MBD3调节干细胞多能性和重编程机制的研究进展

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摘要 MBD3(methyl CpG binding domain 3)是甲基CpG结合域蛋白家族的成员之一, 也是NuRD(nucleosome remodeling and deacetylase complex)的核心亚单位之一。MBD3蛋白可以结合非甲基化DNA, 通过MBD蛋白结构域或与NuRD结合发挥作用。MBD3通过参与调节染色质结构和激活转录过程, 调节胚胎干细胞的多能性和谱系分化, 对于胚胎发育和分化十分关键。MBD3在体细胞和神经干细胞重编程中也发挥着重要作用。此外, 在缺氧环境下MBD3还能影响细胞代谢调控。该文围绕MBD3诱导DNA去甲基化、调节染色质结构、调控转录、调节胚胎干细胞的多能性和谱系分化、在重编程中的作用以及缺氧环境中的对细胞代谢的影响等展开论述, 以期为多能干细胞的表观遗传研究及重编程技术的优化提供参考。

关键词 MBD3; DNA甲基化; 染色质结构; 转录调控; ESCs多能性; 重编程; 代谢

Progress on the Mechanism of MBD3 Regulating the Pluripotency of Stem Cells and Reprogramming

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Abstract MBD3 (methyl CpG binding domain 3) is a member of the MBD (methyl CpG binding domain) protein family and a core subunit of the NuRD (nucleosome remodeling and deacetylase complex). The MBD3 protein can bind to the unmethylated DNA, functioning through the MBD domain or in combination with NuRD. MBD3 is a key protein for embryonic development and differentiation due to involving in scaffolding chromatin structure and activating transcription processes to regulate the pluripotency and lineage differentiation of embryonic stem cells. MBD3 also plays an important role in the somatic cell and neural stem cell reprogramming. Furthermore, MBD3 affects cell metabolism under hypoxic environment. This paper highlights the roles of MBD3 in DNA demethylation, chromatin structure modelling, transcription regulation, pluripotency maintaining and lineage differentiation of embryonic stem cells, the somatic cell reprogramming and the effect on cell metabolism under hypoxia, aiming to provide a reference for the epigenetic research of embryonic stem cells and the optimization of reprogramming technology.

Keywords MBD3; DNA methylation; chromatin structure; transcription regulation; ESCs pluripotency; reprogramming; metabolism

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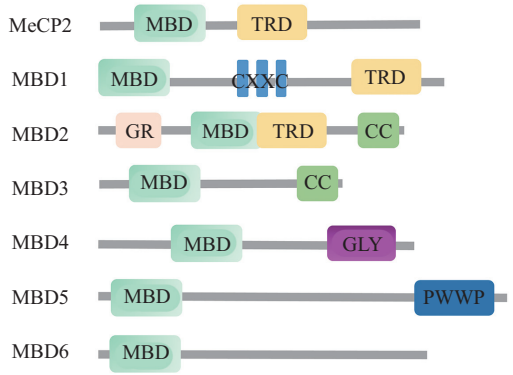
MBD(methyl-CpG-binding domain)蛋白家族与DNA甲基化介导的转录调控密切相关, 目前共发现11个成员, 首先发现的是MeCP2, 它含有N-端的MBD结构域和C-端的转录抑制结构域(transcriptional repression domain, TRD)。随后通过保守的MBD结构域同源性比较先后确定了MBD1~MBD6的蛋白结构(图1和表1), 后来发现的4个成员SETDB1、SETDB2、BAZ2A和BAZ2B则含有类似MBD的结构域[1-3]。

在整个MBD家族中, 缺失TRD结构域的MBD3分子量最小[4], 与MBD2的序列同源性高达70%[4-5], 两者均起源于无脊椎动物的MBD2/3蛋白, 但功能截然相反。两者竞争性地作为核小体重塑和去乙酰化复合物(nucleosome remodeling and deacetylase complex, NuRD)的核心亚基, 且MBD3/NuRD与MBD2/NuRD功能相斥[4,6]。NuRD包含由HDAC1/2、MTA1/2/3和RBBP4/7蛋白组成的去乙酰化酶亚复合物以及由CHD3/4/5、GATAD2A/B和CDK2AP1蛋白组成的重塑亚复合物。MBD2和MBD3将这两部分亚复合物连接成一个整体, 进而使表观遗传修饰的3个主要分支——组蛋白去乙酰化、核小体重塑和选择性识别甲基化DNA有机地结合于NuRD这一个大的复合物上(图2和表2)[7]。由于上述亚基都有不同的同源物, 再加上MBD2和MBD3各有三种亚型, 因此形成的NuRD有多种亚基组合, 在不同的细胞或组织中执行不同的功能[1,8]。



MBD(methyl-CpG-binding domain): 甲基CpG结合域; TRD(transcriptional repression domain): 转录抑制域; GR(glycine-arginine rich domain): 富含甘氨酸–精氨酸的结构域; CC(coiled-coil domain): 卷曲螺旋结构域; CXXC(zinc finger-Cys-x-x-Cys domain): 锌指-Cys-x-x-Cys域; GLY(glycosylase): 糖基化酶; PWWP(Pro-Trp-Trp-Pro): 脯氨酸–色氨酸–色氨酸–脯氨酸。

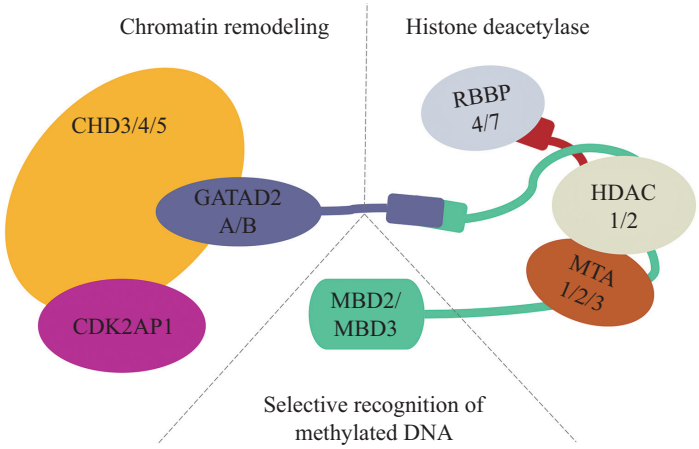
图1 MBD家族成员及其结构域的示意图(根据参考文献[1]修改)

Fig.1 Schematic overview of the MBD family members and their domains (modified from reference [1])

表1 MBD家族成员及其结构域的功能

Table 1 Functions of the MBD family members and their domains

简称 Abbreviations	全称 Full names	功能 Functions
MeCP2	Methyl-CpG binding protein 2	MeCP2 binds to methylated DNA, which is related to transcriptional inhibition
MBD1-6	Methyl-CpG binding domain protein 1-6	MBD1/2/4 bind to methylated DNA, which is related to transcriptional inhibition; MBD5/6 does not bind to methylated DNA, which is related to heterochromatin; MBD3 binds to unmethylated DNA, which is related to transcription activation
MBD	Methyl-CpG-binding domain	MBD binds to methylated CpGs
TRD	Transcriptional repression domain	TRD inhibits transcription
CXXC	Zinc finger-Cys-x-x-Cys domain	CXXC regulates histone and DNA methylation
GR	Glycine-arginine rich domain	Substrate of arginine methyltransferase
CC	Coiled-coil domain	The super secondary structure is formed by the intertwining of α helices, related to MBD2-dependent DNA methylation-mediated gene silencing
GLY	Glycosylase	GLY identifies and removes modified bases from sugar phosphate DNA strands by physical or chemical means
PWWP	Pro-Trp-Trp-Pro	PWWP recognizes histone lysine methyl group, binds histones and DNA, helps to bind nucleosomes and chromatin localization



CHD3/4/5(chromodomain helicase DNA binding protein 3/4/5): 染色体域解旋酶DNA结合蛋白; GATAD2A/B(GATA zinc finger domain 2A/B): GATA锌指结构域2A/B; CDK2AP1(cyclin-dependent kinase 2 associated protein 1): 细胞周期蛋白依赖性激酶2相关蛋白1; RBBP4/7(retinoblastoma binding protein 4/7): 视网膜母细胞瘤结合蛋白4/7; HDAC1/2(histone deacetylase 1/2): 组蛋白脱乙酰酶1/2; MTA1/2/3(metastasis tumor-associated protein 1/2/3): 转移瘤相关蛋白1/2/3; MBD2/3(methyl-CpG binding domain protein 2/3): 甲基CpG结合域蛋白2/3。

图2 NuRD的示意图(根据参考文献[7]修改)

Fig.2 Schematic overview of the NuRD (modified from reference [7])

表2 NuRD及其核心亚基的功能

Table 2 Functions of the NuRD and its core subunits

简称 Abbreviations	全称 Full names	功能 Functions
NuRD	Nucleosome remodeling and deacetylase complex	NuRD has the function of nucleosome remodeling, histone deacetylation and selective recognition of methylated DNA
CHD3/4/5	Chromodomain helicase DNA binding protein 3/4/5	CHD3/4/5 has activity of ATP-dependent chromatin remodeling
GATAD2A/B	GATA zinc finger domain 2A/B	GATAD2A/B interacts with histone tails
CDK2AP1	Cyclin-dependent kinase 2 associated protein 1	CDK2AP1 promotes the recruitment of NuRD at specific sites, replaces SWI/SNF and inhibits transcription
MBD2/3	Methyl-CpG binding domain protein 2/3	MBD2/3 links deacetylase subcomplex and remodeling subcomplex
RBBP4/7	Retinoblastoma binding protein 4/7	RBBP4/7 collaborates with HDAC to participate in the process of chromatin recruitment complex
HDAC1/2	Histone deacetylase 1/2	HDAC1/2 catalyzes lysine deacetylation and mediate gene inhibition
MTA1/2/3	Metastasis tumor-associated protein 1/2/3	MTA1/2/3 plays a key structural role in the formation of the core subcomplex of histone deacetylase composed of MTA, HDAC and RBBP proteins

MBD2有三种亚型, 分别是全长的MBD2A、缺失N-端富含甘氨酸和精氨酸(glycine-arginine rich domain, GR)重复序列的MBD2B以及在睾丸中特异性表达的MBD2C。MBD2与大多数MBD家族蛋白相似, 可以结合甲基化DNA, 通过招募NuRD抑制靶基因转录[9-10]。MBD2不是胚胎发育所必需的, 敲除*Mbd2*的小鼠虽然有发育缺陷但不会导致胚胎死亡[1,4]。但MBD3不同, 尽管它具有MBD结构域, 却是家族中唯一结合非甲基化DNA的蛋白[11], 因为它的MBD结构域中两个关键氨基酸残基分别由Lys30和Tyr34改变为His30和Phe34[12], 于是MBD3结合甲基化CG(methylated CG, mCG)位点的能力减弱, 改为优先结合羟甲基化CG(hydroxymethylated CG, hmCG)位点[5,13], 这使MBD3的生物功能相应地发生了改变, 转为与基因转录激活相关。MBD3也有三种亚型, 分别是MBD3A、MBD3B和MBD3C, 均在胚胎干细胞中特异表达, 其中MBD3B是存在于胚胎干细胞中的主要亚型[14]。MBD3对于胚胎发育至关重要, 敲除*Mbd3*会导致小鼠胚胎死亡[4,15]。

本文结合近十年来的研究结果, 围绕MBD3诱

导DNA去甲基化、调节染色质结构、调控转录、调节胚胎干细胞的多能性和谱系分化、在体细胞及神经干细胞重编程中的作用以及影响缺氧环境中的细胞代谢这些生物学功能进行概述和探讨。

1 MBD3在调节转录中的功能

1.1 MBD3诱导DNA去甲基化

在细胞中DNA甲基化与去甲基化呈现周期性动态变化[16], DNA的甲基化由DNA甲基化酶(DNA methyltransferase, DNMT)家族实现。DNA去甲基化分为主动和被动两种, DNA主动去甲基化过程由TET(ten-eleven translocation)家族、活化诱导脱氨酶/载脂蛋白B mRNA编辑酶复合物(activation-induced cytidine deaminase/apolipoprotein B mRNA-editing enzyme complex, AID/APOBEC)以及胸腺嘧啶DNA糖基化酶(thymine DNA glycosylase, TDG)介导完成。目前认为, MBD3参与DNA主动去甲基化, 因为它在细胞核中的扩散特性与DNA主动去甲基化有关[17], 且偏向于在未甲基化的中等CpG密度且有NF-Y转录因子结合位点的启动子区域, 诱导基因组DNA去甲基化[18]。

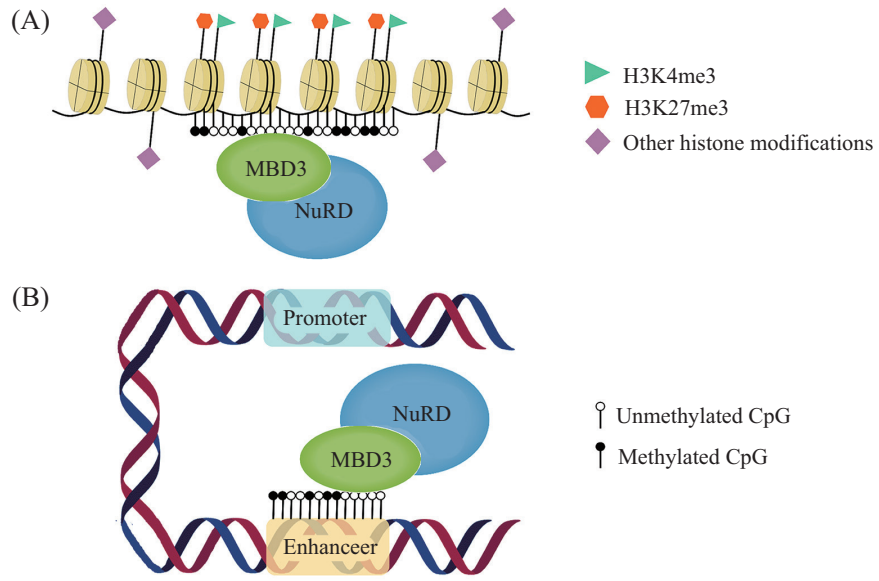
以rRNA启动子为例, MBD3在核仁中与上游结合因子共定位, 与未甲基化的rRNA启动子结合, 使该区域维持在未甲基化状态, 保持其高转录活性[18-19]; 敲低*Mbd3*使该区域的甲基化DNA增多, RNA聚合酶I(RNA polymerase I, Pol I)募集减少, 导致pre-rRNA的转录水平降低[19]。但目前对于MBD3是如何诱导DNA去甲基化的以及MBD3是否能够诱导由RNA聚合酶II(RNA polymerase II, Pol II)进行转录的基因去甲基化仍是未知的。

最近发现的MBD3L2(MBD3-like 2 protein), 与MBD3的区别仅在于缺少MBD结构域, 为研究MBD3提供了参考。MBD3L2在TET酶介导的5-甲基胞嘧啶(5-methylcytosine, 5mC)氧化生成5-羟甲基胞嘧啶(5-hydroxymethyl-cytosine, 5hmC)的过程中, 能够增强TET2与特定靶点之间的亲和力, 特异性促进TET2蛋白的酶活性, 但对TET1和TET3无效[9,20], 同时招募MBD3L2和TET2的区域多数是与癌症及细胞代谢调控相关基因且5mC水平较低的启动子元件[20]。此外, MBD3与DNMT1在细胞周期中同时转录, MBD3制衡DNMT1的作用, 诱导细胞周期相关基因的启动子CpG岛(CpG islands, CGIs)DNA去甲基化, 以防DNMT1对细胞周期相关基因过度甲基化[16]。最近有研究证明, MBD3在神经发育过程中能与常染色质中积累的5hmC共定位并招募H3K4me2(histone H3 dimethylated at lysine 4)和Pol II, 介导RNA转录[21], 但是MBD3是否能通过诱导Pol II转录基因去甲基化介导转录仍未知。

1.2 MBD3调控转录过程

一般认为, MBD蛋白家族是转录抑制因子, 介导异染色质形成和转录沉默[1,22]。以MBD2为例, MBD2/NuRD将常染色质组蛋白修饰转化为抑制性组蛋白修饰, 导致染色质的开放状态转变为紧密状态, 从而介导甲基化CpG岛区域或侧翼区域的染色质浓缩而使转录沉默[3,23-24]。MBD3调节染色质结构的模式完全不同于MBD2, MBD3的C末端酸性区域富含天冬氨酸/谷氨酸, 与Z-DNA(左旋型DNA)竞争性结合Zα(结合Z-DNA的蛋白结构域), 但MBD3的C末端结构域与MBD结构域形成异二聚体, 削弱MBD3同Z-DNA之间的相互作用, 增强了Z-DNA与Zα的亲和力, 从而使不能并入核小体的Z-DNA构象稳定, 使转录起始位点附近的核小体占据率降低, 为转录提供开放的染色质环境, 从而增加Pol II的募集, 最终激活转录[7,25-26]。MBD3还能够通过诱导核小体重构, 进而改变其他转录因子的结合和基因表达, 但是核小体重构的结果是增加转录还是减少转录主要取决于遗传背景[7]。

利用染色体免疫共沉淀测序技术(chromatin immunoprecipitation followed by sequencing, ChIP-seq)在小鼠和人细胞水平上对MBD3进行的功能分析也验证了其调控转录的功能[1]。MBD3通过NuRD来调节靶基因表达, MBD3在活性基因富含CpG的启动子区富集, 优先定位于以H3K4me3(histone H3 trimethylated at lysine 4)标记的启动子区且在转录起始位点丰度最高, 但MBD3也在H3K27me3(histone H3 trimethylated at lysine 27)修饰的启动子处富集, 与转录起始位点处未甲基化的CGIs结合, 在一定水平上减轻基因沉默的程度, 进而维持转录的二价性[3,6,23,26-27](图3A)。MBD3还可以与增强子结合, 使增强子在三维空间中更接近启动子和基因体[26,28](图3B)。此外, 与MBD3结合的富含CpG的启动子以及活跃基因的增强子区域的DNA甲基化水平是动态转换的[16,28]。这种启动子周期性转换甲基化状态的模式很可能是某些启动子周期性转录过程的内在调节机制[1]。通常



A: MBD3调节基因的转录二价性; B: MBD3与增强子结合而促进基因转录。

A: MBD3 regulates the transcriptional bivalence of genes; B: MBD3 promotes the transcription of gene by binding to the enhancer.

图3　MBD3调控转录的机制

Fig.3　The mechanism of MBD3 regulating transcription

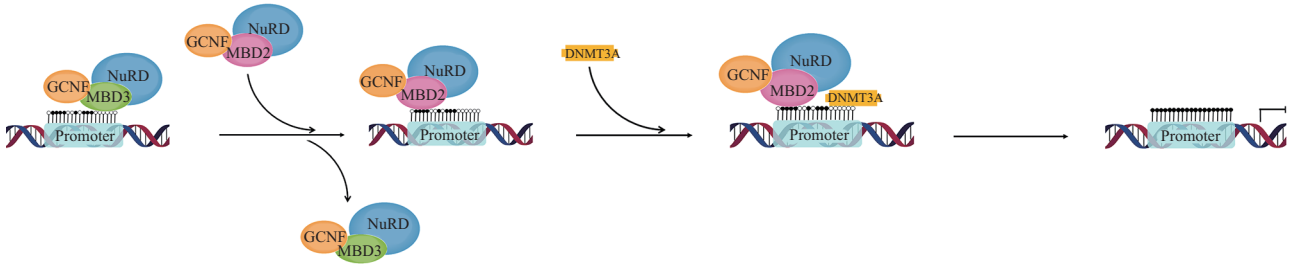


图4　ESCs谱系分化时*Oct4*基因沉默的机制

Fig.4　The mechanism of *Oct4* silencing during lineage differentiation of ESCs

情况下启动子甲基化与转录沉默相关, 但一些启动子可以同时保持甲基化状态和转录活性[29-30], 这些启动子的特殊情况是否与MBD3诱导DNA去甲基化相关还有待进一步验证。

2　MBD3调节ESCs的多能性和谱系分化

MBD3通过调节或抑制多能性相关基因的转录, 进而调节胚胎干细胞(embryonic stem cells, ESCs)的多能性和谱系分化。一方面, MBD3/NuRD是维持ESCs自我更新的核心转录因子(如OCT4和NANOG)转录所需的调控元件[31-34]。NuRD的核心亚单位CDK2AP1将MBD3/NuRD招募至小鼠ESCs的*Wnt*基因启动子区域, 从而在ESCs的多能性中发挥作用[31]。ESCs中表达的MBD3C还可以依靠独特的N-端50个氨基酸区域与组蛋白H3结合蛋白WDR5(WDTrp-Asp repeat domain 5)特异性相互作用, 间接在H3K4me3、染色质重塑和靶基因转录激活中发挥作用[8,35]。另一方面, ESCs中活跃增强子和启动子区的MBD3/NuRD也是限制多能性基因表达并实现谱系分化所必需的调节因子[36-38]。当ESCs进入特定的发育轨道即发育谱系发生时其多能性消失, 维持多能性的转录因子也随之沉默[14]。以转录因子OCT4为例, 它是通过生殖细胞核因子(germ cell nuclear factor, GCNF)实现基因沉默的, MBD3/NuRD通过将MBD结构域与GCNF结合从而被*Oct4*启动子招募, 启动基因抑制, 随后才能通过GCNF将MBD2招募到启动子区的甲基化CpG位点, 进一步维持基因沉默, 最后招募DNMT3A进行彻底的甲基化修饰, 实现基因的永久沉默(图4)[33]。在ESCs中敲减或敲除*Mbd3*时, 一些多能性基因(如*Oct4*和*Nanog*)能够维

持表达, 但无法进行谱系分化, 因为胚胎着床前表达的基因(如*Oct4*)不能被完全沉默[14-15,36,39-40]。这表明, MBD3对于维持ESCs的自我更新和多能性不是必要的, 但对于ESCs的分化和谱系发育是必需的。MBD3/NuRD能够启动*Oct4*基因抑制可能是因为MBD3在ESCs中和HDAC1共同结合在*Oct4*基因上, 从而介导*Oct4*的组蛋白去乙酰化, 辅助转录抑制过程, 从而促进ESCs的正常分化[41]。MBD3与CD-K2AP1的物理相互作用也参与*Oct4*的表观沉默, 通过促进*Oct4*启动子的甲基化下调ESCs分化过程中*Oct4*的表达[42]。此外, MBD3的三种亚型均能在小鼠的ESCs中表达, MBD3A、MBD3B和MBD3C虽然在结构上存在一定差异, 但都有相同的螺旋卷曲(coiled-coil, CC)结构域, 因此维持ESCs谱系限定的能力相同[14,43]。

3 MBD3在重编程中具有双重作用

3.1 MBD3阻碍体细胞重编程

在体细胞重编程产生诱导多能干细胞(induced pluripotent stem cells, iPSCs)的过程中会发生一系列如DNA甲基化和染色质重塑的表观遗传修饰改变[44], 重新获得具有干细胞特征的常染色质结构[45-46]。MBD3通过沉默多能性基因和维持正常体细胞增殖阻碍体细胞进行重编程。NuRD在重编程中发挥着重要的作用, 表现为下调NuRD的表达有利于重编程[45]。其中, MBD3是细胞获得多能性的主要障碍, 过表达*Mbd3*可使体细胞建立异染色质特征并沉默包括*Oct4*和*Nanog*在内的ESCs特异性标记基因, 从而抑制iPSCs的诱导过程[45]。反之, 沉默*Mbd3*能够消除多能性基因的转录抑制从而消除表观遗传记忆[47], 提高重编程效率, 促进iPSCs的形成[45]。这表明, MBD3/NuRD在发育过程中促进ESCs分化, 因此在重编程中减少其表达反而能促进体细胞恢复到多能干细胞状态[48-49]。RAIS等[50]研究证实，MBD3是细胞获得多能性的主要障碍。外胚层干细胞(epiblast stem cells, EpiSCs)在合适的培养条件下会自发地恢复为ESCs样细胞, 因此RAIS等选择这样的“二次”重编程系统, 发现MBD3缺失能够显著增强EpiSCs向ESCs逆转的效率[47], 并且几乎每个细胞都有可能产生ESCs样细胞[50-51]。此外, 敲除*Mbd3*也能促进原始生殖细胞向多能干细胞转化[50-51]。不仅如此, MBD3缺失能使大多数小鼠和人类体细胞在OCT4、SOX2、KLF4和C-MYC作用下重编程[50-51]。

在重编程的初始阶段细胞迅速诱导增殖以获得ESCs样细胞周期, 敲减*Mbd3*能够增强细胞增殖能力[47,52], 但完全敲除该基因会使体细胞无法增殖, 因而无法进行重编程[49-50,53-54]。因此, 在通过降低MBD3促进OCT4、SOX2、KLF4和C-MYC介导的重编程中, 应当注意只有在关键的重新编程早期时不完全敲除*Mbd3*的活性才能促进重编程[50,53]。而将*Mbd3*$^{-/-}$体细胞进行重编程则不会有促进效果[49-50,53]。究其原因, 细胞增殖是重编程早期阶段的重要过程[55], 重编程起始时的体细胞在MBD3完全耗尽后不能在体外继续增殖[54], 因而无法进入重编程, 这与很多通过不完全缺失染色质调节因子促进iPSCs生成相似[56-57]。此外, MOR等[53]证实, MBD3/NuRD对多能性的抑制作用能够通过GATAD2A进行干扰但不影响体细胞的增殖能力, 从而促进确定性重编程进程。

3.2 MBD3促进神经干细胞重编程

虽然MBD3/NuRD在体细胞重编程中起着关键的阻碍作用, 但是却能促进神经干细胞(neural stem cells, NSCs)的重编程进程。在小鼠的神经发生过程中, 神经前体细胞(neural precursor cells, NPCs)在适当的发育阶段对细胞外信号作出反应, 以启动特定细胞系的转录[58-59]。MBD3/NuRD通过抑制NPCs和神经元中的部分转录过程, 促进细胞系选择和分化, 但不指导神经干细胞NSCs的遗传谱系限定[59], 过表达*Mbd3*会阻断NPCs的神经元分化[60], NPCs中敲除*Mbd3*则导致神经发生过程中某些类型细胞分化缺陷[59]。MBD3也可以与Smek(suppressor of Mek null)相互作用调节自身稳定性, 阻断神经发生相关基因募集MBD3/NuRD, 从而促进皮质神经发生[60]。DOS SANTOS等[49]在重编程的不同时间点条件敲除*Mbd3*, 发现MBD3/NuRD在*Klf4*和*Nanog*介导的NSCs重编程过程中起关键作用, 是NSCs转变为重编程中间产物pre iPSCs以及iPSCs所必需的。

综上所述, 不同的重编程环境和不同的重编程系统, 使MBD3在转录因子介导的体细胞重编程过程中发挥着不同但至关重要的作用。此外, 在体细胞克隆胚胎水平上也证明了这一点, 例如猪体细胞核移植克隆胚胎中过表达*MBD3*能够提高囊胚率并增加囊胚的细胞数量, 同时降低*NANOG*、*OCT4*和*LINE1*的DNA甲基化, 使其接近猪体内受精胚胎的甲基化水平[15]。

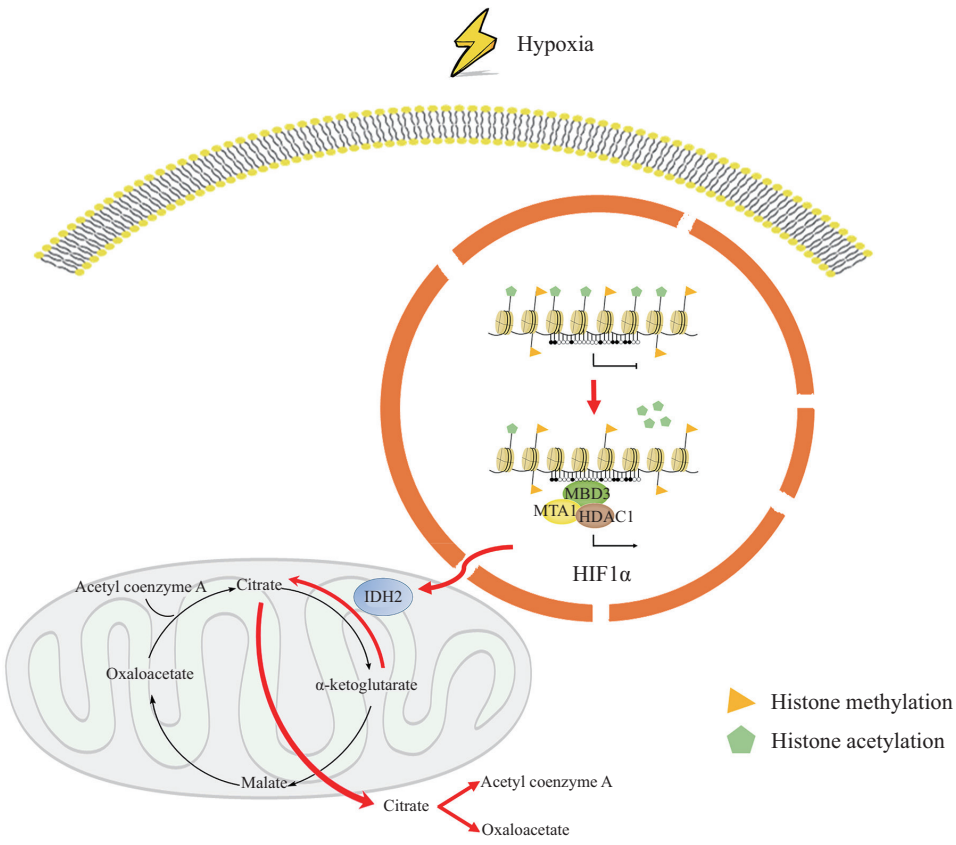


图5 MBD3影响缺氧环境中细胞代谢的机制

Fig.5 The mechanism of MBD3 affecting cell metabolism in hypoxic environment

4 MBD3影响缺氧环境中的细胞代谢

在常氧条件下, 由葡萄糖提供的乙酰辅酶A与草酰乙酸是柠檬酸盐的主要来源, 而谷氨酰胺则是三羧酸循环回补途径所必需的[61-62]。但在缺氧条件下, 与MBD3相关的MTA1招募HDAC1使低氧诱导因子(hypoxia inducible factor 1α, HIF1α)去乙酰化, 增强HIF1α的稳定性和转录活性, 从而调节HIF1α的反式激活功能[63]。HIF1α组成型表达后, 通过异柠檬酸脱氢酶2(isocitrate dehydrogenase 2, IDH2)促进谷氨酰胺衍生的α-酮戊二酸(α-ketoglutarate, αKG)还原羧化, 同时削弱谷氨酰胺氧化, 从而使谷氨酰胺向柠檬酸盐转化, 成为柠檬酸盐再生的主要来源。IDH2将谷氨酰胺衍生的αKG还原羧化形成异柠檬酸, 再异构为柠檬酸[61,64]。还原代谢产生的柠檬酸进一步产生Ac-CoA和OAA[62,65], 而Ac-CoA不仅是合成脂肪酸的原料[64,66], 也是组蛋白乙酰转移酶(histone acetyl transferase, HAT)的底物[66](图5)。

在缺氧环境中, p53、p21以及HIF1相互作用, 通过反馈机制共同调节细胞代谢[67]。*CDKN1A*(cyclin-dependent kinase inhibitor 1A)编码$p21^{Waf/Cip1}$, 而由原癌基因*Zbtb7*编码的原癌蛋白FBI-1(factor binding to the inducer of short transcripts of human immunodeficiency virus-1)能够抑制p53途径和CDKN1A表达。MBD3能够与FBI-1相互作用, 从而被招募到*CDKN1A*启动子中, 增强FBI-1对*CDKN1A*的转录抑制作用。具体地说, MBD3是先将NuRD-HDAC直接招募至FBI-1上, 再间接地将与NuRD-HDAC复合体、DNMTs和HP1(heterochromatin protein 1)相互作用的原癌蛋白Bcl-6辅阻遏物(BCL-6 corepressor, BCoR)也招募至FBI-1上, 不仅增强了FBI-1与BCoR的相互作用, 还增强了*CDKN1A*的甲基化抑制[68]。

5 结语与展望

MBD3作为MBD蛋白家族的重要成员, 在DNA去甲基化、核小体重塑、组蛋白修饰、维持ESCs自我更新与多能性、重编程以及细胞代谢等生物学过程中发挥着重要的调控功能, 逐渐成为表观遗传学领域的研究热点之一, 但目前仍有许多科学问题亟待解决, 如目前仅局限于研究人类和小鼠的MBD3蛋白, 其他哺乳动物中MBD3蛋白生物学功能的研

究极少。因此, MBD3相关的科研仍有很大的发展空间, 未来的研究可能揭示MBD3在细胞代谢中具体的生物功能和在维持正常细胞DNA甲基化稳态中的功能, 以及考虑以MBD3为靶点治疗人类疾病并在疾病预后中发挥作用。随着高通量测序、代谢组学以及生物信息学等新技术的发展, MBD3蛋白的深入研究将势必探索和发现新的调控网络、阐明表观遗传调控机制, 推动生命科学的发展。

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