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Multiple Functions of Dynamic Histone Acetylation

James R. Davie and Michael J. Hendzel

Department of Biochemistry and Molecular Biology, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba R3E OW3, Canada

Abstract Besides its role in organizing nuclear DNA, the nuclear matrix is involved in specific nuclear functions, including replication, transcription, and RNA splicing. It is becoming increasingly evident that nuclear processes are localized to distinct regions in the nucleus. For example, transcriptionally active genes and RNA transcripts are found in discrete transcription foci. Current evidence suggests that nuclear matrix–bound transcriptionally active DNA sequences are in nucleosomes with dynamically acetylated histones. Histone acetylation, which precedes transcription, alters nucleosome and chromatin structure, decondensing the chromatin fibre and making the nucleosomal DNA accessible to transcription factors. Histone acetyltransferase and histone deacetylase, which catalyze this rapid acetylation and deacetylation, are associated with the internal nuclear matrix. We hypothesize that these enzymes play a role in maintaining the association of the active chromatin domains with the internal nuclear matrix at sites of ongoing transcription. © 1994 Wiley-Liss, Inc.

Key words: histone acetylation, transcriptionally active chromatin, nuclear matrix

HIERARCHIES OF CHROMATIN STRUCTURE

In eukaryotic cells, nuclear DNA exists as a hierarchy of chromatin structures, resulting in compaction of nuclear DNA about 10,000-fold. The repeating structural unit in the extended 10 nm fibre form of chromatin is the nucleosome [van Holde, 1988]. The nucleosome consists of 146 bp of DNA wrapped around a protein core of the histones H2A, H2B, H3, and H4 (core histones). These histones are arranged as an $(H3\text{-}H4)_2$ tetramer and two H2A-H2B dimers positioned on each face of the tetramer. The DNA joining the nucleosomes is called linker DNA, and it is to the linker DNA that the H1 or linker histones bind. The 10 nm fibre is compacted further into the 30 nm fibre. Linker histones and amino-terminal regions ("tails") of the core histones maintain the higher order folding of chromatin [Garcia Ramirez et al., 1992]. The chromatin fibre is organized into loop domains, with the base of the loop attached to the nuclear matrix (Fig. 1). The DNA regions attached to the nuclear matrix are referred to as matrix (or scaffold) association regions (MARs or SARs). The nuclear matrix, which consists of residual nucleoli, surrounding nuclear pore-lamina complex and internal nuclear matrix, is operationally defined as the nuclear structure remaining after the salt extraction of nuclease treated nuclei [Berezney, 1991]. Cytochemical localization studies show that most of the DNA loop attachment sites are to the internal nuclear matrix, with the remainder being bound to the nuclear pore-lamina [Zini et al., 1989]. MARs at the base of the loops are considered as stable binding sites and appear to be evolutionarily conserved. Internal nuclear matrix proteins that bind to MARs include topoisomerase II and attachment region-binding protein [Laemmli et al., 1992]. Lamin B, a major component of the nuclear pore-lamina, also binds to MAR sites [Luderus et al., 1992].

TRANSCRIPTIONALLY ACTIVE CHROMATIN DOMAINS

The structure of transcriptionally active chromatin differs from that of the bulk of the genome in susceptibility to digestion by nucleases (e.g., DNase I). The preferential DNase I sensitivity of active gene chromatin includes the coding portion of the gene plus upstream and downstream adjacent nontranscribed DNA sequences. The boundaries of the DNase I sensitive domain comap with MARs (Fig. 1). Thus, the nuclease sensitive chromatin domain constitutes a chro-

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Address reprint requests to J.R. Davie, Department of Biochemistry and Molecular Biology, Faculty of Medicine, University of Manitoba, Winnipeg, MB R3E OW3, Canada.

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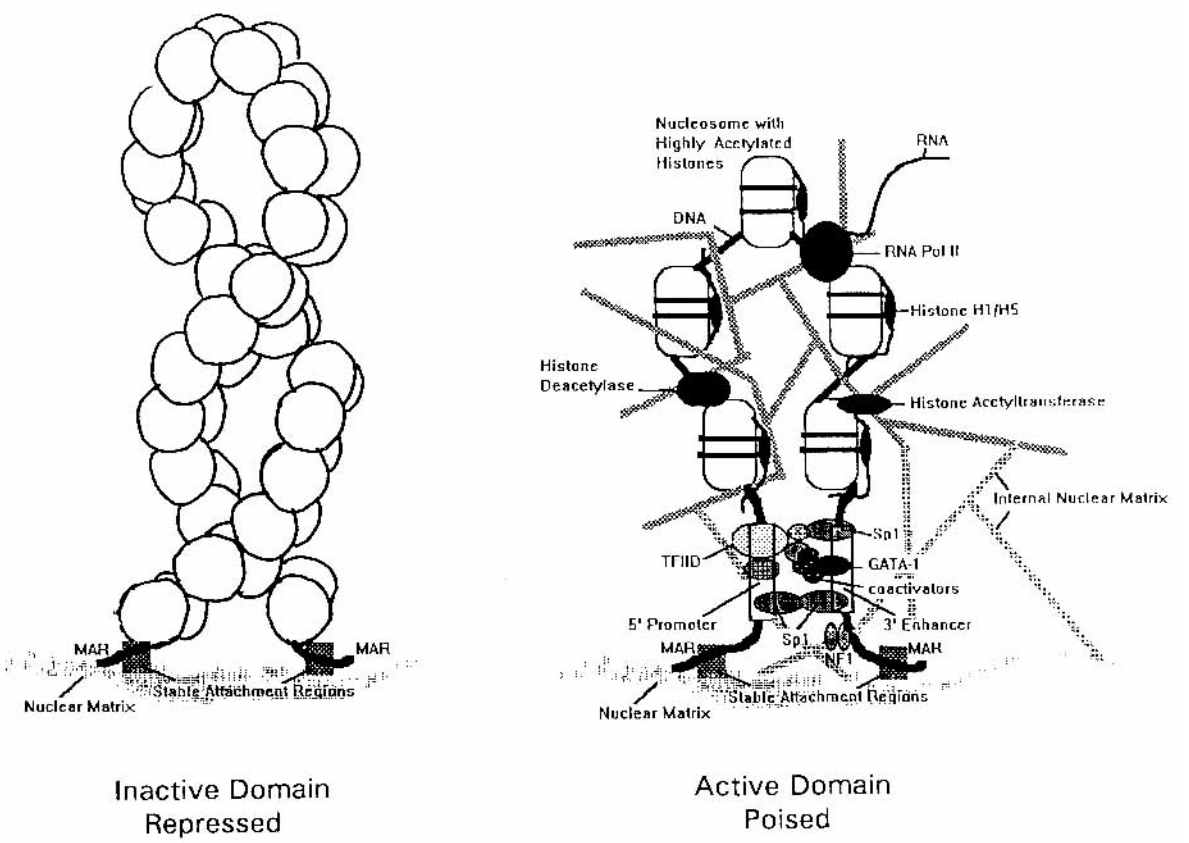

Fig. 1. A model for transcriptionally active and repressed chromatin. Condensed and decondensed chromosomal loops are shown for transcriptionally inactive and active domains, respectively. At the base of the loops are nuclear matrix association regions (MARs). Multiple dynamic attachment sites between the transcriptionally active domain and the internal nuclear matrix are presented. For the inactive domain nucleosomes are depicted as open circles.

mosomal loop, representing a unit of gene regulation.

The chicken β-globin domain, for example, consists of four genes, arranged as 5′ ρ-, β^H-, β^A-, and ϵ-globin 3′. The 5′ boundary of the β-globin DNase I sensitive domain has been mapped to 10 kb 5′ to the ρ-globin gene, while the 3′ boundary of the domain has not yet been mapped [Rocha et al., 1984]. In adult chicken immature erythrocytes the adult β^H- and β^A-globin genes are transcriptionally active, while the embryonic genes ρ- and ϵ-globin genes are not. Hence, the ϵ-globin gene chromatin, which is referred to as being in a poised state, is transcriptionally inactive but sensitive to DNase I.

Transcriptionally active gene chromatin has a soluble and insoluble nature: that is, active DNA sequences are found in two types of chromatin fragments, those that are soluble in 150 mM NaCl and/or 2 mM $MgCl_2$ and in chromatin fragments that remain associated with the residual nuclear material (the nuclear matrix). In adult chicken immature erythrocytes, transcriptionally active (e.g., β-globin, histone H5) and poised (e.g., ϵ-globin) DNA sequences are present in the salt-soluble chromatin fragments [Delcuve and Davie, 1989]. The extent of salt solubility of these active/poised chromatin fragments parallels their sensitivity to DNase I. In adult chicken immature erythrocyte chromatin, DNA sequences within the β-globin DNase I sensitive domain are salt soluble [Rocha et al., 1984]. DNA sequences outside the 5′ boundary of the domain are neither DNase I sensitive nor salt soluble. Therefore, the salt solubility of chromatin fragments defines the same transcriptionally active β-globin domain as does DNase I.

In contrast to the salt solubility properties of transcriptionally active and poised chromatin, the transcribed DNA sequences partition preferentially with the nuclear matrix–attached chromatin fragments [Andreeva et al., 1992]. Adult chicken immature erythrocyte nuclear matrix–bound chromatin fragments are enriched in transcriptionally active β-globin and histone H5, but not poised ϵ-globin, DNA sequences [Delcuve

and Davie, 1989]. We postulate that the soluble active chromatin fragments of immature erythrocytes were originally attached to the internal nuclear matrix. The instability of the chicken erythrocyte internal nuclear matrix may result in the release of nuclear matrix bound transcriptionally active chromatin [Hendzel et al., 1992]. Interestingly, the partitioning of inducible genes with the residual nuclear material is related to their transcriptional activity [Stratling et al., 1986]. Actively transcribed chromatin regions are thought to be immobilized on the nuclear matrix by multiple dynamic attachment sites [Andreeva et al., 1992]. Evidence has recently been presented that sequence-specific DNA binding proteins (e.g., Sp1, CCAAT, Oct-1) are associated with the nuclear matrix [van Wijnen et al., 1993]. These factors would surely contribute to the nuclear matrix attachment of transcriptionally active genes.

HISTONE ACETYLATION AND TRANSCRIPTIONALLY ACTIVE CHROMATIN

The four core histones are reversibly acetylated at the ϵ-amino groups of specific lysine residues located in the basic N-terminal tail (Fig. 2). Histone acetylation and deacetylation are catalyzed by histone acetyltransferases and deacetylases, with the level of acetylation being governed by the net activities of these two enzymes. This postsynthetic modification is associated with several processes, including transcription, DNA replication, and DNA repair. We will focus on the relationship between histone acetylation and transcription. In understanding the role of dynamic histone acetylation in transcription, the adult chicken immature and mature erythrocyte system has been most informative. These cells do not replicate and are arrested in the G_0 phase of the cell cycle. Thus, the metabolically active acetylation observed in these cells

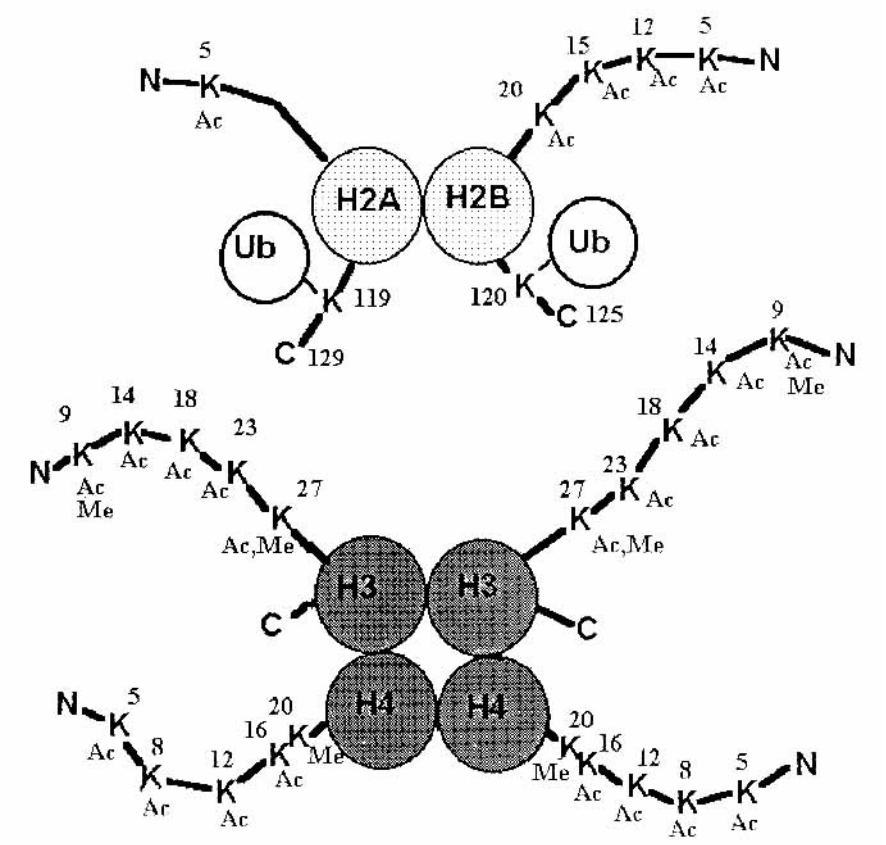

Fig. 2. Sites of reversible acetylation on the core histones. The core histones are reversibly acetylated at specific lysine residues in their amino-terminal domains. Histones H2A and H2B are also reversibly ubiquitinated, and histones H3 and H4 are reversibly methylated. Ac, Me, and Ub show the sites of reversible acetylation, methylation, and ubiquitination, respectively. The N-terminal and C-terminal histone tails and the globular regions, which are depicted as shadowed circles, of the histones are shown.

may be assigned to transcription rather than replication processes.

In unravelling the relationship between histone acetylation and transcription, inhibitors of histone deacetylase have been most helpful. Sodium butyrate has been the most widely used of the histone deacetylase inhibitors. However, this inhibitor lacks specificity and has multiple effects on nuclear function. Specific histone deacetylase inhibitors, trichostatin A and trapoxin, have recently come into use. Studies with these three inhibitors show that the reversible nature of histone acetylation has a crucial role in cell cycle control and differential gene expression [Kijima et al., 1993].

Several groups have provided correlative evidence that acetylated histones are associated with transcriptionally active/poised chromatin. Direct evidence comes from the studies of Crane-Robinson and colleagues in which they used an antibody that recognized the epitope ϵ-acetyl lysine in immunoprecipitation studies [Clayton et al., 1993]. In 5 day chick embryo erythrocytes, the transcriptionally active ρ- and inactive (poised) β^A-globin DNA sequences were in acetylated nucleosomes as were the active β^A- and inactive (poised) ρ-globin genes of 15 day chicken embryo erythrocytes. These studies provide evidence that core histone acetylation precedes transcription [Clayton et al., 1993].

The DNase I sensitivity and salt solubility properties of transcriptionally active/poised gene chromatin are in part due to histone acetylation. Chromatin with hyperacetylated histones has an increased sensitivity to DNase I digestion. The solubility of transcriptionally active/poised gene chromatin fragments in 3 mM $MgCl_2$ and/or 150 mM NaCl is linked to the acetylation status of their core histones, with induction of hyperacetylation increasing the salt solubility of this chromatin [Ridsdale et al., 1990]. The observation that the DNA sequences of the entire DNase I–sensitive β-globin domain in chicken erythrocytes are found in salt-soluble chromatin fragments predicts that the β-globin chromosomal domain is associated with acetylated nucleosomes.

Histone acetylation is a dynamic process. Acetylation occurs at more than one rate, as does the subsequent deacetylation. One population of core histones is characterized by rapid hyperacetylation ($t_{1/2}$ = 7 min for monoacetylated histone H4) and rapid deacetylation ($t_{1/2}$ = 3–7 min). This highly dynamic acetylation-deacetylation is limited to 15% (hepatoma tissue culture cells) of the core histones [Covault and Chalkley, 1980]. A second population is acetylated ($t_{1/2}$ = 200–300 min for monoacetylated H4) and deacetylated at a slower rate ($t_{1/2}$ = 30 min). Approximately 2% of the genome of adult chicken immature erythrocytes participates in active acetylation and deacetylation. The bulk of the chicken erythrocyte genome, which does not take part in active acetylation, is associated with monoacetylated and unacetylated histones. Although both rates of acetylation are observed in mature erythrocytes, there is only one rate of acetylation ($t_{1/2}$ of approximately 12 min for monoacetylated histone H4) in adult chicken immature erythrocytes. However, there are two populations of core histones (H3 and H4) participating in this rapid acetylation. One population of rapidly acetylated histone becomes hyperacetylated (e.g., to the tetraacetylated form of histone H4) in the presence of sodium butyrate. Upon removal of the inhibitor, the hyperacetylated histone species are rapidly deacetylated ($t_{1/2}$ = 5 min). We refer to this type of active acetylation as dynamic, class 1 acetylation [Hendzel et al., 1991]. The other population of the rapidly acetylated histones (H3 and H4) achieves only low levels of acetylation (e.g., mono- and diacetylated forms of histone H4) in the presence of sodium butyrate. In the absence of butyrate, these histones are slowly deacetylated. We refer to this type of acetylation as class 2 acetylation. Dynamically, class 1 acetylated histones are bound principally to active DNA [Ip et al., 1988; Boffa et al., 1990; Hendzel et al., 1991]. Further, the core histones of the nuclear matrix associated chromatin fragments of adult chicken immature erythrocytes had a strong bias for the dynamic, class 1 type of acetylation [Hendzel et al., 1991]. Similar observations were made using a different protocol to separate transcriptionally active chromatin from inactive and poised chromatin of hepatoma tissue culture cells [Ip et al., 1988]. The strong preference of the dynamically acetylated class 1 histones towards active gene-enriched chromatin regions was not apparent with class 2 acetylated histones. Class 2 acetylated histones were located primarily in poised and active chromatin regions. These results suggest that in an active gene domain only regions of the domain engaged in transcription are associated with core his-

tones taking part in class 1 acetylation [Hendzel et al., 1991]. We anticipate that the active β^A-globin, but not the poised ϵ-globin, DNA sequences will be found in nucleosomes undergoing rapid acetylation and deacetylation.

FUNCTIONS OF HISTONE ACETYLATION

Transcriptionally active/poised chromatin is associated with H1 histones [Garrard, 1991]. As the H1 (linker) histones play a key role in the stabilization of the higher order folding of the chromatin fibre, what prevents the transcriptionally active chromatin regions from accepting a higher order structure? Reconstitution experiments suggest that core histone acetylation alters the capacity of the H1 histones to condense transcriptionally active/poised chromatin [Ridsdale et al., 1990]. Chromatin fragments stripped of H1 histones are soluble in 150 mM NaCl, whereas chromatin fragments reconstituted with H1 histones aggregate and precipitate (referred to as exogenously added linker histone-induced precipitation). Reconstitution experiments revealed that active/poised chromatin fragments are much more resistant than repressed chromatin fragments to exogenously added linker histone-induced precipitation in 0.15 M NaCl. By incubating cells in the presence or absence of sodium butyrate, the acetylation level of dynamically acetylated core histones bound to active/poised DNA can be manipulated. Active/poised chromatin fragments with unacetylated histones were unable to resist exogenously added linker histone-induced salt precipitation [Ridsdale et al., 1990].

Removal of the basic amino-terminal tails of the core histones, which contain the sites of acetylation, does not prevent the H1 histones from binding to the chromatin fibre. But removal of the tails interferes with the capacity of the linker histones to condense chromatin. Thus, core histone acetylation may have the same effect on altering H1 histone action as does removal of the N-terminal tail [Ridsdale et al., 1990]. Considering that transcriptionally active DNA is bound to dynamically acetylated core histones suggests that these nuclear matrix–attached chromatin regions are continually condensing and decondensing.

Core histone acetylation alters histone-DNA contacts and nucleosome structure. We propose that the liberation of DNA from the nucleosome and/or change in nucleosome structure may alter the path of the DNA entering and leaving the nucleosome which in turn may modify the interaction between the H1 histone and nucleosomal/linker DNA. Current evidence suggests that dynamic acetylation also increases the lability of H2A-H2B dimers in transcriptionally active nucleosomes, a process that allows remodelling of the nucleosome by the incorporation of variants of histones H2A and H2B (e.g., H2A.Z) [Li et al., 1993; Perry et al., 1993]. These changes in nucleosome structure make available binding sites for *trans*-acting factors [Turner, 1993].

NUCLEAR LOCATION OF HISTONE ACETYLTRANSFERASE AND DEACETYLASE

The observation that rapid acetyl group turnover occurs primarily with histones of active gene chromatin predicted that histone acetyltransferase and histone deacetylase would be localized in the active gene chromatin domains. Both histone acetyltransferase and deacetylase are present in the active/poised gene-enriched, 0.15 M NaCl-soluble chicken erythrocyte chromatin fragments [Chan et al., 1988; Hendzel et al., 1991]. This population, however, represents only a minor proportion of the total nuclear histone deacetylase activity. Most of the histone deacetylase remains insoluble following the release of micrococcal nuclease digested chromatin fragments from the nucleus. When nuclei were fractionated using several different nuclear matrix isolation protocols and several tissue sources (chicken erythrocytes, chicken liver, trout liver, trout hepatocellular carcinomas), histone deacetylase activity was consistently found associated with the nuclear matrix. If however, nuclear pore-lamina complexes were isolated, histone deacetylase activity was completely solubilized. These results show that histone deacetylase is a component of the internal nuclear matrix. Consistent with these results, the histone deacetylase of HeLa cells was located in a high molecular weight fraction with characteristics of the nuclear matrix [Hay and Candido, 1983].

The retention of several proteins to the nuclear matrix appears to depend on intermolecular disulfide bonds that are formed during the isolation of nuclear matrices [Kaufmann et al., 1991]. Our observations argue that in vitro oxidation is not responsible for the association of histone deacetylase with the nuclear matrix [Hendzel, 1993]. Nuclear matrices isolated in the presence or absence of iodoacetamide retained similar levels of histone deacetylase activity.

Loidl's group found that nuclear matrices of *Physarum* and *Zea mays* retain low levels of histone deacetylase activity [Brosch et al., 1992]. The reasons for the discrepancy between their results and ours are unknown. However, we have observed that preparations with RNase activity have lower levels of histone deacetylase activity associated with their nuclear matrices (unpublished observations). The lack of RNase inhibitors and the inclusion of reducing agents in their nuclei isolation buffers may explain the discrepancy. Also, the vertebrate histone deacetylases are much more sensitive to inhibition by sodium butyrate than either plant cells or *Physarum*, showing that these enzymes are not identical. It is possible that the association of the vertebrate and plant histone deacetylases with the nuclear matrix differ, such that the vertebrate, but not the plant, deacetylases will remain bound to the nuclear matrix following 2 M NaCl extraction.

MODEL FOR HISTONE ACETYLTRANSFERASE AND DEACETYLASE IN TRANSCRIPTION FOCI

As with the histone deacetylase, histone acetyltransferase is associated with the internal nuclear matrix [Hendzel, 1993]. We propose that both histone acetyltransferase and deacetylase are attached to the internal nuclear matrix at sites of transcription (Fig. 3). In this model the core histones of transcriptionally active nucleosomes are frequently in contact with either the histone acetyltransferase or deacetylase, resulting in the dynamic class 1 acetylation that is observed in active chromatin regions. The connection of transcriptionally active chromatin with these nuclear matrix–bound enzymes would serve to maintain the nuclear location of the transcribed genes. Further, links between transcriptionally active chromatin and the nuclear matrix–bound enzymes and transcription factors would contribute to the insoluble characteristics of active chromatin.

Our observations are consistent with what we now know about the organization of transcriptionally active gene loci within the nucleus. If dynamic histone acetylation in the $G_0/G_1/G_2$ phases of the cell cycle is predominantly associated with transcriptionally active gene loci, then the histone deacetylases and histone acetyltransferases should colocalize with transcribing chromatin within the nucleus. Recently, it has been

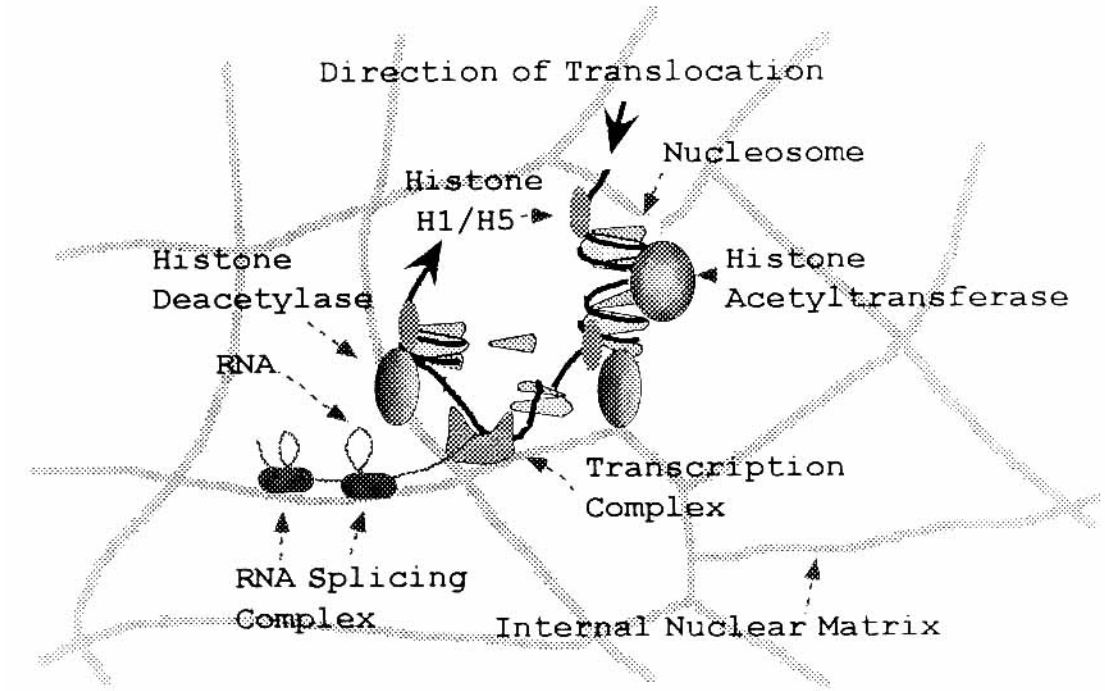

Fig. 3. Model for the association of nuclear matrix–bound histone acetyltransferase and deacetylase with transcribed chromatin. Histone acetyltransferase, histone deacetylase, transcription machinery, and RNA processing machinery are shown associated with the internal nuclear matrix. Histone acetyltransferase and deacetylase are depicted as continually contacting nucleosomes, catalyzing rapid reversible acetylation. The DNA is shown moving through the transcription complex [Jackson et al., 1993]. Histone H1 is removed and the nucleosome is disassembled before encountering the transcription machinery.

shown that RNA polymerase II transcription localizes to discrete nuclear compartments, called transcription foci, which are thought to contain several transcribed genes per focus [Jackson et al., 1993; Wansink et al., 1993]. This suggests that histone acetyltransferases and histone deacetylases should be targeted to these nuclear compartments to function predominantly on transcribed chromatin. The association of these enzymes with the nuclear matrix may be the mechanism of spatially compartmentalizing these enzymes and thereby facilitating their interaction with transcribing chromatin. Since transcription also appears to be a nuclear matrix-*associated process* [Jackson et al., 1993; Wansink et al., 1993], all these processes may be spatially organized in relation to the chromatin domain. Spatial organization of these processes could add an additional level of efficiency to the system that would not otherwise be possible.

FUTURE DIRECTIONS

How does transcriptionally active chromatin get selectively recruited to the nuclear matrix? We are beginning to get a glimpse about the mechanisms by which these processes might occur. The associations of histone acetyltransferase, histone deacetylase, and *trans*-acting factors with the nuclear matrix provide mechanisms for the recruitment of potentially active genes to nuclear matrix, leading to the generation of transcript domains or foci. The *trans*-acting factors would attract the general transcription factors and establish the transcription machinery. The RNA processing machinery would then be recruited to these sites. Immunolocalization studies with antibodies to histone acetyltransferase and deacetylase, which has not yet been purified, and in situ hybridization with probes to transcribed genes will be powerful approaches to testing this model. Further, we will need to know the signals by which the histone acetyltransferase, deacetylase, and *trans*-acting factors are targeted to the nuclear matrix and how these signals are influenced during the cell cycle and different cellular states. There are several isoforms of the histone acetyltransferase and deacetylase, and perhaps only a subset of them is associated with the nuclear matrix. The substrate specificity and the specific lysine residues used by these nuclear matrix–bound enzymes need to be determined to understand their specific functions in the regulation of gene expression.

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