

胎盘发育过程中的表观遗传学改变及其相关疾病

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摘要: 胎盘介于胎儿与母体之间, 是维持胎儿宫内生长发育的重要器官。在胎盘的正常发育过程中, 子宫正常蜕膜化、滋养层细胞粘附与侵袭、胎盘血管生成与形成、胎盘印记基因表达都受到表观遗传修饰(如 DNA 甲基化、组蛋白修饰、非编码 RNA 等)的调控。研究已经证实环境因素如重金属、化合物、现代辅助生殖技术、营养物质均可导致胎盘上多种基因的表观遗传修饰异常。此外, 胎盘基因表达存在性别差异也可能与表观遗传修饰有关。目前, 在临床上可运用产前 DNA 甲基化水平分析技术检测异常的表观遗传修饰, 并在疾病早期发现并做出诊断, 从而为疾病预防及治疗提供依据。本文对胎盘正常发育过程中表观遗传修饰的调控及环境因素所致的胎盘基因表观遗传改变进行了综述, 以期对胎盘相关疾病的诊断与治疗提供借鉴和参考。

关键词: 胎盘; 表观遗传; 印记基因; 环境因素; 产前诊断

Epigenetic regulation and related diseases during placental development

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Abstract: The placenta is vital to fetal growth and development, as it bridges the fetus and the mother. Genome-wide epigenetic regulations (e.g., DNA methylation, histone modifications, non-coding RNAs) participate in many aspects of placenta development, including decidua of the uterus, trophoblast cell adhesion and invasion, angiogenesis and placental imprinted gene expression. Environmental factors during pregnancy, such as heavy metals, chemical compounds, modern assisted reproductive technology and the nutrient conditions, may cause abnormal placental epigenetics. Furthermore, sex differential expression of placental genes also contributes to

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epigenetic modifications. As prenatal DNA methylation analysis can detect abnormal epigenetic modifications, it is a potential diagnosis tool for early stage diseases and may help disease intervention and treatment. Here, we review not only regulations of epigenetic modifications during development of the placenta, but also the influences of environmental factors. The potential value for diagnosis and treatment is also discussed.

Keywords: placenta; epigenetic; imprinted gene; environmental factors; medical diagnosis

胎盘是连接胎儿与母体并维持胎儿在子宫内生长发育的重要器官。目前,研究已经证实表观遗传机制在胎盘的正常发育及其功能的维持中发挥着重要的作用^[1]。表观遗传修饰可在不改变 DNA 核苷酸序列的情况下,通过 DNA 甲基化、组蛋白修饰、RNA 调控与染色质重塑等方式来调控相关基因表达,从而改变胎盘相关蛋白的合成和功能形成,调节胎盘发育及适应性改变^[2,3]。同时,表观遗传修饰在胎盘发育中所起的作用可被外界环境因素所影响,从而导致胎盘相关疾病的发生。本文对胎盘发育过程中表观遗传的修饰、环境因素所致胎盘基因表观遗传的改变、胎盘表观遗传修饰的性别差异进行了综述,并探讨了表观遗传修饰在诊断与治疗胎盘相关疾病方面的借鉴意义与参考价值。

1 表观遗传修饰与胎盘发育

胎盘由胎儿部分的绒毛膜和母体部分的基蜕膜共同组成。胎盘发育贯穿整个妊娠期,表观遗传调控伴随其间。各表观遗传修饰方式对胎盘发育的影响不同,主要包括 DNA 甲基化修饰、组蛋白修饰及非编码 RNA 等。

1.1 DNA 甲基化修饰与胎盘发育

DNA 甲基化主要由 DNA 甲基转移酶(DNA methyltransferases, DNMTs)介导,以 S-腺苷甲硫氨酸为甲基供体,将甲基转移到胞嘧啶第五位碳原子,其中 CpG 岛是 DNA 甲基化发生的主要区域。由于 CpG 岛多位于基因的启动子区,CpG 岛的甲基化可对一些转录因子与基因调控区的结合产生干扰。哺乳动物在生殖细胞发育期和胚胎发育早期均会发生基因组全局范围的 DNA 甲基化重排,即移除已有的表观遗传标记,分别建立胚胎和胎盘的 DNA 甲基化模式^[4]。“印记基因”指那些在传递过程中一方表达而另一方不表达的亲源性等位基因。印记基因调控主

要通过 CpG 岛甲基化进行。就胎盘而言,人类染色体上第 11 位的印记基因 *PHLDA2* 主要在胎盘表达,其表达量与胎儿出生体重呈负相关^[5]。胎盘组织其他印记基因 *ILK2*、*NNAT*、*CCDC86* 和 *PEG10* 基因的表达上调,*MEST*、*MEG3*、*GATM*、*GNA*、*DHCR24*、*ZNF331*、*CDKALI* 以及 *PLAGL1* 基因的表达下调则与胎儿的生长受限有关^[6,7]。

1.2 组蛋白修饰与胎盘发育

染色质以核小体为基本组成单位,每个核小体包括一个组蛋白八聚体(由 H2A、H2B、H3、H4 构成),组蛋白亚基的氨基端游离出来,称为氨基端尾巴(或组蛋白尾巴),可发生乙酰化、甲基化等共价修饰。组蛋白修饰酶包括组蛋白甲基转移酶(histone methyltransferases, HMTs)、组蛋白乙酰转移酶(histone acetyltransferases, HATs)和组蛋白去乙酰化酶(histone deacetylases, HDACs)等。组蛋白修饰在胎盘发育中的基本作用是调控基因表达。例如,H2B 的泛素化可以影响 H3K4 和 H3K79 的甲基化^[8,9];DNA 甲基化位点可以募集诸如组蛋白去乙酰化酶等具有抑制功能的复合物,同时去除该位点附近的组蛋白乙酰化标记^[10];组蛋白修饰 H3K9me 能够促进 DNA 甲基化的进程^[11]。卵裂期组蛋白 3 精氨酸的甲基化可决定胚胎多能干细胞的分化^[12];蛋白复合体 PcG(polycomb group)作为起抑制基因转录作用的蛋白,可催化 H3K27 甲基化,在维持羊膜、绒毛膜正常形成上起重要作用,并且能影响滋养层巨细胞的分化^[13]。

1.3 非编码 RNA 与胎盘发育

非编码 RNA(non-coding RNA, ncRNA)指不编码蛋白质的 RNA,包括微小 RNA(microRNA, miRNA)和长链非编码 RNA(long non-coding RNA, lncRNA)等。胎盘滋养层细胞的增殖与低氧有关,miRNAs 的生物合成途径可受低氧水平影响。在不同低氧浓

度暴露时间下, 离体增殖期胎盘滋养层细胞中 miRNAs 合成相关的酶类表达量, 随着低氧暴露时间的增加亦呈线性增加。伴随这些酶类的改变, 低氧环境下滋养层细胞的 miR-93 表达上调而 miR-424 表达下调^[14]。lncRNAs 与胎盘的脂质代谢、血管生成、凋亡、感染及炎症反应的信号通路有关。研究表明, lncRNAs 可进入核内作用于染色质, 通过 RNA-DNA 碱基配对的方式, 锚定并引导 DNA 表观遗传修饰。例如, 胎盘中 *Kcnq1ot1* 可定位于染色质并在对印记基因群进行抑制性的组蛋白修饰中发挥作用^[15,16]。

2 胎盘功能发育中的表观遗传调控

在胎盘功能发育的表观遗传调控相关研究中, 研究人员一方面从表观遗传修饰对关键基因的必要性修饰作用着手, 另一方面从异常表观遗传修饰所致的病理现象出发, 分别从正、反两方面揭示表观遗传调控机制在胎盘功能发育中的重要作用。

2.1 子宫蜕膜化的表观遗传调控

越来越多的研究发现, 在子宫内蜕膜化过程中, 表观遗传修饰特别是 DNA 甲基化与组蛋白修饰, 参与对子宫蜕膜化过程的调控^[17-19]。在正常的月经周期中, 雌、孕激素的下降可导致子宫内膜的剥脱及撤退性出血。雌、孕激素除了可以使人内膜基质细胞(endothelial stroma cells, ESCs)经历与月经周期同步化的改变外, 还可通过下调 *DNMTs* 表达参与调控子宫内膜蜕膜化^[20,21]。用 5-氮杂胞苷(5-azacytidine, 5-AZA)和 dibutyryl-cAMP (db-cAMP)/estradiol/medroxy-progesterone acetate (MPA)分别处理人 ESCs 后, 发现两组细胞均发生部分蜕膜化^[22,23], 其中 5-AZA 可耗竭 *DNMTs* 而抑制 DNA 甲基化。另外, 在内膜蜕膜化过程中, *IGF1* 结合蛋白、催乳素是预示 ESCs 蜕膜化的标记物, 用环磷酸腺苷处理 ESCs 后发现, 这两种标记物启动子区的 H3K27 乙酰化水平均明显增加^[19,24,25], 提示子宫内膜的蜕膜化过程还受到组蛋白修饰的调节。

2.2 滋养层细胞分化与功能的表观遗传调控

胚胎植入前的胚泡期包括滋养层及内细胞群。内细胞群发育为胚胎, 滋养层决定胚胎植入并且分

化为胎盘滋养层细胞。研究发现, 组蛋白修饰方式可通过调控染色质的结构改变胞核形态的方式来影响细胞分化。如合体滋养层细胞的 H3K9me3 和 H3K27me3 修饰水平低于细胞滋养层细胞, 但 H4K20me3 修饰却更加丰富^[26]。

对滋养层细胞系而言, *Oct4* 与其 *DNMT1* 依赖性分化有关^[27]; *Syncytin-1* (*ERVWE1*)和 *Syncytin-2* (*ERVFRDE1*)在多核合体滋养层中的特异性表达依赖于体细胞中 5'-长末端重复序列(long terminal repeats, LTRs)的 CpG 岛甲基化水平。在体细胞中其甲基化水平高, 基因表达沉默, 促进多核合体滋养层形成胎盘绒毛^[28,29]。用 5-AZA 处理各妊娠期的老鼠, 发现 5-AZA 可影响滋养层细胞的增殖^[30]。这提示 DNA 甲基化异常可致合体滋养层形成受阻。另一方面, 用 5-AZA 处理绒毛膜癌细胞后可发现其侵袭性降低^[31]。实际上, 胎盘形成过程与肿瘤形成过程具有一定的相似性^[32]。例如, 表达于肿瘤的肿瘤抑制基因 *Maspin*、*RASSF1A* 与 *APCL* 的 DNA 甲基化和组蛋白修饰, 在胎盘形成过程中呈现动态改变^[33]。提示 DNA 甲基化对于滋养层细胞植入子宫内膜也具有重要意义。

除 DNA 甲基化修饰外, 滋养层与内细胞群的功能也受到组蛋白修饰的调控。在对滋养层细胞系转录因子 *CDX2*、*GATA3* 的研究发现, 染色质 H3K-27me3 修饰的相关因子可致 *CDX2* 和 *GATA3* 表达增加。这种增加有利于胚胎的植入, 相反其表达缺失则可导致胚泡难以植入子宫内膜^[34]。

2.3 胎盘血管形成的表观遗传调控

胎盘与母体间物质交换依赖于母-胎交界面血管的发生与形成。生理性的局部低氧可促进胎盘的血管生成。细胞对于低氧的反应主要依赖于低氧诱导因子(hypoxia inducible factor, *HIF*)转录复合体的激活, 它可以通过结合于低氧反应元件(hypoxia responsive elements, *HRE*)而调控基因的表达。其中 *HREs* 位于基因启动子区或与基因本身紧密相邻。受到调控的基因产物可作用于内皮细胞(endothelial cell, EC)从而影响其增殖分化与迁移, 进而影响新的血管生成。*HIF* 即可通过结合于胎盘生长因子(placental growth factor, *PlGF*)基因启动子区的 *HREs*

而影响其表达,后者是 EC 基因表达产物之一,在血管生成上具有重要作用。Sandro 等^[35]比较了低氧与正常氧压下的两组人脐静脉内皮细胞中 *PIGF* 启动子区 DNA 甲基化与组蛋白乙酰化水平,结果提示低氧条件下 *HREs* 可通过增强染色质 H3、H4 组蛋白乙酰化修饰,上调 *PIGF* 表达。

先兆子痫是胎盘血管生长发育的异常状态。大量研究表明,这种异常状态的产生可能与基因的表现遗传修饰异常有关。如,转录因子 *PDX1* 可抑制 *TBX15* 启动子区甲基化及 mRNA 表达,导致血管源性的宫内发育迟缓表现^[36]; *TBXAS1* 启动子甲基化水平的减少与先兆子痫特征性的血液凝集素增加有关^[37]; *HOXA13* 启动子区的高甲基化与胎盘血管网的形成障碍有关^[38]; *MMP1* 基因的低甲基化可导致血管相关胶质代谢紊乱^[39]。以上研究说明,表现遗传修饰参与胎盘血管的正常生成与塑形,在血管形成中可能占有重要地位。

2.4 印记基因在胎盘发育中的表现调控

表现遗传修饰调控胎盘印记基因的表达,其中 DNA 甲基化修饰起主要作用。通过敲除印记基因、检测印记基因异常表达等手段可对印记基因如何调控胎盘发育进行研究,从而揭示了印记基因在胎盘发育中的重要性,进而体现了早期印记基因正常表现调控的重要意义^[40,41]。

通过基因敲除的方法已经证实印记基因(*Ascl2*、*Phlda2* 和 *Peg10* 等)在小鼠胚胎滋养层细胞的增殖、分化以及胎盘的血管生成、营养物质转运等方面的重要作用^[42-44];敲除参与胎盘发生的父源性印记基因 *Igf2* 和 *Peg3* 出现胎盘的整体结构及重量减少(迷路层尤为显著),胎盘体积缩小^[45];敲除母源性印记基因 *Grbl0*(主要表达在卵黄囊和迷路层)可造成胎盘体积增大^[46];敲除 *Dnmt1* 与 *Dnmt3L* 的小鼠亦会出现多种形态缺陷,如绒毛膜尿囊融合缺陷及胎盘迷路形成障碍^[47-49]。

葡萄胎分为完全型和部分型葡萄胎。完全型葡萄胎的染色体核型为二倍体,且均来自于父系,而部分型葡萄胎的染色体多为三倍体,其中两条染色体多来自于父方。研究发现 *p57KIP2*、*IPL*、*HASH2* 等印记基因与葡萄胎的发生有关^[50]。*p57KIP2* 与 *IPL*

均为父源性印记基因。*p57KIP2* 基因在人类正常胎盘组织的滋养细胞和绒毛间质细胞表达,但在完全型葡萄胎的滋养细胞及绒毛间质细胞不表达;*IPL* 基因在人类正常胎盘组织的细胞滋养细胞高表达,但在完全型葡萄胎的细胞滋养细胞不表达。依此可鉴别完全型葡萄胎、部分型葡萄胎以及其他妊娠滋养细胞疾病。*HASH2* 基因在有恶变倾向的完全型葡萄胎中表达,在无恶变倾向的完全型葡萄胎中不表达,提示 *HASH2* 基因可能与完全型葡萄胎的恶变相关^[51,52]。研究还发现,*p57KIP2*^{-/+}(母源等位基因敲除,父源等位基因完整)孕鼠胎盘组织中,*p57KIP2* 基因表达缺失可致孕鼠出现高血压、蛋白尿、凝血异常、血小板减少、肾脏受损等子痫前期样表现,提示子痫前期可能与印记基因 *p57KIP2* 缺失有关^[53,54]。

以上研究说明,印记基因在胎盘发育中不可或缺,早期印记基因的甲基化表现遗传调控在胎盘发育中占有重要地位。

3 环境因素对胎盘表现遗传的影响

3.1 孕期重金属暴露对胎盘发育表现遗传的影响

重金属镉在环境中普遍存在。人类镉的摄入主要是通过含镉的植物或海产品,其次是接触烟草及工业废气。研究发现,孕期镉暴露可致母血全基因组 DNA 高甲基化和胎儿血全基因组 DNA 低甲基化^[55];另一研究报道发现,镉暴露可致母血 81 个基因高甲基化、11 个基因低甲基化,胎儿血 90 个基因高甲基化、1 个基因低甲基化^[56]。在一项对鸡胚镉处理的研究中发现,参与胚胎从头甲基化的 *DNMTs*(包括 *DNMT3A*、*DNMT3B*)均出现表达降低^[56]。这种降低对哺乳动物而言可影响胎盘形成,虽然其具体表现遗传机制目前并不明确。

锰是胎儿生长发育的必需元素之一,其过度摄入或缺乏均可导致疾病产生。Carmen 等^[57]收集锰暴露胎儿的指甲和胎盘,并分析 CpG 岛甲基化改变与锰剂量之间的关系后,发现 713 个等位基因的 CpG 岛 DNA 甲基化程度与锰的剂量呈依赖关系,其中包括胎盘血管生成相关的 *VEGF*、滋养层细胞分化及胎盘发育相关的 *PARP1* 和 *NEUROD1*、先兆子痫相关的 *CYR61*。说明锰在胎盘的富集可能通过表现遗传机制改变胎盘的功能。

另外, 重金属三价铬暴露可使父系基因组表观遗传修饰改变, 这种改变可直接通过生殖细胞发生跨代遗传效应, 从而增加子代各组织癌症发生风险^[58]。

3.2 孕期化合物暴露对胎盘发育表观遗传的影响

尼古丁在孕妇吸烟或被动吸烟过程中极易被摄入。作为孕妇较易接触到的有害毒物, 尼古丁可直接扰乱胎盘功能, 例如影响绒毛膜滋养层细胞的迁移与侵袭等。尼古丁可通过改变胎盘正常表观遗传修饰而增加胎儿出生后对心血管疾病、糖尿病等的易感性^[59]。尼古丁不仅可致胎盘相关基因 DNA 甲基化的显著改变, 还可引起全基因组甲基化修饰的改变^[60]。综合不同研究, 以孕期尼古丁暴露的妊娠期妇女为研究对象, 从特定基因或全基因组层面对尼古丁暴露下的胎盘进行 DNA 甲基化水平差异性检测时, 出现 DNA 甲基化修饰异常的基因包括: *HSD11B2*^[61]; *GTF2H2C*、*GTF2H2D*^[62]; *RUNX3*^[63]; *HTR2A*^[64]; *CYP1A1*、*TX5*、*FUT11*、*TUSC3*、*FAN1*、*ZNF671*、*PURA*、*GTF2H2*、*GCA*、*GPR135*、*HKR1*^[65,66]; *NR3C1*^[64]; 重复序列元件 *LINE-1* 和 *AluYb8*^[67]。

饮酒是日常生活行为, 年轻女性饮酒率逐年增加^[68]。妊娠期间饮酒可致母胎乙醇暴露。在乙醇暴露的小鼠模型中, Haycock 等^[69]发现, 胎盘 *H19* 印记基因控制区的 DNA 甲基化因乙醇暴露而出现缺失, *H19* 印记基因控制区的紊乱可能与胎儿生长发育迟缓机制有关。Wilhelm-Benartzi 等^[70]在针对孕期暴露于乙醇的人胎盘组织甲基化水平的检测中即发现, *LINE-1* 与 *AluYb8* 的甲基化水平表现异常。上述研究均说明乙醇暴露可致胎盘功能基因的表达改变, 从而引起胎盘功能异常。

双酚 A(bisphenol A, BPA)是一种广泛使用的有机化工原料, 是苯酚和丙酮的重要衍生物, 主要是用来合成环氧树脂。大多数暴露于 BPA 者, 其血 BPA 水平可达到 0.5~10 ng/mL^[71]。在生物模型中发现, 持续 BPA 暴露可致大脑功能、代谢、生殖、行为以及免疫功能异常。Bartolomei 等^[72]使小鼠在卵泡发育晚期与胚胎发育早期暴露于 BPA, 发现其受精后第 9.5 天与 12.5 天的胚胎及胎盘内印记基因表达被明显干扰, 包括 *Snrpn*、*Ube3a*、*Igf2*、*Kcnq1ot1*、*Cdkn1c* 和 *Ascl2*, 同时胎盘出现全基因组甲基化水平的降低。

3.3 辅助生殖技术对胎盘发育表观遗传的影响

现代辅助生殖技术 (assisted reproductive technology, ART) 的运用可影响胎盘发育。在对小鼠 ART 的研究中发现, 卵细胞的体外培养与授精、胚胎转移、用于培养胚胎的介质、增加氧浓度均可导致种植后胎盘特异性印记基因的缺失。与此同时, 对应用 ART 操作小鼠的所有胎盘转录体进行研究时发现, 大量的胎盘基因转录体表达发生下调, 而印记基因及与 X 染色体相关的基因相比于其他基因却发生了上调^[73]。依此说明, 印记基因的 DNA 甲基化水平可能减少。

体外授精与培养也可影响人滋养层细胞在胎盘形成过程中相关基因的下调, 尤其是 *Igf2*^[74,75]。动物实验中, ART 过程可导致胎盘亲源性 DMRs 区域如 *H19*、*MEST*、*Snrpn*、*Peg3*、*Kcnq1ot1*、*PLAGL1* 甲基化减少以及重复序列的缺失^[76~83], 同时伴有 mRNA 表达增加^[82]。对 ART 胎儿进行基因检测发现, 严重印记基因甲基化缺失可致严重疾病, 如 *SNRPN* 甲基化缺失可致 Angelman 综合征^[84], *KCNQ1OT1* 甲基化缺失可致 Beckwith-Wiedemann 综合征及 *PEG1/MEST* 甲基化缺失可致 Silver-Russell 综合征^[85,86]。

ART 除了影响胚胎 DNA 甲基化外, 尚有研究发现其还可影响参与构成胎盘的子宫内膜容受性相关基因 *HOXA10* 启动子的表观遗传修饰^[87]。此外, 在对牛 ART 的研究中发现, 与人工授精相比, 经过体外授精与受精卵培养的胎盘中, miRNAs 普遍下调^[88]。

3.4 营养物质对胎盘发育表观遗传的影响

越来越多的研究表明, 营养物质可能直接影响胎盘基因表观遗传修饰的调节, 从而影响基因的表观遗传状态。葡萄糖在母体与胎儿之间的转运通过葡萄糖转运体 (GLUT) 实现, 其各亚型在胎盘均有表达, 且其表达在妊娠期间具有动态性。对妊娠期间 *GLUT* 启动子区甲基化水平进行检测, 发现这种动态性可能与表观遗传调控有关^[89]。进一步研究发现, 其与不同时期母体血糖浓度有关^[90]。在母体异常血糖浓度条件下, 母体高血糖可致胎盘 *GLUT* 高表达, 也可导致胎盘脂联素基因甲基化的改变, 从而影响糖、脂代谢。研究还发现, 孕期母体血糖可影响胎

盘 *PPAR γ* 辅助激活因子-1 α (*PPAR γ co-activator 1 α*) 启动子的 DNA 甲基化水平^[91]。最近一项实验验证, 母体糖耐量的降低还可导致胎盘 *IGF1R*、*IGFBP3* 甲基化与 mRNA 表达水平的异常^[92]。

膳食中的甲基供体及辅助因子(如叶酸、胆碱和维生素 B₁₂)参与了机体 S-腺苷甲硫氨酸底物的甲基化, 可通过影响 DNA 甲基化而改变基因表达^[93], 因此在叶酸、维生素 B₁₂ 缺乏实验中出现胎盘全基因组及特异性基因(如 *VEGF*、*FLT1*、*KDR*)甲基化水平的改变^[94,95]。母体叶酸、维生素 B₁₂、脂肪酸的缺乏也可通过甲基化机制影响脂质代谢基因 *PPAR* 的表达^[96]。同理, 锌亦可能参与甲基化的生成与调节, 即通过参与 DNMT 和 HDAC 等表观修饰酶的构成, 而影响表观遗传修饰调控过程^[97]。N-氨甲酰谷氨酸、精氨酸则可能通过影响 miRNAs(包括 miR-15b/16、miR-221/222)的表达而影响胎盘血管的生成与形成^[98]。具有生物活性的维生素 D 则可因维生素 D 羟化酶启动子区发生甲基化而活性受抑, 从而导致胎盘功能不全而诱发先兆子痫等^[99, 100]。

3.5 精神因素对胎盘发育表观遗传的影响

妊娠期间孕妇所经受的精神压力、精神性疾病可影响胎儿成长后的心理与行为, 这一影响可能源于胎盘相关 DNA 甲基化修饰所致的稳定表型改变。Marsit 等^[101]在一项探究应激反应基因群 *FKBP5*、*HSD11B2*、*NR3C1*、*ADCYAP1R1* 的 DNA 甲基化修饰改变与新生儿神经行为结果的研究中发现, 产前暴露于精神压力的孕妇, 其胎儿糖皮质激素(glucocorticoid, GC)应激反应基因的甲基化修饰改变可延续至出生后, 并持续影响胎儿出生后应对及适应环境压力。这一结果在另一研究中同样得到证实^[102]。上述参与 GC 应激反应的基因均表达于胎盘, 其中 *FKBP5* 可减少 GC 胞内的应答反应, *NR3C1* 参与编码 GC 受体, *HSD11B2* 参与灭活 GC, *ADCYAP1R1* 是一种应激相关的神经递质受体。由此可知, 精神因素所致的胎儿生长发育不良可能与表观遗传修饰改变所致的胎盘功能异常有关。

4 胎盘发育过程中表观遗传修饰的性别差异

研究表明在配子形成时期, 雄性和雌性配子甲基化程度的明显差异导致了基因组印记现象的产

生, 从而决定了个体生长发育的不同^[103]。如上所述, 当涉及到环境改变时, 如营养供应改变、激素暴露、尼古丁暴露、重金属暴露等, 均出现基因表观遗传修饰呈现性别差异的现象。

运用基因芯片微列阵的方法比较雌、雄胎盘基因的表达, 发现雌性相比于雄性出现免疫相关基因(如 *JAK1*、*IL2RB*、*Clusterin*、*LTBP*、*CXCL1*、*IL1RL1*)表达的显著上调^[104]。另有一项关于胎盘母体侧蜕膜组织基因的分析中发现, 肾素-血管紧张素系统中 *ACE1*、*ACE2* 在雌性胎儿胎盘表达更显著^[105]。研究分析还发现, 雌、雄性别差异可致正常胎盘的转录本表达存在差别, 例如, 关于胎盘细胞滋养层、合体滋养层、动静脉内皮 4 种细胞类型转录本表达水平与胎儿性别的关系研究中发现, 这些与免疫及炎症相关的基因如 *HLA-DQB1*、*HLA-DQA1*、*HCP5*、*NOS1*、*FSTL3*、*PAPPA*、*SPARC*、*FCGR2C*、*CD34*、*HLA-F* 和 *BCL2*, 其表达水平均存在显著的性别差异^[106]。最近一项研究发现, 胎盘所分泌的瘦素同样具有性别差异, 并且这种差异与瘦素编码基因 *LEP* 启动子区的 DNA 甲基化程度有关^[107]。这一结果提示上述各研究所示的性别差异现象的机制可能均与表观遗传修饰有关。

普遍认为, 胎盘表观遗传的性别差异起源于印记基因调控在原始生殖细胞早期阶段的差异, 如性别差异性表达可能与性染色体有关, 即 X 染色体的选择性失活^[108]、特异性基因在 X 染色体上的表达^[109]、Y 染色体相关基因的表达^[110]。表观遗传修饰中的 DNA 甲基化及非编码 RNA 的参与对于性别差异性表达的影响已经有较多的报道, 但组蛋白修饰与性别差异的关系尚只在牛胎盘滋养层细胞中有报道^[111]。

5 产前胎盘表观遗传修饰异常检测

近年来, 通过对绒毛和羊水进行 DNA 甲基化水平检测, 可以评估因 DNA 甲基化异常导致的胎盘功能障碍^[112]。母血中无创胎儿 DNA 表观遗传学标记物在非侵入性产前检测中亦引起人们的广泛兴趣, 有些病症如 21 三体综合征与 DNA 甲基化、基因表达之间的相关性越来越明确。因此, 利用基因甲基化水平的改变来推断疾病的发生发展已成为可能。

有研究对全基因组及特异性基因位点的 DNA 甲基化改变进行检测, 发现可将先兆子痫发生的诊断追溯至发病之初^[113]。对 *IGF2/H19* 印记基因控制区进行 DNA 甲基化检测, 可预知宫内发育迟缓的发生^[114]。印记基因相关综合征如 Prader-Willi/Angelman syndrome (PWS/AS)、Silver-Russell syndrome 和 Beckwith-Wiedemann syndrome 同样可以通过检测绒毛与羊水样本的表观遗传修饰改变而预知^[115]。对 18-三体、21-三体胎儿的诊断也可通过采集母血检测胎儿 DNA 甲基化水平进行^[116,117]。对暴露于烟草(尼古丁)妇女的胎盘进行相关 DNA 甲基化检测, 可推测尼古丁对胎儿健康所造成的潜在影响^[118]。而上面所提及的 *LINE-1* 和 *AluYb8* 同样被认为可以作为诊断孕期尼古丁暴露所致巨大儿的表观遗传修饰标记物^[67]。尚有研究通过对大量 CpG 位点的评估, 发现了一组新的胎盘及胎儿特异性表观遗传学标记物, 并将这些标记物应用于非侵入性手段进行产前诊断^[119]。因此, 胎盘表观遗传修饰改变的检测对于疾病的产前诊断具有一定的可行性及重要意义。

6 结语与展望

本文综述了胎盘生长发育过程中的表观遗传修饰现象, 阐述了基因表观遗传修饰改变与胎盘、胎儿疾病的相关性及胎盘表观遗传修饰产前检测的临床运用(图 1)。实际上, 虽然产前表观遗传诊断在临床上已有运用, 但其运用范围尚较局限, 其技术也尚未完全成熟。与此同时, 正因为外源性因素导致的表观遗传学改变往往较为广泛, 预示了表观遗传学治疗的困难性, 立足于表观遗传学的介入治疗尚且任重道远。最近有研究报道, 人胎盘绒毛膜板起源的干细胞可治疗四氯化碳所致的大鼠肝损伤, 其机制可能与激活 *IL-6/STAT3* 信号通路及改变 *IL-6R*、*IL-6*、*STAT3* 和 *SOCS3* 的表观遗传修饰有关^[120]; 短时程、周期性的诱导 *Oct4*、*Sox2*、*Klf4* 和 *c-Myc* (*OSKM*) 表达, 通过表观遗传修饰改变细胞重编程状态, 可以延缓衰老导致的细胞水平和生理水平的相关症状, 进而延长细胞生命^[121]。提示通过表观遗传修饰的改变实现疾病的治疗存在着一定可能性。研究中

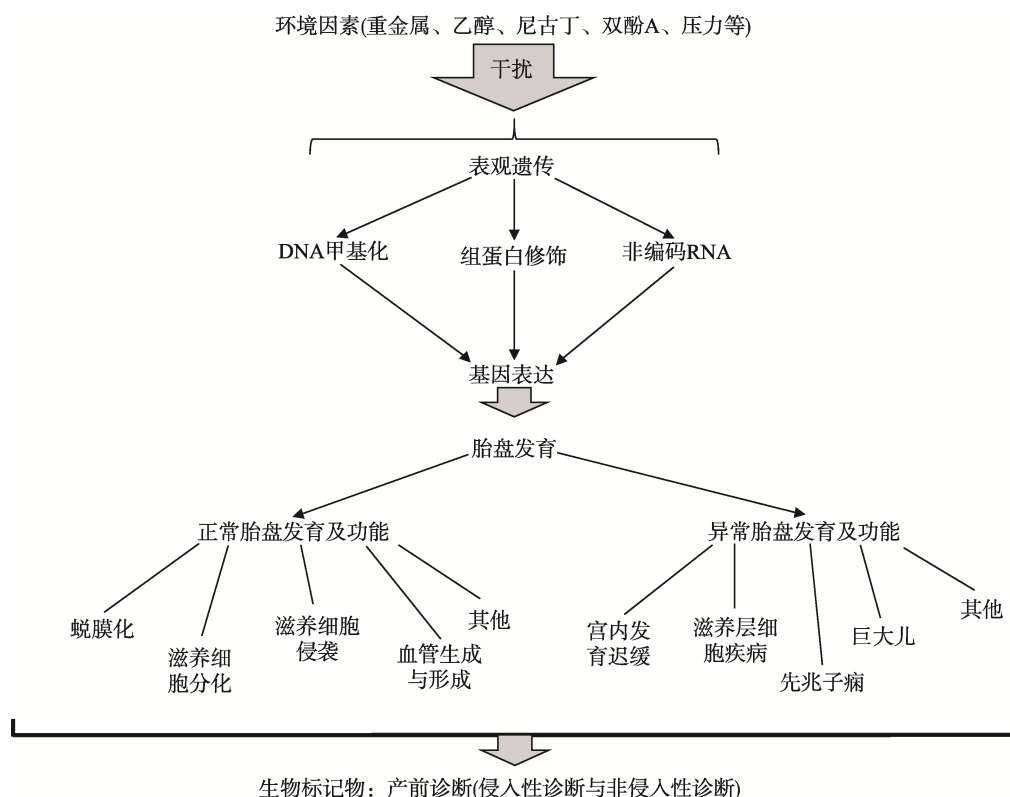


图1 胎盘发育过程中表观遗传学改变及其相关疾病

Fig. 1 Epigenetic regulation and related diseases during placental development

广为运用的 5-AZA 可通过耗竭 DNMTs 而影响 DNA 甲基化修饰过程, 但因其缺乏组织特异性, 而影响了其临床运用。因此, 人为介入胎盘表观遗传修饰并进行相关疾病治疗这一领域仍然存在大片空白。提示, 人们未来仍需要进行更多临床相关机制与应用的研究。

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