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# Understanding "Active" Chromatin: A Historical Perspective of Chromatin Remodeling

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**ABSTRACT:** Two phenomena have long been observed to correlate with transcriptionally active chromatin: increased histone acetylation and increased sensitivity to nucleases, including specific patterns of nuclease hypersensitivity in the promoters of active or inducible genes. Work in recent years has at last identified protein complexes required to form these hallmarks of active chromatin: histone acetyltransferases (HATs) and ATP-dependent chromatin remodeling complexes. This review traces the history of these discoveries, including the development of essential tools that allowed the major advances in the field, and describes the current understanding of the interactions between HATs and ATP-dependent remodelers.

**KEY WORDS:** histone acetylation, chromatin, SWI-SNF, GCN5, DNase I

## I. UNDERSTANDING THE STRUCTURE OF ACTIVE CHROMATIN: DNASE I HYPERSENSITIVE SITES

When early studies revealed that DNA in the eukaryotic nucleus was compacted via its association with histones, researchers immediately recognized that this condensed structure would have a major impact on the regulation of gene expression and other protein-DNA transactions. As early experiments indicated that histones remain present in actively transcribed regions (Axel et al., 1974; Lacy and Axel, 1975), it seemed that chromatin in these regions must exist in an altered conformation or organization that was more permissive for transcription. In groundbreaking experiments, Weintraub and Groudine described a way to detect a conformational difference between active and inactive chromatin — active chromatin displays an enhanced sensitivity to nucleases such as DNase I (Weintraub and Groudine, 1976). The discovery that active and potentially active loci exhibited a general increased sensitivity to nucleases quickly led to a new higher-resolution mapping of chromatin structure. In addition to general DNase I sensitivity, DNase I hypersensitive sites — discrete sites of exquisite accessibility — were identified in the 5′ regions of *Drosophila* heat shock genes (Wu, 1980). Subsequently, DNase I hypersensitive sites were identified in the 5′ and 3′ regions of an array of genes in higher eukaryotes, and such hypersensitivity soon became a hallmark of active genes and genes poised for tissue-specific expression (Groudine and Weintraub, 1982; Stalder et al., 1980; Weintraub, 1983; Weintraub et al., 1981; Wu and Gilbert, 1981). DNase I hypersensitive sites were also found in the promoters of active and inducible genes in yeast (Almer and Horz, 1986; Almer et al., 1986; Bergman and Kramer, 1983; Lohr, 1984; Lohr and Hopper, 1985; Perez-Ortin et al., 1986; Proffitt, 1985; Sledziewski and Young, 1982; Szent-Gyorgyi et al., 1987). As in higher eukaryotes, some of these hypersensitive sites correlate with the transcriptional state of the gene, while others were constitutive.

A number of models were proposed to explain the formation of hypersensitive sites. Several early theories involved changes in the structure or composition of chromatin. For example, re-

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searchers in the Weintraub laboratory detected an enrichment of the high mobility group (HMG) proteins HMG-14 and HMG-17 in active chromatin, and the presence of these proteins appeared to correlate with DNase I sensitivity (Weisbrod et al., 1980; Weisbrod and Weintraub, 1979; Weisbrod and Weintraub, 1981). While these HMG proteins are now understood to bind to nucleosomes and influence chromatin compaction (for review see Bustin et al., 1995), their role in hypersensitive site formation is less clear (Li et al., 1997). Other altered structures that were proposed included "half" or "split" nucleosomes based on nuclease mapping studies that showed reduced nucleosome repeat lengths in active genes (Ryoji and Worcel, 1985; Lee and Garrard, 1991). Another popular proposal was that active chromatin was enriched in nucleosomes depleted for H2A/H2B dimers (Feinstein and Moudrianakis, 1986; Gonzalez and Palacian, 1989).

Other early theories explored enzymatic models for hypersensitive site formation. One early model to explain how hypersensitive sites might be formed posited that a DNA gyrase-like enzyme might drive a change in the topology of a chromatin domain, which would lead to hypersensitive site formation (Villeponteau et al., 1984). These "gyrase" models were also consistent with other studies of Weintraub and colleagues who showed that DNase I hypersensitive sites also tended to be hypersensitive to S1 nuclease or to reaction with chemicals such as chloroacetaldehyde, which detect single-stranded or conformationally strained DNA (Kohwi-Shigematsu et al., 1983; Larsen and Weintraub, 1982; Weintraub, 1983). These studies led to models proposing that promoter regions contained sequence elements that could adopt altered DNA structures, such as cruciforms, Z-DNA, or other non-B-form conformations, which could act as sinks for unconstrained torsional stress. Such torsional stress was hypothesized to be produced by gyrase-like enzymes and led to an intensive search for a eukaryotic gyrase.

Several studies that used the topoisomerase II catalytic inhibitor, novobiocin, were consistent with such gyrase models for formation of "active" chromatin. Early studies from Worcel and colleagues indicated that a Pol III transcription factor, TFIIIA, could induce a novobiocin-sensitive, positive gyration of chromatin in vitro, and that this gyration seemed to be responsible for DNase I hypersensitivity (Kmiec et al., 1986; Kmiec and Worcel, 1985). Likewise, Martinson and colleagues showed that addition of novobiocin to chicken erythrocyte nuclei could reverse the DNase I sensitivity of the active β-globin gene (Villeponteau et al., 1984). Similar results were obtained in the lower eukaryotes *Dictyostelium* and *Physarum*, in which inhibition of topoisomerase II-like activities specifically reduced the nuclease hypersensitivity of the rRNA gene promoters (Borde and Duguet, 1996; Ness et al., 1986). Further, topoisomerase II-induced cleavage sites in the *Physarum* histone H4 locus coincide spatially (but not temporally) with DNase I hypersensitive sites (Borde and Duguet, 1998), and likewise topoisomerase II-induced cleavage sites co-map with some DNase hypersensitive sites in the *Drosophila* hsp70 promoter (Rowe et al., 1986). However, despite the clear importance of topoisomerase II in DNA replication and chromosome condensation/decondensation (for reviews see Wang, 1996; Warburton and Earnshaw, 1997), eukaryotes lack an equivalent to the classic prokaryotic DNA gyrase, and most of the old novobiocin studies relating to DNase I hypersensitive site formation are generally considered to be inherently flawed. Unexpectedly though, topoisomerase II was identified recently as a subunit of the ATP-dependent remodeling enzyme, CHRAC (Varga-Weisz et al., 1997). Although inhibition of topoisomerase II activity does not appear to affect the ability of CHRAC to enhance the accessibility of chromatin, topoisomerase II does appear to contribute to the ability of CHRAC to alter nucleosome spacing, consistent with previous reports of a role for topoisomerase II on nucleosome spacing (To and Kmiec, 1990). It is also interesting to note that another ATP-dependent remodeling enzyme, SWI/SNF, has been shown to influence plasmid supercoiling in vitro (Quinn et al., 1996), and SWI/SNF remodeling itself appears to create torsional stress, and its remodeling is blocked by some catalytic inhibitors of topoisomerase II (I. Gavin and C. L. P., unpublished results). It may be that future studies will lead to a reinterpretation of the old "gyrase" literature.

al., 1992) and human (hSWI/SNF or BAF complex) (Kwon et al., 1994), and to the identification and purification of other members of the ATP-dependent family of remodeling complexes such as NURF (Tsukiyama and Wu, 1995), CHRAC (Varga-Weisz et al., 1997), ACF (Ito et al., 1999), NURD (Xue et al., 1998), and RSC (Cairns et al., 1996). In vitro experiments have led to a number of insights into the mechanism of ATP-dependent remodeling (for recent reviews see Kingston and Narlikar, 1999; Peterson, 1998) and, as described in detail below, a hint of a role for these remodeling enzymes in hypersensitive site formation.

### B. Do ATP-Dependent Remodelers Form DNase I Hypersensitive Sites?

In many cases the formation of hypersensitive sites has been shown to require the concerted action of a site-specific transcriptional activator and an ATP-dependent chromatin remodeling enzyme. For example, Wu and colleagues reconstituted a *Drosophila* heat shock promoter into chromatin (Becker et al., 1991; Becker and Wu, 1992) and found that hypersensitive site formation required binding of the GAGA transcription factor as well as the activity of an ATP-dependent remodeling complex, NURF (nucleosome remodeling factor) (Tsukiyama et al., 1994; Tsukiyama and Wu, 1995). Likewise, the formation of DNase I hypersensitive sites at the yeast *PHO8* locus in vivo requires the PHO4 activator as well as the SWI/SNF complex (Gregory et al., 1999), and a persistent DNase I hypersensitive site can be reconstituted in a purified system composed of only DNA, histones, yeast SWI/SNF, and a derivative of the GAL4 activator (Owen-Hughes et al., 1996).

Emerson and colleagues have also been able to reconstitute the in vitro formation of DNase I hypersensitive sites and regulated transcription for the chicken (Barton and Emerson, 1996) and human (Bagga et al., 1998) β-globin loci. Both the chicken and human β-globin loci have long been classic models for the study of the formation and function of DNase I hypersensitive sites that are activated during development (Baron, 1997; Bieker, 1998; Groudine et al., 1983; Groudine and Weintraub, 1981; Orkin, 1995). As expected, transcription and the formation of specific hypersensitive sites in the human β-globin in vitro system require the binding of erythroid cell-specific activators. However, the formation of a key hypersensitive site by the activator NF-E2 requires ATP, suggesting that an ATP-dependent nucleosome remodeling enzyme that was present in the reconstituted system was required for hypersensitive site formation (Armstrong and Emerson, 1996; Bagga et al., 1998). Subsequently, these workers showed that the ability of the activator EKLF to bind chromatin, form hypersensitive sites, and activate transcription depends on a human SWI/SNF-related remodeling complex (Armstrong et al., 1998; Bagga et al., 1998). Consistent with these in vitro studies, recently Lee et al. have shown that human SWI/SNF is recruited to the β-globin gene in vivo by a mechanism that is independent of EKLF, but requires a functional LCR and binding sites for the NF-E2 transcription factor (Lee et al., 1999).

What is the structure of a DNase I hypersensitive site and how might ATP-dependent remodeling enzymes drive their formation? What now appears clear is that DNase I hypersensitive sites are the read-out for a number of different chromatin structures that include the presence of nucleosome-free regions, positioned nucleosomes, DNA-bound nonhistone proteins, and perhaps the presence of some type of "remodeled" nucleosome with an altered conformation. ATP-dependent remodeling complexes are able to enhance the mobility of nucleosomes, which could lead to nucleosome-free regions. Alternatively, ATP-dependent remodeling could enhance the binding of nonhistone proteins to nucleosomal sites that then reinforce or create boundaries between positioned nucleosomes. Each of these events would ultimately perturb the regularity and folding of the nucleosomal array, thus leading to the enhanced reactivity of DNA to DNase I.

## II. UNDERSTANDING THE ROLE OF HISTONE ACETYLATION: ANTIBODIES AND ACTIVATORS

### A. Finding Patterns of Acetylation

As early as 1964, Allfrey et al. proposed a link between the reversible acetylation of histone

## A. Identification of ATP-Dependent Chromatin Remodelers

While chromatin mapping studies were pursued in both yeast and higher eukaryotes, yeast genetics ultimately led to the identification of the holy grail of the chromatin world — enzymes that control transcription by modulating chromatin structure. Two genetic screens identified six genes that are now known to comprise half of the 11-subunit, 2-megadalton SWI/SNF complex. The *SWI* genes (*SWI1*, *SWI2*, and *SWI3*) were identified as positive regulators of the *HO* gene (which encodes an endonuclease required for mating type switching) (Stern et al., 1984), while the *SNF* genes (*SNF2* {=*SWI2*}, *SNF5*, *SNF6*, and *SNF11*) were isolated as mutants required for the transcription of the *SUC2* gene, an invertase required for growth on raffinose and sucrose (SNF stands for sucrose nonfermenting) (Neigeborn and Carlson, 1984). These two sets of genes were linked when Nasmyth and colleagues partially sequenced the *SWI2* gene and found to their surprise that it was identical to the *SNF2* gene that had been sequenced previously by the Carlson group (Laurent et al., 1991). Subsequent studies demonstrated that *swi* mutants exhibited *Snf* phenotypes and vice versa. The link to chromatin came from the discovery that suppressors of SWI (*SIN*; **SWI-in**dependent) (Sternberg et al., 1987) and SNF (*SSN*; suppressors of snf) (Neigeborn et al., 1986) included mutations in genes that encode chromatin components, such as histone H3 (*sin2*).

The SWI/SNF complex was purified from yeast (Cairns et al., 1994; Cote et al., 1994; Peterson et al., 1994) and shown to be an ATPase that could use the energy of ATP hydrolysis to increase the accessibility of nucleosomal DNA to transcription factors (Cote et al., 1994). These studies opened the door for purification of homologous SWI/SNF complexes from *Drosophila* (*brm* complex) (Papoulas et al., 1998; Tamkun et

**TABLE 1**
**A Timeline of Hallmark Advances in the Chromatin Remodeling Field**

| Year | Advance | References |
|---|---|---|
| 1964 | Relationship between gene expression and acetylation and methylation of histones proposed | Allfrey et al. |
| 1965 | Histones first purified by acid extraction | Phillips and Johns |
| 1974 | Chromatin structure proposed to consist of a repeated unit of DNA and histones | Kornberg |
| 1976 | Active chromatin is sensitive to nuclease digestion | Weintraub and Groudine |
| 1977 | Biochemical isolation of nuclear scaffold | Paulson et al. |
| 1984 | Yeast genetics identify SWI/SNF subunits and GCN5 | Stern et al., Neigeborn and Carlson, Georgakopoulos and Thireos |
| 1988 | First use of chromatin immunoprecipitation to map acetylated histones at active genes in vivo | Hebbes et al. |
| 1991 | First high-resolution structure of histone octamer | Arents et al. |
| 1994 | Purification of the first ATP-dependent chromatin remodeling complex, yeast SWI/SNF | Peterson et al., Cote et al., Cairns et al. |
| 1995 | Purification of the first nuclear histone acetyltransferase, Tetrahymena p55 | Brownell and Allis |
| 1996 | Purification of the first histone deacetylases | Carmen et al., Taunton et al. |
| 1997 | High-resolution structure of the nucleosome | Luger et al. |

heterochromatin (Braunstein et al., 1996). Importantly, mutational analysis of the histone H4 tail allowed these researchers to show that this pattern of H4 acetylation is required for transcriptional silencing. A summary of some of the observed specific patterns of acetylated histone isoforms is presented in Table 2.

## D. Identification of Histone Acetyltransferases

Despite intense interest in histone acetylation, one key advance long eluded researchers: the purification of nuclear histone acetyltransferases (HATs). This breakthrough was finally achieved through the development of an in-gel assay for HAT activity that allowed the identification of the first nuclear HAT from *Tetrahymena* macronuclei (Brownell and Allis, 1995). When this HAT was cloned and sequenced, it was found to be homologous to the yeast *GCN5*, which previously had been identified as a transcriptional coactivator (Brownell et al., 1996). This discovery opened the door for purification of native Gcn5p-dependent (and independent) HAT complexes from yeast (Eberharter et al., 1998; Grant et al., 1997; Pollard and Peterson, 1997; Saleh et al., 1997), as well as the cloning of GCN5 homologs from human (Candau et al., 1996) and *Drosophila* (Smith et al., 1998). The development of the in-gel assay for HAT activity also led to the discovery that many previously identified transcription factors and coactivators are actually histone acetyltransferases, such as CBP/p300 (Bannister and Kouzarides, 1996; Ogryzko et al., 1996), P/CAF (Blanco et al., 1998), TAF(II)250 (Mizzen et al., 1996), ACTR (Chen et al., 1997), SRC-1 (Spencer et al., 1997), BRCA2 (Siddique et al., 1998), and others. In addition, the identification of GCN5 as a HAT finally allowed direct evidence to be obtained that the HAT activity of GCN5 is required for its transcriptional activation function (Wang et al., 1998), and that activation by GCN5 correlates with specific acetylation of histones in target promoters (Krebs et al., 1999; Kuo et al., 1998).

Much of the current research on HATs addresses two major questions: first, how are HATs recruited to their target genes in vivo?; second,

**TABLE 2**
**Patterns of Histone Acetylation In Vivo**

| Acetylation/isoform | Site(s) | Organism/cell type | Ref. |
|---|---|---|---|
| Hyperacetylated core histones | Macronucleus | Tetrahymena | Gorovsky, 1973 |
| Hyperacetylated H4 | α-D-globin | Chicken erythrocytes | Hebbes, 1988 |
| Hyperacetylated H4 | Polytene puffs | Insect salivary glands | Turner, 1990 |
| Hypoacetylated core histones | Telomeres | Yeast | Braunstein, 1993 |
| Hyperacetylated H4lysine 12, hypoacetylated H3, H4 | Mating type cassettes | Yeast | Braunstein, 1996 |
| Hypoacetylated H4, H3, H2A | Inactive X chromosome | Female mammals | Jeppesen, 1993, Belyaev, 1996 |
| Hyperacetylated H4lysine 16 | Hyperactive male X chromosome | *Drosophila* | Bone, 1994 |
| Hyperacetylated H4lysine 12 | Centric heterochromatin | *Drosophila* | Turner, 1992 |
| Hyperacetylated H4 | Active somatic 5S rRNA genes | *Xenopus laevis* | Howe, 1998 |
| H3lysines9/14 | Induced HIS3 promoter | Yeast/amino acid starved | Kuo, 1998 |
| H3lysines9/14, hyper H4 | HO promoter | Yeast/early G1 | Krebs, 1999 |

tails and the regulation of transcription (Allfrey et al., 1964). Numerous studies supporting a correlation between histone hyperacetylation and transcriptionally active chromatin followed this proposal. In 1966, Allfrey and colleagues showed that when lymphocytes are treated with the mitogen phytohaemaglutinin, the resumption of transcription is preceded by a striking increase in acetylation levels of core histones (Pogo et al., 1966). Likewise, it was shown in *Tetrahymena* that acetylation of core histones occurs only in the transcriptionally active macronucleus, not in the silent micronucleus (Gorovsky et al., 1973). The discovery that transcriptionally active chromatin was preferentially sensitive to DNase I digestion (Weintraub and Groudine, 1976) allowed another correlation to be made: active chromatin released by low levels of DNase I digestion is enriched in acetylated histones (Sealy and Chalkley, 1978; Vidali et al., 1978). These and other related studies supported a general connection between active chromatin and core histone acetylation, but these experiments addressed properties of bulk chromatin rather than of specific genes.

## B. Acetylation In Vivo: Patterns of Specific Histone Acetylation

In the mid-1980s new tools were developed that allowed researchers to correlate histone acetylation with specific transcriptionally active loci. Antibodies were generated that could distinguish between acetylated and unacetylated forms of histones (Hebbes et al., 1988; Muller et al., 1987; Pfeffer et al., 1986). Crane-Robinson and colleagues used this class of antibodies to immunoprecipitate chromatin containing acetylated histones from chicken embryo erythrocytes. Using probes recognizing α-D-globin, an actively transcribed gene in this cell type, they were able to show that this active gene, but not an inactive control, was 15- to 30-fold enriched in chromatin associated with acetylated histone H4 (Hebbes et al., 1988). This was the first published example of the use of the powerful "chromatin immunoprecipitation (ChIP)" assay to examine patterns of acetylation in vivo. This assay has been refined over the years and is currently in widespread use in the chromatin field to assess protein-DNA interactions in vivo (see below). The usefulness of antibodies against acetylated histones led to an explosion of studies, using both immunoprecipitation and immunolabeling techniques, to further elucidate the links between acetylation and gene expression. Acetylated H4 was shown to be localized within the borders of transcriptionally active puffs on insect polytene chromosomes (Turner et al., 1990). Transcriptional silencing at yeast telomeres and mating-type cassettes was shown to strictly correlate with hypoacetylation of histones at these loci (Braunstein et al., 1993). Similarly, the inactive X chromosome in female mammals was found to be characterized by hypoacetylated H4 (Jeppesen and Turner, 1993). The early results connecting hyperacetylation and general DNase I sensitivity were confirmed by showing that core histone acetylation and nuclease sensitivity co-map in the 33-kb transcriptionally active chicken β-globin locus (Hebbes et al., 1994).

## C. Acetylation In Vivo: Patterns of Different Isoforms of Acetylated Histones

Further refinements followed the characterization of antibodies that could distinguish different acetylated isoforms of histones. Studies using these antibodies allowed a new idea to emerge: not only are differences in overall acetylation levels important, but that acetylation at specific lysines can be critical. For example, the single male X chromosome in *Drosophila*, which is expressed at elevated levels as a result of dosage compensation, is the site of localization of an isoform of histone H4 acetylated specifically at lysine 16 (Bone et al., 1994). In addition, although histone H4 is hypoacetylated at three out of four acetylatable lysines in *Drosophila* centric heterochromatin, lysine 12 is significantly acetylated in these regions (Turner et al., 1992). A similar story has emerged in yeast. While histones H3 and H4 are hypoacetylated overall at the yeast mating-type cassettes, Braunstein et al. showed that H4 is significantly acetylated at lysine 12 in this silenced chromatin — identical to the acetylation pattern seen in *Drosophila* centric

ATP-dependent remodeling activity directly stimulates NURD's ability to deacetylate nucleosomes (Tong et al., 1998). These results, and the interactions between SWI/SNF and SAGA, suggest one role of ATP-dependent remodelers could be to make histone tails available to either HATs or HDACs.

Clearly, the interplay between chromatin remodeling and histone acetylation/deacetylation is complex and ever-changing. Many important tools and studies over the last 3 decades have teased out many of the distinguishing features and players in the dance between chromatin structure and gene expression. Today we are in the position to follow the changing of partners and the order of steps that lead to the seamless choreography of chromatin dynamics in vivo.

## REFERENCES


Allfrey VG, Faulkner R, Mirsky AE (1964): Acetylation and methylation of histones and their possible role in the regulation of RNA synthesis. Proc Natl Acad Sci USA 51:786–794.

Almer A, Horz W (1986): Nuclease hypersensitive regions with adjacent positioned nucleosomes mark the gene boundaries of the PHO5/PHO3 locus in yeast. EMBO J 5:2681–2687.

Almer A, Rudolph H, Hinnen A, Horz W (1986): Removal of positioned nucleosomes from the yeast PHO5 promoter upon PHO5 induction releases additional upstream activating DNA elements. EMBO J 5:2689–2696.

Arents G, Burlingame RW, Wang BC, Love WE, Moudrianakis EN (1991): The nucleosomal core histone octamer at 3.1 A resolution: a tripartite protein assembly and a left-handed superhelix. Proc Natl Acad Sci USA 88:10148–10152.

Armstrong JA, Bieker JJ, Emerson BM (1998): A SWI/SNF-related chromatin remodeling complex, E-RC1, is required for tissue-specific transcriptional regulation by EKLF in vitro. Cell 95:93–104.

Armstrong JA, Emerson BM (1996): NF-E2 disrupts chromatin structure at human beta-globin locus control region hypersensitive site 2 in vitro. Mol Cell Biol 16:5634–5644.

Axel R, Cedar H, Felsenfeld G (1974): Chromatin template activity and chromatin structure. Cold Spring Harb Symp Quant Biol 38:773–783.

Bagga R, Armstrong JA, Emerson BM (1998): Role of chromatin structure and distal enhancers in tissue-specific transcriptional regulation in vitro. Cold Spring Harb Symp Quant Biol 63:569–576.

Bannister AJ, Kouzarides T (1996): The CBP co-activator is a histone acetyltransferase. Nature 384:641–643.

Baron, MH (1997): Transcriptional control of globin gene switching during vertebrate development. Biochim Biophys Acta 1351:51–72.

Barton MC, Emerson BM (1996): Regulated gene expression in reconstituted chromatin and synthetic nuclei. Methods Enzymol 274:299–312.

Becker PB, Rabindran SK, Wu C (1991): Heat shock-regulated transcription in vitro from a reconstituted chromatin template. Proc Natl Acad Sci U S A 88:4109–4113.

Becker PB, Wu C (1992): Cell-free system for assembly of transcriptionally repressed chromatin from *Drosophila* embryos. Mol Cell Biol 12:2241–2249.

Bergman LW, Kramer RA (1983): Modulation of chromatin structure associated with derepression of the acid phosphatase gene of *Saccharomyces cerevisiae*. J Biol Chem 258:7223–7227.

Bieker JJ (1998): Erythroid-specific transcription. Curr Opin Hematol 5:145–150.

Blanco JC, Minucci S, Lu J, Yang XJ, Walker KK, Chen H, Evans RM, Nakatani Y, Ozato K (1998): The histone acetylase PCAF is a nuclear receptor coactivator. Genes Dev 12:1638–1651.

Bone JR, Lavender J, Richman R, Palmer MJ, Turner BM, Kuroda MI (1994): Acetylated histone H4 on the male X chromosome is associated with dosage compensation in *Drosophila*. Genes Dev 8:96–104.

Borde V, Duguet M (1998): DNA topoisomerase II sites in the histone *H4* gene during the highly synchronous cell cycle of *Physarum* polycephalum [published erratum appears in Nucleic Acids Res 1998 Oct 15; 26(20): following 4789]. Nucleic Acids Res 26:2042–2049.

Borde V, Duguet M (1996): In vivo topoisomerase II cleavage sites in the ribosomal DNA of *Physarum* polycephalum. Biochemistry 35:5787–5795.

Braunstein M, Rose AB, Holmes SG, Allis CD, Broach JR (1993): Transcriptional silencing in yeast is associated with reduced nucleosome acetylation. Genes Dev 7:592–604.

Braunstein M, Sobel RE, Allis CD, Turner BM, Broach JR (1996): Efficient transcriptional silencing in *Saccharomyces* cerevisiae requires a heterochromatin histone acetylation pattern. Mol Cell Biol 16:4349–4356.

Brownell J, Allis CD (1995): An activity gel assay detects a single, catalytically active histone acetyltransferase subunit in *Tetrahymena* macronuclei. Proc Natl Acad Sci USA 92:6364–6368.

Brownell JE, Zhou J, Ranalli T, Kobayashi R, Edmondson DG, Roth SY, Allis CD (1996): *Tetrahymena* histone acetyltransferase A: a homolog to yeast Gcn5p linking histone acetylation to gene activation. Cell 84:843–851.

Bustin M, Trieschmann L, Postnikov YV (1995): The HMG-14/-17 chromosomal protein family: architectural elements that enhance transcription from chromatin templates. Semin Cell Biol 6:247–255.

Cairns BR, Kim Y-J, Sayre MH, Laurent BC, Kornberg RD (1994): A multisubunit complex containing the SWI1/ADR6, SWI2/SNF2, SWI3, SNF5, and SNF6 gene prod-

how does histone acetylation in a promoter actually contribute to transcriptional activation? A number of studies have suggested that HAT complexes can be directly targeted by site-specific activators (Ikeda et al., 1999; Utley et al., 1998; Wallberg et al., 1999). While this mode of recruitment is not surprising, the proposed functions of acetylation itself are more controversial. While it is clear that hyperacetylation can have dramatic effects on higher-order chromatin structure in vitro and in vivo (for review see Hansen 1997), it seems likely that in some cases site-specific acetylation events might control the binding of non-histone proteins to the chromatin fiber, such as site-specific activators or repressors.

Both the recruitment of an acetyltransferase and the function of acetylation have begun to be addressed in vivo at the complex yeast *HO* gene, whose expression requires two site-specific activators (SWI5 and SWI4/6), a GCN5-containing HAT complex (SAGA), and the SWI/SNF complex. SAGA recruitment to *HO* requires the SWI5 activator as well as the remodeling activity of SWI/SNF. An intact SAGA complex is required for binding of the SWI4/6 activator (Cosma et al., 1999), and nucleosomes in the *HO* promoter are specifically acetylated across the 1-kb region containing the ten SWI4/6 binding sites (Krebs et al., 1999). Acetylation by SAGA could serve several functions. It might serve the more traditionally imagined function of stabilizing an unfolded nucleosomal array that was established by SWI/SNF. Alternatively, it could directly contribute to the binding or activation of SBF.

## III. HATS AND ATP-DEPENDENT REMODELERS: WORKING TOGETHER AND APART

While many studies address the effects of either histone acetyltransferases or ATP-dependent remodelers, there is considerable evidence that in many cases these different complexes work together. This connection is most clear in yeast. Three genes from the original screen that yielded *SWI1*, *SWI2*, and *SWI3* turn out to be components of HATs: GCN5, *ADA2* and *ADA3* (*SWI9*, *SWI8*, and *SWI7*, respectively) (Pollard and Peterson, 1997). Double mutants between SWI/SNF and SAGA components are inviable, and the genes that are known to require the SWI/SNF complex for their expression also require a GCN5-dependent HAT complex. As described above, GCN5-dependent acetylation of the HO upstream regulatory region requires prior chromatin remodeling by the SWI/SNF complex (Krebs et al., 1999). It is not known if this interrelationship is maintained at all genes that require both SWI/SNF and SAGA for their expression. However, GCN5 activity seems to contribute to global, genome-wide acetylation of histone H3 during S phase, and these acetylation events do not require SWI/SNF (Krebs et al., 1999). Likewise, the *PHO5* gene, whose expression does not require SWI/SNF, does require GCN5's HAT activity, at least in a *pho80*-background (Gregory et al., 1998). Intriguingly, recent studies suggest that SWI/SNF remodeling may only be a prerequisite for recruitment of GCN5 activity when acetylation events must occur during late mitosis when chromatin is maximally compacted (Krebs and Peterson, unpublished results).

A connection between ATP-dependent remodeling and histone acetyltransferases is not specific to yeast, but occurs in mammalian cells as well. Nuclear hormone receptors, such as the glucocorticoid receptor, interact both with human SWI/SNF complex and several histone acetyltransferases, such as CBP/p300 and SRC1. As described in an earlier section, the transcription factor EKLF, which requires the activity of a human SWI/SNF to induce a DNase I hypersensitive site at the β-globin locus (Armstrong et al., 1998; Bagga et al., 1998), also interacts with three HATs in vivo: CBP, p300, and P/CAF. Surprisingly, CBP/p300 can acetylate EKLF itself in vitro, and this acetylation increases EKLF's ability to activate β-globin in vivo (Zhang and Bieker, 1998). It has not been tested whether EKLF's interaction with HATs leads to increased histone acetylation in the β-globin promoter as well.

Recent studies have revealed that not only do ATP-dependent remodelers cooperate with HATs, they may also act in concert with histone deacetylases (HDACs) (Tong et al., 1998; Wade et al., 1998; Xue et al., 1998; Zhang et al., 1998). It appears that in the case of one complex, NURD,

Kwon H, Imbalzano AN, Khavari PA, Kingston RE, Green MR (1994): Nucleosome disruption and enhancement of activator binding by a human SWI/SNF complex. Nature 370:477–480.

Lacy E, Axel R (1975): Analysis of DNA of isolated chromatin subunits. Proc Natl Acad Sci USA 72:3978–3982

Larsen A, Weintraub H (1982): An altered DNA conformation detected by S1 nuclease occurs at specific regions in active chick globin chromatin. Cell 29:609–622

Laurent BC, Treitel MA, Carlson M (1991): Functional interdependence of the yeast SNF2, SNF5, and SNF6 proteins in transcriptional activation. Proc Natl Acad Sci USA 88:2687–2691

Lee CH, Murphy MR, Lee JS, Chung JH (1999): Targeting a SWI/SNF-related chromatin remodeling complex to the beta-globin promoter in erythroid cells [in process citation] Proc Natl Acad Sci USA 96:12311–12315

Lee MS, Garrard WT (1991): Transcription-induced nucleosome 'splitting': an underlying structure for DNase I sensitive chromatin. EMBO J 10:607–615

Li Y, Strahler JR, Dodgson JB (1997): Neither HMG-14a nor HMG-17 gene function is required for growth of chicken DT40 cells or maintenance of DNaseI-hypersensitive sites. Nucl Acids Res 25:283–288

Lohr D (1984): Organization of the GAL1-GAL10 intergenic control region chromatin. Nucl Acids Res 12:8457–8474

Lohr D, Hopper JE (1985): The relationship of regulatory proteins and DNase I hypersensitive sites in the yeast GAL1-10 genes. Nucl Acids Res 13:8409–8423

Luger K, Mader AW, Richmond RK, Sargent DF, Richmond TJ (1997): Crystal structure of the nucleosome core particle at 2.8 A resolution [see comments]. Nature 389:251–260

Mizzen CA, Yang XJ, Kokubo T, Brownell JE, Bannister AJ, Owen-Hughes T, Workman J, Wang L, Berger SL, Kouzarides T, Nakatani Y, Allis CD (1996): The TAF(II)250 subunit of TFIID has histone acetyltransferase activity. Cell 87:1261–1270.

Muller S, Isabey A, Couppez M, Plaue S, Sommermeyer G, Van Regenmortel MH (1987): Specificity of antibodies raised against triacetylated histone H4. Mol Immunol 24:779–789

Neigeborn L, Carlson M (1984): Genes affecting the regulation of SUC2 gene expression by glucose repression in *Saccharomyces* cerevisiae. Genetics 108:845–858.

Neigeborn L, Rubin K, Carlson M (1986): Suppressors of SNF2 mutations restore invertase derepression and cause temperature-sensitive lethality in yeast. Genetics 112:741–753.

Ness PJ, Parish RW, Koller T (1986): Mapping of endogenous nuclease-sensitive regions and of putative topoisomerase sites of action along the chromatin of *Dictyostelium* ribosomal RNA genes. J Mol Biol 188:287–300

Ogryzko VV, Schlitz RL, Russanova V, Howard BH, Nakatani Y (1996): The transcriptional coactivators p300 and CBP are histone acetyltransferases. Cell 87:953–959.

Orkin SH (1995): Regulation of globin gene expression in erythroid cells. Eur J Biochem 231:271–281

Owen-Hughes T, Utley RT, Cote J, Peterson CL, Workman JL (1996): Persistent site-specific remodeling of a nucleosome array by transient action of the SWI/SNF complex. Science 273:513–516.

Papoulas O, Beek SJ, Moseley SL, McCallum CM, Sarte M, Shearn A, Tamkun JW (1998): The *Drosophila* trithorax group proteins BRM, ASH1, and ASH2 are subunits of distinct protein complexes. Development 125:3955–3966.

Paulson JR, Laemmli UK (1977): The structure of histone-depleted metaphase chromosomes. Cell 12:817–828.

Perez-Ortin JE, Estruch F, Matallana E, Franco L (1986): DNase I sensitivity of the chromatin of the yeast SUC2 gene for invertase. Mol Gen Genet 205:422–427

Peterson CL (1998): SWI/SNF complex: dissection of a chromatin remodeling cycle. Cold Spring Harb Symp Quant Biol 63:545–552.

Peterson CL, Dingwall A, Scott MP (1994): Five SWI/SNF gene products are components of a large multisubunit complex required for transcription enhancement. Proc. Natl. Acad. Sci. USA 91:2905–2908.

Pfeffer U, Ferrari N, Vidali G (1986): Availability of hyperacetylated H4 histone in intact nucleosomes to specific antibodies. J Biol Chem 261:2496–2498

Pogo BG, Allfrey VG, Mirsky AE (1966): RNA synthesis and histone acetylation during the course of gene activation in lymphocytes. Proc Natl Acad Sci USA 55:805–812.

Pollard KJ, Peterson CL (1997): Role for ADA/GCN5 products in antagonizing chromatin-mediated transcriptional repression. Mol Cell Biol 17:6212–6222

Proffitt JH (1985): DNase I-hypersensitive sites in the galactose gene cluster of *Saccharomyces* cerevisiae. Mol Cell Biol 5:1522–1524

Quinn J, Fyrberg AM, Ganster RW, Schmidt MC, Peterson CL (1996): DNA-binding properties of the yeast SWI/SNF complex. Nature 379:844–847

Rowe TC, Wang JC, Liu LF (1986): In vivo localization of DNA topoisomerase II cleavage sites on *Drosophila* heat shock chromatin. Mol Cell Biol 6:985–992

Ryoji M, Worcel A (1985): Structure of the two distinct types of minichromosomes that are assembled on DNA injected in *Xenopus* oocytes. Cell 40:923–932.

Saleh A, Lang V, Cook R, Brandl CJ (1997): Identification of native complexes containing the yeast coactivator/repressor proteins NGG1/ADA3 and ADA2. J Biol Chem 272:5571–5578

Sealy L, Chalkley R (1978) DNA associated with hyperacetylated histone is preferentially digested by DNase I. Nucl Acids Res 5:1863–18676.

Siddique H, Zou JP, Rao VN, Reddy ES (1998): The BRCA2 is a histone acetyltransferase. Oncogene 16:2283–2285

Sledziewski A, Young ET (1982): Chromatin conformational changes accompany transcriptional activation of a glucose-repressed gene in *Saccharomyces* cerevisiae. Proc Natl Acad Sci USA 79:253–256.

ucts isolated from yeast. Proc Natl Acad Sci USA 91:1950–1954.

Cairns BR, Lorch Y, Li Y, Zhang M, Lacomis L, Erdjument-Bromage H, Tempst P, Du J, Laurent B, Kornberg RD (1996): RSC, an essential, abundant chromatin-remodeling complex. Cell 87:1249–1260.

Candau R, Moore PA, Wang L, Barlev N, Ying CY, Rosen CA, Berger SL (1996): Identification of human proteins functionally conserved with the yeast putative adaptors ADA2 and GCN5. Mol Cell Biol 16:593–602.

Carmen AA, Rundlett SE, Grunstein M (1996): HDA1 and HDA3 are components of a yeast histone deacetylase (HDA) complex. J Biol Chem 271:15837–15844.

Chen H, Lin RJ, Schlitz RL, Chakravarti D, Nash A, Nagy L, Privalsky ML, Nakatani Y, Evans RM (1997): Nuclear receptor coactivator ACTR is a novel histone acetyltransferase and forms a multimeric activation complex with P/CAF and CBP/p300. Cell 90:569–580.

Cosma MP, Tanaka T, Nasmyth K (1999): Ordered recruitment of transcription and chromatin remodeling factors to a cell cycle and developmentally regulated promoter. Cell 97:299–311.

Cote J, Quinn J, Workman JL, Peterson CL (1994): Stimulation of GAL4 derivative binding to nucleosomal DNA by the yeast SWI/SNF complex. Science 265:53–60.

Eberharter A, John S, Grant PA, Utley RT, Workman JL (1998): Identification and analysis of yeast nucleosomal histone acetyltransferase complexes. Methods 15:315–321.

Feinstein DL, Moudrianakis EN (1986): Thiol reactivity of histone H3 in soluble and DNA-associated histone complexes: evidence for allosteric and torsional regulation. Biochemistry 25:8409–8418.

Finch JT, Lutter LC, Rhodes D, Brown RS, Rushton B, Levitt M, Klug A (1977): Structure of nucleosome core particles of chromatin. Nature 269:29–36.

Georgakopoulos T, Thireos G (1992): Two distinct yeast transcriptional activators require the function of the GCN5 protein to promote normal levels of transcription. EMBO J 11:4145–4152.

Gonzalez PJ, Palacian E (1989): Interaction of RNA polymerase II with structurally altered nucleosomal particles. Transcription is facilitated by loss of one H2A H2B dimer. J Biol Chem 264:18457–18462.

Gorovsky MA, Pleger GL, Keevert JB, Johmann CA (1973): Studies on histone fraction F2A1 in macro- and micronuclei of *Tetrahymena pyriformis*. J Cell Biol 57:773–781.

Grant PA, Duggan L, Cote J, Roberts SM, Brownell JE, Candau R, Ohba R, Owen-Hughes T, Allis CD, Winston F, Berger SL, Workman JL (1997): Yeast Gcn5 functions in two multisubunit complexes to acetylate nucleosomal histones: characterization of an Ada complex and the SAGA (Spt/Ada) complex. Genes Dev 11:1640–1650.

Gregory PD, Schmid A, Zavari M, Lui L, Berger SL, Horz W (1998): Absence of Gcn5 HAT activity defines a novel state in the opening of chromatin at the PHO5 promoter in yeast. Mol Cell 1:495–505.

Gregory PD, Schmid A, Zavari M, M, M n. t, and W H r (1999): Chromatin remodeling at the PHO8 promoter requires SWI-SNF and SAGA at a step subsequent to activator binding. EMBO J 18:6407–6414.

Groudine M, Kohwi-Shigematsu T, Gelinas R, Stamatoyannopoulos G, Papayannopoulou T (1983): Human fetal to adult hemoglobin switching: changes in chromatin structure of the beta-globin gene locus. Proc Natl Acad Sci USA 80:7551–7555.

Groudine M, Weintraub H (1981): Activation of globin genes during chicken development. Cell 24:393–401.

Groudine M, Weintraub H (1982): Propagation of globin DNAase I-hypersensitive sites in absence of factors required for induction: a possible mechanism for determination. Cell 30:131–139.

Hebbes TR, Clayton AL, Thorne AW, Crane-Robinson C (1994): Core histone hyperacetylation co-maps with generalized DNase I sensitivity in the chicken beta-globin chromosomal domain. EMBO J 13:1823–1830.

Hebbes TR, Thorne AW, Crane-Robinson C (1988): A direct link between core histone acetylation and transcriptionally active chromatin. EMBO J 7:1395–1402.

Ikeda K, Steger DJ, Eberharter A, Workman JL (1999): Activation domain-specific and general transcription stimulation by native histone acetyltransferase complexes. Mol Cell Biol 19:855–863.

Ito T, Levenstein ME, Fyodorov DV, Kutach AK, Kobayashi R, Kadonaga JT (1999): ACF consists of two subunits, Acf1 and ISWI, that function cooperatively in the ATP-dependent catalysis of chromatin assembly. Genes Dev 13:1529–1539.

Jeppesen P, Turner BM (1993): The inactive X chromosome in female mammals is distinguished by a lack of histone H4 acetylation, a cytogenetic marker for gene expression. Cell 74:281–289.

Kingston RE, Narlikar GJ (1999): ATP-dependent remodeling and acetylation as regulators of chromatin fluidity [In Process Citation]. Genes Dev 13:2339–2352.

Kmiec EB, Ryoji M, Worcel A (1986): Gyration is required for 5S RNA transcription from a chromatin template. Proc Natl Acad Sci USA 83:1305–1309.

Kmiec EB, Worcel A (1985): The positive transcription factor of the 5S RNA gene induces a 5S DNA-specific gyration in *Xenopus* oocyte extracts. Cell 41:945–953.

Kohwi-Shigematsu T, Gelinas R, Weintraub H (1983): Detection of an altered DNA conformation at specific sites in chromatin and supercoiled DNA. Proc Natl Acad Sci USA 80:4389–4393.

Kornberg RD (1974): Chromatin structure: a repeating unit of histones and DNA. Science 184:868–871.

Krebs JE, Kuo MH, Allis CD, Peterson CL (1999): Cell cycle-regulated histone acetylation required for expression of the yeast *HO* gene. Genes Dev 13:1412–1421.

Kuo MH, Zhou J, Jambeck P, Churchill ME, Allis CD (1998): Histone acetyltransferase activity of yeast Gcn5p is required for the activation of target genes in vivo. Genes Dev 12:627–639.

Wu C, Gilbert W (1981): Tissue-specific exposure of chromatin structure at the 5′ terminus of the rat preproinsulin II gene. Proc Natl Acad Sci USA 78:1577–1580

Xue Y, Wong J, Moreno GT, Young MK, Cote J, Wang W (1998): NURD, a novel complex with both ATP-dependent chromatin-remodeling and histone deacetylase activities. Mol Cell 2:851–861

Zhang W, Bieker JJ (1998): Acetylation and modulation of erythroid Kruppel-like factor (EKLF) activity by interaction with histone acetyltransferases. Proc Natl Acad Sci USA 95:9855–9860

Zhang Y, LeRoy G, Seelig HP, Lane WS, Reinberg D (1998): The dermatomyositis-specific autoantigen Mi2 is a component of a complex containing histone deacetylase and nucleosome remodeling activities. Cell 95:279–289

Smith ER, Belote JM, Schiltz RL, Yang XJ, Moore PA, Berger SL, Nakatani Y, Allis CD (1998): Cloning of *Drosophila* GCN5: conserved features among metazoan GCN5 family members Nucl Acids Res 26:2948–2954.

Spencer TE, Jenster G, Burcin MM, Allis CD, Zhou J, Mizzen CA, McKenna NJ, Onate SA, Tsai SY, Tsai M-J, O'Malley BW (1997): Steroid receptor coactivator-1 is a histone acetyltransferase Nature 389:194-198

Stalder J, Larsen A, Engel JD, Dolan M, Groudine M, Weintraub H (1980): Tissue-specific DNA cleavages in the globin chromatin domain introduced by DNAase I Cell 20:451–460

Stern M, Jensen RE, Herskowitz I (1984): Five SWI genes are required for the expression of the HO gene in yeast J Mol Biol 178:853–868.

Sternberg PW, Stern MJ, Clark I, Herskowitz I (1987): Activation of the yeast *HO* gene by release from multiple negative controls Cell 48:567–577

Szent-Gyorgyi C, Finkelstein DB, Garrard WT (1987): Sharp boundaries demarcate the chromatin structure of a yeast heat-shock gene. J Mol Biol 193:71–80

Tamkun JW, Deuring R, Scott MP, Kissinger M, Pattatucci AM, Kaufman TC, Kennison JA (1992): Brahma: a regulator of *Drosophila* homeotic genes structurally related to the yeast transcriptional activator SNF2/SWI2 Cell 68:561–572

Taunton J, Hassig CA, Schreiber SL (1996): A mammalian histone deacetylase related to the yeast transcriptional regulator Rpd3p Science 272:408–411

To RQ, Kmiec EB (1990): Assembly of transcriptionally active chromatin in vitro: a possible role for topoisomerase II. Cell Growth Differ 1:39–45.

Tong JK, Hassig CA, Schnitzler GR, Kingston RE, Schreiber SL (1998): Chromatin deacetylation by an ATP-dependent nucleosome remodelling complex Nature 395:917–921.

Tsukiyama T, Becker PB, Wu C (1994): ATP-dependent nucleosome disruption at a heat-shock promoter mediated by binding of GAGA transcription factor [see comments] Nature 367:525–532.

Tsukiyama T, Wu C (1995): Purification and properties of an ATP-dependent nucleosome remodeling factor. Cell 83:1011–1020.

Turner BM, Birley AJ, Lavender J (1992): Histone H4 isoforms acetylated at specific lysine residues define individual chromosomes and chromatin domains in *Drosophila* polytene nuclei. Cell 69:375–384

Turner BM, Franchi L, Wallace H (1990): Islands of acetylated histone H4 in polytene chromosomes and their relationship to chromatin packaging and transcriptional activity J Cell Sci 96:335–346.

Utley RT, Ikeda K, Grant PA, Cote J, Steger DJ, Eberharter A, John S, Workman JL (1998): Transcriptional activators direct histone acetyltransferase complexes to nucleosomes. Nature 394:498–502.

Varga-Weisz PD, Wilm M, Bonte E, Dumas K, Mann M, Becker PB (1997): Chromatin-remodeling factor CHRAC contains the ATPases ISWI and topoisomerase II [published erratum appears in Nature 1997 Oct 30; 389(6654):1003]. Nature 388:598–602.

Vidali G, Boffa LC, Bradbury EM, Allfrey VG (1978): Butyrate suppression of histone deacetylation leads to accumulation of multiacetylated forms of histones H3 and H4 and increased DNase I sensitivity of the associated DNA sequences Proc Natl Acad Sci USA 75:2239–2243

Villeponteau B, Lundell M, Martinson H (1984): Torsional stress promotes the DNAase I sensitivity of active genes Cell 39:469–478.

Wade PA, Jones PL, Vermaak D, Veenstra GJ, Imhof A, Sera T, Ise C, Ge H, Shi YB, Hansen JC, Wolffe AP (1998): Histone deacetylase directs the dominant silencing of transcription in chromatin: association with MeCP2 and the Mi-2 chromodomain SWI/SNF ATPase. Cold Spring Harb Symp Quant Biol 63:435–445.

Wallberg AE, Neely KE, Gustafsson JA, Workman JL, Wright AP, Grant PA (1999): Histone acetyltransferase complexes can mediate transcriptional activation by the major glucocorticoid receptor activation domain [in process citation]. Mol Cell Biol 19:5952–5959

Wang JC (1996): DNA topoisomerases Annu Rev Biochem 65:635–692

Wang L, Liu L, Berger SL (1998): Critical residues for histone acetylation by Gcn5, functioning in Ada and SAGA complexes, are also required for transcriptional function in vivo. Genes Dev 12:640–653

Warburton PE, Earnshaw WC (1997): Untangling the role of DNA topoisomerase II in mitotic chromosome structure and function Bioessays 19:97–99.

Weintraub H (1983): A dominant role for DNA secondary structure in forming hypersensitive structures in chromatin. Cell 32:1191–1203

Weintraub H (1983): Tissue-specific gene expression and chromatin structure. Harvey Lect 79:217–244

Weintraub H, Groudine M (1976): Chromosomal subunits in active genes have an altered conformation Science 193:848–856.

Weintraub H, Larsen A, Groudine M (1981): Alpha-globin-gene switching during the development of chicken embryos: expression and chromosome structure Cell 24:333–344

Weisbrod S, Groudine M, Weintraub H (1980): Interaction of HMG 14 and 17 with actively transcribed genes. Cell 19:289–301.

Weisbrod S, Weintraub H (1979): Isolation of a subclass of nuclear proteins responsible for conferring a DNase I-sensitive structure on globin chromatin Proc Natl Acad Sci USA 76:630–634.

Weisbrod S, Weintraub H (1981): Isolation of actively transcribed nucleosomes using immobilized HMG 14 and 17 and an analysis of alpha-globin chromatin. Cell 23:391–400

Wu C (1980): The 5′ ends of *Drosophila* heat shock genes in chromatin are hypersensitive to DNase I Nature 286:854–860.