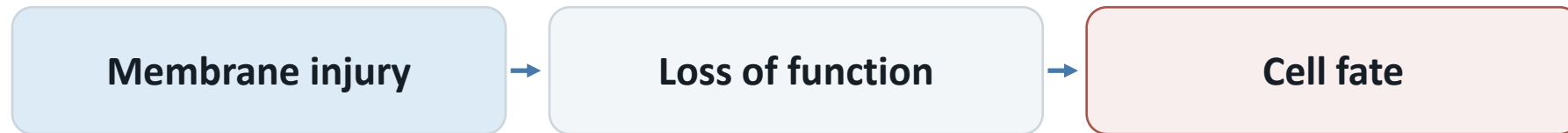


Membrane Damage

Mechanisms, organellar consequences, and clinicopathologic interpretation



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Learning objectives

- Explain how selective permeability is lost during cell injury.
- Trace the four major biochemical mechanisms of membrane damage.
- Distinguish plasma, mitochondrial, and lysosomal membrane effects.
- Connect membrane disruption to morphology, necrosis, and biomarkers.

Membranes are a common target in cell injury

Selective barrier

Organelle function

Cell integrity



Permeability failure

An early and widespread feature of cell injury; Overt damage characterizes progression toward necrosis.

Membrane injury is not limited to the cell surface

Plasma membrane

Maintains cellular contents and regulated exchange.

Mitochondrial membranes

Sustain oxidative phosphorylation; Regulate cell-death pathways.

Lysosomal membrane

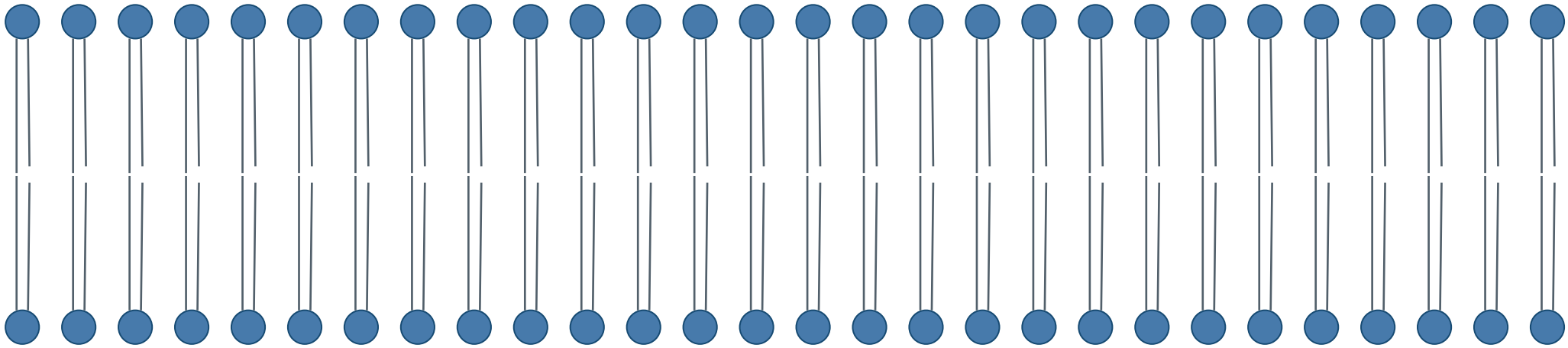
Sequesters degradative hydrolases from cytosol.

Other organellar membranes

Damage can disrupt compartment-specific biosynthesis and transport.

Phospholipid bilayer: The essential physical barrier

Extracellular fluid



Cytosol

Polar head groups face aqueous compartments; Hydrophobic tails form the low-permeability interior.

Selective permeability is a functional property

Intact membrane

- Maintains ion gradients and cellular solutes
- Separates cytosol from extracellular space
- Supports compartment-specific reactions

Injured membrane

- Gradient preservation becomes unreliable
- Water and ions redistribute
- Intracellular components may escape

Membrane integrity and membrane transport are distinct

Barrier

The lipid bilayer provides a physical permeability barrier.

Transport proteins

Channels and pumps determine controlled solute flux.

ATP supply

Energy depletion impairs active transport before rupture is necessary.



Membrane injury: A continuum rather than a single event



The initial functional disturbance may be reversible; Profound membrane disruption is associated with irreversible injury.

Reversible versus irreversible membrane injury

Reversible injury

- Cell swelling (hydropic change)
- Blebbing; Blunting or loss of microvilli
- Membrane remains capable of recovery

Irreversible injury / necrosis

- Profound membrane dysfunction
- Plasma and organelle membrane disruption
- Cellular leakage and enzymatic digestion

Four major biochemical mechanisms

Reactive oxygen species

Peroxidize membrane lipids.

Reduced synthesis

Energy failure limits phospholipid production.

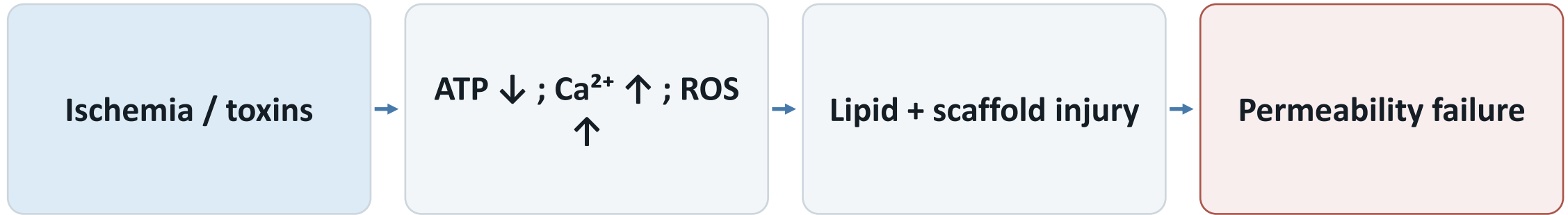
Accelerated breakdown

Ca²⁺-activated phospholipases degrade phospholipids.

Cytoskeletal disruption

Ca²⁺-activated proteases sever membrane anchors.

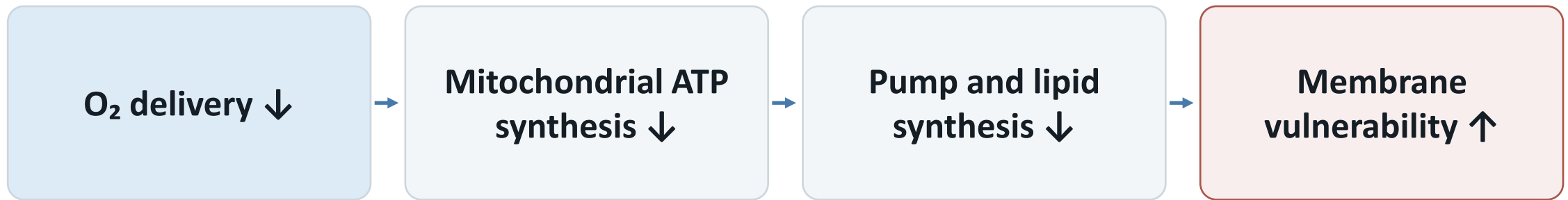
Multiple mechanisms amplify the same injury



A single insult can engage several pathways. Do not assume each pathway operates in isolation.

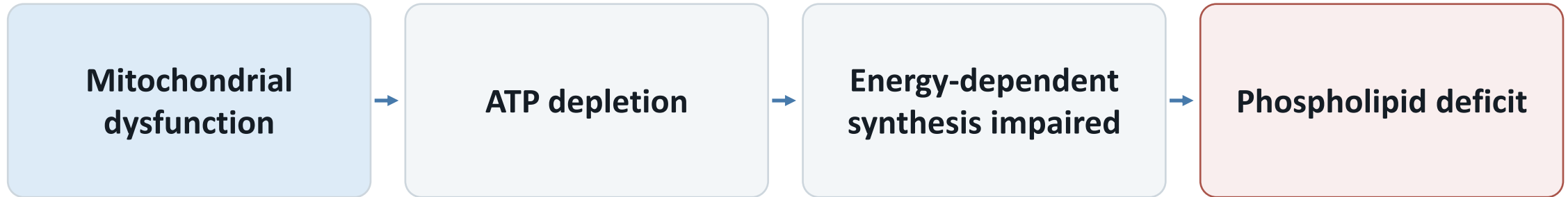
Ischemia couples energy and membrane injury

Hypoxic / ischemic cell



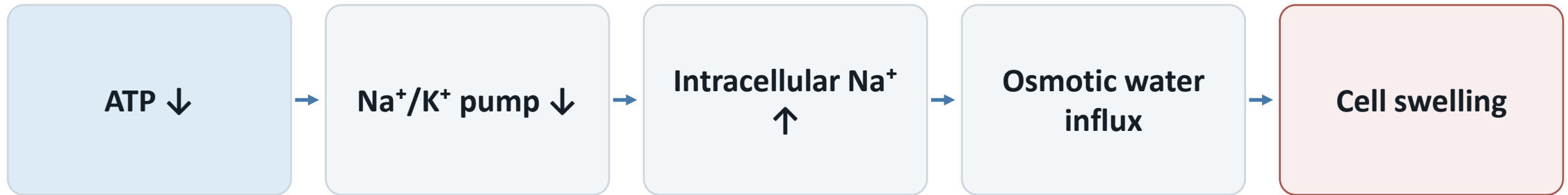
Increased cytosolic Ca^{2+} can simultaneously accelerate enzymatic membrane damage.

ATP depletion reduces phospholipid biosynthesis



The synthesis defect may involve several cellular membranes, including mitochondrial membranes.

Na^+/K^+ -ATPase failure produces cell swelling



This is an early transport failure and does not itself prove irreversible membrane rupture.

Swelling converts tether injury into mechanical stress

Swelling

Osmotically driven water entry expands the injured cell.

Detachment

Protease injury weakens membrane–cytoskeleton links.

Rupture risk

The membrane becomes susceptible to stretching and rupture.



Phospholipid synthesis depends on cellular energy

Normal turnover

Biosynthesis helps preserve the bilayer despite ongoing lipid renewal.

Hypoxic injury

Reduced oxidative phosphorylation lowers ATP availability.

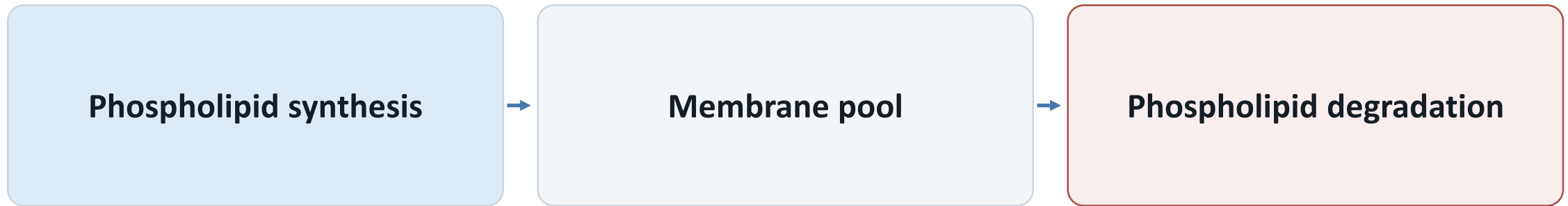
Synthesis impairment

Energy-dependent lipid production and reacylation are compromised.

Net result

Membrane homeostasis cannot be maintained under sustained insult.

Membrane maintenance is a balance of synthesis and loss



Injury shifts balance toward depletion

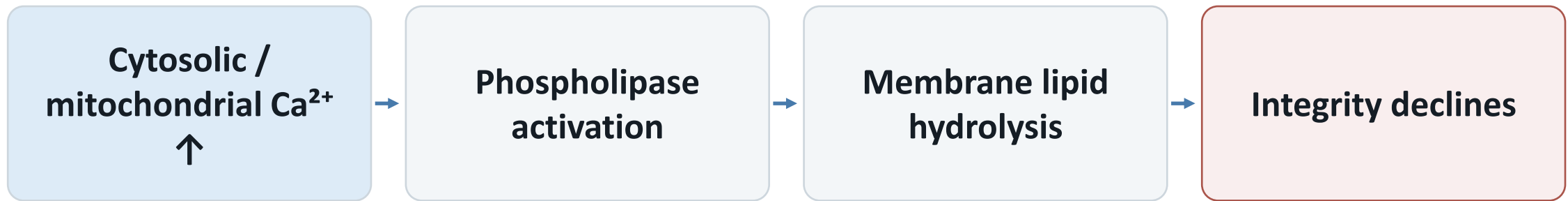
Calcium overload accelerates membrane injury



Elevated cytosolic Ca²⁺ simultaneously accelerates lipid and cytoskeletal injury.

Calcium-dependent phospholipases attack the bilayer

Enzymatic lipid damage



The source associates increased phospholipid degradation especially with severe injury.

Phospholipid degradation generates active by-products

Unesterified fatty acids

Accumulate as membrane phospholipids are degraded.

Lysophospholipids

Detergent-like amphipathic products disturb bilayer structure.

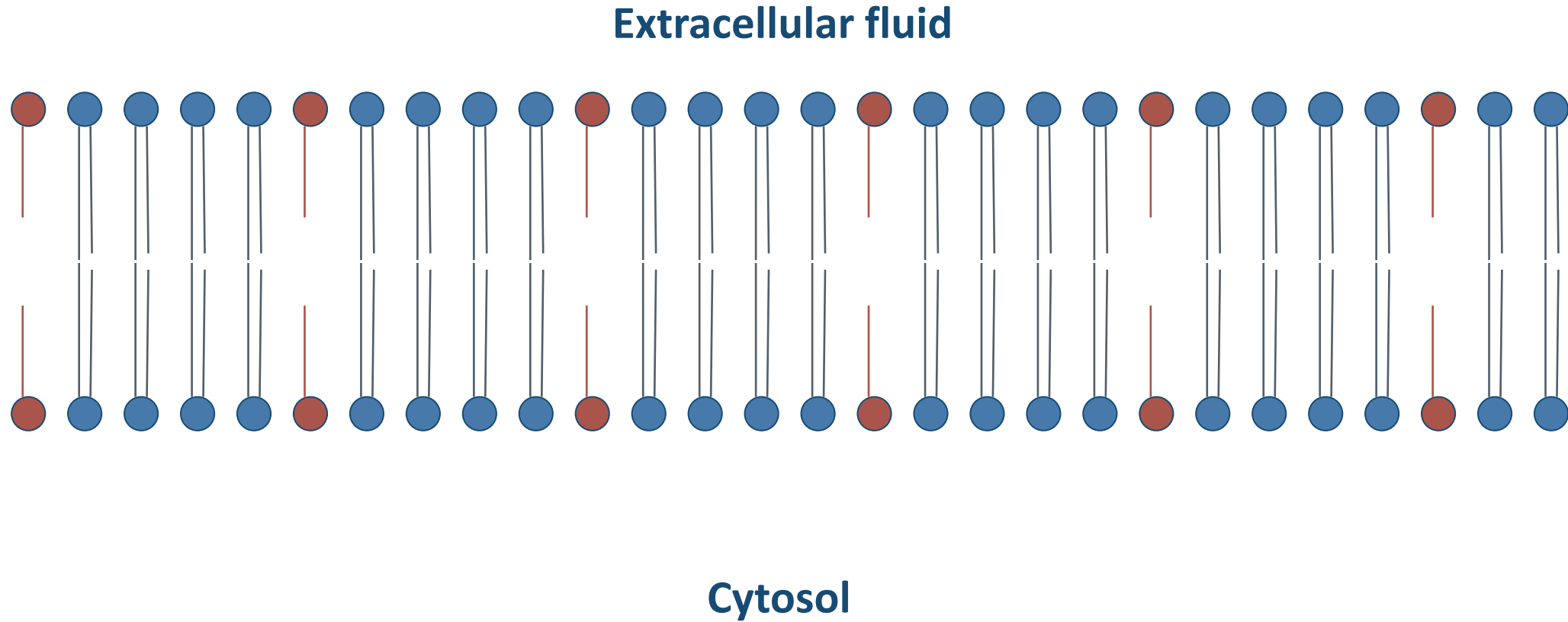
Acylcarnitine

Additional lipid-related breakdown product noted in injured cells.

Shared consequence

Increased permeability and altered electrophysiologic behavior may follow.

Lipid breakdown products disrupt bilayer packing



Simplified bilayer schematic: Altered lipid composition compromises barrier organization.

Why do detergent-like lipids alter permeability?

Amphipathic products

Free fatty acids and lysophospholipids accumulate after hydrolysis.



Bilayer insertion / exchange

Products may enter or exchange with the phospholipid bilayer.



Permeability change

Normal lipid packing and functional barrier behavior can change.

Membrane damage can change electrophysiology

Healthy barrier

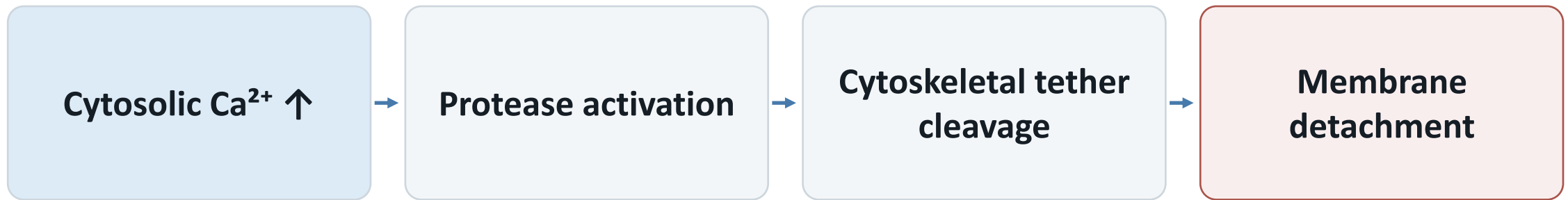
- Ordered ion separation across membrane
- Controlled channel-mediated movements
- Electrochemical gradients maintained

Lipid-disrupted barrier

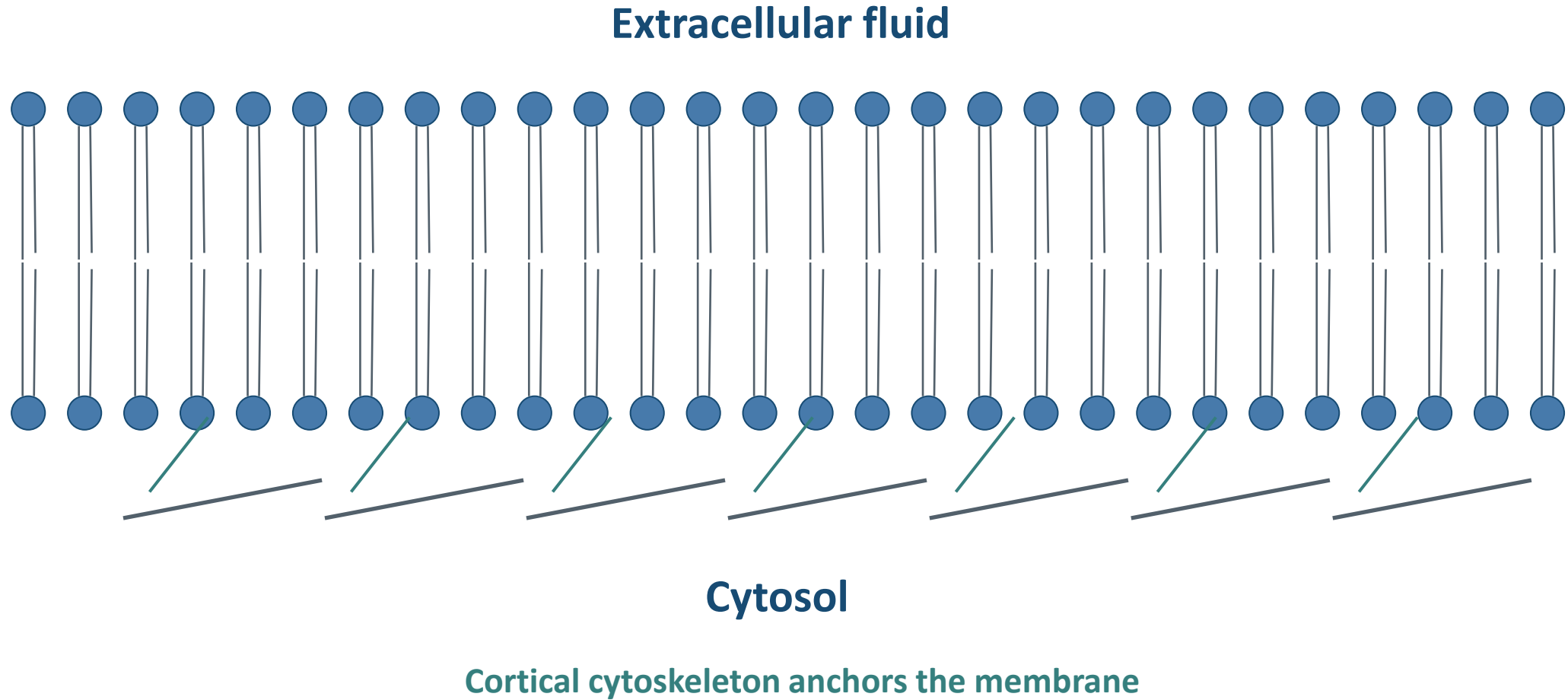
- Abnormal ionic permeability may develop
- Uncontrolled transmembrane flux is possible
- Electrophysiologic properties may change

Proteases damage the membrane–cytoskeleton linkage

Structural pathway



Cytoskeletal anchoring stabilizes the membrane



Membrane detachment increases susceptibility to rupture

Anchor disruption

Cytoskeletal proteolysis reduces mechanical support.



Surface deformation

Swelling and stress can exaggerate membrane blebs.



Fragile membrane

Detached plasma membrane may stretch and rupture.

Myocardial cells illustrate swelling-associated fragility

Stated

Swelling-exacerbated cytoskeletal damage is particularly relevant in myocardial cells.

Mechanistic reason

A membrane mechanically supported by filaments becomes fragile after detachment.

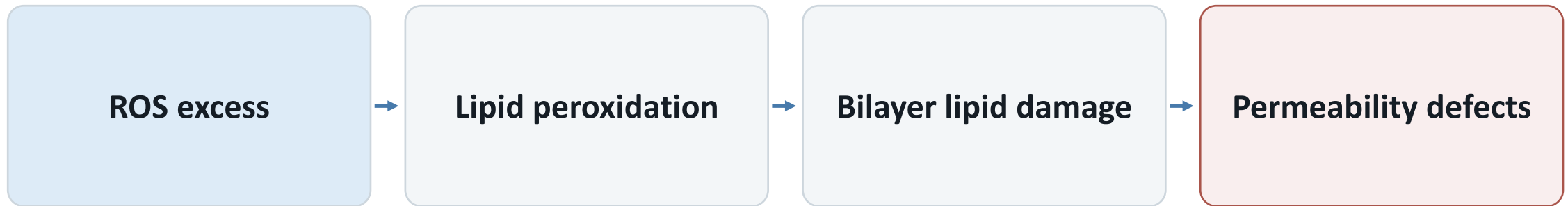
Pathologic implication

Severe ischemic injury may lead to rupture and release of intracellular proteins.

Avoid oversimplification

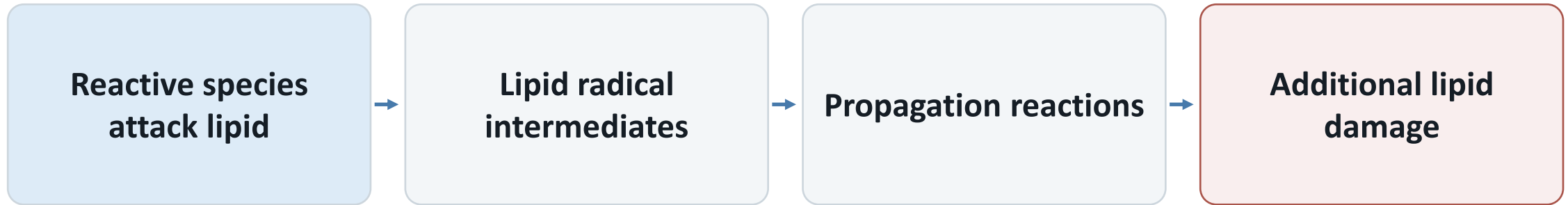
Ischemic injury involves mitochondrial, lipid, and calcium-dependent mechanisms together.

Reactive oxygen species injure membrane lipids



Lipid peroxidation is one of the four mechanisms highlighted in the source membrane-injury section.

Lipid peroxidation can propagate injury



This illustrates the chain-reaction property of oxidative membrane injury; No kinetic magnitudes are implied.

Reperfusion can add a second oxidative insult

During ischemia

- Oxygen delivery is reduced
- ATP depletion and Ca^{2+} loading develop
- Cellular membranes become vulnerable

Upon reperfusion

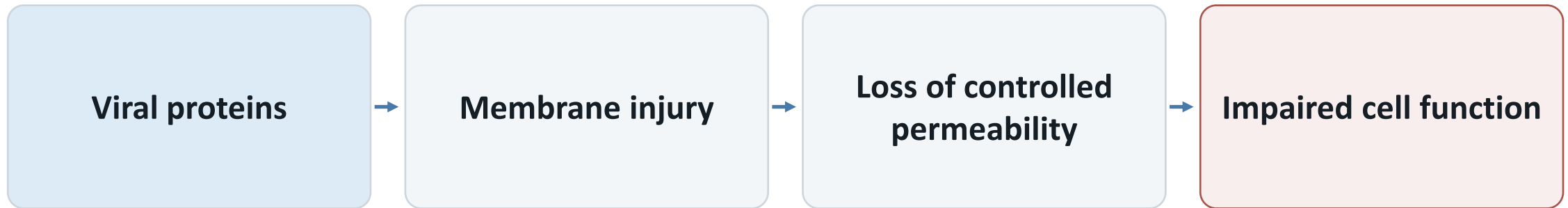
- ROS may increase
- Pre-existing lipid injury may be amplified
- Membrane damage can progress despite restored flow

Direct plasma membrane injury: Bacterial toxins



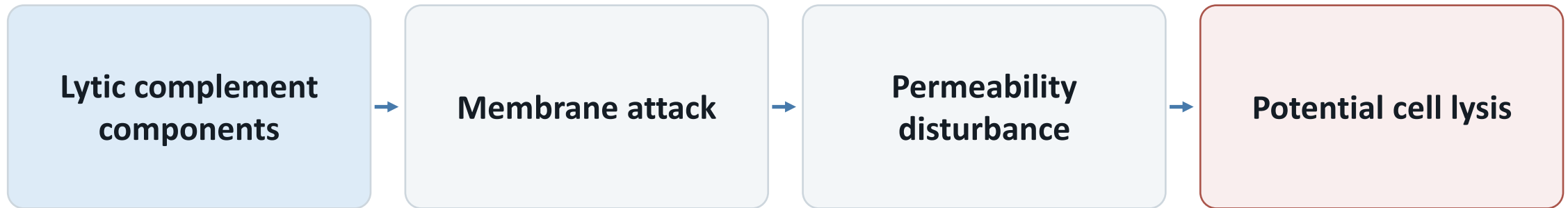
Bacterial toxins among agents capable of directly damaging the plasma membrane.

Direct plasma membrane injury: Viral proteins



The effects are agent- and context-dependent; Not every viral protein has a membrane-lytic role.

Direct plasma membrane injury: Lytic complement



Direct complement-associated membrane damage is distinct from ATP-dependent lipid synthesis failure.

Physical and chemical agents can disrupt membranes

Physical stressors

Injurious physical agents may damage membrane structure directly.

Chemical exposures

Certain chemicals can compromise the plasma membrane.

Direct mechanism

Barrier injury need not begin with impaired phospholipid synthesis.

Convergent endpoint

Direct and indirect injury can produce loss of cellular integrity.

Biochemical versus direct routes to membrane injury

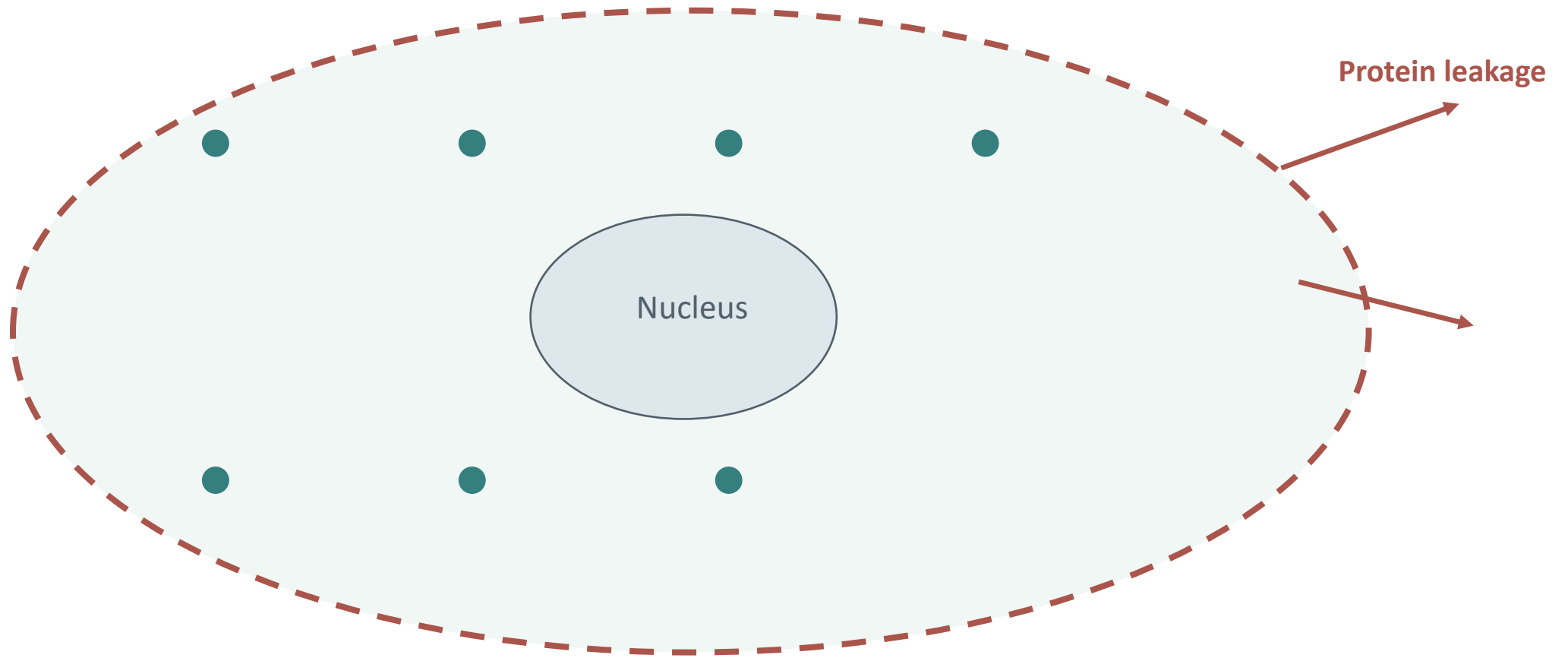
Indirect biochemical routes

- ROS-mediated lipid peroxidation
- ATP-related synthesis deficit
- Ca^{2+} -mediated lipid/scaffold injury

Direct membrane insults

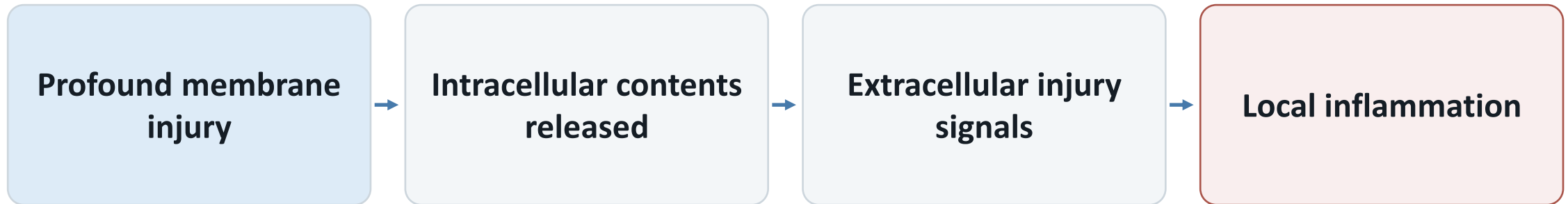
- Lytic bacterial factors or viral proteins
- Complement-mediated lysis
- Selected physical / chemical agents

The plasma membrane: Permeability and leakage



Plasma membrane failure disrupts transport and permits escape of cellular contents in necrosis.

Plasma membrane rupture connects injury to inflammation



This sequence helps distinguish necrosis from typically noninflammatory apoptosis.

Mitochondrial membranes affect cell survival

Inner membrane dysfunction

Loss of membrane potential impairs oxidative phosphorylation.

Reduced ATP synthesis

Energy depletion impairs ion pumps and phospholipid maintenance.

Oxidative stress

Injured mitochondria can contribute to ROS generation.

Protein release

Outer-membrane permeabilization may engage apoptosis under defined conditions.

Mitochondrial permeability transition and necrosis



Mitochondrial permeability transition is not the same event as plasma membrane rupture.

Outer mitochondrial permeabilization differs from lysis

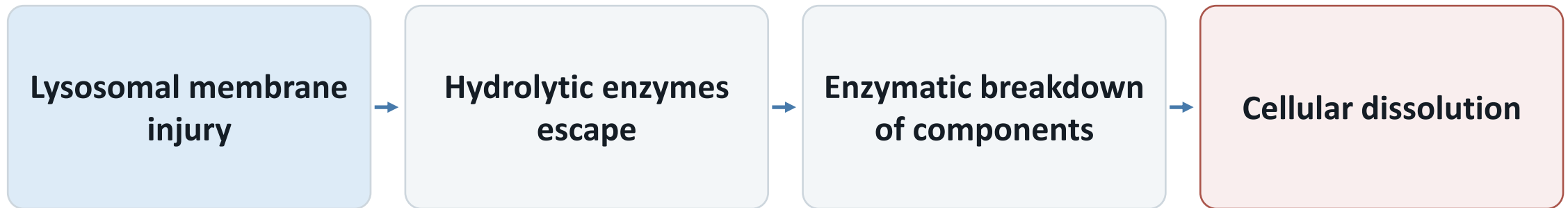
Permeability transition

- Disrupts mitochondrial electrochemical potential
- Compromises ATP formation
- Contributes to necrotic cell injury

BAX/BAK-mediated permeabilization

- Allows release of proapoptotic proteins
- Activates intrinsic apoptotic pathway
- Does not require early plasma membrane rupture

Lysosomal membrane damage releases hydrolases



Lysosomal leakage is a major mechanism of digestion during necrosis.

Organelle-specific outcomes are related but not identical

Plasma membrane

Loss of controlled exchange; Leakage of cytosolic proteins.

Mitochondrial inner membrane

Impaired proton gradient and ATP generation.

Mitochondrial outer membrane

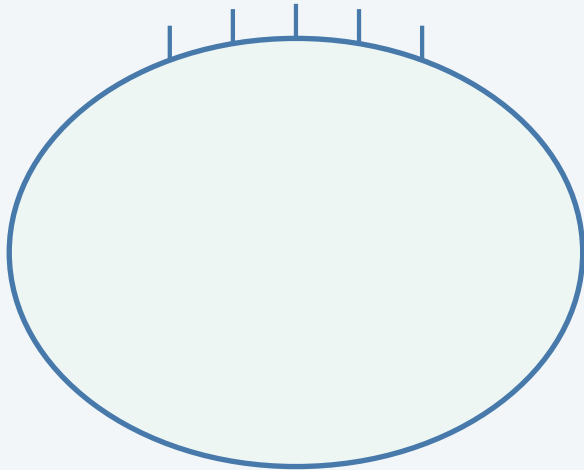
Release of apoptotic proteins in intrinsic apoptosis.

Lysosomal membrane

Release of hydrolases and cellular digestion.

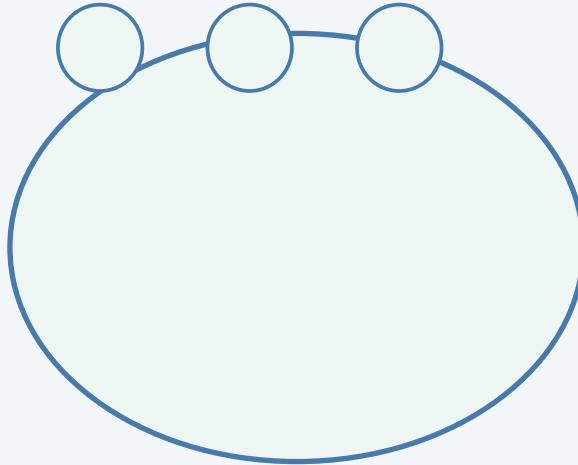
Early surface morphology: Blebs and lost microvilli

Normal surface



Intact cell boundary

Reversible injury



Blebbing; Microvillar changes

Progressive injury



Marked fragility / disruption

Myelin figures indicate membrane-derived lipid debris

Damaged membranes

Organelle and plasma membranes release phospholipid material.



Phospholipid whorls

Lamellar phospholipid aggregates can appear as myelin figures.

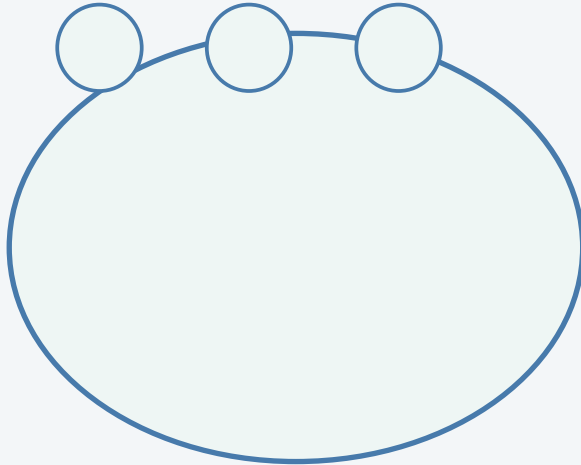


Debris clearance

Debris may be digested further or cleared by phagocytes.

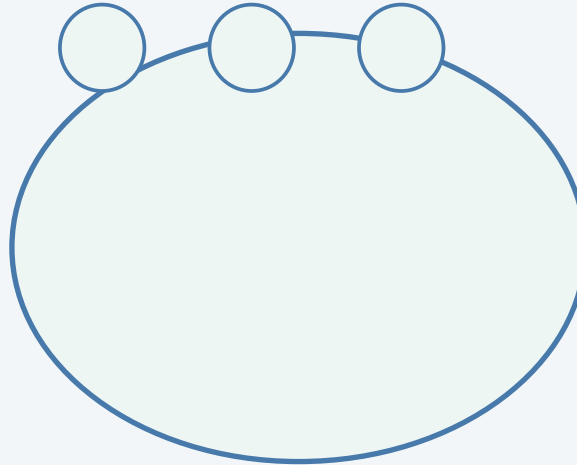
Ultrastructure changes with progression toward necrosis

Early injury



Blebs; Microvillus loss

Late injury



Organelle swelling

Necrosis



Membrane discontinuity

Membrane integrity helps distinguish cell-death patterns

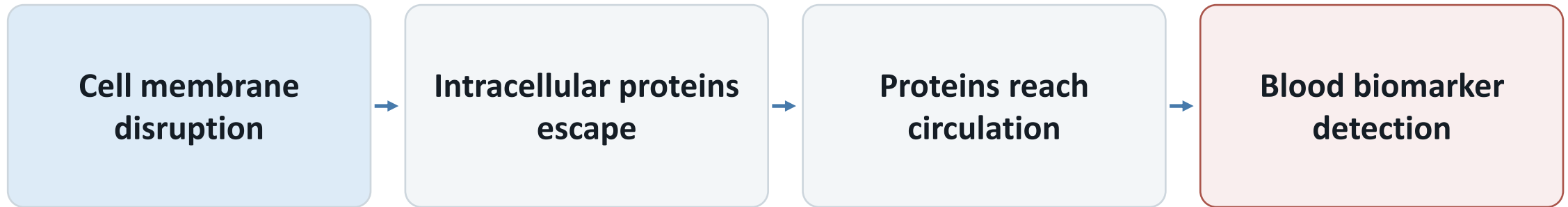
Necrosis

- Plasma membrane disrupted
- Contents digest and leak
- Inflammation often follows

Apoptosis

- Plasma membrane initially preserved
- Contents packaged in apoptotic bodies
- Little or no adjacent inflammation

Extracellular enzyme or protein release is measurable



Tissue-associated biomarkers are clinical readouts of cellular injury, not direct microscopy of membrane pores.

Cardiac injury: Membrane leakage and troponin

In severe myocardial injury, intracellular cardiac troponin can enter the circulation as cardiomyocyte membrane integrity is lost.

Reasoning

1. Why does a cytosolic or structural protein appear in blood?
2. Why should this be interpreted with clinical context?

Teaching focus: Membrane disruption provides the basic mechanism of biomarker release.

Hepatocellular injury: Transaminase leakage

Hepatocytes express transaminases. When hepatocytes are damaged and lose membrane integrity, these intracellular enzymes may appear in increased concentrations in blood.

Reasoning

1. What physical barrier has failed?
2. Does an enzyme elevation alone specify the mechanism of injury?

Teaching focus: The biochemical marker reports damage, not one unique etiology.

Is functional pump failure equivalent to membrane rupture?

Energy-dependent transport failure

- Na^+ pump activity declines with ATP loss
- Cellular swelling may follow
- May occur during reversible cell injury

Physical membrane disruption

- Loss of integrity is profound
- Cellular contents can leak out
- Typically associated with necrosis

Integrated ischemic injury: Three converging routes

Energy

↓ O₂ → ↓ ATP → reduced pumps and phospholipid synthesis.

Calcium

↑ Cytosolic Ca²⁺ → phospholipases and proteases.

Oxidants

ROS excess → membrane lipid peroxidation.

Cell structure

Swelling plus loss of cytoskeletal tethers → rupture risk.

Case: Ischemic tubular epithelial injury

A proximal tubular cell develops swelling, apical surface blebs, and loss of microvilli after reduced perfusion. Organelles remain identifiable.

Reasoning

1. Which alterations favor an early or potentially reversible stage?
2. How can ATP depletion explain the cell swelling?

Teaching focus: Membrane changes form a continuum; Blebs alone do not establish necrosis.

Case discussion: Tubular-cell membrane changes

Interpretation: Predominantly early (potentially reversible) injury

- ATP-dependent ion transport is impaired, so osmotic water accumulates.
- Blebbing and microvillus loss are described reversible ultrastructural changes.
- Irreversible injury requires profound, sustained mitochondrial and membrane dysfunction.

Case: Calcium-mediated damage during ischemia

An ischemic cardiac myocyte has ATP depletion, increased intracellular Ca^{2+} , swelling, and a disrupted submembrane filament network.

Reasoning

1. Which two calcium-activated enzyme families explain lipid and scaffold injury?
2. Why can swelling intensify the consequence of scaffold damage?

Teaching focus: An insult simultaneously affects the bilayer and its mechanical supports.

Case discussion: Calcium, lipids, and tethers

Two synergistic mechanisms explain the membrane vulnerability

- Phospholipases increase membrane phospholipid degradation.
- Proteases cleave cytoskeletal membrane anchors.
- Swelling exacerbates detachment and favors stretching and rupture.

Case: Injury after restoration of blood flow

After restoration of oxygen delivery to previously ischemic cells, oxidant stress increases and membrane dysfunction worsens.

Reasoning

1. What ROS-mediated chemical process targets phospholipids?
2. Why can mitochondrial dysfunction and prior calcium loading matter?

Teaching focus: Reperfusion-associated ROS may add to pre-existing ischemic injury.

Case discussion: Oxidant-mediated lipid damage

ROS-mediated lipid peroxidation is the target mechanism

- Oxidant excess attacks membrane lipids and can propagate damage.
- Lipid injury combines with ATP depletion and calcium-mediated pathways.
- Reperfusion is not guaranteed to restore cells already past irreversibility.

Mechanism identification: Choose the proximal lesion

Hypoxia → ATP depletion

Reduced phospholipid synthesis + pump dysfunction.

Cytosolic Ca²⁺ rise

Phospholipase / protease activation.

ROS accumulation

Lipid peroxidation.

Lytic complement activity

Direct plasma membrane attack.

Membrane injury: Five mechanistic conclusions

- Loss of selective permeability precedes overt membrane breakdown in many injuries.
- ROS, ATP deficiency, and Ca^{2+} -activated enzymes converge on membrane lipids.
- Protease-mediated cytoskeletal detachment increases mechanical fragility.
- Plasma, mitochondrial, and lysosomal membrane injury produce distinct consequences.
- Profound membrane dysfunction and leakage characterize necrotic injury.

Core reference and interpretation boundaries

Primary textbook

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 2, “Membrane Damage,” p. 47.

Context used within Chapter 2

Reversible cell injury and necrosis (pp. 36–39); mechanisms of cell injury and mitochondrial dysfunction (pp. 45–47); oxidative stress (pp. 48–50).