综述
Review

妊娠期镉暴露致新生儿端粒长度缩短和儿童心血管代谢健康损害的研究进展

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摘要：

妊娠期镉暴露是一个不可忽视的公共卫生问题，可能增加新生儿端粒长度缩短和儿童心血管代谢健康损害的风险，近年来受到诸多研究者关注。本文回顾了近年来国内外有关妊娠期镉暴露、新生儿端粒长度缩短和儿童心血管代谢异常三者关联的研究，简述了妊娠期镉暴露导致新生儿端粒长度缩短的可能机制。目前研究结果指出，妊娠期镉暴露与新生儿端粒长度缩短和儿童心血管代谢异常有关，并且新生儿端粒长度缩短也与儿童心血管代谢异常有关，表明新生儿端粒长度可能是反映妊娠期镉暴露导致儿童心血管代谢异常的生物标志物。另外，妊娠期镉暴露加速新生儿端粒长度缩短的机制包括炎症反应、线粒体功能障碍、抗氧化剂消耗/抗氧化酶失活和 DNA 甲基化等，这些生物学机制通过某些因子与儿童心血管代谢异常相关联，包括肥胖、血压偏高、空腹血糖受损、血脂异常，提示儿童心血管代谢异常可能在生命早期就被规划，但相关研究仍然较少。未来应进一步研究妊娠期镉暴露、端粒长度和子代心血管代谢三者的关联，同时研究端粒长度在其中的中介效能和相关生物学机制，从而为预防心血管代谢性疾病提供早期生物学信息。

关键词：镉暴露；端粒长度；生命早期；心血管代谢健康

Research progress on shortened telomere length in newborns and impaired cardiovascular metabolic health in children caused by exposure to cadmium during pregnancy

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Abstract:

Cadmium exposure during pregnancy is a non-negligible public health problem which may increase the risk of shortened telomere length in newborns and cardiovascular metabolic health damage in children, and has attracted attention from many researchers in recent years. This article reviewed recent studies both domestically and internationally on the associations among cadmium exposure during pregnancy, shortened telomere length in newborns, and cardiovascular metabolic abnormalities in children, and briefly outlined possible mechanisms of shortened telomere length in newborns by cadmium exposure during pregnancy. Current research results showed that cadmium exposure during pregnancy is related to shortened telomere length in newborns and cardiovascular metabolic abnormalities in children, and shortened telomere length in newborns is also related to cardiovascular metabolic abnormalities in children. It suggested that telomere length in newborns may be a biomarker reflecting cardiovascular metabolic abnormalities in children caused by cadmium exposure during pregnancy. In addition, the current potential mechanisms of cadmium exposure during pregnancy accelerating neonatal telomere length shortening include inflammatory reaction, mitochondrial dysfunction, antioxidant consumption/antioxidant enzyme inactivation, and DNA methylation, and these biological mechanisms are associated with cardiovascular metabolic abnormalities through certain factors, such as obesity, elevated blood pressure, impaired fasting blood glucose, and dyslipidemia in children, suggesting that cardiovascular metabolic abnormalities in children may be programmed in early life, but there are still few relevant studies. In the future, research should be conducted on the association among cadmium exposure during pregnancy, telomere length, and offspring cardio

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vascular metabolism, as well as possible mediating efficacy and related biological mechanisms of telomere length, aiming to provide early-life biological information for the prevention of cardiovascular and metabolic diseases.

Keywords: cadmium exposure; telomere length; early life; cardiovascular metabolic health

心血管代谢性疾病(cardiovascular and metabolic diseases, CVMD)是指代谢异常与心血管损害之间有较为明确因果关系的一种临床综合征,其发病风险表现为一个连续体,是全球主要死亡因素,常见 CVMD 有高血压、动脉粥样硬化和内皮功能障碍等[1–2]。近年来,儿童 CVMD 的发病风险采用心血管危险因素聚集(cardiometabolic risk factor clustering, CMRF)[3]来判定,其中代谢危险因素包括腹型肥胖、血压偏高、空腹血糖受损和血脂异常等。心血管代谢健康损害即指儿童具有上述一个或多个代谢危险因素,处于心血管疾病发生高风险的一种代谢异常状态。CVMD 影响因素繁多,除传统遗传因素、饮食因素和生活行为因素外,环境有害金属暴露对 CVMD 的影响也受到越来越多研究者的关注。据报道,镉暴露与成人动脉粥样硬化、高血压、内皮损伤和白细胞端粒长度(leucocyte telomere length, LTL)缩短有关,这些因素可能增加 CVMD 和其他衰老相关疾病的风险[4–5]。但由于儿童患 CVMD 的可能性较低,大部分儿童仅处于心血管代谢异常状态,且与成年期相比,在生命早期接触环境有害物质对儿童 LTL 的影响更大[6–7],所以大量研究者开始关注妊娠期镉暴露与新生儿 LTL 和儿童心血管代谢的关联。本文旨在综述妊娠期镉暴露与新生儿 LTL 的关联及可能机制,以及新生儿 LTL 作为生物标志物来反映妊娠期镉暴露导致的儿童心血管代谢异常。

1 妊娠期镉暴露与新生儿 LTL 缩短

在普通人群中,镉暴露与 LTL 较短有关[5]。这种关联也存在于新生儿人群中。缅甸一项纳入 409 对母婴的出生队列研究表明,母亲产前镉暴露与新生儿脐带血 LTL 之间存在独立负相关关系,新生儿脐带血 LTL 在母亲尿镉浓度的最低和最高四分位数组之间相差 17%[8]。在美国波士顿和纽约出生队列研究中,Cowell 等[9]分析 100 对母子后发现,母亲孕期尿金属混合物与新生儿脐带血 LTL 呈负相关,对负关联有贡献的前几位金属包括钡(35.4%)、镉(24.5%)和铅(26.9%),不过这种负关联可以通过摄入抗氧化剂缓解,如摄入适量硒,可能对人类初始 LTL 有益[10]。2013—2015 年中国武汉地区进行的一项包含 410 对母婴的出生队列研究同样发现,在调整潜在混杂因素后,妊娠期镉暴露与新生儿脐带血 LTL 呈负相关,尿镉浓度每增加 1 倍,新生儿 LTL 就会缩短 6.83%;分层分析结果显示,产前尿镉水平与新生儿脐带血 LTL 的负相关关系在女婴中更为显著,表明与男婴相比,女婴 LTL 更容易受到母亲妊娠期镉暴露的影响[11]。尽管各项研究在不同国家和地区进行,但得出的结果相似,都表明妊娠期镉暴露会增加新生儿 LTL 缩短的风险。

2 妊娠期镉暴露导致 LTL 缩短的机制

镉暴露会破坏人体主要代谢过程,诱导活性氧(reactive oxygen species, ROS)产生,诱发炎症反应、线粒体功能障碍、抗氧化剂消耗/抗氧化酶失活和 DNA 甲基化,导致 LTL 缩短。

2.1 炎症反应

实验发现,妊娠期镉暴露可激活小鼠胎盘和人滋养层细胞中的蛋白激酶 B(protein kinase B, PKB/AKT)信号,诱导炎症细胞因子产生增加,如肿瘤坏死因子-α(tumor necrosis factor, TNF-α)、白细胞介素-8(interleukin-8, IL-8)和白细胞介素-6(interleukin-6, IL-6)等[12]。另有动物实验表明,与没有镉暴露的小鼠相比,早期暴露于镉的小鼠肝脏组织表现出更严重的炎症反应[13]。体外细胞实验显示,高水平炎症反应与外周血单核细胞端粒长度缩短的风险增加有关[14]。在美国波士顿和纽约出生队列研究中,Colicino 等[15]发现有 3 种炎症标志物水平与脐带血 LTL 呈负相关,分别为 Beta 神经生长因子(Beta-nerve growth factor, BNGF)、半胱天冬酶-8(caspase-8, CASP8)和 TNF 相关活化诱导细胞因子(TNF-related activation-induced cytokine, TRANCE),其中 CASP8 贡献最大。美国南加州出生队列研究同样发现,妊娠期较高 TNF-α/IL-10 值(IL-10 为抗炎细胞因子)与新生儿 LTL 缩短显著相关[16],与妊娠期间 TNF-α/IL-10 比值最低四分位数相比,处于最高四分位数母亲的后代 LTL 平均缩短 10%。可见,炎症反应可能是联结镉毒性与 LTL 缩短的一种机制。

2.2 线粒体功能障碍

线粒体是镉毒性的作用靶点之一,镉暴露会抑制线粒体电子传递链呼吸复合物 II,使线粒体腔室内 ROS 增加,导致线粒体内膜通透性改变[17]。动物实验发现,当复合物 I 和复合物III受到抑制且琥珀酸浓度

较低时，复合物 II 在大鼠骨骼肌线粒体中可通过黄素位点高速生成 ROS，导致线粒体功能障碍[18]，其中过度产生的 ROS 会导致端粒损伤[19]，端粒损伤也会通过影响抑癌基因 *p53* 和过氧化物酶增殖物激活受体共激活物 1α（peroxisome proliferator-activated receptor-gamma coactivator 1 alpha, PGC-1α）的表达来损伤线粒体[20]，表明线粒体功能障碍和端粒损伤间存在相互作用。Cao 等[21]研究也发现，镉可通过激活线粒体介导的内在凋亡途径，使线粒体膜电位下降，增加细胞内 ROS，导致细胞氧化应激加剧，同时氨基末端激酶（jun N-terminal kinase, JNK）、细胞外信号调节激酶（extracellular-signal-regulated kinase, ERK）和 p38 蛋白激酶（p38 mitogen-activated protein kinase, p38MAPK）的磷酸化分别增强，激活丝裂原活化蛋白激酶（mitogen-activated protein kinase, MAPK）信号通路，最终导致细胞凋亡。

2.3 抗氧化剂消耗和抗氧化酶失活

谷胱甘肽（glutathione, GSH）是细胞中主要氧化还原缓冲液，镉可通过消耗细胞内 GSH 或抑制抗氧化酶来增加细胞氧化应激风险[22]，细胞内 GSH 含量降低引起的氧化应激可使 LTL 缩短，导致细胞衰老凋亡[23]。早有动物实验发现，镉会降低大鼠皮层神经元内的 GSH 水平，介导 ROS 形成而导致细胞凋亡[24]。也有人类细胞实验指出，镉处理后，人成骨细胞内 ROS 水平增加，GSH 含量降低，超氧化物歧化酶（superoxide dismutase, SOD）和过氧化氢酶（catalase, CAT）活性降低，细胞氧化还原应激加剧[25]。最近 Cirmi 等[26]在使用氯化镉处理小鼠后发现，小鼠 GSH 含量和谷胱甘肽过氧化物酶（glutathione peroxidase, GPx）活性显著降低，导致细胞衰老凋亡，并且镉还降低了凋亡调节因子 B 淋巴细胞瘤 2（B-cell lymphoma 2, Bcl2）水平，提高了 *p53* 和凋亡调节因子 B 细胞淋巴瘤 2 相关 X 蛋白（B-cell lymphoma 2 related X protein, Bax）水平。在脐带血中，血浆 *p53* 水平增加 2.42%与 LTL 缩短 10%相关[27]，*p53* 可能在生命早期促进细胞衰老。

2.4 DNA 甲基化

人体基因组在早期胚胎发育过程中会经历甲基化重编程，若这时期母亲内部环境不佳，如母亲体内镉浓度较高，可能会干扰早期胚胎发育的去甲基化和再甲基化过程[28]。在一项包含 2 个队列的全表观基因组研究中，Everson 等[29]发现 17 个与镉相关的差异 DNA 甲基化位点，其 DNA 甲基化水平与 3 个炎症信号传导基因表达相关，分别为 TNF-α 诱导蛋白 2（TNF alpha induced protein 2, TNFAIP2）、酰基辅酶 A 硫代酯酶 7（acyl-CoA thioesterase 7, ACOT7）和视黄酸受体相关孤立受体 α（retinoic acid receptor-related orphan receptor alpha, RORA）。在母子环境健康（Mothers and Children's Environmental Health, MOCEH）队列研究中，Park 等[30]分析产前镉暴露与 DNA 甲基化关联，在调整混杂因素后，发现孕产妇妊娠早期血镉浓度与婴儿 2 个差异 DNA 甲基化位点（cg05537752 和 cg24904393）显著相关。新生儿 LTL 的遗传调控由 DNA 甲基化介导和修饰[31]，表明妊娠期镉暴露可能通过调控 DNA 甲基化来介导新生儿 LTL 变化。

3 妊娠期镉暴露和早期儿童 LTL 缩短与儿童心血管代谢异常的关联

妊娠期镉暴露可通过炎症反应等机制导致新生儿 LTL 缩短，并且妊娠期镉暴露和生命早期儿童 LTL 缩短也与儿童心血管代谢异常有关（见图 1），因此，可推测早期儿童 LTL 可能是妊娠期镉暴露导致儿童心血管代谢异常的生物标志物。

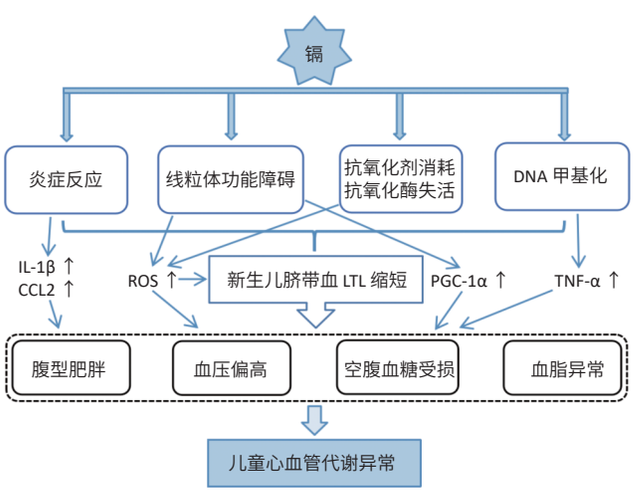

图 1 镉致新生儿 LTL 缩短机制和儿童心血管代谢异常途径

Figure 1 Mechanisms of cadmium-induced LTL shortening in newborns and pathways of cardiovascular metabolic abnormalities in children

3.1 妊娠期镉暴露和早期儿童 LTL 缩短与儿童肥胖的关联

流行病学研究表明，镉暴露与肥胖患病率之间存在关联[32]。镉暴露可以通过增强 IL-6、白细胞介素-1β（interleukins-1 beta, IL-1β）和 C-C 基序趋化因子配体 2（C-C motif chemokine ligand 2, CCL2）等促炎因子表达，扰乱脂肪细胞功能，严重影响关键溶质载体家族 30、39 转运体和金属硫蛋白基因，参与肥胖等多种

代谢异常疾病[33]。Green 等[34]研究发现，怀孕期间母亲血镉浓度与后代青少年肥胖风险增加独立相关，此研究结果也在斑马鱼模型中得到再现，在该模型中，镉暴露水平与母亲孕期血镉水平相近时，会导致斑马鱼肥胖风险增加。有证据表明，儿童肥胖也与 LTL 缩短有关[35]。一项纳入 1 396 对母子的出生队列研究发现[36]，8 岁（6~11 岁）儿童肥胖与其 LTL 缩短有关，儿童体重指数（body mass index, BMI）的 z 分数每增加 1 个单位，LTL 约缩短 1.21%（95%CI：0.30%~2.11%）。Kjaer 等[37]研究也发现，学龄前儿童 LTL 缩短与其 9 岁时肥胖相关。可见，妊娠期镉暴露和早期儿童 LTL 缩短与儿童肥胖存在关联，早期儿童 LTL 可能是未来肥胖风险的预示指标。

3.2 妊娠期镉暴露和早期儿童 LTL 缩短与儿童血压偏高的关联

心脏和血管系统极易受到环境因素的影响，镉暴露的效应目标之一就是心血管系统[38]。动物实验发现，小鼠孕期镉暴露会导致组织缺氧、ROS 产生增加以及金属稳态改变，这些机制途径与心脏和心血管系统发育异常有关，从而导致后代小鼠心脏重量增加，并且后代小鼠在成年后易患高血压[39]。人群研究表明，尿镉浓度越高，高血压发生风险就越高[40]。而儿童早期血压升高又与其出生时 LTL 缩短相关，脐带血 LTL 每减少 1 个四分位数，儿童 4~6 岁时舒张压约升高 1.54 mmHg[41]，另有证据显示，新生儿脐带血单核细胞端粒长度每缩短 10%，儿童 4 岁时收缩压约升高 0.35 mmHg[42]，表明在一定程度上，儿童心血管健康在出生时就被编程。在中国一项 1∶1 匹配病例-对照研究中，高血压组尿镉水平明显高于对照组，而高血压组 LTL 明显短于对照组；中介效应分析表明，LTL 是镉暴露与高血压之间潜在的部分中介因子[43]。可见，新生儿 LTL 可作为妊娠期镉暴露导致儿童血压升高的生物标志物。

3.3 妊娠期镉暴露和早期儿童 LTL 缩短与儿童空腹血糖受损的关联

在普通人群中，慢性环境镉暴露与糖尿病前期和糖尿病风险增加有关[44]，空腹血糖受损正处于糖尿病前期，此时空腹血糖高于正常（≥6.1 mmol·L^{-1}），但尚未达到糖尿病水平。动物实验发现，母代小鼠在妊娠期接触镉后，后代小鼠会在青春期出现高血糖，在成年期出现糖耐量受损，可能机制是镉暴露上调了后代肝糖异生过程中关键蛋白表达，包括 p-环磷腺苷效应元件结合蛋白（cAMP-response element binding protein, p-CREB）和 PGC-1α，并且提高了子代小鼠肝脏中氧化应激相关蛋白水平，包括还原型烟酰胺腺嘌呤二核苷酸磷酸氧化酶 2（nicotinamide adenine dinucleotide phosphate oxidase 2, NOX2）和血红素加氧酶-1（heme oxygenase-1, HO-1）[45]。有证据显示，儿童胰岛素抵抗[46]和血糖升高[47]与 LTL 呈显著负相关，表明儿童 LTL 缩短与葡萄糖稳态改变有关，LTL 缩短的儿童可能会伴随着空腹血糖受损等糖尿病前期症状。在糖尿病前期患者中，非 α-生育酚对 TNF-α 介导的 LTL 缩短有保护作用[48]，饮食摄入非 α-生育酚可能为延缓糖尿病发病提供新途径。可见，炎症和氧化应激介导的 LTL 缩短可作为识别儿童空腹血糖受损的早期生物标志物。

3.4 妊娠期镉暴露和早期儿童 LTL 缩短与儿童血脂异常的关联

血脂异常是常见的代谢异常疾病，包括总胆固醇（total cholesterol, TC）、甘油三酯（triglyceride, TG）和低密度脂蛋白胆固醇（low density lipoprotein cholesterol, LDL-C）升高和/或高密度脂蛋白胆固醇（high density lipoprotein cholesterol, HDL-C）降低等，但其临床早期症状不明显，难以自我察觉。流行病学研究表明，金属混合物暴露与 TC、TG 和 LDL-C 呈正相关，与 HDL-C 呈负相关，其中铅和镉与 LDL-C 表现出协同关联[49]。动物实验也发现，镉可减弱脂质摄取受体的表达，从而导致 TG 和有害载脂蛋白协同升高[50]。这与最近一项 meta 分析结果相吻合，即镉暴露与 HDL-C 降低和 TG 升高显著相关[51]。在美国一项出生队列研究中，高胆固醇血症中年患者在出生时脐带血端粒长度明显较短，这可能提示高胆固醇血症的病因源于生命早期，其中血脂异常可能在儿童时期就已开始发展[52]，但目前关于新生儿 LTL 与儿童血脂异常关联的研究很稀少，需要队列研究来进一步探索。

总体上说，儿童 CMRF 各组分发病对靶器官的损伤在儿童早期就已开始，并且其发生和进展具有较高的聚集性和隐匿性，即 CMRF 各组分可以同时发生，但也常因在儿童早期没有临床症状而不被重视。

4 结论

综上所述，母亲妊娠期镉暴露与新生儿 LTL 缩短存在关联，其中镉毒性引起的炎症反应、线粒体功能障碍、抗氧化剂消耗/抗氧化酶失活和 DNA 甲基化等机制可能起重要作用，另外，妊娠期镉暴露和早期儿童 LTL 缩短均与儿童心血管代谢异常有关，包括儿童肥胖、血压偏高、空腹血糖受损和血脂异常等，表明早

期儿童 LTL 可能是反映妊娠期镉暴露导致儿童心血管代谢异常的生物标志物。因此，孕妇可在妊娠期间摄入适量抗氧化膳食，以缓解氧化促炎因子对子代健康的影响。减少妊娠期镉暴露对保护新生儿 LTL 至关重要，这将有助于防止端粒早期磨损，降低儿童心血管代谢异常风险。未来可借助动物实验或出生队列研究进一步阐明新生儿 LTL 在妊娠期镉暴露与儿童心血管代谢异常关联中的中介效能和相关生物学机制。

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