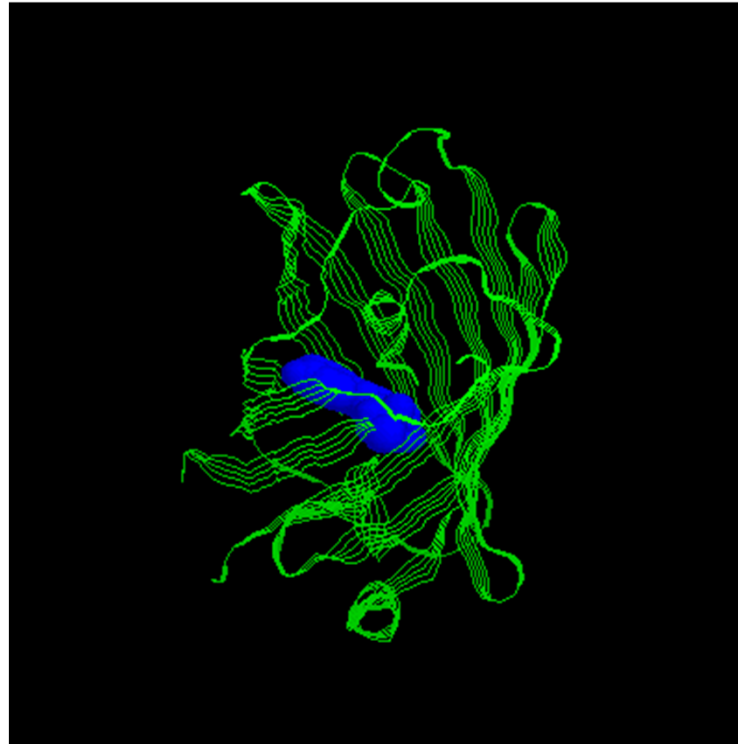


Protein structure and function



- The main structural component of cells.
- The main functional molecules.

Proteins

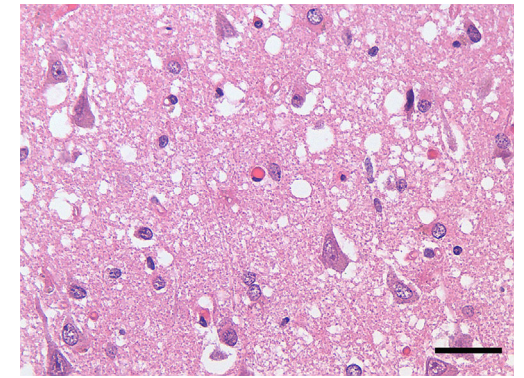
- **A major component of the cell**
- **Building blocks and molecules which carry out cellular function: Enzymes, transport, communication, movement, storage, regulation**
- **About 5,000 different proteins in each human cell**
 - Huge heterogeneity
 - Some are common in all cell types, others are specific to a particular cell type
 - Some are abundant, others are found in only a few copies per cell

Protein structure determines function

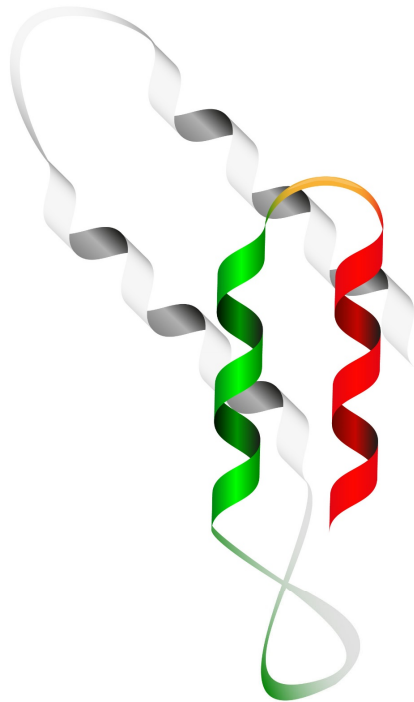
Can diseases be caused by defects in protein structure?



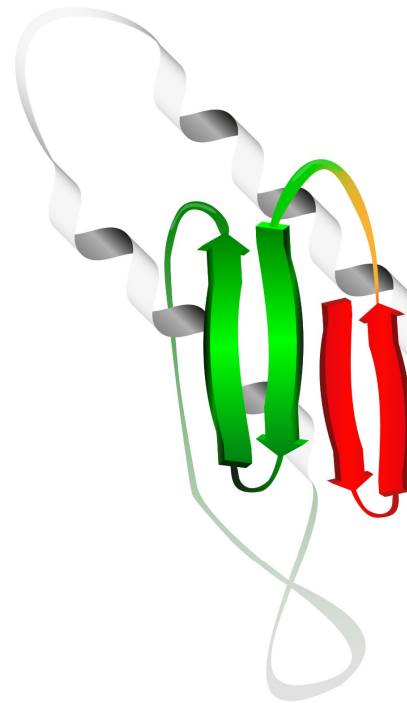
Spongiform encephalopathy (Mad cow disease, Creutzfeldt–Jakob disease)



PrP^C
is a normal protein



PrP^{Sc}
the disease-causing form of the
prion protein



Same amino-acid sequence, different structure

The disease-causing form leads the normal protein to misfolding

The disease-causing form is very stable: **transmissible**

Protein misfolding and disease

Different proteins, a shared problem: abnormal folding and aggregation



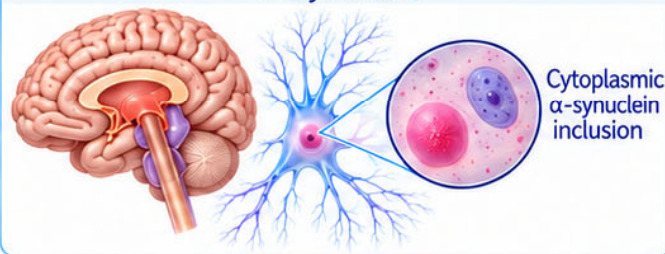
Alzheimer's disease

Amyloid- β and tau



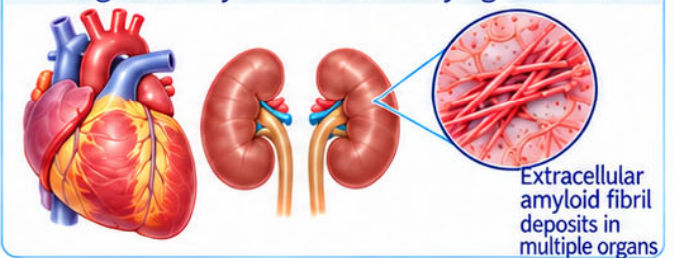
Parkinson's disease

α -Synuclein



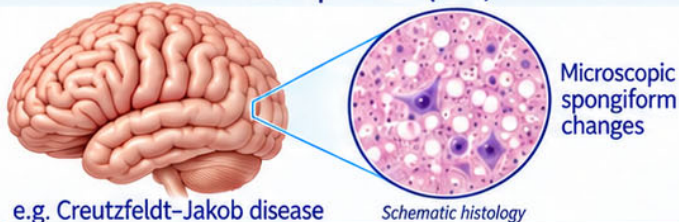
Systemic amyloidosis

e.g. transthyretin or antibody light chains



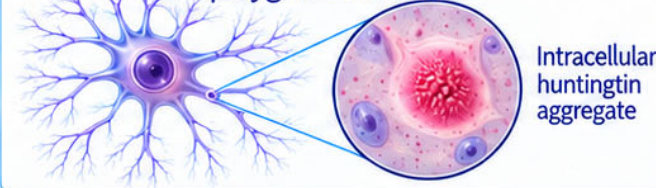
Prion diseases

Prion protein (PrP)



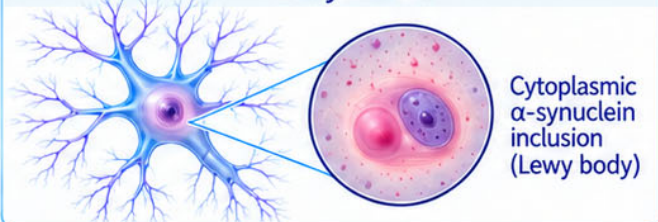
Huntington's disease

Huntingtin with expanded polyglutamine tract



Lewy body dementia

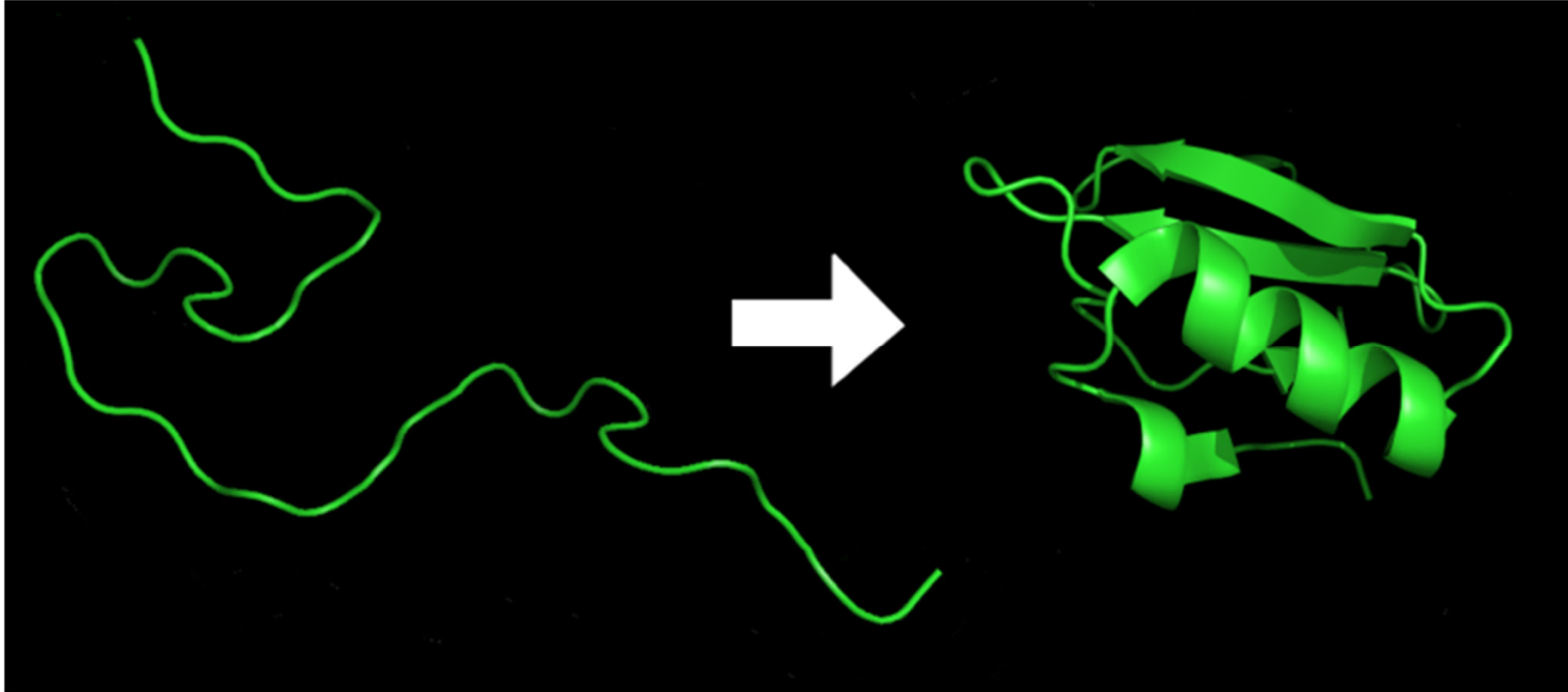
α -Synuclein



Abnormal protein conformations can disrupt cell and tissue function.

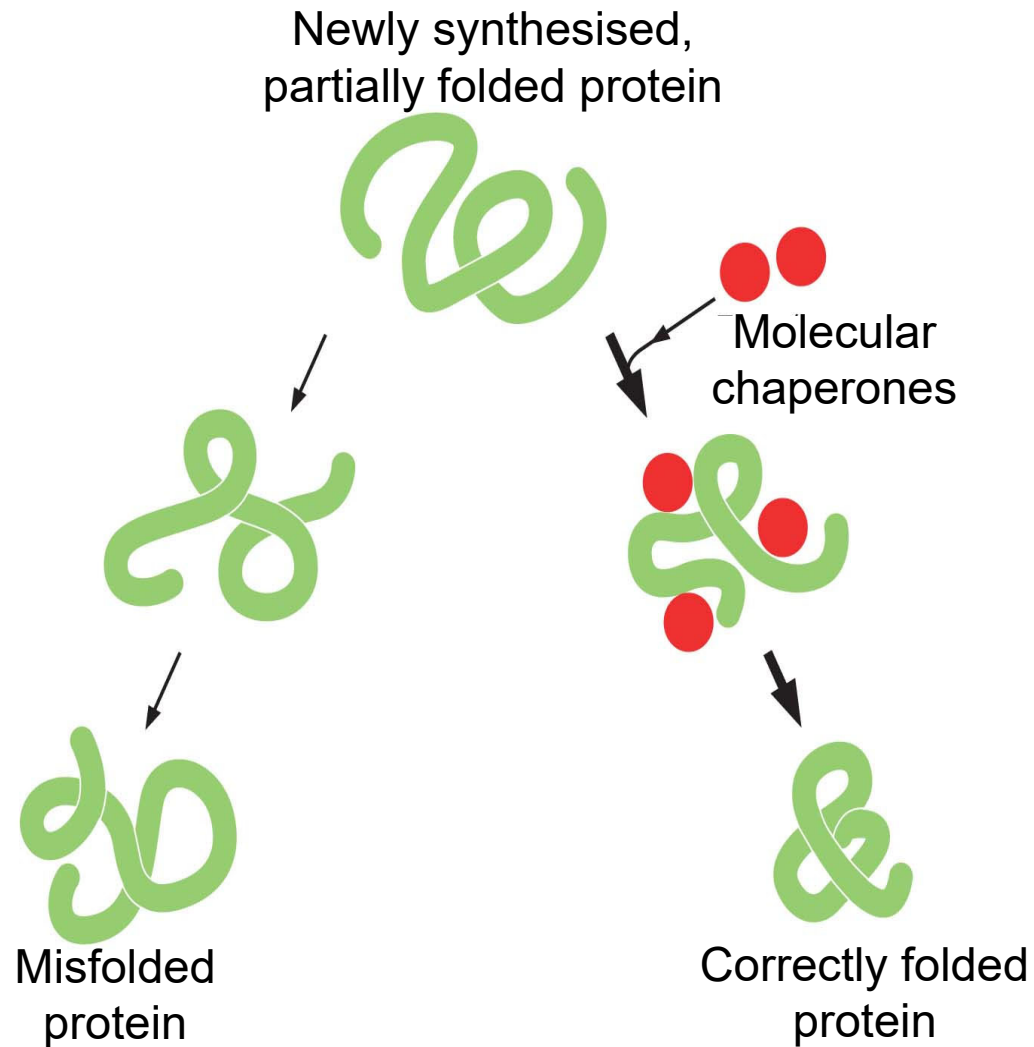
Misfolding and aggregation contribute to disease; visible aggregates are not always the toxic species.

Proteins fold into a stable conformation that enables a specific function

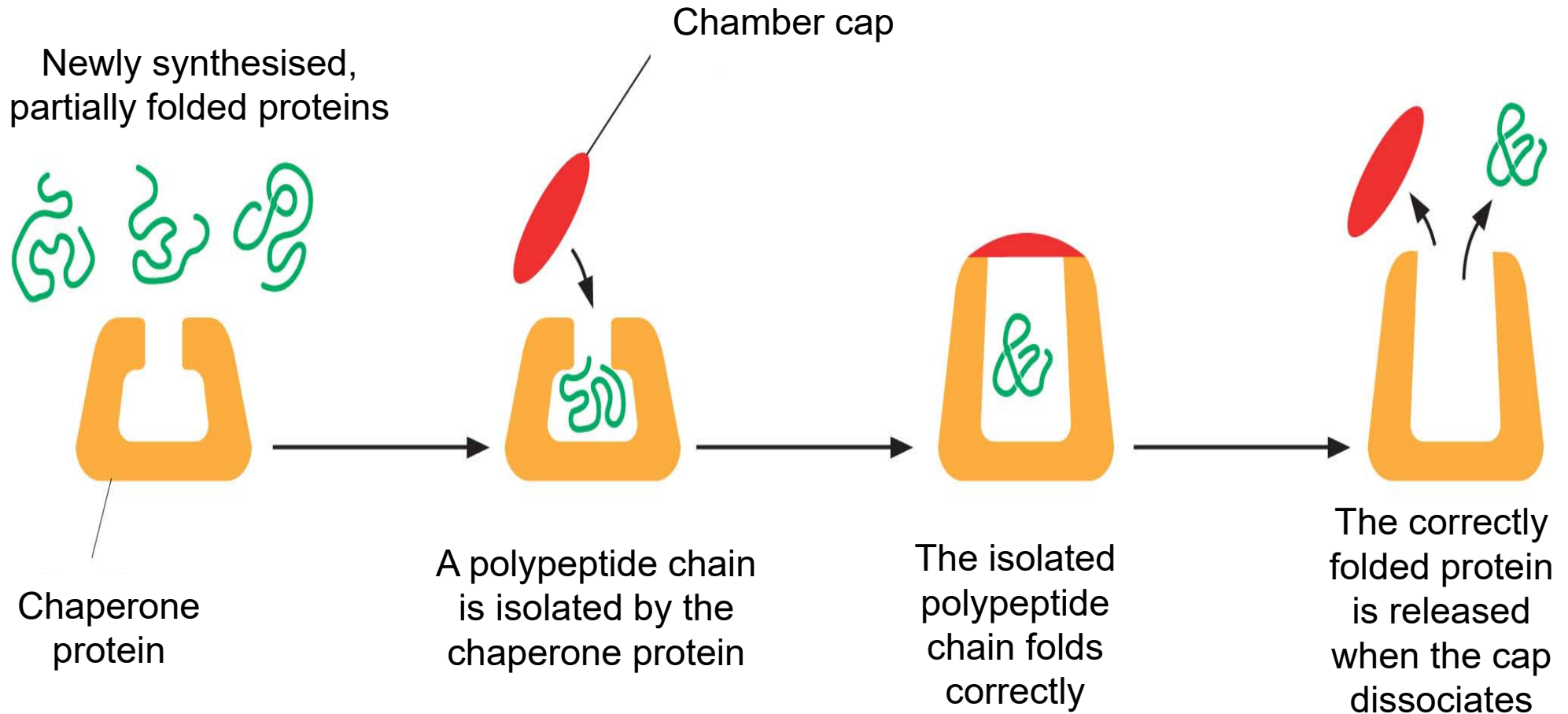


The amino acid sequence contains all the information for protein structure and function

In cells, molecular chaperones help proteins fold

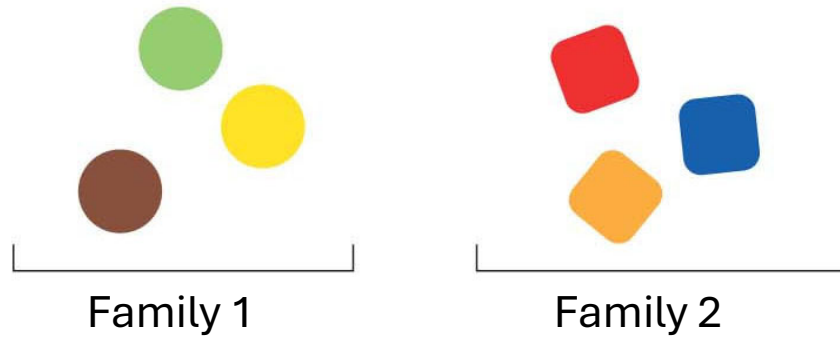


Molecular chaperones help proteins fold



Other chaperones act as isolation chambers that help a polypeptide fold. The chaperone cylinder forms a closed chamber in which a newly synthesised polypeptide chain can fold without the risk of aggregation with other polypeptides in the crowded cytoplasm. This system also requires energy from ATP hydrolysis, mainly for the binding and subsequent release of the cap that seals the chamber.

- Proteins are classified into families with similar structures- why?



They have a common evolutionary origin:

similar by decent = homologues

Many proteins are evolutionarily related

Homologous proteins (homologues): substantial structural and functional similarity due to common evolutionary origin.

The degree of amino-acid conservation indicates evolutionary divergence and/or a sequence essential for survival.

Orthologous proteins (orthologues): a category of homologous proteins

Corresponding proteins in different species,
derived from a common gene in an ancestral species and performing similar functions
E.g. human and mouse β -globin

Paralogous proteins (paralogues): a category of homologous proteins

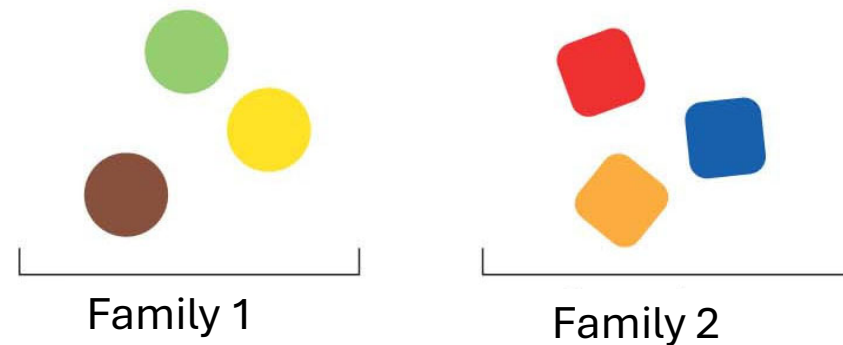
Homologous proteins within the same species;
in an ancestral species, **an original gene was duplicated**.
They have similar structure and often perform similar functions
E.g. human α - and β -globin

Critical thinking question

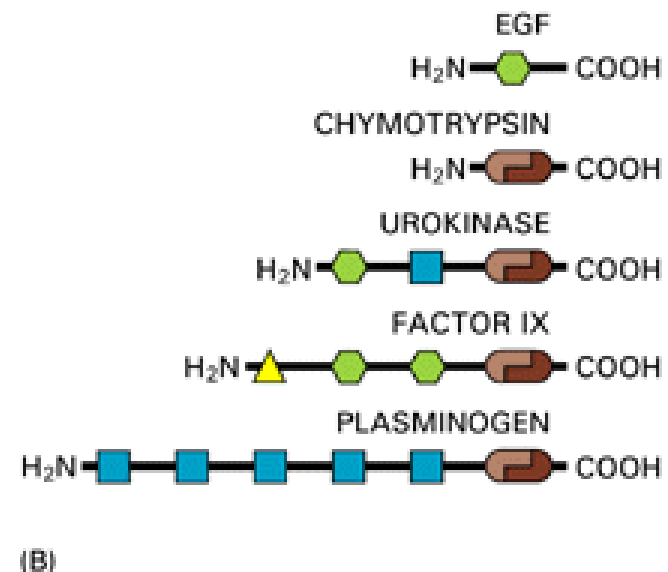
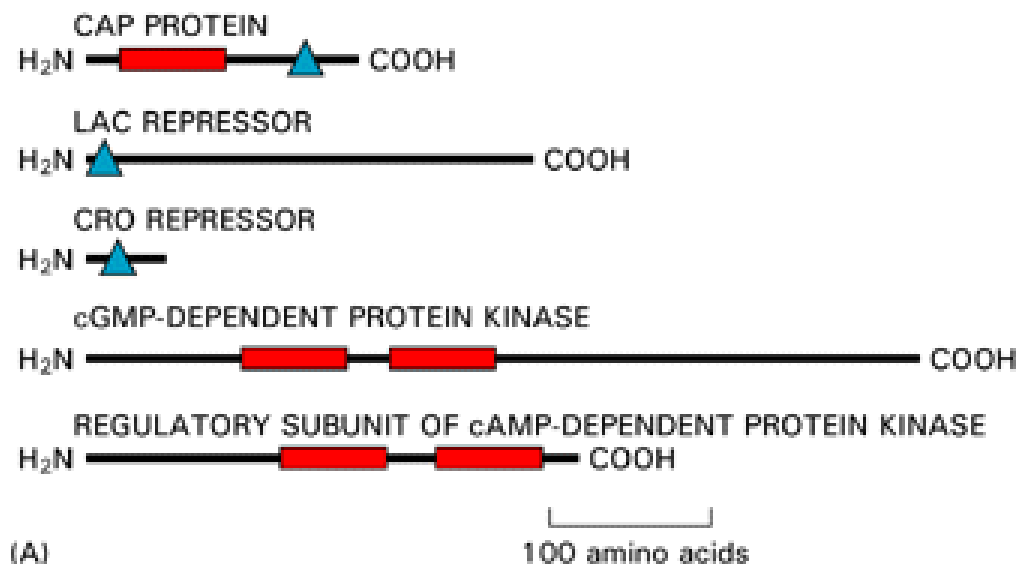
When is, in your opinion, a mutation in a human gene more likely to lead to disease:

- if it changes an amino acid that has been conserved during evolution, or
- if it changes an amino acid found only in the human protein?

- Proteins are classified into families with similar structures
- They have a common evolutionary origins: homologues



- Proteins contain motifs and **domains** also found in many other proteins (e.g. ATP binding and hydrolysis, DNA binding). Why?



Consider the following statements

- Stable folding is essential for protein function
- The ability to change structure is essential for protein function

Protein structure is dynamic

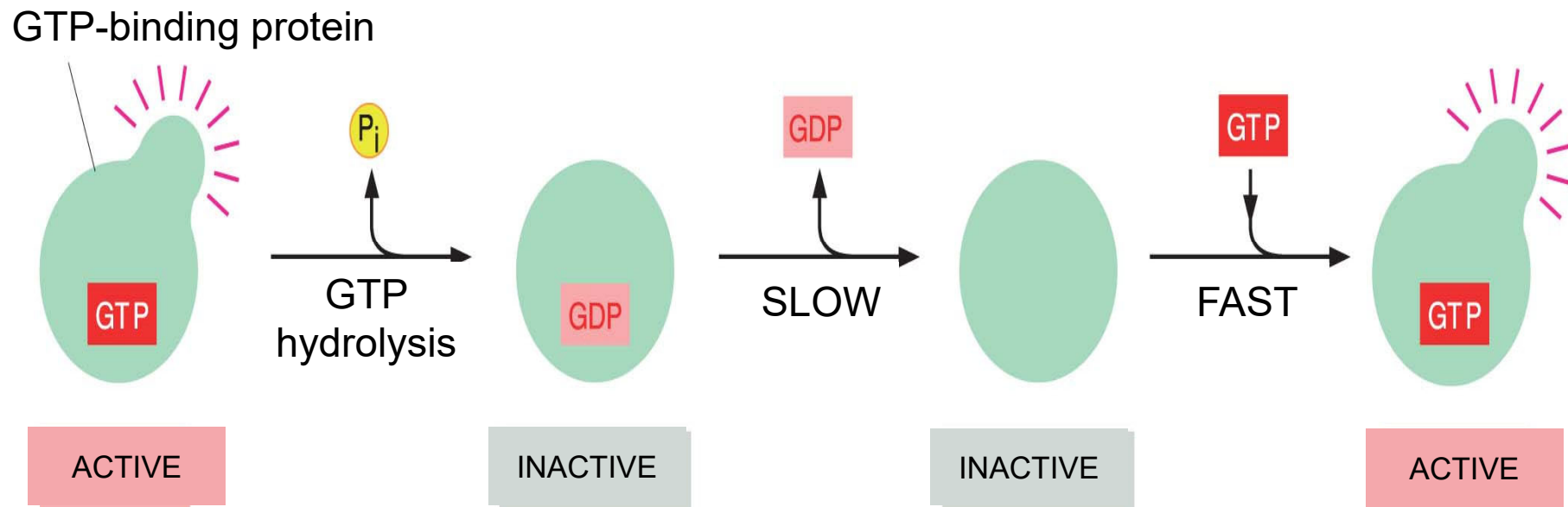
How is protein structure changed in a regulated way
after synthesis

Ways to regulate proteins

Binding of another molecule or protein partner

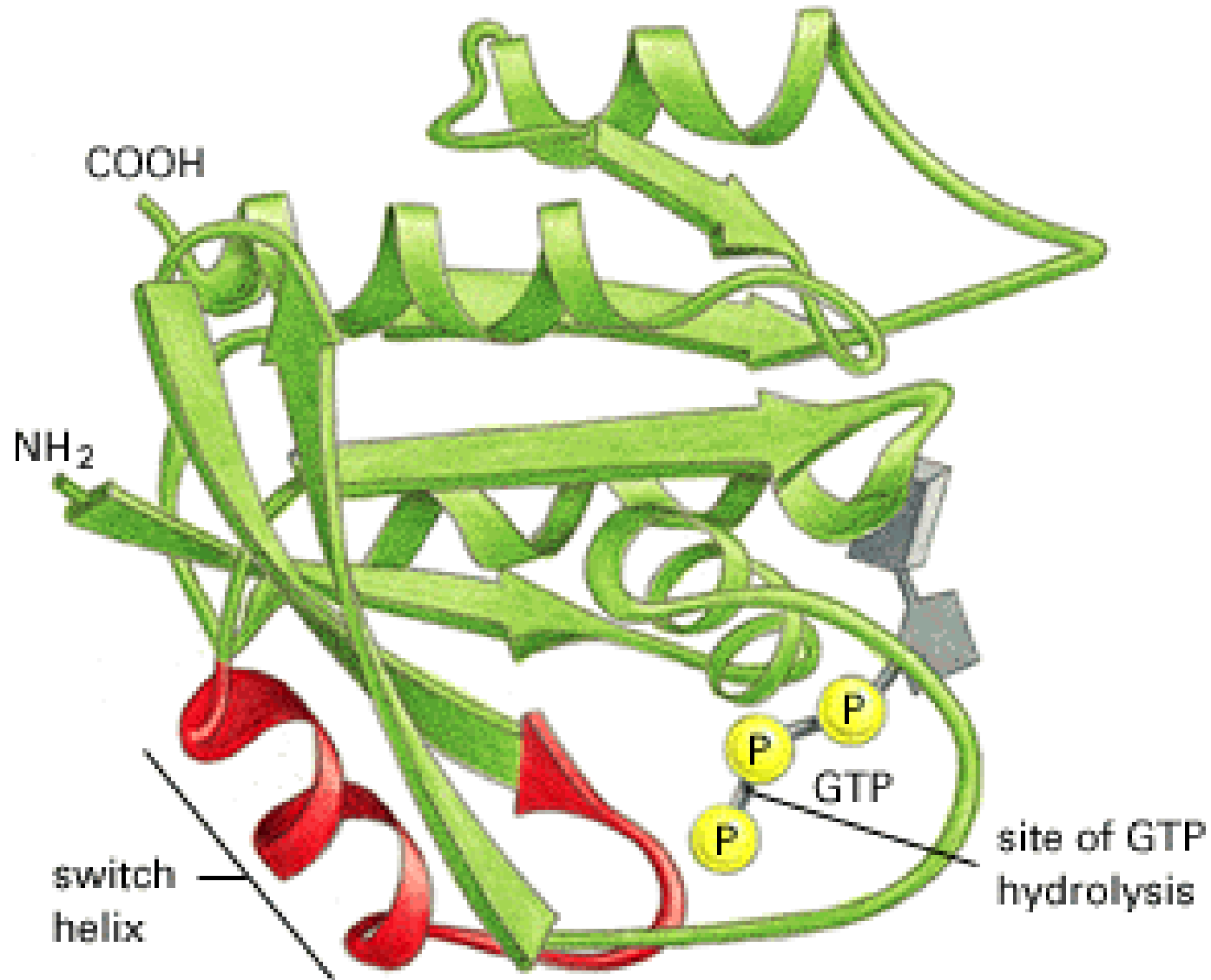
Binding and hydrolysis of nucleoside triphosphates (GTP, ATP) change protein conformation

(example: molecular switches)

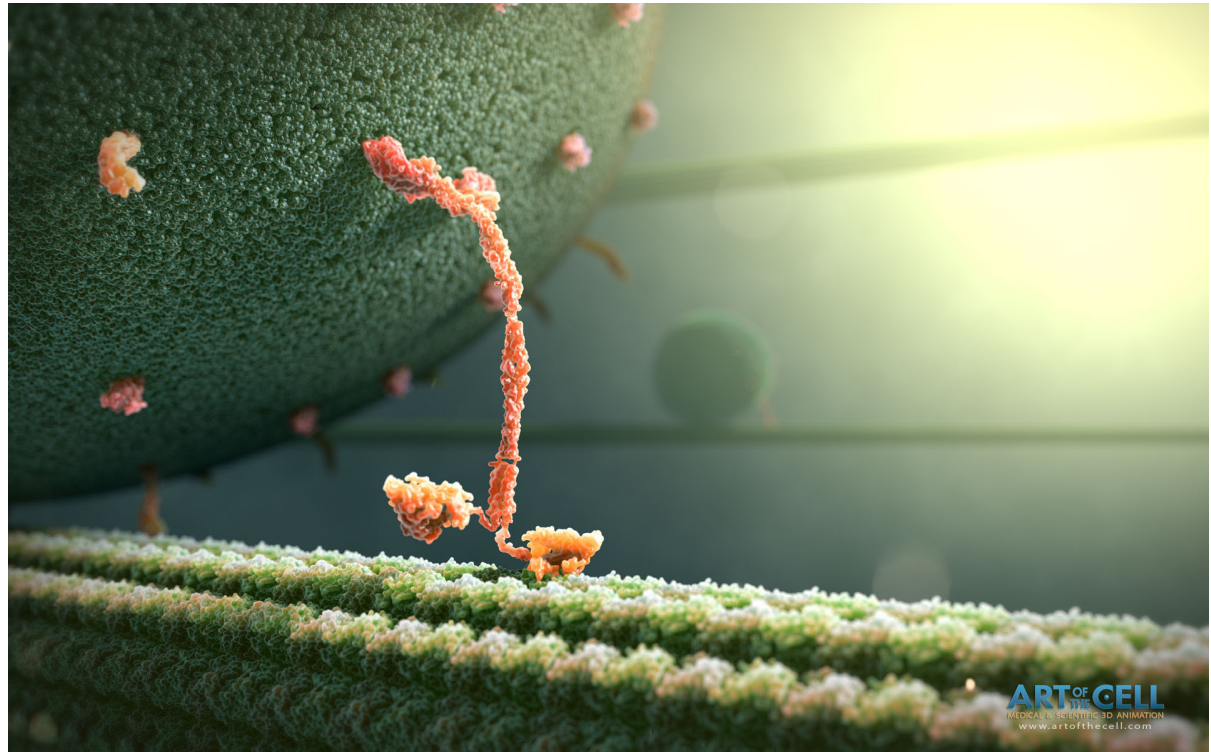
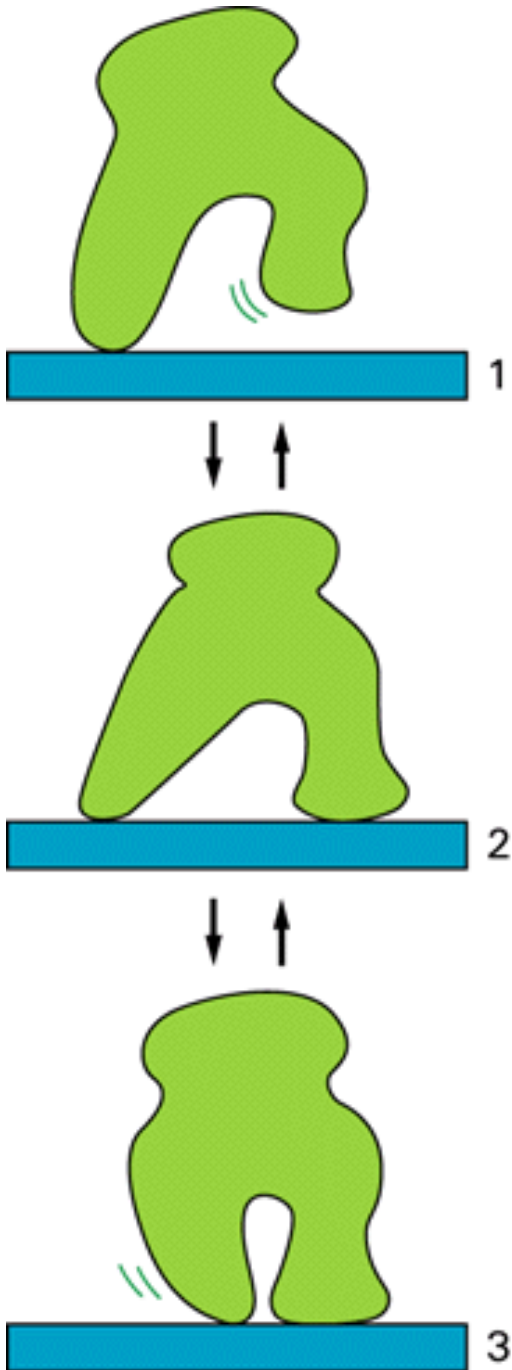


GTP-binding proteins act as molecular switches. A G protein requires tightly bound GTP to be active (ON). It switches off by hydrolysing bound GTP to GDP and inorganic phosphate (P_i), adopting an inactive conformation (OFF). Reactivation requires the tightly bound GDP to dissociate: a slow step accelerated by other signalling proteins. Once GDP dissociates, it is rapidly replaced by GTP and the protein returns to its active conformation.

**Ras (encoded by a proto-oncogene)
is regulated by GTP hydrolysis**



Nucleotide hydrolysis gives direction to biological processes



How is protein structure changed in a regulated way after synthesis?

Ways to regulate proteins

Binding of another molecule or protein partner
nucleotide binding and hydrolysis

Side-chain modification – post-translational modifications

Post-translational modifications

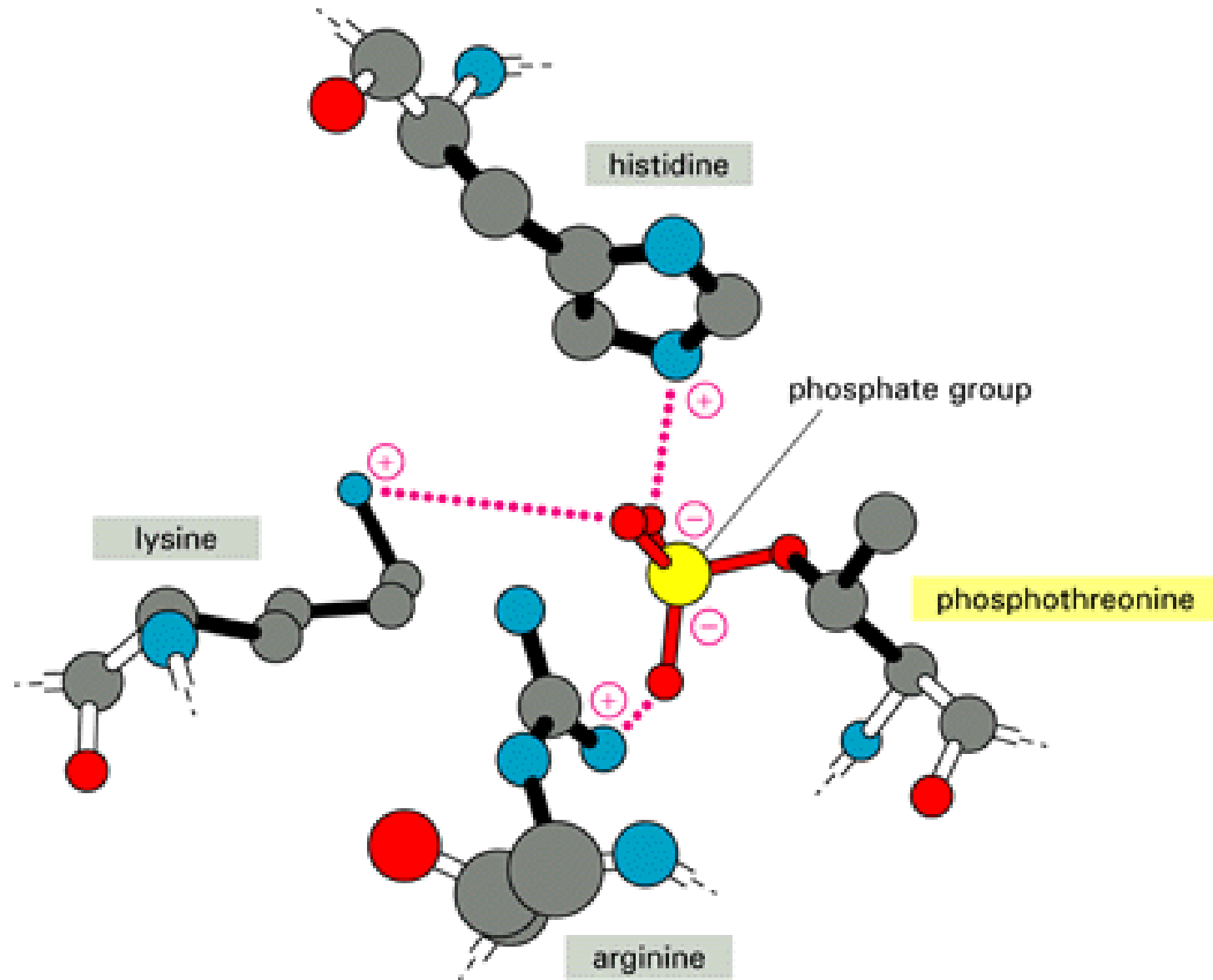
Changes to amino acid side chains:

adding groups (covalently) alters their properties → different interactions

Different structure = different function

- **Phosphorylation** = addition of phosphate groups to serine, threonine and tyrosine side chains

Changes in structure and interactions with other molecules through phosphorylation



At any given time, more than one-third of the proteins in a human cell are phosphorylated!

Post-translational modifications

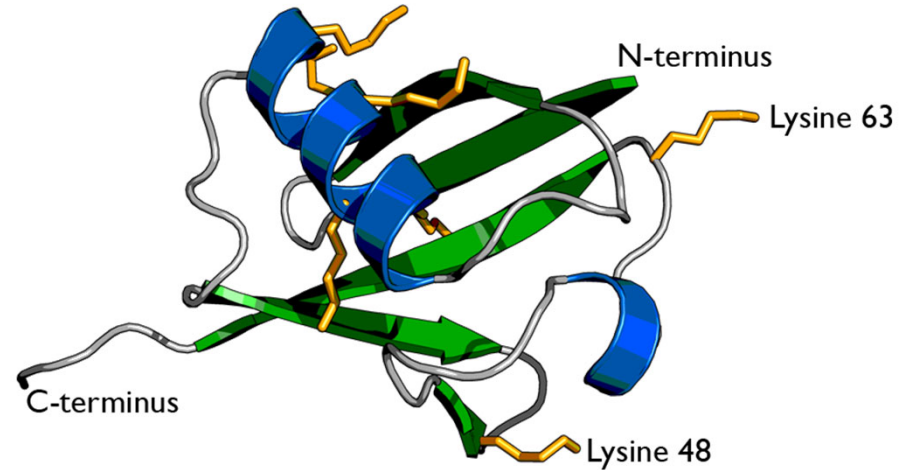
Changes to amino acid side chains: adding groups alters their properties → different interactions

Different structure = different function

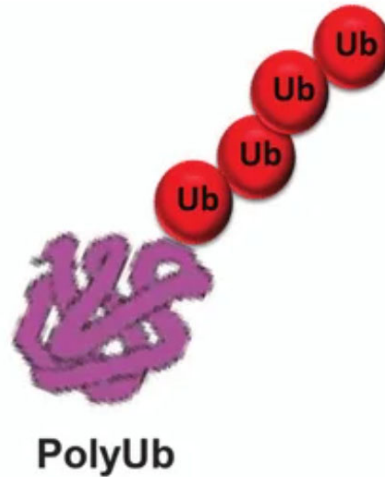
- Phosphorylation = addition of phosphate groups to serine, threonine and tyrosine side chains
- Methylation, acetylation = addition of methyl/acetyl groups to side chains, mainly lysine (K) (e.g. histones and transcriptional regulation)
- Ubiquitination (targets proteins for degradation)

Ubiquitination

Addition of a small protein (ubiquitin) to a lysine side chain



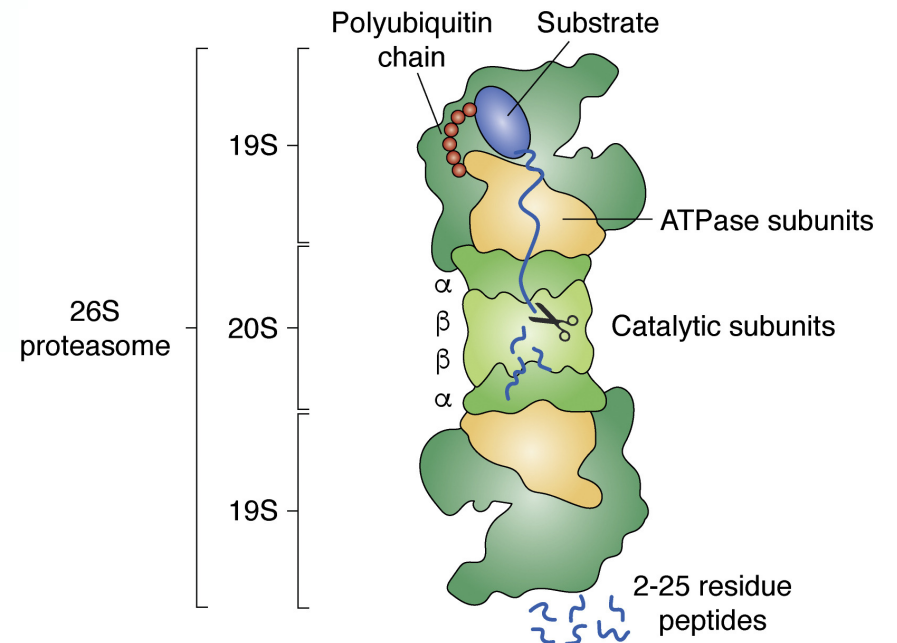
Mono-ubiquitination



Polyubiquitination



Proteolysis (in the proteasome)

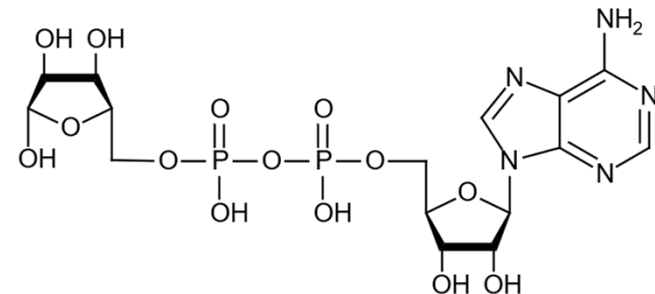


Post-translational modifications

Changes to amino acid side chains: adding groups (**covalently**) alters their properties → different interactions

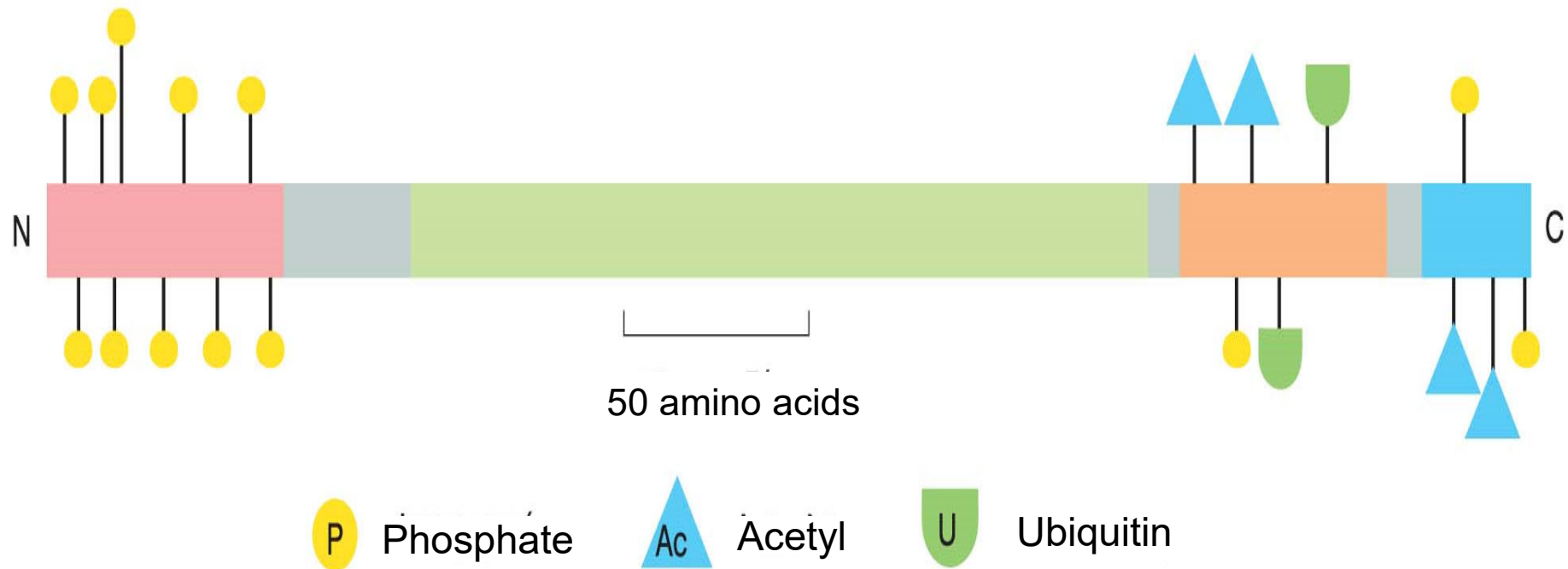
Different structure = different function

- Phosphorylation = addition of phosphate groups to serine, threonine and tyrosine side chains
- Methylation, acetylation = addition of methyl/acetyl groups to side chains, mainly lysine (K) (e.g. histones and transcriptional regulation)
- Ubiquitination (polyubiquitination targets proteins for degradation)
- SUMOylation, NEDDylation
- PARylation (a modified nucleotide is added)
- farnesylation, palmitoylation (a lipid is added)



Multiple post-translational modifications can coexist on one protein

SOME KNOWN MODIFICATIONS OF p53



Post-translational modification at multiple sites regulates protein behaviour. The diagram shows some covalent modifications that regulate the activity and degradation of p53, which controls the cellular response to DNA damage (see Chapter 18). These modifications do not all occur at the same time. Colours along the protein represent distinct domains, including a DNA-binding domain (green) and a domain that activates gene transcription (pink). All the modifications shown occur in relatively unstructured regions of the polypeptide chain.

How is protein structure changed in a regulated way after synthesis?

Ways to regulate proteins

Binding of another molecule or protein partner
nucleotide binding and hydrolysis

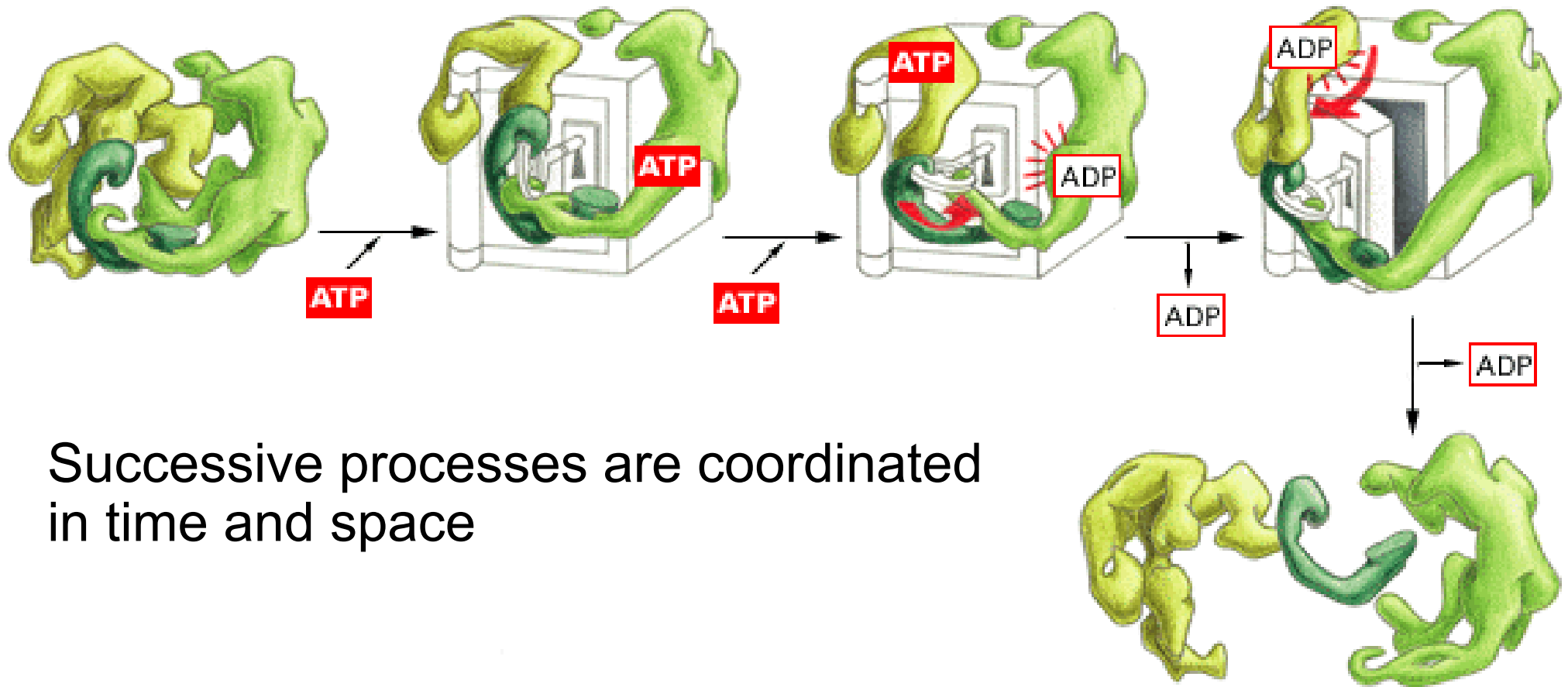
Side-chain modification – post-translational modifications

Proteolytic cleavage

Protein degradation (proteolysis)

Protein machines

Large protein complexes that carry out cellular functions in a coordinated way



Successive processes are coordinated in time and space

Examples: DNA replication, transcription, protein synthesis

Main Points

- Proteins are the structural building blocks and functional molecules of the cell
- The amino acid sequence determines protein conformation and function
- Transient, controlled changes in protein conformation are often essential for activity
- Cells regulate proteins through post-translational modifications (phosphorylation, acetylation, ubiquitination)
- Proteins work together to form protein machines
- Defects in protein conformation can have devastating consequences for the organism
 - * Sickle cell anaemia
 - * Spongiform encephalopathy (BSE, mad cow disease)