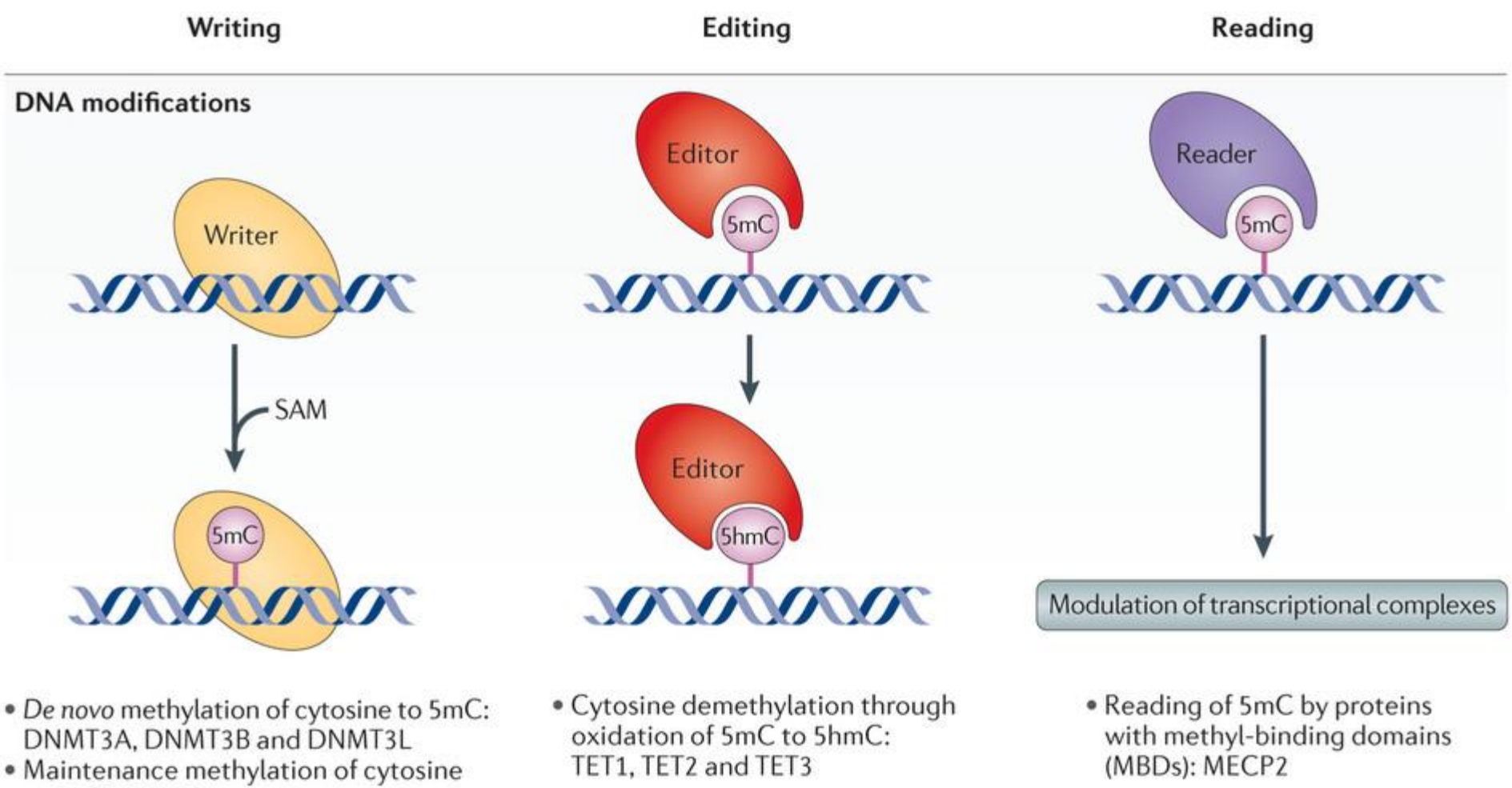
Chemical aspects of the cell

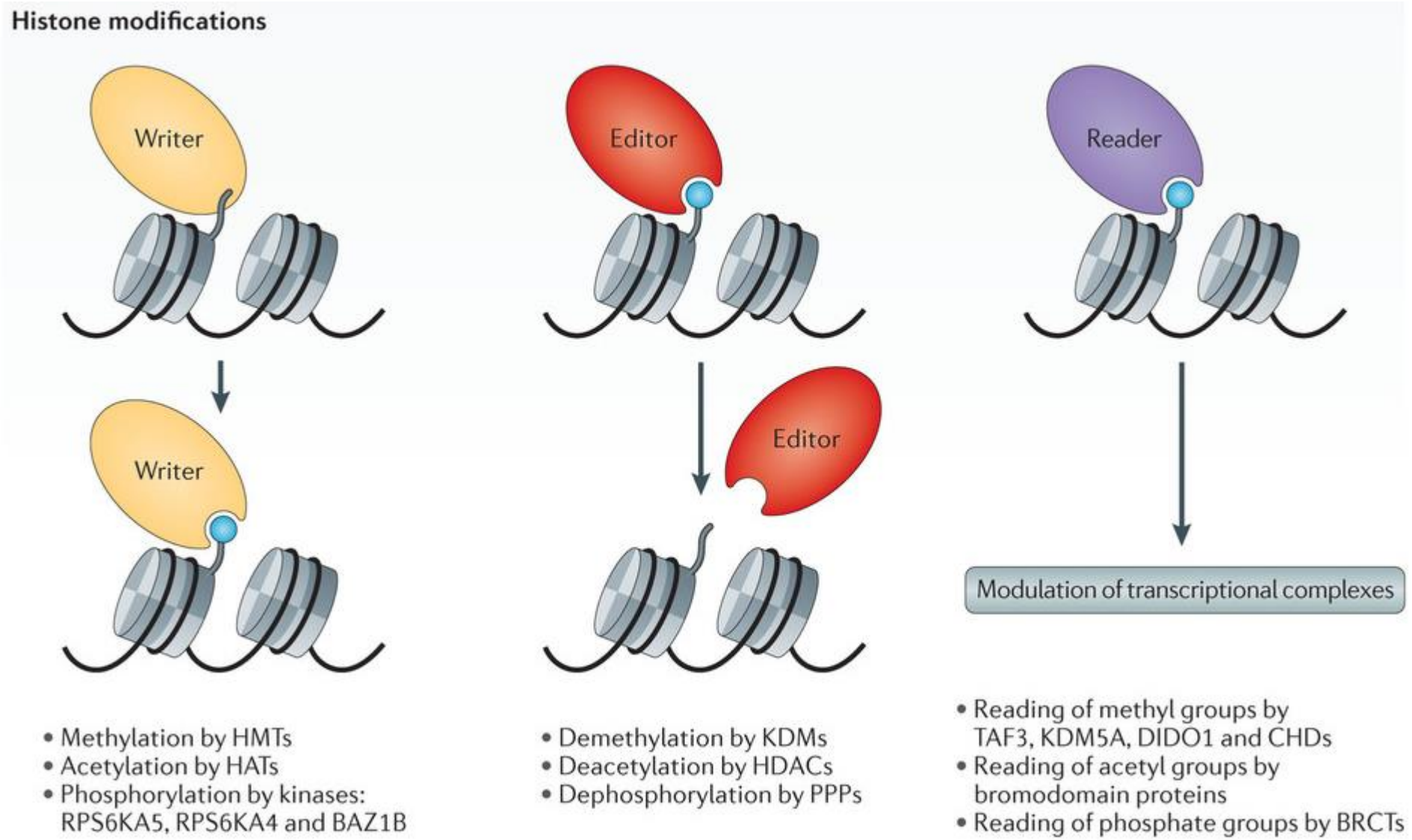
Epigenetics and post-translational modifications

Modification of DNA and histones



Plass, C. et al. *Nat. Rev. Genetics* **2013**, *14*, 765-780

Modification of DNA and histones



Plass, C. et al. *Nat. Rev. Genetics* **2013**, *14*, 765-780

Histone modifications

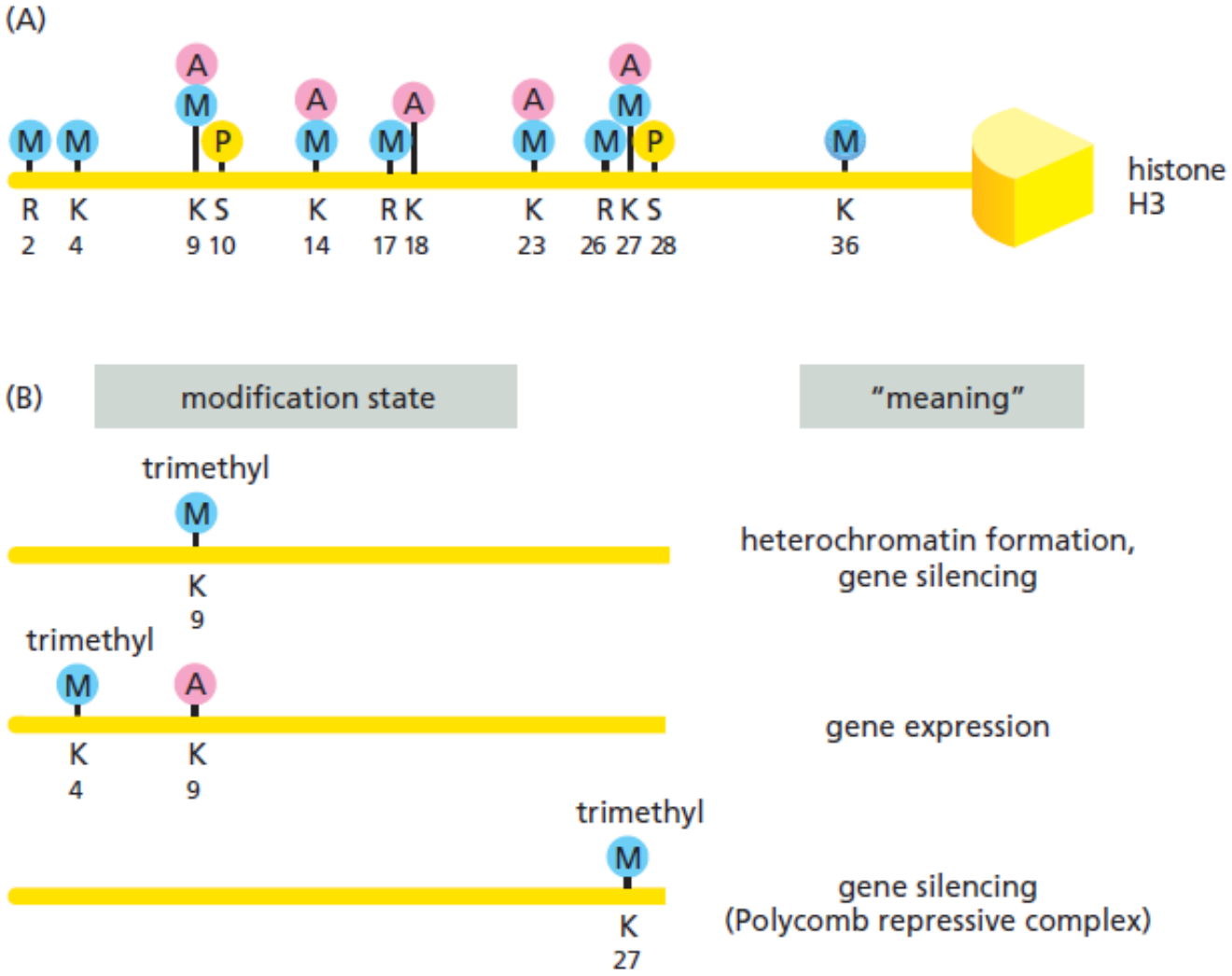


Figure 4–39 Some specific meanings of histone modifications.

Covalent modifications of histones

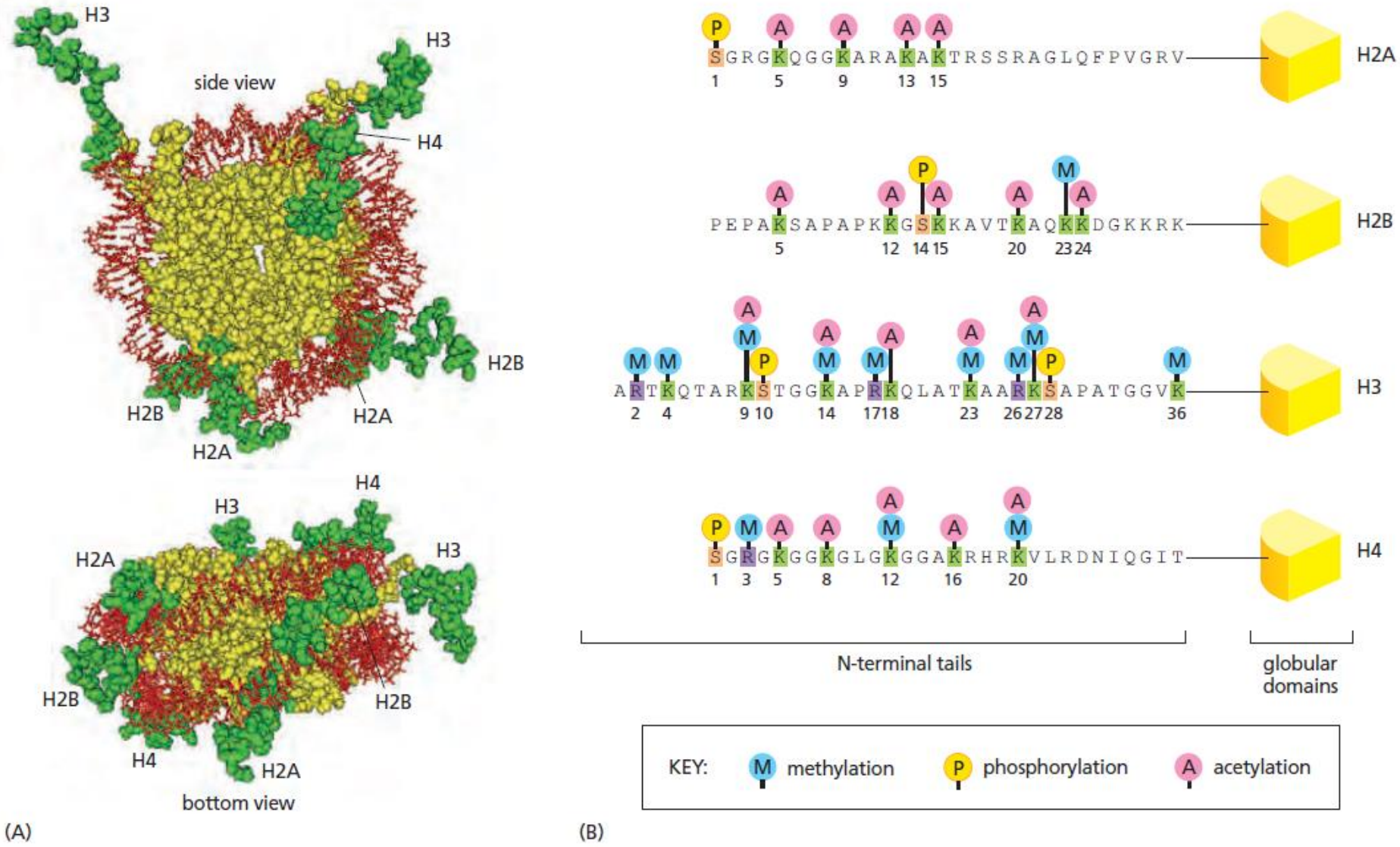


Figure 4–34 The covalent modification of core histone tails.

PI3K and epigenome

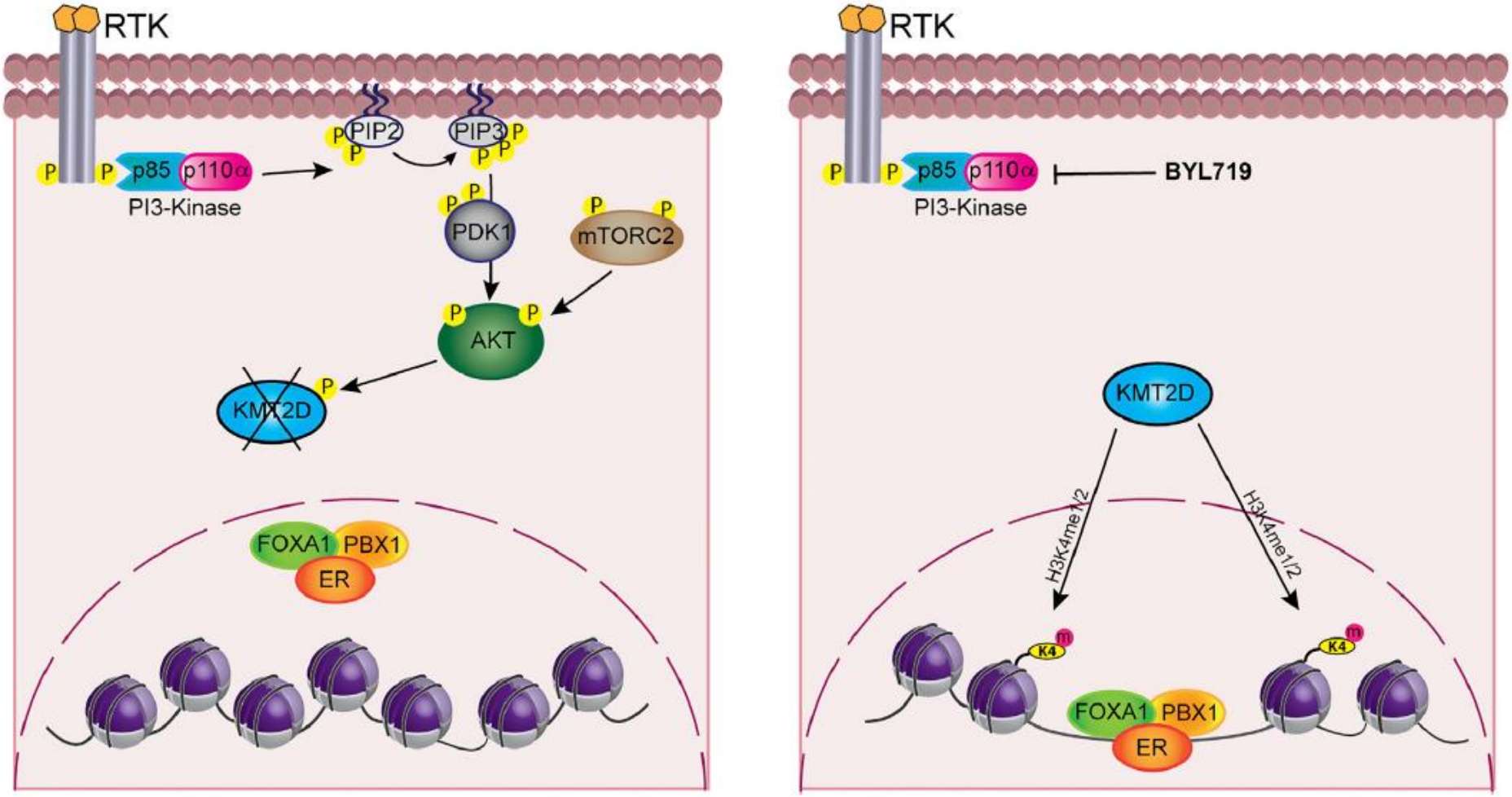


Figure 1. Activation of ERα-Dependent Transcriptional Programs by PI3K Inhibition

Toska et al. suggest a model in which PI3K pathway activation triggers downstream activation of AKT and the phosphorylation of KMT2D, inhibiting its methyltransferase activity. This results in reduced levels of mono- and di-methylated H3K4 (H3K4me1/2) and decreased chromatin accessibility. As a consequence, binding of the ERα-FOXA1-PBX1 complex is attenuated at chromatin, and transcriptional activation of ERα target genes is reduced (left). In contrast, PI3Kα-specific inhibition by BYL719 results in the methylation of H3K4 by KMT2D, increased chromatin accessibility, ERα-FOXA1-PBX1 complex binding at chromatin, and ERα target gene expression (right). RTK, receptor tyrosine kinase; P, phosphorylated sites.

Koren, S.; Bentires-Alj, M. *Cancer Cell* **2017**, *31*, 616-618.

Modification of rRNA

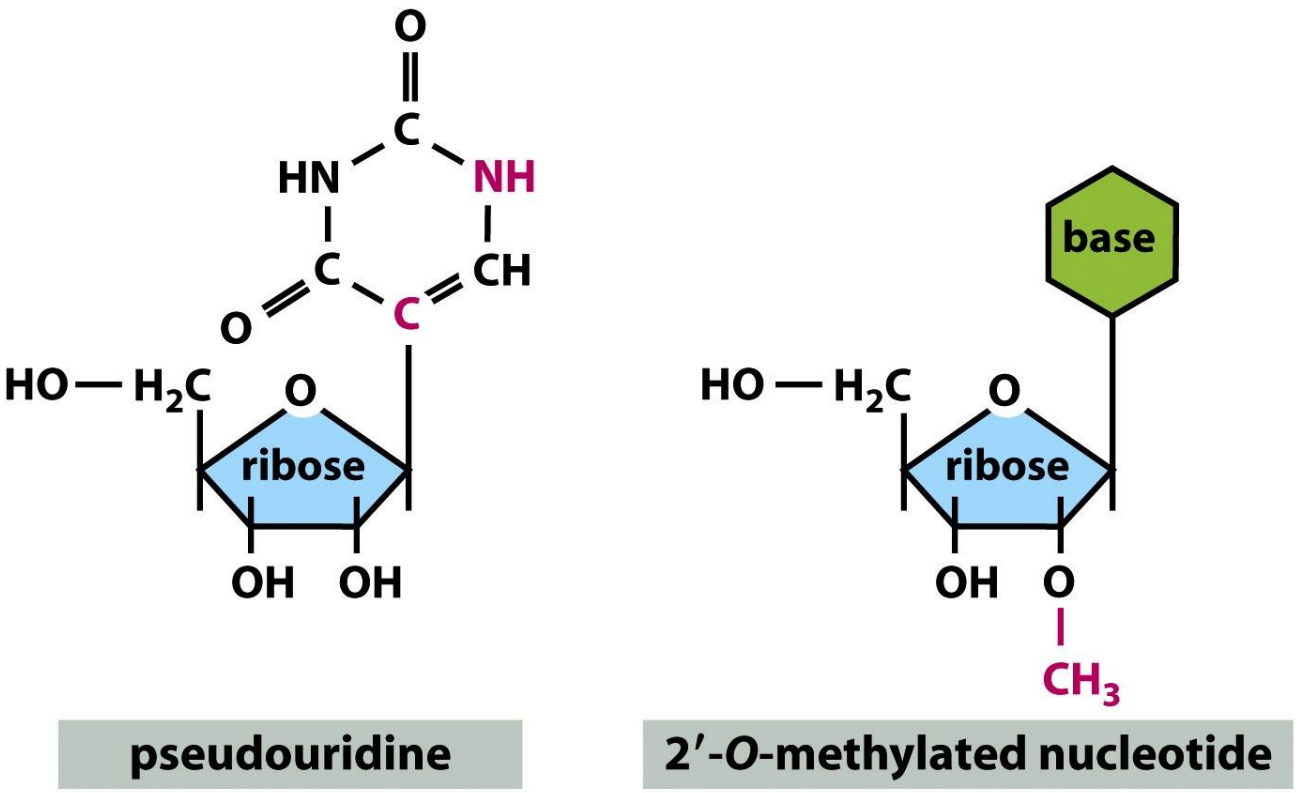
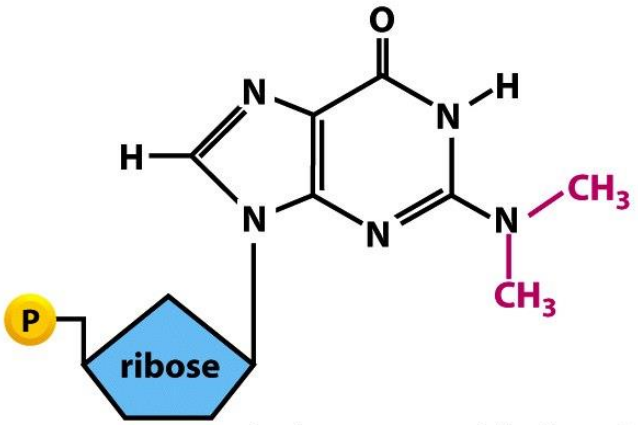
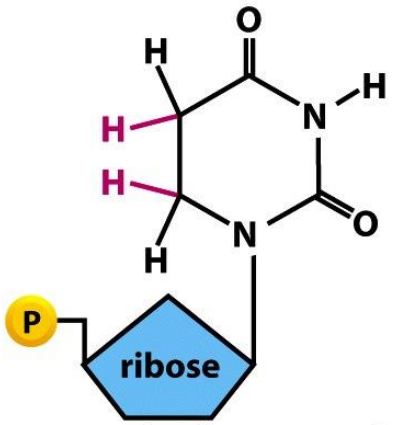


Figure 6–41 Modifications of the precursor rRNA by guide RNAs. (A) Two prominent covalent modifications made to rRNA; the differences from the initially incorporated nucleotide are indicated by *red* atoms. Pseudouridine is an isomer of uridine; the base has been "rotated," and is attached to the *red* C rather than to the *red* N of the sugar (compare to Figure 6–5B). (B) As indicated, snoRNAs determine the sites of modification by base-pairing to complementary sequences on the precursor rRNA. The snoRNAs are bound to proteins, and the complexes are called snoRNPs (small nucleolar ribonucleoproteins). snoRNPs contain both the guide sequences and the enzymes that modify the rRNA.

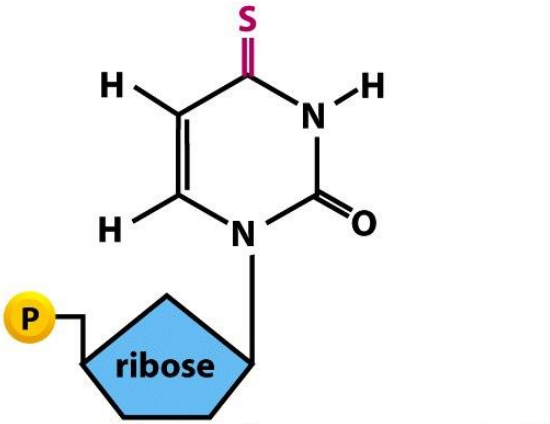
Modifications of tRNA



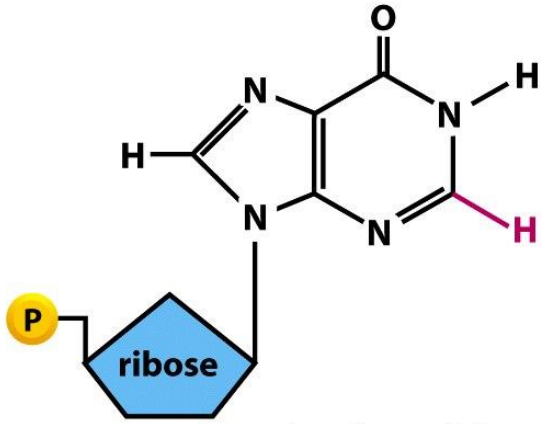
two methyl groups added to G
(*N,N*-dimethyl G)



two hydrogens added to U
(dihydro U)



sulfur replaces oxygen in U
(4-thiouridine)



deamination of A
(inosine)

In most tRNA molecules, about 10% of the nucleotides are modified. Inosine is sometimes present at the wobble position in the tRNA anticodon.

Figures 6-53 *Molecular Biology of the Cell*

Post-translational modifications (PTM)

PTMs involving addition of functional groups

Addition by an enzyme *in vivo*

Hydrophobic groups for membrane localization

- myristoylation (a type of acylation), attachment of myristate
- palmitoylation (a type of acylation), attachment of palmitate
- isoprenylation or prenylation, farnesylation, geranylgeranylation
- glypiation

Cofactors for enhanced enzymatic activity

- lipoylation (a type of acylation)
- flavin moiety (FMN or FAD) may be covalently attached
- heme C attachment via thioether bonds with cysteines
- phosphopantetheinylation
- retinylidene Schiff base formation

Post-translational modifications (PTM)

Modifications of translation factors

- diphthamide formation
- ethanolamine phosphoglycerol attachment
- hypusine formation

Smaller chemical groups

- acylation, e.g. *O*-acylation (esters), *N*-acylation (amides), *S*-acylation (thioesters), acetylation, formylation
- alkylation, e.g. methyl, ethyl
- amidation at C-terminus
- amide bond formation: amino acid addition
- butyrylation
- gamma-carboxylation
- glycosylation & polysialylation
- malonylation
- hydroxylation
- iodination
- nucleotide addition

Post-translational modifications (PTM)

Smaller chemical groups (continuation)

- phosphate ester
- propionylation
- pyroglutamate formation
- *S*-glutathionylation
- *S*-nitrosylation
- *S*-sulfenylation
- *S*-sulfinylation
- *S*-sulfonylation
- succinylation
- sulfation

Non-enzymatic additions *in vivo*

glycation
carbamylation
carbonylation

Post-translational modifications (PTM)

Non-enzymatic additions *in vitro*

- biotinylation
- carbamylation
- oxidation
- pegylation

Other proteins or peptides

ISGylation, SUMOylation, ubiquitination, Neddylation, Pupylation

Chemical modification of amino acids

- citrullination or deimination
- deamidation
- eliminylation

Structural changes

- disulfide bridges
- proteolytic cleavage
- isoaspartate formation
- racemization
- protein splicing

Acetylation and methylation reactions

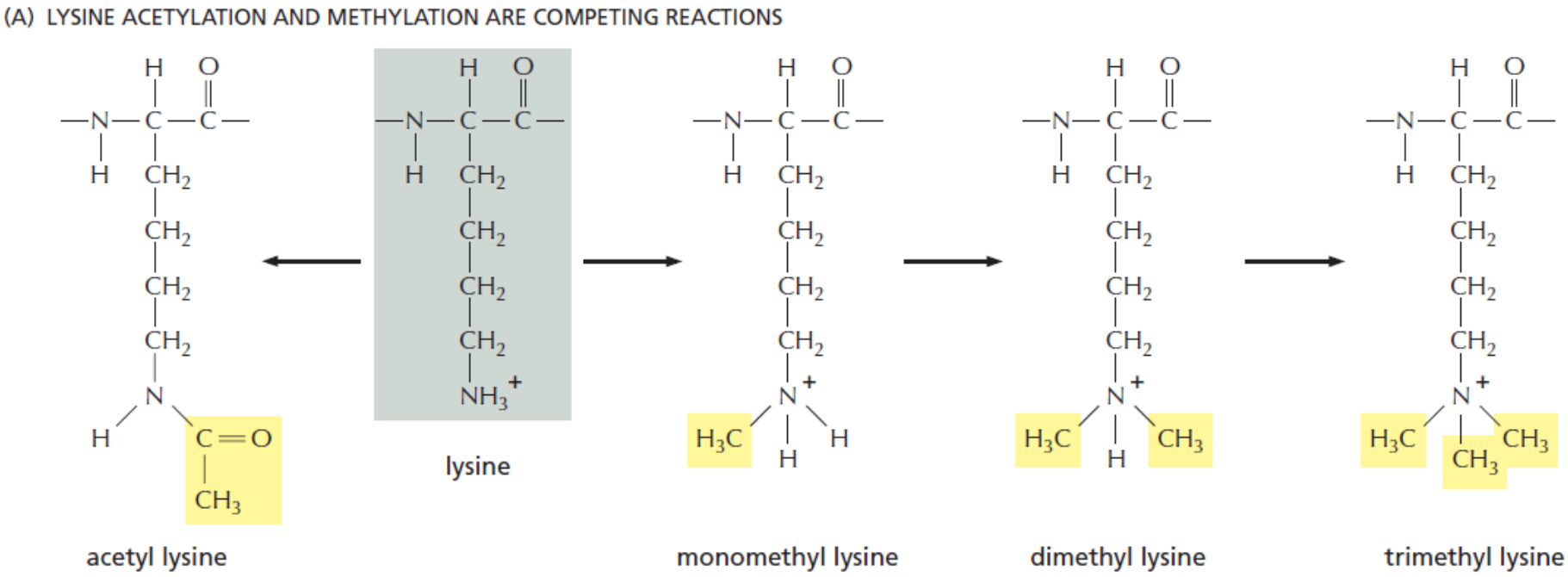


Figure 4–33 Some prominent types of covalent amino acid side-chain modifications found on nucleosomal histones

Methylation and nucleosome

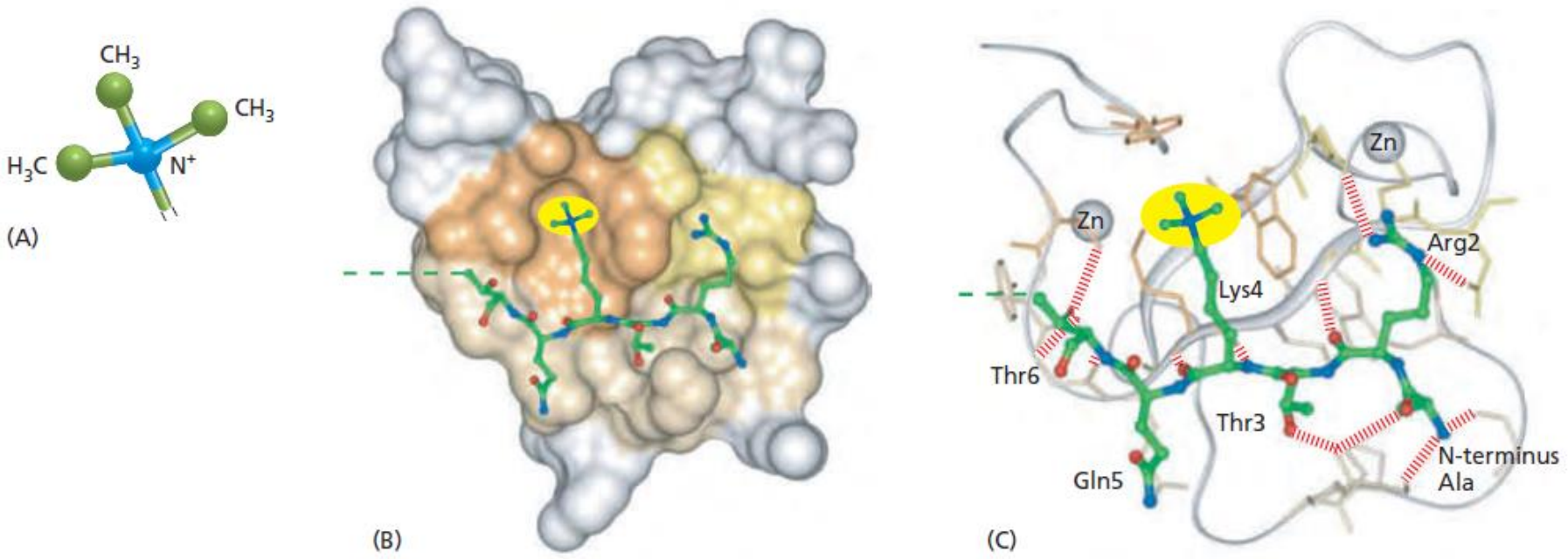
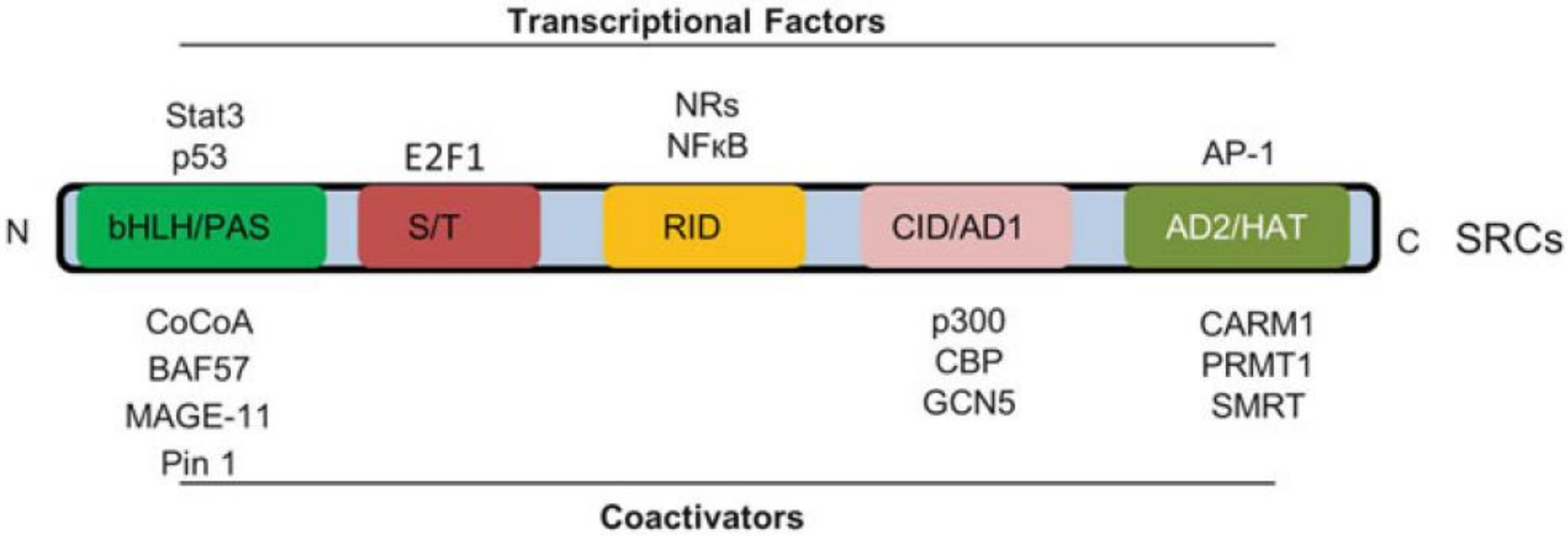


Figure 4–36 How a mark on a nucleosome is read. The figure shows the structure of a protein module (called an ING PHD domain) that specifically recognizes histone H3 trimethylated on lysine 4.

Phosphorylation sites

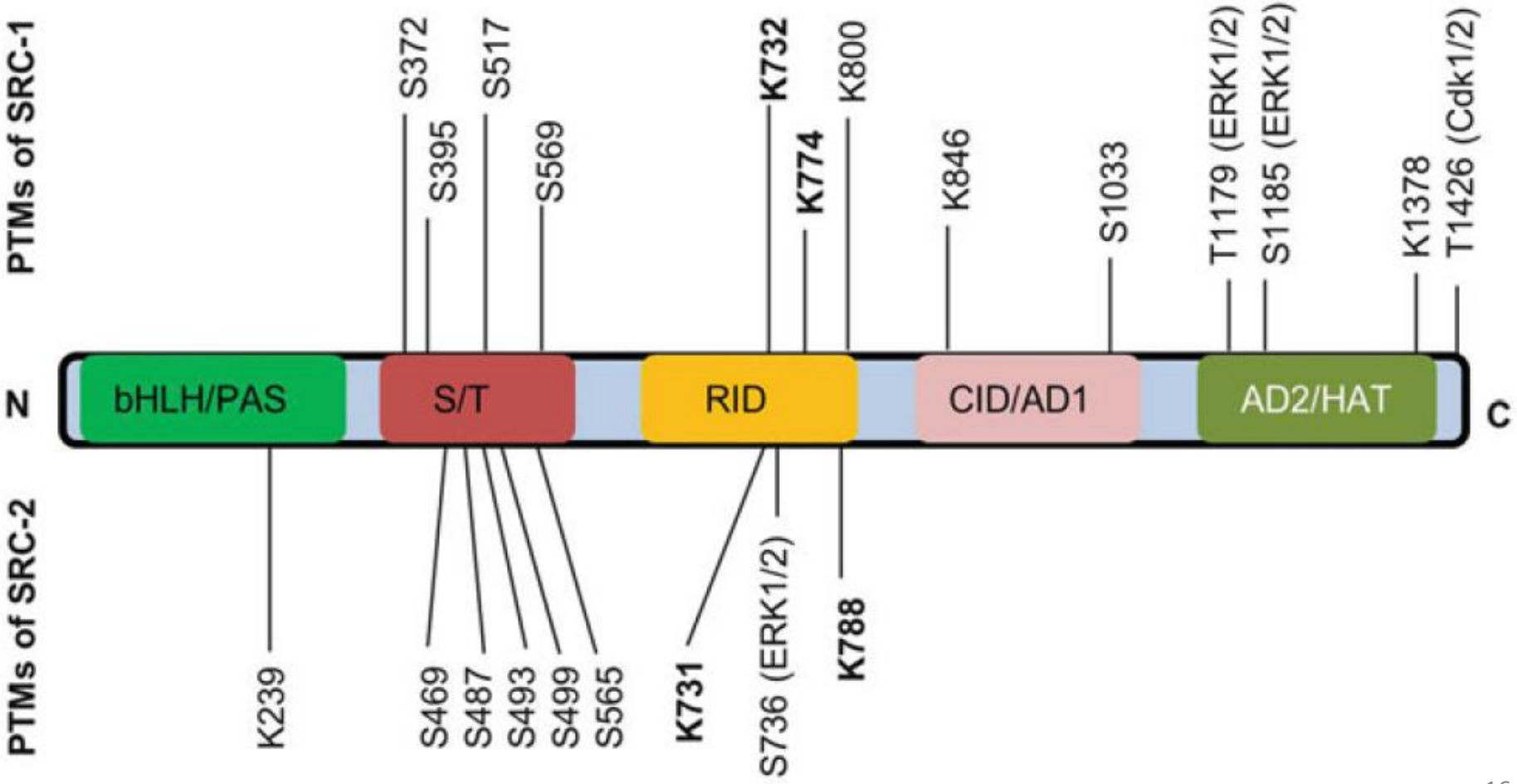
Structural domains and transcriptional interacting partners of Steroid Receptor Coactivators (SRCs)



Kumar, H. Nuclear Signaling Pathways and Targeting Transcription in Cancer. Humana Press. 2014.

Phosphorylation sites

Hormones stimulate target gene transcription not only by activating hormone receptors via direct binding, but also by activating protein kinases that subsequently phosphorylate hormone receptors and coregulators including SRCs.
PTMs of SRC-1 and SRC-2.



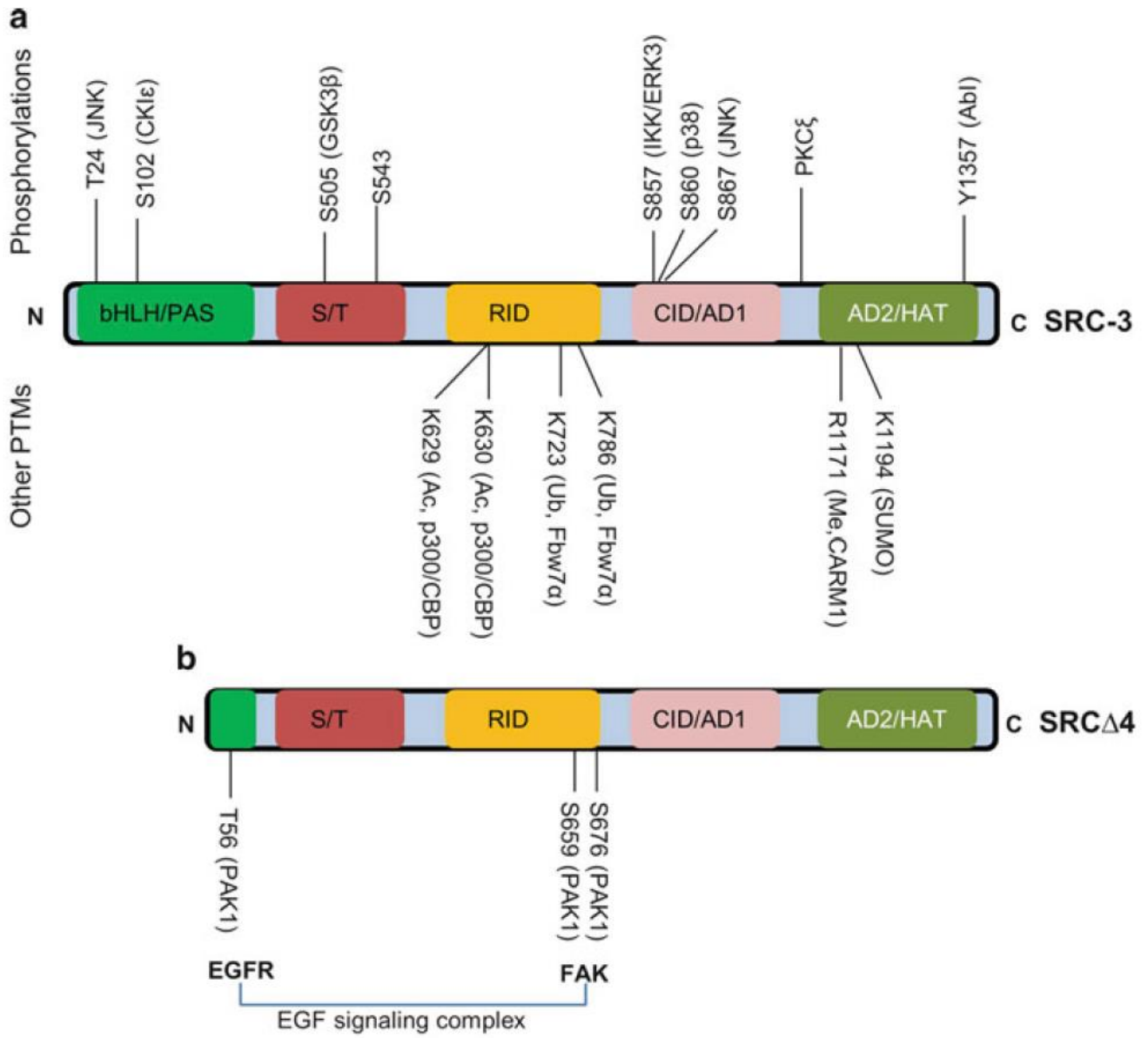
Kumar, H. Nuclear Signaling Pathways and Targeting Transcription in Cancer. Humana Press. 2014.

Phosphorylation sites

PTMs of SRC-3 and SRC-3Δ4.

(a) Selected phosphorylation sites with ubiquitination (Ub), sumoylation (SUMO), or acetylation (Ac), and arginine (R) residue with methylation (Me) of SRC-3. In the “( )” are also shown certain modifying enzymes for each specific PTM.

(b) Phosphorylation codes of SRC-3Δ4.



Kumar, H. Nuclear Signaling Pathways and Targeting Transcription in Cancer. Humana Press. 2014.