PML (promyelocytic leukemia)

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Abstract

Review on PML, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: MYL, RNF71, TRIM19
HGNC (Hugo): PML
Location: 15q24.1

DNA/RNA

Description

PML is composed of 9 exons. Exons 7 and 8 can be divided into exons 7a, 7b, 8a and 8b.

Transcription

Transcription of PML generates 22 transcripts (splice variants) with at least 11 different isoforms (PMLI, PMLIa, PMLII, PMLIIa, PMLIII, PMLIV, PMLIVa, PMLV, PMLVI, PMLVIIa, PMLVIIb). Names of PML isoforms are based on the original nomenclature defined by Jensen et al., 2001.

Pseudogene

No pseudogenes have been reported so far.

Protein

Description

Alternative splicing of PML gives rise to several isoforms with different molecular weight: PMLI is the longest isoform and is composed of 882 amino acids, while the shortest is PMLVIIb (435 amino acids).

PML belongs to the family of the tripartite motif (TRIM).

The RBCC/TRIM motif is present in all PML isoforms and is encoded by the exons 1-3.

The RBCC domain is composed of a RING finger domain (R), two B-boxes domains (B1 and B2) and an α-helical coiled-coil domain (CC).

The RING finger motif is a conserved cysteine-rich zinc-binding domain found in several classes of proteins.
The RING domain of PML is involved in the formation of the PML nuclear bodies (PML-NBs, see below) and in several others PML functions. Adjacent to the RING domain lay two cysteine-rich domains named B-boxes: these two domains have been proposed to work as second zinc-binding domain and they are involved in PML-NBs formation and in several others PML functions. The coiled-coil domain mediate PML homo- and hetero-dimerization. The CC domain is also essential for PML-NBs formation and PML functions. A nuclear localization signal (NLS) is present in the isoforms but not in PMLVIIb. The SUMO interacting motif (SIM) of PML is required for the recognition and binding of SUMOylated proteins (Jensen et al., 2001; Nisole et al., 2013). The SIM domain also contains the PML degron, involved in the CK2-dependent PML degradation (Scaglioni et al., 2006). PML undergoes several post-translational modifications. Several kinases phosphorylate PML on serine and threonine residues regulating its functions (Bernardi et al., 2004; Hayakawa and Privalsky, 2004; Scaglioni et al., 2006; Yang et al., 2006). SUMOylation is the most intensely studied post-translational modification of PML. Both SUMO1 and SUMO2/SUMO3 bind covalently to PML. SUMOylation facilitates PML-NBs formation promoting tumor suppressive response PML-dependent, but also promotes leukemogenesis by the SUMOylation of PML-RARA. Finally, SUMOylation also promotes ubiquitin-mediate degradation of PML and PML-RARA (Fu et al., 2005; Shen et al., 2006; Lallemand-Breitenbach et al., 2008; Kamitani et al., 1998a; Kamitani et al., 1998b; Rabellino et al., 2012). Ubiquitination regulates PML functions and activity and deregulation of PML appears to be the common mechanism accounting for PML loss in tumors (reviewed in Rabellino and Scaglioni, 2013). Finally, PML can be also acetylated (Hayakawa et al., 2008). PML is the major constituent of the PML-NBs. PML-NBs are highly dynamic nuclear structures tightly bound to the nuclear matrix. Several functions of PML are related to the PML-NBs functions (reviewed in Bernardi et al., 2007). More than 150 different proteins have been shown to localize into PML-NBs (Van Damme et al., 2010).
Schematic representation of PML isoform IV protein domains. R = RING-finger domains, aa 55-91; B1, B2 = B-boxes 1 aa 124-166 and 2 aa 184-228; CC = α-helical coiled-coil domain, aa 233-360; N = nuclear localization signal, aa 428-442; SIM = SUMO interacting motif, 508-518; D = degron. The three major SUMOylation sites (K60, K160 and K442) are indicated, as well as the major phosphorylation sites (T28, S36, S40, S480, T482, S517).

**Expression**

PML is ubiquitously expressed.

**Localisation**

Nuclear (PML-I-VI) and cytoplasmic (PML-VIIb).

**Function**

PML has been implicated in several cellular functions.

**Cellular senescence:** PML is a key regulator of cellular senescence. PML is involved in oncogenic-induced senescence (OIS) K-RAS dependent in a p53 dependent way (de Stanchina et al., 2004; Ferbeyre et al., 2000; Pearson et al., 2000; Scaglioni et al., 2012). PML is also involved in Rb-dependent senescence (Mallette et al., 2004).

**Apoptosis:** PML promotes apoptosis primarily by its ability to interact with p53 (Wang et al., 1998). Moreover, a pro-apoptotic function has been also attributed to the cytoplasmic isoform of PML (Giorgi et al., 2010).

**Neoangiogenesis:** PML represses HIF1 transcription, blocking de novo angiogenesis (Bernardi et al., 2006).

**Cell migration:** PML is involved in the regulation of cell migration by the negatively regulating of β-1 integrins (Reineke et al., 2010).

**DNA damage response:** several proteins involved in DNA repair have been report to reside into PML-NBs. Therefore, PML is also involved in DNA-repair, even though the mechanisms are still not completely clear (reviewed in Dellaire and Bazett-Jones, 2004).

**Anti-viral response:** several viral proteins interact with PML and the PML-NBs; moreover, several reports implicate PML and PML-NBs in anti-viral response (reviewed in Geoffroy and Chelbi-Alix, 2011).

**Hematopoietic stem cell maintenance:** PML has been reported being involved in hematopoietic stem cell maintenance by the regulation of the fatty acid oxidation (Ito et al., 2008; Ito et al., 2012). Several functions of PML are related to its ability to form PML-NBs.

**PML-NBs** have been involved in tumor suppression, senescence and apoptosis, DNA-damage response, cell migration, neoangiogenesis and anti-viral response (reviewed in Bernardi et al., 2007).

**Homology**

PML is conserved in Amniota (source: HomoloGene).
Mutations

Note
PML-RARA is the product of the chromosomal translocation t(15;17) and it causes acute promyelocytic leukemia (APL) (de Thé et al., 1990; Goddard et al., 1991; Kakizuka et al., 1991; Pandolfi et al., 1991).

Germinal
No germinal mutations of PML have been reported.

Somatic
At least 65 different somatic mutations have been described. All the informations in this regard can be found at the COSMIC website.

Implicated in

Acute promyelocytic leukemia (APL)

Note
(de Thé et al., 1990; Goddard et al., 1991; Kakizuka et al., 1991; Pandolfi et al., 1991)

Disease
The balanced chromosomal translocation t(15;17)(q24;q21) causes APL by driving the synthesis of the PML-RARA oncoprotein. This translocation drives the production of three different PML-RARA variants, depending on the length of the PML module: a short variant PML(S)-RARA, an intermediate variant PML(V)-RARA and a long variant PML(L)-RARA. Generally, 70% of the APL patients carry the PML(L)-RARA variant, followed by the PML(S)-RARA variant (20%) and the PML(V)-RARA (10%) (Melnick and Licht, 1999). PML staining in APL cells show a characteristic pattern commonly named "microspeckles" due to the fact that PML-RARA disrupts the PML-NBs. PML-RARA acts as a transcriptional repressor of RARA target genes. At the same time PML-RARA physically interacts with PML, impairing its tumor-suppressive functions. Combined, these features lead to the aberrant self-renewal of hematopoietic stem cells and block of differentiation of myeloid precursor cells at the promyelocytic stage (de Thé et al., 2012). APL is a distinct subtype of acute myeloid leukemia (AML), is a rare condition though extremely aggressive and malignant. Clinically, APL symptoms tend to be similar to AML. APL is characterized by a severe coagulopathy, including disseminated intravascular coagulation (DIC).

Prognosis
APL is normally treated with the combination of retinoic acid (ATRA) and arsenic trioxide (ATO). This therapy leads to the remission of the disease in more than 90% of the cases. Notably, APL was the first malignant disease cured with targeted therapy (Lo-Coco et al., 2013).

B-cell acute lymphoblastic leukemia (B-ALL)

Note
(Nebral et al., 2007; Qiu et al., 2011; Kurahashi et al., 2011)

Disease
The transcription factor PAX5 is required for development and maintenance of B-cell. Several chromosomal translocations involving PAX5 have been described, including the t(9;15)(p13;q24) in which the 5' region of PAX5 is fused to PML. So far, two cases of B-ALL PAX5-PML-dependent have been reported. The fused PAX5-PML oncoprotein has a dominant-negative effect on both PML and PAX5, inhibiting PAX5 activation of B-cell specific genes and disrupting PML-NBs formation.

Prognosis
Kurahashi and colleagues suggest that B-ALL PAX5-PML dependent could be treated with ATO (Kurahashi et al., 2011).

Various cancers

Note
Several reports indicate a reduced PML expression in several cancer types (Gurrieri et al., 2004; Rabellino et al., 2012; Rabellino and Scaglioni, 2013).
Disease
PML protein expression was reduced or abolished in prostate adenocarcinomas (63% [95% confidence interval CI = 48% to 78%] and 28% [95% CI = 13% to 43%], respectively), colon adenocarcinomas (31% [95% CI = 22% to 40%] and 17% [95% CI = 10% to 24%]), breast carcinomas (21% [95% CI = 8% to 34%] and 31% [95% CI = 16% to 46%]), lung carcinomas (36% [95% CI = 15% to 57%] and 21% [95% CI = 3% to 39%]), lymphomas (14% [95% CI = 10% to 18%] and 69% [95% CI = 63% to 75%]), CNS tumors (24% [95% CI = 13% to 35%] and 49% [95% CI = 36% to 62%]), and germ cell tumors (36% [95% CI = 24% to 48%] and 48% [95% CI = 36% to 60%]) but not in thyroid or adrenal carcinomas (Gurrieri et al., 2004). In all the cases, PML mRNA levels are comparable to the healthy tissues and the PML gene is rarely mutated, but the protein levels of PML are reduced. This correlates with several reports that underline the role of PML degradation in tumor progression and maintenance (reviewed in Rabellino and Scaglioni, 2013).

Prognosis
In most of the cases, loss of PML is associated with tumor progression, like was reported for prostate cancer, breast cancer and CNS tumors (Gurrieri et al., 2004).

Breakpoints
Note
Breakpoint at q24, responsible of translocation t(15;17)(q24;q21).

References


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