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How can genome changes other than mutations be inherited?

精子中表观遗传机制及环境对父源表观遗传影响概述

李文静, 王司清, 蓝斐*

复旦大学生物医学研究院表观遗传实验室, 医学表观遗传与分子代谢国际科技合作基地, 上海 200032
* 联系人, E-mail: fei_lan@fudan.edu.cn

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摘要 一般认为生命繁衍的过程包括遗传信息的传递和环境因素对优势个体的选择. 然而, 近年来的一些证据提示, 生命体还可主动适应环境因素并发生传代现象, 配子以及受精后的表观遗传机制在此过程中扮演的角色虽存争议, 但已经逐渐成为生物学研究热点之一. 自2009年起, 人们认识到精子中存在丰富的表观遗传信息, 如DNA和组蛋白修饰, 以及小非编码RNA. 后续研究进一步发现环境因素, 如饮食、压力、化学试剂暴露等, 可能通过影响精子表观遗传谱, 进而影响后代的表型. 由于卵子方面的研究较为有限, 本文将主要对精子发生及受精过程中表观遗传信息的调控进行概述, 并讨论环境因素通过影响精子表观遗传信息传递给后代的可能机制.

关键词 精子发生, 受精过程, DNA 甲基化, 组蛋白修饰, 小非编码 RNA, 环境因素

生命的孕育是一个复杂的过程. DNA作为生命信息的载体, 能够将遗传信息传递给下一代. 子代在继承亲代遗传信息的同时, 也会表现出不同于亲代表型的变异. 这些变异除了是由DNA变异引起外, 还可能是由于DNA序列或者是其染色质上的翻译后修饰以及非编码RNA表达的改变所导致, 最近的研究结果提示, 部分改变还可以遗传给下一代. 这种不改变DNA序列但可以遗传给后代的遗传现象称为表观遗传(epigenetics)[1], 主要研究对象包括DNA甲基化、组蛋白修饰(histone modifications)、非编码RNA (non-coding RNAs, ncRNAs)等, 其中任何一方面的异常都将影响染色质结构和基因的表达[2].

精子发生(spermatogenesis)至成熟的精子形成(sperm formation)及精卵结合完成受精过程(fertilization), 是复杂的细胞分化及生理过程, 在这个过程中持续进行着大量的表观遗传学调控[2~6]. 精母细胞经过广泛且特异的表观遗传修饰建立以及染色质重塑运动, 最终分化并产生具有特定表观遗传谱的精子, 成熟精子中的表观遗传修饰进而在胚胎的发育中发生着有序的动态调控[7~10]. 而且研究发现, 一部分父源的表观遗传信息的改变还可能通过精子传递给后代[8,11~13].

近年来, 越来越多的研究表明, 环境的选择性压力会通过表观遗传机制影响基因的表达调控并传递给子细胞及后代. 环境因素如化学试剂暴露、空气质量、饮食、压力、情绪、恐惧等在细胞重编程过程中会引起精子表观遗传信息的改变, 进而传递给后代[11~14]. 因此, 研究环境因素引起的父源表观遗传信息改变机制对于研究生物群体对环境的响应规律(部分内容可能涉及进化)及一些相关疾病的研究有

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重要的意义.

1 精子中的表观遗传学修饰

1.1 精子发生、受精及早期胚胎发育过程中DNA甲基化图谱概述

DNA甲基化(DNA methylation)是表观遗传学的重要组成部分, 在生物体内普遍存在. 常被甲基化修饰的是胞嘧啶第5位碳原子(5mC). 5mC形成途径有两种: (ⅰ) DNA半保留复制后由UHRF1 (ubiquitin-like, containing PHD and RING finger domains 1)招募维持性甲基化酶DNMT1, 催化半甲基化DNA双链中未甲基化链的甲基化, 称为维持甲基化(maintenance methylation)[15~21]; (ⅱ) 由从头修饰的甲基化酶DNMT3a和DNMT3b催化未甲基化DNA双链的从头甲基化(*de novo* methylation)[22~25]. DNA甲基化在调控基因转录, 转座子沉默以及维持遗传印记、X染色体的失活等方面发挥重要作用.

而DNA去甲基化的发生机制则包括被动和主动去甲基化两类. 细胞可通过抑制DNMT1的表达或催化活性来阻断DNA的甲基化维持, 或在细胞分裂过程中降低基因组中甲基化胞嘧啶的密度, 实现DNA被动去甲基化. 这种被动去甲基化机制是小鼠(*Mus musculus*)胚胎发育过程中原生殖细胞(primordial germ cell)去除基因组亲本DNA甲基化的关键机制[26]. 与被动去甲基化相比, DNA的主动去甲基化是一个迅速的、并且独立于细胞分裂的过程, 是由TET (ten-eleven-translocation)双加氧酶家族催化介导, 将5mC氧化为5′胞嘧啶羟甲基修饰5hmC (5-hydroxymethylcytosine), 以及进一步的氧化产物5fC (5-formylcytosine)和5caC (5-carboxylcytosine)[27,28]. 基因组DNA甲基化与去甲基化是表观遗传学的重要组成部分, 它在指导受精卵发育成早期胚胎、进而发育成完整个体过程中起着重要的作用[26,29].

精确的甲基化调控, 使精子在不同成熟阶段建立合适的染色质环境, 也使后续发育阶段保持基因印记、使生殖细胞重建基因印记, 同时防止转座子激活引起的基因组不稳定性. 哺乳动物受精后, 父源DNA迅速主动去甲基化, 而母源DNA在分裂过程中缓慢地被动去甲基化. 受精卵基因组DNA去甲基化过程存在异质性, 即在相同发育阶段的不同受精卵中, 基因组DNA的甲基化程度有显著差异[30]. 关于DNA甲基转移酶, 除了前文提及的DNMT1, DNMT3a, DNMT3b之外, 最新研究在小鼠体内发现第4种DNA甲基转移酶Dnmt3C. 研究发现, Dnmt3C存在于雄性生殖细胞中、并甲基化和沉默年轻转座子, 帮助维持雄性生育力[31]. 但在灵长类生物中, *DNMT3C*的同源基因并不存在, 提示其功能可能被其他DNMTs取代[31]. 在DNA去甲基化方面, 研究也发现TET家族蛋白在精子发生及早期胚胎发育过程中有重要的调控作用[28,32,33].

在哺乳动物中, 受精前后精子和卵细胞中DNA甲基化动态变化如下: 受精前, 精子和卵母细胞的基因组DNA高度甲基化, 且精子DNA甲基化程度显著高于卵母细胞; 受精后, 精子和卵母细胞均发生大规模去甲基化, 且父源DNA去甲基化速度快于母源DNA去甲基化速度[30,34]. 父源DNA在2细胞末期已基本完成大规模主动去甲基化, 该过程被证实是由来自卵细胞的TET3蛋白介导的主动去甲基化完成的[33]. 而母源DNA则在囊胚期完成大规模去甲基化. 在着床前的囊胚阶段, 胚胎的DNA甲基化水平降到最低点, 只有少量区域的DNA甲基化维持高水平, 如印记基因[35,36]. 囊胚期后, 干细胞开始进入分化阶段, DNA甲基化上升, 逐步建立各种体细胞的DNA甲基化模式. 在胚胎干细胞分化为原始生殖细胞的过程中, DNA甲基化发生整体上调. 原始生殖细胞基因组高度甲基化, 随后原始生殖细胞迁移到生殖脊, 分化为生殖母细胞, 基因组DNA发生第二次大规模去甲基化, 包括印记基因的DNA甲基化被擦除, 而部分重复序列尤其是内源逆转录病毒保持DNA甲基化. 而生殖母细胞在进一步产生成熟生殖细胞后, DNA甲基化又上调, 建立生殖细胞的DNA甲基化模式, 印记基因的DNA甲基化也在此过程中被重建[7,34,36,37]. DNA甲基化的动态调控贯穿于精子发生的整个过程, 其有序恰当的完成是精子正常发生的保障[38~40].

近年来, 关于精子中DNA甲基化在脊椎动物受精作用及早期胚胎发育中的研究取得了重要的进展. 研究发现, 斑马鱼(*Danio rerio*)受精后, 子代大规模重写母源的DNA甲基化图谱, 选择性继承父源的精子DNA甲基化图谱[41,42]. 斑马鱼子代胚胎继承父代的甲基化图谱可以调控基因的时序表达, 对于指导胚胎的早期发育具有重要的意义. 哺乳动物受精后也需要使父源DNA和母源DNA具有相似的DNA甲基

化图谱，但机制与斑马鱼不同[43]. 哺乳动物的胚胎发育过程经历了两次大规模DNA甲基化擦除并重建的过程，在这个过程中DNA的甲基化是高度动态的(图1)[37,43]. 对于印记基因，其DNA甲基化状态在原始生殖细胞发育、生殖细胞形成过程中，被擦除后重建；而在其他体细胞中，印记基因的DNA甲基化状态一直保留了下来，继承了父母的印记[35].

1.2 精子发生、受精及早期胚胎发育过程中组蛋白修饰

在精子发生、受精及胚胎发育过程中，伴随多种组蛋白修饰的动态调控[44,45]，包括组蛋白甲基化、乙酰化、磷酸化等. 组蛋白甲基化修饰主要调控基因的表达以及染色质高级结构. 在人的精子中，与转录激活相关的组蛋白修饰H3K4me2和H3K4me3主要分布

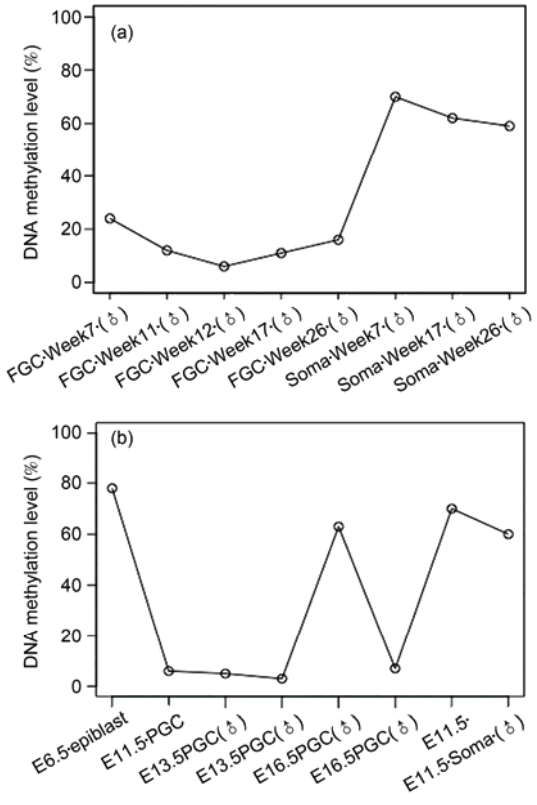

图 1 哺乳动物生殖细胞中DNA甲基化重编程动态变化(数据来自文献[37]). (a) 人类生殖细胞; (b) 小鼠生殖细胞. FGC: 胚胎生殖细胞(fetal germ cells); Soma: 性腺体细胞(gonadal somatic cells); PGC: 原始生殖细胞(primordial germ cells)

Figure 1 Endogenous DNA methylation reprogramming in mammalian germline (Data from [37]). (a) Human germline; (b) mouse germline. FGC: fetal germ cells; Soma: gonadal somatic cells; PGC: primordial germ cells

在与发育相关的基因的转录起始位点以及父源表达的印记基因位点，与抑制相关的组蛋白修饰H3K27me3则富集在配子形成及早期胚胎中受抑制的启动子上[5]；组蛋白乙酰化，可被精原干细胞中的蛋白酶体亚基PA200所识别，使核小体形成一个比较宽松的结构，是精子组蛋白被降解并被鱼精蛋白转换的先决条件[46,47]. 组蛋白磷酸化如H4S1ph等会调控染色质结构的折叠、压缩和解聚等过程[48,49]，进而影响精子染色质的性质[50,51]，此位点磷酸化修饰缺失会对受精过程及子代的发育产生很大的影响[49,52]. 此外，最近的研究发现精子发生过程中H3K4me3, H3K27me3, H3K27ac组蛋白修饰还与染色质可及性(chromatin accessibility)相关[37]. 精子发生过程中，精子中约90%~96%的组蛋白最终会通过乙酰化介导的降解途经丢失[47]，剩余的基因组仍以核小体形式存在，包含有常见组蛋白和睾丸特异性组蛋白变体(见下段)[53]，并在受精过程中将其所携带的组蛋白修饰带入受精卵[5]. 这些残余的精子组蛋白如何逃离乙酰化降解的机制及其意义，仍需进一步研究.

如上文提及，精子中有多种组蛋白变体，如H1的变体H1t, H1T2 HILS1, H2A和H2B的变体TH2A, TH2B, ssH2B, H2A.B.bd, H2BL1, H2BL2, H2AL1-H2AL3及H3的变体H3t, H3.3. 这些组蛋白变体大都与核小体包装密切相关，并参与鱼精蛋白转化组装及染色质重排等生物过程[53~55]. 在线虫(*Caenorhabditis elegans*)中研究发现，组蛋白H2A变体HTAS-1是精子特异的，受精完成后仍会保留[56]. 最近研究发现，H3.3是哺乳动物精子中的主要变体，在精子形成过程中对染色质状态的调控及配子细胞的发育具有重要作用[57]. 精子发生过程中为什么需要使用不同的组蛋白变体，它们在精子发生及重编程过程中有何作用，还需进一步研究.

精子组蛋白修饰的异常可能导致后代胚胎发育异常. 在一个通过精巧设计的实验中，过表达单拷贝H3K4去甲基化酶*LSD1/KDM1A*，导致精子H3K4me2水平下降(并不改变CpG处的DNA甲基化)[8]. 该设计的巧妙之处在于减数分裂后有半数的精子携带有完全正常的*LSD1*拷贝数，其受精产生的后代也具备正确的基因组DNA，但由于这些精子中H3K4me2低水平，其产生的后代胚胎致死量为20%左右，出生的后代有10%左右出现严重的表型异常，如颅骨发育异常、水肿、肠出血等；其F2后代又有5%左右出现这

些严重的表型异常[8]，表明精子的组蛋白H3K4me2修饰的准确建立对后代发育十分重要并可传代.

值得说明的是, 2016年Xie研究组[58,59]、Gao研究组[60]、Arne Klunglandh和Bin Ren研究组[61]突破了少量细胞表观谱分析的技术瓶颈，分别在*Nature*和*Molecular Cell*上发表文章，展示了受精后及胚胎发育早期组蛋白修饰的变化细节，以及染色质开放程度对基因表达的调控，完整地勾勒出早期胚胎发育过程中从配子到囊胚时期的两种组蛋白修饰H3K4me3和H3K27me3动态变化的表观遗传学图谱，并且证明早期胚胎具有非常独特的表观调控机制和模式[58~61]. 他们发现，精卵细胞的H3K4me3在受精后到2细胞末期之间发生去甲基化，而精子的很多H3K4me3信号又在4细胞期到囊胚内细胞团的父母源基因组上重现[58]. 这些研究在一定程度上阐述了组蛋白修饰(主要是H3K4me3和H3K27me3)在受精后的调控规律，为下一步研究表观遗传学信号的传代机制奠定基础.

1.3 精子中的非编码RNA

在精子发生及受精过程中，微小RNA (miRNA)、内源小RNA (endo-siRNA)，以及与Piwi蛋白相互作用的piRNA (piwi interacting RNA)等小非编码RNA (small noncoding RNA, sncRNA)也参与调控[11,62~64]. 此外，有研究发现tRNA来源的小RNA在成熟精子中高度富集[13,14,65].

在物种进化过程中高度保守的miRNA在睾丸及雄性生殖细胞中表达具有偏好性[66,67]. 一些miRNA如*miRNA-221*，*miRNA-203*和*miRNA-34b-5p*在精子发生过程中阶段性特异表达[68]，同时miRNA在成熟和不成熟的睾丸中表达模式不同[69]. miRNA参与精子发生过程中多种调控作用，包括减数分裂和p53有关通路在内的许多重要的生物学现象[10,70]. 此外，研究发现在原始生殖细胞、精原细胞中，调控细胞周期的*miR-290-miR295*簇高表达，对其原始生殖细胞、精原细胞正常增殖是必需的[71]. 还有研究发现果蝇(*Drosophila melanogaster*)中内源siRNA也参与精子发生过程[52].

piRNA (PIWI-interacting RNA)是继miRNA之后发现的一类在高等物种生殖系统中阶段性特异存在的小分子非编码RNA[72,73]. 在精子发生过程中，piRNA只出现在粗线期的精母细胞及精子细胞中，而成熟精子中则没有[74~76]. 粗线期piRNA与其结合蛋白MIWI和脱腺苷酶CAF1组成pi-RISC复合物，该基因沉默复合体通过基因转录后调控作用抑制与精子发生异常的相关基因表达，指导精子细胞中mRNA大规模地脱腺苷酸化及降解[77]. 在精子形成后期，piRNA作为“配体”调控其结合蛋白PIWI/MIWI复合体泛素化修饰，从而触发并诱导其结合蛋白经APC/C-泛素化降解[78]，在精子形成后期piRNA与MIWI蛋白以协同模式被共同清除.

piRNA在染色质水平和转录后水平沉默转座子、逆转座子等DNA移动元件，参与异染色质的形成，在生殖干细胞自我维持和分化命运的决定、减数分裂及配子形成等过程中发挥重要作用. 一方面，piRNA通过与逆转录转座子的RNA配对，招募PIWI复合体，降解逆转录转座子RNA，从而抑制其活性[79,80]. 另一方面，piRNA, Piwi蛋白复合物招募*de novo* DNA甲基化转移酶DNMT3A，DNMT3B，辅助蛋白DNMT3L，以及H3K9甲基转移酶SETDB1，H3K9me3识别子HP1a，H3K4me2去甲基化酶LSD1，对逆转录转座子(retrotransposon)进行DNA从头甲基化、形成异染色质，在转录层面抑制其活性[81~83]. 此外，piRNA形成所需的Tdrd家族基因的突变，可导致小鼠生殖细胞发育受阻，胚胎发育异常[84].

2012年，中国科学院动物研究所段恩奎研究组[65]发现，tRNA来源的小RNA在成熟精子中高度富集. 这种tsRNA在附睾形成，由附睾体输送至成熟的配子，抑制逆转录转座子MERVL的表达[14]；此外，父代的高脂饮食的影响也会通过精子tsRNA传递给后代，tsRNA结合代谢相关基因的启动子，使后代胚胎代谢相关基因表达失调，进而出现葡萄糖耐受下降、胰岛素抵抗等代谢紊乱表型[13,85].

目前，小非编码RNA在精子发生与遗传过程中，还有很多问题需要深入研究，如sncRNA靶向mRNA与DNA的机制、sncRNA与染色质修饰的调控网络、sncRNA在精子成熟与受精过程中的选择性保留与传递机制、受精后父母源sncRNA对胚胎发育进行持续调节的机制、胚胎发育过程中的组织特异性调节机制等.

2 环境因素可改变父源表观遗传信息并形成传代遗传

环境对生物体的进化有重要的影响，除了造成DNA突变外，环境还能诱导精子发生表观遗传学改变，并且已有证据提示一些表观遗传的改变可遗传

到下一代, 不过表观变异的遗传随代数增多逐渐稀释. 这似乎给予了拉马克的“获得性遗传”学说一种分子机制上的支持, 但是学术界针对此论点——表观遗传在进化中的作用——的争论依然十分激烈. 因此, 研究环境对精子表观遗传的影响, 及对父源表观遗传信息的调控, 对于深入理解生命如何进化有着十分重要的意义, 而现在只是窥探了冰山的一角.

如上所述, 在饮食方面, 父代小鼠的高脂饮食或低蛋白饮食, 会通过影响精子tsRNA传递给子代, 影响子代胚胎*Gm8773*, *Alx4*等代谢相关28个基因表达[13,14]. 一些环境诱导的疾病也会影响后代的表观遗传信息. 高脂肪饮食诱导的前期糖尿病会改变小鼠精子的甲基化图谱, 在一定程度上传递给后代, 使后代出现葡萄糖耐受不良和胰岛素抵抗, 从而增加了后代患糖尿病的可能性[86]. 在果蝇中研究也发现了对父亲饮食的干预会引发后代染色质状态的改变和隔代遗传肥胖[87]. 此外, 还有如恐惧、情绪、精神创伤、环境压力等环境因素, 也会对精子产生表观遗传学影响, 通过精子microRNA *MiR-375*影响后代的恐惧行为和糖代谢[88]. 进一步研究发现, 这可能是由于后代海马区的DNA甲基化上升、组蛋白修饰H4K5ac, H3K14ac, H3K4me2和H3K36me3下降导致的[89]. 最近李小英研究组[12]的研究发现, 束缚应激的心理压力可以引起精子中*Sfmbt2*启动子区域发生高甲基化, 使位于内含子的抑制PEPCK蛋白表达功能的*miR-466b-3p*表达下调, 从而导致PEPCK蛋白的含量增加, 同时研究发现精子中*Sfmbt2*基因的甲基化变化可遗传给后代, 导致后代出现高血糖症状.

随着工业技术发展, 环境污染物对精子影响也正在被了解. 将新生儿时期的雄性大鼠(*Rattus norvegicus*)暴露于双酚A (bisphenol A, BPA, 用于合成聚碳酸酯塑料和环氧树脂的常见化工原料), 会导致其生育力低下, 可能是通过某种机制影响DNA甲基转移酶的表达, 改变精子的表观基因组, 导致生育力降低[90]. 还有研究发现, 在成熟男性尿液中检测出的DNA甲基化及去甲基氧化产物5mdC (5-methyl-2′-deoxycytidine)及5hmdC (5-hydroxymethyl-2′-deoxycytidine)与邻苯二甲酸酯化学试剂暴露有关, 研究还发现, 5mdC与5hmdC与精子的浓度等一些质量指标有一定的相关性[91]. 同时子宫内环境也会影响精子的表观遗传信息. 有研究报道, 宫内营养不良会扰乱胎儿成熟后的精子甲基化, 并影响子代、孙代的新陈代谢, 提高子代、孙代罹患肥胖症和2型糖尿病的风险[92].

此外, 空气质量与温度均可以影响精子浓度及精子数量[93]. 有关环境参数对精子影响的研究发现, 空气温度(低温)与精子浓度及总的精子数量成反比; 空气湿度对精子的数量和质量没有太大影响; $PM_{2.5}$直接影响精子的总量; PM_{10}直接影响精子的容量及形态, 但并不影响精子的浓度和精子活力[93]. 空气质量对精子的影响是直接还是间接造成, 且环境因素在改变精子数量及质量的同时, 是否也改变精子的表观遗传信息, 并遗传给后代, 还有待于进一步的研究.

环境因素改变精子的微小RNA, DNA甲基化或组蛋白修饰, 通过受精遗传给后代, 调控后代基因表达, 影响其表型, 从而生物群体在繁衍过程中产生对环境的跨多代响应, 并可能形成主动进化模式. 因此, 了解环境因素引起精子表观遗传信息的机制, 对于进化规律的研究及一些获得性性状的遗传疾病研究有重大的意义.

3 展望

了解精子表观遗传信息的建立以及动态调控规律, 对于研究精子的发生机制及父源遗传信息对胚胎发育的影响, 甚至群体进化规律的研究至关重要. 此外, 还对于人们认识细胞内蛋白质代谢调控和细胞重编程的表观遗传机制具有重要的学术意义, 为相关的代谢性、心血管, 以及生殖与发育疾病的预防和诊断提供理论基础. 同时环境对精子的表观遗传信息的影响以及传代机制为获得性性状的遗传(主动进化)提供了可能的分子基础.

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Summary for “精子中表观遗传机制及环境对父源表观遗传影响概述”

Sperm epigenome and its potential role in transgenerational inheritance

LI WenJing, WANG SiQing & LAN Fei*

Key Laboratory of Epigenetics of Shanghai Ministry of Education, International S&T Cooperation Program of Medical Epigenetics and Molecular Metabolism, Institutes of Biomedical Sciences, Fudan University, Shanghai 200032, China
* Corresponding author, E-mail: fei_lan@fudan.edu.cn

Epigenetics regulation is generally referred to DNA methylation, histone modification and non-coding RNA, which play important roles in chromatin management and gene expression. Recent studies have found that sperm genome is dynamically regulated by a variety of epigenetics mechanisms. More importantly, emerging evidences suggest that certain epigenetics information could be transmitted from sperm to offspring for limited generations. Here, we have overviewed the epigenetics mechanisms involved in spermatogenesis and after fertilization, and the potential underlining mechanisms of epigenetic inheritance.

In the first part, we summarized the current understanding of the regulation of DNA methylation, histone modification and small non-coding RNA in spermatogenesis and early embryonic development.

This part started from the establishment of sperm DNA methylome and the reprogramming of paternal DNA methylome after fertilization. We briefly described how DNA methylation is regulated by DNMT and TET proteins, and its role in silencing repetitive elements and imprinting genes. We also summarized the two rounds of reprogramming of DNA methylation after fertilization. During the first round of reprogramming, most DNA methylation signature from germ cells is erased, and somatic DNA methylome is then re-established. The second round occurring from primordial germ cells to germ cells, during which DNA methylation at imprinted genes is erased, and germ cell specific DNA methylome is then re-established. It is generally believed that the two rounds of reprogramming establish the proper DNA methylome for germ cell formation.

We then reviewed the specific pattern and functional involvement of sperm histone modifications and histone variants. During sperm maturation, most histones undergo acetylation-mediated degradation and replaced by protamine, resulting in only ~10% genome with retained nucleosomes. The remaining nucleosomes contain canonic histones and various histone variants, including TH2A, TH2B, H3t, H3.3, etc. Importantly, sperm histones are also modified, such as H3K4me3, H3K27me3, H3K27ac and H4S1ph. Some modifications are deposited to developmental genes and imprinting loci, while others are thought to control sperm genome accessibility and compaction. Exemplified by transgenerational developmental defects caused by sperm H3K4me2 disruption, proper histone modification patterning in sperm is thought to be critical for early development. We also summarized the recent discoveries in the regulation of H3K4me3 and H3K27me3 from fertilized mouse oocytes to ICM, revealing a highly dynamic and regulated nature of histone modification during early development.

The recent progresses of small non-coding RNA regulation in sperm are also included in this review. For instance, piRNAs are required for heterochromatin formation and gene silencing, especially retrotransposon silencing during spermatogenesis; certain miRNAs, like *miR-290-miR295* and *miRNA-34b-5p*, are required for proper meiosis and cell cycle regulation during spermatogenesis; importantly, tRNA-derived small RNAs (tsRNAs) in sperm were found responsive to paternal diet and able to influence the offspring’s metabolism.

In the second part, we focused on the environmental impacts on sperm epigenome and potential mechanisms of transgenerational inheritance. To date, several studies have implied that diet, pressure and chemical exposure can alter sperm epigenome, which could potentially be inherited through generations. For example, paternal diet is demonstrated to affect offspring’s metabolism. Paternal physiological stress, such as restraint stress or early trauma, could influence offspring’s metabolism or behavior through altered paternal sperm DNA methylation and miRNAs. Additionally, altered sperm DNA methylation has been observed in male rats suffered from utero undernourishment, which could contribute to the high risk of type II diabetes in the offspring.

Taken together, we just started to understand the potential role of epigenetics involving in the transgenerational response to environmental changes. Future epigenomic investigations of sperm, as well as oocyte and zygote, should provide more mechanistic insights in how environment could influence the genome and how the effect might be inherited.

spermatogenesis, fertilization, DNA methylation, histone modification, small non-coding RNA, environmental factor

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蓝斐

1999年获得复旦大学生物化学系学士学位, 2002年获得复旦大学肿瘤分子生物学硕士学位, 2008年获得美国哈佛大学细胞发育博士学位. 2008~2012年任美国星座制药研究员. 2012年入选青年千人计划, 任复旦大学生物医学研究院教授, 博士生导师, 并任附属中山、儿科医院兼职教授. 入选上海市千人计划, 东方学者, 获“上海市优秀学术带头人”称号及“谈家桢生命科学奖(创新奖)”. 在表观遗传领域中组蛋白甲基化的可逆调控以及识别机制方向做出重要贡献. 提出“增强子过度活化态”、“组蛋白变体甲基化信号”以及“赖氨酸零甲基化态”理论. 攻读博士学位期间曾发现多类组蛋白去甲基化酶. 发表SCI论文30余篇, 总引用次数6000余次. 在成果转化方面, 曾参与两类美国食品药品监督管理局(Food and Drug Administration, FDA)(一期)表观遗传药物的开发.