



中国临床医学

Chinese Journal of Clinical Medicine

ISSN 1008-6358

CN 31-1794/R

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引用本文:

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DOI: 10.12025/j.issn.1008-6358.2023.20222140

· 综 述 ·

胎盘中过氧化物酶体增殖物激活受体 γ 对母胎健康的影响进展



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引用本文 白 帆, 张佳玲, 桂永浩. 胎盘中过氧化物酶体增殖物激活受体 γ 对母胎健康的影响进展 [J]. 中国临床医学, 2023, 30(1): 127-136. BAI F, ZHANG J L, GUI Y H. The effect of peroxisome proliferator-activated receptor γ in placenta on maternal and fetal health: recent progress[J]. Chin J Clin Med, 2023, 30(1): 127-136.

〔摘要〕 过氧化物酶体增殖物激活受体 γ (peroxisome proliferator-activated receptor γ , PPAR γ) 是一种配体依赖的核受体转录因子, 参与脂肪细胞分化、葡萄糖稳态和免疫反应等多种生物学过程。近年来, 越来越多的研究强调了 PPAR γ 在哺乳动物胎盘中的重要作用。本文总结了 PPAR γ 在胎盘发育和病理性妊娠中的作用以及环境污染物通过 PPAR γ 对胎盘的毒性作用, 以期提高对 PPAR γ 在胎盘中作用的认识, 阐释 PPAR γ 对母胎健康的重要意义。

〔关键词〕 过氧化物酶体增殖物激活受体 γ ; 胎盘; 妊娠期糖尿病; 子痫前期

〔中图分类号〕 R 714 **〔文献标志码〕** A

The effect of peroxisome proliferator-activated receptor γ in placenta on maternal and fetal health: recent progress

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〔Abstract〕 Peroxisome proliferator-activated receptor γ (PPAR γ) is a nuclear receptor of ligand-dependent transcription factor involved in diverse biological processes including adipocyte differentiation, glucose homeostasis, and immune response. In recent years, a growing number of studies have highlighted the essential role of PPAR γ in the mammalian placenta. This article reviews the recent progress in the research of PPAR γ in the development of placenta, pathological pregnancy and the toxic effects of environmental pollutants on the placenta through PPAR γ , in order to improve the awareness of PPAR γ in the placenta and illuminate the significance of PPAR γ in pregnancy.

〔Key Words〕 peroxisome proliferator-activated receptor γ ; placenta; gestational diabetes mellitus; preeclampsia

过氧化物酶体增殖物激活受体 (peroxisome proliferator-activated receptors, PPARs) 属于核激素受体超家族成员, 包括 PPAR α 、PPAR β/δ 和 PPAR γ 3 种亚型, 主要调节人体脂肪细胞分化、脂质代谢、胰岛素敏感性、葡萄糖平衡和炎症免疫反应等^[1-2]。其中, PPAR γ 在哺乳动物胎盘中的作用得到广泛研究。早在 1999 年, Barak 等^[3]发现 PPAR

γ 在小鼠胎盘中的表达时间明显早于其在胚胎中的表达时间, PPAR γ 丢失而引起异常发育的胎盘成为胚胎致死的直接、独立原因。PPAR γ 调控胎盘中不同滋养层谱系和不同分化阶段的基因表达, 影响滋养细胞的生物学行为、胎盘结构和血管发育, 参与处理整个妊娠期能量代谢和免疫调节^[4-5], 对子代的发育和健康产生长期影响^[3,6-8]。

〔收稿日期〕 2022-11-26 **〔接受日期〕** 2022-12-31

〔基金项目〕 上海市高水平地方高校建设项目——儿童发育与健康(DGJFYJK01), 复旦大学双一流建设学科重点项目——儿童早期健康与维护平台建设(XM06221237). Supported by the Shanghai Local High level University Construction—Child Development and Health Project (DGJFYJK01) and Key Project of Fudan University “Double First Class”—Construction of an Innovation Platform for Early Childhood Health and Maintenance (XM06221237).

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1 PPAR γ 在胎盘发育中的作用

PPAR γ 在妊娠早期的胎盘中被激活,通过调节其下游的胶质细胞缺失因子1 (glial cell missing 1, GCM1) 和人内源性逆转录病毒基因产物合胞素 1、合胞素 2, 启动干细胞样滋养层祖细胞分化为合体滋养层细胞,并在整个妊娠期间促进、维持细胞滋养层细胞向合体滋养层细胞的分化、融合以及胎盘结构的形成^[9-11]。PPAR γ 通过调节胎盘合成并分泌的妊娠相关血浆蛋白 A (pregnancy-associated plasma protein-A, PAPP-A)^[12]、人绒毛膜促性腺激素 (human chorionic gonadotropin, hCG)^[13]、赖氨酰氧化酶^[14]等,直接参与绒毛外滋养层细胞侵袭的基因表达,来抑制滋养层细胞侵袭。然而,完全阻断其表达会由于减少蜕膜巨噬细

胞的正常极化,导致蜕膜巨噬细胞浸润不足而引起滋养层侵入和胎盘发育不良,增加胚胎丢失率^[15]。

PPAR γ 能促进毛细血管样小管的形成和稳定,介导胎盘血管生成,控制胎盘绒毛生长和循环建立^[16]。小鼠胎盘滋养层干细胞中 PPAR γ 丢失后,血管内皮生长因子 (vascular endothelial growth factor, VEGF) 及其受体表达下调,血管形成障碍,无法发育出正常的胎盘迷路结构,导致小鼠胎盘迷路区畸形、母体血窦扩张破裂,造成胚胎死亡^[3, 17-19]。此外,PPAR γ 是胎盘脂质代谢的关键调节因子,调控胎盘脂肪生成、脂肪酸摄取与转运^[20-21],同时在胎盘中通过调控核因子- κ B (NF- κ B) 的激活、核转位、降解发挥抗炎作用,避免炎症诱导胎儿宫内发育迟缓和死亡^[22-24]。PPAR γ 在正常胎盘发育中的作用见图 1。

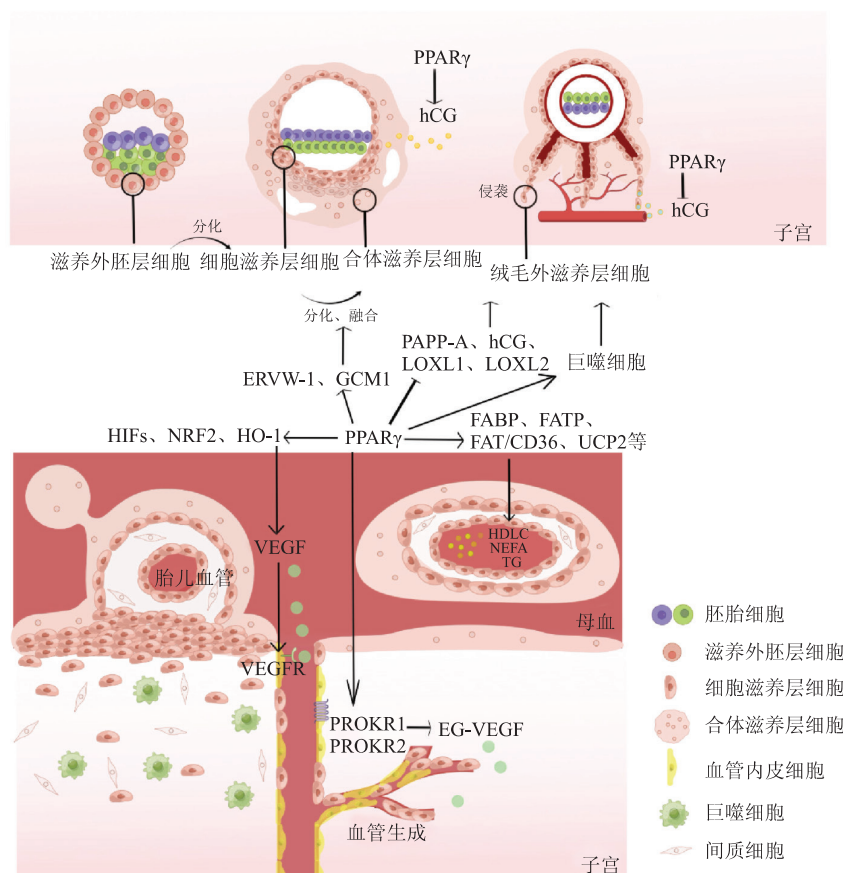


图 1 PPAR γ 在正常胎盘发育中的作用

hCG:人绒毛膜促性腺激素;PAPP-A:妊娠相关血浆蛋白A;LOXL1:赖氨酰氧化酶样蛋白1;LOXL2:赖氨酰氧化酶样蛋白2;ERVW-1:内源性反转录病毒W组成员1;GCM1:胶质细胞缺失因子1;HIFs:缺氧诱导因子;NRF2:核因子E2相关因子2;HO-1:血红素氧化酶-1;FABP:脂肪酸结合蛋白;FATP:脂肪酸转运蛋白;FAT/CD36:脂肪酸转位酶;UCP2:解偶联蛋白2;VEGF:血管内皮生长因子;VEGFR:内皮细胞生长因子受体;HDLc:高密度脂蛋白胆固醇;NEFA:非酯化脂肪酸;TG:三酰甘油;PROKR:前动力蛋白受体;EG-VEGF:内分泌腺源性血管内皮生长因子。

2 PPAR γ 在病理性妊娠中的作用

PPAR γ 参与了多种病理性妊娠过程,对妊娠患者胎盘和蜕膜的病理研究及基因组、转录组分析发现,PPAR γ 异常可引起炎症和免疫反应异常,与流产、胎膜早破、早产显著相关^[25-29]。此外,PPAR γ 可以通过影响胎盘侵袭、胎盘合体滋养层和血管形成、脂质代谢,导致妊娠期糖尿病(gestational diabetes mellitus, GDM)、子痫前期(preeclampsia, PE)、HELLP综合征和胎儿宫内生长受限^[9]。胎盘中PPAR γ 表达下调可能改变了滋养细胞增殖、分化和侵袭之间的平衡,导致滋养细胞疾病(如葡萄胎和绒毛膜癌)的发生^[30]。近年来,胎盘中PPAR γ 相关的病理性妊娠以GDM和先兆子痫为主。

2.1 GDM 绒毛不成熟、血管生成增加和胎盘重量增加是GDM最常见的胎盘异常特征^[31],这将对子代的生长、器官发育和成年后慢性代谢性疾病进展产生影响^[32-33]。糖代谢和脂质代谢的紊乱是GDM的重要特征,高血糖和高血脂相互影响,加重胰岛功能障碍^[34]。患有孕前期糖尿病的大鼠,会产生宫内重编程,使得胎盘哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)信号通路激活、PPARs表达减少、胎盘中促氧化/促炎环境增加,出现胎儿过度生长。值得关注的是,GDM还可产生代际传递,其雌性后代在妊娠时更容易出现GDM^[35]。多项研究发现:GDM的孕妇胎盘中PPAR γ 的蛋白表达量减少^[6, 36-37],并且与子代幼年期血糖升高表现出相关性^[6];而在非GDM孕妇胎盘中PPAR γ 表达水平增加时,则会增加巨大儿的发生风险^[38]。激活PPAR γ 可以促进PI3K-PKB/AKT通路,提高滋养细胞对胰岛素的敏感性^[39]。向GDM妊娠大鼠饮食中添加橄榄油,可以提高PPAR γ 活性,阻止结缔组织生长因子和基质金属蛋白酶2水平增加,防止胎盘脂质过氧化,减轻GDM大鼠的胎盘功能障碍^[37]。在人类GDM患者也可以见到类似效果,富含特级初榨橄榄油的饮食能够降低孕妇血中三酰甘油、减少体重增加,并通过激活/调节PPAR γ 通路诱导胎盘的抗炎作用^[40]。

然而,Suwaki等^[41]发现,用链脲佐菌素诱导的糖尿病妊娠小鼠胎盘中PPAR γ 的表达量增加,在高糖条件下培养人绒毛膜癌滋养层细胞系BeWo细胞,其PPAR γ 的表达和hCG的产生也增加,但该部分结果仅在过高浓度的葡萄糖暴露环境中可见。体外高糖环境将诱导滋养细胞中C1q/肿瘤坏死因子相关蛋白6(C1q/tumor necrosis factor-related protein 6, CTRP6)和其下游的PPAR γ 上调,敲低CTRP6可以抑制高糖环境诱导的PPAR γ 过表达,提高滋养细胞的存活、侵袭和迁移能力^[42-43],不过此部分研究结果尚未得到体内验证。PPAR γ 的表达变化常伴随胎盘中多种脂肪酸转运/结合蛋白的改变,从而调控胎盘脂肪生成,脂肪酸摄取、转运和代谢,因此,胎盘中PPAR γ 调节妊娠过程中母胎之间的糖代谢、脂质代谢,以及实现对母胎间能量物质的供需调控,成为近年来的研究热点。PPAR γ 异常表达常被认为是引起GDM的原因,或胎盘在GDM患者高血糖、高血脂、高胰岛素环境下的适应性改变,使得PPAR γ 可能成为治疗GDM的一个重要靶点。

2.2 PE 子痫前期主要发生在妊娠20周以后,表现为高血压、蛋白尿、水肿,常伴孕妇多脏器功能损害。胎盘绒毛结构异常、胎盘血管发育障碍,是PE的核心病理基础^[44]。众多研究表明,PPAR γ 通过多种机制在PE的发生和发展中起保护作用(图2)。

2.2.1 调节血管内皮功能 可溶性fms样酪氨酸激酶1(soluble fms-like tyrosine kinase-1, sFlt-1)是PE发展中的重要因素^[45]。抑制胎盘中PPAR γ 的表达可以降低血浆VEGF的水平,并通过降低GCM1表达,诱导合体滋养层细胞分化异常区产生强sFlt-1,使胎盘中分离母胎循环的血管间膜增厚。过多的胎盘sFlt-1被分泌到母体循环中,结合循环中的VEGF和胎盘生长因子(placental growth factor, PLGF),阻止它们与内皮细胞表面受体相互作用,抗血管生成,并使母体血管收缩,引起妊娠期高血压^[10, 46-48]。过量sFlt-1能诱导氧化和炎症环境,进一步降低胎盘中PPAR γ 的表达^[49],促进PE发展。使用PPAR γ 的高度选择性激动剂噻唑烷二酮类药物罗格列酮^[1],能激活胎盘中PPAR γ ,

直接或通过 GCM1 间接降低胎盘和循环中的 sFlt-1、可溶性内皮因子 (soluble endoglin, sEng)、内皮素-1 (endothelin-1, ET-1), 升高 PLGF 等蛋白的分泌^[10, 50-51], 缓解血管收缩状态、促进血管生成, 并有效降低血压以及微量白蛋白与肌酐的比值^[52]。此外, PPAR γ 被活化后能促进内皮细胞 NO 信号传递, 或上调成纤维细胞生长因子 2, 刺激 NO 合成和释放, 敏化 NO 的生物有效性^[51, 53-54],

有效舒张血管。血管舒张有利于母体血液流向胎盘植入部位, 一旦中断, 就会导致胎盘缺血^[55]。PPAR γ 通过影响维持血管舒缩状态和血管生成平衡的多种关键蛋白的分泌, 维持正常血管内皮细胞功能和血管舒张状态, 有利于改善 PE 孕妇的高血压以及对子代的不利结局, 如死胎、胎儿宫内生长受限、子代远期非感染性慢性疾病的发生^[7-8]。

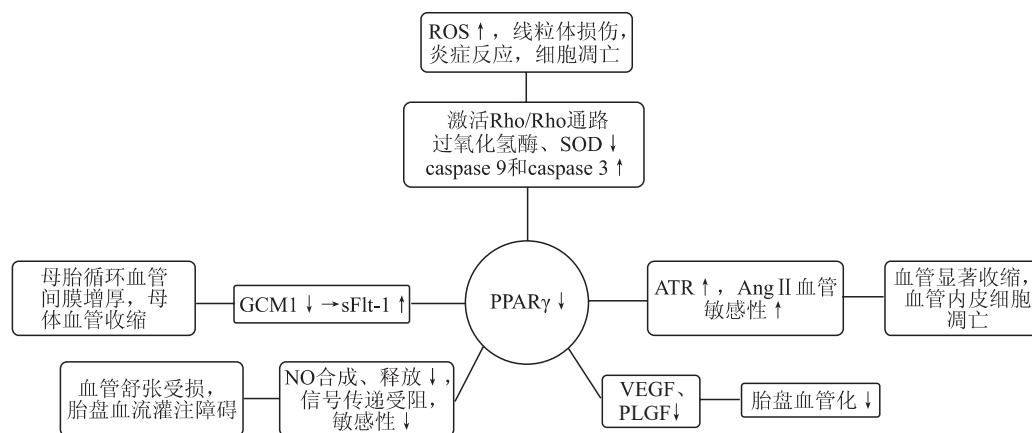


图2 PPAR γ 在子病前期中的作用和机制

2.2.2 调节肾素-血管紧张素系统 (renin-angiotensin-aldosterone system, RAAS) 在正常妊娠中, 母体血容量扩张激活母体循环和子宫胎盘单位的 RAAS, 以调节水盐平衡^[56], 血管紧张素 II (angiotensin II, Ang II) 是 RAAS 的主要效应物质, 其功能多由 Ang II 1 型受体 (angiotensin II type 1 receptor, AT1R) 介导, 正常妊娠中 AT1R 表达下调可以降低血管对升压物质的反应性, 并减弱 Ang II 的升压效应^[56]。RAAS 及其组分的异常与 PE 的发病密切相关, 还会影响胎儿各脏器发育^[57]。

PPAR γ 可以抑制 AT1R 的表达, 并通过多种途径降低血管对 Ang II 的反应性。2-甲氧基雌二醇 (2-methoxyestradiol, 2-ME) 是雌二醇在体内的生理代谢产物, 经邻苯二酚氧甲基转移酶 (catechol-O-methyltransferase, COMT) 甲基化而成。2-ME 与 PPAR 配体结构相似, 可以呈 PPAR γ 依赖性抑制基础和 Ang II 诱导的 AT1R 水平^[58], 防止孕妇在妊娠中血压升高。重度 PE 患者血浆 2-ME 水平与胎盘 COMT 活性显著降低, 并影响胎儿生长, 诱导胎儿生长受限^[59]。G 蛋白信号传导调节因子 5

(regulator of G protein signaling 5, RGS5) 在 PE 患者子宫肌层血管中的表达明显受到抑制, 导致血管对 Ang II 的敏感性增加^[60]。PPAR γ 可以与 RGS5 启动子附近的 PPAR 反应元件 (PPRE) 结合, 激活 RGS5 的表达, 钝化 Ang II 介导的蛋白激酶 C 的激活, 保留大电导 Ca^{2+} 激活的 K^{+} 通道活性, 从而对微循环中的肌源性张力提供严密的控制^[60-61], 改善血管功能和血压。PPAR γ 能直接抑制由 Ang II 介导的血管内皮功能紊乱和细胞凋亡^[62], 并在 Ang II 拮抗因子 Ang1~7 的刺激下表达增加, 减轻患者 PE 症状^[63]。但过高的 Ang II 也可以诱导 PPAR γ 核输出, 或通过泛素-蛋白酶体依赖性降解 PPAR γ ^[64], 减小 PPAR γ 对 Ang II 血管敏感性的抑制作用。PPAR γ 主要通过调控 RAAS 中关键效应因子 Ang II 来缓解 PE 症状, 其主要效应在于降低血管收缩, 保持内皮细胞活性。此外, RAAS 还同时调控着交感神经活性和醛固酮释放, 至于胎盘中 PPAR γ 是否会参与影响妊娠中 RAAS 该部分的功能改变, 目前还鲜有研究报道。

2.2.3 影响胎盘氧化应激 抗氧化系统改变以及

线粒体功能障碍是PE胎盘功能不全的标志,氧化应激加剧内皮细胞障碍,导致不良妊娠结局^[65]。在缺氧条件下,罗格列酮呈剂量依赖性上调妊娠早期胎盘外植体过氧化氢酶和超氧化物歧化酶的表达,增加缺氧下滋养层细胞株JEG-3细胞的线粒体膜电位,降低半胱氨酸天冬氨酸蛋白酶(caspase)-9和caspase-3活性,提高缺氧时滋养细胞存活率^[66]。内皮细胞中PPAR γ 表达缺失时,通过激活Rho/Rho激酶信号通路,打破氧化还原稳态,更容易出现由Ang II引起的血管内皮功能障碍^[67]。Huang等^[68]发现,从PE患者胎盘中分离出的滋养细胞Rho家族GTP酶3(Rnd3)下调,导致活性氧(reactive oxygen species, ROS)生成过多、质子的呼吸链泄漏、线粒体损伤和细胞凋亡。增加Rnd3表达时,可以与PPAR γ 相互作用,促进PPAR γ -UCP2级联,挽救Rnd3介导的线粒体功能障碍。PPAR γ 具有减少氧化应激、保护线粒体功能、防止细胞凋亡的功能,在多篇文献中报道,PPAR γ 还发挥重要抗炎作用,这对维持胎盘功能具有重要意义。

动物实验发现,给大鼠或小鼠使用PPAR γ 特异性拮抗剂后能明显诱导出典型的动脉血压升高、蛋白尿等PE症状^[48, 69],伴随母体内皮功能障碍,血小板聚集增加,活化的血小板产生更多活性氧,诱发胎盘氧化应激和炎症反应,其幼崽体重显著下降^[48, 70]。在人体中也发现孕妇血清具有激活PPAR γ 的能力,重度PE患者血清PPAR γ 激活剂水平明显降低,并且可以在临床诊断PE前几周甚至前几个月就已经出现^[71]。相应的,PPAR γ 在PE孕妇胎盘组织中也出现表达下调^[72],这预示着PPAR γ 有望成为治疗PE的潜在靶标。在小鼠妊娠中后期激活PPAR γ 能改善胎盘血管化,并能明显预防缺氧妊娠下的胎儿宫内生长受限^[7],但也有研究发现从妊娠早期开始就长期暴露于过量罗格列酮的妊娠小鼠,其海绵滋养层厚度和迷路血管表面积反而减少,也将导致胎儿生长受限^[73],其可能原因是胎盘PPAR γ 被过早、过度激活后会促进滋养层细胞过度分化,耗竭细胞滋养层细胞群的前体细胞;或改变了促血管生成和抗血管生成因子的平衡,进而干扰胎盘血管化。这使得在临床上使

用药理学调控PPAR γ 表达以实现预防和治疗PE、胎儿生长受限受到限制。为真正实现罗格列酮的临床应用价值,需要确定其剂量阈值和给药时间,或以PPAR γ 为切入点,找出其相互分子中更具特异性的疾病治疗靶点。

3 环境因素通过PPAR γ 影响胎盘和胎儿

孕期母体环境污染物暴露使部分有生殖发育毒性的物质穿过胎盘屏障进入胎儿循环,环境中的污染物在胎盘中PPAR γ 的介导下发挥毒性作用。

3.1 邻苯二甲酸酯类化合物 广泛存在的内分泌干扰物邻苯二甲酸酯及其代谢物呈脂溶性,能透过胎盘屏障,通过干扰激素受体影响胎盘功能。邻苯二甲酸二(2-乙基己基)酯(DEHP)是一种常见的邻苯二甲酸酯类化合物,DEHP暴露会干扰由PPAR γ 控制的信号通路,影响滋养层细胞的分化,导致胎盘血管形成和葡萄糖转运受损^[74],并加重妊娠期间的炎症反应,引起胎膜早破^[75],通过PPAR γ /PTEN/Akt信号通路抑制胚胎发育,表现出胚胎毒性^[76]。邻苯二甲酸单乙基己酯(MEHP),是DEHP的生物活性代谢物之一,是激活PPAR γ 的高亲和性配体,对PPAR γ 转录活性表现出“U”型剂量反应效应,通过影响MAPK通路和hCG的分泌,干扰人细胞滋养层细胞的分化和胎盘脂质代谢^[77],通过PPAR γ -MMPs通路抑制滋养细胞侵袭^[78],有增加早产或PE发生的风险。

3.2 其他污染物 另一种广泛应用于肥皂、牙膏等个人护理产品中的内分泌干扰物三氯生(triclosan, TCS)也具有发育毒性,使用PPAR γ 激动剂罗格列酮可以减轻TCS对胎盘的损伤,避免由TCS引起的胎盘重量减轻和功能障碍、胎儿身高和体质量降低^[79]。常见增塑剂磷酸三苯酯(triphenyl phosphate, TPhP)及其代谢产物在胎盘中蓄积后,以激活PPAR γ 作为分子起始事件,诱导激素分泌紊乱、干扰胎盘血管生成、促进细胞凋亡,并使PPAR γ 及其调节的脂质转运相关蛋白水平升高,引起脂质积累,诱导内质网应激和细胞凋亡,缩短妊娠时间,增加死胎率^[8, 80]。然而,尽管不同剂量TPhP的暴露都能通过PPAR γ 发挥毒性,但高、低剂量暴露表现出不一致的表型和妊娠

结局,而PPAR γ 在其中的参与度仍不明确。全氟辛酸磺酸(perfluorooctane sulfonate, PFOS)暴露使孕鼠胎盘直径减小、胎儿体质量减少,激活或过表达PPAR γ 可以挽救由PFOS诱导减少的HTR8/SVneo和JEG-3细胞增殖、迁移,减少炎症反应^[81]。镉暴露使胎盘三酰甘油、脂肪酸转运/结合蛋白、PPAR γ 、低氧诱导因子-1 α (hypoxia-inducible factor-1 α , HIF-1 α)水平下降,导致胎儿生长受限^[82]。母体烟草烟雾暴露会呈性别差异性改变胎盘中PPAR γ 和脂肪酸转运蛋白表达,使雄性胎鼠体中 ω -6和 ω -3脂肪酸的比例增加,脐动脉收缩期与舒张期流速比值(SD)增大,提示胎盘功能不全^[83]。

环境毒素暴露通过改变PPAR γ 的表达或活性,影响滋养层细胞功能和胎盘形成,破坏脂肪酸的稳态、引起脂质过氧化,诱导炎症反应,表现出发育毒性、损伤胎盘和胎儿的发育,影响妊娠结局。然而,外源性化学物质通过胎盘介导发育损害的机制仍需进一步探索。

综上所述,PPAR γ 在胎盘中的异常表达可能参与了病理性妊娠和环境污染对胚胎毒性的发生发展过程,但其中大多数机制仍未明确。胎盘中PPAR γ 在转录或转录水平后的改变,以及不同性质或浓度的配体对其在不同妊娠阶段胎盘中活性的影响,都可能通过改变正常的胎盘结构或功能而引起不良妊娠结局,对子代的健康产生危害。希望未来能进一步在合适的疾病动物模型和临床样本上探讨PPAR γ 在胎盘滋养层细胞分化、增殖中的作用及分子机制,了解胎盘中PPAR γ 对能量底物的调控和对母体环境及胎儿需求的响应,并在妊娠期间使用PPAR γ 药理学调控、进行风险评估研究以改善妊娠结局,为有效预防和治疗胎盘来源性疾病提供更多可能的方向,从而提高妊娠质量和母婴健康。

利益冲突: 所有作者声明不存在利益冲突。

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• 消 息 •

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