综述

无膜亚细胞器PML核体的分子组装机制及其在癌症和感染性疾病中的研究进展

蒋雁翎[1,2] 陈立[1]* 蒙国宇[2]*

([1]昆明理工大学医学院, 昆明 650500; [2]上海血液学研究所/医学基因组国家重点实验室/国家转化医学中心(上海)/上海交通大学医学院附属瑞金医院, 上海 200025)

摘要 早幼粒细胞白血病蛋白(promyelocytic leukemia protein, PML)最早在急性早幼粒细胞白血病(acute promyelocytic leukemia, APL)患者体内被发现。PML本身是一种抑癌蛋白, 也是PML核体(PML nuclear bodies, PML NBs)的核心组成部分。PML NBs可以介导转录调控、蛋白修饰、细胞的衰老和凋亡等多种重要的细胞生物学过程。在APL的治疗中, 针对PML的靶向治疗已经被证明是一种有效的治疗方式。已有大量的研究表明, PML蛋白和PML核体不仅在APL的发病和治疗中起着重要作用, 同时也在多种癌症的发生、发展以及病毒感染中发挥着重要作用。该文回顾了PML领域近年来的研究突破, 从PML的形成、相分离、翻译后修饰再到PML在多种癌症和病毒感染中的作用, 以此提示PML在癌症靶向、病毒感染的治疗上或许还有更多的应用潜能。

关键词 PML核体; 组装机制; 癌症; 病毒感染

A Systematic Review on the Mechanism of PML Nuclear Body Assembly and Its Functions in Cancers and Pathogenic Infection

JIANG Yanling[1,2], CHEN Li[1]*, MENG Guoyu[2]*

([1]*Kunming University of Science and Technology of Medicine, Kunming 650500, China*; [2]*Shanghai Institute of Hematology, State Key Laboratory of Medical Genomics, National Research Center for Translational Medicine, Rui-Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China*)

Abstract PML (promyelocytic leukemia protein) was first discovered in patients with APL (acute promyelocytic leukemia). PML itself is a tumor suppressor protein and a core component of PML NBs (PML nuclear bodies). PML NBs can mediate various important cellular biological processes such as transcriptional regulation, protein modification, cell senescence and apoptosis. In the treatment of APL, targeted therapy for PML has been shown to be an effective treatment modality. A large number of studies have shown that PML proteins and PML nucleosomes not only play an important role in the pathogenesis and treatment of APL, but also play an important role in the occurrence, development and viral infection of various cancers. This article reviews the research breakthroughs in the field of PML in recent years, from the formation of PML, phase separation, post-translational modification to the role of PML in various cancers and viral infections, suggestive of more possibilities that PML can be used in cancer targeting and viral infection therapy.

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*通讯作者。Tel: 021-64370045-610730, E-mail: guoyumeng@shsmu.edu.cn

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*Corresponding authors. Tel: +86-21-64370045-610730, E-mail: guoyumeng@shsmu.edu.cn

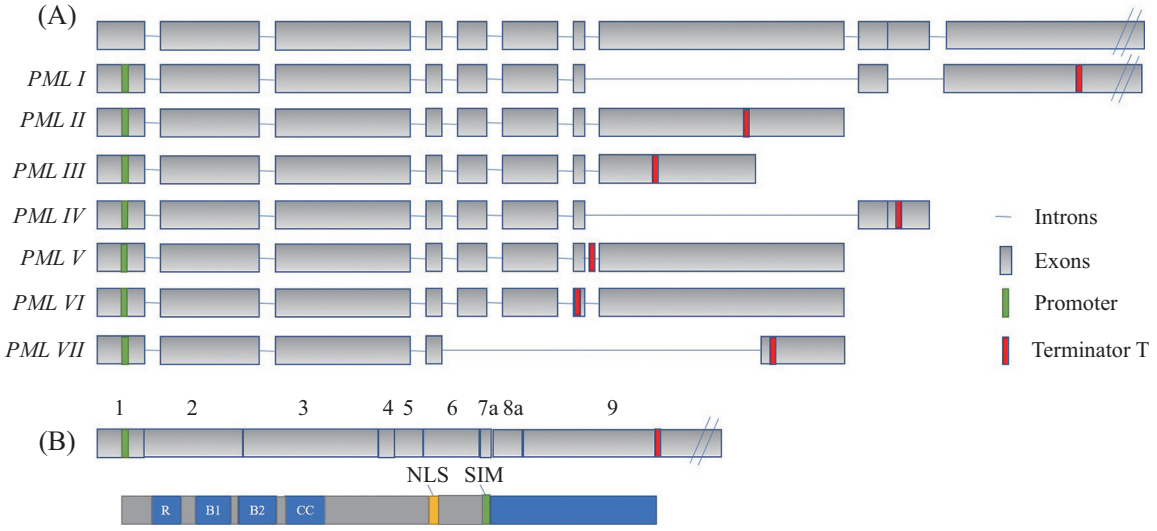
Keywords PML nucleosome; assembly mechanism; cancer; viral infection

1 PML蛋白与PML核体

据报道, 2020年全球新增癌症病例约1 930万例, 癌症死亡病例近1 000万例[1]。癌症的控制是当前医学界亟待解决的问题。近年来, 人们对癌症发病的分子机制的认知有显著提高, 这就可以开发更多的靶向药物控制癌症的发展。针对早幼粒细胞白血病蛋白(promyelocytic leukemia protein, PML)的靶向治疗在急性早幼粒细胞白血病(acute promyelocytic leukemia, APL)的治疗中已经被证明是有效的。这也激发了科研工作者对除APL以外的PML疾病的探索。

PML是一种抑癌蛋白, 最早在1例急性早幼粒细胞白血病患者中发现, 所以被命名为早幼粒细胞白血病蛋白[2]。又因其具有TRIM蛋白家族的共同特征, 即拥有三个连续的保守RBCC结构域, 又被称为TRIM19蛋白。RBCC结构域是由一个RING结构域、两个B-box结构域以及一个卷曲螺旋结构域组成的, 位于PML蛋白的N末端。RBCC结构域对维持PML的结构和功能起着至关重要的作用[3-4]。*PML*基因含有9个外显子, 位于PML蛋白的C末端, 由于选择性剪切形成了至少7种异构体[5], 这些异构体有助于PML核体(PML nuclear bodies, PML NBs)的形成[6]。PML I至PML V都包含RBCC结构域、核定位信号(nuclear localization signal, NLS)、SUOM相互作用位点(SUMO interacting motif, SIM)[7]。*PML I*型至*PML V*型共同含有的区域包括外显子1~7a, 不同的只是7b-9号外显子。而*PML I*至P*ML VI*的1~6号外显子是相同的, 都包含RBCC结构域和NLS, *PML VI*不具有SIM。而*PML VII*只有1~4号外显子, 且与其他六种PML亚型相同, 不具有NLS和SIM, 所以*PML VII*不会像其他六种PML亚型一样被聚集在细胞核[4], 也不能与SUMO化修饰的蛋白相互作用(图1A)。图1B上半部分是*PML I*的外显子结构示意图, 下半部分是经翻译、翻译后修饰之后的PML蛋白的结构域示意图。

PML NBs是主要由PML蛋白构成的超级蛋白复合体, 是存在于细胞核内的无膜细胞器[8], 参与DNA损伤修复、转录调控、干细胞的自我更新、调节P53的稳定性、细胞的增殖和凋亡, 以及细胞对病毒感染的防御等多种重要的细胞过程[9-13]。PML蛋白在白血病以及多种实体瘤的发生和转移过程中都起着非常重要的调控作用[14-16]。在APL病人体内, PML蛋白的活性丧失, PML的N-端和RARα的C末端融合形成了融合蛋白PML-RARα, PML-RARα蛋白是促进APL发生的主要因素[17]。在APL的治疗中, 三氧化二砷(arsenic trioxide, ATO)和全反式维甲酸已经被证明是有明显疗效的药物, 其缓解率可以达到



A: *PML*基因以及七种亚型的结构示意图。B: 以*PML I*为例的*PML*结构域示意图。

A: schematic diagram of the structure of the *PML* gene and seven subtypes; B: schematic diagram of *PML* structural domain using *PML I* as an example.

图1 *PML*基因结构示意图

Fig.1 Schematic diagram of *PML* gene structure

95%[18-19], 而三氧化二砷和全反式维甲酸作用的靶点就是PML-RARα蛋白。近年来, 聚焦在PML蛋白和PML NBs上的研究越来越多, 对于PML的组装机制、PML在多种癌症发生发展的分子机制以及PML在病毒感染中的作用都取得了突破性的进展。本文在此总结近年来PML蛋白和PML核体的结构、组装和其在体内发挥的功能等科研进展, 以期为各类癌症和病毒感染的治疗提供新思路。

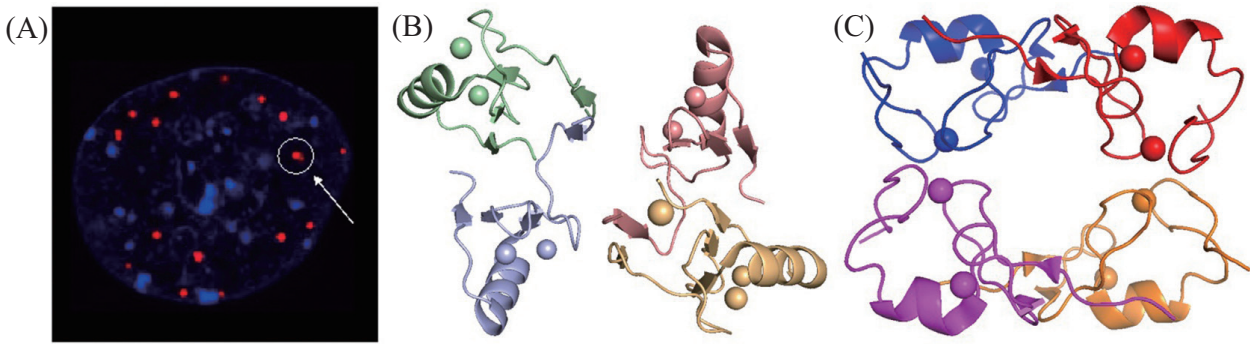
2 PML核体的形成、相分离及翻译后修饰

2.1 PML核体的形成

PML NBs是核小体的一种, 属于无膜细胞器, 是染色质的基本组成单位, 每个细胞核通常有5~30个PML核体[20], 如图2A所示, 每一个红色荧光点代表一个PML NBs。PML NBs组装的第一步主要是由PML单体间的共价二硫键相互作用以及RBCC结构域之间的非共价相互作用驱动的[21-23]。近期有研究表明, PML RING的四聚是PML组装中非常重要的步骤, 一旦PML RING四聚体的结构被破坏, PML核体将无法进行生物合成[24]。另外, 有关PML RING和B1域的结晶学研究发现了一种协同机制, 在PML RING四聚之后, PML B1-box可以促进PML的高度聚合, 影响PML核体的组装[25]。PML RING和PML B1-box的结构图如图2B和图2C所示(数据来源于CRSB PDB, https://www.rcsb.org/)。这些PML多聚体在RBCC结构域突变的PML重组的MEF PML细胞中不存在, 这说明RBCC结构域对PML核体的形成是至关重要的[26]。PML RING、B1-box、B2-box以及CC结构域的协同作用可能使PML二聚化、四聚化、多聚化, 并最终组装成球状结构。然而, PML-SUOM的突变体因为缺乏PML-SIM的相互作用, 因而不能形成PML多聚体和PML NBs, 与引入MEF PML时的结构完全相同[26]。这凸显了PML SUMO-SIM相互作用在PML NB形成的初始步骤中的非关键作用。同时, 在特定的PML蛋白亚型中, C末端基序对PML核体的形成起着重要的调节作用[27]。在完成上述过程之后, 就会进行UBC9的招募, UBC9是迄今为止已知的唯一一种SUMO E2结合酶, 它依赖于PML的RBCC寡聚[24]。然后, UBC9介导的PML SUMO化通过分子间SUMO-SIM相互作用调节来加强PML-PML相互作用[28]。然后, 经过SUMO化之后的PML通过SIM促使伙伴蛋白的招募, 进而形成成熟的PML NBs。值得注意的是, 锌可以增强PML NBs的高阶结构所需的磷酸化SIMs与SUMO-SIM的相互作用。同时, 细胞内锌水平的增加可以显著促进衰老细胞中PML NBs的形成以及提高PML NBs中SUMO蛋白的水平[29]。同时, PML NBs通过招募伴侣, 主要通过SUMO2/3链的形成, 支持SUMO化[30]。

2.2 液–液相分离

液–液相分离(liquid-liquid phase separation, LLPS)是近年来新发现的一种液滴间的相互作用, 在一定的浓度阈值以上, 一些蛋白质可能发生相分离并形成与周围环境具有不同组成的液滴[31-32], 进而形成一个相对稳定的动态结构。相分离的机制为无膜细胞器的组装提供了分子基础, 可能在核仁等的形成中发挥着重要作用[33]。PML蛋白组装成PML



A: PML核体, 每个红色荧光的小点就是一个PML核体。B: PML B1-box四聚体示意图[25], 每一种颜色为一个B1单体。C: RING四聚体示意图[24], 每一种颜色为一个RING单体(B和C数据来源于CRSB PDB, https://www.rcsb.org/)。

A: PML NBs, each red fluorescent dot is a PML NB. B: schematic diagram of PML B1-box tetramer[25], each color is a B1 monomer. C: schematic diagram of RING tetramer[24], each color is a RING monomer (B and C data from CRSB PDB, https://www.rcsb.org/).

图2 PML核体及部分结构示意图

Fig.2 Schematic diagram of PML nucleus and part of the structure

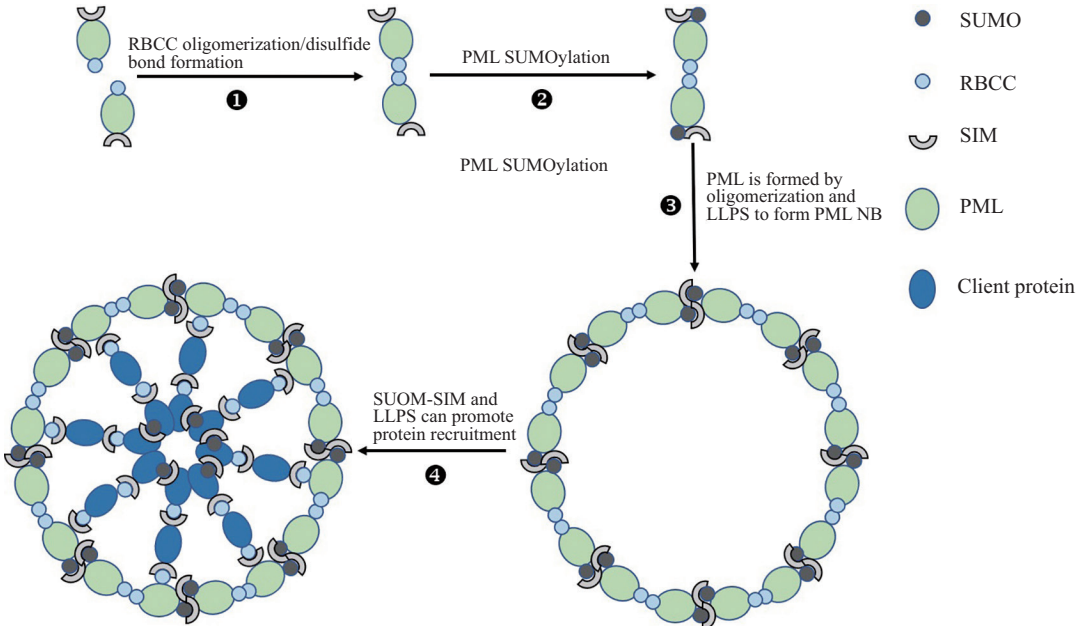


图3 PML核体的组装机制(根据参考文献[36]改编)

Fig.3 Mechanism of assembly of PML NBs (modified from the reference [36])

NBs的过程也涉及到液–液相分离。有研究表明, 聚合物poly SUMO-poly SIM会形成SUMO-SIM液滴, SUMO-SIM的相互作用是PML NBs形成的重要但非必需因素[34-35], PML和多种伙伴蛋白都存在SUMO-SIM相互作用[36]。真核细胞中有很多无膜结构的亚细胞器, 如早幼粒细胞白血病蛋白小体(PML body)、细胞质加工小体(P小体)、卡哈尔体(Cajal body)、核仁等[37-39]。已经有研究表明, 液–液相分离在细胞质加工P小体、卡哈尔体以及核仁的形成中都发挥着相当重要的作用[40-43], 这些研究证明, 在上述的无膜细胞器中都有液–液相分离的现象发生, 已经有研究表明, PML单体氧化的半胱氨酸残基之间的共价二硫键以及RBCC结构域之间的非共价相互作用可以驱动PML相互作用, 形成中空的球状结构[24,44-45], 伙伴蛋白通过SUMO作为分子黏合剂被招募到PML NBs(图3)。SUMO化将改变蛋白质的分离阈值, 这可能是PML发生相分离的重要调节因素, 导致PML形成不同大小、数量和位置的核体[46]。此外, SUMO-SIM相互作用和伙伴蛋白可能允许PML在应对细胞外压力时进入不同的相分离。

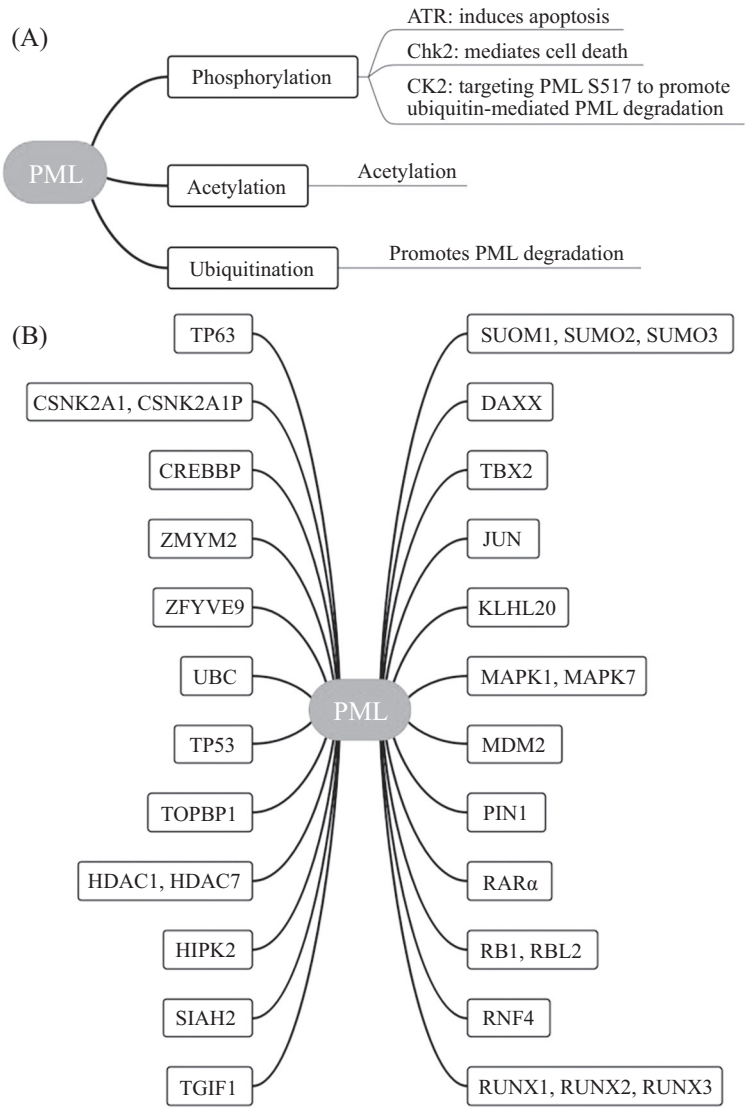
2.3 翻译后修饰

除SUMO化外, PML NBs的形成过程中还存在其他翻译后修饰(post-translational modification, PTM), 如磷酸化、乙酰化和泛素化。PML磷酸化可以由ATR、Chk2、CK2等激酶催化[48-50]。作为对DNA损伤的反应, PML通过Chk2磷酸化来介导细胞死亡, PML通过ATR磷酸化PML诱导细胞凋亡, PML通过MDM2隔离调节PML的亚核定位和P53的稳定性[48]。在多种肿瘤中, CK2的上调可以直接靶向PML S517, 促进泛素介导的PML的降解, 从而否定其肿瘤抑制特性[50]。P300催化的PML K487和K515位点的乙酰化在曲古菌素A(trichostatin A, TSA)诱导的细胞凋亡中起重要作用[51]。砷剂治疗急性早幼粒细胞白血病的分子机制是砷剂能够诱导产生SUMO E3泛素连接酶RNF4, 而RNF4可以促进PML的降解[52]。同时, PML是一种活性氧(reactive oxygen species, ROS)传感器, PML的表达会降低ROS水平, 甚至作为ROS的清除剂, 能将PML核体的形成与P53的激活联系在一起[53]。总而言之, PML蛋白通过这些翻译后修饰形成PML NBs, 才能发挥其生物学功能。据报道, PML能和大约160多种蛋白质直接或间接地相互作用[54]。图4A是PML NBs翻译后修饰的三种方式, 图4B为文献报道较多的数十种能和PML发生相互作用的蛋白(信息源自于BIOGRID, http://www.thebiogrid.org/)。

3 PML与肿瘤的关系

3.1 PML与白血病

前面已经提到, PML蛋白是在急性早幼粒细胞



A: PML NBs翻译后修饰的三种方式。B: 与PML发生相互作用的部分蛋白(数据来源于BIOGRID, http://www.thebiogrid.org/)。

A: three ways to modify PML NBs after translation. B: some proteins that interact with PML (data from BIOGRID, http://www.thebiogrid.org/).

图4 PML NBs翻译后修饰的三种方式

Fig.4 Three ways to modify PML NBs after translation

白血病患者体内被发现的。已经有研究证明, PML/RARα和PML之间的相互作用可显著扰乱PML-PML的相互作用以及PML NBs的形成, 并通过NHEJ和HRR途径损害DNA损伤修复[55]。同时, 急性早幼粒细胞白血病的发病也和PML-RARα功能增强有着密不可分的关系, 作为构成PML一部分的DAXX通过K160 SUMO化招募PML/RARα[56], 而KDM5A通过抑制H3K4me2, 从而抑制PML-RARα靶基因表达和APL细胞的分化[57]。APL患者一般肥胖或超重, 并伴有代谢紊乱, 而这是由于过氧化物酶体增殖物激活受体α(peroxisome proliferator-activated receptor-α, PPARα)与PML/RARα融合蛋白协同作用, 促进了高甘油三酯血症与急性早幼粒细胞白血病的发生造成的[58]。同时, 精氨酸甲基转移酶5(protein arginase methyltransferase 5, PRMT5)通过使RNF4在Arg164位甲基化来减弱PML-RARα与其泛素E3连接酶RNF4之间的相互作用, 抑制其泛素化和降解, 从而促进APL的发生[59]。PML还能作为维甲酸和Pin1抑制剂的靶点, 通过激活P53、促进NPM-1c的降解、抑制Pin1的过度表达来治疗急性髓系白血病(acute myeloid leukemia, AML)[60]。核仁伴侣核磷蛋白1(nucleophosmin 1, NPM1)和PML中的两个反应性半胱氨酸相互作用, 导致PML NB组装受损, 从而促进细胞生长, 而放线菌素D靶向诱导的线粒体可

在急性髓细胞白血病治疗中恢复PML诱导的细胞衰老，放线菌素D和抗肿瘤药物venetoclax协同靶向线粒体，从而导致癌细胞产生PML依赖的生长停滞，并清除白血病[61]。

3.2 PML与其他肿瘤

PML蛋白是公认的抑癌蛋白[47]，但是近年来有研究表明，PML对部分肿瘤的发生发展反而有促进作用。例如，PML对胶质母细胞瘤(glioblastoma multiforme, GBM)的发生、发展起着重要作用。SOX9是一种与脑胶质瘤相关的转录因子，有研究表明，PML与*SOX9*启动子结合，直接调控GBM细胞中*SOX9*的转录，以维持胶质母细胞瘤细胞的活性[62]。PML也可以通过抑制SLIT1(进化保守的具有趋化活性的糖蛋白家族成员)促进细胞的迁移[63]，PML的异常表达还能增加GBM对化疗药物雷帕霉素(Rapamycin)的耐药性并阻断药物诱导的细胞凋亡[64]。PML还能通过转录调控HIF1A靶基因来促进三阴性乳腺癌(triple-negative breast cancer, TNBC)细胞的迁移、侵袭和转移[65]，通过抑制PML的表达也能抑制三阴性乳腺癌的发展[66]。有文献指出，PML I过表达促进了雌激素受体α(estrogen receptors α, ERα)阳性的MCF-7乳腺癌(breast cancer, BC)细胞的增殖、迁移、侵袭和非锚定生长[67]，而PML IV的过度表达则有效地抑制了BC细胞的肿瘤生长[68]。不可否认的是，PML在抑制癌症的发生发展中也起着不可忽视的作用。在肝癌的治疗中，PML表达水平增加会延长肝癌切除后的生存期，降低肝癌的复发率，但PML的高表达会抑制ATO在肝癌(hepatocellular carcinoma, HCC)细胞中的抗肿瘤作用[69]。此外，PML能够通过调控线粒体代谢，增强人卵巢癌的化疗敏感性[70]，PML的失活还能促进前列腺癌的发展[71]，癌蛋白WDR4可以通过泛素化对PML进行负调节，经过泛素化的PML可以激活相关的下游基因，通过促进免疫抑制和转移前肿瘤微环境来促进肺癌的进展[72]。

PML II能够调控I型干扰素诱导的细胞死亡，PML II还可以正向调节干扰素α诱导的促凋亡蛋白表达，ERK、AKT两种信号通路与多种癌细胞系的增殖、存活相关，PML II可以通过调控ERK、AKT的信号转导来促进癌细胞的凋亡[73]。PML IV是目前研究得最多的一种PML亚型，肠道病毒71型(enterovirus 71, EV71) 3C酶可裂解PML IV并抑制PML NBs的产生[74]。同时PML IV支持端粒延长替代机制(alterative lengthening of telomere, ALT)，PML IV能够通过SUMO-SIM介导的相互作用来诱导ALT相关PML小体(ALT-associated PML bodies, APBs)的形成，然后PML IV与端粒连接，可以诱导APB和端粒聚集[75]，进而使端粒得以延长，细胞得以永生。而这种端粒延长替代机制会引起神经母细胞瘤发生[76]。在乳腺癌中，PML IV的过表达能够直接抑制癌基因转录因子FOXM1(forkhead box subclass M1)的表达，同时能够作用于FOXM1上游的肿瘤抑制因子FOXO3(forkhead box O3)，FOXO3能够抑制FOXM1的表达，PML IV通过促进FOXO3的表达来抑制FOXM1的表达，从而抑制三阴性乳腺癌细胞的增殖[77]。PML IV特异性地与一种被称之为ARF的关键性P53调节因子相结合并增强P53与SUMO-1的结合，导致P53的稳定和激活，从而促进细胞的凋亡[78]。PML IV在病毒感染中也起着不可忽视的作用，具体将在下文进行说明。PML IV在肿瘤中的作用机制如图5所示。

4 PML在病毒感染中的作用

PML不仅在肿瘤的发生、发展中起着不可忽视的作用，最近有大量研究表明，PML在病毒感染中也起着至关重要的作用(表1)。DAXX是PML NBs中的一种支架蛋白，它可以抑制DNA病毒和逆转录病毒的复制，是SARS-CoV-2和SARS-CoV在人类细胞中复制的有效抑制因子[79]。同样作为PML NBs组成成分之一的microrchidia家族CW型锌指3(MORC family CW-type zinc finger protein 3, MORC3)和PML协同作用，抑制早期基因启动子(major immediate early enhancer/promoter, *MIEP*)的活性和即时早期蛋白1(immediate-early protein 1, *IE1*)的表达，从而抑制人类巨细胞病毒(human cytomegalovirus, HCMV)的复制[80]，而DAXX则会促进HCMV感染[81]，有相关报道表明，DAXX可以促进蛋白质的折叠[82]，或许内皮细胞可能需要DAXX的这种活性来支持HCMV复制。同时有研究表明，当细胞被HCMV感染后，干扰素和DNA损伤信号会诱导PML NBs发生剧烈的重排效应，使其形成一个笼状结构，这种笼状结构的PML NBs能够捕获新组装的病毒衣壳[83]。而在人类疱疹病毒6B(human herpes virus-6B, HHV-6B)中，PML NBs对HHV-6B的IE1蛋白的多重SUMO化起着重要作用，并且PML在HHV-6B整合到染色体中发挥重要作用，PML能够协助IE1定位到端粒上，进而帮助HHV-6整合到染色体中[84]。PML还

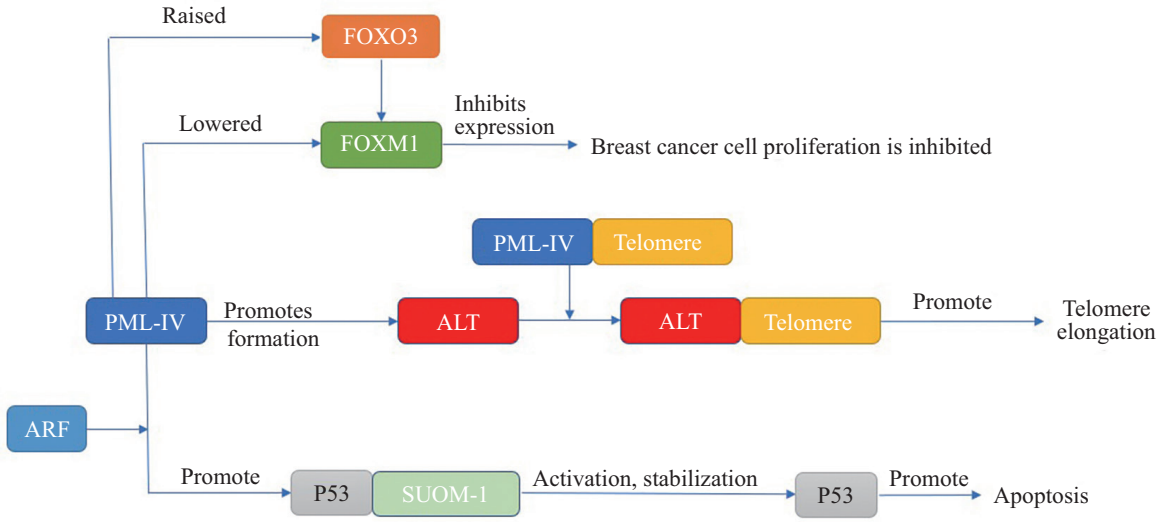


图5 PML IV在肿瘤中的作用机制

Fig.5 Mechanism of action of PML IV in tumors

表1 PML在病毒感染中的作用

Table 1 The role of PML in viral infection

PML相关成分 PML related ingredients	病毒类型 Virus type	作用 Function	参考文献 References
DAXX	SARS-CoV-2, SARS-CoV	Inhibits the replication of DNA viruses and retroviruses	[79]
MORC3	HCMV	Inhibits the activity of MIEP and the expression of IE1	[80]
PML NBs	HCMV	HCMV-infected cells prompt interferon and DNA damage signals to induce PML NBs rearrangement to form a cage-like structure that captures the newly assembled viral capsid	[83]
Daxx	HCMV	Promotes the expression of IE gene in HCMV	[81]
PML NBs, PML	HHV-6B	Assists IE1 in localizing to telomeres, which in turn helps HHV-6 integrate into chromosomes	[84]
PML	IAV	Inhibits the replication of IAV by enhancing the expression of FBXW7 in anti-influenza virus immunity	[12]
PML	HAdV	PML II promotes HAdV value-added, and PML III and PML IV inhibit HAdV value-added; PML I promotes HAdV infection, and PML V inhibits HAdV infection. HAdV can recombine PML NBs containing PML subtypes other than PML II	[85]
PML III, PML IV	DENV	PML III and PML IV inhibit the replication of DENV, and DENV can also change the structure of PML NBs by being recruited by PML III and PML IV	[86]
PML IV	EMCV	PML IV isolates the polymerase of the encephalomyocarditis virus in PML NBS, preventing its activity and inhibiting viral replication	[87]
PML NBs	VZV	The capsid protein of varicella zoster virus is isolated in PML NBs, thereby inhibiting virus replication	[88]
PML	ZIKV	Aromatic hydrocarbon receptors activated by ZIKV infection inhibit endogenous immunity driven by PML and inhibit ZIKV replication	[89]
PML NBs	HSV	Type I interferons can induce the formation of PML NBs, promoting the reactivation of HSV virus latent in neuronal cells	[90]
PML NBs	HPV	The PML protein retains HPV DNA that enters the cell in the nucleus for subsequent efficient transcription	[91]
PML	HCV	The formation of HCV is inseparable from PML	[92]

能通过增强FBXW7在抗流感病毒免疫中的表达抑制甲型流感病毒(influenza A virus, IAV)的复制[12]。在PML的几种亚型中, PML II能够促进人腺病毒(human adenovirus, HAdV)的增殖, 而PML III和PML IV抑制HAdV的增殖。在HAdV的感染过程中, PML I能促进HAdV感染, 而PML V能够抑制HAdV的感染。反过来, HAdV可以重组含有PML II以外的PML亚型的PML核体[85], 也有研究表明, PML III和PML IV能抑制登革热病毒(dengue virus, DENV)的复制, DENV也能通过被PML III、PML IV招募而改变PML NBs的结构[86], PML IV还能将脑心肌炎病毒(encephalomyocarditis virus, EMCV)的聚合酶隔离在PML NBs中, 阻止该聚合酶的活性[87], 水痘带状疱疹病毒(varicella-zoster virus, VZV)的衣壳蛋白也能被PML NBs隔离[88], 从而抑制病毒的复制。同时, PML能够抑制寨卡病毒(Zika virus, ZIKV)的复制, ZIKV感染诱导犬尿氨酸的产生, 从而激活芳香烃受体(arylhydrocarbonreceptor, AHR), AHR又抑制了由PML驱动的内源性免疫, 从而抑制了ZIKV的复制[89]。当单纯疱疹病毒(herpes simplex virus, HSV)长期潜伏在神经元细胞中时, I型干扰素能够诱导原本没有PML NBs的神经元细胞形成PML NBs, 而PML NBs能够促进潜伏在神经元细胞中的HSV病毒的重新激活[90]。在人乳头瘤病毒(human papilloma virus, HPV)感染人体的过程中, PML蛋白可以将进入细胞中的HPV DNA保留在细胞核中, 以便后续*HPV* DNA的高效转录[91]。另外, 丙型肝炎病毒(hepatitis C virus, HCV)的形成离不开PML[92]。

5 总结

PML蛋白虽然因急性早幼粒细胞白血病而得名, 但其在疾病中的作用绝不仅限于急性早幼粒细胞白血病, 目前已有大量研究阐明了PML蛋白在不同癌症的发生、发展中的分子机制, 也有大量文献报道了PML在病毒感染中的作用。目前, PML的部分生物学功能得以阐明, 也为肿瘤治疗以及病毒感染的治疗提供新的思路。但是, PML的许多功能以及相关的分子机制、完整的三维空间结构、相分离对PML作用的影响等目前尚不明确, 还有待进一步挖掘。

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