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Activation of *G0S2* is coordinated by recruitment of PML/RARα and C/EBP to its promoter during ATRA-induced APL differentiation

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Abstract

All-*trans* retinoic acid (ATRA) binds the promyelocytic leukemia/retinoic acid receptor α (PML/RARα) fusion protein and is an effective oncogene-targeted therapy for acute promyelocytic leukemia (APL). However, the molecular basis of PML/RARα-mediated transcriptional control during ATRA-induced differentiation is unclear. Previous studies have shown that the PML/RARα fusion protein behaves as a type II nuclear receptor, binding to DNA regardless of ligand status. Here, we performed a series of chromatin immunoprecipitation (ChIP)-quantitative PCR (qPCR) experiments, demonstrating that there is an additional mode of action of PML/RARα, wherein PML/RARα does not bind DNA in the absence of ATRA but binds DNA and activates adjacent genes in the presence of ATRA. This mode of action is similar to that of a type I nuclear receptor and is highlighted by activation of G0/G1 switch gene 2 (*G0S2*) during ATRA-induced neutrophil differentiation of leukemia cell lines (NB4 and PR9) and primary human APL cells. C/EBP occupancy of the *G0S2* promoter was elevated in parallel with recruitment of PML/RARα in ATRA-treated NB4, PR9, and primary APL cells. Furthermore, we verified that the p30 isoform of C/EBP is crucial for activation of *G0S2* and that PML/RARα interacts physically and cooperates functionally with C/EBP to up-regulate *G0S2*. Our data not only demonstrate a new mode of action of PML/RARα but also suggest a novel model in which PML/RARα synergizes with C/EBP to reactivate the C/EBP target *G0S2*, thereby contributing to ATRA-mediated APL differentiation and potentially, clinical remission.

Supporting Information