

Mitochondrial Damage

Mechanisms of cellular injury and death

From ATP failure to necrosis and intrinsic apoptosis

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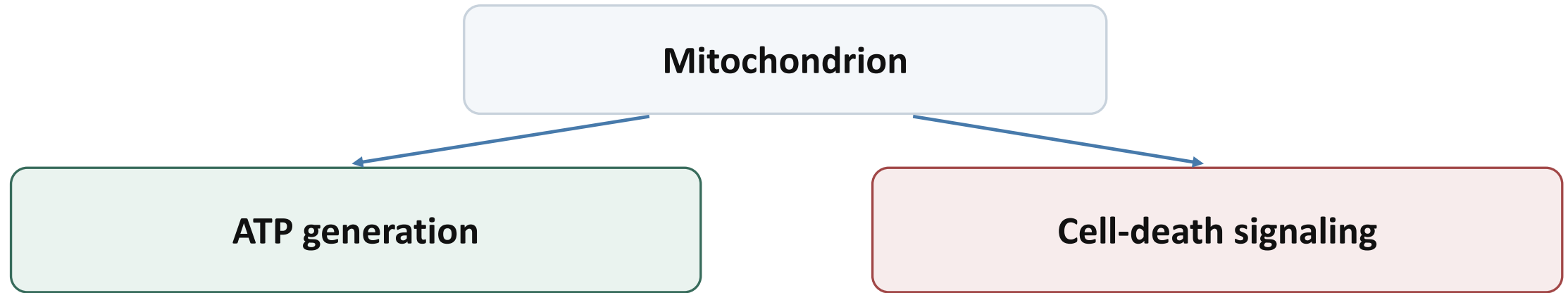
Learning outcomes

By the end of this lecture, explain:

- Why oxygen deprivation, ROS, Ca^{2+} , and toxins injure mitochondria
- How ATP loss causes osmotic, metabolic, and synthetic disturbances
- Why ROS formation and mitochondrial protein leakage change cell fate
- How MPTP-associated necrosis differs from intrinsic apoptosis

Mitochondria link injury to cell fate

Mitochondria both generate life-sustaining energy and participate in cell-death signaling.



- Failure of energy production disrupts ATP-dependent cellular functions.
- Release of mitochondrial proteins can initiate intrinsic apoptosis.

Cell injury has multiple interconnected targets

Mitochondria are one major target within a network of cellular injury.

Mitochondria

Membranes

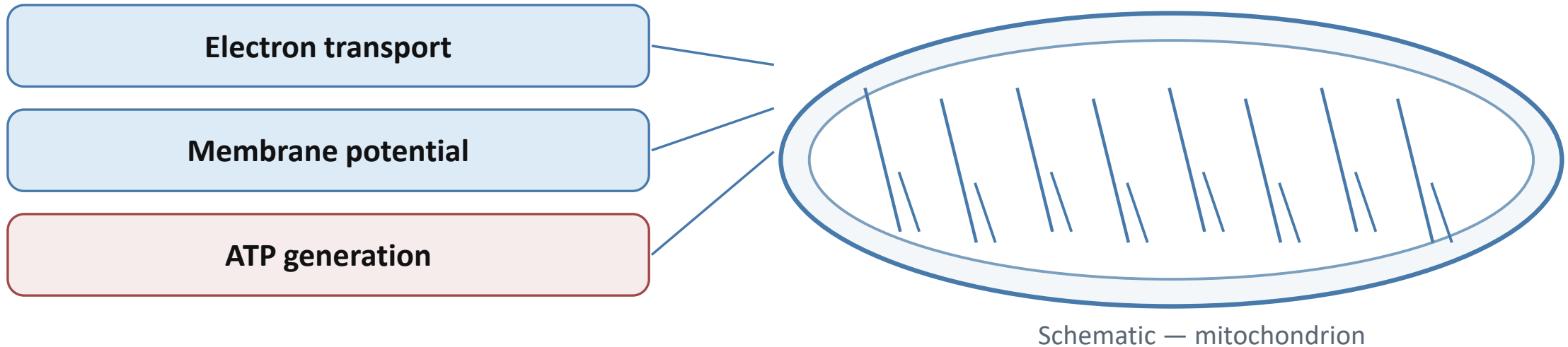
Endoplasmic reticulum

Nucleus

- Plasma membranes, ER protein handling, and DNA are also vulnerable.
- A single insult can damage several components simultaneously.

Normal mitochondria support oxidative phosphorylation

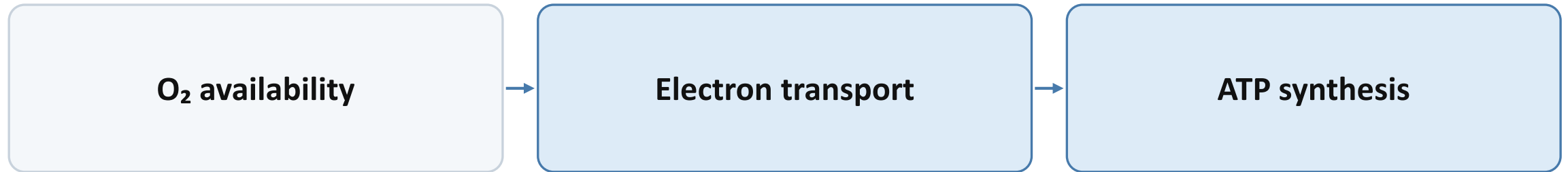
Mitochondrial electron transport couples oxygen reduction to ATP synthesis.



- ADP phosphorylation supplies most cellular ATP under aerobic conditions.
- Energy-dependent membrane transport and biosynthesis rely on this ATP.

Oxygen sustains mitochondrial ATP production

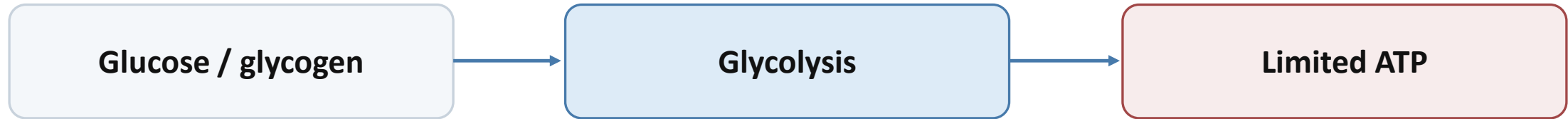
The electron transport system reduces oxygen during oxidative phosphorylation.



- Reduced oxygen supply disrupts mitochondrial energy generation.
- Oxidative phosphorylation is especially important in nondividing cells.

Glycolysis is a less efficient backup

Cells can generate ATP by glycolysis when oxygen is absent.



- Glucose can come from extracellular fluid or glycogen stores.
- Compared with oxidative phosphorylation, glycolysis produces less ATP.

Two pathways contribute to cellular ATP

The relative importance of the pathways changes during oxygen deprivation.

Oxidative phosphorylation

Mitochondrial location

Uses oxygen

Major ATP source

Glycolysis

Cytosolic pathway

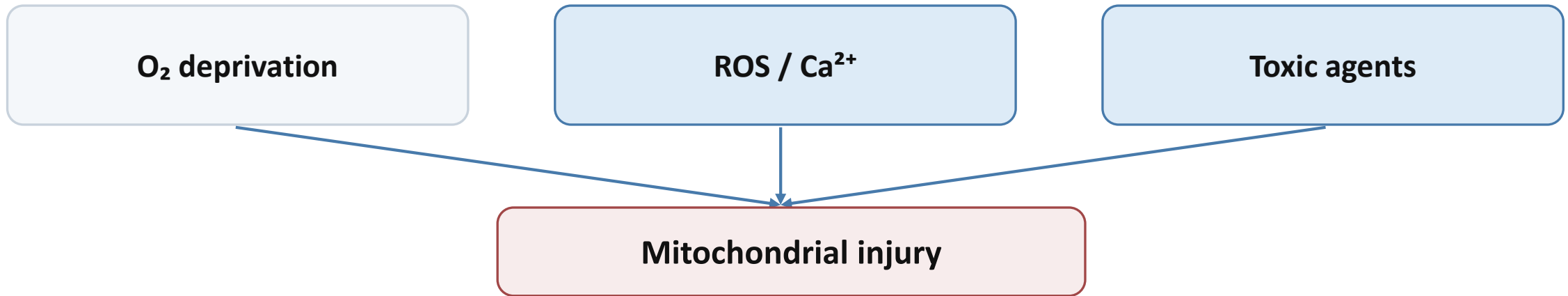
Can function without oxygen

Smaller ATP yield

- Oxidative phosphorylation is oxygen dependent.
- Glycolysis can continue without oxygen but cannot fully replace mitochondrial output.

Mitochondria sense diverse injurious stimuli

Different insults converge on mitochondrial dysfunction.



- Hypoxia and ischemia restrict oxygen supply.
- Reactive oxygen species (ROS), increased Ca²⁺, and toxins also damage mitochondria.

The nature and duration of injury matter

Mitochondrial injury is not automatically irreversible.

Brief / mild injury

Limited perturbation

Recovery possible

Reversibility depends on context

Severe / prolonged injury

Progressive dysfunction

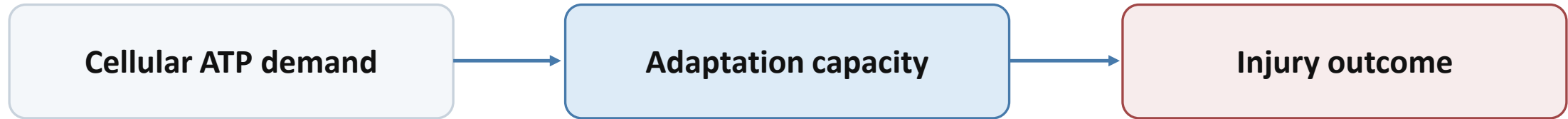
Irreversible damage

Cell death may follow

- Mild or brief injury may remain reversible.
- Sustained severe injury can progress to irreversible dysfunction and death.

Tissue vulnerability differs

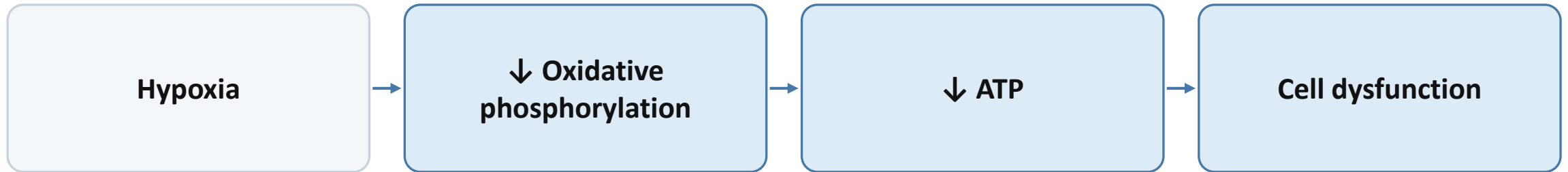
The injured cell's demands and adaptability influence consequences.



- Cells with high aerobic ATP requirements have less tolerance for loss of energy supply.
- The same insult can produce different responses in different tissues.

Hypoxia directly threatens oxidative phosphorylation

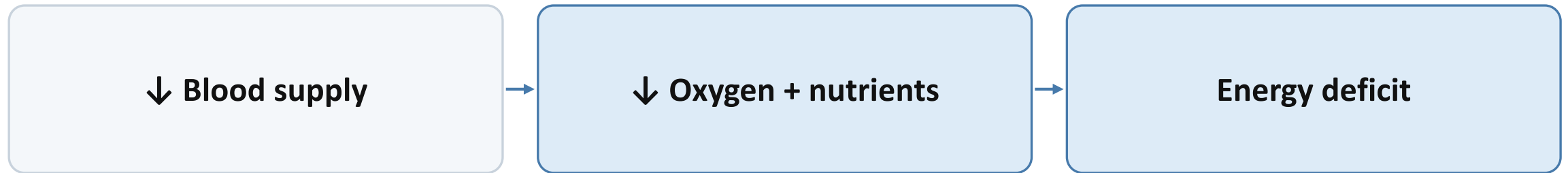
Oxygen shortage impairs mitochondrial ATP synthesis.



- Reduced ATP causes multiple downstream cellular abnormalities.
- Hypoxia may also stimulate compensatory glycolysis.

Ischemia also compromises nutrient delivery

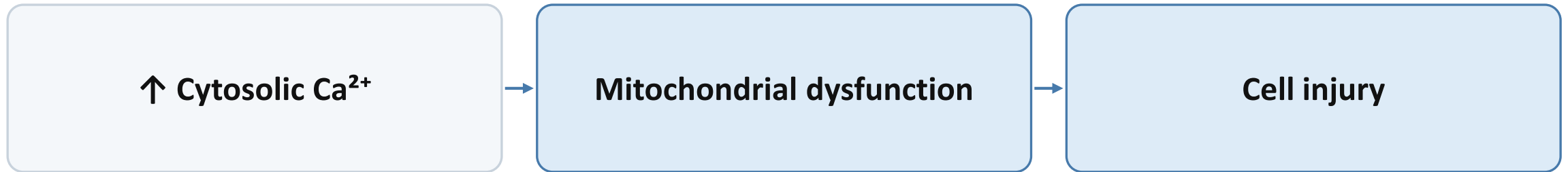
A perfusion deficit restricts both oxygen and metabolic substrates.



- Reduced oxygen limits oxidative phosphorylation.
- Reduced nutrient supply restricts compensation through glycolysis.

Raised cytosolic Ca^{2+} injures mitochondria

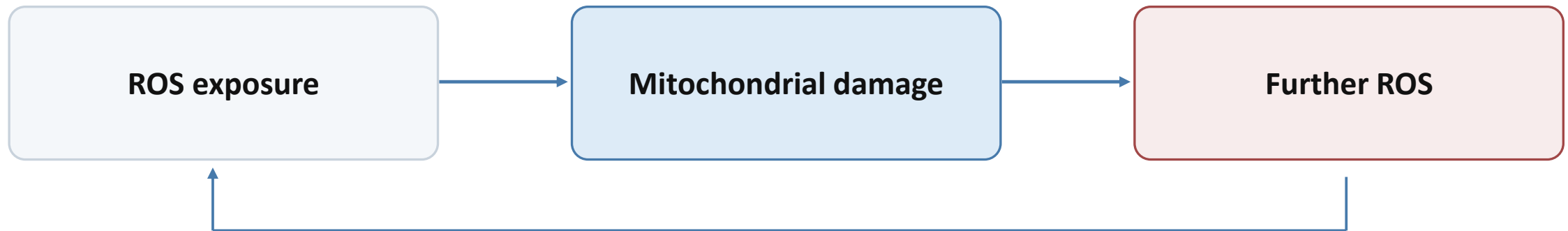
Increased cytosolic Ca^{2+} is a mitochondrial damaging stimulus.



- Mitochondrial disturbance can amplify the consequences of cell injury.
- Calcium-related injury also intersects with membrane damage.

Reactive oxygen species target mitochondria

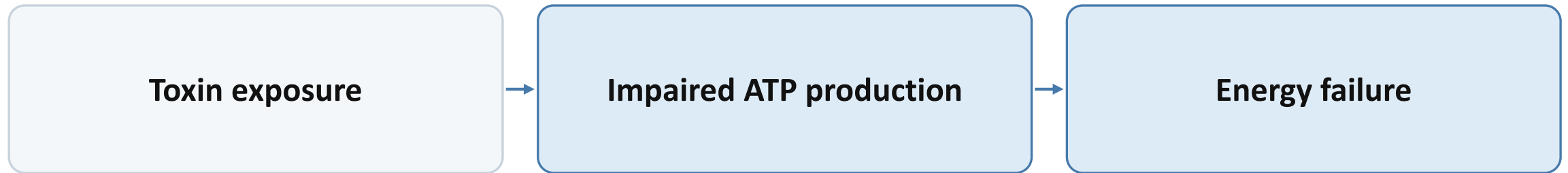
ROS are both causes and consequences of mitochondrial injury.



- ROS can injure cellular components including mitochondrial structures.
- Incomplete oxidative phosphorylation can increase ROS production.

Some toxins reduce ATP production

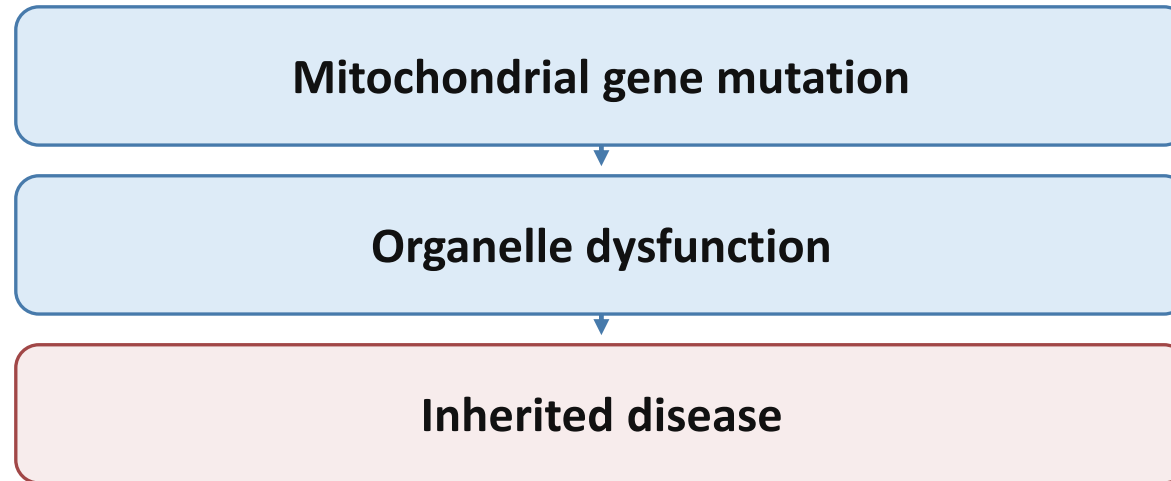
Chemical injury may compromise mitochondrial energy synthesis.



- Cyanide as an example of a toxin causing ATP depletion.
- This can occur despite the presence of oxygen in the environment.

Mitochondrial gene mutations are an additional route

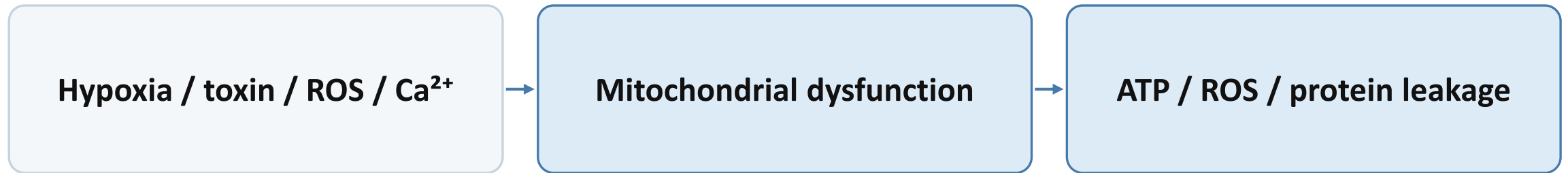
Inherited mitochondrial gene defects can lead to disease.



- This is a distinct mechanism from acute oxygen deprivation or poisoning.
- Specific mitochondrial genetic syndromes are covered elsewhere.

Distinct insults can converge on one organelle

Mitochondrial dysfunction integrates metabolic, oxidative, and toxic injury.



- Different initiating events need not produce completely different downstream consequences.
- ATP loss, ROS generation, and death signaling may coexist.

Three major consequences organize the topic

Mitochondrial injury can produce energy failure, oxidative damage, and apoptotic signaling.

ATP depletion

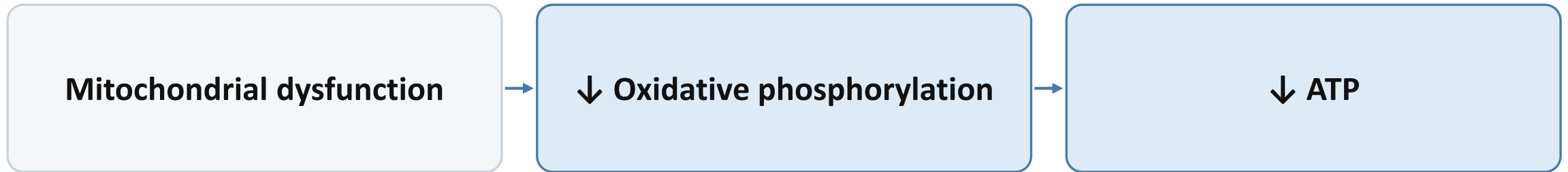
ROS generation

Protein leakage

- ATP depletion primarily contributes to functional failure and necrosis.
- ROS increases injury; Release of proteins favors intrinsic apoptosis.

ATP depletion begins with impaired production

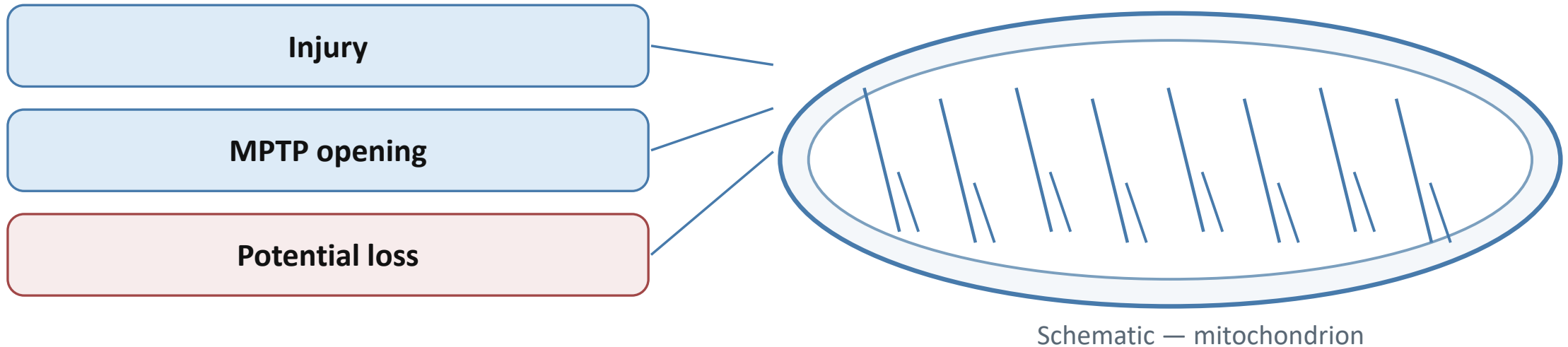
Mitochondrial damage decreases oxidative phosphorylation.



- Energy supply falls before many later structural consequences appear.
- ATP loss can also result from inadequate oxygen, nutrients, or certain toxins.

Mitochondrial permeability transition worsens injury

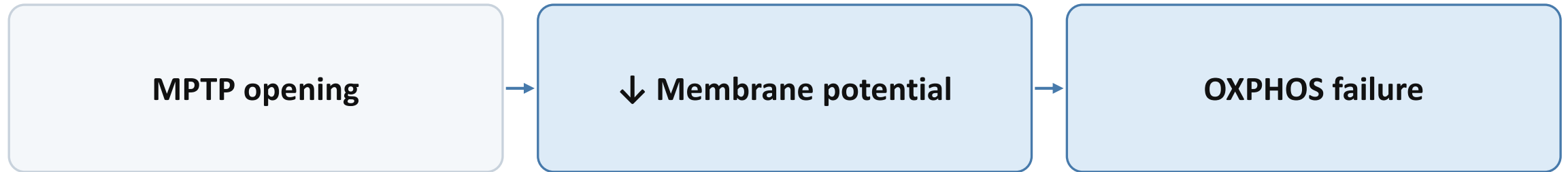
Mitochondrial damage can lead to formation of a high-conductance channel.



- Robbins calls this the mitochondrial permeability transition pore (MPTP).
- Pore opening links mitochondrial injury to loss of membrane potential.

Membrane potential is essential for ATP synthesis

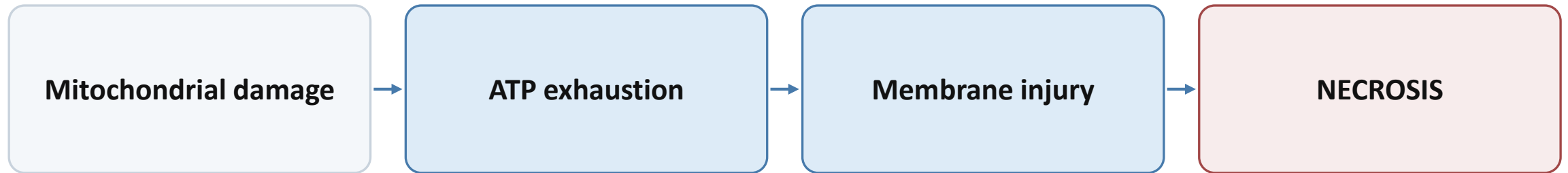
MPTP opening dissipates the mitochondrial membrane potential.



- The electrochemical state necessary for oxidative phosphorylation is lost.
- Failure of ATP production then becomes progressive.

Energy failure can culminate in necrosis

Progressive ATP depletion is a central route from mitochondrial dysfunction to necrosis.



- The pathway disrupts ion transport, biosynthesis, and membrane maintenance.
- Terminal injury includes irreversible damage of cellular membranes.

ATP powers more than contraction or movement

Nearly every cellular synthetic and degradative pathway depends on ATP.

Transport

Protein synthesis

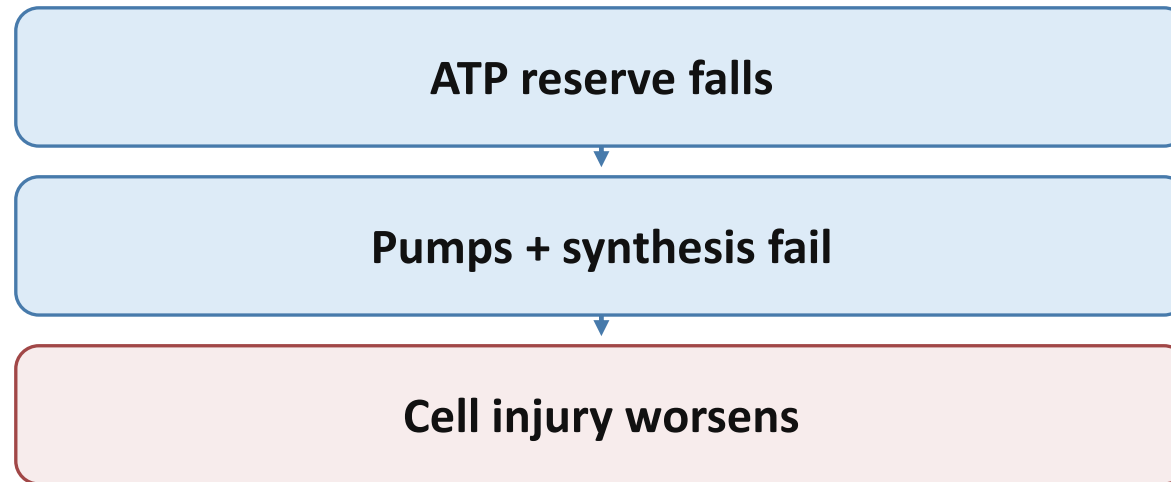
Lipogenesis

Phospholipid turnover

- Major examples: Membrane transport, protein synthesis, and lipogenesis.
- Phospholipid turnover also uses energy-dependent reactions.

Severe ATP loss has widespread cellular effects

Major abnormalities when ATP falls to 5%–10% of normal.



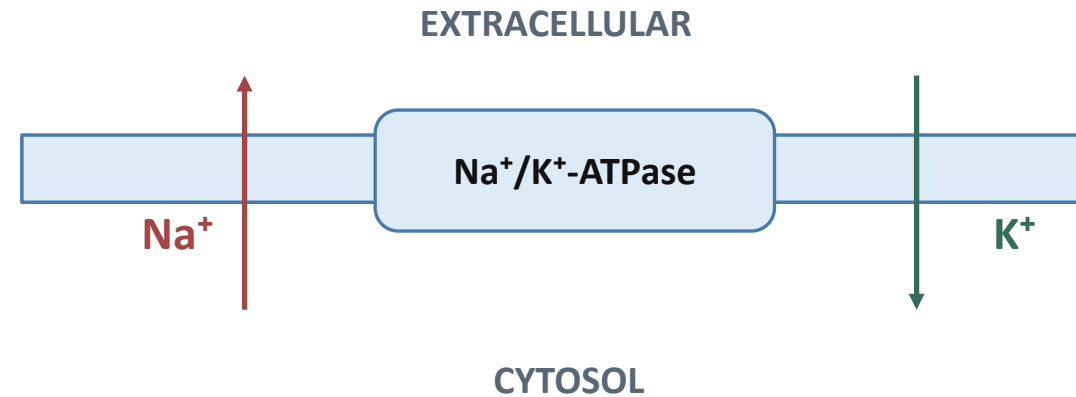
- This figure represents a textbook description, not a diagnostic clinical threshold.
- Multiple essential processes become impaired at this degree of energy depletion.

Na^+/K^+ -ATPase requires continuous ATP

The plasma-membrane sodium pump maintains transmembrane ion gradients.

ATP available

Na^+/K^+ -ATPase active



Schematic — movements across plasma membrane

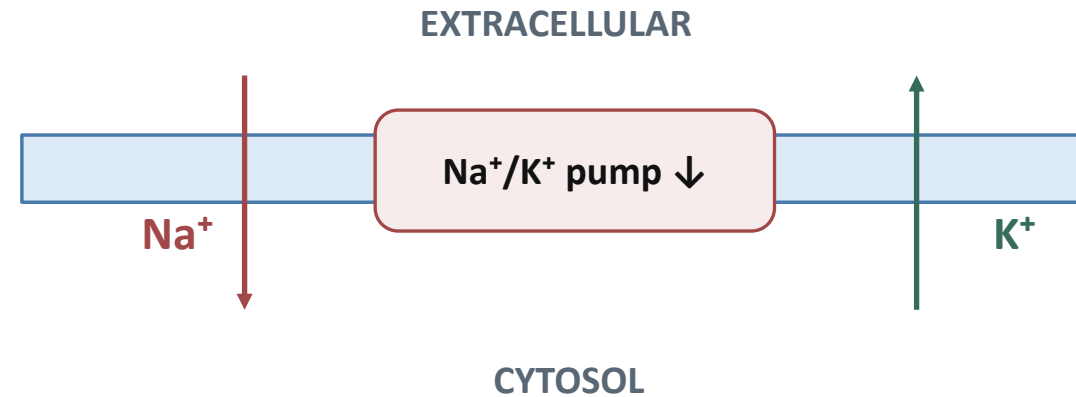
- Normal function opposes Na^+ accumulation inside cells.
- ATP depletion diminishes activity of this energy-dependent transporter.

Pump failure changes cellular ion balance

ATP shortage lowers Na^+/K^+ -ATPase activity.

↓ ATP

↓ Sodium pump activity

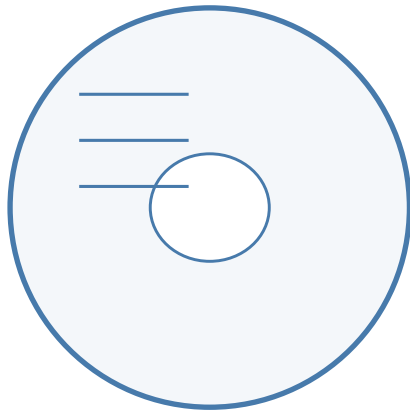


Schematic — movements across plasma membrane

- Na^+ enters and accumulates intracellularly.
- The intracellular K^+ concentration falls.

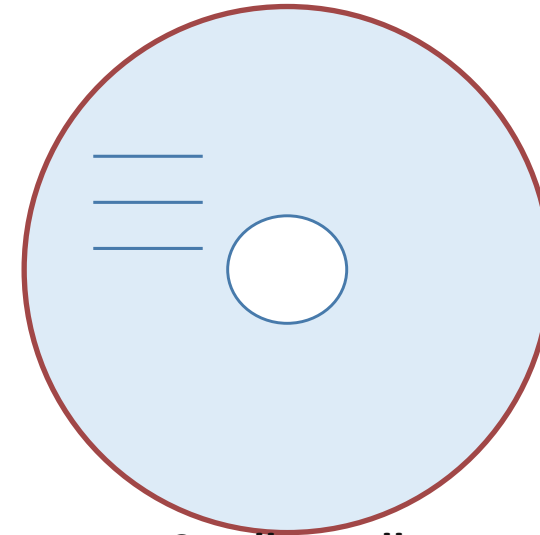
Water follows the intracellular solute gain

Net solute retention creates an osmotic drive for water entry.



Normal cell

Schematic — osmotic water accumulation

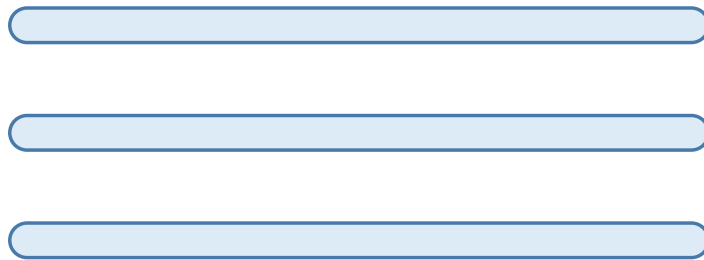


Swollen cell

- The cell swells as intracellular water accumulates.
- This is a key early manifestation of cell injury.

Endoplasmic reticulum also dilates

ATP-depletion–related ionic and water imbalance affects organelles.



Normal ER



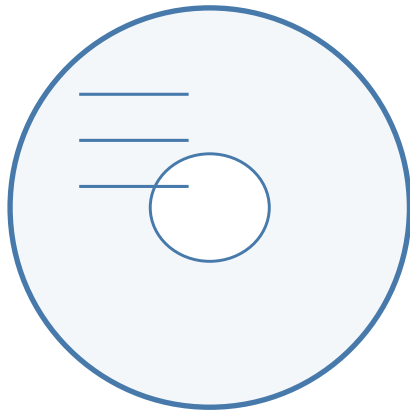
Dilated ER

Schematic — luminal dilation of endoplasmic reticulum

- Robbins explicitly links sodium pump failure to ER dilation.
- Cellular swelling and ER dilation are part of the reversible-injury spectrum.

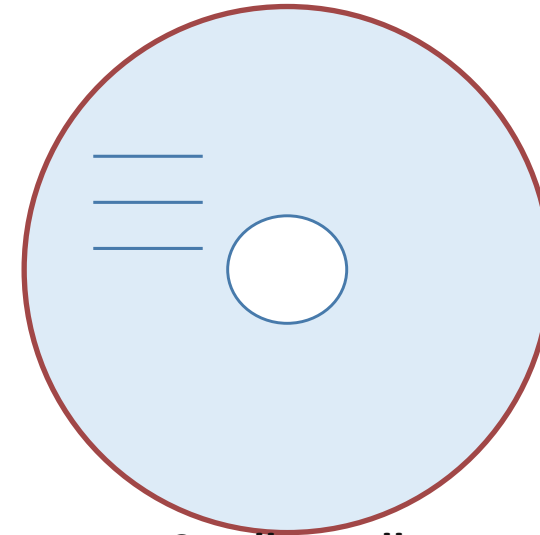
Cell swelling reflects altered homeostasis

The sequence explains a classic early morphology of cell injury.



Normal cell

Schematic — osmotic water accumulation

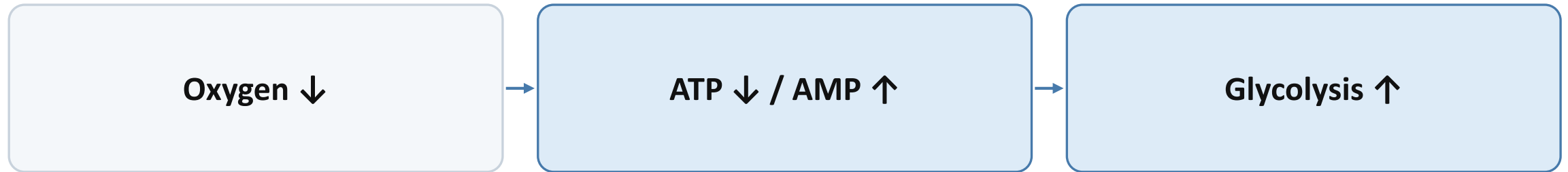


Swollen cell

- ATP failure is the initiating biochemical defect.
- Ion imbalance and osmosis translate the defect into visible cellular enlargement.

Oxygen deprivation triggers metabolic adaptation

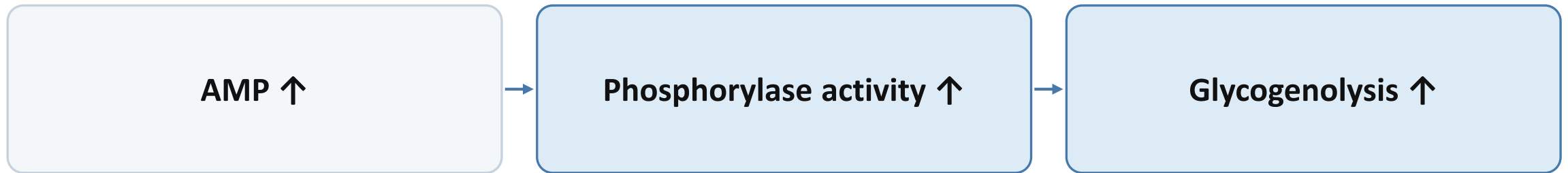
Declining oxidative phosphorylation shifts ATP production toward glycolysis.



- Cellular AMP increases as ATP declines.
- The response attempts to preserve energy supply rather than correct the initiating oxygen deficit.

Energy shortage activates glycogen mobilization

Rising AMP to increased phosphorylase activity.



- Glycogen breakdown supplies glucose for energy generation.
- This is a compensatory response during oxygen shortage.

Phosphofructokinase promotes glycolytic flux

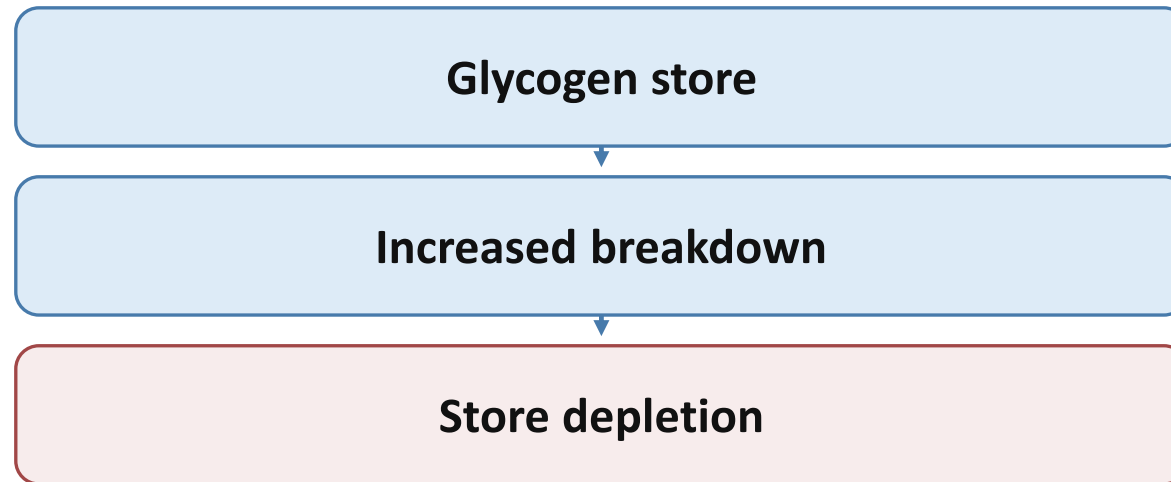
Injury-related energy changes increase glycolytic activity.



- Increased phosphofructokinase activity.
- The pathway provides ATP even when oxygen is limited.

Glycolytic compensation uses finite glycogen stores

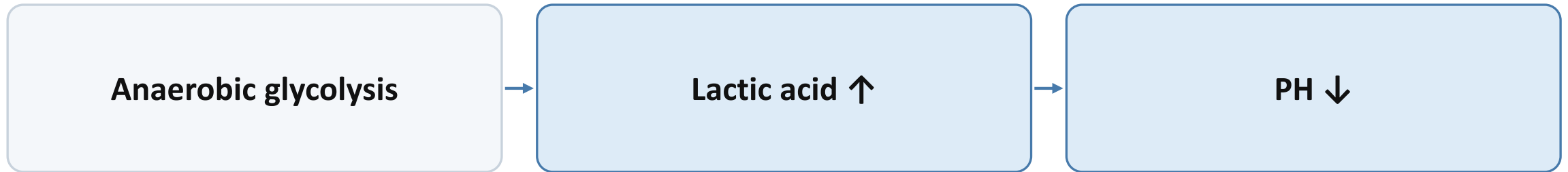
Sustained anaerobic glycolysis consumes cellular glycogen.



- Stored glycogen can be depleted rapidly during ischemic stress.
- The compensatory route cannot fully maintain normal ATP generation.

Anaerobic metabolism causes lactate accumulation

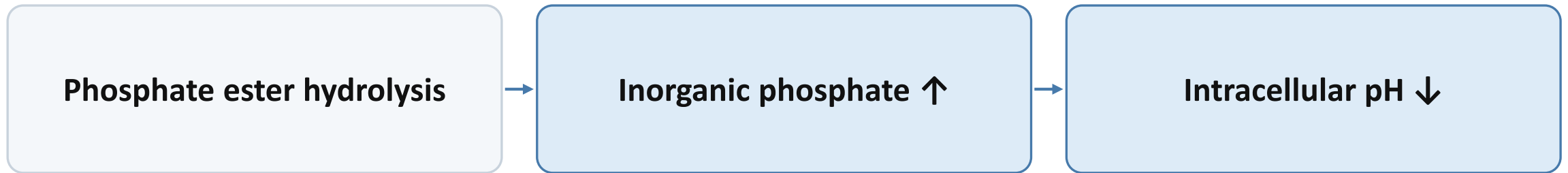
Glycolysis in the absence of adequate oxygen produces lactic acid.



- The biochemical consequence accompanies energy compensation.
- This contributes to intracellular acidification.

Inorganic phosphate also contributes to acidification

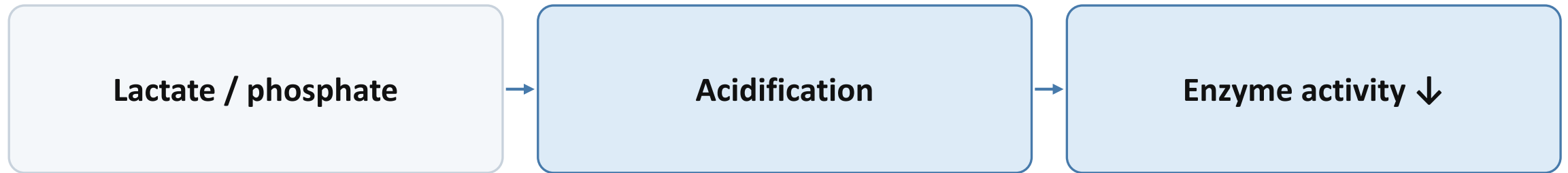
Hydrolysis of phosphate esters produces inorganic phosphate.



- Lactate and phosphate accumulation with lower intracellular pH.
- Metabolic and ionic disturbances occur in parallel.

Low intracellular pH impairs enzyme function

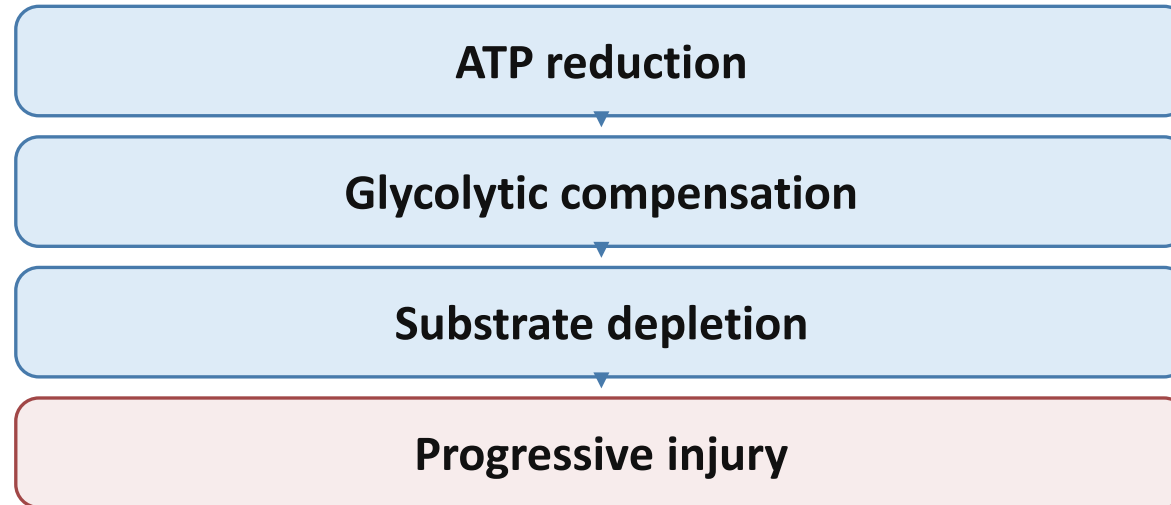
Acidification reduces activity of many cytosolic enzymes.



- Glycolysis is therefore a partial rescue with secondary biochemical costs.
- This connects ATP loss to wider metabolic dysfunction.

Energy deficit becomes self-limiting

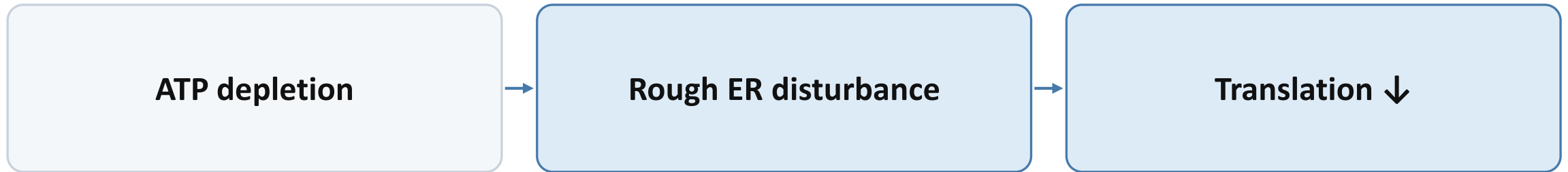
Compensatory glycolysis does not avert injury indefinitely.



- Glycogen stores fall while ATP production remains limited.
- Persistent hypoxia shifts the balance toward severe metabolic and structural damage.

Protein synthesis is an ATP-dependent process

Sustained ATP loss disrupts the protein synthetic apparatus.



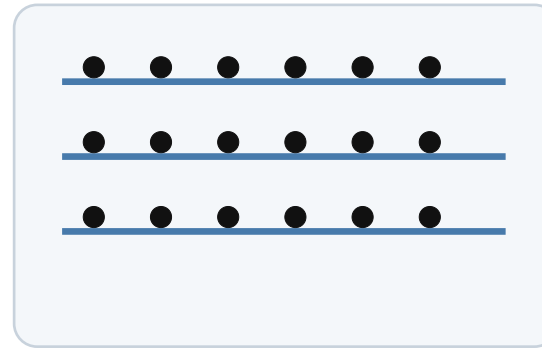
- Structural effects involve rough endoplasmic reticulum and polysomes.
- The result is reduced cellular protein synthesis.

Ribosomes detach from rough ER

Prolonged energy depletion alters ribosome–ER association.

Sustained ATP ↓

Ribosome detachment



Ribosomes attached



Ribosomes detached

Schematic — changes in translation apparatus

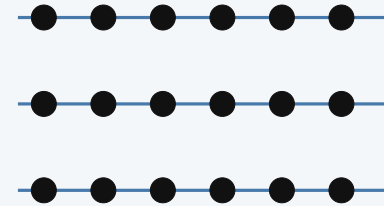
- This represents a structural change in the machinery of protein production.
- Loss of attached ribosomes impairs synthesis of proteins handled by rough ER.

Polysomes dissociate as injury progresses

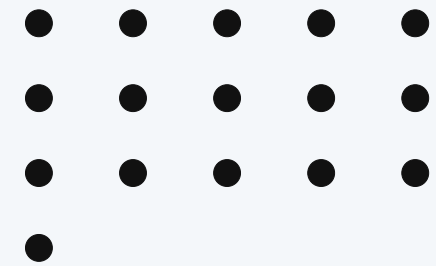
Ribosomal complexes are disrupted during severe energy failure.

Energy depletion

Polysome dissociation



Intact polysomes



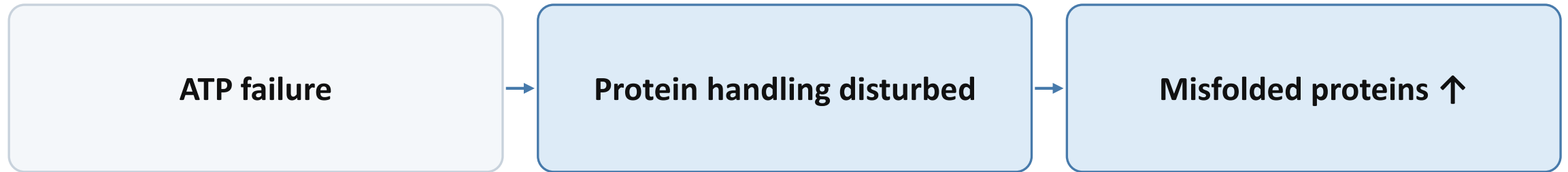
Dissociated ribosomes

Schematic — changes in translation apparatus

- Dissociation of polysomes.
- Ribosome detachment and polysome disruption both reduce translation.

Protein misfolding may add further injury

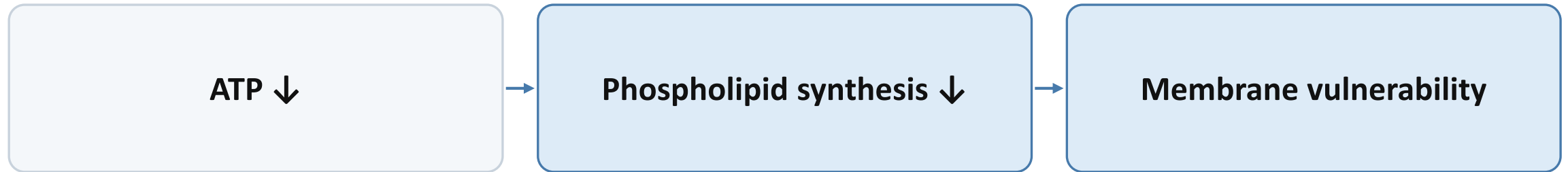
ATP depletion may increase the burden of misfolded proteins.



- The ER is a major site of protein-handling stress.
- This links mitochondrial energy failure to injury at another organelle.

ATP also supports membrane lipid maintenance

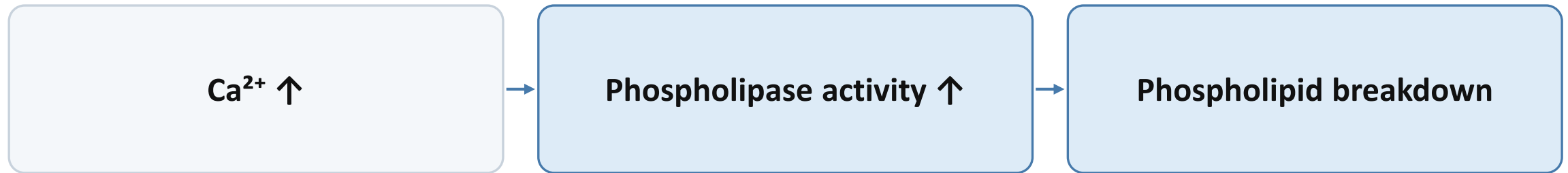
Phospholipid turnover depends on energy-consuming reactions.



- Impaired ATP production can reduce phospholipid synthesis.
- Compromised membrane maintenance increases susceptibility to injury.

Calcium and phospholipases worsen membrane injury

Membrane damage can develop through several interacting processes.



- Ca²⁺-dependent phospholipases can increase phospholipid breakdown.
- ATP depletion, ROS, and membrane injury are mechanistically interconnected.

Severe injury damages multiple cellular membranes

Energy failure progresses beyond reversible swelling.

**Mitochondrial
membrane**

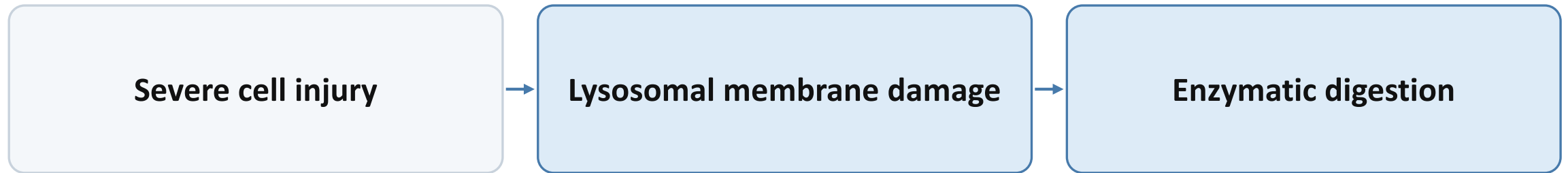
Lysosomal membrane

Irreversible injury

- Irreversible damage to mitochondrial and lysosomal membranes marks advanced injury.
- Loss of cellular membrane integrity contributes to necrotic death.

Lysosomal membrane injury amplifies necrotic damage

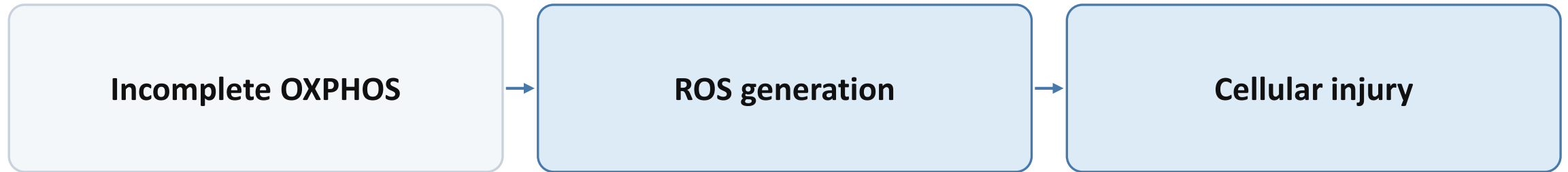
Lysosomal damage is part of the terminal injury sequence.



- Compromised lysosomes release degradative enzymes within injured cells.
- Lysosomal and mitochondrial injury often coexist in severe necrosis.

Incomplete oxidative phosphorylation generates ROS

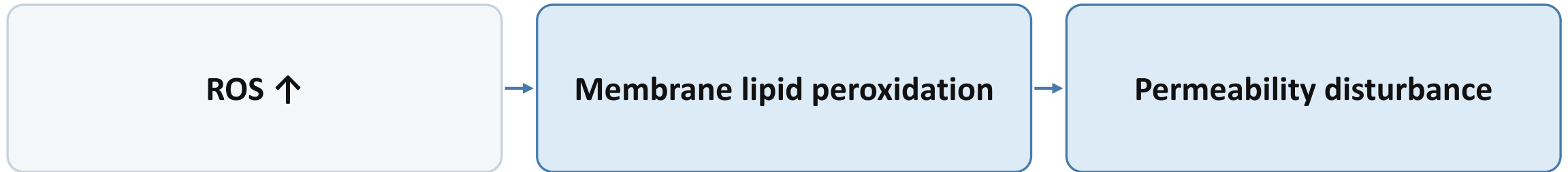
Disrupted mitochondrial electron transport can form reactive oxygen species.



- ROS are a major second consequence of mitochondrial dysfunction.
- The resulting damage extends beyond the mitochondrion itself.

ROS can damage membrane lipids

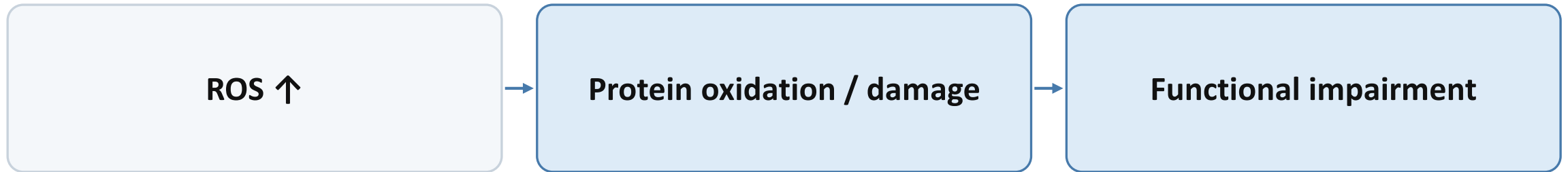
Lipid peroxidation compromises membrane integrity.



- This creates another route from mitochondrial dysfunction to membrane damage.
- A damaged membrane loses normal barrier properties.

ROS can modify cellular proteins

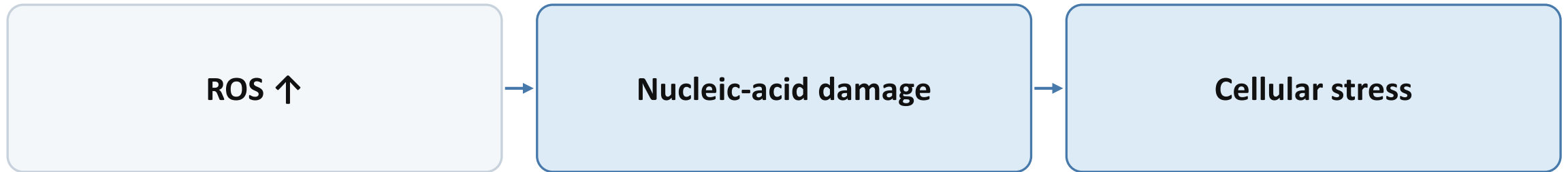
Oxidative injury affects proteins as well as membrane lipids.



- Proteins are one class of molecular targets identified by Robbins.
- Protein damage contributes to loss of normal cellular function.

ROS can injure nucleic acids

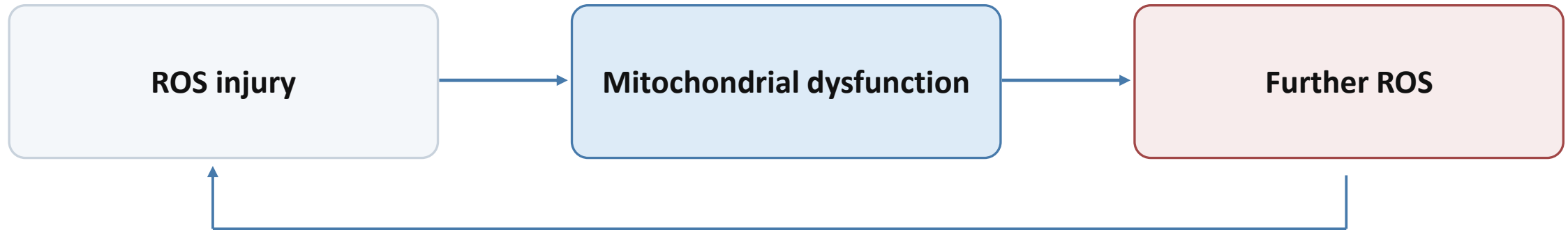
Nucleic acids are also vulnerable to reactive oxygen species.



- Oxidative damage is not confined to mitochondrial DNA.
- The precise consequence depends on the site and extent of damage.

Mitochondrial dysfunction and ROS can reinforce injury

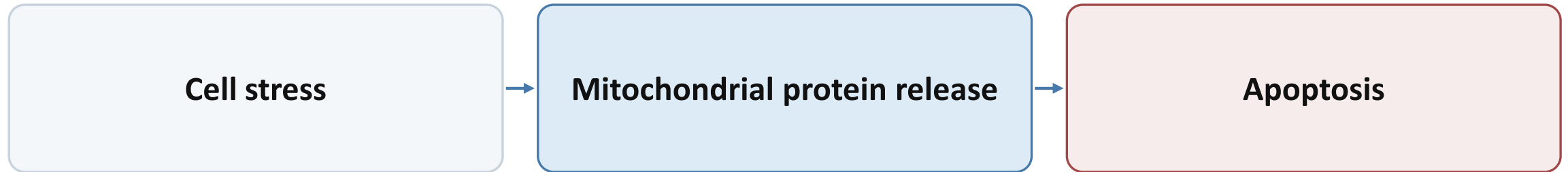
ROS are both an upstream insult and a downstream product of disturbed respiration.



- The relationship helps explain the amplification of severe cellular injury.
- This is a conceptual feedback loop, not a quantitative kinetic model.

Mitochondria also regulate intrinsic apoptosis

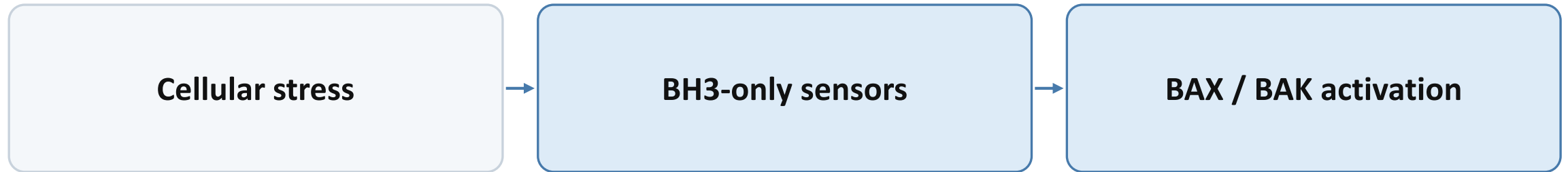
Mitochondrial proteins participate in programmed cell-death signaling.



- This pathway differs from energy depletion leading to necrosis.
- Loss of survival signals and damage can activate pro-apoptotic machinery.

BH3-only sensors respond to cellular stress

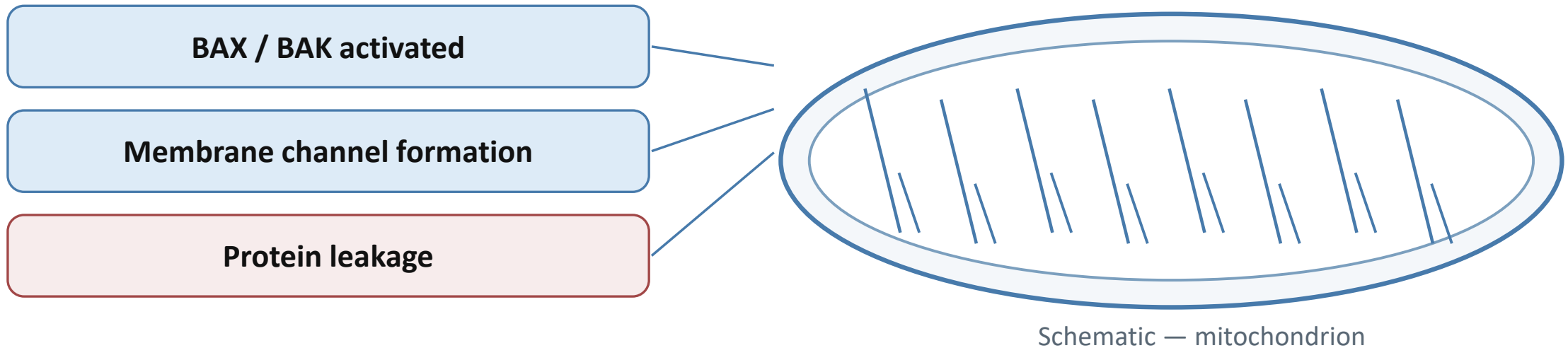
Intrinsic apoptosis uses regulated BCL2-family proteins.



- Growth-factor withdrawal, DNA damage, and protein misfolding may activate BH3-only sensors.
- These signals relieve restraint on the pro-apoptotic effectors BAX and BAK.

BAX and BAK form mitochondrial membrane channels

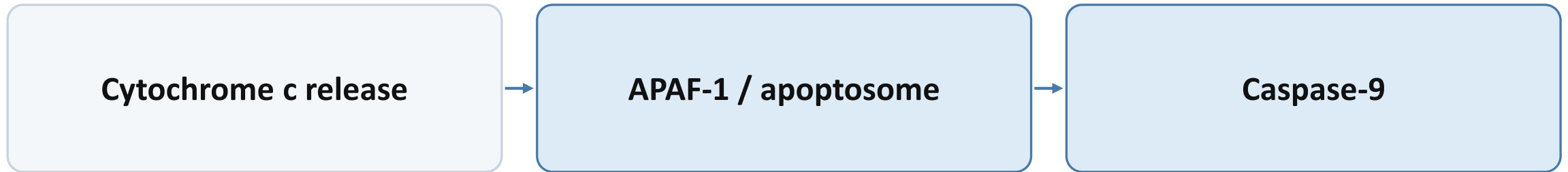
Pro-apoptotic BAX and BAK enable release of mitochondrial proteins.



- Channel formation as an initiating event of the intrinsic pathway.
- Their action is specific to mitochondrial membranes.

Cytochrome c leakage activates the apoptotic machinery

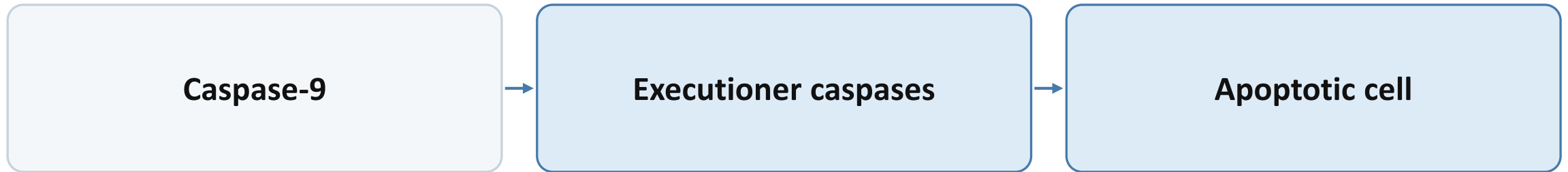
Release of mitochondrial cytochrome c triggers downstream assembly of the apoptosome.



- APAF-1 participates in apoptosome formation.
- The cascade activates initiator caspase-9.

Caspases execute intrinsic apoptosis

Initiator caspases activate downstream executioner caspases.



- Executioner caspases dismantle cellular proteins and structures.
- Programmed fragmentation differs from necrotic membrane rupture.

BCL2-family balance regulates mitochondrial permeabilization

Pro- and anti-apoptotic signals determine whether the intrinsic pathway proceeds.

Anti-apoptotic restraint

BCL2 and BCL-XL

Help maintain mitochondrial integrity

Oppose inappropriate apoptosis

Pro-apoptotic signaling

BH3-only sensors respond to stress

BAX / BAK become activated

Mitochondrial proteins are released

- Anti-apoptotic BCL2-family proteins help preserve mitochondrial integrity.
- Stress-responsive sensors and BAX/BAK favor mitochondrial protein release.

MPTP and BAX/BAK channels have different implications

Mitochondrial membrane changes do not constitute one interchangeable event.

MPTP-related injury

Loss of membrane potential
ATP synthesis failure
Progression toward necrosis

BAX/BAK-mediated injury

Mitochondrial protein leakage
Cytochrome c / caspases
Intrinsic apoptosis

- MPTP opening disrupts membrane potential and ATP synthesis.
- BAX/BAK channels permit protein release that activates intrinsic apoptosis.

Necrosis and apoptosis have distinct proximal mechanisms

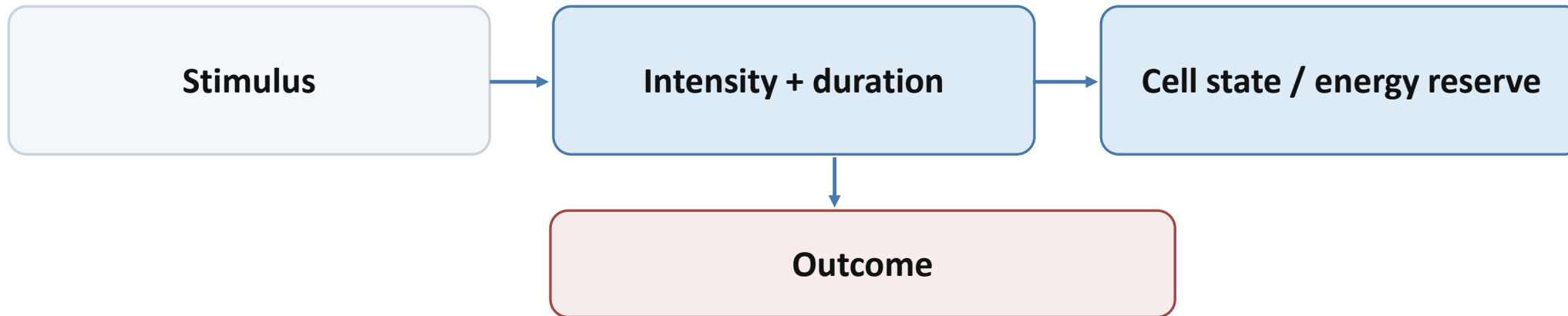
Both pathways can involve mitochondria, but they diverge mechanistically.

Necrotic route	Apoptotic route
Severe ATP depletion	BAX/BAK channel formation
Membrane damage	Caspase cascade
Loss of cell integrity	Ordered fragmentation

- Necrosis: Progressive energy failure and irreversible membrane injury.
- Apoptosis: Regulated protein release and caspase activation.

Why one insult may produce different outcomes

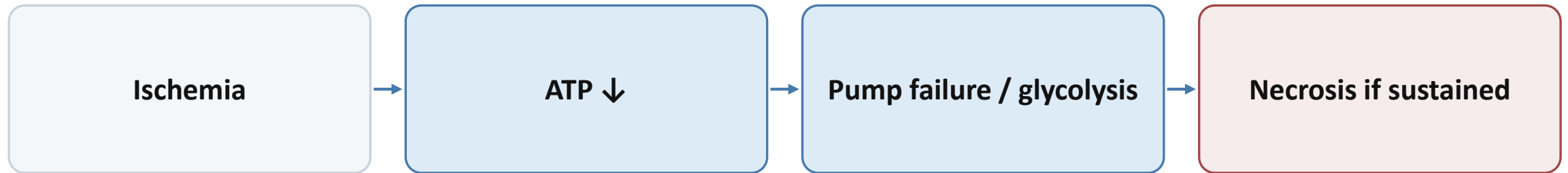
Cell fate depends on injury severity and cellular context.



- Mild injury may be reversible; Severe sustained injury often causes necrosis.
- Some stresses engage the mitochondrial intrinsic apoptosis pathway.

Clinical reasoning: Sudden oxygen deprivation

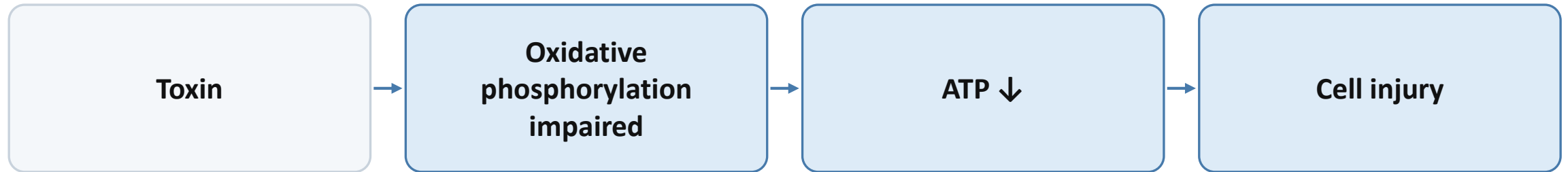
Illustrative scenario: Tissue becomes acutely hypoxic after loss of perfusion.



- Predict an early fall in oxidative phosphorylation and ATP.
- Then predict increased glycolysis, cell swelling, and—if severe—necrosis.

Clinical reasoning: Cyanide exposure

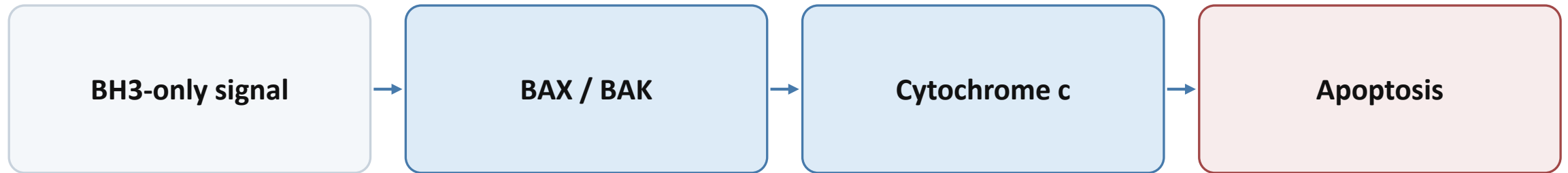
Illustrative scenario: A toxin blocks effective mitochondrial ATP generation.



- Identify the proximate metabolic problem: ATP failure.
- Predict ion pump dysfunction and cellular swelling as consequences.

Clinical reasoning: Protein-handling stress

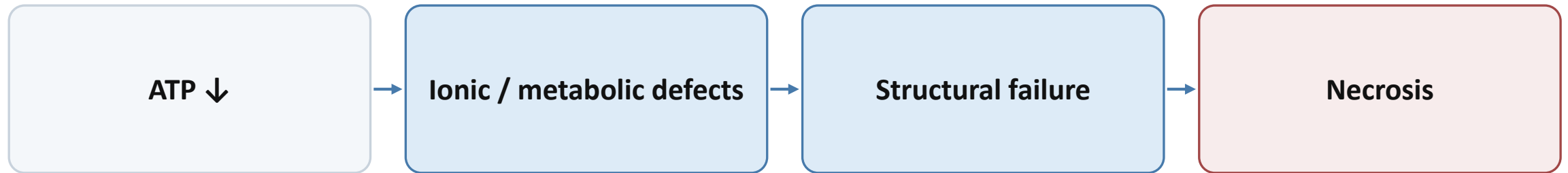
Illustrative scenario: Cellular stress activates BH3-only proteins.



- Predict BAX/BAK-dependent mitochondrial protein release.
- Then identify the apoptosome–caspase sequence as the death pathway.

Integrated sequence: From mitochondrial dysfunction to necrosis

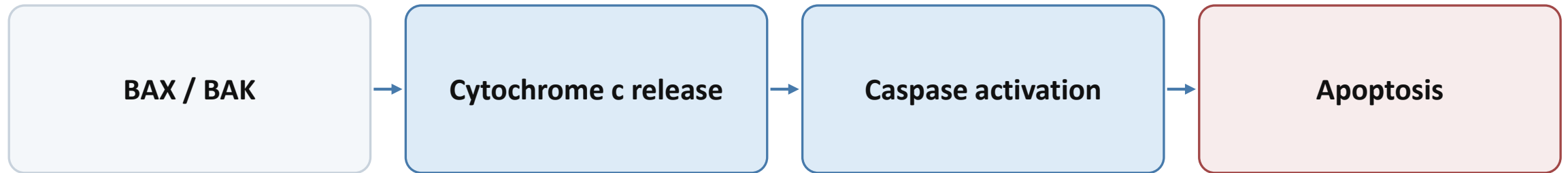
A multistep mechanism explains why ATP depletion is so damaging.



- Pump failure causes swelling; Metabolic adaptation produces lactate and acidity.
- With persistence, protein synthesis and membranes are irreversibly injured.

Integrated sequence: Mitochondrial route to apoptosis

Intrinsic apoptosis uses regulated mitochondrial membrane permeabilization.



- BAX/BAK channel formation releases cytochrome c.
- Apoptosome and caspase activation produce apoptotic dismantling.

The central distinction

Mitochondrial injury leads to different cell-death pathways depending on the dominant mechanism.

Energy failure → necrosis

Protein release → apoptosis

- Loss of membrane potential and ATP favors necrotic injury.
- Release of mitochondrial proteins through BAX/BAK channels favors apoptosis.

Knowledge check: Match the mechanism

Use the initiating mitochondrial event to predict the downstream abnormality.

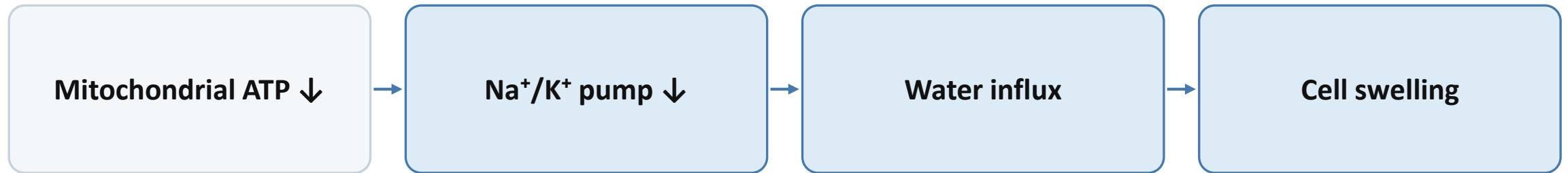
MPTP → membrane potential / ATP?

BAX/BAK → mitochondrial protein release?

- MPTP opening: What happens to membrane potential and ATP?
- BAX/BAK channel formation: Which apoptotic signaling event follows?

Knowledge check: Explain cell swelling

Reconstruct the causal chain from a mitochondrial defect to a visible morphologic change.



Discussion: Trace the mechanism step by step

- Why does intracellular Na⁺ rise when ATP falls?
- Why does the increase in intracellular solute enlarge the cell?

Mechanisms to retain

A small set of linked mechanisms explains the central pathology.

ATP / pumps

MPTP / $\Delta\psi_m$

ROS

BAX / BAK

- Mitochondrial impairment → ATP depletion → pump and synthetic failure.
- MPTP → loss of membrane potential; Incomplete OXPHOS → ROS.
- BAX/BAK → protein release → intrinsic apoptosis.

Source and scope

Primary teaching source

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026).

Chapter 2: Cell Injury, Cell Death, and Adaptations.

Core section: Mitochondrial Damage (pp. 46–47).

Adjacent context: Mechanisms of Cell Injury, Membrane Damage, and Intrinsic Apoptosis.

Illustrations are original editable teaching schematics; no clinical or histologic specimens are depicted.