

端粒在生命早期不良环境和代谢性疾病关系中的作用

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摘要: 大量流行病学和动物实验研究显示,除了生活方式和基因遗传外,生命早期不良因素暴露可能通过对胎儿端粒长度的影响,进而增加其成年后代谢性疾病的发生风险。然而早期不良因素暴露使代谢性疾病风险增加的机制尚不清楚。端粒生物学信息探索可能为预测生命早期不良环境暴露及产后健康问题提供新的途径。

关键词: 端粒; 端粒酶; 宫内因素; 代谢性疾病

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Role of telomeres in the relationship between early life adverse environments and metabolic diseases

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Abstract: Numerous epidemiological and animal experimental studies have shown that in addition to lifestyle and genetic inheritance, exposure to adverse factors in early life may increase the risk of metabolic diseases in adult offspring by affecting fetal telomere length. However, the mechanism by which early exposure to adverse factors increases the risk of metabolic diseases is still unclear. Exploring telomere biological information may provide new avenues for predicting adverse environmental exposure in early life and postnatal health issues.

Keywords: telomeres; telomerase; intrauterine factors; metabolic diseases

随着新生儿救治水平和儿童保健能力的提高,高危儿存活率大幅度上升。然而,由于受到宫内环境中不利因素的影响,高危儿在产后面临着一系列问题,如营养、生长发育和疾病等,这也是健康和疾病起源理论(the developmental origins of health and disease, DOHaD)的真实写照。强调除生活方式和基因遗传外,生命早期经历不良因素可使机体发生适应性调节,导致身体结构、功能等改变,从而增加对成年期肥胖、糖尿病和高血压等代谢性疾病的易感性。

宫内环境因素与新生儿端粒生物学的关系已被广泛探讨。怀孕期间母亲生活方式、压力和妊娠期并发症等会影响新生儿初始端粒长度。这些发现反映了生命早期不良因素暴露对新生儿初始端粒长度的影响。此外,许多研究认为新生儿端粒长度可以

预测成年后代谢性疾病的风险。本文就生命早期不良因素对端粒的影响、端粒和代谢性疾病的关系进行综述,以期探索子代生命早期不良因素和成年后代谢性疾病的关系提供新思路。

1 端粒和端粒酶

端粒位于真核细胞的染色体末端,是由端粒DNA和端粒结合蛋白组成的复合体,其主要功能是防止染色体重组、融合和降解等,从而维持染色体和基因组的完整和稳定。在哺乳动物中,端粒都是由高度保守的串联重复序列(TTAGGG)组成的,方向为5'→3'。由于DNA复制不完全和端粒酶抑制,可导致染色体末端缺损,从而出现“末端复制问题”^[1]。

端粒酶是一种核糖核蛋白复合体,主要由端粒酶RNA成分(telomerase RNA component,

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TERC)、端粒酶相关蛋白和端粒酶催化亚基(telomerase reverse transcriptase, TERT)组成^[2]。端粒酶以自身的 RNA 为模板,逆转录合成端粒重复序列添加到染色体末端,从而调节或维持端粒长度。端粒酶的活性在人类发育过程中受到高度调控,除恶性肿瘤细胞及某些细胞,如外周血单核细胞、成纤维细胞和干细胞等,绝大多数正常细胞由于人端粒酶催化亚基(human telomerase reverse transcriptase, hTERT)转录受到抑制作用而缺乏端粒酶活性,故在大部分正常细胞中端粒酶活性可忽略。

出生时端粒长度和随后的端粒缩短速率是成年期端粒长度的主要决定因素,其中端粒的缩短速率取决于氧化应激和 DNA 损伤。如果机体无法上调抗氧化防御或激活端粒修复机制,将会加速缩短端粒长度。当端粒 DNA 缩短到 Hayflick 界限时,就会导致端粒功能失调,细胞停止分裂并逐渐衰老^[3]。因此,端粒被广泛接受为衰老和年龄相关疾病的生物标志物。

2 端粒长度的影响因素

研究表明,端粒长度具有遗传性,在很大程度上是在成年之前决定的,而早期生活环境因素是整个生命过程中端粒长度的主要决定因素。其中,产前决定因素,如空气污染、压力和妊娠期并发症等被证明是影响子代端粒长度的重要因素,本节重点讨论这些最相关的产前决定因素。

2.1 遗传 子代端粒长度在一定程度上是由遗传决定的,白端粒长度的遗传力在 36%~82%。Delgado 等^[4]发现亲子间白细胞端粒长度(leukocyte telomere length, LTL)具有相关性,且近亲属间的 LTL 相关性强于远亲属间 LTL 相关性。这些结果表明端粒长度具有高度可遗传的性状。有研究推测来自父亲配子细胞的端粒长度可影响子代的端粒长度,精子细胞端粒长度随男性年龄增长而增长,且父亲生育时的年龄与后代端粒长度呈正相关^[5]。此外,非端粒区域的遗传变异也可影响端粒长度。多项研究已证实 *TERT*、*TERC*、*DKC1* 和 *OBFC1* 基因突变与端粒长度相关^[6-8]。

2.2 空气污染 研究显示生命早期空气污染暴露与端粒长度呈负相关。Harnung Scholten 等^[9]通过收集孕妇住宅地和工作地点的空气污染数据,发现母亲产前颗粒物 $\leq 10\mu\text{m}$ (PM_{10})、二氧化硫、黑碳等空气污染物暴露与脐带血端粒长度呈负相关。Kaa-li 等^[10]研究了妊娠期间因燃烧固体燃料而产生的家庭空气污染暴露史与新生儿端粒长度的关系,发现

产前颗粒物 $\leq 2.5\mu\text{m}$ ($\text{PM}_{2.5}$)暴露史与子代出生时的相对端粒长度缩短相关。空气污染导致端粒缩短的机制多认为与氧化应激相关。由于端粒含有丰富的鸟嘌呤碱基,活性氧可通过诱导鸟嘌呤碱基氧化而使 8-羟基-2'-脱氧鸟嘌呤(8-Oxo-7,8-dihydro-2'-deoxyguanosine, 8-oxodG)积累,且这种氧化损伤不能被有效修复,导致端粒单链断裂、复制叉运动停滞而加剧端粒缩短^[11]。Lee 等^[12]发现产前抗氧化剂的摄入可改善宫内空气污染暴露和新生儿端粒长度之间的负性关系,反向验证了上述猜想。

2.3 吸烟 目前,已有多项研究支持宫内烟雾暴露与后代短端粒相关。Ip 等^[13]证明产前烟草暴露与儿童端粒长度存在剂量-反应关系,母亲孕期香烟烟雾暴露时间越长,更程度的氧化应激会加快端粒磨损速率,儿童端粒长度就越短。此外,Pham 等^[14-15]研究发现产前或产后 1 个月内烟雾暴露与后代出现早期注意缺陷多动障碍症状独立相关。而 Camlin 等^[16]通过建立产前香烟烟雾暴露的动物模型,发现宫内烟雾暴露会损害雌性后代的生育能力,子代小鼠卵母细胞数量和质量降低。上述研究提示宫内香烟烟雾暴露可通过氧化应激缩短胎儿端粒长度,改变胎儿发育轨迹,影响后代远期健康。

2.4 食物 Baskind 等^[17]发现与非母乳喂养相比,6 月龄婴儿母乳喂养与 3~5 岁时较长的端粒长度相关,母乳喂养的抗炎和免疫保护作用解释了这一现象。多名研究者认为食用有色水果、绿叶蔬菜、鱼类和多不饱和脂肪酸等可降低氧化应激对儿童和青少年端粒长度的影响;相反,乳制品、谷物和高血糖负荷的饮食会因更高的氧化应激和炎症而诱发端粒长度缩短^[18-19]。此外,Chen 等^[20]研究显示高巧克力摄入量与青少年较长的白细胞端粒相关,巧克力中的黄烷醇具有抗氧化性,并可上调内皮一氧化氮合酶活性,从而避免缩短端粒。

2.5 压力 孕期母亲压力应激对胎儿端粒生物学系统会产生“编程”影响。母亲高应激状态与后代端粒长度缩短相关,不同水平的宫内应激暴露对端粒长度会产生明显影响^[21]。此外,不同的宫内压力应激暴露时间节点和压力承受时间对后代端粒长度有不同影响,震后怀孕或出生的后代端粒长度显著短于震时出生的后代^[22]。母亲更长时间暴露于压力会导致灾后出生的儿童端粒长度缩短,即母亲应激暴露会对胎儿端粒长度产生累积效应。此外,这些后代的收缩压、体质量指数和血糖等显著高于未经地震应激者的后代。宫内胎儿暴露于急性和慢性压力环境时,母体或胎盘激素和氧化应激相关介质

通过母体-胎盘-胎儿循环进入胎儿体内,诱导胎儿细胞分裂增加而加速端粒缩短速率,子代易出现代谢性改变^[23]。

2.6 肥胖 Baskind 等^[17]发现 6 月龄婴儿肥胖与 3 岁时短端粒长度相关,且前 6 个月内的体重增长、2、3 和 5 岁时的儿童肥胖与 3~5 岁儿童端粒长度无关联。然而,Prasad 等^[24]研究显示,相比于母亲妊娠期体重增加高于或等于美国妇产科学院(American College of Obstetrics and Gynecology, ACOG)推荐值,母亲孕期增重不足会对新生儿端粒长度有负面影响,但其他研究显示孕期增重和子代端粒长度无关^[24]。此外,有多项研究支持孕前母亲体重会影响子代端粒长度。Wei 等^[25]发现孕前超重母亲所生新生儿的脐带血端粒长度和胎盘端粒长度显著短于孕前体重正常母亲所生的新生儿。San-Cristobal 等^[26]发现肥胖母亲减重手术前后所生儿童端粒长度有明显差异,减重后所生后代端粒长度显著长于减重前所生后代。这是由于母亲减重后脂质代谢改善,出现低密度脂蛋白胆固醇(low density lipoprotein cholesterol, LDL-C)水平降低、LDL 颗粒变小以及高密度脂蛋白胆固醇(high density lipoprotein cholesterol, HDL-C)水平增加,从而减轻由氧化应激和炎症引起的 DNA 断裂和端粒磨损。

2.7 宫内生长受限 Goumy 等^[27]研究显示宫内发育迟缓(intra-uterine growth retardation, IUGR)与羊水样本和绒毛膜绒毛样本的端粒长度较短相关。Toutain 等^[28]研究显示妊娠合并 IUGR 胎盘滋养细胞的端粒长度显著短于妊娠未合并 IUGR 的对照组。Biron-Shental 等^[29]进一步发现,IUGR 胎盘滋养细胞内 hTERT mRNA 显著降低,SAHF 和端粒捕获显著增加。这可能表明 IUGR 胎盘滋养细胞内存在对缩短端粒的代偿性反应,从而维持端粒稳态。

2.8 辅助生殖技术 当前,有关辅助生殖技术对端粒长度影响的研究较少。Minamoto 等^[30]研究发现与自然受孕相比,接受辅助生殖技术妊娠出生的新生儿端粒长度明显较短,但也有研究认为体外受精技术对新生儿的平均端粒长度无影响。Wang 等^[31]发现与自然受孕儿童相比,应用囊胚期胚胎移植技术出生的儿童 LTL 更短,但卵裂期移植组的 LTL 与自然妊娠组相当。这可能说明胚胎移植过程本身不会导致后代端粒长度缩短,但从卵裂期到囊胚期发生的端粒延伸可能受到干扰,最终改变子代的端粒长度^[32]。

3 端粒和代谢性疾病

端粒长度和端粒酶活性是研究端粒动态变化与疾病发生风险相关性的常用指标。大量研究表明,端粒长度与细胞寿命及多种疾病相关,如糖尿病、高血压和心血管疾病等。

3.1 端粒和糖尿病关系 许多研究显示 1 型糖尿病(type 1 diabetes mellitus, T1DM)和 2 型糖尿病(type 2 diabetes mellitus, T2DM)均与端粒长度缩短相关。Cheng 等^[33]发现 T1DM、T2DM 患者的端粒显著缩短。Sampson 等^[34-35]研究通过对比 2 型糖尿病患者和无糖尿病的健康人,虽均发现 2 型糖尿病患者端粒长度更短,但前者未观察到端粒长度的变化与血糖控制、外周胰岛素抵抗和炎症相关;后者则发现端粒缩短与 2 型糖尿病的氧化应激标志物有关,端粒长度变化与胰岛素抵抗呈负相关。两人研究结局的不同可能是由于种族差异,后者研究对象为印度人群,其对胰岛素耐受性更强,对 2 型糖尿病更易感^[36]。但最近研究显示相比于胰岛素抵抗,胰岛素分泌受损在印度人群 T2DM 发病中起更大作用^[17,37]。

生命早期暴露于高血糖环境的子代不仅可出现端粒缩短,还可出现远期健康问题。Hjort 等^[38]评估了患有妊娠期糖尿病(gestational diabetes mellitus, GDM)母亲的 9~16 岁后代与同龄对照组的端粒长度,发现 GDM 组后代端粒长度较短,且女性后代的空腹胰岛素水平、胰岛素抵抗指数(homeostasis model assessment of insulin resistance, HOMA-IR)与端粒长度呈负相关,认为短端粒长度可以预测 GDM 女性后代中 2 型糖尿病及其相关代谢特征和疾病发展。此外,Yan 等^[39-40]发现子代宫内糖尿病暴露与后代代谢性疾病和青春期发育相关,可出现肥胖风险增加,心脏代谢不良和女童青春期发育提前。

Tesovnik 等^[41]对 61 名 T1DM 青少年进行纵向研究发现,相对于血糖控制良好组,血糖控制不佳组的相对端粒长度加速磨损,且糖化血红蛋白、血糖变异系数、8-硝基鸟嘌呤水平显著升高。Tamura 等^[42]研究发现 2 型糖尿病患者胰岛 α 和 β 细胞中的端粒长度显著缩短,且长端粒优先损耗,糖化血红蛋白与 α 和 β 细胞中的端粒长度呈负相关。此外,Kuhl 等^[43]通过对端粒酶 RNA 成分(TERC)基因缺乏的小鼠和正常小鼠先后进行腹腔葡萄糖耐量和胰岛素耐量试验,确认 TERC 基因缺乏小鼠存在胰岛素分泌受损,且实验组小鼠胰岛的平均端粒长度明

显减少。综合上述研究,高血糖环境诱发的氧化应激会导致端粒酶活性降低和端粒长度缩短,随之胰岛功能障碍和胰岛素分泌异常,进一步出现葡萄糖耐量受损、高血糖,从而形成恶性循环。

3.2 端粒和高血压关系 多数研究认为高血压患者可出现端粒长度缩短。Cheng 等^[44-45]发现原发性高血压患者的白细胞端粒长度明显短于正常者。Gao 等^[46]对 510 名 40~80 岁患者进行端粒长度的初步研究,发现端粒长度与收缩压和脉压均呈负相关,而与舒张压呈正相关。但也有研究显示在调整年龄后,端粒长度不是高血压的影响因素,部分研究并未发现脉压、收缩压、舒张压和端粒长度之间存在一定的相关性,因此目前端粒长度与高血压的关系尚不明确,仍有待研究^[47]。

此外,宫内高血压暴露史可使后代端粒长度缩短。Tellechea 等^[48]研究发现妊娠期高血压孕妇端粒长度显著较短,并且新生儿端粒长度与孕母妊娠动脉血压呈显著负相关,这说明新生儿端粒长度受到母亲妊娠动脉血压状况的显著影响。宫内暴露于不良环境的后代有更高的心血管风险。Laganović 等^[49]发现出生为小于胎龄儿(small for gestational age, SGA)的男性成年人的脉压和颈动脉内膜-中膜厚度明显高于出生正常的成年人,且 SGA 组的成人收缩压和心率有升高趋势。

Cao 等^[50]发现原发性高血压大鼠(spontaneously hypertensive rats, SHR)主动脉血管内皮细胞中的端粒酶活性和内皮细胞的增殖速度均明显高于正常大鼠,且在 SHR 大鼠血管内皮细胞增殖期间,端粒长度增加并保持稳定。这提示早期端粒酶活性上调、端粒长度增加和维持参与了血管内皮细胞的增殖。然而,Mouraret 等^[51]虽发现肺动脉高压小鼠肺组织 TERT 活性、TERT mRNA 和相关蛋白表达水平升高,但未发现端粒长度与肺动脉高压严重程度之间的相关性。研究者认为端粒酶通过独立于端粒延伸的功能在内皮细胞增殖和肺动脉高压中发挥作用。据此推测:在高血压发病前,端粒酶活性上调,这会通过涉及或不涉及端粒延长机制来促进血管内皮细胞增殖,从而出现过早的细胞老化,引起血管弹性减弱,加快高血压的发生和进展^[52]。

综上,生命早期不利因素的影响可通过引起端粒和端粒酶的变化,导致细胞早衰和功能障碍,引起多种代谢性疾病的发生。但目前大多研究是通过动物实验或横断面临床研究而得以验证的,尚需进一步开展大规模前瞻性临床队列研究。此外,通过探讨端粒长度和端粒酶活性变化可能是将生命早期不

良因素暴露和远期代谢综合征联系起来的机制之一,以期对高危儿生长发育进行早期干预,在发育窗口期规范生活方式,提高后代的健康水平,降低后代成年后相关代谢性疾病的发生和发展风险。

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