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The Role of PML in the Nervous System

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Abstract The promyeloctic leukemia protein PML is a tumor suppressor that was originally identified due to its involvement in the (15;17) translocation of acute promyelocytic leukemia. While the majority of early research has focused upon the role of PML in the pathogenesis of leukemia, more recent evidence has identified important roles for PML in tissues outside the hemopoietic system, including the central nervous system (CNS). Here, we review recent literature on the role of PML in the CNS, with particular focus on the processes of neurodevelopment and neurodegeneration, and propose new lines of investigation.

Keywords PML · PML nuclear body · CNS · Neural stem cell · Neurodegeneration

The Promyelocytic Leukemia Protein: What is Known

PML Origins

The PML gene was originally identified at the breakpoint of the *t*(15;17) chromosomal translocation that is observed in acute promyelocytic leukemia (APL), a distinct subtype of myeloid leukemia. This reciprocal translocation results in two fusion genes, PML-RARα and RARα-PML, which are both expressed in the leukemic cells. PML/RARα retains most of the domains of its parental proteins and is the main oncogenic event of APL [1, 2]. It is believed to act by exerting a block hemopoietic differentiation at the promyelocytic stage thus lending the leukaemic blasts a marked proliferation and survival advantage [3, 4].

Understanding the functions of the tumor suppressor PML has subsequently become an area of intense research. While basic aspects of PML biology remain elusive, accumulating evidence demonstrates PML has tumor suppressive functions beyond APL in non-hemopoietic tumors. In addition, the identification of novel roles for PML in the control of cellular senescence and stem cell self-renewal has extended our insight into PML's diverse function.

PML Structure

PML is a member of the tripartite motif (TRIM) family of proteins [5]. Similar to other members, it harbors a distinctive zinc-finger domain termed the really interesting gene (RING) domain, followed by two additional zinc fingers called B-boxes and an alpha helical Coiled-Coil motif (CC), which are collectively referred to as the RBCC domain. RING domains often have E3 ligase activity for ubiquitin or SUMO, a feature that extends to a number of TRIM family proteins [6, 7]. It is currently unclear whether PML can act as an E3 ligase. While the function of the B-box is less well understood, coiled coils are well established for their role in oligomerization [8]. Indeed, the RBCC domain as a whole plays an important role in mediating protein–protein interactions and is vital to coordinate PML and PML-RARα oligomerization [9–11]. This self-association used by PML and TRIM family proteins is fundamental to their individual functions.

The human *PML* gene consists of nine exons that are alternatively spliced to give at least 12 transcripts, most of which encode a distinct protein [12–15]. Each PML isoform shares an identical N-terminal region containing

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the RBCC/TRIM motif but differs in the C-terminal. This C-terminal diversity is responsible for generating the variety of PML binding interfaces for different factors. All nuclear PML isoforms contain a nuclear localization signal (NLS) in exon 6 and localize both to the nucleoplasm and to a nuclear body (PML-NB), a large protein complex tethered by high-order PML multimers (see below). Cytoplasmic PML isoforms, which are deficient in exon 6 and lack a function NLS, also exist [16, 17]. A single PML isoform, PML-I expresses a nuclear export signal, in addition to the NLS, and thus is able to shuttle between the nucleus and the cytoplasm. PML-I is the most highly expressed isoform and shares the highest homology with the murine isoforms, suggesting it is likely to be evolutionary the oldest isoform. PML-I also harbors a putative exonuclease-III (EXOIII) domain, which is likely to be important for interactions with nucleic acids and chromatin tethering. PML-I also contains a domain responsible for nucleolar localization [18]. The most studied isoform, PML-IV, been suggested to interact specifically with p53, leading to induced senescence in primary human fibroblasts [19] and apoptosis in other cellular settings [20].

Posttranslational modification of PML, via phosphorylation and SUMOylation, adds further structural and functional complexity [21–23]. Phosphorylation of PML on Tyr and Ser residues can occur via DNA damage or stress-activated kinases such as ATM, ATR, CHK2, HIPK2, CK2, and ERK [24, 25]. This posttranslational modification is believed to regulate PML stability, PML-NB biogenesis, and partner recruitment [24–27]. Conjugation of PML to the ubiquitin-like protein SUMO (SUMOylation) is the most recognized modification and is critical for PML-NB morphogenesis (see below).

PML Nuclear Body

Within the cell, PML is found associated with a sub-nuclear structure known as the PML-NB, which is a spherical object with a diameter for 0.1–1 μm [28]. Typically five to 15 bodies per nucleus are observed in cell lines and primary cells although alterations in stress conditions (e.g., viral infections, heat shock), the cell cycle, and chromatin changes may modulate the structure and number of PML-NBs [29]. PML is the essential component and organizer of the PML-NB, recruiting additional partner proteins to reside constitutively or transiently within this domain [4, 26]. Electron microscopy has revealed that PML-NBs are ring-like protein structures in nature that do not contain RNA or DNA at their center [29, 30]. However, PML-NBs do make extensive contacts with chromatic fibers through protein-based threads that extend from the core of the bodies, stabilizing the position and integrity of the PML-NBs in the nucleus [31]. Indeed, immunofluorescence in situ hybridization experiments have shown that PML-NBs associate non-randomly with genomic regions which are particularly rich in genes and are transcriptionally active [32]. Moreover, PML may be associated with some specific chromosomal loci, for example the MHC class I gene cluster region for which PML-NBs were proposed to modulate chromatin architecture and transcription [33, 34].

SUMOylation of PML facilitates homo-dimerization (via the CC) and recruitment of other PML-NBs components including the transcriptional co-repressor DAXX [26]. PML is able to directly bind both SUMO and the SUMO-conjugating enzyme UBC9, permitting SUMOylation of PML on three lysine residues (K65 in the RING domain, K160, and K490 in the NLS) [21, 35–37]. These SUMOylations are critical for the formation of the PML-NB and PML mutants, which are unable to be SUMOylated, fail to recruit classical PML interacting proteins, including the transcriptional repressor Daxx [26, 27].

Little was known about the regulation of PML-NB dynamics and biogenesis until studies utilizing Arsenic Trioxide, an effective therapeutic agent in APL [38, 39], provided valuable insight into the mechanisms regulating PML-NB formation. Arsenic Trioxide is able to regulate the partitioning of PML between the nucleoplasm and nuclear matrix in a ROS-dependent manner, uniquely promoting in a sequential manner intermolecular disulfide formation to form PML-NBs, PML SUMOylation, partner recruitment, and PML degradation [40, 41]. The demonstration that ROS can regulate NB biogenesis in vivo raises the exciting possibility that PML may act as a ROS sensor and further strengthens the role of PML in DNA damage response and senescence.

PML Expression in Non-Neural Tissues

Within tissues, PML expression has been shown to vary depending on the tissue and cell type, as well as the differentiation and activation stage of the particular cell [42–44]. For example, within the hemopoietic system, PML is much less abundant in circulating monocytes and granulocytes compared with early myeloid precursors [43, 45]. Tight regulation of PML expression is also observed in the developing mammary gland. High levels of both PML isoform I and II are present in virgin glands and during gestation, reducing during lactation and early involution, before returning to virgin-like levels in late involution [46]. In addition, different tissues often show variable expression of PML transcripts and PML isoforms due to the ability of PML to be altered both transcriptionally and also posttranscriptionally through alternative splicing.

Based upon the observation that PML expression varies considerably between cell types, both within the normal and disease setting, much research has focused on identi-

fying the regulators of PML expression. Various factors including cell cycle (where higher levels of PML are present in G1 phase), heat shock and γ irradiation have all been shown to modulate PML expression [4, 29]. The promoter of PML harbors one interferon-stimulated response element (ISRE) and one interferon-γ-activated (GAS) site and can, therefore, be upregulated at the transcriptional level by types I and II interferons, resulting in an increase in PML-NB size and number [15]. This has led to the notion that PML may be a target for the immune and antiviral effects of IFN and as such might act as a mediator of IFN activity through its role in IFN-induced apoptosis [15, 47]. In addition, the PML ISRE and GAS sites can also serve as binding sites for a family of transcriptional factors known as signal transducer and activator of transcription (Stat) [46, 48]. In this respect, it was shown that the tight regulation of PML expression in the developing mammary gland is orchestrated through three members of the Stat family (Stat1, Stat3, and Stat5/6), which are key for functional development of the breast [46].

Replicative senescence and Ras-induced cell arrest can also lead to an increase in size and number of PML-NBs [49, 50]. This increase is mediated by p53-mediated transcriptional upregulation of PML [51]. Since PML can also function upstream of p53 in inducing senescence and apoptosis (see below) these findings indicate a positive-feedback loop between PML and p53 exists [51].

PML Functions

To date, PML has been shown to influence or regulate a number of cellular processes including transcription, apoptosis, senescence, response to DNA-damage, and stem cell renewal. This diverse functionality is achieved in part, by ability of PML to interact with an increasingly large number protein partners.

DNA Damage Response

PML-NBs mediate a number of important checkpoint responses following DNA damage. This is believed to be facilitated by the numerous DNA repair and checkpoint proteins with localize to PML-NBs including ATR, CHK2, and MRE11 (meiotic recombination-11) which dissociate from PML-NBs upon DNA damage, and BLM helicase, ATM, BRCA1, and phosphorylated histone H2AX which colocalize with PML following DNA damage [29]. In tumor cells that maintain telomere length by the alternative lengthening mechanism (ALT), PML is found in ALT-associated PML bodies (APBs) [52]. APBs contain telomeric DNA and regulators of DNA damage response and recombination [52]. In these cells, PML regulates APB formation [52] and the response to telomeric stress [53]. Overall, while the role of PML as a storage site for DNA repair proteins is well known, it remains to be determined whether PML plays a direct role in DNA repair/recombination.

Transcriptional Regulation

Given that many transcriptional regulators localize to PML-NBs, it has been suggested that PML-NBs may act as sites of transcriptional regulation, controlling the availability or activity status of transcription factors [27]. This has been further strengthened by the observation that PML-NBs often lie near highly acetylated chromatin [30]. In addition, PML-NBs may also control transcriptional activity by participating in chromatin remodeling, given the ability of PML-NBs to associate with chromatic fibers. In this respect, recent studies have shown that PML may regulate chromatin architecture [33]. Furthermore, PML-NBs have been recently reported to associate with the histone variant H3.3, potentially through the interaction with Daxx, a key regulator of H3.3 [54, 55]. PML colocalizes also with the Daxx-interacting protein ATRX, which is a chromatin-remodeling factor involved in H3.3 loading as well [54]. PML-NBs have also been observed to colocalize with transcription repressors and heterochromatin bound proteins, leading to the notion that PML-NBs are involved in transcriptional repression [27, 56]. The suggestion that PML is able to act as both a positive and negative regulation of transcription highlights the heterogeneous nature of PML-NBs and their ability to regulate different events at any given time.

Cell Cycle and Cellular Senescence

Several studies have demonstrated that overexpression of PML induces cell cycle arrest in cancer cell lines [57–59]. This is associated with increased levels of the retinoblastoma protein (pRb), and an arrested cell cycle, principally at G1 phase [49, 59, 60]. It is proposed that PML exerts its functions through interactions with other tumour suppressors, such as p53 and pRb [61–63]. PML-mediated regulation of pRb has been suggested to occur through direct targeting, along with the protein phosphatase PP1a, to the PML-NB [64]. Similarly, p53 function can be regulated and enhanced through direct localization to the PML-NB and changes in its posttranslation modifications [65, 66]. Additionally, a large number of p53-modifying enzymes (CBP, HDM2, HIPK2, and HAUSP) can also be found within the PML-NB [66]. However, p53 can also be indirectly stabilized following PML-dependent Mdm2 sequestration to nucleoli on DNA damage [24, 66]. The observation that PML−/− cells demonstrate impaired ability to undergo senescence highlights the important role PML

plays in regulating p53 function; however, further work is required to fully explore the complexity of the mechanisms by which this is achieved [49–51]. As mentioned, in primary mouse embryo fibroblasts undergoing RAS V12-driven senescence, RAS induces an upregulation of PML in addition to relocalization of p53 and pRb to NBs, and PML-dependent post-translational modification of p53 (phosphorylation in Ser15 an acetylation in Lys382) [19]. Additionally, PML expression is also associated with the activation of the p16/pRb pathway, thus suggesting that PML coordinately modulates the p53 and pRb master regulator pathways of senescence. However, in this respect, it still remains to be determined whether PML plays a role in regulating aging and whether this occurs through its action on post-mitotic cells such as neurons within the central nervous system. Indeed, while a growing body of evidence points to the central role of accumulating DNA damage in the aging process of post-mitotic neurons and in numerous neurodegenerative diseases, it remains unclear whether a correlation exists between PML function, DNA damage, and neuronal dysfunction within the aging brain.

More recent work indicates that PML can interact with other major oncogenic pathways such as the PI3K/Akt pathway [67]. In particular, PML is able to recruit and interact with the protein phosphatase PP2a, thereby promoting dephosphorylation and inhibition of the nuclear function of Akt. This inhibition of Akt leads to suppression of its prosurvival and promitogenic functions [67]. Furthermore, reduction of PML gene dosage in PTEN animals leads to increased Akt phosphorylation, and transition to invasive carcinoma, strengthening the suggestion of a genetic interaction between the two pathways [67]. Together, these findings further confirm PML's involvement within an increasing tumor-suppressive network.

Regulation of Cell Death

A role for PML in cell death has been indicated by studies demonstrating that cells derived from PML KO mice have profound defects in executing cell death by different stimuli [20, 68, 69]. Given the important role that PML plays in the regulation of p53 (see above), it is perhaps not surprising that subsequent studies identified PML as an important factor in the regulation of p53-dependent apoptotic pathways [20, 68]. PML regulates p53 at multiple levels: (1) it recruits p53 to the PML-NBs to promote its acetylation and/or phosphorylation [19, 50, 70]; it indirectly promotes p53 stabilization by sequestering MDM2 into the nucleolus [24]. In addition, PML is a p53 target gene itself [51]. However, PML is also able to induce apoptosis in a p53-independent manner [68]. It is unknown whether these interactions occur directly within the PML-NBs or are mediated indirectly by PML itself. Another protein thought to be important for the role of PML in apoptosis is the PML-NB associated protein, Daxx, which was first implicated as a modulator of Fas-induced apoptosis. The role of Daxx in apoptosis is not entirely clear, since it has been reported to both enhance and to suppress apoptosis. In this respect, the ability of Daxx to regulate pro-apoptotic or anti-apoptotic activity in the PML-NBs may cell-type specific [71, 72]. Like for other tumor suppressors, it is still unclear which among PML's two main functions, cell death or cell cycle regulation, is predominant in the control of tissue homeostasis and transformation.

PML Role in Cancer

Following the identification of PML's involvement in the *t* (15;17) translocation of APL, a large volume of research focused upon its role in the pathogenesis of leukemia. More recently, accumulating evidence suggests that PML has tumor-suppressive functions beyond APL in various solid tumors of different histological origins. Indeed, PML expression appears to be lost or reduced in many different human neoplasms, from hemopoietic tumors to carcinomas. In particular, a recent tissue microarray study that investigated PML expression in cancers of different histological origins, identified loss of PML expression in 17% of colon adenocarcinomas, 21% of lung tumors, 27% of prostate adenocarcinomas, 31% of breast adenocarcinomas, 49% of CNS tumors, 49% of germ cell tumors, and 68% of non-Hodgkin's lymphomas [73]. While a lack of expression was apparent at the protein level, PML mRNA appeared to be normally expressed, and no mutations were found in any of the samples analyzed [73]. Additionally, immunohistochemistry studies have shown loss of PML expression in breast carcinomas [44], gastric cancer [74], small cell lung carcinoma [75], and in invasive epithelial tumors [76]. Interestingly, Gurrieri et al. demonstrated that loss of PML correlates with higher tumor grading in breast adenocarcinomas, prostate carcinomas, and CNS tumors, which confirmed previous data from gastric cancers [73, 74]. However, other immunohistochemistry studies have reported variable expression of PML in different human tumors and, in some cases, even overexpression of PML [44, 77]. Additional tissue microarray studies, employing a combination of PML antibodies, alongside gene expression analysis may prove insightful in investigating this apparent discrepancy.

Role of PML in the Nervous System

PML Expression

PML expression at the transcript level is very low in the postnatal mouse brain [78]. In the developing brain, we

have shown that the PML protein is highly enriched in germinal areas [64] (Fig. 1a). These include the ventricular zone of the neocortex, the hippocampus [64], and the cerebellum (our unpublished results). In these regions, PML accumulates in both the nucleoplasm and the PML-NB. Cytoplasmic localization is undetectable, suggesting that PML cytoplasmic isoforms are not expressed in the developing brain. Indeed, only nuclear isoforms 1 and 2 are readily detected. PML expression was absent in postmitotic cells in developing cortex, cerebellum, and hippocampus [64], with the exception of Purkinje neurons (our unpublished data). Neural progenitor cells isolated from the neocortex (E15.5) retain PML nuclear staining [64]. Mirroring what is seen in vivo, induction of differentiation in cultured neural progenitors results in PML downregulation at both protein and transcript levels ([64] and our unpublished data). These findings indicate that PML expression is associated with the immature state of neural progenitors. This is in agreement with a previous study showing that PML is highly enriched in immature hemopoietic progenitors [79]. Interestingly, in adult mouse brains PML becomes re-expressed in the cortex and hippocampus. PML has been found expressed in the adult human brain, such as in neurons of the substantia nigra [80, 81], in supraoptic neurons [82], and in sensory ganglion neurons [83]. PML-NBs are often associated with intranuclear inclusions in normal and pathological conditions (see below).

Role of PML in Neural Stem Cells

We have shown that loss of PML affects brain development [64]. In particular, PML-deficient embryos show decreased thickness of the cortical wall, although the overall layered structure of the cortex is unaffected. This effect is readily detected at birth, while differences in cortex thickness in adult brains are not as pronounced, suggesting the existence of compensatory mechanisms. PML loss promotes increased cycling in neural precursors, thus leading to the expansion of the ventricular zone. This effect is limited to one specific subtype of neural precursors, radial glial cells. In contrast, transition to basal progenitors is impaired. As a result, PML-deficient cortices show decreased neurogenesis, thus leading to a thinner cortical wall. However, it is unknown whether the affects of PML loss on brain development lead to behavioral changes in the PML KO mouse. The changes in proliferation and differentiation properties induced by PML loss can be recapitulated in vitro in neural stem cell cultures, thus indicating that the effects observed in vivo are indeed cell intrinsic. At the molecular level, PML loss leads to phosphorylation of the pRb, thus inactivating a key G1/S checkpoint. PML had been previously shown to associate with pRb in hemopoietic cells and cell lines [61]. In neural precursors, PML regulates pRb by inducing its targeting to the PML-NB and subsequent dephosphorylation by protein phosphatase 1 (PP1) (Fig. 1b). In the absence of PML, both PP1 and pRb are delocalized to the nucleoplasm and cytoplasm. It is presently unknown whether this is the sole mechanism by which PML regulates cell fate in neural precursors, and this is the current focus of our laboratory. In this respect, PML colocalises with the chromatin-remodeling protein ATRX (see above), which regulates transition through mitosis in the developing cortex [84, 85]. Mutations of ATRX cause the ATR-X syndrome, which is characterized by brain retardation. Interestingly, a number of disease-associated mutants of ATRX are severely impaired in their ability to localize to PML-NBs [86], thus suggesting that PML may regulate ATRX normal function.

A number of recent studies have highlighted a more general role of PML in stem cells. For instance, PML regulates differentiation of progenitors of the mammary gland, thus affecting gland development [46, 87]. Furthermore, PML maintains quiescence in adult hemopoietic stem cells (HSCs). Interestingly, the tumor suppressor p53, which can associate with PML, has been recently shown to control cell fate in HSCs [88], thus suggesting that PML could modulate stem cell function through interaction with multiple tumor suppressors. Finally, other members of the TRIM family, TRIM11 and TRIM32, have been shown to play a role in neural progenitors [89, 90]. Although mechanisms of action are different, it is possibly that a degree of compensation between TRIM family members exists in the CNS.

Role of PML in Differentiated Cells of the CNS

As mentioned above, PML is expressed in neural precursors of the embryonic and postnatal CNS, but it is excluded from neurons and macroglia. However, at least the hippocampus and cortex of adult mouse brain reacquire PML expression, thus suggesting that PML may play a role in postmitotic cells as well (our unpublished data). It is presently unknown whether the pattern of isoform expression is different between the adult and developing brain. Several reports have shown that PML colocalizes with intracellular aggregates formed by aggregation-prone proteins found in neurodegenerative diseases. In particular, early reports showed that PML is found associated in cells with nuclear aggregates formed by mutant Ataxin-1, Ataxin-3, and Ataxin-7, which have been implicated in the pathogenesis of Spinocerebellar Ataxia Type 1 (SCA1) and 2 (SCA7), respectively [91–93]. This association was later confirmed in primary patient samples of SCA1, SCA7, SCA3, SCA17, and DRPLA [94–96]. Notably, PML is highly expressed in terminally differentiated Purkinje

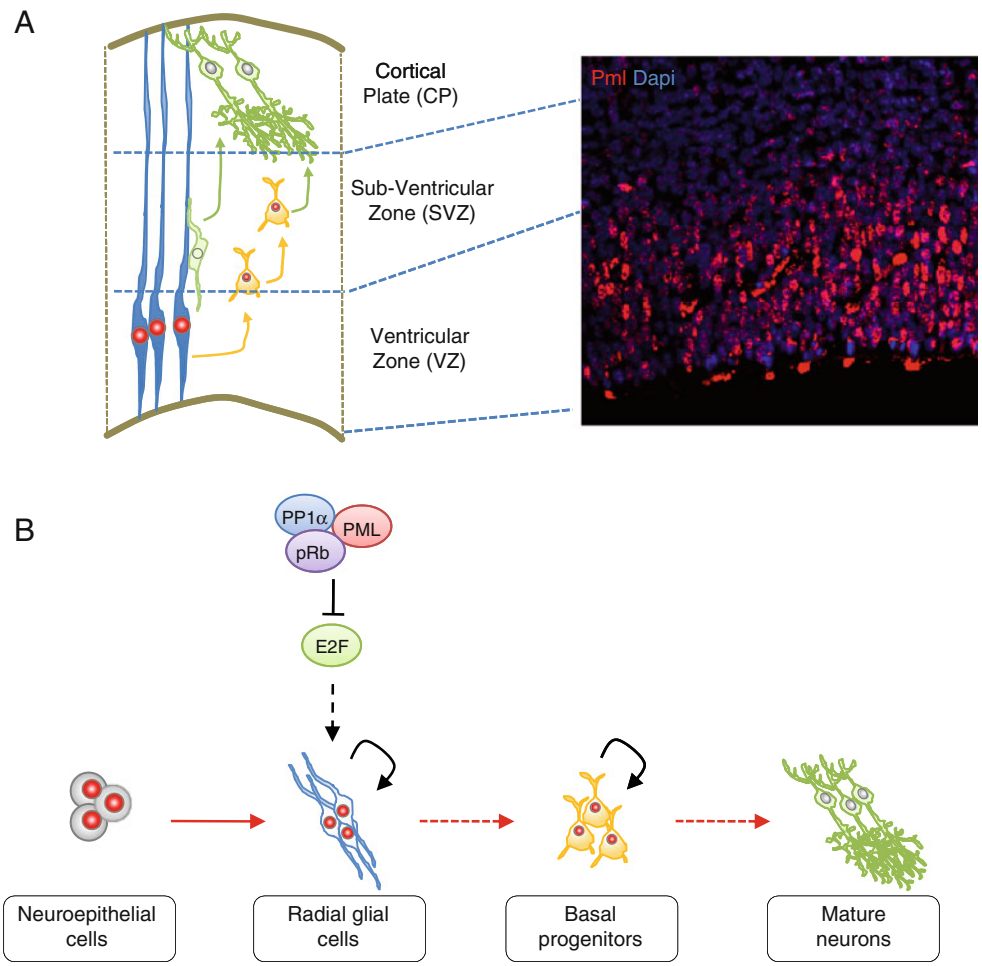

Fig. 1 PML expression is restricted to neural progenitor/stem cells (NPCs) within the embryonic cortex and regulates their functions through interactions with pRb. **a** Schematic showing the neurogenic niche of the embryonic cortex. Radial glial cells (*blue*) are in the ventricular zone, intermediate progenitor cells (IPCs, *yellow*) are mainly in the subventricular zone (SVZ) and newly generated neurons (*green*) are found in the cortical plate (CP). Pml expression (*red*) is restricted to the radial glial cells and intermediate progenitor cells. **b** Within these NPCs, Pml is required to promote PP1α–mediated dephosphorylation of pRb, which then blocks the pro-proliferative effects of E2F transcription factors

neurons (our unpublished results), which are the cell type mostly affected in SCA. Tissues from frontotemporal dementia patients also showed association of ubiquitin nuclear inclusions with PML-NBs [97]. Colocalization with intranuclear inclusion Marinesco bodies was reported in non-degenerative conditions [98].

What would be the role of PML in intranuclear inclusions of neurodegenerative diseases? PML-positive inclusions contain ubiquitin and in some cases proteasome subunits, thus suggesting that these aggregates could be caused by aberrant proteasomal function (Fig. 2). Alternatively, they could represent active sites of proteasomal degradation. In this respect, it is still unclear whether inclusions positively or negatively affect the proteasome [99] and more in general if alterations of the proteasome contribute to neurodegeneration in polyglutamine-associated diseases. PML has been shown to be targeted for degradation by the proteasome [100], and PML-NBs recruit 11S proteasome subunit in normal conditions [101]. Furthermore, a recent report has revealed the mechanism underlying PML and PML-NBs degradation by the proteasome: this is dependent on elevation of ROS levels leading to formation of disulfide bonds and ubiquitin-dependent breakdown [40, 102]. Cellular redox control is one of the potential mechanisms underlying the pathogenesis of polyglutamine-associated diseases [99], thus suggesting that formation of PML inclusions in dysfunctional neurons could be related to changes in ROS levels accompanied by impaired proteasomal function. As PML is believed to regulate the response to DNA damage (see above), it is conceivable that it could regulate activation of checkpoints downstream ROS-induced DNA damage. A number of studies have proposed that specialized PML-NB called clastosomes [103] could play a protective role in preventing accumulation of polyglutamine proteins, potentially through a mechanism involving the GTPase CRAG [104, 105].

PML has been shown to affect the function of the acetyltransferase CBP, which is inactivated in polyglutamine diseases [106, 107]. It is therefore possible that alterations of PML-NBs could affect chromatin remodeling and transcription through modulation of CBP function. However, this does not exclude that PML alterations may affect both proteasomal regulation and transcriptional control, as the interplay between the two processes is well established.

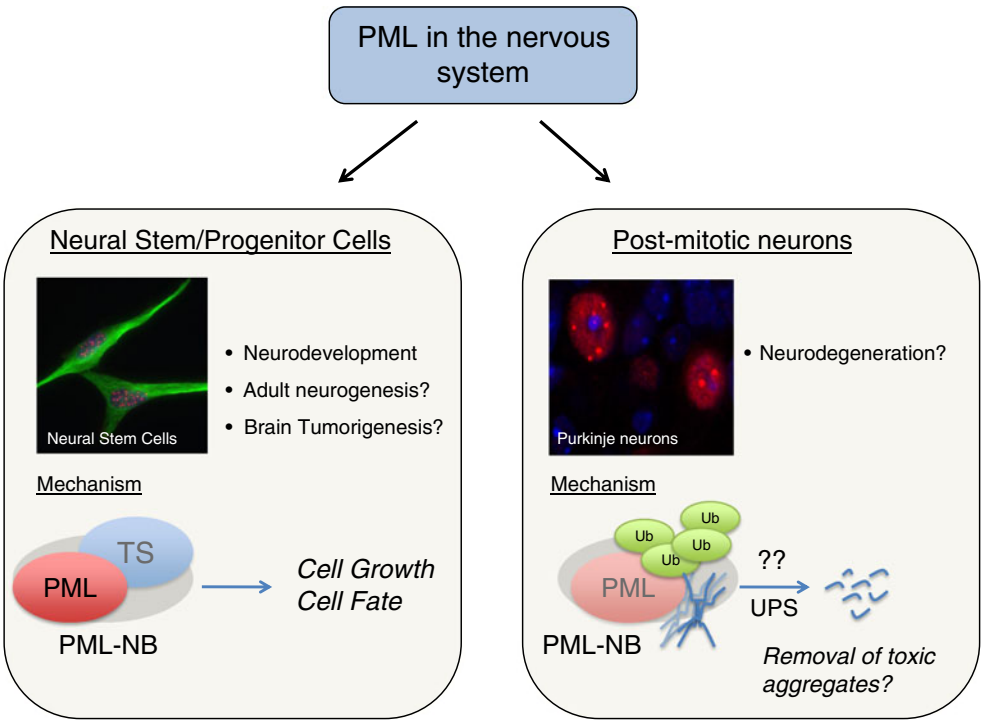

Fig. 2 The role of PML in the nervous system. Within neural stem/progenitor cells NPC, PML interacts with and regulates other tumor suppressors (TS), thus mediating vital NPC functions such as proliferation. Within post-mitotic neurons, PML has been found associated with intranuclear inclusion of neurodegenerative diseases, suggesting it may play an important role in mediating degradation of aberrant proteins by the proteasome

It is of note that PML has been shown to be upregulated in a stroke model, suggesting that it may play a role in the tissue response to this type of brain injury [108]. The authors of this report suggest that PML may be involved in promoting cell death in this context. However, it cannot be excluded that it may represent a protective signal.

As most of the functional studies described above used in vitro systems, there is urgent need to determine the effect of PML loss or gain of function in models of neurodegenerative diseases. The ability of PML to modulate degradation of mutant proteins in these conditions would suggest a protective role against neurodegeneration. As a result, PML loss in neurodegeneration-prone animal models should result in aggravation of the phenotype. Finally, it would be key to investigate what role PML plays in neurons in physiological settings. In this regard, no studies have yet investigated whether PML loss affects neuronal function and if neurological abnormalities are present in PML-deficient animals. Due to PML role in neural stem cells, it would be desirable to conditionally inactivate PML in post-mitotic neurons. This model is not yet available to the research community.

Conclusions and Future Directions

Recent studies have shown that PML regulates brain development and in particular affect stem cell function. This has clear implications for brain cancer research, as transformation of neural stem cells leads to brain cancer. In this respect, PML expression has been reported to be lost in oligodendroglial tumors and medulloblastoma [73], suggesting that its loss may contribute to tumor development. However, PML inactivation is not sufficient to promote brain cancer in the mouse [109]. Therefore, loss of PML could modulate tumorigenesis in the context of other oncogenic lesions. The role of PML in neural stem cells may also carry implications for regenerative medicine. Although cell replacement-based therapy for neurodegeneration conditions has stirred a not yet solved debate [110], the ability of transplanted neural stem cells to nurse damaged circuits may show promise [111]. Modulation of PML expression may be used to promote expansion of neural stem cells in vitro and/or modulate their multipotency. Furthermore, PML status could affect generation of induced pluripotent stem cells, which represent a powerful tool for modeling disease pathogenesis and for drug screening [110]. It is of note that arsenic trioxide has been recently proposed to affect PML nuclear body formation and PML degradation [112]. Thus, modulation of PML function could be achieved pharmacologically.

The association between PML expression/localization in dysfunctional neurons in neurodegeneration conditions prompts further investigation into the involvement of PML in the pathophysiology of the adult brain. It is conceivable that the association between PML and the proteasome may have functional consequences on the pathogenicity of toxic aggregates in neurodegeneration conditions such as SCA and Huntington's disease. As mentioned above, this hypothesis has to be tested in reliable models of these diseases.

Is PML function different in neural stem cells versus postmitotic neurons? The multitude of functions attributed to PML is of no help. The existence of multiple PML splice variants may indicate that their differential expression could underlie changes in PML function. However, some of the functions could be shared in the two cell types. For instance, the ability of PML to regulate the proteasome could result in changes in toxic aggregates levels, thus modulating stem cell function.

Addressing these and other questions would be key to move the PML field forward in the coming years.

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