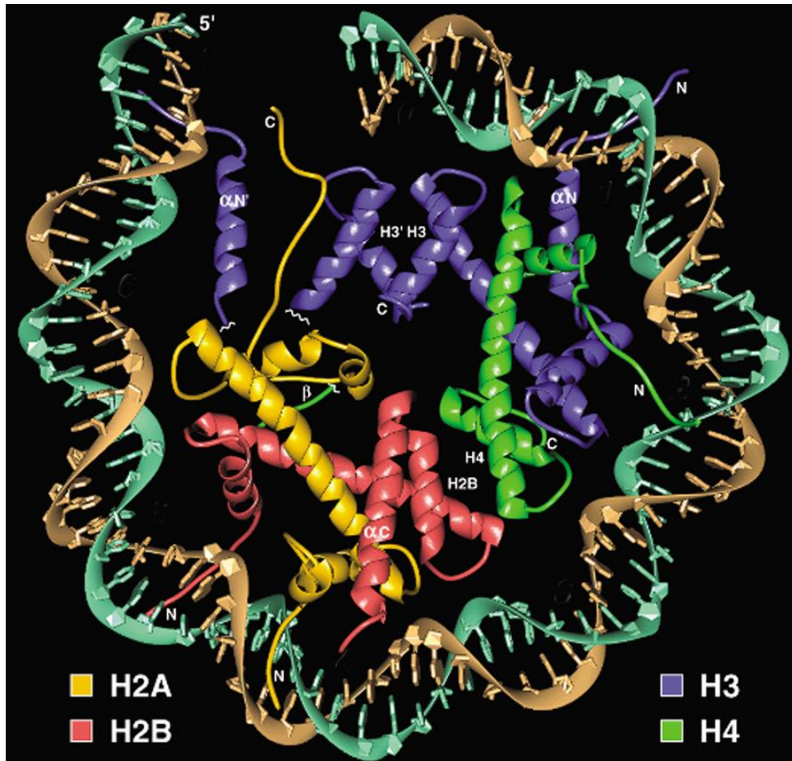


Unit 5

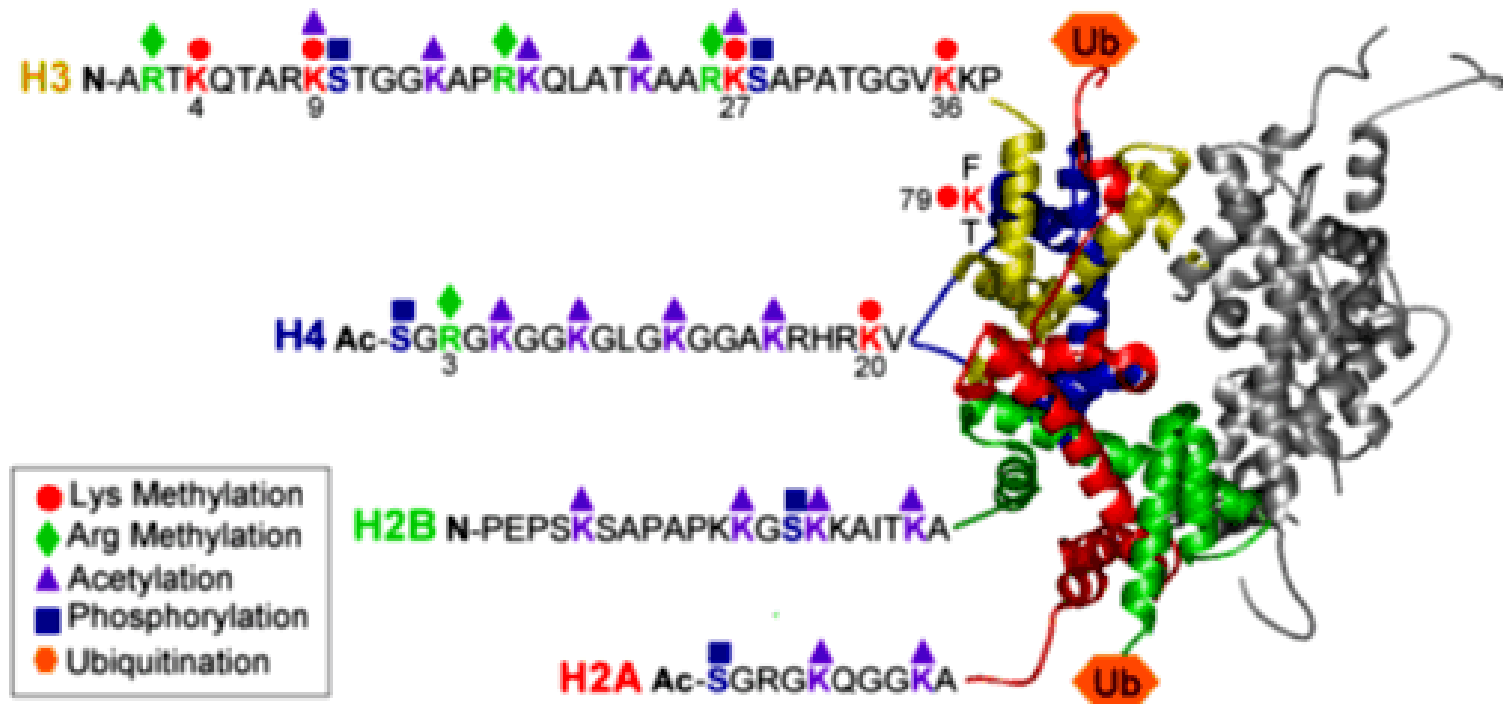
Molecular Biology , Sem III

Changes in Chromatin Structure

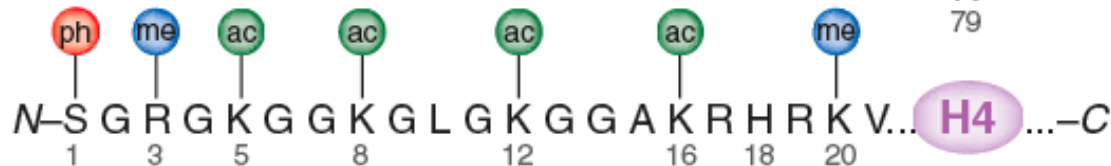
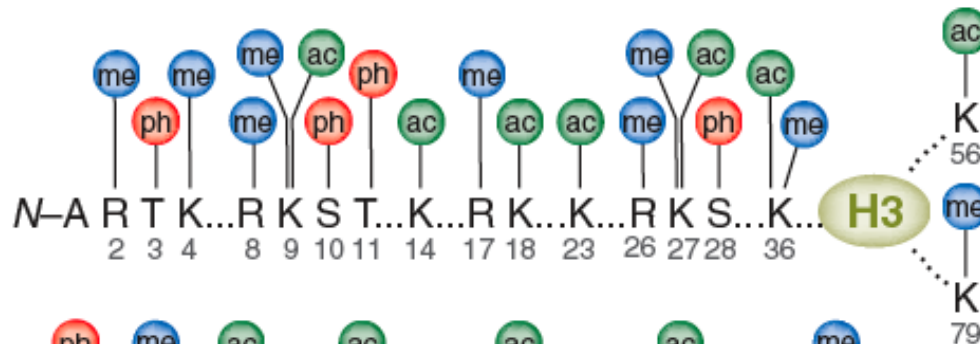
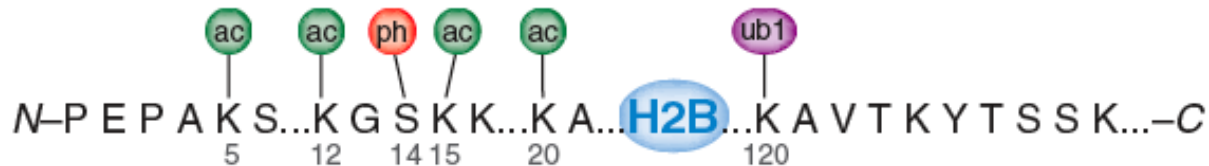
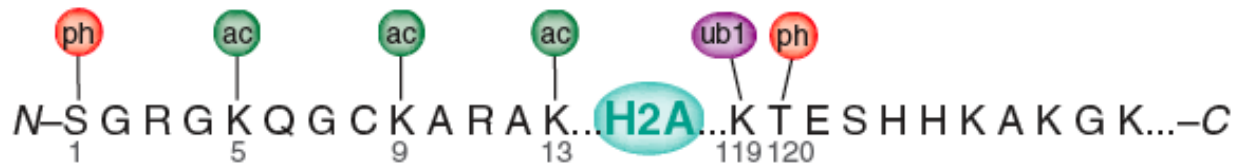
Histone



Histone modifications



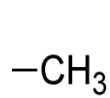
Types of Histone Modifications



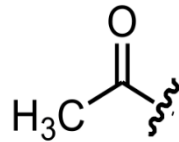
Specific modifications (acetylation, methylation, etc):

- ✓ What are the residues/positions which are that are frequently modified
- ✓ Enzymes that add/remove the modification
- ✓ Biological roles

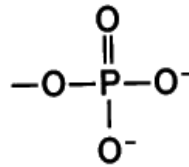
Features of Histone Modifications



Methyl



Acetyl



Phospho



Ubiquitin

Covalently attached groups (usually to histone tails)

Types of Histone Modifications

Table 1. Different Classes of Modifications Identified on Histones

Chromatin Modifications	Residues Modified	Functions Regulated
Acetylation	K-ac	Transcription, Repair, Replication, Condensation
Methylation (lysines)	K-me1 K-me2 K-me3	Transcription, Repair
Methylation (arginines)	R-me1 R-me2a R-me2s	Transcription
Phosphorylation	S-ph T-ph	Transcription, Repair, Condensation
Ubiquitylation	K-ub	Transcription, Repair

Acetylation

- **Many lysine residues can be acetylated**
 - mainly on histone tails (sometimes in core)
- **Can be part of large acetylation domains**
- **Modifying enzymes:**
 - often multi-enzyme complexes
 - can modify multiple residues
- **Well correlated with transcriptional activation**
- **Other roles (chromatin assembly, DNA repair, etc.)**

Histone Acetyl Transferases (HATs/KATs)

- Two general types:
 - **Type B:** cytoplasmic (newly synthesized histones) HAT1
 - **Type A:** nuclear (GNAT, MYST – HAT superfamilies)

Type B	Enzymes that Modify Histones	Residues Modified
	Acetyltransferase	
	HAT1	H4 (K5, K12)

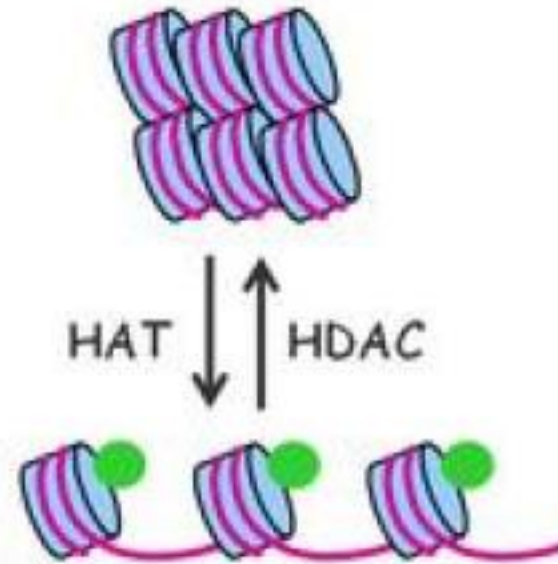
HDAC - Histone Deacetylases

HAT - Histone Acetyl Transferase

- amino groups of lysine side chains
- unacetylated histones tend to repress transcription
- acetylated histones tend to activate transcription

Histone Deacetylases (HDACs)

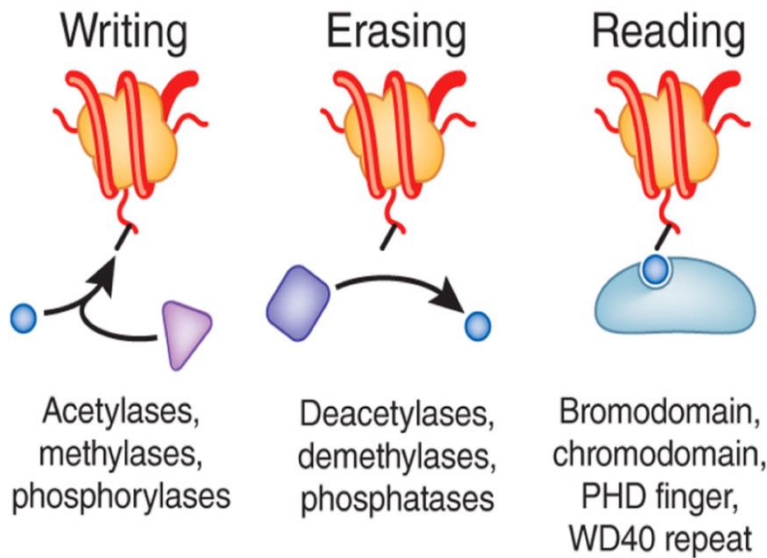
- Multi-enzyme complexes
- Targeted by transcriptional repressors
- Deacetylate histone tails



Acetylation: functions

- Acetylation of histone tails neutralizes some of the positive charge, causing them to relax their grip on the DNA.
- Reduces nucleosome cross-linking - the interaction between histones in neighboring nucleosome. (eg. H4 in one nucleosome and H2A-H2B dimer in the next one).
- Also some TFs recognize acetylated histones. eg. TAFII250 has a double bromodomain and recognizes low level acetylated histones. Once bound it is a HAT and increases acetylation.

Histone modifiers



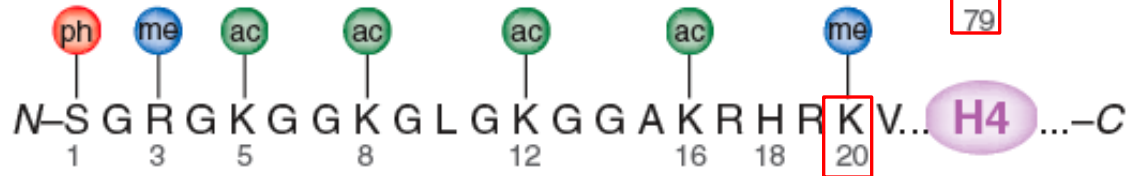
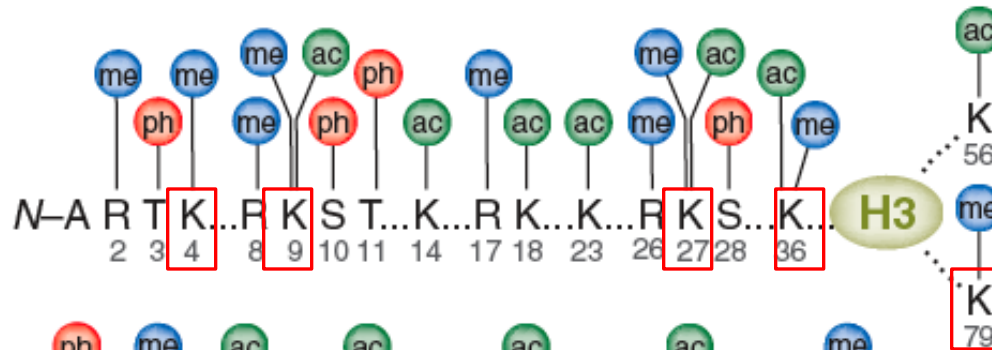
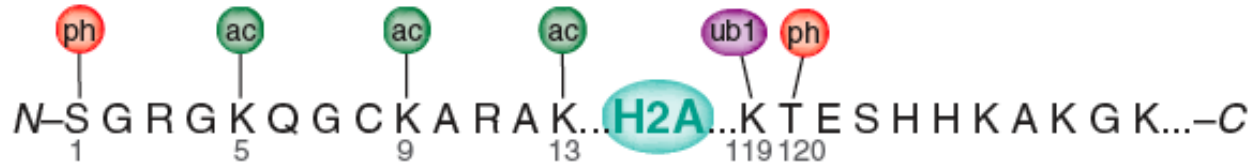
Writers: enzymes that add a mark

Readers: proteins that bind to and “interpret” the mark

Erasers: enzymes that remove a mark

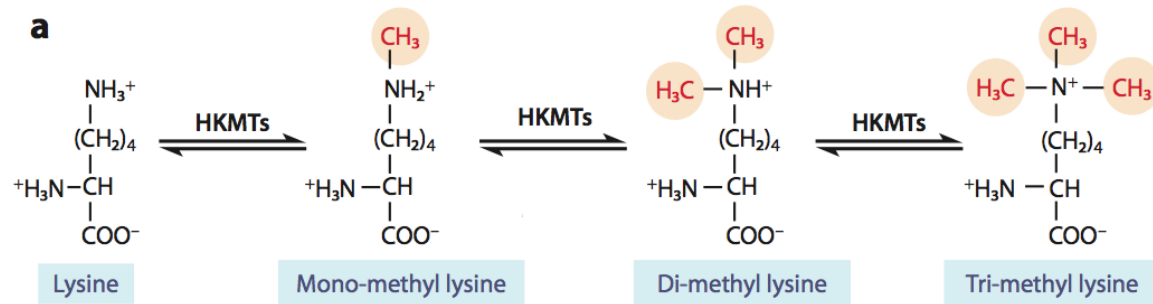
Residue	Modification	Modifying Enzyme
Lysine	Acetylation Deacetylation	HAT HDAC
Lysine	Methylation Demethylation	HMT HDM
Serine/Threonine	Phosphorylation Dephosphorylation	Kinase Phosphatase
Arginine	Methylation Demethylation	PRMT Deiminase/Deimethylase

Lysine Methylation



Lysine Methylation

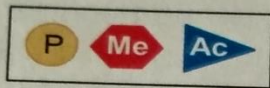
- **Many lysine residues can be methylated**
 - Mainly on histone tails (sometimes in core)
 - Can be mono-, di-, or tri-methylated



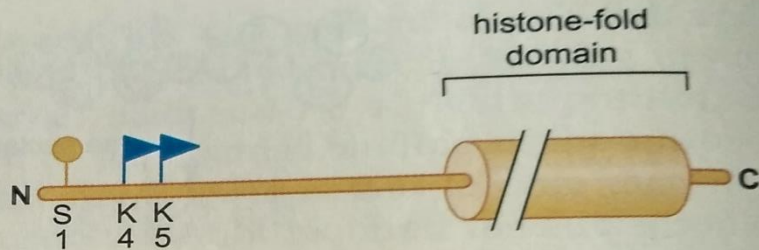
- **Depending on residue and number of methyl groups, can be associated with active or repressive transcription**
- **Other roles**
 - Transcriptional elongation
 - Pericentromeric heterochromatin
 - X chromosome inactivation

Lysine Methyltransferases: KMTs

- **Enzymes very specific**
 - Target a certain lysine on a certain histone
- Put on mono, di, and/or tri methyl (me, me₂, me₃)
- Many contain SET domains (me-transferase)
- HMT (Histone methyl transferases) HDM (Histone demethylases)
- **'Readout' is very specific**
 - Ex. H3K4me₁ vs. H3K4me₃



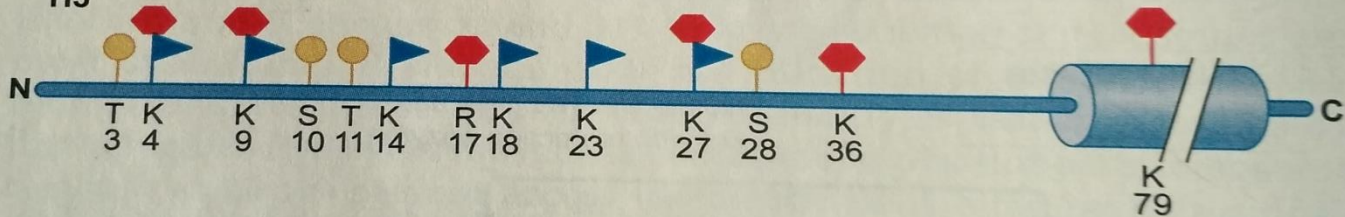
H2A



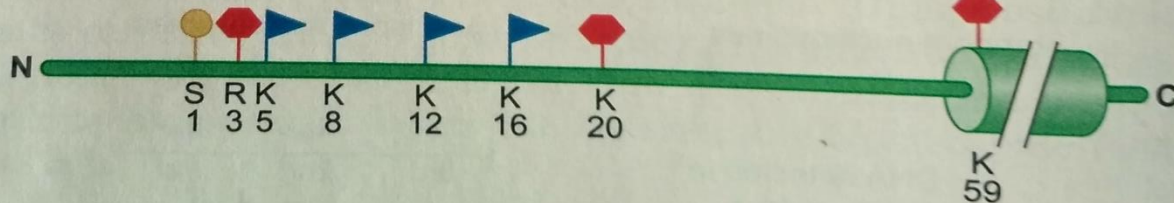
H2B

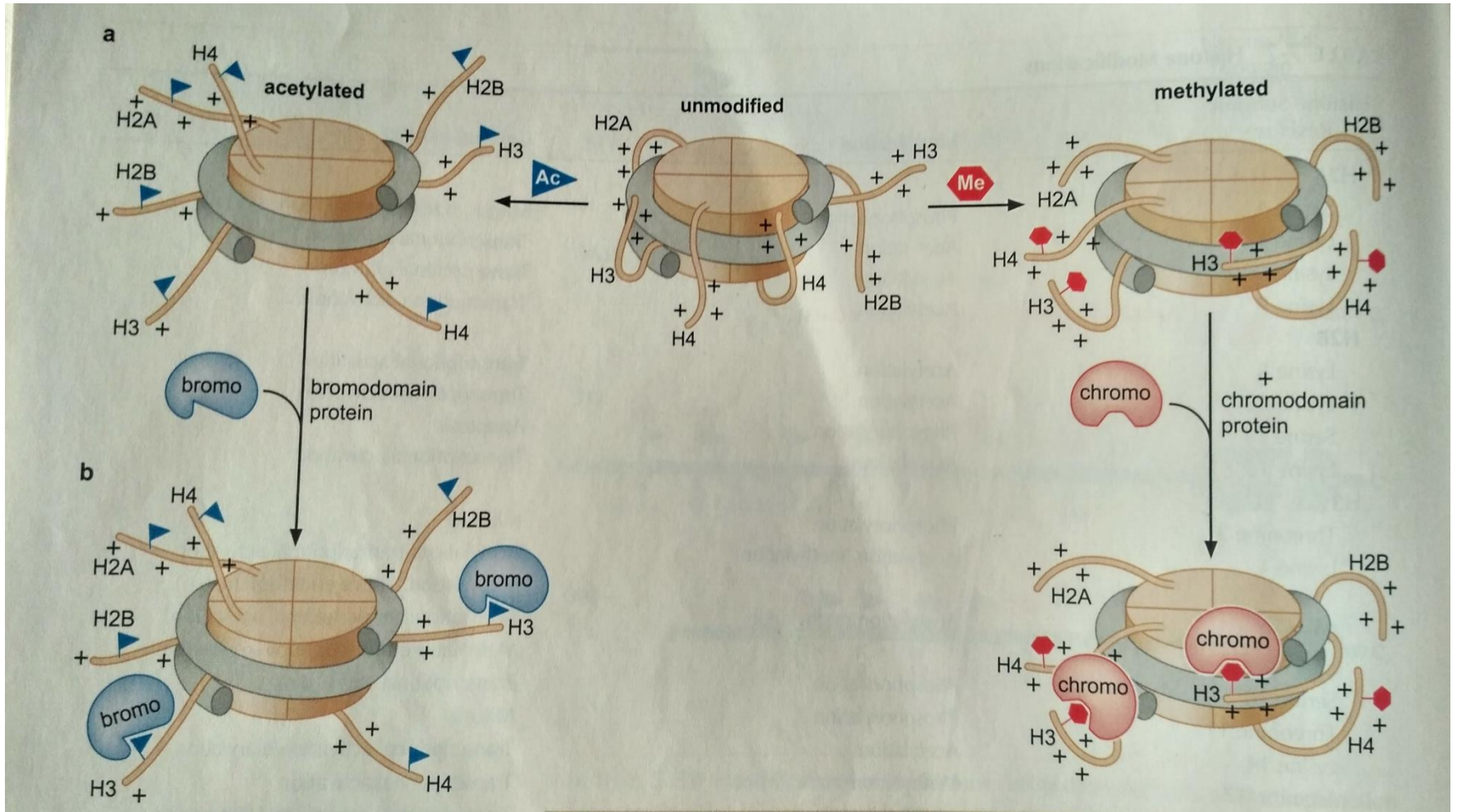


H3



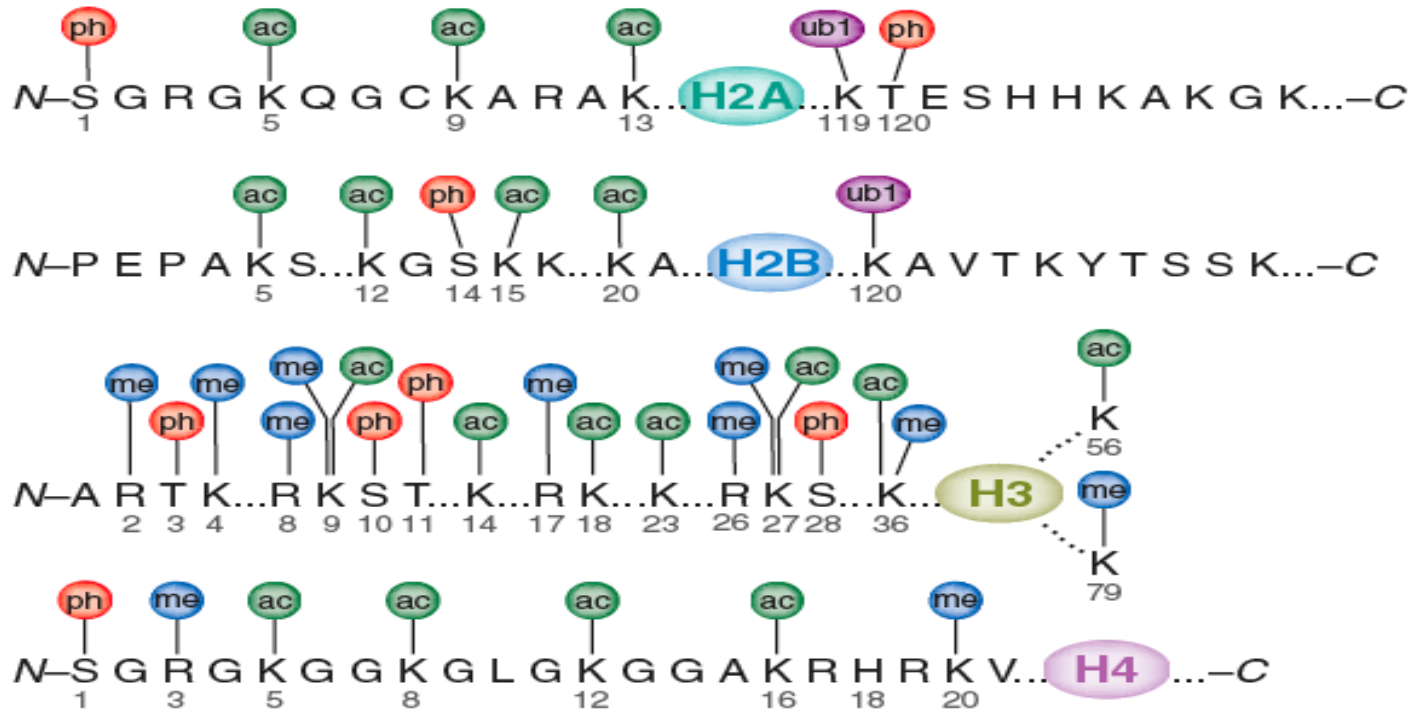
H4





Effect of histone tail modifications

Serine/Threonine Phosphorylation

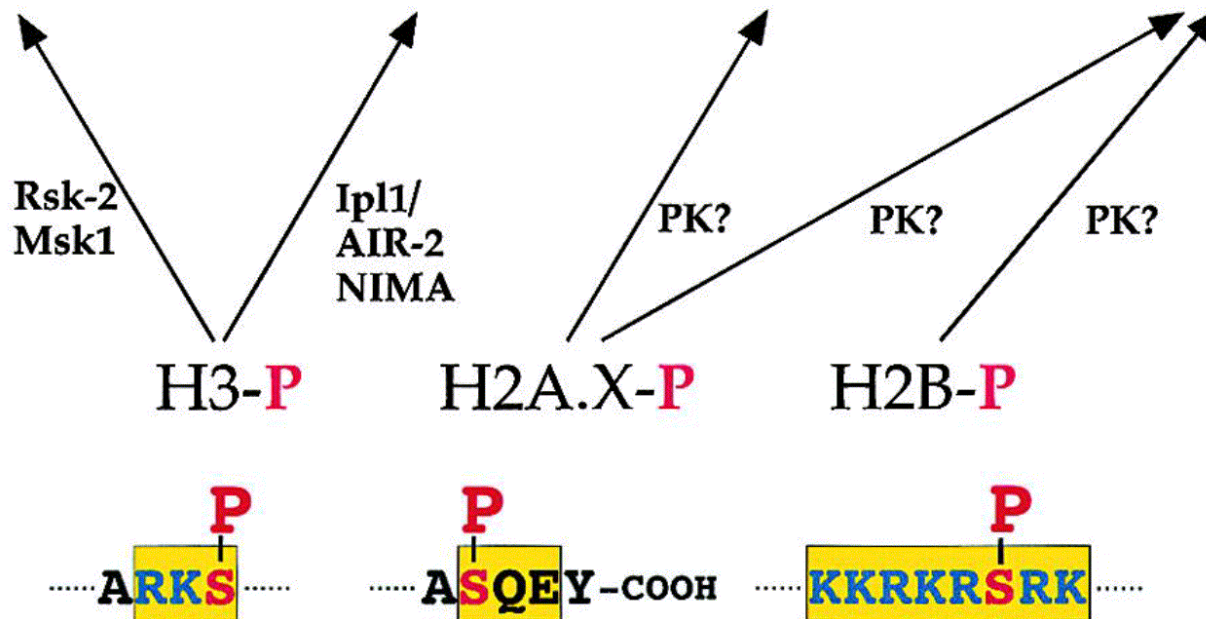


- Kinases phosphorylate
- Phosphatases remove

Eg: H3S10P during mitosis, Kinases: Aurora B, Phosphatase: PP1

Roles of Ser/Thr Phosphorylation

Transcription Mitosis DNA breaks/repair Apoptosis



Overview

- Covalent and reversible
- Dynamic
- Usually occur on histone tails
- Modifying enzymes:
 - Redundancy: A single position can be modified by multiple different enzymes
 - Specificity: Some enzymes (like HMTs) can target only one residue and some (like HATs) can target many
- Histone PTMs recruit other proteins to DNA via specific domains
 - Bromo (Ac)
 - Chromo/PHD (Me)
 - 14-3-3 (Ph)
- Participate in regulation of many processes
 - transcription
 - DNA repair
 - chromatin assembly
 - long-range packaging (heterochromatin formation, silencing)
- Readout frequently depends on the context