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·基础研究·

牙胚间充质细胞中敲除Setd2对牙齿早期发育的影响

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【摘要】　目的　探讨牙胚间充质细胞中特异性敲除含SET结构域蛋白2（Setd2）对牙齿早期发育的影响，为牙发育异常疾病的病因探索提供研究基础。**方法**　本实验已获得武汉大学动物实验中心伦理委员会批准，将C57BL/6J背景的$Wnt1^{Cre}$小鼠与$Setd2^{flox/flox}$小鼠交配，获得敲除Setd2的实验组（$Wnt1^{Cre}$；$Setd2^{flox/flox}$）及对照组（$Setd2^{flox/flox}$）。分别于小鼠胚胎期第13.5天（E13.5）、第15.5天（E15.5）、第18.5天（E18.5）收取小鼠胚胎尾部组织进行聚合酶链式反应（PCR）基因型鉴定，取胚胎头部制备石蜡切片观察下颌第一磨牙牙胚发育情况。采用免疫组织化学染色验证牙胚间充质细胞中Setd2的敲除情况；通过苏木素-伊红（HE）染色及肾囊膜培养分析在牙胚间充质细胞中敲除Setd2对牙齿发育的影响；使用Ki67染色和末端脱氧核苷酸转移酶介导的脱氧尿苷三磷酸缺口末端标记（TUNEL）染色分析特异性敲除Setd2对牙胚间充质细胞增殖和凋亡的影响；使用免疫荧光染色观察特异性敲除Setd2对蛋白H3第36位赖氨酸位点的三甲基化修饰（H3K36me3）的影响。**结果**　PCR基因型鉴定结果显示，实验组表现为$Setd2^{flox/flox}$纯合子单条带（266 bp）及$Wnt1^{Cre}$特征性单条带，对照组仅表现为$Setd2^{flox/flox}$纯合子单条带（266 bp）。免疫组织化学染色结果显示，实验组牙胚间充质细胞中Setd2被成功敲除；HE染色及肾囊膜培养结果显示，与对照组相比，E15.5及E18.5实验组特异性敲除Setd2导致牙胚变小、间充质细胞凝聚增加（E15.5，$P<0.05$；E18.5，$P<0.01$）；Ki67染色结果显示，E13.5及E15.5实验组与对照组间牙胚间充质细胞的细胞分裂比例差异均无统计学意义（E13.5，$P=0.694$；E15.5，$P=0.503$）；而TUNEL染色结果显示，E13.5及E15.5实验组牙胚间充质细胞凋亡率均高于对照组（$P<0.001$）；免疫荧光染色结果显示，E13.5、E15.5及E18.5实验组牙胚间充质细胞的H3K36me3修饰缺失（$P<0.000\ 1$）。**结论**　牙胚间充质细胞中Setd2的特异性敲除可通过影响H3K36me3修饰导致细胞凋亡增加，从而导致小鼠牙齿早期发育异常，表现为牙胚变小。

【关键词】　Setd2基因；　牙胚；　间充质细胞；　牙体发育异常；　细胞凋亡；　组蛋白甲基转移酶类；　表观遗传
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Effect of Setd2 knockout in dental germ mesenchymal cells on early tooth development

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【Abstract】　Objective　To investigate the effect of specific deletion of SET-domain-containing 2 (Setd2) in dental germ mesenchymal cells on early tooth development and provide a research basis for exploring the etiology of dental de-

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velopmental disorders. **Methods**　This study was approved by the Animal Care and Ethical Committee of Wuhan University. $Wnt1^{Cre}$ mice with a C57BL/6J background were crossed with $Setd2^{flox/flox}$ mice to generate the Setd2 knockout experimental group ($Wnt1^{Cre}$; $Setd2^{flox/flox}$) and the control group ($Setd2^{flox/flox}$). Tail tissues of mouse embryos were collected at embryonic day (E) 13.5, E15.5, and E18.5 for polymerase chain reaction (PCR)-based genotyping, and embryonic heads were collected for paraffin sectioning to observe the development of the first mandibular molar germs. Immunohistochemical (IHC) staining was performed to verify the specific knockout of Setd2 in dental germ mesenchymal cells; hematoxylin and eosin (HE) staining and subrenal culture were used to evaluate the effect of Setd2 knockout in dental germ mesenchymal cells on tooth development; Ki67 staining and a terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay were employed to evaluate the effects of specific Setd2 knockout on the proliferation and apoptosis of dental germ mesenchymal cells; immunofluorescence (IF) staining was conducted to observe the impact of Setd2 knockout on the trimethylation of lysine 36 on histone 3 (H3K36me3). **Results**　PCR-based genotyping showed that the experimental group presented a single band (266 bp) for the $Setd2^{flox/flox}$ homozygote and a characteristic band for $Wnt1^{Cre}$, while the control group only showed a single band (266 bp) for the $Setd2^{flox/flox}$ homozygote. IHC staining confirmed the successful knockout of Setd2 in dental germ mesenchymal cells of the experimental group; HE staining and subrenal culture demonstrated that specific knockout of Setd2 in the experimental group led to reduced size of tooth germs and increased condensation of mesenchymal cells at E15.5 and E18.5 (E15.5, $P < 0.05$; E18.5, $P < 0.01$); Ki67 staining showed no statistically significant effect on the proportion of division of dental germ mesenchymal cells between the experimental and control groups at E13.5 and E15.5 (E13.5, $P = 0.694$; E15.5, $P = 0.503$); the TUNEL assay demonstrated increased apoptosis of dental germ mesenchymal cells in the experimental group at both E13.5 and E15.5 ($P < 0.001$); IF staining revealed the absence of H3K36me3 modification in the dental germ mesenchymal cells of the experimental group across E13.5, E15.5, and E18.5 ($P < 0.000\ 1$). **Conclusion**　Specific knockout of Setd2 in dental germ mesenchymal cells leads to increased cell apoptosis by impairing H3K36me3 modification, resulting in early developmental defects in mouse teeth characterized by reduced tooth germ volume.

【Key words】 Setd2 gene; tooth germ; mesenchymal cells; tooth abnormalities; apoptosis; histone methyltransferases; epigenetics

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牙齿发育起始于胚胎期上皮与颅神经嵴来源间充质细胞的特异性识别、募集与聚集，经历蕾状期、帽状期、钟状期的早期形态发生过程[1]，并通过成牙本质细胞[2-3]、成釉细胞等矿化组织特异性细胞的定向分化、功能协作及细胞外基质的有序沉积与矿化，最终完成牙体组织的构建与萌出[4]。牙齿发育的任一环节发生调控异常，均可能导致牙齿数目异常[5]、牙本质发育不全[6-7]等多种先天性口腔疾病，严重影响患者的口腔健康与生活质量[8]。近年来，表观遗传调控在牙齿发育中的作用逐渐成为研究热点[9]。其中，组蛋白甲基化作为关键的表观遗传修饰方式，通过调控靶基因转录，在细胞命运决定中发挥关键作用[10-11]。含SET结构域蛋白2（SET-domain-containing 2，Setd2）是哺乳动物体内主要负责催化组蛋白H3第36位赖氨酸位点的三甲基化修饰（trimethylation of lysine 36 on histone H3，H3K36me3）的甲基转移酶，在基因转录调控[12-13]、DNA损伤修复[14]及RNA剪接[15]等生物学过程中发挥重要作用。Setd2在成牙本质细胞中高表达[16]，但目前关于Setd2在牙齿早期发育中的具体作用尚不明确，限制了对牙齿发育表观遗传调控网络的全面理解。

颅神经嵴细胞是牙齿间充质的主要前体细胞[17]，$Wnt1^{Cre}$工具鼠可特异性标记其来源的牙胚间充质细胞[18-19]。本研究通过将$Wnt1^{Cre}$小鼠与$Setd2^{flox/flox}$小鼠交配，获得的$Wnt1^{Cre}$；$Setd2^{flox/flox}$小鼠可在牙胚间充质细胞中表达Cre重组酶，该酶能特异性识别Setd2基因两侧的LoxP位点，实现Setd2基因的特异性敲除，旨在探究Setd2对牙齿早期发育的影响，以进一步完善牙齿发育的表观遗传调控网络，为牙发育异常相关疾病的病因研究及治疗提供新的实验依据和潜在靶点。

1　材料和方法

本实验遵循国家《实验动物管理条例》及《实验动物福利伦理审查指南》的相关规定，已获得武

汉大学动物实验中心伦理委员会批准(动物伦理审查号:WP20220046)。

1.1　主要试剂和仪器

通用型组织固定液(中性)(G1101-500ML,赛维尔,中国);PBS(G0002-15,赛维尔,中国);乙二胺四乙酸(ethylenediamine tetraacetic acid,EDTA)二钠盐(10009717,沪试,中国);吐温-20(ST825,碧云天,中国);1 mol/L Tris-HCl(pH 8.0)(ST787,碧云天,中国);2×聚合酶链式反应(polymerase chain reaction,PCR)预混液(10102,翌圣,中国);50×Tris乙酸盐EDTA(Tris acetate-EDTA,TAE)缓冲液(ST716,碧云天,中国);琼脂糖(BS081,Biosharp,中国);100 bp DNA ladder(10507ES60,翌圣,中国);二氨基联苯胺显色试剂盒(DAB显色试剂盒)(DAB-0031,迈新,中国);免疫组化试剂盒(KIT-9706,迈新,中国);苏木素(G1004,赛维尔,中国);伊红(BL703A,Biosharp,中国);胃酶修复液(DIG-3009,迈新,中国);驴抗兔免疫球蛋白G(594 Donkey anti-Rabbit IgG)(ANT030,Antgene,中国);含Setd2兔单克隆抗体(89680,Cell Signaling Technology,美国);Ki67/增殖细胞核抗原相关抗原兔单克隆抗体(Ki67/MKI67 Rabbit mAb)(NB110-89717SS,NOVUS,美国);组蛋白H3第36位赖氨酸三甲基化兔单克隆抗体[Histone H3(trimethyl K36)Rabbit mAb](ab9050,Abcam,美国);一步法末端脱氧核苷酸转移酶介导的脱氧尿苷三磷酸缺口末端标记(terminal deoxynucleotidyl transferase dUTP nick end labeling,TUNEL)原位细胞凋亡检测试剂盒(绿色,FITC)(E-CK-A320,Elabscience,中国);抗荧光淬灭封片液[含4',6-二脒基-2-苯基吲哚2-(4-Amidinophenyl)-6-indolecarbamidine dihydrochloride,DAPI)](P0131,碧云天,中国)。PCR扩增仪(T100,Bio-Rad,美国);数字病理切片扫描仪(Pannoramic MIDI,3D HISTECH,匈牙利);正置显微镜(BX53,奥林巴斯,日本)。

1.2　实验方法

1.2.1　实验动物　本实验所用小鼠均为C57BL/6J背景,其中$Setd2^{flox/flox}$小鼠由武汉大学周严教授馈赠,$Wnt1^{Cre}$工具鼠由武汉大学何淼教授惠赠。为构建实验模型,将$Wnt1^{Cre}$小鼠与$Setd2^{flox/flox}$小鼠交配,获得牙胚间充质细胞特异性敲除Setd2的实验组小鼠($Wnt1^{Cre}$;$Setd2^{flox/flox}$)12只及同窝对照组小鼠($Setd2^{flox/flox}$)12只用于后续实验。所有小鼠均饲养于武汉大学动物实验中心,采用无特定病原体(specific pathogen-free,SPF)环境进行饲养与繁殖,饲养条件如下:环境温度为20~24 ℃,相对湿度为40%~70%,采用12 h光照/12 h黑暗循环模式(光照时间段为7:00~19:00),小鼠可自由摄食、饮水。

1.2.2　凝胶电泳检测小鼠基因型　采用二氧化碳过量吸入安乐死方法(30%~70%容器体积/min的二氧化碳置换率)分别处死妊娠13.5 d(E13.5)、15.5 d(E15.5)、18.5 d(E18.5)的雌性小鼠各3只后,取出小鼠胚胎,分离头部并固定,同时剪取尾部组织进行基因型鉴定:将组织置于200 μL 50 mmol/L氢氧化钠溶液中,95 ℃金属浴裂解30 min;加入20 μL 1 mol/L Tris-HCl(pH 8.0)中和混匀,14 000 g、4 ℃离心10 min,取上清液作为基因组DNA模板进行PCR扩增。PCR产物采用1×TAE缓冲液配制的2%琼脂糖凝胶进行电泳检测(90 V恒压水平电泳30 min)。凝胶成像系统采集图像并判读基因型:$Setd2^{flox/flox}$纯合子为266 bp单条带,$Wnt1^{Cre}$阳性为特征性单条带。鉴定后获得E13.5、E15.5、E18.5实验组和对照组小鼠各3只用于后续实验。引物序列见表1,PCR扩增程序见表2。

表1　小鼠基因型鉴定引物序列

Table 1　Primer sequences for mouse genotyping

Genotype	Forward	Reverse
$Setd2^{flox/flox}$	5'-TGTTTGTGTTGACAATGAGC-3'	5'-TGATGCAAATTCATGAGGTA-3'
$Wnt1^{Cre}$	5'-CAGCGCCGCAACTATAAGAG-3'	5'-CATCGACCGGTAATGCAG-3'

Setd2: SET-domain-containing 2

1.2.3　免疫组织化学染色检测牙胚Setd2表达　选取经基因型鉴定筛选获得的实验组与对照组E13.5、E15.5、E18.5小鼠胚胎头部(每组每个时间点3只小鼠),脱矿,脱水,石蜡包埋,切片。石蜡切片60 ℃烤片2 h,脱蜡入水,PBS冲洗。胃酶修复30 min,PBS再次冲洗;按照免疫组化试剂盒相关步骤进行后续操作:内源性过氧化物酶阻断剂37 ℃孵育20 min,PBS冲洗;非特异性染色阻断剂

表2　PCR扩增程序
Table 2　PCR amplification programs

Genotype	Program
$Setd2^{flox/flox}$	95 ℃, 5 min; 35 cycles (95 ℃, 30 s; 53 ℃, 30 s; 72 ℃, 30 s); 72 ℃, 5 min; 10 ℃, hold
$Wnt1^{Cre}$	95 ℃, 5 min; 35 cycles (95 ℃, 30 s, 60 ℃, 30 s, 72 ℃, 30 s); 72 ℃, 7 min; 10 ℃, hold

Setd2: SET-domain-containing 2

37 ℃孵育1 h；去除阻断剂，滴加Setd2一抗（1∶200），同时设置滴加PBS的组别作为阴性对照，4 ℃湿盒孵育过夜，PBS冲洗；生物素标记的羊抗兔IgG聚合物37 ℃孵育1 h，PBS冲洗；链霉菌抗生素蛋白-过氧化物酶37 ℃孵育20 min，PBS冲洗。其后配置DAB显色剂滴加于组织，显色后使用PBS终止；滴加苏木素衬染，流水冲洗反蓝[20]；梯度乙醇脱水后，二甲苯透明，中性树胶封片。使用数字病理切片扫描仪对切片进行扫描观察，阳性信号表现为棕黄色颗粒。

1.2.4　苏木素-伊红（hematoxylin and eosin，HE）染色观察牙胚形态　石蜡切片60 ℃烤片2 h后，脱蜡入水，PBS冲洗。依次使用苏木素及伊红染色，梯度乙醇脱水，二甲苯透明，中性树胶封片[21]。使用数字病理切片扫描仪完成切片扫描后，通过Case Viewer软件进行组织形态学观察，并使用ImageJ软件完成牙胚横截面积测量与细胞定量分析。

1.2.5　肾囊膜培养实验观察牙齿形态　采用二氧化碳过量吸入安乐死法处死妊娠E14.5的雌性小鼠3只后，取出小鼠胚胎，分离下颌第一磨牙牙胚暂存于预冷的PBS，同时剪取尾部组织进行基因型鉴定。以8~10周龄C57BL/6J小鼠为受体，移植经基因型鉴定筛选获得的实验组与对照组牙胚各3枚分别至小鼠肾被膜下，每只小鼠左侧肾囊膜植入1枚实验组牙胚，右侧肾囊膜植入1枚实验组牙胚[22]。培养4周后，收集肾下移植物，观察分析。

1.2.6　免疫荧光染色检测牙胚相关蛋白表达　石蜡切片60 ℃烤片2 h，脱蜡入水，PBS冲洗；37 ℃温箱胃酶修复30 min，PBS冲洗；滴加3%牛血清白蛋白（bovine serum albumin，BSA），37 ℃湿盒封闭1 h；去除封闭液，分别滴加H3K36me3一抗（1∶200）和Ki67一抗（1∶200），4 ℃湿盒孵育过夜，含吐温-20的PBS（PBS with Tween-20，PBST）冲洗；滴加按比例稀释后的荧光二抗（1∶200），37 ℃孵育1 h，PBST冲洗；滴加含DAPI的封片剂封片[23]。正置荧光显微镜下观察并拍摄相关蛋白在小鼠牙胚间充质细胞中的荧光定位与表达强度，阳性信号为细胞核内特异性红色荧光。

1.2.7　TUNEL染色检测细胞凋亡水平　石蜡切片60 ℃烤片2 h，脱蜡入水，PBS冲洗；滴加蛋白酶K，37 ℃湿盒孵育20 min，PBS冲洗；滴加TdT平衡缓冲液，37 ℃湿盒平衡20 min；滴加对应标记工作液，37 ℃湿盒避光孵育60 min，PBS冲洗；滴加含DAPI的封片剂封片。正置荧光显微镜下观察并拍摄小鼠牙胚间充质区域凋亡细胞的分布，凋亡阳性细胞呈现细胞核内特异性绿色荧光。

1.3　统计学分析

本研究所有实验均独立重复至少3次。实验数据以均数 ± 标准差（$\bar{x} \pm s$）表示，采用GraphPad Prism软件（9.5.0）进行统计学分析。采用双因素方差分析（two-way ANOVA），事后采用Sidak检验进行同一时间点的组间两两比较。$P < 0.05$为差异有统计学意义。

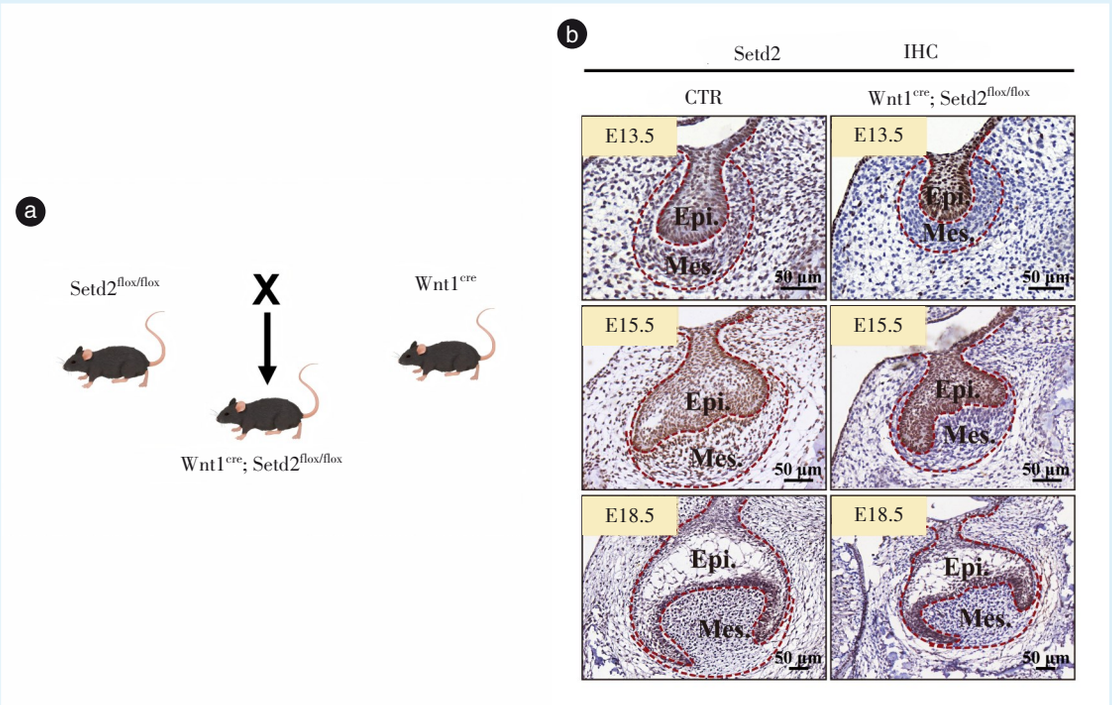
2　结　果

2.1　$Wnt1^{Cre}$；$Setd2^{flox/flox}$小鼠的构建与验证

通过Cre-LoxP系统将$Wnt1^{Cre}$小鼠与$Setd2^{flox/flox}$小鼠交配繁育，PCR基因型鉴定结果显示，实验组表现为$Setd2^{flox/flox}$纯合子单条带（266 bp）及$Wnt1^{Cre}$特征性单条带，对照组仅表现为$Setd2^{flox/flox}$纯合子单条带（266 bp）；筛选获得颅神经嵴来源间充质细胞中Setd2特异性敲除的实验组（$Wnt1^{Cre}$；$Setd2^{flox/flox}$）及Setd2未敲除的对照组（$Setd2^{flox/flox}$）（图1a）。纯合小鼠出生后死亡，因此选取E13.5、E15.5、E18.5的小鼠下颌第一磨牙切片进行免疫组织化学染色。结果显示，Setd2在对照组小鼠牙胚间充质中呈阳性表达，而在$Wnt1^{Cre}$；$Setd2^{flox/flox}$小鼠牙胚间充质细胞中被完全敲除，表明条件性敲除模型的成功构建（图1b）。

2.2　$Wnt1^{Cre}$；$Setd2^{flox/flox}$小鼠牙胚变小

对E13.5、E15.5、E18.5对照组小鼠和实验组小鼠的下颌第一磨牙切片进行HE染色观察，结果显示实验组牙胚发育时序未受明显影响，仍经历蕾状期、帽状期至钟状期的牙齿早期形态发生过程。



a: schematic of the breeding strategy to generate Wnt1^{Cre}; Setd2$^{flox/flox}$ mice. Setd2$^{flox/flox}$ mice were crossed with Wnt1^{Cre} mice to obtain the offspring with conditional knockout of Setd2 in cranial neural crest-derived cells. b: immunohistochemical staining of Setd2 in the first mandibular molar germs from control and Wnt1^{Cre}; Setd2$^{flox/flox}$ mice at E13.5 (bud stage), E15.5 (cap stage), and E18.5 (bell stage). The tooth germ is composed of dental epithelium (enamel organ) and dental mesenchyme (including dental papilla and dental follicle). The red dashed lines outline the dental epithelium and dental mesenchyme; the tissue outside the dashed lines is the maxillofacial connective tissue surrounding the tooth germ (non-tooth germ tissue). The brown granules represent positive Setd2 expression: robust Setd2 positivity was detected in both the dental epithelium and mesenchyme of control tooth germs across all examined developmental stages; in the experimental group, Setd2 expression was retained exclusively in the dental epithelium, with complete loss of positive signal in the dental mesenchyme, confirming the specific knockout of Setd2 in the dental germ mesenchymal cells of Wnt1^{Cre}; Setd2$^{flox/flox}$ mice. Experimental mice (Wnt1^{Cre}; Setd2$^{flox/flox}$) were generated by crossing Wnt1^{Cre} mice with Setd2$^{flox/flox}$ mice, resulting in specific knockout of Setd2 in dental germ mesenchymal cells. Control mice (CTR) were littermates with Setd2$^{flox/flox}$ mice. IHC: immunohistochemical; E: embryonic day; Epi.: epithelium; Mes.: mesenchyme; Setd2: SET-domain-containing

Figure 1　Generation and validation of Wnt1^{Cre}; Setd2$^{flox/flox}$ mice

图1　Wnt1^{Cre}; Setd2$^{flox/flox}$小鼠的构建与验证

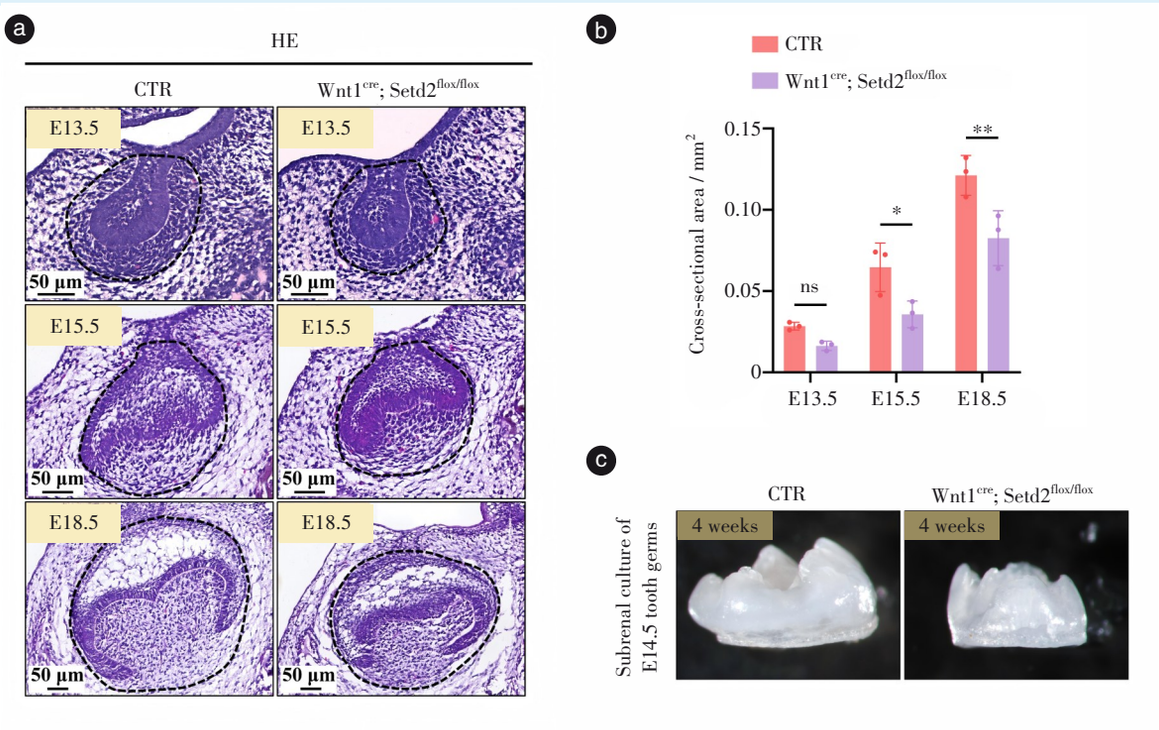
对牙胚横截面面积进行定量分析发现，E13.5时实验组与对照组小鼠牙胚面积差异无统计学意义，E15.5时实验组牙胚面积小于对照组（$P < 0.05$），且该差异持续至E18.5并进一步增大（$P < 0.01$）（图2a、2b）。为排除体内整体发育微环境的干扰，取出E14.5对照组和实验组小鼠下颌第一磨牙牙胚进行肾囊膜培养，培养4周后体式显微镜观察显示，实验组牙胚发育形成的牙齿体积显著小于对照组，而牙尖数量及形态未出现明显异常（图2c）。以上结果表明，牙胚间充质细胞中Setd2的特异性敲除不影响牙齿早期发育的形态发生进程及时序调控，但会显著抑制牙胚的体积生长，最终导致牙胚发育偏小。

2.3　Setd2的条件性敲除导致牙胚间充质细胞凝聚增加

对E13.5、E15.5对照组小鼠和实验组小鼠下颌第一磨牙HE染色切片进行间充质区域的细胞数量及区域面积定量分析，结果显示实验组下颌第一磨牙牙胚间充质细胞数量及区域面积低于对照组小鼠（图3a、3b），而间充质细胞密度则显著高于对照组（E13.5，$P < 0.05$；E15.5，$P < 0.001$）（图3c）。以上结果表明，Setd2在颅神经嵴来源细胞中的条件性敲除会导致间充质细胞凝聚增加，影响牙胚正常发育。

2.4　Setd2的条件性敲除导致牙胚间充质细胞凋亡增加

为进一步探究Wnt1^{Cre}; Setd2$^{flox/flox}$小鼠牙胚间充质细胞发生变化的机制，对E13.5、E15.5对照组



a: representative HE staining images of the first mandibular molar germs from control and Wnt1^{Cre}; Setd2$^{flox/flox}$ mice at E13.5 (bud stage), E15.5 (cap stage), and E18.5 (bell stage). The black dashed lines outline the boundaries of the tooth germs. b: quantitative analysis of cross-sectional area about tooth germs based on HE stained sections. n = 3. Two-way ANOVA showed significant main effects of genotype (F = 25.71, P < 0.001) and embryonic stage (F = 79.29, P < 0.001), with no significant interaction between the two factors (F = 2.196, P = 0.154). Post hoc Sidak test showed that: ns (not significant), *P < 0.05, **P < 0.01. c: representative images of subrenal culture of the first mandibular molar germs from control and Wnt1^{Cre}; Setd2$^{flox/flox}$ mice after 4 weeks of transplantation. The tooth volume of the experimental group was significantly smaller than that of the control group, with no obvious abnormality in cusp number and morphology. Experimental mice (Wnt1^{Cre}; Setd2$^{flox/flox}$) were generated by crossing Wnt1^{Cre} mice with Setd2$^{flox/flox}$ mice, resulting in specific knockout of Setd2 in dental germ mesenchymal cells. Control mice (CTR) were littermates with Setd2$^{flox/flox}$ mice. HE: hematoxylin and eosin; E: embryonic day; Setd2: SET-domain-containing 2

Figure 2　Conditional knockout of Setd2 in dental germ mesenchymal cells inhibits tooth germ development

图2　Setd2在牙胚间充质细胞中的条件性敲除抑制牙胚发育

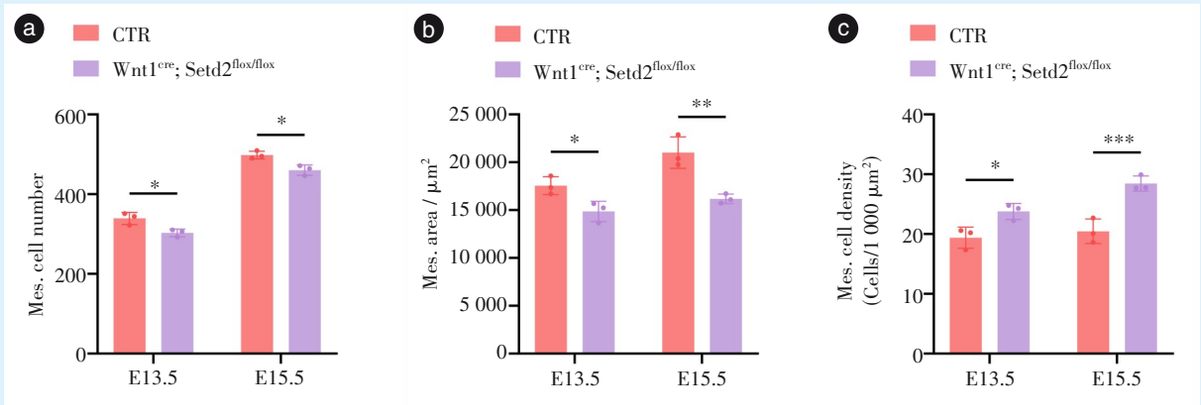
小鼠和实验组小鼠的下颌第一磨牙牙胚切片进行免疫荧光染色。Ki67染色结果显示，实验组Ki67阳性细胞比例与对照组相比差异无统计学意义（E13.5，P=0.694；E15.5，P=0.503），提示Setd2敲除对牙胚间充质细胞的细胞分裂比例无明显影响（图4a）。TUNEL染色结果显示，Setd2条件性敲除后，实验组小鼠牙胚间充质细胞中TUNEL阳性细胞比例显著高于对照组（E13.5，P < 0.000 1；E15.5，P < 0.001），表明Setd2的条件性敲除可导致Wnt1^{Cre}; Setd2$^{flox/flox}$小鼠牙胚间充质细胞凋亡水平增加（图4b）。

2.5　H3K36me3在Wnt1^{Cre}; Setd2$^{flox/flox}$小鼠牙胚间充质细胞中表达缺失

H3K36me3是Setd2介导的主要组蛋白修饰。免疫荧光结果显示，E13.5、E15.5、E18.5对照组小鼠下颌第一磨牙牙胚中，H3K36me3在牙胚上皮及间充质中呈强阳性表达；而在Wnt1^{Cre}; Setd2$^{flox/flox}$小鼠中，H3K36me3在牙胚上皮中仍呈阳性表达，在牙胚间充质细胞中表达则显著缺失，仅在少量非颅神经嵴来源的间充质细胞中可见残留阳性信号（图5）。

3　讨　论

Setd2自被发现以来，其生物学功能相关研究已覆盖肿瘤发生[24]、干细胞稳态维持[25]、组织器官发育[26]等多个领域。现有研究表明，Setd2介导的H3K36me3修饰在骨髓间充质细胞分化[27-28]、造血干细胞自我更新[29]等过程中发挥不可或缺的作用。此外，Setd2功能缺失常与组织发育异常及疾病发生相关，其突变可导致肿瘤细胞恶性增



Quantitative analysis of dental germ mesenchymal cells in the first mandibular molar germs from control and Wnt1^{Cre}; Setd2$^{flox/flox}$ mice at E13.5 and E15.5 (Analyzed by ImageJ software). a: total mesenchymal cell number in the first mandibular molar germs from control and Wnt1^{Cre}; Setd2$^{flox/flox}$ mice at E13.5 and E15.5. n = 3. b: the mesenchymal area of the first mandibular molar germs from control and Wnt1^{Cre}; Setd2$^{flox/flox}$ mice at E13.5 and E15.5. n = 3. c: mesenchymal cell density the first mandibular molar germs from control and Wnt1^{Cre}; Setd2$^{flox/flox}$ mice at E13.5 and E15.5. n = 3. Two-way ANOVA showed significant main effects of genotype (Mes. cell number: F = 28.24, P < 0.001; Mes. area: F = 34.07, P < 0.001; Mes. cell density: F= 42.62, P < 0.001) and embryonic stage (Mes. cell number: F = 517.2, P < 0.001; Mes. area: F = 13.87, P = 0.006; Mes. cell density: F = 9.255, P = 0.016), with no significant interaction between the two factors (Mes. cell number: F = 0.009, P = 0.926; Mes. area: F = 2.761, P = 0.135; Mes. cell density: F = 3.61, P = 0.094). Post hoc Sidak test showed that: *P < 0.05, **P < 0.01, ***P < 0.001. Experimental mice (Wnt1^{Cre}; Setd2$^{flox/flox}$) were generated by crossing Wnt1^{Cre} mice with Setd2$^{flox/flox}$ mice, resulting in specific knockout of Setd2 in dental germ mesenchymal cells. Control mice (CTR) were littermates with Setd2$^{flox/flox}$ mice. Mes.: mesenchymal; E: embryonic day; Setd2: SET-domain-containing 2

Figure 3　Conditional knockout of Setd2 leads to an increased condensation of dental germ mesenchymal cells in Wnt1^{Cre}; Setd2$^{flox/flox}$ mice

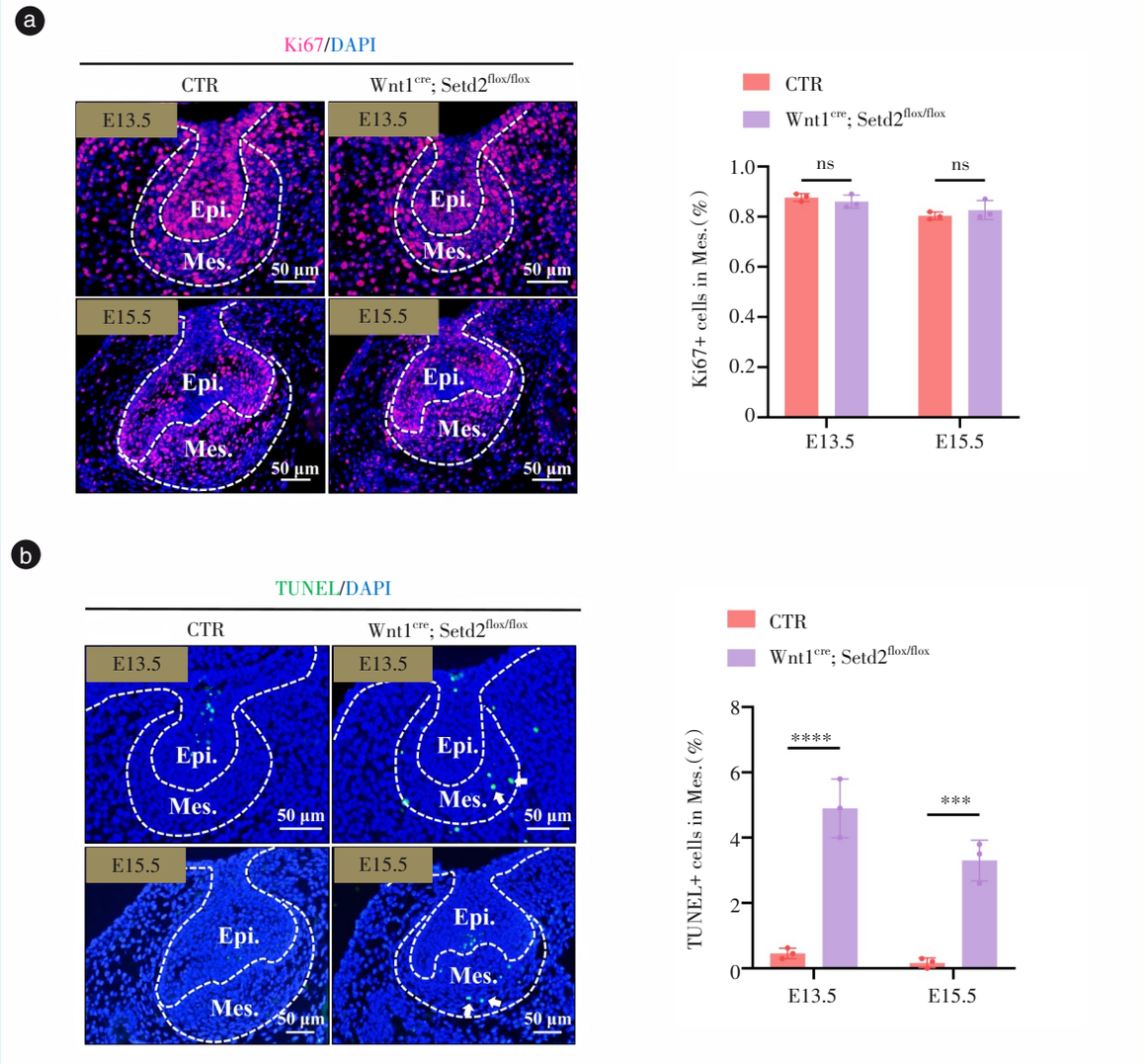
图3　Setd2的条件性敲除导致Wnt1^{Cre}；Setd2$^{flox/flox}$小鼠牙胚间充质细胞凝聚增加

殖[30-31]、骨骼发育畸形[32]等表型，提示该基因在组织器官发育中具有核心调控作用，但其在牙齿发育过程中的功能尚未明确。本研究通过Cre-LoxP系统构建了牙胚间充质细胞Setd2条件性敲除模型，首次揭示了该基因在牙齿早期发育中的关键作用，提出Setd2-H3K36me3轴是牙胚正常生长发育的重要调控通路，其功能缺失可导致牙胚体积缩小，为牙齿早期发育的表观遗传调控机制提供了新的实验证据。

牙齿发育依赖多种信号通路的持续双向通信以及转录因子的时序性精准调控[33-34]，两者协同介导细胞增殖速率调控、谱系定向分化、程序性凋亡启动[35]及细胞外基质的合成与分泌等关键生物学事件[36]。既往研究已证实，牙胚间充质在牙齿大小的调控中发挥核心作用[37-38]，本研究结果与这一结论高度契合，进一步阐明了牙胚间充质细胞功能异常是牙齿发育缺陷的重要诱因。值得注意的是，肾囊膜培养实验结果显示，Wnt1^{Cre}；Setd2$^{flox/flox}$实验组小鼠牙胚体外发育形成的牙齿虽体积显著小于对照组，但牙尖的数量及形态未发生明显改变，证实间充质中Setd2特异性调控牙胚的体积生长而非形态构建，为解析牙齿发育中大小与形态的差异化调控机制提供了新靶点。

本研究进一步探讨了Setd2敲除导致牙胚体积缩小的细胞学机制。Ki67染色结果显示，实验组与对照组牙胚间充质细胞分裂比例差异无统计学意义；而TUNEL染色结果显示，实验组细胞凋亡率显著升高。这表明Setd2条件性敲除导致的细胞凋亡增加是牙胚变小的核心原因，该结果与Setd2在其他组织中通过影响细胞凋亡调控细胞稳态的功能一致[39-40]。

Setd2作为一类甲基转移酶，其核心功能在于催化H3K36me3修饰，而组蛋白甲基化作为关键的表观遗传调控方式，可参与调控牙的发育及多种口腔疾病的发生发展进程[41]。本研究通过免疫荧光染色检测发现，在实验组小鼠的牙胚间充质细胞中H3K36me3表达几乎完全消失，而上皮细胞中仍有阳性表达。因此，Setd2在牙胚间充质中可能通过H3K36me3修饰影响细胞稳态，且其功能具有细胞特异性。本课题组前期已证实，Setd2在成牙

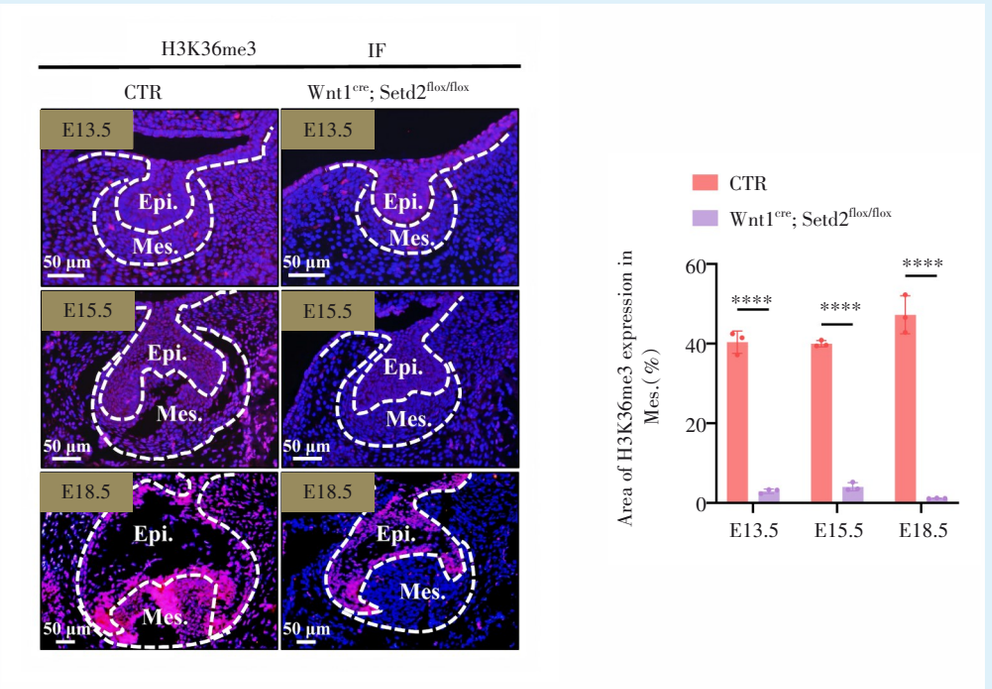


a: representative immunofluorescence staining images of Ki67 in the first mandibular molar germs from control and $Wnt1^{Cre}$; $Setd2^{flox/flox}$ mice at E13.5 and E15.5. The white dashed lines outline the dental epithelium and dental mesenchyme. The quantitative analysis (right) shows the percentage of Ki67-positive mesenchymal cells; no significant difference was observed, suggesting no obvious change in the proportion of cell division. n = 3. Two-way ANOVA showed a significant main effect of embryonic stage (F = 13.13, P = 0.007), but no significant main effect of genotype (F = 0.0512 , P = 0.827), and no significant interaction (F = 1.846, P = 0.211). Post hoc Sidak test showed that: ns (not significant). b: representative TUNEL staining images of the first mandibular molar germs from control and $Wnt1^{Cre}$; $Setd2^{flox/flox}$ mice at E13.5 and E15.5. The white dashed lines outline the dental epithelium and dental mesenchyme. The white arrows indicate TUNEL-positive signals. The quantitative analysis (right) shows the percentage of TUNEL-positive mesenchymal cells. n = 3. Two-way ANOVA showed significant main effects of genotype (F = 137.9, P < 0.001) and embryonic stage (F = 8.58, P = 0.019), with no significant interaction between genotype and embryonic stage (F = 4.122, P = 0.077). Post hoc Sidak test showed that: ns (not significant), ***P < 0.001, ****P < 0.000 1. Experimental mice ($Wnt1^{Cre}$; $Setd2^{flox/flox}$) were generated by crossing $Wnt1^{Cre}$ mice with $Setd2^{flox/flox}$ mice, resulting in specific knockout of Setd2 in dental germ mesenchymal cells. Control mice (CTR) were littermates with $Setd2^{flox/flox}$ mice. E: embryonic day; Epi.: epithelium; Mes.: mesenchyme; TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labeling; DAPI: 2-(4-Amidinophenyl)-6-indolecarbamidine dihydrochloride; Setd2: SET-domain-containing 2

Figure 4　Conditional knockout of Setd2 leads to increased apoptosis of dental germ mesenchymal cells in $Wnt1^{Cre}$; $Setd2^{flox/flox}$ mice

图4　Setd2的条件性敲除导致$Wnt1^{Cre}$; $Setd2^{flox/flox}$小鼠牙胚间充质细胞凋亡增加

本质细胞中高表达，通过调控Ⅺ型胶原蛋白α2链（collagen type XI alpha 2 chain，Col11a2）、信号素3E（semaphorin 3E，Sema3e）等基因转录激活AKT丝氨酸/苏氨酸激酶1（AKT serine/threonine kinase 1，



Representative IF staining images of H3K36me3 in the first mandibular molar germs from control and Wnt1^{Cre}; Setd2$^{flox/flox}$ mice at E13.5 (bud stage), E15.5 (cap stage), and E18.5 (bell stage). H3K36me3-specific positive signals were visualized as red fluorescence: H3K36me3 positivity was detected in both the dental epithelium and mesenchyme of control tooth germs across all examined developmental stages; in the experimental group, H3K36me3 expression was retained exclusively in the dental epithelium, with loss of positive signal in the dental mesenchyme. Cell nuclei were counterstained with DAPI and appeared blue. The white dashed lines mark the boundary between the tooth germ epithelium and mesenchyme. The quantitative analysis (right) of the percentage area of H3K36me3-positive signals in the dental mesenchyme of control and Wnt1^{Cre}; Setd2$^{flox/flox}$ mice at E13.5, E15.5, and E18.5 (analyzed by ImageJ software) confirmed the loss of H3K36me3 modification in the dental germ mesenchymal cells of the experimental group. n = 3. Two-way ANOVA showed a significant interaction effect between genotype and embryonic stage (F = 8.288, P = 0.006), no significant main effect of embryonic stage (F = 2.08, P = 0.168), and a highly significant main effect of genotype (F = 1 309, P < 0.001). Post hoc Sidak test showed that: ****P < 0.000 1. Experimental mice (Wnt1^{Cre}; Setd2$^{flox/flox}$) were generated by crossing Wnt1^{Cre} mice with Setd2$^{flox/flox}$ mice, resulting in specific knockout of Setd2 in dental germ mesenchymal cells. Control mice (CTR) were littermates with Setd2$^{flox/flox}$ mice. IF: immunofluorescence; DAPI: 2-(4-Amidinophenyl)-6-indolecarbamidine dihydrochloride; E: embryonic day; Epi.: epithelium; Mes.: mesenchyme; Setd2: SET-domain-containing 2; H3K36me3: trimethylation of lysine 36 on histone H3

Figure 5　H3K36me3 expression is lost in the dental germ mesenchyme cells of Wnt1^{Cre}; Setd2$^{flox/flox}$ mice

图5　H3K36me3在Wnt1^{Cre}; Setd2$^{flox/flox}$小鼠牙胚间充质细胞中表达缺失

AKT1）信号通路，维持牙本质矿化过程[16]。该研究聚焦于牙齿发育后期的矿化阶段，而本研究则探究了Setd2缺失在牙齿早期发育中的作用及相关机制，完善了Setd2-H3K36me3轴在牙齿发育不同阶段的作用机制。这一研究不仅揭示了Setd2调控牙齿发育的表观遗传基础，更为后续深入探析相关分子机制提供了关键参考依据。

本研究采用小鼠模型进行机制探究，虽然小鼠牙发育与人类高度相似，但物种差异仍可能导致研究结果的临床转化受限，未来需通过人牙胚组织样本验证Setd2及H3K36me3的表达模式与功能相关性，为临床转化提供更坚实的实验依据。此外，本研究尚未明确Setd2-H3K36me3轴调控细胞凋亡的下游靶基因及核心信号通路，相关分子机制仍有待通过多组学联合分析及功能验证实验进一步深入挖掘。

综上所述，本研究发现牙胚间充质细胞中Setd2特异性缺失会导致牙胚体积减小、间充质细胞凝聚异常及凋亡增加，这一过程可能受H3K36me3修饰水平调控。这一发现进一步拓展了Setd2在牙齿发育不同阶段的功能谱，提示该基因可能贯穿牙胚早期形态发生至后期矿化成熟的全过程，为临床牙发育异常的病因研究提供了新的分子靶点，也为相关疾病的基因诊断提供了理论依据，有助于推动先天性口腔疾病精准医疗的发展。

【Author contributions】 Sheng J performed the experiments, analyzed the data and drafted the article. Niu JX performed the experiments and revised the article. Yuan GH designed the study and revised the article. All authors read and approved the final manuscript as submitted.

【Ethics Statement】 All animal experiments were conducted in accordance with the national Regulations for the Administration of Laboratory Animals and the Guidelines for Ethical Review of Laboratory Animal Welfare. The study protocol was approved by the Ethics Committee of the Animal Experiment Center of Wuhan University (Approval No. WP20220046).

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【Competing interests】 All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from the National Natural Science Foundation of China (No. 82170914 and No. 82370913) for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

【Data availability statement】 The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author upon reasonable request.

【Generative AI statement】 The authors declared that generative AI was not used in the creation of this manuscript.

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