Alterations in Subnuclear Trafficking of Nuclear Regulatory Factors in Acute Leukemia

Shari Meyers[1]* and Scott W. Hiebert[2]

[1]Department of Biochemistry and Molecular Biology, LSUHSC and the Feist-Weiller Cancer Center, 1501 Kings Hwy, Shreveport, Louisiana 71130
[2]Department of Biochemistry, Vanderbilt University School of Medicine, 21st and Garland, Nashville, Tennessee 37232

Abstract   The nuclear matrix plays an important role in the functional organization of the nucleus in part by locally concentrating regulatory factors involved in nucleic acid metabolism. A number of nuclear regulatory proteins initially identified due to their involvement in human cancer are localized to discrete nuclear matrix-attached foci and correct nuclear partitioning likely plays a role in their function. Two such examples are promyelocytic leukemia (PML) and acute myelogenous leukemia-1 (AML-1; Runx1). PML, the target of the t(15;17) in acute PML, is localized to PML nuclear bodies (also termed Nuclear Domain 10 and PML oncogenic domains), a nuclear matrix-associated body whose function appears to be quite complex, with probable roles in cancer, apoptosis, and in acute viral infections. In t(15;17)-containing leukemic cells, the PML nuclear bodies are disrupted, but reform when the leukemic cells are induced to differentiate in the presence of all-trans retinoic acid. *AML1* (*RUNX1*) is a key regulator of hematopoietic differentiation and AML1 proteins are found in nuclear compartments that reflect their roles in transcriptional activation and repression. The t(8;21), associated with AML, results in a chimeric transcription factor, AML-1/ETO (eight twenty one), that remains attached to the nuclear matrix through targeting signals contained in the ETO protein. When co-expressed, ETO and AML-1/ETO co-localize to a nuclear compartment distinct from that of AML1 or PML nuclear bodies. Interestingly, enforced expression of ETO or AML-1/ETO changes the average number of PML nuclear bodies per cell. Thus, chromosomal translocations involving *AML1* result in altered nuclear trafficking of the transcription factor as well as other changes to the nuclear architecture. J. Cell. Biochem. Suppl. 35:93–98, 2000. © 2001 Wiley-Liss, Inc.

Key words: transcription regulatory proteins; acute promyelocytic leukemia (APL); acute myelogenous leukemia (AML); eight-twenty one (ETO); nuclear structure

In the past 30 years the view of the nucleus as composed of nucleoplasm and chromatin has evolved as ordered structures such as the nuclear matrix were identified [Berezney and Coffey, 1974]. Advances in light and electron microscopy techniques, coupled with the localization of individual proteins has revealed that the nucleus is an organized structure and many nuclear proteins have specific sub-nuclear addresses [reviewed in Cardoso and Leonhardt, 1998; Lamond and Earnshaw, 1998]. The nuclear matrix, the non-chromatin nuclear scaffolding, is an integral player in the organization of structure and function in the nucleus performing regulatory roles in DNA replication, transcription, and RNA processing by locally concentrating regulatory factors [reviewed in Strouboulis and Wolffe, 1996; Cardoso and Leonhardt, 1998; Stein et al., 1999]. In cancerous cells, there are marked changes in the structure, size and internal organization of the nuclei [reviewed in Nickerson, 1998]. These changes may be the result of direct changes in the nuclear matrix and/or sub-nuclear localization of regulatory proteins. Because nucleic acid metabolism is organized through DNA and protein contacts with the nuclear matrix, disruption in nuclear architecture can affect the assembly of regulatory protein complexes required for correct gene expression [Stein et al., 1999].

A number of nuclear proteins initially identified due to their involvement in human cancer

are localized to discrete nuclear matrix-attached foci. Two such examples are promyelocytic leukemia (PML) and acute myelogenous leukemia-1; (AML-1; Runx1) [de The et al., 1990; Miyoshi et al., 1991]. PML, the target of the t(15;17) in acute promyelocytic leukemia (APL), is localized to PML nuclear bodies (also termed Nuclear Domain 10 and PML oncogenic domains), a nuclear matrix-associated body whose function appears to be quite complex, with probable roles in cancer, apoptosis, and in acute viral infections [reviewed in Melnick and Licht, 1999; Maul et al., 2000]. The AML1 (RUNX) family of transcription factors consists of three members all sharing structural and functional similarity with the *Drosophila* protein, Runt [reviewed in Speck and Stacy, 1995; Lutterbach and Hiebert, 2000]. These proteins contain a nuclear matrix-targeting signal (NMTS) that directs AML1 proteins to nuclear matrix-associated domains [Zeng et al., 1997]. *AML1* (*RUNX1*) is a key regulator of hematopoietic differentiation and the gene is a frequent target of chromosomal rearrangements in acute leukemias [reviewed in Speck and Stacy, 1995; Lutterbach and Hiebert, 2000]. Chromosomal translocations involving *PML* and *AML1* result in altered nuclear trafficking of these important regulatory factors as well as other changes to the nuclear architecture. This review will focus on the latest findings concerning the appropriate trafficking of transcription regulatory factors and their disruption in acute leukemia.

PML Nuclear Bodies

PML is a member of the RING-B-Box-Coiled-coil (RBCC) family of proteins and functions as a growth suppressor [Reddy et al., 1992; Le et al., 1996]. PML localizes to a discrete set of subnuclear bodies that appear as speckles under immunofluorescence microscopy [Dyck et al., 1994; Weis et al., 1994]. The properties and assembly of PML nuclear bodies have been recently reviewed [Maul et al., 2000] and will only be briefly discussed here. The ring finger/B-box region is involved in localization of PML into nuclear bodies and mutations in critical cysteine residues in the ring finger abolish proper localization and growth suppression [reviewed in Maul et al., 2000]. The typical mammalian nucleus contains 10–20 PML nuclear bodies of varying size (0.3–1.0 μm) [reviewed in Maul et al., 2000]. A number of cellular insults alter the number and distribution of PML nuclear bodies including heat shock, viral infection, and malignant transformation [Melnick and Licht, 1999]. In particular, there is interest in understanding how and why PML nuclear bodies undergo alterations in cancer.

Several proteins are known to co-localize to PML nuclear bodies including Sp100, Sp110, and Sp140, SUMO-1/PIC1, and Daxx, among others [reviewed in Maul et al., 2000]. SUMO-1 is a small ubiquitin-related protein, modifying PML and Sp100 [Sternsdorf et al., 1997; reviewed in Maul et al., 2000]. The Sp100 proteins are a group of closely related transcriptional regulators. For example, a Sp110-DNA binding domain fusion was demonstrated to activate transcription of a reporter gene [Bloch et al., 2000]. Moreover, Sp110 enhanced all-*trans* retinoic acid (ATRA)-mediated expression of a reporter gene containing a retinoic acid response element [Bloch et al., 2000]. Daxx was cloned as an enhancer of Fas-mediated apoptosis [Kiriakidou et al., 1997; Yang et al., 1997]. Interestingly, Daxx is found localized to PML nuclear bodies likely through direct interactions with PML [Zhong et al., 2000]. Daxx association with PML nuclear bodies has been linked to its ability to enhance Fas-induced cell death [Torii et al., 1999; Zhong et al., 2000]. Recently, Daxx was reported to be a repressor of PAX3 and to interact with ETS1 to repress ETS1 target genes [Hollenbach et al., 1999; Li et al., 2000]. Therefore, the composition of the PML nuclear body is complex, housing both transcriptional activators and repressors whose activity may depend on their subnuclear localization.

Studies performed in PML$^{-/-}$ MEFs demonstrated that PML is required for nuclear body formation and integrity [Zhong et al., 2000]. In the absence of PML, Sp100, Daxx, and SUMO-1 all fail to accumulate to PML nuclear bodies [Zhong et al., 2000]. The PML protein is SUMOylated at three lysine residues and the role of SUMOylation on PML nuclear body formation has been investigated. Whereas the SUMOylated form of PML is tightly associated with the nuclear matrix, the unmodified form is not. A PML protein that can not be SUMOylated, 3M-PML, forms fewer nuclear bodies on average that does wild-type PML in PML$^{-/-}$ MEFs, suggesting that SUMOylation is an intra-nuclear targeting modification for PML to localize to nuclear bodies [Zhong et al., 2000]. Further, Daxx accumulation at PML nuclear

bodies requires that PML be SUMOylated [Ishov et al., 1999; Maul et al., 2000].

In t(15;17)-containing acute promyelocytic leukemia, PML is fused to the retinoic acid receptor-α protein (RARα), and the resultant PML-RARα protein disrupts PML nuclear bodies and redistributes their components into smaller microspeckles [de The et al., 1991; Weis et al., 1994]. ATRA treatment of t(15;17)-containing cells results in degradation of PML-RARα, the reformation of PML bodies and the differentiation of the leukemic cells [reviewed in Melnick and Licht, 1999]. Likewise, arsenic trioxide (As_2O_3), which induces clinical remission of APL in ATRA resistant patients, causes a rapid reformation of PML bodies [Zhu et al., 1997; Zhang et al., 2000].

AML (RUNX) Proteins are Directed to Functional Subnuclear Compartments

AML-1B is the largest splice variant of AML-1 [reviewed in Lutterbach and Hiebert, 2000] and can activate and repress transcription through protein contacts. AML-1B attaches to the nuclear matrix though a 31 amino acid peptide, the nuclear matrix-targeting signal (NMTS), residing in the C-terminus [Zeng et al., 1997]. The NMTS is distinct from the nuclear localization signal (NLS) and is sufficient to direct a heterologous nuclear protein to the matrix [Zeng et al., 1997]. The crystal structure of the NMTS was recently determined to 2.7 A resolution by X-ray crystallography. The NMTS forms a finger-shaped loop region (loop I), a hinge-shaped glycine rich turn (GIGIG), and a β-strand (Strand II) [Tang et al., 1999]. The GIGIG may permit rotation between Loop I and Strand II to promote attachment to the nuclear matrix [Tang et al., 1999]. The NMTS is conserved within the AML1 family, all of which are attached to the nuclear matrix [Zeng et al., 1997], suggesting that sub-nuclear localization is critical for the function of these factors.

AML-1B localized to a few prominent subnuclear foci and smaller evenly distributed foci that co-localized with a subset of RNA polymerase II_0. By contrast, a mutant, AML-1B L-D 148, that failed to bind to DNA or to CBFβ, the AML-1 heterodimeric partner, failed to co-localize with RNA polymerase II_0 [Zeng et al., 1998]. Moreover, inhibition of transcription with actinomycin D blocked co-localization of AML-1B with RNA polymerase II_0. Thus, proper nuclear targeting, promoter recognition, and recruitment of RNA polymerase II_0 are linked. The AML-1B foci did not overlap with nuclear speckles containing SC35, which defines bodies that are highly enriched in RNA splicing factors [Zeng et al., 1998]. Because only a subset of AML-1B is associated with RNA polymerase II_0, matrix attachment alone is not sufficient to support AML-1B driven transcriptional activation, although the NMTS is required for some transcriptional activation functions [Zeng et al., 1998].

The RUNX family of proteins can also repress transcription through protein contacts with the mSin3 and Groucho/TLE co-repressors [reviewed in Lutterbach and Hiebert, 2000]. RUNX proteins contain a conserved C-terminal VWRPY motif that mediates the interaction with the Groucho/TLE repressors [reviewed in Lutterbach and Hiebert, 2000]. The VWRPY motif is required for repression of the multidrug resistance promoter and AML-1 cooperates with LEF to repress transcription by binding Groucho [Levanon et al., 1998]. TLE-1 and TLE-2 proteins exhibit a punctate distribution throughout the nucleus and are nuclear matrix attached [Javed et al., 2000]. Double label immunofluorescence microscopy of cells transiently transfected with TLE and AML-1B cDNAs shows that 40–70% of AML-1B foci associate with TLE-1 and TLE-2 in both whole cell and nuclear matrix- intermediate filament (NMIF) preparations. In addition, an AML-3 protein lacking the VWRPY motif or the NMTS does not co-localize with TLE proteins [Javed et al., 2000]. Thus, the AML1 proteins are compartmentalized in the nucleus in association with proteins involved in transcriptional activation and repression.

ETO, the AML1 Translocation Partner in t(8;21) Leukemia, Encodes a Nuclear Matrix Attached Transcriptional Regulator

A number of chromosomal alterations effecting the AML1 gene have been detected in acute leukemias, including the t(12;21), and the t(8;21) [reviewed in Lutterbach and Hiebert, 2000]. In the t(8;21), associated with acute myelogenous leukemia, a portion of the AML1 gene is joined to ETO [Miyoshi et al., 1991]. The resultant hybrid product, AML-1/ETO retains the AML1 DNA binding domain, but the C-terminus of AML-1B is replaced with most of the ETO protein [reviewed in Lutterbach and Hiebert, 2000]. ETO does not bind to DNA but

TABLE I. Function and Localization of ETO Interacting Proteins

Protein	Function	Found in ETO foci
HDACs	Transcriptional repression	Yes
SMRT	Transcriptional repression	Yes
N-CoR	Transcriptional repression	Not known
mSin3A	Transcriptional repression	Yes
Atrophin 1	Transcriptional repression involved in neurodegenerative disease	Yes
PLZF	Transcriptional repression involved in acute promyelocytic leukemia	Not known
AML-1/ETO	Transcriptional repression results from the t(8;21)	Yes

interacts with the nuclear hormone co-repressors N-CoR and SMRT, mSin3A and mSin3B, and histone deacetylases-1 and -2 [reviewed in Lutterbach and Hiebert, 2000], suggesting that ETO functions as a co-repressor (Table I). In fact, ETO cooperates with the promyelocytic leukemia zinc finger protein (PLZF) to repress transcription [Melnick et al., 2000].

Because the t(8;21) fusion removes the AML-1 NMTS, the localization of both ETO and AML-1/ETO has been intensely investigated. ETO contains a non-canonical NLS within AA 241–280 [Odaka et al., 2000]. This region is both sufficient and required for nuclear localization and the NLS is retained in AML-1/ETO [Odaka et al., 2000]. Both ETO and AML-1/ETO are tightly associated with the nuclear matrix [Le et al., 1998; McNeil et al., 1999]. Using epitope-tagged ETO for immunoflourescence studies in whole cell and NM-IF preparations from transiently transfected Saos-2 cells, ETO was localized to distinct sub-nuclear compartments separate from those of AML-1B [McNeil et al., 1999]. In addition, green fluorescent protein (GFP) tagged ETO was both diffusely localized and found in distinct sub-nuclear foci of living cells and the punctate distribution was retained in paraformaldehyde fixed cells [Odaka et al., 2000]. When ETO was analyzed for sub-nuclear localization following transient transfection and detected by using an antibody raised against the zinc-finger portion of ETO [Odoka et al., 2000], the protein was again detected in nuclear foci. ETO proteins deleted for the zinc-finger region formed these sub-nuclear foci to a greater extent than wild-type protein (much less diffuse staining was visible). Further analysis demonstrated that an internal deletion of amino acids 114-216 precluded GFP-ETO from forming nuclear foci [Odaka et al., 2000].

By using dual color fluorescence microscopy, ETO-containing bodies did not co-localize with either speckles containing SC35 or with PML nuclear bodies in hematopoietic K562 cells [Odaka et al., 2000]. However, ETO co-localizes with Atrophin-1, the dentato-rubral and pallido-luysian atrophy gene product, and may act as an Atrophin-1 co-repressor [Wood et al., 2000] (Table I). Atrophin/ETO-containing sub-nuclear particles co-localize with mSin3A and histone deacetylases, but not N-CoR [Wood et al., 2000]. The ETO-containing structures were of similar size and number to PML bodies, but these foci were distinct from PML-containing structures [Wood et al., 2000].

The AML-1 NMTS is removed by the t(8;21), and AML-1/ETO is directed to nuclear foci that overlap with ETO, but not with AML-1B, when transiently expressed [McNeil et al., 1999; Odaka et al., 2000]. These results suggest that in t(8;21)-containing leukemia, AML-1/ETO will localize to ETO sub-nuclear addresses (Table I). It is likely that this alteration in nuclear address changes the number and type of contacts that the fusion protein makes with co-repressors. While this result might have been anticipated from the localization of targeting sequences in AML-1B and ETO, it was not expected that expression of AML-1/ETO would alter other sub-nuclear structures. However, the average number of PML nuclear bodies was increased in Saos-2 cells transiently made to express AML-1/ETO, but not in cells expressing AML1. Like AML1/ETO, ETO-expressing Saos-2 cells also showed increases in the average number of PML nuclear bodies per cell. Although the number of PML nuclear bodies increased per cell, the size of PML bodies remained constant [McNeil et al., 2000]. Thus, it is possible that at least some of AML-1/ETO phenotypes observed in t(8;21)-containing leukemic cells result from reorganization of PML nuclear bodies and perhaps other structures. Given that AML-1/ETO binds co-repressors to repress the

transcription of many AML-1-regulated genes, it will be critical to determine whether re-routing of intranuclear trafficking is required for repression or whether disruption of the nuclear architecture contributes to the leukemic phenotype in other ways.

SUMMARY

We are just beginning to understand the spatial and functional organization of the nucleus in the normal and diseased state. A number of transcription regulatory factors are nuclear matrix attached and localize to discrete subnuclear compartments. One of the best studied of these is PML, a protein required for the organization of the PML nuclear body. In t(15;17) acute promyelocytic leukemia, PML bodies are disrupted, suggesting that loss of the proper localization of the protein components of PML bodies is intimately linked to leukemogenesis. In t(8;21)-containing leukemia, AML-1/ETO is redirected away from AML-1 containing nuclear foci and into ETO-containing nuclear bodies. In contrast to the disruption of PML bodies by PML-RARα, AML-1/ETO does not appear to disrupt ETO nuclear bodies. Interestingly, both AML-1/ETO and ETO effect the number of PML nuclear bodies, suggesting that in t(8;21)-containing leukemia there is modified trafficking of PML and associated proteins. One immediate issue is to define the ETO NMTS, and then to test its role in the biologic function of AML-1/ETO. One possible drawback regarding most of the data presented here concerning the subnuclear localization of ETO and its interacting proteins is that the experiments were carried out with cells engineered to express the proteins of interest. Clearly, reagents powerful enough to look at endogenous proteins are necessary for a clear description of how ETO and AML-1/ETO traffic in the nucleus. Ultimately, it will be critical to understand the links between transcriptional regulation and leukemogenesis and sub-nuclear targeting of the normal and chromosomal translocation fusion proteins.

ACKNOWLEDGMENTS

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