REGULATION BY POST-TRANSLATIONAL MODIFICATION

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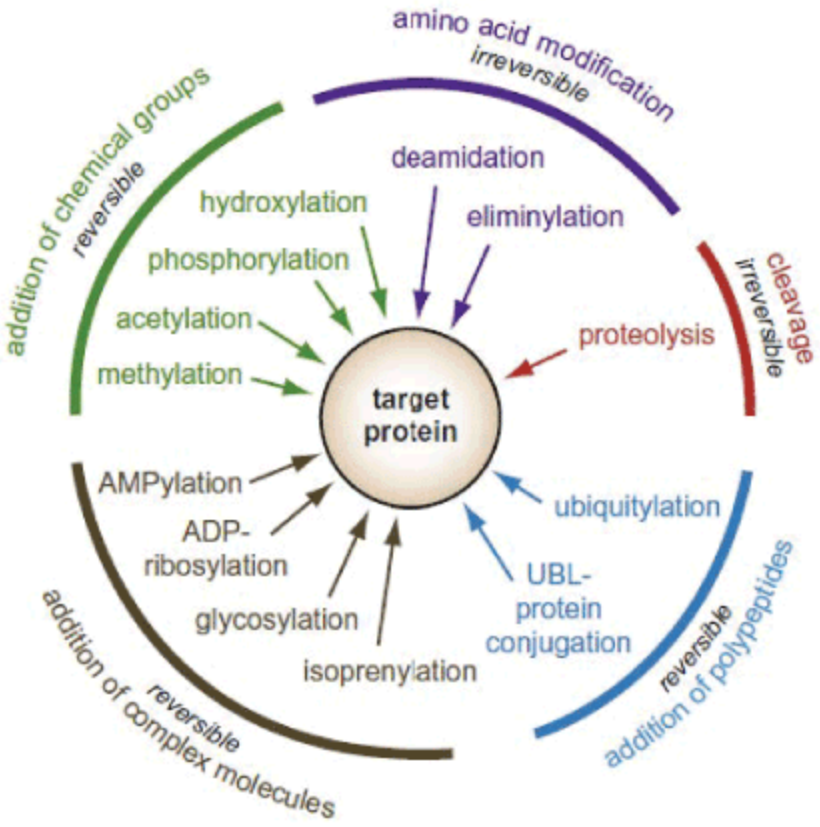
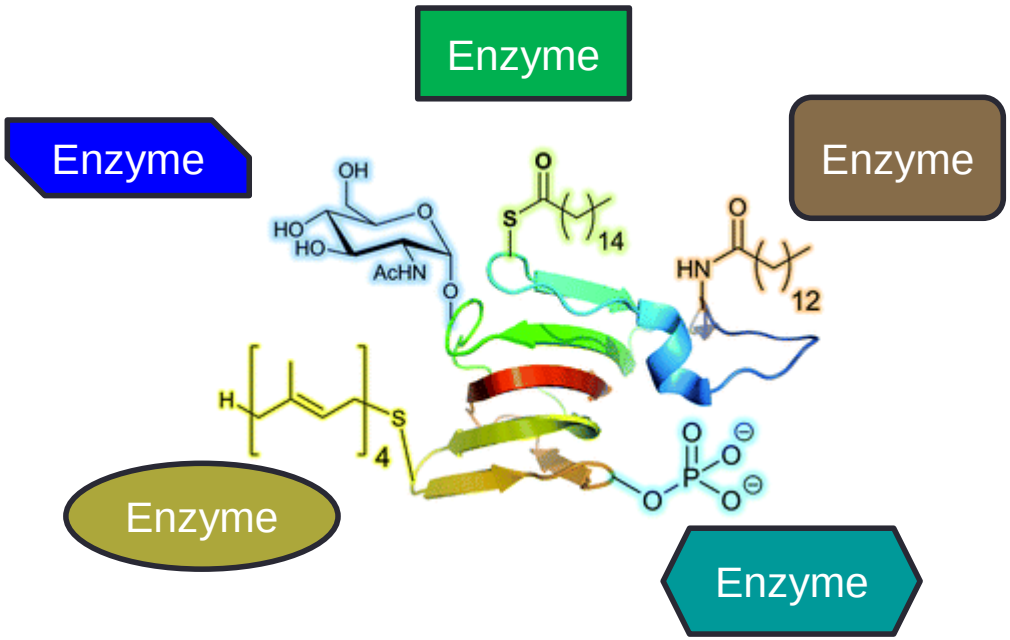
SUSTC

Post-translational modification

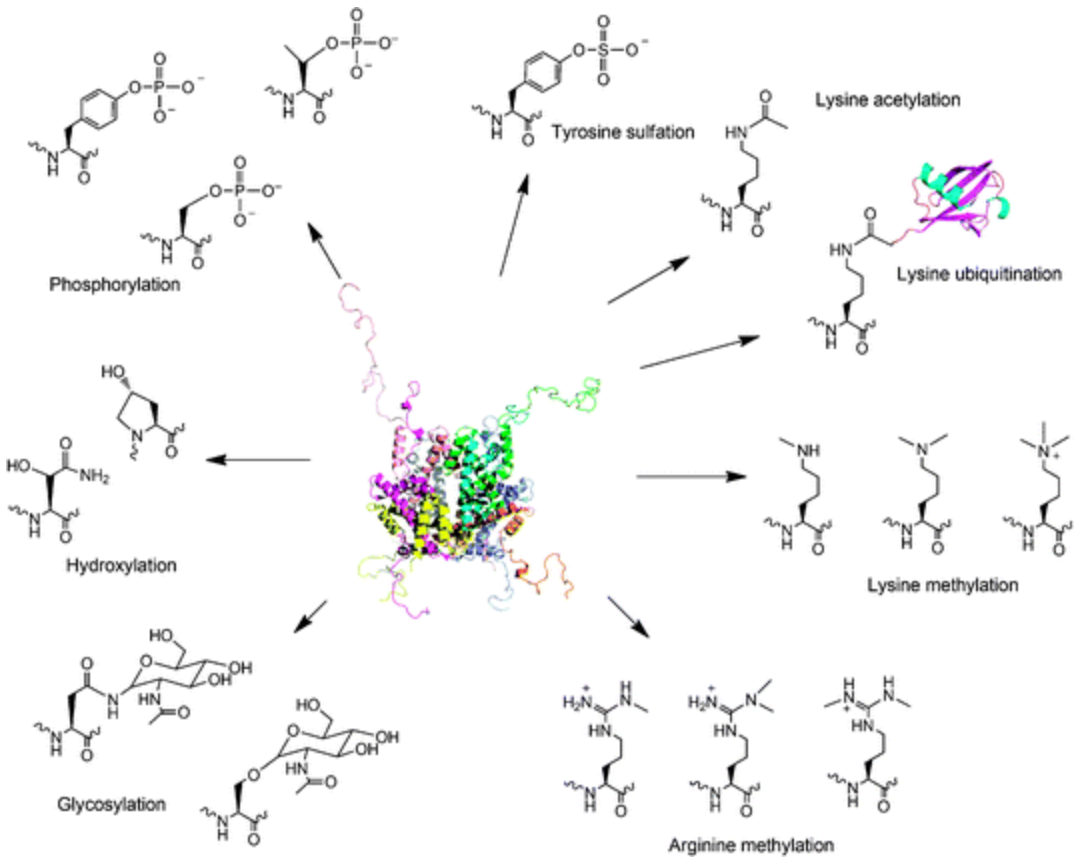


Addition of chemical groups

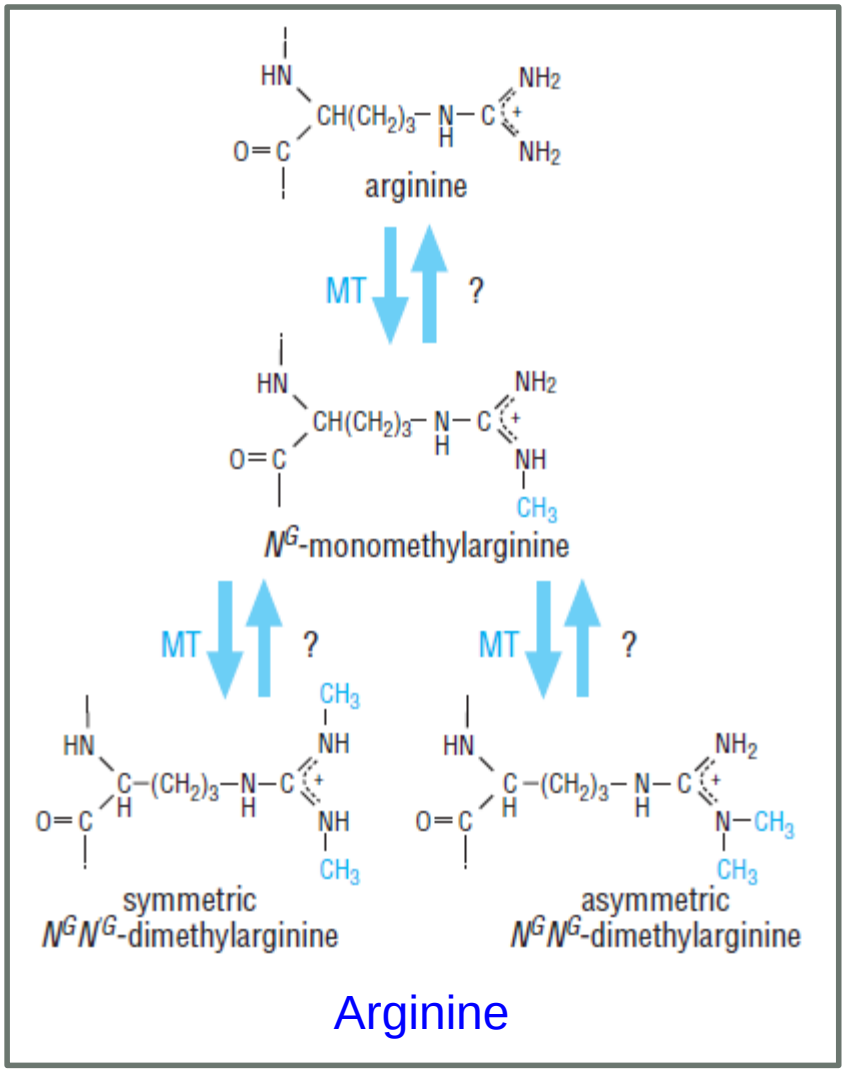
- Phosphorylation
- Methylation
- Acetylation
- Nitrosylation
- Hydroxylation
- …

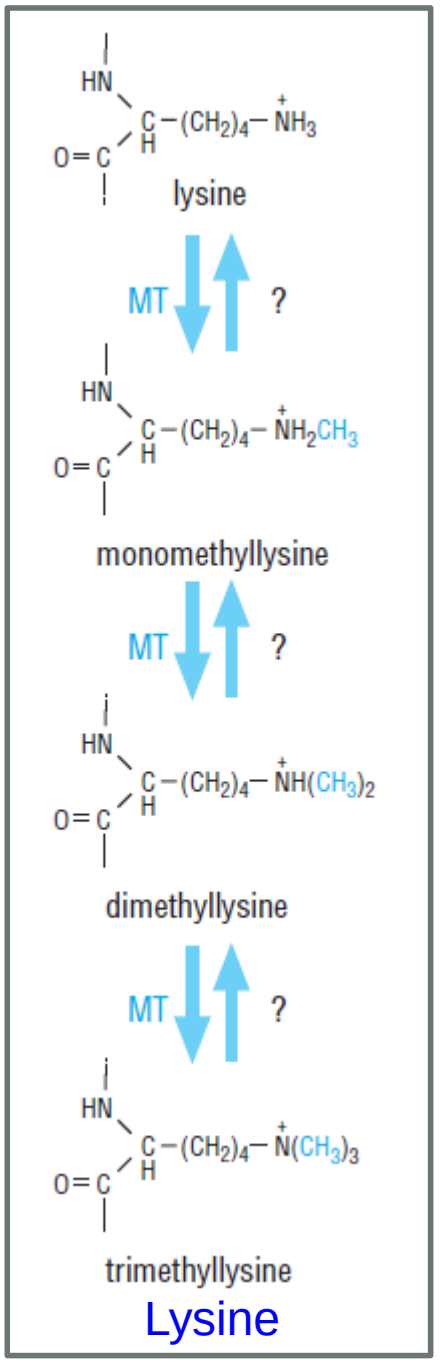


Amino acid specificity in modification



Methylation

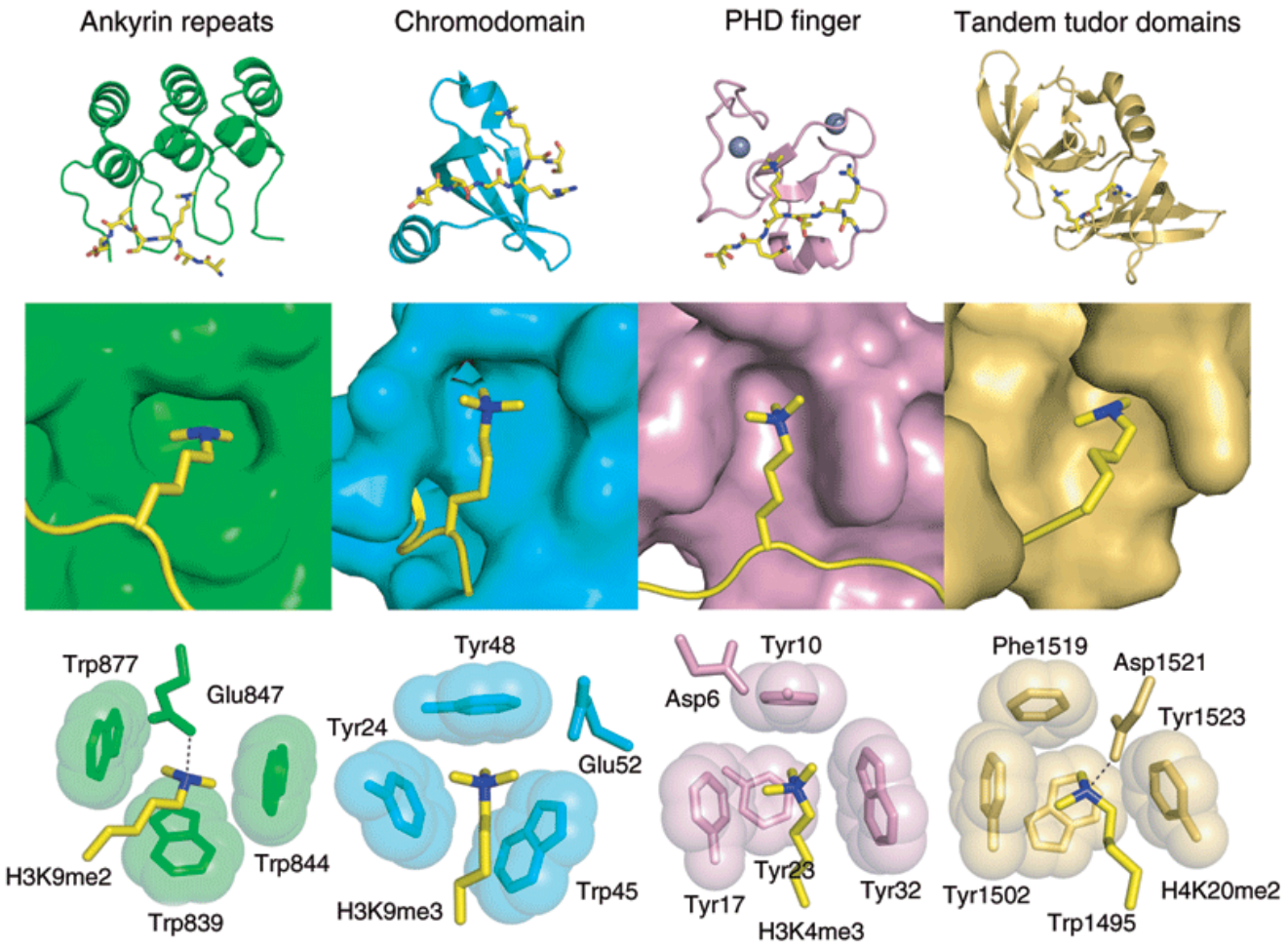




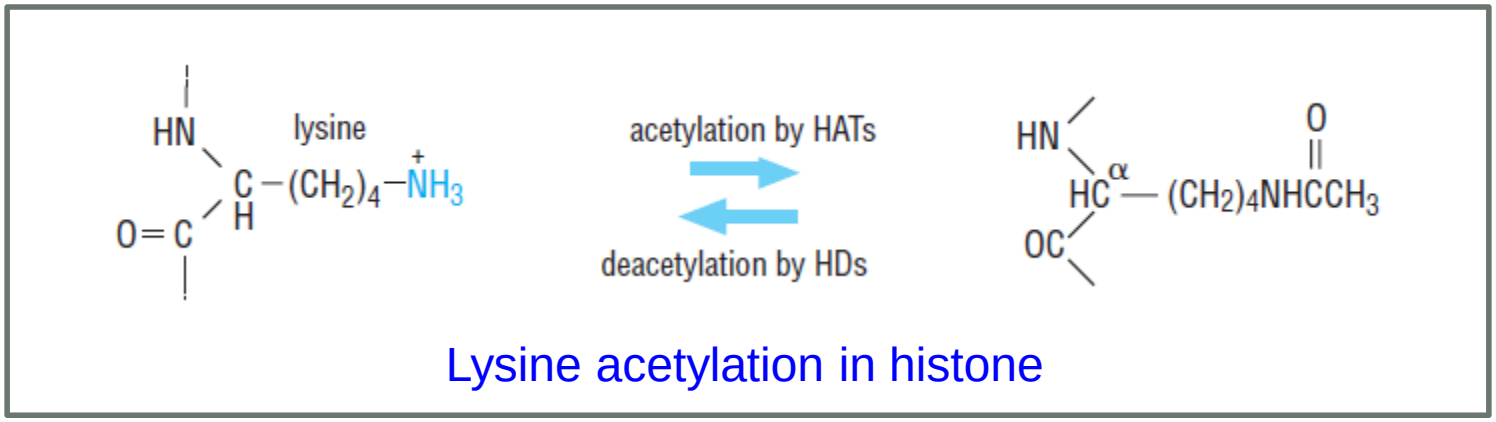
Regulation by methylation

- A common modification of proteins in eukaryotic nuclei
  - Histone
  - Heterogeneous nuclear ribonucleoprotein (hnRNP)
    - Arginine methylation
- Methyltransferase (“writer”)
  - Using *S*-adenosylmethionine as the methyl donor
- Demethylase (“eraser”)
- Effects by methylation on Lys/Arg
  - No changes on the overall charge
  - Altering the steric interactions the group can make
  - Eliminating possible hydrogen-bond donors
- Methylation on Lys/Arg creating a new and highly specific protein binding site and altering the protein-protein interaction

Methyl-lysine readers



N-acetylation



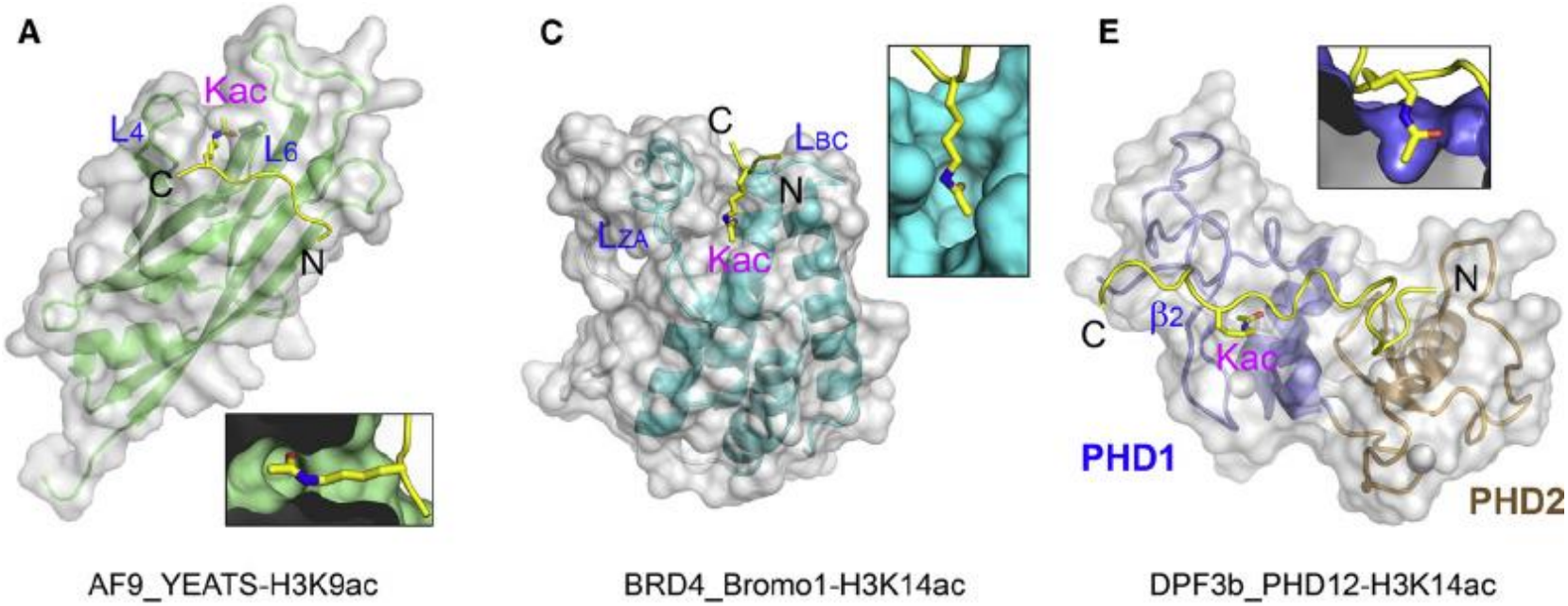
Lysine acetylation in histone

- Acetyltransferases
  - Using an acetyl group from acetyl-CoA
  - Amino terminus of protein backbone can be modified by sequence specific N-acetyltransferases
  - Lysine sidechain of histone can be modified by other specific acetyltransferases
- Deacetylase

Regulation by N-acetylation

- Histone methylation may induce either an active or an inactive state of chromatin
  - Depending on the position and the nature of the methyl group
- Histone acetylation is always associated with an active state of chromatin
  - Promoted by chromatin-remodeling enzymes recruited to the DNA by proteins containing bromodomains that specifically recognize acetylated lysines
- Unlike methylation, acetylation changes the charge on Lys
- Similar with methylation, acetylation on Lys creating a unique chemical group for protein-protein interaction

Acetyl-lysine readers

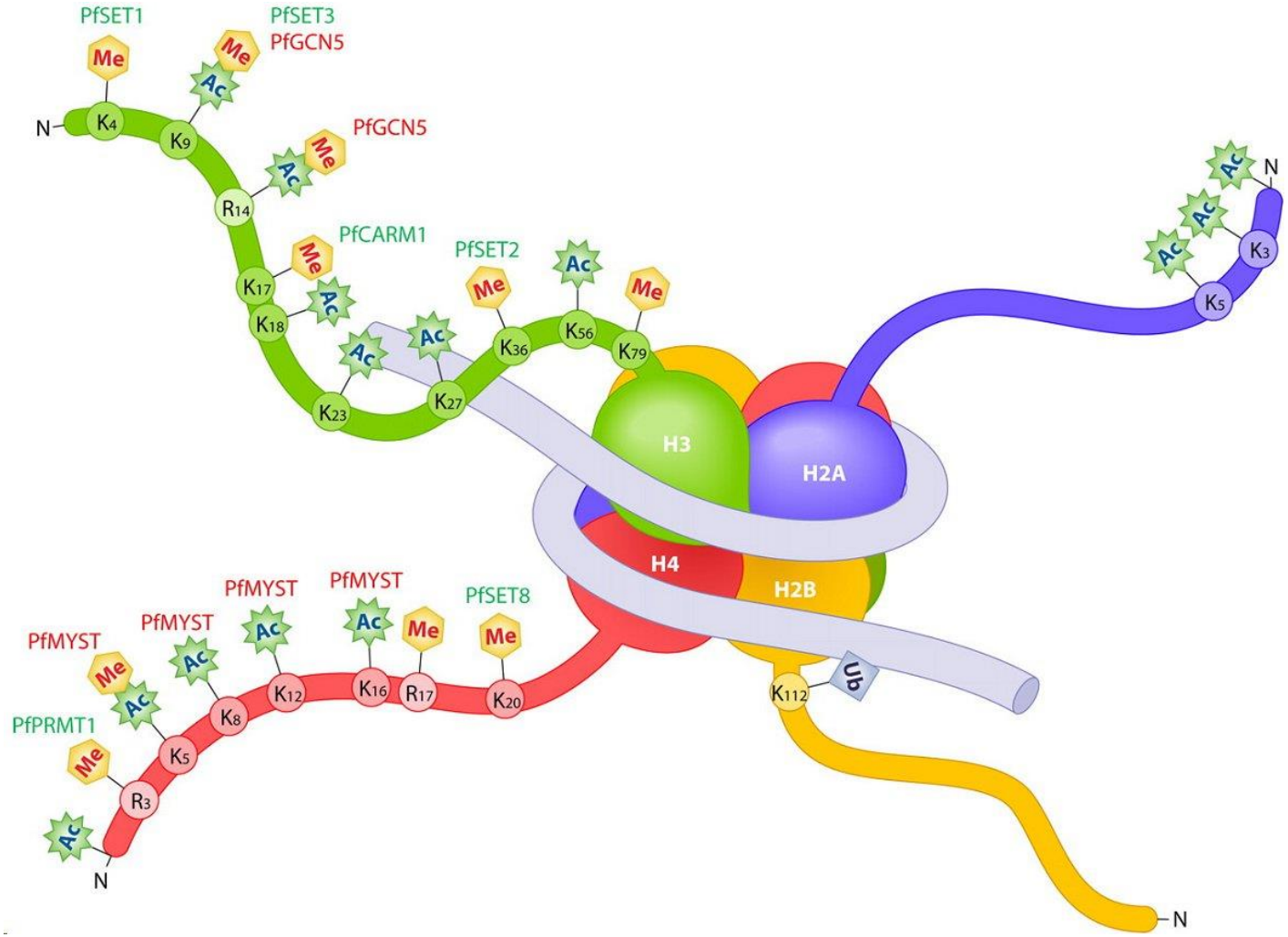


AF9_YEATS-H3K9ac

BRD4_Bromo1-H3K14ac

DPF3b_PHD12-H3K14ac

Histone is highly modified by methylation and acetylation



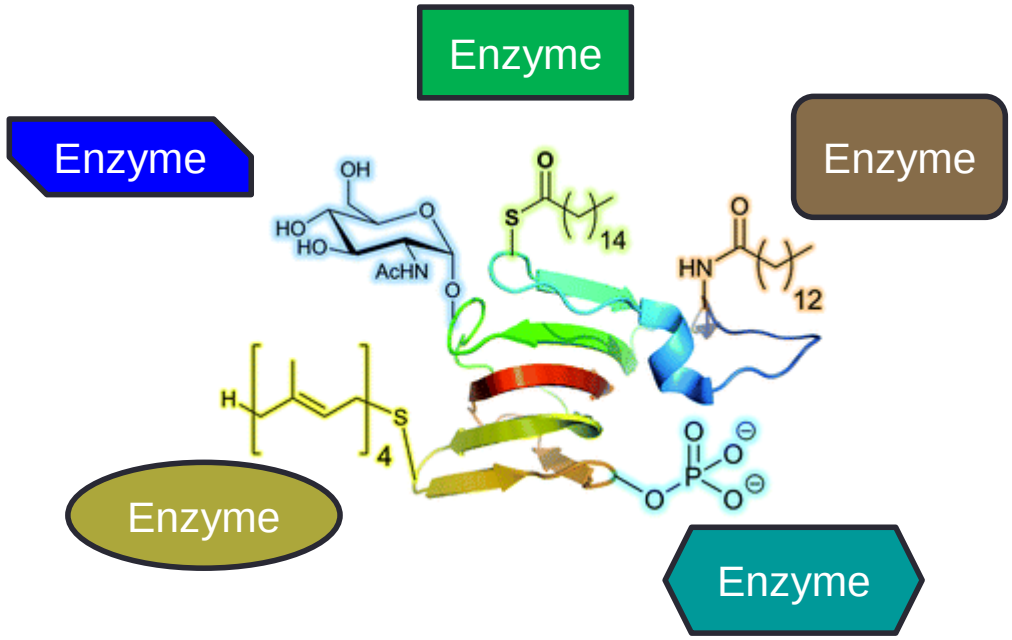
Histone modification and epigenetics

Cell Signaling Technology

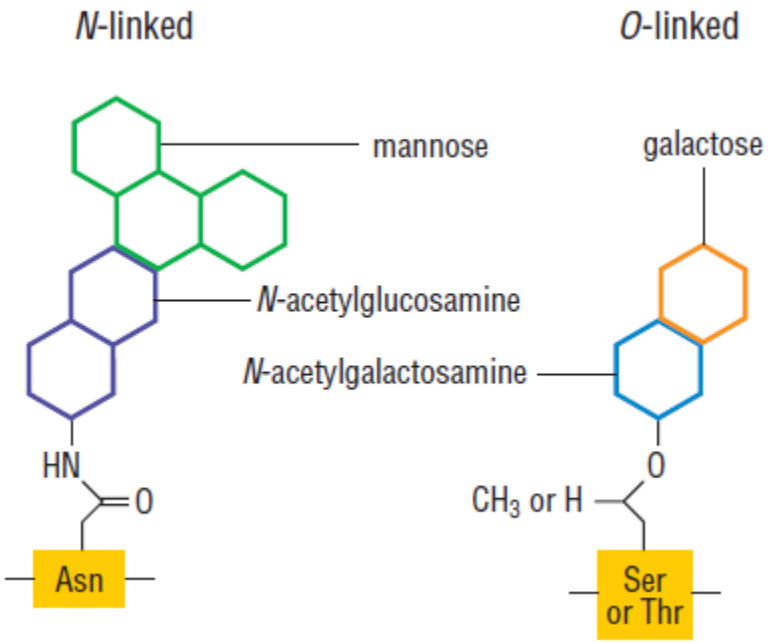
Epigenetics Regulation & Associated Product Offerings

Addition of complex molecules

- Proteins can be modified by other large biomolecules
- By glycan
  - Glycosylation
- By lipid (lipidation)
  - Myristoylation
  - Palmitoylation
  - Prenylation
  - …
- By nucleotide
  - ADP-ribosylation
  - …



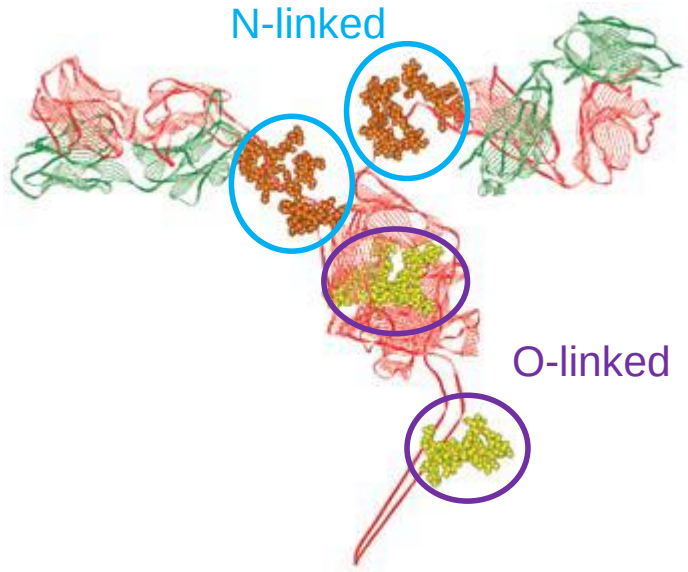
Glycosylation



- Glycosylation
  - Attaching carbohydrate chains (oligosaccharides) to asparagine, serine and threonine residues on protein surfaces
  - The most complex and diverse post-translational modification
  - N-linked (Asn) or O-linked (Ser/Thr) types

Regulation by glycosylation

- Functions for sugars attached to proteins
  - Providing recognition sites that tag glycoproteins for recognition by other proteins
  - Shielding large areas of the protein surface, therefore providing protection from proteases and nonspecific protein–protein interactions
  - In some cases, oligosaccharides increase the solubility of nascent glycoproteins and prevent their aggregation

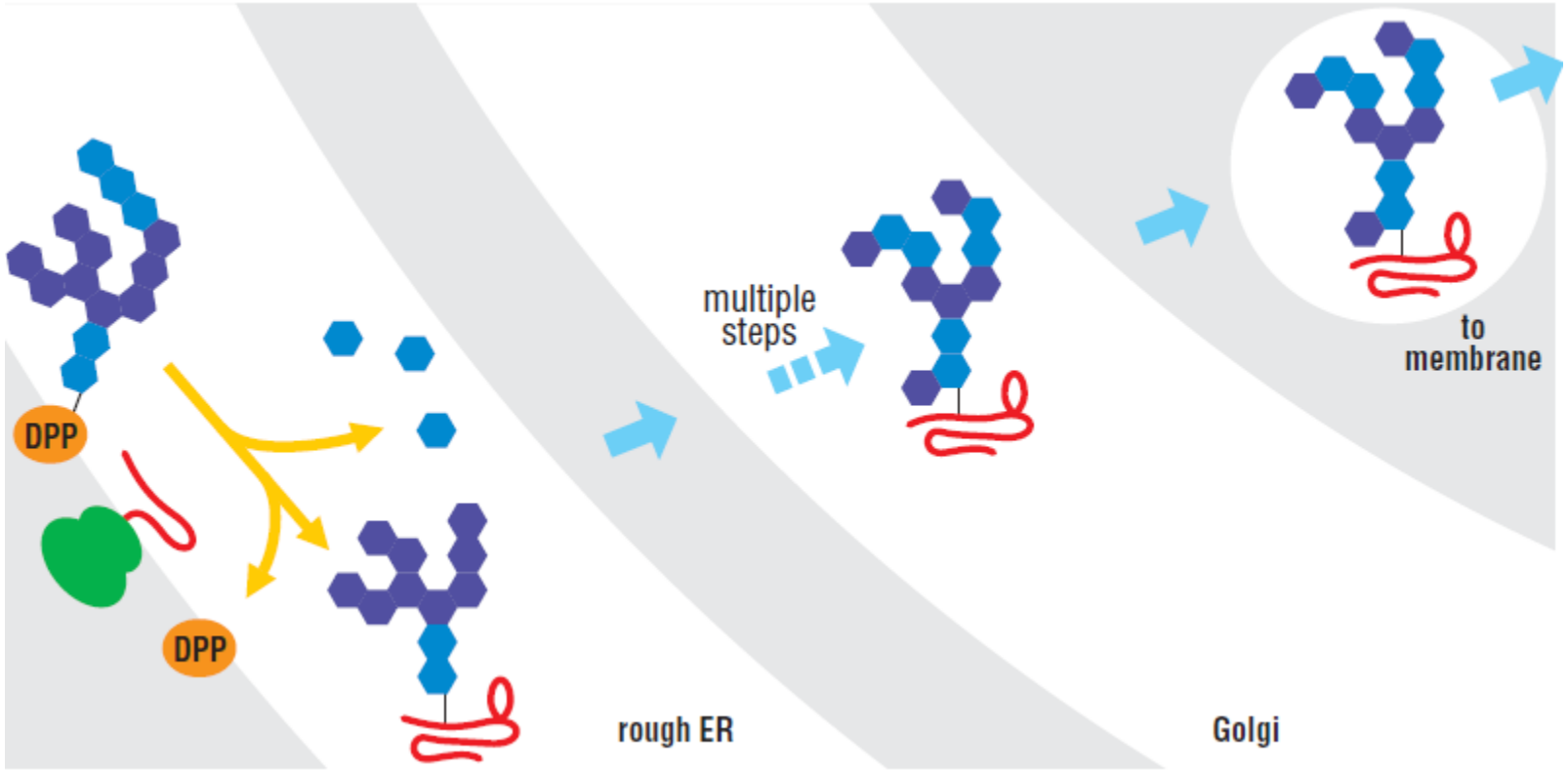


IgA protects mucosal surfaces from pathogens

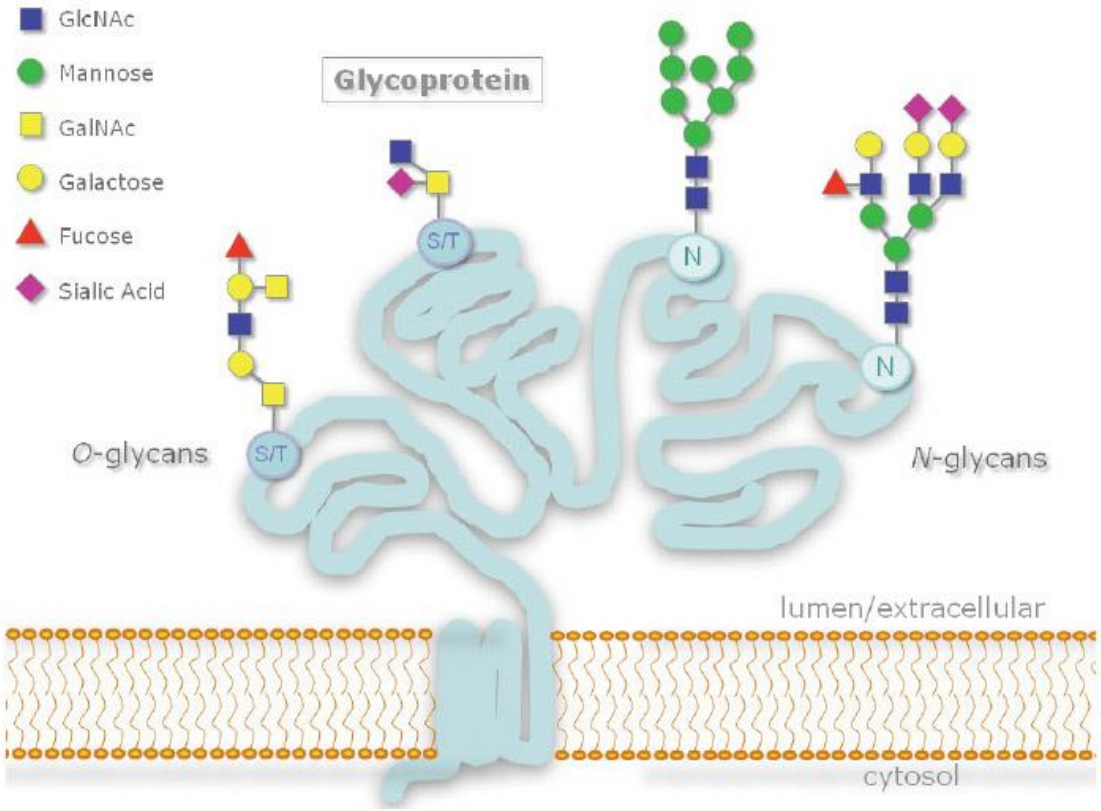
- Protecting vulnerable regions of the molecule from proteolysis
- Providing binding sites for bacteria, thereby protecting the mucosal surface from infection

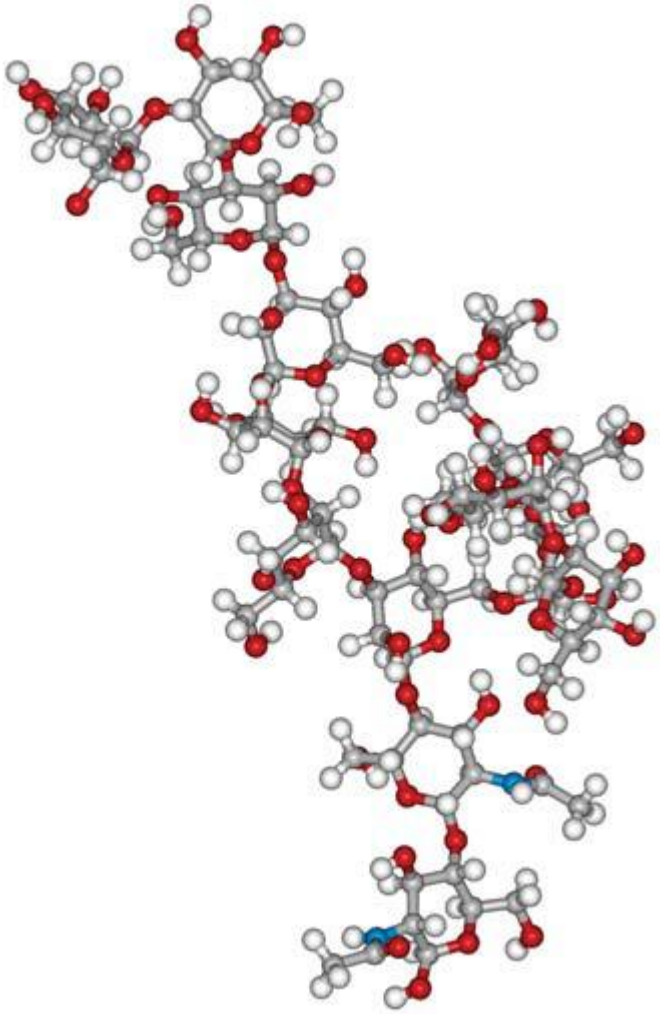
Oligosaccharide processing in cell

- Almost all secreted and membrane-associated proteins of eukaryotic cells are glycosylated
- Oligosaccharide processing on newly synthesized glycoprotein



Diverse and complex structures of oligosaccharides on glycoproteins

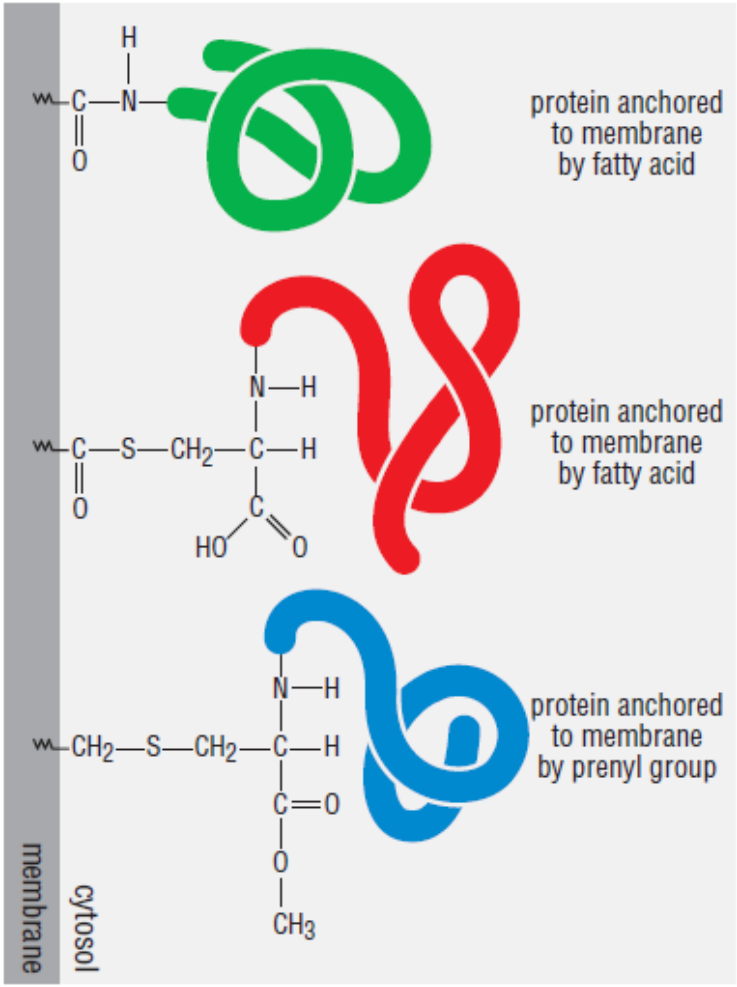




The structure of Glc3Man9GlcNac2

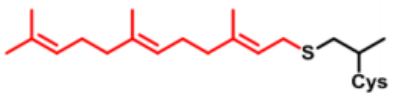
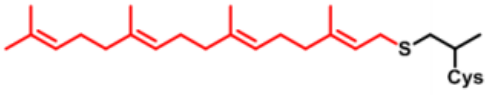
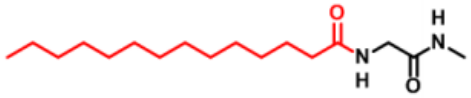
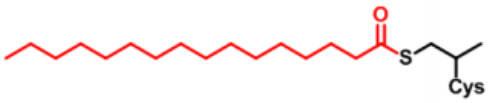
Lipid modification (lipidation)

- Protein targeting by lipid modification
  - Covalent attachment of lipids targets proteins to membranes and other proteins



Four types of lipid modifications

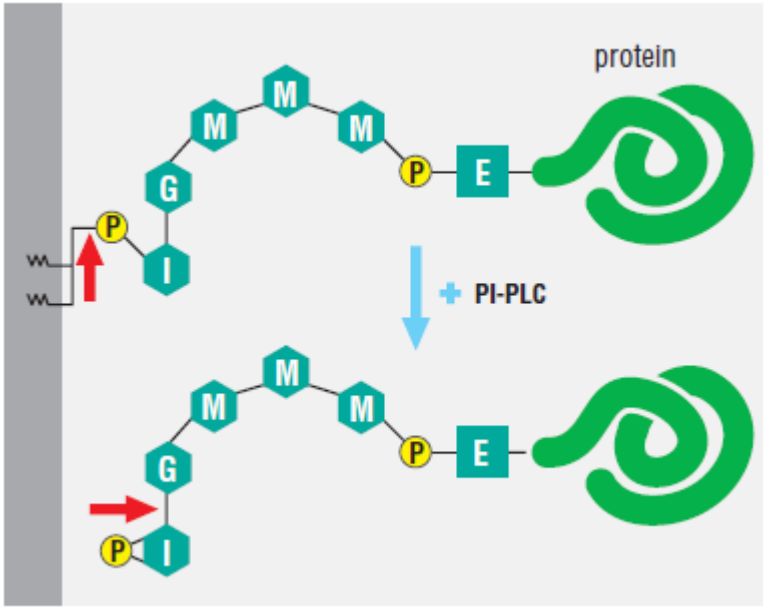
- Classification of lipid modification according to the identity of the attached lipid
  - Myristoylation
  - Palmitoylation
  - Prenylation

Lipid Modifications		Signals	Enzymes
Prenylation	Farnesylation 	—CaaX	Farnesyltransferase Geranylgeranyltransferase I
	Geranylgeranylation 	—CC or —CXC (Rab proteins only)	Geranylgeranyltransferase II
N-myristoylation		MGxxS—	N-myristoyltransferase
Palmitoylation		Poorly defined	Palmitoylatransferase

  - The modification by a glycosylphosphatidylinositol (GPI) anchor
    - Attached to the C-terminus of a protein

GPI anchoring

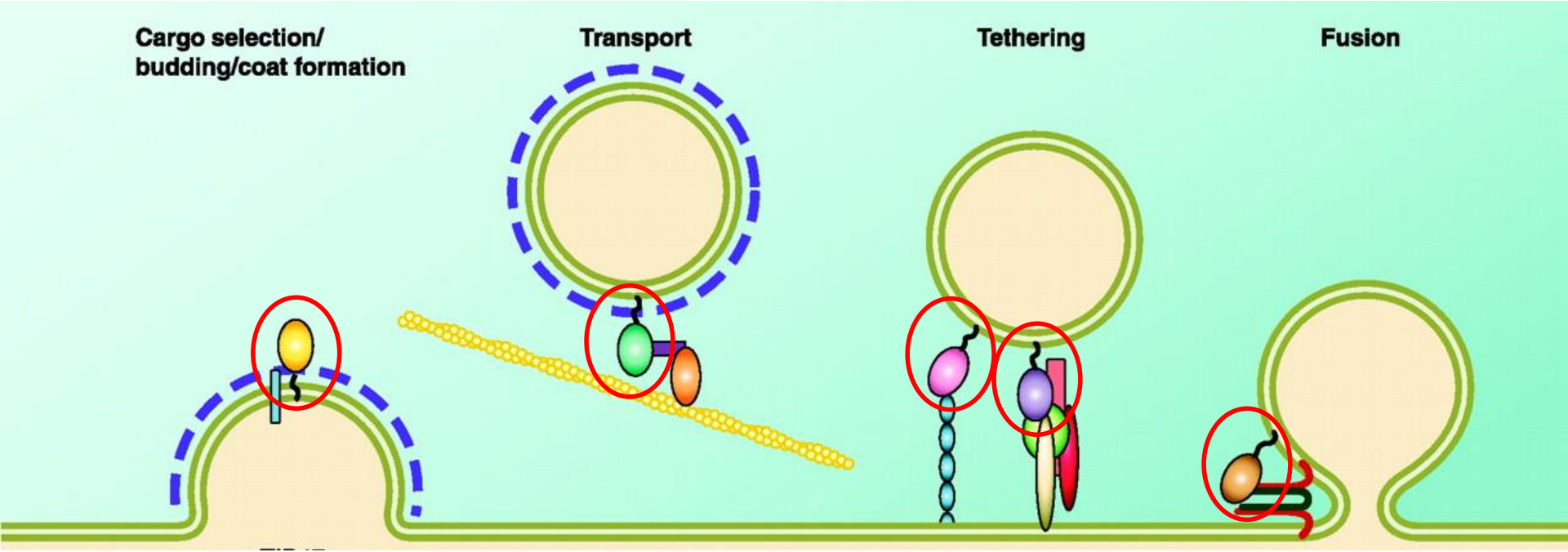
- A way for protein of glycoprotein transport by vesicle (ER-Golgi)
- GPI modification is reversible
- PLC cleavage is a releasing mechanism

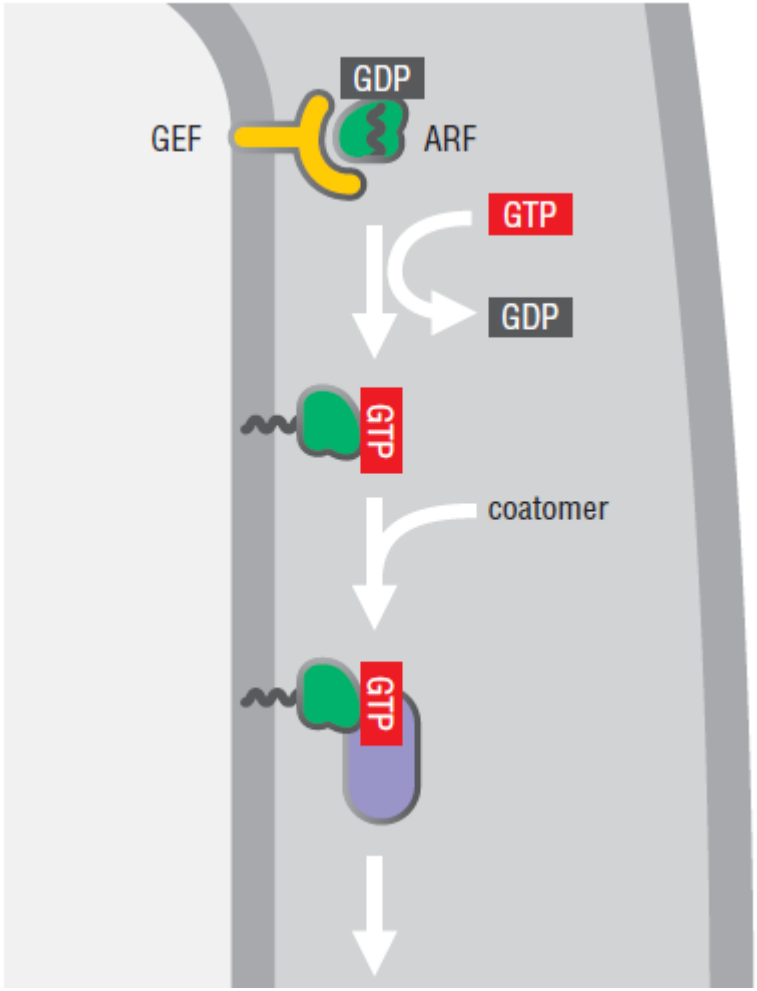


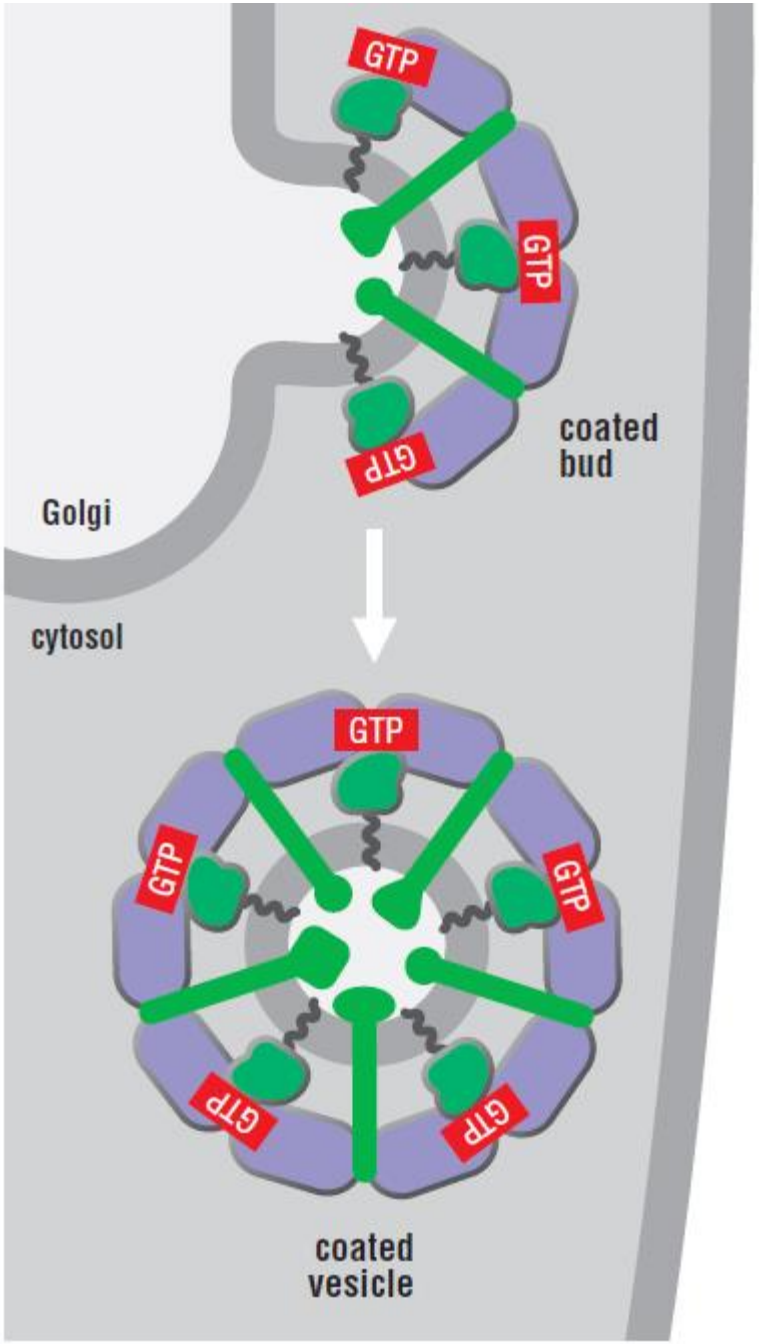
The protein is connected through an amide linkage to a phosphoethanolamine molecule (E-P) that is attached to a core tetrasaccharide composed of three mannose sugars (M) and a single glucosamine sugar (G).
The tetrasaccharide is in turn attached to phosphatidylinositol (I)

GTPase and lipid modification

- Some GTPases are reversibly associated with internal membranes of the cell via lipid modification
- Rab GTPases
  - A large family of small GTPases, regulating membrane traffic
    - vesicle formation, movement, tethering, and membrane fusion
  - Directing transport vesicles between the membrane-bounded compartments of the cell




GDP
GEF
ARF
GTP
GDP
GTP
coatomer
GTP


GTP
GTP
GTP
coated
bud
Golgi
cytosol
GTP
GTP
GTP
GTP
GTP
coated
vesicle