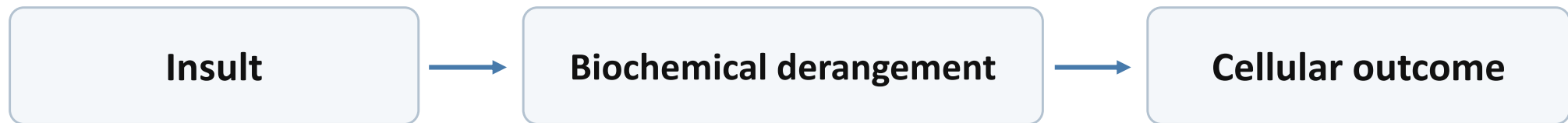


Mechanisms of Cell Injury

From biochemical derangement to cellular dysfunction and death



Dr Abu Suraih Sakhri

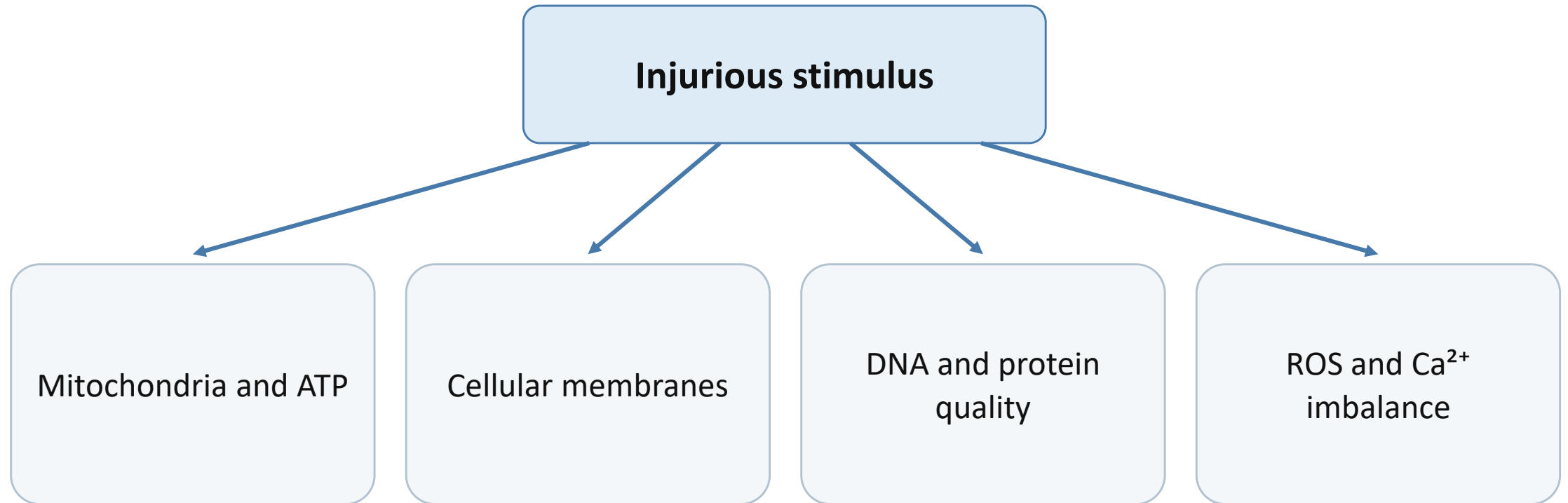
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Learning objectives

- Relate the intensity and duration of an insult to reversible or irreversible injury.
- Identify the key cellular targets and the consequences of damaging each.
- Trace ATP, membrane, oxidative, DNA, and calcium disturbances to cell death.
- Integrate mechanisms in ischemic and chemical injury.

Cell injury is a network of linked failures



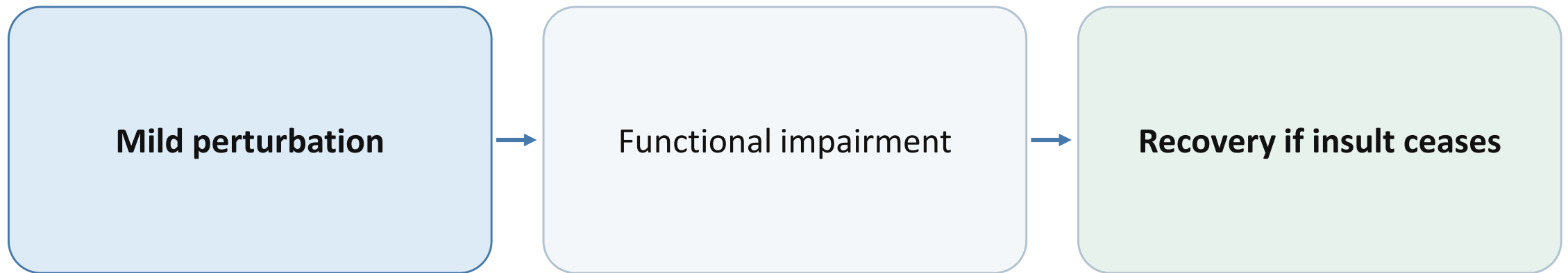
The same insult can damage several essential systems at once.

Principle 1: The nature of the insult matters

- An insult is not defined by its name alone: Mechanism and intensity influence the response.
- Low-dose chemical exposure may permit recovery; A greater dose may cause death.
- A brief reduction in perfusion may be reversible; Prolonged ischemia may not.

Dose and duration must be interpreted together.

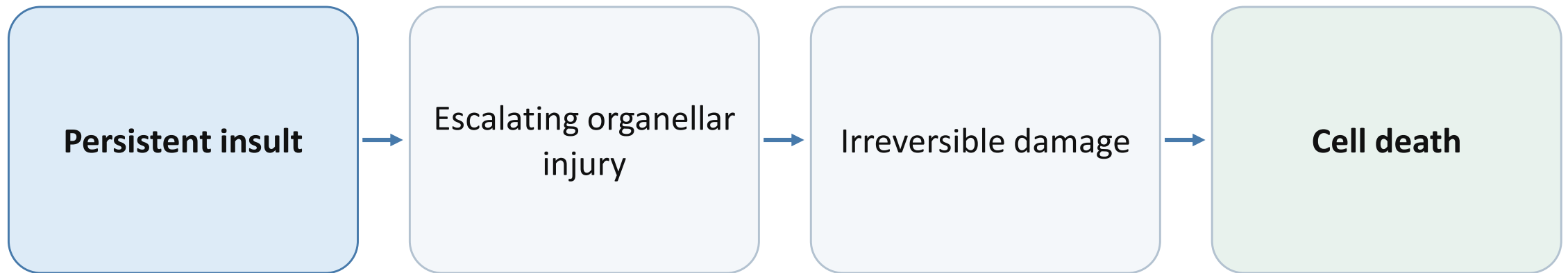
Severity changes the injury outcome



Mechanistic sequence — schematic

Low-intensity injury may remain reversible.

Prolonged injury crosses a threshold



Mechanistic sequence — schematic

A gradual deterioration can culminate in necrosis or apoptosis.

Brief and prolonged ischemia

Brief ischemia

- ATP falls before cell structure is destroyed
- Swelling and dysfunction may be reversible
- Restored perfusion can rescue viable cells

Prolonged ischemia

- Energy deficit deepens
- Membrane and mitochondrial damage become severe
- Irreversibly injured cells undergo death

Principle 2: The cell determines its vulnerability

- Cell type and differentiated function influence injury thresholds.
- Nutritional and hormonal state modify resilience.
- Metabolic demand and ability to adapt are critical.
- Equivalent exposures need not produce equivalent outcomes.

Metabolic demand shapes ischemic injury

Skeletal muscle

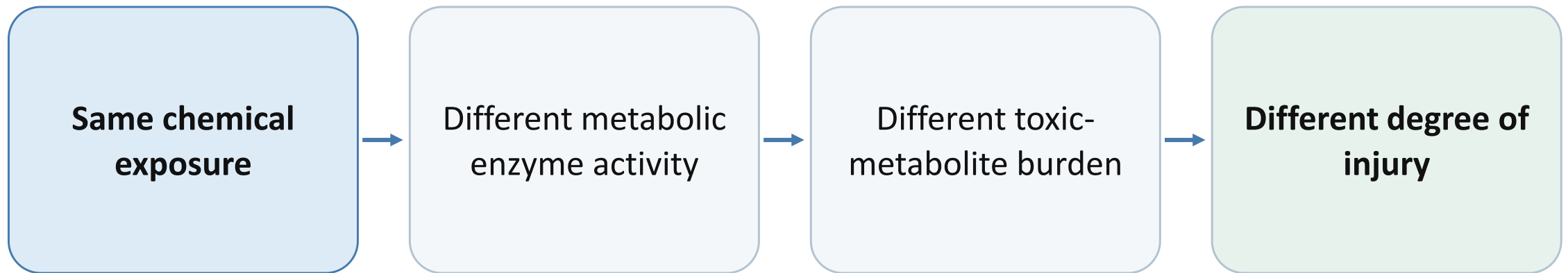
- Activity can be reduced during hypoperfusion
- Energy demand may decline with rest
- Functional state influences survival

Cardiac myocyte

- Continuous contractile demand limits rest
- ATP depletion rapidly compromises function
- Energy-dependent integrity is essential

Vulnerability partly reflects whether demand can be reduced.

Individual toxicity may differ



Mechanistic sequence — schematic

The source uses carbon tetrachloride to illustrate metabolic variability.

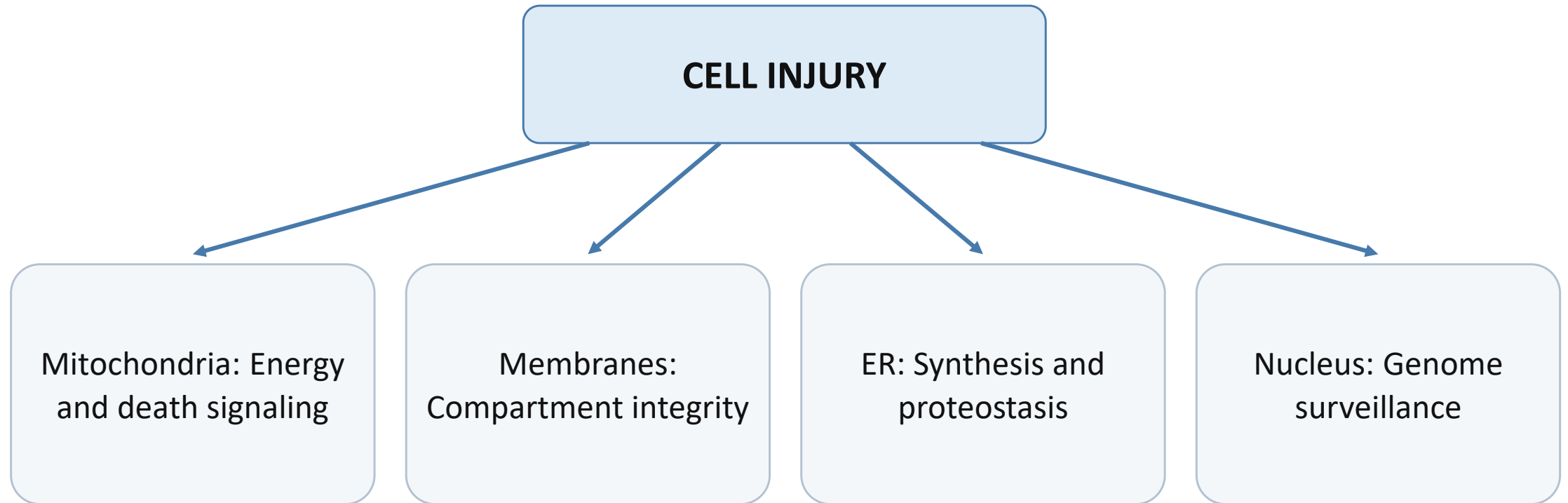
Genetic variation can change toxic responses

- Metabolic enzymes may convert a parent chemical to toxic products.
- Enzyme polymorphisms may alter the extent of activation.
- Identical exposure does not guarantee identical cellular injury.
- This is susceptibility variation, not proof that every difference is genetic.

Principle 3: Cell injury is mechanistically interconnected

- A single stimulus can injure multiple organelles simultaneously.
- Mitochondrial failure can amplify ionic, oxidative, and membrane disturbances.
- Secondary biochemical derangements can sustain injury after the initiating event.
- A single dominant molecular cause often cannot be assigned.

Four essential cellular targets



Distinct abnormalities generate overlapping consequences.

Target injury predicts a characteristic consequence

Cellular target	Primary impairment	Dominant consequence
Mitochondria	Oxidative phosphorylation	ATP depletion / death signaling
Plasma membrane	Selective permeability	Ion imbalance and leakage
ER / protein machinery	Synthesis and folding	Proteostatic stress
Nucleus	DNA integrity	Arrest, repair, or apoptosis

Why ATP is central to viability

- ATP supports active ion transport and osmotic stability.
- Protein synthesis and lipid turnover require energy.
- Metabolic pathways and cellular housekeeping depend on ATP.
- Failure of ATP-dependent functions explains many early injury changes.

Two routes to ATP generation

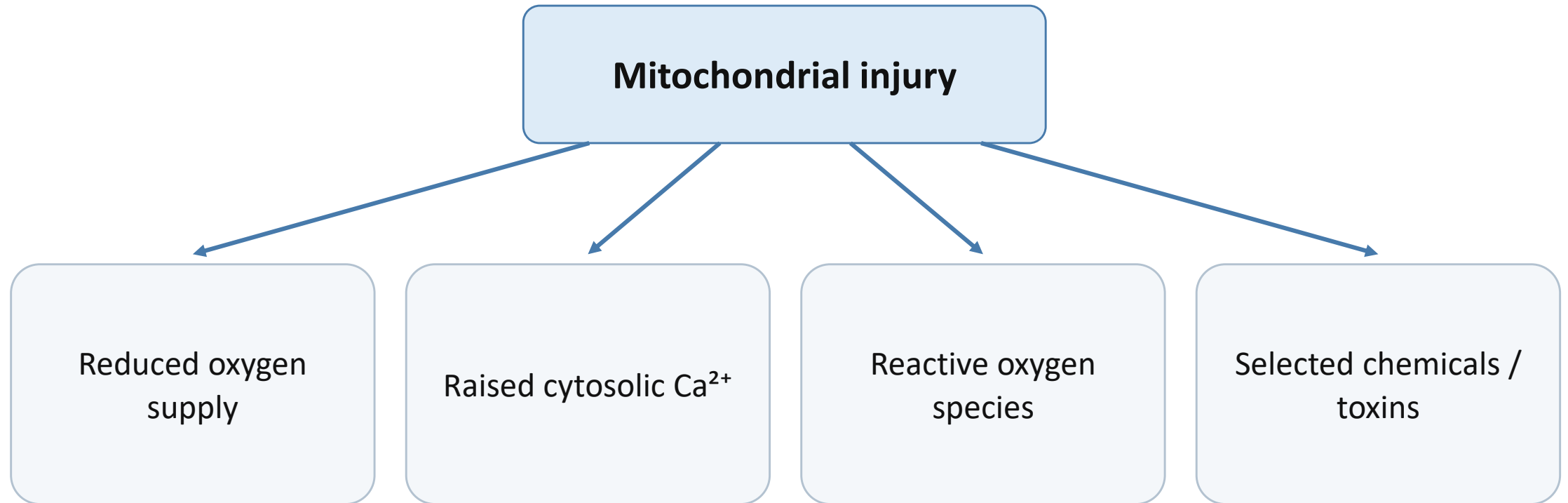
Oxidative phosphorylation

- Mitochondrial electron transport uses oxygen
- Dominant ATP source in many mammalian cells
- Sensitive to ischemia and respiratory toxins

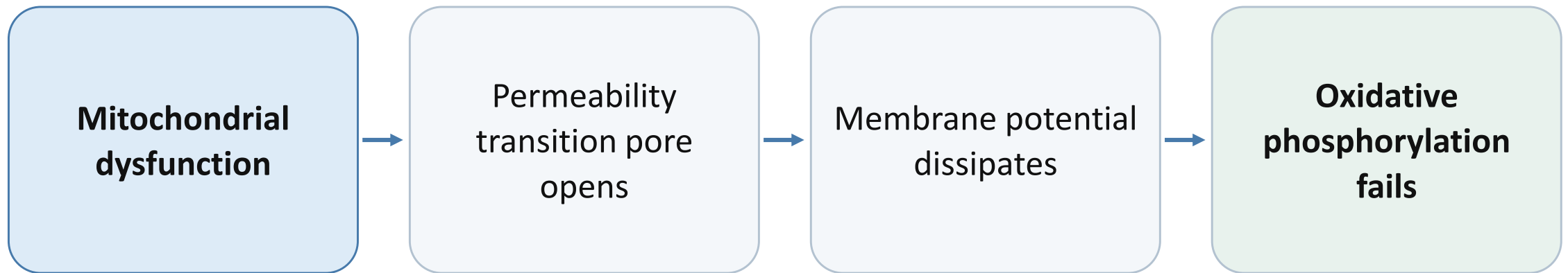
Glycolysis

- Uses glucose or glycogen-derived substrate
- Can generate ATP without oxygen
- Lower total ATP yield than respiration

Mitochondria are exposed to diverse insults



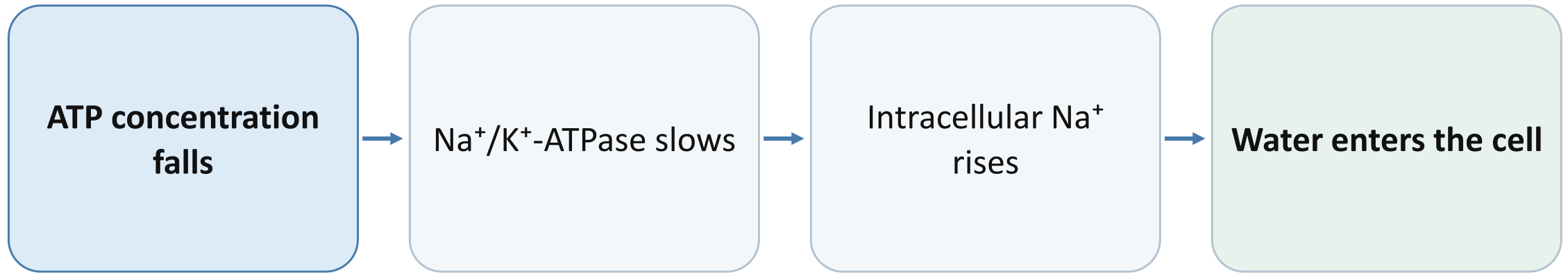
Permeability transition drives energy failure



Mechanistic sequence — schematic

Progressive ATP depletion favors necrotic cell death.

ATP depletion undermines the sodium pump



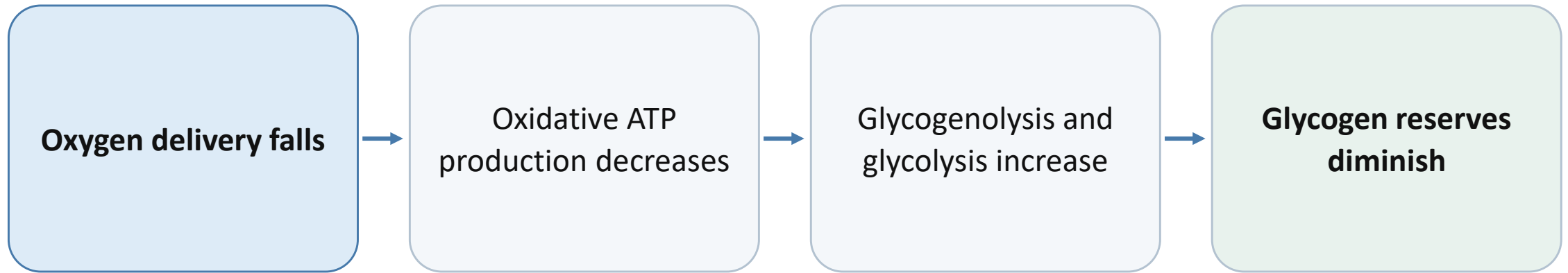
Mechanistic sequence — schematic

Cell swelling is a characteristic change of reversible injury.

Why cells swell during early injury

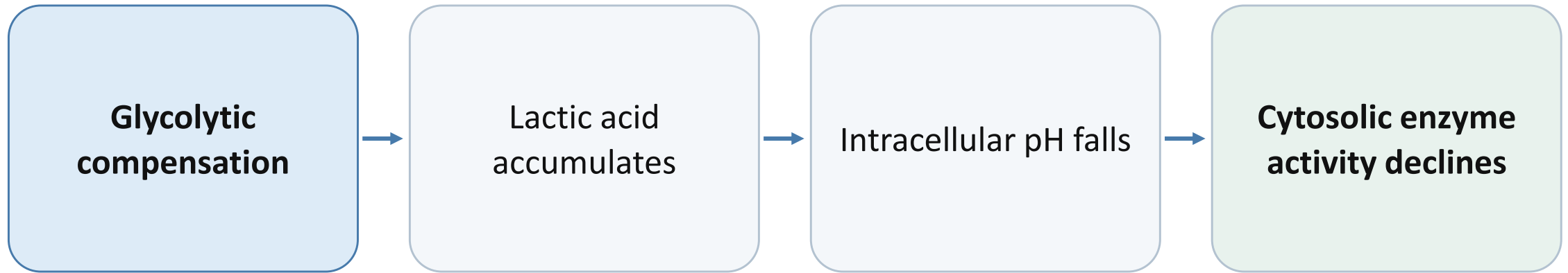
- Active extrusion of sodium requires ATP.
- Reduced pump activity promotes intracellular sodium accumulation.
- The net gain of intracellular solute draws water osmotically.
- Cell and endoplasmic reticulum swelling can follow.

Ischemia redirects energy metabolism



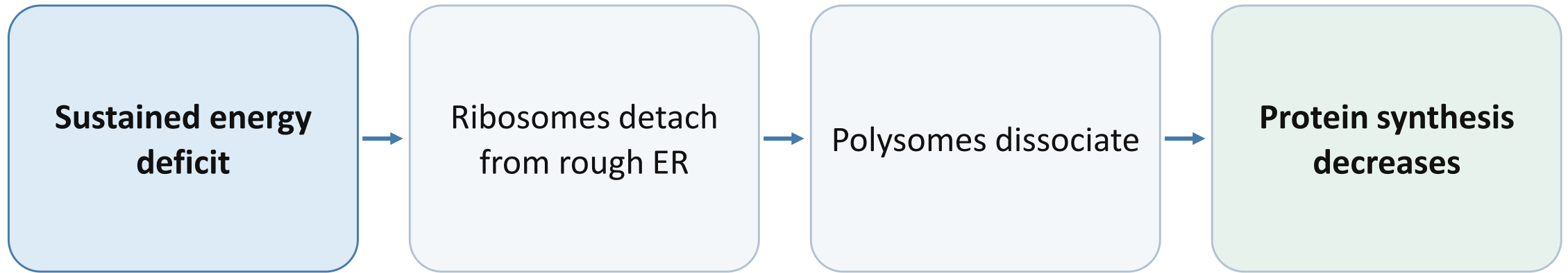
Mechanistic sequence — schematic

Anaerobic metabolism promotes acidosis



Mechanistic sequence — schematic

Prolonged ATP loss suppresses translation

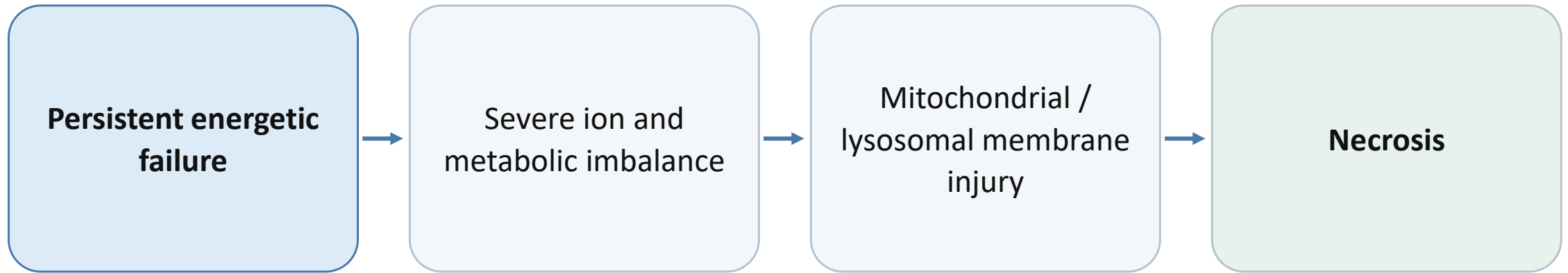


Mechanistic sequence — schematic

Protein synthesis and proteostasis fail together

- Rough-ER disruption diminishes new protein synthesis.
- Misfolded proteins can accumulate during cellular stress.
- Severe, unresolved protein stress can become a cell-death signal.
- This pathway connects an organellar disturbance to the injury response.

ATP depletion progresses toward necrosis



Mechanistic sequence — schematic

Mitochondria can promote two death routes

Necrosis-linked route

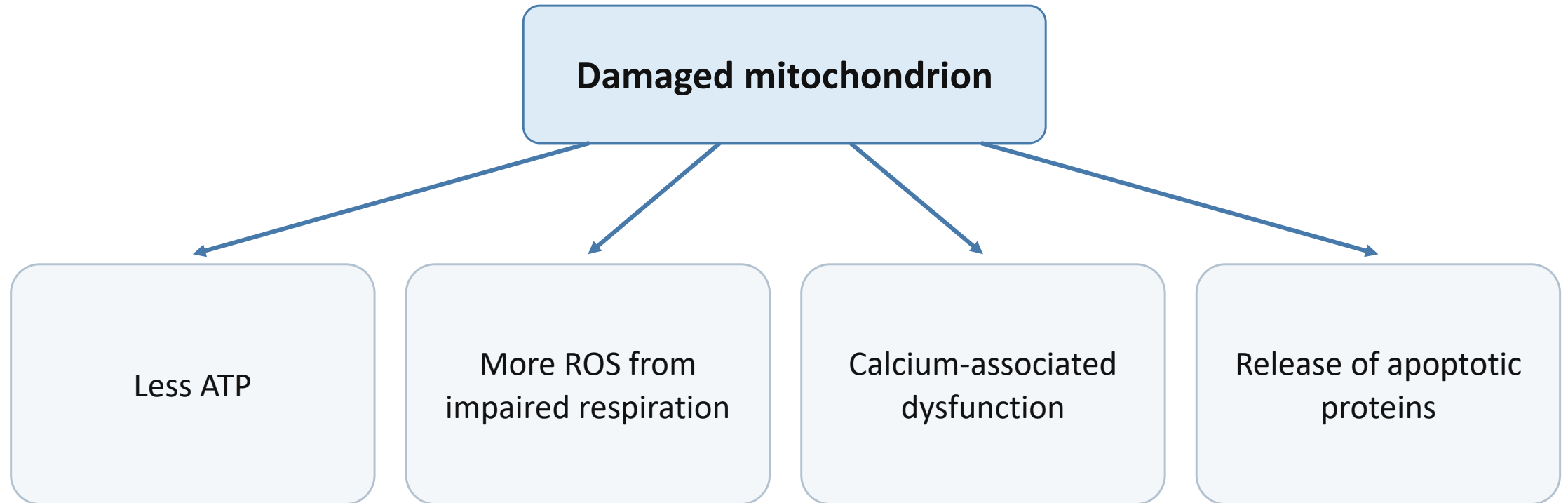
- Permeability transition dissipates membrane potential
- Oxidative ATP formation fails
- Advanced energy collapse promotes necrosis

Apoptosis-linked route

- BAX and BAK form membrane channels
- Pro-apoptotic mitochondrial proteins escape
- Intrinsic apoptotic pathway is activated

The initiating mitochondrial event determines the downstream program.

Mitochondria sit at a biochemical crossroads

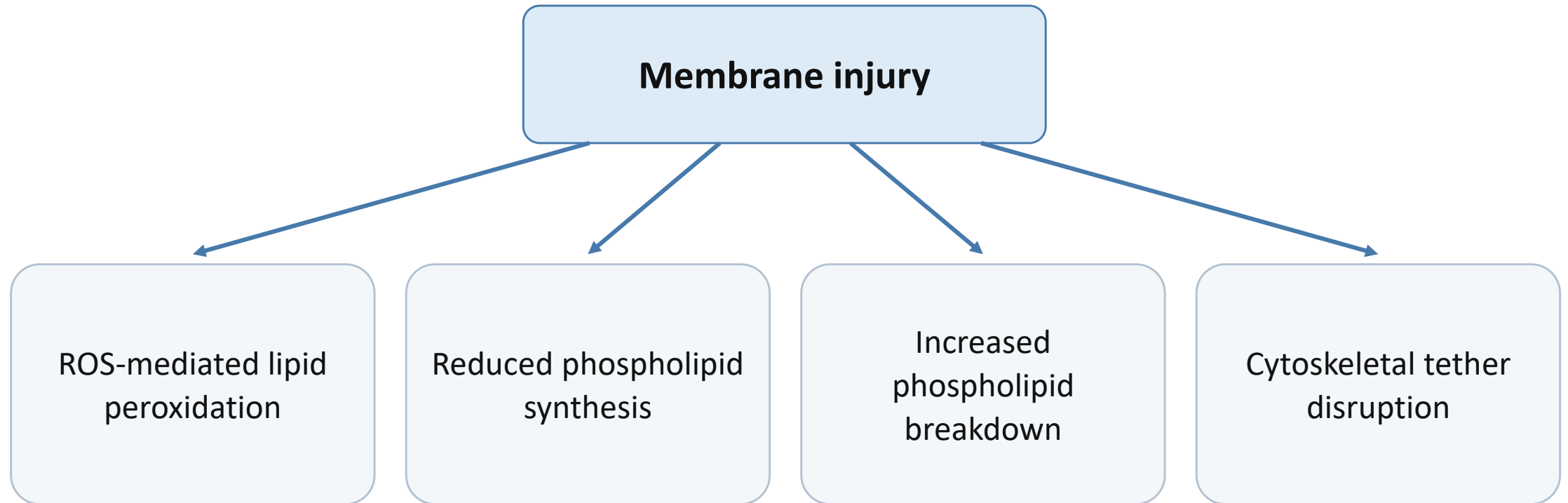


Mitochondrial injury is not synonymous with necrosis only.

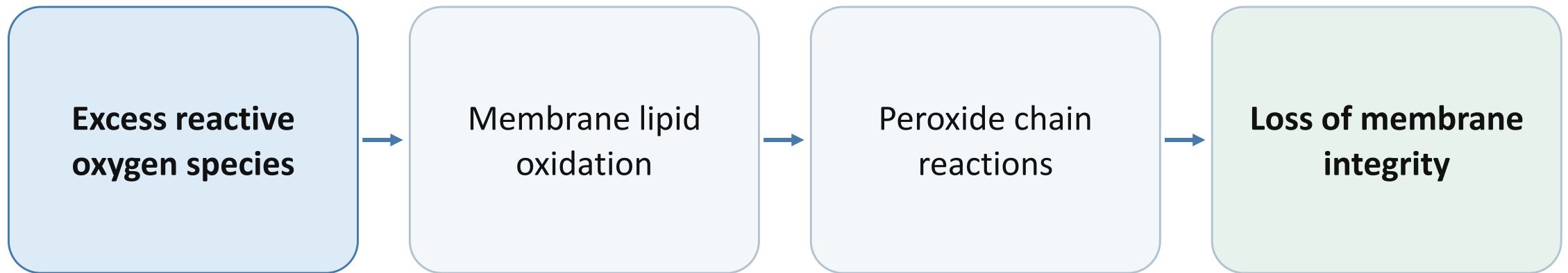
Membrane damage is a shared injury endpoint

- Most forms of severe injury disrupt selective membrane permeability.
- Plasma, mitochondrial, and lysosomal membranes may all be affected.
- Loss of barrier function impairs ionic and biochemical compartmentation.
- Apoptosis is an important exception to early overt membrane disruption.

Four mechanisms weaken cellular membranes

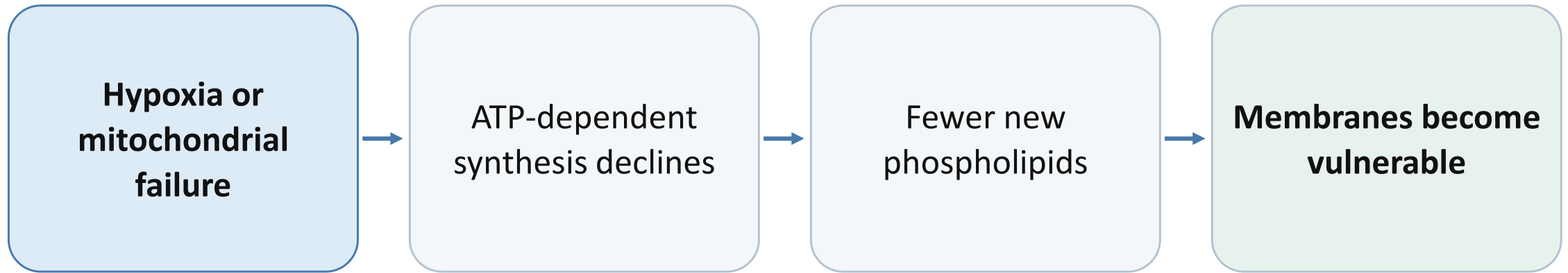


Oxidants destabilize lipid bilayers



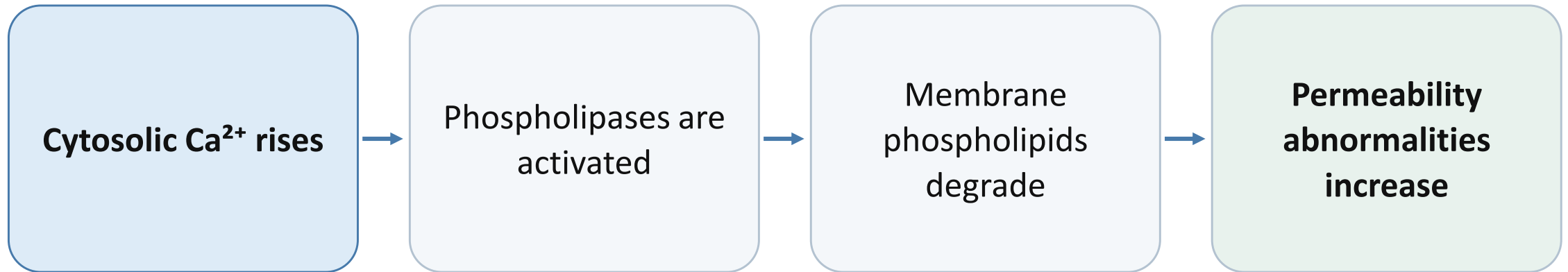
Mechanistic sequence — schematic

Energy failure impedes membrane renewal



Mechanistic sequence — schematic

Calcium accelerates phospholipid breakdown

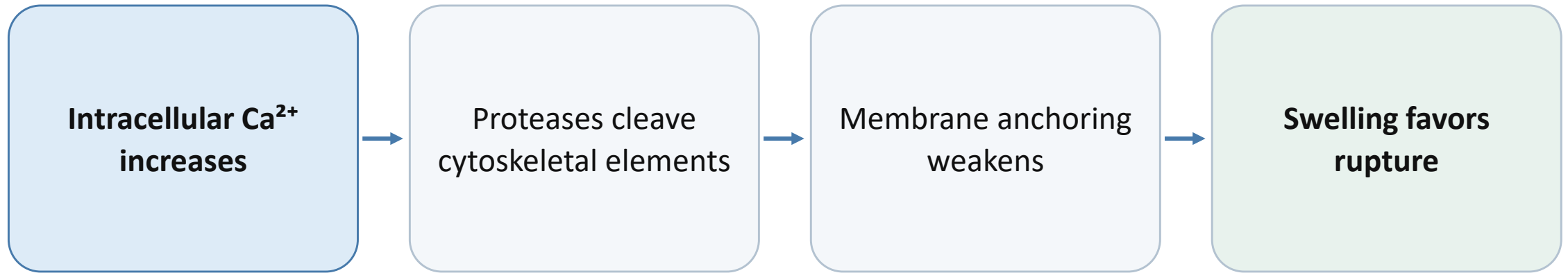


Mechanistic sequence — schematic

Lipid breakdown products amplify injury

- Free fatty acids and lysophospholipids accumulate after phospholipid degradation.
- These molecules can have detergent-like effects.
- Insertion into membrane bilayers alters permeability and function.
- Membrane lipid injury therefore generates additional damaging products.

Protease activity disconnects the cell surface



Mechanistic sequence — schematic

Membrane compartment determines the clinical signal

Membrane	Consequent failure	Illustrative result
Plasma membrane	Barrier loss	Cell contents may leak
Mitochondrial membranes	Bioenergetic disruption	ATP collapse / death signals
Lysosomal membrane	Enzyme compartment disruption	Self-digestion contributes to necrosis

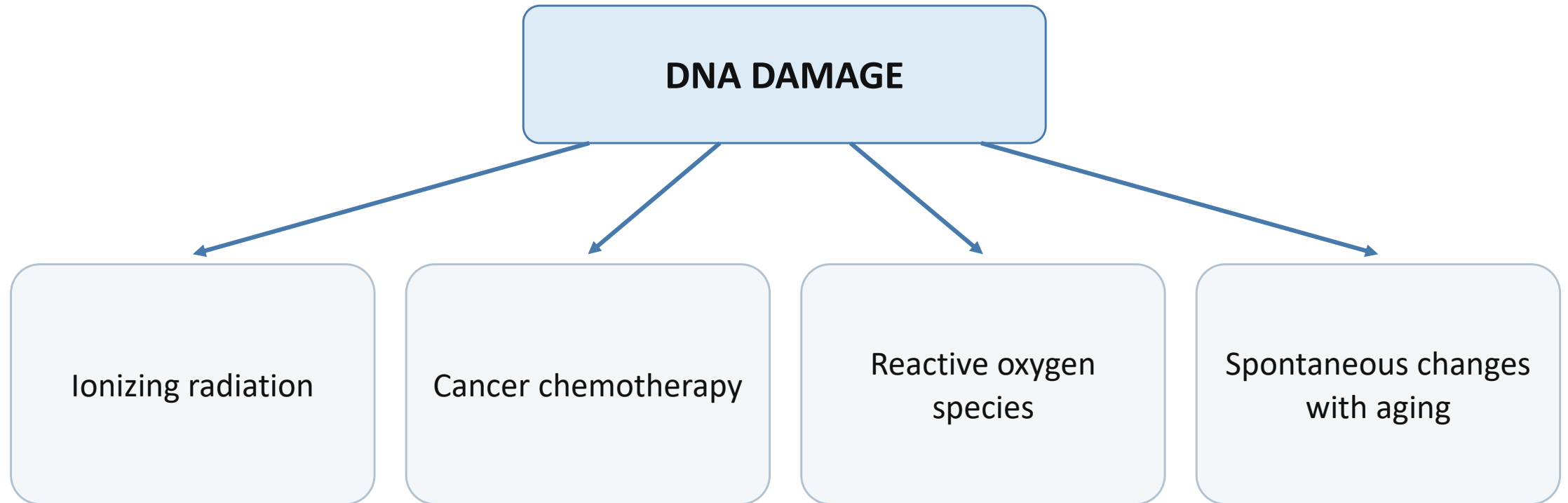
Plasma membrane loss is a major step toward necrosis

- Severe membrane permeability defects abolish ion gradients.
- Cellular constituents escape from damaged cells.
- The loss of a continuous plasma membrane distinguishes advanced necrotic injury.
- This barrier failure complements mitochondrial energy collapse.

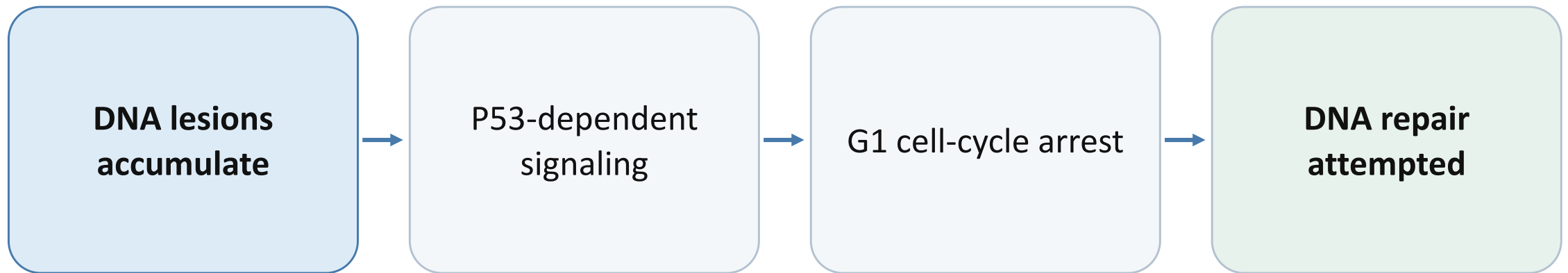
Lysosomal membrane disruption worsens necrosis

- Lysosomes compartmentalize degradative enzymes.
- Severe injury can disrupt lysosomal membrane integrity.
- Released enzymes participate in degradation of cellular constituents.
- The effect converges with plasma and mitochondrial injury.

Nuclear DNA can be injured in several ways



DNA surveillance can impose a protective arrest



Mechanistic sequence — schematic

DNA repair success versus failure

Damage can be repaired

- P53-mediated cell-cycle arrest allows time
- Repair mechanisms correct lesions
- Cell may resume cycling

Damage remains extensive

- Unrepaired lesions persist
- P53 activates mitochondrial apoptosis
- Potentially abnormal cells are removed

The p53 response limits propagation of damaged DNA

- DNA damage activates cell-cycle checkpoints and repair.
- Irreparable injury can trigger mitochondrial apoptosis.
- Failure to arrest or eliminate damaged cells permits genetic instability.
- Defective p53 signaling is linked to many cancers.

Oxidative stress is a balance failure

- Low ROS levels are generated during normal cell metabolism.
- Intracellular scavenging usually limits their accumulation.
- Increased formation or impaired removal produces oxidative stress.
- Excess oxidants damage lipids, proteins, and nucleic acids.

Physiologic ROS versus oxidative stress

Controlled ROS

- Low concentrations can support signaling
- Antioxidant defenses maintain equilibrium
- Production and removal remain balanced

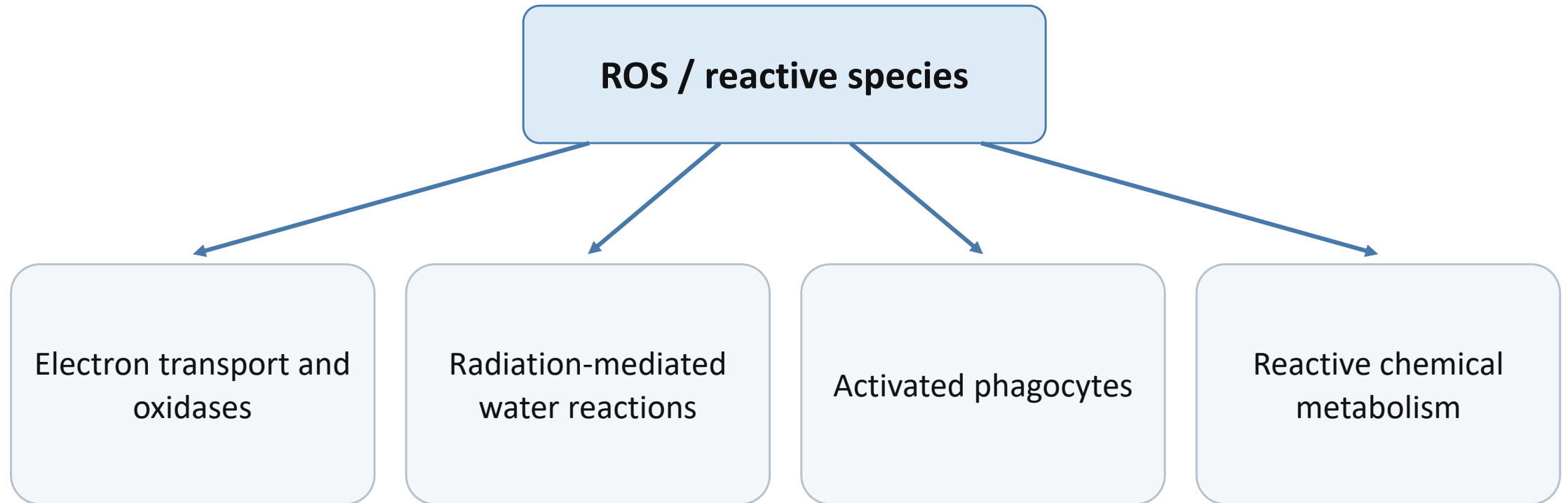
Excess ROS

- Scavenging capacity is exceeded
- Macromolecules undergo oxidative modification
- Cell injury or death can follow

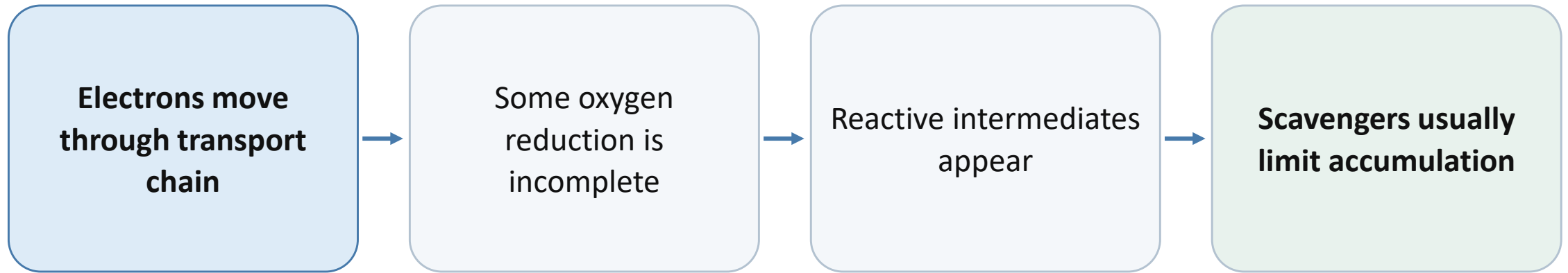
Why free radicals react so readily

- Free radicals have an unpaired electron in an outer orbital.
- They can alter adjacent proteins, lipids, carbohydrates, or DNA.
- Some reactions yield new radical species and propagate damage.
- Hydrogen peroxide is a reactive oxidant but not itself a free radical.

Cellular sources of damaging oxidants

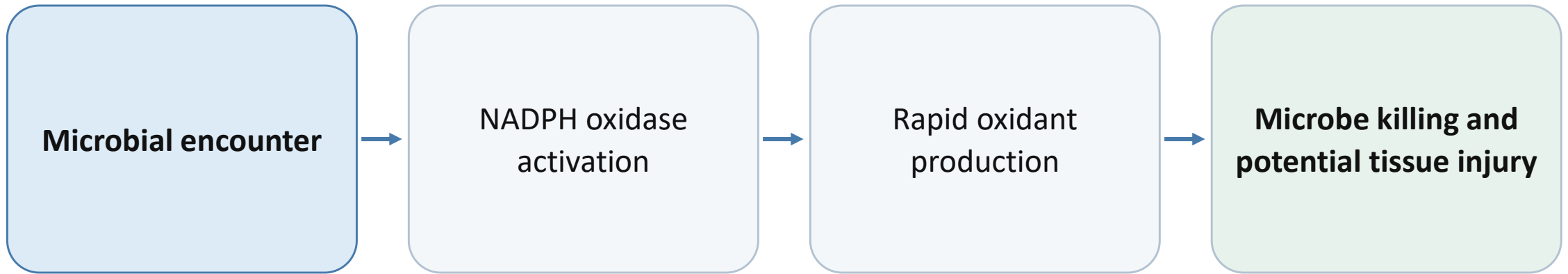


Mitochondrial respiration can form ROS



Mechanistic sequence — schematic

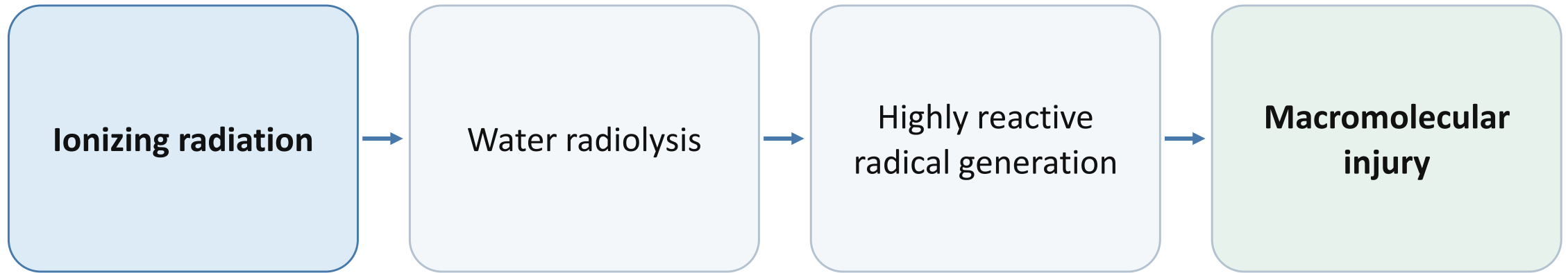
Inflammatory cells deliberately produce ROS



Mechanistic sequence — schematic

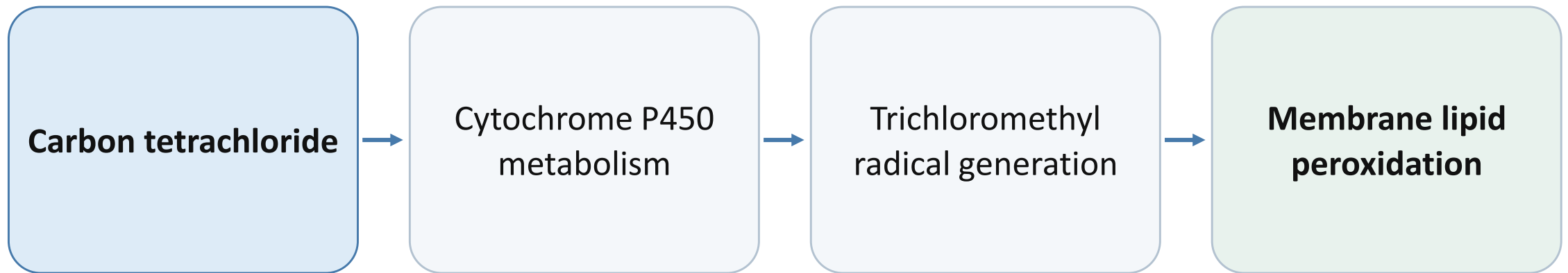
A defense mechanism can contribute to collateral injury.

Radiation can generate hydroxyl radicals



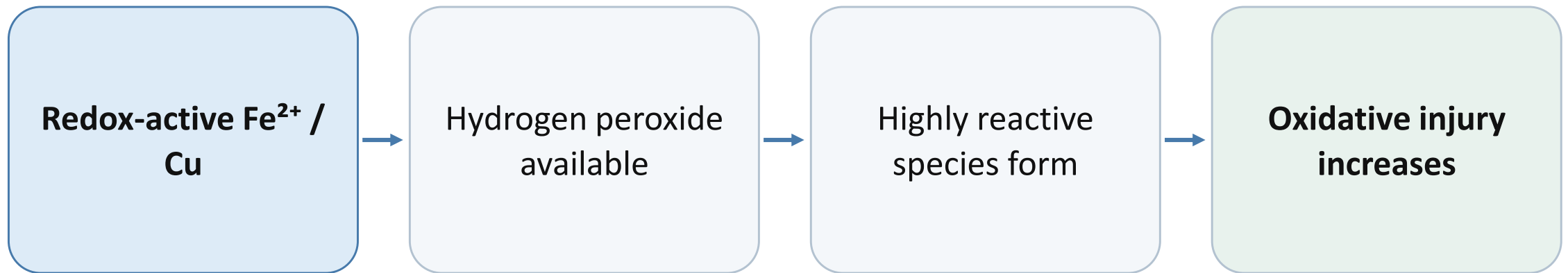
Mechanistic sequence — schematic

Chemical bioactivation yields reactive radicals



Mechanistic sequence — schematic

Transition metals catalyze oxidant formation



Mechanistic sequence — schematic

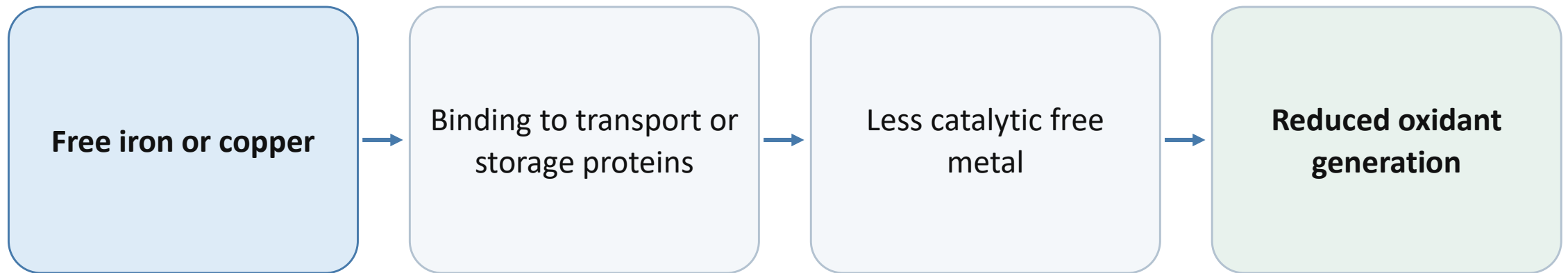
Selected reactive species have distinct chemistry

Species	Source or route	Important property
Superoxide ($\text{O}_2\bullet^-$)	Electron leakage; phagocyte oxidase	Converted by SOD
Hydrogen peroxide (H_2O_2)	Superoxide dismutation; oxidases	Can diffuse and form stronger oxidants
Hydroxyl radical ($\bullet\text{OH}$)	Fenton reaction; radiolysis	Extremely reactive
Peroxynitrite (ONOO^-)	Superoxide plus nitric oxide	Damages multiple macromolecules

Antioxidants prevent runaway oxidation

- Cells use small-molecule antioxidants to scavenge radicals.
- Vitamin E and vitamin A are lipid-soluble examples.
- Ascorbic acid and glutathione act in aqueous cellular environments.
- Antioxidant action complements enzymatic ROS disposal.

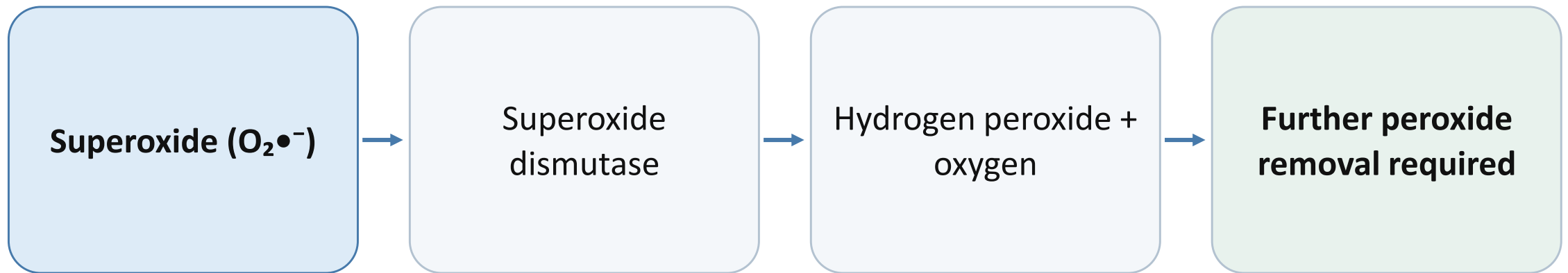
Metal-binding proteins limit radical chemistry



Mechanistic sequence — schematic

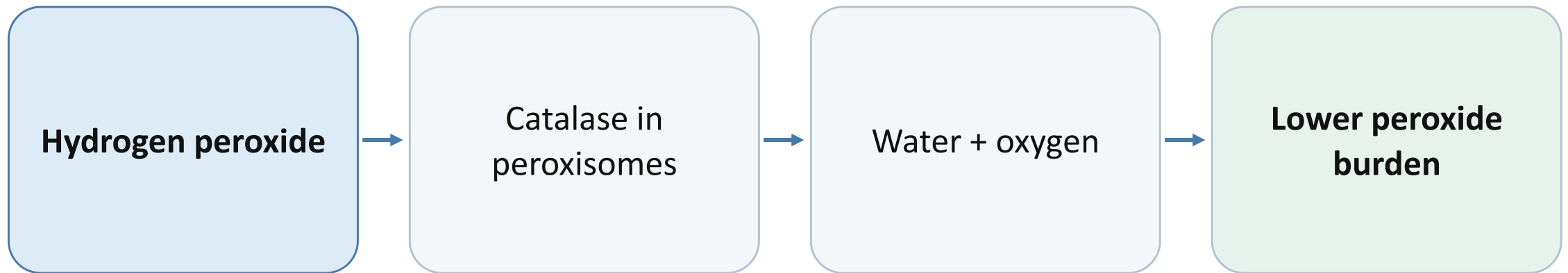
Examples include ferritin, transferrin, lactoferrin, and ceruloplasmin.

Superoxide dismutase limits superoxide



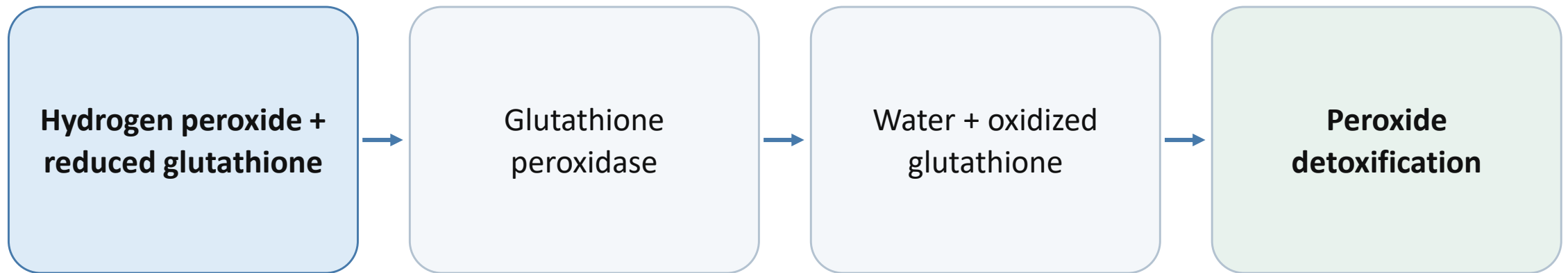
Mechanistic sequence — schematic

Catalase removes hydrogen peroxide



Mechanistic sequence — schematic

Glutathione peroxidase consumes reducing power

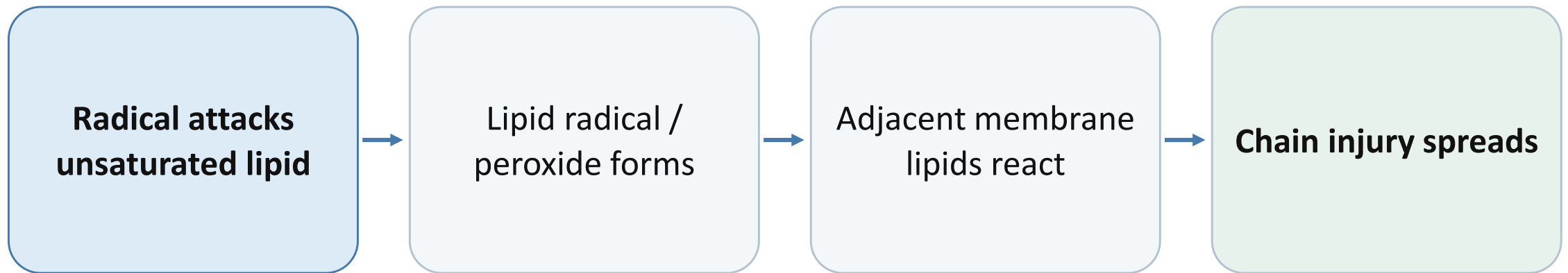


Mechanistic sequence — schematic

Reduced and oxidized glutathione report redox state

- Reduced glutathione is denoted GSH; Oxidized glutathione is GSSG.
- Glutathione peroxidase uses GSH to detoxify peroxide.
- The cellular GSSG:GSH balance reflects oxidative state.
- Loss of reducing capacity limits oxidant defense.

Lipid peroxidation can propagate itself

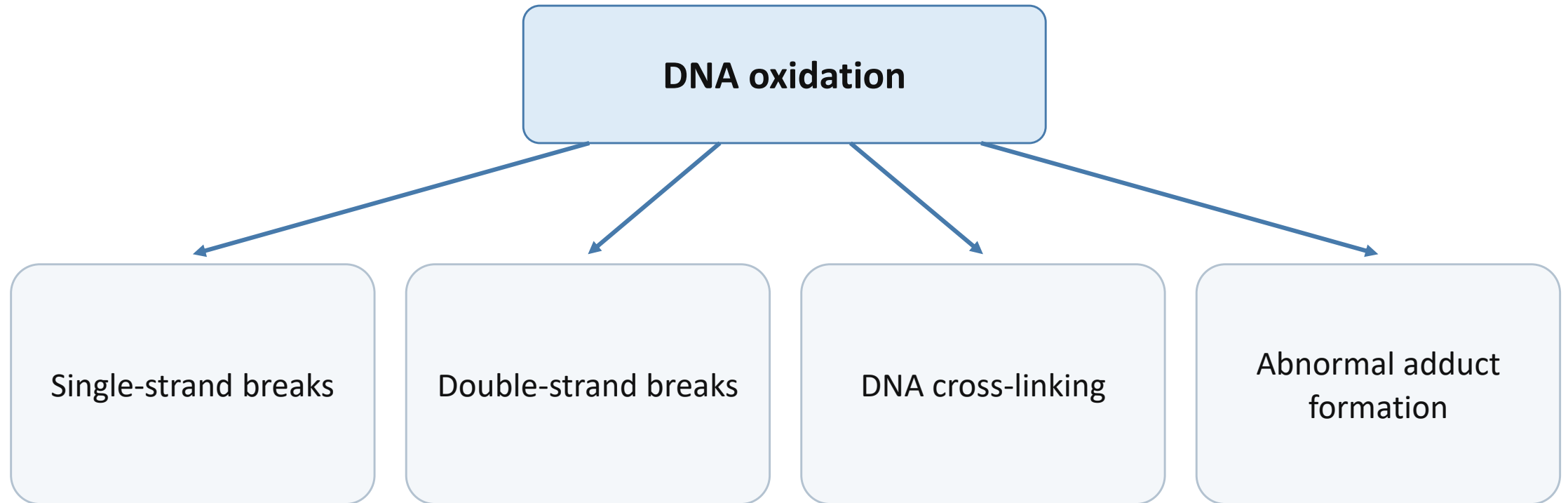


Mechanistic sequence — schematic

Protein oxidation changes activity and structure

- Oxidation can alter amino acid side chains or the protein backbone.
- Covalent cross-links can distort protein conformation.
- Enzyme active sites and structural-protein function may be lost.
- Misfolded or damaged proteins may undergo increased degradation.

Oxidative DNA injury has multiple manifestations



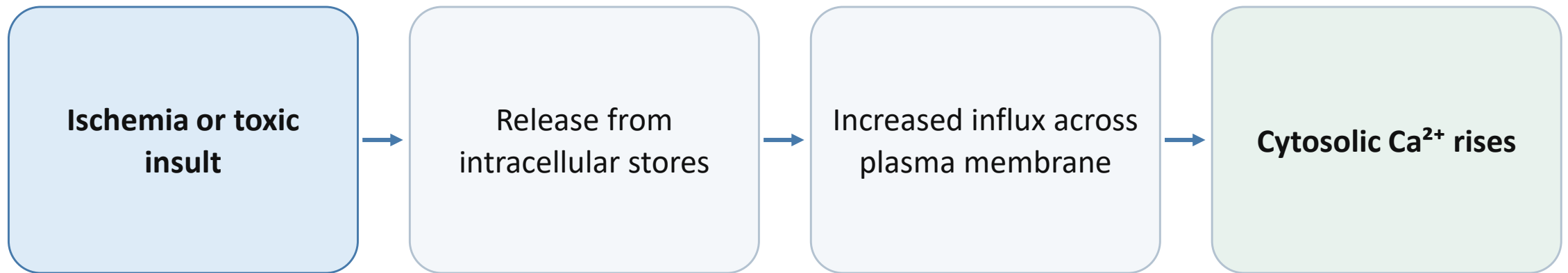
ROS attack three classes of macromolecules

Target	Representative lesion	Cellular consequence
Membrane lipids	Lipid peroxidation	Loss of permeability control
Proteins	Oxidation / cross-links	Dysfunction and degradation
DNA	Breaks / adducts	Damage response or mutation

Calcium gradients must remain tightly controlled

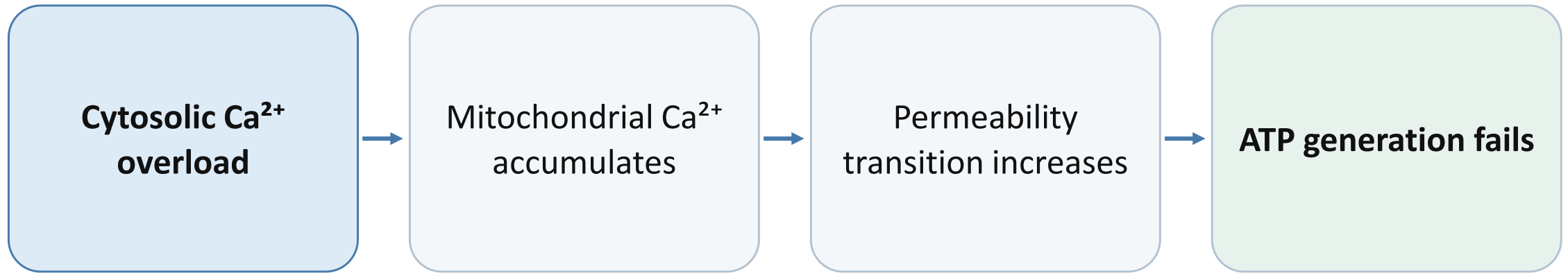
- Cytosolic free Ca^{2+} is normally very low compared with extracellular Ca^{2+} .
- The ER and mitochondria sequester much of the intracellular calcium.
- Calcium acts as a useful second messenger at controlled concentrations.
- Sustained cytosolic calcium elevation promotes injury; Its precise in vivo contribution remains incompletely established.

Two sources produce cytosolic Ca^{2+} overload



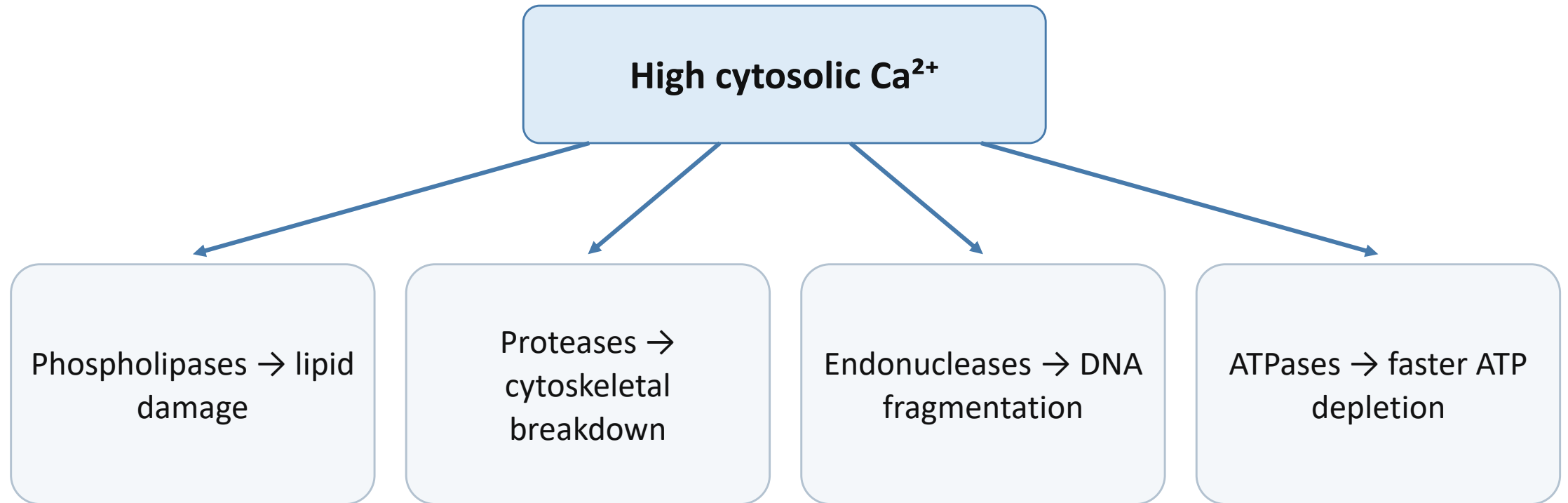
Mechanistic sequence — schematic

Calcium excess damages mitochondria

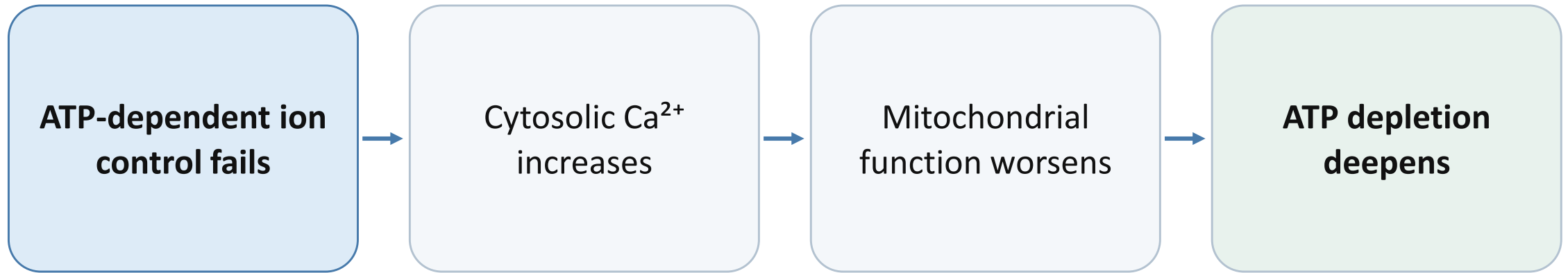


Mechanistic sequence — schematic

Excess calcium activates injurious enzymes



Energy and calcium injury reinforce one another



Mechanistic sequence — schematic

This sequence is a reinforcing loop, not a single isolated lesion.

Multiple lesions converge on limited outcomes

Trigger	Intermediate injury	Possible outcome
Energy failure	Ion pump loss; cell swelling	Reversible injury → necrosis
Mitochondrial protein release	Intrinsic apoptotic signaling	Apoptosis
DNA injury / misfolded proteins	Stress sensing and failed repair	Apoptosis
ROS / elevated Ca^{2+}	Membrane and organelle damage	Severe dysfunction / death

Hypoxia and ischemia are not equivalent

Hypoxia

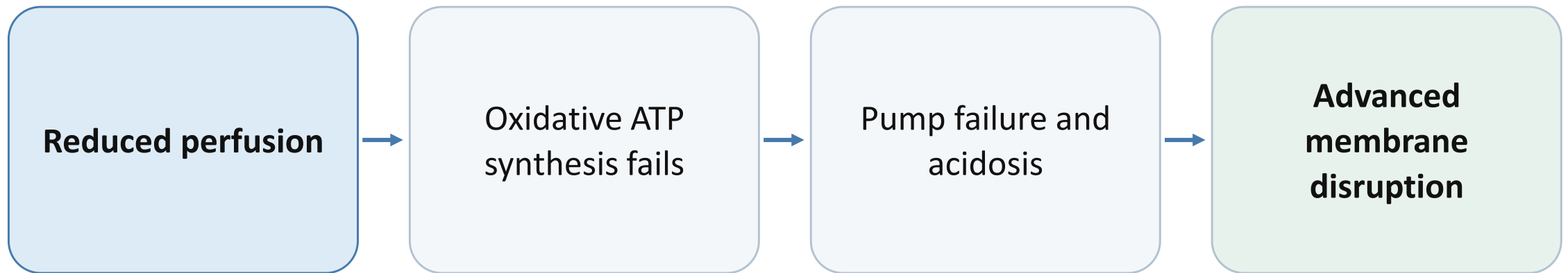
- Oxygen supply is reduced
- Blood flow may remain intact
- Glycolytic substrates can still arrive

Ischemia

- Tissue perfusion is reduced
- Both oxygen and substrate delivery suffer
- Waste metabolites are less effectively removed

Ischemia often produces more rapid and severe damage.

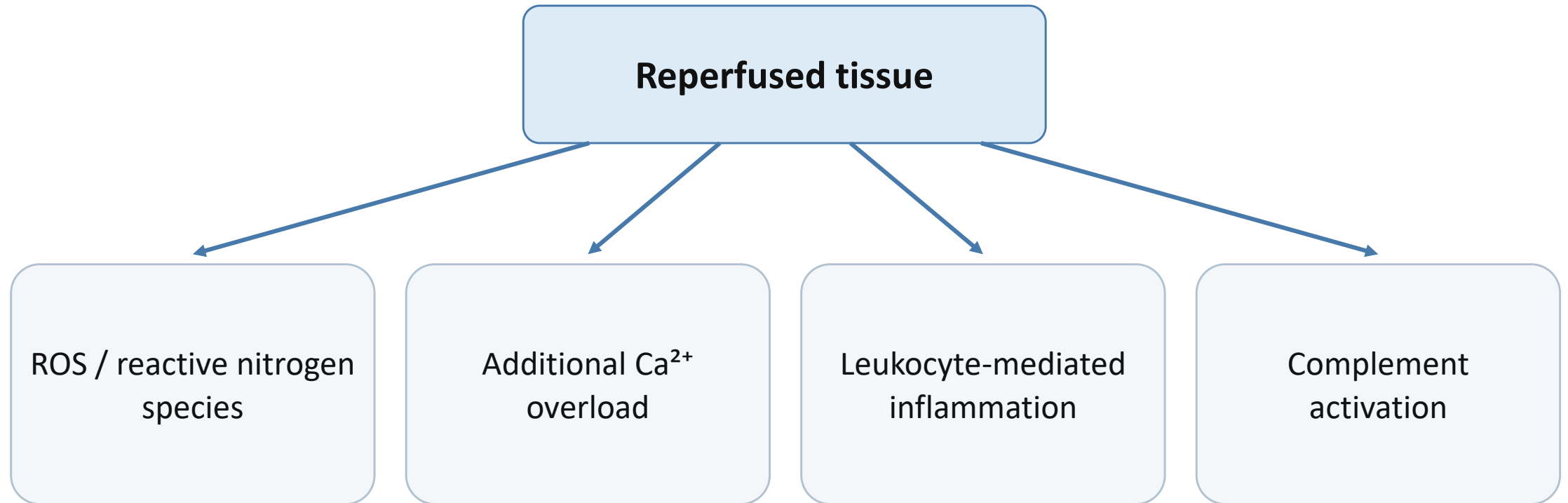
The ischemic injury sequence is mechanistically coherent



Mechanistic sequence — schematic

Early stages may reverse; Severe persistent injury proceeds to necrosis.

Reperfusion can add a second wave of damage



Two general pathways of chemical injury

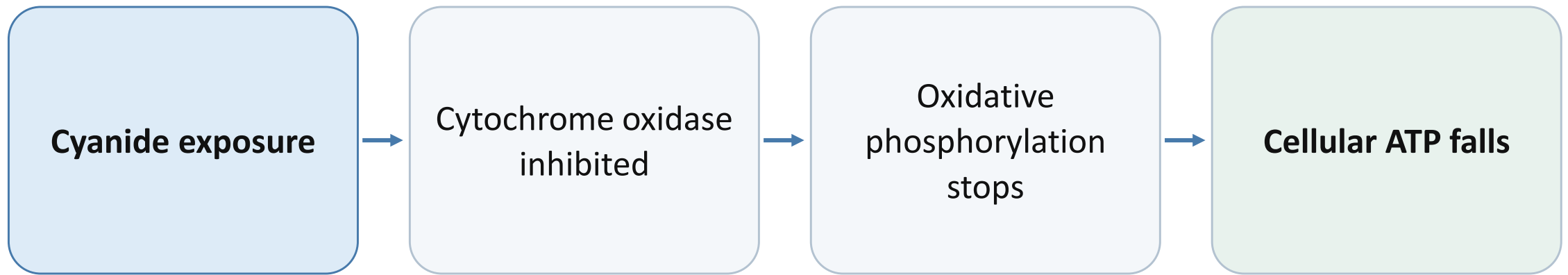
Direct-acting toxicants

- Bind or inhibit essential cell constituents
- Mercury disrupts membrane protein function
- Cyanide inhibits mitochondrial respiration

Metabolic activation

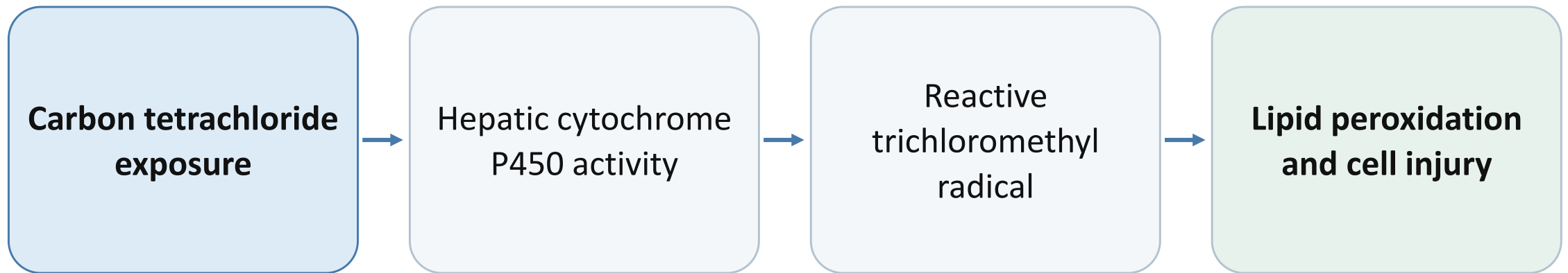
- Parent chemical converted to a reactive metabolite
- Cytochrome P450 frequently participates
- Radicals and covalent binding damage cells

Cyanide produces an energy catastrophe



Mechanistic sequence — schematic

Carbon tetrachloride damages liver-cell membranes



Mechanistic sequence — schematic

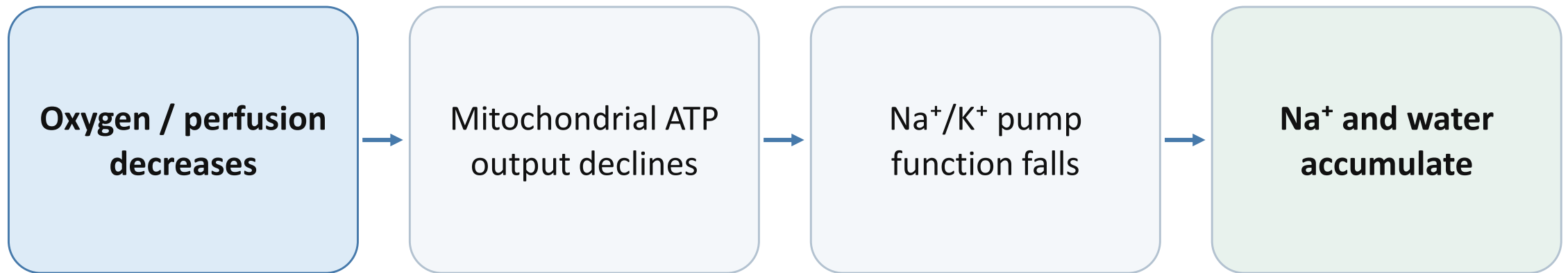
Case 1: Abrupt loss of perfusion

A tissue region experiences arterial occlusion. Early cells are swollen but have not yet lost plasma-membrane integrity.

Questions for interpretation

1. Which bioenergetic defect occurs first?
2. What explains the swelling?
3. Why can rapid reperfusion restore viability?

Case 1: Connect the findings to mechanisms



Mechanistic sequence — schematic

Preserved membrane integrity supports the possibility of reversibility.

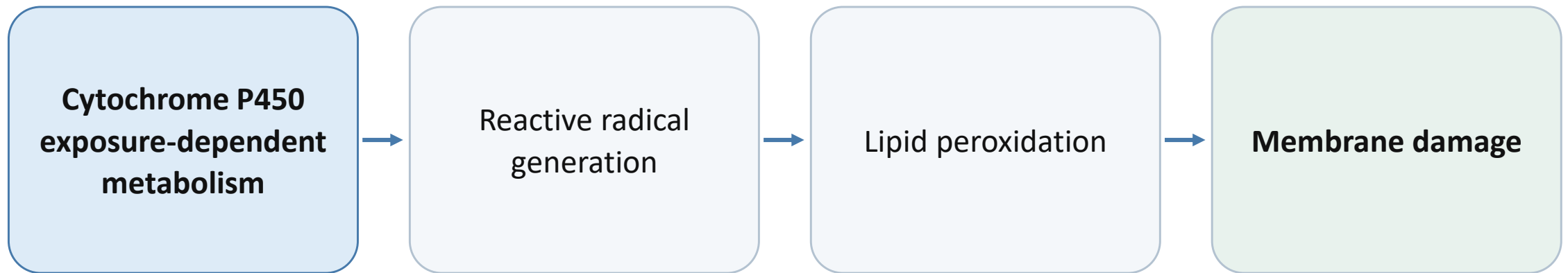
Case 2: Toxic-metabolite injury

Two persons have similar carbon tetrachloride exposure but show different degrees of hepatocellular injury.

Questions for interpretation

1. Which enzymatic system activates the toxin?
2. What kind of molecular intermediate is formed?
3. Why might the outcomes differ?

Case 2: Trace toxic activation



Mechanistic sequence — schematic

Interindividual variation in metabolic activation can modify injury severity.

A unified framework for cell injury

Primary defect	Detectable cellular change	Implication
ATP depletion	Swelling; synthesis failure	May be reversible initially
Membrane injury	Permeability loss; leakage	Favors necrotic injury
DNA / proteostasis stress	Cell-cycle arrest / stress programs	Repair or apoptosis
ROS and Ca ²⁺ overload	Amplified organelle injury	Multiple modes of cell death

Synthesis: Three principles to retain

- Insult identity, severity, and duration jointly influence injury.
- Cell type, energy needs, and adaptability shape susceptibility.
- Several reinforcing mechanisms can operate simultaneously.
- Injury to mitochondria, membranes, ER, and DNA leads to overlapping dysfunction.

References and source boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026). Chapter 2.
- Primary section: “Mechanisms of Cell Injury,” pp. 45–46.
- Mechanistic context: mitochondrial and membrane damage; DNA damage; ROS; calcium homeostasis, pp. 46–50.
- Selected clinical integration: hypoxia / ischemia, reperfusion, and chemical injury, pp. 50–51.