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

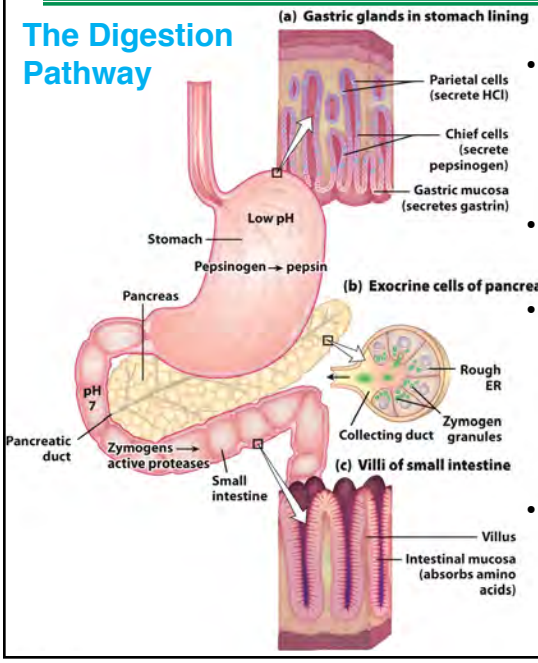
Protein Catabolism

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 are scarce (starvation, diabetes mellitus).
- Carnivores use amino acids for energy more than herbivores, plants, and most microorganisms

Protein Catabolism

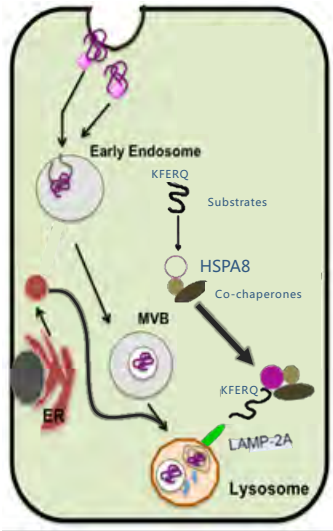
The Digestion Pathway



- Pro-enzymes are secreted (zymogens) and the environment activates them by specific proteolysis.
- Pepsin hydrolyzes protein into peptides in the stomach.
- Trypsin and chymotrypsin hydrolyze proteins and larger peptides into smaller peptides in the small intestine.
- Aminopeptidase and carboxypeptidases A and B degrade peptides into amino acids in the small intestine.

Protein Catabolism

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 types of cathepsin proteases.
- In the secondary lysosome, proteins (and other macromolecules) are hydrolyzed into amino acids and internalized into the cell.

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

Protein Catabolism

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 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.
[a]Half-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 euk 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
- Ubiquinated proteins are cleaved by the 26 S proteasome complex.
  - The proteosome is ATP-dependent.
- In *E. coli*, **Lon** (for "long form," an ATP-dependent protease) hydrolyzes defective or short-term peptides.
  - CLp-P (20S), CLp-A (19S), CLpX