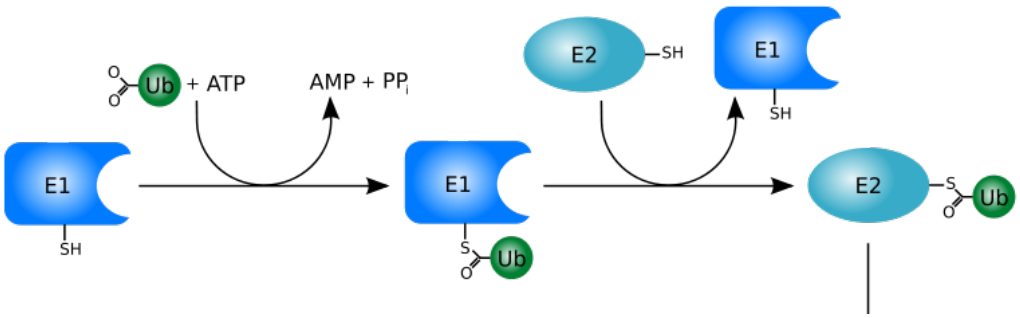
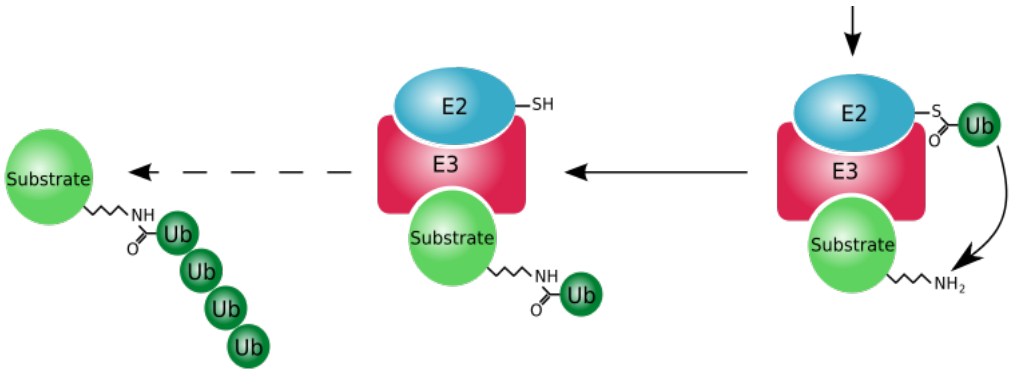
CONCEPT: PROTEIN DEGREDATION

Ubiquitin-Proteasome Pathways

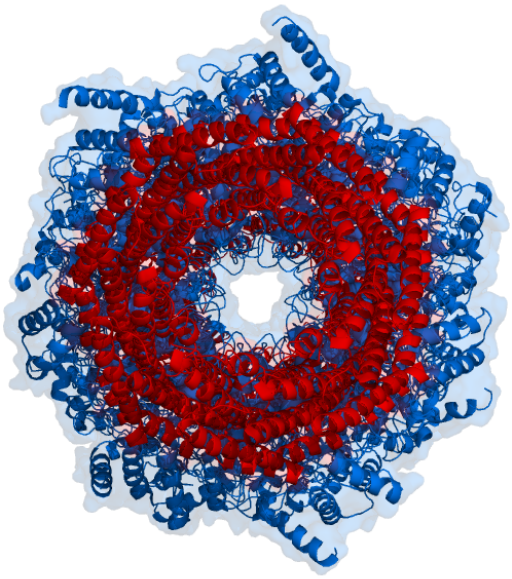
- The **proteasome** is a multisubunit protein complex that is able to _____ proteins
  - □ Proteins labeled with **ubiquitin** protein are targeted to the proteasome
    - Ubiquitin is a 76 amino acid protein conserved across all eukaryotic organisms
    - Proteins can be labeled with one (mono) or more than one (poly) ubiquitin proteins
  - □ This pathway occurs in steps and requires energy from ATP
    1. Ubiquitin is activated by the E1 ubiquitin activation enzyme
    2. Activated ubiquitin then binds to the E2 ubiquitin conjugating enzyme



    3. Then this complex is attached onto the target protein via E3 ubiquitin ligase
       - Each E3 recognizes a different substrate protein – it "selects" the correct protein
    4. The ubiquitinated protein is recognized by the outside of the proteasome
    5. The protein is unfolded and fed through the inside of the cylindrical proteasome
       - Contains ATP-dependent **proteases** which chop up the protein into short peptides
       - The entire protein is bound until it is entirely cut



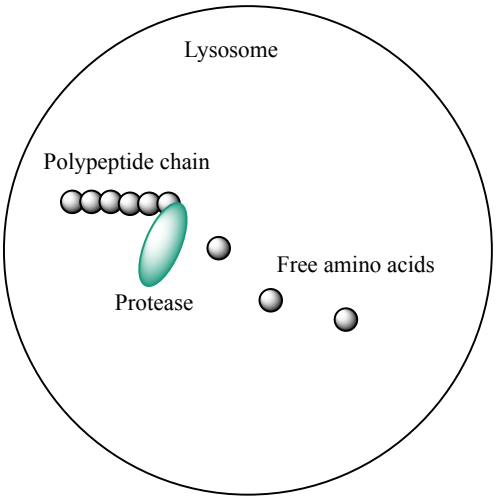
EXAMPLE: Proteasome structure



Lysosomal Pathway

- The **lysosome** breaks down proteins
  - □ The lumen of the lysosome contains _____ that chop up proteins
  - □ *Autophagy* is the process of cell death, and involves a lot of protein destruction via lysosomes
  - □ Can rapidly respond to nutrients and external signals

EXAMPLE: Lysosomal protein degradation



Degradation Regulation

● Protein degradation _____ the amount of protein in the cell at a certain time

□ One reason for regulation is that a protein's lifespan can vary from seconds to decades

- Proper proteins levels are crucial for certain chemical reactions

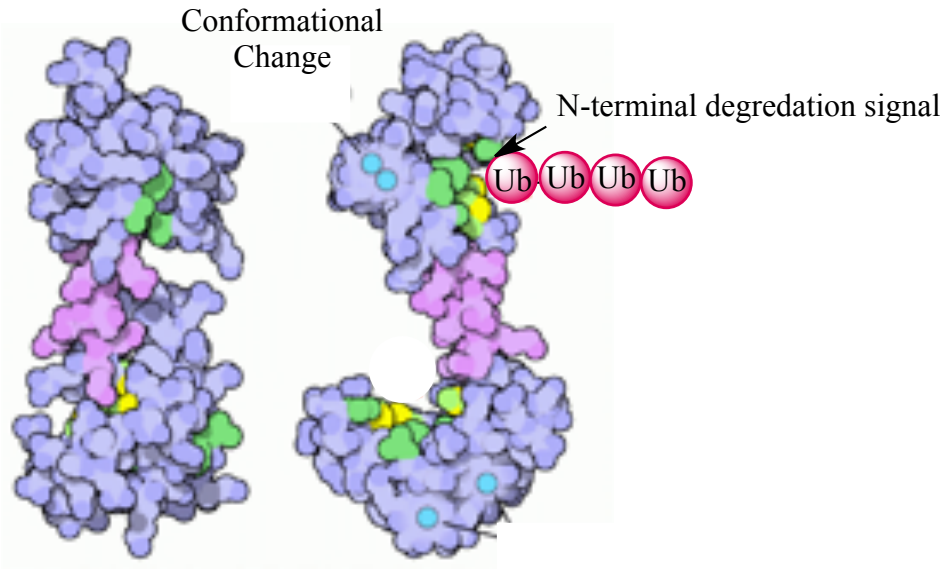
- An **N-terminal degradation signal** is a hidden signal released when its time for degradation

- Ubiquitin binds this region

□ A second reason for regulation is proteins occasionally _____

- Abnormally folded proteins can form aggregates in the cell and cause disease

EXAMPLE: A conformational change releases an N-terminal degradation signal which becomes ubiquitinated



PRACTICE

1. Which of the following is not associated with protein degradation?
    a. Ubiquitin-proteasome pathway
    b. Lysosomal pathway
    c. 5' Cap
    d. N-terminal degradation signal

2. Which protein is responsible for attaching a ubiquitin molecule onto a protein to target it for degradation?
    a. E1 ubiquitin activation enzyme
    b. E2 ubiquitin conjugating enzyme
    c. E3 ubiquitin ligase
    d. E4 ubiquitin attachase

3. True or False: Before entering the proteasome the protein marked for degradation is unfolded.
    a. True
    b. False

4. What is the name of the signal released by some proteins when they can be degraded?
    a. Ubiquitin binding signal
    b. N-terminal degradation signal
    c. C-terminal degradation signal
    d. Proteosome signal