

Protein Folding

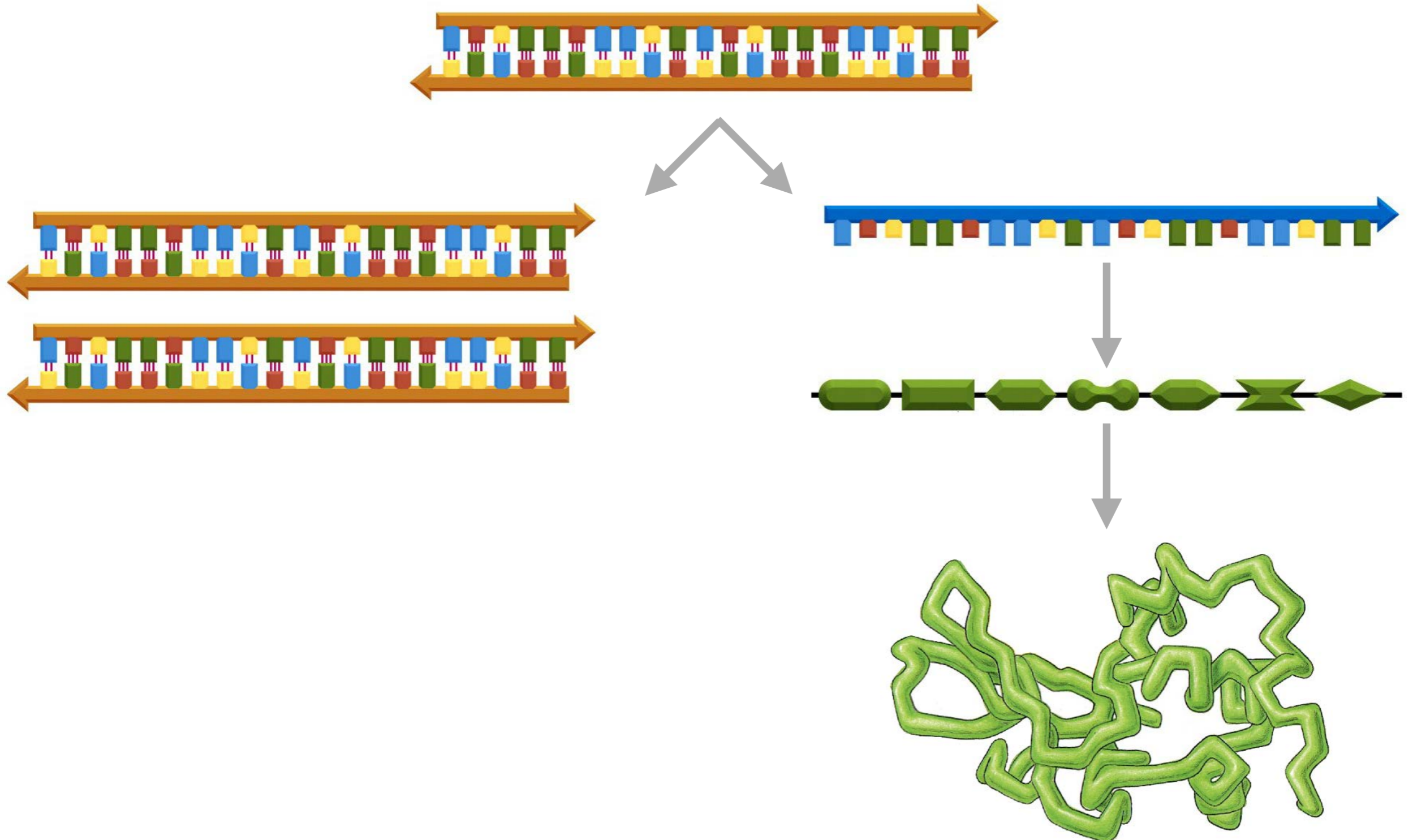
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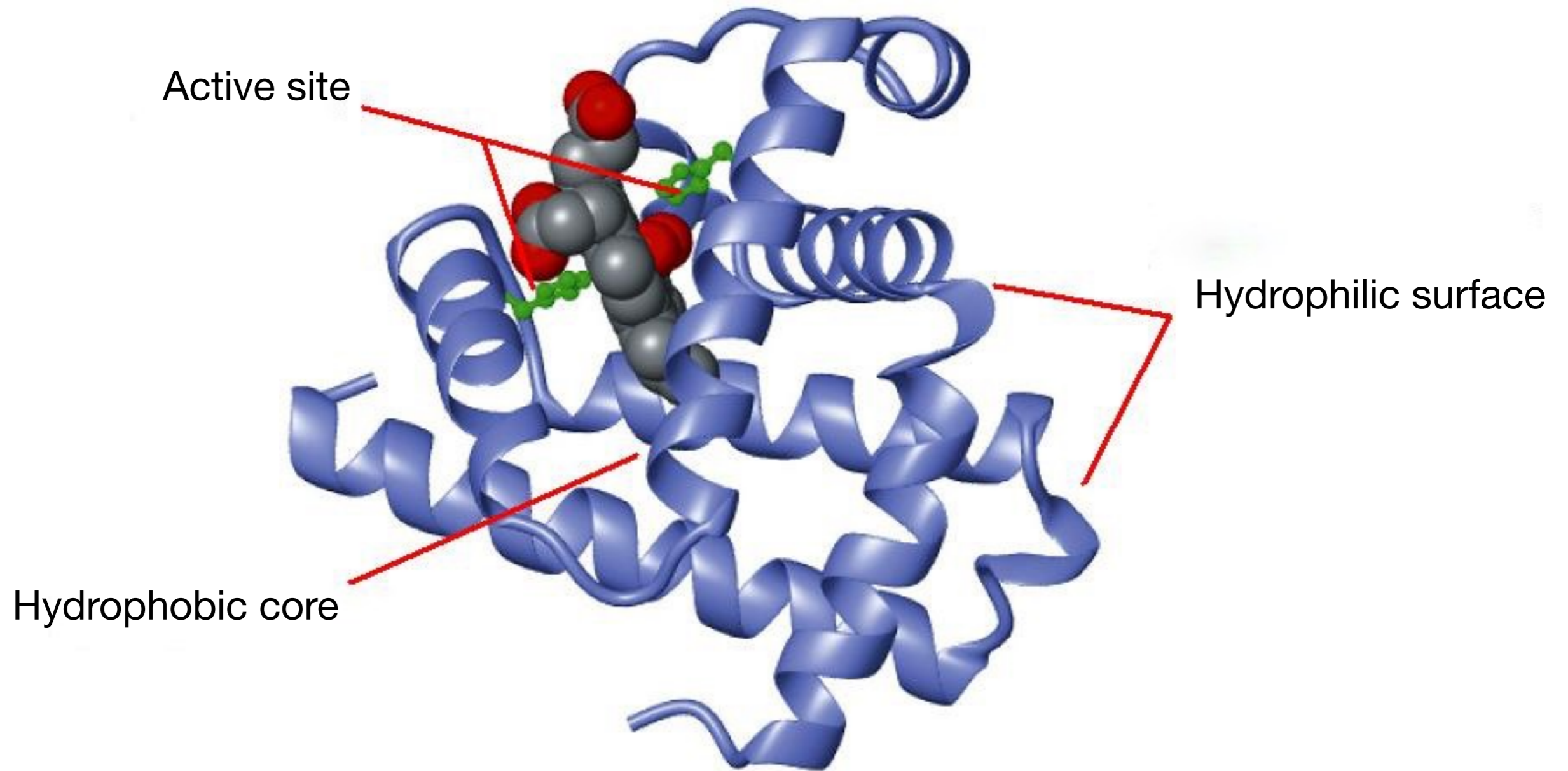
What we'll talk about...

- Protein folding and chaperones
- Finding and degrading unfolded proteins in cytosol and ER
- Unfolded protein response in the ER

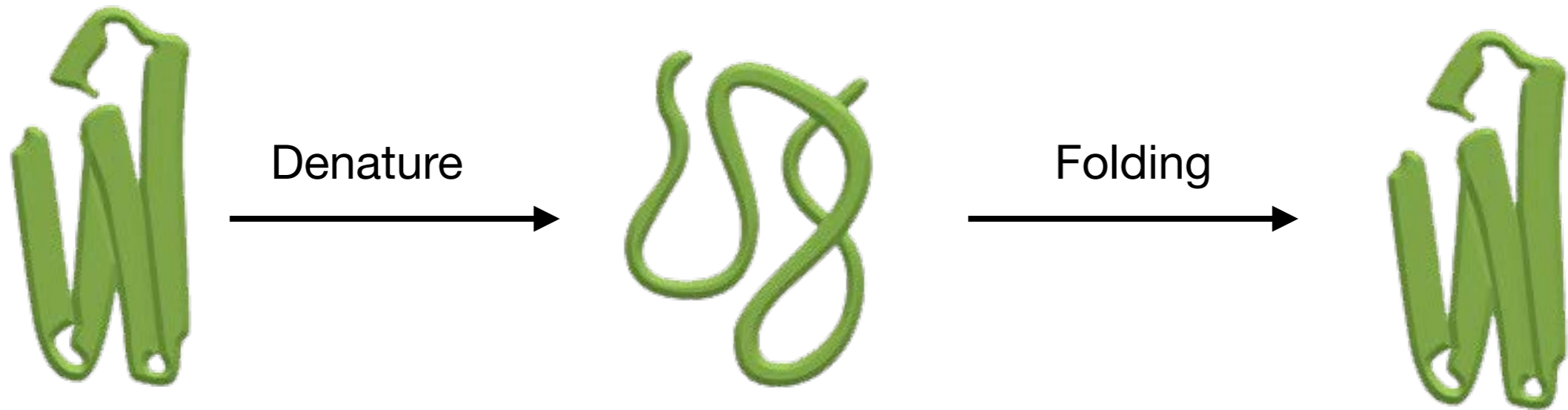
Biochemical pathways are prone to errors.



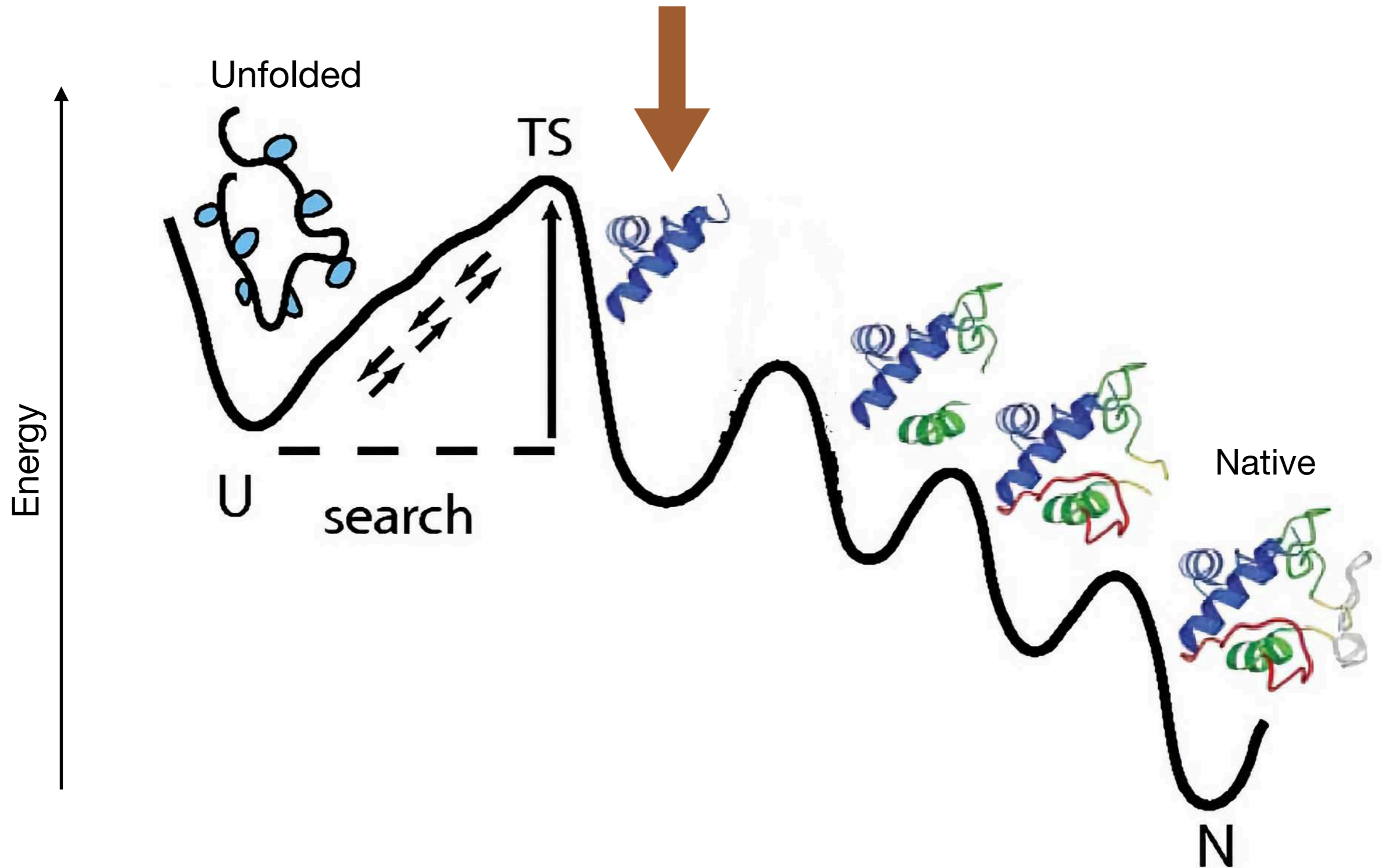
Hydrophobic amino acids maintain three-dimensional structure of proteins.



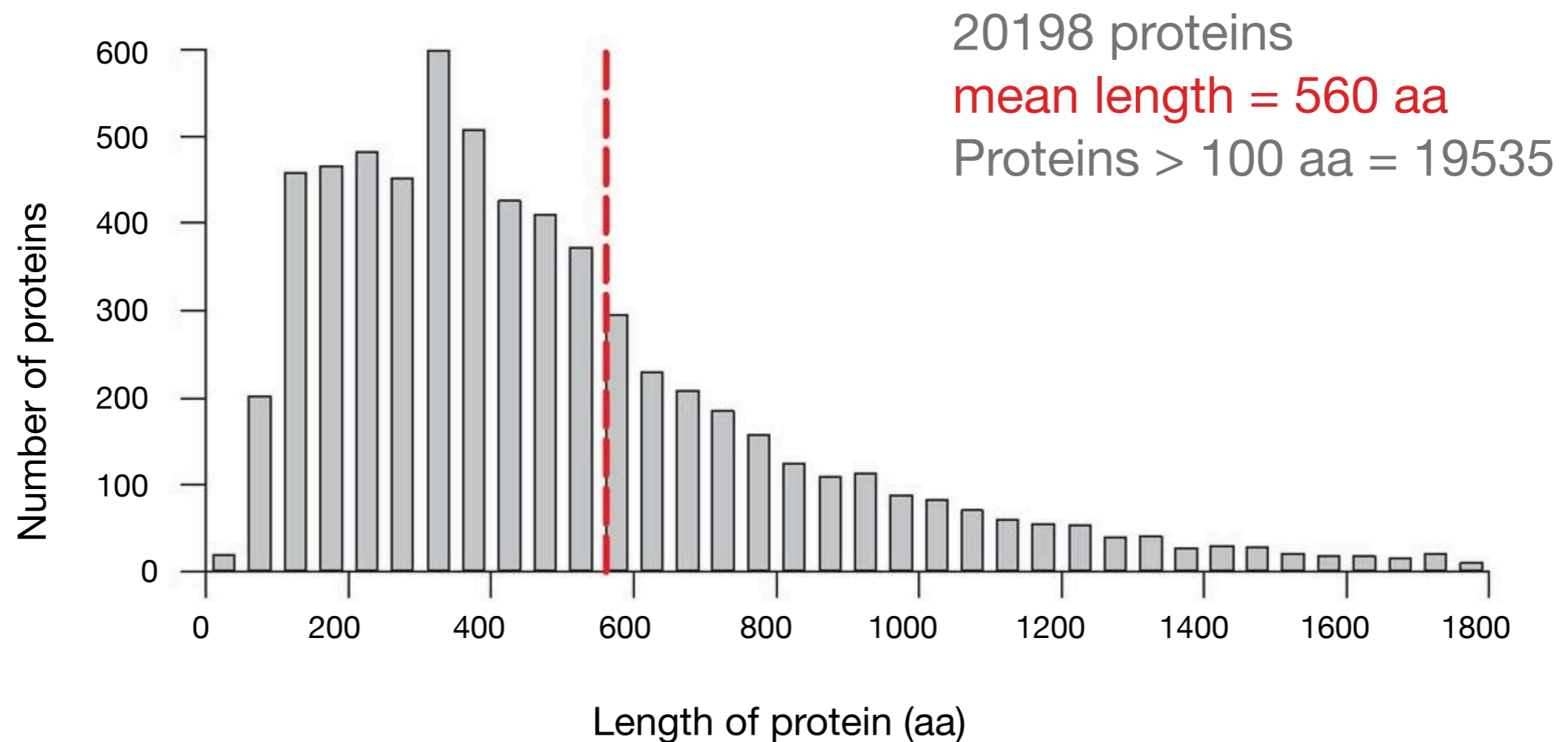
Proteins shorter than 100 amino acids can spontaneously fold into 3-D structure.



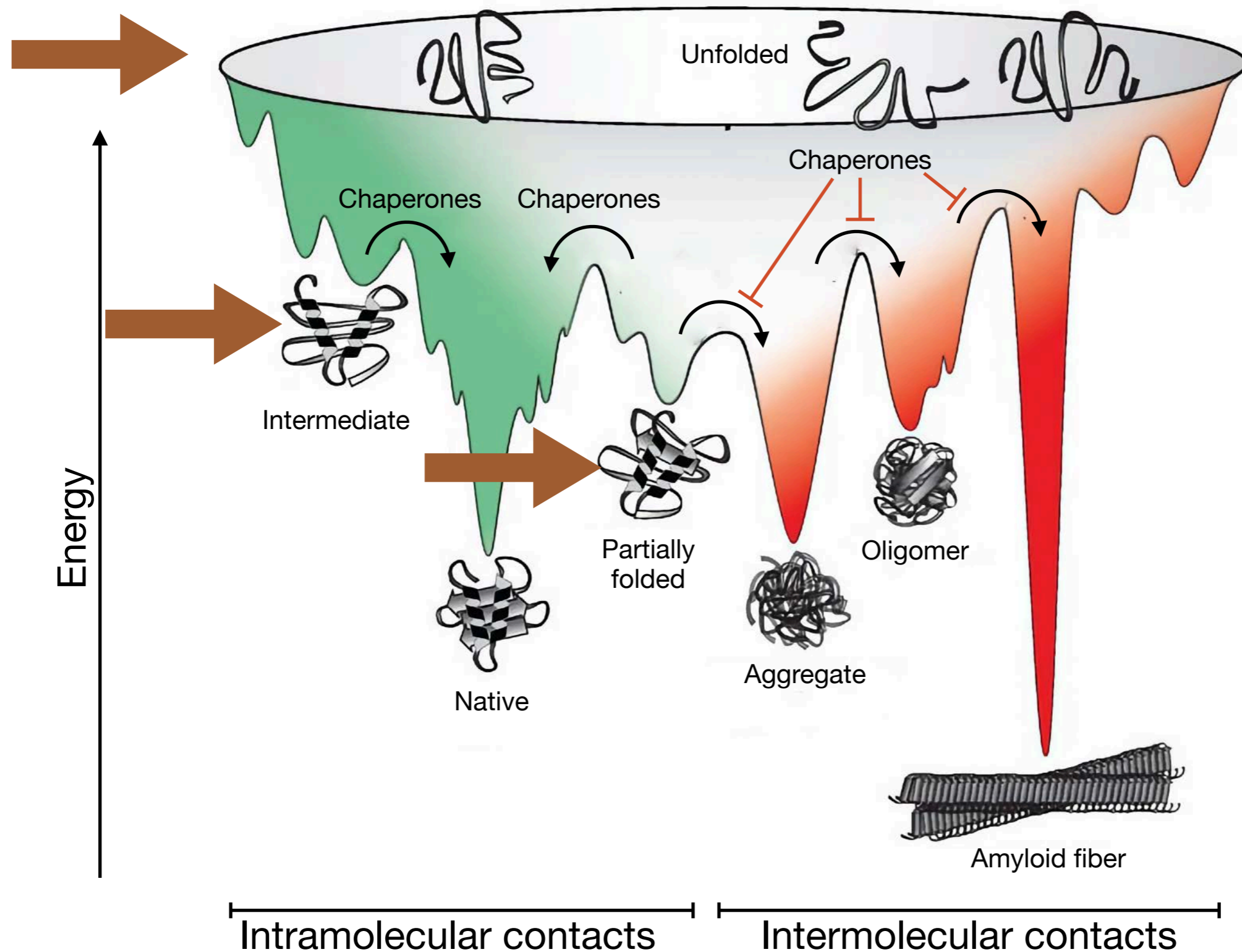
Small proteins appear to follow one path to their native structures.



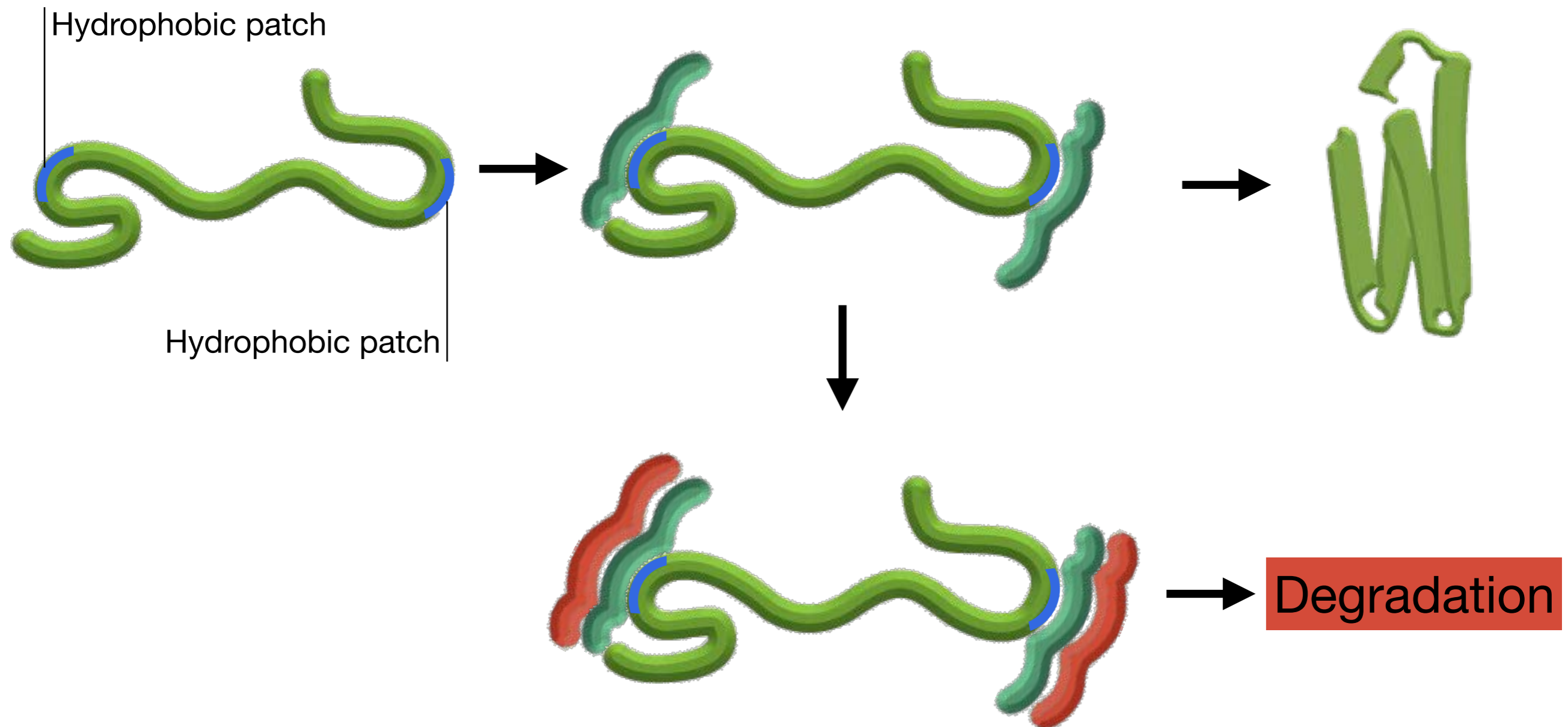
96% of human proteins are longer than 100 amino acids.



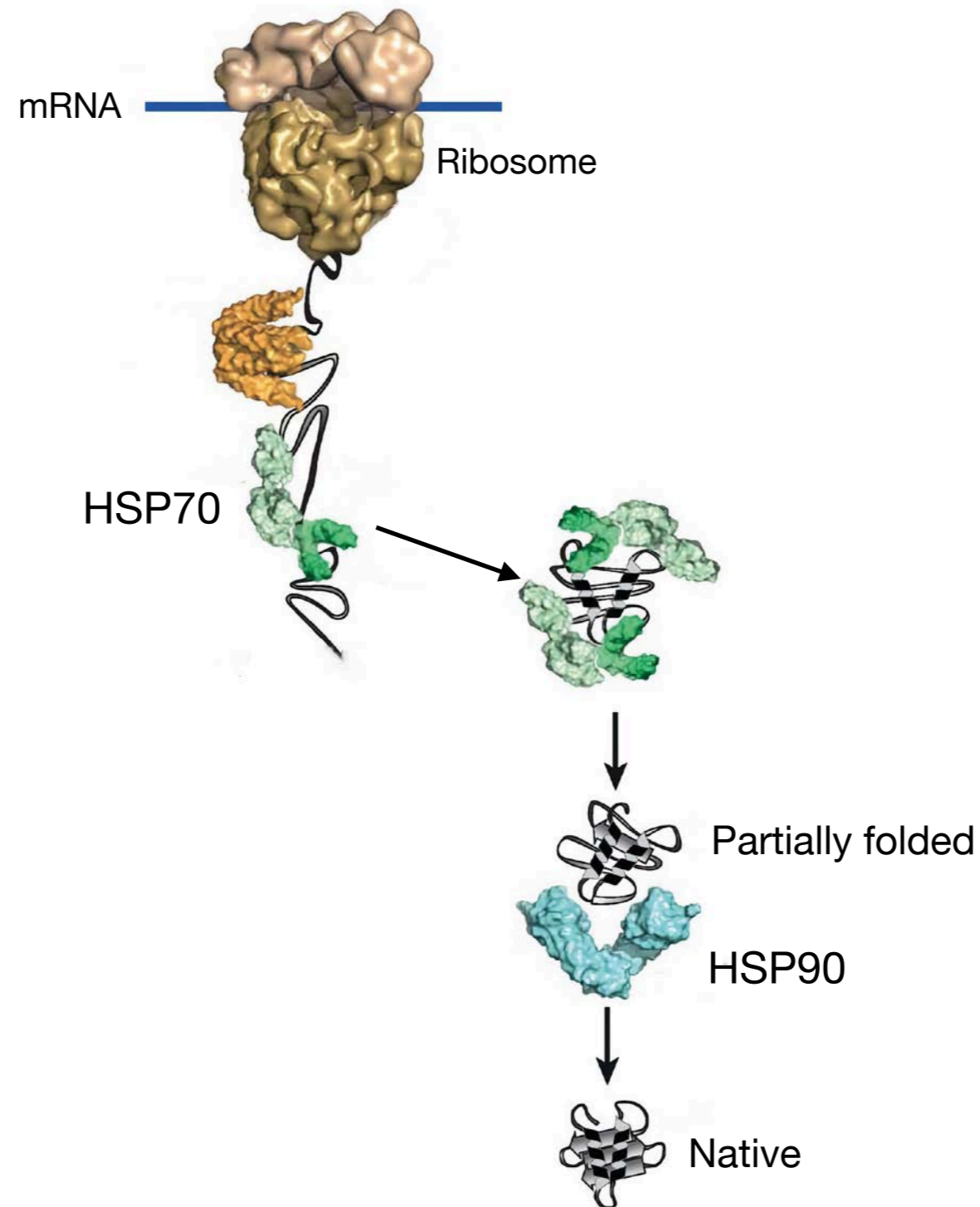
Large proteins follow several folding pathways that can lead to multiple states.



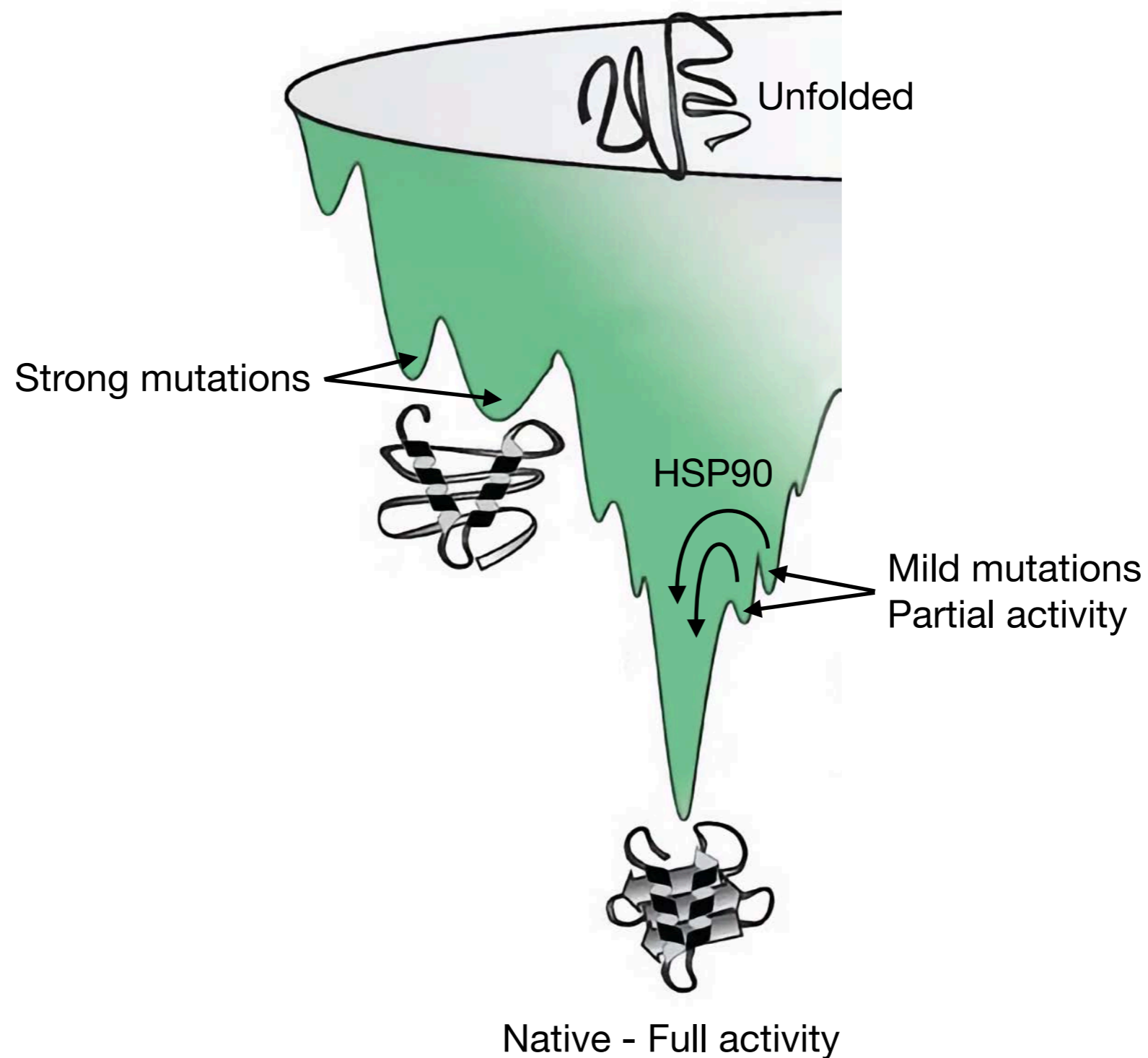
Chaperones bind hydrophobic domains to mediate folding or recruit degradation machinery.



Heat-shock proteins mediate different steps in protein folding pathways.



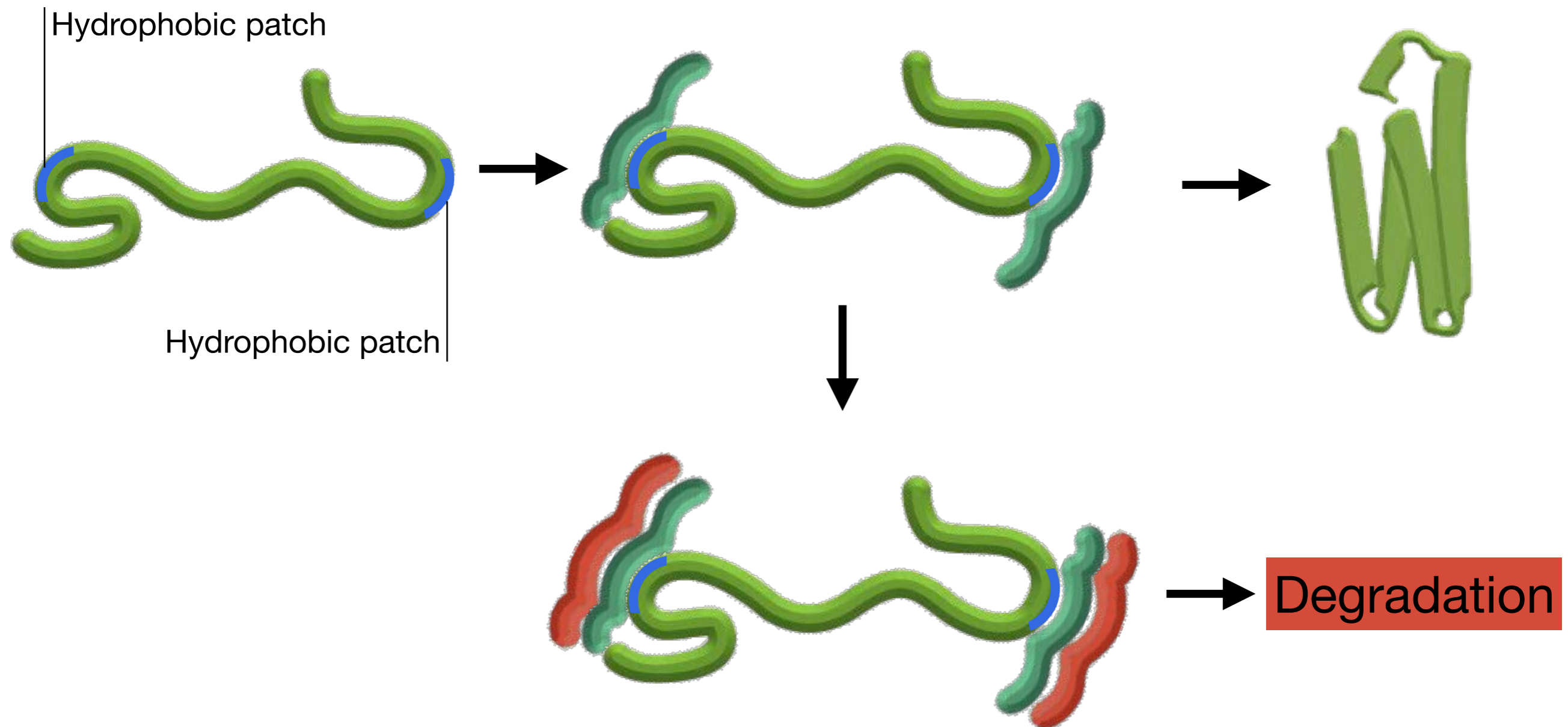
HSP90 converts proteins with mild mutations to their native structures to restore full activity.



Cellular Control of Unfolded Proteins

Protein degradation

Chaperones bind hydrophobic domains to mediate folding or recruit degradation machinery.



Chains of ubiquitin mark proteins for degradation.

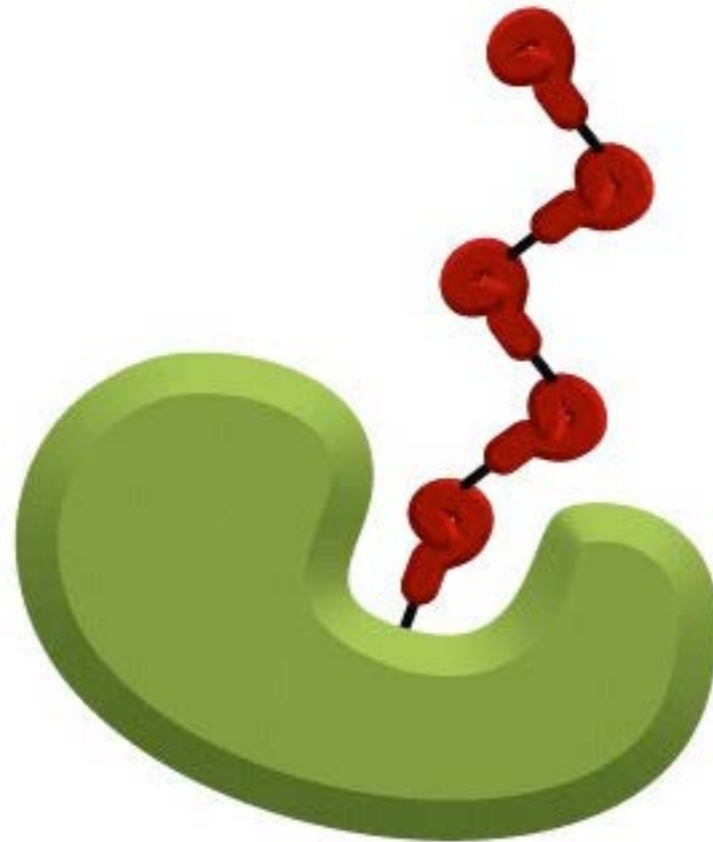
Ubiquitin



The pattern of ubiquitins on proteins have different biological meanings.



Histone
regulation

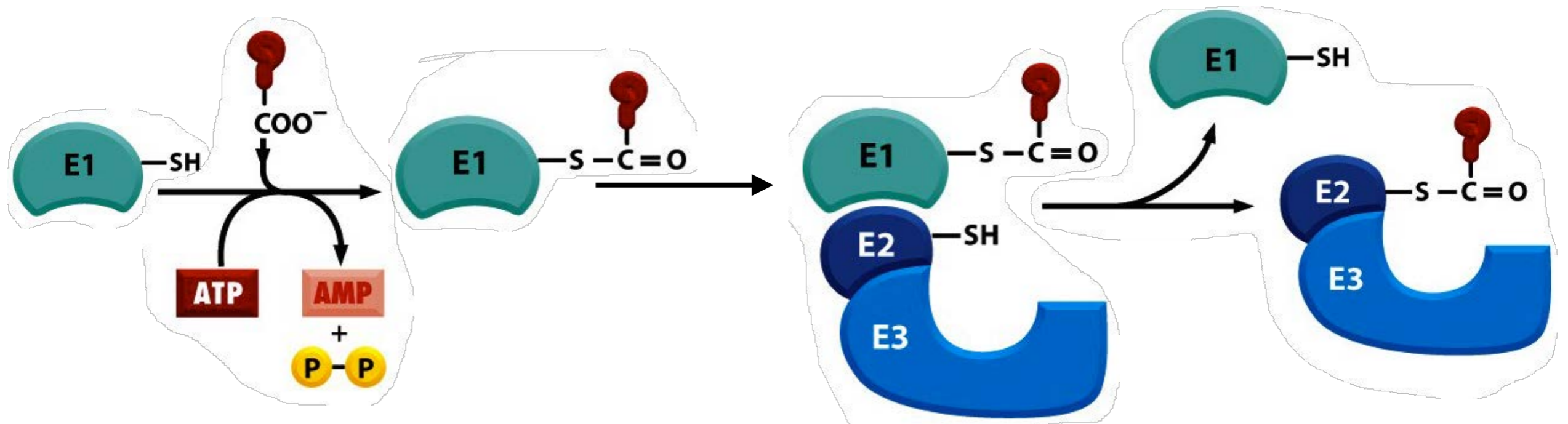


Degradation

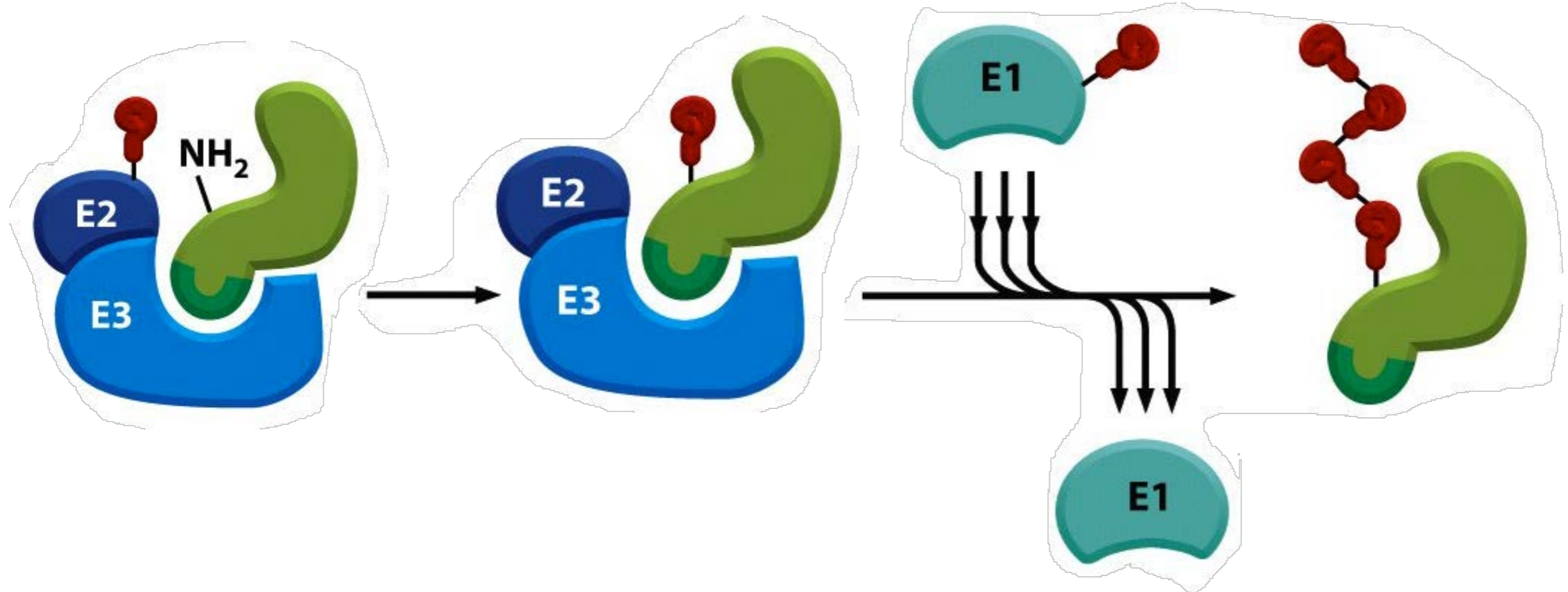
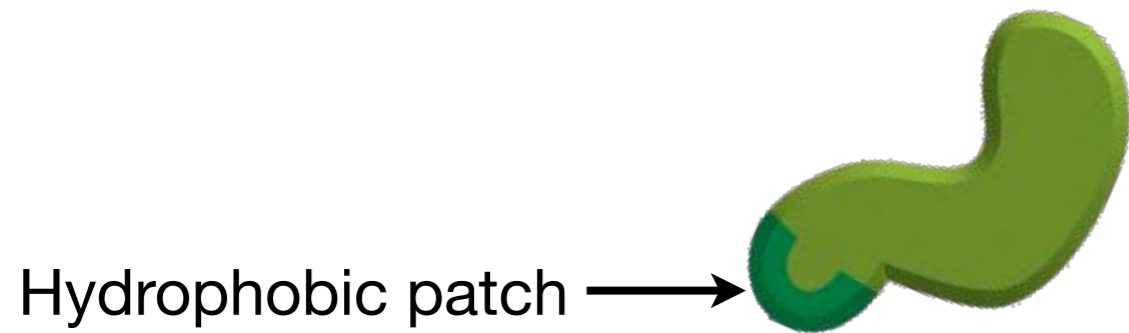


Endocytosis

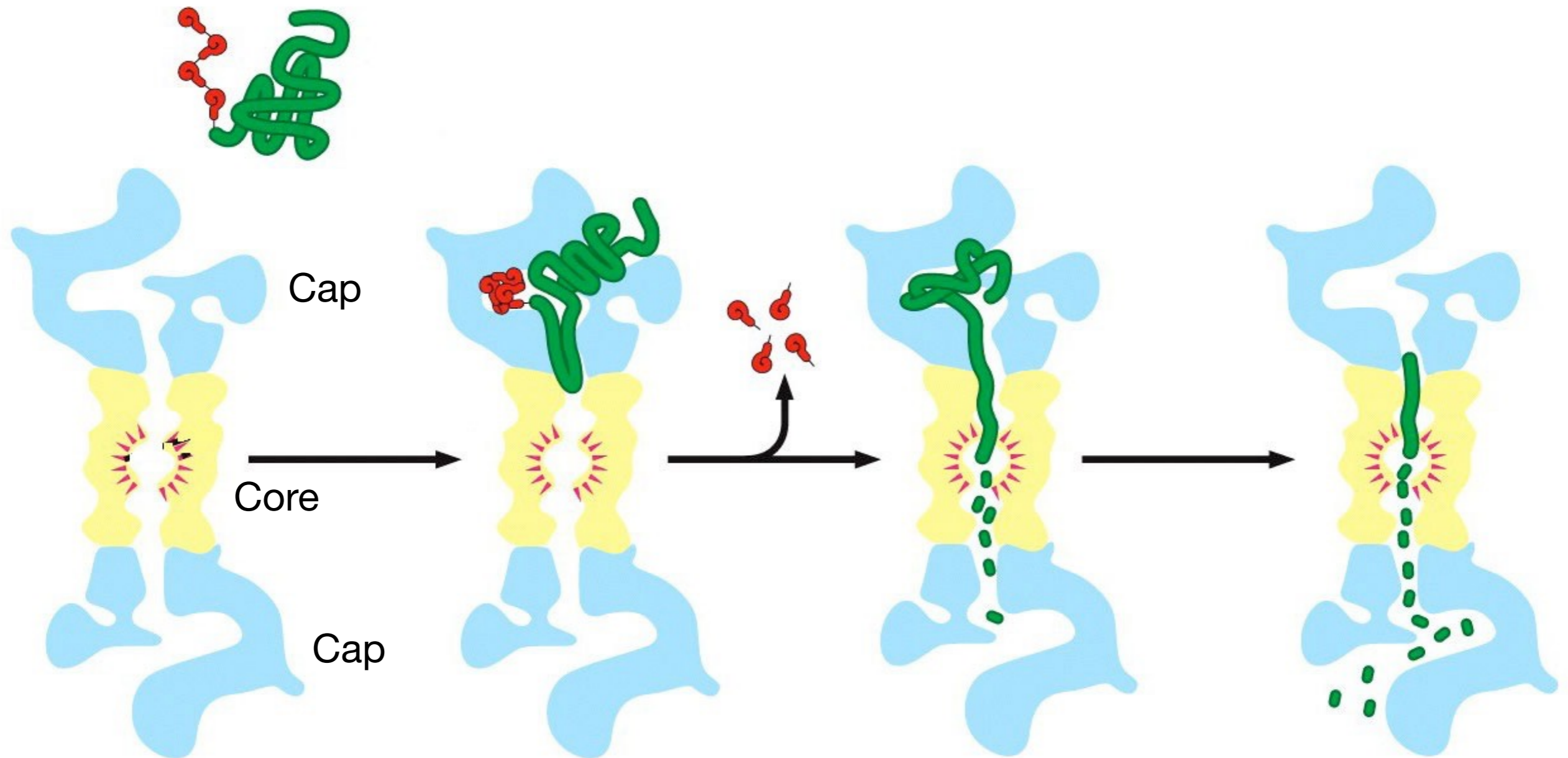
Three enzymes mediate ubiquitylation of proteins.



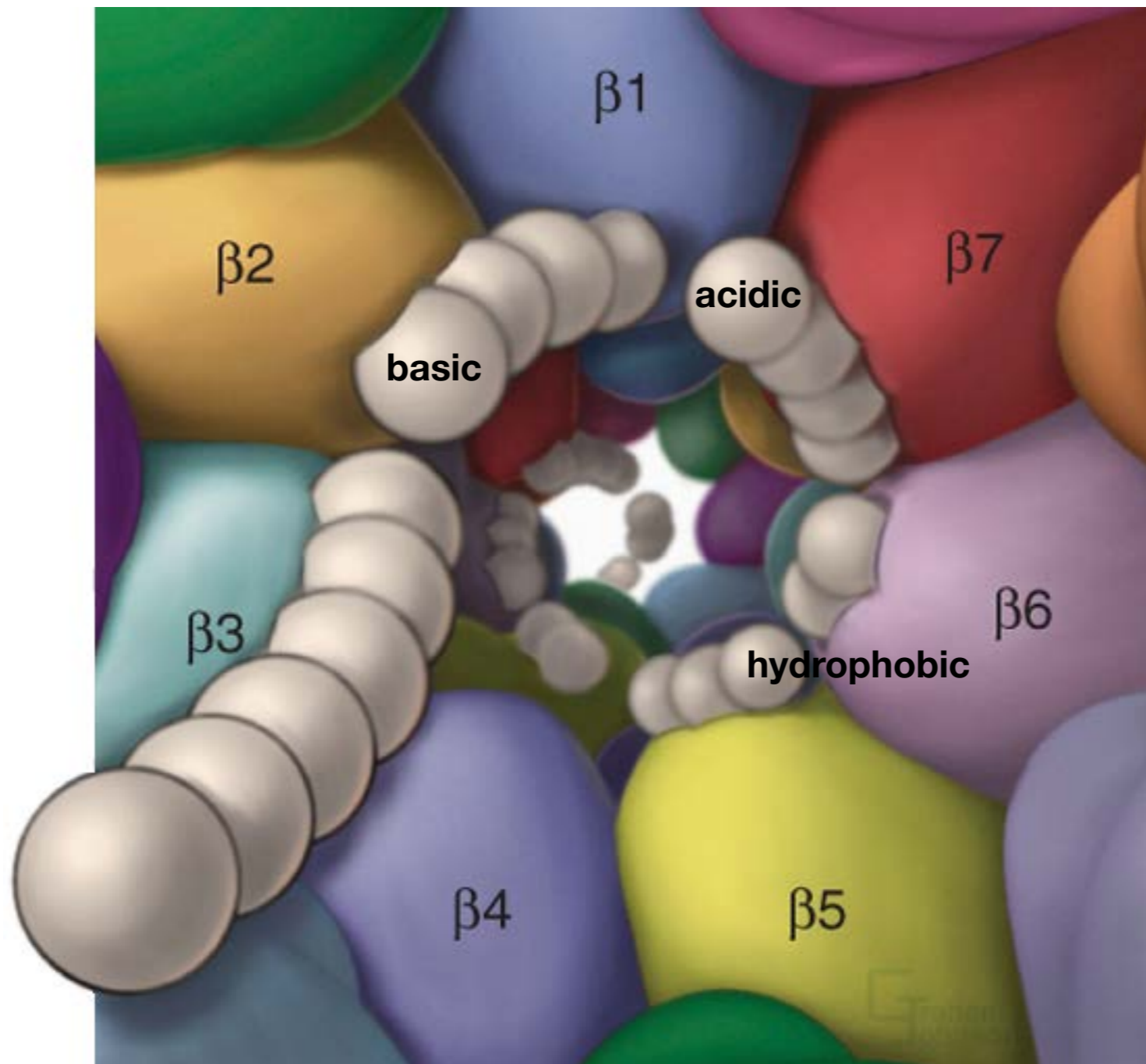
E2 and E3 target specific proteins for ubiquitylation.



Proteasome is a large complex of proteins that digests ubiquitylated proteins.

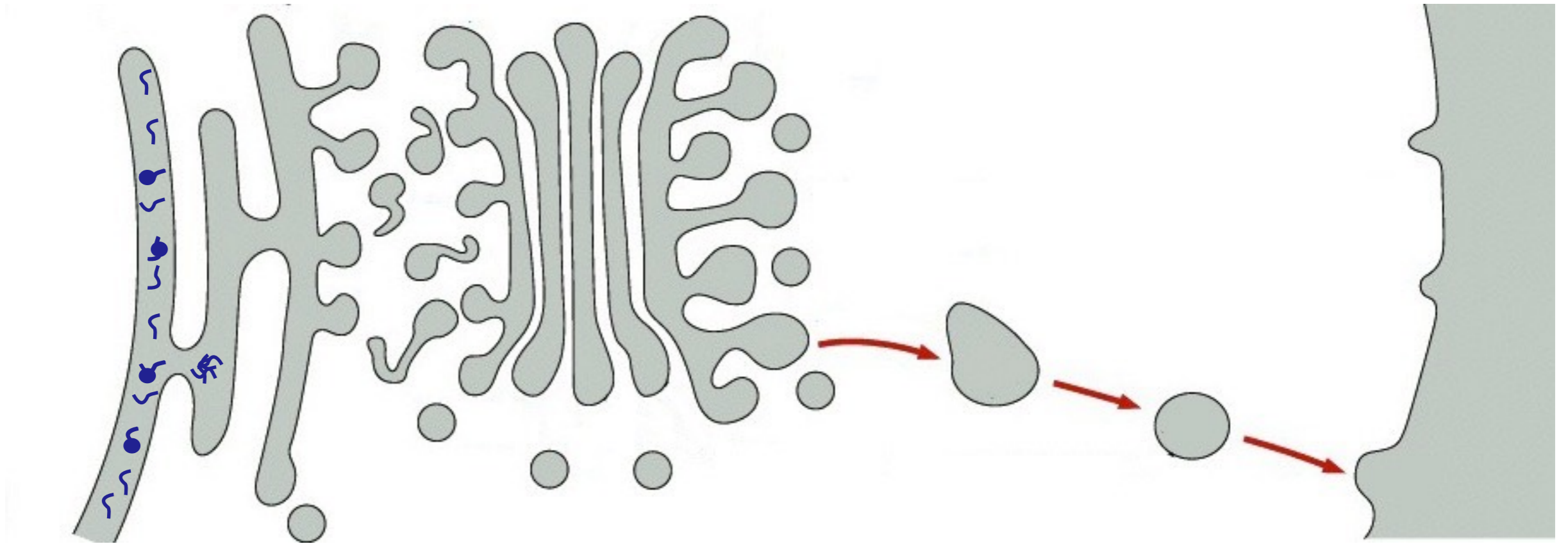


Proteasome contains several proteases that cleave at specific sites in proteins.

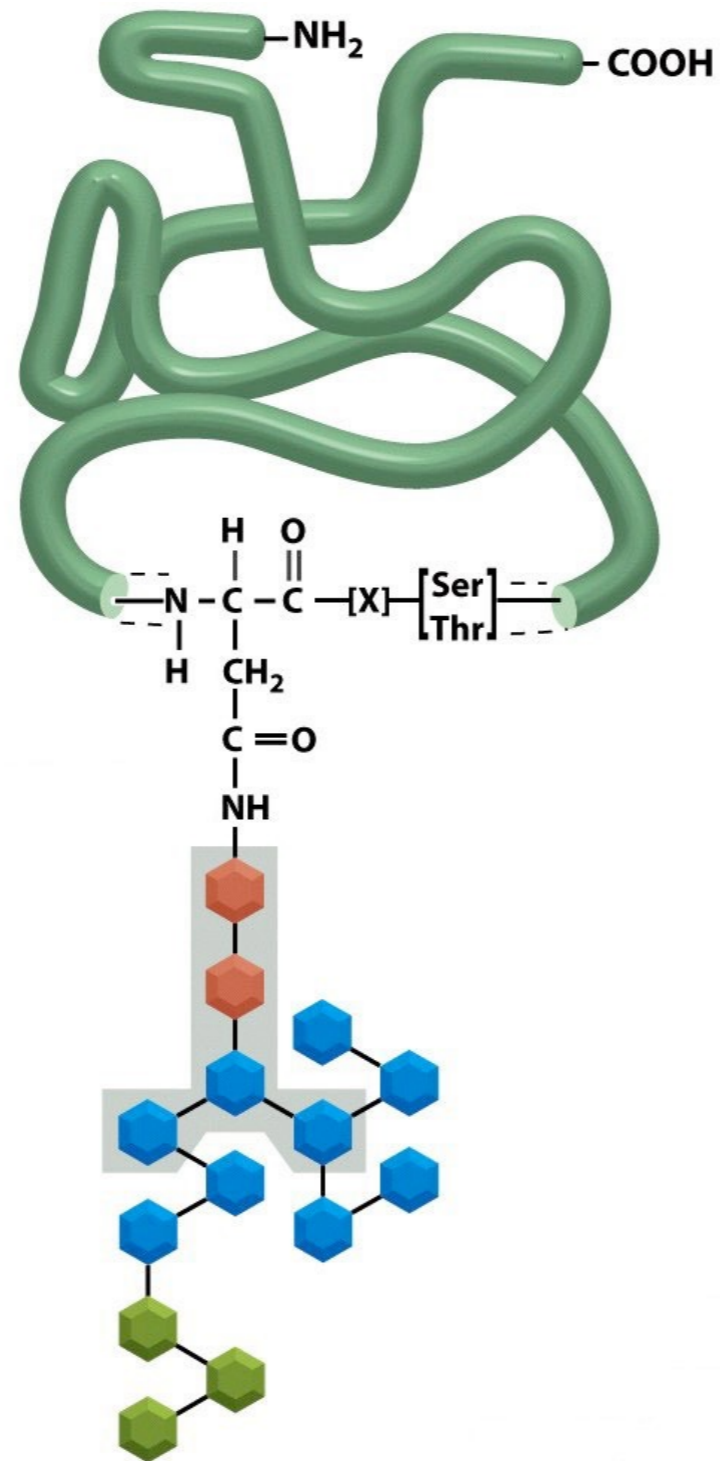





Recognizing and responding to unfolded proteins in the ER.

Secretory cells are susceptible to accumulation of unfolded protein in their ER.

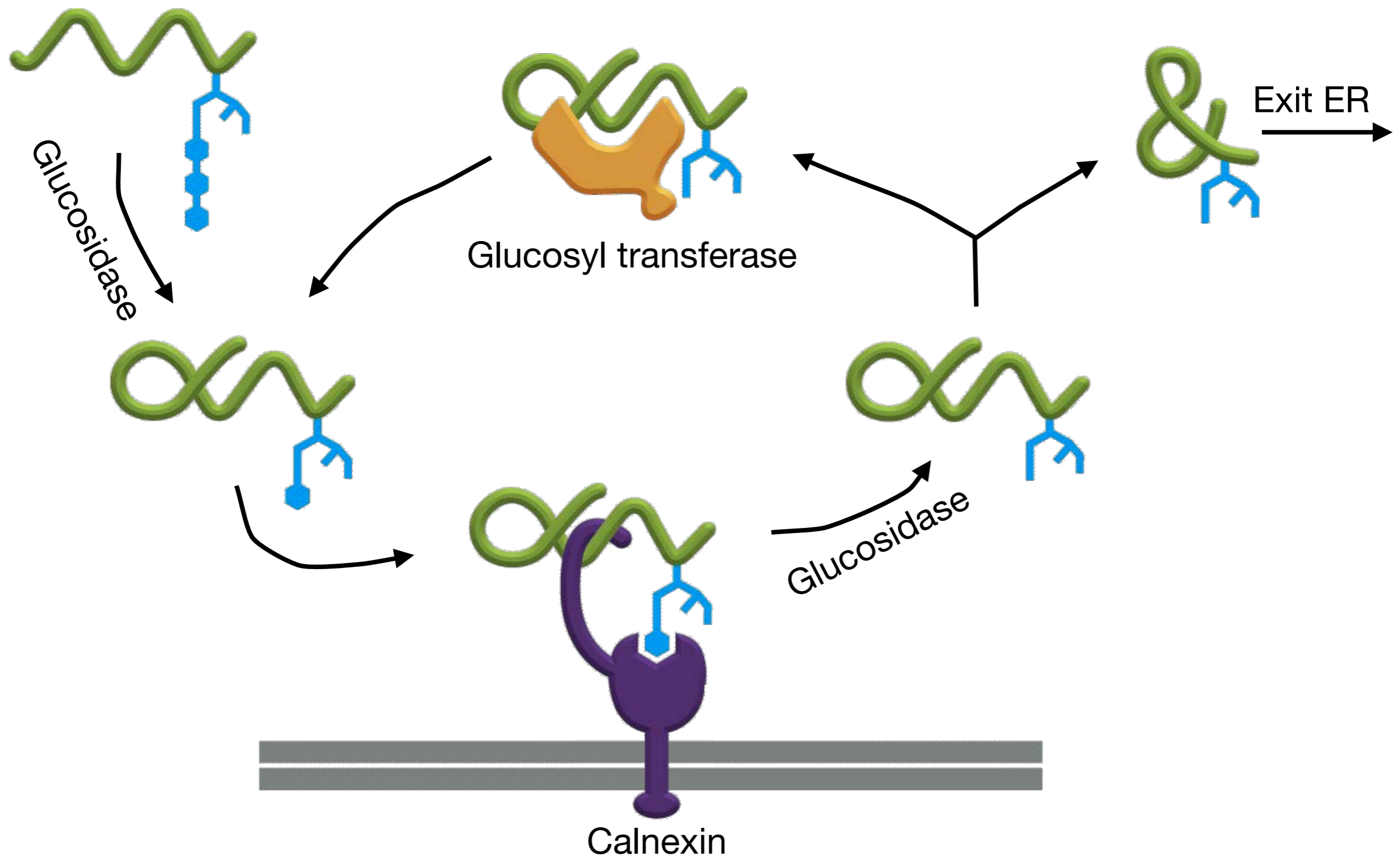


The pattern of sugars on glycosylated proteins marks them as unfolded proteins in the ER.

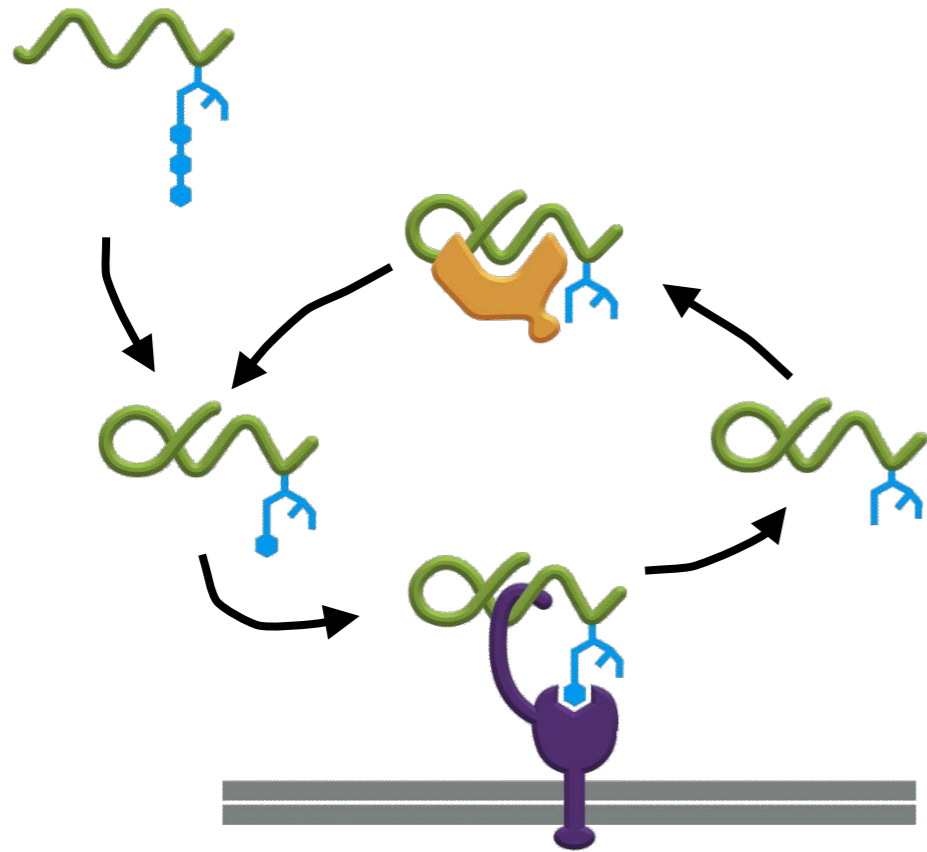


-  Glucose
-  Mannose
-  N-acetylglucosamine

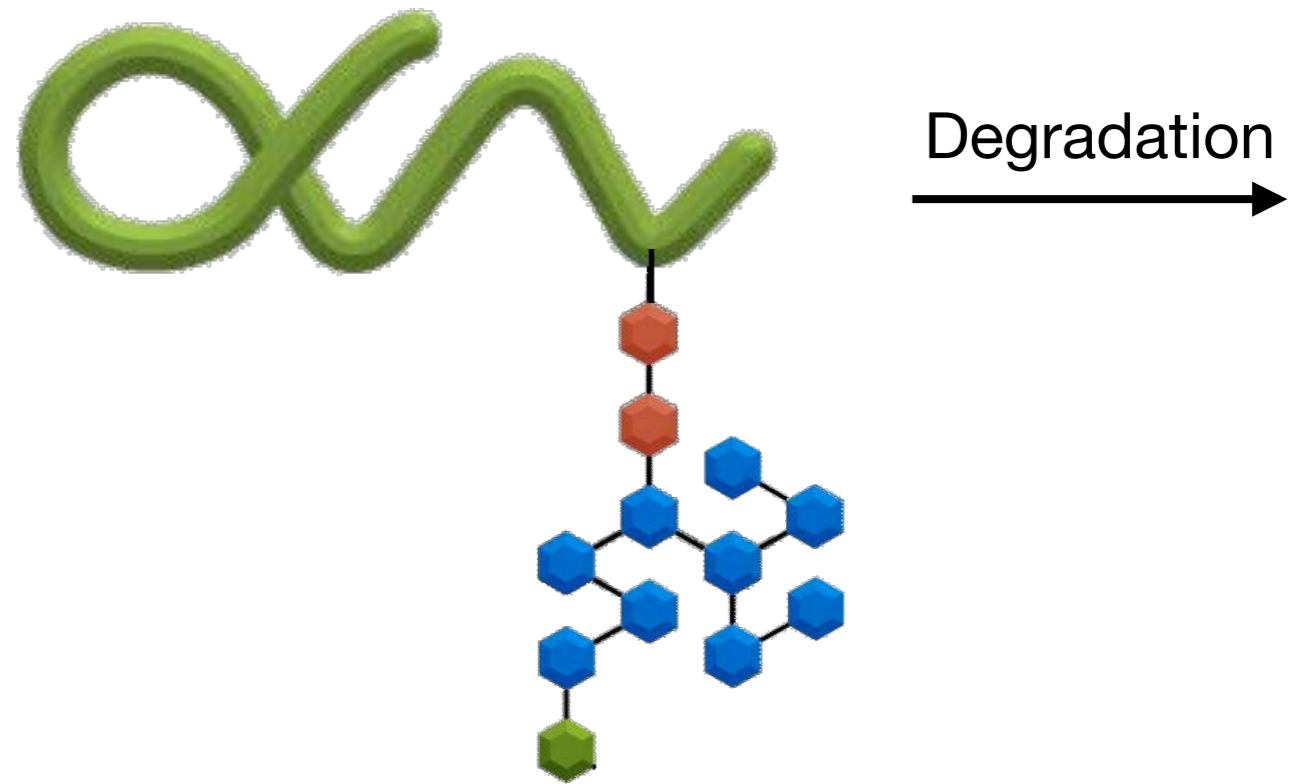
Calnexin and glucosyl transferase prevent unfolded proteins from leaving the ER.



Mannosidase triggers degradation pathway for ER proteins.

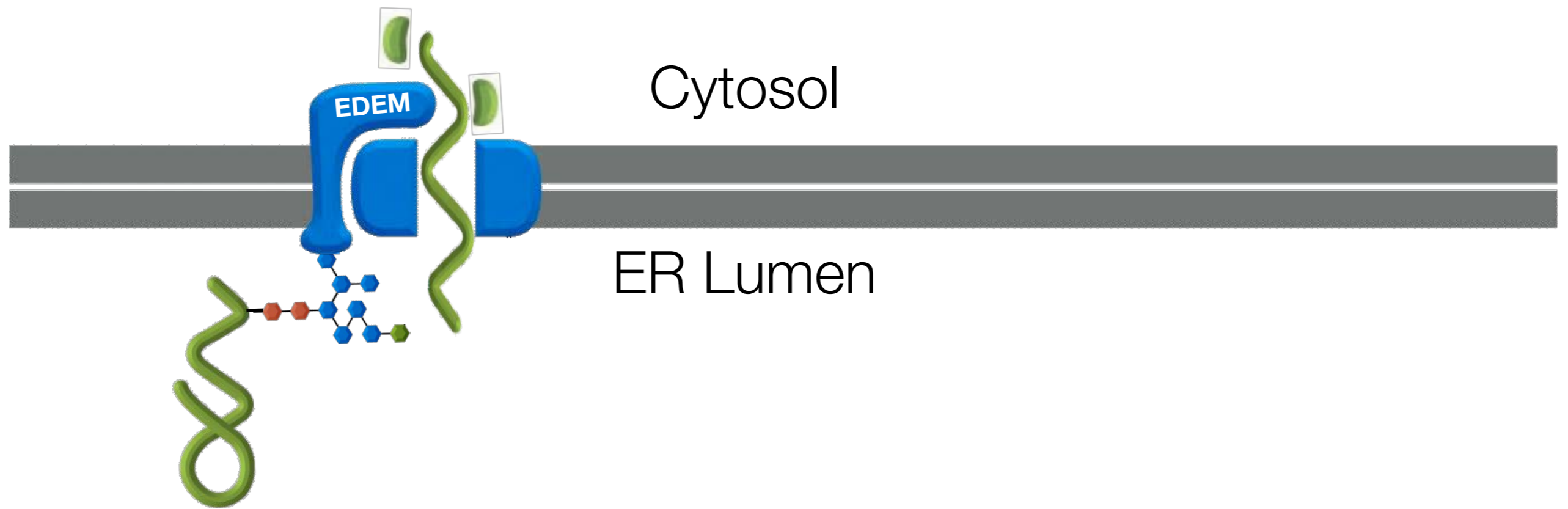


Folding Pathway

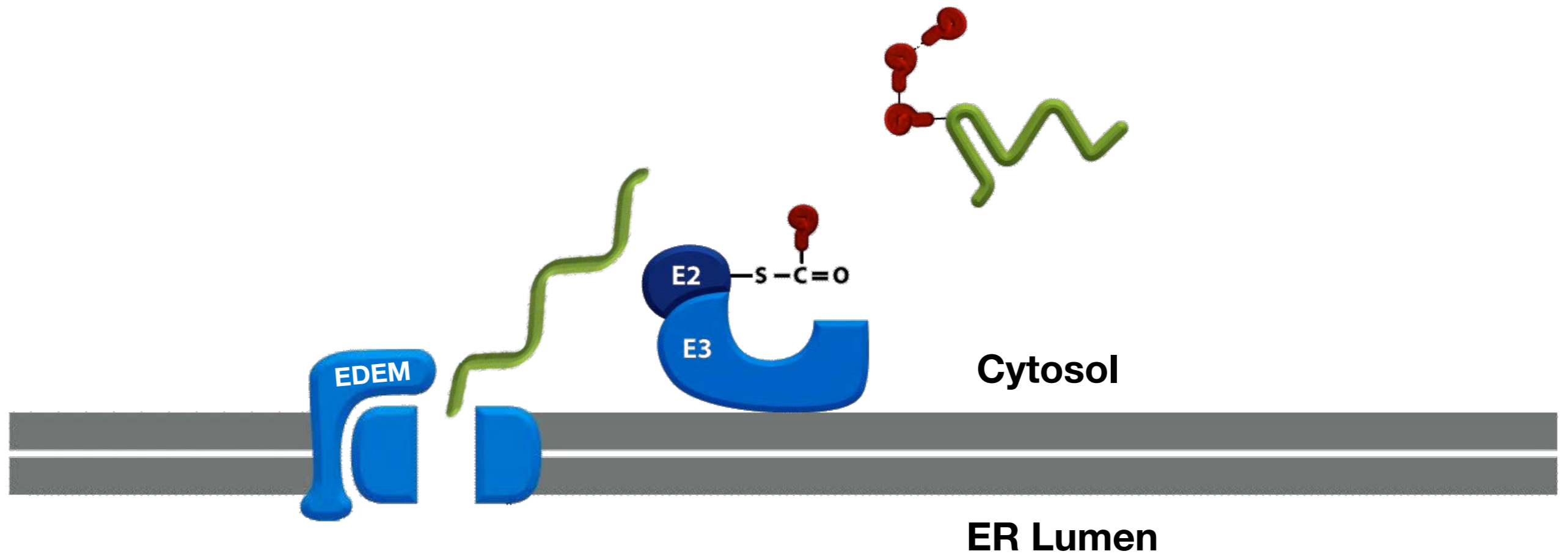


Mannosidase

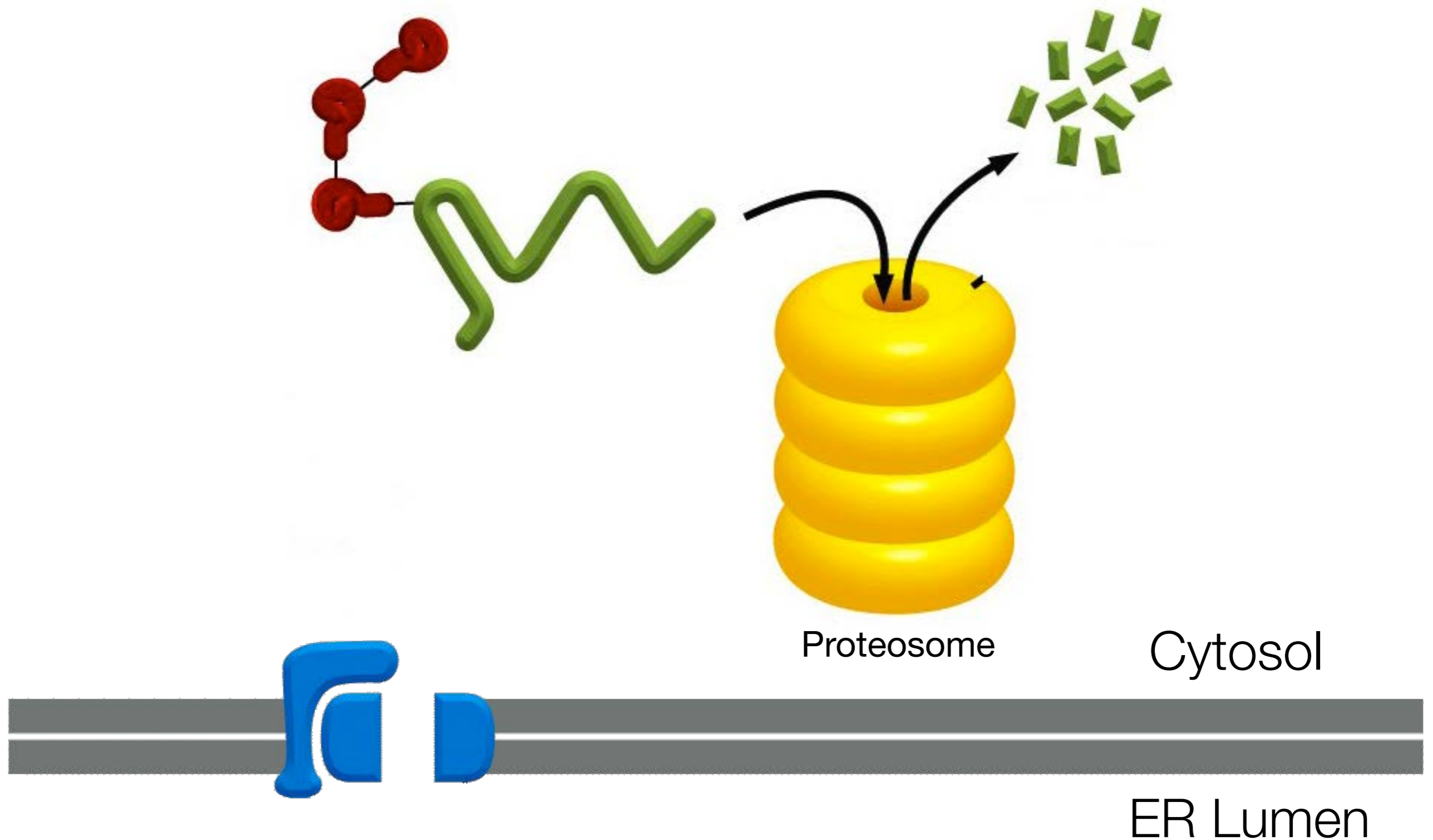
EDEM and retrotranslocator export unfolded proteins from lumen of ER.



Ubiquitin ligases on ER membrane tag unfolded proteins with ubiquitin.

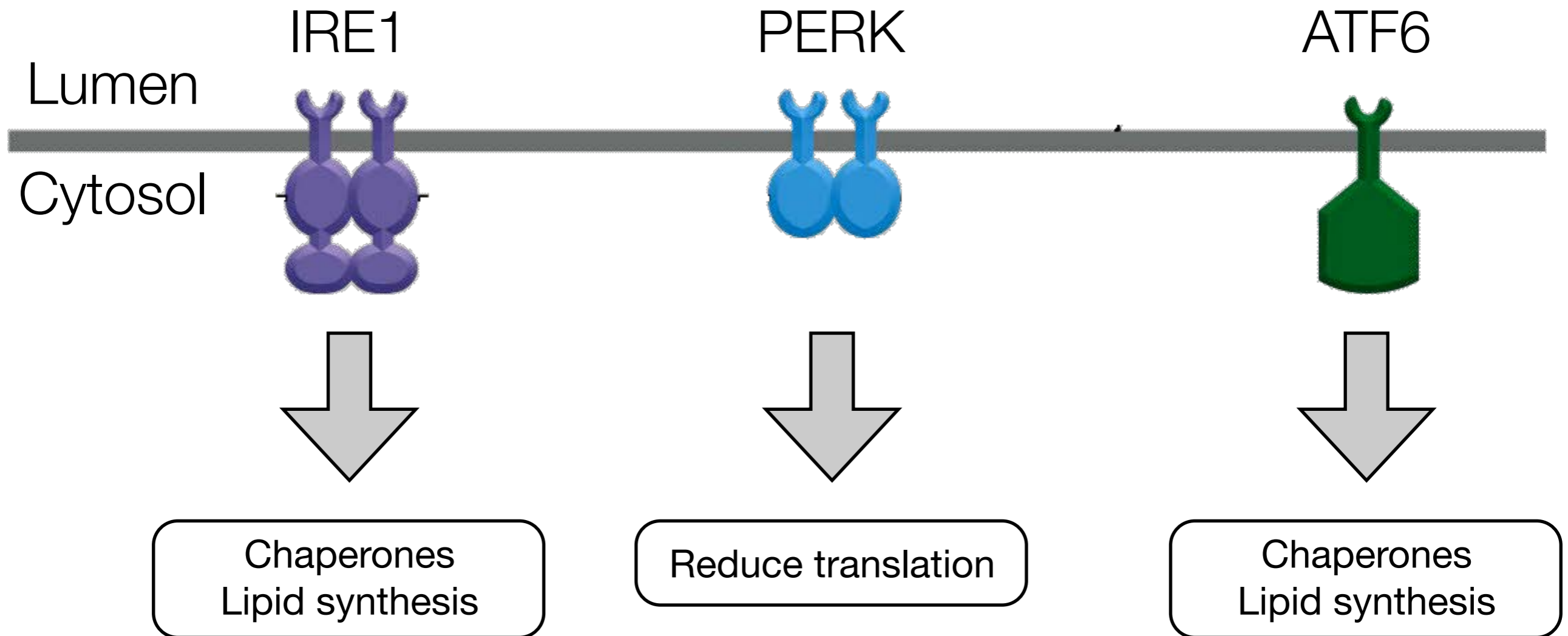


Proteasome in cytosol degrades unfolded ER proteins.

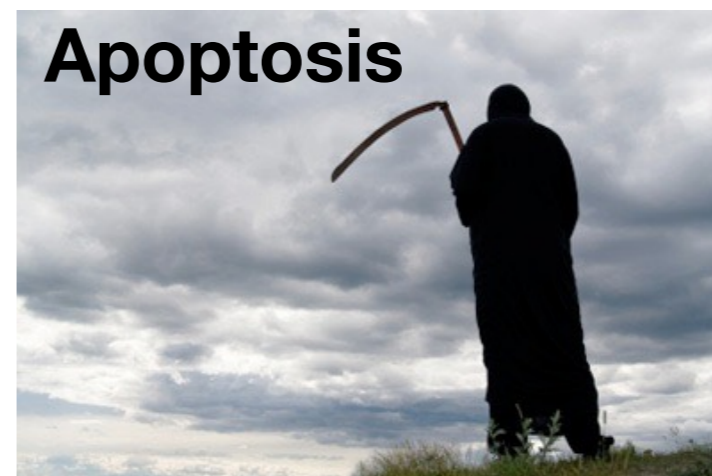
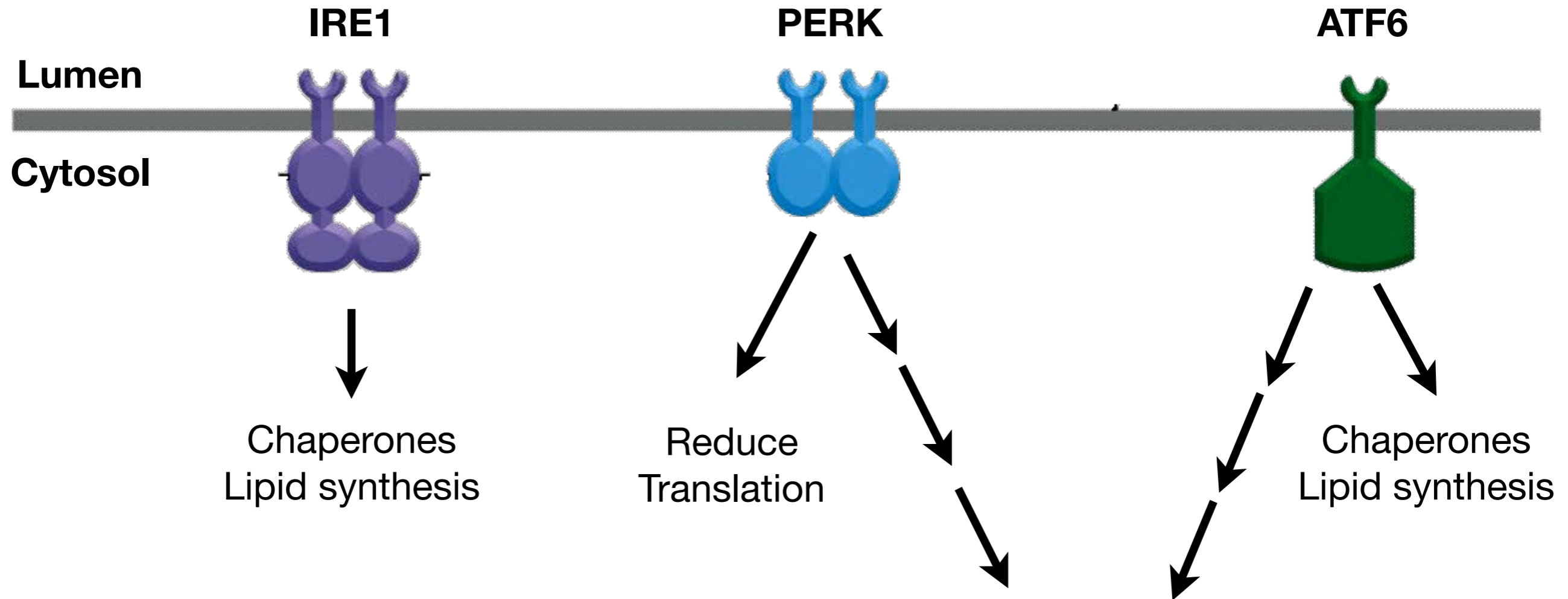


Responding to accumulation of unfolded proteins in the ER

Three sensors detect amount of unfolded protein in ER and generate response.



Prolonged activation of PERK and ATF6 trigger the apoptosis pathway.



Take home points...

- Chaperones bind hydrophobic domains in proteins to prevent aggregation and help folding.
- HSP90 can mask some genetic mutations by helping proteins find correct three-dimensional structure.
- Unfolded proteins in the cytosol are tagged by ubiquitin and degraded by proteasome.
- The ER retains unfolded proteins and eventually extrudes it for degradation.
- Excess unfolded protein in the ER triggers the unfolded protein response.