

Protein degradation

Protein degradation

- A way to digest what was brought by endocytosis
- A way to discard unnecessary proteins
 - Discard synthesis and folding mishaps
- Slow or stop biochemical reaction
- Regulate metabolism
 - Autophagy
- Present internalized antigens in the immunological cells

Two types of protein degradation

- Lysosomal
 - Proteases in an acidic organelle
- Cytosolic
 - In proteasomes, multienzyme complexes in the cytoplasm
- Protein degradation is energy consuming process!!!

Lysosome

- Major digestive organelle for both cytosolic and extracellular molecules
 - Heterophagy
 - Autophagy
- Single membrane
- Acidification needed for proper activity
 - Vacuolar H⁺ pump

Lysosome

- Contains many hydrolytic enzymes (hydrolases)
 - Proteases, lipases, glycosidases
- All enzymes tagged with mannose-6-phosphate for targeting into lysosomes from ER

Degradation in lysosomes

- Proteins are delivered via endocytic pathway
- Five different mechanisms
 - Endocytosis
 - Crinophagy
 - Macroautophagy
 - Microautophagy
 - Direct translocation from cytosol

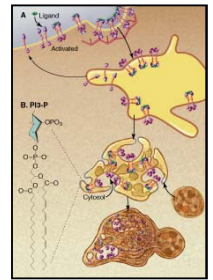
Degradation in lysosomes - endocytosis

- Internalization of receptors as a mean of limiting membrane signaling
 - Internalization of activated receptors to end a signaling event
 - Down-regulation of biologic response by lysosomal breakdown of receptors



Receptor down-regulation

- Most membrane receptors are internalized in the receptor mediated endocytosis
 - For some receptors internalization requires receptor occupation by a ligand
 - For others ligand binding is not necessary



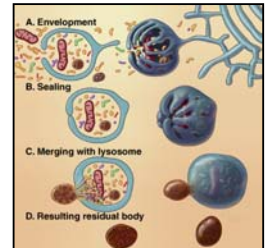
Delivery to lysosomes - autophagy

- Autophagy – consumption of own cytoplasmic components
 - Micro- and macro-
- Housekeeping but usually in response to starvation
- Micro - small vesicles that form during multivesicular bodies formation are digested



Delivery to lysosomes - autophagy

- Macro – large amounts of cytoplasm containing organelles are caught in a vacuole and digested



Delivery to lysosomes - autophagy

- Starvation is a stimulus for autophagy
- In hepatocytes periodic differences according to insulin/glucagon levels



Delivery to lysosomes - crinophagy

- Direct fusion of lysosomes with secretory vesicles
- A fast way to limit/end secretion from the cell (save substrates)
- A way to remove granules with damaged proteins



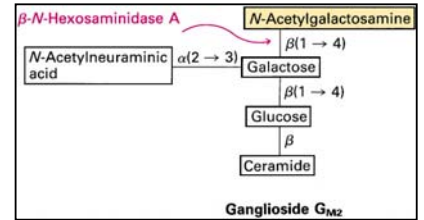
Delivery to lysosomes – direct translocation

- Response to prolonged starvation
- Selective – saves essential proteins (they would have been destroyed in autophagy)
 - Special sequence selects for degradation



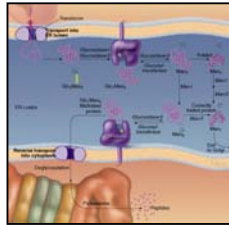
Lysosomal storage diseases

- Tay-Sachs disease is a genetic defect in one of specific lysosomal hydrolases



Remember unfolded protein response?

- Misfolded or unassembled proteins are retained in the ER bound to chaperones or lectins
- They are transported back to cytosol for degradation in the ubiquitin-**proteasome** pathway



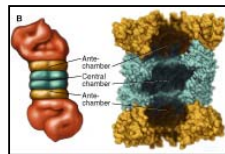
Proteasome – the cellular chamber of doom

- Large **multienzyme complexes** for protein degradation
 - Tunnel like macromolecule with protease activity, not an organelle
 - Located both in cytoplasm and nucleoplasm
- Contain many proteases
 - Degrade proteins by breaking them to small peptides and amino acids
 - Death of a Thousand Cuts



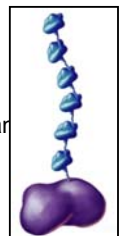
Proteasome – molecular structure

- Core region of 4 rings 7 subunits each form a tunnel
- 2 regulatory subunits at the ends
 - Cap the structure and prevent stray proteins from entering
 - Unfold doomed proteins and inject them into the tunnel



Ubiquitination – molecular kiss of death

- Targets proteins to proteasomes
- Selective linkage of the chain of ubiquitins to protein destined for degradation
- Mostly quality control for misfolded and abnormal proteins
- But also as means for regulation of intracellular signaling molecules



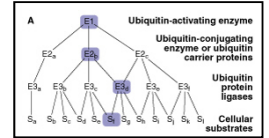
Ubiquitin

- Tiny (76 aa) cytosolic protein
- Covalently added to proteins destined for degradation
- Added post-translationally to lysine residues
 - ATP needed



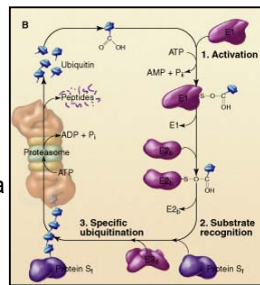
Ubiquitination

- Tightly regulated 3 step enzymatic process
 - Activation of ubiquitin (E1)
 - Conjugation to E2
 - Substrate recognition and ubiquitin transfer (E3 – ubiquitin ligase)



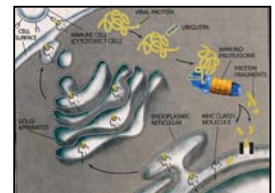
Ubiquitination

- Polyubiquitination – additional ubiquitins added to preceding ubiquitin
- Proteasome's cap deubiquitinates the protein before entry into a proteasome
 - Ubiquitin is recycled



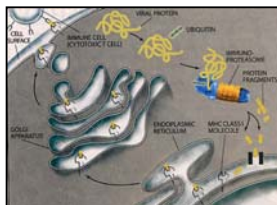
Immunoproteasomes

- Only in higher vertebrates
- Always associated with TAP (transporter associated with antigen presentation) in the ER
- Induced by γ interferon
- Antigen is cut into small pieces



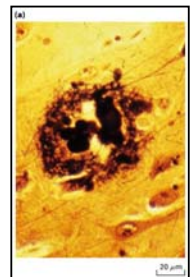
Immunoproteasomes

- Peptides resulting from proteasome degradation are transported to ER and bind to MHC molecules (transporter!)
- MHC-peptide complex is secreted and presented to T lymphocytes



Misfolded proteins are implicated in degenerative diseases

- An amyloid plaque in Alzheimer's disease is a tangle of defective protein filaments that have not been degraded



Lipid degradation and turnover



- 3 separate pathways for
 - Phosphoglycerides
 - Glycolipids
 - Cholesterol
- Outer leaflet lipids are degraded in lysosomes by lysosomal hydrolases

Lipid degradation and turnover



- Inner leaflet lipids are broken down by phospholipases and remodeled into new lipids
- Molecules created by phospholipases serve as second messengers in intracellular signaling cascades