Hans Journal of Biomedicine 生物医学, 2024, 14(2), 201-211
Published Online April 2024 in Hans. https://www.hanspub.org/journal/hjbm
https://doi.org/10.12677/hjbm.2024.142022

Hans汉斯

核因子红细胞系2相关因子2 (Nrf2)在病理性妊娠中的作用

焦芙蓉[1]，徐翰婷[2]，陈雪梅[1*]

[1]重庆医科大学，公共卫生学院，生殖与发育教育部国际合作联合实验室，重庆
[2]重庆医科大学，基础医学院，生殖与发育教育部国际合作联合实验室，重庆

收稿日期：2024年3月11日；录用日期：2024年4月11日；发布日期：2024年4月19日

摘　要

活性氧的产生和抗氧化还原系统之间的稳态平衡在维持正常妊娠中发挥重要作用，氧化还原系统的失衡会导致各种不良妊娠结局。核因子红细胞系2相关因子2 (nuclear factor erythroid 2-related factor 2, Nrf2)是一种抗氧化关键转录因子，活化的Nrf2可与抗氧化反应元件ARE结合激活各种抗氧化基因，增强细胞的先天抗氧化状态，维持机体氧化还原动态平衡，从而减少怀孕期间各种不利因素对母体及胎儿细胞的氧化应激和炎症损伤。本研究对Nrf2在先兆子痫、IUGR、流产、早产、妊娠期GDM和代谢综合征以及预防孕期环境毒素诱导的不良妊娠结局中的作用进行综述，并分析Nrf2在各种不良妊娠结局(APOs)中可能的作用机制。

关键词

Nrf2，氧化应激，不良妊娠结局，生殖毒性

The Role of Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) in Pathological Pregnancy

Furong Jiao[1], Hanting Xu[2], Xuemei Chen[1*]

[1]Joint International Research Laboratory of Reproduction & Development, School of Public Health and Management, Chongqing Medical University, Chongqing
[2]Joint International Research Laboratory of Reproduction & Development, College of Basic Medicine, Chongqing Medical University, Chongqing

Received: Mar. 11th, 2024; accepted: Apr. 11th, 2024; published: Apr. 19th, 2024

*通讯作者 Email: chenxuemei@cqmu.edu.cn

文章引用: 焦芙蓉, 徐翰婷, 陈雪梅. 核因子红细胞系 2 相关因子 2 (Nrf2)在病理性妊娠中的作用[J]. 生物医学, 2024, 14(2): 201-211. DOI: 10.12677/hjbm.2024.142022

Abstract

The homeostatic balance between the production of reactive oxygen species and the antiredox system plays an important role in maintaining a normal pregnancy, and the imbalance of the redox system leads to a variety of adverse pregnancy outcomes. Nuclear factor erythrocyte 2 related factor 2 (Nrf2) is a key antioxidant transcription factor, activated Nrf2 can combine with antioxidant response element ARE activate various antioxidant genes, enhance the innate antioxidant status of cells, maintain the body redox dynamic balance, during pregnancy to reduce various adverse factors on the maternal and fetal cell oxidative stress and inflammation damage. In this study, the role of Nrf2 in pre-eclampsia, IUGR, abortion, preterm birth, GDM and metabolic syndrome during pregnancy, and prevention of environmental toxin-induced adverse pregnancy outcomes during pregnancy were reviewed, and analyzed the possible mechanisms of Nrf2 in various adverse pregnancy outcomes (APOs).

Keywords

Nrf2, Oxidative Stress, Adverse Pregnancy Outcome, Genotoxicity

1. 引言

妊娠期可通过胎儿体重、腹围、羊水等生理指标的变化来反应妊娠状态[1] [2] [3]。在此期间，活性氧(ROS)和抗氧化系统之间的稳态平衡是母体细胞维持稳态和胎儿细胞成长发育的重要机制，是确保成功妊娠的重要前提[4]。生理水平的 ROS 可促进正常妊娠过程中子宫、胎盘组织的重塑和生长，然而过量的 ROS 生成是一种病理性的改变，可能导致不良妊娠结局(APO)的发生[5] [6]。过量 ROS 生成和氧化还原失衡与许多 APO 有关，包括不孕、流产、早产(PTB)、宫内生长受限(IUGR)、先兆子痫(PE)和妊娠糖尿病(GDM) [7] [8]。抗氧化系统的缺乏会导致脂质过氧化产物水平升高，造成血管内皮破坏，影响滋养层细胞侵袭，进而导致先兆子痫[9] [10] [11]。缺氧诱导的氧化应激(OS)与滋养层细胞凋亡有关，滋养层细胞凋亡会减少母体向胎儿提供氧气和营养物质，从而导致 IUGR [12]。此外，胎膜中炎症反应的加剧也可导致 ROS 的过度产生，导致胎膜细胞衰老，甚至引起胎膜早破和早产(PTB)的发生[12] [13]。

事实上，机体内存在着多种途径有助于 ROS 的平衡，这里主要介绍的是由核因子红细胞系 2 相关因子 2 (nuclear factor erythroid 2-related factor 2, Nrf2)/Kelch 样 ECH 相关蛋白 1 (Keap1)通路介导的内源性抗氧化应激相关机制[14]。Nrf2 是一种抗氧化关键转录因子，是外源性有毒物质和氧化应激的感受器，在参与细胞抗氧化应激和外源性有毒物质诱导的主要防御机制中发挥重要的作用。在静息状态下，Nrf2 停留在细胞质中，与其抑制蛋白 Keap1 结合，使 Nrf2 发生多泛素化和蛋白酶体降解，以维持细胞内 Nrf2 稳态[15]。当细胞处于应激状态时，氧化/亲电应激将通过 PKC、MAPK、PI3K/Akt 等激酶参与调控 Nrf2 的丝氨酸或苏氨酸残基磷酸化来激活 Nrf2，促进 Nrf2 的蛋白稳定并发生核易位。随后 Nrf2 与细胞核内抗氧化反应元件 ARE 结合，激活其下游一系列抗氧化因子如血红素氧合酶-1 (HO-1)、过氧化物酶增殖物激活受体 γ (PPAR-γ)等，从而调节氧化防御系统，以抵御氧化应激[15] [16] [17]。

Nrf2 已在多种生殖细胞中被检测到，而这些细胞均对高水平的 ROS 敏感。妊娠期间，Nrf2 在子宫

细胞中表达增强，有助于维持子宫细胞中的氧化还原平衡，其水平在产后将逐渐降低[18]。此外，Nrf2介导的抗氧化防御系统被认为在预防 APO 中发挥重要作用[19] [20]。尽管知道 Nrf2 参与 APO 的调控，但其分子机制和功能仍不清楚。为了更好地了解 Nrf2 在妊娠和分娩中的作用，本综述分析了 Nrf2 在不良妊娠结局中所发挥的作用，并阐述了环境毒素对妊娠期间 Nrf2 表达的影响。

2. Nrf2 在先兆子痫病理生理学中的作用

先兆子痫(PE)是指妊娠 24 周后，怀孕女性出现水肿、高血压、蛋白尿，并兼有头痛、眩晕、呕吐、上腹不适、视力障碍或血压收缩高于 160 mmHg 等临床表现的一种多系统进展性疾病。体内外实验和临床研究表明 Nrf2 能在先兆子痫发病前期及中期发挥潜在作用，但具体作用还存在争议。目前大部分临床数据显示，与正常妊娠患者相比，先兆子痫患者的胎盘和血液中 Nrf2 的水平更高[21]-[37]。然而，有其他研究报告称，与正常对照组相比，先兆子痫胎盘的 Nrf2 显著降低[38]。同时，由 Keap1/Nrf2 信号通路调节的超氧化物歧化酶(SOD)、谷胱甘肽过氧化物酶(GPX)和过氧化氢酶(CAT)决定了胎盘组织的抗氧化状态，这些氧化应激相关酶的水平在 PE 胎盘组织中显著降低[32]。然而在孕妇的血浆分析中，PE 组和对照组之间 Nrf2 的含量没有显著差异[24]。

动物研究也提供了大量关于 PE 小鼠模型中 Nrf2 失调的证据。PE 小鼠模型中，沉默 Nrf2 可降低抗氧化因子 HO-1 表达，但不影响先兆子痫病理核心分子 sFlt-1 的表达[39]。Nrf2 的缺失也增加了胎盘中的氧化 DNA 所造成的损伤[40]。此外，研究还指出，Nrf2 的过度激活可能会促进 PE 的病理进展。在 PE 小鼠模型中，Nrf2 过度激活会损害胎盘血管生成，抑制胎儿生长，促进不良母体和新生儿结局的发生[40]。这些证据表明稳定的氧化应激水平对于胎儿胎盘生长至关重要，并间接证实 Nrf2 表达过多或不足都将造成胎盘发生病理性改变。有研究发现，在子痫前期小鼠模型中单独敲低 Nrf2 并不能改善母体和胎儿的结局，单独敲低 sFlt-1 效果也不明显。然而，Nrf2 和 sFlt-1 联合敲低处理能显著减轻 PE 症状，并改善 PE 小鼠模型中母体和胎儿的结局[35]。这表明仅调节抗氧化反应可能不足以预防先兆子痫，而 Nrf2 和 sFlt-1 的协同调控具有控制 PE 病情发展的能力。总的来说，调节 Nrf2 对于预防 PE 及其相关的母体和胎儿并发症的发生具有重要意义，但其具体机制还需进一步研究。

3. Nrf2 在 IUGR 病理生理学中的作用

IUGR 通常是由于母体营养供应不足造成的，其特征是绒毛外滋养层侵袭受损，此时胎儿体重低于同龄平均体重的两个标准差或是同龄体重的第 10 百分位以下。IUGR 与先兆子痫导致的继发性胎盘病变有关。研究认为，胎盘中的 OS 与 IUGR 的发生有着重要关联。一些临床研究显示，与正常妊娠女性相比，PE 和 IUGR 患者胎盘绒毛外滋养细胞中 Nrf2 水平增加[41]。研究发现，IUGR 与抗氧化酶水平降低有关，Nrf2 信号通路的抑制会进一步加重滋养层损害[42]。同时，Nrf2 在 IUGR 双胞胎较小胎儿胎盘中显著激活，可保护较小的胎儿免受 OS 损伤[43]。

动物研究表明，胎盘中的 Nrf2 水平可能调控了 IUGR 的病理生理学状态。在 IUGR 家猪模型中，外源性添加膳食姜黄素能激活 Nrf2 信号通路，增加抗氧化能力，改善仔猪肝脏以及空肠等器官功能，进而减轻 IUGR [44] [45]。有研究发现，在小鼠孕 18 天 Nrf2-KO 组的胎儿体重与 Nrf2-WT 组相比显著降低[46]。IUGR 大鼠模型中，二十二碳六烯酸能激活 Nrf2 信号通路，减轻宫内生长受限大鼠幼崽脾细胞免疫的损害[47]。然而另一项研究发现，虽然 Nrf2 缺失增加了 PAH (妊娠相关高血压)小鼠胎盘中 ROS 的积累，但是 Nrf2 缺乏能通过诱导 PAH 小鼠的胎盘血管生成改善宫内发育迟缓(IUGR)，从而降低 PAH 小鼠的围产期发病率和死亡率；在 Nrf2 药理激活后 PAH 小鼠的围产期发病率和死亡率恶化[48]。总之，这些研究表明，Nrf2 的激活有助于减轻氧化应激，但其对 IUGR 的调控存在双重作用，具体机制还需进一步探究。

4. Nrf2 在流产病理生理学中的作用

OS 是诱导特发性多囊卵巢综合征(PCOS)相关流产发生的因素之一。关于 Nrf2 在特发性复发性流产中的作用的相关证据目前仍十分有限。先前一项涉及特发性复发性流产患者的临床研究发现，Nrf2 rs6721961 多态性基因与特发性复发性流产之间不存在任何关联[49]。然而，另一项针对稽留流产患者的研究显示，绒毛膜绒毛组织中 ROS 呈高水平，而 Nrf2mRNA 转录和蛋白表达降低[50]。而使用 H_2O_2 (一种公认的氧化剂)处理稽留流产患者的绒毛膜滋养层细胞样本，会诱导 ROS 生成和细胞凋亡，且 Nrf2 的表达也随着 H_2O_2 的处理而呈剂量依赖性下降[50]。

动物研究发现，胎盘中 ROS 水平过高、线粒体功能障碍以及抗氧化因子如 SOD1 和 Keap1/Nrf2 的下调都可导致患有多囊卵巢综合征样疾病的妊娠大鼠出现胎儿丢失的现象[51]。使用 N-乙酰半胱氨酸(一种已知的抗氧化剂)处理可增强Keap1/Nrf2 的抗氧化能力，从而提高 PCOS 样妊娠大鼠胎儿存活率。然而，NAC 治疗对对照妊娠大鼠的胎儿存活率存在着负面影响[52]。这一发现表明，生理水平的 ROS 对于妊娠期正常胎盘功能和胎儿存活也是必需的。另一项研究发现，Nrf2 在患有 PCOS 的妊娠大鼠子宫中的表达会显著降低，导致子宫血管生成异常和线粒体功能障碍，干扰子宫中 ROS 产生和抗氧化应激反应的失衡，从而增加流产风险[52]。总之，Nrf2 通过维持氧化还原稳态在预防流产中发挥着重要作用，但其具体分子机制还待进一步探索。

5. Nrf2 在早产病理生理学中的作用

早产是指胎儿在母体妊娠达到 28 周但不足 37 周就分娩的过程，此时娩出的新生儿称为早产儿。宫内炎症是驱动 PTB (早产)的重要病因之一，氧化应激与 PTB 的发生密切相关。多项临床研究表明 Nrf2 的表达与 PTB 之间存在着关联。Lim 等人报道，Nrf2 基因在早产分娩和非早产分娩妇女的胎膜均存在表达。自然足月分娩后，Nrf2 基因总蛋白和核蛋白表达均显著降低。而与无组织绒毛膜羊膜炎的非早产妇女胎膜相比，早产妇女的绒毛膜组织中 Nrf2 基因的表达显著降低[48]。

体内和体外研究表明，Nrf2 与母体和胎儿细胞的炎症反应及氧化应激有关。Nrf2 缺陷小鼠胎盘的氧化应激和炎性细胞因子水平增加，导致小鼠的早产易感性增加[53]。有研究发现罗格列酮给药能通过激活 Nrf2 及其下游 HO-1 下调炎症和上调抗氧化反应能预防 PTB 的发生[54]。另一项研究发现，Nrf2 被证明在人胎膜中具有抗炎作用。通过 siRNA 沉默原代羊膜细胞中的 Nrf2 会导致由 IL-1β、TNF-α、鞭毛蛋白和 Poly (I:C)诱导的 IL-6 与 IL-8 的表达和释放显著增加，从而导致 PTB 风险增加[55]。凝血酶会增加人羊膜间充质细胞中基质金属蛋白酶-1 (MMP-1)、MMP-9 和前列腺素－内过氧化物合酶 2 (环氧合酶-2 [COX-2])的表达。MMP 的增加可能导致胶原蛋白降解和胎膜过早破裂，COX2 的上调可能导致宫颈过早成熟，导致怀孕小鼠早产[56]。用 Nrf2 激活剂，马来酸二乙酯或 15-脱氧-Δ12，14-前列腺素 J2 进行预处理，发现 Nrf2 被激活后可显著降低凝血酶诱导的羊膜间充质细胞内 COX-2、IL-1β、IL-6、IL-8 和 MMP-1 的表达，减轻凝血酶对胎膜的不良促炎作用，继而显著降低凝血酶诱导的 PTB 风险[57]。氧化应激多是通过促进炎症而增加 PTB 风险。有研究发现氧化应激会诱导怀孕小鼠胎膜的无菌炎症，抑制 Nrf2 转录后，会显著提高羊膜上皮细胞中的 ROS 水平，促进炎症相关因子 IL-6 与 IL-8 的分泌，进而增加 PTB 风险[58]。这些结果说明，Nrf2 能通过干预氧化应激和炎症相关因子的分泌进而降低 PTB 风险。

6. Nrf2 在妊娠期 GDM 和代谢综合征病理生理学中的作用

妊娠期 GDM 是指由于妊娠后母体糖代谢异常而首次发生的糖尿病，是妊娠期常见的合并症之一。一些研究已经报道了 Nrf2 在妊娠期糖尿病和妊娠期代谢综合征中的作用。临床研究表明，肥胖和正常妊娠期 GDM 患者胎盘中均存在过度 OS，Nrf2 表达降低的现象[59] [60]，这将影响后代的葡萄糖和脂质代

谢[60]。而另一项研究显示出相反的结果，妊娠期 GDM 患者胎盘组织中 OS 相关蛋白，如 Nrf2、HO-1 和 NQO1 的表达则是显著增加[61]。一项动物研究发现，妊娠期 GDM 小鼠胎盘表现出较高的 ROS 水平并激活 Nrf2 信号，并且该 Nrf2 信号的改变与自噬有关。这些 DM (糖尿病)诱导的效应最终将导致小鼠胎盘的发育缺陷，包括胎盘连接区扩大和迷路区变窄[62]。

妊娠合并代谢综合征是妊娠合并肥胖、糖尿病、高血压、高脂血症等疾病的症候群，是人体蛋白质、脂肪、碳水化合物等物质发生代谢素乱的病理状态，会导致母亲和儿童未来患慢性病疾病的风险增加[63]。Zheng 等研究了母体 25-羟基维生素 D 缺乏症在其后代代谢综合征发展中的作用。他们观察到抑制 Nrf2/CBR1 途径表达是 OS 导致母体及后代发生代谢综合征的原因之一[64]。

目前，多项研究指出，Nrf2 可以作为一种潜在的治疗靶点，用以治疗 GDM 和代谢综合征患者可能造成的母婴结局。研究指出，二甲双胍可在胎盘、人脐静脉内皮细胞和母体血液中下调 NF-kB (P65)和上调 Nrf2 表达，恢复 GDM 所致的胎盘血管生成障碍[65]；叔丁基对苯二酚(THBQ)可增加 Nrf2 的表达水平，上调下游抗氧化酶 HO-1 和 SOD2 的表达，从而显著降低 GDM 小鼠血糖水平，提高胰岛素水平，改善葡萄糖和胰岛素耐量，提高后代的存活率[66]。

7. Nrf2 在预防孕期环境毒素致病中的作用

不同环境毒素，如空气污染物、内分泌干扰物(BPA 和 BDE-47)、杀虫剂及有机磷酸盐等化学物质，对妊娠期间的母体及胎儿具有显著的毒性作用。研究发现，胎儿宫内发育迟缓、低出生体重和早产等不良妊娠结局与孕期环境毒素的暴露有关[67]。有研究指出，收集生活在高度工业化环境中孕妇的血液样本进行检测，发现血液样本中 Nrf2 水平降低，而氧化应激标志物含量显著增加[68]。事实上，Nrf2/ARE (OS)通路的适应性激活为胎儿提供了针对外源性化学物毒性的保护[69]。然而，同一研究小组后来进行的一项研究发现，暴露于有机磷酸盐的女性与对照组妇女的胎盘组织中 Nrf2 水平并没有显著差异[70]。另一项研究显示，居住在多环芳烃水平较高地区的早产患者胎盘中的 Nrf2 的水平则显著减少[71]。

双酚 A(BPA)和 2，2′4，4′-四溴二苯醚(BDE-47)等内分泌干扰物也被证明会影响 Nrf2 的表达。在 OS 状态下，BPA 会损害 Nrf2 的表达和核易位，抑制滋养层细胞的死亡，影响妊娠期间胎盘的正常发育[72]。一项针对人滋养层细胞系的体外研究表明，与对照组相比，用 Nrf2 诱导剂预处理能防止 BDE-47 诱导的 ROS 产生和促炎细胞因子反应等毒性效应，减少 IL-6 的释放和 NF-κB 的激活，增加抗氧化基因的表达[73]。有趣的是，Nrf2 的激活可以防止外源性化合物所诱导的胚胎毒性。Harris 等人证明，用 Nrf2 诱导剂二硫醚-3-硫酮(D3T)预处理，可以保护小鼠胚胎免受 OS 的侵害，维持细胞内正常的氧化还原水平以实现胚胎形态发育正常[74]。一项关于 HTR 细胞的体外研究表明，五味子乙素通过激活 Nrf2，促进其与 ARE 的结合，上调其下游基因 HO-1 和 SOD 的表达，减弱苯并(a)芘(BaP)所诱导的 HTR 毒性细胞作用[75]。另有研究发现硫化氢可上调 Nrf2 的表达来减弱 CSE 诱导的大鼠胎盘氧化损伤[76]。

8. 调控 Nrf2 水平的化合物在怀孕期间能对妊娠结局产生有益作用

一些能与 Nrf2 相互作用或参与调控 Nrf2 的化合物和药物已被研究作为预防妊娠并发症(如先兆子痫和早产)的潜在疗法。补充姜黄素具有抗氧化和调节滋养层细胞凋亡的作用，而这种效应是由通过激活 Nrf2 信号通路而实现的[77]。补充白藜芦醇能够增加血浆中 Nrf2 的含量，以及促进胎盘中 Nrf2 的核易位[26] [27] [28] [29]。萝卜硫素预处理也可增加 Nrf2 表达[34]，并诱导滋养层细胞和人脐静脉内皮细胞中 Nrf2 的活化和核易位[29]。其他分子，如索法酮[23]、辛伐他汀[78]、水飞蓟宾[33]和维生素 C，也具有上调 Nrf2 表达的能力。在人胎盘和小鼠模型中，褪黑素处理可提高胎盘组织中 Nrf2 水平[28]-[37]。Nrf2 途径的激活，能保护滋养层细胞免受缺氧/复氧引起的氧化损伤和细胞死亡[79]。

饱和脂肪酸和不饱和脂肪酸在胎盘的炎症和抗氧化能力中扮演着不同的角色。这些脂肪酸的作用受胎盘组织和细胞中 Nrf2 表达的影响。亚油酸是一种多不饱和脂肪酸，可维持胎盘功能并抑制胎盘中的炎症和 OS 产生，而棕榈酸(一种饱和脂肪酸)可增加 OS 的产生并降低胎盘的抗氧化能力。亚油酸和棕榈酸均使 Nrf2 的活性提高了 50%以上[80]。另一项研究发现，使用多不饱和脂肪酸(PUFA)处理 BeWo 细胞，特别是花生四烯酸和二十二碳六烯酸，会增加抗氧化蛋白 HO-1 的表达。然而，用靶向 Nrf2 的 siRNA 处理 BeWo 细胞会减弱 PUFA 对 HO-1 的诱导[81]。

9. 讨论

OS 和炎症是诱导多种不良妊娠结局发生的主要病理生理机制。OS 可由多种危险因素诱发，其中最常见的一种是吸烟。尽管许多报告记录了 OS 在妊娠中的作用，以及通过饮食和其他干预措施治疗 OS 的潜在外源性方法，但很少有人研究 OS 的内源性反应，确定导致 OS 的 ROS 调节因子，或将其视为靶向干预的领域。在妊娠期间，Nrf2 有助于妊娠细胞的抗氧化反应。Nrf2 的其他功能包括促进细胞存活，防止细胞死亡和胎盘异常血管生成[40]。这些功能在早期胎盘形成中很重要，有助于预防先兆子痫。Nrf2 还显示出抗炎特性，这也解释了其为何具有预防 APOs 的能力[44]。

根据本综述的内容，我们认为 Nrf2 水平不足和过量都可能导致不良妊娠结局的发生。由于 OS 失衡，Nrf2 水平不足可能导致 OS 增加[19] [32]。同样，Nrf2 水平过高可能导致异常量的氧化还原当量积累，这也可能对妊娠组织有害[82]。为了维持怀孕期间氧化还原稳态，妊娠组织中足够水平的 Nrf2 至关重要，这将促进适当的抗氧化反应以维持必要的体内平衡，以确保怀孕期间良好的母亲和胎儿结局。

虽然大量的研究调查了妊娠和分娩期间 Nrf2 的水平，但关于 Nrf2 的了解仍存在空白。由于相互矛盾的结果，目前的临床证据还没有统一的定论，即一些研究表明 Nrf2 具有保护作用，而另一些研究表明 Nrf2 与妊娠并发症没有直接关联。在不同妊娠并发症中导致 Nrf2 失调的分子途径尚不清楚，且大多数研究主要集中在胎盘组织上，只有少数研究调查了 Nrf2 在其他母体和胎儿妊娠组织(如胎膜、子宫颈和子宫)中的作用。此外，显示 Nrf2 作为预防妊娠并发症的治疗靶点的潜力的数据主要基于体外研究。由于该模型在模拟体内微环境方面的局限性，这些结果可能不适用于人类，有必要进行更多的临床前和临床研究，以阐明 Nrf2 的机制作用，并开发新的治疗策略来控制妊娠并发症并改善妊娠结局。

10. 结论

OS 和炎症在正常妊娠过程中发挥重要作用，如参与胎盘发育期的组织和血管重塑。而在病理条件下，OS 和炎症也会导致组织损伤。深入研究这一过程的调节因子及其功能，对于认识各种妊娠相关疾病的发病机制，以及制定针对这些关键靶分子的治疗策略至关重要。Nrf2 是参与细胞抗氧化反应的关键分子之一，很少有人研究其在生殖过程中的重要性。本综述分析了围产期医学和生殖免疫学领域的相关研究，这些研究显示了 Nrf2 在各种生殖组织中所发挥的作用。然而，仍需进一步的研究才能更好地了解 Nrf2 作为妊娠和分娩期间抗氧化剂分子的重要功能和确切的分子机制。

参考文献

[1] Marshall, N.E., Abrams, B., Barbour, L.A., *et al*. (2022) The Importance of Nutrition in Pregnancy and Lactation: Lifelong Consequences. *American Journal of Obstetrics & Gynecology*, **226**, 607-632. https://doi.org/10.1016/j.ajog.2021.12.035

[2] Papageorghiou, A.T., Kennedy, S.H., Salomon, L.J., *et al*. (2018) The INTERGROWTH-21 Fetal Growth Standards: Toward the Global Integration of Pregnancy and Pediatric Care. *American Journal of Obstetrics & Gynecology*, **218**, S630-S640. https://doi.org/10.1016/j.ajog.2018.01.011

[3] Nabhan, A.F. and Abdelmoula, Y.A. (2008) Amniotic Fluid Index versus Single Deepest Vertical Pocket as a Screen-

ing Test for Preventing Adverse Pregnancy Outcome. *Cochrane* Database Syst Rev, No. 3, CD006593. https://doi.org/10.1002/14651858.CD006593

[4] Shi, M., Chen, Z., Chen, M., *et al*. (2021) Continuous Activation of Polymorphonuclear Myeloid-Derived Suppressor Cells during Pregnancy Is Critical for Fetal Development. *Cellular & Molecular Immunology*, **18**, 1692-1707. https://doi.org/10.1038/s41423-021-00704-w

[5] Joo, E.H., Kim, Y.R., Kim, N., Jung, J.E., Han, S.H. and Cho, H.Y. (2021) Effect of Endogenic and Exogenic Oxidative Stress Triggers on Adverse Pregnancy Outcomes: Preeclampsia, Fetal Growth Restriction, Gestational Diabetes Mellitus and Preterm Birth. *International Journal of Molecular Sciences*, **22**, Article 10122. https://doi.org/10.3390/ijms221810122

[6] Quan, J.H., Gao, F.F., Ma, T.Z., *et al*. (2023) *Toxoplasma gondii* Induces Pyroptosis in Human Placental Trophoblast and Amniotic Cells by Inducing ROS Production and Activation of Cathepsin B and NLRP1/NLRP3/NLRC4/AIM2 Inflammasome. *The American Journal of Pathology*, **193**, 2047-2065. https://doi.org/10.1016/j.ajpath.2023.08.016

[7] Menon, R., Boldogh, I., Urrabaz-Garza, R., *et al*. (2013) Senescence of Primary Amniotic Cells via Oxidative DNA Damage. *PLOS ONE*, **8**, e83416. https://doi.org/10.1371/journal.pone.0083416

[8] Duhig, K., Chappell, L.C. and Shennan, A.H. (2016) Oxidative Stress in Pregnancy and Reproduction. *Obstetric Medicine*, **9**, 113-116. https://doi.org/10.1177/1753495X16648495

[9] Al-Gubory, K.H., Fowler, P.A. and Garrel, C. (2010) The Roles of Cellular Reactive Oxygen Species, Oxidative Stress and Antioxidants in Pregnancy Outcomes. *The International Journal of Biochemistry & Cell Biology*, **42**, 1634-1650. https://doi.org/10.1016/j.biocel.2010.06.001

[10] Sağol, S., Özkinay, E. and Özşener, S. (1999) Impaired Antioxidant Activity in Women with Pre-Eclampsia. *International Journal of Gynecology & Obstetrics*, **64**, 121-127. https://doi.org/10.1016/S0020-7292(98)00217-3

[11] De Oliveira, L.G., Karumanchi, A. and Sass, N. (2010) Preeclampsia: Oxidative Stress, Inflammation and Endothelial Dysfunction. *Revista Brasileira de Ginecologia e Obstetrícia*, **32**, 609-616. https://doi.org/10.1590/S0100-72032010001200008

[12] Menon, R. and Richardson, L.S. (2017) Preterm Prelabor Rupture of the Membranes: A Disease of the Fetal Membranes. *Seminars in Perinatology*, **41**, 409-419. https://doi.org/10.1053/j.semperi.2017.07.012

[13] Moore, T.A., Ahmad, I.M. and Zimmerman, M.C. (2018) Oxidative Stress and Preterm Birth: An Integrative Review. *Biological Research for Nursing*, **20**, 497-512. https://doi.org/10.1177/1099800418791028

[14] Ma, Q. (2013) Role of Nrf2 in Oxidative Stress and Toxicity. *Annual Review of Pharmacology and Toxicology*, **53**, 401-426. https://doi.org/10.1146/annurev-pharmtox-011112-140320

[15] Bellezza, I., Giambanco, I., Minelli, A. and Donato, R. (2018) Nrf2-Keap1 Signaling in Oxidative and Reductive Stress. *Biochimica et Biophysica Acta* (*BBA*)—*Molecular Cell Research*, **1865**, 721-733. https://doi.org/10.1016/j.bbamcr.2018.02.010

[16] Kweider, N., Wruck, C.J. and Rath, W. (2013) New Insights into the Pathogenesis of Preeclampsia—The Role of Nrf2 Activators and Their Potential Therapeutic Impact. *Geburtshilfe und Frauenheilkunde*, **73**, 1236-1240. https://doi.org/10.1055/s-0033-1360133

[17] Kweider, N., Huppertz, B., Kadyrov, M., Rath, W., Pufe, T. and Wruck, C.J. (2014) A Possible Protective Role of Nrf2 in Preeclampsia. *Annals of Anatomy*, **196**, 268-277. https://doi.org/10.1016/j.aanat.2014.04.002

[18] Lu, J., Wang, Z., Cao, J., Chen, Y. and Dong, Y. (2018) A Novel and Compact Review on the Role of Oxidative Stress in Female Reproduction. *Reproductive Biology and Endocrinology*, **16**, Article No. 80. https://doi.org/10.1186/s12958-018-0391-5

[19] Hussain, T., Tan, B., Liu, G., *et al*. (2017) Modulatory Mechanism of Polyphenols and Nrf2 Signaling Pathway in LPS Challenged Pregnancy Disorders. *Oxidative Medicine and Cellular Longevity*, **2017**, Article ID: 8254289. https://doi.org/10.1155/2017/8254289

[20] Hadley, E.E., Richardson, L.S., Torloni, M.R. and Menon, R. (2018) Gestational Tissue Inflammatory Biomarkers at Term Labor: A Systematic Review of Literature. *American Journal of Reproductive Immunology*, **79**, e12776. https://doi.org/10.1111/aji.12776

[21] Kweider, N., Fragoulis, A., Rosen, C., *et al*. (2011) Interplay between Vascular Endothelial Growth Factor (VEGF) and Nuclear Factor Erythroid 2-Related Factor-2 (Nrf2): Implications for Preeclampsia. *Journal of Biological Chemistry*, **286**, 42863-42872. https://doi.org/10.1074/jbc.M111.286880

[22] Pang, H., Huang, Y., Liu, Z., *et al*. (2011) Effect of Lipoxin A_4 on Lipopolysaccharide-Induced Endothelial Hyperpermeability in Human Umbilical Vein Endothelial Cell. *Chinese Journal of Obstetrics and Gynecology*, **46**, 199-204. https://doi.org/10.1100/tsw.2011.98

[23] Onda, K., Tong, S., Nakahara, A., *et al*. (2015) Sofalcone Upregulates the Nuclear Factor (Erythroid-Derived 2)-Like

2/Heme Oxygenase-1 Pathway, Reduces Soluble fms-Like Tyrosine Kinase-1, and Quenches Endothelialdys Function: Potential Therapeutic for Preeclampsia. *Hypertension*, **65**, 855-862. https://doi.org/10.1161/HYPERTENSIONAHA.114.04781

[24] Chigusa, Y., Kondoh, E., Mogami, H., *et al*. (2016) Nrf2 Activation Inhibits Thrombin-Induced COX2 and PGE2 in Human Amnion Mesenchymal Cells. *Placenta*, **46**, 112. https://doi.org/10.1016/j.placenta.2016.08.040

[25] Li, J., Zhou, J., Ye, Y., *et al*. (2016) Increased Heme Oxygenase-1 and Nuclear Factor Erythroid 2-Related Factor-2 in the Placenta Have a Cooperative Action on Preeclampsia. *Gynecologic and Obstetric Investigation*, **81**, 543-551. https://doi.org/10.1159/000451025

[26] Gurusinghe, S., Cox, A.G., Rahman, R., *et al*. (2017) Resveratrol Mitigates Tro-Phoblast and Endothelial Dysfunction Partly via Activation of Nuclear Factor Erythroid 2-Related Factor-2. *Placenta*, **60**, 74-85. https://doi.org/10.1016/j.placenta.2017.10.008

[27] Onda, K., Tong, S., Beard, S., *et al*. (2017) Proton Pump Inhibitors Decrease Soluble fms-Like Tyrosine Kinase-1 and Soluble Endoglin Secretion, Decrease Hypertension, and Rescue Endothelial Dysfunction. *Hypertension*, **69**, 457-468. https://doi.org/10.1161/HYPERTENSIONAHA.116.08408

[28] Hobson, S.R., Gurusinghe, S., Lim, R., *et al*. (2018) Melatonin Improves Endothelial Function *in Vitro* and Prolongs Pregnancy in Women with Early-Onset Preeclampsia. *Journal of Pineal Research*, **65**, e12508. https://doi.org/10.1111/jpi.12508

[29] Caldeira-Dias, M., Montenegro, M.F., Bettiol, H., *et al*. (2019) Resveratrol Improves Endothelial Cell Markers Impaired by Plasma Incubation from Women Who Subsequently Develop Preeclampsia. *Hypertension Research*, **42**, 1166-1174. https://doi.org/10.1038/s41440-019-0243-5

[30] Cox, A.G., Gurusinghe, S., Abd Rahman, R., *et al*. (2019) Sulforaphane Improves Endothelial Function and Reduces Placental Oxidative Stress *in Vitro*. *Pregnancy Hypertension*, **16**, 1-10. https://doi.org/10.1016/j.preghy.2019.02.002

[31] Knyazev, E.N., Zakharova, G.S., Astakhova, L.A., Tsypina, I.M., Tonevitsky, A.G. and Sukhikh, G.T. (2019) Metabolic Reprogramming of Trophoblast Cells in Response to Hypoxia. *Bulletin of Experimental Biology and Medicine*, **166**, 321-325. https://doi.org/10.1007/s10517-019-04342-1

[32] Feng, H., Wang, L., Zhang, G., Zhang, Z. and Guo, W. (2020) Oxidative Stress Activated by Keap-1/Nrf2 Signaling Pathway in Pathogenesis of Preeclampsia. *International Journal of Clinical and Experimental Pathology*, **13**, 382-392.

[33] Guo, H., Wang, Y. and Liu, D. (2020) Silibinin Ameliorats H_2O_2-Induced Cell Apoptosis and Oxidative Stress Response by Activating Nrf2 Signaling in Trophoblast Cells. *Acta Histochemica*, **122**, Article 151620. https://doi.org/10.1016/j.acthis.2020.151620

[34] Langston-Cox, A., Muccini, A.M., Marshall, S.A., *et al*. (2020) Sulforaphane Improves Syncytiotrophoblast Mitochondrial Function after *in Vitro* Hypoxic and Superoxide Injury. *Placenta*, **96**, 44-54. https://doi.org/10.1016/j.placenta.2020.05.005

[35] Li, L., Li, H., Xue, J., Chen, P., Zhou, Q. and Zhang, C. (2020) Nanoparticle-Mediated Simultaneous Downregulation of Placental Nrf2 and SFlt1 Improves Maternal and Fetal Outcomes in a Preeclampsia Mouse Model. *ACS Biomaterials Science & Engineering*, **6**, 5866-5873. https://doi.org/10.1021/acsbiomaterials.0c00826

[36] Yang, S., Zhang, R., Xing, B., Zhou, L., Zhang, P. and Song, L. (2020) Astragaloside IV Ameliorates Preeclampsia-Induced Oxidative Stress through the Nrf2/HO-1 Pathway in a Rat Model. *American Journal of Physiology-Endocrinology and Metabolism*, **319**, e904-e911. https://doi.org/10.1152/ajpendo.00357.2020

[37] Zuo, J. and Jiang, Z. (2020) Melatonin Attenuates Hypertension and Oxidative Stress in a Rat Model of L-NAME-Induced Gestational Hypertension. *Vascular Medicine*, **25**, 295-301. https://doi.org/10.1177/1358863X20919798

[38] Chigusa, Y., Tatsumi, K., Kondoh, E., *et al*. (2012) Decreased Lectin-Like Oxidized LDL Receptor 1 (LOX-1) and Low Nrf2 Activation in Placenta Are Involved in Preeclampsia. *The Journal of Clinical Endocrinology & Metabolism*, **97**, e1862-e1870. https://doi.org/10.1210/jc.2012-1268

[39] Tong, S., Kaitu'u-Lino, T.J., Onda, K., *et al*. (2015) Heme Oxygenase-1 Is Not Decreased in Preeclamptic Placenta and Does Not Negatively Regulate Placental Soluble fms-Like Tyrosine Kinase-1 or Soluble Endoglin Secretion. *Hypertension*, **66**, 1073-1081. https://doi.org/10.1161/HYPERTENSIONAHA.115.05847

[40] Nezu, M., Souma, T., Yu, L., *et al*. (2017) Nrf2 Inactivation Enhances Placental Angiogenesis in a Preeclampsia Mouse Model and Improves Maternal and Fetal Outcomes. *Science Signaling*, **10**, eaam5711. https://doi.org/10.1126/scisignal.aam5711

[41] Acar, N., Soylu, H., Edizer, I., *et al*. (2014) Expression of Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) and Peroxiredoxin 6 (Prdx6) Proteins in Healthy and Pathologic Placentas of Human and Rat. *Acta Histochemica*, **116**, 1289-1300. https://doi.org/10.1016/j.acthis.2014.07.012

[42] Kweider, N., Huppertz, B., Wruck, C.J., *et al*. (2012) A Role for Nrf2 in Redox Signalling of the Invasive Extravillous Trophoblast in Severe Early Onset IUGR Associated with Preeclampsia. *PLOS ONE*, **7**, e47055.

https://doi.org/10.1371/journal.pone.0047055

[43] Wu, J., He, Z., Gao, Y., Zhang, G., Huang, X. and Fang, Q. (2017) Placental NFE2L2 Is Discordantly Activated in Monochorionic Twins with Selective Intrauterine Growth Restriction and Possibly Regulated by Hypoxia. *Free Radical Research*, **51**, 351-359. https://doi.org/10.1080/10715762.2017.1315113

[44] Yan, E., Zhang, J., Han, H., *et al*. (2019) Curcumin Alleviates IUGR Jejunum Damage by Increasing Antioxidant Capacity through Nrf2/Keap1 Pathway in Growing Pigs. *Animals* (*Basel*), **10**, Article 41. https://doi.org/10.3390/ani10010041

[45] Niu, Y., He, J., Ahmad, H., *et al*. (2019) Dietary Curcumin Supplementation Increases Antioxidant Capacity, Upregulates Nrf2 and Hmox1 Levels in the Liver of Piglet Model with Intrauterine Growth Retardation. *Nutrients*, **11**, Article 2978. https://doi.org/10.3390/nu11122978

[46] Kweider, N., Huppertz, B., Rath, W., *et al*. (2017) The Effects of Nrf2 Deletion on Placental Morphology and Exchange Capacity in the Mouse. *The Journal of Maternal-Fetal & Neonatal Medicine*, **30**, 2068-2073. https://doi.org/10.1080/14767058.2016.1236251

[47] Jiang, W., Wan, L., Chen, P. and Lu, W. (2021) Docosahexaenoic Acid Activates the Nrf2 Signaling Pathway to Alleviate Impairment of Szui(2020) Excessive Reactive Oxygen Species Induce Apoptosis via the APPL1-Nrf2/HO-1 Antioxidant Signalling Pathway in Trophoblasts with Missed Abortion. *Life Sciences*, **254**, Article 117781. https://doi.org/10.1016/j.lfs.2020.117781

[48] Khadzhieva, M.B., Lutcenko, N.N., Volodin, I.V., Morozova, K.V. and Salnikova, L.E. (2014) Association of Oxidative Stress-Related Genes with Idiopathic Recurrent Miscarriage. *Free Radical Research*, **48**, 534-541. https://doi.org/10.3109/10715762.2014.891735

[49] Luan, X., Yan, Y., Zheng, Q., *et al*. (2020) Excessive Reactive Oxygen Species Induce Apoptosis via the APPL1-Nrf2/HO-1 Antioxidant Signalling Pathway in Trophoblasts with Missed Abortion. *Life Sciences*, **254**, Article 117781. https://doi.org/10.1016/j.lfs.2020.117781

[50] Zhang, Y., Zhao, W., Xu, H., *et al*. (2019) Hyperandrogenism and Insulin Resistance-Induced Fetal Loss: Evidence for Placental Mitochondrial Abnormalities and Elevated Reactive Oxygen Species Production in Pregnant Rats That Mimic the Clinical Features of Polycystic Ovary Syndrome. *The Journal of Physiology*, **597**, 3927-3950. https://doi.org/10.1113/JP277879

[51] Hu, M., Zhang, Y., Guo, X., *et al*. (2019) Hyperandrogenism and Insulin Resistance Induce Gravid Uterine Defects in Association with Mitochondrial Dysfunction and Aberrant Reactive Oxygen Species Production. *American Journal of Physiology-Endocrinology and Metabolism*, **316**, e794-e809. https://doi.org/10.1152/ajpendo.00359.2018

[52] Sussan, T.E., Sudini, K., Talbot Jr., C.C., *et al*. (2017) Nrf2 Regulates Gene-Environment Interactions in an Animal Model of Intrauterine Inflammation: Implications for Preterm Birth and Prematurity. *Scientific Reports*, **7**, Article No. 40194. https://doi.org/10.1038/srep40194

[53] Kadam, L., Gomez-Lopez, N., Mial, TN., *et al*. (2017) Rosiglitazone Regulates TLR4 and Rescues HO-1 and NRF2 Expression in Myometrial and Decidual Macrophages in Inflammation-Induced Preterm Birth. *Reproductive Sciences*, **24**, 1590-1599. https://doi.org/10.1177/1933719117697128

[54] Zhang, W., Li, M., Li, N. and Liu, Z. (2020) Regulation of Keap-1/Nrf2 Signaling Pathway Is Activated by Oxidative Stress in Patients with Premature Rupture of Membranes. *Medical Science Monitor*, **26**, e921757. https://doi.org/10.12659/MSM.921757

[55] Mogami, H., Keller, P.W., Shi, H. and Word, R.A. (2014) Effect of Thrombin on Human Amnion Mesenchymal Cells, Mouse Fetal Membranes, and Preterm Birth. *Journal of Biological Chemistry*, **289**, 13295-13307. https://doi.org/10.1074/jbc.M114.550541

[56] Chigusa, Y., Kishore, A.H., Mogami, H. and Word, R.A. (2016) Nrf2 Activation Inhibits Effects of Thrombin in Human Amnion Cells and Thrombin-Induced Preterm Birth in Mice. *The Journal of Clinical Endocrinology & Metabolism*, **101**, 2612-2621. https://doi.org/10.1210/jc.2016-1059

[57] Gusar, V.A., Timofeeva, A.V., Chagovets, V.V., *et al*. (2022) Interrelation between miRNAs Expression Associated with Redox State Fluctuations, Immune and Inflammatory Response Activation, and Neonatal Outcomes in Complicated Pregnancy, Accompanied by Placental Insufficiency. *Antioxidants* (*Basel*), **12**, Article 6. https://doi.org/10.3390/antiox12010006

[58] Duan, Y., Sun, F., Que, S., Li, Y., Yang, S. and Liu, G. (2018) Prepregnancy Maternal Diabetes Combined with Obesity Impairs Placental Mitochondrial Function Involving Nrf2/ARE Pathway and Detrimentally Alters Metabolism of Offspring. *Obesity Research & Clinical Practice*, **12**, 90-100. https://doi.org/10.1016/j.orcp.2017.01.002

[59] Manoharan, B., Bobby, Z., Dorairajan, G., *et al*. (2019) Increased Placental Expressions of Nuclear Factor Erythroid 2-Related Factor 2 and Antioxidant Enzymes in Gestational Diabetes: Protective Mechanisms against the Placental Oxidative Stress? *European Journal of Obstetrics & Gynecology and Reproductive Biology*, **238**, 78-85.

https://doi.org/10.1016/j.ejogrb.2019.05.016

[60] Zhang, C., Yang, Y., Chen, R., *et al*. (2019) Aberrant Expression of Oxidative Stress Related Proteins Affects the Pregnancy Outcome of Gestational Diabetes Mellitus Patients. *American Journal of Translational Research*, **11**, 269-279.

[61] He, M.-Y., Wang, G., Han, S.-S., *et al*. (2016) Nrf2 Signalling and Autophagy Are Involved in Diabetes Mellitus-Induced Defects in the Development of Mouse Placenta. *Open Biology*, **6**, Article 160064. https://doi.org/10.1098/rsob.160064

[62] McAninch, D., Bianco-Miotto, T., Gatford, K.L., *et al*. (2020) The Metabolic Syndrome in Pregnancy and Its Association with Child Telomere Length. *Diabetologia*, **63**, 2140-2149. https://doi.org/10.1007/s00125-020-05242-0

[63] Zheng, J., Liu, X., Zheng, B., *et al*. (2020) Maternal 25-Hydroxyvitamin D Deficiency Promoted Metabolic Syndrome and Downregulated Nrf2/CBR1 Pathway in Offspring. *Frontiers in Pharmacology*, **11**, Article 97. https://doi.org/10.3389/fphar.2020.00097

[64] Sun, C.C., Lai, Y.N., Wang, W.H., *et al*. (2020) Metformin Ameliorates Gestational Diabetes Mellitus-Induced Endothelial Dysfunction via Downregulation of P65 and Upregulation of Nrf2. *Frontiers in Pharmacology*, **11**, Article 575390. https://doi.org/10.3389/fphar.2020.575390

[65] Song, H., Xu, Y., Yang, X., Rong, X., Wang, Y. and Wei, N. (2019) Tertiary Butylhydroquinone Alleviates Gestational Diabetes Mellitus in C57BL/KsJ-Lep db/+ Mice by Suppression of Oxidative Stress. *Journal of Cellular Biochemistry*, **120**, 15310-15319. https://doi.org/10.1002/jcb.28798

[66] Srám, R.J., Binková, B., Dejmek, J. and Bobak, M. (2005) Ambient Air Pollution and Pregnancy Outcomes: A Review of the Literature. *Environmental Health Perspectives*, **113**, 375-382. https://doi.org/10.1289/ehp.6362

[67] Nagiah, S., Phulukdaree, A., Naidoo, D., *et al*. (2015) Oxidative Stress and Air Pollution Exposure during Pregnancy: A Molecular Assessment. *Human & Experimental Toxicology*, **34**, 838-847. https://doi.org/10.1177/0960327114559992

[68] Chiapella, G., Flores-Martín, J., Ridano, M.E., *et al*. (2013) The Organophosphate Chlorpyrifos Disturbs Redox Balance and Triggers Antioxidant Defense Mechanisms in JEG-3 Cells. *Placenta*, **34**, 792-798. https://doi.org/10.1016/j.placenta.2013.06.007

[69] Chiapella, G., Genti-Raimondi, S. and Magnarelli, G. (2014) Placental Oxidative Status in Rural Residents Environmentally Exposed to Organophosphates. *Environmental Toxicology and Pharmacology*, **38**, 220-229. https://doi.org/10.1016/j.etap.2014.06.001

[70] Suter, M.A., Aagaard, K.M., Coarfa, C., *et al*. (2019) Association between Elevated Placental Polycyclic Aromatic Hydrocarbons (PAHs) and PAH-DNA Adducts from Superfund Sites in Harris County, and Increased Risk of Preterm Birth (PTB). *Biochemical and Biophysical Research Communications*, **516**, 344-349. https://doi.org/10.1016/j.bbrc.2019.06.049

[71] Ponniah, M., Billett, E.E. and de Girolamo, L.A. (2015) Bisphenol A Increases BeWo Trophoblast Survival in Stress-Induced Paradigms through Regulation of Oxidative Stress and Apoptosis. *Chemical Research in Toxicology*, **28**, 1693-1703. https://doi.org/10.1021/acs.chemrestox.5b00093

[72] Park, H.-R. and Loch-Caruso, R. (2014) Protective Effect of Nuclear Factor E2-Related Factor 2 on Inflammatory Cytokine Response to Brominated Diphenyl Ether-47 in the HTR-8/SVneo Human First Trimester Extravillous Trophoblast Cell Line. *Toxicology and Applied Pharmacology*, **281**, 67-77. https://doi.org/10.1016/j.taap.2014.09.015

[73] Harris, C. and Hansen, J.M. (2012) Nrf2-Mediated Resistance to Oxidant-Induced Redox Disruption in Embryos. *Birth Defects Research Part B: Developmental and Reproductive Toxicology*, **95**, 213-218. https://doi.org/10.1002/bdrb.21005

[74] Dong, Q., Hou, H., Wu, J. and Chen, Y. (2016) The Nrf2-ARE Pathway Is Associated with Schisandrin B Attenuating Benzo(a)pyrene-Induced HTR Cells Damages *in Vitro*. *Environmental Toxicology*, **31**, 1439-1449. https://doi.org/10.1002/tox.22149

[75] Zhao, F., Lei, F., Yan, X., Zhang, S., Wang, W. and Zheng, Y. (2018) Protective Effects of Hydrogen Sulfide against Cigarette Smoke Exposure-Induced Placental Oxidative Damage by Alleviating Redox Imbalance via Nrf2 Pathway in Rats. *Cellular Physiology and Biochemistry*, **48**, 1815-1828. https://doi.org/10.1159/000492504

[76] Qi, L., Jiang, J., Zhang, J., Zhang, L. and Wang, T. (2020) Curcumin Protects Human Trophoblast HTR8/SVneo Cells from H_2O_2-Induced Oxidative Stress by Activating Nrf2 Signaling Pathway. *Antioxidants* (*Basel*), **9**, Article 121. https://doi.org/10.3390/antiox9020121

[77] Chigusa, Y., Kawasaki, K., Kondoh, E., *et al*. (2016) Simvastatin Inhibits Oxidative Stress via the Activation of Nuclear Factor Erythroid 2-Related Factor 2 Signaling in Trophoblast Cells. *Journal of Obstetrics and Gynaecology Research*, **42**, 36-43. https://doi.org/10.1111/jog.12876

[78] Sagrillo-Fagundes, L., Bienvenue-Pariseault, J. and Vaillancourt, C. (2019) Melatonin: The Smart Molecule That Differentially Modulates Autophagy in Tumor and Normal Placental Cells. *PLOS ONE*, **14**, e0202458.

https://doi.org/10.1371/journal.pone.0202458

[79] Manuel, C.R., Charron, M.J., Ashby Jr., C.R. and Reznik, S.E. (2018) Saturated and Unsaturated Fatty Acids Differentially Regulate *in Vitro* and *ex Vivo* Placental Antioxidant Capacity. *American Journal of Reproductive Immunology*, **80**, e12868. https://doi.org/10.1111/aji.12868

[80] Ono, K., Furugen, A., Kurosawa, Y., *et al*. (2019) Analysis of the Effects of Polyunsaturated Fatty Acids on Transporter Expressions Using a PCR Array: Induction of XCT/SLC7A11 in Human Placental BeWo Cells. *Placenta*, **75**, 34-41. https://doi.org/10.1016/j.placenta.2018.11.010

[81] Brewer, A.C., Mustafi, S.B., Murray, T.V.A., Rajasekaran, N.S. and Benjamin, I.J. (2012) Reductive Stress Linked to Small HSPs, G6PD, and Nrf2 Pathways in Heart Disease. *Antioxidants & Redox Signaling*, **18**, 1114-1127. https://doi.org/10.1089/ars.2012.4914

[82] Menon, R. and Peltier, M.R. (2020) Novel Insights into the Regulatory Role of Nuclear Factor (Erythroid-Derived 2)-Like 2 in Oxidative Stress and Inflammation of Human Fetal Membranes. *International Journal of Molecular Sciences*, **21**, Article 6139. https://doi.org/10.3390/ijms21176139