DOI：10.12287/j.issn.2096-8965.20220404

·综　　述·

配子—胚胎发育源性疾病的研究进展

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【摘要】“健康和疾病的发育起源”理论（Developmental Origins of Health and Disease，DOHaD）认为，生命早期的不利环境因素导致了成年期慢性疾病的发生。与胚胎、胎儿的宫内发育时期相比，配子的发生和成熟需要几十年的时间，在较长的暴露时间内更易遭受潜在的损伤并传递给子代，导致子代发生先天性异常和慢性成年期疾病的风险增加，并可存在代际传递效应。表观遗传学修饰是指在不改变核苷酸序列的情况下调控基因的表达，该学说的提出为发育源性疾病的机制探索提供了可能。本文总结了近几年在疾病的配子、胚胎及胎儿起源机制方面取得的研究进展，阐述了表观遗传学机制在其中发挥的重要作用，并进一步强调了于孕前及生命早期进行健康干预的重要性，将疾病的一级预防关口前移至了配子发生及胚胎、胎儿的宫内发育阶段。

【关键词】配子；胚胎；获得性遗传；代际传递；表观遗传修饰

中图分类号：[R715.5]　　文献标识码：A　　文章编号：2096-8965（2022）04-0030-07

Research advances of gamete and embryo-fetal origins of adult diseases

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【**Abstract**】The Development Origins of Health and Disease (DOHaD) theory suggests that adverse environmental factors in early life contribute to the development of chronic disease in adulthood. Compared to the intrauterine developmental period of the embryo and fetus, gametes take decades to develop and mature, and are more susceptible to potential damage. Changes in the gametes can be further transmitted to the offspring, leading to an increased risk of congenital anomalies and chronic adult disease in them, and intergenerational transmission effects can exist. Epigenetic modification refers to the regulation of gene expression without altering the nucleotide sequence, and the proposed doctrine offers the possibility of exploring the mechanisms of developmental-derived diseases. This paper summarizes the research progress of the gamete and embryo-fetal origins of diseases, and illustrates the important role of epigenetic mechanisms in this regard, and further emphasizes the importance of health interventions before conception and early in life to shift the primary prevention of diseases to the gametogenesis and intrauterine development of embryos and fetuses.

【**Keywords**】Gamete; Embryo; Acquired inheritance; Intergenerational/Transgenerational transmission; Epigenetic modification

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收稿日期：2022-10-08；**修回日期**：2022-11-09

基金项目：国家自然科学基金面上项目（82088102）；中国医学科学院医学与健康科技创新工程项目（2019-I2M-5-064）；上海市卫健委协同创新集群项目（2020CXJQ01）

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英国流行病学家David Barker于1989年提出了“成人疾病的胎儿起源”假说，认为个体生命早期所经历的不良事件可影响其远期的代谢状况，并可显著增加慢性疾病的发生风险[1]。随着研究的不断开展与深入，这一假说在实践中不断完善，最终发展成为“健康和疾病的发育起源（Developmental Origins of Health and Disease，DOHaD）”理论，为多种疾病的预防及治疗提供了重要的理论基础，并将疾病的一级预防关口前移至个体生命早期及孕前期。

生命早期包括受精卵形成、宫内胚胎和胎儿发育以及出生后的早期阶段，该时期个体所处的环境对于其远期健康有着深远及广泛的影响。近年来的多项流行病学研究及基础研究皆显示，自配子发生至胚胎、胎儿发育阶段，父母不良的生活方式及环境因素可影响子代个体的远期健康，增加其心血管、代谢、免疫及神经等系统疾病的发生风险[2]。由于许多成年期疾病的发育起源可追溯至个体生命早期，甚至亲代的配子发生阶段，因此也被称为“配子–胚胎发育源性疾病”。基于上述背景，本文概述了近年来配子–胚胎发育源性疾病的研究进展，对其未来的研究机遇进行了展望，以期为成年期疾病的生命早期预防提供理论依据及临床指导。

1 配子源性疾病的研究进展

根据DOHaD理论，个体的发育不仅包括宫内的胚胎发育及胎儿成熟阶段，也包括卵母细胞的减数分裂和成熟、精子的发育和分化等配子发生发育的过程，这标志着亲代基因组向胚胎基因组的过渡与重编程[3]，而在此过程中配子所遭受的各类不良因素可导致其出现异常。近年来，越来越多的研究表明，配子的异常可进一步传递至子代，并显著影响子代的发育及远期健康。

1.1 卵源性疾病

基于1944–1945年荷兰大饥荒的研究发现，仅在孕前暴露于饥荒的女性，其子代于成年期出现抑郁症的风险大大增加[4]，该研究将成年期疾病的起源前移至了孕前阶段，并提示孕前的母源性不良因素与疾病风险增加密切相关。近年来的多项流行病学研究显示，女性孕前营养不良会导致其子代出现小于胎龄儿及低出生体重的风险增加[5]；孕前超重或肥胖会增加其子代出现巨大儿的风险，并与子代童年期肥胖、脂质代谢水平异常、神经系统发育障碍以及成年期心血管疾病风险增加等不良结局密切相关[6–8]；孕前吸烟会增加新生儿先天畸形的风险[9]。以上基于人类队列的研究为成年期疾病的配子起源提供了一定的流行病学证据。同时，既往研究显示，不良的饮食和生活习惯会对育龄期妇女的卵巢环境造成不良影响，并进一步影响卵母细胞的质量、基因表达以及早期胚胎的发育[10–12]。基于临床样本的研究发现，孕前超重不仅会导致卵母细胞大小异常、囊胚期细胞数减少[11]，同时也会对卵母细胞的基因表达产生潜在影响，导致其促炎及氧化应激相关基因表达增加[12]。此外，研究发现，孕前期短暂暴露于高水平的环境颗粒物与早期胚胎发育异常及早期流产的发生呈显著正相关[13, 14]。以上流行病学证据为卵源性疾病奠定了坚实的理论基础。近年来，随着动物模型的广泛应用以及体外受精、胚胎移植等技术的蓬勃发展，配子源性疾病的研究与日俱进。早期的研究显示，仅在孕前期给予雌鼠低蛋白饮食可导致其子代于成年期出现血压升高[15]及焦虑样行为异常[16]；孕前期的高糖环境会导致子代小鼠胚胎形态及发育异常[17]。同时，Huypens等[18]研究发现，孕前高脂饮食的雌鼠其子代可于成年期出现肥胖、葡萄糖耐受异常及胰岛素抵抗等代谢系统紊乱的表型，并提出该不良表型可能由母体卵母细胞的异常所介导。以上研究将成年期疾病的母源性起点前移至了孕前阶段，强调了不良因素的孕前期暴露对于子代远期健康的重要性。

1.2 精源性疾病

20余年前，Olshan和Faustman[19]首次提出了由父亲介导的“发育毒性”概念，认为除遗传信息的编码外，父亲于孕前暴露于不良的外界环境同样会对后代的健康造成深远的影响。由于父亲对发育中的后代仅贡献精子，因此，父源性因素影响子代健康的机制大多可直接通过精子的改变加以解释[20]。既往的流行病学研究显示，在荷兰大饥荒时期出生的男性，其子代出现肥胖、慢性代谢性疾病的风险显著增加[21]，该研究表明父源性因素对于子代的远期健康至关重要。此外，其它基于人类队列的研究发现，父亲暴露于肥胖[22, 23]、高龄[24]、精神障碍[25]及有毒化学物质[26]等不良因素可导致子代的不良出生结局，增加其远期疾病的发生风险。然而，基于人类样本的研究往往难以完全控制混杂因素，因此，得益于动物模型，研究者们进一步明确了孕前时期父源性因素在子代中的致病作用。Ng等[27]利

用高脂饮食的大鼠模型，证实父亲的高脂饮食暴露会诱发雌性子代胰岛β细胞功能紊乱，进而导致其出现体重增加、葡萄糖耐受异常以及胰岛素抵抗等代谢异常表现。另有研究显示，新生儿期营养过剩可导致雄性小鼠于成年期出现糖代谢障碍，表现为空腹高血糖、葡萄糖耐受异常及胰岛素抵抗，该异常可进一步传递至子一代甚至子二代小鼠，提示父源性因素对后代的健康具有深远的影响[28]。与父亲肥胖的影响相类似，父亲低蛋白饮食可重编程子代肝脏脂质和胆固醇生物合成的基因表达谱，调控子代肝脏DNA甲基化的水平[29]，并导致其子代成年期脂肪含量增加、血清炎性因子肿瘤坏死因子-α（Tumor Necrosis Factor-α，TNF-α）水平升高，出现低血压、葡萄糖耐受量异常等[30]。除此之外，父亲高糖饮食[31]、心理压力[32, 33]等不良因素皆会对子代健康产生不良影响。

2 胚胎—胎儿源性疾病的研究进展

生命起始于受精卵的形成，而后在母亲子宫内逐步经历自胚胎至胎儿的发育过程。大量流行病学及动物模型研究显示，在宫内发育时期的多种暴露因素都可导致个体远期的不良健康状况，其中，以母体暴露于不良营养因素最为常见与普遍，是当下最为严峻的公共卫生挑战[34]。流行病学研究显示，母体孕期超重或肥胖不仅会导致子代超重[35, 36]、患2型糖尿病风险增加[37]，也会对其心脏的代谢健康[38]、神经系统的发育及功能[39]造成不利的影响，并且会导致其患哮喘风险增高[40]。同样地，母体孕期营养不良同样会影响子代的健康状况，如导致其肺脏发育异常、成年期肺功能下降等[41]。此外，母体孕期维生素D缺乏也可显著影响子代儿童期大脑形态的发育[42]，增加子代患自闭症的风险[43]。除异常的营养状况外，母体孕期暴露于精神压力[44, 45]、感染[46]、尼古丁[47~49]以及环境污染物[50~52]等不良因素也会导致子代的不良健康状态，导致其罹患神经精神疾病、哮喘等疾病的风险大大增加，其中，孕期尼古丁暴露可致女性子代青春期激素紊乱，影响其生殖健康[53]。以上基于人类队列的流行病学研究揭示了宫内环境与远期健康状况之间的密切关系，强调了孕期健康干预对于个人及社会的重要性。

由于人类队列存在诸多的混杂因素，因此，为进一步明确获得性疾病与宫内不良环境之间的关联性，研究者们利用各类动物模型揭示了二者的因果关系。Mitchell等[54]利用猕猴作为研究动物，发现于孕期给予母猴高脂高糖的西式饮食模式会增加后代神经系统发育障碍的风险。基于小鼠的研究显示，母体孕期的高糖暴露会导致后代记忆力损伤，并可持续至少两代[55]。Chen等[56]研究发现，于小鼠生命早期（宫内时期和哺乳期）给予蛋白营养限制饮食可诱导子代小鼠免疫细胞重编程，进而导致其哮喘易感性增加，并且这种效应主要由宫内时期的不良营养状况所介导。Lin等[57]进一步利用孕期高脂饮食的小鼠模型发现了同样的子代结局，即母体孕期高脂饮食也可导致子代小鼠哮喘患病风险增加。以上的基础研究为进一步开展孕期营养干预提供了重要的科学数据。此外，与流行病学研究的结果相一致，除营养因素外，母体孕期遭受的多种不良打击都可对胎儿的宫内发育造成损害，并可能持续至子代成年期。研究显示，母体孕期感染可促进子代免疫激活，导致其结肠炎易感性增加，并可伴随神经系统的发育障碍[58, 59]；孕期尼古丁暴露可致子代小鼠哮喘易感性增加[60, 61]以及大脑线粒体损伤[62]。

3 发育源性疾病的表观遗传调控机制

自DOHaD理论提出后，疾病的配子、胚胎、胎儿起源机制一直是研究的热点及难点，而“表观遗传修饰”概念的提出为其机制的探索点亮了一盏明灯。表观遗传修饰是指在基因的核苷酸序列不发生改变的情况下，可遗传的基因表达变化，包括DNA甲基化、染色质重构及非编码RNA等，它是基因-环境相互作用的潜在载体，能够将环境信号传递给基因组，并调控基因活动[63]。此概念由沃丁顿于1942年首先提出，并被学者们不断完善和补充，为获得性疾病代际遗传的机制研究提供了新的思路，进一步扩充了生物进化理论。由于表观遗传修饰过程常受到环境因素的调控，因此，自孕前的配子发生至宫内胎儿发育阶段的多种暴露都可能影响生命早期的表观遗传重编程过程，导致子代多种疾病的发生风险增加[64]。

大量人类及动物研究显示，父母早期或母体孕期所经历的不良环境暴露可对子代产生深远的影响，并可能存在持久的代际遗传效应。基于人类队列的研究显示，母亲孕期吸烟可导致新生儿的大量基因发生DNA甲基化改变，且该效应可持续至儿童期[65]。Serpeloni等[66]研究发现，妊娠期间遭受精神压力所致的不良影响可持续传递至孙代，并可在

孙代全基因组中观测到多个位点的DNA甲基化变异，提示DNA甲基化改变可作为压力跨代传递的生物机制。与此同时，孕期不良因素暴露对子代表观遗传模式的调控作用也在动物模型上得到了进一步的证实。Cinquina等[67]研究发现，孕前和妊娠期间母体摄入高含量的多不饱和脂肪酸可影响胎儿的大脑发育，并且严重影响子代指示神经元分化的表观遗传检查位点，以上不良影响存在持续性效应，可进一步导致子代小鼠成年期出现焦虑样行为。Jahreis等[68]研究表明，母体于妊娠期暴露于邻苯二甲酸丁苄酯（Butyl Benzyl Phthalate，BBP）可诱导子代$CD4^+$T细胞发生DNA高甲基化，并导致子代小鼠出现严重的哮喘表型，而利用DNA去甲基化剂进行治疗可使哮喘表型得到显著的缓解，进一步证实了孕期不良因素可通过表观遗传机制调控子代的健康状态。

除妊娠期外，孕前生殖细胞的表观遗传标记也可受不良暴露因素的影响而发生改变[69]。Han等[70]研究表明，于孕前给予雌鼠高脂饮食可诱导卵母细胞中Stella蛋白的表达显著下降，破坏子代合子的DNA甲基化重塑，进而导致子代早期胚胎发育迟缓或阻滞。Chen等[71]研究发现，孕前期的高糖环境可诱导雌鼠卵母细胞中DNA双加氧酶TET3表达减少及功能下降，重编程子代胚胎的DNA甲基化谱，进而影响子代成年期胰岛素分泌相关基因的表达，并最终导致子代小鼠出现葡萄糖耐受不良。与母亲不同，父亲所经历的外界因素并不直接参与胚胎的宫内发育过程，因此，研究者们普遍认为父源性因素对子代所带来的不利影响是通过父亲精子的改变来传递的[72]。Gapp等[73]在小鼠模型中揭示了精子表观遗传修饰的改变对于后代行为学及代谢功能的调控作用。他们研究发现，雄鼠早期生活中经历创伤性压力可改变精子miRNAs的表达，而将异常精子的RNAs注入受精后的正常卵细胞中可再现后代的行为学及代谢改变。Watkins等[74]研究发现，雄鼠低蛋白饮食可诱导其精子DNA低甲基化，进而导致后代脂肪含量升高、代谢功能异常以及肠道微生物组成改变。除此之外，多种不良因素，如肥胖、环境污染物、酒精等，都可导致精子的表观遗传修饰变化，并进一步传递至后代[75]。

4 发育源性疾病的研究机遇与展望

虽然个体基因的组成可导致疾病遗传性及患病风险增高，但环境因素，尤其是生命早期以及父亲、母亲配子发生阶段的不良暴露同样至关重要[20]。DOHaD理论的提出使研究者们对疾病病因的探索不再局限于遗传因素或后天经历的外界因素，而是将目光聚焦至其生命早期起源，并发现多种疾病，如糖尿病、哮喘、神经精神疾病等，都可定义为发育源性疾病，其调控因素及发生机制尚处于探索的起步阶段。随着表观基因组技术的发展，小鼠及人类配子和胚胎中的表观遗传重编程过程逐渐为人们所认识，为进一步研究发育源性疾病的潜在机制提供了巨大的可能性。除表观遗传外，母乳[76]、菌群[77]等同样影响着子代远期的健康状况，为发育源性疾病的机制提供了研究线索及思路。如前所述，父源性因素通过精子的改变介导子代的不良表型，具有直接性；然而，母源性影响不仅包括孕前阶段，也包括妊娠期，其过程长久且遭受的不良打击混杂。如今，大多数有关母源性因素的人类队列研究尚不能将环境变化对宫内胎儿发育的直接影响与其所诱导的卵母细胞重编程完全区分开来，只能依赖动物研究填补这一空白。在未来，需要研究者们进一步明确各类不良因素的窗口期，并深入对配子–胚胎发育源性疾病进行机制探索，为疾病的生命早期起源提供更多证据及线索，从而将疾病的一级预防窗口前移至个体生命早期，在孕期甚至孕前即进行健康干预及指导，更大程度地减轻个人及社会的疾病负担。

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