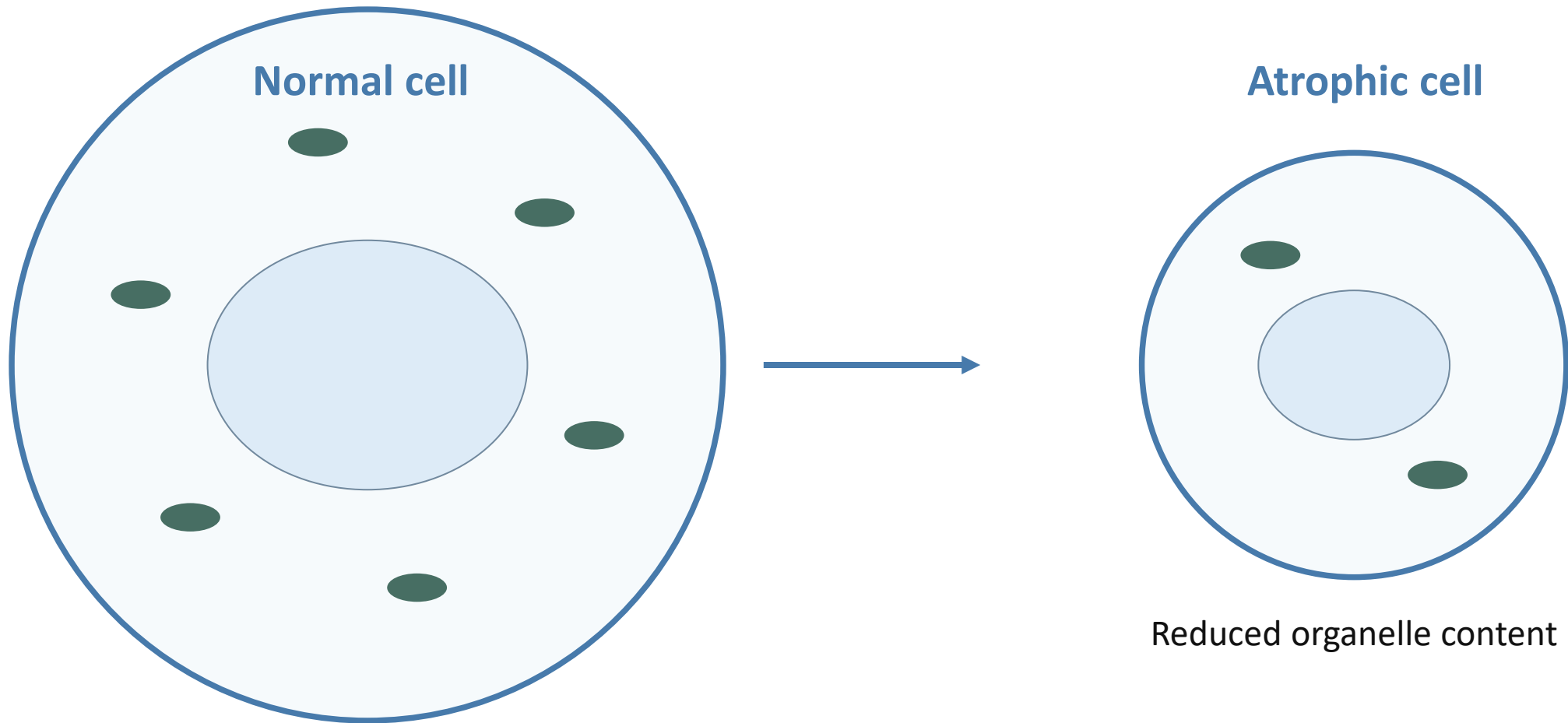


Mechanisms of Atrophy



Higher organelle content

Reduced organelle content

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Protein homeostasis shifts toward a smaller, metabolically economical cell

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Learning objectives

- Explain atrophy as an adaptive reduction in cellular size and sometimes cell number.
- Distinguish reduced protein synthesis from increased protein degradation.
- Trace the ubiquitin–proteasome and autophagy pathways.
- Connect the molecular mechanisms to disuse, cachexia, endocrine withdrawal, and morphologic changes.

Atrophy: The defining structural change

- Atrophy reduces the size of an organ or tissue through smaller cells and, with progression, fewer cells.
- Early atrophy commonly reflects shrinkage of surviving cells rather than immediate cell death.
- The decreased structural mass typically accompanies diminished metabolic and functional activity.

Atrophy may be physiologic or pathologic

Physiologic involution

Occurs as part of normal development.

Robbins examples: Notochord and thyroglossal duct involution.

A regulated tissue-remodeling context.

Pathologic atrophy

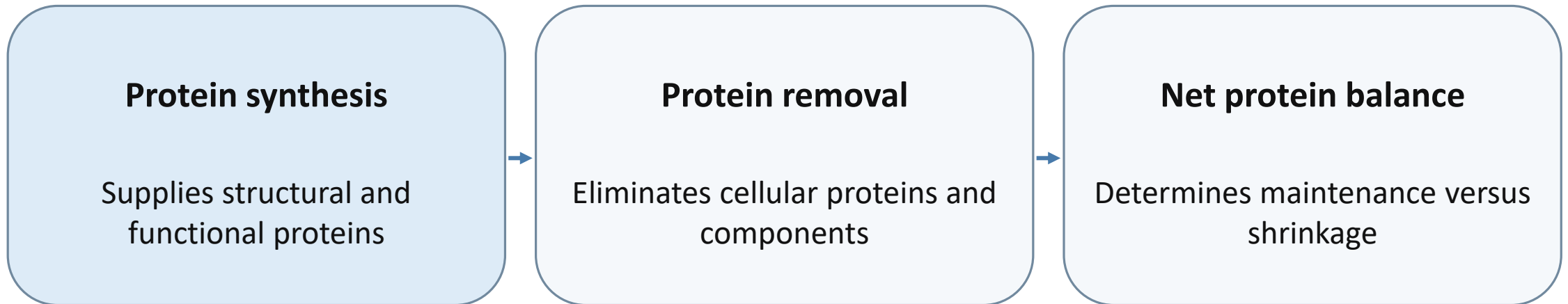
Occurs with inadequate workload, nutrients, blood supply, or trophic signals.

Can be localized or generalized.

May eventually include apoptosis.

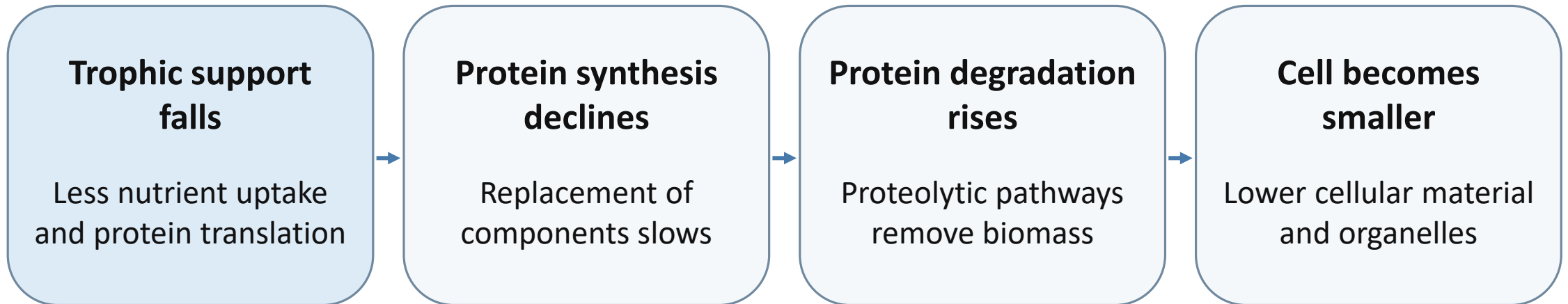
Protein balance determines cellular size

Two opposing processes normally maintain cellular biomass



Schematic

The two central changes in atrophy



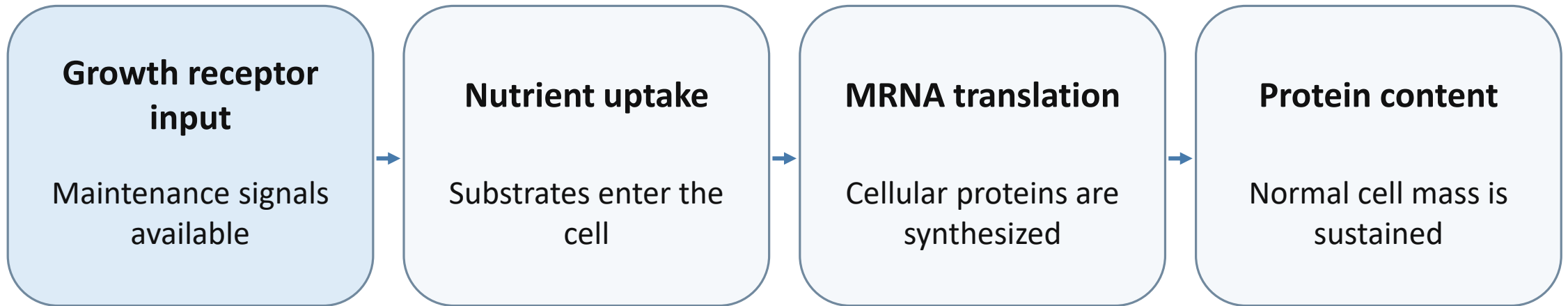
Schematic

Reduced trophic signaling: An upstream trigger

- Trophic signals support cellular growth and maintenance.
- Growth receptor signaling enhances nutrient uptake and mRNA translation.
- Withdrawal of trophic stimulation therefore reduces the supply of newly synthesized proteins.

Growth signals connect environment to proteins

Loss of one or more inputs can shift the balance toward atrophy



Schematic

Protein synthesis falls when input is inadequate

- Diminished nutrient availability limits the material needed to sustain cellular proteins.
- Reduced growth receptor–dependent trophic signals diminish translation.
- Even without extensive cell death, reduced synthesis permits gradual shrinkage as proteins turn over.

Cell maintenance versus atrophic adaptation

Adequate support

Protein synthesis is maintained.

Normal cellular structures are replenished.

Cell size and functional capacity are preserved.

Inadequate support

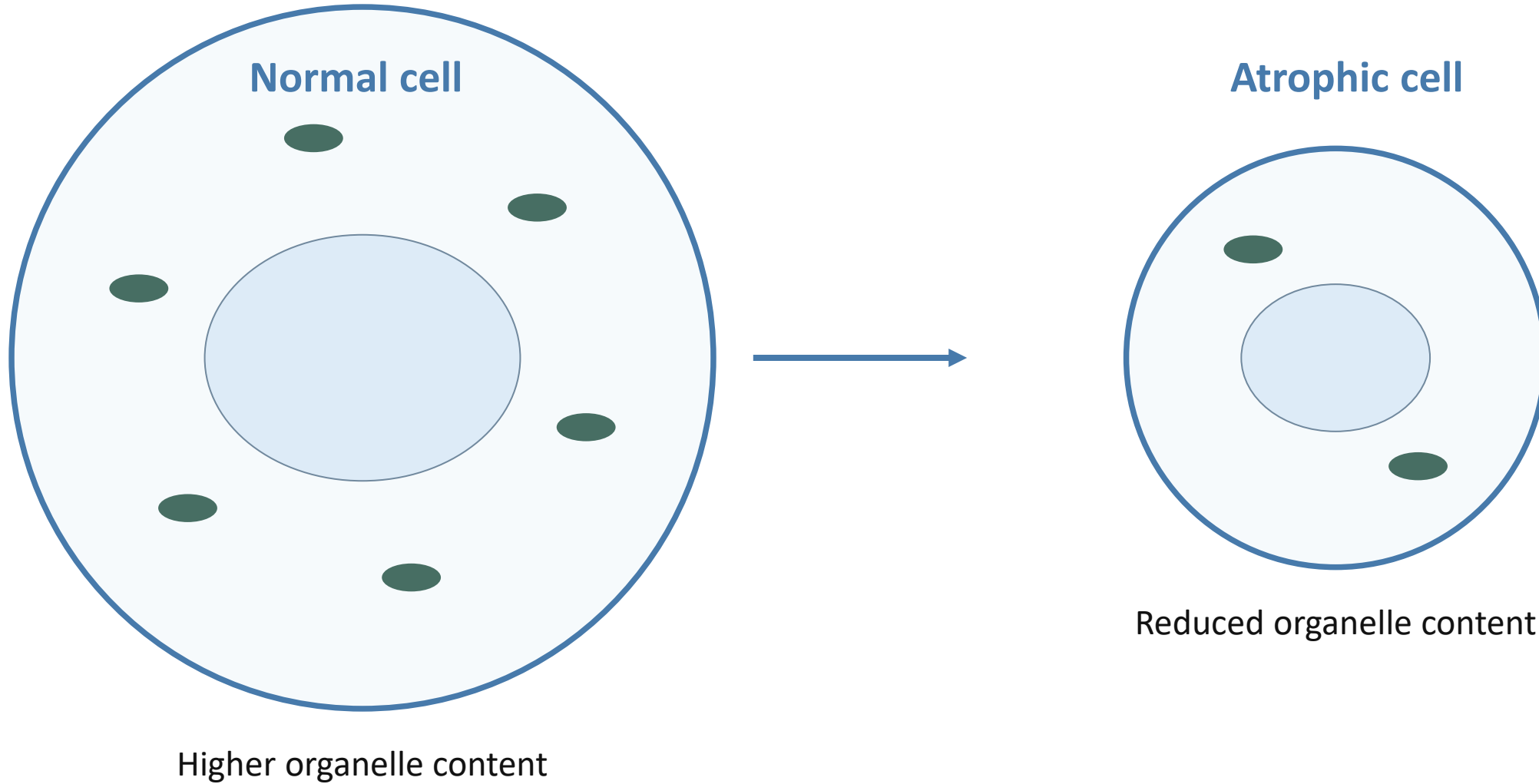
Protein replenishment decreases.

Degradation exceeds synthesis.

Cell size and energy demand decrease.

Atrophy is a change in cellular steady state, not necessarily immediate irreversible injury.

Cells adapt by reducing their structural inventory



Original simplified cell schematic — not a photomicrograph

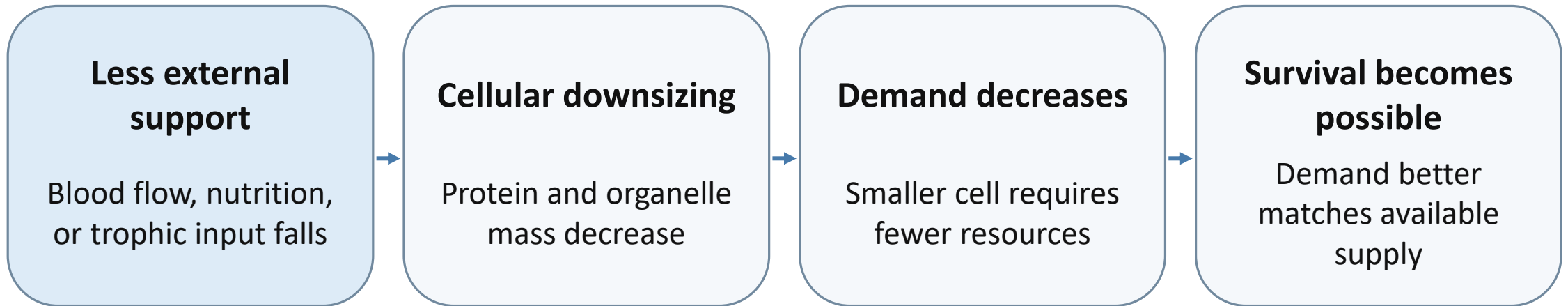
Why fewer organelles help an atrophic cell

- Mitochondria, rough endoplasmic reticulum, and other components impose maintenance costs.
- Lower organelle content reduces the resource demands of the cell.
- The smaller cell may remain viable despite diminished nutrition or trophic input.

Atrophic skeletal muscle: Ultrastructural changes

- Skeletal muscle fibers contain fewer mitochondria.
- Myofilament content decreases as fiber size falls.
- Rough endoplasmic reticulum is reduced.
- These changes help explain reduced muscle bulk and contractile function.

Adaptive downsizing restores a new equilibrium



Schematic

Early atrophy is often a survival response

- Atrophic tissues initially function less well, but cell death can be minimal.
- Reduced cell size conserves limited metabolic resources.
- Survival reflects a new balance between available support and maintenance demands.

Early versus advanced atrophy

Early adaptive phase

Smaller cells are still viable.

Cell function is reduced.

Potential to recover when the stressor is relieved.

Advanced/prolonged injury

Some cells may be lost by apoptosis.

Tissue mass may decline from both shrinkage and cell loss.

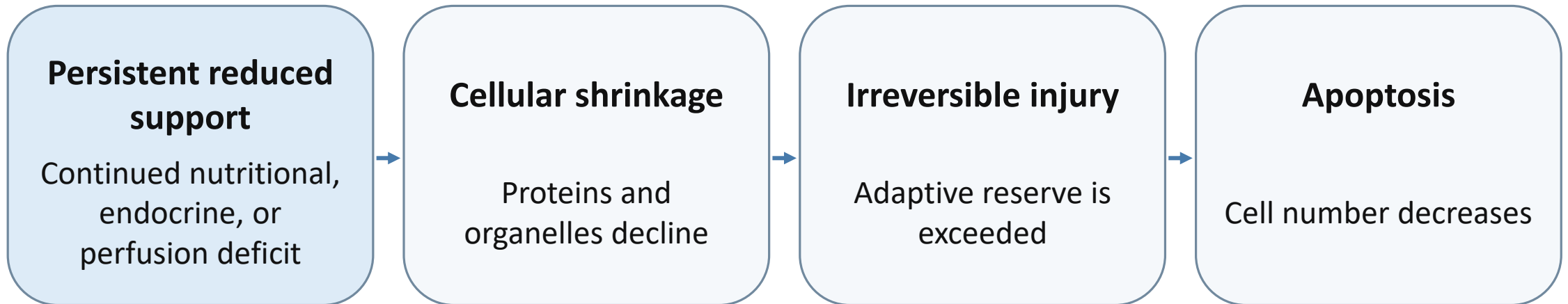
Not every component is readily reversible.

Reversibility depends on injury duration and severity

- The initial decrease in skeletal-muscle cell size during disuse can reverse when activity resumes.
- Prolonged disuse is associated with muscle-fiber loss as well as smaller fibers.
- Chronic severe ischemia may pass from adaptation to irreversible cell injury.

Prolonged stress may culminate in cell loss

The last two stages are possible outcomes—not inevitable in every case

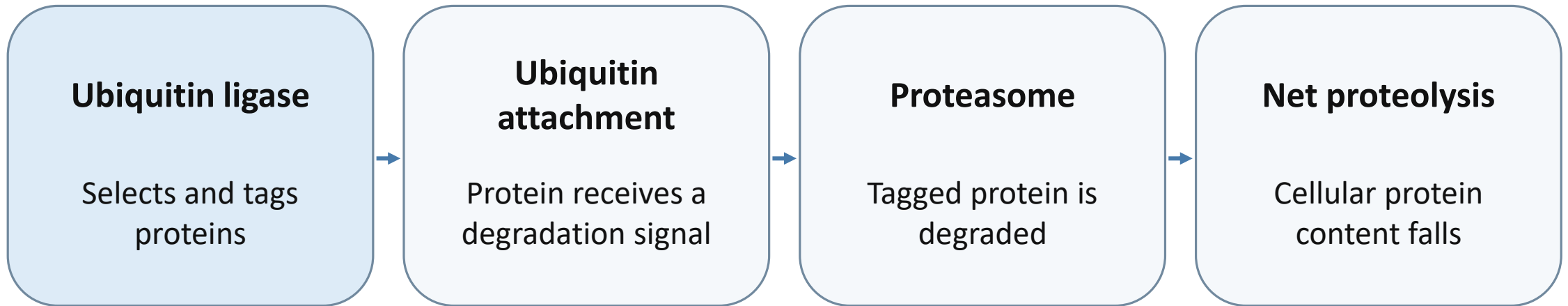


Schematic

Protein degradation: The other half of atrophy

- A decrease in synthesis alone does not describe the full atrophic response.
- Increased protein degradation as a central companion process.
- The principal route for degrading cellular proteins is the ubiquitin–proteasome pathway.

Ubiquitin–proteasome pathway: Overview



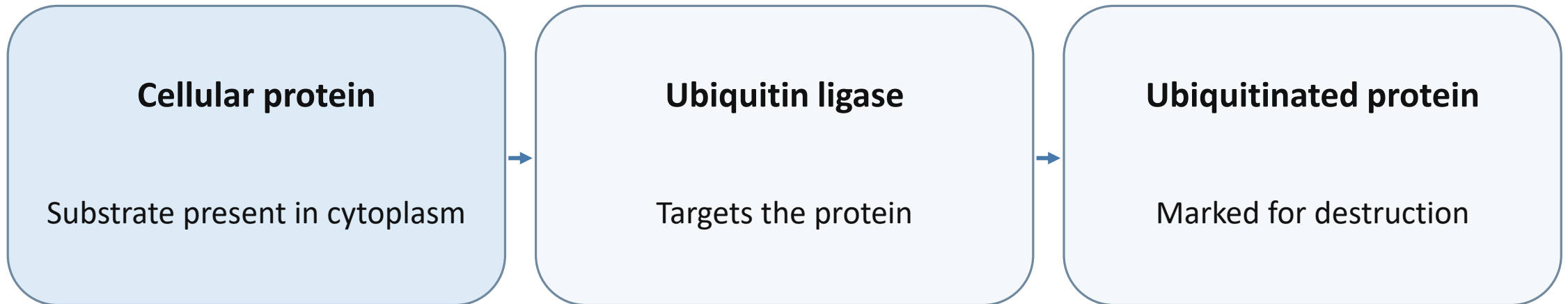
Schematic

Ubiquitin marks proteins for destruction

- Ubiquitin is a small peptide attached to cellular proteins.
- Ubiquitin ligases carry out the targeting step.
- The tag directs the selected protein toward proteasomal degradation.

Ubiquitin ligases are the targeting step

The targeting step links upstream atrophic stimuli to protein removal



Schematic

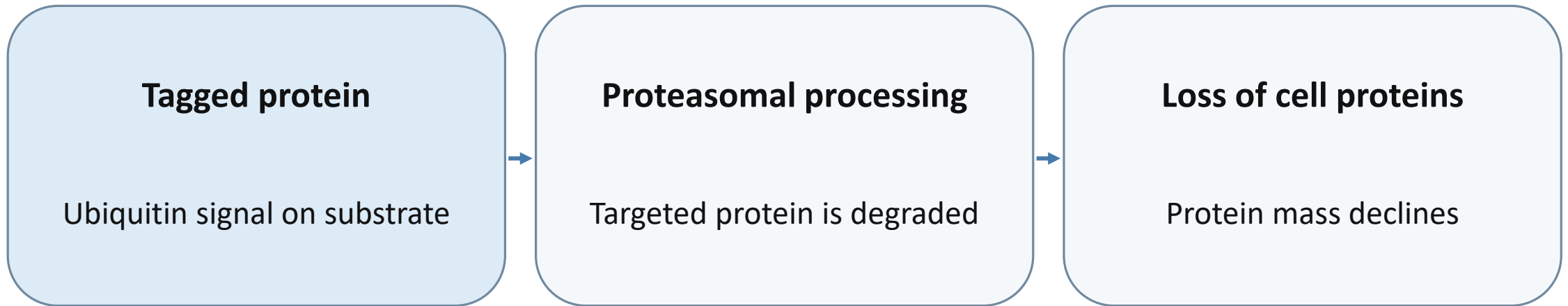
Disuse can promote proteolytic targeting

- Reduced workload is an established cause of tissue atrophy.
- In disuse, ubiquitin ligases may be activated.
- Increased tagging and removal of proteins contributes to reduced muscle-fiber content.

Nutrient deficiency also promotes proteolysis

- Nutrient deficiency can activate ubiquitin ligases.
- Protein catabolism supplies substrates when normal energy reserves are insufficient.
- Skeletal muscle wasting in severe nutritional deficiency reflects this broader catabolic state.

Proteasomes execute the degradation signal



Schematic

Synthesis and ubiquitin-mediated breakdown differ

Reduced synthesis

Less replenishment of cell proteins.

Linked to diminished trophic stimulation.

Alters the input side of protein balance.

Increased breakdown

Greater removal of existing proteins.

Linked to ubiquitin ligase activation.

Alters the output side of protein balance.

Both mechanisms may operate simultaneously within an atrophying cell.

Disuse atrophy: From unloading to fiber loss

- Immobilization or prolonged bed rest reduces workload on skeletal muscle.
- Protein synthesis falls relative to degradation as muscle fibers shrink.
- With prolonged disuse, some muscle fibers may disappear by apoptosis.

Clinical correlation: Immobilized skeletal muscle

CLINICAL OBSERVATION

A limb remains immobilized in a cast. Its skeletal muscle becomes visibly smaller.

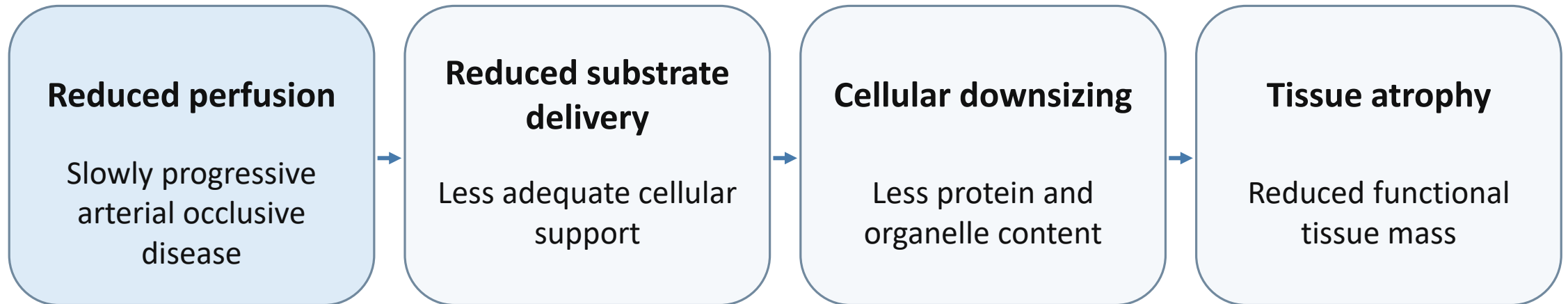
MECHANISTIC INTERPRETATION

- Lower workload favors atrophy of muscle fibers.
- Proteolytic pathways are important to the loss of protein mass.
- Early size loss may reverse when normal activity resumes.

Denervation atrophy: Loss of nerve-dependent support

- Normal skeletal-muscle metabolism and function depend on an intact nerve supply.
- Damage to supplying nerves causes the innervated muscle fibers to atrophy.
- The trigger differs from disuse, but decreased cellular maintenance is the shared outcome.

Chronic ischemia drives adaptive reduction in demand



Schematic

Cerebral atrophy: Gross consequences of tissue loss

- Cerebral atrophy associated with reduced blood supply in late adult life.
- Loss of brain substance narrows the gyri and widens the sulci.
- This gross description is an example of tissue-level effects; It does not identify a unique molecular cause.

Malnutrition and cachexia: Overlapping contexts

Profound malnutrition

Protein-calorie deficiency follows depletion of other reserves.

Muscle proteins become an energy source.

Marked skeletal-muscle wasting follows.

Cancer/chronic inflammation

Catabolic states can accelerate proteolysis.

Ubiquitin–proteasome pathway is implicated.

Reduced intake alone need not explain all wasting.

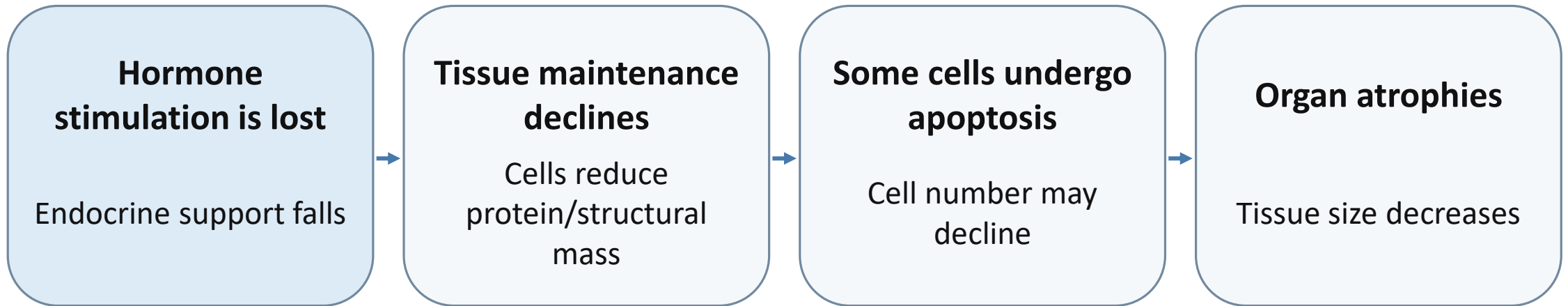
Cancer-related cachexia engages proteolytic pathways

- Accelerated proteolysis in cancer-related cachexia to the ubiquitin–proteasome pathway.
- Protein loss produces skeletal-muscle wasting in a systemic catabolic environment.
- The word “implicated” matters: The text states that the pathway is thought to contribute.

Inflammatory mediators can accompany wasting

- Some cachectic states involve chronic overproduction of TNF.
- TNF as a proposed contributor to appetite suppression and lipid depletion.
- These processes can culminate in muscle atrophy; The role described is context-dependent.

Endocrine withdrawal can initiate tissue atrophy



Schematic

Examples of hormone-dependent tissue atrophy

- After menopause, reduced estrogen stimulation is associated with atrophy of endometrium, vaginal epithelium, and breast.
- The prostate may atrophy after chemical or surgical castration.
- In endocrine organs, hormone withdrawal may be accompanied by apoptosis as well as cell shrinkage.

Pressure atrophy: Mechanical compression and perfusion

- Expanding lesions can compress surrounding uninvolved tissue.
- Pressure-induced atrophy probably to impaired local blood supply.
- In this setting, sustained compression is the initiating circumstance, whereas ischemia is the proposed intermediary.

Different triggers converge on common cell responses

Reduced support or use

Disuse or denervation

Nutrient deficiency

Reduced blood supply

Altered regulation or environment

Hormone withdrawal

Mechanical compression

Systemic catabolic signals

Distinct causes converge on protein turnover, organelle loss, and sometimes apoptosis.

Autophagy: Intracellular self-digestion

- Autophagy delivers cytoplasmic material to lysosomes for degradation.
- The process can eliminate organelles and cellular debris.
- During nutrient deprivation, recycled material helps the stressed cell survive.

Proteasome and autophagy are distinct routes

Ubiquitin–proteasome

Targets selected cellular proteins.

Ubiquitin tagging guides degradation.

Principal route for protein breakdown in atrophy.



Autophagy–lysosome

Sequesters cytoplasmic material.

Can remove organelles and aggregates.

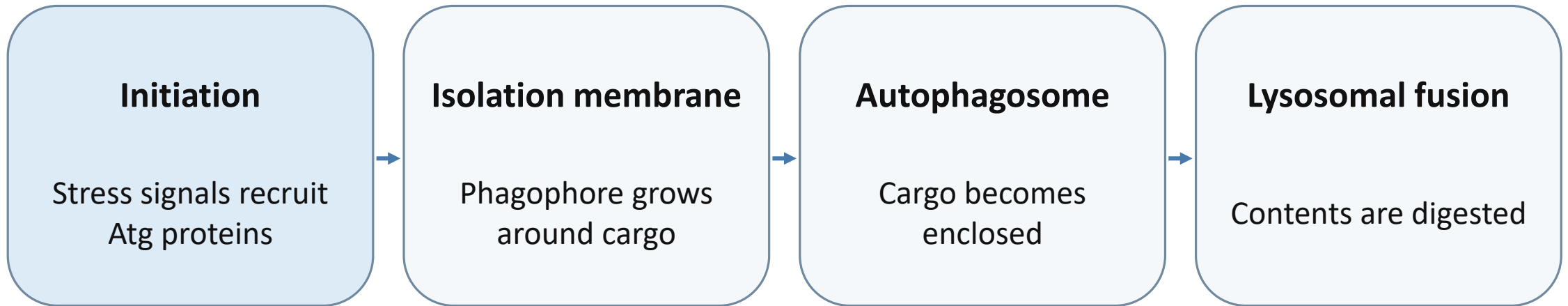
Often increases alongside atrophy.

Both routes change cellular composition; Their cargo and machinery differ.

Autophagy is induced by cellular stress

- Nutrient deprivation and growth factor depletion can activate the pathway.
- Autophagy also occurs with hypoxia, oxidative stress, and organelle or membrane damage.
- Its prominence in atrophic cells reflects a survival strategy under limited resources.

Autophagy proceeds through coordinated stages



Schematic

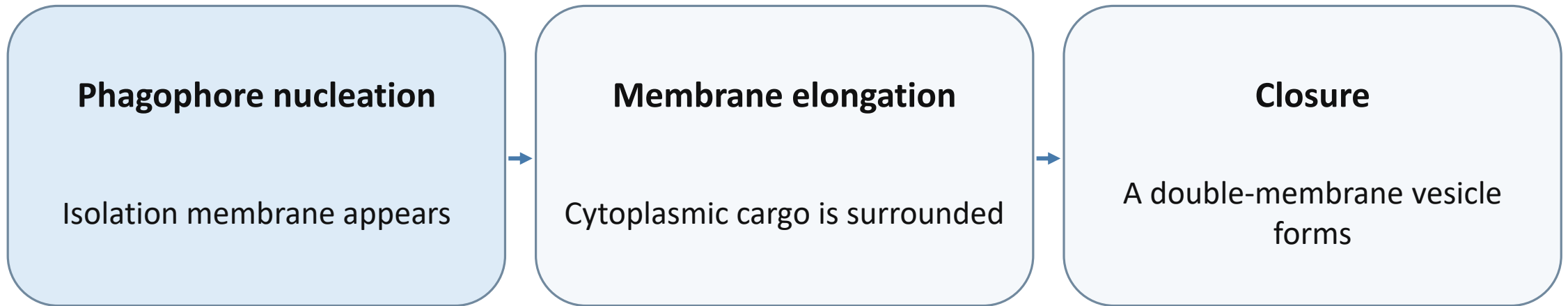
Autophagy-related proteins organize initiation

- Products of more than 30 Atg genes have been identified in the text.
- Environmental cues activate an initiation complex.
- Atg proteins are recruited hierarchically to organize the nascent isolation membrane.

The phagophore is the isolation membrane

- A nascent membrane surrounds selected cytoplasmic material.
- The membrane is believed to derive from the endoplasmic reticulum.
- Other membranes, including the plasma membrane and mitochondria, may also contribute.

Membrane elongation encloses cellular cargo



Schematic

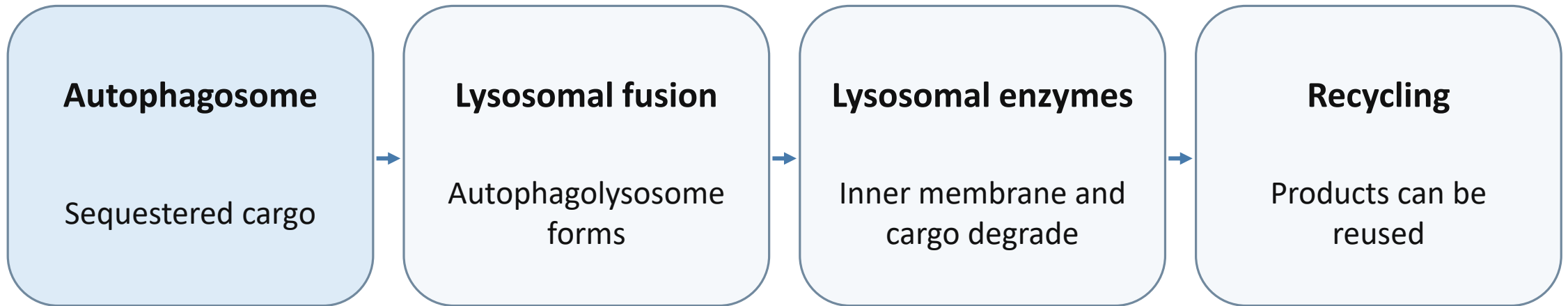
LC3 lipidation participates in vesicle formation

- Autophagy uses coordinated ubiquitin-like conjugation systems.
- These promote covalent attachment of phosphatidylethanolamine (PE) to LC3.
- Lipidated LC3 increases during autophagy and is useful for identifying cells in which the process is occurring.

Autophagosomes are not empty vacuoles

- Newly formed autophagosomes sequester cytosol and organelles.
- Their double-membrane boundary separates cargo from the remaining cytoplasm.
- The cargo is delivered for subsequent lysosomal breakdown.

Fusion with lysosomes permits digestion



Schematic

Autophagy supplies metabolites during starvation

- Cellular constituents are digested into reusable products.
- Recycling helps maintain essential functions despite external nutrient deprivation.
- This explains why self-digestion can promote cellular survival rather than simply signal death.

Autophagy also supports organelle quality control

- The pathway contributes to turnover of endoplasmic reticulum, mitochondria, and lysosomes.
- It helps clear intracellular aggregates that accumulate in aging and stress.
- Cargo loading is selective rather than indiscriminate, according to the source.

Atrophy and autophagy are related but not synonymous

Atrophy

A tissue/cellular response: Reduced cellular mass.

Protein synthesis decreases and degradation increases.

May involve autophagy, proteasomes, and apoptosis.

Autophagy

A degradation-and-recycling pathway.

Forms autophagosomes and engages lysosomes.

Also operates outside atrophy and during normal stress responses.

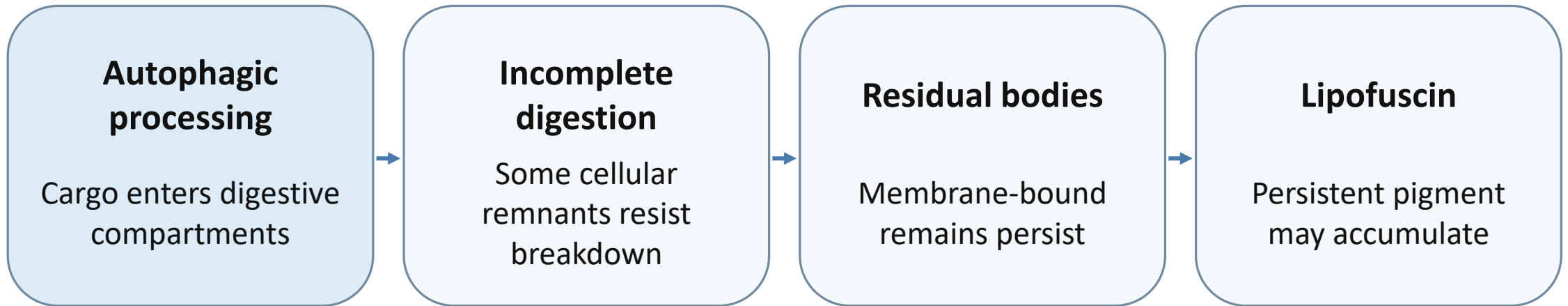
Autophagic vacuoles increase in many atrophic cells

- Increased autophagy in many settings of atrophy.
- Atrophic cells may show greater numbers of autophagic vacuoles.
- This observation aligns with the ongoing removal and recycling of intracellular constituents.

Residual bodies: Incomplete degradation

- Some material within autophagic compartments resists digestion.
- Indigestible residue may persist within membrane-bound cytoplasmic bodies.
- These persistent structures are termed residual bodies.

From autophagic turnover to residual pigment

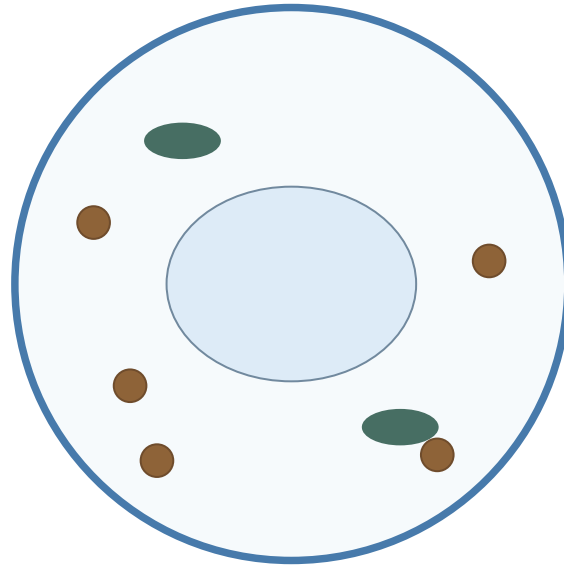


Schematic

Lipofuscin is an example of residual bodies

- Lipofuscin granules as a persistent residual material.
- These granules may remain in the cytoplasm after autophagic digestion.
- Accumulated lipofuscin reflects persistent intracellular residue rather than an active protein synthesis product.

Brown atrophy: Pigment adds a visible change



Reduced organelle content

Schematic only: Brown discoloration reflects sufficient accumulation of lipofuscin

What “brown atrophy” does—and does not—mean

- Brown discoloration may occur when lipofuscin accumulates in sufficient amounts.
- The pigment accompanies atrophy; It is not the defining cause of cell shrinkage.
- The degree of brown color alone is not a quantitative readout of proteolysis.

Atrophy is distinct from cell death

Cellular atrophy

The surviving cell becomes smaller.

Protein and organelle content decline.

Often an adaptive response to low support.

Apoptotic cell loss

Cells are eliminated, reducing cell number.

Can emerge after prolonged disuse or severe ischemia.

Also contributes after hormone withdrawal.

Applied case: Cancer-associated wasting

CLINICAL OBSERVATION

A patient with cancer develops progressive loss of skeletal-muscle mass.

MECHANISTIC INTERPRETATION

- A systemic catabolic state can accelerate proteolysis.
- Robbins implicates ubiquitin–proteasome protein degradation.
- Autophagy may coexist; No single process should be assumed to explain all wasting.

Applied case: Endocrine organ involution

CLINICAL OBSERVATION

After withdrawal of hormonal stimulation, a previously hormone-responsive tissue becomes smaller.

MECHANISTIC INTERPRETATION

- Diminished trophic support reduces cell maintenance.
- Cells may shrink as protein balance changes.
- Apoptosis can contribute to a reduction in cell number.

A mechanistic checklist for interpreting atrophy

Ask about the trigger

Is workload or innervation reduced?

Is perfusion or nutrition inadequate?

Is endocrine/trophic stimulation withdrawn?

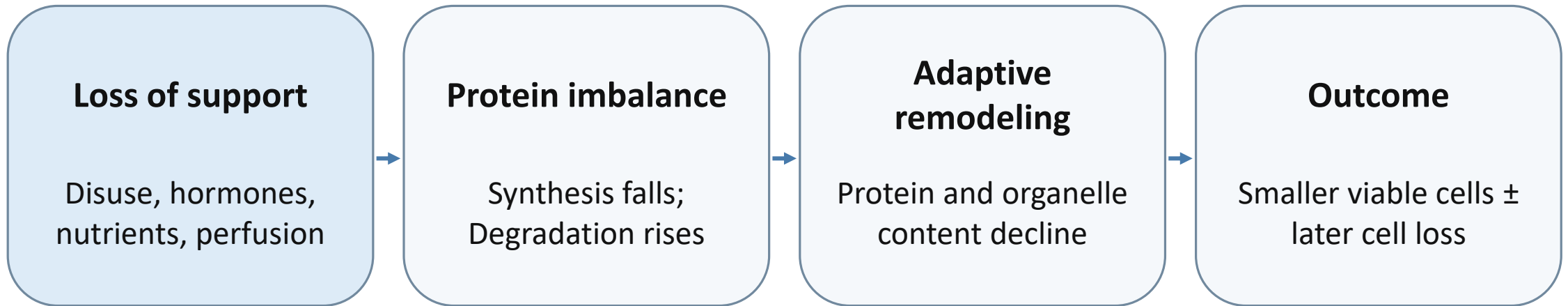
Ask about the cellular response

Does protein synthesis decrease?

Is ubiquitin-mediated degradation increased?

Is autophagy evident; Has apoptosis occurred?

Integrative model: Causes converge on shrinkage



Schematic

Five statements to retain

- Atrophy is primarily a change in cellular biomass, not necessarily immediate cell death.
- Reduced trophic signaling decreases nutrient uptake and protein synthesis.
- Ubiquitin ligases and proteasomes provide a major degradation pathway.
- Autophagy removes and recycles cell contents; Indigestible residue may persist as lipofuscin.
- Severe or prolonged stress can culminate in apoptosis and irreversible loss of tissue.

Primary reference and source boundaries

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026).
- Chapter 2: “Atrophy” and “Mechanisms of Atrophy,” printed pages 54–55.
- Chapter 2: “Autophagy,” printed pages 34–35; text and the accompanying mechanism description.
- All figures in this lecture are original editable schematics, not reproductions of textbook or patient specimens.