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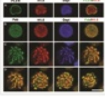
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PML Nuclear bodies: the cancer connection and beyond

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ABSTRACT

Promyelocytic leukemia (PML) nuclear bodies, membrane-less organelles in the nucleus, play a crucial role in cellular homeostasis. These dynamic structures result from the assembly of scaffolding PML proteins and various partners. Recent crystal structure analyses revealed essential self-interacting domains, while liquid–liquid phase separation contributes to their formation. PML bodies orchestrate post-translational modifications, particularly stress-induced SUMOylation, impacting target protein functions. Serving as hubs in multiple signaling pathways, they influence cellular processes like senescence. Dysregulation of PML expression contributes to diseases, including cancer, highlighting their significance. Therapeutically, PML bodies are promising targets, exemplified by successful acute promyelocytic leukemia treatment with arsenic trioxide and retinoic acid restoring PML bodies. Understanding their functions illuminates both normal and pathological cellular physiology, guiding potential therapies. This review explores recent advancements in PML body biogenesis, biochemical activity, and their evolving biological roles.

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Introduction

The nucleus of eukaryotic cells is a dense environment home for several key cellular processes. It plays a pivotal role in gene expression, DNA repair, RNA synthesis, and cell cycle control. Such processes are tightly regulated in a spatiotemporal manner to secure the biological functions essential for cell homeostasis or response to extracellular stimuli. This spatiotemporal regulation is optimized by the cellular localization of proteins and molecules into subcellular compartments, which leads to the sequestration or exclusion of certain proteins into a microenvironment that may favor some biochemical reactions. Such compartmentalization has been extensively described through membranous organelles such as the mitochondria or Golgi apparatus in the cytoplasm, but it may also be insured by non-membranous organelles, referred to as nuclear bodies, commonly present in the nucleus [1,2]. Disruption of PML bodies can be detrimental to cell homeostasis and is involved in diseases such as cancer [3]. Unlike some nuclear bodies that are dedicated to specific biological processes, PML bodies have diverse functions. They are altered in

several diseases, ranging from viral infections to cancer [4]. PML bodies also play an important role in protein post-translational modifications such as SUMOylation, which subsequently influences protein activity and function. In this sense, we can note a resemblance between PML bodies and the Golgi apparatus. Both play a role in protein processing and trafficking within the cell. PML bodies are implicated in cargo protein modifications or degradation, as well as sequestration within the nucleus. On the other hand, Golgi manages post-translational modifications, sorting and delivery of proteins and lipids in the cytoplasm [5]. PML bodies are instrumental in the regulation of the cell's internal processes, while the Golgi apparatus coordinates the delivery of proteins to the appropriate cellular destinations. The distinct responsibilities of PML bodies and the Golgi apparatus in comparison to other organelles exemplify the complexity of the cell's protein management systems.

In this review, we focus on PML bodies as important organelles in the complex system of the cell. The links between PML bodies and viruses are not detailed here as recent reviews have explored

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this active research field [6,7]. PML bodies have been extensively investigated in cancer research, especially acute myeloid leukemia (AML) and acute promyelocytic leukemia (APL). Several therapies for APL have emerged, implicating nuclear bodies, as reviewed recently [8]. We will approach the formation of PML bodies, their importance, and molecular modifications, and end by shedding light on some of the various roles they play in different processes in the cell.

PML: from protein to nuclear bodies

PML nuclear bodies biogenesis

PML proteins were brought to light by the discovery of a chromosomal translocation, creating a fusion protein in the context of acute promyelocytic leukemia [9]. Member of the tripartite motif (TRIM) protein family, PML, exhibits an RBCC structure (RING finger, B-Box, and coiled-coil domains) [10,11], which is essential for PML bodies assembly and interaction with various molecules [12–14]. In mammalian cells, PML is found in the nucleus in two main fractions: a diffuse nucleoplasmic fraction, a fraction assembled into nuclear bodies (PML bodies) [4,15]. It is also found in some cytoplasmic compartments, such as mitochondria [16]. PML

bodies are multiprotein structures organized in a core-shell manner [15,17] with a size ranging from 0.2 to 1 μm , distributed in the nucleus (up to 30 bodies per nucleus) [18,19]. The assembly of PML bodies occurs in several steps: PML self-assembly through noncovalent interactions of RBCC domains [14,20,21] drives the formation of the spherical PML polymeric shell. Subsequently, PML SUMOylation leads to partner proteins recruitment [21,22]. These steps are illustrated in Figure 1. Super-resolution microscopy and 3D reconstruction elucidated the accumulation of partner proteins inside the core of the PML bodies structures [21,23].

In the past few years, the field of membrane-less organelles has been explored through the lens of liquid-liquid phase separation. Even though significant advances in this field have emerged in the past few years, the link between biomolecular condensate assembly by LLPS and its function remains unclear [24]. Some studies have suggested a link between the assembly dynamics of proteins and their function [25–27]. The model of organelle formation by LLPS proposes the presence of a critical concentration of proteins in a confined space, beyond which structural assembly occurs via several weak and reversible interactions of proteins [28]. This process results in the formation of liquid structures with high fluidity and reversible

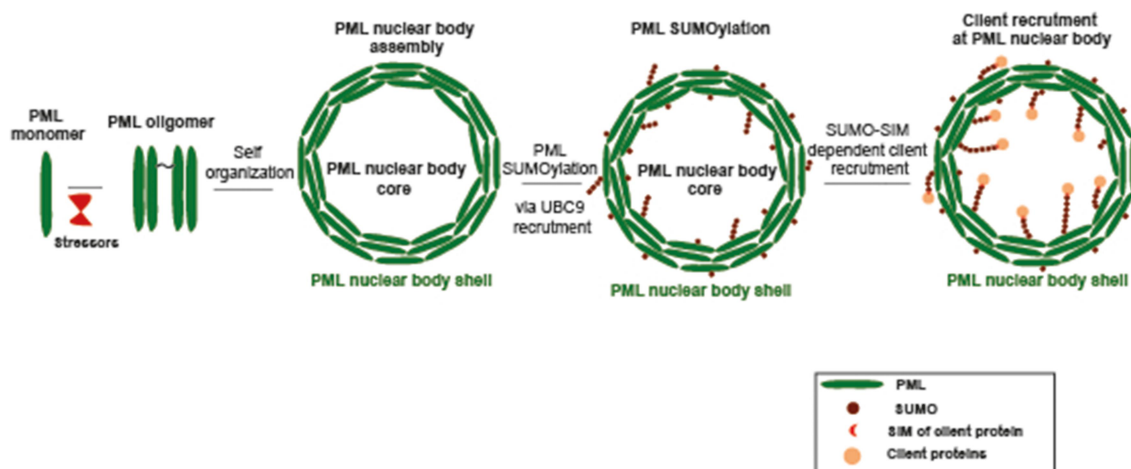


Figure 1. Illustration showing stepwise PML nuclear body biogenesis. PML nuclear body biogenesis begins with the initial oxidation-induced PML linking via covalent disulfide bonds inducing PML oligomerization. PML self organizes into PML nuclear bodies with a PML shell. This initial seeding step is highly affected by cellular redox status. In the second step, multimeric PML proteins recruit UBC9 (not illustrated), and the body's shell becomes heavily SUMOylated. In the third step, SUMO-conjugated PML recruits SIM-containing client proteins via non-covalent SUMO/SIM interactions. This is followed by partner SUMOylation in the NB inner core (step not illustrated), which leads to partner sequestration through enhanced SUMO/SIM interactions. Several client proteins are recruited to the inner core of the PML bodies such as SP100, RNF4, DAXX, P53 and others.

interactions, or solids with no fluidity and irreversible interactions [29]. Some nuclear organelles form following this LLPS model, such as the nucleolus and P bodies; nevertheless, this model failed to explain the assembly of PML bodies. Part of the challenge relies on the formation of a core-shell structure that solely depends on PML protein assembly, which seems to diverge from the proposed membrane-less organelles assembly theories. *In vitro* approaches helped investigate the role of LLPS in the formation of several organelles but did not provide sufficient evidence for PML bodies. A recent study by our team showed that PML bodies formation exhibits some hallmarks of LLPS: PML de-mixes from the nucleoplasmic fraction at a threshold concentration into bodies, these bodies can fuse and relax into one body, and PML dynamically exchanges between bodies and the nucleoplasm. Nevertheless, the presence of an immobile fraction of PML at the bodies and the core-shell structure challenges the classical LLPS model as a simple model for PML bodies assembly [30].

Zooming at the RBCC domain of the PML showed some differences from other TRIM family domains. The PML RING domain, unlike the RING domain of other TRIM, undergoes tetramerization, which favors interaction with UBC9 and is necessary for the biogenesis of PML bodies [14]. It has been proposed that ATO may bind to PML in the ring domain and replace a zinc atom [31]. B1 box has been proposed to multimerize via hydrophobic interactions [13]. Interestingly, the B2 structure was solved recently [30], and the study identified a key alpha helix controlling trimerization via hydrophobic interactions that dictate typical PML bodies assembly dynamics. Focusing on cysteine 213 and using a series of subtle mutations, a triad of C213 is highlighted, which functions as a rheostat for PML bodies assembly. In the case of free sulfur loss on this residue or a mutation into a very hydrophobic residue, there is a shift from liquid-like bodies to gel-like bodies. Interestingly, the ATO atom can bind three sulfur residues, highjacking the C213 trio to freeze the dynamics of PML bodies assembly [30].

PML and SUMOylation

The PML protein undergoes several post-translational modifications; SUMOylation being one of the most important modifications in which the small ubiquitin-like modifier (SUMO) bonds covalently onto three main target PML lysines (K65, K160, and K490) [32]. K65 SUMOylation stabilizes UBC9 [33], K490 seems to be involved in the nuclear localization of PML (S. T [34], while K160 is the central SUMOylation site for the PML protein, which is necessary for the formation of bodies and the recruitment and localization of partner proteins [15,22]. SUMOylation of PML is dispensable for the formation of spherical PML shells as cells expressing a mutant PML with no SUMOylation sites or a deleted SIM domain still form core-shell bodies [33,35,36].

PML recruits UBC9 to PML bodies. UBC9 is a single SUMO-conjugating enzyme, particularly active upon stress, such as in ATO-promoted PML bodies. The concentration of UBC9 in PML bodies has two consequences. First, creating a PML shell that is highly SUMOylated (PML seems to be one of the most SUMOylated proteins in the cell) leading to the recruitment of other partner proteins via SUMO/SIM interactions [33,37]. The SIM domain is essential for recruiting partner proteins to PML bodies [21]. Interaction with partner proteins is tuned according to different stimuli (oxidative stress, viral infection, and transformation) [38,39], while PML bodies regulate their post-translational modifications, SUMOylation, and ubiquitination [40]. Among the proteins recruited by PML is RNF4, which induces the recruitment of ubiquitin onto the poly SUMO chains that target PML to the proteasome for degradation. Recently, it was suggested that proteasome-mediated degradation of SUMOylated PML was mediated by P97/VCP segregase. Using proteomic analysis of PML bodies, this study showed that PML is associated with P97/VCP, and this association is proposed to be involved in ATO-induced PML degradation in cancer therapy [41].

Second, UBC9 retention in the PML body core favors partner protein SUMOylation. First suggested by [21] a paper focusing on SP100 and HipK2, two well-known PML bodies-associated proteins, then demonstrated by unsupervised

proteomic analysis [40] *in vivo*. In this study, SUMO proteomics was performed using different systems: APL, in which PML bodies are disrupted and treated with ATO at different times after injection in mice to follow PML bodies reformation; mouse ESCs, where PML and SUMO are highly expressed; and liver tissues treated or not treated with PolyI:C and ATO to increase PML expression and PML bodies assembly. Proteomic results identified proteins with increased SUMOylation induced by PML bodies assembly, such as KAP1. This PML bodies-regulated SUMOylation affects the function exerted by these proteins [35,40].

In adult T-cell leukemia treatment, a combination of interferon and ATO is used to induce expression of PML and formation of PML bodies. Such a treatment in combination with classical chemotherapy enables the degradation of specific oncogenic protein TAX via the SUMO-ubiquitin pathway thus significantly improving the prognosis of patients [42,43].

PML and oxidative stress

Oxidative stress inducers, such as ATO, regulate PML bodies formation. Other *in vivo* oxidative stress-inducing agents as doxorubicin, paraquat, and irradiation, induce an increase in the number and size of PML Bodies. This change in PML bodies is not correlated with an increase in PML concentrations, indicating that oxidation of PML induces PML body formation [20,21]. PML was described as a ROS sensor. The PML protein contains free cysteines that are prone to oxidation. Upon oxidative stress, the accumulation of ROS induces the formation of disulfide bonds between PML proteins, thereby securing their multimerization [44]. Previous studies have shown that PML bodies are heavily present in macrophages, endothelial cells, fibroblasts, and inflammatory tissues, reinforcing the idea that PML oxidation plays a role in PML bodies biogenesis [45]. The role of these disulfide bonds in PML body formation remains unclear, and the partial oxidation of PML cysteines may have different consequences depending on the modified cysteines.

C213 oxidation controls PML bodies assembly and dynamics under normal conditions and stress [30]. *In vivo* studies have shown that the response

to oxidative stress occurs through the activation of p53 pathways and regulates the basal level of ROS [20]. Nevertheless, p53 plays the role of an antioxidant under basal conditions, and the role of a prooxidant under stress conditions, thus paving the way for apoptosis [46]. With this dual role, p53 is considered as a regulator of the ROS balance, and its antioxidant function participates in its tumor suppressor activity. CCl₄ known to induce oxidative stress, resulting in fibrosis and activated pathways, has been shown to depend on C213 in PML [30].

Some prone to oxidation cysteine, such as C389, engages in disulfide bonds with oncoproteins in myeloid leukemia [47,48]. The oxidation of C389 induces its link with NPM1c oncoprotein, which also contains free cysteine. In mice, in response to oxidative stress, PML is localized in the nucleoplasm in a diffused pattern and assembles through intermolecular covalent bonds, thereby strengthening the weak interactions of the coiled-coil domain. In NPM1c AML, therapy disrupting NPM1c-PML C389 disulfides induces the reestablishment of PML bodies and induces the p53/senescence pathway [48]. Focusing on the PML structure and modifications, this study highlights the therapeutic advantage of the ROS sensor.

PML and cellular processes

PML: a broad spectrum of functions

Although the PML protein is not essential for the cell, *Pml* knockout mice are prone to develop tumors much more than normal mice [49]. PML loss is implicated in the progression of prostate, colon, breast, and lung cancers, whereas low levels of PML are associated with poor prognosis [50,51]. PML bodies have diverse roles in a variety of biological processes, briefly summarized in Figure 2, such as senescence, apoptosis, DNA repair, and stem cell renewal [17,52–54]. This diversity is assumed to be mediated by a variety of proteins that interact with PML and traffic through PML bodies. Many studies have reported crosstalk between PML and the proapoptotic/pro-senescence P53 protein [55] and its regulators (CBP, ARF) [56,57], or with the DNA repair proteins TRF2 and BLM [58], or SP100, with various implications in tumorigenesis,

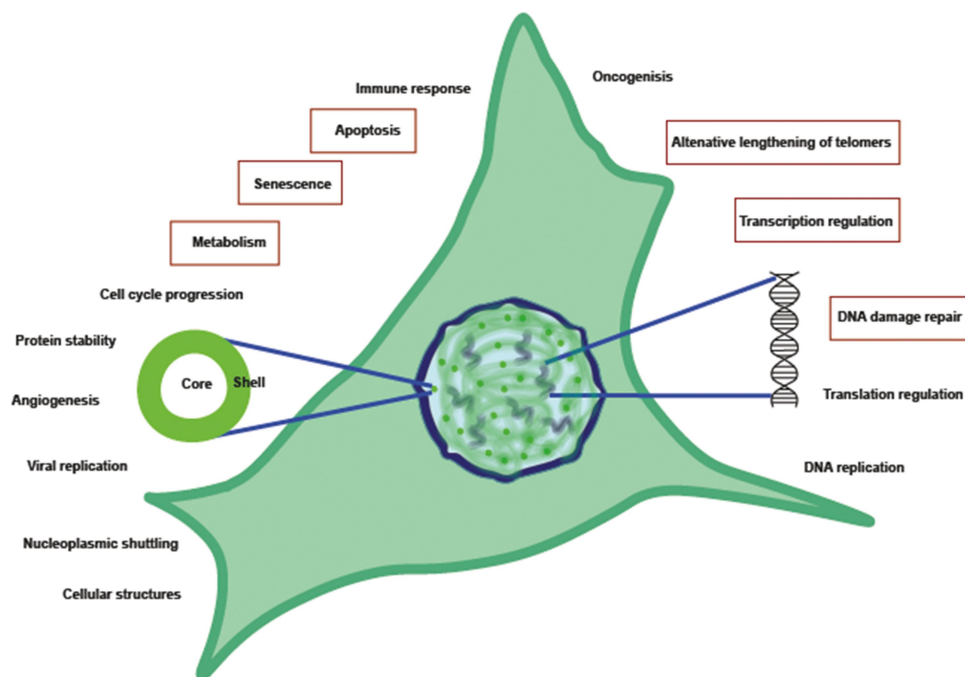


Figure 2. Schematic representation of a cell where the nucleolus is represented in blue, diffuse PML fraction in the nucleus represented in light green, and PML nuclear bodies as green dots. On the left of the cell, a zoom on the PML bodies with a list of some major processes PML/PML nuclear bodies affect. Similarly, on the right side of the cell a zoom on a DNA structure with a list of some processes PML affects through DNA interaction. Processes detailed in the manuscript are surrounded by red boxes.

immunity, and transcriptional regulation [59,60]. In this section, we focus on some key PML functions and recent advances on the contribution of PML in the fields of transcriptional regulation, metabolism, DNA repair, and ALT senescence and apoptosis. Recent advances have been made in understanding the contribution of PML to translational regulation through eIF4E [61,62], mTOR activity [55,63], and mitosis [64]. Advances in these fields will not be discussed in the future sections.

Regulation of transcription

For several years, the idea of transcriptional regulation by PML bodies has been presented on the table. PML would play a dual role, either directly or indirectly activating transcription. Indeed, transcription can be regulated via PML bodies or by the direct binding of PML to DNA. Several studies have elucidated using ChIP that PML is recruited to the promoter region [55,65], and one study proposed that the association between PML bodies and specific loci plays a role in the three-dimensional organization of the chromatin, thus

creating a favorable environment for associated gene expression [6]. PML can associate with heterochromatin region PADs, where it induces heterochromatic organization in PADs and induces pro-metastatic gene expression in subregions of PADs depleted of PML. Such a function of nucleoplasmic PML was observed in triple-negative breast cancer cells, suggesting a potential role of nucleoplasmic PML in gene regulation [66].

Among the first PML bodies identified, the resident protein was the histone chaperone DAXX. Interestingly, PML bodies can regulate the sorting of histone H3, as a pool of histone H3 is recruited to the bodies via DAXX and may be delivered for subsequent incorporation into chromatin by the DAXX/ATRX complex [67,68]. Another study showed that PML associates with H3.3 poor regions in the chromatin, suggesting different roles between the PML protein and PML bodies [69]. Nevertheless, loss of PML modified the incorporation of the H3.3 histone variant by the DAXX/ATRX complex at PADs. Altogether, these studies suggest an important role for PML in the organization of heterochromatin and PADs

through the DAXX/ATR complex [69]. Another histone chaperone that is regulated by PML is HIRA [70]. The distribution of HIRA in the nucleus is regulated by PML and PML partner protein SP100. PML functions as a chromosomal hub regulating ISGs transcription and thus HIRA-mediated H3.3 deposition at ISGs during the inflammatory response process [71]. PML is also associated with senescence-associated heterochromatin foci and is considered a marker of senescent cells.

Several studies favor the scenario where PML indirectly modulates transcription by sequestering some transcriptional regulators into the bodies, thus blocking their access to chromatin. This model has been proposed for CBP, N-CoR, DAXX, and PAX3, which localize to PML bodies in response to various stimuli [18,72–74]. More recently, ATR-regulation of DAXX has been described to promote its sequestering into PML bodies. When DAXX is maintained in bodies, levels of H3.3 are regulated in interphase via CENP-A at the kinetochore. This study shows an indirect role of PML in protecting centromere identity and ensuring mitotic fidelity [75].

Mechanistically, PML can also induce post-translational modifications of transcriptional regulators. In mESCs, PML favors SUMOylation of both the KAP1 repressive complex and transcription factor DPPA2 [76]. SUMOylation blocks DPPA2 and activates KAP1, leading to a coordinated action that represses both endogenous retroviral elements and genes activated at the 2-cell stage of early embryogenesis. Thus, PML opposes the 2CL transition of mESCs by coordinating SUMOylation. These recent findings suggest that PML regulates transcription factors through post-translational modifications.

Cellular metabolism

Metabolic dysfunction is a common consequence of oncogenes. Several studies have shed light on the direct link between PML and metabolism. PML is upregulated in the hepatocytes of obese patients, correlating with fatty liver syndrome [77]. This suggests a role for PML in hepatic function in response to obesity, which is likely expressed as a response/adaptation mechanism to

counterbalance an increase in adipogenesis. Moreover, PML plays an essential role in hematopoietic stem cells through regulating the β -oxidation of fatty acids (FAO), leading to the identification of the peroxisome proliferator-activated receptor (PML-PPAR γ -FAO) [78], essential for the asymmetric division of hematopoietic stem cells which has a key role in the maintenance of autorenewal of stem cells [79]. The PML-PPAR γ -FAO pathway is upregulated in some cancers, such as breast cancer, enabling cells to escape apoptosis using ATP produced by fatty acid oxidation as an energy resource to survive [80]. Interestingly, fatty acid oxidation uses lipid esters present in lipid droplets, which are associated in their turn with PML bodies, to regulate PPAR γ [81]. Indeed, recent studies have pointed out that certain cells accumulate lipid droplets in the nucleus, and PML associates with their surface [82,83]. These structures contain lipid biosynthesis enzymes at their surface, suggesting a possible implication for fatty acid synthesis and regulation.

In addition, PML has been implicated in the regulation of mitochondrial biogenesis. Under oxidative stress, PML bodies form and activate PGC-1 α , which in its turn promotes mitochondrial respiration by inducing electron transport chain complex synthesis. This increased the sensitivity of ovarian cancer cells to chemotherapy [84]. A novel study using a leukemia cell model elucidated the importance of mitochondrial integrity, which is influenced by PML bodies. The absence of PML affects mitochondrial fitness, resulting in impaired response to chemotherapy [48]. Altogether, PML protein and/or PML body-regulated mitochondrial metabolism opens new perspectives on the contribution of PML to cancer.

DNA repair and ALT

PML bodies are sensitive to DNA damage and act as sensors for the detection of DNA damage and repair. In response to radiation, a rapid increase in their number was observed [85], in addition to a gradual increase in their presence at the DNA break site. PML is also involved in the DNA repair mechanism; PML depletion drastically diminishes the homologous recombination process [86], and several double-strand break detection factors and

repair-implicated proteins are localized at the PML bodies [4]. Expression of a RING mutant of PML abolishing PML body formation induces defects in the activation of both the homologous recombination DNA repair pathway and non-homologous end joining pathway [87]. Super-resolution microscopy showed PML recruitment juxtaposed to a persistent DNA damage site. This recruitment is proposed to occur via the RNF168-53BP1 pathway to induce DNA repair [88]. PML regulates the DNA damage repair process via post-translational modifications of key actors in this process. It can play a regulatory catalytic role by SUMOylating proteins implicated in the DNA damage response, such as BRCA1-BARD1, and inducing their degradation. This regulatory effect is coordinated with the SENP protease, which de-conjugates SUMO [89]. PML plays a role in regulating the ubiquitination and control of BLM, a helicase known to unwind several DNA structures, such as the G-quadruplex ([90]. PML proteins can also operate on their own; as shown by recent findings demonstrating PML proteins presence in rapidly forming nuclear bodies in response to replication-related single-strand breaks [91]. These fast forming structured nuclear bodies are thought to strategically concentrate various proteins crucial for the repair mechanism in close proximity to the break site. This implicates a potential role of nucleoplasmic PML in DNA repair, expanding beyond the conventional PML bodies role.

Another process implicating PML and DNA repair is the alternative lengthening of telomers. Commonly in cancers, telomere shortening is compensated via the activity of telomerase, which synthesizes telomeric DNA by an inverse transcription mechanism [92,93]. In cells lacking telomerase, ALT promotes telomere maintenance [94]. PML bodies serve as hubs to promote efficient telomere-specific homology-directed repair [95]. Telomeres of such cells are physically associated with abnormal nuclear bodies, which are referred to as ALT-associated promyelocytic leukemia bodies (APBs) and can organize and concentrate telomeric repetitions [96]. Interestingly, APBs recruit proteins implicated in double-stranded DNA breaks, homologous recombination, and stalled replication fork repair, thus inducing DNA synthesis during ALT via a PML-dependent mechanism [96–99]. At the

APB, sequestering the repair machinery could promote a self-perpetuating loop of ALT activity [100]. Many questions remain unanswered regarding the relationship between PML and DNA repair as well as ALT. Future research should clarify many essential points to broaden our understanding of these processes.

Apoptosis and senescence

The contribution of PML to apoptosis has been the focus of many studies in the field of cancer. PML has been implicated in sensing oxidative stress and is involved in the response to it. Indeed, mouse embryonic fibroblasts deficient in PML have been shown to accumulate ROS. At the same time, the activation of p53 is mediated by PML and induces apoptosis. PML bodies associate with the p53 gene locus, and at the same time PML is a direct target gene of p53 [101]. In the absence of stress, p53 is polyubiquitinated by Mdm2 and degraded by proteasome. In contrast, cellular stress (DNA damage, radiation, and oncogene expression) induces an activation and stabilization of p53 [102]. PML blocks p53 polyubiquitination and degradation by sequestering Mdm2 into the nucleus [103]. Overall, p53 and most of its post-translational regulators are recruited to PML bodies [57,104]. Notably, the acetyltransferase MOZ, which acetylates p53 and activates it, as well as the kinase HIPK2, which phosphorylates a key p53 serine residue, are recruited to PML bodies in response to stress [105–107]. Recently, the TRAIL-2 receptor was shown to localize at PML bodies with p53. This localization of TRAIL-2 decreases the p53 protein levels, suggesting an effect on p53 degradation. PML knockdown abolishes TRAIL-2-mediated regulation of p53 levels [108]. Moreover, most of the p53 regulatory proteins are SUMOylated, and PML bodies can promote and coordinate their SUMOylation depending on the physiological state of the cell to finely tune P53 activity [57,76].

PML also contributes to p53-mediated senescence. PML was initially linked to senescence, as several studies have shown that the KRAS oncogene induces PML-dependent senescence [109]. Mechanistically, expression of the KRAS G12V oncogene in human fibroblasts induced PML and

nuclear body formation, the latter favoring p53 acetylation through CBP colocalization within the bodies [110,111]. In addition, senescence can be induced by the overexpression of PML IV alone, which is related to the hyperphosphorylation of Rb as well as the phosphorylation of p53, and the re-localization of these two proteins to PML nuclear bodies [110]. Both PML overexpression and interferon treatment-induced senescence [111,112]. Interestingly, PML-mediated senescence regulation is directly linked to p53/p21 and p16/Rb pathway regulation and regulates p53-induced senescence using the same mechanisms of post-translational modifications used for apoptosis [113]. PML IV binds specifically to ARF which interacts with UBC9 and stabilizes it, UBC9 in its turn SUMOylates p53. Such post-translational modifications of p53 induce its stabilization and activation, thus initiating senescence [57]. Additionally, PML can regulate senescence via Rb/E2F, where PML sequesters the Rb/E2F complex in the bodies, inducing cell cycle arrest [57,65,65,114,115]. An interesting study showed that under stress conditions, cells could transiently form cilia to reach PML bodies and initiate a senescence response. This route implicates modifications of proteins, such as SUMOylation, that would interact with PML bodies, which in turn initiates senescence [116]. In a model of myeloproliferative neoplasms (MPNs), JAK2^{V617F}-driven, a combination of ATO and interferon promotes efficient PML bodies assembly, leading to clearance of the disease in mice through activation of p53-mediated senescence [117, 118].

Concluding remarks

The story of PML briefly summarized here represents only a small part of its intricate life. These dynamic nuclear structures play a central role in orchestrating several cellular processes, highlighting their importance in both physiological functions and in the context of diseases. Despite the significant progress made in understanding PML bodies and their multifaceted roles, several questions remain unanswered. Knowing that SIM is a common motif, the specific mechanisms governing the complex interplay between PML bodies and various cellular components are still under investigation. The evolving field and

interdisciplinary nature of research in this area, combining new technologies such as advanced proteomic techniques, cell biology, and most recently, biophysics, and super-resolution microscopy, have contributed to a deeper investigation into PML bodies biology and understanding of them. New approaches can be used to understand the link between the three essentials: core-shell structure, PML bodies assembly dynamics, and function. Understanding the link between the three essentials will not only uncover the mechanisms underlying their disorganization but also manipulate these organelles that are seen as key tumor suppression checkpoints. The biophysical parameters driving PML bodies assembly and dynamics are related to biochemical and oncogene-induced senescence functions under various conditions. Hence, PML bodies may be ideal models for investigating the functional aspects of LLPS in cancer. Solving these interconnections could help in identifying how to harness PML bodies to promote tumor regression.

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Authors contributions


Majdouline Abou-Ghali wrote the manuscript and Valérie Lallemand-Breitenbach supervised and reviewed the manuscript.

Data availability statement

Data sharing is not applicable to this article, as no new data were created or analyzed in this study.

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