

铁死亡在膝骨关节炎性滑膜炎中的作用机制

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摘要: 铁死亡是一种新发现的细胞死亡形式, 与多种疾病的发生密切相关, 尤其在炎症反应方面具有重要的调控作用。膝关节滑膜炎(knee synovitis, KS)是膝骨关节炎(knee osteoarthritis, KOA)发病过程中重要的病理改变。KS造成的炎症微环境异常容易诱发铁死亡, 而铁死亡又可通过触发机体非特异性免疫、脂氧合酶、环氧化产物等参与调节滑膜炎反应, 对KOA的发生发展、治疗及转归有着重要的影响。本文回顾了有关铁死亡在膝骨关节炎性滑膜炎作用机制方面的进展与突破, 阐述了铁过载、铁死亡相关基因以及脂质过氧化物代谢与滑膜炎的相关性, 探讨了铁死亡在KOA中的潜在作用机制, 以为KOA的防治提供新的思路与方法。

关键词: 膝骨关节炎; 滑膜炎; 铁死亡

Mechanism of Ferroptosis in knee osteoarthritis synovitis

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Abstract: Ferroptosis, a newly discovered form of cell death, is closely associated with the development of several diseases and has an important regulatory role in the inflammatory response in particular. Knee synovitis (KS) is an important pathological change in the pathogenesis of knee osteoarthritis (KOA). The abnormal inflammatory microenvironment caused by KS can easily induce ferroptosis, which in turn can participate in regulating the synovial inflammatory response by triggering the body's nonspecific immunity, lipoxygenase, and epoxidation products, and has an important impact on the development, treatment and regression of KOA. This article reviews the progress and breakthroughs in the mechanism of ferroptosis in osteoarthritic synovitis of the knee, describes the relevance of iron overload, ferroptosis-related genes and lipid peroxide metabolism to synovial inflammation, and explores the potential mechanism of ferroptosis in KOA, with the aim of providing new ideas and methods for the prevention and treatment of KOA.

Key Words: knee osteoarthritis; synovitis; ferroptosis

膝骨关节炎(knee osteoarthritis, KOA)是以关节软骨退行性改变和关节滑膜炎反应为主要病理特征的慢性、增龄性关节疾病。该病具有发病率高、病程长、阶梯性明显、发生发展阶段性清晰及致残率高等特点, 严重影响着中老年人群

生活质量, 已成为威胁社会及人类健康的难治性疾病^[1,2]。KOA的发病机制复杂, 与增龄、肥胖、性别、劳损、创伤、关节畸形、基因易感性等多种因素密切相关, 是多种原因综合作用所致关节损伤的结果^[3]。随着研究的不断深入, 发现膝关节

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滑膜炎(knee synovitis, KS)在KOA的发生发展过程中起重要作用,促炎症细胞因子的释放是导致滑膜炎、软骨基质破坏的重要病理因素,滑膜炎、活化的滑膜巨噬细胞以及炎症因子继而诱导了关节软骨的降解和破坏性反应,促进了骨性关节炎的进展^[4]。Goldenberg等^[5]的研究证实,在KOA患者的膝关节滑膜中存在着大量的炎症细胞,IL-6、IL-8、TNF- α 等炎症介质水平明显升高。在众多炎症性疾病中,铁死亡被认为是发病的重要诱因,铁死亡能触发机体非特异性免疫(non-specific immunity, NS),释放白介素-1 β (interleukin 1 beta, IL-1 β)、白介素-18(interleukin-18, IL-18)等炎症介质,进而激活机体炎症反应^[6]。随着KOA滑膜炎的发生,研究发现,铁死亡可通过脂氧合酶(lipoxygenase, LOX)和环氧化酶-2(cyclooxygenase-2, COX-2)参与调节滑膜炎反应^[7,8],与KOA的发生密切相关。目前关于铁死亡调节KOA滑膜炎的研究主要从铁死亡过程中铁代谢紊乱、产生的过氧化物代谢、花生四烯酸代谢、炎症因子等方面展开。本文将围绕这几个方面分析探讨铁死亡在KOA滑膜炎的生理病理机制,以期丰富完善KOA滑膜炎发病机制的认识,为临床的相关治疗提供理论依据。

1 铁死亡的概述

铁是机体必不可少的微量元素之一,广泛参与体内的多种生物学过程,对机体健康的维持至关重要^[9]。正常情况下,铁代谢处于动态平衡以满足机体的需要,一旦出现铁代谢紊乱、含量异常就会导致各种损伤与疾病的发生。在病理状态下,铁过载以芬顿反应的形式产生大量的活性氧(reactive oxygen species, ROS),进而造成DNA、细胞器和蛋白质的损伤,激活更为严重的生化反应,诱导铁死亡的发生。铁死亡是一种铁依赖性的非细胞凋亡形式的细胞死亡,以细胞内ROS的堆积为特征^[10],在形态学、代谢学、遗传学和分子生物学等方面不同于其他的细胞死亡形式^[11],与骨退行性疾病、肝癌、肾损伤等疾病的发生密切相关。铁死亡的发生机制复杂,主要受谷胱甘肽过氧化物酶4(glutathione peroxidase 4, GPX4)的调控^[12]。GPX4是一种能够有效减少生物膜中过氧化

脂质的酶,可以催化还原型谷胱甘肽变为氧化型谷胱甘肽^[13],从而发挥细胞抗氧化作用,其被抑制甚至失活会直接导致脂质过氧化物积累进而诱发细胞铁死亡^[14]。铁依赖性ROS的积累、GSH水平的降低和GPX4的失活造成细胞内脂质氧化物代谢障碍是铁死亡的实质^[15]。因此,铁死亡的发生主要涉及铁稳态及脂质过氧化代谢等方面的异常,且受多种蛋白分子与信号通路的调控,而抗氧化酶GPX4是铁死亡发生中的关键调控因子^[16]。

2 铁死亡对KS的影响

膝关节滑膜分泌的滑液可润滑和修复受损的关节,其对稳定关节内部结构具有重要作用,膝关节软骨、半月板等结构均受到滑膜的保护^[17]。另外,滑膜下丰富的毛细血管可营养关节软骨、通过微循环清理关节软骨的代谢物质^[18]。铁元素参与机体能量生成、血液循环、遗传物质的合成、新陈代谢、大分子物质的组成等诸多过程,机体内铁平衡的关键是维持“游离铁”水平的相对稳定^[19],体内“不稳定铁”的过量可产生过量的ROS,从而损害细胞^[20]。而在KOA引起的关节炎症性疾病中,膝关节滑膜组织中确实存在铁过载的情况^[21],铁过载可触发膝关节滑膜的氧化应激反应,升高滑膜细胞内ROS含量,进一步诱导细胞铁死亡^[22],加剧原有的病理进程。

2.1 铁过载与滑膜炎的相关性

食物中的铁(Fe^{2+} 或 Fe^{3+})经十二指肠吸收入血后,血液中铁与转铁蛋白(transferrin, Tf)结合,将铁摄入细胞内,输送给全身组织^[23]。当具有铁氧化酶作用的膜铁转运蛋白(ferroportin, FPN)数量减少或功能不足时,FPN无法将 Fe^{2+} 从细胞内运输到血浆中^[24],2种机制相互协调平衡以维持循环中“不稳定铁”的水平。在维持膝关节滑膜正常功能活动中,铁代谢发挥着重要的调节作用。由于年龄的增长,机体代谢能力下降,膝关节本身的退变容易导致局部循环障碍、动脉压增大而使滑膜增厚、循环减少,引起滑膜炎性刺激,进一步导致滑膜组织中铁排泄障碍,铁离子在膝关节滑膜中持续积累,即造成关节滑膜中铁过载环境^[25]。膝关节滑膜中铁过载,一方面,促进铁的芬顿反应,而使滑膜组织产生大量的ROS^[26];另一

方面,铁过载使ROS产生烟酰胺腺嘌呤磷酸二核苷酸氧化酶(nicotinamide adenine phosphate dinucleotide oxidases, Noxs)、脂氧合酶(lipoxygenases, LOX)、细胞色素p450(cytochrome P450, CYP450)酶等活性增加,以促使滑膜组织产生大量的ROS^[27],滑膜细胞内过量ROS生成进一步促使铁死亡的发生。铁过载诱发铁死亡可能破坏滑膜微环境,抑制滑膜成纤维样细胞(fibroblast-like synoviocytes, FLS)的功能。铁死亡能触发机体非特异性免疫而释放IL-1 β , IL-1 β 可活化FLS,产生基质金属蛋白酶-1(matrix metalloproteinase-1, MMP-1)、基质金属蛋白酶-13(matrix metalloproteinase-13, MMP-13),MMP-1和MMP-13与滑膜炎症反应和膝关节软骨退变密切相关^[28];此外,IL-1 β 还可促进FLS中COX-2的表达以促使前列腺素E2(prostaglandin E2, PGE2)的分泌,从而加剧KOA的滑膜炎症反应^[29](图1)。

2.2 铁代谢相关基因通过铁死亡调控KS

多种基因参与了铁代谢的调控,维持其在机体的动态平衡。Billesbølle等^[30]的研究显示,铁调素(hepcidin, Hpc)属于铁代谢的调节因子,Hpc的表达受铁调素调节蛋白(hemojuvelin, HJV)的调

节,敲除小鼠肝脏HJV后可引起铁死亡,给予含铁饮食后,可明显改善铁死亡。Brissot等^[31]的研究发现,HJV基因突变容易导致铁过载,在遗传性血色素沉着病引起的KS中,也存在着铁过载。此外,血色病基因(hemochromatosis gene, HFE)与转铁蛋白受体2基因(transferrin receptor 2, TFR2)的突变也与铁超载性KS相关^[32]。线粒体在细胞能量代谢中起着核心作用,细胞发生铁死亡时线粒体在形态上发生变化,随着铁离子在线粒体膜上的累积,会出现脂质过氧化反应而激活铁死亡^[33]。位于线粒体上的线粒体铁蛋白(mitochondrial ferritin, FtMt)是一种调节铁稳态的储铁蛋白,可调节细胞内铁代谢,减少线粒体内所产的ROS,发挥保护细胞的功能。正常细胞FtMt表达较低,当细胞内FtMt表达升高,可降低细胞内氧化应激水平,而抑制铁死亡对细胞具有保护作用。Wang等^[34]的研究证实,FtMt能够抑制Erastin诱导的铁死亡。在膝关节滑膜组织中,FtMt表达升高可抑制铁死亡,这可能有助于减轻因铁死亡激活而导致的滑膜炎症反应。

沉默调节蛋白2(recombinant sirtuin 2, SIRT2)在细胞代谢与炎症演变等生物学过程中具有重要

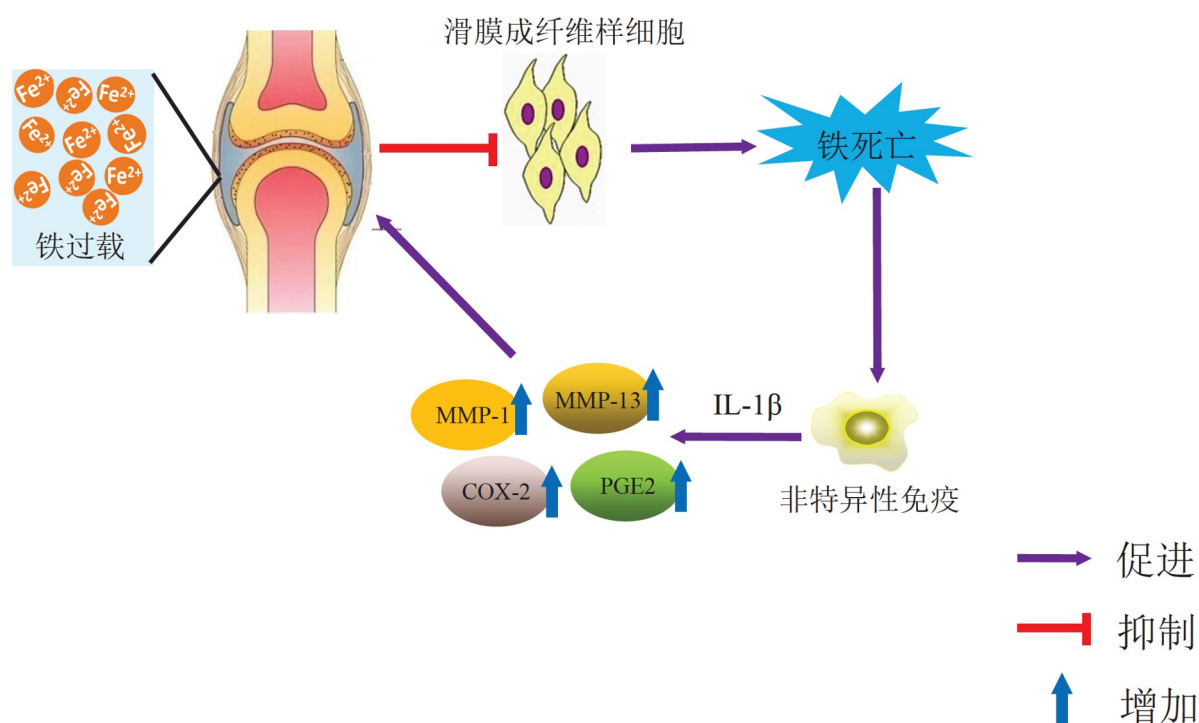


图1 膝关节滑膜组织中铁过载诱导铁死亡与滑膜炎症的示意图

治疗多通过抑制关节滑膜炎症达到治疗目的, 其治疗效果也较为有限, 故在基础研究与临床桥接方面富有巨大的挑战性。随着对铁死亡与膝骨关节炎性滑膜炎反应相互作用机制研究的不断深入, 铁死亡通过调节滑膜免疫、炎症细胞、炎症介质、铁代谢、脂质过氧化物等分子机制也将逐渐被揭示, 以调控铁代谢与抑制铁死亡作为切入点, 是KOA研究的新方向, 有助于临床防治思路的拓展和新型的药物研发。

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