

CONTROL OF PROTEIN FUNCTION IN CELL

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SUSTC

Regulation is everywhere



Traffic



Finance

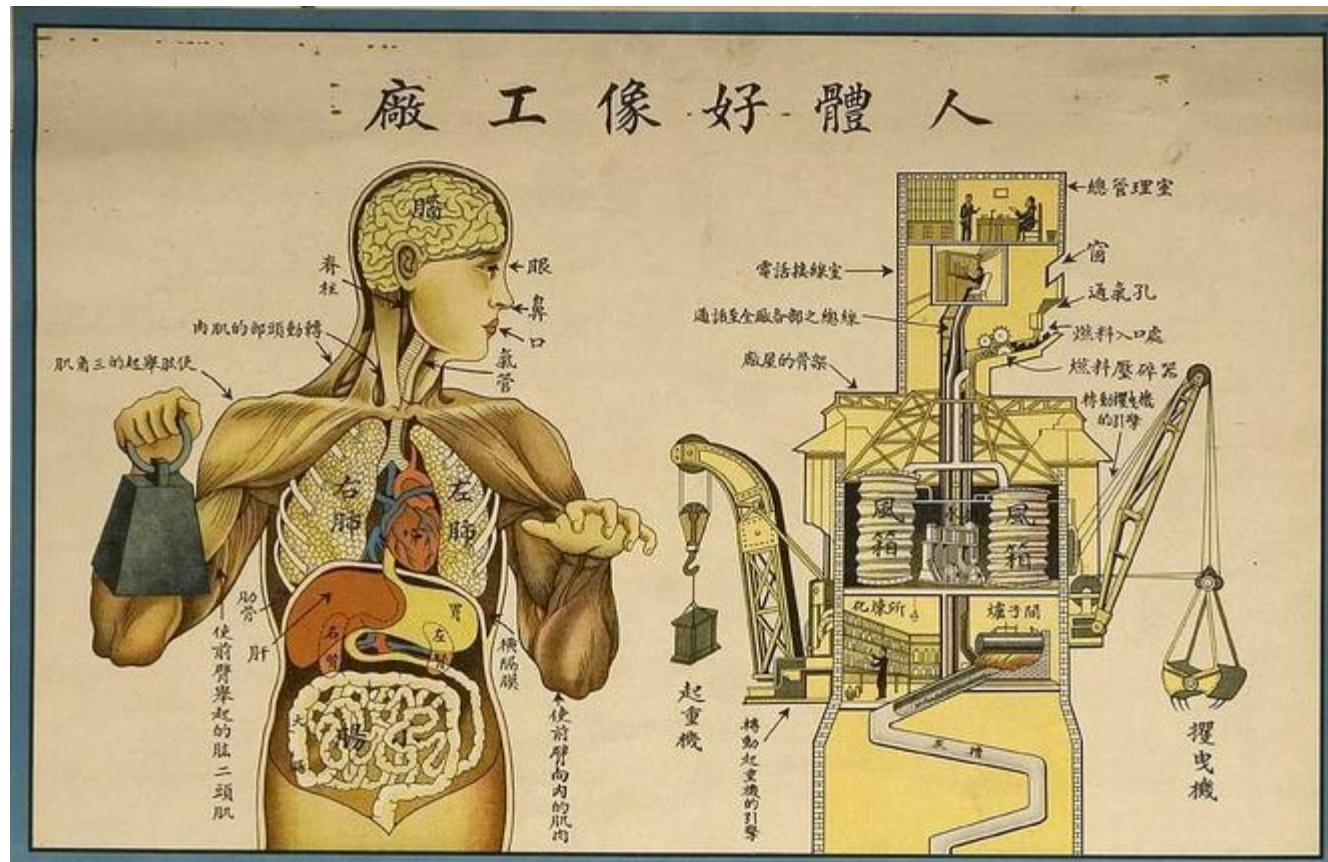


Logistics

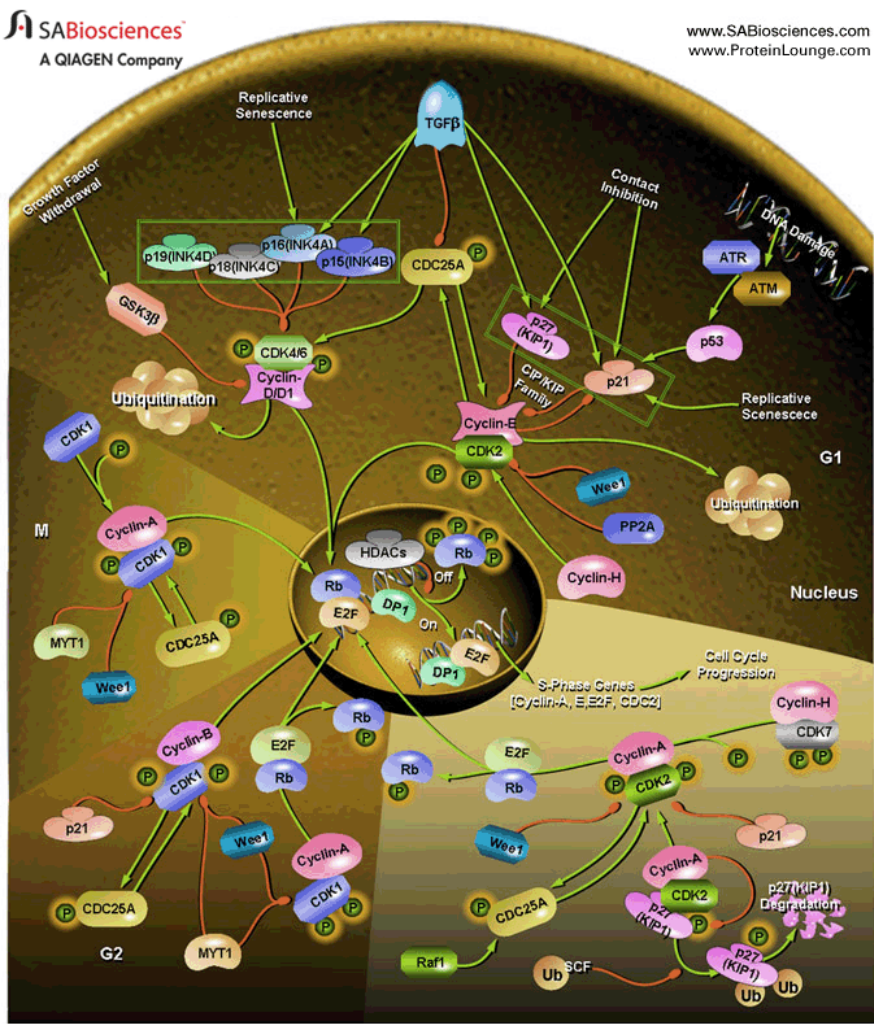


Interpersonal relationship

Body is a highly delicate machine



Regulation is vital for cellular function



**DON'T PANIC.
EVERYTHING IS
UNDER CONTROL**

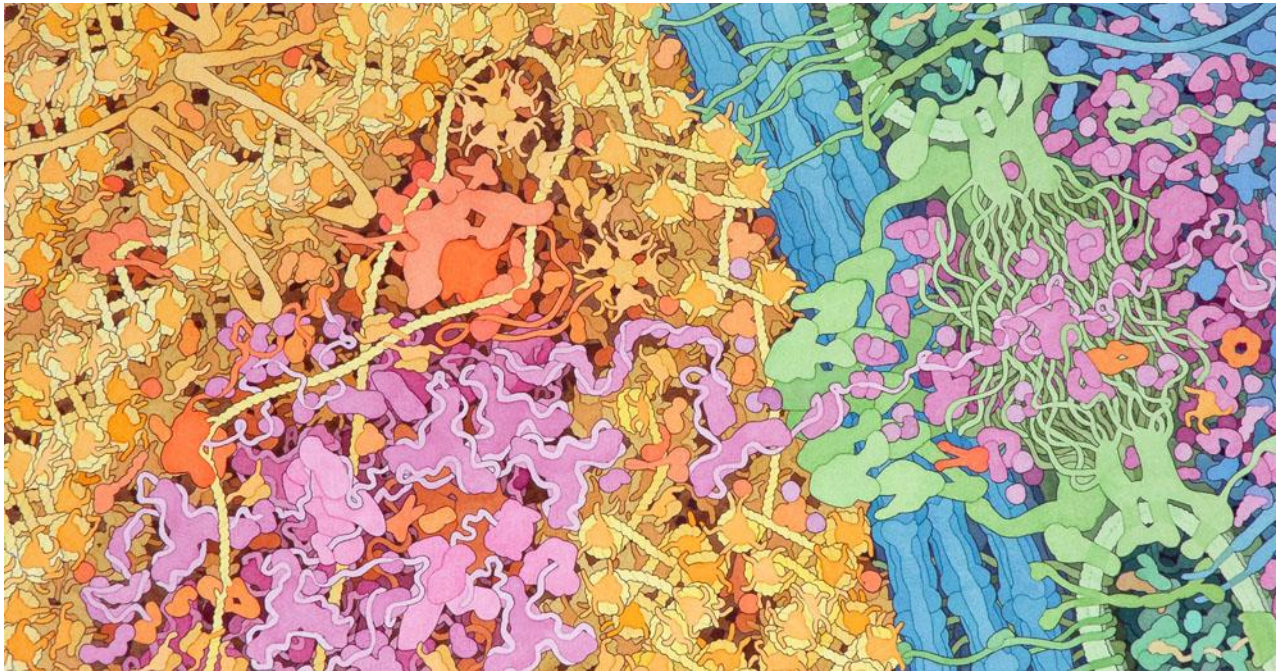


Protein function is precisely regulated in cell

- Gene expression regulation
- Transcriptional regulation
- Translational regulation
- Protein regulation

Proteins play functions in a highly crowded environment

- A typical bacterial cell
 - Containing ~250,000 protein molecules
 - Size: ~1 μm in length



Mechanisms of regulations

- Regulation by location
- Regulation by molecules
- Regulation by covalent modification
- Regulation by protein quantity and lifetime
- Combination of different regulation mechanisms

Regulation by location

- Protein can be targeted to specific locations
 - Tissue
 - Cell
 - Cellular compartments
 - Molecular complexes
- Not all proteins are absolutely specific and may have multi-function
- Protein can be targeted by
 - Signal sequence
 - Chemical modification
- Protein is usually **maintained in an inactive conformation** when it is not in the location where it is needed

Regulation by molecules

- Protein function can be controlled by the binding of **effector** molecules
- The binding of effectors may induce conformational changes that produce inactive or active forms of the protein
- Effectors are ranged from proton to macromolecule
 - Protein-ligand interaction
 - Protein-protein interaction
- Effectors are most common in enzyme, for examples
 - Competitive inhibitor to the active site
 - Allosteric effector to the remote site

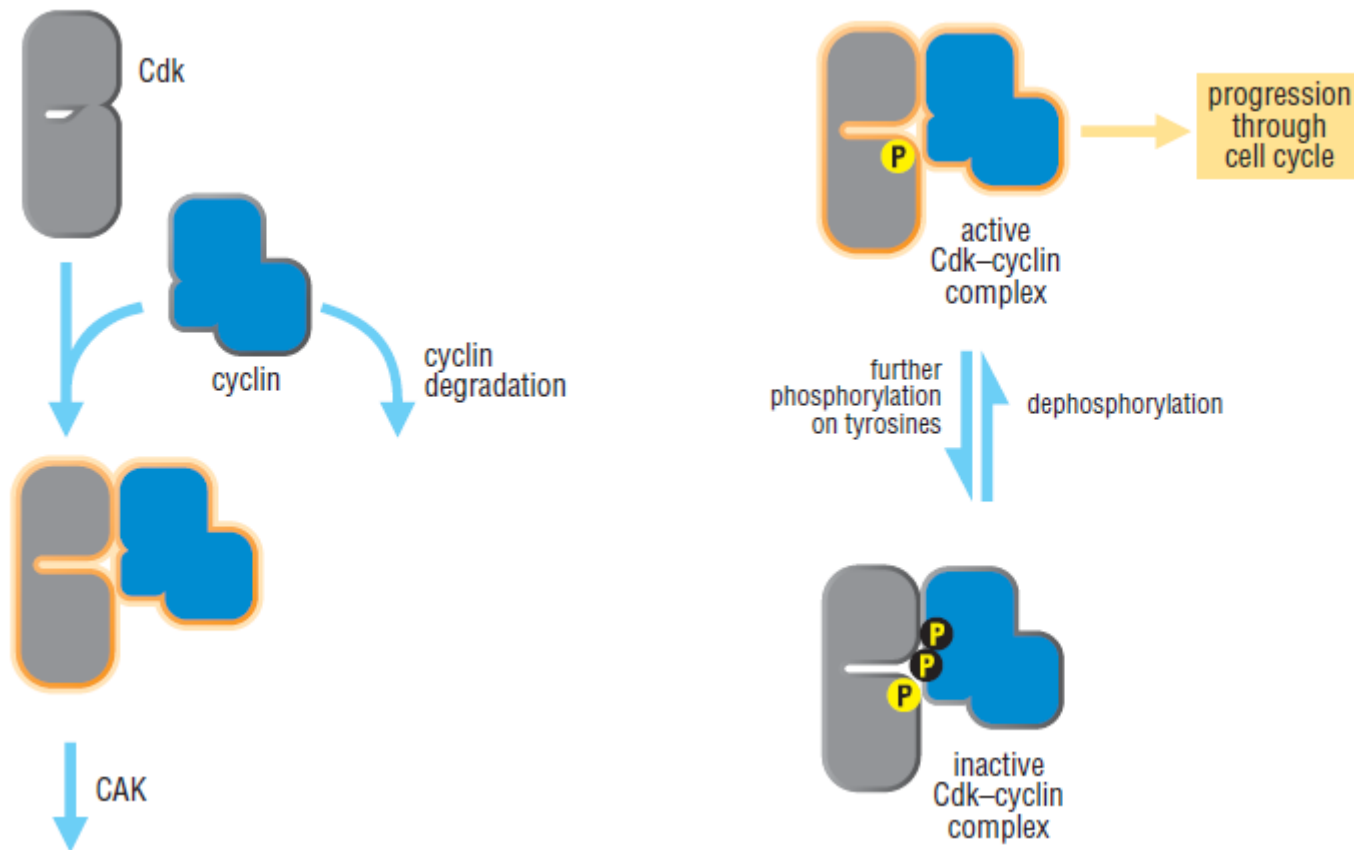
Regulation by covalent modification

- Binding of effector may lead to covalent changes in a protein
- The common way for covalent modification is post-translational modification
 - Phosphorylation/Dephosphorylation
 - Glycosylation
 - Methylation
 - Acetylation
 - ...
- Such modifications may either activate or inactivate the protein
- Signal cascade by covalent modification for signal amplification

Regulation by protein quantity and lifetime

- Control protein lifetime at post-translational level
 - Protease (lysosome)
 - Proteasome
- Protein digestion by lysosome
 - Protein targeting
 - Location
- Specific protein degradation by proteasome
 - Covalent attachment
 - Modification

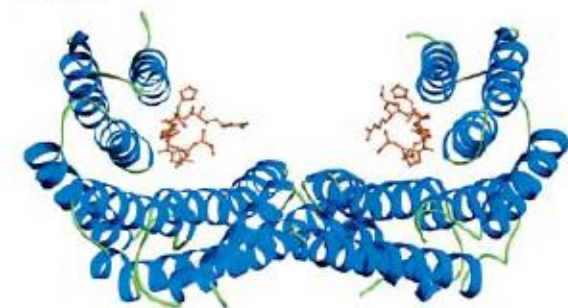
Combination of different regulation mechanisms



Protein interaction domains

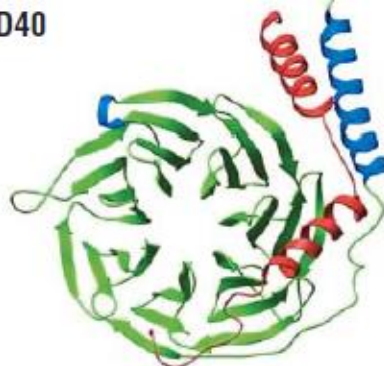
- The flow of information within the cell is regulated and integrated by the combinatorial use of small protein domains that recognize specific ligands
- **Interaction domain** / recognition module
 - Folded modules
 - 35-150 residues in length
 - Many of them having their C- and N-termini close together in space, while the ligand-binding site being located on the opposite face, which allow an interaction domain to be inserted into a loop region
- Interaction domain can be classified by sequence, structure, and ligand-binding properties
 - SH3, WW and EVH1
 - Recognizing proline-rich sequences
 - SH2 and PTB
 - Recognizing phosphotyrosine containing sequences
 - 14-3-3, FHA, PBD and WD40
 - Recognizing phosphoserine and phosphothreonine motifs
 - PH, PX and FYVE
 - Recognizing phospholipids

14-3-3



Example: 14-3-3
Function: protein-protein interactions
Specificity: phosphotyrosine

WD40



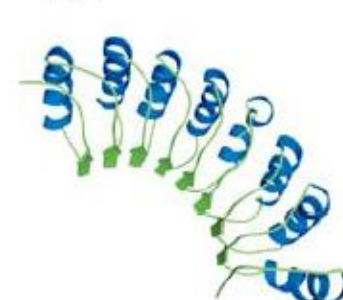
Example: G protein beta subunit
Function: protein-protein interactions;
 a stable propeller-like platform to which
 proteins bind either stably or reversibly
Specificity: various

EF-hand



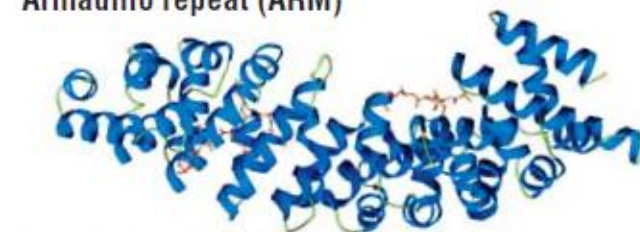
Example: Calmodulin
Function: calcium binding
Specificity: Ca²⁺

LRR



Example: Rpn1
Function: protein-protein
 interactions
Specificity: various

Armadillo repeat (ARM)



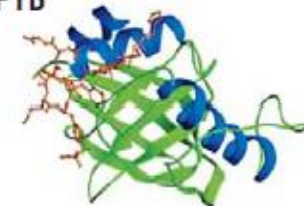
Example: Importin alpha
Function: protein-protein interactions
Specificity: various

SNARE



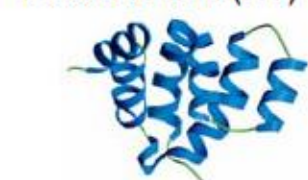
Example: SNAP-25B
Function: protein-protein interactions
 in intracellular membrane fusion
Specificity: other SNARE domains

PTB



Example: Shc
Function: protein-protein
 interactions
Specificity: phosphotyrosine

Death domain (DD)



Example: FADD
Function: protein-protein
 interactions in pathway that
 triggers apoptosis
Specificity: other DD domains
 through heterodimers

ANK (ankyrin repeat)



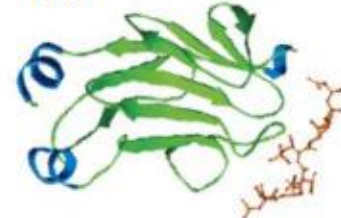
Example: Swi6
Function: protein-protein
 interactions
Specificity: various

C2



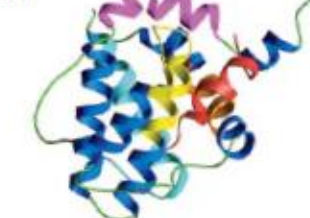
Example: PKC
Function: electrostatic switch
Specificity: phospholipids

FHA



Example: Rad53
Function: protein-protein
 interactions
Specificity: phosphotyrosine

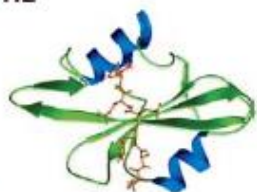
BH



Example: Bcl-XL
Function: protein-protein
 interactions
Specificity: Other BH domains
 through heterodimers

BIO446 Protein Structure and Function

SH2



Example: Src
Function: protein-protein interactions
Specificity: phosphotyrosine

SH3



Example: Sem5
Function: protein-protein interactions
Specificity: proline-rich sequences

PH



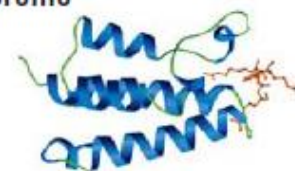
Example: PLC-δ
Function: recruitment of proteins to the membrane
Specificity: phosphoinositides

SAM



Example: EphA4
Function: protein-protein interactions via homo- and heterodimers
Specificity: other SAM domains

Bromo



Example: P/CAF
Function: protein-protein interactions in chromatin remodeling
Specificity: acetylated lysine

PDZ



Example: PSD-95
Function: protein-protein interactions, often involving transmembrane proteins or ion channels
Specificity: -XXXV/I-COOH

GYF



Example: CD2
Function: protein-protein interactions
Specificity: proline-rich sequences

Chromo



Example: Mouse modifier protein 1
Function: protein-protein interactions in chromatin remodeling
Specificity: methylated lysine

FYVE



Example: Vps27p
Function: Regulation of signaling
Specificity: phosphatidylinositol-3-phosphate

RING finger



Example: c-Cbl
Function: protein-protein interactions in ubiquitin-dependent degradation and transcription regulation
Specificity: various

WW



Example: Pin1
Function: protein-protein interactions
Specificity: proline-rich sequences

LIM



Example: CRP2
Function: protein-protein interactions, usually in transcription regulation
Specificity: various

F-box



Example: Skp2
Function: protein-protein interactions in ubiquitin-dependent protein degradation
Specificity: various

C1



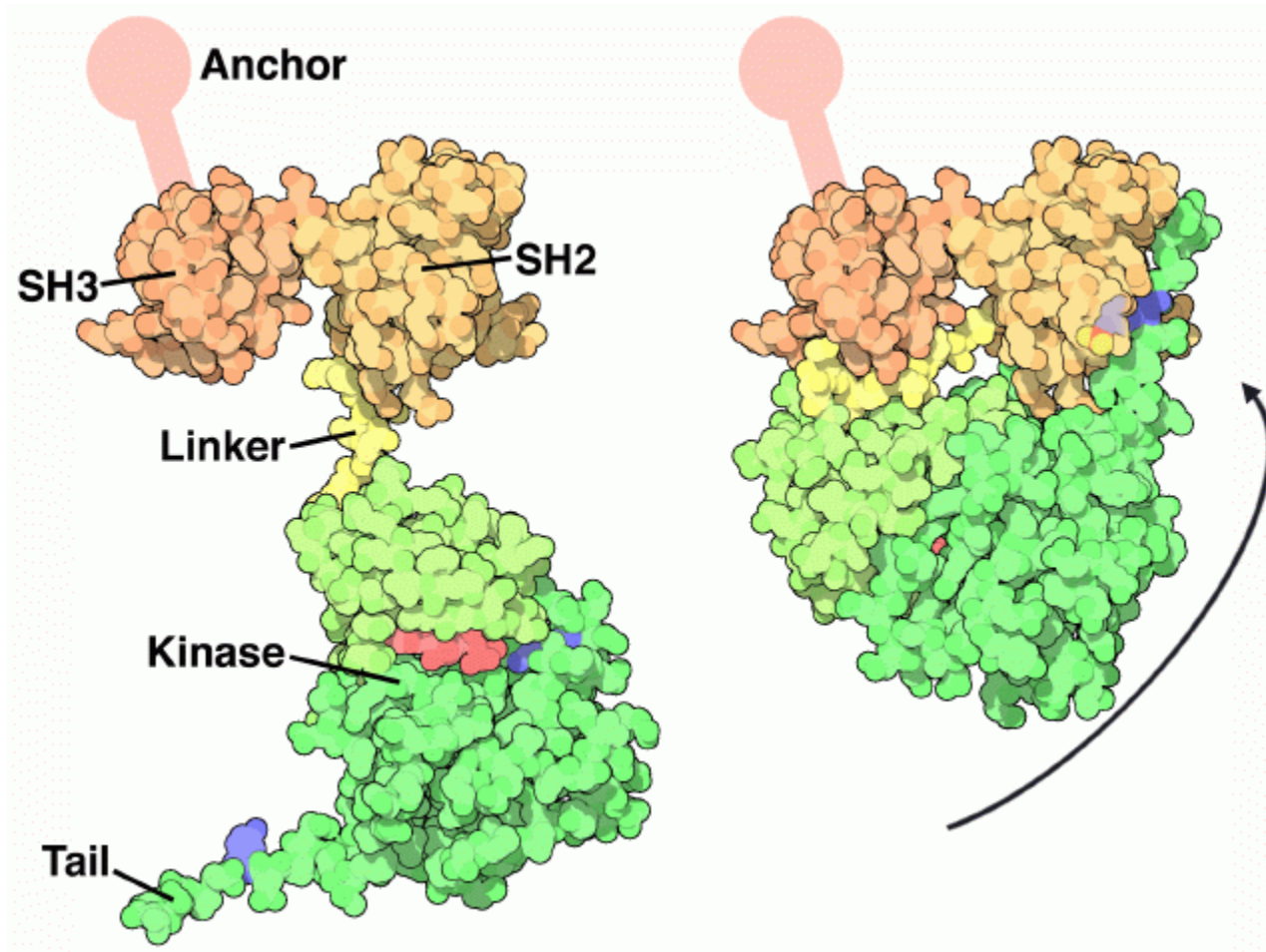
Example: PKC
Function: recruitment of proteins to the membrane
Specificity: phospholipids

Fibronectin



Example: Fibronectin III
Function: protein-protein interactions in cell adhesion to surfaces
Specificity: RGD motif of integrins

Src Tyrosine Kinase



PDB101 link: <http://pdb101.rcsb.org/motm/43>