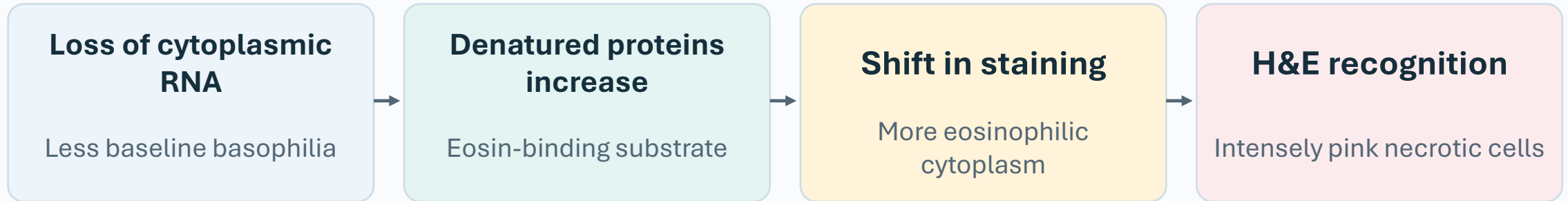


Intact nuclei; Cytoplasmic baseline



Hypereosinophilia; Nuclear loss

Why necrotic cytoplasm becomes more pink



Glassy cytoplasm: A second appearance

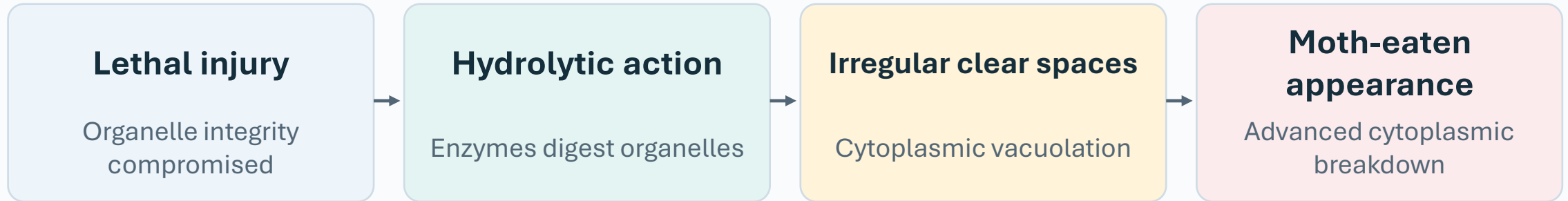
Observation

Necrotic cytoplasm may become relatively smooth and homogeneous.

Pathologic correlate

This appearance largely with loss of cytoplasmic glycogen particles.

When organelles are digested, vacuoles appear



Myelin figures originate from damaged membranes

Source material

Injured phospholipid-rich cellular membranes.

Appearance

Whorled membrane-derived phospholipid precipitates.

Subsequent fate

Phagocytosis or breakdown into fatty acids; Residues may calcify.

Ultrastructural features of necrosis

Compartment	Electron microscopy appearance
Cell membrane	Discontinuities or frank breaks
Organelle membranes	Discontinuities and severe injury
Mitochondria	Marked dilation, including large amorphous densities
Cytoplasm	Myelin figures and amorphous debris
Proteins	Fluffy aggregates of denatured material

Light microscopy and electron microscopy

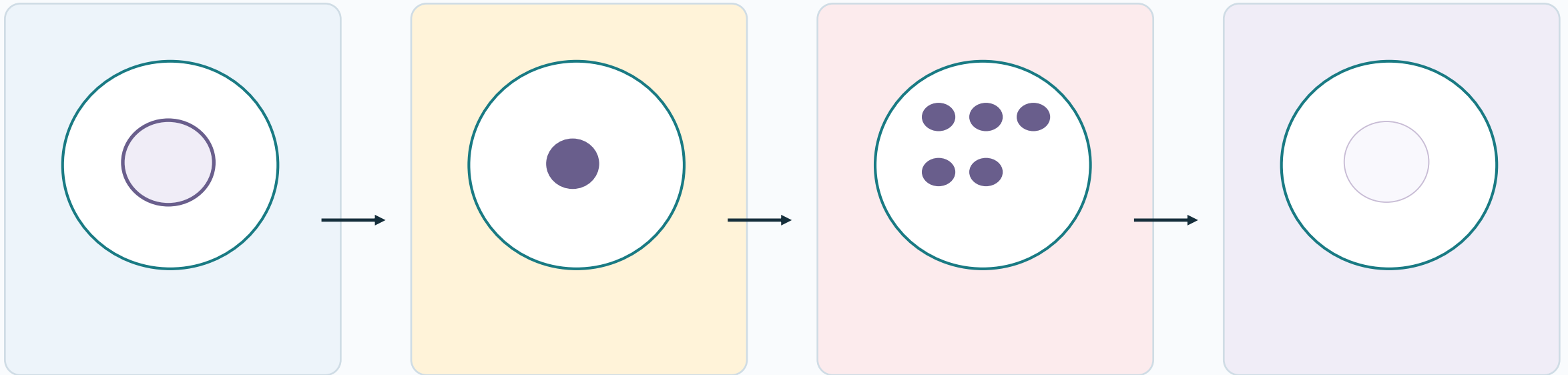
Light microscopy (H&E)

- Marked cytoplasmic eosinophilia.
- Variable vacuolation and a homogeneous appearance.
- Nuclear pyknosis, fragmentation, or loss.

Electron microscopy

- Plasma and organelle membrane breaks.
- Severely altered mitochondria.
- Myelin figures and electron-dense cellular debris.

The three principal nuclear changes



Intact nucleus

Distinct nuclear
chromatin

Pyknosis

Small, hyperchromatic
nucleus

Karyorrhexis

Nuclear fragmentation

Karyolysis

Progressive nuclear
fading

Schematic nuclear appearances; All three nuclear endpoints need not be present simultaneously.

Pyknosis: Dense nuclear shrinkage

Pyknosis is nuclear shrinkage with conspicuous chromatin condensation and basophilia.

- Nuclear volume decreases.
- Chromatin forms a small, dark, condensed mass.
- Pyknosis is not unique to necrosis; It may also occur in apoptosis.

Karyorrhexis: Fragmented nucleus

Karyorrhexis denotes fragmentation of a pyknotic nucleus.

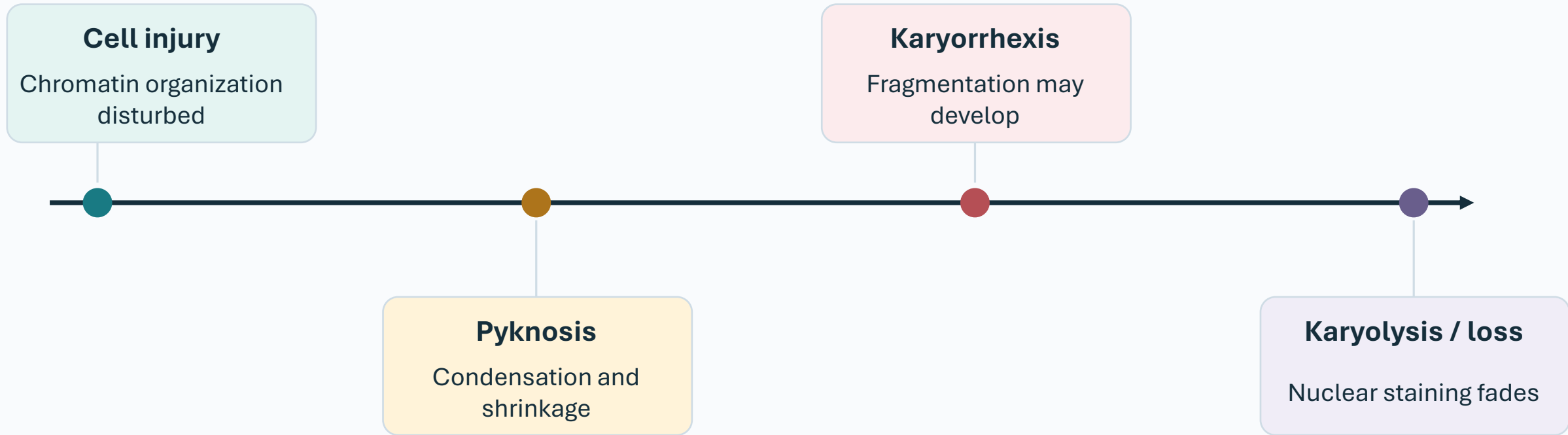
- The condensed chromatin separates into fragments.
- Intact nuclear continuity is lost.
- The finding supports cell death when read in the correct morphologic context.

Karyolysis: Loss of nuclear staining

Karyolysis is progressive fading of nuclear basophilia during DNA degradation.

- Endonuclease-mediated breakdown reduces stainable nuclear DNA.
- The nucleus can become difficult to identify.
- Ultimately, nuclear material may disappear from the necrotic cell.

Nuclear disappearance is a temporal process



Nuclei of necrotic cells can disappear over roughly 1–2 days; Patterns are not a rigid universal sequence.

Avoid overinterpreting a single nuclear sign

Pyknosis alone

Not exclusive to necrosis; Apoptotic cells may also show chromatin condensation.

Karyorrhexis

Supports nuclear breakdown, but interpret alongside the surrounding cell and tissue.

Karyolysis

Fading nuclear staining usually indicates substantial DNA degradation.

Integrative diagnosis

Combine nuclear, cytoplasmic, membrane, and tissue-inflammatory features.

Necrosis compared with reversible injury

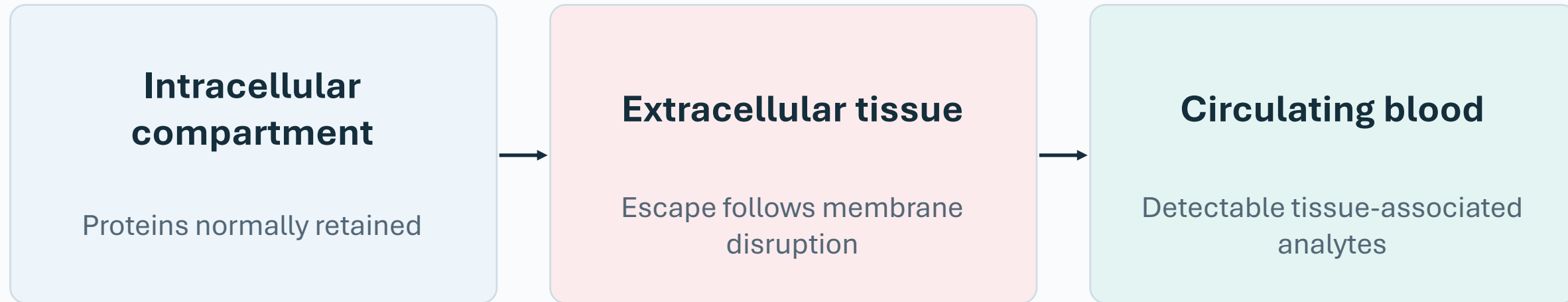
Feature	Potentially reversible injury	Necrosis
Cell boundary	Blebbing may occur; Integrity can persist	Major barrier failure; Contents escape
Energy system	Mitochondrial dysfunction may recover	Severe failure does not recover
Cytoplasm	Swelling and vacuolation	Denaturation and enzymatic digestion
Nucleus	May remain identifiable	Pyknosis, fragmentation, or fading
Inflammation	Not intrinsic to every early injured cell	Common local response to DAMP release

Necrosis contrasted with apoptosis

Characteristic	Necrosis	Apoptosis
Typical context	Severe pathologic injury	Regulated death pathway
Cell membrane	Disrupted, with leakage	Initially intact; Apoptotic bodies enclosed
Cell contents	Leak into surroundings	Packaged for phagocytic removal
Inflammation	Frequently prominent	Usually minimal / absent
Tissue response	Proteolysis and inflammatory cleanup	Rapid phagocytosis of bodies

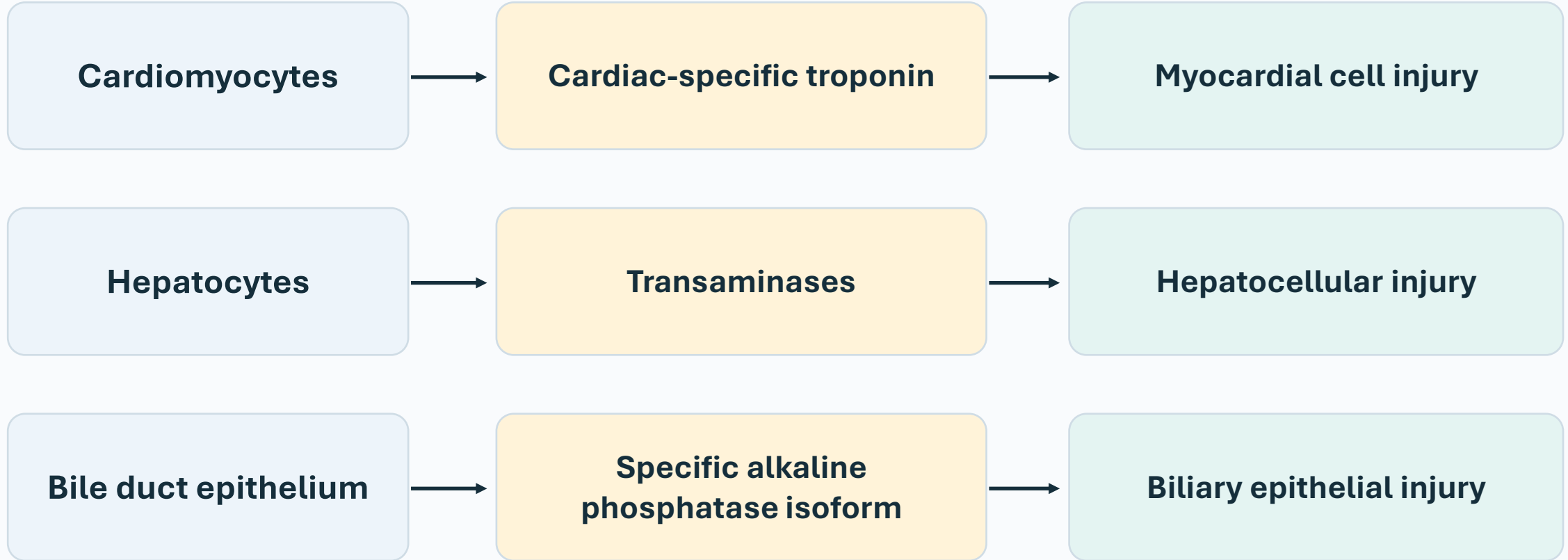
Tissue injury becomes a blood-test signal

Three linked spaces



Biomarker detection relies on membrane leakage and access of the analyte to circulation.

Biomarkers track different cellular origins



Specificity varies: A circulating analyte is interpreted with clinical context, not in isolation.

Cardiac-specific troponins

Cell of origin

Cardiac myocytes express cardiac-specific variants of the contractile protein troponin.

Clinical implication

Released troponins are sensitive markers used in serial testing for myocardial cell injury.

Hepatocyte transaminases

Source tissue

Hepatocytes contain the transaminases used as serum indicators of hepatocellular injury.

Interpretive limitation

Elevated transaminases indicate hepatocellular injury, not a unique cause or stand-alone proof of necrosis.

Biliary alkaline phosphatase isoforms

Relevant tissue

Bile duct epithelial cells express a characteristic alkaline phosphatase isoform.

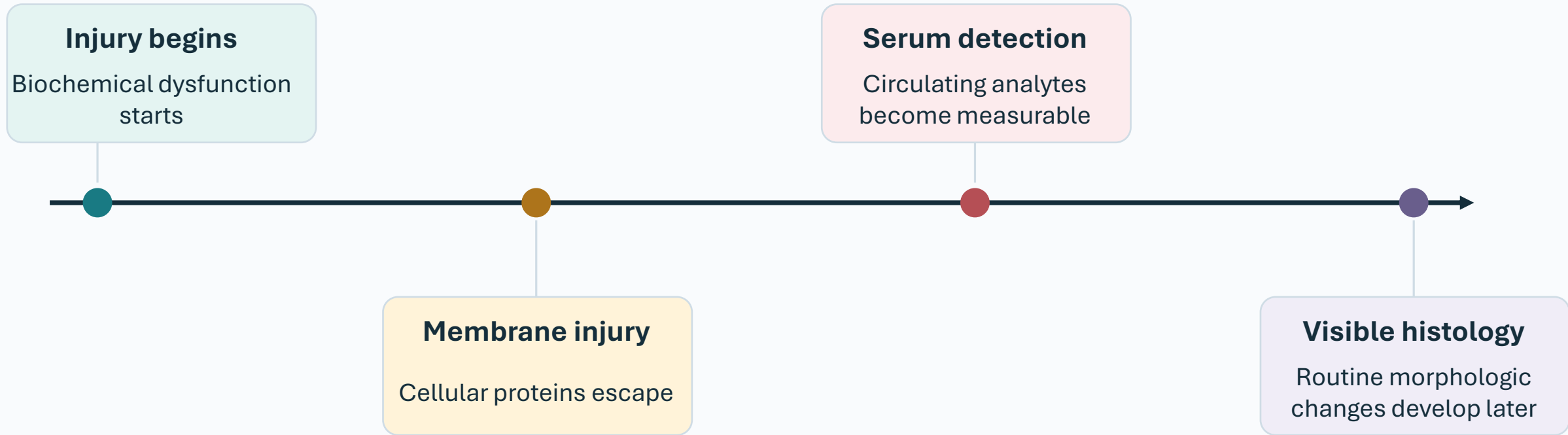
Clinical use

Increased circulating activity may indicate biliary injury; Other ALP sources must be considered.

Serum markers: What can be inferred?

Observed finding	Supported implication	Not established by marker alone
Cardiac troponin rise	Myocardial cellular injury	Specific mechanism without clinical data
Transaminase elevation	Hepatocyte damage	Etiology or tissue histologic pattern
ALP elevation	Potential hepatobiliary source	Exclusive bile duct provenance
Serial change over time	Dynamic injury information	Exact morphologic timing of every cell

Biochemistry can precede visible necrosis



The timing is conceptual; The exact interval depends on organ, insult, and test sensitivity.

Myocardial troponin may rise before histology

That cardiac-specific troponins may be detectable as early as 2 hours after myocardial cell necrosis.

- Biochemical evidence can predate unmistakable light-microscopic changes.
- Serial serum troponin testing has a central role in myocardial infarction assessment.
- Absolute timing varies with assay, clinical course, and sampling.

Membrane leakage does not specify a single etiology

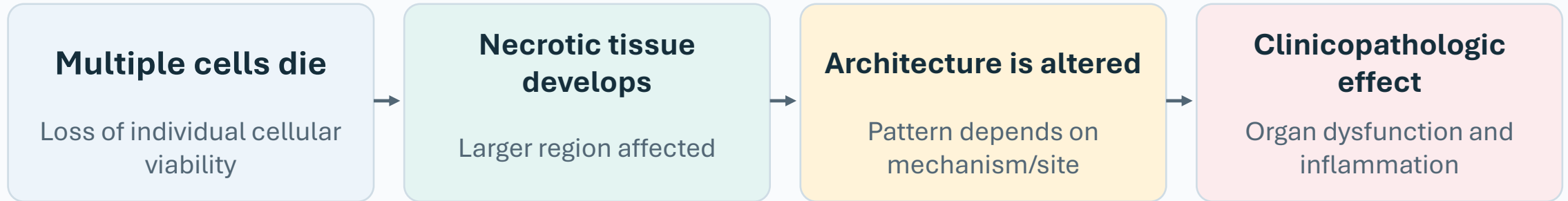
What a marker can support

- Presence of tissue-associated intracellular protein in circulation.
- A biologically plausible cell-injury process.
- Change over time with repeated testing.

What else must be integrated

- Symptoms and relevant clinical findings.
- Organ-specific physiological assessment.
- Alternative sources and assay-related limitations.

From dead cells to tissue-level necrosis



Tissue patterns are a separate classification

Coagulative pattern

Typical of ischemic necrosis in many solid organs; Preserved outlines may remain transiently.

Liquefactive pattern

Digestion predominates; Classic settings include brain infarcts and certain infections.

Other patterns

Distinctive settings include gangrene, caseous, fat, and fibrinoid change; Developed in Topic 22.

Case: Ischemic myocardial injury

A patient with a coronary occlusion has elevated serial cardiac troponin concentrations, but an early myocardial sample does not yet show unmistakable cell death by routine light microscopy.

Is this temporal combination compatible with myocardial necrosis?

- Yes — a circulating marker can precede clear H&E findings.
- No — histologic necrosis must always appear first.

Myocardial case: Interpretation

Yes. Biochemical and histologic manifestations have different delays.

- Cellular proteins can escape into blood after membrane injury.
- Necrotic morphology requires additional time to develop at light-microscopic scale.
- Correlate serial troponins with symptoms, ECG, and other clinical evidence.

Case: Acute proteolytic pancreatic injury

Severe pancreatic injury is accompanied by escape of active proteases into local tissue. Surrounding cells become irreversibly damaged and recruit inflammatory cells.

What feature makes this an example of necrosis?

- Protease-associated cell destruction with leakage and inflammation.
- Intracellular triglyceride accumulation alone.

Pancreatic case: Interpretation

Uncontrolled proteolytic injury can contribute to cell destruction and necrosis.

- Protease escape in pancreatitis as an illustrative necrotic trigger.
- Membrane disruption releases tissue contents and inflammatory signals.
- This mechanism should not be generalized to every necrotic disease.

Knowledge check: The irreversibility boundary

Which pair most strongly characterizes the irreversible transition?

(A) Persistent mitochondrial failure and profound membrane dysfunction.

(B) Mild cell swelling and ribosomal detachment alone.

(C) Reduced intracellular triglyceride and normal ATP.

(D) Intact membranes with rapid apoptotic body clearance.

Irreversibility check: Answer

Persistent mitochondrial failure + severe membrane disturbance.

- The threshold is not defined by one exact time or one isolated lesion.
- Severe loss of oxidative phosphorylation and membrane homeostasis are consistent features.
- Lysosomal membrane injury contributes to enzymatic dissolution.

Knowledge check: Nuclear morphology

Which term describes the fading of nuclear basophilia caused by DNA breakdown?

(A) Pyknosis.

(B) Karyorrhexis.

(C) Karyolysis.

(D) Hydropic change.

Nuclear change check: Answer

Karyolysis describes nuclear fading.

- Pyknosis denotes condensation and shrinkage.
- Karyorrhexis denotes fragmentation.
- Karyolysis reflects loss of stainable DNA and may precede nuclear disappearance.

Knowledge check: Inflammatory trigger

Why can necrotic tissue produce an inflammatory response without microbes?

(A) DAMP release activates resident and recruited host cells.

(B) Apoptotic bodies must invariably rupture before being cleared.

(C) Every necrosis focus is caused by bacteria.

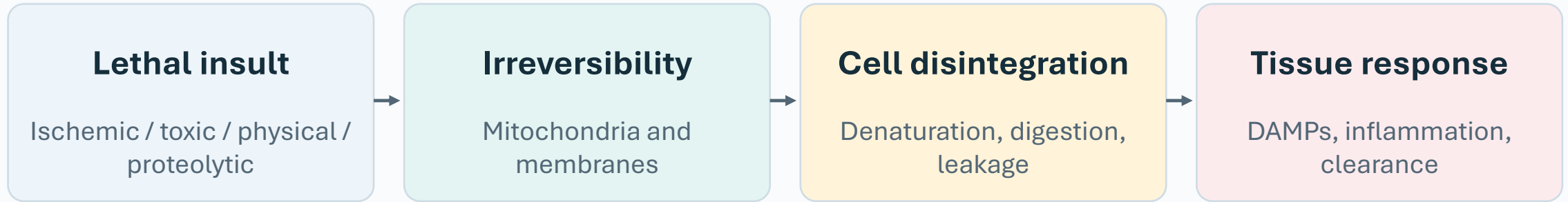
(D) The plasma membrane remains fully intact indefinitely.

DAMP check: Answer

Released endogenous danger signals can activate innate immune sensing.

- ATP and uric acid are examples named.
- Macrophages and other host cells recognize damaging extracellular signals.
- Cytokines, proteolysis, and phagocytosis support the subsequent response.

Integrated necrosis mechanism



Necrosis: Five durable conclusions

- Necrosis follows severe pathologic injury with irreparable cellular damage.
- Persistent mitochondrial dysfunction and profound membrane damage mark irreversibility.
- Cellular proteins denature; Lysosomal and inflammatory enzymes digest dead cells.
- DAMP leakage stimulates inflammation, while intracellular proteins may become serum biomarkers.
- Necrotic cytoplasm and nuclei show characteristic H&E and ultrastructural alterations.

Primary source and figure provenance

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026), Chapter 2, “Necrosis,” p. 38.
- Adjacent textual context: “Progression of Cell Injury and Death,” p. 35.
- Adjacent morphology: “Patterns of Tissue Necrosis—Morphology,” pp. 38–39.
- All mechanism and morphology graphics are original native editable PowerPoint schematics.
- No source photomicrograph is reproduced; schematics are not clinical or histologic specimens.