Chromatin and Epigenetic Regulation Pathways

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from Cell Signaling Technology

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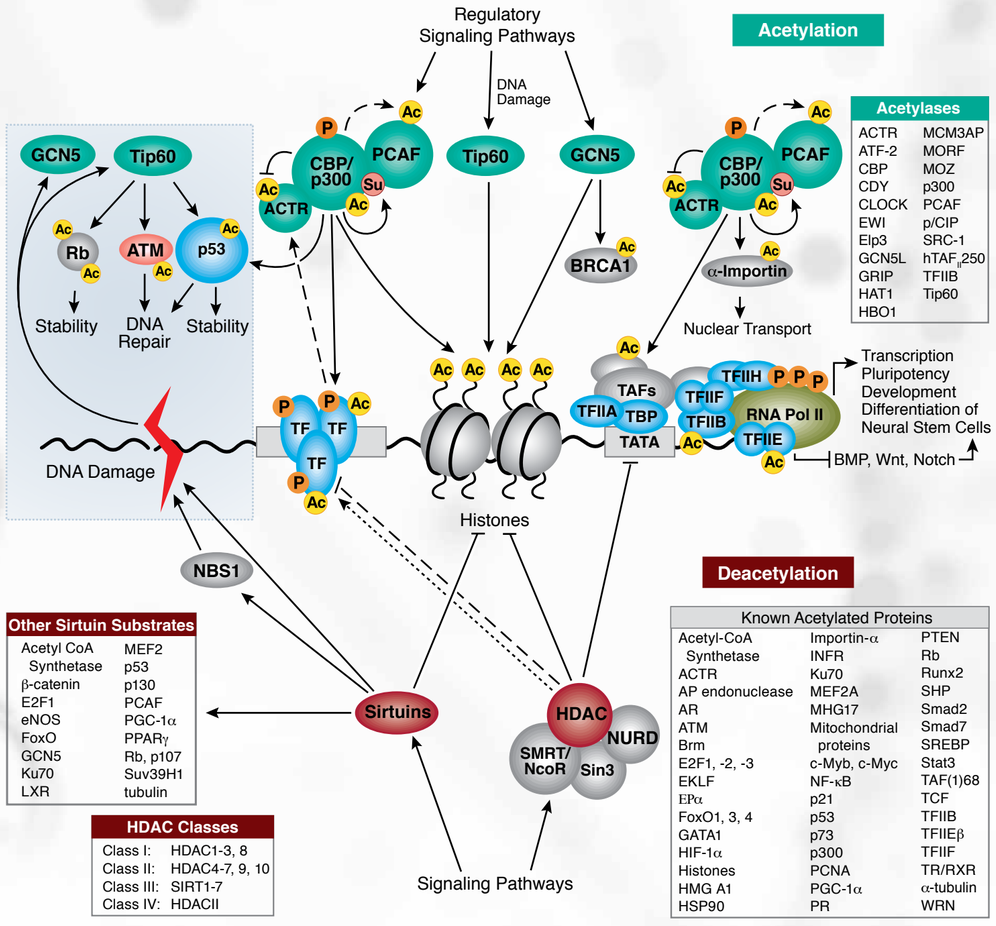
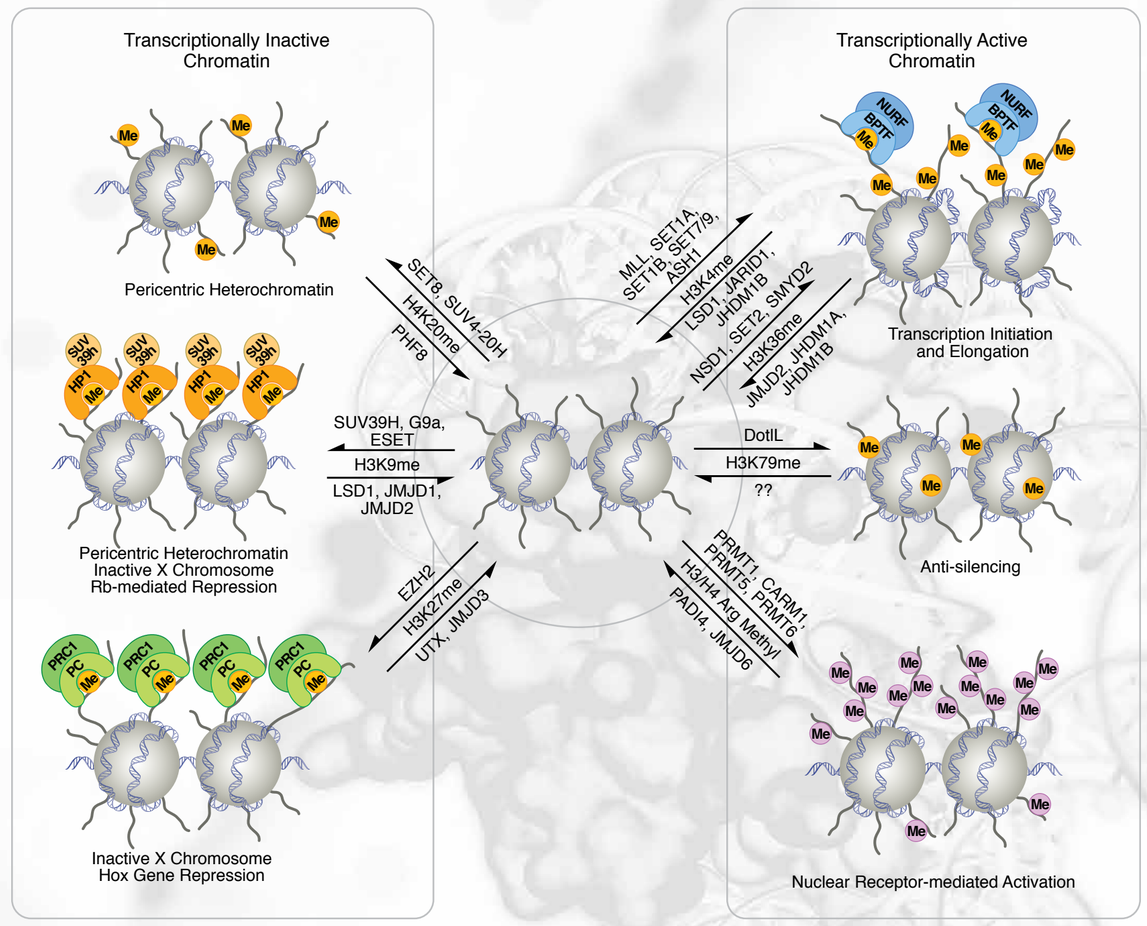
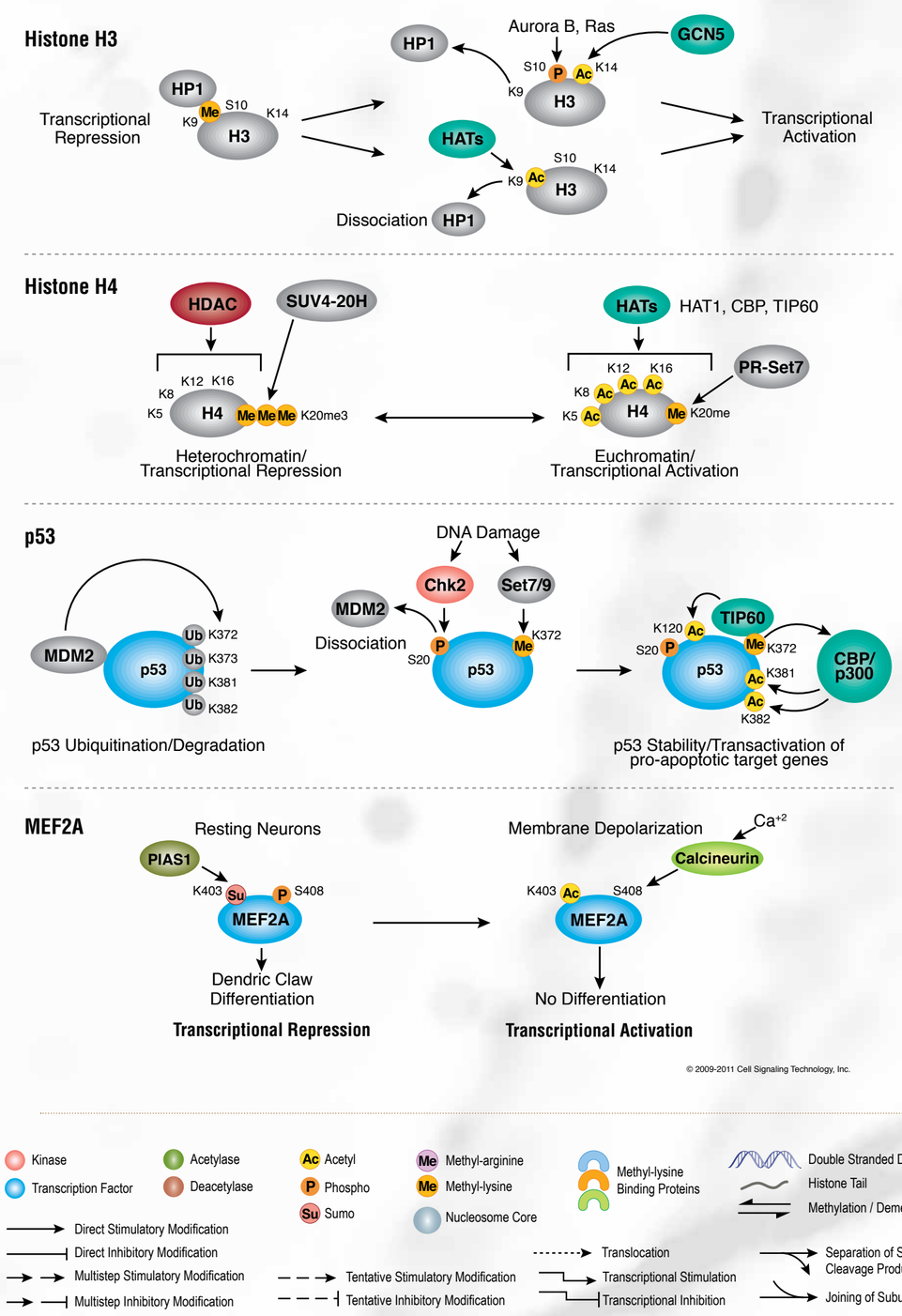
Protein Acetylation



Histone Methylation



Examples of Crosstalk Between Post-translational Modifications



Kinase
Transcription Factor
Acetylase
Deacetylase
Ac Acetyl
P Phospho
Su Sumo
Me Methyl-arginine
Me Methyl-lysine
Nucleosome Core
Methyl-lysine Binding Proteins
Double Stranded DNA
Histone Tail
Methylation / Demethylation
Direct Stimulatory Modification
Direct Inhibitory Modification
Multistep Stimulatory Modification
Multistep Inhibitory Modification
Tentative Stimulatory Modification
Tentative Inhibitory Modification
Translocation
Transcriptional Stimulation
Transcriptional Inhibition
Separation of Subunits or Cleavage Products
Joining of Subunits

Histone Modification Table

Acetylation

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
		Esa1	transcriptional activation	10082517
H2B	Lys5	p300, ATF2	transcriptional activation	9880483, 10821277
	Lys11 (S. cerevisiae)	Gcn5	transcriptional activation	11545749
	Lys12 (mammals)	p300/CBP, ATF2	transcriptional activation	9880483, 10821277
	Lys15 (mammals)	p300/CBP, ATF2	transcriptional activation	9880483, 10821277
	Lys16 (S. cerevisiae)	Gcn5, Esa1	transcriptional activation	11545749
	Lys20	p300	transcriptional activation	9880483
H3	Lys4 (S. cerevisiae)	Esa1	transcriptional activation	10082517
		Hpa2	unknown	10600387
	Lys9	unknown	histone deposition	7862667
		Gcn5, SRC-1	transcriptional activation	10026213, 9296499
	Lys14	unknown	histone deposition	7862667
		Gcn5, PCAF	transcriptional activation	9880483, 12353039
		Esal, Tip60	transcriptional activation	10082517, 10096020
			DNA repair	12353039, 10966108
		SRC-1	transcriptional activation	9296499
		Elp3	transcriptional activation (elongation)	11904415
		Hpa2	unknown	10600387
		hTFIIIC90	RNA polymerase III transcription	10523658
		TAF1	RNA polymerase II transcription	8980232
		Sas2	euchromatin	12626510
		Sas3	transcriptional activation (elongation)	11731478
		p300	transcriptional activation	9880483
	Lys18	Gcn5	transcriptional activation, DNA repair	10026213
		p300/CBP	DNA replication, transcriptional activation	9880483, 12498683
	Lys23	unknown	histone deposition	7862667
		Gcn5	transcriptional activation, DNA repair	10026213
		Sas3	transcriptional activation (elongation)	11731478
		p300/CBP	transcriptional activation	9880483, 12498683
	Lys27	Gcn5	transcriptional activation	11545749
	Lys56 (S. cerevisiae)	Spt10	transcriptional activation	15882620
			DNA repair	16015338
H4	Lys5	Hat1	histone deposition	8858151
		Esal, Tip60	transcriptional activation	10082517, 10096020
			DNA repair	12353039, 10966108
		ATF2	transcriptional activation	10821277
		Hpa2	unknown	10600387
		p300	transcriptional activation	9880483
	Lys8	Gcn5, PCAF	transcriptional activation	9880483, 8805705
		Esal, Tip60	transcriptional activation	10082517, 10096020
			DNA repair	12353039, 10966108
		ATF2	transcriptional activation	10821277
		Elp3	transcriptional activation (elongation)	11904415
		p300	transcriptional activation	9880483
	Lys12	Hat1	histone deposition	8858151
			telomeric silencing	10982821
		Esal, Tip60	transcriptional activation	10082517, 10096020
			DNA repair	12353039, 10966108
		Hpa2	unknown	10600387
		p300	transcriptional activation	9880483
	Lys16	Gcn5	transcriptional activation	8805705
		MOF (D. melanogaster)	transcriptional activation	9155031
		Esal, Tip60	transcriptional activation	10082517, 10096020
			DNA repair	12353039, 10966108
		ATF2	transcriptional activation	10821277
		Sas2	euchromatin	10096020, 11545749
	Lys91 (S. cerevisiae)	Hat1/Hat2	chromatin assembly	15808514

Biotinylation

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

Methylation

Histone	Site	Histone-modifying Enzymes	Proposed Function	PMID
H1	Lys26	Ezh2	transcriptional silencing	16127177, 15099518
H3	Lys4	Set1 (S. cerevisiae)	permissive euchromatin (di-Me)	11751634
		Set7/9 (vertebrates)	transcriptional activation (tri-Me)	11779497
		MLL, ALL-1	transcriptional activation	12453419, 14603321
		Ash1 (D. melanogaster)	transcriptional activation	12397363
	Arg8	PRMT5	transcriptional repression	15485929
	Lys9	Suv39h, Clr4	transcriptional silencing (tri-Me)	10949293, 11283354
		G9a	transcriptional repression, genomic imprinting	11316813
		SETDB1	transcriptional repression (tri-Me)	11959841
		Dim-5 (N.crassa), Kryptonite (A. thaliana)	DNA methylation (tri-Me)	11713521, 12194816
		Ash1 (D. melanogaster)	transcriptional activation	12397363
	Arg17	CARM1	transcriptional activation	12498683
	Lys27	Ezh2	transcriptional silencing	12351676
			X inactivation (tri-Me)	
		G9a	transcriptional silencing	11316813
	Lys36	Set2	transcriptional activation (elongation)	12773564
	Lys79	Dot1	euchromatin	12123582
			transcriptional activation (elongation)	12667454
			checkpoint response	15525939
H4	Arg3	PRMT1	transcriptional activation	11448779
		PRMT5	transcriptional repression	15485929
	Lys20	PR-Set7	transcriptional silencing (mono-Me)	12086618
		Suv4-20h	heterochromatin (tri-Me)	15145825
		Ash1 (D. melanogaster)	transcriptional activation	12397363
		Set9 (S. pombe)	checkpoint response	15550243
	Lys59	unknown	transcriptional silencing	12937907

Phosphorylation

Histone	Site	Histone-modifying Enzymes	Proposed Function	PMID
H1	Ser27	unknown	transcriptional activation, chromatin decondensation	16127177, 15099518
H2A	Ser1	unknown	mitosis, chromatin assembly	15133681
		MSK1	transcriptional repression	15010469
	Thr119 (D. melanogaster)	NHK1	mitosis	15078818
	Ser122 (S. cerevisiae)	unknown	DNA repair	15781691
	Ser129 (S. cerevisiae)	Mec1, Tel1	DNA repair	11140636, 15458641
	Ser139 (mammalian H2AX)	ATR, ATM, DNA-PK	DNA repair	11673449, 11571274, 14627815
H2B	Ser10 (S. cerevisiae)	Ste20	apoptosis	15652479
	Ser14 (vertebrates)	Mst1	apoptosis	12757711
		unknown	DNA repair	15197225
	Ser33 (D. melanogaster)	TAF1	transcriptional activation	15143281
H3	Thr3	Haspin/Gsg2	mitosis	15681610
	Ser10	Aurora-B kinase	mitosis, meiosis	9362543, 10975519
		MSK1, MSK2	immediate-early gene activation	12773393
		IKK-α	transcriptional activation	12789343
		Snf1	transcriptional activation	11498592
	Thr11 (mammals)	Dlk/Zip	mitosis	12560483
	Ser28 (mammals)	Aurora-B kinase	mitosis	11856369
		MSK1, MSK2	immediate-early activation	12773393, 11441012
H4	Ser1	unknown	mitosis, chromatin assembly	15133681
		CK2	DNA repair	15823538

Sumoylation

Histone	Site	Histone-modifying Enzymes	Proposed Function	PMID
H2A	Lys126 (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

Ubiquitination

Histone	Site	Histone-modifying Enzymes	Proposed Function	PMID
H2A	Lys119 (mammals)	Ring2	spermatogenesis	15386022
H2B	Lys120 (mammals)	UbcH6	meiosis	16307923
	Lys123 (S. cerevisiae)	Rad6	transcriptional activation	10642555
			euchromatin	

Protein Acetylation

Pathway Description: Protein acetylation plays a crucial role in regulating chromatin structure and transcriptional activity. Many transcriptional coactivators possess intrinsic acetylase activity, while transcriptional corepressors 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 CARM1 (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[var]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 surface 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 methyl-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 JHDM1 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-, di- 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.

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