4 Molecular Genetics of Acute Promyelocytic Leukemia

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Introduction

In 1957, Dr. L.K. Hillestad published a case series describing three patients with a rapidly lethal form of acute myeloid leukemia characterized by the accumulation of promyelocytes in the peripheral blood and bone marrow and coagulopathy, leading to hemorrhage, which he termed acute promyelocytic leukemia (APL) [1]. The first signal of disease control came in the 1970s with the application of anthracyclines to the treatment of APL. *All-trans*-retinoic acid (ATRA) entered the stage in 1985 [2–4] and was followed shortly thereafter by mapping of the hallmark genetic translocation t(15;17) to the retinoic acid receptor alpha (RARα) [5–10]; thus, commenced an era of molecular genetic study into APL. Arsenic trioxide (ATO) entered the clinic in 1994 [11–14] and laid the foundation for the seminal Phase II trial of ATRA and ATO by Estey and colleagues [15] followed by the landmark Phase III trial of the combination by Lo-Coco and colleagues in 2013 [16]. APL is an unparalleled story—the first example of a malignancy cured by targeted therapy. Alongside profound molecular insights lies a history rooted in traditional Chinese medicine with therapy informing science and science informing therapy leading to phenomenal success against this once-fatal disease.

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PML-RARα/RARα-PML and Other APL Translocations in Leukemogenesis

APL is associated with balanced and reciprocal translocations characterized by involvement of the RARα gene on chromosome 17 [5, 17–19]. To date, nine different translocation partners have been identified (atlastgeneticsoncology.org) including fusions with PLZF t(11;17) (q23;q21) [20], NPM1 t(5;17)(q32q21) [21], and NuMA t(11;17)(q13,q21) [22], the so-called "X" partner genes for RARα [23]. PML is by far the dominant partner gene with t(15;17) being present in 98% of cases (Fig. 4.1) [20]. An early question in the field was whether the oncoproteins encoded by such translocations were necessary and sufficient for leukemogenesis. Transgenic mouse models of APL were instrumental in addressing this fundamental question [24–28]. This approach was also utilized to address the role of reciprocal translocations, such as RARα-PML and RARα-PLZF, in the initiation and progression of disease [29–31].

In 1997 multiple groups successfully recapitulated the salient features of human APL in

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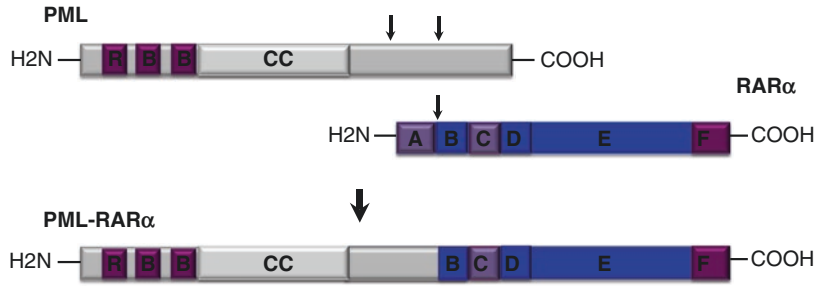

Fig. 4.1 Schematic of the PML-RARα fusion oncoprotein with functional domains. For PML, the RING (R), B boxes (B), and coiled-coil (CC) domains are indicated. For RARα, the DNA-binding domain (C) and ligand-binding domain (E) are indicated, and A, B, D, and F represent additional motifs

transgenic mouse models engineered to express the fusion PML-RARα oncoprotein under the control of myeloid-specific promoters, thus demonstrating that PML-RARα mediates leukemogenesis [24–26]. Interestingly, the models displayed a long latency and incomplete penetrance in developing acute leukemia suggesting that a "second hit" was involved; as we discuss below, RARα-X, the reciprocal product of the translocation, can act as a "second hit." The preleukemic stage in these transgenic models was characterized by myeloproliferation with the accumulation of myeloid progenitors in the bone marrow and spleen. Few additional genetic hits were identified in these models consistent with the notion that PML-RARα is the main driver of the disease, albeit not sufficient. This is coherent with a unique feature of APL, the consistent incidence of the disease across ages, which suggests that a single genetic event drives transformation [32]. Additional oncogenic events such as activation of fms-related tyrosine kinase through the FLT3-ITD mutation, NRAS mutation, and MYC overexpression promote disease penetrance or progression in mice and humans [33].

That the X-RARα translocations are disease-defining events was first hinted at by the differential response to ATRA and chemotherapy observed in patients harboring t(11;17) compared to t(15;17) APL, poor and favorable, respectively [34, 35]. That a distinct biology is prescribed by t(11;17) was also captured in the PLZF-RARα transgenic mouse model which developed disease reminiscent of a myeloproliferative neoplasm (Fig. 4.2); myeloid precursors retained the ability to terminally differentiate, and myeloid cells at different stages of maturation accumulated in the bone marrow and spleen [25]. This was cemented by seminal, preclinical studies showing that ATRA, ATO, and ATRA plus ATO prolonged survival in PML-RARα transgenic mice, whereas PLZF-RARα transgenic mice fail to attain complete remission in response to any of the three treatments (Fig. 4.2) [36]. Subsequent generation of the NPM-RARα TM allowed comparison with the PML- and PLZF-RARα TMs. In addition to cytomorphologic differences, the NPM-RARα TM also responded to treatment with ATRA or ATO like the PML-RARα TM, but different from the PLZF-RARα TMs. Interestingly, the NPM-RARα fusion oncoprotein was localized to the nucleolus suggesting possible interference with native NPM function [28]. Thus, X-RARα translocations and the encoded fusion proteins drive distinct biologic programs, and this translates into differential response to therapy.

As previously noted, translocations in APL are balanced and reciprocal. This begs the question—does RARα-X play an active role in leukemogenesis or is it merely a passenger? TMs again provided insights into the biologic role of RARα-Xs (Fig. 4.2). As with X-RARα, one size does not fit all. RARα-PML/PML-RARα TM displays increased penetrance of disease [29] consistent with an oncogenic role for RARα-PML. As noted above, PLZF-RARα TM develops disease that is MPN-like and falls short of leukemia;

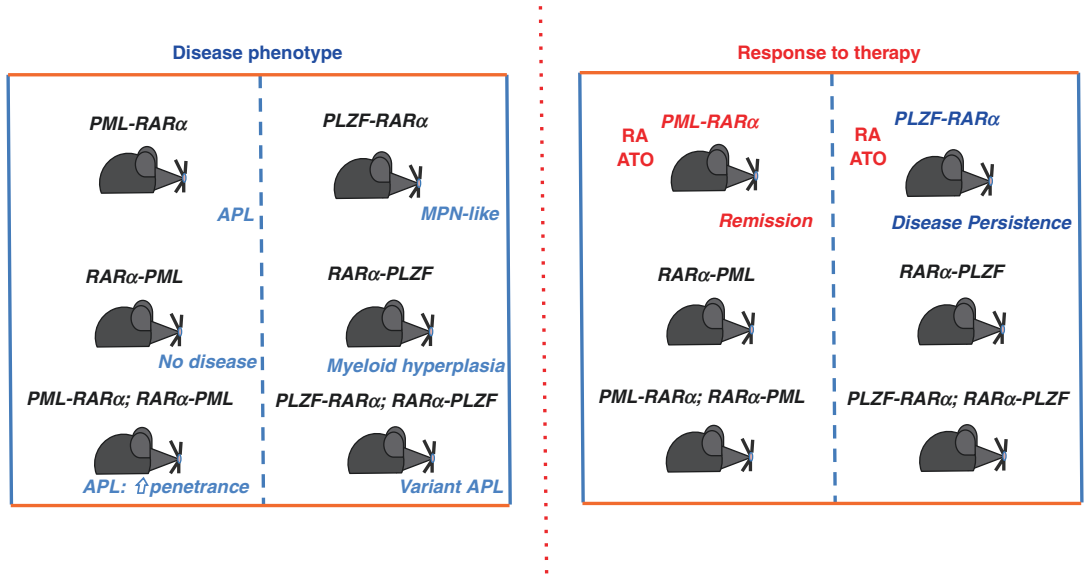

Fig. 4.2 Murine X-RARα and RARα-X transgenic models (TMs) recapitulate human APL and predict response to curative combination therapy. TMs bearing X-RARα, RARα-X, or both were generated (where X is either PML or PLZF). TMs reveal that the X partner protein modulates disease phenotype and dictates response to therapy

RARα-PLZF TM develop myeloid hyperplasia, but strikingly RARα-PLZF/PLZF-RARα TM develop APL-like disease [30]. In this regard, it is worth noting that RARα-PLZF expression is pervasive in t(11;17) human APL [34, 37].

Another layer of molecular detail was added by studies investigating whether transcriptional repression or activation by PML-RARα is required for leukemogenesis. Interestingly, the breakpoint for the RARα gene is consistently within the same intron [38] and results in preservation of the DNA-binding, ligand-binding, and RXR-binding domains. With multiple translocations involving RARα leading to the same phenotypic disease, the classical model of APL pathogenesis centers on suppression of RA signaling through repression of RARα target genes by a PML-RARα with dominant-negative activity. This model is in line with RARα regulation of myeloid differentiation, the block in differentiation seen in APL cells, and the ensuing differentiation of APL cells in response to pharmacologic retinoic acid. In support of this model, X-RARα proteins retain the ability to heterodimerize with RXR and bind to DNA RARE and the RA ligand, like the native RARα protein [39, 40]. Lending further support to the model, multiple lines of evidence indicated that X-RARα act as "super repressors" secondary to increased affinity for nuclear corepressors and histone deacetylases (HDAC) [41–43]. At pharmacologic doses of RA, the PML-RARα oncoprotein dissociates from corepressors/HDAC and transactivates RARα target genes (Fig. 4.3). And again, X-RARα specificity was observed since RA did not disrupt the PLZF-RARα interaction with corepressors. Interestingly, HDAC inhibitors did overcome transcription repression in the case of both PML-RARα and PLZF-RARα [41–43]. Investigators searched for the molecular basis for the observed "super repressor" activity of X-RARα. Oligomerization of X-RARα emerged as key to the repressive activity [44–46], and this was postulated to be due to more effective competition with native RARα for RXR binding as well as recruitment of X-moiety corepressors in the case of PML [47, 48].

The pivotal role of the X-moiety of the fusion oncoprotein in APL pathogenesis was further highlighted by studies by Kogan and

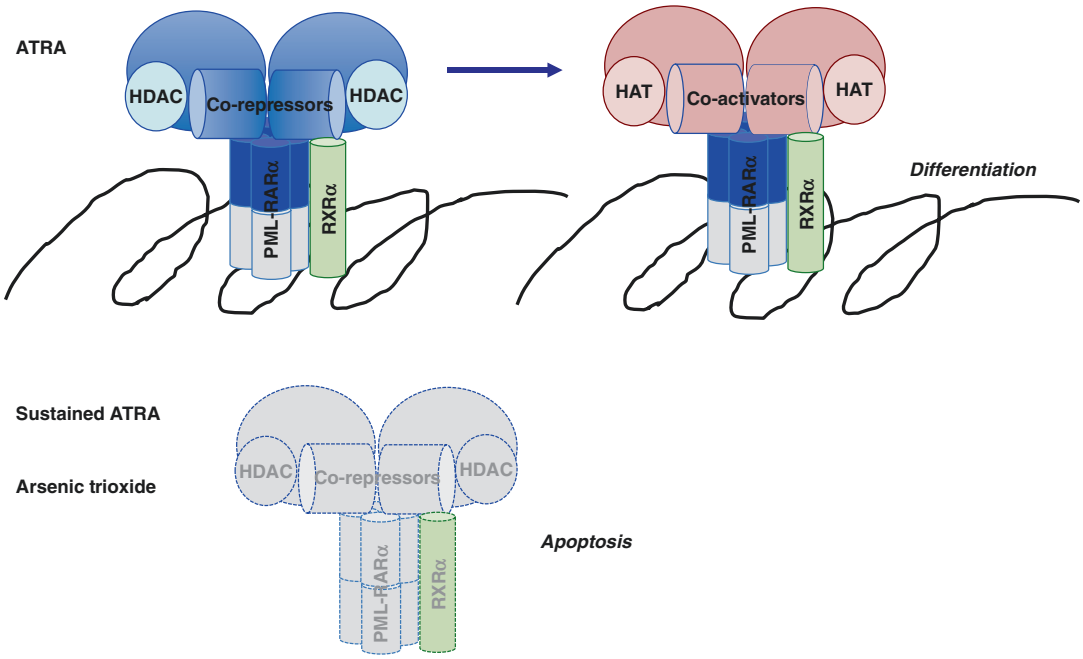

Fig. 4.3 ATRA and arsenic trioxide converge on PML-RARα to eliminate APL. ATRA prompts exchange of corepressors for coactivators and results in blast differentiation. Both ATRA and arsenic trioxide induce PML-RARα degradation, which is required for eradication of disease

colleagues demonstrating that transgenic mice expressing mutant RARα, unable to bind RA and thus activate transcription, do not develop leukemia challenging an RARα-centric paradigm. The same RARα mutation when engineered into PML-RARα resulted in myeloid leukemia albeit with differences compared to the original PML-RARα transgenic mice and unresponsive to RA-induced differentiation; this study demonstrated that lack of or aberrant activation of RARα target genes is not sufficient for the development of APL. However, the RARα mutant studies by Kogan et al. did not exclude the possibility that "super repression" of basal transcription levels of RARα targets in hematopoietic cells is the central transcriptional event in APL [23]; future studies would further elaborate this issue (discussed below). In PML-RARα, the functional domains of PML, the RING finger and coiled-coil domains, are retained suggesting that the PML moiety of the oncoprotein plays a specific and critical role in oncogenesis. Notably, the impressive clinical activity of single agent ATO, which does not lead to transactivation of RARα target genes [33], signaled that APL pathogenesis extended beyond an aberrant RARα pathway.

Multiple lines of evidence indicate that a central aspect of APL pathogenesis is functional impairment of PML. PML-RARα dominant-negative activity renders APL cells resistant to multiple apoptotic pathways mediated by the native PML protein [49]. A hallmark of t(15;17) APL cells is disruption of PML-NBs with reconstitution of the NBs upon treatment with RA or ATO [50–53]. Disruption of PML-NBs is a major mechanism by which PML-RARα results in functional impairment of PML with implications on p53 signaling, the PTEN-Akt pathway and other pathway, as we will also discuss below [54–58]. In an elegant proof of principle, Rego and colleagues demonstrated that homozygous or heterozygous deletion of PML accelerates the

onset and increase the penetrance of leukemia in the PML-RARα TM [59]. Likewise, homozygous genetic deletion of PLZF had a profound effect on the phenotype of the PLZF-RARα TM, which now did display arrest at the promyelocyte stage of differentiation [30, 60]. Collectively, these genetic experiments provided evidence that APL pathogenesis and, specifically, the signature block at the promyelocytic stage of differentiation involve disruption of both native X and RARα activity.

More recently, several lines of evidence point to gain-of-function PML-RARα activity. Using ChIP-seq, Martens and colleagues profiled PML-RARα genomic binding sites in human APL and described a landscape characterized by the acquisition of de novo DNA binding sites by a heterotetramer composed of PML-RARα and RXRα. Many of the de novo binding sites overlapped with sites recognized by other nuclear receptors known to play a role in myeloid differentiation and stem cell self-renewal such as RARγ, the thyroid hormone receptor, and the vitamin D receptor [61]. Moreover, most RXRα was bound to PML-RARα raising the possibility that sequestration of RXRα, which has been implicated in myeloid lineage determination [62], plays an important role in the pathogenesis of APL. Transcriptional output by the PML-RARα oncoprotein is additionally regulated at the level of posttranslational modification. Sumoylation of the PML moiety, which has been shown to participate in APL initiation [63], results in transcriptional repression by the oncoprotein, and this may be mediated by sumoylation-dependent recruitment of cofactors such as the death domain-associated protein (DAXX) [64, 65]. Ex vivo, DAXX is required for immortalization and transcription repression [63]. As far as posttranslational modification of the RARα moiety, phosphorylation adds multiple layers of regulation including a possible nexus at S369 for cross talk with the MAPK signaling pathway with S369 being phosphorylated by RA-activated MSK1 [66].

Oncoprotein-Mediated Response to Therapy and Beyond

Transgenic models of APL demonstrated that the fusion oncoprotein is necessary for leukemogenesis. They also established that the specific X-RARα oncoprotein confers response or lack thereof to RA-induced differentiation. As in human t(15;17) APL, administration of RA to the hCG-PML-RARα TM, at a dose comparable to what would be used in patients, resulted in a transient complete remission with blast differentiation observed in vitro and in vivo [24–26]. The hCG-PLZF-RARα by contrast never achieved a complete remission upon treatment with RA [36, 41] nor with single agent ATO or the combination of ATO and RA, which in the hCG-PML-RARα TM induced complete remission and prolonged survival, respectively (Fig. 4.2). These studies revealed the power of these TMs as tools to [1] obtain mechanistic insights into APL biology and [2] model the response to therapy.

ATRA is able to evoke degradation of the PML-RARα oncoprotein through the RARα moiety as the RA-elicited negative feedback mechanism is preserved (Fig. 4.3) [67]. Liposomal preparations of ATRA, which yield sustained higher levels of intracellular ATRA than the conventional preparation, result in improved rates of cure for patients. This suggests that prolonged exposure to ATRA is required for elimination of the oncoprotein in patients [68, 69], which may be mediated via a low affinity interaction with the 26S proteasome subunit, SUG1 [70]. Zhu et al. found that RARα point mutations abrogating RXR binding and mutation of the AF-2 domain disrupted RA-prompted RARα degradation and surmised that an allosteric signal is sent from the DNA-binding domain to the AF-2 domain, consistent with a model in which degradation is couple to transcriptional activation. On the other hand, when synthetic retinoids are utilized as agonists, PML-RARα transactivation is uncoupled from proteolysis, and this allowed Ablain and colleagues to make the critical observation that transactivation in the

absence of proteolysis accomplishes differentiation, but not elimination of disease. Strikingly, retinoid-differentiated APL blasts, which still possess PML-RARα, retain leukemia-initiating capacity in serial transplantation experiments.

We recently reported on a novel aspect of ATRA-induced PML-RARα proteolysis involving binding, inactivation, and degradation of the prolyl isomerase, Pin1. Pin1 regulates the prolyl isomerization of many oncogenes and tumor suppressors and, in so doing, integrates multiple pathways toward the development of cancer exerting proto-oncogenic roles. Surprisingly, ATRA emerged as the top hit in a high-throughput screen for Pin1 inhibitors. Pin1, itself, appears to dock at PML-RARα's pS581-proline motif, which was previously demonstrated to be required for PML-RARα proteolysis, resulting in stabilization of the oncoprotein. Multiple approaches were used to abrogate Pin1 activity: Pin1 silencing, ATRA, additional Pin1 inhibitors, in both murine APL and human APL cell lines, and all resulted in PML-RARα degradation in vitro and in vivo. Finally, silencing Pin1 or pharmacologic inhibition of Pin1 in vivo resulted in increased disease-free survival and/or significant reduction in disease burden in APL mouse models [71].

Retinoic Acid Signaling

The field of retinoic acid signaling is inextricably bound to the story of PML-RARα. RA acts principally by signaling through its receptor, RARα. RA is obtained directly from the extracellular medium or converted through a set of oxidative steps, from vitamin A. All-trans-retinoic acid is the most common isomer of RA. CYP26 members carry out the degradation of RA, and the intracellular availability of RA is further regulated by protein binding such as to CRABPs in the cytosol [72]. RARs, that is, RARα, RARβ, and RARγ, belong to the retinoid subfamily nuclear receptor superfamily of steroid hormones along with retinoic acid X receptor (RXR). Nuclear receptors function as intracellular receptors with some encountering their ligand in the cytoplasm and others in the nucleus. Their functional domains include ligand-independent activation function (AF-1), a DNA-binding domain and ligand-binding domain (LBD), a dimerization domain, and a ligand-dependent AF-2 domain involved in co-regulator binding and transactivation. The receptors bind to hormone-response elements on their target genes, and in the classic model, ligand binding results in exchange of corepressors for coactivators and, in so doing, leads to target gene activation. On DNA, RARα is found as a heterodimer with the retinoic acid X receptor alpha (RXRα); efficient binding of DNA requires dimerization with RXR. Together they bind to RA-responsive elements (RAREs) [73]. Interestingly, receptor-independent mechanisms of action of RA have also been described such as direct activation of kinases in the cytoplasm by RA [74]. In addition, the recent finding of inhibition and degradation of the prolyl isomerase, Pin1 [71], by RA raises the possibility that signaling pathways relying on proline-directed phosphorylation may be indirectly regulated by RA.

Posttranslational modification of RARα by phosphorylation is a further layer of control with resulting changes in conformation and activity [66, 75, 76]. In the absence of ligand, DNA-bound RARα represses transcription of its target genes. RA engages the ligand-binding domain of RARα prompting a conformational change and the exchange of corepressors such as SMRT/NCoR for coactivators [77, 78]. Steroid hormone receptor signaling is coupled with a negative self-regulatory function in which prolonged exposure to hormone results in catabolism of the receptor. Notably, RA-receptor engagement also prompts a negative feedback mechanism resulting in proteasome-mediated RARα degradation [67, 79].

Early on, scientists observed that the pro-differentiating activity of RA is retained with certain cancer cell lines [80, 81] including APL cell lines [82]. Remarkably, treatment of APL blasts from patients induces terminal differentiation into granulocytes [83]. Starting in the 1980s, in a transformative step for the field, APL patients were treated with all-trans-retinoic acid (ATRA) and saw improved remission rates and survival [2–4]. Subsequently, Longo et al. mapped the breakpoint in t(15;17) [5, 19] to the RARα gene which had recently been cloned [84, 85], and t(15;17) was

shown to produce an aberrant form of RARα [10] opening the floodgates of investigation into the role of RARα in the pathogenesis of APL [5–10].

Promyelocytic Leukemia Gene

The promyelocytic leukemia gene, *PML* (also called *MYL*, *RNF71*, *PP8675*, or *TRIM19*), was originally identified based on its involvement in the t(15;17) chromosomal translocation of APL [7–10]. However, the discovery of the PML-RARα oncoprotein quickly led to the study of PML in its own right. *PML* encodes a homo- or hetero-multimeric protein with wide tissue expression and is required for the proper assembly of subnuclear macromolecular structures, called PML nuclear bodies (PML-NBs) [56, 86]. PML-NBs are discrete nuclear foci, 0.2–1.0 μm wide, with a typical number 1−30 bodies per nucleus, and are dynamic and heterogeneous structures [87]. The observation that the oncogenic PML-RARα protein disrupts PML-NBs in a treatment-reversible manner with two clinically effective therapies, retinoic acid (RA) and arsenic, drew instant excitement from the scientific community [50, 51, 53, 88], and it was later concluded that the restoration of tumor suppressive function of PML-NBs by RA and arsenic is essential for APL regression [36, 50, 57, 58, 89, 90]. Through its scaffold properties, PML recruits an ever-growing number of partner proteins (in the range of 70–100) into PML-NBs, including p53 [55], AKT [57], mTOR [91], PTEN [58], and SIRT1 [92], providing a possible explanation for the involvement of PML in many aspects of normal physiology and pathology, including senescence, apoptosis, stem cell self-renewal, metabolism, and, importantly, tumor suppression. PML and PML-NBs have been proposed to concentrate the partner proteins together with many posttranslational modifying enzymes facilitating their posttranslational modifications, notably sumoylation, leading to partner activation, degradation, and sequestration (Fig. 4.4) [93, 94].

The physiological roles of PML and PML-NBs are still a matter of debate, and the related

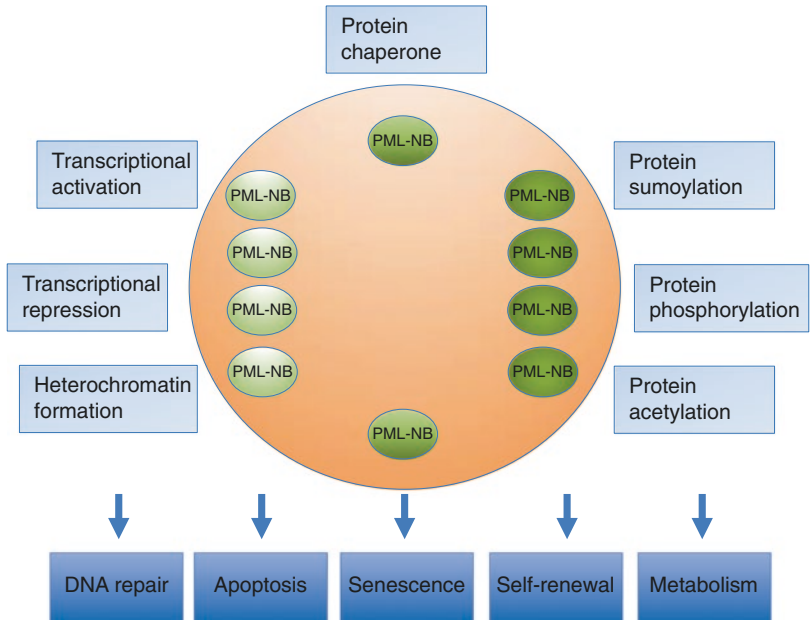

Fig. 4.4 The functions of PML and PML-NBs. PML and PML-NBs have been described as structures that regulate several, diverse cellular functions, including DNA repair, apoptosis, cellular senescence, stem cell self-renewal, and metabolism. The biochemical means used by PML and PML-NBs to regulate so many functions are varied and can be categorized into three main groups: protein chaperone activity, posttranslational modification of proteins, and regulation of nuclear activities such as transcriptional regulation and chromatin organization

research was greatly facilitated by the generation and analysis of Pml knockout (*Pml*$^{-/-}$) mice and cells that have provided direct genetic evidence and experimental tools linking Pml to a variety of biological processes [88]. Although *Pml*$^{-/-}$ mice are viable, they are more susceptible to cancer-promoting and stress-related insults and exhibit resistance to p53-dependent and p53-independent apoptosis [88, 95, 96].

Furthermore, PML and NBs are frequently lost in both leukemia and solid tumors [97], consistent with their prevalent tumor suppressive functions. Surprisingly, however, recent data have also demonstrated a selective pro-self-renewal and pro-survival role of PML in specific contexts, mainly due to its role in maintaining normal hematopoietic (HSC) and neuronal stem cell pool or leukemia-initiating cells (LICs) [92, 98, 99].

Here we briefly summarize PML functions in APL pathogenesis and response to therapy as well as the recent new findings on this multifunctional protein. The functions of PML and PML-NBs in other contexts and mechanisms underlying arsenic-mediated degradation of PML and PML/RARα have been extensively reviewed elsewhere [93, 94].

PML has a well-established role in apoptosis and cell senescence. The cells derived from *Pml*$^{-/-}$ mice have profound defects in executing cell death by different stimuli [90, 96]. Mechanistically, PML is an important factor in the regulation of both p53-dependent and p53-independent apoptotic pathways. PML activates p53 by promoting its acetylation and phosphorylation through recruitment of p53 into PML-NBs [54, 95, 96]. In addition, PML can induce apoptosis through p53-independent mechanisms. A discrete accumulation of cytoplasmic PML at the mitochondria-associated membranes of the endoplasmic reticulum facilitates transfer of calcium to the mitochondria and induces apoptosis in a p53-indepenent manner [90]. Moreover, PML can contribute to Fas-induced apoptosis through recruitment of FLICE-associated huge protein (FLASH) into PML-NBs [100]. It is therefore possible that NB disruption by PML/RARα could promote leukemia cell survival by inhibiting apoptosis. Along with apoptosis, PML regulates cellular senescence in both p53-dependent and p53-independent manner [55, 101]. PML was also implicated in the induction of premature senescence because Ras-induced senescence depends on PML-promoted p53 acetylation and subsequent activation [55]. Interestingly, recent studies have showed that among PML isoforms, only PML IV activates p53, leading to senescence when overexpressed due to its specific C-terminus motif that interacts with ARF and protects p53 from MDM2-driven degradation [102].

Furthermore, a newly defined PML/PP1α/Rb pathway is involved in the induction of senescence in a p53-independent manner [101]. The role of PML in the regulation of apoptosis and cell senescence is critical not only for understanding APL initiation but also the basis of response to therapy. Indeed, NB reformation in response to RA or arsenic treatments tightly correlates with enhanced cellular apoptosis and senescence. Importantly, this specific response is highly specific for PML/RARα, but not PLZF/RARα-driven APL [36, 103, 104], suggesting that restoration of normal function of PML and PML-NBs is critical for APL clearance.

However, it is also worth noting that PML plays a crucial role in maintaining normal HSC and LIC (described in detail below) [92, 98, 99]. Thus, NB reformation uncoupled from degradation could represent a double-edge sword and a liability for APL clearance, in that it would allow for the persistence of leukemia-initiating cells and ultimately lead to disease persistence or relapse. This is consistent with what has been observed in the clinic with single agent ATO leading to high rates of cure presumably because arsenic triggers initial NB reformation with PML degradation immediately ensuing while RA does not affect PML degradation and, in the clinic, leads to transient responses.

The role of PML in HSC self-renewal was first suggested by ex vivo studies in which PML-RARα resulted in increased self-renewal of myeloid progenitors [105]. PML has now been

demonstrated to play an important role in normal hematopoiesis and in non-APL myeloid neoplasms. Our group and others have shown that PML is required for the maintenance of cancer-initiating cells [98, 106, 107]. In bone marrow mononuclear cells, PML is most highly expressed in the stem cell/progenitor compartment. Deletion of PML initially leads to normal HSC and LIC cycling and expansion of these pools. However, over time, both in vitro and in vivo, loss of PML leads to exhaustion of HSC and LICs [98].

Chronic myeloid leukemia is a paradigmatic stem cell disorder and consistent with prior observations that leukemia-initiating cells co-opt normal stem cell self-renewal mechanisms, in a retroviral BCR-ABL murine model, CML leukemia-initiating cells (LIC) collapse in the absence of PML or upon pharmacologic ablation of PML via arsenic trioxide [98]. Subsequent studies revealed that PML mediates stem cell maintenance by regulating lipid metabolism, thus revealing a specific HSC metabolic requirement. PML accomplishes this by acting upstream of a PPARδ-fatty acid oxidation pathway required for asymmetric division of HSC [99]. These interesting findings raise the possibility that LIC exhaustion in myeloid malignancies, including APL, could be induced by interfering with fatty acid metabolism, through PPAR-directed therapy or PML targeting drugs, such as ATO.

A metabolic dimension to PML-regulated cell biology in solid tumors was also recently uncovered. In breast cancer, a PML-PPARα-fatty acid oxidation pathway allows cells to withstand metabolic stress and survive loss of attachment. In primary patient samples, high PML expression is correlated with high-grade histology and reduced disease-free survival; accordingly, poor prognosis, triple negative breast cancers are enriched in the PML group. Consistent with the molecular studies, tumors with elevated PML levels exhibited an activated PPARα signaling gene expression signature [92]. The above described metabolic function of Pml in breast cancer suggests that in a subset of solid tumors, targeting Pml-directed metabolic programs may open new therapeutic avenues for patients.

Conclusions

The story of APL has by now paved the way to contemporary molecular oncology. It represents a paradigmatic example of a journey of discovery toward the cure, where genetic and molecular analyses, mouse modeling efforts, and preclinical and clinical trials converged toward disease eradication. This paradigm has by now inspired a generation of investigators and oncologists and has been exported above and beyond leukemia to any realm of cancer research and care.

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