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# PML Nuclear Bodies

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PML nuclear bodies are matrix-associated domains that recruit an astonishing variety of seemingly unrelated proteins. Since their discovery in the early 1960s, PML bodies have fascinated cell biologists because of their beauty and their tight association with cellular disorders. The identification of PML, a gene involved in an oncogenic chromosomal translocation, as the key organizer of these domains drew instant interest onto them. The multiple levels of PML body regulation by a specific posttranslational modification, sumoylation, have raised several unsolved issues. Functionally, PML bodies may sequester, modify or degrade partner proteins, but in many ways, PML bodies still constitute an enigma.

## PML BODIES, AN INTRODUCTION

PML nuclear bodies (NBs) are spheres of 0.1–1.0 μm in diameter found in most cell-lines and many tissues. They belong to the nuclear matrix, an ill-defined super-structure of the nucleus proposed to anchor and regulate many nuclear functions, including DNA replication, transcription, or epigenetic silencing (Stuurman et al. 1990). The PML protein is the key organizer of these domains that recruits an ever-growing number of proteins, whose only common known feature to date is their ability to be sumoylated (Bernardi and Pandolfi 2007). PML and NBs were proposed to fine-tune a wide variety of processes, through facilitation of partner protein posttranslational modifications (notably sumoylation itself) resulting in partner sequestration, activation, or degradation. Several NBs subtypes have been defined on morphological bases, which all contain an electron-dense shell and an inner core.

PML NBs came to the forefront with the observation that the oncogenic PML/RARA protein disrupts them in a treatment-reversible manner (Daniel et al. 1993; Dyck et al. 1994; Koken et al. 1994; Weis et al. 1994; Zhu et al. 1997). PML NBs are regulated by cellular stress: viral infection (Everett 2006), DNA-damage, transformation (Koken et al. 1995; Terris et al. 1995; Gurrieri et al. 2004), and oxidative stress (Yamada et al. 2001a; Villagra et al. 2006). Moreover, transcription of PML and several genes encoding partner proteins is dramatically enhanced by interferons. Yet, *pml*-/- mice, which cannot assemble NBs, develop normally and live well, demonstrating that NBs are dispensable for most basic biological functions.

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Nevertheless, recent data has implicated PML in the control of cellular senescence and stem cell self-renewal, extending the fields of investigation of PML function (Ferbeyre et al. 2000; Pearson et al. 2000; Salomoni and Pandolfi 2002; Ito et al. 2008).

## HISTORICAL OVERVIEW

As for several other nuclear structures, electron microscopy and auto-antibodies were the two founding fathers of the field. Work from several pioneers in the early 1960s noted the presence of dense spherical objects by electron microscopy (de Thé et al. 1960). Two classes were morphologically described: Empty ones (fibrillar) and granular ones, with an inner microgranular material proposed to be ribonucleoproteins (Fig. 1). PML NBs were later observed by immunofluorescence using autoimmune sera from primary billiary cirrhosis patients. These allowed the identification of the first NB-associated protein, SP100 (Szostecki et al. 1990), and an initial characterization of these structures (Ascoli and Maul 1991).

Identification of an anti-nuclear matrix antibody, which labeled the same structures as SP100 (Stuurman et al. 1992), drew the first link between these bodies and the nuclear matrix. The localization of PML, a protein fused to the retinoic acid receptor α(RARA) in the PML/RARA oncoprotein of acute promyelocytic leukemia (APL), to the same nuclear dots as SP100, renewed interest for these domains. The observation that in APL cells PML/RARA disrupted these domains drew instant excitement from the scientific community (Daniel et al. 1993; Dyck et al. 1994; Koken et al. 1994; Weis et al. 1994). Moreover, PML bodies were restored by two different anti-APL therapies, retinoic acid and arsenic trioxide, later shown to trigger PML/RARA degradation (Quignon et al. 1997; Zhu et al. 2001), identifying the first striking parallel between the status of the bodies and that of the cell. Many further studies showed that PML bodies altered in stress conditions, notably viral infections, heat shock, and

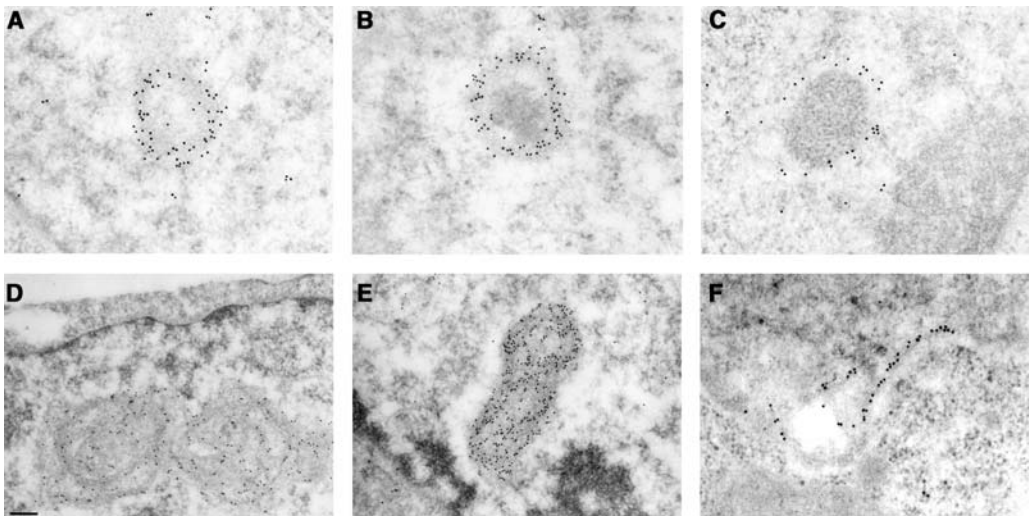


**Figure 1.** Different types of PML bodies. Immuno-gold electron microscopy of PML NBs in CHO cell line stably overexpressing PML. (*A*, *B*, *C*) "Classical" PML NBs. PML is distributed on a dense electron shell (*A*, *B*) or on light halo (*C*), that can contain a microgranular inner core (*B*, *C*) or not (*A*). (*D*, *E*) PML body in arsenic trioxide-treated cell. Note the absence of the inner core and the enrolled fibrillar aspect of the body (*D*). (*F*) PML-II targets the inner membrane region of the nuclear envelope in *pml*-/- MEF cells. Images courtesy of Edmond and Francine Puvion (CNRS, Villejuif, France).

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exposure to heavy metals (Everett 2001; Dellaire and Bazett-Jones 2004; Everett 2006).

PML bodies recruit an ever-increasing number of partner proteins (now in the range of 100), one of the most studied being DAXX, a potent repressor of transcription and modulator of apoptosis. Critically, PML is the actual organizer of the bodies (Ishov et al. 1999; Zhong et al. 2000a; Lallemand-Breitenbach et al. 2001). Among these recruited proteins, one deserves a special mention: an ubiquitin-like protein named SUMO, as PML conjugation by SUMO plays a critical role in recruitment of partners, many of which are sumoylated themselves. Recent studies have focused on more fundamental cell-biology issues: Dynamics of the bodies (Eskiw et al. 2003, Muratani et al., 2002, Chen et al., 2008), relation to other nuclear components (Wang et al. 2004; Batty et al. 2009; Russell et al. 2009), mode of assembly (Shen et al. 2006), and determinants of partner recruitment and actual function in cellulo and in vivo.

## THE PML PROTEINS

PML is a member of the TRIM/RBCC family of proteins, many members of which are ubiquitin ligases that generate subcellular structures through autoassembly (Reymond et al. 2001; Meroni and Diez-Roux 2005). Transcription of the *PML* gene is tightly controlled by interferons α/β or γ, but also by p53 (Stadler et al. 1995; de Stanchina et al. 2004), which both yield a dramatic increase in the number and the size of the bodies. PML harbors an amino-terminal RING finger that directly binds the SUMO E2 ligase UBC9 (Duprez et al. 1999), two RING-like domains, the B boxes (Tao et al. 2008), and a coiled-coil mediating homodimerization (Kastner et al. 1992). For other RBCC/TRIM family members, partner binding-specificity often relies on the carboxyl terminus. For PML, a variety of carboxy-terminal domains generated by alternative splicing yield isoforms (Jensen et al. 2001). When expressing single PML isoform in *pml*-/- cells, distinct types of PML NBs were observed, implying that isoform-specific sequences contact different nuclear constituents that influence morphogenesis (Beech et al. 2005; Condemine et al. 2006; Weidtkamp-Peters et al. 2008) (Table 1). Yet, because of the coiled-coil, all endogenous isoforms colocalize. The most abundant (but perhaps least studied) isoform, PML-I, harbors an exonuclease-III domain, that targets PML to nucleolar caps in stressed or senescent cells (Condemine et al. 2007). In addition to the nuclear localization signal (NLS) present in all PML isoforms, PML-I harbors a nuclear export signal (NES) that allows shuttling of all isoforms between the two compartments through heterodimer formation (Henderson and Eleftheriou 2000; Beech et al. 2005; Condemine et al. 2006). The most extensively studied isoform, PML-IV, induces senescence in primary human fibroblasts (Bischof et al. 2002) and apoptosis in many other cellular settings, at least in part through p53 activation (Guo et al. 2000).

**Table 1.** PML isoforms with specific localizations.

| PML isoform: | Specific localization in *pml* -/- cells: |
|---|---|
| PML I | Nucleolar upon stress, cytoplasm |
| PML II | Fibrillar/nuclear envelope (lamina?) |
| PML IV | Nucleolar upon stress |
| PML V | Thick shell/nuclear matrix tethering |
| PML VII | Cytoplasmic/early endosomes |

The expression of PML isoforms in *pml*-/- cells reveals specific localizations, suggesting that the carboxy-terminus drives interactions with specific unidentified partners. From (Beech et al. 2005; Condemine et al. 2006; Weidtkamp-Peters et al. 2008).

PML undergoes several critical posttranslational modifications, notably phosphorylation and sumoylation. PML sumoylation has been implicated in NB-morphogenesis. DNA damage- or stress- activated kinases like ATM, ATR, CHK2, HIPK2, CK2, or ERK phosphorylate PML, possibly regulating PML stability, NB biogenesis and partner association (Engelhardt et al. 2003; Hayakawa and Privalsky 2004; Scaglioni et al. 2006; Gresko et al. 2009) and contributing to DNA repair or apoptosis control.

## MORE THAN ONE PML BODY!

It is generally assumed that "PML NBs" designates a single object. However, there is considerable evidence that PML bodies are diverse.

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Indeed, PML aggregates onto different sites to create an unsuspected repertoire of PML-accumulating domains in response to a variety of stresses (Eskiw et al. 2003; Bernardi and Pandolfi 2007). Before engaging in the catalog of structures that contain PML, one has to realize that contrarily to the common appreciation, the overwhelming majority of the PML protein pool in a cell is actually *not* NB-bound. In most cell lines, even in vivo, more than 90% of PML has a diffuse nuclear localization, not associated with the nuclear matrix or NBs (Lallemand-Breitenbach et al. 2001) (P. Hemmerich, personal communication). The most extensively studied factor modulating PML distribution has been arsenic trioxide (see later discussion), although several DNA-damage-activated kinases are also important. Stress-induced aggregation may promote aggregation of typical NBs or conversely disperse them into microspeckles (see Table 2). The differences among these bodies can be based on morphology or content, yielding a much more dynamic view of PML than previously thought.

## Structure of the Classical Body

The classical PML body is a spherical object with a diameter of 0.1–1 μm, which may or may not have a micro-granular centre. These bodies, from five to 15 per nucleus in cell-lines, are mostly proteinaceous in nature and do not in general contain RNA or DNA (Boisvert et al. 2000). PML forms the outer shell of the

**Table 2.** PML NBs are sensitive to cellular stress.

| Stress | | PML NB phenotypes | SUMO colocalization | Cell types | Ref |
|---|---|---|---|---|---|
| **IFNs** | | Increased number and size | Increased | All | Stadler, 1995 |
| **$As_2O_3$** | | Large PML shell, decreased number | Increased | All | Zhu, 1997<br>Lallemand-Breitenbach, 2001 |
| **$CdCl_2$/heat shock** | | Dispersed micro-bodies | No | All | Eskiw, 2003 |
| **Proteasome Inhibition** | | Nucleolus | Yes | Primary | Condemine, 2007<br>Mattsson K, 2001 |
| | | Increased number and size | Increased | Transformed | Lallemand-Breitenbach, 2001<br>Everett, 1999 |
| **Actinomycin-D** | | Large, Peri-nucleolar | ? | Primary + transformed | Janderova-Rossmeislova, 2007<br>Condemine, 2007 |
| | | Dispersed micro-bodies | Yes | Transformed | Eskiw, 2004 |
| **DNA Damage** | Doxo, IRgamma, UVc | Large, perinucleolar | Yes | Primary transformed | Bernardi, 2004<br>Condemine, 2007<br>Kurki, 2003 |
| | UVc, alkylators, staurosporine DNase | Dispersed micro-bodies | Yes | Primary transformed | Salomoni, 2005,<br>Condemine, 2007<br>Eskiw, 2003<br>Eskiw, 2004 |

List of exogenous agents that perturb PML NB organization; the status of PML sumoylation followed by NB localization is indicated. The phenotype of PML NBs is dependent on the type of stress and cellular context (transformed cell lines or primary cells).

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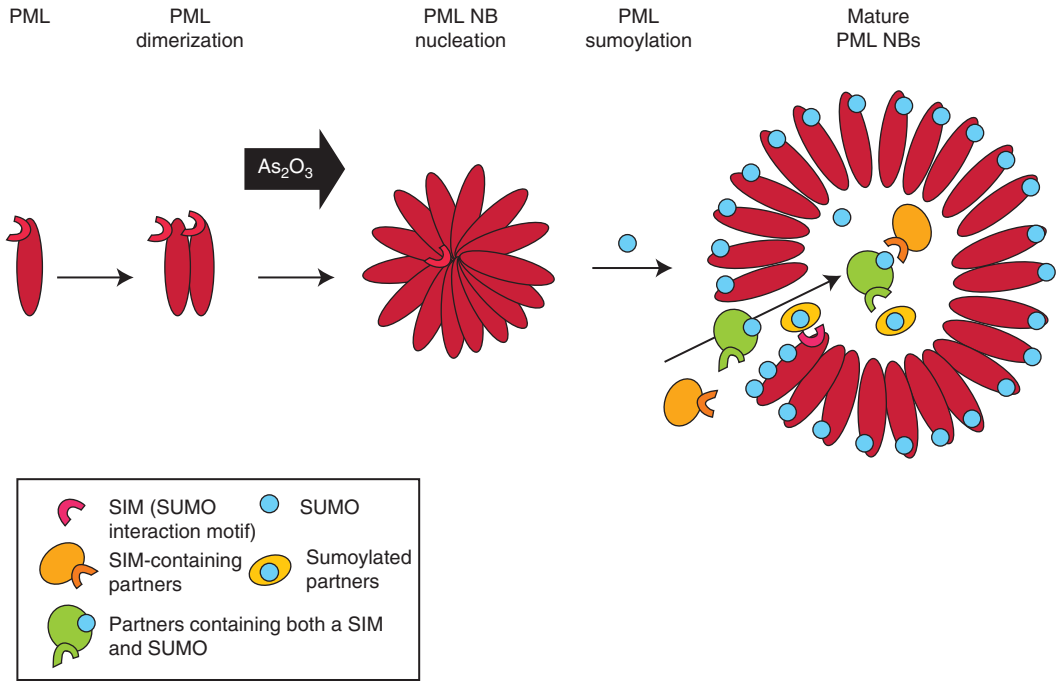


**Figure 2.** Schematic representation of PML NB biogenesis. PML proteins first dimerize through the RBCC domains and then multimerize to nucleate NBs. PML sumoylation then leads to organization in spherical body. SIM-containing or sumoylated partners (or both) are recruited by the SUMO or SIM of PML into the inner core of the body.

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bodies and partners are usually inside, which is easily shown after PML/partner overexpression (Guiochon-Mantel et al. 1995) (Figs. 1, 2). Like several other bodies, PML NBs are present in the interchromosomal space (Bridger et al. 1998), likely explaining why they are often found close or adjacent to other bodies (Wang et al. 2004; Sun et al. 2005; Batty et al. 2009; Russell et al. 2009). Although devoid of DNA, PML NBs may be associated with some specific chromosomal loci, like MHC class I gene cluster region for which PML NBs were proposed to modulate chromatin architecture and transcription (Shiels et al. 2001; Wang et al. 2004; Kumar et al. 2007). One elegant study has found a PML body constantly juxtaposed to a repressor locus, underscoring the links with transcriptional regulation (Tsukamoto et al. 2000). Conversely, chromatin changes occurring during transcription or the cell cycle may modulate PML NBs structure and number (Eskiw et al. 2004; Wang et al. 2004; Ching et al. 2005). PML NBs are profoundly modified during many virus infections (Everett 2006). They may, for example, accumulate viral genomes at their periphery or within their central core during infection of quiescent cells (Everett et al. 2007).

## PML NBs, Telomeres and DNA Damage

Alternative lengthening of telomeres (ALT)-associated PML bodies (APBs) are larger structures observed in cell-lines that do not express telomerase and maintain telomere length by homologous recombination. APBs contain two types of DNA double-strand break repair and homologous recombination factors, the Rad50/Mre11/NBS1 complex and Rad51/Rad52, together with the replication factor A (RPA), the helicase BLM and the telomeric repeat-binding factors TRF1 and TRF2 (Wu et al. 2000; Wu et al. 2003). APBs harbor actively replicating telomeres in the S/G2

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phase of the cell cycle. Almost all these proteins are sumoylated. Association of the SUMO ligase SMC5/6 complex with APBs is required for TFR1/2 sumoylation and cell survival (Potts and Yu 2007). Recent studies have argued for a role of PML in facilitating these processes (Jiang et al. 2007; Draskovic et al. 2009).

PML is phosphorylated by several DNA-damage activated kinases, including ATM, ATR, HIPK2, or CHK2. Several studies have implicated PML in DNA-repair, through the recruitment to or release from NBs of many proteins like BLM (Bischof et al. 2001), the Mre11 complex (Carbone et al. 2002), WRN, or TOPBP1 (Dellaire and Bazett-Jones 2004). Some of these proteins are localized in NBs in unstressed conditions, whereas others are only associated with NBs after DNA-damage. Although NBs partially overlap with γH2AX foci, their possible localization on the damage sites is still disputed (Boe et al. 2006). Initial studies localized NBs with BLM on BrdU-positive putative DNA repair sites after irradiation (Bischof et al. 2001). Yet, in later reports, PML-NBs were proposed to retain BLM away from DSB through BLM sumoylation, which could be released by phosphorylation (Eladad et al. 2005; Rao et al. 2005). In response to DNA damage, PML NBs appear to sense the damaged sites, yielding an increased number of microbodies by a fission mechanism. The exact role of PML (bystander or actor) in theses diverse processes is still unclear. Yet, *pml-/-* cells have a very high rate of sister chromatin exchange (Zhong et al. 1999), implying that PML regulates at least some aspects of homologous recombination.

## Nucleolus and RNAs

Electron microscopy studies noted that a subset of bodies contains a granular core, typical for the presence of ribonucleoproteins (Dupuy-Coin et al. 1972). Some of these granular bodies were proposed to bud from the nucleolus (Dupuy-Coin and Bouteille 1972). This most likely reflects the presence of specific RNA-binding proteins and is often observed in hormone-stimulated primary cells (Vagner-Capodano et al. 1982). What determines the presence of the micro-granular core inside PML NBs is unknown. We have observed this granular core in a subset of PML-labeled structures (Fig. 1). The nature of this micro-granular core deserves a renewed exploration. Some studies showed the presence of nascent RNA within a subset of the bodies (LaMorte et al. 1998; Fuchsova et al. 2002; Kiesslich et al. 2002), whereas others did not (Boisvert et al. 2000). Finally, a series of papers has linked PML bodies and mRNA export and translation through eukaryotic translation initiation factor 4E (Lai and Borden 2000; Cohen et al. 2001; Culjkovic et al. 2006; Borden and Culjkovic 2009). Heterogeneity of the results may reflect analysis of different cellular systems, but these issues clearly deserve additional studies.

In primary or senescent cells, others and we have observed larger structures that contain nucleolar elements, senescence-associated NBs (SANBs) (Condemine et al. 2007; Janderova-Rossmeislova et al. 2007). Interestingly, in this setting, NB-associated proteins are not present within the inner core, but directly on the PML shell (Condemine et al. 2007). Formation of these domains requires PML-I, which contains a nucleolar targeting domain, possibly the exonuclease-III homology domain (Condemine et al. 2007). The nucleolar constituent recognized by this domain and the consequence of PML delocalization for nucleolar function are unknown. Yet, upon genotoxic stress or inhibition of transcription, ATR-mediated PML phosphorylation relocalizes PML to nucleolar caps, where PML was proposed to sequester the p53 ubiquitin ligase MDM2 (Bernardi et al. 2004; Shav-Tal et al. 2005) (Table 2).

## Other Subnuclear Compartments

Studies performed in human embryonic stem cells (HESC) have revealed a further unsuspected heterogeneity in PML NBs (Butler et al. 2009). PML NBs assemble in "rosettes" surrounding DNA centromeres or are distributed in tracks bridging two centromeres. These tracks can cross the nucleus and were frequently observed filing lamina gaps at the nuclear envelope. These PML structures do not contain SUMO, SP100, or DAXX proteins and their role in stem cell fate remains to be explored. The

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PML-II isoform is associated with the inner membrane of nuclear envelope in somatic cells (Condemine et al. 2006) (Fig. 1). NBs are associated with centromeres in proteasome inhibitor-treated cells in the G2 phase of the cell cycle (Everett et al. 1999a). Finally, NBs containing pericentromeric satellite DNA together with HP1, BRCA1, ATRX, and DAXX were proposed to play a role in the re-establishment of the condensed heterochromatic state of late-replicating satellite DNA in ICF syndrome and possibly in normal cells (Luciani et al. 2006).

### Cytoplasmic PML

Among PML isoforms some are devoid of NLS and yield purely cytoplasmic bodies, when expressed in *pml-/-* cells. Similarly, because PML-I has a nuclear export signal, it forms some cytoplasmic PML-labeled bodies (Condemine et al. 2006). Cytoplasmic PML was proposed to regulate TGFβ signaling by controlling the association of Smad2/3 with SARA and accumulation of SARA and TGFβ-receptor in the early endosomes (Lin et al. 2004) (Table 1).

## NB DYNAMICS

### Basal Status

NBs have been the focus of several studies using imaging technologies such as FRET or FRAP (Tsukamoto et al. 2000). These have shown that PML is a stable component of the bodies and that partner proteins are more mobile, although they are transiently retained in NBs (Boisvert et al. 2001; Weidtkamp-Peters et al. 2008). The exchange rates of the different PML isoforms between NBs and nucleoplasm showed a clear difference for PML-V, which forms peculiar thick-shelled NBs and might anchor NBs onto the nuclear matrix (Condemine et al. 2006; Weidtkamp-Peters et al. 2008). The bodies themselves are not very mobile, although fusions and fissions can be observed through the cell cycle progression (see later discussion). Some bodies labeled by GFP-SP100 are smaller and more dynamic than typical PML NBs (Muratani et al. 2002; Wiesmeijer et al. 2002). Telomeres quickly get in and out of APBs, whereas their PML shell is quite immobile (Molenaar et al. 2003; Jegou et al. 2009), similar to that of SANBs (Condemine et al. 2007). When interpreting these studies, one has to remember that some were performed in transiently transfected cells where posttranslational modifications, which are essential determinants of partner residence, are unlikely to be complete.

### Cell-Cycle Analysis

Analyses of NBs during the cell cycle have provided evidence for duplication by a fission mechanism during S phase (Dellaire et al. 2006c) and have dissected NB reformation during the M/G1 transition (Dellaire et al. 2006b; Chen et al. 2008). During mitosis, PML proteins remain aggregated, but are phosphorylated, become desumoylated and release partners (Everett et al. 1999b). Before nuclear membrane breakdown in prometaphase, PML NBs lose their chromatin-tethering, resulting in increased mobility (Chen et al. 2008). Yet, FRAP performed during mitosis showed that PML proteins did not exchange, demonstrating that mitotic bodies are highly stable (Dellaire et al. 2006c). PML associates with nuclear membranes and nucleoporins during mitosis, facilitating reformation of the nuclear envelope during the telophase/G1 transition (Puvion-Dutilleul et al. 1995; Jul-Larsen et al. 2009). Finally, during telophase to G1 transition, SP100 and DAXX re-enter the nucleus and then bind preformed NBs, SP100 first and later DAXX, consistent with the critical role of PML in NB-nucleation.

### Stress Response

Apart from arsenic trioxide that promotes NB formation (see below), heat shock or heavy metals induce reversible NB fragmentation by budding of highly mobile micro-bodies that are devoid of SUMO and most partners (Table 2). In contrast, transcriptional inhibition or DNA damage induce formation of microspeckles or nucleolar caps depending on the type of cells (transformed or primary), with a maintained

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SUMO-colocalization (Table 2) (Eskiw et al. 2003; Nefkens et al. 2003; Dellaire et al. 2006a). Single cell studies after stress recovery have shown that the initial size, location, and number of NBs was somehow restored, suggesting that NBs may assemble on predetermined sites. A full exploration of the role of PML phosphorylation for the regulation of PML mobility and NB formation would be important to clarify these issues.

## IS SUMO THE NB-ASSEMBLY GLUE?

SUMO is conjugated to target proteins on the side chain of lysine residues, creating a branched peptide and significantly changing the binding properties of the protein. SUMO has been implicated in multiple pathways, mostly as a regulator of protein interactions (Hay 2005). Conjugated SUMO may interact with a short motif, known as the SUMO interaction motif (SIM) (Minty et al. 2000; Hecker et al. 2006). SUMO-1 was first identified as a PML partner in a two-hybrid screen (Boddy et al. 1996). PML was shown to be sumoylated on three lysine residues: K65 in the RING finger, K160 in the B1 box, and K490 in the NLS. PML also contains a SIM. Accordingly, intermolecular interactions between the PML SUMO and SIM were proposed to underlie NB biogenesis (Matunis et al. 2006; Shen et al. 2006). Sumoylation-defective *Ubc9*-/- cells indeed show NB defects (Nacerddine et al. 2005). Moreover, because most partner proteins associated with classical PML NBs are sumoylated and many contain a SIM, SIM/SUMO interactions may also account for partner recruitment as well as sequestration.

Studies on NB-biogenesis have been greatly facilitated by arsenic trioxide. Arsenic trioxide, a very potent therapeutic agent in APL (Zhu et al. 2002; Kogan 2009), was first shown to target PML/RARA for degradation through its PML moiety (Chen et al. 1997; Zhu et al. 1997; Muller et al. 1998; Shao et al. 1998). Arsenic trioxide is the only factor that regulates the partitioning of PML between the nucleoplasm and the nuclear matrix, promoting in a sequential manner NB-formation, PML sumoylation, partner recruitment, and PML degradation (Lallemand-Breitenbach et al. 2001; Lallemand-Breitenbach et al. 2008) (Fig. 2). Critically, PML sumoylation on K160/K65 follows matrix-targeting and is required for partner recruitment (Ishov et al. 1999; Zhong et al. 2000a; Lallemand-Breitenbach et al. 2001). Yet, how arsenic trioxide initiates the SUMO-independent transfer from the soluble diffuse nucleoplasmic form toward the insoluble matrix fraction and why matrix association is followed by sumoylation of these two sites remains unexplained to date.

SUMO/SIM interactions were initially proposed to underlie both formation of the PML mesh and recruitment of partners. Although appealing, this model has been significantly challenged by recent evidence. Specific PML isoforms that do not harbor the SIM yield normal bodies (Weidtkamp-Peters et al. 2008). Conversely, analysis of several partner proteins has shown that their SIM is essential, whereas their sumoylation is dispensable for NB-targeting (Takahashi et al. 2005; Lin et al. 2006; Cho et al. 2009). Taken together, SIM/SUMO are unlikely to play a fundamental role in PML aggregation to create the PML mesh, but may be critical for partner recruitment.

## WHAT ARE THE FUNCTIONS OF NBs?

PML influences or regulates key processes such as transcription, apoptosis, senescence, response to DNA-damage or resistance to micro-organisms, which have all been extensively reviewed elsewhere (Salomoni and Pandolfi 2002; Everett 2006; Bernardi and Pandolfi 2007; Bernardi et al. 2008). Two novelties have emerged: (1) the protective role of PML, DAXX, and SP100 against many viral infections (Everett et al. 2006; Tavalai et al. 2006; Everett et al. 2008; Tavalai et al. 2008; Kyratsous and Silverstein 2009), at least in the absence of the viral proteins that disrupt NBs; (2) the role of PML in normal or cancer stem cell fate (Ito et al. 2008; Li et al. 2009; Regad et al. 2009). PML-enforced stem cell self-renewal may rely on its ability to modulate the AKT pathway through regulation of AKT phosphorylation or through the localization of its regulator PTEN (Trotman et al. 2006; Song et al. 2008; Ito et al. 2009). TR2, a modulator of the critical Oct4

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stem cell transcriptional regulator, is dependent on PML for its sumoylation (Park et al. 2007; Gupta et al. 2008). The importance of PML in "stemness" highlights the distinctly uncommon morphology of NBs in ES cells (Butler et al. 2009) and questions the nature of the PML isoforms that they actually express.

How are these functions actually achieved? The current models envision PML as glue, whose major function is to recruit and concentrate partners within NBs. Recruitment of partners together with many protein-modifying enzymes, could, in principle, enhance posttranslational modifications, yielding activation, sequestration or degradation. There is evidence to support all three of these processes (Fig. 3).

## Partner Posttranslation Modifications

Perhaps the most studied posttranslational modifications have been those on the tumor suppressor p53. A striking finding has been the concentration of p53-modifying enzymes (CBP, HDM2, HIPK2, and HAUSP) within NBs. PML-enhanced acetylation, sumoylation, and phosphorylation occurring in NBs all appear to enhance p53 function. In that respect *pml*-/- cells are distinctly impaired in their ability to undergo senescence (Ferbeyre et al. 2000; Pearson et al. 2000; de Stanchina et al. 2004), whereas conversely PML-IV overexpression triggers senescence by a pathway involving both p53 and Rb (Bischof et al. 2002; Mallette et al. 2004; Bischof et al. 2005). The complexity of the multiple mechanisms through which PML enhances p53 function and some apparent contradictions in the published data plea for a renewed exploration of this critical issue in primary cells, using siRNA or gene excision rather than PML/partner overexpression.

Kinase activity may be affected by translocation into NBs: PP2A dephosphorylates p-Akt

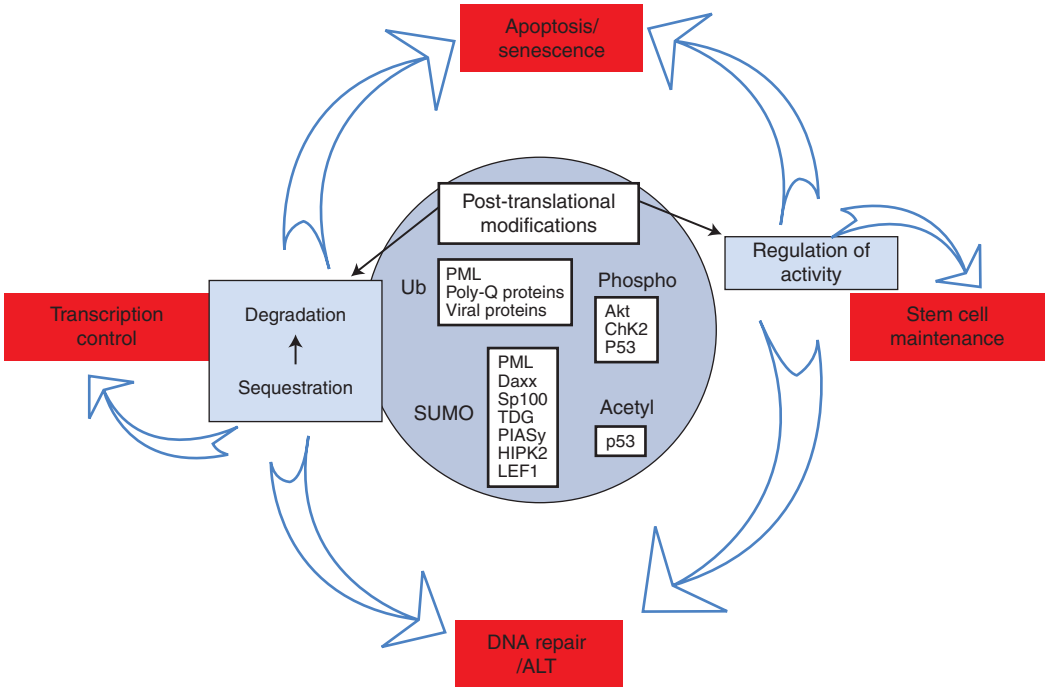


**Figure 3.** A general function for PML NBs: Integrated posttranslational protein modifications? PML NBs regulate posttranslational modifications of partner proteins like sumoylation, ubiquitination, but also phosphorylation or acetylation. These modifications regulate a wide variety of partners, leading to modulation of biological processes like transcription, apoptosis/senescence, DNA repair, or ALT and stem cell self-renewal.

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within PML NBs (Trotman et al. 2006), whereas PP1A was proposed to dephosphorylate RB (Regad et al. 2009). In contrast, recruitment into NBs may favor auto-phosphorylation of some kinases, such as CHK2 (Yang et al. 2002; Yang et al. 2006).

There are also some indications that PML can directly enhance global protein sumoylation in yeast (Quimby et al. 2006) and NBs were proposed to enhance sumoylation of specific partner proteins (Park et al. 2007). Because many NB-associated proteins contain a SIM, this may enhance partner sequestration within NBs.

## Partner Sequestration

Sequestration or "depot" was the first proposed function of PML NBs (Negorev and Maul 2001). This sequestration is evident by the relative accumulation of the nucleoplasmic and the NB-associated form of PML-partners, which very significantly varies between individual partners and levels of PML expression, as well as sumoylation. A well-studied sequestered partner is DAXX, a potent repressor that partitions between sumoylated proteins, including PML and many transcription factors. Sequestration of DAXX by NB-associated, sumoylated PML releases transcriptional repression by DNA-bound sumoylated transcription factors (Li et al. 2000; Lehembre et al. 2001; Lin et al. 2003; Lin et al. 2006). Sequestration of DAXX also regulates apoptosis. In particular, DAXX enhances Fas-triggered caspase activation, possibly through release of ASK1 kinase activity (Torii et al. 1999; Zhong et al. 2000b; Salomoni and Khelifi 2006), although opposite results have been observed in other cell-types (Meinecke et al. 2007). Sequestration of DAXX may also modulate other critical regulators, such as HAUSP, ultimately deubiquitinating the PTEN tumor suppressor (Song et al. 2008). In any case, DAXX, which exerts pro- or anti-apoptotic functions, is a critical partner of PML involved in many of it properties (Maul et al. 2000).

A related situation is the concentration of histones and their chaperones in senescent cells. Formation of a specific type of heterochromatin that silences proliferation-associated genes, senescence-associated heterochromatin foci (SAHF), is one of the first known senescence-associated events. The latter is initiated by the concentration of two histone chaperones HIRA and ASF1a, together with the heterochromatin protein HP1, within PML NBs (Zhang et al. 2005; Ye et al. 2007a; Ye et al. 2007b). What initiates their translocation into NBs and how transient concentration of heterochromatin-associated histones and their chaperones into NBs later favor SAHF formation is not understood.

## Partner Degradation

Several unstable proteins have been localized to PML bodies (Anton et al. 1999; Smith et al. 2004), whereas proteins that are impaired in their degradation aggregate with PML, SUMO, and ubiquitin (Yamada et al. 2001b). NBs concentrate proteasomes and ubiquitin (Fabunmi et al. 2001; Lallemand-Breitenbach et al. 2001; Lafarga et al. 2002; Lallemand-Breitenbach et al. 2008). Arsenic trioxide-induced PML degradation has linked PML bodies and protein degradation. Arsenic trioxide triggers an initial sumoylation of K160, followed by proteasome-dependent degradation, a very controversial proposal at the time this was discovered (Zhu et al. 1997; Lallemand-Breitenbach et al. 2001). Yet, identification of a yeast SUMO-dependent ubiquitin ligase (Geoffroy and Hay 2009) and realization that its human ortholog RNF4 localizes to NBs (Hakli et al. 2005) led to renewed interest in these findings. The initial arsenic trioxide-induced K160 sumoylation triggers a secondary polyubiquitination by RNF4 and proteasome-mediated degradation in NBs (Lallemand-Breitenbach et al. 2008; Tatham et al. 2008). There is also some evidence for partner degradation within NBs (Kitagawa et al. 2006; Qin et al. 2006; St-Germain et al. 2008), but how general this is and what the specific signals are that promote partner degradation within NBs is currently unknown.

Note that for the same pathway, a combination of those different mechanisms may cooperate. For example, modulation of p53 function

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may involve both enhanced p53 modifications and HDM2 sequestration. Similarly, regulation of AKT function involves both dephosphorylation in NBs and sequestration of the DAXX/HAUSP regulators of PTEN activity, to control the critical AKT/TOR/FOXO pathway for stem cell fate (Ito et al. 2009).

## CONCLUDING REMARKS AND OPEN QUESTIONS

Because PML can aggregate with so many cellular components, forced overexpression can yield many artifacts, notably by titration of partners or aggregation of unstable proteins (Takahashi et al. 2004; Bernardi and Pandolfi 2007). Paradoxically, there are only few studies in which PML functions were investigated in stable transfectants or in *pml*-/- cells or in which siRNA were used to inactivate the endogenous PML proteins. Even these experimental approaches preclude assessing the role of the bodies *per se*, compared with that of the diffuse nucleoplasmic fraction of PML. For example, PML-IV-initiated senescence is unaffected by the viral protein CMV IE1, which disrupts NBs (Ahn and Hayward 1997; Bischof et al. 2002). Separating the PML NB functions from those of unassembled PML may be difficult until ad hoc mutants are described.

Another critical issue concerns isoforms. The vast majority of studies have used the PML-IV isoform, which is expressed at very low levels in most cell lines (Stuurman et al. 1992; Condemine et al. 2006), questioning their actual relevance. Finally, future studies will have to address the paradoxical critical role of PML in multiple key processes and the surprisingly modest phenotype of *pml*-/- mice. Perhaps one clue to this issue is that stress response has not been fully explored in these animals, despite some important contributions (Wang et al. 1998) and that stem cell defects may have relatively few manifestations in adults.

The PML field has been extremely active, yielding over the past years a large number of remarkable results. Yet, some very fundamental issues remain to be explained. What is the biochemical and physiological basis for NB-assembly? What is the micro-granular core? What are the specific functions of different isoforms? Why are so many NB-associated proteins transcriptionally controlled by interferons, including PML itself (Stadler et al. 1995; Grötzinger et al. 1996; Engelhardt et al. 2001; Fabunmi et al. 2001)? These issues will certainly be clarified in the years to come, maintaining a vivid and exciting field.

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# PML Nuclear Bodies

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