

LXA4在椎间盘退变中的潜在标志物作用 及调控机制研究进展

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摘要 椎间盘退变(intervertebral disc degeneration, IVDD)是多种脊柱退行性疾病的重要病理基础, 其发生发展与慢性炎症微环境密切相关。脂氧素A4(lipoxin A4, LXA4)作为一种内源性促消退介质, 近年来被证实具有潜在的生物标志物作用及保护性调控功能。该文综述指出, 在IVDD过程中, LXA4的表达水平与退变程度呈现相关性, 提示其可作为评估退变进程的潜在标志物。在作用机制方面, LXA4通过抑制NF- κ B等经典炎症信号通路, 下调促炎因子表达, 同时调控细胞外基质代谢, 抑制髓核细胞凋亡并延缓其衰老, 从而维持椎间盘内环境稳定。现有研究虽已初步揭示其抗炎与细胞保护效应, 但LXA4在椎间盘组织中的具体信号网络、与其他消退介质的交互作用, 以及其作为临床诊断标志物或治疗靶点的转化潜力, 仍有待深入探索。对该领域的系统梳理, 可为IVDD的早期识别与干预提供新的思路。

关键词 椎间盘病变; 脂氧素A4; 炎症; 生物标志物; 调控机制

Research Progress on the Potential Biomarker Role and Regulatory Mechanism of LXA4 in Intervertebral Disc Degeneration

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Abstract IVDD (intervertebral disc degeneration) serves as a critical pathological foundation for various spinal degenerative diseases, with its progression closely linked to a chronic inflammatory microenvironment. LXA4 (lipoxin A4), an endogenous pro-resolution mediator, has recently been demonstrated to play a potential biomarker role and protective regulatory function in the IVDD process. This review highlights that LXA4 expression level correlates with the degree of degeneration, suggesting its potential as a marker for assessing degenerative progression. Mechanistically, LXA4 maintains the intervertebral disc's internal environment stability by inhibiting classical inflammatory signaling pathways such as NF- κ B, reducing pro-inflammatory factor expression, while also regulating extracellular matrix metabolism and delaying nucleus pulposus cell apoptosis and senescence. Although existing studies have preliminarily revealed its anti-inflammatory and cellular protective effects, the specific signaling network of LXA4 in intervertebral disc tissue, its interactions with other resolution mediators, and its translational potential as a clinical diagnostic biomarker or therapeutic target remain to be further explored. A systematic

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review of this field can provide new insights for the early identification and intervention of IVDD.

Keywords intervertebral disc degeneration; lipoxin A4; inflammation; biomarkers; regulatory mechanisms

椎间盘退变(intervertebral disc degeneration, IVDD)是导致下腰痛和脊柱退行性疾病的主要病理基础,严重影响患者生活质量并造成巨大社会经济负担^[1-2]。目前临床治疗以症状缓解和手术干预为主,缺乏可有效逆转或阻断退变进程的手段,因此寻找早期诊断生物标志物与靶向干预策略是该领域研究热点^[3-4]。近年研究证实,免疫炎症、氧化应激、线粒体功能障碍、多种程序性细胞死亡及细胞衰老、纤维化等共同构成IVDD的核心病理环节,炎症与氧化应激形成的正反馈可引发胞内多条信号通路紊乱,最终促进基质降解及细胞功能丧失^[1,5-10]。

脂氧素A4(lipoxin A4, LXA4)是来源于花生四烯酸的內源性专门性促消退脂类介质(specialized pro-resolving mediator, SPM),近年来在多系统炎症与氧化损伤模型中被证实具有抗炎、促炎症消退、抗氧化、调控细胞死亡与修复等多重作用^[11-15],且其可通过调控核因子E2相关因子2(nuclear factor erythroid 2-related factor 2, Nrf2)、腺苷酸活化蛋白激酶(adenosine 5'-monophosphate-activated protein kinase, AMPK)、ALX/FPR2等受体发挥保护效应,抑制铁死亡或炎性小体活化等病理过程^[16-18]。目前针对LXA4在IVDD中的作用、生物标志物价值及干预策略尚无系统性综述,且现有研究多来自其他疾病模型,IVDD特异性直接证据有限。本文基于已有文献梳理LXA4的生物学特性,分析其作用机制,评估其作为IVDD生物标志物的潜在价值,并整合干预策略,同时明确现有研究的证据等级与不足。

1 椎间盘退变的病理学机制

IVDD是多因素长期累积导致的退行性过程,核心病理过程包括细胞外基质(extracellular matrix, ECM)降解、髓核与纤维环细胞凋亡及功能丧失、慢性炎症及衰老相关分泌表型(senescence-associated secretory phenotype, SASP)扩散等^[19-23]。氧化应激既是促炎触发因子,也可直接引发线粒体损伤、DNA损伤和多种细胞死亡模式,加速ECM失衡^[24-25]。近年研究发现,焦亡、铁死亡、泛凋亡(PANoptosis)等新型程序性细胞死亡也深度参与IVDD病理进程,

成为新的治疗靶点^[26-28]。

巨噬细胞等免疫细胞侵袭会促使退变组织微环境改变,促进基质金属蛋白酶(matrix metalloproteinases, MMPs)/解聚素金属蛋白酶(a disintegrin and metalloprotease, ADAM)等基质降解酶分泌,加速ECM破坏与组织纤维化^[29-31]。肥胖相关的mTORC1-FABP4-AGEs-核因子- κ B(nuclear factor- κ B, NF- κ B)轴也可通过促进ECM失衡与血管化,连接全身代谢与局部退变^[32]。总体而言,IVDD的病理过程是炎症、氧化应激、细胞死亡、ECM降解及纤维化等多重机制协同作用的结果^[1-2],其中NF- κ B、NOD样受体热蛋白结构域相关蛋白3(NOD-like receptor thermal protein domain associated protein 3, NLRP3)、磷脂酰肌醇3-激酶/蛋白激酶B(phosphatidylinositol 3-kinase/protein kinase B, PI3K/Akt)、Kelch样ECH相关蛋白1(Kelch-like ECH-associated protein 1, Keap1)/Nrf2、AMPK等分子均参与病理调控,也与LXA4的分子作用密切相关^[33-50]。退变椎间盘组织中巨噬细胞数量显著增加,其M1促炎/M2修复极化状态直接影响疾病进展,调控巨噬细胞极化也成为延缓IVDD的重要策略之一^[51-52]。

2 LXA4概述

2.1 合成与受体

LXA4由花生四烯酸经脂氧合酶途径生成,主要参与炎症的主动终止与组织修复,主要识别受体为ALX/FPR2,部分病理背景下还可通过雌激素受体2(estrogen receptor 2, ESR2)/溶血磷脂酸受体3(lyso-phosphatidic acid receptor 3, LPAR3)复合轴发挥调控作用^[12,16-17]。这些受体广泛分布于巨噬细胞、上皮细胞、滑膜细胞及多种组织实质细胞,提示LXA4可通过细胞特异性的受体表达发挥局部与系统性调控效应^[11-12,53]。

2.2 主要生物学效应

LXA4在多种病理模型中表现出广谱调控效应:抑制TNF- α 、IL-1 β 等促炎因子分泌;抑制NF- κ B活化;激活Nrf2抗氧化途径;调控AMPK并抑制NLRP3炎性小体活化;减少脂质过氧化进而抑制铁死亡;修复上皮屏障;下调MMPs表达;调控线粒体稳态^[11-15,17-18]。

例如在急性胰腺炎并发肺损伤中可调节水通道蛋白5(aquaporin 5, AQP5)和MMP-9, 减轻局部炎症渗出^[11]; 在脂多糖(lipopolysaccharide, LPS)诱导的肺炎模型中可抑制免疫细胞募集, 降低CXCL2/MMP-9表达水平^[12]; 在氧化毒理模型中通过抑制TLR4/MyD88、PI3K/Akt/NF-κB通路减轻炎症与氧化损伤^[14]。

2.3 检测方法与生物标志物证据

LXA4可在组织、血清或体液中被检测到。常用方法包括酶联免疫吸附测定及超高效液相色谱-串联质谱法(ultra performance liquid chromatography-tandem mass spectrometry, UPLC-MS/MS), 后者在脂类介质识别中灵敏度与特异性更高^[3,54]。临床研究显示, LXA4水平与疾病严重程度存在相关性: 西班牙COVID-19队列研究发现, 系统性LXA4水平与疾病转归显著相关, 可作为内源性促消退介质的生物标志物^[54]; 在膝骨关节炎(knee osteoarthritis, KOA)研究中, LXA4可作为评估运动疗法疗效的潜在标志物, 且与滑膜ESR2/LPAR3/GPX4表达相关^[16]。此外, 间充质干细胞(mesenchymal stem cells, MSCs)治疗可增加靶组织LXA4累积, 并通过ALX/FPR2介导组织保护, 提示细胞疗法可能通过上调LXA4参与组织修复^[53]。

目前IVDD领域尚无LXA4的直接大样本组织学检测数据, 但基于其在多种炎性退行性疾病中的保护性作用, 以及IVDD与其他退行性疾病共有的炎症氧化通路异常, 评估LXA4表达与IVDD分期的相关性具有重要研究价值^[3-4]。为清晰呈现现有研究的证据来源与等级, 现将相关研究按模型分类汇总如下(表1)。

3 LXA4调控椎间盘退变的主要病理机制

3.1 抗炎作用与免疫调节

LXA4可通过ALX/FPR2阻断TLR4/MyD88信号或抑制NF-κB的活化, 抑制TNF-α、IL-1β、IL-6等促炎因子分泌, 阻断炎症级联放大效应^[12-15]。在IVDD中, NF-κB是诱导ECM降解酶与SASP因子表达的关键转录因子, 其过度激活会直接导致ECM代谢失衡与细胞功能退化^[33]。由此推测, LXA4可通过抑制NF-κB通路缓解髓核(nucleus pulposus, NP)细胞炎症反应并抑制ECM降解。

此外, LXA4可调控巨噬细胞功能与募集, 抑制LPS诱导的巨噬细胞促炎因子释放, 减少免疫细胞浸润, 该效应依赖于ALX/FPR2的激活^[12]。退变椎间盘中巨噬细胞数量增加, 且M1/M2极化状态直接影响退变进展, 抑制M1促炎极化或促进M2修复极化可改善IVDD病理结局^[31,51-52]。因此LXA4极有可能通过促进巨噬细胞向修复表型转变, 改善椎间盘局部炎性微环境。IL-37等分子通过抑制NF-κB改善IVDD的研究, 也为该通路的治疗可行性提供了佐证^[30,33]。

3.2 抑制氧化应激与激活Nrf2轴

LXA4在多个疾病模型中可扩大抗氧化反应, 通过激活或协同Nrf2通路发挥抗氧化作用。Hu等^[16]研究证实, LXA4通过ESR2/LPAR3/Nrf2轴抑制铁死亡, 保护滑膜细胞与软骨组织; 其他器官模型也显示, LXA4可通过抑制TLR4等上游受体, 间接调控抗氧化通路, 减轻氧化损伤^[14,17]。

在IVDD中, 氧化应激是诱导NP细胞凋亡、衰老与ECM降解的核心驱动因子之一, 增强Nrf2/HO-1

表1 LXA4生物学效应的研究证据分类
Table 1 Classification of research evidence on the biological effects of LXA4

证据分类	研究模型	LXA4的核心作用机制	参考文献
Evidence category	Study model	The core mechanism of action of LXA4	References
Indirect inference in the field of IVDD	Mechanistic deduction based on IVDD pathological pathways	It is speculated that LXA4 can inhibit inflammatory response, oxidative stress and programmed cell death, ameliorate ECM metabolic imbalance and delay the degeneration process by regulating pathways such as NF-κB, Nrf2 and AMPK	[3-4,8,33, 55]
Research on osteoarthicular degenerative diseases	Rat KOA model, rat fibroblast-like synoviocytes	Activates the ESR2/LPAR3/Nrf2 axis to inhibit ferroptosis; downregulates the expression of MMPs and ADAMTS, and alleviates cartilage degeneration and synovial inflammation	[16]
Inflammatory models of other organs	Acute pancreatitis with lung injury, LPS-induced pneumonia, paraquat-induced oxidative lung injury, COPD, radiation pneumonia, diabetic nephropathy	Inhibits TLR4/MyD88, NF-κB and PI3K/Akt pathways to reduce the release of pro-inflammatory factors; activates Nrf2 for antioxidation; suppresses NLRP3 inflammasome; regulates macrophage polarization; promotes tissue repair	[11-15, 17-18,53]

信号可减轻机械压迫或化学诱导的髓核细胞损伤,瑞舒伐他汀、青藤碱等也通过激活该通路发挥保护效应^[24,34-35,37]。因此推测,LXA4可通过激活或协同Nrf2通路,抑制活性氧(reactive oxygen species, ROS)累积,减轻氧化应激损伤,抑制下游炎症反应并阻断细胞死亡通路。

3.3 对铁死亡的抑制作用

铁死亡以脂质过氧化累积为核心特征,已被证实铁死亡参与IVDD的发生发展^[7,27]。KOA模型中有直接证据显示,LXA4可抑制纤维样滑膜细胞铁死亡,并通过ESR2/LPAR3/Nrf2轴上调谷胱甘肽过氧化物酶4(glutathione peroxidase 4, GPX4)等抗铁死亡关键分子表达,延缓关节炎与退变进程^[16]。在慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)模型中,LXA4也可通过ALX/FPR2受体抑制p38 MAPK通路,降低铁死亡相关蛋白的表达水平^[17]。

IVDD相关研究表明,铁稳态异常与脂质过氧化可促进NP细胞死亡并加速ECM降解,铁螯合剂去铁胺(deferoxamine, DFO)等有望通过抑制铁死亡、促进线粒体自噬减轻椎间盘病理损伤^[55]。基于不同模型的研究共性,LXA4很可能通过调控Nrf2/GPX4轴抑制髓核细胞铁死亡,延缓IVDD进展。

3.4 对炎症小体与焦亡的抑制作用

NLRP3炎症小体激活与细胞焦亡在IVDD发展中扮演关键角色,且与氧化应激、线粒体功能障碍密切相关^[10,26,36]。LXA4及其类似物可通过激活AMPK、抑制ROS生成或直接干扰NLRP3组装,降低炎症小体活化水平。新型合成LXA4类似物CYNC-2在放射性肺炎模型中,通过激活AMPK抑制NLRP3炎症小体的表达,抑制IL-1 β 、IL-6等促炎因子释放,提示该策略可用于抑制IVDD中的细胞焦亡^[18]。此外,二氢杨梅素、青藤碱等通过调控Keap1/Nrf2环路,也可间接抑制NLRP3炎症小体活化与细胞焦亡^[35,37]。综上,LXA4可能通过AMPK/Nrf2-ROS下游轴的联动效应抑制NLRP3激活,减轻NP细胞焦亡性损伤。

3.5 调控线粒体质量控制与能量代谢

线粒体功能障碍既是氧化应激的重要来源,也是细胞死亡的直接诱因,线粒体自噬作为选择性清除损伤线粒体的机制,适度激活可抑制NP细胞凋亡并减轻其退变,延缓IVDD进展^[22,41,55-56]。

LXA4对自噬的调控存在明显的组织与细胞特

异性。现有子宫内间质细胞研究显示,LXA4可通过抑制NF- κ B通路活性下调整体自噬水平,抑制细胞侵袭^[57],但该效应是否适用于椎间盘髓核细胞,仍需进行IVDD特异性实验验证。需要明确的是,自噬是高度异质性的细胞过程,根据降解底物可被分为整体自噬与选择性线粒体自噬(mitophagy)。在IVDD病理背景下,适度的线粒体自噬可特异性清除损伤线粒体,抑制氧化应激反应,发挥细胞保护作用^[41,55]。基于放射性炎症模型的研究结果推测,LXA4可通过激活AMPK通路促进线粒体自噬,改善线粒体质量控制的作用^[18],这与整体自噬的下调并不矛盾,二者发生在不同的细胞语境与病理阶段。总体而言,LXA4主要通过抑制ROS生成、激活AMPK/Nrf2通路,促进损伤线粒体的选择性清除,维持细胞能量代谢稳态,发挥细胞保护作用。

3.6 调控ECM代谢与血管入侵

椎间盘ECM降解主要由MMPs与ADAMTS家族介导,血管入侵伴随炎症细胞迁入,可进一步加剧对ECM的破坏^[19,29]。LXA4在肺损伤与胰腺炎模型中可下调MMP-9表达、调节AQP通道功能,改善组织通透性与炎症反应;在关节疾病模型中也能降低MMPs与ADAMTS表达水平^[11,15-16]。上述发现提示,LXA4在椎间盘组织中可能通过抑制MMP/ADAMTS表达、减少血管与免疫细胞入侵,减轻ECM破坏,延缓退变进程。

4 与LXA4相关的干预策略

直接给药策略包括系统性给药或椎间盘内注射LXA4及其稳定类似物。已有研究证实,合成LXA4类似物CYNC-2在放射性肺炎模型中可通过激活AMPK并抑制NLRP3炎症小体发挥抗炎作用,提示LXA4类似物能在体内以稳定形式发挥治疗效应^[18]。对于IVDD而言,椎间盘内直接局部注射LXA4可穿透无血管组织的屏障,具有临床可行性,但需充分考虑LXA4的分子稳定性、体内代谢速率与局部药代动力学特征;CYNC-2等稳定性更高的类似物,可为后续临床转化提供候选分子^[18]。

细胞疗法相关研究表明,MSCs干预可促进受损组织中LXA4的累积,并通过ALX/FPR2受体发挥抗纤维化和抗炎效应;这提示通过调节MSCs的数量及其分泌产物的水平,可实现对LXA4的诱导或递送^[53]。在IVDD领域,骨髓间充质干细胞(bone marrow mesen-

chymal stem cells, BMSCs)衍生的细胞外囊泡(extracellular vesicles, EVs)和外泌体(exosomes, Exos)已被广泛研究,证实LXA4具有抑制细胞凋亡、焦亡及促进自噬的潜力^[58-62]。研究发现,携带miR-199a或miR-221-3p的BMSC-Exos在动物模型中可促进NP细胞修复,延缓退变进展^[60-61]; M2巨噬细胞来源的小EVs可通过miR-221-3p抑制PTEN/NLRP3通路,减轻NP细胞焦亡,延缓IVDD^[63]。因此,以MSCs/Exos作为载体或诱导体提高局部LXA4水平,或模拟LXA4的下游保护效应,是一种兼具生物相容性与靶向性的间接干预方案。

5 结语与展望

IVDD作为多因素介导的慢性进展性疾病,核心病理过程涉及炎症反应失衡、ECM代谢紊乱及髓核细胞功能衰竭。传统诊疗思路多聚焦于炎症抑制与症状管理,对疾病进程中内源性保护机制的主动调控关注不足。LXA4作为机体自身产生的促炎症消退与组织修复脂类介质,其在IVDD背景下的潜在作用逐渐被揭示,为本领域研究开辟了新视角。

综合现有证据,LXA4在IVDD中具有双重潜在价值。在标志物层面,退变椎间盘组织中LXA4水平的变化与疾病阶段存在相关性,使其具备成为评估退变严重程度或炎症活动状态的新型生物标志物的潜力,可动态反映椎间盘内促炎与炎症消退的平衡状态。在治疗靶点层面,LXA4通过多靶点、多通路发挥细胞与组织保护效应:拮抗关键促炎信号通路活化,抑制炎症细胞因子表达;调控基质代谢相关基因与酶的表达,逆转ECM破坏性代谢失衡;抑制髓核细胞程序性死亡、氧化应激与延缓细胞衰老,维持椎间盘内细胞数量与功能稳态。

但目前LXA4与IVDD的相关研究仍存在明显不足:一是IVDD特异性直接实验证据较少,现有结论多基于骨关节疾病及其他器官炎症模型推导,其在椎间盘细胞中的具体受体分布、下游信号网络及效应强度,仍需体内外实验验证;二是LXA4对自噬等细胞过程的调控具有组织特异性,其在椎间盘微环境中的具体作用模式尚未明确,易出现机制推论的偏差;三是LXA4在体内代谢迅速,针对椎间盘组织的靶向递送系统研究较为匮乏,限制了LXA4应用于IVDD的临床转化。

未来研究需重点从以下方向推进:第一,开展

IVDD特异性体内外实验,明确LXA4在髓核、纤维环及软骨终板细胞中的具体调控机制,验证其对不同程序性细胞死亡方式、ECM代谢的直接效应;第二,深入探索LXA4与microRNA等非编码RNA的交互调控,以及其对髓核细胞代谢重编程的影响,结合组学技术丰富机制网络;第三,关注LXA4在椎间盘源性疼痛中的调控作用,探索其与UCHL3-HMGB1等疼痛相关通路的关联,拓展临床应用场景;第四,开发稳定性更高的LXA4类似物及椎间盘靶向递送系统,推动其从基础研究向临床应用转化。此外,还需探讨LXA4与消退素、保护素等其他促消退介质的协同作用,构建更完整的椎间盘炎症-消退调控网络,为IVDD的精准防治提供新的策略与靶点。

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