

CATABOLISM III:

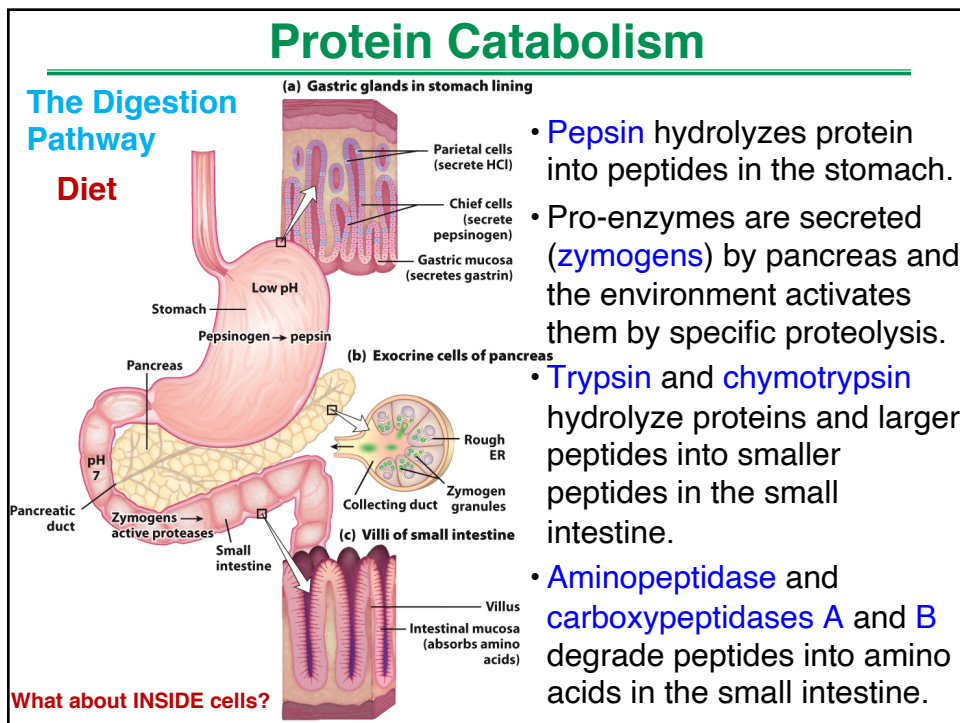
Digestion and Utilization of Proteins

- Protein degradation
- Protein turnover
 - The ubiquitin pathway
 - Protein turnover is tightly regulated
- Elimination of nitrogen
 - By fish, flesh and fowl
 - How is the N of amino acids liberated and eliminated?
- How are amino acids oxidized for energy

Protein Catabolism

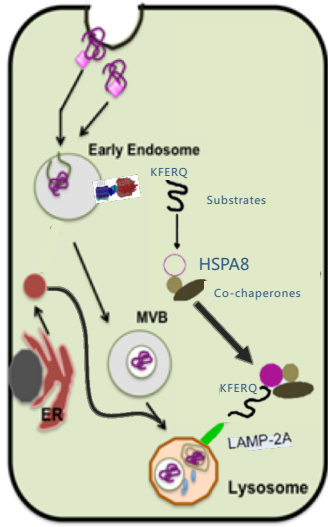
Sources of AMINO ACIDS:

- **Dietary amino acids** that exceed body's protein synthesis needs
- **Excess amino acids** from protein turnover (e.g., proteolysis and regeneration of proteins)
- **Proteins in the body can be broken down** (muscle wasting) to supply amino acids for energy when carbohydrates and fat are scarce (starvation, diabetes mellitus, cancer).
- Carnivores use amino acids for energy more than herbivores, plants, and most microorganisms



Protein Catabolism In cells: turnover

The Lysosomal Pathway



- **Endocytosis**, either receptor-mediated, phagocytosis, or pinocytosis, engulfs extra-cellular proteins into vesicles.
- These internal vesicles fuse as an **early endosome**.
- This early endosome is acidified by the vATPase ("v" for vesicular).
- Components that are recycled, like receptors, are sequestered in smaller vesicles to create the **multivesicular body (MVB)**, sometimes called a **late endosome**.
- If set for degradation, it will fuse with a **primary lysosome** (red) which contains many cathepsin-type proteases.
- In the **secondary lysosome**, proteins (and other macromolecules) are hydrolyzed into amino acids and internalized into the cell.

If some **cellular** proteins have a KFERQ motif, they are degraded through a chaperone-mediated autophagy pathway..... This leads us to the main mechanism of cellular-protein turnover.....

Protein Catabolism In cells: turnover

Protein Turnover (within cell):

- Half-lives of proteins range from seconds to days to even months.

Examples:

- Hemoglobin is long lived.
- Defective proteins are short lived, as are many regulatory proteins that respond to rapidly changing needs (e.g., cyclins).

• But all proteins are eventually degraded; **Protein Degradation Is Inevitable**

TABLE 27-9 Relationship between Protein Half-Life and Amino-Terminal Amino Acid Residue

Amino-terminal residue	Half-life ^a
Stabilizing	
Ala, Gly, Met, Ser, Thr, Val	> 20 h
Destabilizing	
Gln, Ile	~30 min
Glu, Tyr	~10 min
Pro	~7 min
Asp, Leu, Lys, Phe	~3 min
Arg	~2 min

Source: Information from A. Bachmair et al., *Science* 234:179, 1986.

^aHalf-lives were measured in yeast for the β -galactosidase protein modified so that in each experiment it had a different amino-terminal residue. Half-lives may vary for different proteins and in different organisms, but this general pattern appears to hold for all organisms.



Alexander Varshavsky

What is this ubiquitination?

N-end rule

Found it was ATP dependent

Found a protein associated:
called it ubiquitin

The N-end rule applied to ubiquitination

Protein Catabolism

Protein Turnover (within cell): Ubiquitination

- In eukaryotes, proteins are linked to the protein **ubiquitin**; found everywhere in all eukaryotic cells (hence the name)
 - Ubiquitin is very highly conserved among all eukaryotes.
 - Only 3 substitutions among all species
 - Works via activating enzyme, E1, conjugating enzyme, E2, and ligating enzyme, E3.
- Ubiquitinated proteins have many fates, but the best known is their fate in the **26 S proteasome complex**.
 - The proteasome is ATP-dependent.
- In *E. coli*, **Lon** (for “long form,” an ATP-dependent protease) hydrolyzes defective or short-term peptides.
 - It is part of CLp-P (20S), CLp-A (19S), CLpX

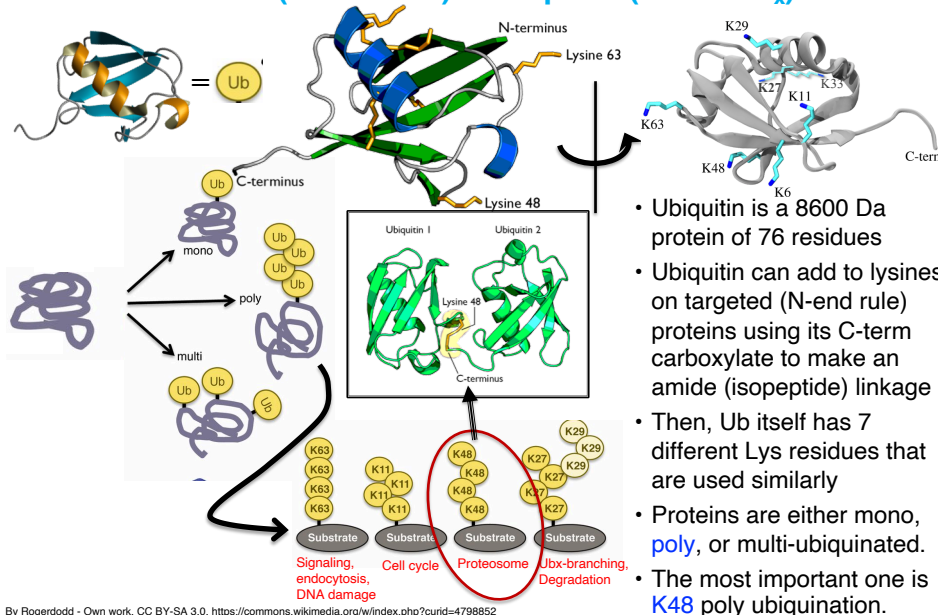
The Nobel Prize in Chemistry 2004



Aaron Ciechanover Avram Hershko Irwin Rose

Protein Catabolism

Protein Turnover (within cell): Ubiquitin (Ub or Ub_x)



Protein Catabolism

Protein Turnover (within cell): Ubiquitination

Attachment of Ubiquitin to Target Proteins

