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Review

The functional roles of PML nuclear bodies in genome maintenance

Hae Ryung Chang[a,1], Anudari Munkhjargal[a,1], Myung-Jin Kim[a], Seon Young Park[a], Eunyoung Jung[a], Jae-Ha Ryu[b], Young Yang[a], Jong-Seok Lim[a], Yonghwan Kim[a,*]

[a] Department of Biological Sciences, Sookmyung Women's University, Seoul 04310, Republic of Korea
[b] Research Center for Cell Fate Control, Sookmyung Women's University, Seoul 04310, Republic of Korea

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ABSTRACT

In the nucleus, there are several membraneless structures called nuclear bodies. Among them, promyelocytic leukemia nuclear bodies (PML-NBs) are involved in multiple genome maintenance pathways including the DNA damage response, DNA repair, telomere homeostasis, and p53-associated apoptosis. In response to DNA damage, PML-NBs are coalesced and divided by a fission mechanism, thus increasing their number. PML-NBs also play a role in repairing DNA double-strand breaks (DSBs) by homologous recombination (HR). Clinically, the dominant negative PML-RARα fusion protein expressed in acute promyelocytic leukemia (APL) inhibits the transactivation of downstream factors and disrupts PML function, revealing the tumor suppressor role of PML-NBs. All-*trans* retinoic acid and arsenic trioxide treatment has been implemented for promyelocytic leukemia to target the PML-RARα fusion protein. PML-NBs are associated with various factors implicated in genome maintenance, and are found at the sites of DNA damage. Their interaction with proteins such as p53 indicates that PML-NBs may play a significant role in apoptosis and cancer. Decades of research have revealed the importance of PML-NBs in diverse cellular pathways, yet the underlying molecular mechanisms and exact functions of PML-NBs remain elusive. In this review, PML protein modifications and the functional relevance of PML-NB and its associated factors in genome maintenance will be discussed.

1. Introduction

The nucleus of a eukaryotic cell is a highly-organized organelle composed of several substructures [1]. Some of these substructures are often called nuclear bodies, which include Cajal bodies, nuclear speckles, polycomb bodies, paraspeckles, and promyelocytic leukemia nuclear bodies (PML-NBs). PML mRNA and protein is expressed in most human organs and in over 60 species according to the public databases The Human Protein Atlas, ProteomicsDB, and Ensembl [2–5]. The nucleolus is where rRNA is generated and Cajal bodies are implicated in assembly and modification of small nuclear RNP (ribonuclear protein) [6]. PML-NB is composed mainly of the PML protein, a known tumor suppressor [7–10]. PML-NBs are about 0.3 − 1.0 μm in size, and the number of nuclear bodies varies from 5 − 30 per nucleus [11]. Over the years, PML-NBs have been continuously highlighted for their role in multiple cellular functions including protein modification, transcriptional regulation, viral infection response, DNA-damage response, DNA repair, cell proliferation, senescence, and apoptosis [12–16]. Many protein factors involved in these processes have been found at the PML-NBs, and disruption of the PML protein results in aberrations of critical cellular functions, leading to human diseases such as acute promyelocytic leukemia (APL) [17]. The *PML* gene encodes the tumor suppressor protein PML, and a t(15;17) translocation results in a PML-RARα fusion protein, which is found in majority of APL. The fusion protein is dominant negative, disrupting PML-NB formation and transcription of RARα downstream genes [18]. Removal of the *PML* gene is not lethal; $PML^{-/-}$ mice are viable [19]. However, other studies revealed that PML knockdown eventually leads to increased genome instability, and $PML^{-/-}$ mice developed more tumors than $PML^{+/+}$ mice, and there were also longer-term side effects that could lead to cancer [20,21]. These are clear evidence that PML and PML-NBs play a significant role in genome maintenance, and further studies showed that PML-NBs are involved in the DNA damage response and DNA repair [22]. The roles of PML-NBs in the cell are versatile, and this review will focus mainly on the role of PML-NBs in genome maintenance pathways including DNA damage sensing, DNA repair, telomere maintenance, and apopto-

Abbreviations: PML-NB, promyelocytic leukemia nuclear body; DSBs, DNA double-strand breaks; HR, homologous recombination; APL, acute promyelocytic leukemia; ALT, alternative lengthening of telomere; APB, ALT-associated PML bodies

* Corresponding author at: 100 Cheongpa-Ro 47 Gil, Yongsan-Gu, Seoul 04310, Republic of Korea.
E-mail address: yhkim@sookmyung.ac.kr (Y. Kim).

[1] These authors contributed equally to this work.

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sis. DNA damage sensing and repair are essential parts of genome maintenance that require multiple factors. Functional roles of PML-NB in genome maintenance pathways, and the associated binding partners are discussed in this review.

2. PML protein and nuclear bodies

2.1. Domains of PML protein and isoforms

The PML protein, also known as TRIM19, is a member of the tripartite motif protein family (TRIM), comprised of a RING-B-Box-Coiled-coil (RBCC) domain located in exons 1–3, and a SUMO-binding domain or SUMO-interacting motif (SIM) found in exon 7a, which play an important role in nuclear body formation [13,23–25]. There are seven isoforms of PML designated as PML I − VIIb by Jensen et al. with a few variations, or isoform PML 1 − 11 by the NCBI nomenclature (The Jensen nomenclature will be used hereafter) [13,25,26]. These isoforms are a result of alternative splicing, all sharing the same N-terminal region but differing at the C-terminal end [13,25,26]. The varying C-terminal end determines each isoform's interaction partners and specific function. For example, all isoforms have a nuclear localization signal (NLS) except PML VIIb, the shortest isoform, which is found in the cytosol. PML I is the longest isoform and the only isoform with a Nuclear Export Signal (NES), and is distributed both in the nucleus and the cytoplasm [25]. The SIM domain is found only in PML I − V. Authors often do not specify which isoforms are being studied, but to this date, PML IV is the most commonly used isoform [27]. PML is mostly in the diffused (RIPA-soluble) fraction, suggesting that some PML proteins exist independently of PML-NBs, while others form nuclear bodies, requiring protein SUMOylation [25,28–31]. The presence of the SIM domain and the modification of many of PML-NB-associated proteins imply that SUMOylation is important for interaction [31]. In addition, PML is phosphorylated by several kinases such as extracellular regulated kinase (ERK), checkpoint kinase-2 (CHK2), ataxia telangiectasia mutated (ATM) and Rad3-related (ATR), and casein kinase-2 (CK2) [13]. The role of phosphorylation will be discussed in Section 3.2 in more detail.

2.2. SUMO-interaction motif (SIM) and nuclear body formation

PML-NB is not a static structure, but a dynamic one, and the size and number of the nuclear bodies change in response to cellular stress or DNA damage [32–35]. PML forms a homodimer, and even the PML-RARα fusion protein forms a dimer through the PML protein, but not RARα [8]. Unlike normal PML-NBs, PML-RARα forms microparticulates in the nucleus. When retinoic acid (RA) is added to cells, these microparticulates break down and start to form nuclear bodies that resemble PML-NB. Arsenic trioxide (As_2O_3) also degrades PML-RARα fusion protein, and is used for APL treatment [36,37]. A review by Van Damme et al. states that there are about 166 proteins associated with PML-NB with various functions such as transcription regulation, cell cycle, virus-host interaction, the DNA damage response, DNA repair, and apoptosis, among others [27]. About 57% of these proteins reside in the nucleus, about 33% shuttle between the nucleus and the cytoplasm, and about 9% are cytoplasmic [27]. Among them, PML-associated factors implicated in genome maintenance, telomere homeostasis, and apoptosis are illustrated in Fig. 1 and listed in Table 1. Of the many proteins present in the PML-NBs, PML, Sp100, and Daxx are some of the permanent residents [22,24]. It has been continuously suggested that one of the important functions of the PML-NB is to serve as storage for many nuclear proteins [13,15,22,38,39]. Of these proteins, RAD51 and Mre11 are involved in DNA damage repair, and also co-localize with PML at the telomere region in cells undergoing alternative lengthening of telomeres (ALT) [38,40–44]. Although numerous proteins localize to the PML-NB, no nucleic acids have been found, indicating that the nuclear bodies found near DNA are most likely due to protein-DNA interactions with a PML-interacting protein [45,46]. One exception is at the telomere, which will be discussed further in the telomere section. Table 1 describes the main PML-NB-interacting proteins discussed in several subsequent sections below.

SUMO-1 was initially identified through a yeast-two hybrid screen, giving it its earlier name, PML-interacting clones (PIC1) [47]. Independently of covalent protein modification, the SIM domain of PML can interact with SUMO and SUMOylated proteins. Shen et al. identified that both the SIM and the RING domains of PML are critical for PML-NB formation and suggested a model for nuclear body assembly [24]. The authors suggest that PML mainly forms a homodimer during mitosis, which is primarily deSUMOylated. During interphase, PML is SUMOylated, allowing the SIMs of PML to interact with each other and the RBCC domain, forming a large assembly of PML proteins.

2.3. Formation of PML-NBs by a fission mechanism

When considering PML-NB formation, nuclear body division or *de novo* formation are two main possibilities. The number of PML-NB increases during S phase in U2OS cells, which is not necessarily due to increased PML protein expression, as PML-protein expression peaks during the G1 phase [48]. The nuclear body becomes unstable during S phase, divides by fission, and redistributes into chromatin fibers. As mentioned above, PML is deSUMOylated during S phase, which likely alters the structure of PML-NB and interacting proteins. It is possible that deSUMOylation contributes to nuclear body fission, as only the RBCC domain is available for PML dimerization, which favors PML-NB fission. In addition, PML-NBs co-localize and migrate with chromatin fibers during S phase, supporting the idea that PML-NBs are involved in DNA damage response and repair.

3. SUMOylation and its significance in PML degradation and PML-NB maintenance

3.1. SUMOylation and nuclear body integrity

SUMOylation is an essential part of PML-NB function during both nuclear body assembly and PML degradation. PML is modified by SUMO at three main amino acid residues: Lys65, Lys160, and Lys490 [49]. SUMOylation at Lys65 and Lys160 are associated with PIAS1/SENP5, leading to PML degradation, and SUMOylation at Lys490 is associated with RanBP2/SENP5, related to PML-NB assembly and maintenance [50]. SUMOylation is essential for nuclear body formation of PML [29,31]. In the study by Zhong et al., authors used $PML^{-/-}$ and $PML^{+/+}$ mouse-derived cell lines to observe PML-NB foci formation by immunofluorescence (IF) imaging [31]. According to this study, diffused SUMO-1 fluorescent signal is visible in the nuclear region in both cell-lines, but in the $PML^{+/+}$ cells, SUMO-1 forms distinctive foci that co-localize with PML-NBs. The authors also found that when the three lysine residues were substituted by arginine (3M-PML), the 3M-PML was no longer SUMOylated, and the nuclear foci representing PML-NBs significantly reduced in number, showing a direct correlation between PML SUMOylation and nuclear body formation. SUMOylation is also critical for protein–protein interactions. 3M-PML does not co-localize with Daxx, SUMO-1, or Sp100, implying the significance of SUMOylation and protein interaction of the PML-NB-residing proteins [31]. Additionally, Sp100, CBP, ISG20, and Daxx foci are visible in $PML^{+/+}$ cells, but not in the $PML^{-/-}$ cells. Daxx, Sp100, and SUMO-1 foci are visible when $PML^{-/-}$ cells are transfected with PML. Multiple studies have shown that PML SUMOylation is not only required for nuclear body formation, but also for recruiting resident proteins [51].

3.2. PML phosphorylation and SUMOylation

The SUMOylation of PML seems to be dependent on the phosphorylation of the serine residues in the protein. Treatment with calyculin A,

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