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·综述·

# 甲基化修饰在牙周炎中作用的研究进展

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【摘要】 牙周炎是发生于牙齿支持组织的慢性炎症性疾病，是重大的全球性公共卫生问题之一。甲基化修饰包括DNA甲基化、组蛋白甲基化和RNA的$m^6A$修饰等，是由甲基转移酶、去甲基化酶和结合蛋白等共同调控的可逆过程。牙周炎中异常的甲基化修饰抑制Toll受体2表达导致口腔菌群失调，通过C-C基序趋化因子配体、Fc-γ受体介导的吞噬作用、NF-κB等信号通路破坏宿主正常免疫调节功能，引起牙周组织局部免疫炎症反应失衡；多种甲基化修饰还调节Runt相关转录因子2和成骨细胞特异性转录因子Osterix、核因子-κB配体等表达，干扰破骨细胞和成骨细胞分化，破坏骨稳态，引发牙槽骨吸收。甲基化相关的生物标志物具有牙周炎筛查和预后评估的潜力。目前研究已发现牙周炎中众多异常甲基化位点，然而具体的信号通路及完整的表观遗传因子网络有待阐明。本文对DNA甲基化修饰在牙周炎发生发展中的作用进行综述，探讨其在牙周炎病因学、诊断标志物筛选及靶向治疗中的潜在价值，以期为牙周炎的防治研究提供新的思路。

【关键词】 牙周炎；　DNA甲基化；　组蛋白甲基化；　RNA甲基化；　免疫炎症反应；　牙周膜干细胞；　成骨分化；　生物标志物
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**Research progress on the role of methylation modifications in periodontitis**

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【Abstract】 Periodontitis is a chronic inflammatory disease that affects the tooth-supporting tissues, and it constitutes a major global public health concern. Methylation modifications, including DNA methylation, histone methylation, and RNA $m^6A$ modification, represent reversible processes coordinately regulated by methyltransferases, demethylases, and binding proteins. In periodontitis, aberrant methylation modifications suppress Toll-like receptor 2 expression, leading to oral microbial dysbiosis. These modifications further disrupt normal immune regulatory functions through C-C motif chemokine ligands, Fc-γ receptor-mediated phagocytosis, and NF-κB signaling pathways, resulting in localized immune - inflammatory imbalance in periodontal tissues. In addition, various methylation modifications regulate the expression of Runt-related transcription factor 2 (RUNX2), osteoblast-specific transcription factor Osterix (OSX), and receptor activator of nuclear factor-κB ligand (RANKL), thereby interfering with osteoclast and osteoblast differentiation, disrupting bone homeostasis, and ultimately driving alveolar bone resorption. Methylation-related biomarkers demonstrate promising potential for periodontitis screening and prognostic evaluation. While numerous abnormally methylated sites have been identified in periodontitis, the precise signaling pathways and comprehensive epigenetic regulatory networks re-

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main to be fully elucidated. This review systematically summarizes the functional roles of DNA methylation modifications in the pathogenesis of periodontitis and explores their potential value in etiological studies, diagnostic biomarker discovery, and targeted therapeutic interventions, with the aim of providing novel perspectives for periodontitis prevention and treatment strategies.

**【Key words】** periodontitis; DNA methylation; histone methylation; RNA methylation; immune and inflammatory response; periodontal ligament stem cell; osteogenic differentiation; biomarker

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第四次全国口腔健康流行病学调查结果显示我国35岁以上成年人中62.3%患有不同程度牙周炎，而中重度牙周炎的比例高达30.6%[1]，牙周炎已成为我国常见且突出的口腔健康问题之一。表观遗传修饰是指在不改变DNA序列的前提下，通过化学修饰来调控基因表达的过程[2]。甲基化修饰是表观遗传调控的核心机制之一。常见的甲基化修饰包括DNA甲基化、组蛋白甲基化和RNA甲基化。研究发现免疫炎症反应相关的异常甲基化修饰干扰宿主识别病原菌的能力，影响牙周免疫炎症基因正常表达，破坏免疫细胞功能，使宿主免疫稳态失调[3]。本文对甲基化修饰在牙周炎进展中的作用进行综述，为牙周炎防治相关研究提供思路和参考。

## 1　甲基化修饰方式

### 1.1　DNA甲基化

在真核生物中，DNA甲基化通常是在胞嘧啶的碳5位上添加甲基基团，这种修饰发生在基因启动子区域富含胞嘧啶-磷酸-鸟嘌呤（cytosine-phosphate-guanine，CpG）双核苷酸对的区域，即CpG岛上，启动子区域异常高甲基化导致基因沉默且可以在细胞间稳定遗传[4]。DNA甲基化调控涉及DNA甲基转移酶（DNA methyltransferase，DNMT）和DNA去甲基化酶10-11易位酶（ten-eleven translocases，TET）[5-6]。Niu等[7]研究发现DNA中5-甲基胞嘧啶通过直接抑制基因组中G-四链体结构形成，抑制基因转录。此外，其它的DNA甲基化形式，如$N^6$-甲基腺嘌呤参与转录、复制、DNA的损伤修复等，Cheng等[8]鉴定发现MT-A70家族蛋白腺嘌呤甲基转移酶2（adenine methyltransferase 2，AMT2）和AMT5介导其从头甲基化。DNA甲基化作为较为稳定的一种表观遗传修饰方式，在多种口腔疾病中得到广泛研究。

### 1.2　组蛋白甲基化

组蛋白的共价修饰参与染色质结构和功能的调控，赖氨酸残基甲基化作为常见的组蛋白修饰方式被认为是染色质活性或非活性的标志物[9]。组蛋白H3赖氨酸4（histone H3 lysine 4，H3K4）、H3K36和H3K79的甲基化介导基因正向调控，而H3K9、H3K27、H4K20甲基化则与转录抑制相关[10]。Fukuda等[11]发现在哺乳动物细胞中，H3K27me3在H3K9甲基化缺失后保护异染色质构型。Lu-Culligan等[12]发现组蛋白H4的同一氨基酸残基先单甲基化再乙酰化，形成$N^{\varepsilon}$-乙酰基-$N^{\varepsilon}$-甲基赖氨酸，在活性转录起始位点标记染色质。在牙周炎模型中，H3K9、H3K27甲基化抑制剂显著促进了牙周膜成纤维细胞中成骨标志物Runt相关转录因子2（Runt-related transcription factor 2，RUNX2）和成骨细胞特异性转录因子Osterix（OSX/SP7）的表达，靶向组蛋白甲基化标志物用于诱导成骨分化和促进骨再生在牙周治疗中表现出一定潜力[13]。

### 1.3　RNA甲基化

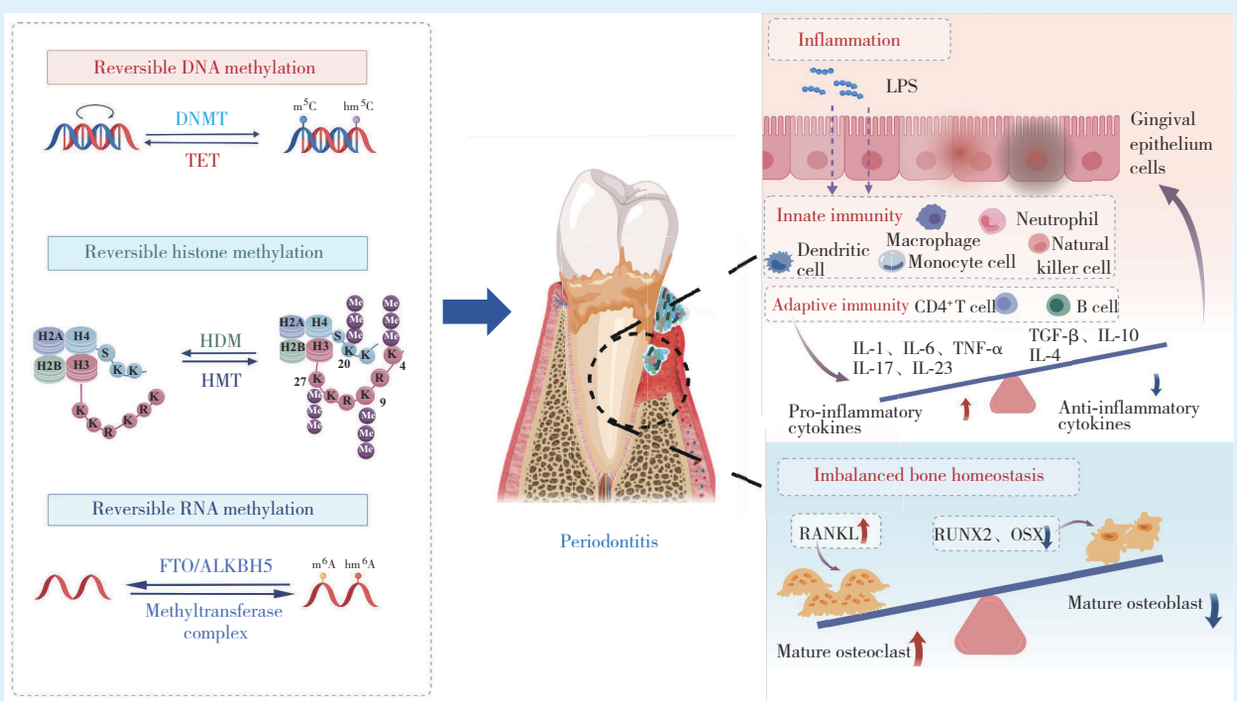
真核生物中发现最早和最常见的一种甲基化修饰方式为$N^6$-甲基腺苷（$N^6$-methyladenosine，$m^6A$），通过影响mRNA剪接、翻译、稳定性和长非编码RNA介导的表观遗传过程，在基因表达、肿瘤发生等多种生物过程中发挥重要作用[14-15]。$m^6A$“书写者”甲基转移酶复合物、“擦除者”去甲基化酶和“阅读者”结合蛋白之间的动态相互作用共同调控$m^6A$修饰的可逆过程[16-19]。除了mRNA外，$m^6A$也修饰染色质RNA，如调节环状RNA（circular RNA，circRNA）的翻译、促进其核输出和降解，与染色质相互作用影响基因组稳定性和转录活性[20]。近来研究发现甲基转移酶样3（methyltrans-

ferase like 3，METTL3）催化的 m$^6$A 修饰在口腔上皮细胞等自我更新的体细胞组织中发挥关键作用，METTL3 缺失抑制 H3K4 甲基转移酶 mRNA 的降解，促进分化程度更高、祖细胞样程度更低的转录表型，导致广泛的基因表达失调[21]。

此外，DNA 甲基化、组蛋白甲基化和 m$^6$A 修饰之间存在广泛的相互作用调控基因表达[22]。Li 等[23]发现含 YTH 结构域蛋白 1（YTH domain-containing protein 1，YTHDC1）募集赖氨酸去甲基化酶 3B（lysine demethylase 3B，KDM3B）到 m$^6$A 相关的染色质区域，导致 H3K9me2 去甲基化，促进基因表达。Sun 等[24]发现 YTHDC2 可募集 DNA 去甲基化酶 TET1，通过去除 LTR7/HERV-H 基因组位点的 5-甲基胞嘧啶阻止表观遗传沉默，进而抑制人胚胎干细胞的神经分化。多项研究也发现 H3K27、H3K36、H3K4 参与 DNMT3 的变构调控，DNA 甲基化和组蛋白赖氨酸甲基化间的失衡与人类神经发育障碍和多种癌症有关[25]。多种甲基化修饰间广泛的相互作用参与染色质活性调节、发育障碍和多种癌症的发生，然而不同甲基化修饰之间是否通过相互作用参与牙周炎的发生发展仍然未知。

## 2　甲基化修饰与牙周炎

现有研究发现，甲基化修饰会通过影响机体全身及牙周局部的免疫炎症反应、成骨分化和破骨分化等过程，增加牙周炎易感性[26]（图 1）。此外，多种甲基化修饰还可以作为预测牙周炎活动性的潜在分子生物标志物[27]。




DNA methylation, histone methylation and RNA methylation are involved in the occurrence and development of periodontitis. They disrupt immune-inflammatory homeostasis by up-regulating pro-inflammatory cytokines and down-regulating anti-inflammatory cytokines. At the same time, they interfere with bone homeostasis and promote alveolar bone resorption by promoting osteoclast differentiation and inhibiting osteoblast differentiation. DNMT: DNA methyltransferase; TET: ten-eleven translocases; HDM: histone demethylase; HMT: histone methyltransferase; FTO: fat mass and obesity-associated protein; ALKBH5: human AlkB homolog 5; m$^5$C: 5-methylcytosine; hm$^5$C: 5-hydroxymethylcytosine; m$^6$A: N6-methyladenosine; hm$^6$A: N6-hydroxymethyladenosine; LPS: lipolyaccharide; IL: interleukin; TNF-α: tumor necrosis factor-α; TGF-β: transforming growth factor-β; RUNX2: Runt-related transcription factor 2; RANKL: receptor activator of nuclear factor-kappa B ligand; OSX: Osterix

Figure 1　Methylation modifications and periodontitis

**图 1**　甲基化修饰与牙周炎

### 2.1　免疫炎症反应

龈下菌斑微生物、遗传和环境等多种因素共同参与牙周炎的发生和进展，炎症、免疫和防御系统是牙周炎发病机制中的主要因素，相关基因的变化会影响机体对牙周炎的易感性[28-29]。牙菌斑作为牙周炎的始动因子，细菌病原体相关分子模

式与模式识别受体结合激活单核吞噬细胞、抗原呈递细胞、辅助性T(T helper, Th)细胞等多种免疫细胞,释放促炎细胞因子,进而激活核因子-κB配体(receptor activator of nuclear factor-kappa B ligand, RANKL)表达和基质金属蛋白酶(matrix metalloproteinase, MMP)分泌,破坏牙周组织[30]。

2.1.1　临床样本中异常的甲基化修饰位点　众多研究发现牙周炎患者与健康人群的临床样本间存在明显的差异甲基化修饰位点,参与牙周炎的免疫炎症反应过程。首先,牙周健康者和牙周炎患者牙龈组织局部甲基化水平存在显著差异。Zhao等[31]鉴定出牙周健康者和牙周炎患者牙龈组织中668个基因的DNA甲基化水平存在差异,牙周炎患者牙龈组织中低甲基化基因主要与免疫、炎症、细胞迁移、经典细胞信号、细胞增殖和细胞连接相关,高甲基化基因主要参与调节细胞损伤过程。

Zhang等[32]对69名健康者和241例牙周炎患者的牙龈组织进行微阵列数据分析,在23个$m^6A$调节因子中,$m^6A$结合蛋白YTHDC1显著减少、甲基转移酶复合体亚基Wilms肿瘤1相关蛋白和去甲基化酶AlkB同源物5(Alk B homolog 5, ALKBH5)显著增加,在牙周炎免疫微环境中还观察到ALKBH5与单核细胞浸润丰度呈正相关,研究提示$m^6A$相关的调节因子可能在塑造牙周炎的免疫反应、激活免疫炎症通路和免疫细胞浸润中发挥重要作用。

Wang等[33]对4名健康者和4例牙周炎患者的牙龈组织进行$m^6A$微阵列分析,鉴定出458个mRNA的差异$m^6A$甲基化位点,Delta/Notch样表皮生长因子相关受体(Delta/Notch-like epidermal growth factor-related receptor, DNER)基因和G蛋白核仁2(G protein nucleolar 2, GNL2)基因在牙周炎中表达水平显著降低,且与$m^6A$甲基化水平正相关。DNER是与Notch1受体相互作用的跨膜蛋白,慢性炎症状态下可增加干扰素-γ(interferon-γ, IFN-γ)的分泌。在牙周炎中,IFN-γ介导多种促炎功能,通过放大局部免疫炎症反应,控制破骨细胞生成促进牙槽骨吸收[34];GNL2促进核糖体生物发生和蛋白质合成,参与调节细胞周期,对干细胞的生长和发育十分重要[33],牙周炎中GNL2水平的降低可能会抑制PDLSCs的增殖迁移能力。因此,未来需要探究DNER和GNL2在牙周炎中参与调节免疫炎症反应和PDLSCs增殖分化的具体作用机制。

此外,一项全表观基因组关联研究调查了外周血白细胞中CpG特异性DNA甲基化与牙周病之间的关联,锌指蛋白57基因的低甲基化和同源异型盒基因A4(homeobox A4, HOXA4)中的高甲基化在重度牙周炎更显著[35]。锌指蛋白与抗原呈递和免疫反应调节相关,而HOXA4在牙周炎中的作用有待阐明[35-36]。这提示,甲基化修饰与牙周炎局部和全身免疫状态密切相关,是调控牙周炎免疫炎症反应和疾病进展的重要表观遗传修饰之一。

2.1.2　TLR2和甲基化修饰　临床研究中异常的甲基化修饰可导致口腔菌群失调,破坏宿主正常免疫调节功能,干扰炎性细胞因子分泌,引发免疫炎症反应。

首先,DNA甲基化参与调节牙周炎中Toll样受体2(Toll-like receptors 2, TLR2)的表达。先天免疫反应通过模式识别受体识别细菌脂多糖(lipolyaccharide, LPS)、脂蛋白、脂磷壁酸、细菌DNA等病原体相关分子模式,其中TLR2在识别病原体和启动宿主免疫炎症反应方面发挥关键作用[37]。牙龈卟啉单胞菌(*Porphyromonas gingivalis*, *P. gingivalis*)与牙龈上皮细胞长期相互作用可以增加细胞中TLR2启动子的甲基化水平并抑制TLR2表达,进而降低细胞对细菌的识别能力,通过影响先天免疫反应导致菌群失调[38]。

此外,部分研究通过检测外周血白细胞中TLR2相关差异甲基化位点揭示牙周炎对全身免疫状态的影响[39-40]。Cárdenas等[39]综述了不同外周免疫细胞相关的DNA甲基化模式,TLR2基因被确定为牙周炎相关的潜在风险标志物。Shaddox等[40]对局限性侵袭性牙周炎患者不同类型的外周免疫细胞进行DNA甲基化模式分析,发现淋巴细胞和单核细胞中TLR调节因子基因在严重程度不同的牙周炎中具有不同的甲基化模式,相较于中度局限性侵袭性牙周炎患者,重度患者中髓样分化因子88、丝裂原活化蛋白激酶激酶激酶7、受体相互作用丝氨酸/苏氨酸蛋白激酶2、白细胞介素-6受体(interleukin-6 receptor, IL-6R)等促炎基因和IL-1受体相关激酶1结合蛋白1、过氧化物酶体增殖物激活受体-α、Fas相关死亡结构域蛋白等抗炎基因均表现较低的DNA甲基化水平。结果表明牙周炎相关的甲基化修饰调控基因表达可影响全身免疫状态。总之,TLR2表达失调引起宿主对牙周致病菌的反应改变可能会加剧炎症反应并增加牙周炎的易感性。

2.1.3　细胞因子和甲基化修饰　细胞因子相关基因的甲基化模式在健康者和牙周炎患者之间存在显著差异。对20名健康个体和20例广泛性牙周炎患者牙龈组织样本进行差异甲基化分析，广泛性牙周炎与信号转导和转录激活因子5（signal transducer and activator of transcription 5，STAT5）的DNA低甲基化有关，该基因在不同细胞因子（如IL-2、IL-3、IL-7等）的产生中发挥作用[41]。Cárdenas等[39]综述了不同外周免疫细胞相关的DNA甲基化模式，C-C基序趋化因子配体2（C-C motif chemokine ligand 2，CCL2）、IL-4、肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）、IL-6、IL-8等40多个基因被确定为牙周炎相关的潜在风险标志物。Zhang等[32]对69名健康者和241例牙周炎患者的牙龈组织进行微阵列数据分析，牙周炎中细胞因子和TNF家族成员受体反应活跃，Cbl原癌基因样1与细胞因子活性负相关，$m^6A$结合蛋白ELAV样蛋白1与TNF家族成员受体正相关，表明$m^6A$修饰在牙周局部免疫微环境中发挥重要作用，参与牙周组织稳态调节及疾病发生。此外，在牙周组织细胞中发现甲基化相关酶与牙周炎相关炎症因子可以互相作用。Huang等[42]发现敲低牙周膜细胞（periodontal ligament cells，PDLCs）中METTL3和METTL14有利于降低*P. gingivalis*的LPS诱导的IL-6水平。Seutter等[43]发现IL-1和前列腺素E2会降低人牙龈成纤维细胞（gingival fibroblasts，GFs）中DNMT3a和去甲基化酶TET1表达水平，但IL-1β增加DNMT1表达。用TNF-α、IL-1β处理人PDLCs构建体外炎症环境，观察到$m^6A$甲基化修饰基因富集于mRNA加工、剪接和组蛋白修饰等生物过程[44]。IL-6、IL-8、IFN-γ等免疫炎症反应相关基因在牙周炎组织中甲基化水平降低[45-46]，炎症环境下细胞因子甲基化水平的异常改变会干扰中性粒细胞、巨噬细胞等免疫细胞的正常功能，加重牙周组织破坏。

2.1.4　免疫细胞、非免疫细胞和甲基化修饰　单核细胞、巨噬细胞、淋巴细胞等免疫细胞在牙周炎不同阶段的甲基化模式同样差异显著[47]。Zhang等[32]对69个健康者和241例牙周炎患者牙龈组织样本进行分析发现，牙周炎患者和健康者间17个$m^6A$调节因子表达存在显著差异，牙周炎患者中临床特征无明显差异的样本间$m^6A$调节因子的表达存在显著差异，因此根据$m^6A$调节因子表达水平将牙周炎分为3个亚型并分析其免疫微环境间的差异，在亚型1中免疫细胞浸润水平较低，而亚型2中表现更高水平的活化B细胞、树突状细胞、自然杀伤细胞、中性粒细胞、Th1细胞、Th17细胞等浸润，在亚型3中则表现出活化的$CD4^+$ T细胞、肥大细胞和Th2细胞浸润，亚型2表现出更为活跃的免疫反应和IL-6/STAT3通路的激活，这提示$m^6A$调节因子可以区分健康和牙周炎样本且$m^6A$修饰参与调节牙周炎的免疫微环境，基于免疫特性的牙周炎分型有望提供更加精确的治疗策略。

巨噬细胞与牙龈上皮细胞和树突状细胞形成的防线通过清除非自身抗原发挥作用，研究发现牙周致病菌引起人β-防御素2和CCL20的甲基化改变，TLR2基因启动子区域高甲基化，IL-6、IL-8、IFN-γ、TNF-α基因启动子区域的异常甲基化模式均可以间接影响巨噬细胞介导的免疫反应[48]。Fc-γ受体主要存在于免疫细胞，在传递炎症和非炎症信号方面发挥双重作用[49]，Kang等[50]研究发现相比于单纯牙周炎患者，伴有2型糖尿病的牙周炎患者Fc-γ受体相关基因呈现显著低甲基化，外周血单核细胞RNA分析表明该基因在单核细胞中显著上调，提示靶向Fc-γ受体介导的吞噬作用信号通路有望成为伴2型糖尿病牙周炎患者的潜在治疗策略。Th17细胞在牙周炎的炎性骨吸收和组织损伤中发挥重要作用，Huang等[51]通过体外实验表明*P. gingivalis*的LPS诱导含jumonji结构域的组蛋白去甲基化酶3（histone demethylases jumonji domain containing 3，JMJD3）表达，进而通过调节STAT3-RORc信号通路促进Th17细胞分化，阐明了JMJD3在*P. gingivalis* LPS促进Th17细胞分化的重要作用，但JMJD3调节STAT3-RORc信号通路的具体机制有待进一步研究。综上，异常甲基化修饰可引起免疫炎症相关基因表达水平异常，干扰免疫细胞正常功能，破坏宿主免疫稳态，但相关信号通路仍需进一步探索。

此外，多项研究也表明甲基化修饰调控GFs的免疫炎症反应。Lagosz-Cwik等[52]研究发现用DNMT抑制剂地西他滨处理GFs，GFs增殖能力下降，CCL20、MMP1、MMP9、MMP13表达增加和细胞间黏附分子-1表达上调，表明DNA甲基化影响牙周炎GFs的活力和炎症反应。训练有素的免疫力会增加对刺激的炎症反应，导致慢性炎症性疾病的进展[53]。Liu等[54]研究表明*P. gingivalis*的LPS通过PI3/AKT通路诱导GFs获得训练免疫，促炎细胞因子IL-6和TNF-α分泌增加和基因的增强子区

域H3K4me1水平升高，该研究解释了牙周炎复发性和持续性的新机制，为牙周炎的治疗提供了新的策略。

2.1.5　*P. gingivalis*和甲基化修饰　研究发现，龈下菌斑微生物可以直接或间接影响牙周组织细胞的DNA甲基化和组蛋白甲基化水平，触发炎症反应和逃避宿主的防御机制[55]。Barros等[56]通过*P. gingivalis*刺激牙龈上皮细胞模型，研究发现三种细胞间连接复合物E-钙粘蛋白、血小板亲和蛋白2、紧密连接蛋白1的DNA甲基化水平增加。组蛋白甲基化也参与*P. gingivalis*与宿主的相互作用。*P. gingivalis*的LPS刺激GFs可通过PI3K/AKT通路使细胞代谢转向糖酵解，导致IL-6、TNF-α分泌增加。且在牙周炎患者GFs中IL-6和TNF-α增强子区域观察到H3K4me1水平显著增加[54]。Fan等[57]用*P. gingivalis*的外膜囊泡（outer membrane vesicles，OMVs）刺激人PDLCs，结果表明OMVs中sRNA45033靶向色素框同源蛋白5基因并抑制其表达，进而降低p53基因的H3K9me3水平，促进细胞凋亡。此外，*P. gingivalis*及其产物（如LPS、OMVs、短链脂肪酸等）通过DNA甲基化、组蛋白修饰等过程调节牙龈上皮细胞、巨噬细胞和PDLSCs等细胞中细胞凋亡和免疫炎症反应相关基因的表达（表1）。

**表1**　牙龈卟啉单胞菌及其产物在牙周炎中引起的表观遗传变化

Table 1　Epigenetic modifications induced by *Porphyromonas gingivalis* and its products in periodontitis

| Stimulating | Epigenetic changes | Cell types | Vivo experiment | Effectors | Signaling axis |
|---|---|---|---|---|---|
| *P.g*[58] | DNA methylation | | BALB/C mice and C57BL/6 mice | Numerous DMRs | PI3K/Akt, Wnt |
| *P.g*-OMVs[57] | Histone methylation | hPDLCs | SD rats | Upregulation of P53, caspase-3, NOXA, PUMA, IL-1β, IL-6, and NLRP3; downregulation of PHF | p53/Bcl-2/Bax |
| *P.g*-LPS[59] | Histone methylation | hPDLCs | C57BL/6 mice | Upregulation of TLR4 and downregulation of PHF8 and osteogenic markers | LPS-TLR4-PHF8 |
| *P.g*[56] | DNA methylation | hGECs | | Upregulation of DNA methylation levels in CDH1, PKP2, TJP1 | |
| *P.g*-LPS[60] | Histone methylation | hPDLSCs | C57BL/6 mice | Increased transcription of IL-1β, IL-6, and MMP2; increased protein expression of IL-1β and IL-6 | NF-κB/p65 |
| *P.g*-LPS[61] | Histone methylation | THP-1, HOK-16B | Mice | Elevation of TNF-α, IL-1β, IL-6, and NF-κB signaling levels induced by KDM3C knockout | NF-κB |
| LPS[62] | Histone methylation | hPDLSCs | Nude mice | Downregulation of COL1A1, COL3A1, and RUNX2 expression; upregulation of CCL, DEFA4, and IL-1β gene expression | |
| Butyric acid[63] | Histone acetylation | hGFs | | Upregulation of cytochrome c-related caspase and TNF-α | Caspase 8/9 |
| *P.g*-LPS[64] | DNA methylation, histone acetylation | hPDLSCs | | Downregulation of DNMT1, HDAC1; upregulation of p300, NF-κB, and HDAC2 | |
| *P.g*-LPS[65] | DNA methylation | hPdLFs | | Higher methylation in the promoter regions of 25 ECM-related genes | |
| LPS[66] | Histone acetylation, DNA methylation | NOK-SI cells | Wild-type mice | | p300/CBP/NF-κB |

DMRs: differentially methylated regions; IL: interleukin; *P.g*: *Porphyromonas gingivalis*; LPS: lipopolysaccharide; OMVs: outer membrane vesicles; hPDLCs: human periodontal ligament cells; hPDLSCs: human periodontal ligament stem cells; hGECs: human gingival epithelial cells; hGFs: human gingival fibroblasts; CDH1: E-cadherin; PKP2: plakophilin 2; TJP1: tight junction protein 1; SETD1: SET domain -containing methyltransferases 1; THP1: Tohokuhospital pediatrics-1; HOK-16B: human oral keratinocyte-16B; hBD2: human β-defensin 2; HaCaT: immortalized human keratinocytes; DNMT: DNA methyltransferase; hPdLFs: human periodontal fibroblast cells; NOK-SI: normal human oral keratinocytecells; NF-κB: nuclear factor-κB; TLR: Toll-like receptor; NOXA: NADPH oxidase activator 1; PUMA: p53 upregulated modulator of apoptosis; NLRP3: NOD-, LRR-, and pyrin domain-containing protein 3; Bcl-2: B cell lymphoma 2; PHF8: PHD finger protein 8; MMP: matrix metalloproteinase; KDM: lysine demethylase; COL1A1: collagen type I alpha 1 chain; DEFA4: defensin alpha 4; TNF-α: tumor necrosis factor-α; RUNX2: Runt-related transcription factor 2; CCL: C-C motif chemokine ligand; HDAC: histone deacetylase; ECM: extracellular matrix

2.2　成骨分化和破骨分化

在牙周炎中，异常的甲基化修饰下调PDLSCs的成骨潜能并促进破骨细胞分化，破坏骨形成与骨吸收的动态平衡[67]。在PDLSCs成骨分化过程中，RUNX2和OSX分别是成骨早期和后期的主要转录因子[68-69]。研究表明，RUNX2和OSX的表达受到DNA甲基化、组蛋白甲基化和m$^6$A修饰的调节。

2.2.1　DNA甲基化与成骨分化　RUNX2基因的甲基化水平与PDLSCs的成骨能力相关。Assis等[70]发现高成骨潜能的PDLSCs（h-PDLSCs）相较于低成骨潜能的PDLSCs（l-PDLSCs），成骨诱导3 d后RUNX2、OSX基因表达增加；成骨诱导21 d后DNMT1、DNMT3B、TET1、TET3基因表达降低，OSX基因表达增加，进一步用DNMT1抑制剂RG108诱导l-PDLSCs去甲基化可以使细胞中DNMTs表达减少和RUNX2表达增加，增强l-PDLSCs成骨能力。Ferreira等[71]将来自牙周膜的间充质细胞成骨诱导10 d后，h-PDLCs相较于l-PDLCs，DNMT3a、TET1、TET3基因转录水平降低，RUNX2基因低甲基化和转录增加。上述研究表明降低RUNX2基因的甲基化水平可潜在提高PDLSCs和PDLCs的成骨能力。此外，Li等[72]的研究表明转化生长因子-β1通过DNA甲基化介导的PRKAG2基因沉默触发活性氧产生、DNA损伤，通过DNA损伤应答相关的共济失调毛细血管扩张突变蛋白信号通路引起PDLSCs中G2细胞周期停滞，减弱其再生潜力，对PDLSCs增殖分化产生负向调控。

2.2.2　组蛋白甲基化与成骨分化　组蛋白甲基化修饰可以影响PDLSCs中RUNX2和OSX转录相关的成骨分化过程。赖氨酸去甲基化酶5B（lysine demethylase 5B，KDM5B/jumonji AT-rich interactive domain 1B，JARID1B）作为转录抑制因子，通过使RUNX2基因启动子处H3K4me3和H3K4me2去甲基化抑制RUNX2基因活性，是实现PDLSCs成骨分化的关键因子[73]。Ferreira等[74]诱导不同成骨潜能的PDLCs成骨分化10 d后发现，h-PDLCs中JARID1B表达下调，H3K4me3、RUNX2、OSX表达上调，Pearson相关性分析表明JARID1B基因表达与RUNX2、OSX基因表达相关。研究也发现KDM5A在LPS处理的人PDLSCs中高表达，并可与miR-495-3p启动子结合，通过H3K4me3的去甲基化抑制miR-495-3p表达，增强HOXC8并限制牙周炎中PDLSCs的成骨分化、增殖和迁移[75]。Shao等[76]利用*P. gingivalis*的LPS处理人PDLSCs研究发现，炎症微环境下赖氨酸特异性去甲基化酶1（lysine specific demethylase 1，LSD1/KDM1A）表达上调，并特异性促进H3K4me2去甲基化，抑制OSX转录，减弱PDLSCs的成骨分化。结果表明，上述组蛋白去甲基化酶负向调节RUNX2、OSX转录，抑制成骨分化，有望通过抑制上述靶点作为牙周再生治疗的潜在策略。

2.2.3　m$^6$A修饰与成骨分化　m$^6$A修饰在PDLSCs成骨分化中调节RUNX2表达的作用机制也得到了初步研究。牙周炎症微环境下，METTL3可促进lncRNA CUTALP的表达和稳定性，抑制miR-30b-3p，上调RUNX2表达促进牙周炎患者PDLSCs的成骨分化[77]。此外，m$^6$A结合蛋白通过增强m$^6$A修饰的mRNA的稳定性，提高mRNA的翻译效率。Zhou等[78]发现METTL3靶向RUNX2 mRNA 3'-UTR，胰岛素样生长因子2 mRNA结合蛋白1（insulin-like growth factor 2 mRNA-binding proteins 1，IGF2BP1）作为m$^6$A结合蛋白进一步识别RUNX2 mRNA的m$^6$A位点，从而增强骨髓间充质干细胞（bone marrow mesenchymal stem cells，BMSCs）中m$^6$A修饰的RUNX2 mRNA的稳定性，上调RUNX2表达促进BMSCs成骨分化。Huang等[79]发现在PDLSCs成骨分化过程中，METTL3上调PDLSCs中RUNX2的m$^6$A修饰，IGF2BP1识别和结合m$^6$A区域增加RUNX2 mRNA稳定性，上调RUNX2表达促进PDLSCs的成骨分化。相关研究揭示了IGF2BP1在促进mRNA稳定性和翻译中的重要作用，METTL3通过IGF2BP1/m$^6$A/RUNX2信号轴增强细胞的成骨分化能力，有待探究更多促进成骨分化的m$^6$A标志物[79]。目前，circRNA相关的m$^6$A修饰主要集中于免疫、生殖系统、肌细胞发生发育和恶性肿瘤，在口腔疾病中研究较少[15]。大多数研究通过体外实验探究circRNAs在牙周炎中的作用，评估牙周炎患者中circRNAs的表达水平，但缺少circRNA m$^6$A修饰与牙周炎间关系的研究[80]。现有研究表明，circRNA作为竞争性内源性RNA，通过充当miRNA海绵减轻PDLSCs的炎症反应，促进其成骨分化。如体外研究发现circ_0062491通过调节miR-498/细胞因子信号转导抑制因子6轴减轻LPS诱导的PDLSCs的凋亡和炎症反应[81]。Yu等[82]的体外和体内研究表明，牙周炎患者中高表达的circMAP3K11可靶向负调控miR-511-3p，从而逆转miR-511-3p对TLR4的抑制作用，circMAP3K11通过调节miR-511-3p/TLR4轴促进炎症微环境中

PDLSCs的增殖、凋亡和迁移。上述研究表明circRNAs在牙周炎中发挥重要作用，但circRNA的m$^6$A修饰对牙周炎的调控作用仍有待探究。

2.2.4　甲基化修饰与破骨分化　骨骼稳态的维持依赖于骨吸收与骨形成的平衡，破骨细胞的分化过程也受到甲基化修饰的调控。研究表明，敲除骨髓谱系或巨噬细胞/破骨细胞前体中LSD1/KDM1A可以增加IFN-β表达并减少破骨细胞分化，实现小鼠骨量增加[83]。He等[84]通过LPS和RANKL构建炎性破骨细胞生成模型，研究发现，FTO以含YTH结构域家族蛋白2依赖性方式增加破骨细胞前体细胞中S期相关蛋白细胞周期蛋白依赖性激酶2（cyclin-dependent kinase 2，CDK2）和Cyclin A2的mRNA稳定性，上调CDK2、Cyclin A2表达和下调DNA损伤相关蛋白γ-H2AX、p-Chk2和p-p53的表达，促进破骨细胞增殖并抑制细胞凋亡；动物实验表明，FTO抑制剂FB23-2可减少破骨细胞形成，减轻牙周炎小鼠骨破坏。提示FTO有望成为治疗牙周炎的潜在靶点。此外，在种植体的骨整合微环境中，m$^6$A甲基化参与成骨细胞外泌体中circ_0008542的转录后调控。具体机制为METTL3促进circ_0008542靶向miRNA-185-5p，上调RANK基因表达，促进破骨细胞分化，ALKBH5通过去甲基化抑制circ_0008542与miRNA-185-5p结合，减少破骨细胞分化和骨吸收[85]。以上研究表明circRNA的m$^6$A修饰参与调节破骨细胞分化和骨吸收，但目前多数研究仅为甲基化修饰参与调节破骨细胞或成骨细胞分化提供了证据。在牙周炎症微环境下，甲基化修饰对破骨细胞和成骨细胞稳态的影响及作用机制仍有待研究。

2.3　*牙周炎生物标志物*

探索精确预测和识别牙周炎活动性的生物标志物对于牙周炎的筛查和预后评估具有重要意义[86]。牙龈、龈沟液等样本的甲基化水平可反映牙周炎活动状态，作为潜在的生物标志物用于牙周炎筛查和预后评估[87-88]。研究对基因本体数据库、京都基因与基因组百科全书数据库、蛋白质-蛋白质相互作用STRING数据库中慢性牙周炎患者牙龈活检样本的甲基化数据集进行生物信息学分析，结果发现，低甲基化基因主要与细胞外基质、细胞趋化性和髓系白细胞迁移过程相关，高甲基化基因则与角质形成细胞分化、角化、表皮发育、皮肤发育过程相关[87]。三个低甲基化基因IL-1β、激酶插入结构域受体、MMP9基因和三个高甲基化基因角膜锁链蛋白、桥粒芯糖蛋白1、角蛋白2基因是牙周炎潜在的生物标志物[87]，其在牙周炎筛查、诊断和预后评估中的应用价值值得进一步探索。

另有研究发现，牙周炎患者唾液的小细胞外囊泡中整体5-甲基胞嘧啶相较于牙周健康者显著增加，在区分牙周炎和牙周健康之间具有高度敏感性和特异性（*AUC*=1）[89]。Wang等[90]将基因表达综合数据库中183份牙周炎患者和64份健康对照者牙龈组织样本的基因表达数据和CpG甲基化数据进行加权基因共表达网络分析，免疫炎症相关基因（巨噬细胞清道夫受体-1、神经调节蛋白1、外周髓鞘蛋白2、丝氨酸/苏氨酸激酶3、内质网氨肽酶2）启动子CpG位点的甲基化水平在牙周炎患者中降低，基因表达显著高于健康对照组，基于这5个免疫基因构建的牙周炎诊断模型预测性能优异（*AUC*=0.95，灵敏度=90%，特异性=100%）。多数研究以牙龈组织或血液为样本分析牙周炎患者和健康者之间的甲基化差异，唾液、龈沟液等体液具有容易重复获取、无创等特点，用于牙周炎筛查和预后评估的随机临床试验的统计效力、可重复性和操作可行性能够增加甲基化生物标志物的临床相关性[91]。

目前牙周炎患者诊断及预后评估依赖牙周探针和影像学检查确定牙周袋探诊深度、探诊出血、牙槽骨丧失程度等信息，通过多种参数评估疾病严重程度，但无法检测疾病当前的活动状态[92]。通过表观遗传变化预测牙周炎易感性、进展速度或严重程度是牙周炎筛查和预后评估的一种潜在策略[93]。使用特异性甲基化DNA、组蛋白或RNA作为牙周炎预后生物标志物的研究仍处于起步阶段，牙周炎严重程度、年龄、吸烟状况等混杂因素无法在小队列中得到匹配，需要多项具有独立外部验证能力的大型队列和足够检验效能的研究来证明其可行性[94]。其次，龈沟液等体液在采样方法、样本存储条件、检测方法、统计学分析等方面的差异限制了相关生物标志物的临床应用价值[95]。单一生物标志物的诊断能力不足且缺乏统一的诊断标准，需要建立统一的操作标准和方案确保结果的可重复性和可比较性，开发临床可靠的标准化检测方法[96]。随着更多可靠生物标志物的发现及表观遗传因子网络的建立，有望从全新角度实现牙周炎及其它疾病的早期发现、治疗和预后评估。

## 3　小　结

DNA甲基化、RNA的m$^6$A修饰和组蛋白甲基化从表观遗传修饰、转录和转录后水平参与牙周炎的免疫炎症反应及PDLSCs的成骨分化过程(图1),展现出在疾病早期发现、诊断和预后评估的潜力。目前研究重点关注DNA甲基化在牙周炎中的作用,已在牙周炎患者中检测出众多基因存在差异甲基化位点。

未来,一方面需要对当前报道的众多异常甲基化基因在牙周炎中的作用进行充分验证,阐明不同甲基化修饰在牙周炎中的作用机制及多种甲基化修饰间的相互作用,识别牙周炎发生发展中的稳定基因座标志物,构建完整的表观遗传因子网络。另一方面,目前虽然有多项研究将DNMT抑制剂地西他滨、姜黄素、RG-108等用于降低炎症基因的甲基化水平,减少牙周组织破坏,但以甲基化水平为诊断指标或者靶向炎症基因的甲基化进行牙周炎治疗仍处于理论水平,有待进一步通过体内实验及临床试验验证药物的有效性,开发更多DNA甲基化抑制剂等表观遗传治疗药物,从而实现传统治疗与表观遗传疗法相结合。

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