

Cellular Waste Disposal:

Lysosomes and Proteasomes

Intracellular catabolism, protein quality control, and cellular recycling

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Learning outcomes

By the end of the session, explain:

- How lysosomal acid hydrolases reach their destination
- How endocytosis, phagocytosis, and autophagy deliver cargo
- How ubiquitin targets proteins for proteasomal degradation
- Why defects in intracellular disposal cause cellular dysfunction
- How these mechanisms connect to selected diseases

Cellular housekeeping is an active process

Cells must remove, remodel, and reuse material continuously.

Catabolism supports proteostasis, organelle renewal, and resource recovery.

- Waste can originate outside or inside the cell
- Distinct pathways handle particles, organelles, and proteins

What needs to be degraded?

Substrate origin and physical scale help determine the disposal route.

Extracellular cargo

Internalized molecules, fluid
and debris

Cellular structures

Aged or damaged organelles

Proteins

Denatured, misfolded and
short-lived regulatory proteins

Two complementary intracellular degradation systems

Lysosomal degradation

Membrane-delimited cargo; Endosomes, phagosomes, autophagosomes



Hydrolytic enzymes

Acid hydrolases

Proteasomal degradation

Predominantly selected cytosolic proteins; Ubiquitin-dependent targeting



Proteolytic core

Proteasome

Both systems support cellular quality control and nutrient recycling.

Three routes converge on lysosomal digestion

Endocytosis

External molecules / fluid



Phagocytosis

Large particles / microbes



Autophagy

Internal organelles / complexes



Lysosome

Hydrolysis → breakdown products → salvage

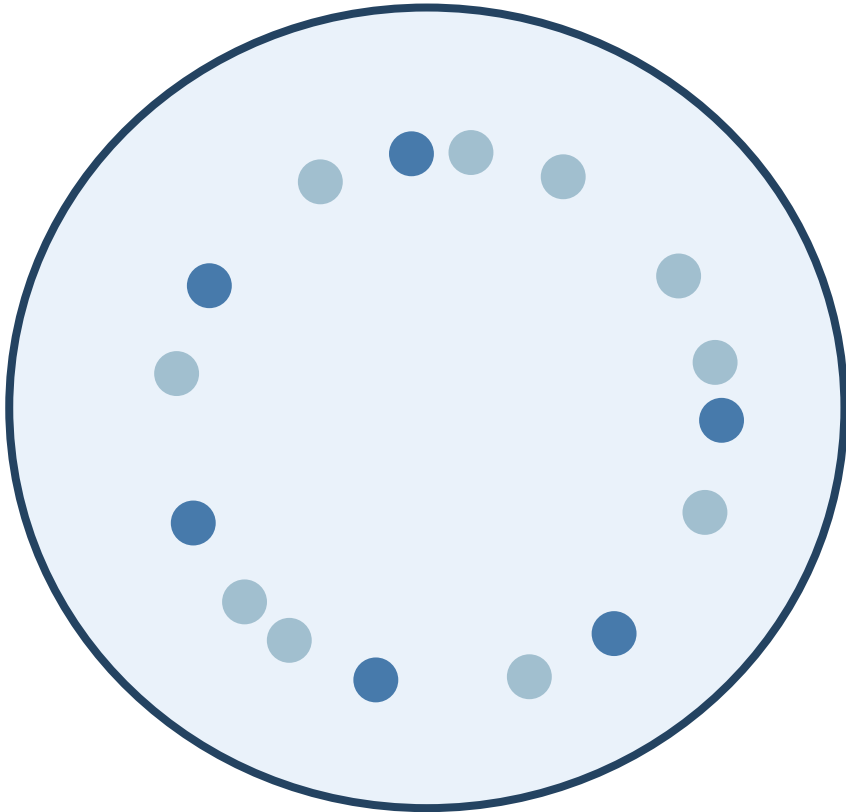
Lysosomes contain acid hydrolases

Approximately 40 types of hydrolases operate in the lysosomal lumen.

These enzymes break complex substrates into smaller recoverable products.

- A membrane maintains a distinct digestive compartment
- An acidic lumen optimizes enzyme activity

The lysosome: An acidic digestive compartment



LYSOSOMAL LUMEN

Acidic environment ($\approx$ pH 5)

- Multiple classes of acid hydrolases
- Membrane-enclosed catabolism
- Products can be recycled by the cell

Major families of lysosomal hydrolases

Different substrate chemistries require different hydrolytic activities.

Proteases

Digest proteins

Nucleases

Digest nucleic acids

Lipases

Digest lipid substrates

Glycosidases

Cleave carbohydrate bonds

Phosphatases

Remove phosphate groups

Sulfatases

Remove sulfate groups

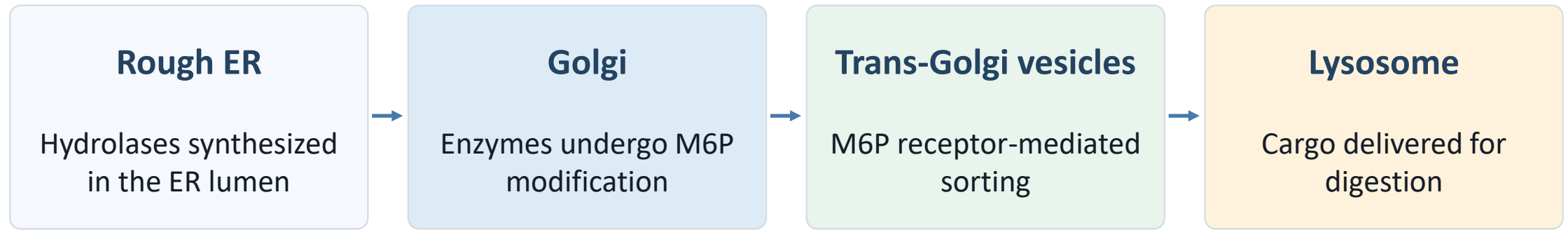
Why an acidic lumen matters

Lysosomal enzymes function optimally at approximately pH 5.

Endosomal compartments become progressively more acidic along the transport route.

- Enzyme activation is coupled to organelle maturation
- Compartmentalization helps localize digestive activity

Lysosomal enzymes begin in the secretory pathway



Lysosomal hydrolases have to be synthesized and correctly trafficked before they can act.

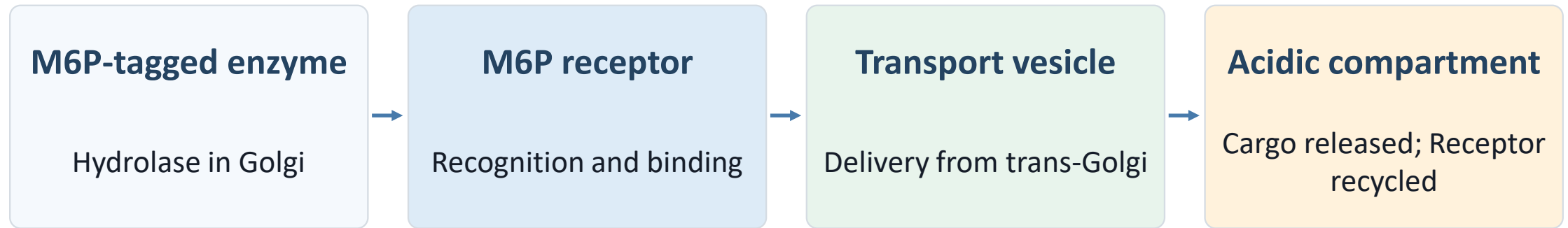
Mannose-6-phosphate is a sorting address

M6P marks newly synthesized lysosomal hydrolases.

This modification is placed on the enzymes in the Golgi apparatus.

- The M6P tag provides a recognition signal
- A defect in the address can disrupt delivery despite enzyme synthesis

M6P receptors mediate lysosomal enzyme delivery



Correct protein sorting is as important as catalytic enzyme synthesis.

Two different lysosomal failure mechanisms

Defect	Immediate event	Result
Catalytic enzyme defect	Hydrolase missing or inactive	Specific substrate cannot be digested
M6P tagging defect	Hydrolases misdirected	Many lysosomal enzymes fail to reach target

Clinical principle: Sorting defects mimic enzyme deficiencies

M6P pathway failure can deprive lysosomes of multiple hydrolases.

Illustrative correlation: I-cell disease (mucopolidosis II).

- Failure to create the recognition marker causes enzyme misdirection
- The enzymes may be secreted instead of targeted to lysosomes

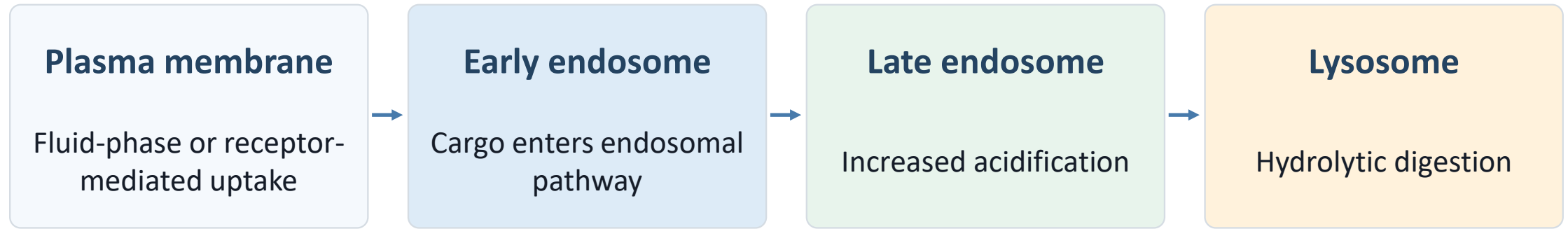
Heterophagy begins with material outside the cell

The cell internalizes external cargo and transfers it to lysosomes.

Endocytosis and phagocytosis are complementary routes.

- Endocytosis conveys soluble cargo and small vesicular contents
- Phagocytosis handles large particles and microorganisms

Endocytosis routes soluble material toward lysosomes



The material has crossed the plasma membrane before reaching the lysosome.

Fluid-phase versus receptor-mediated endocytosis

Fluid-phase uptake

- Bulk sampling of surrounding fluid
- Internalization does not require a specific cargo receptor
- Material enters endosomal compartments

Receptor-mediated uptake

- Cell-surface receptor binds selected ligand
- Allows selective concentration of cargo
- Material enters endosomal compartments

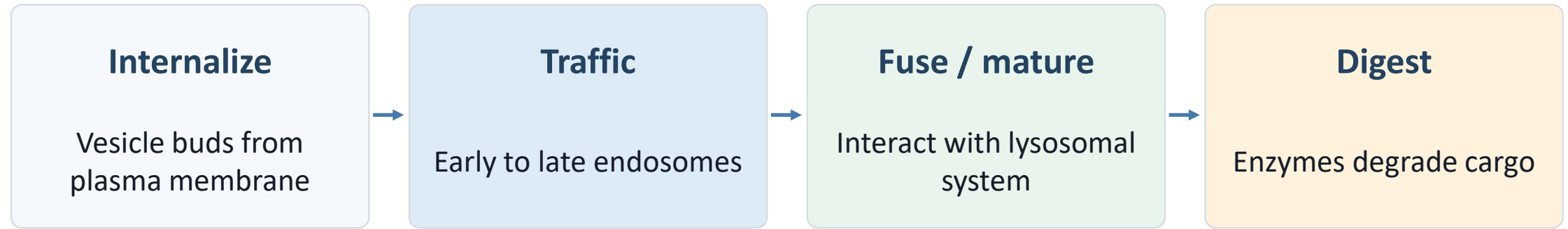
Endosome maturation couples transport to acidification

Early endosome → late endosome → lysosome.

Proteolytic enzymes become increasingly active in later acidic compartments.

- Transport and maturation are linked events
- The lysosome is the final digestive destination

Heterophagic cargo reaches an endolysosomal compartment



The endolysosomal pathway coordinates uptake, sorting and degradation.

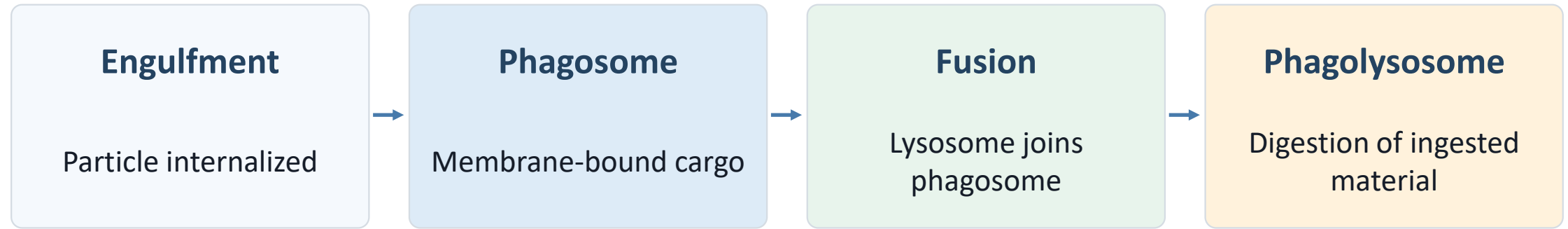
Phagocytosis handles large particles

Professional phagocytes engulf microorganisms and bulky debris.

Macrophages and neutrophils are principal examples.

- The engulfed material first resides in a phagosome
- The phagosome subsequently interacts with lysosomes

Phagocytosis ends in a phagolysosome



Vesicle fusion exposes internalized organisms or debris to acid hydrolases.

Phagocytic cells couple uptake to degradation

Macrophages

- Recognize and ingest debris and microorganisms
- Contain a developed lysosomal system
- Clear extracellular material

Neutrophils

- Engulf microorganisms
- Deliver phagosome contents to degradative compartments
- Support immediate cellular defense

Endocytosis versus phagocytosis

Feature	Endocytosis	Phagocytosis
Typical cargo	Fluid or ligand-bound molecules	Large debris / microorganisms
Intermediate	Endosome	Phagosome
Terminal digestion	Lysosomal compartment	Phagolysosome
Typical cells	Many cell types	Macrophages; Neutrophils

Autophagy is lysosome-directed self-digestion

Cytoplasmic structures are sequestered for subsequent lysosomal degradation.

Unlike heterophagy, the cargo initially resides inside the cell.

- Aged or damaged organelles can be removed
- Large cytosolic complexes can also be eliminated

Signals associated with autophagy

The pathway serves both routine quality control and stress adaptation.

Nutrient depletion

Recycling helps support survival

Intracellular stress

Damaged structures require turnover

Infection-related stress

Autophagy contributes to protective responses

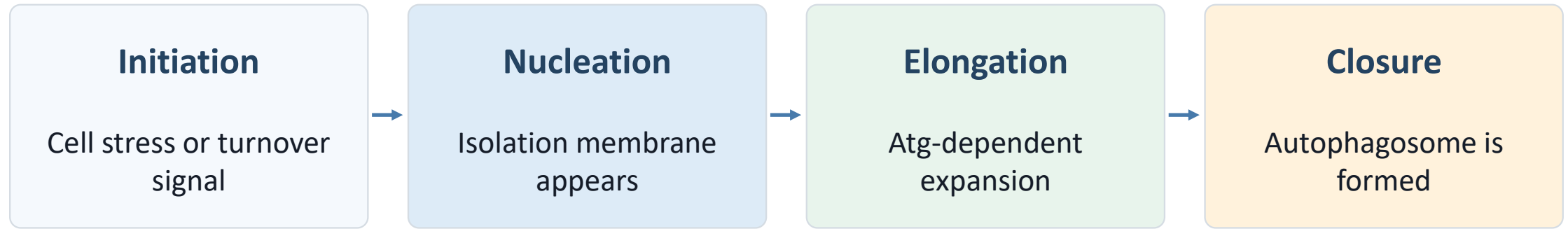
Autophagy begins with an isolation membrane

A phagophore grows around selected cytosolic material.

The ER is an important membrane source description.

- Other cellular membranes may contribute to phagophore formation
- Sequestration precedes lysosomal fusion

Atg proteins coordinate autophagosome formation



Autophagy-related gene products organize the membrane remodeling steps.

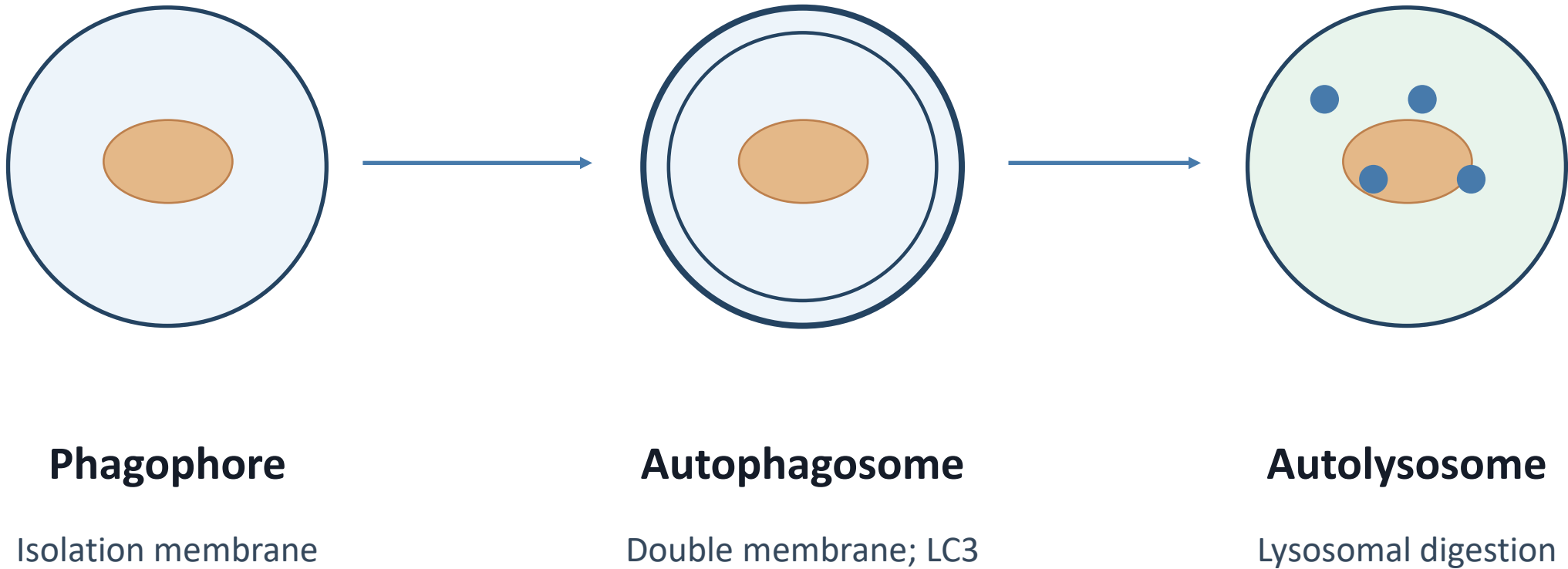
An autophagosome has a double membrane

The cargo becomes enclosed before lysosomal digestion begins.

The double-membrane vesicle is a defining morphologic stage.

- Cytosolic components lie within the enclosed compartment
- Fusion with a lysosome supplies degradative capacity

Autophagy: Encapsulate, fuse, digest



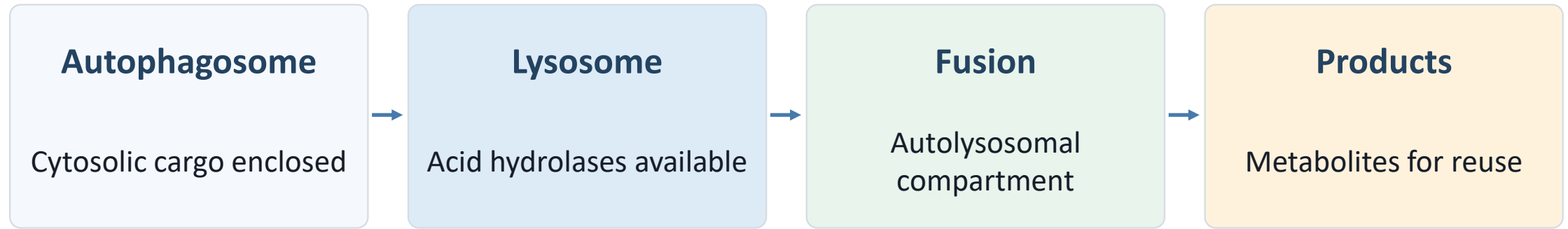
LC3 is associated with the autophagic membrane

Microtubule-associated protein light chain 3 (LC3) participates in autophagosome formation.

The textbook scheme depicts LC3 on the autophagic compartment.

- LC3 is a mechanistic marker in the source figure
- Its presence alone does not define the downstream endpoint of degradation

Autophagosome maturation enables digestion



The autophagosome does not digest cargo efficiently in isolation.

Autophagic degradation releases reusable metabolites

Lysosomal hydrolysis converts sequestered cargo into smaller molecules.

These can re-enter the cell's metabolic pools.

- Autophagy is therefore both degradative and salvage-oriented
- Recycling becomes especially relevant during nutrient deprivation

Starvation activates a nutrient-salvage response

Autophagy helps maintain cellular viability under nutrient stress.

Cells mobilize constituents that are no longer essential or functional.

- The pathway supplies metabolites from internal sources
- Survival benefit depends on the cellular context

Autophagy supports intracellular quality control

Defunct organelles and bulky protein complexes require organized clearance.

This removal limits persistence of damaged cellular structures.

- Turnover is part of ordinary maintenance
- Impaired clearance can compound cellular injury

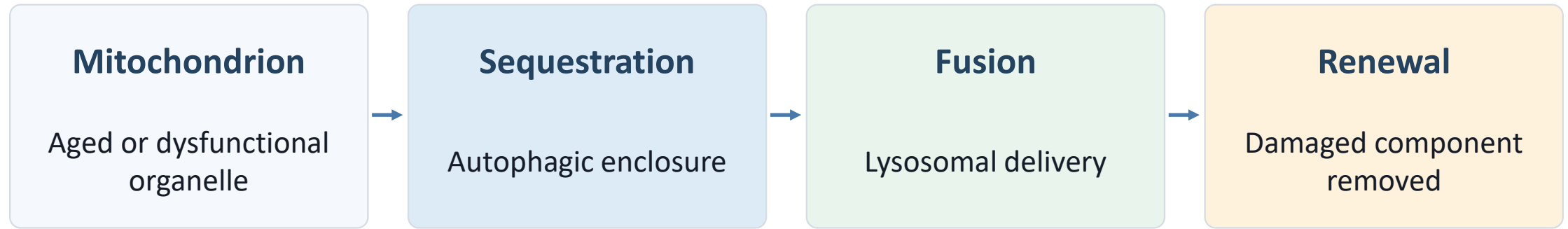
Mitophagy targets dysfunctional mitochondria

Mitochondrial turnover is a specialized form of autophagy.

Damaged mitochondria are delivered to lysosomes for degradation.

- Mitophagy is a mitochondrial quality-control pathway
- Defective clearance can allow dysfunctional mitochondria to persist

How mitophagy contributes to cellular health



Autophagy is not limited to protein digestion: Entire organelles can be recycled.

Autophagy also contributes to host defense

Some intracellular infections activate the autophagic pathway.

Infection response as one of its protective functions.

- Cargo is enclosed within an autophagic compartment
- Digestion ultimately requires lysosomal activity

Three lysosomal delivery routes: Final comparison

Route	Where cargo originates	Delivery intermediate
Endocytosis	Outside cell: Fluid or ligands	Endosome
Phagocytosis	Outside cell: Large particles	Phagosome
Autophagy	Inside cell: Organelles / complexes	Autophagosome

The lysosome is both a disposal and a recovery site

Hydrolytic products can return to the cytosol for reuse.

Lysosomal digestion does not necessarily mean permanent nutrient loss.

- Metabolite salvage supports cellular metabolism
- Some material can exit through lysosomal exocytosis

Lysosomal exocytosis provides an outward route

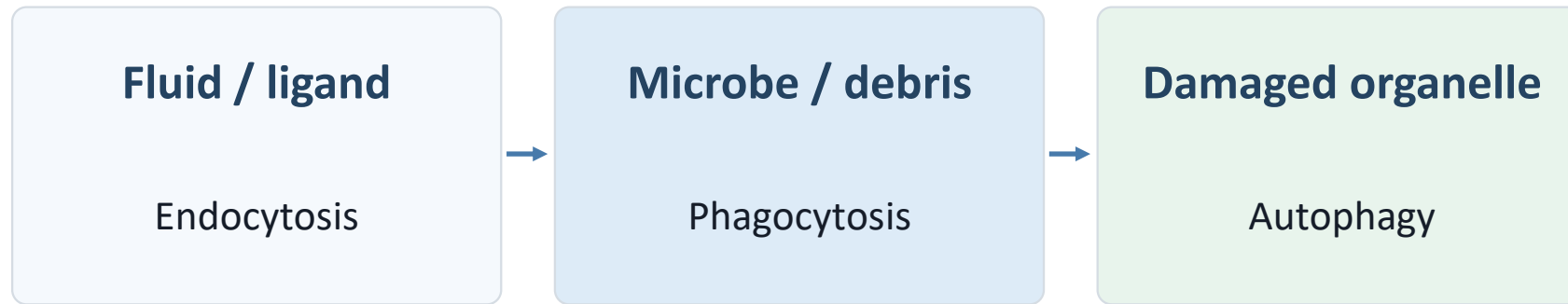
Lysosomal contents can be discharged into the extracellular space.

Both intracellular salvage and lysosomal exocytosis.

- Exocytosis differs from degradation occurring inside a lysosome
- Lysosomes participate in membrane dynamics as well as catabolism

Choose the lysosomal route by cargo origin

Cargo characteristics determine the entrance pathway.



All three pathways converge on acid hydrolase–mediated digestion.

Proteasomes degrade selected intracellular proteins

The proteasome is a cytosolic multisubunit proteolytic complex.

It handles misfolded proteins and proteins whose lifespan must be tightly controlled.

- Protein turnover is selective rather than indiscriminate
- Unlike autophagy, the canonical substrate is an individual protein

What proteins enter proteasomal degradation?

The pathway connects protein quality control with precise regulation.

Denatured proteins

Altered by stress or chemical injury

Misfolded proteins

Failed to achieve a stable conformation

Regulatory proteins

Molecules whose concentrations control signaling

A stressed protein can be rescued or degraded

Chaperone-assisted folding

- Chaperones assist nascent proteins in achieving useful conformation
- Successful folding permits continued protein function
- Quality control prevents unnecessary loss

Proteasomal disposal

- Persistent abnormal proteins are targeted for elimination
- Covalent ubiquitin labeling often precedes degradation
- Proteolysis avoids accumulation of defective proteins

Sources of protein denaturation

The degradation machinery disposes of proteins that cannot remain functional.

Age-related damage

Senescence-associated protein alterations

Heat or UV

Extrinsic physical stress

Reactive oxygen species

Oxidative injury

Chemical stress

Destabilization of folded conformations

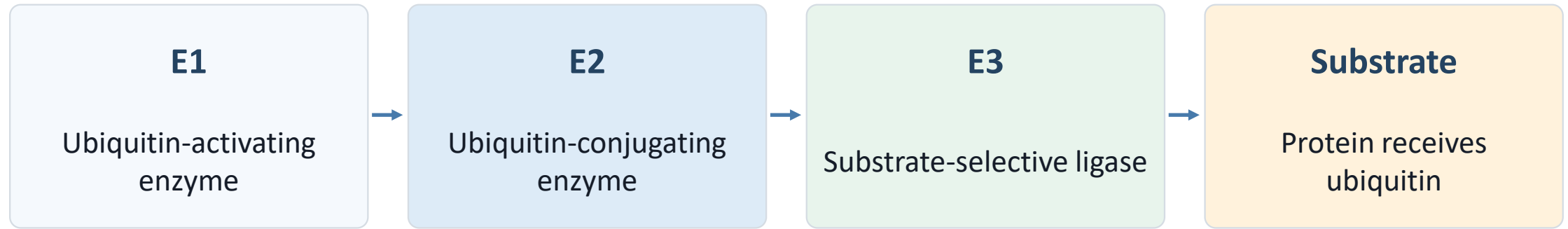
Ubiquitin serves as a degradation signal

A small protein, ubiquitin, is covalently attached to selected substrates.

Many proteasomal targets are recognized through polyubiquitin chains.

- Labeling is regulated by dedicated enzyme machinery
- Substrate selection helps control protein lifespan

Ubiquitin conjugation requires E1, E2 and E3



A multistep enzyme system allows regulated protein targeting.

E1 activates ubiquitin

The first stage prepares ubiquitin for transfer through the conjugation machinery.

E1 participates upstream of substrate-specific tagging.

- Activation is an enabling step rather than the final degradation event
- The proteasome acts after the targeting cascade

E2 conveys activated ubiquitin

E2 conjugating enzymes operate between E1 and E3 in the tagging system.

The sequential organization underlies ubiquitin transfer to selected targets.

- E2 contributes to ubiquitin transfer
- Targeting specificity depends substantially on the associated E3 machinery

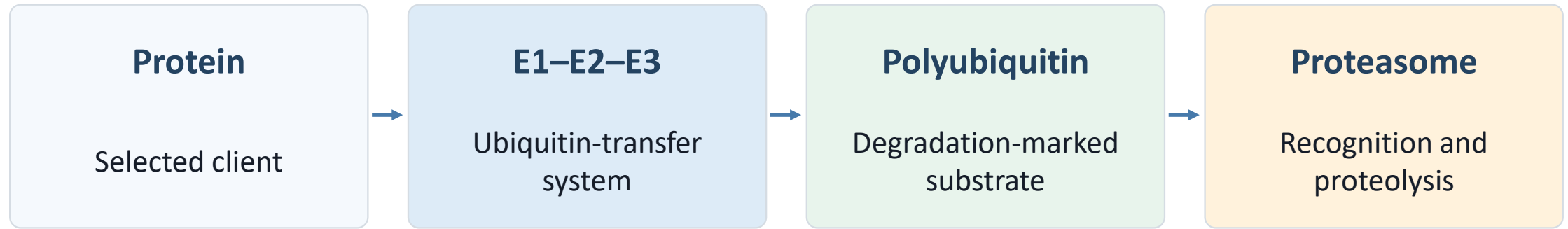
E3 ligases help select the protein substrate

E3 ligase activity links ubiquitin to the protein chosen for removal.

This step connects cell state and signaling to selective destruction.

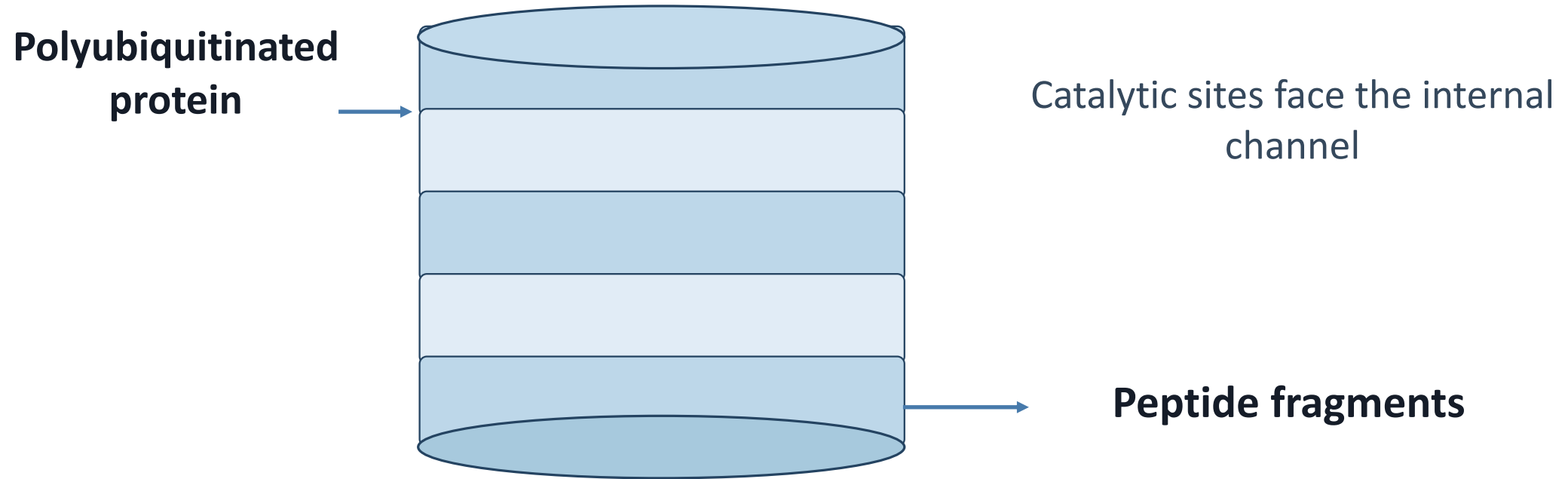
- Different proteins can have regulated lifespans
- Errors in targeting can alter steady-state protein abundance

Polyubiquitination licenses proteasomal turnover



The ubiquitin tag acts upstream of protein unfolding and proteolysis.

The proteasome: A proteolytic cylinder



Proteins are unfolded and threaded into the core

Proteasomal substrates are unfolded before digestion

Polyubiquitinated proteins are directed into the proteasome core.

Their polypeptide chains are threaded into the proteolytic cylinder.

- Catalytic sites face the hollow central core
- The compartment generates small peptide products

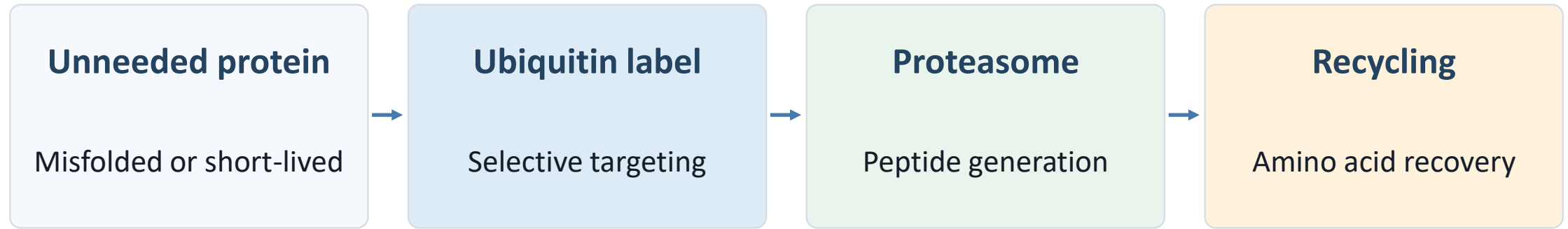
The proteasome produces short peptides

The source describes fragments of approximately 6–12 amino acids.

Further breakdown can release free amino acids for reuse.

- Proteolysis supports amino-acid recycling
- Fragment generation can also provide peptides for immune processing

Proteasomal protein turnover closes a recycling loop



This is primarily a protein-centered degradation route.

Proteasomal turnover regulates signaling

Destroying a regulatory protein can terminate or change a cell signal.

Transcription factors and signaling molecules are prominent examples.

- Protein half-life can modulate cellular responses
- Degradation is therefore a mechanism of regulation, not only waste removal

Proteasomal peptides contribute to antigen processing

Proteasome-derived peptides can enter the MHC class I presentation pathway.

This links cytosolic protein turnover to adaptive immune recognition.

- Antigen presentation is an additional use of generated peptides
- The processing pathway is conceptually distinct from bulk lysosomal digestion

Lysosomes and proteasomes: Distinct mechanisms

Characteristic	Lysosome	Proteasome
Primary cargo	Endocytic / phagocytic contents; Organelles	Selected intracellular proteins
Sorting route	Vesicle trafficking; Autophagy	Often ubiquitin labeling
Digestive machinery	Acid hydrolases	Core proteolytic activities
Physical context	Membrane-bound compartment	Multisubunit protein complex
Typical end products	Metabolites for salvage	Short peptides → amino acids

How to assign a substrate to its pathway

Cellular problem	Predominant route	Rationale
Ingested bacterium	Phagolysosome	Particle engulfment
Damaged mitochondrion	Autophagy–lysosome	Whole organelle removal
Short-lived transcription factor	Ubiquitin–proteasome	Regulated protein turnover
Internalized soluble ligand	Endosome–lysosome	Endocytic entry

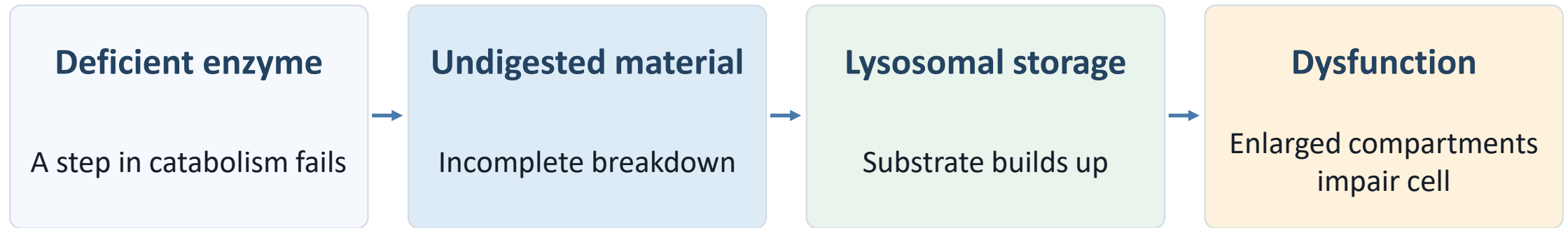
Clinical extension: Lysosomal storage disorders

A missing or nonfunctional lysosomal component causes incomplete substrate degradation.

Storage results when substrates accumulate within lysosomes.

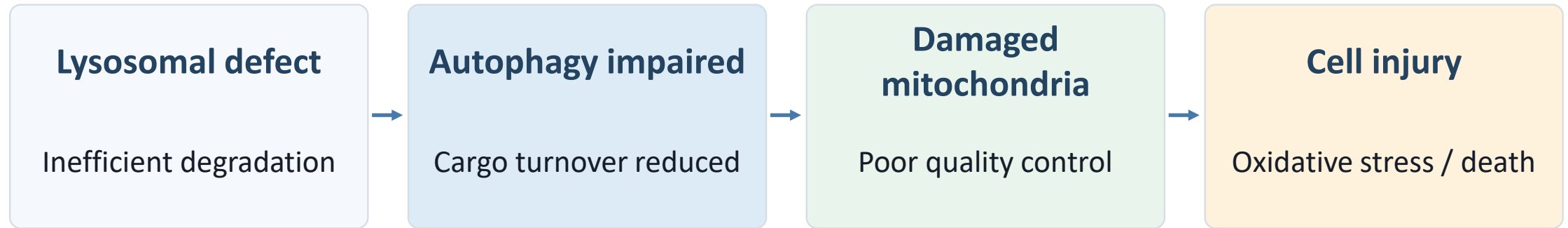
- This is a failure of catabolism, not excess substrate production alone
- Accumulation can compromise cellular function

Primary accumulation in lysosomal storage disorders



Stored material depends on which degradative step is impaired.

Secondary injury follows defective autophagic clearance

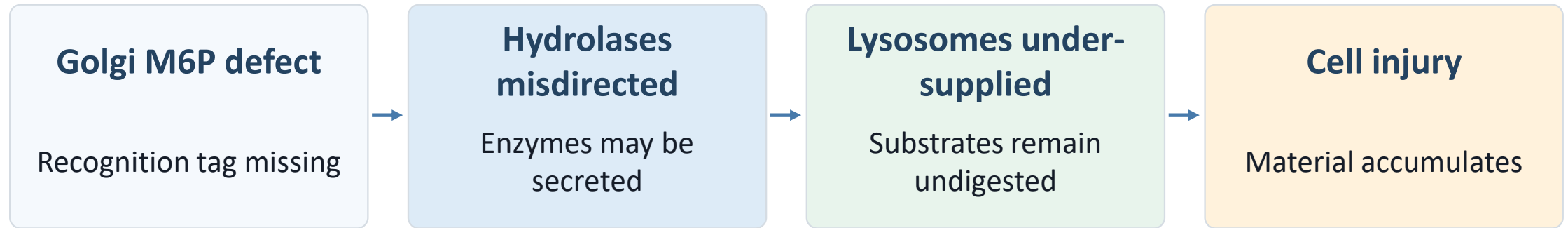


The source links primary lysosomal storage with secondary organelle and protein accumulation.

Why different storage disorders affect different organs

Stored substrate / function	Tissue consequence
Gangliosides enriched in neural tissue	Neuronal storage can predominate
Widely distributed mucopolysaccharides	Multisystem involvement
Macrophage-rich organs with stored substrates	Hepatic and splenic enlargement may occur

I-cell disease: A protein-sorting defect



This illustrates why intracellular trafficking is integral to lysosomal function.

Three mechanistic strategies in lysosomal storage disease

Therapeutic approaches illustrate the different failure points; Applicability is disease-specific.

Enzyme replacement

Supply functional activity

Substrate reduction

Lower the degradative load

Molecular chaperones

Stabilize eligible misfolded
enzyme variants

Clinical extension: Proteasome inhibitors in myeloma

Myeloma plasma cells synthesize large quantities of immunoglobulin chains.

Disturbed protein folding increases reliance on proteasomal disposal.

- Blocking the proteasome can cause misfolded proteins to accumulate
- The resulting stress can trigger apoptosis in susceptible cells

Application 1: Loss of lysosomal targeting

CLINICAL APPLICATION

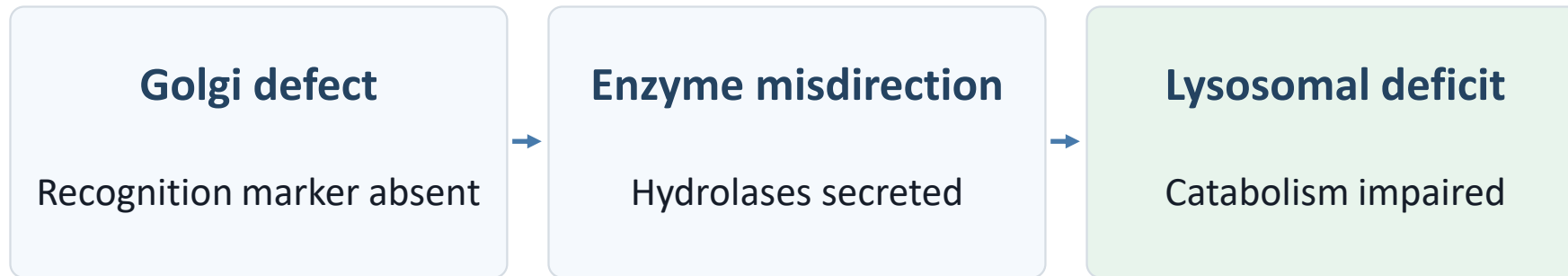
A cell synthesizes several acid hydrolases normally, but many fail to reach lysosomes and are secreted instead.

Which intracellular step is most directly defective?

- A. Tagging or recognition of mannose-6-phosphate
- B. E3-mediated ubiquitination
- C. Formation of phagosomes

Application 1: Mechanism explained

Correct answer: A — mannose-6-phosphate targeting



M6P-mediated trafficking is essential even when hydrolase synthesis is intact.

Application 2: Turnover of a regulatory protein

CLINICAL APPLICATION

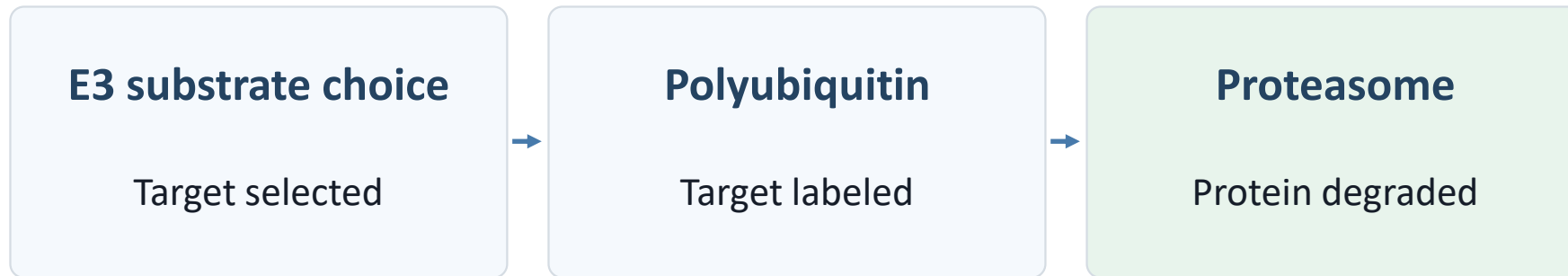
A transcription factor must be rapidly removed once a cellular signal terminates.

Which pathway best provides selective protein turnover?

- A. Phagocytosis followed by lysosomal fusion
- B. E1/E2/E3-directed proteasomal degradation
- C. Autophagy of an entire mitochondrion

Application 2: Mechanism explained

Correct answer: B — ubiquitin–proteasome pathway



Selective turnover is a key mechanism for adjusting signaling-protein abundance.

Application 3: Damaged mitochondria

CLINICAL APPLICATION

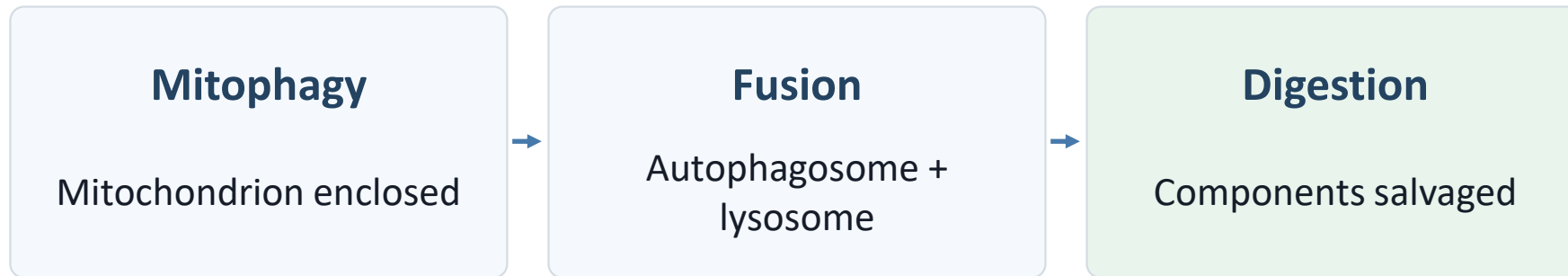
A stressed cell needs to remove a dysfunctional mitochondrion while recycling its constituent molecules.

Which pathway directly handles this whole-organelle cargo?

- A. Autophagy followed by lysosomal fusion
- B. Endocytosis of extracellular fluid
- C. Direct proteasomal entry of the organelle

Application 3: Mechanism explained

Correct answer: A — autophagic lysosomal turnover



Proteasomes act mainly on selected proteins, not intact organelles.

Essential points to retain

Cellular waste disposal is selective and compartmentalized:

- Lysosomes digest endocytic, phagocytic and autophagic cargo
- Acid hydrolases require correct M6P-dependent trafficking
- Autophagy supports organelle renewal and nutrient salvage
- Ubiquitin–proteasome degradation controls protein quality and lifespan
- Disrupted catabolism or targeting can produce cellular disease

Sources and scope

Primary teaching source

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Chapter 1, pp. 13–14; Fig. 1.10.

Correlative sections from the same textbook

- Chapter 2, pp. 34–35: autophagy and isolation-membrane stages
- Chapter 5, pp. 134–137: M6P trafficking and storage disorders
- Chapter 13, p. 555: proteasome vulnerability in myeloma