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·综述·

组蛋白乙酰化/甲基化在口腔疾病中的研究进展

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【摘要】 组蛋白乙酰化和甲基化能影响染色质构象，进而调控多种生物学活动。异常的组蛋白乙酰化和甲基化修饰与多种口腔疾病的发生发展有关。在牙的发育过程中，组蛋白乙酰化和甲基化修饰有序地升高或降低，调控牙的发育，氟离子能够破坏组蛋白乙酰化和甲基化修饰的平衡，这可能与氟牙症的发生有关。此外，组蛋白乙酰化和甲基化修饰也参与调控了口腔的炎症性疾病，炎症微环境下，组蛋白乙酰转移酶GCN5表达下降，使Dickkopf 1（DKK1）表达下降，从而激活Wnt/β-catenin通路，最终抑制牙周膜干细胞的成骨分化。Zeste增强子同源物2（enhancer of zeste homolog 2，EZH2）与H3K27me3在炎症牙髓组织和牙髓细胞中下降，抑制EZH2可抑制炎症刺激导致的人牙髓细胞中白细胞介素-1b、白细胞介素-6和白细胞介素-8的表达。组蛋白乙酰化/甲基化修饰能够与多条信号通路相互作用，促进口腔肿瘤的发生发展，并与唾液腺肿瘤的高侵袭性有关。靶向组蛋白乙酰化和甲基化相关酶的小分子药物能调控组蛋白甲基化/乙酰化修饰水平，在口腔颌面部疾病治疗中展现出应用潜能，例如组蛋白去乙酰化酶抑制剂——伏立诺他，其既能够抑制炎症的相关细胞因子的分泌，还能促进成牙本质细胞分化并形成牙本质相关基质，展现出了在保髓治疗中的潜力。了解组蛋白乙酰化/甲基化修饰在口腔疾病发生发展中的作用，有助于推进表观遗传修饰在口腔疾病的研究深入，提供新的疾病诊疗视角。

【关键词】 组蛋白修饰；　组蛋白甲基化；　组蛋白去甲基化；　组蛋白乙酰化；　组蛋白去乙酰化；　组蛋白去甲基酶抑制剂；　组蛋白去乙酰化酶抑制剂；　氟牙症；　牙周炎；　牙髓炎
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Research progress on histone acetylation/methylation in oral diseases

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【Abstract】 Histone acetylation and methylation can affect chromatin conformation and regulate a variety of biological activities. Abnormal histone acetylation and methylation modifications are related to the occurrence and development of a variety of oral diseases. Histone acetylation and methylation increase or decrease in an orderly manner to regulate the development of teeth. Fluoride ions can destroy the balance between histone acetylation and methylation, which may be related to the occurrence of dental fluorosis. In addition, histone acetylation and methylation are involved in the regulation of oral inflammatory diseases. In the inflammatory microenvironment, the expression of histone acetyltransferase GCN5 decreases, and the expression of Dickkopf 1 (DKK1) decreases, activating the Wnt/β-catenin pathway and ultimately inhibiting the osteogenic differentiation of periodontal ligament stem cells. Enhancer of zeste homolog 2 (EZH2) and H3K27me3 levels were decreased in inflamed dental pulp tissues and cells. EZH2 inhibition inhibited the expres-

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sion of interleukin (IL)-1b, IL-6 and IL-8 in human dental pulp cells under inflammatory stimulation. Histone acetylation/methylation modifications can interact with multiple signaling pathways to promote the occurrence and development of oral tumors and are related to the high invasiveness of salivary gland tumors. Small molecule drugs targeting histone acetylation and methylation-related enzymes can regulate the level of histone methylation/acetylation and have shown potential in the treatment of oral and maxillofacial diseases. For example, the histone deacetylase inhibitor vorinostat can inhibit the secretion of inflammation-related cytokines; it also promotes the maturation of odontoblasts and the formation of dentin-related matrix, demonstrating its potential in pulp preservation. Understanding the role of histone acetylation/methylation modifications in the occurrence and development of oral diseases will help promote research on epigenetic modifications in oral diseases and provide new perspectives for disease diagnosis and treatment.

【Key words】 histone modification; histone methylation; histone demethylation; histone acetylation; histone deacetylation; histone demethylase inhibitors; histone deacetylase inhibitors; dental fluorosis; periodontitis; pulpitis

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在真核细胞中，DNA常以染色质的形式存在。染色质的基本单位为核小体，由147 bp的DNA分子包绕四种核心组蛋白（H2A、H2B、H3、H4）组成的八聚体而构成。染色质的结构并非一成不变，而是会响应相应的信号进行动态调节。组蛋白乙酰化和甲基化修饰在这种调节中起关键作用。组蛋白的乙酰化和甲基化修饰依赖于各种酶及蛋白复合体对组蛋白进行翻译后修饰（posttranslational modifications，PTMs），而这些修饰能够影响染色质结构，进而在不改变DNA序列的情况下调控DNA转录和细胞生物学活动。伴随着高通量蛋白组学的发展，对于组蛋白修饰的研究逐渐深入，组蛋白修饰与多种疾病的关系也逐渐被揭晓[1]。本文将聚焦组蛋白乙酰化修饰与甲基化修饰与口腔多种疾病的关系，以及目前针对这两种组蛋白修饰开发的药物在口腔颌面部疾病中的应用进行综述，为后续口腔疾病的病因探索与治疗提供新思路。

1　组蛋白乙酰化与甲基化修饰

1.1　组蛋白乙酰化修饰

组蛋白乙酰化是由组蛋白乙酰转移酶（histone acetyltransferases，HATs）和组蛋白去乙酰化酶（histone deacetylases，HDACs）动态调控的组蛋白PTM。HATs以乙酰辅酶A（CoA）为供体，在组蛋白的赖氨酸残基加上乙酰基，能够改变染色质构象，有助于转录调节蛋白接近DNA。组蛋白乙酰化主要通过两种方式促进转录，一是能直接或间接地改变染色质构象，增加转录子的可及性；二是乙酰化的组蛋白能募集多种效应蛋白以促进转录，包括含溴结构域蛋白（BRD）和转录起始因子TFIID亚基1（TAF1）等[2]。根据HATs的功能域结构，又可以将其分为五种，包括GCN5相关N-乙酰基转移酶家族、MYST家族、p300/CBP、TAF250、类固醇受体辅激活蛋白家族[2-3]。HDACs能够将组蛋白去乙酰化，发挥着与HATs相反的作用。HDAC1是最早发现，也是研究最多的组蛋白去乙酰化酶。与HDAC1序列同源性最高的称为Ⅰ类HDAC，包括HDAC1、2、3、8；Ⅱ类包括HDAC4、5、6、7、9和10；Ⅳ类HDAC目前仅发现了一种，即HDAC11。Ⅰ类、Ⅱ类和Ⅳ类都是锌依赖性的[4]。Ⅲ类HDACs又称Sirtuins，与锌依赖的HDACs不同，其只能在NAD^+存在的情况下发挥作用[5]。除了HDACs和HATs，组蛋白的乙酰化还受到代谢的影响。例如HATs的乙酰基供体乙酰CoA的水平升高，组蛋白乙酰化水平也将随之上升[6]。Sirtuins（SIRTs）蛋白的活性需要NAD^+的参与，NAD^+及相关代谢物的细胞生物利用度会影响SIRTs活性，进而影响组蛋白去乙酰化[7]。

1.2　组蛋白甲基化修饰

组蛋白不同位点的不同程度甲基化将对染色质结构和DNA转录产生不同的影响。H3K4，H3K36和H3K79的双、三甲基化与基因激活有关，H3K9和H3K27甲基化则通常与抑制基因有关[8]。基因转录的激活或抑制有赖于组蛋白修饰的“阅读器”，即效应蛋白的参与。效应蛋白能识别组蛋白甲基化并将相关信息传递到下游事件，以调控

基因表达的关键因素。例如，ATP依赖的染色质域解旋酶DNA结合蛋白1（CHD1）通过其两个N端染色质结构域识别H3K4me2和H3K4me3响应组蛋白甲基化，改变染色质构象，打开局部染色质结构，促进DNA转录[9]。

组蛋白的赖氨酸甲基化是一个动态变化的过程，由组蛋白赖氨酸甲基转移酶（histone lysine methyltransferases，HKMTs）催化，并被赖氨酸去甲基化酶（lysine demethylases，KDM）去除[10]。目前发现的HKMTs中，可以根据其甲基转移酶活性的结构域分为两大类：一类是含SET结构域HKMTs，包括EZH2（Enhancer of zeste homolog 2），SET和MYND结构域蛋白3（SMYD3），SETD1B（SET domain containing 1B）等，另一类是不含SET结构域的DOT1L组蛋白甲基转移酶，仅负责H3K79的甲基化修饰[11]。组蛋白赖氨酸去甲基化酶根据其结构也可以分为两大类，一类是赖氨酸特异性去甲基化酶（lysine-specific demethylase ，LSD，包括LSD1和2），其仅能使单、双甲基化的赖氨酸去甲基化；另一类是含jumonji结构域的去甲基化酶，如KDM2B（Lysine demethylase 2B），KDM6B（Lysine demethylase 6B）等[11]。另外，组蛋白甲基转移酶的甲基供体S-腺苷甲硫氨酸的水平也可以影响组蛋白甲基化的水平[12]。

2　组蛋白乙酰化/甲基化修饰与口腔颌面部疾病

2.1　组蛋白乙酰化/甲基化修饰与口腔颌面部发育相关疾病

组蛋白乙酰化/甲基化修饰参与调控口腔颌面部重要器官——牙的发育。在成牙本质细胞分化的过程中，HDAC3降低，而p300升高，相应位点的H3K9ac和H3K27ac升高[13]。有研究发现，使用HDAC抑制剂能够促进牙髓干细胞（dental pulp stem cell，DPSCs）相关成骨基质的表达[14]。此外，在DPSCs分化过程中起关键调控作用的转录因子也有可能与组蛋白乙酰化相互作用，调控DPSCs分化。例如KLF4（Krüppel-like factor 4）可以通过与牙本质基质蛋白1（dentin matrix protein 1，DMP1）和Sp7的启动子结合以及在成牙本质细胞分化的不同阶段在DMP1和Sp7的启动子处募集P300或HDAC3，参与牙本质形成[15]。在成釉细胞系中，氟化物能够增强p300的活性，使P53基因处发生组蛋白乙酰化，造成成釉细胞的生长抑制[16]。而在牙囊细胞中条件性的敲除HDAC4，将会影响小鼠牙根发育，使小鼠牙根明显变短[17]。

定向为成牙谱系的神经嵴细胞在牙本质涎磷蛋白（dentin sialophosphoprotein，DSPP）基因和牙本质基质蛋白1（dentin matrix protein 1，DMP1）基因启动子上有H3K27三甲基化修饰，而当成牙谱系的细胞向牙髓祖细胞定向时，H3K27me3下降，DSPP与DMP1表达[18]。EZH2通过调控β-catenin启动子上的H3K27me3水平，下调Wnt/β-catenin信号通路，在人牙髓细胞矿化过程中起负向调控作用[19]。将人骨肉瘤细胞系暴露于氟会导致EZH2升高，在转换生长因子β受体2（transforming growth factor beta receptor Ⅱ，TGFBR2）和SMAD3启动子处H3K9三甲基化水平异常升高，进而使一系列成骨、成软骨、胶原相关的基因表达下调，这提示氟牙症可能是由于氟影响了牙齿发育过程中正常的组蛋白修饰[20]。在小鼠磨牙牙胚的发育过程中也出现了KMT2D的有序表达，且研究发现KMT2D可能通过经典Wnt/β-catenin信号通路影响成牙本质细胞的增殖和分化[21]。KMT2D突变导致的歌舞伎综合征所伴随的牙数目、形态异常可能与此相关[22]。KDM5A则能够下调成牙本质分化相关基因处的H3K4me3，抑制DPSCs牙源性分化[23]。牙根的发育也与组蛋白甲基化相关，在小鼠中敲除EZH2将导致小鼠上皮根鞘发育受损，无法正常地形成磨牙牙根[24]。

2.2　组蛋白乙酰化/甲基化修饰与口腔颌面部炎症性疾病

大量研究表明组蛋白乙酰化/甲基化在多种炎症相关的疾病中参与调控[25]。在口腔颌面部的炎症性疾病——牙周炎中，有研究表明，相较于正常的牙龈组织，牙周炎患者的牙龈组织中HADC1的表达上升，这种上升与聚集组织内表达肿瘤坏死因子的细胞有关[26]。牙龈假单胞菌的脂多糖（lipopolysaccharide，LPS）可导致人牙龈上皮细胞中p300/CBP的激活和核因子-κB（NF-κB）的积累进而导致H3K9乙酰化水平的快速升高[26]。炎症微环境下，组蛋白乙酰转移酶GCN5表达下降，在DKK1（Dickkopf-1）启动子处H3K9和H3K14乙酰化降低，DKK1表达下降，从而激活Wnt/β-catenin通路，最终抑制PDLSCs的成骨分化[27]。在LPS刺激下，牙周膜细胞中能观察到成骨相关基因启动子处的H3K27发生三甲基化修饰以及炎症介质启动子处H3K4发生三甲基化修饰[28]。LPS诱导牙周膜细胞中SETD1B表达上调，增加IL6和IL1B基因的启动

子处H3K4me3水平，促进IL6和IL1B基因转录[29]。在牙髓炎的相关研究中，SIRT6可能是牙髓炎的负调控因子，能够通过抑制TRPV1活性抑制牙髓细胞的促炎因子的表达，负性调控牙髓炎[30]。EZH2与H3K27me3在炎症牙髓组织和牙髓细胞中减少而KDM6B表达增加，抑制EZH2可抑制炎症刺激导致的人牙髓细胞中IL-1b，IL-6和IL-8的表达[31]。

2.3　组蛋白乙酰化和甲基化修饰与口腔颌面部肿瘤

口腔颌面部肿瘤的发生常常会有各种诱因导致多种遗传和表观遗传改变[32]，有数据表明相较于正常的口腔角质形成细胞，口腔鳞状细胞癌（oral squamous cell carcinoma，OSCC）细胞的HDACs表达上升[33]，HDACs增加或HATs活性降低而导致的基因表达异常与OSCC患者的侵袭性和不良预后相关[34]。HDAC1在OSCC组织和细胞中过表达，并可以通过调控miR-154-5p/PCNA信号来促进OSCC的生长和进展[35]，并通过在热休克蛋白β7（HSPβ7）启动子处去乙酰化组蛋白，抑制其表达，进而促进OSCC增殖[33]。也有研究报道，过表达HDAC2可增强缺氧诱导因子1α（HIF-1α）蛋白的稳定性，增加OSCC侵袭和迁移能力[36]。TGF-β1能促进CBP介导的整合素β6（ITGB6）启动子处的组蛋白H3和H4高乙酰化，以及募集RNA聚合酶Ⅱ到ITGB6启动子，促进转录因子与ITGB6启动子的结合，进而增强OSCC细胞的侵袭性[37]。

同样地，异常的组蛋白甲基化与肿瘤发生发展也有关[38]。研究发现一系列参与调控OSCC细胞的生长、存活和迁移的基因存在异常组蛋白甲基化[36]。组蛋白甲基转移酶SMYD3能够通过增加高迁移率族蛋白A2基因（HMGA2）的启动子H3K4me3来增强HMGA2的转录，推动OSCC的发生[39]。信号转导及转录激活因子3（STAT3）在OSCC中高表达，有研究发现其能通过信号转导增加组织中EZH2的表达，而EZH2表达增加又反过来增加STAT3的表达，二者相互作用，促进OSCC的侵袭[40]。长链非编码RNA—MRPL23-AS1能聚集EZH2，使上皮性钙黏蛋白基因启动子处组蛋白发生H3K27me3，抑制其表达，进而促进腺样囊性癌（adenoid cystic carcinoma，ACC）的肺部转移[41]。抑制LSD1功能将从表观遗传的途径减弱口腔癌的生长和转移[42]。此外，在唾液腺肿瘤中，组蛋白H3K9乙酰化和甲基化水平异常升高可能与实体型ACC预后不良有密切关系，高水平的H3K9三甲基化可能与黏液表皮样癌（mucoepidermoid carcinoma，MEC）的高度侵袭性特征相关[43]。

3　基于组蛋白乙酰化/甲基化修饰的药物开发

3.1　靶向组蛋白乙酰转移酶/去乙酰化酶的药物

靶向组蛋白去乙酰化酶催化域的去乙酰化酶抑制剂（HDAC inhibitor，HDACI）——伏立诺他（Vorinostat，suberoylanilide hydroxamic acid，SAHA）在2006年被FDA批准用于治疗皮肤T细胞淋巴瘤[44]。SAHA在唾液腺肿瘤ACC中进行了二期临床试验，但是ACC对于SAHA的响应非常有限[45]。虽然单药效果有限，但SAHA搭配其他抗癌药物一同使用能在OSCC治疗中发挥更强的抗癌效果[46]。此外，在牙髓炎的相关研究中，SAHA既能够抑制炎症的相关细胞因子的分泌，还能促进成牙本质细胞分化并形成牙本质相关基质[47]。

曲古抑菌素A（Trichostatin A，TSA）作为HDACI能够通过调节细胞周期调节因子和凋亡调节蛋白的表达来抑制OSCC细胞生长和诱导细胞凋亡[48]，此外研究发现TSA促进人牙髓干细胞增殖和成牙本质分化，促进成牙本质的形成[13]。

恩替诺特（Entinostat）作为HDACI展现出了对OSCC增殖的抑制作用，能触发氧自由基的产生并诱导细胞凋亡[49]。此外，另一种HDACI——Quisinostat在实验中证明能上调细胞凋亡相关蛋白的表达，下调细胞增殖相关蛋白的表达，抑制舌癌细胞的生长，诱导其凋亡[50]。西达本胺（Chidamide）能阻滞细胞周期在G2/M期，有效抑制ACC细胞的生长和增殖[51]。

3.2　靶向组蛋白甲基转移酶/去甲基化酶的药物

针对EZH2的抑制剂——他泽斯他（Tazemetostat，EPZ6438）已被FDA批准用于成人和青少年局部晚期或转移性上皮样肉瘤，但其单独在口腔颌面部疾病中的应用尚无报道，与pembrolizumab联合用于HNSCC正在进行二期临床试验[52]。另一种靶向EZH2的小分子抑制剂DZNep，在动物实验中已证明能减缓舌癌异种移植瘤的生长，与组蛋白去乙酰酶抑制剂合用能增强其对OSCC细胞的毒性[53]。另外有研究发现即使在炎症环境下，DZNep能够通过抑制EZH2功能促进牙周膜干细胞的成骨向分化，展现出用于牙周炎治疗的潜力[54]。研究者还开发了针对LSD的小分子抑制剂，如GSK-LSD1。在口腔颌面部肿瘤中，有研究表明GSK-LSD1能抑制OSCC侵袭相关基因的表达[55]。

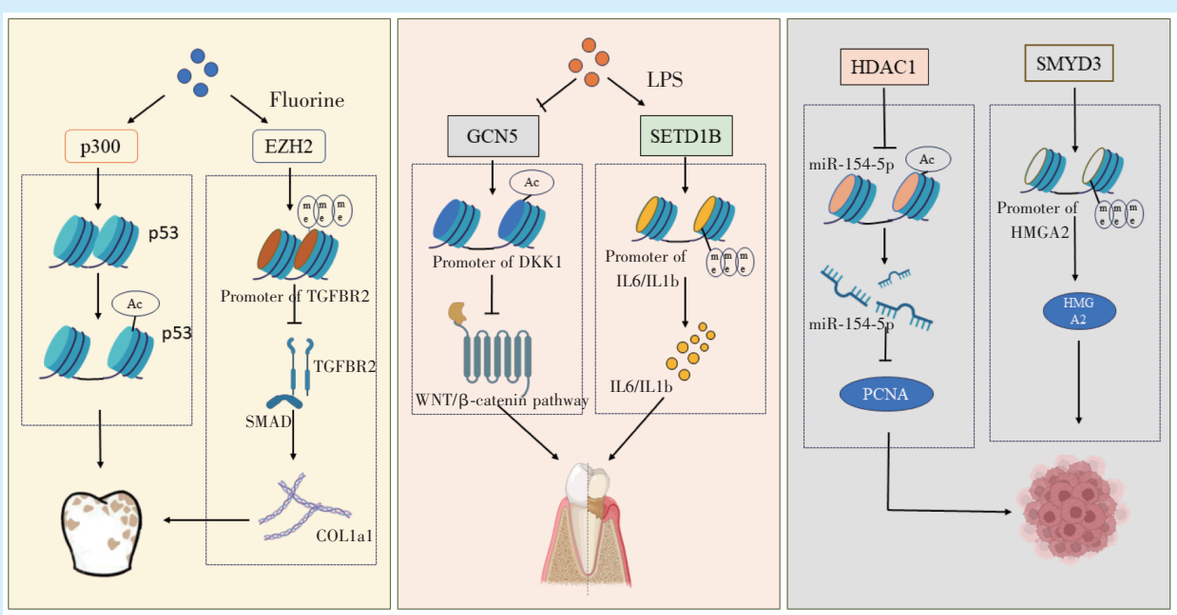
3.3　其他

除了上述提到的直接作用于组蛋白乙酰化/甲

基化修饰酶的药物外，JQ1作为BRD4抑制剂，作用于阅读蛋白BRD4，能够升高MMP2基因处的H3K27ac，进而抑制OSCC细胞系在体内的增殖、迁移和侵袭[56]。此外，JQ1还展现出了抗炎能力，在小鼠牙周炎模型中，全身给予JQ1显著抑制了病变牙龈组织中炎症细胞因子的表达[57]。烟酰胺属于维生素B族，同时也是Ⅲ类组蛋白去乙酰化酶的抑制剂，能够通过恢复破骨细胞生成，明显改善Runx2+/−颅骨锁骨发育不良综合征小鼠中的延迟出牙[58]。

4　总结与展望

组蛋白乙酰化/甲基化修饰的异常在口腔颌面部疾病的发生发展都发挥着重要作用。随着对组蛋白乙酰化/甲基化修饰研究的深入，靶向组蛋白修饰的药物在口腔颌面部疾病的治疗中展现出了巨大潜能。但是许多生物学过程所涉及的组蛋白修饰并非单一的某种修饰的升高或降低，这给针对组蛋白PTMs的药物的疗效带来了不确定性以及脱靶效应。因此相较于将基于组蛋白乙酰化/甲基化修饰的药物应用于口腔颌面部疾病临床治疗，研究者们更多的是将各种小分子抑制剂用于实验室研究中，以探明组蛋白乙酰化/甲基化修饰在口腔颌面部疾病发生发展中可能的机制（图1）。高通量测序的运用将大大推进对组蛋白修饰与基因、疾病之间关系的研究，有助于靶向组蛋白乙酰化/甲基化修饰治疗的安全性和有效性提高。



This figure illustrates the molecular mechanisms of histone acetylation/methylation involved in typical oral developmental diseases, inflammatory diseases and cancer. The first box shows the role played by these two types of histone modifications in the development of dental fluorosis. The second box shows the role the two types of histone modifications play in development of periodontitis. The third box shows the role the two types of histone modifications play in development of oral cancer. The effect of histone acetylation/methylation modification on the opening/closing of DNA transcription will be reflected by the distance between the two nucleosomes. LPS: lipopolysaccharide; IL: interleukin; DKK1: Dickkopf 1; Ac: acetylation; Me: methylation; HDAC: histone deacetylases; EZH2: enhancer of zeste homolog 2

Figure 1　Mechanisms of histone acetylation/methylation involved in oral diseases

图1　组蛋白乙酰化/甲基化参与口腔疾病发生发展的机制

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参考文献

[1] Millán-Zambrano G, Burton A, Bannister AJ, et al. Histone post-translational modifications - cause and consequence of genome function[J]. Nat Rev Genet, 2022, 23(9): 563-580. doi:10.1038/s41576-022-00468-7.

[2] Shvedunova M, Akhtar A. Modulation of cellular processes by histone and non-histone protein acetylation[J]. Nat Rev Mol Cell Biol, 2022, 23(5): 329-349. doi:10.1038/s41580-021-00441-y.

[3] He W, Li Q, Li X. Acetyl-CoA regulates lipid metabolism and his-

tone acetylation modification in cancer[J]. Biochim Biophys Acta Rev Cancer, 2023, 1878(1): 188837. doi: 10.1016/j.bbcan.2022.188837.

[4] Bondarev AD, Attwood MM, Jonsson J, et al. Recent developments of HDAC inhibitors: emerging indications and novel molecules[J]. Br J Clin Pharmacol, 2021, 87(12): 4577-4597. doi:10.1111/bcp.14889.

[5] Brancolini C, Gagliano T, Minisini M. HDACs and the epigenetic plasticity of cancer cells: target the complexity[J]. Pharmacol Ther, 2022, 238: 108190. doi:10.1016/j.pharmthera.2022.108190.

[6] Bradshaw PC. Acetyl-CoA metabolism and histone acetylation in the regulation of aging and lifespan[J]. Antioxidants (Basel), 2021, 10(4): 572. doi:10.3390/antiox10040572.

[7] Roh E, Kim MS. Hypothalamic NAD+-sirtuin axis: function and regulation[J]. Biomolecules, 2020, 10(3): e396. doi: 10.3390/biom10030396.

[8] Li Y, Chen X, Lu C. The interplay between DNA and histone methylation: molecular mechanisms and disease implications[J]. EMBO Rep, 2021, 22(5): e51803. doi:10.15252/embr.202051803.

[9] Bulut-Karslioglu A, Jin H, Kim YK, et al. Chd1 protects genome integrity at promoters to sustain hypertranscription in embryonic stem cells[J]. Nat Commun, 2021, 12(1): 4859. doi: 10.1038/s41467-021-25088-3.

[10] Husmann D, Gozani O. Histone lysine methyltransferases in biology and disease[J]. Nat Struct Mol Biol, 2019, 26(10): 880-889. doi: 10.1038/s41594-019-0298-7.

[11] Jambhekar A, Dhall A, Shi Y. Roles and regulation of histone methylation in animal development[J]. Nat Rev Mol Cell Biol, 2019, 20(10): 625-641. doi:10.1038/s41580-019-0151-1.

[12] Wang X, Long Y, Paucek RD, et al. Regulation of histone methylation by automethylation of PRC2[J]. Genes Dev, 2019, 33(19/20): 1416-1427. doi:10.1101/gad.328849.119.

[13] Tao H, Li Q, Lin Y, et al. Coordinated expression of p300 and HDAC3 upregulates histone acetylation during dentinogenesis[J]. J Cell Biochem, 2020, 121(3): 2478-2488. doi:10.1002/jcb.29470.

[14] Liu M, Yang Q, Zuo H, et al. Dynamic patterns of histone lactylation during early tooth development in mice[J]. J Mol Histol, 2023, 54(6): 665-673. doi:10.1007/s10735-023-10154-5.

[15] Tao H, Lin H, Sun Z, et al. Klf4 promotes dentinogenesis and odontoblastic differentiation via modulation of TGF-β signaling pathway and interaction with histone acetylation[J]. J Bone Miner Res, 2019, 34(8): 1502-1516. doi:10.1002/jbmr.3716.

[16] Deng H, Fujiwara N, Cui H, et al. Histone acetyltransferase promotes fluoride toxicity in LS8 cells[J]. Chemosphere, 2020, 247: 125825. doi:10.1016/j.chemosphere.2020.125825.

[17] Yamauchi Y, Cooper PR, Shimizu E, et al. Histone acetylation as a regenerative target in the dentine-pulp complex[J]. Front Genet, 2020, 11: 1. doi:10.3389/fgene.2020.00001.

[18] Francis M, Gopinathan G, Foyle D, et al. Histone methylation: Achilles heel and powerful mediator of periodontal homeostasis[J]. J Dent Res, 2020, 99(12): 1332-1340. doi:10.1177/0022034520932491.

[19] Liu Y, Yang Q. The roles of EZH2 in cancer and its inhibitors[J]. Med Oncol, 2023, 40(6): 167. doi:10.1007/s12032-023-02025-6.

[20] Daiwile AP, Tarale P, Sivanesan S, et al. Role of fluoride induced epigenetic alterations in the development of skeletal fluorosis[J]. Ecotoxicol Environ Saf, 2019, 169: 410-417. doi:10.1016/j.ecoenv.2018.11.035.

[21] Pang L, Tian H, Gao X, et al. KMT2D deficiency disturbs the proliferation and cell cycle activity of dental epithelial cell line (LS8) partially via Wnt signaling[J]. Biosci Rep, 2021, 41(11): BSR20211148. doi:10.1042/bsr20211148.

[22] Wang YR, Xu NX, Wang J, et al. Kabuki syndrome: review of the clinical features, diagnosis and epigenetic mechanisms[J]. World J Pediatr, 2019, 15(6): 528-535. doi:10.1007/s12519-019-00309-4.

[23] Li QM, Li JL, Feng ZH, et al. Effect of histone demethylase KDM5A on the odontogenic differentiation of human dental pulp cells[J]. Bioengineered, 2020, 11(1): 449-462. doi: 10.1080/21655979.2020.1743536.

[24] Jing J, Feng J, Li J, et al. Antagonistic interaction between Ezh2 and Arid1a coordinates root patterning and development via Cdkn2a in mouse molars[J]. Elife, 2019, 8: e46426. doi: 10.7554/elife.46426.

[25] Jiang W, Zhang LX, Tan XY, et al. Inflammation and histone modification in chronic pain[J]. Front Immunol, 2022, 13: 1087648. doi:10.3389/fimmu.2022.1087648.

[26] Suzuki S, Yamada S. Epigenetics in susceptibility, progression, and diagnosis of periodontitis[J]. Jpn Dent Sci Rev, 2022, 58: 183-192. doi:10.1016/j.jdsr.2022.06.001.

[27] Cao J, Zhang Q, Yang Q, et al. Epigenetic regulation of osteogenic differentiation of periodontal ligament stem cells in periodontitis [J]. Oral Dis, 2023, 29(7): 2529-2537. doi:10.1111/odi.14491.

[28] Francis M, Pandya M, Gopinathan G, et al. Histone methylation mechanisms modulate the inflammatory response of periodontal ligament progenitors[J]. Stem Cells Dev, 2019, 28(15): 1015-1025. doi:10.1089/scd.2019.0125.

[29] Francis M, Gopinathan G, Salapatas A, et al. SETD1 and NF-κB regulate periodontal inflammation through H3K4 trimethylation[J]. J Dent Res, 2020, 99(13): 1486-1493. doi:10.1177/0022034520939029.

[30] Hu J, Chen W, Qiu Z, et al. Robust expression of SIRT6 inhibits pulpitis via activation of the TRPV1 channel[J]. Cell Biochem Funct, 2020, 38(5): 676-682. doi:10.1002/cbf.3528.

[31] Zhang H, Fu H, Fang H, et al. Epigenetic regulation of methylation in determining the fate of dental mesenchymal stem cells[J]. Stem Cells Int, 2022, 2022: 5015856. doi:10.1155/2022/5015856.

[32] Chang S, Yim S, Park H. The cancer driver genes IDH1/2, JARID1C/KDM5C, and UTX/KDM6A: crosstalk between histone demethylation and hypoxic reprogramming in cancer metabolism[J]. Exp Mol Med, 2019, 51(6): 1-17. doi:10.1038/s12276-019-0230-6.

[33] Yue HQ, Xu PF, Guo YD, et al. Sodium butyrate inhibits oral squamous cell carcinoma proliferation and invasion by regulating the HDAC1/HSPB7 axis[J]. Neoplasma, 2022, 69(5): 1029-1040. doi:10.4149/neo_2022_220311n270.

[34] Tan Y, Wang Z, Xu M, et al. Oral squamous cell carcinomas: state of the field and emerging directions[J]. Int J Oral Sci, 2023, 15(1):

44. doi:10.1038/s41368-023-00249-w.

[35] Lv Y, Lu J, Liu X, et al. Histone deacetylase 1 regulates the malignancy of oral cancer cells via miR-154-5p/PCNA axis[J]. Biol Chem, 2020, 401(11): 1273-1281. doi:10.1515/hsz-2020-0189.

[36] Vatsa PP, Jindal Y, Bhadwalkar J, et al. Role of epigenetics in OSCC: an understanding above genetics[J]. Med Oncol, 2023, 40(4): 122. doi:10.1007/s12032-023-01992-0.

[37] Jiang Y, Zhou T, Shi Y, et al. A SMYD3/ITGB6/TGFβ1 positive feedback loop promotes the invasion and adhesion of ovarian cancer spheroids[J]. Front Oncol, 2021, 11: 690618. doi:10.3389/fonc.2021.690618.

[38] Marzochi LL, Cuzziol CI, Nascimento Filho CHVD, et al. Use of histone methyltransferase inhibitors in cancer treatment: a systematic review[J]. Eur J Pharmacol, 2023, 944: 175590. doi:10.1016/j.ejphar.2023.175590.

[39] Yang Z, Liu F, Li Z, et al. Histone lysine methyltransferase SMYD3 promotes oral squamous cell carcinoma tumorigenesis via H3K4me3-mediated HMGA2 transcription[J]. Clin Epigenetics, 2023, 15(1): 92. doi: 10.1186/s13148-023-01506-9.

[40] Zheng M, Cao MX, Luo XJ, et al. EZH2 promotes invasion and tumour glycolysis by regulating STAT3 and FoxO1 signalling in human OSCC cells[J]. J Cell Mol Med, 2019, 23(10): 6942-6954. doi:10.1111/jcmm.14579.

[41] Chen CW, Fu M, Du ZH, et al. Long noncoding RNA MRPL23-AS1 promotes adenoid cystic carcinoma lung metastasis[J]. Cancer Res, 2020, 80(11): 2273-2285. doi:10.1158/0008-5472.can-19-0819.

[42] Alhousami T, Diny M, Ali F, et al. Inhibition of LSD1 attenuates oral cancer development and promotes therapeutic efficacy of immune checkpoint blockade and YAP/TAZ inhibition[J]. Mol Cancer Res, 2022, 20(5): 712-721. doi:10.1158/1541-7786.mcr-21-0310.

[43] Lam-Ubol A, Phattarataratip E. Distinct histone H3 modification profiles correlate with aggressive characteristics of salivary gland neoplasms[J]. Sci Rep, 2022, 12(1): 15063. doi:10.1038/s41598-022-19174-9.

[44] Wawruszak A, Borkiewicz L, Okon E, et al. Vorinostat (SAHA) and breast cancer: an overview[J]. Cancers (Basel), 2021, 13(18): 4700. doi:10.3390/cancers13184700.

[45] Malarkey M, Toscano AP, Bagheri MH, et al. A pilot study of volumetric and density tumor analysis of ACC patients treated with vorinostat in a phase II clinical trial[J]. Heliyon, 2023, 9(8): e18680. doi:10.1016/j.heliyon.2023.e18680.

[46] Zhao B, Huang Z, Qin Z, et al. Enhancement of histone deacetylase inhibitor sensitivity in combination with cyclin-dependent kinase inhibition for the treatment of oral squamous cell carcinoma [J]. Cell Physiol Biochem, 2019, 53(1): 141-156. doi: 10.33594/000000126.

[47] Duncan HF, Kobayashi Y, Kearney M, et al. Epigenetic therapeutics in dental pulp treatment: hopes, challenges and concerns for the development of next-generation biomaterials[J]. Bioact Mater, 2023, 27: 574-593. doi:10.1016/j.bioactmat.2023.04.013.

[48] Mesgari H, Esmaelian S, Nasiri K, et al. Epigenetic regulation in oral squamous cell carcinoma microenvironment: a comprehensive review[J]. Cancers (Basel), 2023, 15(23): 5600. doi: 10.3390/cancers15235600.

[49] Marques AEM, do Nascimento Filho CHV, Marinho Bezerra TM, et al. Entinostat is a novel therapeutic agent to treat oral squamous cell carcinoma[J]. J Oral Pathol Med, 2020, 49(8): 771-779. doi: 10.1111/jop.13039.

[50] Wang X, Liu K, Gong H, et al. Death by histone deacetylase inhibitor quisinostat in tongue squamous cell carcinoma via apoptosis, pyroptosis, and ferroptosis[J]. Toxicol Appl Pharmacol, 2021, 410: 115363. doi:10.1016/j.taap.2020.115363.

[51] Pouloudi D, Manou M, Sarantis P, et al. Clinical significance of histone deacetylase (HDAC)-1, -2, -4 and-6 expression in salivary gland tumors[J]. Diagnostics (Basel), 2021, 11(3): 517. doi: 10.3390/diagnostics11030517.

[52] Ettl T, Grube M, Schulz D, et al. Checkpoint inhibitors in cancer therapy: clinical benefits for head and neck cancers[J]. Cancers (Basel), 2022, 14(20): 4985. doi:10.3390/cancers14204985.

[53] Ushio R, Hiroi M, Matsumoto A, et al. Enhanced cytotoxic effects in human oral squamous cell carcinoma cells treated with combined methyltransferase inhibitors and histone deacetylase inhibitors[J]. Biomedicines, 2022, 10(4): 763. doi: 10.3390/biomedicines10040763.

[54] Cheng M, Zhou Q. Targeting EZH2 ameliorates the LPS-inhibited PDLSC osteogenesis via Wnt/β-catenin pathway[J]. Cells Tissues Organs, 2020, 209(4/5/6): 227-235. doi:10.1159/000511702.

[55] Kim D, Kim KI, Baek SH. Roles of lysine-specific demethylase 1 (LSD1) in homeostasis and diseases[J]. J Biomed Sci, 2021, 28(1): 41. doi:10.1186/s12929-021-00737-3.

[56] Yamamoto T, Hirosue A, Nakamoto M, et al. BRD4 promotes metastatic potential in oral squamous cell carcinoma through the epigenetic regulation of the MMP2 gene[J]. Br J Cancer, 2020, 123 (4): 580-590. doi:10.1038/s41416-020-0907-6.

[57] Maksylewicz A, Bysiek A, Lagosz KB, et al. BET bromodomain inhibitors suppress inflammatory activation of gingival fibroblasts and epithelial cells from periodontitis patients[J]. Front Immunol, 2019, 10: 933. doi:10.3389/fimmu.2019.00933.

[58] Yoon H, Kim HJ, Shin HR, et al. Nicotinamide improves delayed tooth eruption in Runx2+/- mice[J]. J Dent Res, 2021, 100(4): 423-431. doi:10.1177/0022034520970471.

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