Journal of Cellular Biochemistry 94:864–869 (2005)

PROSPECTS

Leukemia Fusion Proteins and Co-Repressor Complexes: Changing Paradigms

Robert L. Redner[1]* and Johnson M. Liu[2]

[1]Department of Medicine, University of Pittsburgh School of Medicine, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania
[2]Department of Medicine, Division of Hematology/Oncology, Mount Sinai School of Medicine, New York, New York

Abstract Many cases of acute myelogenous leukemia (AML) are characterized by non-random chromosomal translocations that fuse a DNA-binding protein with a transcriptional regulator, which in turn may aberrantly recruit a co-repressor complex. The similarities in this pattern between different AML chimeric fusions have led to a paradigm that stresses the importance of the co-repressor complex in altering the pattern of expression of genes targeted by the DNA-binding moiety of the fusion. Such findings beg the question of whether the fusion proteins merely serve as anchors to recruit the co-repressor complex or whether they play other significant roles in leukemogenesis. The answers to this question may have therapeutic importance since we now have the ability to target various components of the co-repressor complex, such as the histone deacetylase (HDAC) enzymes. In this Prospect, we wish to highlight some of the complexities and difficulties with the existing molecular paradigm of this challenging group of disorders. J. Cell. Biochem. 94: 864–869, 2005. © 2005 Wiley-Liss, Inc.

Key words: acute myeloid leukemia; co-repressors; HDAC; SMRT; N-COR; PML-RAR; AML-ETO

The majority of cases of acute myelogenous leukemia (AML) are associated with non-random chromosomal translocations [Look, 1997]. Many of these involve the locus encoding a transcriptional activator, leading to expression of a fusion protein that retains the DNA binding motifs of the wild-type protein. In many instances the fusion partner is a transcriptional protein that is capable of interacting with a co-repressor complex. A commonly accepted paradigm (Fig. 1) is that through aberrant recruitment of a co-repressor to a locus of active transcription, the fusion protein alters expression of target genes necessary for myeloid development, thus laying the groundwork for leukemic transformation [Redner et al., 1999]. Potential targeting of this interaction has become a major focus for development of novel therapeutics. All-trans retinoic acid (ATRA) serves as a prototype: by altering co-repressor interaction with the acute promyelocytic leukemia (APL) fusion protein, ATRA effectively induces remissions and has become a mainstay of treatment of this previously fatal disease [Melnick and Licht, 1999]. In this review we will address the question of whether the fusion protein merely serves as an anchor for the co-repressor or whether there is more to these fusion proteins than meets the eye. We will present evidence on the importance of co-repressor recruitment and present several examples that support the hypothesis. We will also present examples of leukemic fusions that do not conform to the paradigm and highlight functions of the fusion proteins that do not bear on their ability to interact with co-repressors yet potentially impact their role in leukemogenesis.

CO-REPRESSOR COMPLEXES

The year 1995 marked the discovery of the co-repressor proteins N-CoR (nuclear co-repressor) [Horlein et al., 1995] and SMRT (silencing mediator of retinoic and thyroid hormone receptors) [Chen and Evans, 1995]. Both were

*Correspondence to: Robert L. Redner, MD, 2.18a Hillman Research Pavilion, 5117 Centre Ave., Pittsburgh PA 15213. E-mail: redner@pitt.edu

Received 14 October 2004; Accepted 15 October 2004
DOI 10.1002/jcb.20368

© 2005 Wiley-Liss, Inc.

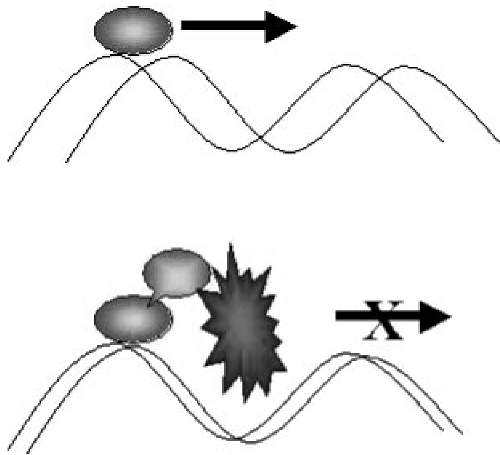

Fig. 1. Cartoon representing alteration in transcription induced by a leukemic fusion protein. The top panel depicts activation of transcription upon site-specific binding to a target promoter. The bottom panel indicates that upon fusion with a second protein, the transcriptional protein becomes a site-specific anchor that tethers a co-repressor complex to the target promoter. The co-repressor, through the action of histone deacetylase, alters local chromatin conformation, to inhibit transcription of target genes.

originally identified as mediators of the repressive effects of unliganded nuclear hormone receptors. They have since been found to mediate the repressive action of a wide range of DNA binding proteins [Privalsky, 2004]. Although derived from different genes, N-CoR and SMRT share $\sim$45% amino acid homology and an overall similar architecture, with homologous interacting domains that mediate binding with the repressor domains of nuclear receptors and other transcriptional proteins [Perissi et al., 1999]. N-CoR or SMRT associate with other members of the co-repressor complex, the full nature of which is yet to be clarified. The key member of this complex is histone deacetylase (HDAC) [Chen and Evans, 1995], which modulates chromatin structure to regulate accessibility of nucleosomal target DNA to the transcriptional machinery. HDACs 3, 4, 5, and 7 have all been shown to participate in the SMRT/N-CoR co-repressor complex [Privalsky, 2004].

Although early reports indicated that N-CoR and SMRT interact with Sin3 to recruit HDACs 1 and 2 to the co-repressor complex [Alland et al., 1997; Heinzel et al., 1997; Laherty et al., 1997], this has since become a subject of controversy. Sin3 interacts with N-CoR and SMRT in vitro, but is often not identified in co-purification from cells [Privalsky, 2004]. Recent reports indicate that Sin3 complexes have different histone target specificity than do N-CoR/SMRT complexes, inducing acetylation of histones H3 and H4 versus H3 alone [Vermeulen et al., 2004]. Is there a difference between SMRT-containing and N-CoR-containing complexes? This is not clear. N-CoR knockout mice are not viable, suggesting that there is incomplete overlap in the function of these two proteins [Jepsen et al., 2000]. Nevertheless, in almost all instances investigated, transcriptional repressors that bind N-CoR also bind SMRT, and vice-versa, although preference for one or the other can be brought out in different assay systems [Privalsky, 2004].

LEUKEMIC FUSIONS

The paradigm of leukemic fusion proteins aberrantly recruiting co-repressor complexes grew from studies in APL. The t(15;17)-(q24;q21.1) translocation that is present in the vast majority of APL patients juxtaposes sequences encoding the N-terminal RING-finger and leucine zipper domains of the PML protein with DNA binding, dimerization, ligand binding, and co-repressor interaction domains derived from the C-terminus of the retinoic acid receptor alpha (RARα) [Melnick and Licht, 1999]. Similar to wild-type RARα, PML-RAR binds to target promoters containing a retinoic acid response element. In its unliganded state, PML-RAR binds N-CoR/SMRT, to actively suppress transcription of target genes. The binding of ligand to wild-type RARα induces repositioning of helix 12, which interferes with SMRT/N-CoR binding, and unveils a co-activator binding site [Privalsky, 2004]. This helix 12 switch controls the conversion of RARα the repressor to RARα the activator. PML-RAR, however, fails to undergo the same conformational change. Rather, PML-RAR continues to bind the co-repressor complex at levels of ligand that induce helix 12 movement in the wild-type receptor, to suppress expression of target genes necessary for myeloid differentiation [Melnick and Licht, 1999]. Pharmacologic levels of ligand are needed to overcome the reticence of PML-RAR to reposition helix 12 and allow expression of the target genes (and myeloid differentiation). Indeed, this clinical observation has altered the approach to patients with APL, and inclusion of retinoic acid in treatment strategies has led to remission rates of nearly

90% [Sanz et al., 1999]. The mechanism underlying the relative ligand insensitivity of PML-RAR is still somewhat clouded: several groups have suggested that this is due to dimerization or possibly oligomerization of the receptor [Lin and Evans, 2000]; this hypothesis implies co-operativity of co-repressor binding, which has not yet been demonstrated.

The PLZF-RAR fusion provides another example of aberrant recruitment of a co-repressor complex. PLZF-RAR is derived from t(11;17)(q23;q21), which characterizes a subset of patients with an APL-like disease [Melnick and Licht, 1999]. PLZF-RAR contains the same RAR sequences as in the PML-RAR fusion protein. PLZF itself is a Kruppel-like protein that acts as a constitutive repressor through N-CoR/SMRT recruitment to its N-terminal POZ domain. This protein interaction domain is also retained in the fusion protein, allowing PLZF-RAR to bind N-CoR/SMRT at two sites: one in its RAR-derived C-terminus (ligand-dependent) and the other in its PLZF-derived N-terminal POZ domain (ligand-independent). It is not known whether PLZF-RAR recruits one or two (or more) co-repressor complexes to targets: lack of change in intensity of co-precipitated N-CoR upon exposure of PLZF-RAR to ligand would suggest that one complex might be tethered to two sites in PLZF-RAR [Guidez et al., 1998]. As might be predicted from this model, PLZF-RAR- expressing blasts do not differentiate in response to even pharmacologic levels of retinoic acid, and t(11;17) patients respond poorly to ATRA [Melnick and Licht, 1999].

AML1-ETO provides a similar, albeit more complex model for aberrant co-repressor recruitment. AML1-ETO is derived from the t(8;21)(q22;q22) translocation seen in a high proportion of patients with AML with moderate differentiation (M2 by the French-American-British classification) [Look, 1997]. AML1 is a transcriptional activator, which functions as a heterodimer with core binding factor beta (CBFβ) to activate transcription of a series of genes that are necessary for myeloid development. ETO, whose wild-type function in cells is still under investigation, can bind to N-CoR/SMRT through its C-terminal Zn-finger domains [Gelmetti et al., 1998; Lutterbach et al., 1998; Wang et al., 1998]. AML1-ETO fuses the AML1 runt domain, which mediates DNA binding, to practically the entirety of ETO. AML1 is a transcriptional activator; AML1-ETO is a transcriptional repressor. Although at first glance, AML1-ETO appears to follow the example (in a ligand-independent fashion) of PML-RAR and PLZF-RAR, there is much more to the story. Indeed, the runt domain itself mediates binding with Sin3 [Lutterbach et al., 2000], and hence the AML1-ETO fusion might interact with two different co-repressor complexes.

TESTS OF THE PARADIGM

The AML1-EVI1 fusion generated by the t(3;21) translocation [Tanaka et al., 1995] serves as a test of the paradigm. It generates a fusion protein that binds neither N-CoR nor SMRT, but rather the co-repressor CtBP [Izutsu et al., 2002]. Like the t(8;21) translocation, the AML1 runt domain is retained in this fusion, and so AML1-EVI1 could be viewed as another example of a fusion protein acting as a tether for a co-repressor. However, despite the fact that both AML1-ETO and AML1-EVI1 recruit a co-repressor complex, the leukemias differ, with AML1-EVI1 being found more often in myelodysplastic syndrome and chronic myeloid leukemia blast crisis than in frank AML [Look, 1997]. AML1-EVI1 mice develop AML [Cuenco et al., 2000], yet AML1-ETO mice do not [de Guzman et al., 2002]. It is interesting to speculate whether the difference in phenotype lies in the alternate DNA binding potential of the AML1-EVI fusion (AML1-EVI1 also contains the DNA binding domain of EVI1), the different specificity of HDACs that ETO or EVI1 recruit to the same runt-domain recognition site, or other non-transcriptional effects of the proteins.

HDAC INHIBITION

Probably the most convincing series of experiments to support the importance of co-repressor tethering comes from the ability of HDAC inhibitors to ameliorate the leukemic phenotype induced by these fusion proteins. Both cell models and transgenic mice harboring PML-RAR or PLZF-RAR show increased tendency to differentiate after exposure to HDAC inhibitors [He et al., 1998]. Indeed, there has been one case report of phenylbutyrate, an HDAC inhibitor, inducing remission in a patient with refractory PML-RAR [Warrell et al., 1998]. Wang et al. [1999] have similarly reported induction of

apoptosis and differentiation with HDAC inhibitors in AML1-ETO expressing cells. Phenylbutyrate, suberoylanilide hydroxamic acid (SAHA), valproic acid, and many other HDAC inhibitors are now in clinical trials targeting myeloid leukemias and other malignancies.

EXCEPTIONS TO THE RULE

Not all leukemic fusion proteins fit into a model of a rearranged DNA-binding domain aberrantly anchoring a co-repressor domain to alter expression of transcriptional targets. For example, HOX proteins [Lenny et al., 1997] are transcriptional activators that regulate development cascades of genes, similar to the homeobox proteins of *Drosophila*. HOXA9, HOXD13, HOXA11, HOXA13, HOXC11, HOXD11, and PMX1 have each been reported rearranged in myeloid leukemias; the common fusion partner for these HOX fusions is NUP98 [Borrow et al., 1996; Raza-Egilmez et al., 1998; Kwong and Pang, 1999; Arai et al., 2000; Gu et al., 2003]. Leukemogenesis is dependent on NUP98 and the HOX DNA binding domains [Pineault et al., 2004]. NUP98 is a member of the nucleoporin gene family. It regulates transport of protein and RNA-protein complexes into and out of the nucleus. NUP98 is not known to bind any member of the co-repressor complexes nor HDAC. The NUP98-Hox fusions induce a leukemic phenotype in mice, but their leukemic potential is enhanced by co-expression of one of the so-called Three Amino-acid Loop Extension (TALE) proteins, such as Meis1 [Pineault et al., 2003]. Although it is unclear how TALE proteins synergize with the NUP-fusions, the TALE-binding domain of HOX proteins is lost in the fusion [Pineault et al., 2003], suggesting that they do not interact directly with the HOX-NUP fusion (and thus would likely not be mediators of co-repressor function).

ALTERNATIVE MECHANISMS

Clearly, the AML1-EVI1 and NUP98-HOX fusions do not fit well with the paradigm that the leukemic fusions merely tether co-repressors to transcriptionally active targets. Indeed, there are several lines of evidence to suggest that other properties of the fusion proteins are important for leukemogenesis.

First, there is evidence that the repertoire of genes to which the fusion proteins bind may differ from the wild-type proteins. Detailed studies [Hauksdottir and Privalsky, 2001; Privalsky, 2004] have shown that the preferred sequence binding element for PML-RAR and PLZF-RAR differs from that for wild-type RARα, suggesting that the transcriptional targets differ.

Second, there have been many observations that suggest that protein–protein interactions by the leukemic fusions may impact genes important for myeloid development. For instance, PML-RAR modulates the myeloid transcriptional regulator C/EBPβ through direct protein interaction, as well as by transcriptional regulation [Duprez et al., 2003]. PML-RAR alters the transcriptional activity of the AP-1 transcription complex [Doucas et al., 1993], as does the AML1-EVI1 fusion [Tanaka et al., 1995]. PML-RAR interacts with DNA methyltransferase [Di Croce et al., 2002], implicating a mechanism for gene regulation independent of co-repressors. AML1-ETO interacts with PU.1 to modulate the transcriptional activity of this important regulator of myeloid development [Vangala et al., 2003]. Recently, AML1-ETO has been reported to form stable interactions with E proteins and inhibit E-protein target gene expression by blocking interaction with p300/CBP [Zhang et al., 2004].

Third, the products of the reciprocal translocation may also play a role in modulating myeloid development. The best example is the RAR-PLZF fusion (reciprocal of PLZF-RAR), which contains seven of the PLZF-DNA binding Zn fingers as well as the N-terminal activating region of RARα. Unlike wild-type PLZF, this protein has no POZ domain, and acts to activate transcription of otherwise repressed target genes [Sitterlin et al., 1997]. RAR-PML has as yet no clear assigned activity, but co-expression with PML-RAR has been shown to enhance the rapidity and frequency with which mice develop leukemia [Pollock et al., 2001].

Fourth, whenever a chromosomal translocation results in a fusion protein, there is decreased expression of the wild-type proteins. There is evidence that the resultant hemizygosity may also play a role in leukemogenesis through decreased dose-intensity of the wild-type proteins. For example, wild-type PML may well play the role of a tumor-suppressor gene [Salomoni and Pandolfi, 2002]: it not only regulates the assembly and function of transcription complexes that mediate tumor suppression, but also regulates apoptotic pathways.

It is difficult to separate the importance of indirect actions of the fusion proteins from those mediated by direct DNA binding. Nevertheless, they serve to confound and complicate a unifying hypothesis for the molecular mechanism underlying acute myeloid leukemia.

ACKNOWLEDGMENTS

We would like to acknowledge the UPCI Hematology-Oncology Writing Group for critical reading of the manuscript. We also apologize to the many authors whose work could not be cited because of size constraints of the manuscript.

REFERENCES

Alland L, Muhle R, Hou H, Jr., Potes J, Chin L, Schreiber-Agus N, DePinho RA. 1997. Role for N-CoR and histone deacetylase in Sin3-mediated transcriptional repression. Nature 387:49–55.

Arai Y, Kyo T, Miwa H, Arai K, Kamada N, Kita K, Ohki M. 2000. Heterogenous fusion transcripts involving the NUP98 gene and HOXD13 gene activation in a case of acute myeloid leukemia with the t(2;11)(q31;p15) translocation. Leukemia 14:1621–1629.

Borrow J, Shearman AM, Stanton VP, Jr., Becher R, Collins T, Williams AJ, Dube I, Katz F, Kwong YL, Morris C, Ohyashiki K, Toyama K, Rowley J, Housman DE. 1996. The t(7;11)(p15;p15) translocation in acute myeloid leukaemia fuses the genes for nucleoporin NUP98 and class I homeoprotein HOXA9. Nat Genet 12:159–167.

Chen JD, Evans RM. 1995. A transcriptional co-repressor that interacts with nuclear hormone receptors. Nature 377:454–457.

Cuenco GM, Nucifora G, Ren R. 2000. Human AML1/MDS1/EVI1 fusion protein induces an acute myelogenous leukemia (AML) in mice: A model for human AML. Proc Natl Acad Sci USA 97:1760–1765.

de Guzman CG, Warren AJ, Zhang Z, Gartland L, Erickson P, Drabkin H, Hiebert SW, Klug CA. 2002. Hematopoietic stem cell expansion and distinct myeloid developmental abnormalities in a murine model of the AML1-ETO translocation. Mol Cell Biol 22:5506–5517.

Di Croce L, Raker VA, Corsaro M, Fazi F, Fanelli M, Faretta M, Fuks F, Lo Coco F, Kouzarides T, Nervi C, Minucci S, Pelicci PG. 2002. Methyltransferase recruitment and DNA hypermethylation of target promoters by an oncogenic transcription factor. Science 295:1079–1082.

Doucas V, Brockes JP, Yaniv M, de The H, Dejean A. 1993. The PML-retinoic acid receptor alpha translocation converts the receptor from an inhibitor to a retinoic acid-dependent activator of transcription factor AP-1. Proc Natl Acad Sci USA 90:9345–9349.

Duprez E, Wagner K, Koch H, Tenen DG. 2003. C/EBPbeta: A major PML-RARA-responsive gene in retinoic acid-induced differentiation of APL cells. Embo J 22:5806–5816.

Gelmetti V, Zhang J, Fanelli M, Minucci S, Pelicci PG, Lazar MA. 1998. Aberrant recruitment of the nuclear receptor corepressor-histone deacetylase complex by the acute myeloid leukemia fusion partner ETO. Mol Cell Biol 18:7185–7191.

Gu BW, Wang Q, Wang JM, Xue YQ, Fang J, Wong KF, Chen B, Shi ZZ, Shi JY, Bai XT, Wu DH, Chen Z, Chen SJ. 2003. Major form of NUP98/HOXC11 fusion in adult AML with t(11;12)(p15;q13) translocation exhibits aberrant trans-regulatory activity. Leukemia 17:1858–1864.

Guidez F, Ivins S, Zhu J, Soderstrom M, Waxman S, Zelent A. 1998. Reduced retinoic acid-sensitivities of nuclear receptor corepressor binding to pml- and plzf-rar-alpha underlie molecular pathogenesis and treatment of acute promyelocytic leukemia. Blood 91:2634–2642.

Hauksdottir H, Privalsky ML. 2001. DNA recognition by the aberrant retinoic acid receptors implicated in human acute promyelocytic leukemia. Cell Growth Differ 12: 85–98.

He LZ, Guidez F, Tribioli C, Peruzzi D, Ruthardt M, Zelent A, Pandolfi PP. 1998. Distinct interactions of pml-rar-alpha and plzf-rar-alpha with co-repressors determine differential responses to ra in apl. Nature Genetics 18: 126–135.

Heinzel T, Lavinsky RM, Mullen TM, Soderstrom M, Laherty CD, Torchia J, Yang WM, Brard G, Ngo SD, Davie JR, Seto E, Eisenman RN, Rose DW, Glass CK, Rosenfeld MG. 1997. A complex containing N-CoR, mSin3 and histone deacetylase mediates transcriptional repression. Nature 387:43–48.

Horlein AJ, Naar AM, Heinzel T, Torchia J, Gloss B, Kurokawa R, Ryan A, Kamei Y, Soderstrom M, Glass CK. 1995. Ligand-independent repression by the thyroid hormone receptor mediated by a nuclear receptor co-repressor. Nature 377:397–404.

Izutsu K, Kurokawa M, Imai Y, Ichikawa M, Asai T, Maki K, Mitani K, Hirai H. 2002. The t(3;21) fusion product, AML1/Evi-1 blocks AML1-induced transactivation by recruiting CtBP. Oncogene 21:2695–2703.

Jepsen K, Hermanson O, Onami TM, Gleiberman AS, Lunyak V, McEvilly RJ, Kurokawa R, Kumar V, Liu F, Seto E, Hedrick SM, Mandel G, Glass CK, Rose DW, Rosenfeld MG. 2000. Combinatorial roles of the nuclear receptor corepressor in transcription and development. Cell 102:753–763.

Kwong YL, Pang A. 1999. Low frequency of rearrangements of the homeobox gene HOXA9/t(7;11) in adult acute myeloid leukemia. Genes Chromosomes Cancer 25: 70–74.

Laherty CD, Yang WM, Sun JM, Davie JR, Seto E, Eisenman RN. 1997. Histone deacetylases associated with the mSin3 corepressor mediate mad transcriptional repression. Cell 89:349–356.

Lenny N, Westendorf JJ, Hiebert SW. 1997. Transcriptional regulation during myelopoiesis. Mol Biol Rep 24:157–168.

Lin RJ, Evans RM. 2000. Acquisition of oncogenic potential by RAR chimeras in acute promyelocytic leukemia through formation of homodimers. Mol Cell 5:821–830.

Look AT. 1997. Oncogenic transcription factors in the human acute leukemias. Science 278:1059–1064.

Lutterbach B, Westendorf JJ, Linggi B, Patten A, Moniwa M, Davie JR, Huynh KD, Bardwell VJ, Lavinsky RM, Rosenfeld MG, Glass C, Seto E, Hiebert SW. 1998. ETO,

a target of t(8;21) in acute leukemia, interacts with the N-CoR and mSin3 corepressors. Mol Cell Biol 18:7176–7184.

Lutterbach B, Westendorf JJ, Linggi B, Isaac S, Seto E, Hiebert SW. 2000. A mechanism of repression by acute myeloid leukemia-1, the target of multiple chromosomal translocations in acute leukemia. J Biol Chem 275:651–656.

Melnick A, Licht JD. 1999. Deconstructing a disease: RARalpha, its fusion partners, and their roles in the pathogenesis of acute promyelocytic leukemia. Blood 93: 3167–31215.

Perissi V, Staszewski LM, McInerney EM, Kurokawa R, Krones A, Rose DW, Lambert MH, Milburn MV, Glass CK, Rosenfeld MG. 1999. Molecular determinants of nuclear receptor-corepressor interaction. Genes Dev 13: 3198–3208.

Pineault N, Buske C, Feuring-Buske M, Abramovich C, Rosten P, Hogge DE, Aplan PD, Humphries RK. 2003. Induction of acute myeloid leukemia in mice by the human leukemia-specific fusion gene NUP98-HOXD13 in concert with Meis1. Blood 101:4529–4538.

Pineault N, Abramovich C, Ohta H, Humphries RK. 2004. Differential and common leukemogenic potentials of multiple NUP98-Hox fusion proteins alone or with Meis1. Mol Cell Biol 24:1907–1917.

Pollock JL, Westervelt P, Walter MJ, Lane AA, Ley TJ. 2001. Mouse models of acute promyelocytic leukemia. Curr Opin Hematol 8:206–211.

Privalsky ML. 2004. The role of corepressors in transcriptional regulation by nuclear hormone receptors. Annu Rev Physiol 66:315–360.

Raza-Egilmez SZ, Jani-Sait SN, Grossi M, Higgins MJ, Shows TB, Aplan PD. 1998. NUP98-HOXD13 gene fusion in therapy-related acute myelogenous leukemia. Cancer Res 58:4269–4273.

Redner RL, Wang J, Liu JM. 1999. Chromatin remodeling and leukemia: New therapeutic paradigms. Blood 94: 417–428.

Salomoni P, Pandolfi PP. 2002. The role of PML in tumor suppression. Cell 108:165–170.

Sanz MA, Martin G, Rayon C, Esteve J, Gonzalez M, Diaz-Mediavilla J, Bolufer P, Barragan E, Terol MJ, Gonzalez JD, Colomer D, Chillon C, Rivas C, Gomez T, Ribera JM, Bornstein R, Roman J, Calasanz MJ, Arias J, Alvarez C, Ramos F, Deben G. 1999. A modified AIDA protocol with anthracycline-based consolidation results in high antileukemic efficacy and reduced toxicity in newly diagnosed PML/RARalpha-positive acute promyelocytic leukemia. PETHEMA group. Blood 94:3015–3021.

Sitterlin D, Tiollais P, Transy C. 1997. The RAR alpha-PLZF chimera associated with Acute Promyelocytic Leukemia has retained a sequence-specific DNA-binding domain. Oncogene 14:1067–1074.

Tanaka T, Mitani K, Kurokawa M, Ogawa S, Tanaka K, Nishida J, Yazaki Y, Shibata Y, Hirai H. 1995. Dual functions of the AML1/Evi-1 chimeric protein in the mechanism of leukemogenesis in t(3;21) leukemias. Mol Cell Biol 15:2383–2392.

Vangala RK, Heiss-Neumann MS, Rangatia JS, Singh SM, Schoch C, Tenen DG, Hiddemann W, Behre G. 2003. The myeloid master regulator transcription factor PU.1 is inactivated by AML1-ETO in t(8;21) myeloid leukemia. Blood 101:270–277.

Vermeulen M, Carrozza MJ, Lasonder E, Workman JL, Logie C, Stunnenberg HG. 2004. In vitro targeting reveals intrinsic histone tail specificity of the Sin3/histone deacetylase and N-CoR/SMRT corepressor complexes. Mol Cell Biol 24:2364–2372.

Wang JX, Hoshino T, Redner RL, Kajigaya S, Liu JM. 1998. Eto, fusion partner in t(8-21) acute myeloid leukemia, represses transcription by interaction with the human n-cor/msin3/hdac1 complex. Proceedings of the National Academy of Sciences of the United States of America 95:10860–10865.

Wang J, Saunthararajah Y, Redner RL, Liu JM. 1999. Inhibitors of histone deacetylase relieve ETO-mediated repression and induce differentiation of AML1-ETO leukemia cells. Cancer Res 59:2766–2769.

Warrell RP, He LZ, Richon V, Calleja E, Pandolfi PP. 1998. Therapeutic targeting of transcription in acute promyelocytic leukemia by use of an inhibitor of histone deacetylase. Journal of the National Cancer Institute 90:1621–1625.

Zhang J, Kalkum M, Yamamura S, Chait BT, Roeder RG. 2004. E protein silencing by the leukemogenic AML1-ETO fusion protein. Science 305:1286–1289.