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Review Article

# A Review on PML Nuclear Bodies and their Interaction with Herpesviruses

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**Abstract**

PML nuclear bodies (PNBs) are proteinaceous structures which predominantly reside inside the nuclei of mammalian cells. Their antiviral effects on a wide range of DNA and RNA viruses are shown. Viruses have evolved a diverse range of mechanisms to overcome the antiviral effect of PNBs. In particular, herpesviruses enter into an association with PNBs to control such antiviral effects. An outcome of this association is switching between the two life cycles of the virus. In this manuscript, we have reviewed our current knowledge on the biology of PNBs and the interplay between them and herpesviruses with an emphasis on the factors that affect the life cycle of the virus.

## ABBREVIATIONS

PML: Promyelocytic leukemia protein; PNBs: PML nuclear bodies; MDV: Marek's disease virus; SUMO: small ubiquitin-like modifier; SIM: SUMO-interacting motif; TRIM: tripartite motif; HSV-1: herpes simplex virus-1; CMV: cytomegalovirus; EBV: Epstein-Barr virus; and KSHV: Kaposi's sarcoma –associated herpesvirus.

## PML NUCLEAR BODIES (PNBS)

PML nuclear bodies (PNBs) are referred to multiprotein spherical compartments in the nucleus of mammalian cells ranging in size between 0.1 to 1 µm. They were first described as "discrete punctate nuclear dot" patterns with a number ranging from 7 to 40 in proliferating cells [1]. PNBs are named after their major organizer, PML protein. PML protein was first identified in patients with acute promyelocytic leukemia (APL), an acute myelogenous leukemia where retinoic acid receptor-alpha (RARA) gene on chromosome 17 is involved in a balanced reciprocal translocation with the PML gene on human chromosome 15 [2,3]. Unlike in normal cells, PML protein in APL cells is dispersed across the nucleus and are not in association of the "discrete punctate nuclear" structures (reviewed in [4]). PML protein is the major organizer of PNBs. There are over 60 proteins whose interaction with PML is shown [5,6], and with localization with PML proteins, they produce PNBs. The exact function of PNBs is not clearly understood, but it is thought that PNBs have functional rules in transcription regulation, epigenetic control of gene expression, tumor suppression, apoptosis, DNA replication, DNA repair and anti-viral innate immune response [7-11]. There are several reviews on PNBs describing their biochemistry and molecular biology [12-17]. Here to provide a better understanding of the topic, a brief description of PML protein and its major partners to form PNBs is provided.

## MOLECULAR BIOLOGY OF PML PROTEIN AND ITS PARTNERS

In human, *pml* gene is located on the chromosome 15 and consists of 9 exons giving rise to at least 7 protein isoforms. In *Mus musculus*, pml is located on chromosome 9 and in *Bos taurus*, it is located on chromosome 21. The molecular structure of PML protein makes it a member of tripartite motif (TRIM) proteins family (TRIM19). Like other TRIM proteins, PML protein consists of: a zinc-binding RING finger domain, two B-box domains (B1 and B2), a coiled-coiled domain, nuclear localization signal, SUMO binding motifs and a SUMO-interacting motif (SIM) [18]. It has been shown that mutations in the zinc binding residues of the domain disrupt formation of PNBs. The RING finger domain of PML is essential for the growth suppression, apoptosis and anti-viral activities of PNBs. B-boxes are cysteine/histidine rich protein motifs with zinc binding properties. The zinc binding property of B-boxes has an important role in the formation of PNBs [19]. The coiled-coil domain of PML is required for both homo- and heterodimerization of PML, for PNB formation and growth suppressor effects of PML [20,21].

Death associated protein (DAXX), SP100, alpha-thalassemia mental retardation syndrome, X-linked (ATRX) and small ubiquitin-related protein (SUMO) proteins are the major partners of PML protein in PNBs. A brief description of the proteins is provided below.

SP100, one of the major components of PNBs, is an acidic and phosphorylated nuclear protein with an apparent molecular weight of 100 KDa [22-24]. DAXX was first discovered through

its interaction with Fas and its participation in Fas associated apoptosis [25,26]. It has both cytoplasmic and nuclear distributions. Pro- and anti-apoptotic functions and a role in TGFβ signaling pathways are reported for DAXX [27,28].

ATRX functions as a chromatin remodeling protein and is an essential protein in mice. It associates with the nuclear matrix, pericentromeric heterochromatin and PNBs. ATRX is composed of a plant homeodomain (PHD) zinc finger domain, HP1 binding and a helicase/ATPase domain of SWI2/SNF2. ATRX co-localises with PNBs and it has been shown that amino acids 1498-1651 (targeting domain 1, TD1) and amino acids 1965-2239 (TD2) are responsible for producing punctate structures in the nucleus, but only TD2 participates in localization with PNBs [29]. TD1 contains the DAXX interacting domain. ATRX and histone H3.3 are key regulators of telomeric chromatin integrity in embryonic stem cells [30].

Small ubiquitin-related protein (SUMO) is another important component of PNBs. SUMOylation (a post-translational modification of proteins [31]) of PML and its counterparts is essential for their formation and function. In PML protein, SUMOylation of B-Box1 has been shown that is important in recruiting DAXX to the PML compartments [32-35]. In humans three sites of PML protein (K65, K160 and K490) are shown to be sumoylated by sumo-1, -2 and -3 proteins in a dynamic and reversible manner [36]. SUMOylation of PML in humans requires the E2 sumo conjugating enzyme, Ubc9.

## PNBS AND INNATE IMMUNITY

PNBs respond to the interferon exposure by increasing their number and frequency following herpesvirus infection. It is also reported that PML disperses across the nuclei of cells following infection with HSV [37]. Both of these observations raised the possibility that PNBs are the nuclear depots for different regulatory proteins that could impact defense against virus infection [7,38]. More recently and based on other studies, it has been shown that in cells infected with RNA viruses, over-expression of PML protein inhibits vesicular stomatitis virus (VSV) and influenza virus replication [9].

In DNA viruses, the association of PML proteins with viral DNA was first reported as a cell directed mechanism rather than an event preferred by the virus. PNBs could function as early sites for viral transcription and replication and they accumulate around the genomic content of DNA viruses when viral DNA released into the nucleoplasm [39-42]. The observations were consistent with later findings that reported epigenetic silencing of viral genome as the first line of defense provided by PNBs [11, 43, 44]. To overcome such restrictive mechanisms of PNBs, DNA viruses have evolved various strategies. For example in herpes simplex virus-1 (HSV-1), the mechanism involves localization of viral proteinICP0 with PNBs that result in degradation of PML and disruption of PNBs [45]. Kaposi's sarcoma-associated herpesvirus (KSHV) infection results in disruption of PNBs mediated by LANA2 protein [46]. More recently, antagonistic effect of KSHV tegument protein, ORF75, was shown [38]. Both of IE1 and tegument protein pp71, immediate early proteins of cytomegalovirus (CMV), are involved to overcome restricting effects of PNBs. The IE1 protein inhibits PML protein SUMOylation [47] and pp71 co-localizes with DAXX protein and mediates its proteasomal degradation [48-50]. The effect of pp71 on DAXX protein controls the antivirus silencing of virus genome imposed by DAXX. It is reported that the tegument protein integrated into the virus capsid is sufficient to initiate the mechanism [50].

## VIRAL PROTEINS INTERACTING WITH PNBS

ICP0 protein of HSV-1 was the first viral protein that shows interaction with PNBs [51-53]. ICP0 an immediate early protein and a RING finger ubiquitin E3 ligase protein, is probably the most widely studied protein among the PNB-interacting molecules [51,54-56]. It has been shown that ICP0-deleted HSV-1 virus has a better replication profile in PML-/- or PML depleted cells [57,58]. ICP0 co-localises with PNBs and promotes degradation of SUMOylated forms of PML and SP100 proteins [56,59-63]. This effect of ICP0 will result in the dispersal of PNB components and correlates with the initiation of the lytic phase of the virus [64]. ICP4, an immediate early transcription regulatory protein of HSV-1, is another viral protein which is shown to be associated with PNBs during herpesvirus infection. It is thought that ICP4 in conjunction with viral DNA and PNBs produce replication compartments for the virus [65,66]. ICP27 is another HSV-1 protein which its association with PNBs is shown. ICP27 is a highly conserved protein among herpesviruses and it functions as a viral mRNA export factor and is essential for early and late viral gene expression. It is thought that both ICP27 and ICP4 and their association with PNBs are related with active virus gene expression. VP22, VP13 and VP14 are other HSV-1 proteins that were shown for their association with PNBs [65-67].

As mentioned above, IE1 protein of CMV interacts with PNBs and disrupts the association between them [68]. It is thought that the disruption of PNBs occurs through de-SUMOylation of PML. The exact mechanism of the interaction between IE1 that leads to disruption of PNBs has remained unclear. In Epstein-Barr virus (EBV), tegument protein BKRF4, BZLF-1 and EBNA5 proteins co-localize with PNBs proteins [69-71], while KSHV employs different mechanisms to overcome the restrictive effect of PNBs. One of the mechanisms is mediated by ORF75 tegument protein of KSHV. ORF75 of KSHV belongs to viral protein family formylglycineamid-ribotideamidotransferase enzyme (vFGARAT). It is shown that KSHV ORF75 co-localizes with PNBs in cells undergoing lytic viral replication and it coincides with depletion of ATRX protein from PNBs. Depletion of ATRX in cells infected with ORF75-mutated KSHV can lead to the lytic virus replication [38].

A second mechanism that KSHV employs to overcome restrictive effect of PNBs is to interfere with epigenetic silencing effects of PNBs. Epigenetic alteration of genomic DNA of herpesviruses mediated by PNBs [72] is considered as a restrictive mechanism to overcome virus infection. Methylation of KSHV genomic DNA is an example for such host mediated epigenetic silencing of viruses. To overcome this restrictive mechanism, KSHV employs different strategies. A hallmark of KSHV latency is acquisition of activating (H3K4me3 and H3K9/K14ac) and repressive (H3K27me3) patterns. KSHV-encoded latency associated nuclear antigen (LANA) is a key mediator of virus DNA replication. It associates to chromosomal DNA and tethers to viral episomal DNA during cell division. It is reported

that LANA plays an active role in SP100 re-localization which is associated with accumulation of H3K27me3 modification on the virus genome. As a result, non-ND10 resident SP100 acts as a negative regulator of polycomb repressive complex-2 (PRC2), a key epigenetic regulator [43]. As a result, the virus stablishes its latency life cycle and escapes the antiviral effect of PNBs.

## PML NUCLEAR BODIES IN NON-MAMMALIAN VERTEBRATES

Despite their importance, the presence and role of PNBs in non-mammalian vertebrate are not well studied. From the data that is achieved in mammalian systems and based on the available sequencing data of different organisms, it could be extrapolated that some of the PNB proteins are present in birds and fishes. Possible presence of a *pml-like* gene protein in *Salmo salar* is reported (NCBI Reference Sequence: NW_012362619.1). Possible presence of DAXX protein in *Danio rerio* is reported (NCBI Reference Sequence: NC_007130.6). In chicken (*Gallus gallus domesticus*), the only study which is linked to the presence of PML protein was done by O'Hare and Delany who studied an alternative lengthening of telomeres (ALT) in chicken cells *in vitro* [73]. Based on their study, it was shown that both PML-L and PML proteins produce a punctuated structure in the nucleus of DF-1 cells and both of the proteins co-localize with telomeric repeat protein 2 (TRF2) in DF-1 cells [73].

Sequence alignment of human and chicken PML proteins suggests the presence of two PML genes in the chicken located on the chromosome 10 of chicken. The first gene is annotated as *pml* (GenBank accession number: NC_006097.3) and the second gene is *loc100857563* (GenBank accession number: NC_006097.3). The two genes are located close to each other but are transcribed from distinct promoters and on opposite directions. Eight exons are predicted for the chicken *pml* gene which results in transcription of 4 predicted isoforms PML-X4, -X5, -X6 and -X7. PML-X4 protein shares 37% of amino acid identity with PML-2 of humans. Whereas, PML-X5, -X6 and –X7 are more similar to PML-8 isotype of human. There splicing variants (PML-L- X1, -X2 and -X3) have been predicted that are transcribed from the *pml-l* gene. PML-L-X3 and PML-L-X2 share 35% identity with human PML isoform 1. The roles and dynamics of these isoforms in the PML biology in avian species remain to be elucidated.

## CONCLUDING REMARKS

Among all of non-mammalian vertebrates, avian species possess an important place due to their economic significance and their major differences with mammals.

Marek's disease virus (MDV) is a member of *Herpesviridae* family and a most notable chicken pathogen that produces devastating disease among chicken flocks. Despite all of the effort in designing an efficient vaccine against MDV, we have failed to control Marek's disease spread among chicken species. One major obstacle for this has been lack of a clear understanding of biology and pathogenesis of MDV.

PNBs are complexes made of interferon-inducible factors that exhibit various functions in the nucleus, many of which are restrictive against DNA viruses. Viruses not only overcome these mechanisms, but use them to their advantage to establish infection in the host. LANA protein of KSHV and its association with PNBs is one of such examples [43]. Similar to other herpesviruses discussed in this manuscript, it could be hypothesized that MDV interaction with PNBs may play important role in latent infections through the modulation of epigenetic regulation of the host and the virus. MDV genome in lymphoblastoid cells and tumors show extensive methylation [74]. Further studies are needed to delineate the role of PNBs in virus-host interaction in avian cells.

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