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Role of Histone Deacetylases in Acute Leukemia

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Abstract Accumulating evidence points to a connection between cancer and transcriptional control by histone acetylation and deacetylation. This is particularly true with regard to the acute leukemias, many of which are caused by fusion proteins that have been created by chromosomal translocations. Genetic rearrangements that disrupt the retinoic acid receptor-α and acute myeloid leukemia-1 genes create fusion proteins that block terminal differentiation of hematopoietic cells by repressing transcription. These fusion proteins interact with nuclear hormone co-repressors, which recruit histone deacetylases to promoters to repress transcription. This finding suggests that proteins within the histone deacetylase complexes may be potential targets for pharmaceutical intervention in many leukemia patients. J. Cell. Biochem. Suppls. 30/31:194–202, 1998. © 1998 Wiley-Liss, Inc.

Key words: acute leukemias; hematopoietic cells; histone deacetylase complexes

All the cells present in the bloodstream are derived from a single hematopoietic stem cell [Clark and Keating, 1995; Lenny et al., 1997]. Through the actions of both soluble and adhesive factors, stem cells differentiate through several steps into the mature cells of the lymphoid and myeloid cell lineages [Clark and Keating, 1995; Lenny et al., 1997]. Those cells that are unable to complete their differentiation programs accurately undergo apoptosis [Look, 1997]. Acute leukemias arise when immature hematopoietic cells are blocked from undergoing terminal differentiation and continue to proliferate in an unrestrained manner [Olsson et al., 1996; Grimwade and Solomon, 1997].

Leukemias are associated with specific chromosomal translocations (Fig. 1), which may obviate the need for the multistep mutation of proto-oncogenes and tumor suppressor genes observed in solid tumors [Ruddon, 1995; Look, 1997]. These translocations result either in the generation of a fusion protein or in the aberrant expression of a regulatory protein [Ruddon, 1995; Look, 1997]. In the case of fusion proteins, the gene products can display novel properties and/or exhibit a loss of regulation [Ruddon, 1995]. The activity of fusion proteins must be dominant over that of the wild-type protein(s), as only one allele of each gene is normally affected. Many of these translocations target master regulatory transcription factors that control cellular proliferation, survival, and differentiation [Ruddon, 1995; Look, 1997]. In this review, we explore the convergent mechanisms of transcriptional control of two master regulators, retinoic acid receptor-α (RARα) and acute myeloid leukemia-1 (AML-1), and describe the manner in which fusion proteins created by chromosomal translocations affect transcription of RARα and AML-1 target genes.

RETINOIC ACID RECEPTOR-α

Retinoic acid (RA) is a naturally occurring metabolite of vitamin A [Chen et al., 1995]. Like other retinoids, this compound regulates both cell growth and differentiation in a variety of cell types [Ruddon, 1995; Grimwade and Solomon, 1997]. During normal hematopoiesis, RA stimulates the differentiation of myeloid cells, mainly through the actions of RARα [Grimwade and Solomon, 1997; Kalantry et al., 1997].

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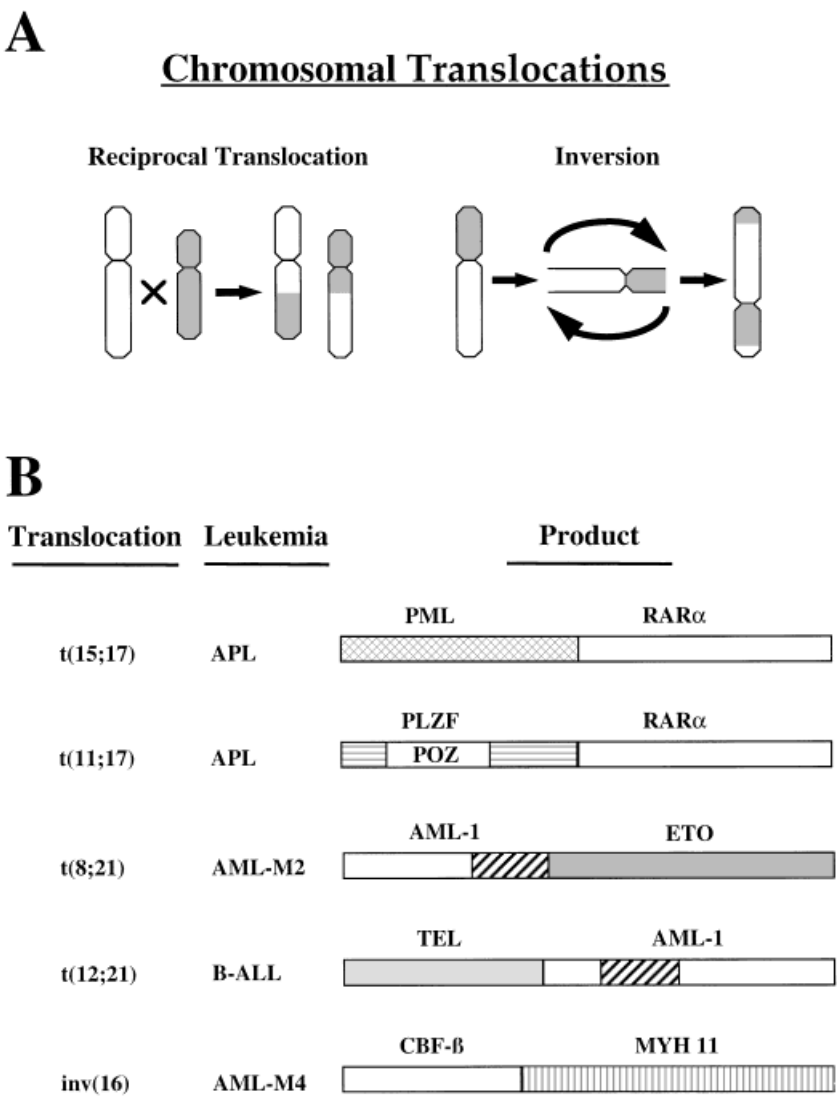

Fig. 1. Chromosomal alterations of the retinoic acid receptor-α (RARα and acute myeloid leukemia-1 (AML-1) genes. **A:** Schematic diagram showing the results of a reciprocal translocation and an inversion. **B:** Representation of the major RARα and AML-1 translocations described and their resulting fusion proteins. *Hatched boxes*, the Runt homology DNA-binding domain of AML-1; *shaded box*, the POZ domain of PLZF. Leukemia designations M2 and M4 refer to specific AML subtypes.

RARα is a type II nuclear hormone receptor that preferentially binds to DNA as a heterodimer with a retinoid-X receptor (RXR) [Ruddon, 1995; Grimwade and Solomon, 1997; Kalantry et al., 1997].

In the absence of ligand, RARα represses target genes by tethering co-repressors such as N-CoR (nuclear co-repressor) and SMRT (silencing mediator of retinoic acid and thyroid hormone receptors) to promoter DNA [Chen and Evans, 1995; Kurokawa et al., 1995] (Fig. 2). These co-repressors are part of one or more large complexes that contain mSin3 proteins and histone deacetylases (HDACs) [Struhl, 1998]. The activity of these enzyme complexes antagonizes that of the histone acetyltransferases (HATs), which have long been associated with transcriptional activation [Struhl, 1998].

Three models have been proposed for the function of acetylation/deacetylation in transcriptional control. HATs are known to acetylate progressively up to four N-terminal lysine residues in each of the four nucleosomal histones [Jeppesen, 1997; Wade et al., 1997; Struhl, 1998]. Acetylation of these amino acids reduces the number of positive charges on the histone octamer that interact with the surrounding, negatively charged DNA [Jeppesen, 1997; Wade et al., 1997; Struhl, 1998]. This destabilizes the DNA–histone interaction, opening the nucleosome structure, which permits transcription [Jeppesen, 1997; Wade et al., 1997; Struhl, 1998]. Conversely, HDACs remove acetyl groups from modified histones, which stabilizes local chromatin structure and leaves the affected promoter sequences inaccessible to the tran-

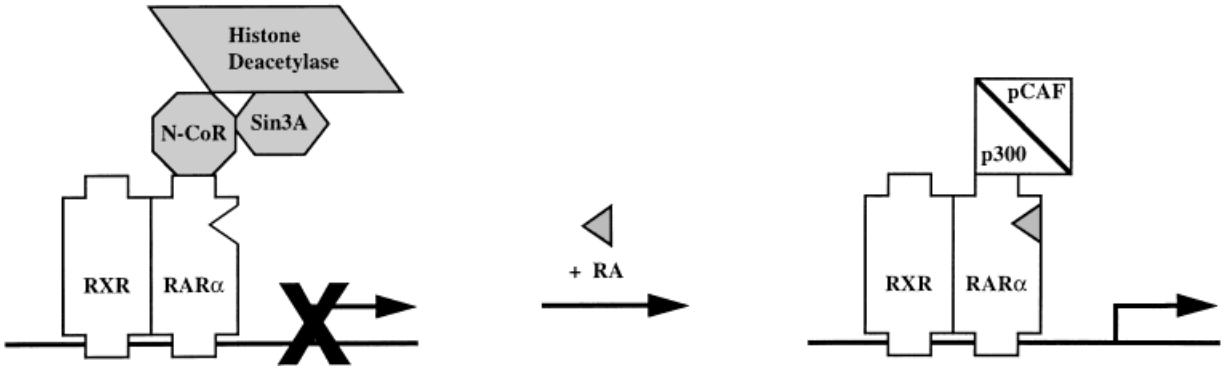

Fig. 2. Regulation of transcription by retinoic acid receptor-α (RARα). In the absence of ligand, the RAR/RXR heterodimer associates with the mSin3A/histone deacetylase complex through interactions with N-CoR or SMRT. The binding of ligand releases the repressor complex, allowing RAR/RXR to recruit the p300/CBP and pCAF histone acetyltransferases, resulting in transcriptional activation.

scription machinery [Jeppesen, 1997; Wade et al., 1997; Struhl, 1998]. A second potential mechanism suggests a role for acetylation/deacetylation in altering the activity of other transcriptional regulators. Consistent with this, both basal and sequence-specific transcription factors have been reported to be acetylated by HATs [Struhl, 1998]. Finally, acetylation may provide a tag for the binding of transcriptional activators to core histones, whereas deacetylation of these residues might unveil a protein interaction site for other repressors.

Although RAR/RXR mediates transcriptional repression by recruiting HDAC complexes, these heterodimers are also ligand-inducible transcriptional activators. In the presence of ligand, N-CoR/SMRT is released, and co-activators such as CBP and p300 are bound [Glass et al., 1997; Wade et al., 1997; Struhl, 1998]. These co-activators, which display HAT activity themselves, act in part by recruiting yet another HAT called pCAF (p300/CBP-associated factor) [Wade et al., 1997; Struhl, 1998]. Why would such a multienzyme complex be necessary? One possibility is that these acetyltransferases will prove to have differing substrate specificities, each of which may be required to bring about the ordered opening of the nucleosomal structure [Struhl, 1998]. By contrast, it has recently been reported that p300 interacts specifically with the nonphosphorylated, initiation-competent form of RNA polymerase II, whereas pCAF interacts with the phosphorylated, elongation-competent form of RNA polymerase II [Cho et al., 1998]. Future experiments will be necessary to determine whether these potential mechanisms are mutually exclusive, or whether they simply represent different facets of a convergent mechanism for the actions of these proteins.

RARα FUSION PROTEINS

In acute promyelocytic leukemia (APL), the RARα gene is disrupted. In most APL patients, a translocation of chromosomes 15 and 17 (t(15;17)) results in the expression of a fusion protein containing the N-terminal portion of the *PML* (promyelocytic leukemia) gene product linked to most of RARα (Fig. 1) [Ruddon, 1995; Kalantry et al., 1997]. In a few cases, a zinc finger-containing protein, promyelocytic leukemia zinc finger (PLZF), is fused to RARα by the t(11;17) [Kalantry et al., 1997] (Fig. 1). As a result of the additional sequences, the RARα fusion proteins are no longer responsive to physiological levels of retinoic acid [Grimwade and Solomon, 1997; Kalantry et al., 1997; He et al., 1998]. Moreover, they interfere with the expression of the RA-inducible genes that promote myeloid differentiation [Ruddon, 1995; Chen et al., 1995; Grimwade and Solomon, 1997; He et al., 1998]. This results in a clonal expansion of cells arrested in the promyelocyte stage of development, the hallmark of APL [Chen et al., 1995; Grimwade and Solomon, 1997; He et al., 1998]. When targeted to the myeloid cell compartment, both fusion proteins induce leukemias in transgenic mice as well [He et al., 1998].

Though pathologically indistinguishable [Lin et al., 1998], the APL caused by the t(15;17) and the t(11;17) differ in their response to high doses of retinoic acid. Leukemic blasts harboring the PML-RARα protein respond to pharmacological doses of *all-trans*-retinoic acid (ATRA)

and differentiate [Chen et al., 1995; Grimwade and Solomon, 1997]. Thus, most of these patients achieve short-term remission with ATRA treatment [Chen et al., 1995; Ruddon, 1995]. However, cells expressing PLZF-RARα are insensitive to ATRA administration, and efforts to cure patients with this agent have been unsuccessful [Chen et al., 1995; Grimwade and Solomon, 1997].

The clinical results have been explained in molecular terms by the observation that in cells expressing PML-RARα, ATRA causes the release of N-CoR/SMRT and the histone deacetylase complex [Grignani et al., 1998; He et al., 1998; Lin et al., 1998] (Fig. 3). By contrast, PLZF-RARα does not completely release the co-repressor complex in the presence of ligand [Grignani et al., 1998; He et al., 1998; Lin et al., 1998]. This is because PLZF can also bind both N-CoR and SMRT by a conserved motif termed the poxvirus and zinc finger (POZ) domain [Grignani et al., 1998; He et al., 1998; Lin et al., 1998] (Figs. 1, 3). The POZ domain is retained in PLZF-RARα, suggesting that the fusion protein binds two co-repressor complexes, only one of which is retinoid sensitive [Grignani et al., 1998; He et al., 1998; Lin et al., 1998] (Fig. 3). Consistent with this observation, Trichostatin A (TSA), a histone deacetylase inhibitor, is capable of restoring RA-responsiveness to PLZF-RARα and of allowing leukemic cells expressing this fusion protein to differentiate in response to ATRA [Grignani et al., 1998; He et al., 1998; Lin et al., 1998] (Fig. 3). These results confirm that the inhibition of RARα-dependent transcription is central to the leukemic phenotype and establish a link between chromatin remodeling enzymes and oncogenesis. These results also suggest that proteins within the HDAC complex are potential targets for pharmaceutical intervention in APL patients.

In addition to inhibiting normal RARα function, the fusion proteins may also affect the activity of the wild-type PML and PLZF pro-

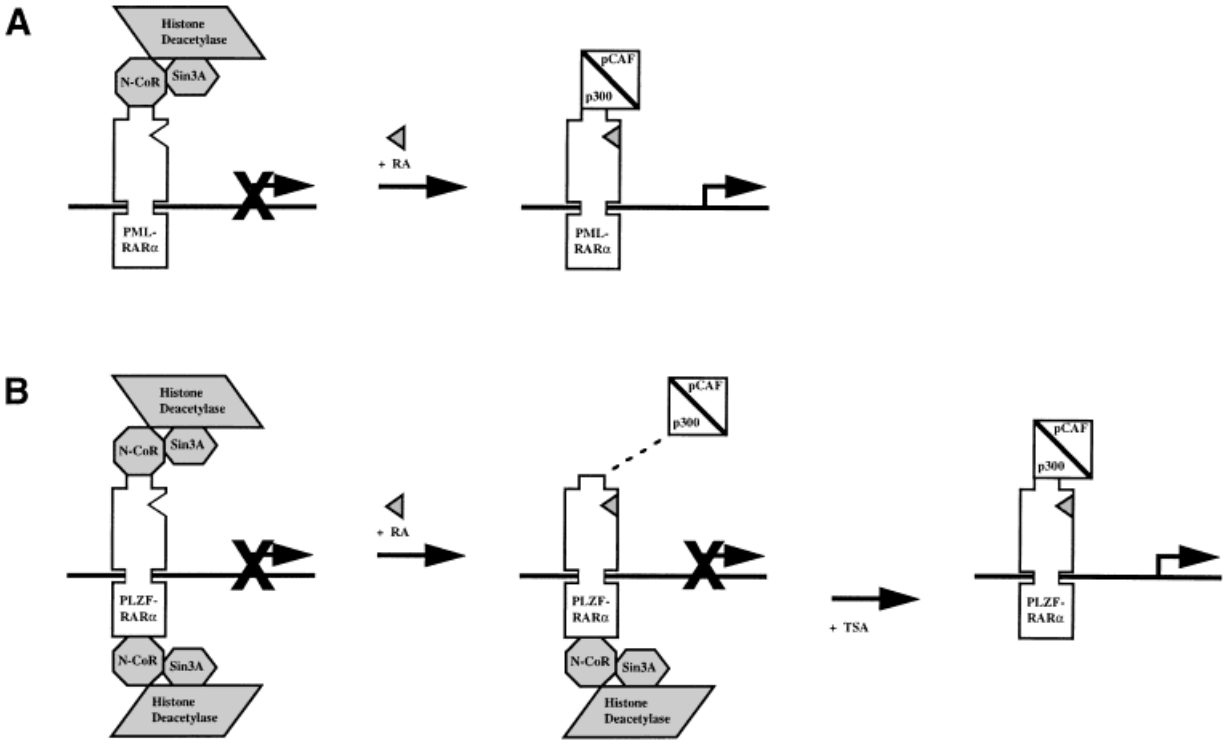

Fig. 3. Model of transcriptional repression by the retinoic acid receptor-α (RARα) fusion proteins. **A:** PML-RARα represses transcription by tethering an HDAC complex to promoter sequences. Administration of pharmacological doses of retinoic acid is sufficient to release the repressor complex, which facilitates the recruitment of co-activators and allows transcription to occur. For simplicity, RXR is not shown. **B:** PLZF-RARα binds two repressor complexes, one of which is RA sensitive. Administration of retinoic acid has no effect on the binding of the repressor complex to the promyelocytic leukemia zinc finger (PLZF) POZ domain, and therefore has no effect on transcription. Co-administration of RA and TSA, however, is sufficient to induce transcriptional activation by the fusion protein. Note that in this case the repressor complex may not actually be released, but rather its activity is inhibited.

teins. The precise function of PML is currently unknown, but PLZF is a DNA-binding transcriptional repressor [Li et al., 1997]. Both PML and PLZF display growth inhibitory properties when expressed in various cell types, and the expression of the endogenous proteins appears to be cell cycle regulated [Kalantry et al., 1997]. These proteins are capable of homodimer formation, and can form heterodimers with their respective RARα fusion proteins as well [Kalantry et al., 1997].

Both PML and PLZF are normally found in a small number of discrete structures called nuclear bodies or PML oncogenic domains (PODs) [Chen et al., 1995; Grimwade and Solomon, 1997; Kalantry et al., 1997]. However, expression of either fusion protein delocalizes both PML and PLZF to a large number of aberrant nuclear microspeckles, similar to those seen in APL blasts [Chen et al., 1995; Kalantry et al., 1997]. Administration of ATRA to cells expressing PML-RARα can restore POD integrity and normal PML localization [Chen et al., 1995; Kalantry et al., 1997]. Thus, PML-RARα and PLZF-RARα may function in a double dominant-negative manner by blocking the actions of both of the wild-type proteins involved in each fusion.

In summary, RA-responsive promoters are maintained in a repressive conformation in the absence of ligand by HDACs (Fig. 2). Upon ligand binding, the co-repressor complex is released from RARα, and the co-activator complex is recruited. Subsequent acetylation of core histones results in nucleosomal remodeling, making the DNA accessible to other transcription factors and permitting transcription to proceed. The RARα fusion proteins maintain target genes in a repressed state, thereby blocking differentiation (Fig. 3).

CHROMOSOMAL TRANSLOCATIONS THAT DISRUPT *AML1*

AML1 was cloned as a gene disrupted by the t(8;21) in acute myeloid leukemia [Lenny et al., 1997] (Fig. 1). Subsequently, its role as the DNA binding component of the enhancer core binding factor (CBF) was uncovered by the identification of the DNA binding site of AML-1 and by the purification and cloning of the murine CBF and polyoma enhancer binding protein 2 (PEBP2) [Meyers and Hiebert, 1995; Speck and Stacy, 1995]. The enhancer core motif is necessary but not sufficient for the tissue-specific expression of various cytokines, cytokine receptors, T-cell receptors, and neutrophil enzymes [Lenny et al., 1997]. AML-1 binds to DNA as a heterodimer with core binding factor-β (CBFβ), which does not bind DNA directly, but increases the affinity of AML-1 for its binding site [Meyers and Hiebert, 1995; Speck and Stacy, 1995].

AML-1/CBFβ form a weak transcriptional activation complex [Lenny et al., 1997; Westendorf et al., 1998]. However, AML-1 strongly activates target promoters by cooperating with other tissue-specific transcription factors [Lenny et al., 1997; Westendorf et al., 1998]. Thus, AML-1 may act as a promoter organizer that physically interacts with neighboring ets, myb, or C/EBP factors to coordinately regulate transcription [Lenny et al., 1997] (Fig. 4). At least a part of the ability of AML-1 to activate transcription also appears to be mediated by physical interactions with CBP and p300 and their associated HAT activities [Kitabayashi et al., 1998] (Fig. 4).

The cloning of AML-1 provided the molecular tools to ask whether other translocations that disrupt chromosomal region 21q22 also affect AML-1. This has led to the identification of chromosomal translocations in addition to the t(8;21), including the t(12;21), t(3;21) and the t(16;21). The t(12;21), which fuses the first 333 amino acids of an ets factor termed TEL (*t*ranslocation, *ets*, *l*eukemia, also known as ETV6) to virtually all of AML-1 [Lenny et al., 1997], is found in up to 25% of childhood B-cell acute lymphocytic leukemias (B-ALLs) [Look, 1997] (Fig. 1). The t(8;21), which fuses the DNA-binding domain of AML-1 to a protein referred to as ETO (*e*ight-*t*wenty-*o*ne, also known as MTG8 and CDR) [Lenny et al., 1997], accounts for 10–12% of AML cases with discernable translocations [Look, 1997]. The recently reported t(16;21) is similar to the t(8;21) in that AML-1 is fused to a gene closely related to ETO, termed myeloid tumor gene 16 (MTG16) [Kitamura et al., 1998]. The t(3;21) fuses AML-1 to a known transcriptional repressor, Evi I [Nucifora and Rowley, 1995]. All fusion proteins that directly target AML-1 retain the Runt homology domain, which is responsible for binding to DNA, as well as for interacting with other transcription factors, including CBFβ [Meyers and Hiebert, 1995; Speck and Stacy, 1995; Lenny et al., 1997].

The importance of AML-1 in human leukemia was further highlighted by the cloning of

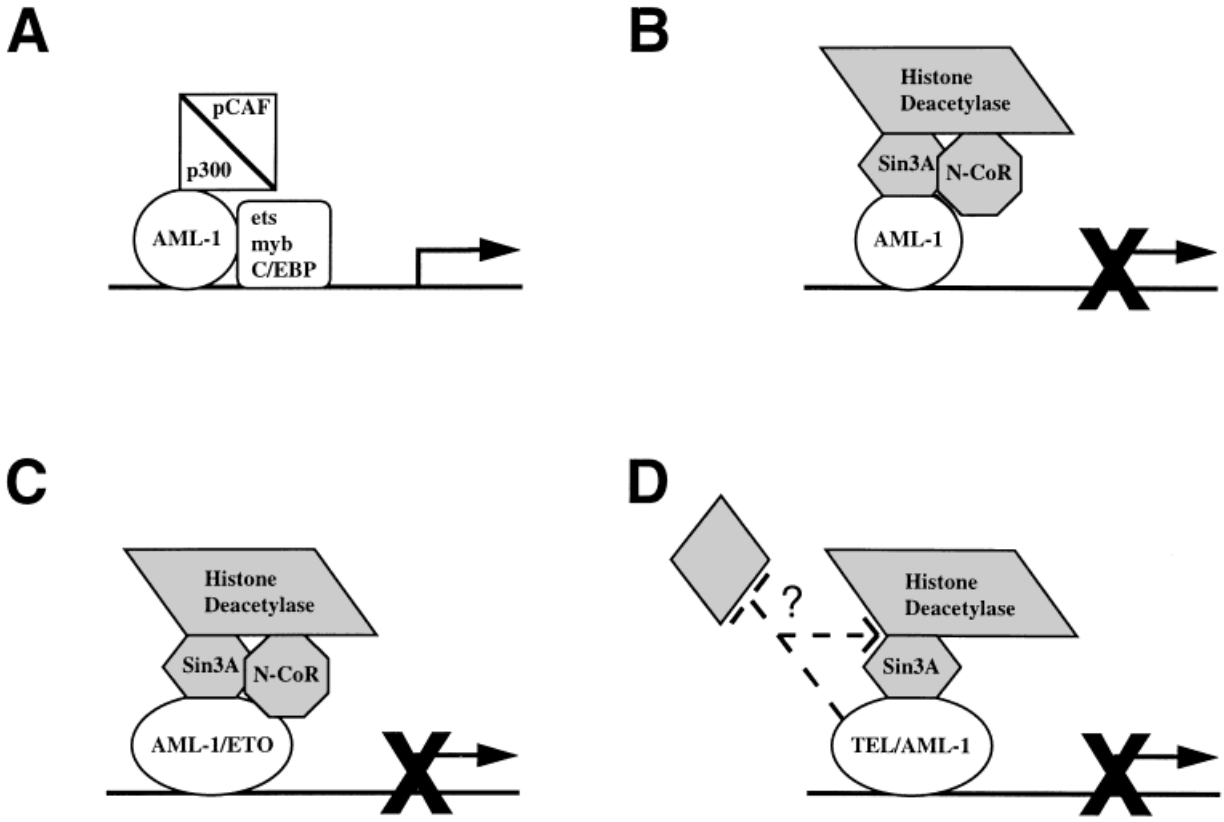

Fig. 4. Acute myeloid leukemia-1 (AML-1) and the AML-1 translocation fusion proteins regulate transcription through interactions with various proteins. **A:** AML-1 activates transcription by recruiting histone acetyltransferases (p300/CBP and pCAF), as well as by interacting with neighboring ets, myb, and/or C/EBP factors. For simplicity, core binding factor-β (CBFβ) is not shown. **B–D:** AML-1 and the AML-1 fusion proteins repress transcription by recruiting histone deacetylase complexes to promoter sequences. It has not been determined whether TEL/AML-1 binds N-CoR.

the inv(16), which is the most frequent translocation in AML, accounting for up to 15% of cases [Look, 1997]. This translocation fuses CBFβ to MYH11, a smooth muscle myosin heavy chain gene. The inv(16) fusion protein retains the ability to interact with AML-1, and is presumed to act through AML-1. Thus, all fusion proteins that affect AML-1/CBFβ appear to promote leukemogenesis by regulating the expression of normally AML-1-responsive genes. In fact, the AML-1/CBFβ transcription factor is the most frequently targeted complex in human acute leukemia [Look, 1997].

The t(8;21), t(3;21), t(12;21), and inv(16) fusion proteins have all been shown to inhibit AML-1-dependent transcription from a number of promoters in transfection studies [Nucifora and Rowley, 1995; Lenny et al., 1997; Westendorf et al., 1998]. This repression has been confirmed in vivo, as transgenic expression of the AML-1/ETO or CBFβ/MYH11 fusion protein results in a phenotype that is identical to that in AML-1 and CBFβ knockout mice— embryonic lethality due to a lack of definitive hematopoiesis [Lenny et al., 1997; Yergeau et al., 1997]. Thus, it appears that transcriptional repression of AML-1 target genes is critical to the function of these translocation fusion proteins.

Synthetic AML-1 dominant repressor proteins block myeloid and erythroid differentiation [Tanaka et al., 1995; Niitsu et al., 1997]. AML-1/ETO also blocks granulocyte colony-stimulating factor (G-CSF)-dependent myeloid differentiation in culture [Westendorf et al., 1998, Kitabayashi et al., 1998]. Both overexpression of AML-1 or antisense oligonucleotides directed against AML-1/ETO can induce differentiation in cells containing this fusion protein [Meyers and Hiebert, 1995; Kitabayashi et al., 1998]. These results argue that AML-1 is a critical regulator of differentiation, and that AML-1/ETO inhibits AML-1-dependent transcription of myeloid differentiation genes.

The evidence that AML-1/ETO represses transcription argued that ETO either acts as a co-repressor or recruits co-repressors to modulate transcription. Very recent evidence indicates that, like RARα and PLZF, ETO interacts with N-CoR and mSin3A and recruits histone deacetylases to repress transcription [Lutterbach et al., 1998a; Wang et al., 1998]. However, it appears that, unlike RARα and PLZF, ETO does not bind DNA. Nearly all of ETO cosediments with mSin3A or N-CoR and up to 25% of ETO can be co-immunoprecipitated with mSin3A. Moreover, ETO makes independent contacts with both mSin3A and N-CoR. Therefore, ETO may function as a component of one or more co-repressor complexes. The t(8;21) takes advantage of this activity by fusing this putative co-repressor to the DNA binding domain of AML-1 [Lutterbach et al., 1998a] (Figs. 1, 4). Histone deacetylase inhibitors inactivate AML-1/ETO in both transcription assays and biological assays [Strom et al., 1998]. Because domains conserved between ETO and MTG16 mediate the interaction of ETO with N-CoR, it is likely that the t(16;21) also represses transcription by recruiting histone deacetylases. Thus, HDAC inhibitors may have therapeutic benefits outside of APL.

The observations that AML-1 can both activate and repress transcription coupled with the similarities between the RARα fusion proteins and AML-1/ETO led to the discovery of an AML-1/mSin3 interaction [Lutterbach et al., 1998b]. The AML-1/mSin3A interaction is required for AML-1-dependent repression of the *p21*$^{waf1/cip1}$ promoter [Lutterbach et al., 1998b]. Because the Runt homology domain and sequences just C-terminal to the Runt domain contribute to mSin3A binding, all the fusion proteins that result from chromosomal translocations that disrupt *AML1* may be able to interact with mSin3 to some degree. This has been confirmed for the t(12;21), which retains the entire mSin3A binding domain and physically interacts with mSin3A [Fenrick et al., 1998]. Thus, AML-1 is analogous to RARα. Both transcription factors are critical regulators of myeloid differentiation, both interact with HATs to activate transcription, and both interact with co-repressor complexes to repress transcription. Nevertheless, the molecular switch that turns AML-1 from a repressor to an activator has yet to be defined.

Although the t(12;21) fusion protein retains the mSin3A binding domain, the TEL sequences that are added by the translocation also contribute to TEL/AML-1-mediated repression (Fig. 4). On promoters where AML-1 acts as a transactivator of transcription, the N-terminus of TEL converts AML-1 into a repressor [Fenrick et al., 1998]. Moreover, the TEL sequences that are linked to AML-1 contain a portable transcriptional repressor domain. Fusion of the TEL residues to a heterologous DNA-binding domain is sufficient to induce sequence-specific transcriptional repression from a minimal SV40 promoter [Fenrick et al., 1998]. However, unlike AML-1, PLZF, and RARα, TEL does not appear to interact with N-CoR or histone deacetylases. This distinct mechanism of repression may provide promoter or cell type specificity that ultimately may explain why this translocation is observed in B-cell acute leukemia, while the other translocations targeting AML-1 are found exclusively in AML.

FUTURE DIRECTIONS

Acute leukemias are the result of unrestrained growth of immature hematopoietic cells whose terminal differentiation has been blocked. For the examples described in this article, this block appears to be due to transcriptional repression of differentiation genes by HDAC enzymes. Fusion proteins that utilize HDACs account for at least 30% of AMLs, 25% of childhood B-ALLs, and >99% of APLs. This argues that HDAC inhibitors could function as "differentiation therapy" reagents for many acute leukemia patients.

Furthermore, histone deacetylase inhibitors induce the differentiation of many types of hematopoietic cells [Niitsu et al., 1997]. We speculate that a component of this action occurs through inhibiting transcriptional repression by RARα and AML-1, permitting expression of RARα and AML-1 target genes that promote differentiation. It follows that HDAC inhibitors may be useful even in leukemias that do not directly target these genes. Histone deacetylase inhibitors have already been used in clinical trials as treatments for brain and prostate tumors as well as β-thalassemia [Collins et al., 1995; Samid et al., 1997; He et al., 1998]. Therapeutic benefits in these studies were realized with few, if any, significant side effects, indicating that such treatment would also be much less toxic than conventional chemotherapeutic

agents. We also note that other nuclear hormone receptors function similarly to RARs and that other AML family members bind mSin3A [Lutterbach et al., 1998b]. As these genes are widely expressed, it is possible that HDAC inhibitors may prove to be effective therapeutic agents in many types of cancer.

The next few years promise to be very enlightening with regard to our understanding of the relationship between chromatin structure and transcriptional activity. We expect significant progress to be achieved in characterizing the activities of HAT and HDAC enzymes in terms of substrate specificity, interaction with other transcription factors, and their own regulation as well. Such studies will not only continue to unravel the role that these enzymes play in transcription, but will also aid in identifying the molecular mechanisms that promote leukemogenesis.

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