综述

妊娠期糖尿病患者基因DNA甲基化的研究进展

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［摘要］妊娠期糖尿病是指患者妊娠前糖代谢正常、妊娠期出现的糖耐量异常，表现为机体脂肪、肌肉等组织对胰岛素的敏感性降低，血糖水平异常，严重影响母体及子代健康。妊娠期糖尿病患者在产后及其子代罹患2型糖尿病及其他代谢性疾病的风险明显增加。研究发现，表观遗传修饰如DNA甲基化参与妊娠期糖尿病的发生及母胎并发症的发生过程。在妊娠期糖尿病患者多种临床标本如胎盘、脐血、外周血与脂肪等组织中，发现多个基因的甲基化水平改变，并可通过“胎儿编程”的方式影响子代终生。该文对妊娠期糖尿病相关基因的DNA甲基化研究进展进行综述。

［关键词］妊娠期糖尿病；表观遗传修饰；DNA甲基化；胎儿编程；代谢模式
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Research progress of DNA methylation in gestational diabetes mellitus

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[Abstract] Gestational diabetes mellitus refers to patients with normal glucose metabolism before pregnancy and getting abnormal glucose tolerance during pregnancy. It is characterized by decreased insulin sensitivity of adipose and muscle tissues and abnormal blood glucose levels in the body. This disease can seriously affect the maternal and fetal health, and the risk of type 2 diabetes mellitus and other metabolic diseases in the postpartum period and the offsprings significantly increased. It has been found that epigenetic modifications such as DNA methylation can be involved in the pathogenesis of gestational diabetes mellitus and the occurrence of maternal and fetal complications. The differences in gene methylation levels appear in the various clinical specimens of patients with gestational diabetes mellitus, such as placentas, umbilical cord blood, peripheral blood and adipose tissues. It can also affect all the lives of the offsprings through “fetal programming”. In this paper, the research progress of DNA methylation in gestational diabetes mellitus is reviewed.

[Key words] gestational diabetes mellitus (GDM); epigenetic modification; DNA methylation; fetal programming; metabolic pattern

妊娠期糖尿病（gestational diabetes mellitus，GDM）为患者妊娠前糖代谢正常、妊娠期出现的糖耐量异常；依据诊断标准及人群不同，其发病率为10%~15%[1]。对于母体而言，GDM患者孕期易并发子痫前期，且远期罹患2型糖尿病（type 2 diabetes mellitus，T2DM）及代谢性疾病的风险大大增加；对于子代而言，其出现巨大儿、早产、胎儿生长受限、围产期死亡及新生儿低血糖等并发症的概率明显增加，且对于胎儿的代谢影响可延续至成年甚至终生[2]，这也是此前易被忽视的GDM危害性。近年来随着对GDM研究的不断深入，“胎儿编程”和“胎源性成人疾病”的概念愈来愈受到重视。研究[3]发现，胎儿早期暴露于GDM母体宫内高血糖环境后，机体代谢模式发生重编程，其影响可延续至子代成年[3]。表观遗传修饰在“胎儿编程”理论中被认为具有重要的作用[4]，而DNA甲基化作为研究最多的表观遗传机制，近年来在GDM中的报道逐步增多。

DNA甲基化指在DNA甲基转移酶的作用下，基因组胞嘧啶和鸟嘧啶组成的串联重复序列（CpG）中的胞嘧啶5′碳位共价键结合一个甲基基团；其通常发生在基因启动子区，可在不改变DNA序列的情况下，调控基因表达水平。研究[5]发现，DNA甲基化参与癌症、心血管疾病、糖尿病等多种疾病的发生，干预其对特定基因的遗传修饰可成为疾病的治疗策略，且对外周血中循环DNA的甲基化水平进行检测可望为疾病的预测与诊断提供帮助。GDM患者胎盘、外周血、脐血及脂肪组织等标本中均出现部分基因甲基化水平的改变，同时GDM患者子代机体组织标本中亦存在某些基因甲基化水平的差异。这些差异引起的基因表达水平与遗传信息

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的改变，可能对GDM的发病、并发症的发生及远期代谢性疾病罹患风险的增加具有重要的影响。本文对目前GDM中相关基因的DNA甲基化研究进展进行综述，以期为临床上GDM新型诊断和治疗手段的开发提供启示。

1　GDM患者基因的DNA甲基化

1.1　胎盘组织

胎盘是孕期母体供应胎儿营养物质、母胎交流的重要枢纽，可分泌多种激素，对维持胎儿的正常生长非常重要。GDM患者宫内高血糖环境可促使胎盘组织形态、结构及功能发生异常改变，对胎儿的生长与代谢模式造成直接影响，而DNA甲基化的遗传修饰方式在其中的作用不容忽视。研究表明，GDM患者胎盘组织DNA甲基化水平发生改变的基因功能多与葡萄糖代谢、生长调控、脂质代谢等相关。如GDM胎盘中非典型notch配体1（δ like non-canonical notch ligand 1，*DLK1*）甲基化水平异常与母体葡萄糖耐量试验2 h血糖水平和新生儿出生体质量具有相关性[6]；过氧化物酶体增殖物激活受体γ辅助激活因子1A（peroxisome proliferator activated receptor γ coactivator 1 α，*PPARGC1A*）与胰十二指肠同源异型基因1（pancreatic and duodenal homeobox 1，*PDX1*）甲基化水平与胎儿葡萄糖代谢均具有一定关联[7]；胰岛素样生长因子2（insulin-like growth factor 2，IGF2）的甲基化水平改变可影响胎儿发育和出生体质量[8]；*PPARGC1A*启动子甲基化水平改变与母体餐后2 h血糖水平及新生儿瘦素水平相关[9-10]；胎盘脂蛋白酯酶（lipoprotein lipase，*LPL*）基因甲基化水平可影响母体和胎儿的脂质谱[11]及子代5岁时的身体成分[12]。此外，另有研究[13]发现，中胚层特异性转录子（mesoderm specific transcript，*MEST*）的异常表观遗传修饰可能会导致GDM患者的子代终生肥胖。6-磷酸葡萄糖脱氢酶（glucose-6-phosphate dehydrogenase，*G6PD*）基因的异常甲基化与高血糖症、氧化应激相关，而胰岛素样生长因子轴相关分子的甲基化改变则直接增加巨大儿的发生风险[14]。此外，GDM环境还可以通过DNA甲基化和基因表达水平变化使胎儿胎盘内皮细胞形态与屏障功能发生损伤[15]。研究者[16]基于生物信息学工具，发现GDM患者胎盘组织中低密度脂蛋白受体相关蛋白1b（LDL receptor related protein 1b，*LRP1B*）等基因可能为胎儿发生代谢模式重编程的候选基因。可见，GDM患者胎盘组织中DNA甲基化水平的变化参与多种病理过程。

1.2　脐血

除胎盘外，脐带对胎儿的正常生长亦发挥着不可替代的作用。脐血标本信息可直接反映胎儿部分相关指标的变化。GDM患者脐血中部分基因启动子区域甲基化水平改变引起的基因表达异常，与机体组织多种生物学功能的损害相关。脐血是临床上预测胎儿并发症的发生、胎儿远期机体代谢模式的重要媒介。如脐血瘦素甲基化水平与巨大儿的发生相关[17]；*IGF2*的甲基化水平改变与胎儿出生体质量具有相关性[8]；巨大儿脐血中Rho蛋白鸟苷酸交换因子11（Rho guanine nucleotide exchange factor 11，*ARHGEF11*）基因的甲基化水平明显降低，与新生儿血糖水平和出生体质量呈负相关[18]。研究[19]还发现，GDM可引起1型糖尿病、主要组织相容性复合体和神经元发育相关途径基因发生表观遗传修饰，这些基因通过DNA甲基化方式参与胎儿代谢编程，对胎儿的生长和发育产生影响。研究[20]发现，人缺氧诱导因子α（hypoxia inducible factor 3 subunit α，*HIF3A*）等基因可能在GDM效应传递给子代的过程中发挥重要作用。此外，脐血中基因DNA甲基水平的改变还可以作为GDM患者诊断的间接指标。如孕产妇GDM的发生与脐血自闭症相关嗅觉受体家族2亚家族L成员13（olfactory receptor family 2 subfamily L member 13，*OR2L13*）基因和细胞色素P450同工酶2E1（cytochrome P450 family 2 subfamily E member 1，*CYP2E1*）基因的甲基化水平降低有关[21]。研究[22]还发现，信号转导蛋白亚基8（COP9 signalosome subunit 8，*COPS8*）等基因在母体发生GDM前已出现甲基化水平的变化，显示DNA甲基化作为临床生物标志物的巨大潜力。与此同时，DNA甲基化方式参与调节脐血淋巴细胞内丙二酰-辅酶A-酰基载体蛋白转氨酶网络，影响细胞脂肪酸合成及胰岛素抵抗[23]；在胎儿脐血中分离出的淋巴细胞中，G蛋白α亚基（GNAS complex locus，*GNAS*）基因甲基化水平较高，其可能与GDM母体与子代代谢疾病风险增加相关[24]。

1.3　外周血

目前，关于GDM患者外周血中全基因组DNA甲基化水平是否存在差异尚有争议。研究[25]表明，患或不患GDM的女性外周血全基因组DNA甲基化水平差异无统计学意义，且基因DNA甲基化水平与空腹血糖水平及胰岛素浓度均无关。而另有研究[26]显示，GDM组和非GDM组患者之间共有1 046个CpG位点（与939个基因相关）甲基化水平具有差异性，这些基因富集于与GDM相关的途径，例如胰岛素抵抗、葡萄糖代谢和炎症；其中前5个CpG位

点的DNA甲基化在GDM组和非GDM组间显示出不同的甲基化模式，并且与母体外周血的血糖水平相关；其中一个CpG位点定位于钙调蛋白结合转录激活因子1（calmodulin binding transcription activator 1，*CAMTA1*）基因；该基因已被证明可调节胰岛素的产生和分泌。此外，不同GDM严重程度的患者孕早期外周血中DNA甲基化水平亦存在差异[27]，且在GDM患者母体外周血中发现白介素10（interleukin 10，*IL10*）的甲基化水平降低，浓度升高[28]。

1.4 脂肪与肌肉组织

与T2DM相似，GDM可影响患者脂肪与肌肉组织对胰岛素的敏感性。研究[29]表明，与正常糖耐量患者相比，GDM患者内脏脂肪组织中肿瘤坏死因子（tumor necrosis factor，*TNF*）和细胞因子信号转导抑制因子3（suppressor of cytokine signaling 3，*SOCS3*）的mRNA表达水平显著增加，伴随着各自启动子甲基化模式的特异性改变。同时，大网膜脂肪组织中*HIF3A*启动子CpG岛的甲基化可促进GDM的胰岛素抵抗[30]，且GDM患者和子代的脂肪组织中胰岛素受体表达的减少亦与其DNA甲基化改变有关[31]。脂肪组织和血细胞中脂联素（adiponectin，C1Q and collagen domain containing，*ADIPOQ*）基因表达和甲基化的改变可影响GDM的病程与新生儿结局[32]。基于基因表达谱和甲基化谱的综合分析发现，间皮素（mesothelin，*MSLN*）基因的表达与其甲基化水平之间呈现典型的负相关，该基因可参与内脏脂肪组织的抗原加工、提呈及GDM相关通路的调控[33]。这些研究显示，GDM患者外周组织胰岛素抵抗的出现很可能源于DNA甲基化的表观遗传修饰。

2 子代基因的DNA甲基化

2.1 脂肪组织、胰腺和胰岛

DNA甲基化异常除了在GDM母体中出现外，在子代中同样存在，并影响子代各组织的功能。研究[34]发现，GDM患者子代内脏脂肪组织中*ADIPOQ*基因甲基化水平增加，基因表达水平降低；胰腺基因组中*GNAS*等基因的DNA甲基化亦发生改变，可能与子代成年后的糖脂代谢异常、T2DM易感性和肥胖有关[35]，且GDM的胰岛素治疗不能完全保护子代免受饮食引起的代谢紊乱。雄性子代小鼠胰岛的全基因组DNA甲基化图谱鉴定出了几个调节胰岛素分泌基因的高甲基化区域；这些基因包括ATP结合盒亚家族C成员8（ATP-binding cassette sub-family C member 8，*Abcc8*）等，其表达降低与胰岛素分泌受损相关[36]。研究还发现，母体宫内高血糖环境引起子代生殖细胞的DNA甲基化重编程，从而形成代际遗传[37-38]，亦可诱发小鼠胎盘中*Dlk1*基因甲基化[39]。此外，GDM患者成年子代肌肉和脂肪组织中*PPARGC1A*基因的表达和DNA甲基化均发生改变[40]；外周血中磷酸二酯酶6A（phosphodiesterase 6A，*PDE6A*）基因与GDM状态相关[38]。可见，在GDM子代中识别出的甲基化改变可能反映疾病发生机制或被利用于开发疾病的生物标志物。

2.2 生殖细胞和部分体细胞

GDM除影响子代胰岛素相关组织与器官外，还可通过DNA甲基化的方式影响其他类型组织的功能。研究显示，GDM中脱嘌呤/脱嘧啶核酸内切酶1（apurinic/apyrimidinic endodeoxyribonuclease 1，*APEX1*）基因甲基化水平的改变能够调节子代上皮干细胞的增殖和自我更新[41]，亦可引起子代神经系统疾病的发生[42]，且子代DNA甲基化模式的改变还与随后的T2DM风险相关[43]。与此同时，GDM患者所育新生儿的内皮集落形成细胞功能受损，其原因在于暴露于GDM宫内环境后内皮集落形成细胞中胎盘特异蛋白8（placenta associated 8，*PLAC8*）基因表达增加，其表达水平与*PLAC8*中17个CpG位点的甲基化状态呈负相关[44]。在心血管系统中，GDM子代沉默信息调节因子1（silent information regulator 1，*Sirt1*）的甲基化水平降低可促进心肌缺血敏感性表型的胎儿编程[45]。更多研究发现，GDM子代原始生殖细胞及睾丸中出现了胰岛素抵抗和脂肪蓄积相关基因酪氨酸激酶（Fyn proto-oncogene，Src family tyrosine kinase，*Fyn*）基因的低甲基化[37]，且子代生长相关并发症的发生可能与脂肪细胞因子如*ADIPOQ*的甲基化水平改变相关[32]。GDM患者及子代不同组织中基因DNA甲基化水平异常改变对母体及子代的影响见表1。

3 总结与展望

DNA甲基化作为一种常见的表观遗传修饰方式，发生机制与局部微环境关系密切，但其确切的调控机制尚不清楚。研究[46]发现，人类GDM胎盘组织中miR-98的上调可靶向抑制甲基CpG结合蛋白2（methyl-CpG binding protein 2，*MECP2*）基因表达，而*MECP2*表达水平的改变影响全基因组的甲基化状态，表明微小RNA的作用可能是DNA甲基化的一种调控模式。尽管目前DNA甲基化发生的原因尚不明确，但是其在GDM的诊断与治

表1　GDM相关组织样本中DNA甲基化水平的改变

Tab 1　Changes of DNA methylation levels in GDM-related specimens

Specimen type	Gene involved in methylation	Impact of changes in methylation levels	Reference
Maternal side of placenta（from the mother，*Homo sapiens*）	*DLK1*	Glycemia	［6］
	PPARGC1，*PDX1*	Fetal glucose metabolism	［7］
	IGF2	Birth weight	［8］
	PPARGC1A	Newborn birth weight	［9-10］
	LPL	Energy homeostasis	［11］
	MEST，*NR3C1*	Obesity	［13］
	G6PD，*IGF*	Hyperglycemia，oxidative stress and fetal macrosomia	［14］
Peripheral blood（from the mother，*Homo sapiens*）	*CAMTA1*	Insulin synthesis and secretion	［26］
	IL10	Inflammation	［28］
	G6PD，*IGF*	Hyperglycemia，oxidative stress and fetal macrosomia	［14］
	NDUFC1，*HAPLN3*，*RHOG*，et al	Cell morphology，cellular organization and cell cycle	［27］
Cord blood（from the mother，*Homo sapiens*）	*OR2L13*，*CYP2E1*	Autism and diabetes	［21］
	IGF2	Fetal growth and newborn birth weight	［8］
	MEST，*NR3C1*	Obesity predisposition	［13］
	HIF3A，et al	Metabolic phenotype	［20］
	ARHGEF11	Macrosomia	［18］
Adipose and omental tissue（from the mother，*Homo sapiens*）	*TNF*，*SOCS3*	Inflamation	［29］
	HIF3A	Insulin resistance	［30］
	MSLN	Antigen process and presentation	［33］
Umbilical cord blood lymphocyte（from the mother，*Homo sapiens*）	*MCAT*	Mitochondrial fatty acid synthesis and insulin resistance	［23］
Fetal side of the placenta（from the offspring，*Homo sapiens*）	*DLK1*	Newborn birth weight	［6］
	LPL	Energy homeostasis	［12］
Adipose tissue（from the offspring，*Homo sapiens*）	*PPARGC1A*	Insulin secretion and metabolic disease	［40］
	ADIPOQ，*RETN*	Metabolic disease	［34］
Muscle（from the offspring，*Homo sapiens*）	*PPARGC1A*	Insulin secretion and metabolic disease	［40］
Dental epithelial stem cell（from the offspring，*Homo sapiens*）	*APEX1*	Proliferation and self-renew	［41］
Pancreas（from the offspring，*Mus musculus*）	*Gnas*，*Fbp2*，*Wnt2*，et al	Glycolipids metabolism	［35］
Pancreatic islet（from the offspring，*Mus musculus*）	*Abcc8*，et al	Insulin secretion	［36］
Heart（from the offspring，*Mus musculus*）	*Sirt1*	Heart ischemia sensitive phenotype	［45］
Placenta（from the offspring，*Mus musculus*）	*Dlk1*，et al	Insulin pathway	［39］
Primordial germ cell（from the offspring，*Mus musculus*）	*Fyn*	Obesity and insulin resistance	［37］

Note: *NR3C1*—nuclear receptor subfamily 3 group C member 1; *NDUFC1*—NADH-ubiquinone oxidoreductase subunit C1; *HAPLN3*—hyaluronan and proteoglycan link protein 3; *RHOG*—RAS homolog family member G; *RETN*—resistin; *Fbp2*—fat body protein 2; *Wnt2*—wingless-type MMTV integration site family member 2.

疗中仍具有重要的应用前景。一方面，DNA甲基化的改变广泛存在于外周血中，并与机体多种指标状态相关，如外周血中循环DNA的甲基化差异可用于监测胰岛β细胞的死亡状况[47]，显示了其作为一种新型生物标志物的巨大潜力；另一方面，DNA甲基化水平改变直接影响基因表达水平，进而促进基因相关功能发生改变，可见该表观遗传修饰方式亦可作为疾病治疗的干预靶点。由于GDM宫内高血糖环境可对胎儿代谢进行重编程，以遗传的方式产生代际间传递，对子代的健康影响严重且持久，DNA甲基化的调控可能成为一种预防GDM母胎危害的策略。随着相关研究不断深入，DNA甲基化有望为临床上GDM的诊断与治疗带来新的启示。

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