Components of the SMRT Corepressor Complex Exhibit Distinctive Interactions with the POZ Domain Oncoproteins PLZF, PLZF-RARα, and BCL-6*

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Many transcription factors function by repressing gene transcription. For a variety of these transcription factors the ability to physically recruit auxiliary proteins, denoted corepressors, is crucial for the ability to silence gene expression. We and others have previously implicated the SMRT corepressor in the actions of the PLZF transcription factor and in the function of its oncogenic derivative, PLZF-retinoic acid receptor (RARα), in promyelocytic leukemia. We report here that PLZF, and a structurally similar transcriptional repressor, BCL-6, can interact with a variety of corepressor proteins in addition to SMRT, including the mSin3A protein and (for PLZF) histone deacetylase-1. Unexpectedly, these additional interactions with corepressor components are nonequivalent for these otherwise similar oncoproteins, suggesting that transcriptional repression by BCL-6 and by PLZF may differ in mechanism. Furthermore, we demonstrate that the oncogenic PLZF-RARα chimera lacks several important corepressor interaction sites that are present in the native PLZF protein. Thus the t(11;17) translocation that creates the PLZF-RARα chimera generates an oncoprotein with potentially novel regulatory properties distinct from those of either parental protein. Our results demonstrate that otherwise similar transcription factors can differ notably in their interactions with the corepressor machinery.

The study of eukaryotic gene regulation has focused primarily on the mechanisms of transcriptional activation. However, many transcriptional factors function not as activators, but as repressors, or can operate bimodally by mediating both negative and positive effects on gene transcription. Transcription factors capable of repression of gene expression include the Ying-Yang-1 protein, the Mad-Max complex, nuclear hormone receptors such as those for thyroid hormone and retinoic acid, the retinoblastoma gene product, the BCL-6 protein, and the PLZF polypeptide (1–13). Although these transcriptional repressors are structurally and physiologically distinct from one another, they share the ability to interact with components of a multiprotein SMRT-N-CoR corepressor complex (3, 5–7, 9–35). In the prevailing model, these DNA-binding transcription factors are thought to operate by tethering corepressor to a target gene; once so tethered, components of the corepressor complex help mediate the actual events involved in transcriptional silencing (reviewed in Refs. 36 and 37).

A number of potential constituents of the SMRT-N-CoR corepressor complex have been identified, including SMRT/N-CoR, mSin3A/B, histone deacetylase (HDAC)1-1/2, retinoblastoma-associated proteins 46 and 48, and several additional polypeptides of unknown function (23, 24, 26, 27, 29, 34, 38, 39). Different transcription factors interact with different corepressor components; nuclear hormone receptors, for example, bind primarily to the SMRT-N-CoR component, whereas Mad-Max binds to the mSin3A/B polypeptide, and Ying-Yang 1 and the retinoblastoma protein appear to preferentially recruit the HDAC subunit (6, 15–24, 26, 27, 29, 34). Notably, it appears that not all of these potential corepressor polypeptides necessarily assemble in the cell into a single corepressor complex. The retinoblastoma protein, for example, appears to recruit HDAC without a detectable co-association with mSin3 (9, 12, 13). Therefore, different forms of corepressor complex, each with a distinct polypeptide composition, may be utilized by different transcription factors. Once recruited to the DNA, the corepressor assemblage mediates gene silencing by multiple mechanisms that may include covalent modification of the chromatin template by the HDAC component (reviewed in Refs. 36 and 37) and inhibitory interactions with general transcription factors, mediated at least in part by the SMRT subunit (40, 41). The specific set of these corepressor components recruited by a given transcription factor is therefore likely to determine the actual mechanism of gene silencing and to influence the nature of the final transcriptional outcome.

The interactions between corepressor complex and the PLZF and BCL-6 proteins are of particular interest. Both PLZF and BCL-6 were initially identified as human oncogenes activated by chromosomal translocations (42–46). PLZF is associated with t(11;17) translocations found in acute promyelocytic leukemias; these translocations result in synthesis of a novel chimeric protein bearing the N-terminal regions of PLZF linked to the central and C-terminal portions of a retinoic acid receptor (RARα) (Fig. 1A) (42, 44, 45). In contrast, BCL-6 is associated with translocations found in human large cell and follicular lymphomas; these latter translocations result in over-expression of an otherwise structurally unaltered BCL-6 protein (4, 43, 46). Both the native PLZF and BCL-6 polypeptides are composed of an N-terminal "POZ" motif linked to a more C-terminal cluster of reiterated C2-H2 "zinc-fingers" (Fig. 1A), and both proteins are able to function as transcriptional repressors (4, 7, 8, 45–48). The POZ domain is thought to function as a site for protein-protein interactions, whereas the zinc-fingers...
proteins were then incubated with 50 mM sponding immobilized GST fusion protein in 200–300 m total DNA to 5
proteins were eluted in 30 m

We wished to better understand the interactions between these POZ domain-containing proteins and the different components of the SMRT corepressor complex. We report here that PLZF and BCL-6 interact not only with SMRT, but also with additional components of the corepressor complex, and that the interaction between otherwise similar transcriptional repression by BCL-6 and by PLZF may differ in mechanism and/or in manifestation. Furthermore, we demonstrate that the PLZF-RARα chimera generates an oncprotein with potentially novel regulatory properties distinct from those of either parental protein. We conclude that otherwise similar transcription factors can differ notably in their interactions with the corepressor machinery, and that these differences appear to result in distinctive transcriptional properties.

EXPERIMENTAL PROCEDURES

In Vitro Protein-Protein Binding Assays—The construction of the glutathione S-transferase (GST)-SMRT fusions were previously described (7, 20). Similar GST fusion constructs, representing various portions of the mSin3A, HDAC-1, PLZF, or BCL-6 coding regions, were constructed by cleavage of the pGEX-KG vector (52) and the target DNA at appropriate restriction sites and ligation using standard recombinant DNA methodology. The GST fusion proteins were expressed in Escherichia coli strain DH5α, and were purified and immobilized to glutathione-agarose as described previously (52).

35S-Radiolabeled PLZF, PLZF (1–456), PLZF-RARα, BCL-6, (1–418), mSin3A, or SMRT were synthesized in vitro by use of a coupled transcription/translation system (TnT kit, Promega). The 35S-labeled proteins were then incubated with 50 μl of a 50% slurry of the corresponding immobilized GST fusion protein in 200–300 μM Heming buffer (40 mM HEPES, pH 7.8, 50 mM KCl, 0.2 mM EDTA, 5 mM MgCl2, 0.1% Triton X-100, 10% glycerol, 1.5 mM dithiothreitol, 1× Complete Protease Inhibitor (Boehringer-Mannheim), and 0.5 mg/ml bovine serum albumin) for 1 h at 4 °C with gentle rocking. The agarose beads were then washed four times with 1 ml each of HEMG buffer in the absence of protease inhibitor and bovine serum albumin. Bound proteins were eluted in 30 μl of 50 mM Tris-Cl (pH 6.8) containing 10 mM glutathione, were resolved by SDS-polyacrylamide gel electrophoresis, and were visualized and quantified by PhosphorImager analysis (Molecular Dynamics Storm System) (7, 53).

Mammalian Repression Assays—The pSG5 GAL4-DNA binding domain (pSG5 GAL4DBD) vector was created by transferring the HindIII to BamHI portion of pG79/2 (CLONTECH) as a blunt end fragment into the similarly treated EcoRI and BamHI sites of pSG5. The pSG5 GAL4DBD open reading frame in the pSG5 vector was subsequently fused in-frame to various subdomains of PLZF or of BCL-6 by use of appropriate restriction sites and standard recombinant DNA subcloning techniques. Transient transfections of CV-1 cells were performed by a calcium phosphate coprecipitation method (7). Each 60-mm plate, representing 2.5 × 106 transfected cells, contained a pGAL (17 mer)-Luc reporter (7), 125 ng of the pSG5-GAL4DBD vector, 500 ng of a pCH110 vector (Amersham Pharmacia Biotech) as an internal β-galactosidase control, and sufficient PUC19 to normalize the total DNA to 5 μg. Luciferase activity was determined after 48 h. using a luciferase assay kit (Promega) and a TD 20/20 luminometer (Turner Design). The relative light units were normalized to the β-galactosidase activity.

PLZF Interacts with Three Distinct Components of the Corepressor Complex, SMRT, mSin3A, and HDAC-1—We have previously reported that PLZF can bind to purified SMRT in vitro, and that this interaction is mediated, in part, by the POZ domain of PLZF (7). Notably, however, this SMRT-PLZF interaction in vitro was relatively weak, in contrast to the much stronger interaction we observed between PLZF and SMRT in vivo by use of a mammalian two-hybrid assay (7). Other researchers have also demonstrated that PLZF and BCL-6 strongly interact with the SMRT corepressor complex in vitro by both two-hybrid and co-immunoprecipitation methodologies (10, 11, 51). We therefore investigated if these enhanced interactions in vivo might reflect a stabilization of the PLZF/SMRT association by additional contacts between PLZF and other components of the corepressor complex.

To address which components of the corepressor complex interact directly with PLZF, we employed a protein-protein binding (“GST-pull-down”) assay. This in vitro strategy was used to avoid the difficulties of distinguishing direct interactions from the indirect (“bridging”) interactions that can occur in a two-hybrid co-immunoprecipitation assay. For our first determinations, radiolabeled SMRT or mSin3A were synthesized in vitro by coupled transcription/translation, and were tested for the ability to bind to different domains of PLZF (Fig. 1A), each synthesized in bacteria as GST fusions and immobilized on an agarose matrix. As expected from prior analysis, SMRT bound to PLZF under these conditions (Fig. 2A), with
the interaction mediated by the PLZF POZ domain (amino acids 1–120); although this SMRT-PLZF interaction was modest, it was clearly above the background binding observed with a nonrecombinant GST control, or with constructs representing the C-terminal domains of PLZF (Fig. 2A). Intriguingly, PLZF was also able to independently bind to mSin3A under the same conditions (Fig. 2B). Notably, this interaction between mSin3A and PLZF was somewhat stronger than that observed between SMRT and PLZF, and was mediated by multiple domains representing both the POZ and zinc-finger regions of PLZF (Fig. 2B).

The interaction between SMRT and PLZF was reciprocal, in that radiolabeled full-length PLZF was able to bind to appropriate GST fusions of SMRT (Fig. 3A, and quantified in Fig. 4A, solid bars). The N-terminal domain of SMRT (amino acids 96–566) mediated the majority of the interaction with PLZF under these conditions, although a secondary interaction could also be observed between PLZF and more C-terminal regions of SMRT (Figs. 3A and 4A), this pattern is quite distinct from that observed for retinoic and thyroid hormone receptors, which interact exclusively with the C-terminal region of SMRT (encompassing amino acids 1055–1495) (18, 20, 21, 30, 53). Little or no PLZF bound to the nonrecombinant GST employed as a negative control, or to an assortment of SMRT mapping outside of the N- and C-terminal interaction domains noted above (Figs. 3 and 4).

Similarly, the interaction between mSin3A and PLZF was also reciprocal, with radiolabeled PLZF binding to GST derivatives of mSin3A (Fig. 3C, and quantified in Fig. 4B, solid bars). The mSin3A molecule is comprised of four repetitive domains believed to represent paired amphipathic helices (denoted PAH-1 through 4), separated by regions of unique sequence (Fig. 1B). Two mSin3A domains, representing amino
In contrast to these parallels between the interactions of BCL-6 and PLZF with SMRT, the interactions of BCL-6 with mSin3A and with HDAC-1 were notably different from those exhibited by PLZF. BCL-6 shared the ability of PLZF to bind to mSin3A, and this interaction mapped to amino acids 1–140 (including the POZ domain) and amino acids 418–706 (including C-terminal zinc-finger motifs) of BCL-6 (Fig. 2D). However, when individual subdomains of mSin3A were tested as GST-fusions in our in vitro assay, BCL-6 interacted exclusively with the PAH-3 region of mSin3A (amino acids 404–545); this was in clear contrast to the behavior of PLZF, which interacted equally with both the PAH-1 and PAH-3 mSin3A domains (compare Fig. 3, C and D, and quantified in Fig. 4B, compare cross-hatched bars to solid bars). Perhaps even more notable was that BCL-6 exhibited little or no ability to bind to HDAC-1, in contrast to the strong interaction observed between PLZF and HDAC-1 in the same assay (compare Fig. 3, E to F, and Fig. 4C, cross-hatched bars to solid bars). Thus, despite sharing a similar architecture and a common ability to recruit SMRT and mSin3A, the detailed contacts with the corepressor complex differ significantly between PLZF and BCL-6.

**Truncation of PLZF by the t(11;17) Translocation in Human Acute Promyelocytic Leukemia Results in the Loss of Several Important Corepressor Interactions That Are Mediated by the Native PLZF Polypeptide**—The t(11;17) translocation implicated in human acute promyelocytic leukemias results in synthesis of a chimeric PLZF-RARα protein containing only the first 456 amino acids of the native PLZF polypeptide (42, 44, 45). We wished to investigate the effects of this PLZF truncation on corepressor recruitment. We therefore first tested the ability of a truncated PLZF construct, limited to amino acids 1–456, to interact with the individual components of the corepressor complex. In contrast to full-length PLZF, the PLZF (1–456) derivative was significantly impaired in its ability to bind to SMRT (compare Fig. 5A to Fig. 4A, solid bars). This was observed principally as a severe inhibition of the ability of the truncated PLZF protein to bind to the N-terminal domain of SMRT (SMRT amino acid 96–566), whereas the weaker interactions observed between the wild-type PLZF and the C-terminal domain of SMRT appeared to be largely preserved in the PLZF (1–456) construct (Fig. 4A and Fig. 5A, solid bars and data not shown). For comparison, we created an analogous C-terminal truncation of BCL-6, comprised of the first 418 amino acids, but lacking most of the C-terminal zinc-finger motifs. In contrast to the effects of truncation on PLZF, the BCL-6 (1–418) truncation exhibited an enhanced interaction with SMRT relative to native BCL-6; this was most evident as a greatly increased binding to GST constructs representing the N-terminal (amino acid 96–566) SMRT domain (compare Fig. 5A to Fig. 4A, cross-hatched bars). Therefore, although the interactions of full-length BCL-6 and PLZF with SMRT appear to be similar, the precise determinants controlling these interactions must in fact differ.

In addition to displaying a severely impaired interaction with SMRT, the PLZF (1–456) truncation also lost the ability to bind to HDAC-1 and to the PAH-3 domain of mSin3, but retained the ability to interact with the PAH-1 mSin3A (amino acids 57–215) domain (compare Fig. 5, B and C, with Fig. 4, B and C, solid bars). Intriguingly, the analogous BCL-6 (1–418) truncation exhibited a similar loss in its ability to bind to the mSin3A PAH-3 domain (and in common with the native BCL-6, failed to bind to either HDAC-1 or the PAH-1 domain of mSin3A).
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mSin3A) (compare Fig. 5, B and C, with Fig. 4, B and C, cross-hatched bars). It should be noted that the truncated BCL-6 (1–418) protein did not lose all interaction with mSin3A; although the PAH-3 contact was the only mSin3A interaction observed when individual PAH mSin3A domains were employed as GST fusions, a GST-BCL-6 (1–140) truncation did nonetheless bind, if modestly, to full-length mSin3A (Fig. 2D). It appears likely that either (i) an interaction surface present in full-length mSin3A is bisected (and thereby inactivated) in the individual GST-PAH domain fusions tested in Fig. 5, or (ii) the interaction detected between the N terminus of BCL-6 and mSin3A may require cooperative contacts with multiple mSin3A interaction surfaces. Taken as a whole, our results indicate that the zinc-finger domains of both BCL-6 and PLZF contribute to the ability of these proteins to interact with mSin3A. In the case of PLZF, but not BCL-6, these C-terminal zinc-finger domains also help stabilize interaction of the proto-oncoprotein with SMRT and with HDAC-1.

Thus, the loss of PLZF C-terminal sequences in the t(11;17) translocation disrupts several corepressor interactions that are conferred by the wild-type PLZF protein. However, the t(11;17) translocation also joins to PLZF a novel and potent SMRT interaction surface contributed by the RARα sequences (16–18, 20–22). We therefore next examined the corepressor interactions mediated by the chimeric PLZF-RARα polypeptide. Given that the RARα interaction with SMRT is inhibited by hormone ligand (16, 17, 20, 54), we performed these experiments both in the presence and absence of all-trans-retinoic acid. The PLZF-RARα chimera displayed corepressor interactions that appeared to be a sum of the interactions observed for the individual PLZF (1–456) and RARα components (Figs. 6 and 7).

Specifically, a strong, hormone-labile interaction was observed between PLZF-RARα and the SMRT (1055–1291) domain, presumably reflecting the contribution of RARα-derived sequences, and a weaker, hormone-independent interaction was observed between PLZF-RARα and the SMRT (96–566) and SMRT (1291–1495) domains that are presumably contacted by the PLZF moiety (Fig. 6A, and quantified in Fig. 7, A and B). The PLZF-RARα construct also interacted with mSin3A in a manner consistent with the sum of the interactions observed individually for the PLZF (1–456) truncation and for the native RARα protein (Fig. 6B and Fig. 7, C and D), whereas neither RARα nor the PLZF-RARα chimera interacted strongly with HDAC-1 (data not shown). We conclude that the PLZF-RARα chimera manifests a novel combination of corepressor contacts that is an incomplete and permuted sum of the contacts observed individually for the native PLZF and RARα proteins.

BCL-6 and PLZF Manifest Distinct Transcriptional Silencing Properties—We wished to determine if the nonidentical interactions observed for BCL-6 and PLZF with the different components of the corepressor complex might result in distinct transcriptional regulatory properties. To more readily permit comparisons, we expressed each protein as a GAL4DBD fusion, and determined the ability of the resulting proteins to repress basal expression of an appropriate GAL4(17-mer) luciferase reporter (Fig. 8). Notably, both full-length PLZF and full-length BCL-6 functioned as strong transcriptional repressors in this assay, inhibiting expression of the reporter gene construct by 40–50-fold. Apparently, therefore, a direct interaction with HDAC-1 is not required for efficient transcriptional silencing by BCL-6. In contrast to the strong repression properties exhibited by the full-length proteins, repression by C-terminal truncations of either PLZF or BCL-6 was impaired. The effect of the C-terminal truncation on PLZF was particularly severe, with the PLZF (1–456) construct mediating only 10% of the repression observed for the full-length PLZF construct. This is consistent with the disruption of PAH-3/mSin3A, SMRT, and
HDAC-1 interactions observed for this truncation in vitro. In contrast, repression by the comparable truncation of BCL-6 (expressing BCL-6 amino acids 1–418), although reduced, was nonetheless nearly half that observed for the wild-type protein. Similarly, still more severely truncated constructs limited to the POZ domain of PLZF exhibit little or no repression in this assay, whereas a near-equivalent construct containing the POZ domain of BCL-6 exhibits clearly detectable repression. We suggest that the C-terminal zinc-finger motifs present in both the BCL-6 and PLZF proteins contribute to transcriptional silencing by both polypeptides, but the C-terminal determinants of PLZF are more crucial for efficient gene silencing than are the corresponding sequences in BCL-6.

**DISCUSSION**

The POZ Domain Proteins PLZF and BCL-6 Interact with Multiple, but Nonidentical Components of the SMRT-N-CoR Corepressor Complex—Both PLZF and BCL-6 were first identified as human oncogenes that can be "activated" in neoplasia by chromosomal translocations. Intriguingly, the requirements for, and consequences of, oncogenic activation differ for the two different proteins. BCL-6 translocations lead to overexpression of an otherwise intact polypeptide, and are associated with follicular and large cell neoplasias (4, 43, 46). PLZF translocations, on the other hand, result in the production of a chimeric PLZF-RARα polypeptide implicated in myeloid leukemias (42, 44, 45). The functions of BCL-6 and PLZF in the normal organism also appear to differ; PLZF has been implicated, in part, in central nervous system development, whereas BCL-6 appears to be required for the formation of the germinal centers of the immune system (55–59). Nonetheless, both of these proteins possess a similar overall architecture, consisting of an N-terminal POZ domain linked to highly reiterated, C-terminal zinc-finger motifs, both BCL-6 and PLZF can bind to defined DNA sequences and mediate repression in transfection assays (4, 7, 8, 46, 48, 50), and as shown here, both proteins exhibit the ability to interact with important components of the SMRT-N-CoR corepressor complex.

We had previously reported that although PLZF interacts with SMRT, this interaction is relatively weak in vitro, and is greatly stabilized in vivo, presumably through interactions with additional components of the corepressor complex (7). Here, we demonstrate that PLZF does indeed make contact with at least two additional components of corepressor complex, namely mSin3A and HDAC-1. These interactions, assayed in vitro, are summarized in Table I. While this work was nearing completion, several other groups, using a variety of two-hybrid and co-immunoprecipitation techniques, demonstrated that PLZF can also interact with these components of the corepressor complex in vivo (10, 11, 51).

Intriguingly, BCL-6 shares the ability of PLZF to contact SMRT and mSin3A, but in contrast to PLZF, BCL-6 interacts only weakly with HDAC-1 (Table I) (25). Thus, PLZF and BCL-6 differ in these properties from one another, and from
other transcription factors that contact primarily a single subunit of the corepressor complex. Why such a multiplicity of interactions? If the corepressor complex is, in fact, a single entity with an unmutable composition, the multiple subunit contacts mediated by PLZF and BCL-6 may simply serve to enhance and stabilize recruitment of the corepressor to a target promoter. Also conceivable is that the multiple contacts made between the POZ proteins and the corepressor complex may serve a regulatory role, with the different subunit contacts regulating the functions of the corepressor complex after it is tethered to a target promoter. Alternatively, it appears likely that multiple forms of the corepressor complex can exist in cells, each with a different subunit composition (9, 12, 13). PLZF, by contacting three different corepressor components, may therefore recruit a "PLZF-specific" corepressor complex to its target promoters that differ in composition from the complexes recruited by BCL-6, by Mad/Max, or by the nuclear hormone receptors.

**Sequences Outside of the Shared POZ Domain Play Critical Roles in Defining Interactions with the Corepressor Complex**—The POZ domain appears to be an important motif for a variety of protein-protein interactions; for example, the POZ domain of PLZF plays a role in the ability of this protein to homodimerize, to heterodimerize with PML, and to localize to the proper subnuclear compartments (47, 49). As reported here, the POZ domain also represents one determinant through which BCL-6 and PLZF interact with components of the SMRT corepressor complex. These results are consistent with previous work indicating that the integrity of the POZ domain is necessary for transcriptional repression by BCL-6 and by PLZF (4, 8, 46, 48, 49). Unexpectedly, however, our work demonstrates that additional protein determinants, including the zinc-finger domain, also participate in the interaction with the corepressor complex by stabilizing the interactions of PLZF and BCL-6 with the PAH-3 domain of mSin3A, and the interactions of PLZF with SMRT and with HDAC-1.

| SMRT       | mSin3A PAH-1 | mSin3A PAH-3 | HDAC-1 |
|------------|--------------|--------------|--------|
| RARα       | ++           | ++           | ++     |
| PLZF       | ++           | ++           | ++     |
| PLZF ΔCα    | /+           | +            | ++     |
| PLZF-RARα  | ++           | ++           | ++     |
| BCL-6      | ++           | ++           | ++     |
| BCL-6 ΔCα  | ++           | ++           | ++     |

* Interaction in the absence of retinoic acid.

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Note Added in Proof—After this manuscript was first prepared, a parallel study was published that, by use of both in vitro and in vivo methodologies, demonstrated a similar multiplicity of interactions and BCL-6, in that C-terminal truncations of the former exhibit only weak repression properties, whereas C-terminal truncations of the latter retain relatively strong repression properties. Finally, the multiplicity of the interactions described here appear to account for the strong overall interaction between PLZF or BCL-6 and the corepressor complex observed in vivo, despite the relatively modest individual nature of the individual interactions that are detected when the separate components of the corepressor complex are tested in vitro.
between PLZF, BCL-6, and the different components of the SMRT-mSin3A-HDAC complex (David, G., Alland, L., Hong, S.-W., Wong, C.-W., DePinho, R. A., and Dejean, A. (1998) Oncogene 16, 2549–2556).

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