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How can genome changes other than mutations be inherited?

表观遗传信息的跨代传递

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摘要 表观遗传是不依赖于DNA序列改变的染色质变化所引起的遗传现象. 表观遗传学作为调控环境诱导的表型的机器, 通过调控基因在时间和空间的特异性表达, 将个体获得的性状传递给子代. 表观遗传信息跨代传递的证据逐年涌现, 亲代饮食、生活经历以及生活习惯等可影响子代的代谢以及对应激的响应, 而表观遗传信息主要由DNA甲基化、小RNA、组蛋白修饰、染色体的状态、转录因子的丰度以及阮病毒等6种载体传递. 本文重点探讨了DNA甲基化和小RNA介导的表观遗传信息跨代传递, 包括印记基因和非印记基因的DNA甲基化改变以及精子中miRNA和tRNA片段介导的后代性状改变. 鉴于外界环境的复杂性和不可控性以及表观遗传修饰的可塑性, 表观遗传信息跨代传递的研究也面临诸多挑战, 但新的方法和测序技术为揭示表观遗传信息的跨代传递的分子机制提供了新的机遇. 基于表观遗传信息的跨代传递, 我们应重新认识体外受精、基于遗传学的药物设计等社会问题对后代潜在的影响, 为预防相关疾病及政策制定提供新的视角.

关键词 表观遗传信息, 跨代传递, DNA 甲基化, 组蛋白修饰, 非编码 RNA, 配子

表观遗传学(epigenetics)一词于1942年由Waddington C. H.创造, 最初指胚胎干细胞由多能性状态分化为终末分化状态的随机发育过程, 强调基因与环境间的关联[1]. 1958年, Nanney D. L.用表观遗传描述不依赖于DNA序列的细胞遗传[2]. 直到2008年冷泉港会议表观遗传学的定义才基本统一, 指DNA序列未发生改变的染色质变化所引起的稳定遗传表型[3].

经典的遗传学认为, 遗传信息从DNA依次流向RNA和执行生物学功能的蛋白质[4], 因而基因与表型可相互对应. 而表观遗传学进一步拓宽了人们对生命遗传信息表达和传递的理解: (1) 基因的表达是受到调控的. 如每个人都携带原癌基因[5], 但并非每个人都患癌症; 当外界环境改变时, 原癌基因启动子或增强子区域表观遗传修饰发生改变, 进而调控原癌基因的表达以及影响癌症的发生[6,7]. (2) 部分获得的性状可遗传给后代. 亲代将环境介导的表观遗传信息传递给子代, 使得子代对类似的环境产生相应的适应性. 表型是基因和环境共同作用的结果, 而表观遗传学是调控环境诱导的表型的机器[8].

1 表观遗传调控方式的可逆性

表观遗传学主要包括DNA甲基化(DNA methylation)、组蛋白修饰以及非编码RNA等, 主要在转录水平调控基因在时间和空间的特异性表达[9]. 表观遗传学可参与肿瘤的发生发展[10]、同卵双胞胎表型差异[11,12]、代谢疾病的发生[13~15]以及细胞生长和凋亡[16,17]等多个生命过程, 这些生命过程的动态性提

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示表观遗传调控的可逆性.

DNA甲基化是指DNA中胞嘧啶上第5位碳上的氢原子被甲基取代的过程. DNA甲基化发生位点通常为CpG二核苷酸, 形成过程分为从头甲基化(*de nevo* methylation)和维持甲基化(maintainance methylation), 分别由DNMT3家族蛋白和DNMT1催化[18]. DNA甲基化比较稳定, 一旦形成则难以直接消除, 目前尚未发现直接的DNA去甲基化酶, 但DNA甲基化可通过多步骤的通路去除. 甲基化的胞嘧啶(5-methylcytosine, 5mC)可被氧化为5-羟甲基胞嘧啶(5-hydromethylcytosine, 5hmC)[19], 并可被进一步氧化为5-醛基胞嘧啶(5-formylcytosine, 5fC)和5-羧基胞嘧啶(5-carboxylcytosine, 5caC)[20], 而5fC和5caC可在糖苷酶的作用下通过BER(Base excision repair)通路还原为胞嘧啶[21~23]. DNA甲基化是一种可逆的修饰, 在早期胚胎发育、基因表达调控、肿瘤发生发展等过程中发挥重要功能[18].

组蛋白(Histone)主要包含H1, H2A, H2B, H3, H4等5种, 其中各2分子的H2A, H2B, H3, H4可聚合成组蛋白八聚体, 约147 bp DNA缠绕组蛋白八聚体表面, 构成染色质的基本单元核小体[24]. 每种组蛋白除拥有与其他组蛋白相互作用的球形结构域外, 还有一个长约20~35个氨基酸残基的末端, 即“组蛋白尾巴”[24]. “组蛋白尾巴”上可发生多种共价修饰, 包括乙酰化、甲基化、磷酸化、泛素化以及ADP核糖基化等[25], 共同构成“组蛋白密码”[26]. “书写者”(writer), “阅读者”(reader)和“擦除者”(eraser)分别负责组蛋白共价修饰的形成、识别和去除[27,28]. 1996年首个组蛋白乙酰化酶[29]和组蛋白去乙酰化酶[30]先后被发现, 随后首个组蛋白H3甲基转移酶[31]、含SET结构域的组蛋白H3甲基转移酶G9a[32]以及首个组蛋白去甲基化酶LSD1[33]相继被发现. 动态的组蛋白修饰水平在基因表达调控、可变剪接、DNA复制以及DNA损伤修复等多种生命过程中发挥重要功能[34].

非编码RNA (noncoding RNAs, ncRNAs)包括rRNA, snRNA, miRNA, siRNA, piRNA, antisense RNA以及tRNA等. 其中rRNA为核糖体的重要组成部分, snRNA为剪接体的重要组分. 成熟的siRNA和miRNA可引导RNA诱导沉默复合物RISC (RNA-induced silencing complex)至与之互补配对的mRNA, 利用Argonaute对mRNA进行剪切[35,36]. piRNA是一类不依赖于Dicer的小RNA, 可特异地引导Piwi蛋白对转座子RNA进行剪切; 同时可以招募组蛋白甲基转移酶到染色质, 促进异染色质形成, 进而同时在转录水平和转录后水平沉默转座子[37,38]. Antisense RNA通过异染色质的形成沉默其对应的基因[39]. 小RNA除了可沉默基因, 我们实验室证实胞核中的miRNA可激活基因转录[40]. tRNA主要参与蛋白的翻译, 最新研究表明, tRNA以及tRNA剪切的片段可参与肿瘤的转移[41,42].

DNA甲基化和组蛋白修饰可随着外界环境的改变而动态变化, 进而调控基因的表达并影响子代的性状[8]; 而miRNA和tRNA可作为表观遗传信息的载体在代际间传递[43~46]. 随着表观遗传现象和机制的揭示, DNA甲基化、组蛋白修饰和ncRNA等在表观遗传信息传递中的功能逐渐被阐明.

2 表观遗传信息跨代传递的复杂性

早在19世纪, 法国生物学家Lamarck J. B.就提出“获得性状遗传”的理论, 但缺乏一定的科学基础. 直到近年来表观遗传信息跨代遗传现象和机理研究的涌现, “获得性状的遗传”的科学性才得以重新认识. 20世纪90年代, 科学家们发现, 在荷兰大饥荒期间经受严重营养不良的母亲, 其子女患精神分裂症的风险更高[47~50]. 类似地, 在1959~1961年间饥荒最严重的地区之一安徽芜湖出生的孩子, 今后患精神分裂症的风险显著升高[51]. 饥荒导致的营养缺陷可能影响胎儿大脑的发育, 但其具体的分子机制还不清楚.

亲代的饮食除了可以影响后代患精神疾病的风险, 还可调控后代的代谢. 营养不良的雌鼠的F_1代出生体重更轻, 并伴随多种代谢缺陷. 即使F1代未经历过环境扰动, 这种代谢表型也可被遗传至F2代[52]. 父亲的前驱糖尿病可导致子代中的葡萄糖耐量受损和胰岛素抵抗[53]. 雄鼠的营养不良可影响子代小鼠胆固醇和脂质代谢[54,55]. 此外, 父亲的精神状态也可影响子代的代谢, 经受精神压力刺激的雄鼠, 其子代糖异生增强, 出现高血糖[56].

亲代的生活经历和习惯也可影响子代的性状. (1) 亲代关怀对子代行为的影响. 母亲对幼崽的关怀对于其成长非常关键, 其中梳理毛发(licking and grooming, LG)以及弓背哺乳(arched-back nursing, ABN)行为被系统研究. 相对于那些给予低水平LG-ABN的雌鼠的成年后代, 给予高水平LG-ABN的雌鼠的成年后代对应激的恐惧和下丘脑-垂体-肾上腺(hypothalamic-

pituitary-adrenal, HPA)响应相对降低[57~60]. (2) 亲代的嗅觉体验可以影响后代的行为和神经网络的结构. 将F0代认知前的小鼠暴露在气味恐惧状态下, 发现F1代与F2代对F0代曾经经历过的气味更加的敏感, 而对其他气味不敏感[61]. (3) 亲代的生活习惯对子代生理和心理的影响. 产前和产后的早期阶段的尼古丁暴露可能会影响很多器官(如大脑)的发育, 并很有可能导致行为和心理的疾病, 如注意力缺陷多动障碍、抑郁和焦虑[62]. 类似地, 孕期的饮酒和吸毒等行为对后代也会产生深远的影响[63~65]. (4) 亲代的经历对子代行为的有益影响. 让新生的雄性小鼠经历两周的亲代应激和亲代隔离, 有助于其子代成年小鼠产生目标导向的行为以及更高的行为敏捷度[66].

表观遗传信息的跨代传递现象逐年揭示, 但其研究过程和结果存在很大的不确定性. 首先, 外界环境的复杂性和不可重复性导致很多实验结果无法重现, 削弱了研究结果的可信度. 此外, 表观遗传对表型的影响是长期积累的结果, 目前动物模型的研究周期可能不足以显示出环境诱导的性状改变. 因此探究表观遗传信息跨代传递的载体和分子机制成为近年来的研究重点.

3 表观信息跨代遗传载体的多样性

无论是大饥荒对后代精神状态的影响, 还是亲代饮食和生活习性对后代代谢以及对应激响应的影响, 都阐明了亲代的信息可以通过不依赖于DNA序列的形式传递给后代, 但具体机制并不清楚. 表观遗传信息的跨代传递需要载体, 表观遗传信息载体主要可分为6类: DNA甲基化、小RNA、组蛋白修饰、染色体的状态、转录因子的丰度以及阮病毒[67,68]. 表观遗传信息载体的多样性提示其跨代传递分子机制的多样性和复杂性.

3.1 DNA甲基化是表观遗传信息跨代传递的媒介

哺乳动物早期胚胎发育过程中DNA甲基化发生两次重编程[69~71], 以擦除来自父母的大部分表观遗传信息, 而部分印记基因可以逃避重编程效应[72]. 但研究表明, 很多非印记基因也可逃避重编程以保留来自亲本的表观遗传信息[73].

印记基因的DNA甲基化改变是表观遗传信息传递的重要媒介. 经历荷兰大饥荒的父母其后代中印记基因*IGF2*的差异性甲基化区域(differentially methylated region, DMR)具有更低的DNA甲基化水平[74]. 孕期营养不良小鼠的F1代雄鼠精子全基因组中111个区域呈现低甲基化, 绝对的甲基化水平与低甲基化的DMR一致. 低甲基化的DMR主要富集在基因间区和CpG岛, 也出现在核小体保留区域, 提示在某些位点孕期营养不良诱导的亲本生殖细胞低甲基化会被传递到染色体中[52].

除了印记基因, 外界环境、亲代饮食和经历可直接影响后代表型相关基因的甲基化. (1) 外界环境对小鼠毛发相关基因的影响. 化学试剂双酚A可调控刺豚鼠毛色相关基因的反转座子上游的甲基化进而影响子代小鼠的毛色, 给雌鼠补充甲基供体都可撤销双酚A的DNA低甲基化作用[75], 而妊娠前后的季节性饮食变化(主要是甲基供体摄取的变化)可影响胎儿中亚稳态表观等位基因的甲基化[76]. (2) 亲代饮食对后代代谢相关基因DNA甲基化的影响. 低蛋白饮食可通过影响其子代肝脏中脂质调控因子*Ppara*增强子区域的甲基化来调控雄鼠子代小鼠的代谢[54]. 高脂饮食可改变雄鼠后代雄鼠胰岛中642个基因的表达发生改变(P<0.01), 这些基因隶属于13个功能簇, 包括阳离子和ATP结合、细胞骨架和细胞内转运等[77]. 差异表达的2492基因(P<0.05)参与钙离子通路、MAPK通路、Wnt信号通路、细胞凋亡和细胞周期[77]. (3) 亲代经历对后代应激响应相关基因DNA甲基化的影响. 亲代的气味感知经历可调控亲代和F1代精子DNA中气味相关基因*Olfr*的甲基化来影响子代对相同气味的敏感度[61]. 亲代的创伤性经历可改变子代中盐皮质激素启动子区域的甲基化以及组蛋白修饰提高子代的行为敏捷度[66], 类似地, 得到更多关爱雌鼠的子代大脑海马区中糖皮质激素受体启动子区域甲基化发生改变, 进而影响子代对应激的响应[78].

无论对于印记基因还是非印记基因, 环境诱导的DNA甲基化的改变具有很强的可塑性. 此外, 由于单一环境的改变可诱导多种基因甲基化的改变, 表观遗传信息跨代遗传的调控网络十分复杂, 有待更多层面的解读.

3.2 ncRNA作为表观遗传信息跨代传递的载体

传统观念认为精子的主要功能是提供来自父本的遗传信息, 但人们在精子中发现了丰富的RNA[79], 包括mRNA, rRNA, piRNA, miRNA以及tRNA等, 提示精子可能具有其他潜在功能. 研究证实, ncRNA可

作为表观遗传信息的载体[80,81].

miRNA作为表观遗传信息跨代传递的载体. 早年创伤性刺激可改变小鼠miRNA的表达, 进而影响后代代谢和行为响应, 将经历过创伤应激的雄鼠精子RNA注射到野生型卵子中可在后代中重现行为和代谢的改变[44]. 进一步探究精子中miRNA介导表观遗传的机制, 9种miRNA在受刺激的父本精子中增加并与子代HPA应激轴反应降低相关[43], 显微注射这9种miRNA可重现后代应激失调[82]. miRNA和DNA甲基化可分别单独作为表观遗传信息的载体, 还可协同作用传递表观遗传信息. 应激可使雄鼠多梳基因*Sfmbt2*启动子区域DNA甲基化升高, 导致内含子miRNA-466b-3p的表达下调, 促进PEPCK的表达, 进而诱发F1代小鼠的高血糖. 这种高血糖可被黄体素拮抗剂RU486逆转, 而给F0代小鼠服用地塞米松可模拟应激刺激的表型[56].

tRNA相关的片段(transfer RNA-related fragments, tRFs)也可作为表观遗传信息传递的载体. 低蛋白饮食可调控精子中tRFs的水平, 在胚胎干细胞和胚胎中, 特定的tRF可抑制多种内源性逆转录因子MERVL相关的基因的表达[45]. 类似地, 高脂饮食可改变精子中tsRNAs (transfer RNA-derived small RNAs)的表达谱和修饰. 将高脂饮食雄鼠精子tsRNA注入正常合子可在F1代产生代谢异常以及其早期胚胎和胰岛中代谢通路基因的表达改变[46].

以上研究证实miRNA和tRF在表观遗传信息跨度遗传中的作用, 随着越来越多的科学家聚焦于精子中sRNA的表观遗传功能, 其他类型的sRNA表观遗传载体和机制有待进一步阐明.

4 表观遗传信息跨代传递研究的问题与挑战

近10年来, 随着测序技术的发展和成熟[83,84], 部分表观遗传信息跨度遗传的分子机制得到揭示, 但目前表观遗传研究依然面临着众多问题和挑战.

DNA甲基化是研究最久的表观遗传信息载体. 虽然已观测到外界环境对精子中DNA甲基化的影响, 但环境诱导的DNA甲基化建立或重塑的通路以及对子代表型的调控通路也有待深入研究, 此外目前缺乏研究环境对DNA甲基化影响的有效手段[85]. 虽然众多研究证实RNA可作为表观遗传信息的载体, 但传递的具体通路和机制还有待进一步研究. 首先, 外界环境信息是如何影响精子中的RNA种类和数量的机制还不清楚; 其次, RNA上可以发生多种形式的共价修饰[86], 部分修饰可逆[87,88], 但RNA修饰对表观遗传信息传递的影响鲜有报道.

研究表观遗传信息跨代传递的通路和分子机制有助于进一步揭示外界环境对后代性状潜在可能的影响, 同时有助于更新对一些社会问题的看法. 不孕不育已成为世界难题, 全球约10%的夫妻有生育困难, 对于年轻健康的夫妻, 利用体外受精技术一个生育周期内怀孕的概率为20%~25%, 一年怀孕的概率接近90%[89]. 体外受精看似是解决这个问题的良策, 但由于受精环境改变, 体外受精的婴儿可能伴随诸多潜在的问题[90]. 目前的药物设计和使用忽视了药物对表观遗传修饰以及对后代健康的潜在影响, 从表观遗传学的角度制定药物开发标准可能是未来的一个方向[91].

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How can epigenetic information be inherited to the next generation?

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Epigenetics refers to the study of stably heritable phenotype resulting from changes in chromatin without alterations in the DNA sequence. Epigenetics regulates specific gene expression in a spatial-temporal manner, and is able to transmit the acquired trait to the next generation. Epigenetics mainly consists of DNA methylation, histone modification and non-coding RNAs, though yet only the former 2 proved to be reversible and all hereditable, implying that epigenetics functions as an adaptive approach to sensing environmental factors.

Evidences of transgenerational epigenetic inheritance, in which the effects that parental diet, life experience and habits have on the progeny's metabolism and their responses to stress have been highly emphasized and extensively studied, have been emerging annually. Epigenetic information is mainly transmitted through 6 carriers, i.e. DNA methylation, small RNAs, histone modifications, chromatin remodelling, transcription factor abundance and prions. Here, we primarily focus on the transgenerational epigenetic inheritance mediated by DNA methylation and small RNAs, discussion on which is divided into two sections: (1) DNA-methylation-mediated transgenerational epigenetic inheritance. Both DNA methylation alteration of imprinted genes (such as *IGF2*) and non-imprinted genes could modulate their expression, further transforming the phenotype. (2) ncRNAs-mediated transgenerational epigenetic inheritance. It's transparent that mammalian sperm contains various ncRNAs, including rRNAs, piRNAs, miRNAs, tRNAs and their fragments. Here, the latter 3 have been confirmed to be involved in transmission of epigenetic information generally triggered by environmental factors. It's highlighted here that DNA methylation and ncRNAs are capable of coordinating each other to collectively contribute to the transgenerational epigenetic inheritance.

Owing to the complexity of the environment and dynamic plasticity of epigenetic modifications, studies on transgenerational epigenetic inheritance face many barriers. Firstly, a substantial amount of results are achieved by epidemiological analysis, the raw data of which could date back to few decades ago. The canonical cases are the 1944–1945 Dutch Hunger Winter and Chinese Famine of 1959–1961. It severely weakens their reliability. Secondly, even a single environmental factor is powerful enough to generate diverse epigenetic alternations in downstream genes. When multiple factors involved in a single study are taken into consideration, it becomes extremely difficult to distinguish the pivotal factors and genes in the regulatory network.

Despite what appears to be a grim situation at hand, the advent of novel methods and technologies continues to shed light on the molecular mechanism of epigenetic inheritance. Lastly, it is essential to concurrently rethink and reevaluate the potential impacts of certain social issues linked to epigenetics, such as *in vitro* fertilization, genetics-based drug design. Understanding these impacts will offer a new angle to be considered in the policy making of related disease prevention.

epigenetic information, transgenerational inheritance, DNA methylation, histone modifications, non-coding RNAs, gametes

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