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氧化应激在激素性股骨头坏死发病机制中的研究进展

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摘　要

大量研究表明，氧化应激参与了激素性股骨头坏死(SONFH)的发病过程。活性氧(ROS)在维持细胞正常功能中起着至关重要的作用，但在氧化应激状态下，过量的ROS会导致多种细胞损伤，引起疾病发生。氧化应激引起血管内皮损伤、间充质干细胞功能障碍、成骨细胞及骨细胞凋亡、破骨细胞过度活化，导致SONFH发生。本文就氧化应激在SONFH发病机制中的研究进展作一综述。

关键词

氧化应激，活性氧，激素性股骨头坏死，发病机制

Research Progress on Oxidative Stress in the Pathogenesis of Steroid-Induced Osteonecrosis of the Femoral Head

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Abstract

Considerable evidence suggests that oxidative stress is involved in the pathogenesis of steroid-

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induced osteonecrosis of the femoral head (SONFH). Reactive oxygen species (ROS) play a crucial role in maintaining normal cellular function, but excessive ROS under oxidative stress conditions can lead to various forms of cellular damage, contributing to disease onset. Oxidative stress induces endothelial injury, dysfunction of mesenchymal stem cells, apoptosis of osteoblasts and osteocytes, and excessive activation of osteoclasts, resulting in the occurrence of SONFH. This review provides an overview of the research progress on oxidative stress in the pathogenesis of SONFH.

Keywords

Oxidative Stress, Reactive Oxygen Species, Steroid-Induced Osteonecrosis of the Femoral Head, Pathogenesis

1. 引言

股骨头坏死是各种原因引起的获得性股骨头缺血性疾病，伴有剧烈疼痛和进行性髋关节功能障碍[1]。随着糖皮质激素(GCs)的广泛应用，激素性股骨头坏死(SONFH)发病率已位居非创伤性股骨头坏死的首位[2]。SONFH 的主要病理特点为软骨下骨微骨折、骨髓水肿和进行性股骨头塌陷[3] [4] [5]。SONFH 的发生起源于微循环障碍和成骨细胞坏死。疾病早期，MRI 能够检测到髓内水肿区域，但 CT 显示软骨下骨微结构没有明显变化。随着骨坏死的发生，修复过程启动，但破骨细胞介导的骨吸收超过了成骨细胞介导的骨形成，导致软骨下骨小梁净流失。随着病情进展，骨量的减少和微结构的改变影响了股骨头的完整性，最终塌陷和畸形[6]。近年的研究表明，氧化应激在 SONFH 的发病过程中起着重要作用，使用抗氧化剂或激活抗氧化基因的表达能够一定程度抑制其病理进展[7] [8] [9] [10] [11]。本文就氧化应激在 SONFH 发病机制中的研究进展进行综述。

2. 氧化应激简述

氧化应激是指活性氧(ROS)的产生与内源性抗氧化防御机制之间的失衡，即 ROS 水平过高。ROS 可分为两类：一是具有未成对电子的氧分子，包括超氧阴离子自由基、羟基自由基、脂质过氧自由基和一氧化氮自由基；二是处于激发态的氧分子，即单线态氧[12]。体内 ROS 主要来源于线粒体呼吸链反应、NADPH 氧化酶(NOX)、黄嘌呤氧化酶(XO)和一氧化氮合酶(NOS)等[13]。生理状态下，ROS 在细胞稳态中起着至关重要的作用。ROS 参与细胞内外的氧化还原平衡调节，维持细胞内环境的稳定性。ROS 作为细胞信号分子，参与调节多种信号通路。线粒体呼吸链中产生的超氧阴离子能够被超氧化物歧化酶(SODs)转化成过氧化氢(H_2O_2)，进而氧化蛋白质上的半胱氨酸残基，以启动氧化还原信号传导[14]。同时，H_2O_2 介导 HIFs、PI3K、NF-κB、MAPK 等通路的激活，参与细胞正常的新陈代谢、生长和增殖等过程[15] [16]。此外，ROS 介导促炎细胞因子(IL-1β, TNFα, IFN)的释放，并作为免疫细胞中重要的第二信使，通过调节细胞间信号传导影响炎症过程[17] [18] [19]。

过量的 ROS 会导致细胞和组织损伤。当细胞内氧化还原平衡失衡时，抗氧化防御系统(如超氧化物歧化酶、谷胱甘肽还原酶等)的活性受损，进一步加剧了氧化应激。过量的 ROS 引发脂质过氧化，破坏细胞膜完整性，影响细胞内外物质的交换和信号传导[20]。ROS 还能氧化蛋白质的硫基、羧基、酰胺基

等，改变其结构和功能，甚至形成氧化蛋白聚集体，导致细胞功能障碍[21]。此外，ROS 还会引发 DNA 单链和双链断裂、碱基修饰和交联等损伤，导致基因突变、染色体异常和细胞死亡。氧化应激使细胞内的凋亡通路过度激活，并通过影响凋亡相关蛋白(如 Bcl-2 家族、Caspase 家族)的表达和活性，诱导细胞凋亡[22]。过量的 ROS 还会导致核因子 κB (NF-κB)和其他炎症信号通路过度激活，促进炎症因子(如肿瘤坏死因子-α、白细胞介素等)的过度释放，进一步加剧细胞和组织损伤[23]。因此，GCs 引起的氧化应激可能是 SONFH 进展的重要原因。

3. 氧化应激在 SONFH 中的作用机制

3.1. 血管内皮细胞损伤

微循环障碍被认为是 SONFH 发生的始动因素，其中血管内皮损伤起着重要作用[24] [25] [26]。血管内皮是覆盖在血管系统表面的单层上皮，是血液和血管壁之间的物理屏障，在维持血管内稳态中发挥着重要作用。

氧化应激会导致内皮功能障碍及程序性死亡(细胞焦亡、铁死亡等) [27]。在 ROS 介导的内皮功能障碍过程中，促炎细胞因子如 IL-1β、IL-18，以及 ICAM-1、VCAM-1 和 E-选择素等细胞粘附分子表达增强，从而引发炎症反应[28]。氧化应激还会激活 NF-κB 通路，促进 TNF-α 等炎症因子表达；炎症因子又反过来促进内皮细胞中线粒体 ROS 生成、NADPH 氧化酶活性和 iNOS 表达，进一步加剧氧化应激及炎症反应，形成恶性循环[29] [30]。NO 是重要的血管扩张剂，对血管具有保护作用。ROS 及炎症因子通过增加超氧化物歧化酶水平导致 NO 失活，从而导致血管屏障破坏、血管舒缩功能障碍，影响局部血流调节和血管活性分子的释放[31] [32]。新的研究表明，天然化合物如苯丙素、黄酮类、萜类和生物碱等可激活 Nrf2/HO-1 减轻氧化应激导致的血管内皮细胞凋亡[33]。综上所述，氧化应激能够介导血管内皮细胞功能障碍或死亡，引起血管屏障破坏、血管痉挛、局部炎症浸润，从而阻碍股骨头正常的血液供应，导致骨组织损伤。

3.2. 间充质干细胞功能障碍

间充质干细胞(MSCs)具有多向分化潜能，可以分化为成骨细胞、软骨细胞、脂肪细胞等多种细胞类型，其成骨分化能力的变化与 SONFH 密切相关[34]。MSCs 通常具有低水平的细胞内 ROS 和高水平的谷胱甘肽。低水平的 ROS 促进 MSCs 成骨分化，氧化应激则会促进成脂分化甚至导致细胞周期停滞和凋亡[35]。SONFH 发生后，坏死区会形成氧化应激微环境，进一步影响 MSCs 的正常功能[36]。

过量的 ROS 通过激活 FOXO 转录因子抑制 Wnt/β-catenin 信号转导，同时通过下调 MSCs 中 Gli 蛋白水平抑制 Hedgehog 信号传导，损害 MSCs 的成骨作用[37] [38]。ROS 还可增加 MSCs 关键成脂转录因子 CCAAT/增强子结合蛋白(C/EBP)和过氧化物酶体增殖物激活受体(PPAR) γ 的表达促进脂肪生成[39] [40]。此外，过量的 ROS 激活 JNK、p38、ERK 等 MAPK 通路，诱导促凋亡蛋白 Bax 和 Caspase-3 的表达，导致 MSCs 凋亡[41]。因此，氧化应激能减少成骨细胞数量，阻碍新生骨形成；同时引起脂肪细胞过度增殖，诱发骨内高压，干扰骨内微循环，进一步加剧骨破坏。

实验证实，硒代蛋氨酸可通过 PTEN/PI3K/AKT 途径调节的抗氧化作用减轻 H_2O_2 诱导的 MSCs 分化障碍[42]。线粒体自噬可以通过破坏线粒体来减少 ROS 的产生，诱导 MSCs 自噬能够促进成骨分化[43]。抗氧化蛋白 PARK7 过表达能减少氧化应激诱导的 MSCs 凋亡[44]。青蒿素通过激活 c-Raf/Erk1/2/p90rsk/CREB 减轻 ROS 诱导的 MSCs 凋亡，而辅酶 Q10 和牛磺熊去氧胆酸则通过调节 Nrf-2/NQO-1 信号通路发挥抗氧化和抗凋亡作用[45] [46] [47]。这些结果表明，氧化应激与 MSCs 的功能障碍密切相关，通过影响骨组织修复能力加速股骨头坏死的发展。

3.3. 成骨细胞分化障碍和骨细胞凋亡

成骨细胞主要由 MSCs 分化产生，在调节骨基质的合成、分泌和矿化中发挥成骨作用[48]。在骨形成的末期，成骨细胞被包裹在骨基质中并成熟为骨细胞，在骨重塑中发挥着至关重要的作用[49]。研究表明，大剂量 GCs 诱导 ROS 产生并导致骨细胞和成骨细胞凋亡，且涉及多种分子机制。GCs 提高成骨细胞内 ROS 水平从而激活 PI3K/AKT/GSK3β 信号通路，进而增加促凋亡基因 cleaved-caspase 3、cleaved-caspase 9 的表达诱导成骨细胞凋亡[50]。GCs 能够激活 p66shc 增加成骨细胞线粒体中 ROS 的生成，从而激活 ROS/PKCβ/p66shc/JNK 信号级联诱导成骨细胞凋亡；而抗氧化剂 N-乙酰半胱氨酸(NAC)或敲除 $p66^{shc}$ 可阻止 JNK 的激活，减轻 GCs 诱导的成骨细胞损伤[51]。FoxO 转录因子家族通过调节抗氧化酶(如 MnSOD 和过氧化氢酶)介导抗氧化作用，应用抗氧化剂或上调 FOXO 表达均可以阻止 GCs 诱导的成骨细胞凋亡[52]。高剂量 GCs 会显著增加成骨细胞中 NOX1 来源的 ROS 生成，进而激活 MAPK 通路诱导成骨细胞凋亡；通过 siRNA 沉默 NOX1 能有效阻碍 ROS 生成和细胞凋亡[53]。此外，外源性 H_2O_2 诱导成骨前体细胞中 ERK 和 NF-κB 激活，增强 Bax 的表达和线粒体膜电位的超极化，抑制成骨标志物如碱性磷酸酶(ALP)、I 型胶原的形成；使用 ERKs 和 NF-κB 特异性抑制剂能逆转这一过程[54] [55]。动物实验显示，经大剂量 GCs 处理后，实验动物股骨头骨小梁密度和厚度降低，骨细胞空洞增加，并观察到氧化损伤诱导的骨细胞凋亡，而激活抗氧化通路能够将其改善[10] [11]，进一步印证了氧化应激在 GCs 诱导的成骨细胞及骨细胞凋亡中起重要作用。

此外，成骨细胞和骨细胞产生的 VEGF 已被证明可以耦合骨形成和血管生成，而氧化应激引起的骨细胞凋亡能够干扰 VEGF 的产生和作用以及破坏内皮血管生成[56] [57]。供血不足带来的缺氧进一步加剧骨细胞凋亡，干扰新骨形成，形成恶性循环，加剧股骨头结构的破坏。

3.4. 破骨细胞过度激活

破骨细胞是源自单核/巨噬细胞谱系并通过单核前体细胞融合产生的多核细胞，是人体内唯一具有骨吸收功能的细胞[58]。破骨细胞活化依赖 NF-κB 配体受体激活剂(RANKL)系列信号转导通路，ROS 在其中起重要调节作用。RANKL 可通过 TRAF6/RAC1/Nox1 信号级联提高破骨前体细胞中的 ROS 水平，进而激活 NF-κB 促进破骨细胞的分化。此外，ROS 可激活丝裂原活化蛋白激酶(MAPKs)，促进 RANKL 诱导的破骨细胞生成[59]。ROS 还可刺激破骨细胞转录因子 c-Fos、NFATc1 的表达，从而促进抗酒石酸磷酸酶(TRAP)和酪蛋白酶 K (CTSK)的合成，导致骨吸收增强[60]。诱导破骨细胞自噬能抑制其分化和骨吸收功能[61]。ROS 清除剂剂罗布麻素、NOX 抑制剂 ML171、黄嘌呤氧化酶抑制剂 DPI 等可抑制骨吸收[62]。诸多天然抗氧化剂如黄酮类、生物碱类、香豆素类等具有抑制破骨细胞活化、减轻骨破坏的作用[63]。GCs 可显著抑制破骨前体细胞中 Nrf2 核转位，阻碍其诱导的抗氧化基因激活，引起氧化应激，而激活 Nrf2 可显著抑制破骨细胞活化并减轻 SONFH 发生[8] [11]。人与动物 SONFH 的股骨头标本均检测到过量 ROS 和过度激活的破骨细胞[6] [64]，进一步证实了 GCs 诱导的氧化应激在破骨细胞活化及 SONFH 中起重要作用。

破骨细胞和成骨细胞相互调节，共同维持骨重塑平衡。成骨细胞与破骨细胞前体细胞的共培养表明，过量的 ROS 通过抑制成骨细胞中 Wnt/β-catenin/OPG 信号通路来降低其对 RANKL 的阻断作用，同时通过激活蛋白激酶(ERKs、JNK 等)增加 RANKL 表达，导致破骨细胞过度活化[65] [66]。成骨细胞分化障碍和破骨细胞过度活化共同导致骨重塑紊乱，加剧股骨头结构的破坏。

4. 小结

SONFH 发病机制十分复杂，涉及诸多学说。迄今为止，关于氧化应激在 SONFH 发生发展中的作用

机制已取得很大进展，但其具体机制仍未完全阐明，还需进行更进一步的基础研究和临床对照研究。可以明确的是，GCs 诱发的氧化应激影响血管内皮细胞、骨髓间充质干细胞、成骨细胞和破骨细胞等正常功能，从而破坏股骨头的血供和骨重塑过程，最终导致股骨头结构破坏。对氧化应激与 SONFH 发生机制的深入研究可为其防治提供理论基础，相信未来有望为患者提供更加安全、有效的治疗新策略。

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