组蛋白甲基转移酶在骨肉瘤中的研究进展

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摘要 组蛋白甲基转移酶(histone methyltransferases, HMTs)主要由一类能催化组蛋白赖氨酸(也可发生于精氨酸、组氨酸、天冬酰胺)甲基化的蛋白质组成, 小部分底物也可以为非组蛋白。组蛋白的甲基化修饰参与染色质的多种调控功能, 包括基因转录调控、基因组稳定性维持、干细胞成熟分化、DNA修复、炎症免疫调节等多种生理过程。目前已发现多种HMTs在骨肉瘤(osteosarcoma, OS)中的异常表达与患者病程及预后密切相关。针对这些HMTs在骨肉瘤细胞中的作用机制, 已有部分高选择性的小分子抑制剂被研制出来, 以期未来应用于临床诊断、预后评估及靶向生物治疗。该文就近年来在骨肉瘤领域的组蛋白甲基转移酶及相关抑制剂的研究现状作一综述。

关键词 骨肉瘤; 组蛋白甲基转移酶; 抑制剂; 表观遗传学

Advances of Histone Methyltransferases in Osteosarcoma

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Abstract Histone methyltransferases are mainly comprised by a class of protein which can catalyze the transfer of methyl groups to specific lysine (also occur in arginine, histidine and aspartic acid) residues on the tails of histones, as well as non-histone proteins. Histone methylation is involved in the various regulatory functions of chromatin, including transcription regulation, genomic stability maintenance, stem cell maturation and differentiation, DNA repair, inflammatory immune regulation and other biological processes. Mounting evidences have identified that the abnormal expression of various HMTs in osteosarcoma (OS) is closely associated with poor prognosis in patients with osteosarcoma. According to the mechanisms of HMTs in OS, some potent, selective small molecule inhibitors have been discovered for applications in clinical diagnosis, prognostic evaluation and biological therapy. This review aims to provide an overview of the molecular mechanisms of HMTs and inhibitors in OS.

Keywords osteosarcoma; histone methyltransferases; inhibitors; epigenetics

骨肉瘤(osteosarcoma, OS)起源于原始成骨间充质细胞, 是最为常见的原发性骨恶性肿瘤, 多见于0~14岁儿童以及65岁以上老年人, 且男性多于女性[1]。骨肉瘤的发病部位多见于长骨干骺端, 例如股骨远端、胫骨近端和肱骨近端[2]。骨肉瘤恶性程度高, 1970年以前高级别骨肉瘤的唯一治疗手段是截肢, 即使经过截肢治疗后仍然有80%的病人死于肿瘤转移, 其中最常见的是肺转移[3]。过去40年中, 术前新辅助化疗联合术后常规化疗的新型治疗方式能够使患肢切除后的骨肉瘤病人总体生存率得到显著提高。近十年来, 90%~95%的骨肉瘤患者可进行保肢手术, 60%~80%的局部病灶患者已经可以长期生存。尽

收稿日期: 2018-04-23 接受日期: 2018-06-11
常州市科技局社会发展项目(批准号: CS2008204)资助的课题
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Received: April 23, 2018 Accepted: June 11, 2018
This work was supported by the Social Development and Science & Technology Fund of Changzhou (Grant No.CS2008204)
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网络出版时间: 2018-08-24 10:33:23 URL: http://kns.cnki.net/kcms/detail/31.2035.Q.20180824.1033.002.html

管如此, 仍然有部分患者因为复发或转移、术后化疗效果不佳、对化疗药物普遍耐药等因素而最终死亡[4]。随着表观遗传学说的不断深入, 关于组蛋白甲基转移酶(histone methyltransferases, HMTs)在骨肉瘤中作用机制的相关研究日益增多。研究发现, 诸多HMTs在骨肉瘤细胞中的异常表达或基因突变与细胞周期调控、上皮–间质转化(epithelial-to-mesenchymal transition, EMT)、细胞凋亡等多种致癌机制密切相关(图1)。因此, HMTs被视为抗骨肉瘤药物研发的又一新靶点。

1 组蛋白甲基转移酶的结构特点

目前基于序列相似性的功能预测, 已发现52种组蛋白赖氨酸甲基转移酶和44种组蛋白精氨酸甲基转移酶[5](表1)。其中, 40多种HMTs证实可催化S-腺苷甲硫氨酸(S-adenosylmethionine, SAM)上的甲基转移至相应的蛋白底物上。从结构上看, HMTs可以被大致分成3种功能酶家族: 包含SET结构域的赖氨酸甲基转移酶、非SET结构域的DOT1L赖氨酸甲基转移酶PRDM家族以及精氨酸甲基转移酶PRMT(protein arginine methyltransferase)家族[6-7]。非SET结构域的DOT1L赖氨酸甲基转移酶PRDM家族含有结构和功能上近似SET的PR结构域, 其中PRDM1型还含有数量不定的C2H2型锌指结构(能特异性识别结合DNA、RNA、蛋白质), PRDM2型没有锌指结构。众多组蛋白甲基转移酶中, 含SET结构域的酶家族占多数, 其名称起源于最初发现表达结构域的三种基因——Su(var)3-9、Enhancer of zeste、Trithorax的缩写[8]。

2 组蛋白甲基转移酶在人类多种癌症中的作用

组蛋白甲基转移酶的异常表达及组蛋白甲基化异常修饰存在于人类诸多肿瘤中, 与患者临床分期、预后复发以及五年生存率密切相关。例如: 在前列腺癌、肺癌、肾癌、乳腺癌、胰腺癌等肿瘤中, H3K4me2修饰水平显著下降, 与肿瘤复发及患者生存率下降密切相关; H3K9me2下调见于胰腺癌, H3K9me3上调可见于胃腺癌; H3K27me3下调见于乳腺癌、胰腺癌、卵巢癌等, 与患者生存率下降有关; H4K20me2下调见于前列腺癌中, 与前列腺癌高复发率有关; H4K20me3及H4R3me2的下调与乳腺癌预后差有关, 同时H4K20me3的下调与淋巴瘤、结肠腺癌的发生发展相关, 具体机制尚待阐明[22-24]。近年来, 越来越多的研究表明, 除组蛋白以外, 一些非组蛋白底物, 如p53、血管内皮生长因子受体(VEGFR)、增殖细胞核抗原(PCNA)、雌激素受体-α(ER-α)、雄激素受体(AR)、核因子-κB(NF-κB)、聚腺苷酸二磷酸核糖转移酶-1(PARP1)等[25-27]亦可被组蛋白甲基转移酶催化。这些底物经过甲基化修饰后, 在细

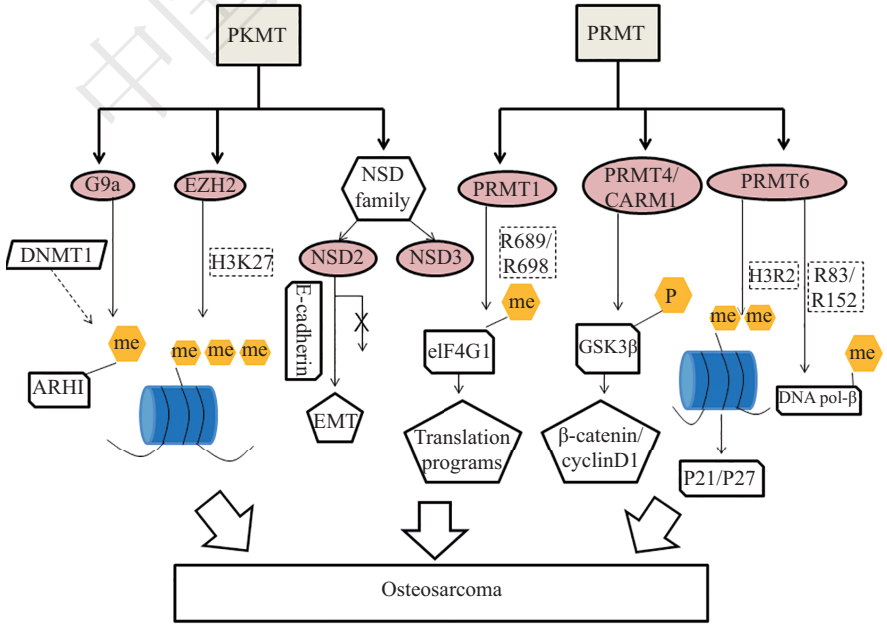

图1 组蛋白甲基转移酶促进骨肉瘤生长的作用机制

Fig.1 The mechanism of promoting tumor growth in osteosarcoma

表1 常见组蛋白甲基转移酶的分类及功能特点

Table 1 Classifications and functional characteristics of common histone methyltransferases

家族 Family	组蛋白甲基转移酶 Histone methyltransferases	其他名称 Aliases	组蛋白甲基化 Histone methylation	非组蛋白甲基化 Non-histone methylation	骨肉瘤相关性文献 Associated references with OS
SMYD (SET and MYND domain-containing proteins)	SMYD2	KMT3C	H3K36	p53, RB1, PARP1, HSP90AB1, ERα	–
	SMYD3	KMT3E	H3K4	VEGFR1, MAP3K2	–
Polycomb complex	EZH2	KMT6A	H3K27	RORα, STAT3	[9]
NSD (nuclear receptor-binding)	NSD1	KMT3B	H3K36	NF-κB	–
	NSD2	WHSC1, MMSET	H3K36	–	[10]
	NSD3	WHSC1L1	H3K36	–	[11]
SETD (SET-domain containing proteins)	SETD1A	KMT2F	H3K4	HSP70	–
	SETD7	KMT7	H3K4	PPP1R12A, p53, NF-κB, E2F1, DNMT1, STAT3	–
	SETD8	KMT5A	H4K20	PCNA, P53	[12-14]
Suppressor of variegation 3-9 homolog	SUV39H2	KMT1B	H3K9, H2AXK134	–	[15]
Euchromatic histone-lysine N-methyltransferase	G9a	EHMT2, KMT1C	H3K9	p53 Lys373, C/EBPβ	[16]
MLL family	MLL	KMT2A	H3K4	–	–
	MLL2	KMT2D	H3K4	–	–
	MLL3	KMT2C	H3K4	–	–
DOT1L	DOT1L	KMT4	H3K79	–	–
PRMT (protein arginine methyl-transferase family)	PRMT1	–	H4R3	MRE11, 53BP1, SAM68	[17]
	PRMT2	–	H3R8	–	–
	PRMT3	–	–	RPS2, p53	–
	PRMT4	CARM1	H3R17	AIB1, p300, CBP, RNA Pol II CTD	[18]
	PRMT5	–	H3R8, H4R3	–	–
	PRMT6	–	H3R2, H3K4	–	[19-20]
	PRMT7	–	H4R3, H2AR3, H3R2	–	–
	PRMT8	–	Unknown	–	–
	PRMT9	–	Unknown	–	[21]

胞调节过程中的生物学作用发生改变, 进而发挥着促进肿瘤或抑制肿瘤的作用。除此以外, HMTs还被证明参与肿瘤免疫逃逸过程进而促进肿瘤发生及进展。如在卵巢癌中, 组蛋白甲基转移酶EZH2及DNA甲基转移酶1(DNMT1)分别修饰H3K27三甲基化(H3K27me3)及DNA甲基化过程, 从而抑制辅助性T细胞1型趋化因子CXCL9及 CXCL10表达, 最终肿瘤细胞逃避免疫监控[28-29]。目前, 以HMTs抑制剂为代表的表观遗传药物可通过提高多种肿瘤免疫过程中关键基因(包括肿瘤相关性抗原、抗原加工递呈组成成分、免疫检定点抑制剂、趋化因子及其他免疫相关基因)的表达, 增加效应T细胞肿瘤浸润, 提高程序性死亡配体1(PD-L1或B7-H1)检定点封锁的疗效, 最终逆转肿瘤免疫抑制, 这种结合表观基因疗法与免疫疗法的抗癌新思路有望明显改善患者最终生存状况[30-31]。

3 组蛋白甲基转移酶与骨肉瘤

3.1 G9a

G9a调控组蛋白H3第9位赖氨酸甲基化修饰,

H3K9的甲基化修饰与基因沉默及异染色质形成有关[32]。组蛋白甲基转移酶G9a和DNA甲基转移酶1(DNMT1)催化人类抑癌基因*ARHI*甲基化, ARHI经过修饰后转录活性降低, 是骨肉瘤发生发展过程中的重要致病因素。抑制G9a及DNMT1能显著减少ARHI甲基化修饰, 增强ARHI在骨肉瘤细胞中调控细胞活性及细胞凋亡的能力[16]。

3.2 EZH2

Enhancer of zeste homolog 2(EZH2)作为多梳抑制复合物2(polycomb repressive complex 2, PRC2)的催化亚基, 催化H3K27三甲基化, 发挥转录抑制的作用[33]。H3K27三甲基化修饰后染色质构象致密化, 导致抑癌基因沉默, 从而推动骨肉瘤进展。EZH2敲除后骨肉瘤晚期肺转移率下降, 同时骨肉瘤细胞针对化疗药顺铂的敏感性提高, 并且EZH2通过下调TSSC3的表达促进骨肉瘤细胞的增殖和迁移, 同时还增强抑制细胞的凋亡能力[9]。

3.3 NSD家族

NSD家族包括NSD1(KMT3B)、NSD2(MMSET/WHSC1)、NSD3(Wolf-Hirschhorn syndrome candidate 1-like 1, WHSC1L1)。该家族组蛋白甲基转移酶主要通过组蛋白H3第36位赖氨酸甲基化调节基因表达[34-35]。NSD2通过抑制E-cadherin表达促进骨肉瘤生长, 并且诱导EMT促进骨肉瘤细胞转移、侵袭[10]。NSD3在骨肉瘤细胞中高表达, 敲低NSD3导致骨肉瘤细胞活性显著下降, 伴随G_2/M期阻滞和凋亡细胞数量增加, 证明NSD3在骨肉瘤的发生发展中起重要的生物学作用, 其具体作用机制尚不明确[11]。

3.4 PRMT1

PRMT1是以组蛋白H4第3位精氨酸为底物催化其单甲基化修饰的组蛋白精氨酸甲基转移酶。PRMT1在骨肉瘤中的表达与肿瘤细胞活性呈正相关, 在肿瘤方面的作用机制主要表现为对基因转录、翻译及翻译后修饰上的全局调控。在*P53*/*Rb*基因-阴性骨肉瘤细胞中, PRMT1介导翻译起始复合物甲基化修饰, 协同eIF4G1、p53共同调控基因翻译过程, 从而促进肿瘤细胞生长, 但PRMT1调控翻译过程的具体机制还有待阐明[17]。

3.5 PRMT4/CARM1

共激活因子相关精氨酸甲基转移酶1(coactivator-associated arginine methyltransferase 1, CARM1)以往在肺癌、乳腺癌及结直肠癌中异常表达, 最新研究发现, CARM1在骨肉瘤细胞中同样过度表达, 并且表达量与其骨肉瘤Enneking分期相关[18]。相对于低级别Enneking分期, CARM1表达在高级别分期显著升高。CARM1通过激活pGSK3β/β-catenin/cyclinD1通路调控细胞周期, 并促进骨肉瘤细胞增殖[18]。

3.6 PRMT6

PRMT6催化组蛋白H3第2位精氨酸非对称性双甲基化且抑制H3K4甲基化修饰。PRMT6在骨肉瘤细胞中通过直接调控下游基因*P21*及*P27*(细胞周期蛋白依赖性激酶CDK抑制剂CIP/KIP家族成员)干预细胞周期, 沉默PRMT6导致G_2/M细胞周期阻滞[19]。PRMT6还特异性催化DNA聚合酶-β(pol-β)第83、152号位点精氨酸甲基化修饰, 增强pol-β与DNA的结合能力, 从而提高pol-β的酶加工活性[36]。此外, PRMT6通过转录抑制Thrombospondin-1(TSP-1), 促进骨肉瘤细胞迁移活性。敲除PRMT6导致TSP1表达升高, 骨肉瘤细胞迁移受到遏制, 当利用中和肽或者TSP-1特异性抗体降低TSP-1水平后骨肉瘤细胞迁移活性恢复, 证明PRMT6通过直接调控TSP-1影响骨肉瘤病程进展[20]。

4 组蛋白甲基转移酶抑制剂研究

近几年, 针对组蛋白甲基转移酶的强效、高选择性、高细胞活性的小分子抑制剂及类似化合物逐渐被提取或合成, 甚至已有抑制剂(如靶向EZH2、DOT1L、PRMT5)已经进入临床试验前期准备阶段。目前, 抑制剂分为底物竞争型抑制剂和辅因子竞争型抑制剂。

4.1 G9a/GLP(G9a-like protein)

自2007年第一个G9a高选择性强效抑制剂BIX-01294被发现以来, 包括UNC-0638[37]、BRD4770[38]、UNC0642[39]、A-366[40]、UNC0224[41]等一系列抑制剂也一一被揭示, 这类抑制剂主要与相关酶竞争性结合底物从而阻断下游反应[42]。

4.2 EZH2

目前已证实, EZH2抑制剂GSK343、MiR-138[43]、TSSC3[9]可以抑制骨肉瘤细胞增殖、转移, 并促进细胞凋亡。GSK343通过抑制EZH2及其靶基因*c-Myc*、*FBP1*(Fuse-binding protein 1)和*H3K27me3*, 抑制EZH2-c-Myc和FBP1-c-Myc信号通路, 最终显著降低骨肉瘤细胞活性[44]。

4.3 PRMT1

目前最具代表性的PRMT1抑制剂为化合物

DB75。DB75可以抑制PRMT1催化的蛋白质ALY(也称THOC4)甲基化修饰过程[45]。DB75还通过抑制PRMT1介导的RBM15(RNA-binding protein 15)第578位精氨酸残基甲基化修饰, 干扰RBM15与SF3B1复合物的结合, 进而调节RNA剪接过程[46]。

4.4 PRMT4/CARM1

在多发性骨髓瘤中, CARM1高选择性小分子抑制剂EZM2302显著抑制组蛋白H3R17及非组蛋白(包括PARP、SMB)的甲基化修饰, 高效抑制肿瘤细胞增殖。EZM2302在小鼠体内具有较适宜的药代动力学特性, 可以通过口服途径进行小鼠体内研究, 对小鼠的肿瘤生长均有明显的抑制作用, 但存在明显剂量依赖现象[47]。

4.5 PRMT6

目前已发现, 化合物EPZ020411是PRMT6的强效小分子抑制剂, 针对PRMT6/8/1的选择性是其他组蛋白甲基转移酶的100倍以上, 并且药物代谢动力学属性适合进行人体体内实验, 有望将其推向临床试验[48]。

5 结语与展望

表观遗传修饰异常与人类恶性肿瘤、炎症、自身免疫性疾病及衰老问题密切相关, 目前诸多组蛋白甲基转移酶被证实与肿瘤相关, 因此调控表观遗传修饰的组蛋白甲基转移酶已经成为人类治疗肿瘤新的靶点, 研究组蛋白甲基转移酶小分子抑制剂具有潜在的应用前景。组蛋白甲基转移酶EZH2抑制剂EPZ-6438和DOT1L抑制剂EPZ-5676已进入I/II期临床试验, 主要针对MLL重组型白血病。其他高效组蛋白甲基转移酶抑制剂也在逐步进入临床试验前期阶段, 有望应用于人类癌症靶向生物治疗。目前在骨肉瘤领域中, 组蛋白甲基转移酶及其抑制剂的具体作用机制尚不明确, 因此, 进一步阐明组蛋白甲基转移酶在骨肉瘤中详细的作用机制, 并发现高效、高选择性、高生物活性的HTMs抑制剂, 有助于在未来推进骨肉瘤的个体化基因及免疫治疗。

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