

# Chromatin and Epigenetic Regulation Pathways

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from Cell Signaling Technology

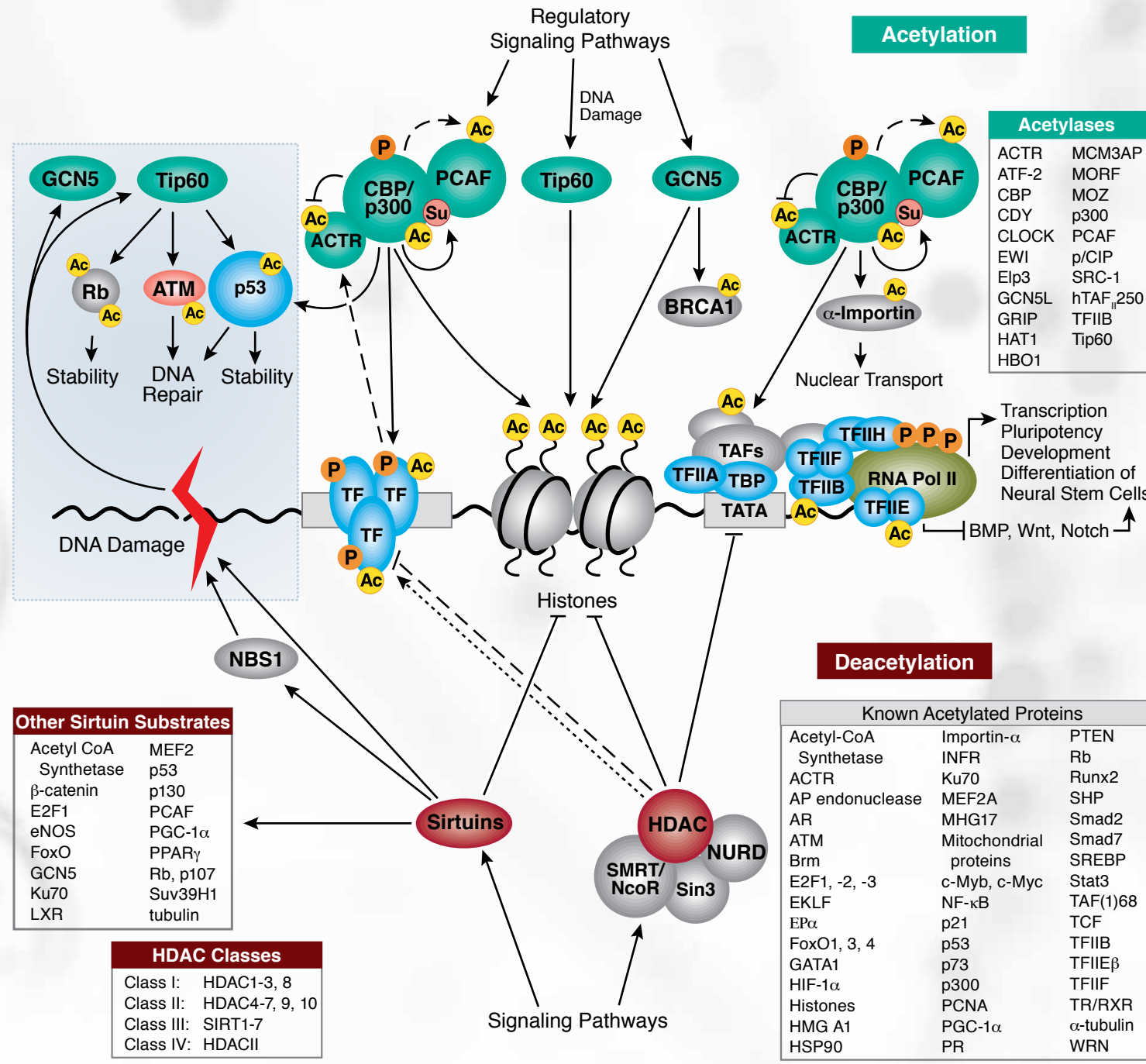
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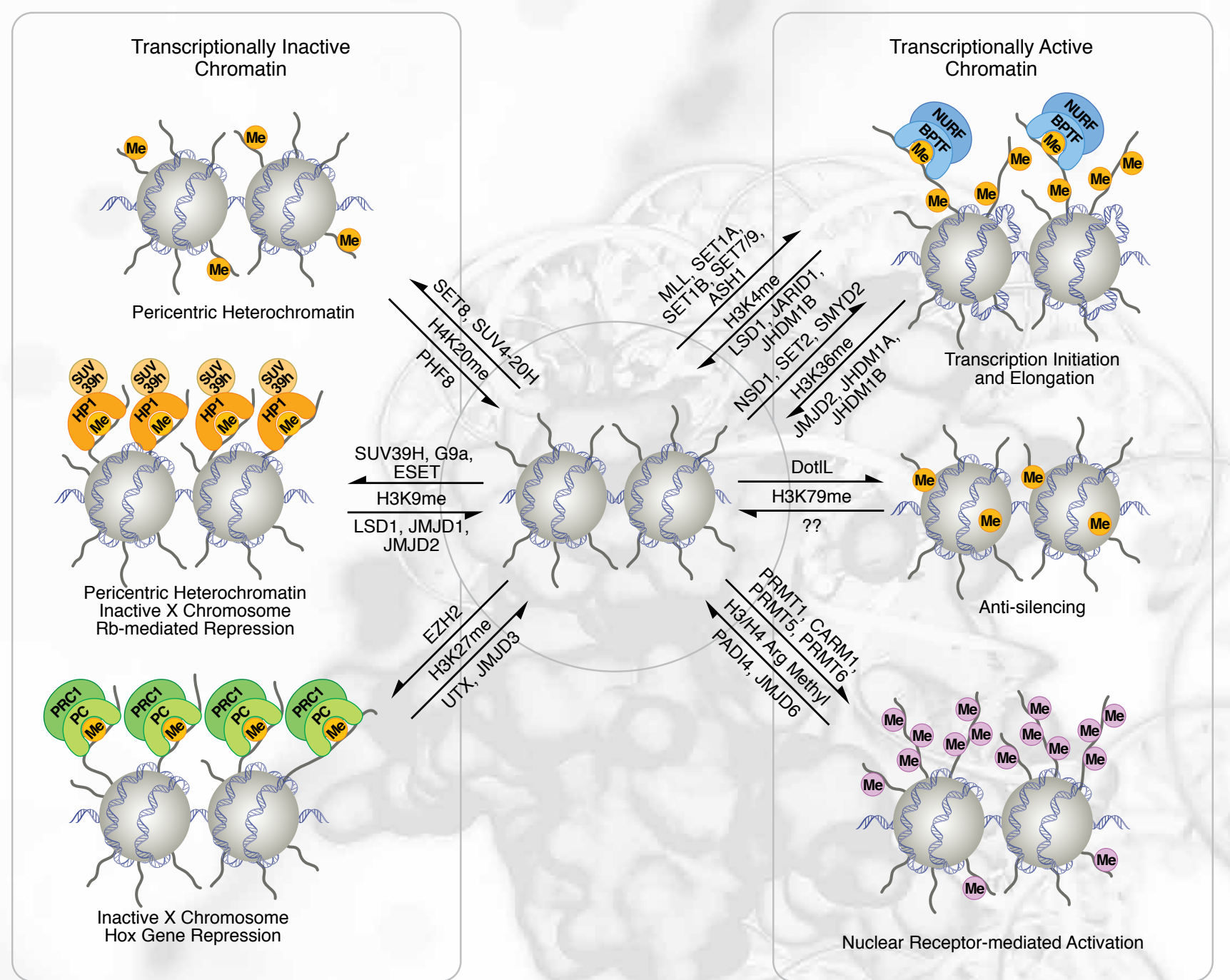
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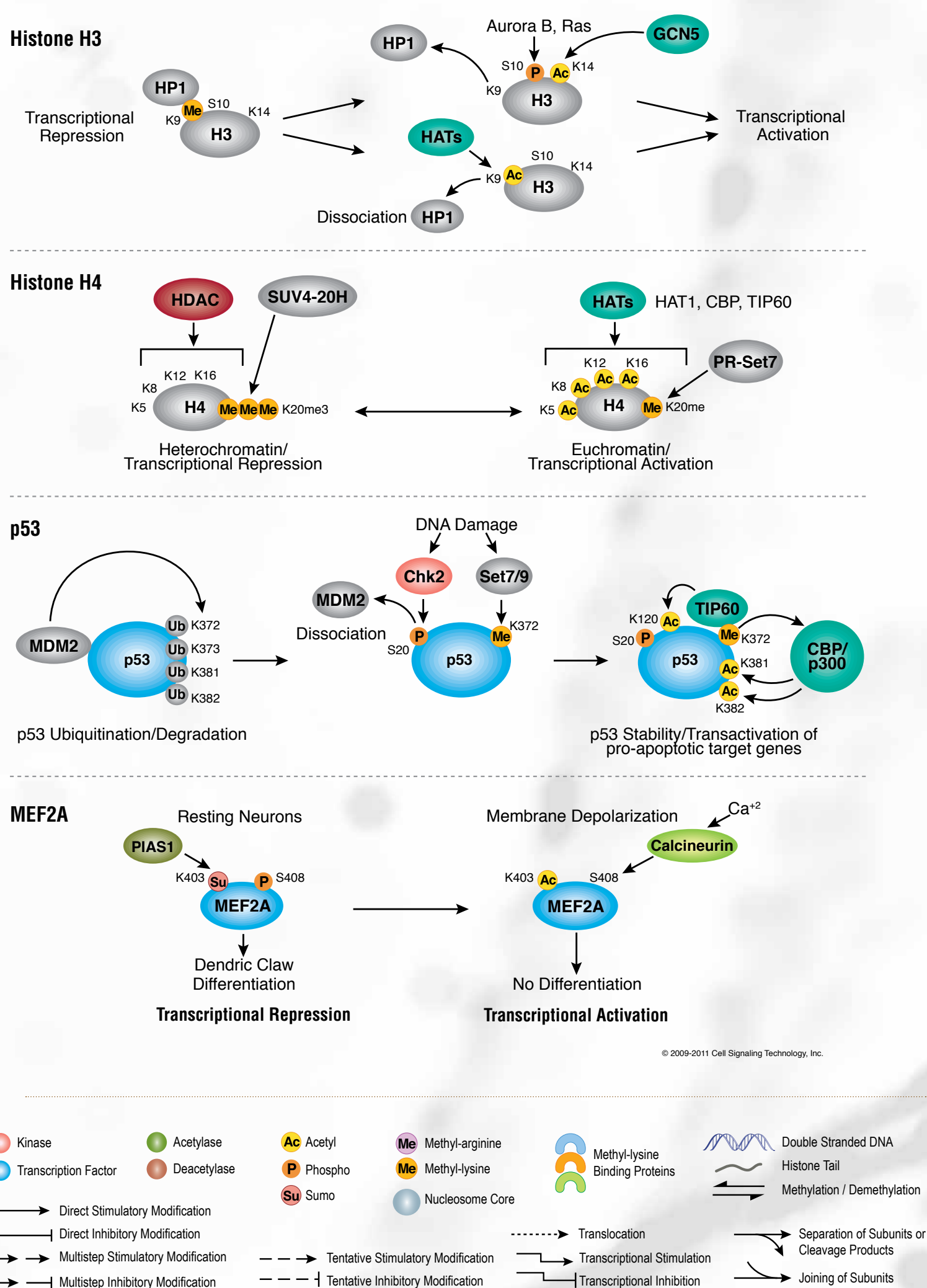
## Protein Acetylation



## Histone Methylation



## Examples of Crosstalk Between Post-translational Modifications



## Histone Modification Table

Histone	Site	Histone-modifying Enzymes	Proposed Function	PMID
H2A	Lys4 (S. cerevisiae)	Esa1	transcriptional activation	10082517
	Lys5 (mammals)	Tip60, p300/CBP	transcriptional activation	10096020, 9880483
	Lys7 (S. cerevisiae)	Hat1	unknown	9427644
H2B	Lys5	p300, ATF2	transcriptional activation	9880483, 10821277
	Lys11 (S. cerevisiae)	Gcn5	transcriptional activation	11545749
	Lys12 (mammals)	p300/CBP, ATF2	transcriptional activation	9880483, 10821277
H3	Lys4 (S. cerevisiae)	Esa1	transcriptional activation	10082517
	Lys9	Hpa2	histone deposition	10600387
	Lys14	Gcn5, SRC-1	transcriptional activation	10026213, 9296499
H4	Lys5	Hat1	histone deposition	8658151
	Lys9	Gcn5	transcriptional activation, DNA repair	10026213
	Lys12	Hat1	histone deposition	8658151

Histone	Site	Histone-modifying Enzymes	Proposed Function	PMID
H1	Lys26	Eh2	transcriptional silencing	1612177, 1509518
H3	Lys4	Set1 (S. cerevisiae)	permissive euchromatin (di-Me)	11751634
	Lys9	Set7/9 (vertebrates)	transcriptional activation (tri-Me)	11779497
	Lys36	Set2	transcriptional silencing (tri-Me)	12351676
H4	Arg3	PRMT1	transcriptional activation	11448779
	Lys20	PR-Set7	transcriptional repression (mono-Me)	12086618
	Lys59	Set9 (S. pombe)	transcriptional silencing	12337907

Histone	Site	Histone-modifying Enzymes	Proposed Function	PMID
H1	Ser27	unknown	transcriptional activation, chromatin decondensation	1612177, 1509518
H2A	Ser1	unknown	mitosis, chromatin assembly	15133681
	Thr119 (D. melanogaster)	NHK1	mitosis	15010469
	Ser122 (S. cerevisiae)	MSK1, MSK2	immediate-early gene activation	12773393
H3	Thr3	Hsp90/Gsp2	mitosis	15681610
	Ser10	Aurora-B kinase	mitosis, meiosis	9326243, 10975519
	Ser28 (mammals)	MSK1, MSK2	immediate-early gene activation	12773393

Histone	Site	Histone-modifying Enzymes	Proposed Function	PMID
H2A	Lys26 (S. cerevisiae)	Ubc9	transcriptional repression	16598039
H2B	Lys6 or Lys7 (S. cerevisiae)	Ubc9	transcriptional repression	16598039
H4	N-terminal tail (S. cerevisiae)	Ubc9	transcriptional repression	14578449

Histone	Site	Histone-modifying Enzymes	Proposed Function	PMID
H2A	Lys19 (mammals)	Ring2	spermatogenesis	15386022
H2B	Lys20 (mammals)	Ubc6	meiosis	16307923
	Lys23 (S. cerevisiae)	Rad6	transcriptional activation, euchromatin	10642555

Histone	Site	Histone-modifying Enzymes	Proposed Function	PMID
H2A	Lys9	biotinidase	unknown	16109483
	Lys13	biotinidase	unknown	16109483
	Lys4	biotinidase	gene expression	16098205
H3	Lys9	biotinidase	gene expression	16098205
	Lys18	biotinidase	gene expression	16098205
H4	Lys12	biotinidase	DNA damage response	15153116, 16177192

**Protein Acetylation**  
**Pathway Description:** Protein acetylation plays a crucial role in regulating chromatin structure and transcriptional activity. Many transcriptional activators possess intrinsic acetylase activity, while transcriptional repressors are associated with deacetylase activity. Acetylation complexes (such as CBP/p300 and PCAF) or deacetylation complexes (such as Sin3, NuRD, NcoR and SMRT) are recruited to DNA-bound transcription factors (TFs) in response to signaling pathways. Histone hyperacetylation by histone acetyltransferases (HATs) is associated with transcriptional activation, whereas histone deacetylation by histone deacetylases (HDACs) is associated with transcriptional repression. Histone acetylation stimulates transcription by remodeling higher order chromatin structure, weakening histone-DNA interactions, and providing binding sites for transcriptional activation complexes containing proteins that possess bromodomains, which bind acetylated lysine. Histone deacetylation represses transcription through an inverse mechanism involving the assembly of compact higher order chromatin and the exclusion of bromodomain-containing transcription activation complexes. Histone hypoacetylation is a hallmark of silent heterochromatin. Site-specific acetylation of a growing number of non-histone proteins, including p53 and E2F, has been shown to regulate their activity, localization, specific interactions, and stability/degradation, therefore controlling a variety of cellular processes, such as transcription, proliferation, apoptosis, and differentiation. At an organismal level, acetylation plays an important role in immunity, circadian rhythmicity, and memory formation. Protein acetylation is becoming a favorable target in drug design for numerous disease conditions.

**Histone Methylation**  
**Pathway Description:** The nucleosome, made up of four histone proteins (H2A, H2B, H3, and H4), is the primary building block of chromatin. Originally thought to function as a static scaffold for DNA packaging, histones have more recently been shown to be dynamic proteins, undergoing multiple types of post-translational modifications. Two such modifications, methylation of arginine and lysine residues are major determinants for formation of active and inactive regions of the genome. Arginine methylation of histones H3 (Arg2, 17, 26) and H4 (Arg3) promotes transcriptional activation and is mediated by a family of protein arginine methyltransferases (PRMTs), including the co-activators PRMT1 and CAPM1 (PRMT4). In contrast, a more diverse set of histone lysine methyltransferases has been identified, all but one of which contain a conserved catalytic SET domain originally identified in the *Drosophila* Su(Hw) [3-9]. Enhancer of zeste, and Trithorax proteins. Lysine methylation has been implicated in both transcriptional activation (H3 Lys4, 36, 79) and silencing (H3 Lys9, 27, H4 Lys20). Unlike acetylation, methylation does not alter the charge of arginine and lysine residues and is unlikely to directly modulate nucleosomal interactions required for chromatin folding. While the mechanisms by which arginine methylation regulates transcription are unknown, lysine methylation coordinates the recruitment of chromatin modifying enzymes. Chromodomains (HP1, PRC1), PHD fingers (BPTF, ING2), Tudor domains (53BP1), and WD-40 domains (WDR5) are among a growing list of methyl-lysine binding modules found in

histone acetyltransferases, deacetylases, methylases and ATP-dependent chromatin remodeling enzymes. Lysine methylation provides a binding site for these enzymes, which then regulate chromatin condensation and nucleosome mobility in order to maintain local regions of active or inactive chromatin. In addition, lysine methylation can block binding of proteins that interact with unmethylated histones or directly inhibit catalysis of other regulatory modifications on neighboring residues. The presence of histone-lysine binding modules in the DNA repair protein 53BP1 suggests roles for lysine methylation in other cellular processes. Histone methylation is crucial for proper programming of the genome during development and misregulation of the methylation machinery can lead to diseased states such as cancer. Until recently, methylation was believed to be an irreversible, stable epigenetic mark that is propagated through multiple cell divisions, maintaining a gene in an active or inactive state. While there is no argument that methylation is a stable mark, recent identification of histone demethylases such as LSD1/AOF2, JMJD1, JMJD2 and JMJD3 has shown that methylation is reversible and provides a rational for how genomes might be reprogrammed during differentiation of individual cell lineages.

**Examples of Crosstalk Between Post-translational Modifications**  
**Pathway Description:** Post-translational modifications (PTMs) have recently emerged as major regulators of protein function. Originally described in histones, these various chemical modifications (methylation, acetylation, phosphorylation, sumoylation, and more) have now been identified in non-histone proteins as well. Early work defined a putative role for each of these modifications, for instance, acetylation correlates with activation and methylation with repression. However, more recent studies indicate that some of these modifications could trigger either activation or silencing in a context dependent manner. For instance, methylation of histone H3 Lys9 correlates with repression, while methylation of H3 Lys4 correlates with activation. Furthermore, each of these moieties can be either mono- or tri-methylated, and depending on the degree of methylation, the biological output will be completely different. Until recently, PTMs were considered independently, under the assumption that their functions would not be related to one another. It is now clear that PTMs work in concert, and the crosstalk between different modifications determines the final biological read-out. In this context, some modifications can influence others, and it appears that specific combinations of these modifications can form a dynamic "code". We provide a few examples of this type of crosstalk above. Although each of the modifications shown here are occurring in cis, there are now clear examples, at least for histones, where modifications in one histone molecule can regulate modifications in other histones in trans. Although there are now many examples of these "functional networks", it is likely that we have just begun to scratch the surface. Better antibodies and novel technologies will help to complete this crosstalk puzzle, for which the specific fine-tuning appears critical to determine life as we know it.