Transcription Through Chromatin – Dynamic Organization of Genes

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In this article, we discuss the dynamic organization of eukaryotic genes into chromatin. Remodeling of chromatin confers it the ability for dynamic change. Remodeling is essential for transcriptional regulation, the first step of gene expression.

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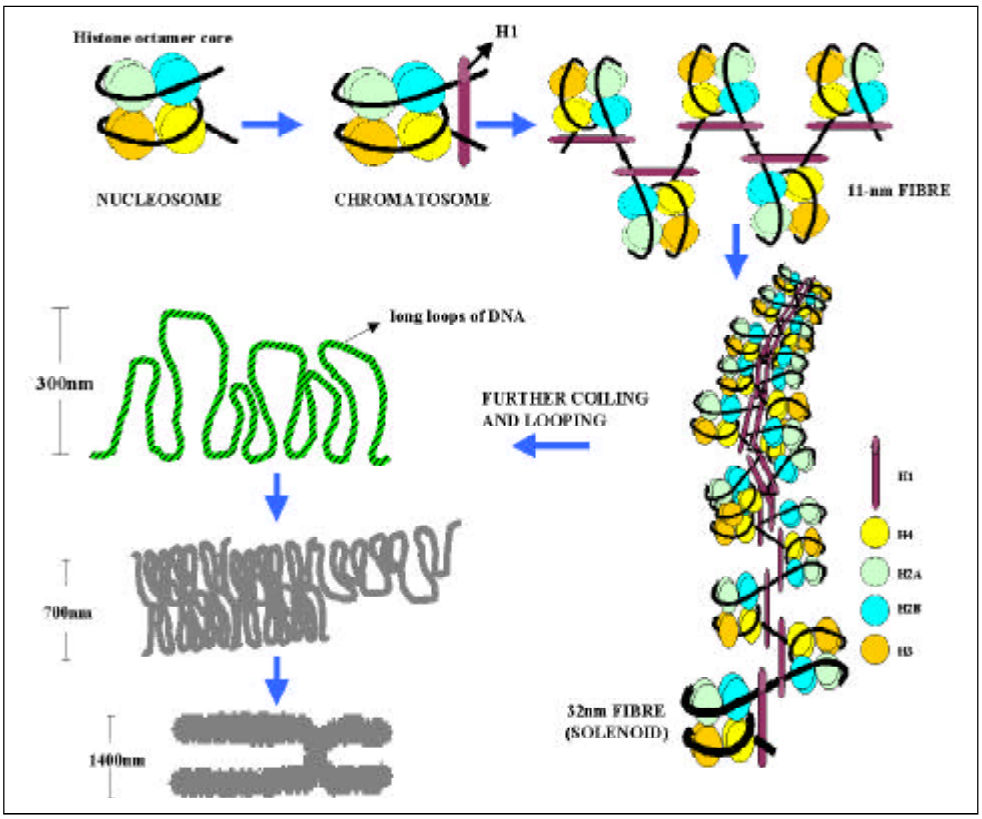
Chromatin Structure and Gene Expression

Transcription is the first step of gene expression in which RNA synthesis occurs from the DNA (gene) template in a series of complex biochemical reactions. In eukaryotes there are three types of RNA polymerases (RNA Pol I, II and III), to synthesize different types of RNA, required for diverse cellular processes. Among these, RNA Polymerase II catalyzes the synthesis of mRNA (RNA that code for proteins). There are more than fifty different proteins involved in the synthesis of mRNA from the DNA template. However, eukaryotic DNA (gene) is not present as open DNA in the cell; rather it is packaged into a highly compact and condensed nucleoprotein structure called chromatin in order to confine the enormous length of DNA to the nucleus. The repeating unit of chromatin, the nucleosome, consists of 147 bp of DNA wrapped twice around an octamer made of 2 copies each of the histones : H2A, H2B, H3, and H4 (*Figure* 1). Recently, X- ray crystallography structure of the nucleosome core has been solved at 2.8 Å resolution which shows that the highly flexible N-terminal tails of each of the histone molecules protrude out from the nucleosome, and the 'globular histone fold domain' in association with DNA, provide the structural organization of nucleosome. Histone H1, also called the linker histone, binds to the DNA at the entry and exit points from the nucleosome. The H1-associated nucleosome particle contains 166 bp of DNA and is



termed as the chromatosome. The 11-nm chromatin filament consists of arrays of regularly spaced nucleosomes. Further folding of the chromatin into higher order structures known as 32-nm filament requires histone H1 (*Figure* 1). The 32-nm filament further folds into the chromatin loop (50-100 Kb) structure, which folds again and again to be compacted into highly condensed chromosomes. In the interphase nucleus each of these chromosomes maintain their identity and location within particular chromosome territories. The scaffold proteins hold the chromatin loop within these territories. The space between two territories is termed as interchromosomal domain (ID). Chromatin may loop out into the ID during transcription. This dynamic arrangement of the nuclei is known as nucleography. The tight packaging of DNA into chromosome solves the problem of accommodating the long DNA molecules within the confines of the nucleus. The organization of DNA

Figure 1. Organization of Chromatin: Two copies each of four different core histones, H3, H4, H2A and H2B (as represented by different colours) forms an octamer. DNA wraps around the octamer and organized into nucleosomal beads. The 11 nm beads on string structure further condensed into 32 nm fibre and so on, with the help of histone H1 and several nonhistone proteins which finally lead to the formation of highly condensed metaphase chromosome.

List of Abbreviations

ACF – ATP dependent Chromatin remodeling Factor
ATF – Activation Transcription Factor
CARM1 – Coactivator-Associated arginine Methyltransferase
CBP – CREB Binding Protein
CHRAC – Chromatin Accessibility Complex
GCN5 – General Control Not repressed
HBO – Histone acetyltransferase Binding to Origin recognition complex
HDAC – Histone Deacetylase
JBP – Janus kinase Binding Protein
MLL – Mixed Lymphoid Leukemia
MOF – Males-absent-On-the-First
MOZ – Monocytic leukemia Zinc finger protein
MYST – MOZ, Ybf2/Sas3, Sas2, and TIP60
NURD – Nucleosome Remodeling and Deacetylase
NURF – Nucleosome Remodeling Factor
PCAF – p300 - CBP Associated Factor
PRMT – Protein arginine N-Methyl Transferase
RSC – Remodels the Structure of Chromatin
SAGA – Spt-Ada-Gcn5-Acetyltranferase
Sas – Something About Silencing
SRC – Steroid Receptor Coactivator

into chromatin has, however, important functional consequences for transcriptional regulation and other DNA template-dependent processes such as replication, repair, recombination and chromosome segregation. In all these phenomena, alteration of chromatin imposes the first level of regulation and is brought about by a process called chromatin remodeling. There are two basic operational mechanisms for chromatin remodeling. One is the covalent modification of core histones and non-histone chromatin proteins while the other is ATP-dependent alteration of the DNA path over the nucleosome. Chromatin remodeling alters the DNA-protein interactions in the nucleosomal structure and regulates all the above-mentioned DNA template-dependent phenomena.

There are three different phases of transcription – initiation, elongation and termination. The chromatin remodeling factors play important roles in all the three different phases of transcription. However, transcription initation is the most complex step of transcription involving a large number of factors (see *Figure* 2). In this review we will more specifically discuss the role of chromatin remodeling in RNA Polymerase II-mediated transcription initiation.

Chromation Remodeling: The Biochemical Steps Involved

Recent advances conclusively show that chromatin, which was once thought to be a static and merely repressive structural entity, is actually highly dynamic and plays an active role in gene expression. It is the chromatin remodeling system, which is responsible for the dynamic structural and functional change of chromatin. Broadly, chromatin remodeling can be classified into two types of modifications:

a) Covalent modifications of the N-terminal tails of four different core histones and
b) ATP-dependent chromatin remodeling which alters the path of DNA over the nucleosome.

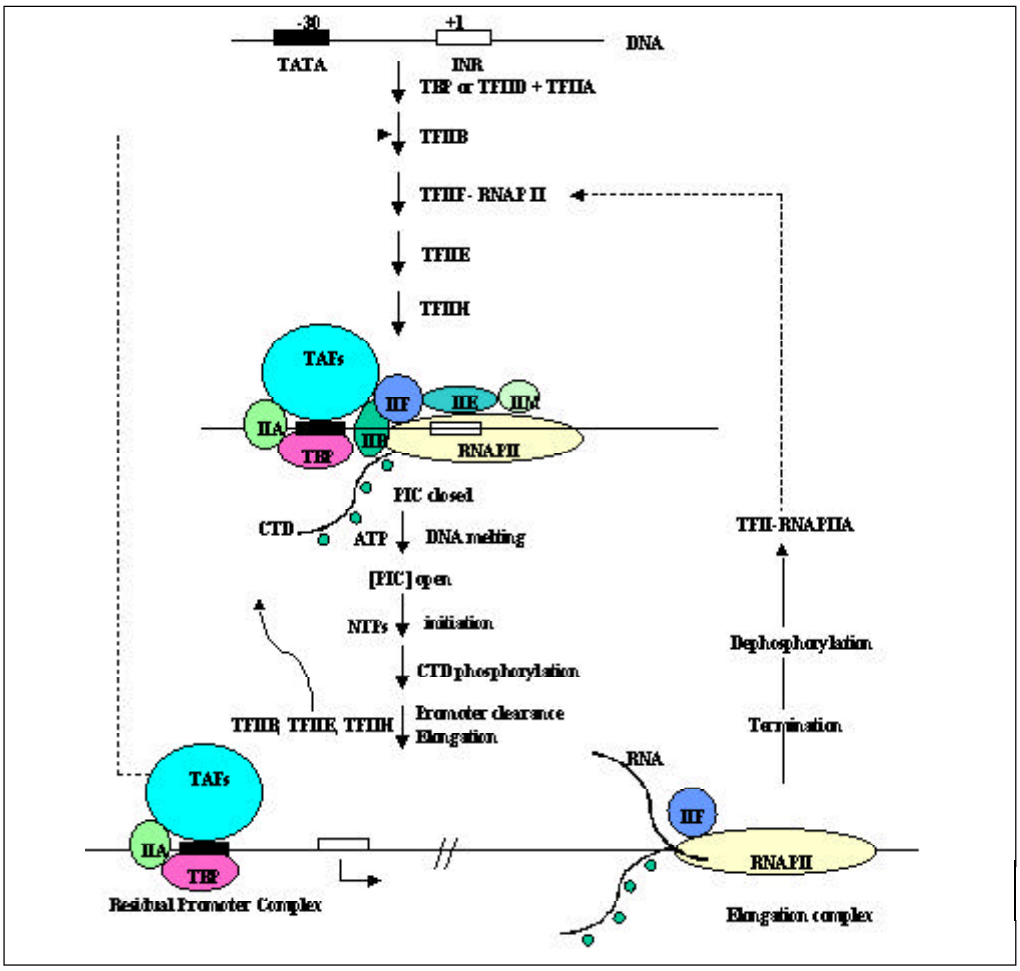


Figure 2. Assembly of Transcription initiation complex on a TATA containing promoter: The single line with boxes represent promoter DNA and the +1 indicates the transcription start site. In relative to +1 the TATA is at -30 position where TFIID (TBP and more than eight other polypeptide TAFs) bind to initiate the assembly. All the other GTFs join the assembly sequentially as represented to form the preinitiation complex (PIC), which is a closed complex with regard to transcriptional initiation. The closed complex opens by ATP-dependent DNA melting with the help of TFIIE and TFIIH (see Table 1). The DNA melting is followed by the formation of first phosphodiester bond (transcription initiation). Soon after this TFIIH phosphorylates the C-terminal domain of the largest subunit of RNA Pol II which leads to promoter clearance (releasing of TFIIB, TFIIE and TFIIH for recycling).

Covalent Modifications of Core Histones in Chromatin

Recently solved high resolution (2.8 Å) crystal structure of the nucleosome, showed that the flexible N-terminal regions of

Factor	Number of subunits	Mw(kDa)	Function
TBP	1	38	core promoter recognition;TFIIB recruitment
TAFs	12	15-250	core promoter recognition; positive and negative regulatory functions
TFIIA	3	12,19,35,55	stabilization of TFIID interactions; anti-repression
TFIIB	1	35	RNA Pol II-TFIIF recruitment; start-site selection by RNA PolII
TFIIF	2	30,74	assist promoter targeting of Pol II;
RNA Pol II	12	10-220	catalyses RNA synthesis; recruitment of TFIIE
TFIIE	2	34,57	TFIIH recruitment; modulation of TFIIH helicase, ATPase and kinase activities ;direct enhancement of promoter melting
TFIIH	9	35-89	helicase activity melts the promoter, CTD kinase activity helps in promoter clearance

Table 1. General transcription initiation factors from human cells.

core histones are projected out from the nucleosome. These N-terminal tails play a significant role in intra- and inter-nucleosomal interactions, and thereby change the chromatin structure, as per the need of the cellular functions. The post-translational covalent modifications of histone tails at lysine and arginine residues are the key players behind the structural changes of chromatin with important functional consequences.

The various modifications are:

i) Acetylation and deacetylation of lysine residues by different histone acetyltransferases (HATs) and deacetylase (HDACs) (*Table* 2 and *Table* 3);
ii) Methylation of lysine and arginine residues by histone methyltransferases (HMTase) (*Table* 4);
iii) Phosphorylation of serine residues by different kinases (*Box* 1).

Acetylation and Deacetylation of Histones: Histone acetylation is a diagnostic feature for transcriptionally active genes. Though the correlation between active genes and histone acety-

HAT	Organism	Function
GCN5/PCAF family		
Gcn5	yeast, human	Coactivator
PCAF	human	Coactivator
MYST family		
Sas2	yeast	Silencing
Sas3	yeast	Silencing
Esa1	yeast	cell-cycle progression
MOF	fruit fly	dosage compensation
MOZ	human	Leukomogenesis
HBO1	human	origin recognition interaction
Tip60	human	HIV-Tat interaction
TAFII250 family	yeast –human	TBP associated factor
CBP/p300	worm-human	global coactivator
SRC family	mice ,human	steroid receptor coactivators
ATF-2	yeast- human	sequence specific DNA binding activator
GNAT related		
Elp3	yeast	Elongation
Hpa2	yeast	Unknown
HAT1	yeast-human	deposition-related(B- type)
TFIIIC	human	RNA Pol III initiation

Table 2. HAT families and their transcription – related functions.

lation has been known for many years (since 1963), it took more than 30 years (1995) to discover the first histone acetyltransferase (HAT), GCN5. It is a nuclear HAT (also called A-type HAT) which catalyzes transcription-related acetylation events. The cytoplasmic, B-type HAT catalyzes acetylation events linked to the transport of newly synthesized histones from the cytoplasm to the nucleus for deposition onto newly replicated DNA. However, since B-type HAT is not involved in transcriptional regulation, we will discuss only A-type HATs.

There was a dramatic development soon after the discovery of GCN5 from the ciliate *Tetrahymena thermophila.* Homologs of GCN5 were cloned and sequenced from numerous organisms such as human, mouse, yeast, *Drosophila* and *Arabidopsis* indicating that its function is highly conserved throughout the eukaryotes. The list of A-type HATs started constantly expanding; this

CLASS	HDACs	Protein length	Function
I	hHDAC1	482 (amino acids)	i. Transcription repression
	hHDAC2	488 ,,	ii. Regulates the function of Class II HDACs
	hHDAC3	428 ,,	iii. Nonhistone protein deacetylation
	hHDAC8	377 ,,	
II	hHDAC4	1084 (amino acids)	i. Genomic organization
	hHDAC5	1122	ii. Developmental specific transcriptional regulation
	hHDAC6	1215	
	hHDAC7	ND	iii. Corepressor function
III	hSIRT1	747 (amino acids)	
	hSIRT2	373	i. Nonhistone protein deacetylation (e.g., p53)
	hSIRT3	399	
	hSIRT4	314	ii. Maintenance of acetylation gradient
	hSIRT5	310	iii. Gene silencing
	hSIRT6	355	
	hSIRT7	400	

Table 3. Different Classes of HDACs.

is given in *Table* 2. Significantly, all the nuclear HATs discovered so far were known to play crucial roles in transcription regulation and a number of them are established transcriptional coactivators.

Most of the HATs function as multiprotein complex in vivo with different specificities for the nucleosomal histones as well as the gene (promoter). For example, GCN5 and its closely related mammalian homolog were found to acetylate histone H3 strongly. Yeast GCN5 is present in a multi-protein complex SAGA. The similar human complex is termed as STAGA. Both the human and yeast complex contain several transcriptionally important proteins which include mediator proteins, and histone like TAFs (TBP associated factor) suggesting their direct involvement in transcriptional regulation. Indeed several groups showed that the HAT activity of GCN5 is essential for transcription of a number of genes. The other very important HATs are p300 and CBP. p300 is a close homolog of CBP. p300/CBP is a

Lysine Methyltransferases	Organism	Substrate	Function
SUV39H1	Human	H3, Lys 9	Heterochromatinization and gene silencing
SUV39H2	Human	H3, Lys 9	Heterochromatinization and gene silencing
MLL	Human	H3, Lys 4	Regulates HOX gene expression
Ash 1	Drosophila	H3 Lys 4, 9 H4 Lys 20	Epigenetic Transcription regulator
Arginine Methyltransferases			
PRMT1	Human	H4 Arg 3	Can cooperate with PRMT4/CARM1
PRMT4/CARM1	Mouse	H3 Arg 2,17,26	Acts as a coactivator of nuclear receptor activity
PRMT5/JBP1	Human	H2A and H4	Cooperate with p300 acetylase to stimulate transcription by nuclear receptor

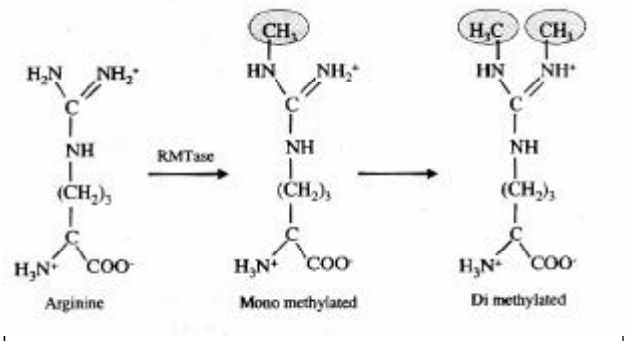
Table 4. Histone methyltransferases.

ubiquitously-expressed, global-transcriptional coactivator which plays critical roles in a wide variety of cellular processes, including cell cycle control, differentiation and apoptosis. The recombinant p300/CBP can acetylate all four histones within nucleosomes, as well as free histones. In the context of HAT dependent transcriptional activation, from chromatin template, p300/CBP acetylate the promoter-proximal histones in a activator-dependent manner.

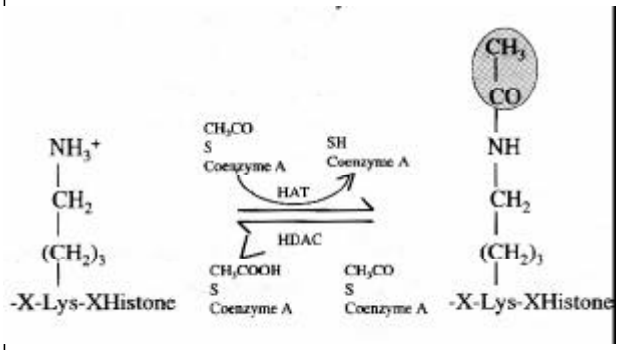
Histone acetylation is a reversible process, thus deacetylases are also an integral part of transcription cycles. Acetylation is associated with activation, whereas deacetylation is correlated with repression. The optimum balance of acetylation and deacetylation of histone regulates gene expression. A number of histone deacetylases (HDACs) have been characterized in the last several years and quite a few of those were known as repressors or correpressors of transcription. To date, three classes of HDACs

Box 1.

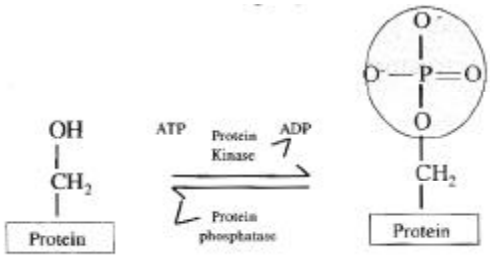
Histone Methylation



Histone Acetylation



Histone Phosphorylation



have been discovered which can be distinguished by their size, catalytic domain, sub cellular localization and mode of action (*Table* 3). Class I human HDACs have homology to yeast Rpd3 (an established transcriptional repressor) and this class includes HDACs 1, 2, 3 and 8, whereas Class II HDACs (HDAC 4, 5, 6, 7, 9 and 10) are similar to yeast Hda1 (another repressor). The class III HDACs are the homologs of yeast Sir-2 family of proteins. These class III enzymes are somewhat unique and require the cofactor NAD+ for deacetylation. The role of class I HDACs in transcriptional repression has been shown clearly. Furthermore the class I HDACs have also shown to be associated with the ATP dependent chromatin remodeling system. Both the class I and class II HDACs can directly interact with the repressor which facilitates the targeted deacetylation of core histones in a gene programmed to be repressed. While class I and class II deacetylases function as corepressors, Sir2p-related proteins appear to be involved in gene silencing. However, Sir2p also functions as a potent deacetylase for some transcriptionally important nonhistone proteins, (e.g., the transcription factor and tumor suppressor p53). The question that remains to be answered is, why are there so many deacetylases? However, like HATs, HDACs are also present as complexes in the cells. It may be associated with ATP dependent remodeling complexes, histone methyltransferase complexes or DNA repair machinery.

Methylation of Histones Though methylation of histones was documented at the same time (1963) as acetylation, methylation is lagging behind acetylation in its functional characterization. However, it is catching up rapidly. In the past two years, several methyltransferases have been discovered and their mechanism of action as well as function have also been elucidated. Histone methylation occurs predominantly at arginine and lysine residues in the amino terminal tails of H3 and H4 (*Table* 4).

Lysine methyltransferases methylate H3(K4, K9, K27) and H4(K20). The SUV39 protein was the first histone methyltransferase to be discovered. It methylates lysine 9 of histone H3. The catalytic domain of the enzyme resides within a highly conserved structure known as SET domain. It was found that any protein having SET-domain flanked by cysteine-rich sequence possesses lysine methylation activity. SUV39 was found to be a transcriptional repressor. The histone methyltransferase activity of SUV39 recruits heterochromatin protein 1 (HP1) which is responsible for condensation of chromatin. SUV39 also interacts with retinoblastoma protein (Rb) and Rb recruits histone deacetylase 1 (HDAC1). Thus, methylation of lysine by SUV39 initiates the chromatin condensation by deacetylation and thereby functions as a gene silencer. However, methylation and subsequent HP1 binding do not occur ubiquitously, but rather in a targeted manner through Rb. Methylation of H3-Lys-4 has a reverse effect on transcription. The H3-Lys-4 methylation correlates with an active state of transcription. The unmodified histone H3-tail binds to the NURD-complex (a HDAC containing repressor complex) which deacetylates the chromatin template and induces the compaction. Methylation of lysine 4 prevents this interaction and keeps the HDACs away. The H3-Lys-4 can be methylated by different enzymes which include human MLL and *Drosophila* Ash1.

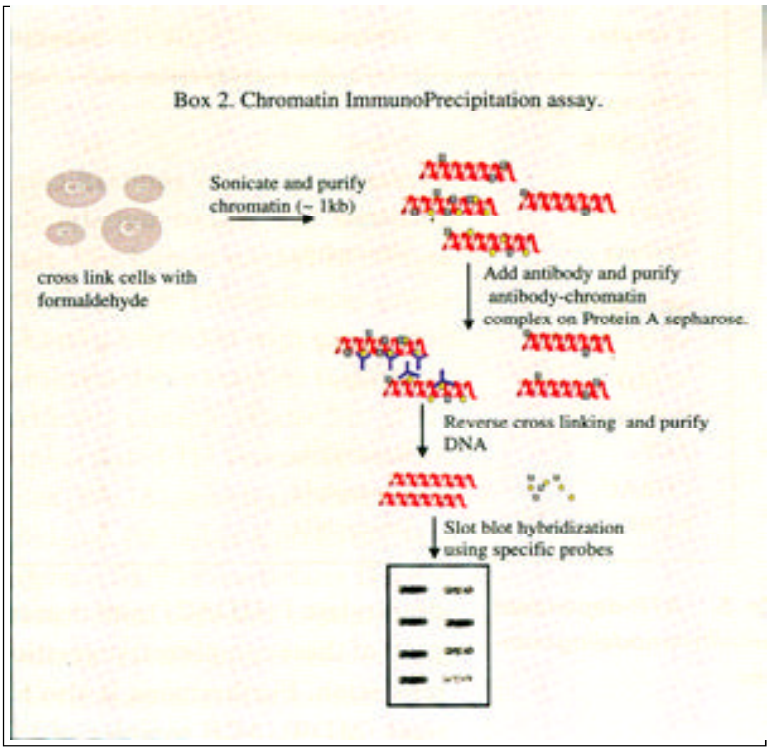
Arginine methyltransferases (AHMTase) also play a critical role in transcriptional regulation. This group of enzymes does not have the SET domain but contains a highly conserved S-adenosyl methionine (SAM) binding site. AHMTase can also methylate

non-histone proteins. However, in this article we will confine our discussion to histone methylation. There are three mammalian histone Arginine methyltransferases that have been well characterized. These are PRMT1, PRMT4/CARM1 and PRMT5/JBP1. PRMT1 prefers to methylate arginine residues in glycine rich regions. It efficiently methylates arginine 3 of histone H4. The PRMT1 methyltransferase has also been shown to mediate methylation of histones *in vivo*. However, the target promoters at which arginine 3 of H4 is methylated have not yet been identified. Presumably, it targets the nuclear receptor stimulated genes. To date, the best substrate reported for PRMT4/CARM1 is histone H3 and the methylation is not in the glycine rich region. *In vitro* CARM1 methylates histone H3 at arginine 2 (minor site) and Arginine 17 and 26 (major sites) in the basic N-terminal region. It directly binds to the coactivator p160 and enhances the coactivation function. Most significantly, CARM1 and p300 show a synergistic effect in their function as coactivators for nuclear receptors. The functional significances of arginine methyltransferases in gene regulation is yet to be elucidated.

Phosphorylation of Histones: Phosphorylation of histone H1 and H3 has long been implicated in chromosome condensation during mitosis. The phosphorylation of H1 is mainly associated with the decompaction of higher ordered chromatin structure whereas H3 phosphorylation (specifically at Serine-10) is directly linked to induction of gene expression of *c-jun*, *c-fos* and *c-myc*. By employing Chromatin Immuno Precipitation assays (*Box* 2) it was shown that newly phosphorylated H3 is associated with *c-fos* and *c-jun* gene promoters. Recently, it was found that RSK-2, a histone kinase, is associated with the Coffin-Lowry syndrome in humans. Another histone kinase is the MSK1, a kinase activated by growth factors and stress stimuli.

ATP-dependent Chromatin Remodeling

The other group of chromatin remodeling machinery which is equally important for the transcription regulation, alters the histone-DNA interactions by changing the path of the DNA



over the nucleosomes in an energy (ATP) dependent manner. Similar to histone acetyltransferases or deacetylases, ATP-dependent remodeling system is present as a multiprotein complex in the cell. There are nine different complexes, which were discovered from different organisms. These complexes could be classified into three different groups based on the type of ATPase present in each complex (*Table* 5). These complexes are partially conserved from yeast to humans. It is still a mystery, why there are so many ATP-dependent chromatin remodeling complexes. Presumably, these complexes are gene and cell cycle specific.

Members of the same family of ATP dependent remodeling complex may have differing roles to play in the cell. This can be gauged from the fact that the SWI/SNF complex and the RSC complex differ in their abundance. The RSC complex, which is present in ten-fold excess is essential for cell viability. The two human SWI/SNF family complexes are highly related in their subunit composition and function, except the ATPase subunit (hBrm/BRG1 and BRM). The BRM protein was found to be involved in transcriptional activation of homeotic genes during development. Mutation in *BRM* questions the viability. Mi2 and NURD complexes are very closely related. Mi2 was first identified as an autoantigen in the human disease, dermatomyositis. The Mi2 complex also contain metastasis (cancer) associated proteins MTA1 and MTA2. Significantly, histone

Complex	Organism	Subunits	ATPase
SWI/SNF family			
SWI/SNF	Yeast	11	SWI2/SNF2
RSC	Yeast	15	STH
hSWI/SNF	Human	~10	hBrm, BRG1
Brahma	Drosophila	>7	BRM
Mi family			
Mi 2	Xenopus	6	Mi2
NURD	Human	>7	Mi2
ISWI family			
ACF	Drosophila	2	ISWI
CHRAC	Drosophila	5	ISWI
NURF	Drosophila	4	ISWI

Table 5. ATP-dependent chromatin remodeling complexes.

deacetylase 1 (HDAC1) and deacetylase 2 (HDAC2) are integral parts of these complexes, suggesting their role in transcriptional repression. Furthermore, it also has methyl DNA binding proteins (MDB). ACF complex of ISWI family stimulate the nucleosomal assembly by modulating the intranucleosomal spacing. It also facilitates transcription factor binding.

Mechanism of Transcription Regulation by Chromatin Remodeling

The functional link between chromatin remodeling and transcriptional regulation is complex. There is no single mechanism which can explain the chromatin remodeling dependent transcriptional regulation. Rather it depends upon the gene, activator or repressor and stages of cell cycle when the gene is expressing. The dynamic change in chromatin structure by histone modification and ATP dependent chromatin remodeling regulates transcription initiation, elongation and repression through the activator and repressor. There are two different classes of activators. The class I activators can bind the packaged nucleosome and able to perturb chromatin structure by recruiting the remodeling system. These include Gal4, Ume6, Pho4 and ER transcription complex, E2F4 and Swi5. The second class of

activators bind to promoter regions only after nucleosomes have been conformationally changed. The activators such as E2Fs and SBF belong to this class.

The coordinated covalent modifications of histone methylation, acetylation and phosphorylation control the optimum gene transcription. For example, the human methyltransferase PRMT1 specifically methylates R3 of H4. This enhances subsequent acetylation of H4 at K8 and 12 by p300 with consequent transcription activation. The other notable example is the yeast serine kinase Snf1 which specifically phosphorylates S10 of H3 at *INOI* promoter. The phosphorylated H3 promoter recruits GCN5 containing HAT complex (SAGA), which acetylates K14. On the other hand the deacetylated H3 tail is a preferred substrate for SUV39 methyltransferase. SUV39 methylates H3(K9) and represses the transcription. Thus different modification events function in a proper concert. However, it is now evident that the order of recruitment of histone modification and ATP-dependent chromatin remodeling systems on a particular promoter depends upon the specific gene and stage of cell cycle. The activator/repressor recruits histone modifying complex or ATP/dependant chromatin remodeling complexes through direct interactions. Based on the order of recruitment of these complexes, genes can be grouped into 3 different classes:

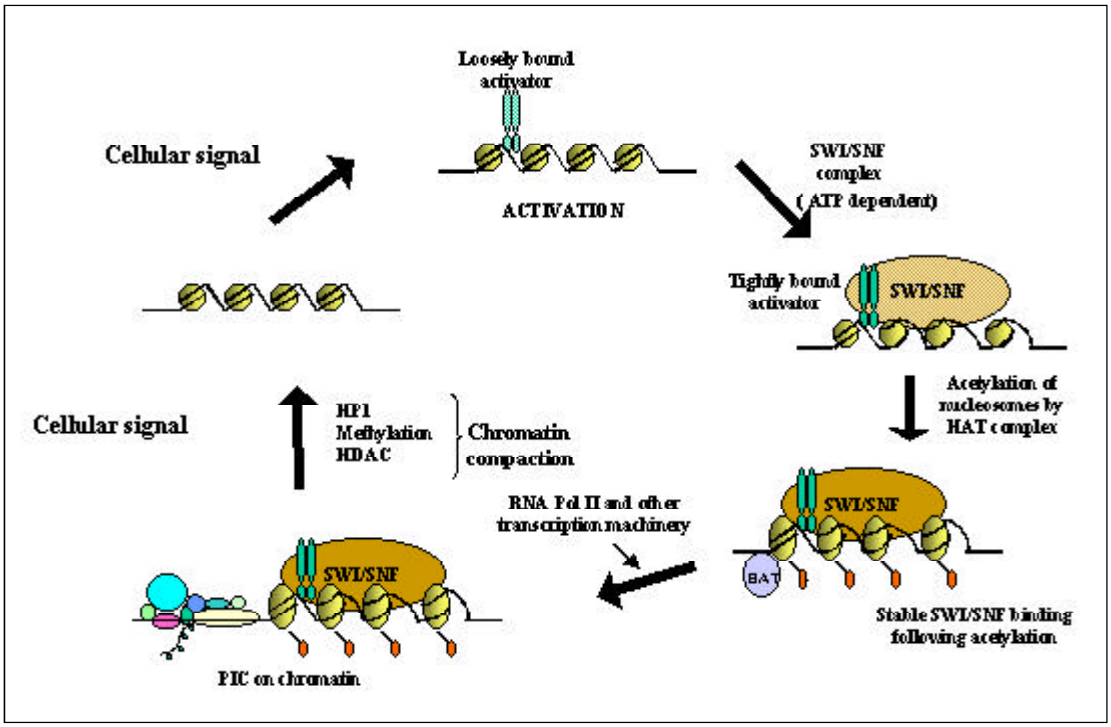
Class I: Histone acetylation is independent of ATP-dependent remodeling where HAT complexes are recruited to the promoter by the activator (e.g., interphase-expressed genes and stimulus dependent genes.).

Class II: Histone acetylation precedes ATP dependent chromatin remodeling. (e.g., *PH08*, *HIS3* and *IFNb*).

Class III: There are few cell cycle dependent genes (e.g., *HO*, *SIC1*, *PCL2* and *PCL9*) which express at the end of mitosis or G1. The ATP dependent chromatin remodeling system is recruited on these genes before acetylation. Presumably the highly condensed mitotic chromatin needs to be opened up before acetylation and transcriptional initiation.

We present here a model for the mechanisms of class III gene activation, where ATP-dependent chromatin remodeling is the first step (*Figure* 3). By employing 'ChIP (Chromatin Immuno Precipitation) assay' (*Box* 2), recruitment of each type of chromatin remodeling system has been found for some genes. Though there are exceptions, for a major group of genes it

Figure 3. Transcription through the chromatin (type III): Transcription regulation by targeted histone acetylation/deacetylation and ATP dependent remodeling. In response to cellular signals, the activator binds loosely to its cognate binding site on the chromatin, which in turn recruits the SWI/SNF complex on the promoter proximal nucleosomes. The ATP dependent chromatin remodeling alters the path of DNA over the nucleosome, facilitating the tighter binding of the activator. The activator then recruits the histone acetyltransferase, which acetylates the nucleosomes, stabilizing the SWI/SNF complex as well as the activator interact and recruits the transcription apparatus to establish active chromatin. Again, in response to cellular signals, repressors are recruited which deacetylates the transcription proteins and histones. Histone deacetylation followed by methylation of promoter DNA by the DNA methyl transferase (DNMT) facilitates the binding of the INHAT (inhibitor of HAT) complex and the methyl DNA binding domain protein to stabilize the repressed state of chromatin. For simplicity, histone methylation and phosphorylation are not included in this model.



was found that after the activator loosely binds to its cognate site on chromatin, the ATP dependent chromatin remodeling complex gets recruited by the activator, which in turn remodels the chromatin structure and aids the activator to bind tightly. The activator then recruits various modifying enzymes (kinases, methyltransferases, acetyltransferases) to make room for the PIC (Preinitiation Complex) (*Figure* 2). The stably bound SWI/SNF complex facilitates repressor binding and recruits the HDACs to repress the chromatin at the termination of transcription (*Figure* 3).

Conclusion

Chromatin is no longer considered an inert repressive structure, rather it plays an active and dynamic role in the regulation of gene expression. An enormous amount of work has been done in the past eight years after the resurrection of the field. These discoveries have answered several intriguing questions regarding the function of chromatin in gene regulation, DNA replication and DNA repair. It has also helped in understanding the mechanism of different human diseases. This opens up the possibilities of a number of new targets for different drugs, especially antineoplastics (anticancer). We will discuss about chromatin remodeling and disease connection in the next article.

Suggested Reading

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