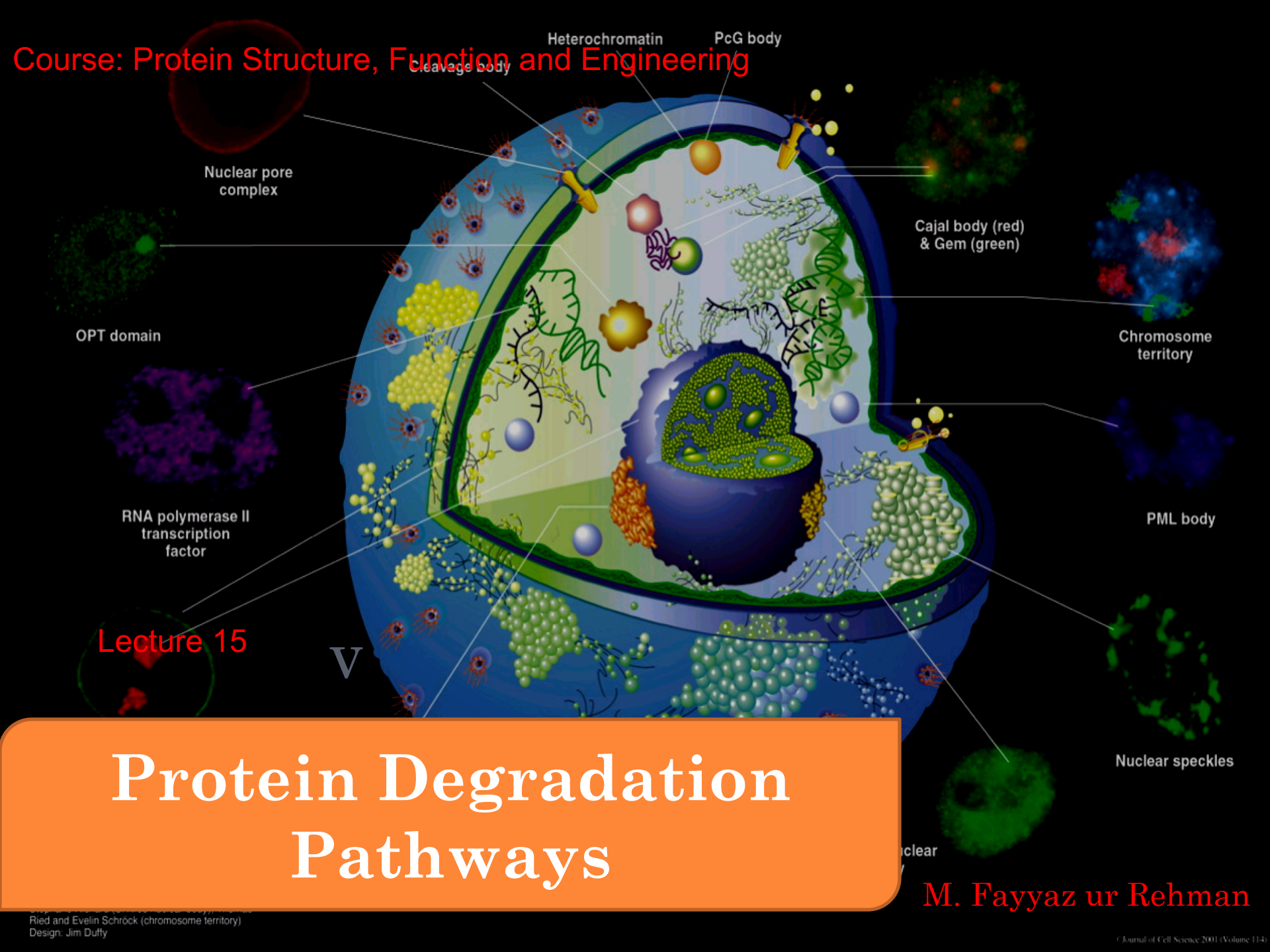
Course: Protein Structure, Function and Engineering



Lecture 15

Protein Degradation Pathways

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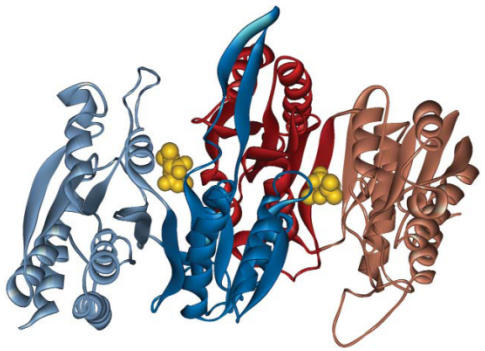
Catalytic sites

- **Occur at domain and subunit interfaces**
- **Can be Predicted**
  - If a protein has more than one **structural domain,**
    - **Then** the catalytic site will nearly always be found at the interface between two of them, or all of them.
  - If the protein is composed of more than one subunit,
    - **Then** the active site will often be found at an intersubunit interface.
  - If Both
    - **Then** , both an interdomain and an intersubunit interface

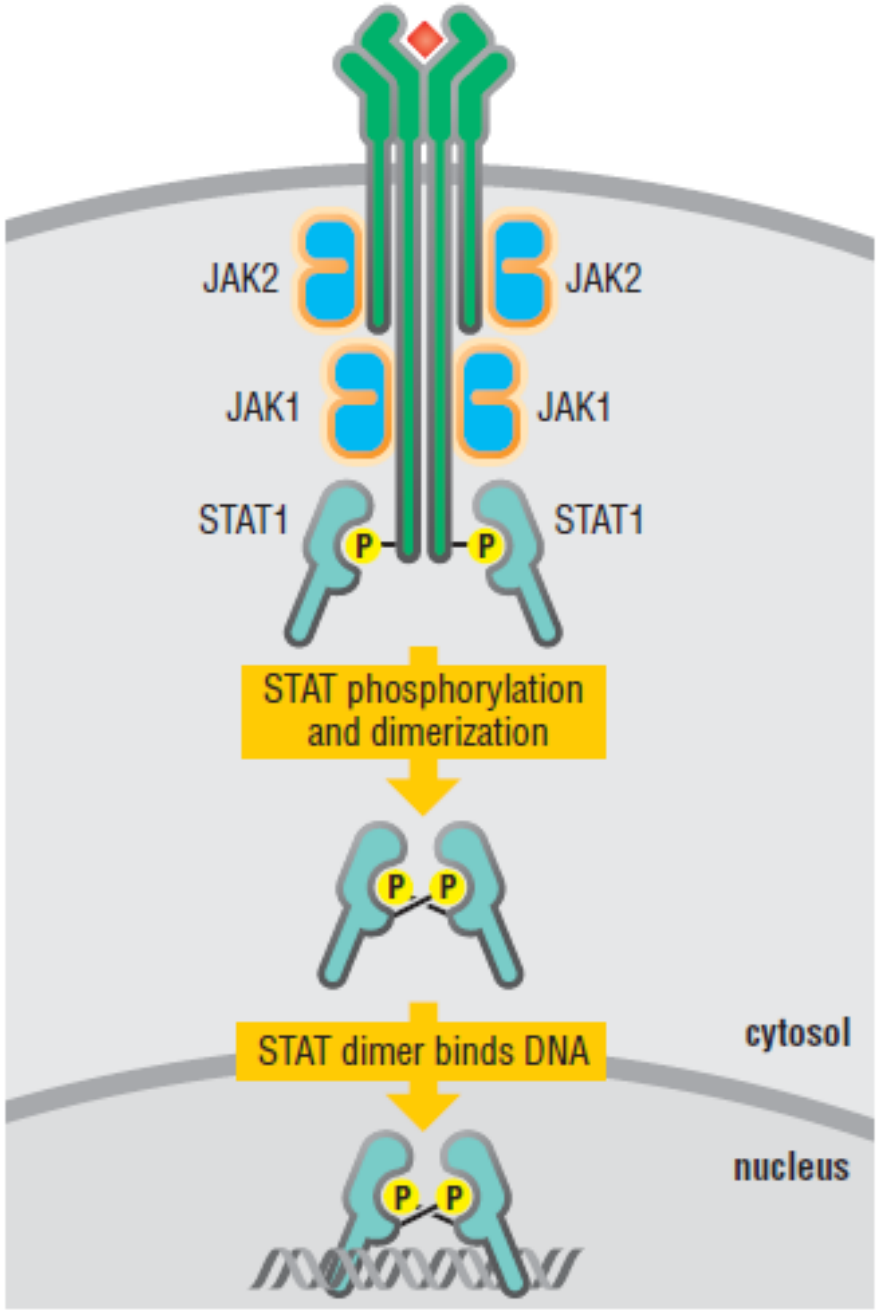


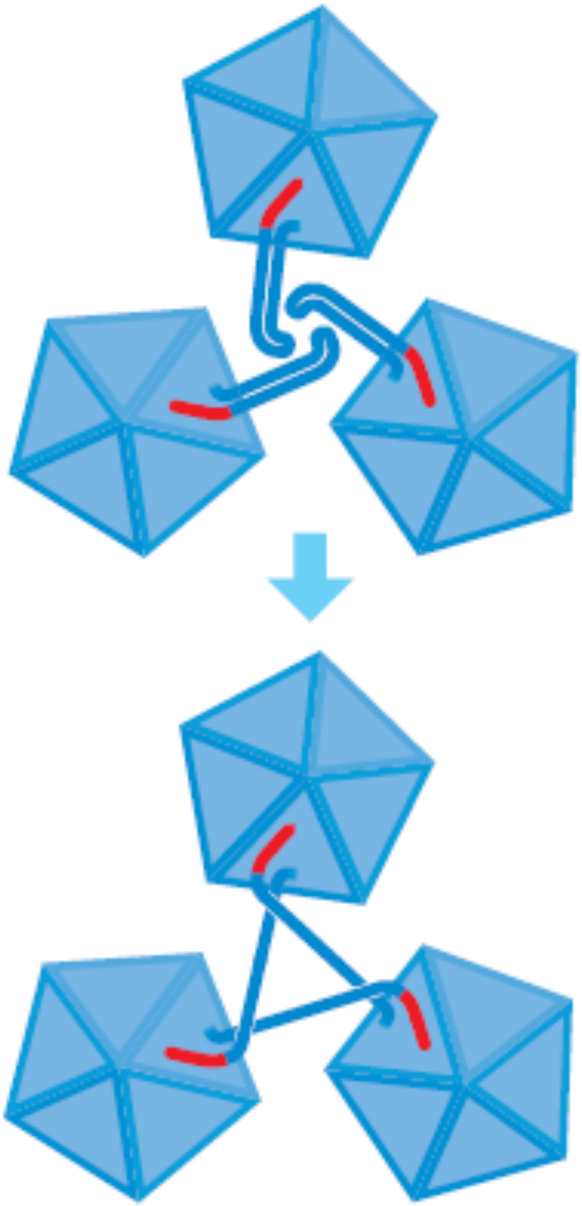
Binding sites, hydrophobic surface

- Protein surfaces are never completely polar
- Ligand-binding sites, however, are generally distinguished by a much higher than average amount of exposed hydrophobic surface area
- **Binding sites for small molecules**
  - concave and partly hydrophobic
  - lead to self-association and indeed they are the basis for oligomerization
  - allow the protein to self-associate.
  - readily associate with a small-molecule ligand

Weak interactions & exchange of partners

- Weak interactions can lead to an easy exchange of partners
- smaller hydrophobic patches that are important in more transient protein–protein interactions
  - Less Hydrophobic
  - two partners can exist independently
- **Partner swapping**
  - Kinases, Phosphatases, and G-protein effectors are targeted to
  - other proteins by specialized modules such as the SH2 domain
  - which recognizes phosphotyrosine-containing peptides on other proteins
- **Domain swapping**
  - Found in viral coat proteins and signal transduction proteins.
  - PAK1 protein kinase
    - each monomer inhibits the active site of the other monomer


JAK2
JAK2
JAK1
JAK1
STAT1
STAT1
P
P
STAT phosphorylation and dimerization
P
P
STAT dimer binds DNA
cytosol
nucleus
P
P



Displacement of water also drives binding events

- Surface Water Molecules
  - interact more or less tightly with the protein surface
- Ligand which is itself surrounded by water molecules to bind to a solvated protein
  - Both water layers must be disrupted and, at least partially, displaced.
  - the protein and the ligand would exchange a layer of waters for favorable interactions with each other

BINDING AFFINITY & BINDING SPECIFICITY

- the affinity, or strength, of such binding and contributions to ligand specificity.
- **The affinity** between a protein and its ligand
  - Chiefly due to hydrophobic interactions which are non-directional,
- **The Specificity** of binding is chiefly due to **anisotropic,** or directional, forces such as hydrogen bonding
- Relative contributions of the different types of interactions to specificity and affinity will clearly vary from case to case

Proteins as frameworks, connectors and scaffolds

- All cells are surrounded by a protein-reinforced membrane
- some have a cell wall that is primarily protein and carbohydrate
- Internal structures within the cell also are made up of particular structural proteins
- In some cases, structural proteins are assisted by DNA, RNA, lipid and carbohydrate molecules
- In other cases the structure is built up from a large number of different proteins.
  - The ribosome
- There is a dynamic character to many of these subcellular structures.
  - Muscle, the structure itself can change shape in response to external stimuli; in other cases, the structural proteins provide a framework for dynamic processes to occur, driven by other types of proteins.
- Some structural proteins form temporary structures that are then destroyed when no longer needed
  - Fibrinogen, the primary component of blood clots

STRUCTURAL PROTEINS ONLY FORM STABLE ASSEMBLIES

- Structural components of cells and organisms are designed to be permanent
  - They are neither altered nor destroyed during the lifetime of the organism.
- Such assemblies can be constructed from proteins alone,
  - as in the case of silk, collagen, elastin or keratin, or the coat proteins of a virus,
- or constructed from protein plus some other component, as in the case of cartilage, which is composed of protein plus carbohydrate.

Structure Stabilization

- There are two ways in which these structures can be stabilized.
- One is by protein–protein interactions alone.
- Such interactions are non-covalent and thus relatively weak in energetic terms, relatively weak in energetic terms.
- To make the assembly take on a particular shape, the interactions also need to be specific.
- One way to achieve a large number of specific weak interactions is
  - to place the complementary surfaces on simple repeating secondary structure elements such as alpha helices and beta strands.
- Stable assemblies are thus often coiled coils of long helices or stacks of beta sheets
- Collagen, the fibrous component of tendons, Variability at the third position in the repeat can impart special local properties
- Silk is an example of a stack of beta sheets

CATALYTIC PROTEINS CAN ALSO HAVE A STRUCTURAL ROLE

- structural proteins very often have cellular functions that require time-dependent changes
- changes are often brought about by changes in the structure of a single component of the multicomponent assembly
- This may be merely the binding of another protein or small molecule—
- as small as a proton if the change is pH-driven as in the conformational changes required for fusion of viruses to cell membranes—
- but is usually a protein-catalyzed chemical transformation such as the hydrolysis of ATP.