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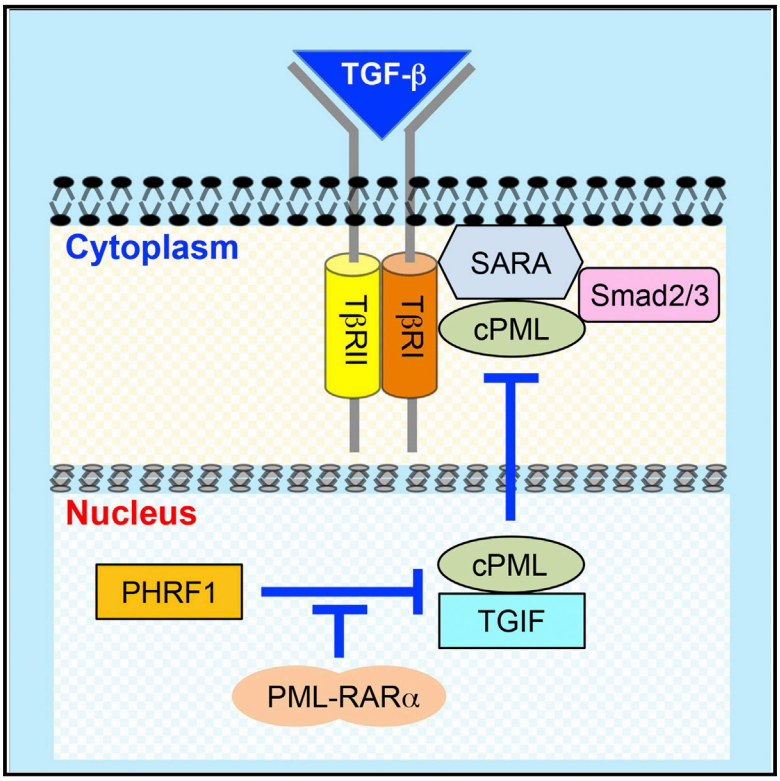
Report

Disruption of the PHRF1 Tumor Suppressor Network by PML-RARα Drives Acute Promyelocytic Leukemia Pathogenesis

Graphical Abstract



Highlights

- PML-RARα stabilizes TGIF by antagonizing PHRF1 activity
- PML-RARα and PHRF1 form mutually exclusive complexes with TGIF
- Enforced expression of PHRF1 restores TGF-β signaling in APL blasts
- Suppression of PHRF1 activity contributes to the pathogenesis of APL

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In Brief

Disruption of the TGF-β tumor suppressor network by PML-RARα contributes to acute promyelocytic leukemia pathogenesis, but the underlying mechanisms remain unclear. Prunier et al. show that PML-RARα associates with and engages TGIF in a complex that compromises its interaction with PHRF1, culminating in TGIF accrual and attenuated TGF-β signaling.

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Disruption of the PHRF1 Tumor Suppressor Network by PML-RARα Drives Acute Promyelocytic Leukemia Pathogenesis

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SUMMARY

PHRF1 functions as an essential component of the TGF-β tumor suppressor pathway by triggering degradation of the homeodomain repressor factor TGIF. This leads to redistribution of cPML into the cytoplasm, where it coordinates phosphorylation and activation of Smad2 by the TGF-β receptor. In acute promyelocytic leukemia (APL), acquisition of PML-RARα is known to impede critical aspects of TGF-β signaling, including myeloid differentiation. Although these defects are thought to rely on suppression of cPML activity, the mechanisms underlying this phenomenon remain enigmatic. Here, we find that an abnormal function of PML-RARα is to interfere with TGIF breakdown, presumably by competing with PHRF1 for binding to TGIF, culminating in cPML sequestration and inactivation. Enforcing PHRF1 activity is sufficient to restore TGF-β cytostatic signaling in human blasts and suppress APL formation in a mouse model of APL, providing proof-of-concept data that suppression of PHRF1 activity by PML-RARα represents a critical determinant in APL pathogenesis.

INTRODUCTION

The PML tumor suppressor plays an important role in constraining both hematological and non-hematological malignancies, yet much remains to be learned about how it is regulated or how it might be inactivated during tumor progression (de Thé et al., 2012; Dos Santos et al., 2013). In the vast majority of acute promyelocytic leukemia (APL) patients, PML is fused to RARα, engendering an oncogenic fusion protein PML-RARα capable of initiating acute leukemia by suppressing differentiation along the myeloid lineage (Grignani et al., 1993; Scaglioni and Pandolfi, 2007). In transgenic mice, ectopic expression of PML-RARα in the myeloid lineage causes leukemia with features of APL, underscoring unequivocally the causal role for PML-RARα acquisition in APL development (Brown et al., 1997). Functionally, PML-RARα was initially thought to act as a transcriptional repressor to antagonize myeloid differentiation and promote APL-initiating cell self-renewal. However, there is accumulating evidence that PML-RARα can also interfere with the ability of the PML isoforms encoded by the intact remaining allele to elicit a variety of tumor-suppressive functions, such as growth arrest and terminal differentiation (de Thé and Chen, 2010; Licht, 2006; Salomoni and Pandolfi, 2002; Scaglioni and Pandolfi, 2007). For instance, PML-RARα has been shown to antagonize cPML activity that is instrumental to integration of the transforming growth factor beta (TGF-β) tumor suppressor program (Lin et al., 2004). Yet, the molecular mechanisms by which PML-RARα disables cPML function in TGF-β signaling remain to be elucidated.

TGF-β signaling is initiated by the formation of a complex consisting of two types of transmembrane Ser/Thr kinase receptor, TβRI and TβRII (Massagué, 2008). TGF-β binding to TβRII induces recruitment and phosphorylation of TβRI, which in turn phosphorylates Smad2 and Smad3 (Smad2/3), a process facilitated by the adaptor protein SARA (Massagué, 2008). The role of cPML in TGF-β signaling is to bridge together Smad2/3 and SARA and bring that complex within the proximity of TβRI (Lin et al., 2004; Seo et al., 2006). Phosphorylation of Smad2/3 induces association with Smad4 and translocation of the complexes to the nucleus, where they regulate expression of TGF-β target genes (Massagué, 2008).

The phosphorylation of Smad2/3 can be limited from the nucleus by TGIF (TG-interacting factor), which belongs to the TALE family of homeodomain proteins. Mechanistically, TGIF interacts with and interferes with the nucleocytoplasmic transit of cPML, thereby precluding assembly of the cPML/SARA complex and concomitant phosphorylation of Smad2/3 (Ettahar et al., 2013; Faresse et al., 2008; Lin et al., 2004; Seo et al., 2006). Besides cPML, TGIF has also been shown to interact with retinoic acid receptor alpha (RARα) and repress its transcriptional activity (Bartholin et al., 2006).

Collectively, these observations underscored an ability of TGIF to associate with both cPML and RARα, raising the question of whether there is any functional interplay between TGIF and