Emerging roles for chromatin remodeling in cancer biology

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Cell proliferation and differentiation are guided by changes in gene expression and require the coordinated efforts of the transcription machinery and chromatin-remodeling factors. However, aberrant regulation of chromatin structure can arise through mutations in chromatin-modifying and -remodeling proteins and can lead to improper gene expression and cancer. This review discusses how mutations in chromatin regulators might affect their targeting or activity, with an emphasis on the important insights revealed by leukemogenic fusion proteins. Understanding the normal and oncogenic role of these factors will be crucial for the design of therapeutic agents.

A TRENDS Guide to Cancer Biology

Chromatin is an important and dynamic regulator of transcription. Genes that are packaged into protein or DNA structures that silence transcription can be remodeled to those that enable transcription in response to cellular signals[1]. Misregulation of chromatin structure can cause incorrect gene activation or improper gene silencing. Recent experiments strongly suggest that certain oncogenic transcription factors, including the leukemogenic fusion proteins MLL–CBP, PML–RAR, PLZF–RAR and MOZ–TIF2, promote oncogenesis by misregulating chromatin structure. In addition, tumor suppressors such as Rb, p53 and Ini1/hSNF5 utilize chromatin remodeling as part of their normal function, and these functions are misregulated in certain cancers. Furthermore, changes in DNA methylation are an almost constant feature of tumors, and methylated DNA is now known to recruit chromatin-modifying complexes that silence transcription. This review looks at key experiments that have connected chromatin misregulation to cancer and addresses some of the major challenges that lie ahead.

Nucleosomes, the basic repeating unit of chromatin structure, comprise an octamer of histone proteins and 147 base pairs of DNA. Nucleosomes repress transcription by blocking the binding of transcription factors and basal transcription machinery to promoter regulatory sequences; thus nucleosome repositioning is required for activation. Repression by nucleosomes is potentiated by the acetylation state of lysine residues in the flexible N-terminal histone 'tails', which extend from the nucleosome particle (Fig. 1). In general, tail hypoacetylation is correlated with transcriptional repression, whereas hyperacetylation is correlated with activation[2]. Acetylation and deacetylation might be similar in concept to phosphorylation and dephosphorylation – a reversible modification that can affect protein–protein interactions. In this regard, histone tails are now believed to function as dynamic platforms for the assembly of transcriptional regulatory factors. In their deacetylated state, tails bind to repressor proteins (such as SSN6/TUP1) that stabilize nucleosomes and promote higher-order structures. By contrast, acetylated tails bind to bromodomains, a motif found on certain factors that promote chromatin remodeling and transcriptional activation[3]. Therefore, altering the acetylation state of a promoter can trigger an important switch in expression. Although changes in acetylation state do not significantly alter the repositioning of nucleosomes, acetylation might promote the recruitment of nucleosome-repositioning factors. Taken together, chromatin structural changes involve both the covalent modification, and repositioning, of nucleosomes (Fig. 1), and both are sources for misregulation.

Factors that mediate chromatin transitions include: (i) histone acetyltransferases (HATs); (ii) histone deacetylases (HDACS); and (iii) adenosine triphosphate (ATP)-dependent nucleosome-remodeling and -repositioning factors ('remodelers')[4]. Interestingly, these three types of factor function as complexes, and each bears one (or two) enzymatic functions and between two and 25 additional

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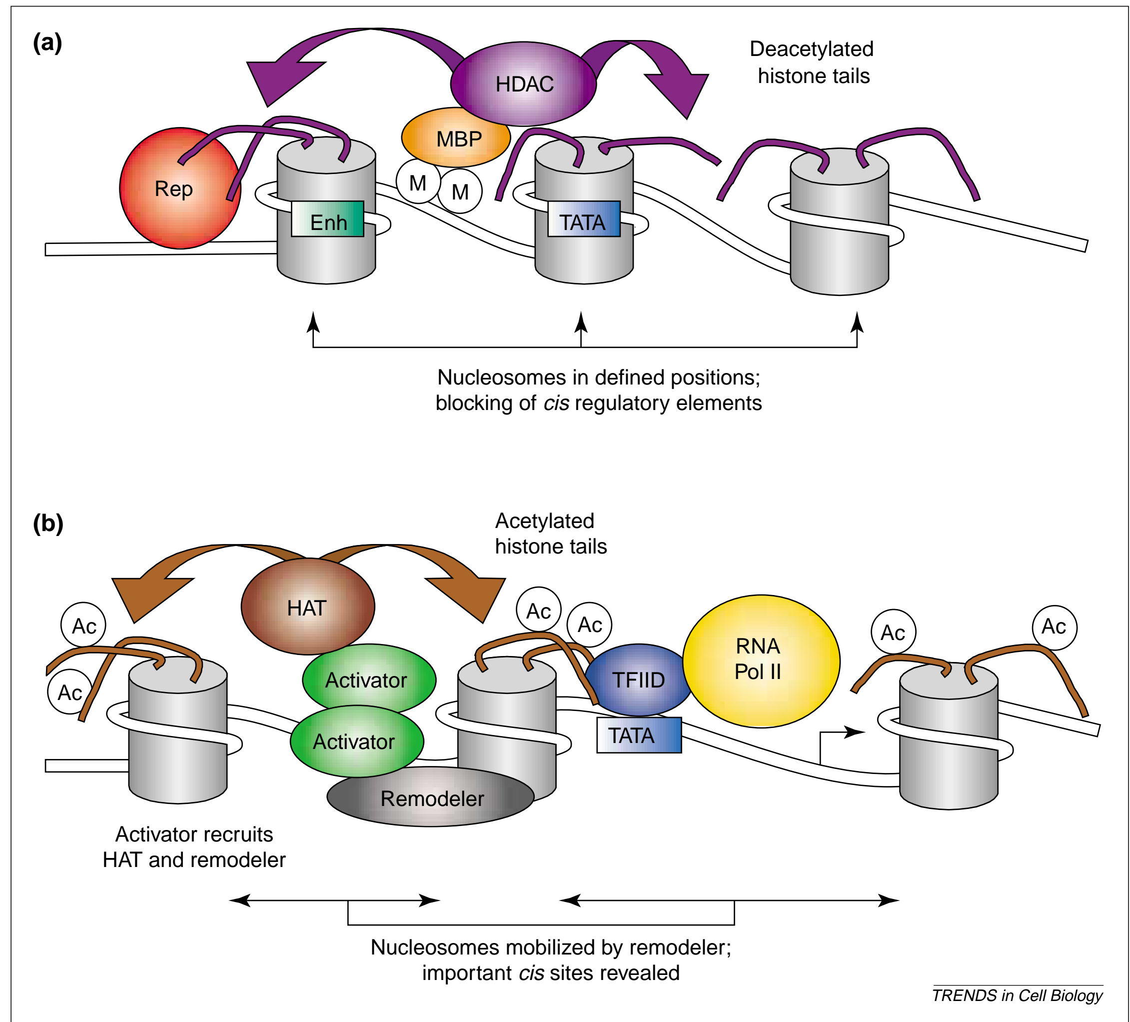

Figure 1. Features of repressed and active chromatin

(a) Repressed chromatin is characterized by stably positioned nucleosomes, deacetylated histone tails and, sometimes, DNA methylation. Histone deacetylase complexes (HDAC) are recruited either by site-specific repressors or by methyl-binding proteins (MBP), which bind to methylated CpG (M). Certain repressor proteins (Rep) bind to tails in their deacetylated state and stabilize nucleosome positioning. Certain remodelers (not shown) might contribute to establishing the positions of nucleosomes over important *cis* elements, such as enhancers (Enh) or the TATA box. **(b)** Active chromatin is characterized by mobile nucleosomes and acetylated (Ac) histone tails. Activators (green) recruit histone acetyltransferase (HAT) complexes and remodelers, which modify and reposition nucleosomes, enabling the binding of activators to enhancers and of general transcription factors such as TFIID and RNA polymerase II (RNA Pol II) to the promoter.

proteins. These proteins regulate the activity of the enzyme, or help link the complex to gene-specific transcriptional regulators that target the complex to particular genes. As will be discussed below, alteration in either the recruitment or the function of any of these three factors can lead to misregulation of transcription, and improper growth decisions can result from defects in either activation or repression of key regulatory genes. Different modes by which chromatin misregulation can lead to cancer are discussed below. This article is not intended to provide a comprehensive review of all possible connections of chromatin to cancer but instead focuses on several key studies that have established important concepts for such connections.

Misregulation of HAT complexes

MLL–CBP fusions

Much of the evidence connecting HAT misregulation to cancer has been revealed through the study of oncogenic fusion proteins. Chromosomal translocations are often associated with acute leukemias, and a significant number of translocations involve genes encoding HATs[5]. One example is MLL–CBP, which causes acute leukemias in humans and involves the fusion of two well-studied factors, human mixed lineage leukemia/trithorax protein (MLL; also known as ALL or HRX) and the CREB-binding protein (CBP).

MLL is a DNA-binding transcriptional regulator that interacts functionally with chromatin-regulating complexes, and is important for maintaining the expression of HOX

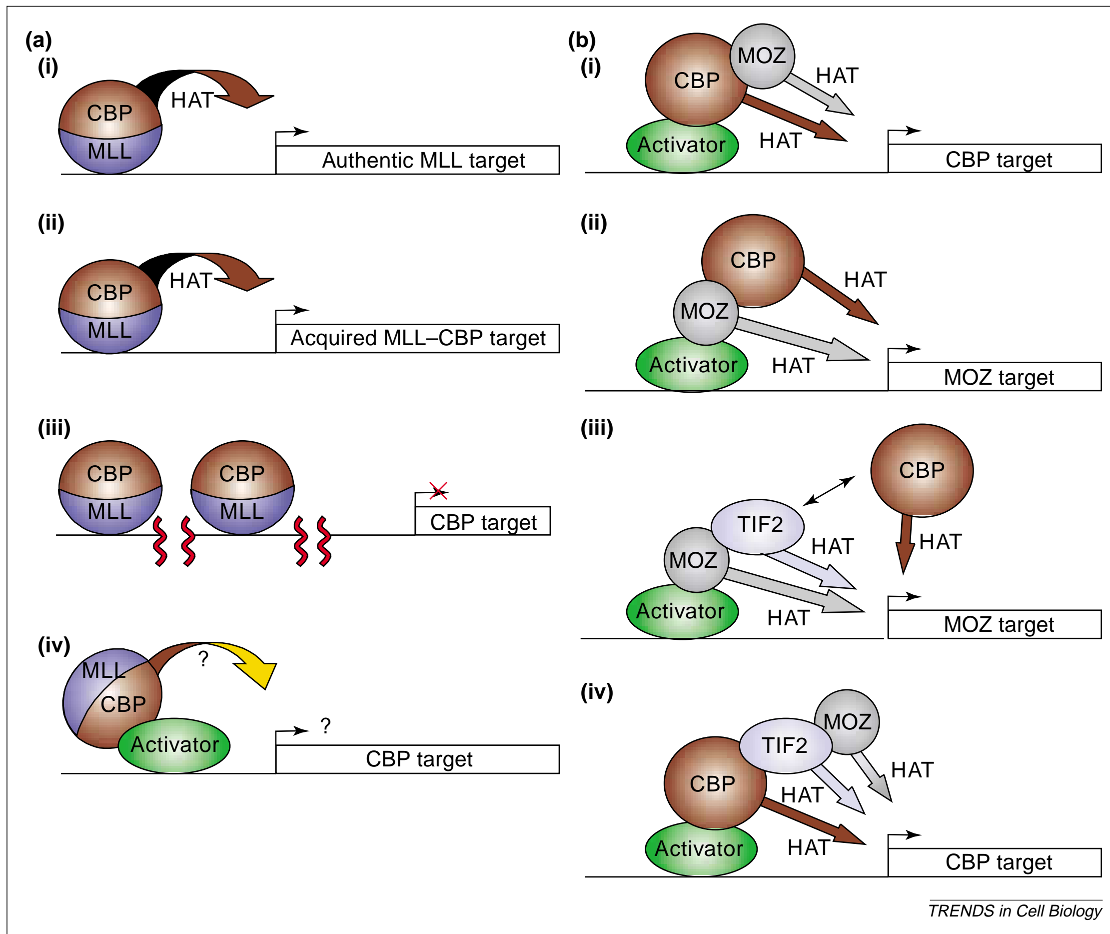

Figure 2. Misregulation of HAT activity

(a) How fusions between human mixed lineage leukemia/trithorax protein (MLL) and CREB-binding protein (CBP) might alter histone acetyltransferase (HAT) activity and transcription. The diagrams show the MLL–CBP fusion operating in different contexts: (i) CBP alters acetylation at MLL targets and activates transcription; (ii) an MLL–CBP fusion finds novel targets, CBP alters acetylation and activates their transcription; (iii) MLL moiety sequesters CBP away from normal CBP targets, causing reduced transcription; (iv) MLL moiety alters CBP acetylation activity at CBP targets, with uncertain consequences. The wavy red lines in (iii) separate distant loci. **(b)** How fusions between monocytic leukemia zinc finger (MOZ) and CBP and between MOZ and transcriptional intermediary factor 2 (TIF2) might alter HAT activity and transcription. The diagrams show MOZ–CBP and MOZ–TIF2 fusions operating in different contexts: (i) MOZ augments HAT activity at CBP-target promoters and activates transcription; (ii) CBP augments HAT activity at MOZ-target promoters and activates transcription; (iii) TIF2 augments HAT activity at MOZ-target promoters and might also recruit CBP HAT activity to activate transcription; (iv) TIF2 and MOZ augment CBP HAT activity at CBP-target promoters and activate transcription. Other variations on these models are possible, such as misregulation of normal TIF2 targets or improper localization of these activities in the cell.

genes, which play central roles in both development and hematopoiesis[6]. MLL can be fused to many translocation partners, including CBP and the closely related p300 protein, as well as AF4, and the related proteins AF9 and ENL[5]. CBP is a large protein that contains a HAT domain, a bromodomain, and several other domains that bind a wide variety of gene-specific activators[7]. CBP also binds several coactivator proteins, many of which are themselves HATs. All MLL–CBP fusions retain the N-terminal DNA-binding domain of MLL and nearly the entire length CBP, including its HAT and bromodomain[5]. Although the DNA-binding domain of MLL is not highly sequence specific, its DNA-binding properties are required for promoting transformation, suggesting that it might recognize aspects of chromatin structure in addition to DNA sequence. CBP-HAT activity is important for transcriptional activation, and the presence of the HAT domain in all oncogenic MLL–CBP fusions strongly suggests that HAT activity is required for oncogenesis, but this remains to be determined experimentally.

One attractive model for transcriptional misregulation by MLL–CBP involves the recruitment of CBP to MLL target sites, resulting in their acetylation and activation (Fig. 2a). As the targets of MLL include HOX genes, their misregulation might underlie leukemogenesis, owing to their role in hematopoesis[6]. However, as only a portion of MLL is present, the fusion protein might also be directed to targets not normally bound by MLL. By either model, the fusion represents a dominant, gain-of-function mutation, in which a central player in transcription has been hijacked (note that the patient still retains one wild-type allele of MLL and CBP). Other models are also consistent with a dominant phenotype. For example, fusion to MLL might alter the acetylation activity of CBP or alter interactions of CBP with other proteins, resulting in misregulation of transcription at CBP targets rather than MLL targets. Another possibility is that the MLL–CBP translocation confers CBP haploinsufficiency, leaving cells with only one normal CBP allele; with MLL–CBP sequestered at MLL-binding sites, there might not be enough CBP for all the important targets.

Recent work suggests that CBP might be an authentic regulator of MLL targets (such as HOX genes) and interact in a regulated fashion with a C-terminal activation domain in full-length MLL[8]. However, this domain is not present in MLL–CBP or in other common MLL fusions. Therefore, the ability to regulate the interaction between CBP and MLL is lost in the MLL–CBP fusion, possibly causing constitutive acetylation of MLL targets.

MOZ, MORF and TIF2 fusions

Another route to transcriptional misregulation involves the fusion of two HAT proteins. CBP is again provided as an example, as it is involved in leukemogenic fusions with the highly related HAT proteins, monocytic leukemia zinc finger (MOZ) and MOZ-related factor (MORF)[9,10]. Importantly, these fusions retain the HAT domains of both proteins, and MOZ and MORF also donate a C_2HC zinc-finger domain. Little is known about the normal or leukemogenic roles of these proteins, although both are highly similar to HATs in both yeast and flies that have known roles in transcriptional regulation[11].

One clear model for misregulation by MOZ–CBP and MORF–CBP is altered (presumably increased) acetylation at CBP targets (Fig. 2b). Alternatively, CBP might also be recruited to as-yet-undefined MOZ or MORF targets. Additional support for a link between CBP target misregulation and MOZ were revealed when leukemogenic translocations were discovered between MOZ and transcriptional intermediary factor 2 (TIF2)[11]. TIF2 has intrinsic HAT activity, and also helps to physically link CBP to nuclear hormone receptors[12]. The resulting MOZ–TIF2 fusions retain the HAT domains of both proteins as well as the C_2HC zinc finger of MOZ and the CBP-interaction domain of TIF2. Two models could explain MOZ–TIF2 oncogenicity; TIF2 might serve to bridge MOZ to CBP (thus again bringing MOZ to CBP targets), or the HAT activity of TIF2 itself might serve to misregulate CBP targets (Fig. 2). Interestingly, the conserved C_2HC zinc finger has recently been shown to recognize the globular region of histones, suggesting that the C_2HC domain and the HAT domain function as a nucleosome-recognition and -modification module[13]. As this module is retained in the leukemogenic fusion proteins, it might play a central role in transcriptional misregulation.

Taken together, misregulation of HAT targeting and activity are emerging as important routes to cancer. HAT proteins are quite diverse and show considerable differences in function and substrate specificity – promising properties for the design of inhibitors specific for individual HATs.

Misregulation of HDAC complexes

RAR fusions and RXR mutations

Studies on RAR have revealed compelling connections between chromatin and cancer. RAR is a transcriptional regulator important for cell differentiation in response to retinoids, and myeloid differentiation in particular[14]. RAR has a heterodimerization partner, termed RXR, and together they regulate both the repression and activation of genes bearing the target sequence, the retinoic acid response element (RARE). In the absence of ligand, the RAR–RXR complex is constitutively bound to RARE sequences, and (via bridging proteins) to the SIN3–HDAC repression complex[15–17].

SIN3–HDAC is a ubiquitous and abundant complex that contains two HDAC proteins (HDAC1 and HDAC2), the scaffolding protein SIN3, and at least eight other proteins with presumed roles in complex targeting and regulation[18]. The SIN3–HDAC complex is conserved from yeast to man and is a necessary cofactor for many site-specific transcriptional repressors. One of the clearest connections of chromatin to cancer, which has been reviewed in detail elsewhere[19], was the discovery that repression by the retinoblastoma tumor suppressor protein (Rb) is mediated by the SIN3–HDAC complex. Briefly, many genes that promote the G1–S transition of the cell cycle contain binding sites for the E2F family of transcription factors. E2F proteins repress these genes by recruiting a complex consisting of Rb, SIN3–HDAC and SWI–SNF complex (an ATP-dependent nucleosome remodeler, discussed later). Many experiments have shown that the HDAC activity of this complex helps repress E2F-dependent genes, providing an important role for chromatin in regulating cell-cycle progression[19].

For RAR–RXR, interaction with SIN3–HDAC requires the bridging protein 'nuclear receptor co-repressor' (N-CoR) or its homolog 'silencing mediator for retinoid and thyroid receptors' (SMRT), which are released from RAR along with SIN3–HDAC upon the binding of ligand[15–17] (Fig. 3). RXR and RAR bind to separate sites on N-CoR–SMRT; however the interaction with RAR might be stronger. Release of N-CoR–SIN3–HDAC from RAR enables the subsequent binding of a TIF2–CBP HAT complex to a domain on RAR that is masked in the absence of ligand. Thus, activation involves the ligand-dependent exchange of an HDAC complex for a HAT complex[17,20].

Interestingly, leukemias can result from the constitutive repression of RAR–RXR targets because of persistent interaction with SIN3–HDAC. Two types of mutation cause this: mutation of a certain region of RXR[21], and fusions (through chromosomal translocation) of RAR to genes such as promyelocytic leukemia (PML) or promyelocitic leukemia zinc finger (PLZF)[22,23]. Wild-type RXR interacts directly with N-CoR–SMRT; however, the RXR mutant RXRα443 binds to N-CoR–SMRT much more strongly[21]. Importantly, reporter constructs bearing RARE sites are not activated in response to retinoic acid in cells expressing RXRα443. However, the combination of retinoic acid and the HDAC inhibitor trichostatin A restores activation, strongly suggesting that histone deacetylation mediates the repression of the RARE reporter[24].

PML–RAR fusions typically consist of nearly full-length PML at the N-terminus and nearly full-length RAR at the C-terminus. The normal function of PML is not well understood. However, PML is known to homodimerize, to interact with HDACs and to localize with transcription

factors in nuclear 'speckles'[25]. PML–RAR fusions retain the regions of RAR required for DNA and ligand binding, and the regions of PML required for HDAC interaction and homodimerization. Importantly, PML–RAR patients often go into remission after a course of treatment with retinoic acid[25]. Recent evidence suggests that the transcriptional misregulation and leukemogenesis resulting from PML–RAR fusions are mediated by homodimerization. Dimerization might allow two N-CoR or SMRT proteins and therefore two SIN3–HDAC complexes to be bound in the repressed state, which might underlie the requirement for higher levels of retinoic acid to shift the equilibrium to the unbound state[24]. In addition, RAR might assume a different conformation in PML–RAR homodimers than in a RAR–RXR heterodimer and therefore interact differently with N-CoR or SMRT and/or respond differently to retinoic acid. Furthermore, a RAR derivative bearing an oligomerization domain at the N-terminus has the same properties as PML–RAR[26].

Fusions of the protein PLZF to RAR might promote leukemogenesis through a similar mechanism. The normal function of PLZF is not known, but a homodimerization motif present in PLZF is retained in PLZF–RAR fusions and might direct PLZF–RAR dimerization. PLZF itself also interacts strongly and directly with SIN3, thus providing another means of recruiting HDACs. Interestingly, SIN3 protein is not released from PLZF–RAR at high concentrations of retinoic acid, and patients bearing this translocation are resistant to retinoic acid therapy.

Taken together, persistent interaction of SIN3–HDAC at RAR targets promotes leukemia and can occur by many modes, including RXR mutations, RAR multimerization and fusion partner interactions (Fig. 3). Because of the multiple connections between retinoic acid signaling and HDAC misregulation, combinations of retinoic acid and HDAC inhibitors are now being tested in the clinic against these and other translocations[27]. Finally, other links between cancer and HDACs have recently emerged, as altered Ras and Ca^{2+}/calmodulin-dependent protein kinase (CaMK) signaling has been shown to dramatically change the nuclear or cytoplasmic distribution of certain HDAC proteins, change gene expression patterns and alter proliferation[28].

DNA methylation and HDAC recruitment

Changes in DNA methylation are almost a constant feature of tumors, making this alteration the most common link between cancer and chromatin. A major step forwards came with the discovery that methylation-associated gene silencing is mediated by HDAC activity[29]. This association is mediated by the methyl CpG-binding proteins MBD1–4 and MeCP2, which bind SIN3–HDAC and recruit them to highly methylated regions. In addition, the DNA methyltransferases (DMTs) themselves interact directly with HDAC enzymes[30–32], suggesting that regions might be concurrently methylated and deacetylated, and therefore silenced. In addition, DMTs interact with sequence-specific repressors, showing that DMTs might act as proteins to bridge repressors to HDACs[32]. This provides a role for DMTs in gene silencing, independent of their methyltransferase activity.

Although the connections of methylation to repression are now clear, the connections to cancer are complex. DNA is generally hypomethylated in cancer cells;

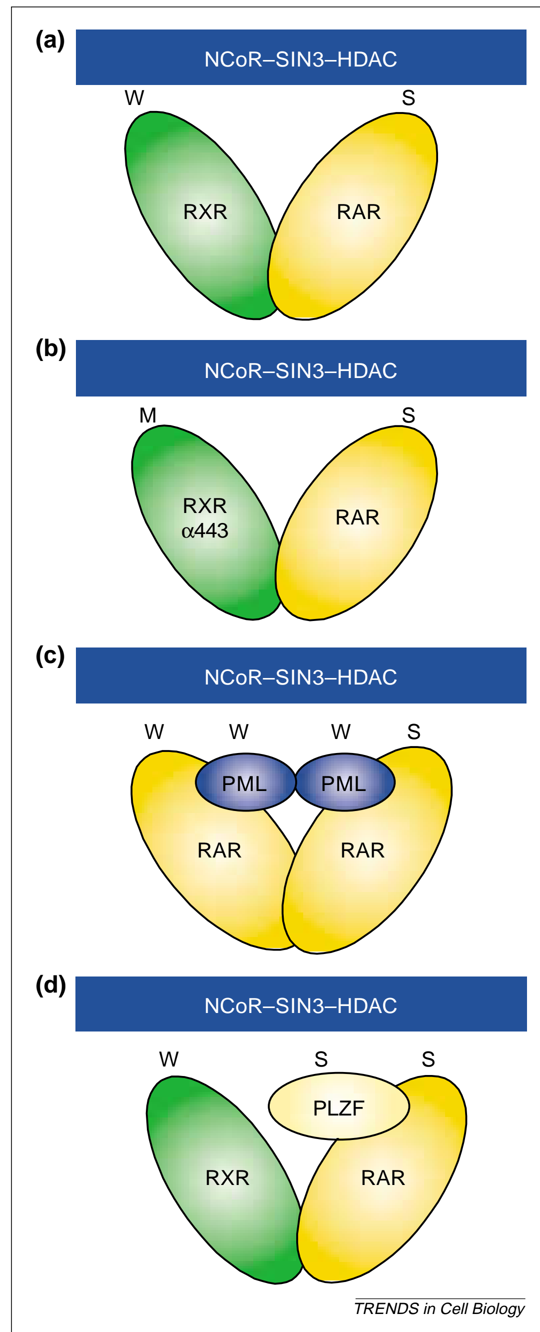

Figure 3. Oncogenic mutations or fusions involving RAR and RXR affect interaction with HDAC-containing complexes

In the absence of ligand (retinoic acid), retinoic acid receptor (RAR)–RXR dimers interact with the SIN3–histone deacetylase (HDAC) complex through the bridging protein N-CoR or silencing mediator for retinoid and thyroid receptors (SMRT). Diagrams show either normal RAR–RXR dimers, or oncogenic derivatives depicting the strength of their interactions with N-CoR–SIN3–HDAC complex in the absence of ligand (W, weak; M, moderate; S, strong). There are several types of alterations that might occur in the presence of ligand: **(a)** Normal RAR–RXR. These normal interactions with HDAC complex are reversed by ligand binding. HDAC is released and activation can occur; **(b)** RXRα443 mutant. Moderate RXR interaction with HDAC complex maintained in the presence of low levels of ligand, but HDAC complex is released with high levels of ligand; **(c)** Fusion between the promyelocytic leukemia protein (PML) and RAR. The PML moiety mediates RAR homodimerization, increased association with HDAC complex, and/or poorer response to ligand. HDAC association is maintained at low levels of ligand, but released at high levels of ligand; **(d)** Fusion between the promyelocytic leukemia zinc-finger protein (PLZF) and RAR. Strong direct association of PLZF with HDAC complex (through SIN3) is independent of ligand, so HDAC association is maintained. In addition, PLZF might mediate homodimerization of PLZF–RAR (not shown).

however, certain types of tumor show localized regions that are hypermethylated[33]. The role of general hypomethylation in oncogenesis is not clear, nor is it known whether it is a cause or consequence of transformation. However, several studies now suggest that the regulatory regions of important negative regulators of the G1–S transition (such as Rb and the cyclin-dependent kinase inhibitor p16), or of genes involved in DNA repair (such as *MLH1*), are abnormally hypermethylated, and therefore silenced in many tumors[33,34]. Taken together, these results point to important roles for methylation in regulating the modification state of chromatin at genes that regulate cell proliferation and genome integrity.

Misregulation of ATP-dependent remodelers

Recent studies have shown strong links between the misregulation of remodelers and cancer. SWI–SNF complexes are a large and well-studied family of remodelers, and most family members are essential, abundant, and highly conserved[1]. SWI–SNF complexes contain an adenosine triphosphatase (ATPase) subunit that can slide nucleosomes along DNA templates, and 8–12 other proteins that assist in regulation and targeting. Remodelers are now emerging as versatile machines that can assist in the establishment, maintenance or removal of repressive chromatin structures.

hSNF5–INI1 mutations

Perhaps the most compelling connection between SWI–SNF and cancer was the discovery that mutations in the hSNF5–INI1 component of human SWI–SNF complex are a consistent feature of rhabdoid tumors, an aggressive cancer of the brain and soft tissues[35]. In fact, *hSNF5–INI1* displays the properties of a tumor-suppressor gene, as sporadic rhabdoid tumors show biallelic loss-of-function mutations, and germline mutations confer an autosomal-dominant syndrome that predisposes patients to a variety of rhabdoid cancers[35,36]. Mutations in hSNF5–INI1 are also associated with acute leukemias, suggesting that sporadic loss of hSNF5–INI1 might also promote proliferation of developing blood cells[37]. Studies suggest that SNF5–INI itself helps regulate the activity and the stability of the ATPase activity of SWI–SNF, and might also assist with targeting. Recent studies have shown that mutations in the ATPase subunit of SWI–SNF, Brg1, are also associated with multiple types of tumors[38]. However, as SWI–SNF is essential, mutations that confer cancer might be those that misregulate a particular mode of SWI–SNF function rather than eliminate activity entirely. Clearly, understanding the precise role of these subunits in SWI–SNF will be necessary for the design of therapeutic agents.

Rb, BRCA1 and Myc associations

Recent work has shown both physical and functional interactions between human SWI–SNF and the tumor suppressors Rb and BRCA1. For example, SWI–SNF enters into the Rb–SIN3–HDAC complex in G1 phase and assists in repressing genes (such as cyclin E) that control the G1–S transition[19,39]. Also striking was the discovery that the human breast cancer susceptibility gene product, BRCA1, is a stable (although substoichiometric) component of human SWI–SNF[40]. Whereas BRCA1 is normally able to synergize with the tumor suppressor and transcriptional activator p53, this synergy is not observed in cells expressing a dominant-negative version of the SWI–SNF ATPase. Finally, c-Myc interacts directly with the hSNF5–INI1 component of SWI–SNF, and c-Myc transactivation requires an intact and active SWI–SNF complex[41]. Taken together, SWI–SNF complexes contain and associate with important tumor-suppressor proteins and cell-cycle regulators, strongly suggesting that misregulation of remodeler targeting or activity can promote cancer.

Concluding remarks

In this review, I have presented several modes by which chromatin misregulation can lead to transcription patterns that can promote transformation. Oncogenic fusion proteins can alter the targeting or association of chromatin-regulating complexes at the promoters of genes controlling proliferation or differentiation. Alternatively, fusions can inappropriately combine two or more HAT domains that might alter the modification state of nucleosomes in promoters and alter gene expression patterns. In addition, changing the DNA methylation patterns of chromosomal regions alters their association with HDACs and therefore the expression levels of genes in those regions. Finally, mutations in chromatin remodelers or associated proteins can confer gene-specific defects in transcriptional regulation that lead to cancer.

Much work remains to be done in identifying the targets of misregulation and in understanding how they promote oncogenesis. For example, rarely have researchers established that the mutant factor directly occupies the promoter of a candidate target gene or that the structure and modification state of that gene is altered in the predicted way. Another important issue is whether misregulation of a chromatin-regulating complex is sufficient for transformation, or whether a 'second hit' is required in other pathways regulating proliferation or apoptosis. Finally, we need to know how chromatin normally regulates transcription to understand how misregulation occurs, and how it can be reversed. Such information could enable the design of specific inhibitors for HATs, HDACs or remodelers that can assist in the treatment of chromatin-related cancers.

Acknowledgements

I apologize to those authors whose important work could not be cited because of space restrictions. I thank Don Ayer, Dan Richardson and Doug Roberts for their helpful comments.

References

1 Workman, J.L. and Kingston, R.E. (1998) Alteration of nucleosome structure as a mechanism of transcriptional regulation. *Annu. Rev. Biochem.* 67, 545–579
2 Strahl, B.D. and Allis, C.D. (2000) The language of covalent histone modifications. *Nature* 403, 41–45
3 Winston, F. and Allis, C.D. (1999) The bromodomain: a chromatin-targeting module? *Nat. Struct. Biol.* 6, 601–604
4 Kingston, R.E. *et al.* (1996) Repression and activation by multiprotein complexes that alter chromatin structure. *Genes Dev.* 10, 905–920
5 Rowley, J.D. (1998) The critical role of chromosomal translocations in human leukemias. *Annu. Rev. Genet.* 32, 495–519
6 Yu, B.D. *et al.* (1998) MLL, a mammalian trithorax-group gene, functions as a transcriptional maintenance factor in morphogenesis. *Proc. Natl. Acad. Sci. U. S. A.* 95, 10632–10636
7 Shikama, N. *et al.* (1997) The p300/CBP family: Integrating signals with transcription factors and chromatin. *Trends Cell Biol.* 7, 230–236
8 Ernst, P. *et al.* (2001) MLL and CREB bind cooperatively to the nuclear coactivator CREB-binding protein. *Mol. Cell. Biol.* 21, 2249–2258
9 Borrow, J. *et al.* (1996) The translocation t(8;16)(p11;p13) of acute myeloid leukaemia fuses a putative acetyltransferase to the CREB-binding protein. *Nat. Genet.* 14, 33–41
10 Panagopoulos, I. *et al.* (2001) Fusion of the MORF and CBP genes in acute myeloid leukemia with the t(10;16)(q22;p13). *Hum. Mol. Genet.* 10, 395–404
11 Sterner, D.E. and Berger, S.L. (2000) Acetylation of histones and transcription-related factors. *Microbiol. Mol. Biol. Rev.* 64, 435–459
12 Voegel, J.J. *et al.* (1998) The coactivator TIF2 contains three nuclear receptor-binding motifs and mediates transactivation through CBP binding-dependent and -independent pathways. *EMBO J.* 17, 507–519
13 Akhtar, A. and Becker, P.B. (2001) The histone H4 acetyltransferase MOF uses a C2HC zinc finger for substrate recognition. *EMBO Rep.* 2, 113–118
14 Chambon, P. (1996) A decade of molecular biology of retinoic acid receptors. *FASEB J.* 10, 940–954
15 Alland, L. *et al.* (1997) Role for N-CoR and histone deacetylase in Sin3-mediated transcriptional repression. *Nature* 387, 49–55
16 Nagy, L. *et al.* (1997) Nuclear receptor repression mediated by a complex containing SMRT, mSin3A, and histone deacetylase. *Cell* 89, 373–380
17 Heinzel, T. *et al.* (1997) A complex containing N-CoR, mSin3 and histone deacetylase mediates transcriptional repression. *Nature* 387, 43–48
18 Ayer, D.E. (1999) Histone deacetylases: transcriptional repression with SINers and NuRDs. *Trends Cell Biol.* 9, 193–198
19 Harbour, J.W. and Dean, D.C. (2000) The Rb/E2F pathway: Expanding roles and emerging paradigms. *Genes Dev.* 14, 2393–2409
20 Nagy, L. *et al.* (1999) Mechanism of corepressor binding and release from nuclear hormone receptors. *Genes Dev.* 13, 3209–3216
21 Zhang, J. *et al.* (1999) A novel role for helix 12 of retinoid X receptor in regulating repression. *Mol. Cell. Biol.* 19, 6448–6457
22 Grignani, F. *et al.* (1998) Fusion proteins of the retinoic acid receptor-alpha recruit histone deacetylase in promyelocytic leukaemia. *Nature* 391, 815–818
23 Lin, R.J. *et al.* (1998) Role of the histone deacetylase complex in acute promyelocytic leukaemia. *Nature* 391, 811–814
24 Lin, R.J. and Evans, R.M. (2000) Acquisition of oncogenic potential by RAR chimeras in acute promyelocytic leukemia through formation of homodimers. *Mol. Cell* 5, 821–830
25 Melnick, A. and Licht, J.D. (1999) Deconstructing a disease: RARalpha, its fusion partners, and their roles in the pathogenesis of acute promyelocytic leukemia. *Blood* 93, 3167–3215
26 Minucci, S. *et al.* (2000) Oligomerization of RAR and AML1 transcription factors as a novel mechanism of oncogenic activation. *Mol. Cell* 5, 811–820
27 Minucci, S. *et al.* (2001) Histone deacetylases: a common molecular target for differentiation treatment of acute myeloid leukemias? *Oncogene* 20, 3110–3115
28 McKinsey, T.A. *et al.* (2000) Signal-dependent nuclear export of a histone deacetylase regulates muscle differentiation. *Nature* 408, 106–111
29 Bird, A.P. and Wolffe, A.P. (1999) Methylation-induced repression – belts, braces, and chromatin. *Cell* 99, 451–454
30 Rountree, M.R. *et al.* (2000) DNMT1 binds HDAC2 and a new co-repressor, DMAP1, to form a complex at replication foci. *Nat. Genet.* 25, 269–277
31 Fuks, F. *et al.* (2000) DNA methyltransferase Dnmt1 associates with histone deacetylase activity. *Nat. Genet.* 24, 88–91
32 Fuks, F. *et al.* (2001) Dnmt3a binds deacetylases and is recruited by a sequence-specific repressor to silence transcription. *EMBO J.* 20, 2536–2544
33 Baylin, S.B. *et al.* (1998) Alterations in DNA methylation: a fundamental aspect of neoplasia. *Adv. Cancer Res.* 72, 141–196
34 Jones, P.A. and Laird, P.W. (1999) Cancer epigenetics comes of age. *Nat. Genet.* 21, 163–167
35 Versteege, I. *et al.* (1998) Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. *Nature* 394, 203–206
36 Sevenet, N. *et al.* (1999) Constitutional mutations of the hSNF5/INI1 gene predispose to a variety of cancers. *Am. J. Hum. Genet.* 65, 1342–1348
37 Shastry, B.S. *et al.* (1984) Altered levels of a 5 S gene-specific transcription factor (TFIIIA) during oogenesis and embryonic development of *Xenopus laevis*. *J. Biol. Chem.* 259, 11373–11382
38 Wong, A.K. *et al.* (2000) BRG1, a component of the SWI-SNF complex, is mutated in multiple human tumor cell lines. *Cancer Res.* 60, 6171–6177
39 Zhang, H.S. *et al.* (2000) Exit from G1 and S phase of the cell cycle is regulated by repressor complexes containing HDAC-Rb-hSWI/SNF and Rb-hSWI/SNF. *Cell* 101, 79–89
40 Bochar, D.A. *et al.* (2000) BRCA1 is associated with a human SWI/SNF-related complex: linking chromatin remodeling to breast cancer. *Cell* 102, 257–265
41 Cheng, S.W. *et al.* (1999) c-MYC interacts with INI1/hSNF5 and requires the SWI/SNF complex for transactivation function. *Nat. Genet.* 22, 102–105