综述

PRMT5在乳腺癌中的研究进展

王丽[1,2] 张景惠[1,2] 卫浩亮[1,2] 李京凯[1,2] 崔旭鑫[1,2] 成帆[1,2] 杨孝来[2]*

([1]甘肃中医药大学药学院, 兰州 730000; [2]甘肃省人民医院药剂科, 兰州 730000)

摘要 蛋白精氨酸甲基转移酶5(protein arginine methyltransferase 5, PRMT5)是蛋白精氨酸甲基化转移酶家族的成员之一, 是在组蛋白和非组蛋白上产生对称二甲基精氨酸的主要II型甲基转移酶。*PRMT5*是一种潜在的致癌基因, 参与基因转录、RNA剪切、DNA复制和DNA损伤修复等多种生物学过程, 在包括乳腺癌在内的多种人类恶性肿瘤中均表达上调, 将其作为新靶点进行抗乳腺癌药物研究有巨大的前景。该文通过查阅大量PRMT5和乳腺癌的相关文献, 综述了PRMT5在乳腺癌中的研究进展, 旨在为后续相关研究提供参考。

关键词 乳腺癌; PRMT5; PRMT5抑制剂; 研究进展

Recent Advances of PRMT5 in Breast Cancer

WANG Li[1,2], ZHANG Jinghui[1,2], WEI Haoliang[1,2], LI Jingkai[1,2], CUI Xuxin[1,2], CHENG Fan[1,2], YANG Xiaolai[2]*

([1]*College of Pharmacy, Gansu University of Chinese Medicine, Lanzhou 730000, China*;
[2]*Department of Pharmacy, People's Hospital of Gansu Province, Lanzhou 730000, China*)

Abstract PRMT5 (protein arginine methyltransferase 5) is a member of PRMTs (protein arginine methyltransferases) family and the primary type II methyltransferase that generates symmetric-dimethyl-arginine on both histone and non-histone proteins. *PRMT5* is a potential oncogene, it has been implicated in the control of many cellular processes such as gene transcription, RNA splicing, DNA replication and DNA damage response. It is overexpressed in numerous human cancers, including breast cancer. Therefore, it has great prospect to be used as a new target for anti-breast cancer drug research. This paper reviews the recent advances of PRMT5 in breast cancer by consulting a large number of relevant literatures on PRMT5 and breast cancer, aiming to provide a reference for subsequent relevant research.

Keywords breast cancer; PRMT5; PRMT5 inhibitor; recent advances

乳腺癌(breast cancer, BC)是世界上女性最常见的癌症之一, 是女性癌症死亡的主要因素[1]。BC的病因具有多因素起源, 包括生育年龄、不良习惯、遗传和环境因素等[2]。根据人表皮生长因子受体2、雌激素受体、孕激素受体的表达水平将BC分为四种分子亚型: Luminal A、Luminal B、HER2阳性、 三阴性乳腺癌[3]。根据其亚型和是否为转移性等来确定BC治疗策略和治疗药物, Luminal A/B型患者使用内分泌治疗, 少数患者使用化疗; HER2阳性患者使用HER2阳性靶向抗体或小分子抑制剂治疗联合化

收稿日期: 2023-03-14 接受日期: 2023-05-22
国家自然科学基金(批准号: 81560595)资助的课题
*通讯作者。Tel: 13893408199, E-mail: yxl1668@vip.163.com
Received: March 14, 2023 Accepted: May 22, 2023
This work was supported by the National Natural Science Foundation of China (Grant No.81560595)
*Corresponding author. Tel: +86-13893408199, E-mail: yxl1668@vip.163.com

疗; 三阴性BC患者仅使用化疗[4]。BC的发生可能是癌细胞中积累的许多突变, 影响了几种信号通路, 这些信号通路能改变增殖和凋亡之间的平衡, 最终导致癌变状态[5]。这些通路或靶点包含表观遗传学的一些内容, 表观遗传学是研究不涉及DNA序列变化且可逆的、可遗传的基因功能变化的科学领域, 包括对DNA的修饰(例如甲基化修饰)和组蛋白的各种修饰[6]。近年来, 研究人员发现表观遗传失调可能导致基因异常表达并最终促进肿瘤的发生发展[7-9]。目前, 对以组蛋白修饰为主的表观遗传学的研究是癌症研究的热点之一。组蛋白修饰主要包括甲基化、乙酰化、磷酸化和泛素化四种类型, 以组蛋白甲基化最为常见且广泛存在于真核生物的多种生命调节过程中[10]。因技术发展暂不成熟, 与被广泛研究的DNA甲基化相比, 组蛋白甲基化在癌症中的研究相对较少。

1 蛋白精氨酸甲基化修饰

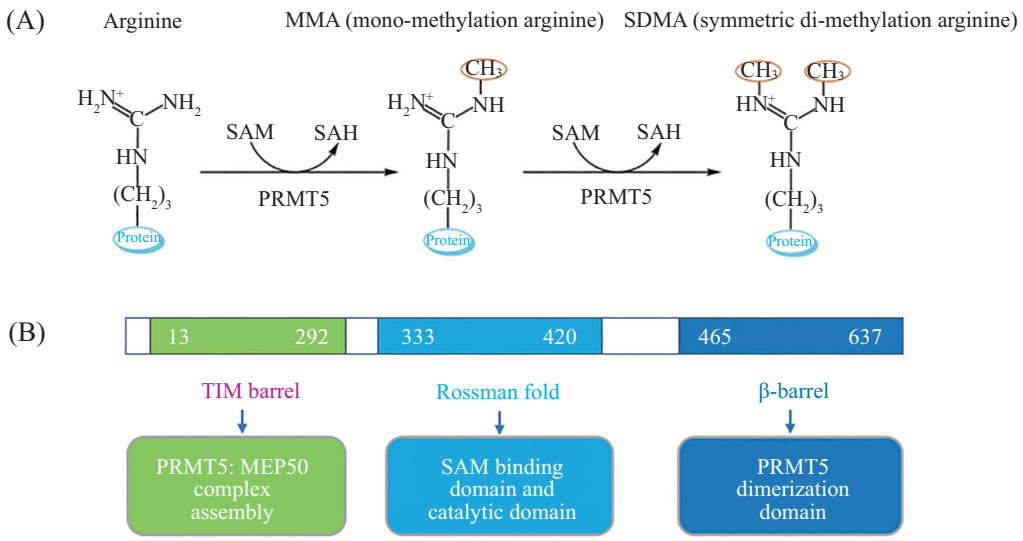
表观遗传修饰对于在不改变DNA密码的情况下以可遗传的方式调节基因表达、细胞分化和功能至关重要[11]。精氨酸甲基化是一种发生在组蛋白、RNA结合蛋白和许多其他细胞蛋白上最常见的翻译后修饰, 由主要发生在真核细胞核蛋白中的蛋白精氨酸甲基转移酶家族(protein arginine methyltransferases, PRMTs)催化, 通过改变蛋白质–蛋白质和蛋白质–核酸相互作用来影响组蛋白、RNA结合蛋白和许多其他细胞蛋白的功能, 在转录调控、RNA剪接、DNA损伤修复、细胞分化和细胞凋亡中起着至关重要的作用[12-14]。PRMTs通过将甲基从*S*-腺苷甲硫氨酸(*S*-adenosyl-*L*-methionine, AdoMet/SAM)转移到精氨酸残基的胍氮原子来催化精氨酸甲基化[15]。甲基化精氨酸残基主要分为三种类型: ω-N^G-单甲基精氨酸(ω-N^G-monomethylarginine, MMA)、ω-N^G,N^G-不对称二甲基精氨酸(ω-N^G,N^G-asymmetric dimethylarginine, ADMA)和ω-N^G,N^G-对称二甲基精氨酸(ω-N^G,N^G-symmetric dimethylarginine, SDMA), MMA、SDMA和ADMA的形成由PRMT催化[16]。哺乳动物中有九种PRMTs, PRMTs按催化的二甲基精氨酸类型进一步分类: I型PRMTs(PRMT1、2、3、4、6、8)将第二个甲基添加到与第一个相同的胍基氮中, 产生ADMA和MMA; II型PRMTs(PRMT5、9)催化SDMA和MMA; III型PRMTs只有PRMT7一种, 主要催化MMA[17]。

越来越多的研究表明在甲基精氨酸蛋白中, 有许多与疾病相关的蛋白质可以作为甲基化底物; MMA、ADMA或SDMA等水平失调会导致个体发育受损, 同时PRMTs的失调与癌症的发生、发展和转移密切相关[18-20]。姜黄素通过降低转录因子Sp1和NF-YA的水平来降低PRMT5-MEP50在MCF-7细胞中的表达水平, 进而抑制癌症的进展[21]。白藜芦醇通过降低PRMT5的催化产物H4R3me2s和H3K-27me3, 增加抑癌因子BRCA1、p53和p21的表达水平来抑制MCF-7细胞的生长[22]。PRMTs参与调节转录、剪接、RNA生物学、DNA损伤反应和细胞代谢等基本过程, PRMTs与多种疾病的发生发展密切相关, 正在成为有希望的治疗靶点, 为众多相关疾病提供新的治疗选择[23]。在九种PRMTs中, PRMT5参与诸多肿瘤的生物学过程, 且最近几年研究较多, 故本文以其为中心进行综述。

2 PRMT5的结构和生物学功能

PRMT5是主要的II型蛋白精氨酸甲基转移酶, 主要存在于哺乳动物细胞的细胞质与细胞核中, 如图1A所示, PRMT5可催化精氨酸残基生成SDMA。PRMT5-MEP50构成独特的异源八聚体复合物, 复合物的核心成分包括WD40蛋白/MEP50/WDR77/p44[24]。PRMT5的结构由N-端的三聚磷酸异构酶(triosephophate isomerase, TIM)桶、中间罗斯曼折叠域(Rossmann fold domain)和C-端β桶组成(图1B)。PRMT5单体独特的N-端TIM桶结构使得其在八聚体复合物的中心形成PRMT5四聚体, 并随后用四个MEP50分子修饰PRMT5四聚体[25]。相对于PRMT5同源二聚体, PRMT5-MEP50复合物对SAM和目标底物表现出更强的亲和力, 导致异质八聚体PRMT5-MEP50复合物的甲基化活性更高[26]。

PRMT5参与基因转录、核糖体生物发生、RNA转运、前mRNA剪接和信号转导[27]。PRMT5被鉴定为是Jak2结合蛋白, 并甲基化组蛋白H2AR3、H4R3、H3R2和H3R8[28]。在细胞核中, PRMT5与COPR5结合可导致H4R3优先于H3R8甲基化, 表明COPR5调节含有PRMT5的核复合物的底物特异性[26,29]; ATP依赖性染色质重塑复合物hSWI/SNF与表观遗传修饰酶PRMT5一起调节*Cyp24a1*的转录, 这在维持钙稳态中起关键作用[30]。在细胞质中, PRMT5通过促进Sm



A: PRMT5生成对称二甲基精氨酸的过程; B: PRMT5的结构和功能领域。

A: process of the generation of symmetric di-methylarginine by PRMT5; B: structural and functional domains of PRMT5.

图1 PRMT5生成对称二甲基精氨酸的过程及其结构和功能领域(根据参考文献[16]修改)

Fig.1 Process of the generation of symmetric di-methylarginine by PRMT5 and their structural and functional domains (modified from reference [16])

剪接体蛋白的甲基化和改变哺乳动物胚胎细胞和原始细胞中RNA的剪接来调节基因表达[31]。STROBL等[32]通过实验证明PRMT5抑制剂EPZ015666通过上调抑癌基因*p53*和AKT/mTOR信号通路来抑制肿瘤, 但同时T细胞代谢会受损。BARCZAK等[33]实验证明PRMT5是E2F1活动的上游调节器, 在与PRMT1竞争中, 它将E2F1上离散的精氨酸残基甲基化, 这不仅影响了癌细胞的生长和分裂, 而且还增加了肿瘤细胞的迁移和侵袭性。近年来, 研究发现PRMT5参与的诸多生物学过程与人类癌症的生长、发展和转移有紧密的关系, 严重影响癌症的进程, 故将PRMT5作为新靶点进行抗癌药物研究极为重要[34]。

3 PRMT5在乳腺癌中的研究进展

*PRMT5*可能作为癌基因在癌症中发挥作用, PRMT5在BC中是过表达的, 它是导致BC发生的重要因素之一[35]。因为BC不同的亚型, PRMT5与肿瘤预后之间的关系具有较高的异质性[36]。

3.1 PRMT5与乳腺癌干细胞

乳腺癌干细胞(breast cancer stem cells, BCSCs)是一类具有肿瘤起始能力, 与BC复发、转移和耐药性密切相关的干细胞亚群。BCSCs对诸多治疗具有一定的抵抗性, 研究发现PRMT5通过上调FOXP1的表达来维持BCSCs增殖和自我更新的能力, 并促进BC的生长, 但有临床研究表明FOXP1和PRMT5与BC的其他生物标志物和疾病的临床进展没有关联[37-39]。

3.2 PRMT5与ER阳性乳腺癌

PRMT5蛋白表达水平与干性具有相关性, PRMT5通过升高MCF-7细胞干性相关调控分子C-Myc、OCT4A和KLF4的蛋白表达水平来增强BC对化疗药物阿霉素的耐药性[40]。实验研究发现, PRMT5通过促进ALKBH5的核转位, 抑制经多柔比星处理的RNA m6A修饰, ALKBH5去除BRCA1的m6A甲基化以稳定mRNA, 这进一步增强了DNA修复能力以降低阿霉素在BC细胞中的疗效[41]。作为E-钙黏蛋白和Vimentin启动子的双重表观遗传调节剂, PRMT5和LSD1协同促进Slug诱导的上皮间充质转化过程和癌细胞的侵袭[42]。细胞质中的抑癌基因*LKB1*通过在苏氨酸残基上磷酸化PRMT5, 降低PRMT5活性, 从而抑制其促进肿瘤生长的作用[43]。PRMT5可介导ULK1和Atg5等自噬蛋白表达的调控, 降低BC细胞对雷帕霉素的敏感性[44]。精氨酸甲基化促进了PRMT5的底物, 即hnRNPA1与前mRNA的结合, PRMT5或hnRNPA1的敲低导致MCF-7细胞的增殖速率减慢[45]。PRMT5通过在R391处直接甲基化MCF-7细胞中的AKT1来激活AKT途径, 以此发挥其致癌功能[46]。circ-PRMT5是一种促进肿瘤生长的circRNA, 其在BC组织和细胞中上

调, 提示预后不良。敲低circ-PRMT5可抑制BC细胞的增殖和血管生成, 增加细胞凋亡水平[47]。circ-PRMT5通过上调TCF7L2来激活PI3K/AKT通路, 促进BC细胞的恶性增殖[48]。PRMT5通过抑制Wnt拮抗剂DKK1和DKK3的表达来促进Wnt/β-Catenin信号转导, 从而促进Wnt/β-Catenin靶基因(包括*C-Myc*、*Cyclin D1*和*Survivin*)的表达, 诱导细胞凋亡[49]。PRMT5可通过维持Treg细胞的功能、促使Treg细胞向BC迁移和FOXP3甲基化来促进肿瘤免疫[50]。PHF1/PRMT5-WDR77/CRL4B复合物上调BC中E-钙黏蛋白、FBXW7和PHF1的表达, 并与E-钙黏蛋白和FBXW7的表达呈负相关, PHF1/PRMT5-WDR77/CRL4B复合物促进了乳腺癌细胞的增殖和侵袭[51]。

3.3 PRMT5与三阴性乳腺癌

在不同病理类型的BC中, 三阴性BC中PRMT5的表达水平最高。在三阴性BC中PRMT5和KLF4蛋白积累最多, PRMT5对KLF4的甲基化导致KLF4稳定, 减少KLF4的降解, 从而促进有丝分裂, 促进肿瘤发生、进展和细胞转化[52]。在BC原位模型中, 升高的PDCD4和PRMT5共表达协同促进了肿瘤快速发展, 这种作用依赖于PRMT5的催化活性和PDCD4在N末端区域内的甲基化位点[53]。HAN等[54]裸鼠致瘤实验表明抑制PRMT5表达可加速BC细胞凋亡, 并通过LXRα/NF-κB p65通路减弱BC细胞的增殖、侵袭和有氧糖酵解能力。PRMT5介导的KLF5在R57处的甲基化阻止了Fbw7γ与KLF5蛋白结合, 从而稳定了KLF5蛋白以促进KLF5下游靶基因的转录, 进而促进三阴性BC细胞的增殖[55]。PHF1通过识别并结合H4R3me2s使CRL4B被PHF1和WDR77所招募, 在靶基因启动子区域形成了复合物PHF1/PRMT5/CRL4B, 复合物参与E-钙黏蛋白和*FBXW4*的转录调控, 促进了三阴性BC的增殖与转移[51]。ZNF326是PRMT5/WDR77复合物的底物, WDR77和PRMT5的缺失导致ZNF326甲基化丧失, 使增殖/迁移相关靶基因异常剪切和降解, 进而降低细胞活力并诱导MDA-MB-231细胞凋亡[56]。PRMT5介导的组蛋白H4R3me2s甲基化水平在HER2和三阴性BC中较低, 验证了PRMT5的低核活性; 三阴性BC表达更高水平的*MEP50* mRNA, *MEP50*和*PRMT5* mRNA水平与TNBC和luminal B型BC的无复发生存率相关[57]。敲低PRMT5可降低MDA-MB-231细胞中Bcl-2表达水平, 促进半胱天冬酶3和PARP表达来参与线粒体凋亡相关蛋白介导的细胞凋亡; PRMT5还与MDA-MB-231细胞中的ki-67呈正相关, PRMT5过表达使S期细胞数目增加, G_2期细胞数目减少, 从而影响了细胞凋亡和细胞周期, 以此来参与BC发生发展[58]。YANG等[59]实验发现在细胞核中, TRAF4通过上调PRMT5的表达来促进BC细胞增殖, 该过程可能与NF-κB信号通路的激活相关。

以上研究证明PRMT5通过多方面对BC的细胞生物学进行调控, 我们需要考虑不同的背景, 在多方面研究PRMT5在BC中的作用。

4 以PRMT5为靶点的抗乳腺癌药物开发

BC严重威胁女性的生命与健康, 寻找新的治疗策略是必要的。表观遗传学为BC治疗研究提供了新的方向和思路, 在BC治疗靶标方面对PRMT5的研究颇多。PRMT5在BC中高表达, 促进了BC的发生发展, PRMT5与乳腺癌的不良预后密切相关。目前, 虽然没有上市的PRMT5抑制剂, 但对其实验研究相对较多。对现有的以PRMT5为靶点的抗BC药物进行总结(表1)。

5 小结与展望

综上所述, PRMT5通过参与基因转录、RNA剪切、DNA复制和DNA损伤修复等多种生物学过程, 影响细胞生物学行为, 因而影响生物个体的生长发育。PRMT5在多种癌症中高表达, 与肿瘤的不良预后密切相关, 这对PRMT5进行抗肿瘤研究具有重要意义。对PRMT5作用机制及其在癌症中表达水平的深入研究是PRMT5抑制剂研究开发的基础。目前, PRMT5在BC中的作用机制尚不明确, 对PRMT5的作用机制以及抑制剂的研究正在进行中, 期望未来针对BC开发出高效低毒的PRMT5抑制剂, 为BC患者提供更有效的治疗途径和药物。

参考文献 (References)

[1] JALALI S, HEIDARI Z, DE COURTEN B, et al. Dietary total antioxidant capacity and odds of breast cancer: a case-control study [J]. Nutr Cancer, 2023, 75(1): 302-9.

[2] GHAFOOR D D. Correlation between oxidative stress markers and cytokines in different stages of breast cancer [J]. Cytokine, 2023, 161: 156082.

[3] ZHANG X M. Molecular classification of breast cancer: relevance and challenges [J]. Arch Pathol Lab Med, 2023, 147(1): 46-51.

[4] WAKS A G, WINER E P. Breast cancer treatment: a review [J]. JAMA, 2019, 321(3): 288-300.

[5] CHRISTOU C, CHRISTODOULOU M I, ZARAVINOS A , et al.

表1 以PRMT5为靶点治疗乳腺癌的小分子抑制剂

Table 1 Small molecule inhibitors targeting PRMT5 for the treatment of breast cancer

化合物 Compound	临床阶段 Clinical phase	作用机制 Mechanism of action	参考文献 Reference
CMP5	Preclinical	Reduce PRMT5 recruitment as well as methylation of H3R8 and H4R3 histones in the promoter regions of DKK1 and DKK3, which consequently results in reduced expression CYCLIN D1 and SURVIVIN	[49]
PJ-68	Preclinical	Protein levels of KLF5 and its targets were decreased *in vivo* and *in vitro* in a dose-dependent manner	[55]
EPZ015666 (GSK3235025)	Preclinical	Apoptosis is triggered by inhibition of PRMT5, regulates cell cycle progression and decreases mammosphere formation; synergistically reduce the expression of vimentin and E-cadherin in MCF-7 cell lines with SP2509	[42,60]
The molecular isomers A, B, C of Tadalafil	Preclinical	Enhance the sensitivity of chemotherapy drugs	[61]
GSK591	Preclinical	Reduce MMA and SDMA levels in MCF-7 cells and leads to inactivation of the AKT pathway	[45]
GSK3326595	II	Block the activation of AKT pathway	[46]
JNJ-64619178	I	Regulate PRMT5-mediated spliceosome activity	[62]
MS4322	Preclinical	PRMT5 expression in MCF-7 cells was decreased in a concentration, time, VHL and proteasome dependent manner	[63]
WX2-43	Preclinical	Block PRMT5-catalyzed methylation to inhibit KLF4-mediated transcription and cell transformation	[52]
EPZ004777	Preclinical	The invasion of Treg cells into breast cancer was reduced, FOXP3 methylation was effectively inhibited, and tumor immunity was promoted	[50]
LLY-283	Preclinical	Selective inhibition of PRMT5 activity *in vivo* and *in vitro*	[64]

Ras suppressor 1 long form (RSU1L) silencing promotes apoptosis in invasive breast cancer cells [J]. Cell Signal, 2023, 101: 110522.

[6] OHSAWA S, UMEMURA T, TERADA T, et al. Network and evolutionary analysis of human epigenetic regulators to unravel disease associations [J]. Genes, 2020, 11(12): 1457.

[7] LU Y J, CHAN Y T, TAN H Y, et al. Epigenetic regulation in human cancer: the potential role of epi-drug in cancer therapy [J]. Mol Cancer, 2020, 19(1): 79.

[8] MARTINEZ L G, ZHANG Y S, NAKATA Y, et al. Epigenetic mechanisms in breast cancer therapy and resistance [J]. Nat Commun, 2021, 12(1): 1786.

[9] ZHU L R, ZHENG W Q, GAO Q, et al. Epigenetics and genetics of hepatoblastoma: linkage and treatment [J]. Front Genet, 2022, 13: 1070971.

[10] 何伶靖, 邹成, 贺琴菊, 等. PRMT5在癌症中的研究进展[J]. 中国细胞生物学学报(HE L J, ZOU C, HE Q J, et al. Recent advances of PRMT5 in cancer [J]. Chinese Journal of Cell Biology), 2021, 43(3): 662-74.

[11] PARK J W, HAN J W. Targeting epigenetics for cancer therapy [J]. Arch Pharm Res, 2019, 42(2): 159-70.

[12] XU J, RICHARD S. Cellular pathways influenced by protein arginine methylation: implications for cancer [J]. Mol Cell, 2021, 81(21): 4357-68.

[13] LOWE T L, CLARKE S G. Human protein arginine methyltransferases (PRMTs) can be optimally active under nonphysiological conditions [J]. J Biol Chem, 2022, 298(9): 102290.

[14] YIN X K, WANG Y L, WANG F, et al. PRMT1 enhances oncogenic arginine methylation of NONO in colorectal cancer [J]. Oncogene, 2021, 40(7): 1375-89.

[15] LORENZON L, QUILLES J C, CAMPAGNARO G D, et al. Functional study of leishmania braziliensis protein arginine methyltransferases (PRMTs) reveals that PRMT1 and PRMT5 are required for macrophage infection [J]. ACS Infect Dis, 2022, 8(3): 516-32.

[16] ZHANG F, KNAPP J K, COLMAN M J R, et al. Global analysis of protein arginine methylation [J]. Cell Rep Methods, 2021, 1(2): 100016.

[17] MOTOLANI A, MARTIN M, SUN M, et al. The structure and functions of PRMT5 in human diseases [J]. Life, 2021, 11(10): 1074.

[18] XU J, RICHARD S. Cellular pathways influenced by protein arginine methylation: implications for cancer [J]. Mol Cell, 2021, 81(21): 4357-68.

[19] JARROLD J, DAVIES C C. PRMTs and arginine methylation: cancer's best-kept secret [J]? Trends Mol Med, 2019, 25(11): 993-1009.

[20] GUCCIONE E, RICHARD S. The regulation, functions and clinical relevance of arginine methylation [J]. Nat Rev Mol Cell Biol, 2019, 20(10): 642-57.

[21] CHATTERJEE B, GHOSH K, SURESH L, et al. Curcumin ameliorates PRMT5-MEP50 arginine methyltransferase expression by decreasing the Sp1 and NF-YA transcription factors in the A549 and MCF-7 cells [J]. Mol Cell Biochem, 2019, 455(1/2): 73-90.

[22] CHATTERJEE B, GHOSH K, KANADE S R. Resveratrol modulates epigenetic regulators of promoter histone methylation and acetylation that restores BRCA1, p53, p21 CIP1 in human breast cancer cell lines [J]. BioFactors, 2019, 45(5): 818-29.

[23] WU Q, SCHAPIRA M, ARROWSMITH C H, et al. Protein arginine methylation: from enigmatic functions to therapeutic targeting [J]. Nat Rev Drug Discov, 2021, 20(7): 509-30.

[24] 全兴萍, 侯晓莹, 孙立. 精氨酸甲基转移酶5在肿瘤发生发展中作用的研究进展[J]. 中国肿瘤生物治疗杂志(QUAN X P, HOU X Y, SUN L. Role and progress of arginine methyltransferase 5 in

tumorigenesis and progression [J]. Chinses Journal of Cancer Biotherapy), 2018, 25(12): 1322-6.

[25] HO M C, WILCZEK C, BONANNO J B, et al. Structure of the arginine methyltransferase PRMT5-MEP50 reveals a mechanism for substrate specificity [J]. PLoS One, 2013, 8(2): e57008.

[26] KRZYZANOWSKI A, GASPER R, ADIHOU H, et al. Biochemical investigation of the interaction of pICln, RioK1 and COPR5 with the PRMT5-MEP50 complex [J]. Chembiochem, 2021, 22(11): 1908-14.

[27] Protein arginine methyltransferase 5: a potential cancer therapeutic target [J]. Cell Oncol, 2021, 44(1): 33-44.

[28] PASTORE F, BHAGWAT N, PASTORE A, et al. PRMT5 inhibition modulates E2F1 methylation and gene-regulatory networks leading to therapeutic efficacy in JAK2 V617F-mutant MPN [J]. Cancer Discov, 2020, 10(11): 1742-57.

[29] PAUL C, SARDET C, FABBRIZIO E. The histone- and PRMT5-associated protein COPR5 is required for myogenic differentiation [J]. Cell Death Differ, 2012, 19(5): 900-8.

[30] SETH-VOLLENWEIDER T, JOSHI S, DHAWAN P, et al. Novel mechanism of negative regulation of 1,25-dihydroxyvitamin D3-induced 25-hydroxyvitamin D3 24-hydroxylase (Cyp24a1) transcription: epigenetic modification involving cross-talk between protein-arginine methyltransferase 5 and the SWI/SNF complex [J]. J Biol Chem, 2014, 289(49): 33958-70.

[31] LI Z W, YU J H, HOSOHAMA L, et al. The Sm protein methyltransferase PRMT5 is not required for primordial germ cell specification in mice [J]. EMBO J, 2015, 34(6): 748-58.

[32] STROBL C D, SCHAFFER S, HAUG T, et al. Selective PRMT5 inhibitors suppress human $CD8^+$ T cells by upregulation of p53 and impairment of the AKT pathway similar to the tumor metabolite MTA [J]. Mol Cancer Ther, 2020, 19(2): 409-19.

[33] BARCZAK W, JIN L, CARR S M, et al. PRMT5 promotes cancer cell migration and invasion through the E2F pathway [J]. Cell Death Dis, 2020, 11(7): 572.

[34] FU S Y, ZHENG Q W, ZHANG D, et al. Medicinal chemistry strategies targeting PRMT5 for cancer therapy [J]. Eur J Med Chem, 2022, 244: 114842.

[35] STOPA N, KREBS J E, SHECHTER D. The PRMT5 arginine methyltransferase: many roles in development, cancer and beyond [J]. Cell Mol Life Sci, 2015, 72(11): 2041-59.

[36] LIANG Z Z, LIU L C, WEN C W, et al. Clinicopathological and prognostic significance of PRMT5 in cancers: a system review and meta-analysis [J]. Cancer Control, 2021, 28: 10732748211050583.

[37] CHIANG K, DAVIES C C. Linking PRMT5 to breast cancer stem cells: new therapeutic opportunities [J]? Mol Cell Oncol, 2018, 5(3): e1441628.

[38] SU H, LIU Y X, ZHANG C H, et al. PRMT5 and FOXP1 expression profile in invasive breast cancer patients undergoing neoadjuvant chemotherapy [J]. Cell Mol Biol, 2020, 66(2): 142-5.

[39] CHIANG K, ZIELINSKA A E, SHAABAN A M, et al. PRMT5 is a critical regulator of breast cancer stem cell function via histone methylation and FOXP1 expression [J]. Cell Rep, 2017, 21(12): 3498-513.

[40] WANG Z, KONG J, WU Y, et al. PRMT5 determines the sensitivity to chemotherapeutics by governing stemness in breast cancer [J]. Breast Cancer Res Treat, 2018, 168(2): 531-42.

[41] WU Y, WANG Z, HAN L, et al. PRMT5 regulates RNA m6A demethylation for doxorubicin sensitivity in breast cancer [J]. Mol Ther, 2022, 30(7): 2603-17.

[42] ZHANG J C, FAN X K, ZHOU Y F, et al. The PRMT5-LSD1 axis confers Slug dual transcriptional activities and promotes breast cancer progression [J]. J Exp Clin Cancer Res, 2022, 41(1): 191.

[43] LATTOUF H, KASSEM L, JACQUEMETTON J, et al. LKB1 regulates PRMT5 activity in breast cancer [J]. Int J Cancer, 2019, 144(3): 595-606.

[44] KONG J, WANG Z, ZHANG Y, et al. Protein arginine methyltransferases 5 (PRMT5) affect multiple stages of autophagy and modulate autophagy-related genes in controlling breast cancer tumorigenesis [J]. Curr Cancer Drug Targets, 2022, 23(3): 242-50.

[45] LI W J, HE Y H, YANG J J, et al. Profiling PRMT methylome reveals roles of hnRNPA1 arginine methylation in RNA splicing and cell growth [J]. Nat Commun, 2021, 12(1): 1946.

[46] YIN S S, LIU L, BROBBEY C, et al. PRMT5-mediated arginine methylation activates AKT kinase to govern tumorigenesis [J]. Nat Commun, 2021, 12(1): 3444.

[47] ABUHAMMAD S, CULLINANE C, MARTIN C, et al. Regulation of PRMT5-MDM4 axis is critical in the response to CDK4/6 inhibitors in melanoma [J]. Proc Natl Acad Sci USA, 2019, 116(36): 17990-8000.

[48] WU D, JIA H Y, ZHANG Z R, et al. Circ-PRMT5 promotes breast cancer by the miR-509-3p/TCF7L2 axis activating the PI3K/AKT pathway [J]. J Gene Med, 2021, 23(2): e3300.

[49] SHAILESH H, SIVEEN K S, SIF S. Protein arginine methyltransferase 5 (PRMT5) activates WNT/β-catenin signalling in breast cancer cells via epigenetic silencing of DKK1 and DKK3 [J]. J Cell Mol Med, 2021, 25(3): 1583-600.

[50] NAGAI Y, JI M Q, ZHU F X, et al. PRMT5 associates with the FOXP3 homomer and when disabled enhances targeted p185 erbB2/neu tumor immunotherapy [J]. Front Immunol, 2019, 10: 174.

[51] LIU R Q, GAO J, YANG Y, et al. PHD finger protein 1 (PHF1) is a novel reader for histone H4R3 symmetric dimethylation and coordinates with PRMT5-WDR77/CRL4B complex to promote tumorigenesis [J]. Nucleic Acids Res, 2018, 46(13): 6608-26.

[52] ZHOU Z, FENG Z W, HU D, et al. A novel small-molecule antagonizes PRMT5-mediated KLF4 methylation for targeted therapy [J]. EBioMedicine, 2019, 44: 98-111.

[53] POWERS M A, FAY M M, FACTOR R E, et al. Protein arginine methyltransferase 5 accelerates tumor growth by arginine methylation of the tumor suppressor programmed cell death 4 [J]. Cancer Res, 2011, 71(16): 5579-87.

[54] HAN X, WEI L L, WU B. PRMT5 promotes aerobic glycolysis and invasion of breast cancer cells by regulating the LXRα/NF-κBp65 pathway [J]. Onco Targets Ther, 2020, 13: 3347-57.

[55] WANG X Y, QIU T, WU Y Y, et al. Arginine methyltransferase PRMT5 methylates and stabilizes KLF5 via decreasing its phosphorylation and ubiquitination to promote basal-like breast cancer [J]. Cell Death Differ, 2021, 28(10): 2931-45.

[56] RENGASAMY M, ZHANG F, VASHISHT A, et al. The PRMT5/WDR77 complex regulates alternative splicing through ZNF326 in breast cancer [J]. Nucleic Acids Res, 2017, 45(19): 11106-20.

[57] SURESH S, VINET M, DAKROUB R, et al. Expression, localization and prognosis association of MEP50 in breast cancer [J]. Cancers, 2022, 14(19): 4766.

[58] WU Y, WANG Z, ZHANG J, et al. Elevated expression of protein arginine methyltransferase 5 predicts the poor prognosis of breast cancer [J]. Tumour Biol, 2017, 39(4): 1010428317695917.

[59] YANG F, WANG J, REN H Y, et al. Proliferative role of TRAF4 in breast cancer by upregulating PRMT5 nuclear expression [J]. Tumour Biol, 2015, 36(8): 5901-11.

[60] VINET M, SURESH S, MAIRE V, et al. Protein arginine methyltransferase 5: a novel therapeutic target for triple-negative breast cancers [J]. Cancer Med, 2019, 8(5): 2414-28.

[61] YANG Z Y, XIAO T, LI Z Z, et al. Novel chemicals derived from Tadalafil exhibit PRMT5 inhibition and promising activities against breast cancer [J]. Int J Mol Sci, 2022, 23(9): 4806.

[62] BREHMER D, BEKE L, WU T F, et al. Discovery and pharmacological characterization of JNJ-64619178, a novel small-molecule inhibitor of PRMT5 with potent antitumor activity [J]. Mol Cancer Ther, 2021, 20(12): 2317-28.

[63] SHEN Y D, GAO G Z, YU X F, et al. Discovery of first-in-class protein arginine methyltransferase 5 (PRMT5) degraders [J]. J Med Chem, 2020, 63(17): 9977-89.

[64] BONDAY Z Q, CORTEZ G S, GROGAN M J, et al. LLY-283, a potent and selective inhibitor of arginine methyltransferase 5, PRMT5, with antitumor activity [J]. ACS Med Chem Lett, 2018, 9(7): 612-7.