

内质网应激介导腰椎间盘突出退变至突出症演进的机制及干预进展

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摘要 腰椎间盘突出(lumbar intervertebral disc degeneration, LIDD)是腰椎间盘突出症(lumbar disc herniation, LDH)的主要病理基础, 内质网应激(endoplasmic reticulum stress, ERS)及未折叠蛋白反应(unfolded protein response, UPR)可能是连接异常机械负荷、营养障碍、氧化应激和炎症微环境与椎间盘细胞命运失衡的关键环节。该文围绕LIDD向LDH演进, 综述PERK、IRE1 α 和ATF6三条UPR通路在髓核、纤维环和软骨终板中的作用。现有研究表明适度UPR有助于维持蛋白质稳态和促进细胞外基质合成; 持续或过度ERS可激活CHOP、JNK/NF- κ B和NLRP3炎症小体等相关信号, 诱导线粒体损伤及Ca²⁺稳态紊乱, 引发包括凋亡、焦亡、坏死性凋亡和铁死亡在内的多种程序性细胞死亡, 以及自噬失衡和细胞衰老, 导致Aggrecan、COL2A1表达水平降低, 使MMPs和ADAMTSs表达水平升高, 进而导致髓核脱水、纤维环屏障破坏和软骨终板营养障碍, 并可能参与突出后免疫炎症反应、组织吸收及痛觉敏化。化学伴侣、UPR分支调节、抗氧化/线粒体保护、外泌体与生物材料局部递送等方向具有研究潜力, 但目前研究主要为体外和动物研究。未来需结合人体组织分期分区验证, 明确ERS的时相和阈值, 并建立精准局部递送与临床转化路径。

关键词 内质网应激; 未折叠蛋白反应; 腰椎间盘突出退变; 腰椎间盘突出症; 细胞外基质; 程序性细胞死亡; 靶向治疗

Endoplasmic Reticulum Stress in the Progression from Lumbar Disc Degeneration to Herniation: Mechanisms and Progress in Intervention

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Abstract LIDD (lumbar intervertebral disc degeneration) is the main pathological basis of LDH (lumbar disc herniation). ERS (endoplasmic reticulum stress) and UPR (unfolded protein response) may be key links connecting abnormal mechanics, nutritional disorders, oxidative stress, and inflammatory microenvironment with disc cell fate imbalance. This article reviews the roles of PERK, IRE1 α and ATF6 UPR pathways in nucleus pulposus, annulus fibrosus and cartilage endplate, focusing on the evolution of LIDD to LDH. Existing studies have shown that moderate UPR helps to

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maintain protein homeostasis and promote extracellular matrix synthesis. Persistent or excessive ERS induces apoptosis, pyroptosis, necroptosis, ferroptosis, autophagy imbalance and senescence, through CHOP, JNK/NF- κ B, NLRP3 inflammasome, mitochondrial damage and Ca^{2+} homeostasis disorder, resulting in decreased expression levels of Aggrecan and COL2A1. The expression levels of MMPs and ADAMTSs are increased, which lead to dehydration of nucleus pulposus, destruction of annulus fibrosus barrier and dystrophy of cartilage endplate, and may be involved in immune inflammation, tissue absorption and pain sensitization after protrusion. Chemical chaperones, UPR pathway modulation, antioxidant and mitochondrial protection, exosome-based therapies, and biomaterial-mediated local delivery have shown therapeutic potential, although current evidence is largely limited to *in vitro* and animal studies. In the future, it is necessary to combine with the validation based on human tissue stages and partitions, clarify the time phase and threshold of ERS, and establish an accurate local delivery and clinical transformation path.

Keywords endoplasmic reticulum stress; unfolded protein response; lumbar intervertebral disc degeneration; lumbar disc herniation; extracellular matrix; programmed cell death; targeted therapy

腰痛是全球疾病负担和功能障碍的重要原因, 2021年全球疾病负担研究显示, 2020年全球约6.19亿人受腰痛影响, 且腰痛是全球致残的首要原因之一, 腰椎间盘突出症(lumbar disc herniation, LDH)是导致腰痛、下肢放射痛及神经根症状的常见脊柱退行性疾病^[1]。研究发现突出并非单纯由一次性机械损伤造成, 而多是在椎间盘长期退变基础上, 由生物学稳态破坏逐步发展为结构性失稳的结果^[2]。正常椎间盘依赖髓核、纤维环和软骨终板三者协同维持负荷传递、应力分散和营养代谢; 任一单元发生持续损伤均可能改变整体力学环境^[3]。椎间盘细胞长期处于低氧、低营养、酸性、高渗和动态机械负荷交织的特殊微环境中, 蛋白质折叠、胶原成熟、蛋白聚糖合成及钙稳态调控对细胞器功能高度依赖^[4]。内质网作为分泌蛋白加工、质量控制和钙储存的核心细胞器, 既参与细胞外基质合成, 又可感知异常机械负荷、代谢紊乱、炎症刺激及氧化应激等微环境变化。当未折叠或错误折叠蛋白在内质网内积聚时, 细胞启动未折叠蛋白反应(unfolded protein response, UPR)以恢复稳态; 若应激持续存在, 则UPR可由保护性反应转向促凋亡、促炎和促基质降解反应^[5]。本文以“微环境刺激-UPR激活-细胞命运异常-细胞外基质破坏-组织力学失稳-突出后炎症与症状-干预边界”为主线, 系统阐述内质网应激(endoplasmic reticulum stress, ERS)介导腰椎间盘突出退变(lumbar intervertebral disc degeneration, LIDD)向LDH演进的病理效应, 以期深化对其发生发展机制的认识, 并为相关防治策略的探索提供理论依据。

1 LIDD向突出症演进的病理基础

1.1 椎间盘结构、营养特点与微环境压力

腰椎间盘由中央髓核、外周纤维环和上下软骨终板构成^[6]。髓核富含Aggrecan、II型胶原和水分, 依赖蛋白聚糖负电荷形成较高渗透压和膨胀压, 以分散轴向压缩负荷; 纤维环以I型胶原为主, 胶原纤维呈层板状交错排列, 承担抗张、抗剪切和抗旋转功能; 软骨终板既参与负荷传导, 又是无血管椎间盘营养扩散和代谢废物清除的重要通道^[7]。因此, 髓核、纤维环和软骨终板不是孤立结构, 而是共同维持“营养-基质-力学”稳态的功能单元。

椎间盘细胞长期处于低氧、低糖、酸性、高渗及动态机械负荷交织的特殊微环境中, 并由此形成一定的适应性表型; 然而, 随着软骨终板通透性下降及机械过载、氧化应激、炎症刺激和代谢异常等因素持续作用, 其细胞稳态更易受到破坏^[8]。内质网在胶原、蛋白聚糖和分泌蛋白加工中负担较重, ATP供应不足、酸性环境、 Ca^{2+} 紊乱和活性氧(reactive oxygen species, ROS)积聚均可削弱内质网蛋白折叠与质量控制能力, 使内质网功能障碍成为退变微环境破坏椎间盘细胞稳态的重要环节^[9]。因此, 维持椎间盘微环境的稳态, 依赖椎间盘内各结构的功能协同与细胞层面的内环境稳定, 任一环节发生异常都可能启动或加速椎间盘退变, 为腰椎间盘突出症的发生发展奠定病理基础。

1.2 从基质代谢失衡到组织力学失稳

LIDD的早期核心改变是细胞外基质合成减少和降解增加^[10]。随着髓核细胞合成Aggrecan、II型胶原等细胞外基质成分的能力下降, 基质金属蛋

白酶-3(matrix metalloproteinase-3, MMP-3)、MMP-13以及含血小板反应蛋白基序的解聚蛋白样金属蛋白酶-4/5(a disintegrin and metalloproteinase with thrombospondin motifs-4/5, ADAMTS-4/5)等基质降解酶表达水平增加,导致细胞外基质合成与降解平衡向分解代谢方向偏移。随之蛋白聚糖丢失和含水量下降,使髓核凝胶样结构逐渐纤维化,膨胀压及轴向负荷分散能力进一步降低^[11]。此时,椎间盘内应力由均匀传递转为局部集中,为纤维环裂隙形成和髓核外移创造了力学基础。

纤维环在应力集中以及反复屈曲、旋转、剪切等异常机械负荷作用下,可出现层板间分离、胶原纤维排列紊乱及放射状裂隙^[12]。后外侧纤维环相对薄弱,后纵韧带对该区域约束有限,退变髓核更易沿薄弱区域迁移,可表现为膨出、突出、脱出或游离。软骨终板硬化或钙化可进一步降低其通透性,阻碍氧、葡萄糖等营养物质经终板向椎间盘内部扩散,使髓核及纤维环细胞面临更严重的缺氧、低糖及酸性代谢压力,从而形成“终板退变-营养障碍-内质网应激-基质降解-力学失稳”的正反馈闭环^[13-15]。这一闭环解释了退变如何转化为突出的过程,但不能单独解释症状轻重,症状还取决于突出物是否突破免疫隔离及其与神经根微环境的相互作用。

1.3 突出后炎症反应与症状异质性

LDH的临床症状由机械压迫、免疫炎症和神经敏化共同决定。部分患者影像学可见明显退变或突出而症状轻微,另一些患者突出体积不大却因炎症反应、神经根水肿或个体痛觉敏化而出现明显疼痛。因此,临床评估应综合影像学表现、病史、体征、神经功能及功能障碍程度,避免单纯依据突出大小制定治疗策略^[16]。

髓核组织在椎间盘内处于相对免疫隔离状态。突出后,髓核暴露于硬膜外空间,可诱导巨噬细胞浸润、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、白细胞介素-1 β (interleukin-1 β , IL-1 β)、白细胞介素-6(interleukin-6, IL-6)等炎症因子释放,并伴随新生血管及神经纤维长入^[17]。适度免疫反应可能参与突出物自发吸收,而过度或持续炎症则可能加重神经根刺激和痛觉敏化。内质网应激可能同时参与突出前的组织结构破坏和突出后的炎症放大,但其生物学效应取决于退变阶段、细胞类型、免疫微环境和应激阈值^[18]。

不同突出亚型的免疫暴露程度存在差异。膨出

及包容性突出仍受到纤维环和后纵韧带的相对限制,而脱出型和游离型髓核组织更易与硬膜外血管、肉芽组织及免疫细胞接触。研究发现,ADAMTS-4主要表达于CD68阳性单核/巨噬细胞,且经后纵韧带脱出型和游离型组织中ADAMTS-4阳性细胞数量明显多于突出型及韧带下脱出型^[19]。在坐骨神经痛患者中,脱出型患者的巨噬细胞浸润程度高于膨出型,并与随访时突出物缩小相关^[20]。这些结果与脱出型和游离型椎间盘突出具有较高自发吸收概率的临床研究结果^[21]一致。而目前现有亚型研究主要检测CD68、ADAMTS-4等免疫或基质降解指标,在同一患者中直接比较葡萄糖调节蛋白78(glucose-regulated protein 78, GRP78)、蛋白激酶R样内质网激酶(protein kinase R-like endoplasmic reticulum kinase, PERK)/磷酸化真核翻译起始因子2 α (phosphorylated eukaryotic translation initiation factor 2 α , p-eIF2 α)、肌醇需求酶1 α (inositol-requiring enzyme 1 α , IRE1 α)、剪接型X盒结合蛋白1(spliced X-box-binding protein 1, XBP1s)、激活转录因子6(activating transcription factor 6, ATF6)和C/EBP同源蛋白(C/EBP homologous protein, CHOP)等内质网应激标志物的证据不足^[22]。因此,现有研究仅能间接支持非包容型突出具有更高层次的免疫暴露和组织重塑,尚不足以据此认为ERS强度随突出分型呈持续递增趋势。未来应开展影像学分型、组织区域、ERS标志物与症状及突出物吸收结局相匹配的配对研究,以进一步验证其关联。

2 内质网应激与UPR: 从适应性保护到失代偿损伤

2.1 椎间盘细胞内质网的功能定位

内质网负责分泌蛋白折叠、糖基化修饰、质量控制及向高尔基体转运等过程,是胶原、蛋白聚糖及多种细胞外基质蛋白合成和初步加工的重要场所。髓核细胞、纤维环细胞和软骨终板细胞均具有较强的细胞外基质合成功能,因此,内质网蛋白加工及分泌能力与椎间盘细胞外基质稳态密切相关^[23]。内质网同时是细胞内重要Ca²⁺储存库,参与机械刺激响应、线粒体功能调控、细胞死亡和炎症信号转导。在椎间盘细胞中,低营养、低氧、酸性、高渗及异常机械负荷可共同增加内质网蛋白折叠压力,破坏钙稳态和氧化还原环境,诱发内质网应激^[24]。由此可见,同一ERS标志物在不同组织区域和阶段的意义并不完全相同,

需结合UPR分支、刺激背景及下游结局共同解释。

2.2 UPR三条经典通路及其病理转向

UPR主要由PERK、IRE1 α 和ATF6三条经典通路介导。在应激早期, GRP78/BiP与PERK、IRE1 α 和ATF6三类跨膜感受器解离, 启动包括抑制蛋白翻译、增强分子伴侣表达和促进内质网相关降解(endoplasmic reticulum-associated degradation, ERAD)在内的适应性反应, 从而帮助细胞恢复蛋白稳态^[25]。

PERK通过磷酸化eIF2 α 暂时抑制整体蛋白翻译, 减少新生肽链进入内质网, 从而减轻其蛋白折叠负荷; 但PERK持续激活可经ATF4上调CHOP表达, 诱导BCL-2相关X蛋白(BCL-2-associated X protein, BAX)与B细胞淋巴瘤-2蛋白(B-cell lymphoma 2, BCL-2)之间的平衡失调, 进而促进线粒体功能障碍和caspase级联反应^[26]。IRE1 α 在适应性应激阶段通过剪接XBP1 mRNA, 生成剪接型XBP1, 后者作为转录因子上调分子伴侣及ERAD相关基因表达, 从而增强内质网蛋白折叠及错误折叠蛋白清除能力; 而在强烈或持续应激条件下, IRE1 α 则可通过JNK、NF- κ B等信号通路促进炎症反应和细胞凋亡^[27]。ATF6经高尔基体剪切后入核, 上调分子伴侣和质控相关基因表达; 其不同椎间盘细胞类型和退变阶段可能兼具保护与损伤双重效应^[28]。

UPR的三条经典通路在椎间盘细胞中既能发挥适应性保护作用, 又可在持续应激条件下转而促进细胞凋亡、炎症反应及细胞外基质降解。为便于后续机制阐述, 本文将内质网应激相关标志物及其在LIDD至突出症进展中的作用汇总于表1。

2.3 适应性与失代偿性内质网应激

内质网应激并非单向致病过程。轻度、短时应激可提高细胞耐受性, 维持胶原和蛋白聚糖加工能力; 持续、强烈或反复应激则可能超过细胞代偿阈值, 使UPR由“修复稳态”转向“诱导损伤”^[29-30]。在人髓核组织中, 与Pfaffmann I-II级的早期组相比, III~V级进展组的内质网扩张及GRP78、CHOP表达更明显^[31]。在人纤维环细胞中, 5%低幅循环牵张(light cyclic stretch, LCS)影响较小, 而15%高幅循环牵张(high cyclic stretch, HCS)可激活GRP78/NOX2/ROS/TXNIP/NLRP3/IL-1 β 信号轴^[32]; 大鼠纤维环20%牵张亦可随时间上调GRP78、CHOP和caspase-12表达^[33]。这些数值依赖细胞来源、负荷频率、持续时间和检测终点, 不能直接外推为患者治疗阈值。

2.4 不同椎间盘细胞的差异化UPR特征

髓核细胞位于椎间盘中央, 长期处于低氧、低营养和高渗微环境中。现有人退变组织及炎症刺激研究发现, PERK和IRE1 α 分支持续激活较为显著, 而ATF6变化相对不一致; 抑制PERK或IRE1 α 信号可部分恢复细胞增殖及基质合成表型^[34]。因此, 分析髓核细胞UPR时, 需重点关注PERK/eIF2 α /ATF4通路由短期翻译抑制向CHOP/NOXA介导凋亡的转变, 并区分IRE1 α /XBP1s介导的适应性反应与持续应激下IRE1 α /JNK/NF- κ B介导的促炎、促凋亡性损伤反应。

纤维环细胞直接受到牵张、剪切及基质硬度变化等力学刺激, ERS可与NOX2/ROS、TXNIP/NLRP3及CHOP/caspase-12等信号通路耦联, 并对高幅或持续机械负荷产生非线性应答^[35]。软骨终板细胞位于椎间盘营养物质扩散的关键界面, 并与终板钙化密切相关。氧化应激模型研究显示, miR-31-5p/ATF6轴可调节ERS相关凋亡和钙化^[36], 提示ATF6可能是终板ERS调控的重要节点, 但现有证据尚不足以证明其不同退变阶段均为主导分支。总体而言, 目前有关不同细胞类型UPR差异的证据主要来自不同模型间的趋势性比较, 仍需在同一患者、同一分级体系下开展髓核-纤维环-软骨终板的配对检测。

3 椎间盘微环境诱发内质网应激的主要因素

3.1 异常机械负荷与机械转导

异常机械负荷是推动退变椎间盘进一步失稳的重要外部因素。持续压缩、反复屈曲、旋转剪切和偏心负荷可通过机械敏感离子通道、整合素/FAK、细胞骨架重构和MAPK/NF- κ B等信号, 将宏观力学刺激转化为细胞器应激^[37]。Piezo型机械敏感离子通道组件1(Piezo-type mechanosensitive ion channel component 1, Piezo1)和瞬时受体电位阳离子通道V亚家族成员4(transient receptor potential cation channel subfamily V member 4, TRPV4)等机械敏感通道激活可引起Ca²⁺内流, 进而影响内质网Ca²⁺的储存与释放; 同时, 细胞骨架张力的改变可影响内质网形态和膜张力, 增加蛋白折叠压力。长期机械过载可促进纤维环细胞死亡、胶原代谢紊乱和裂隙扩展, 使退变椎间盘更容易发生髓核外移^[38]。

3.2 低氧、营养不足与酸性微环境

椎间盘细胞主要依赖软骨终板扩散获得氧、葡

表1 内质网应激相关标志物及其在椎间盘退变至突出症演进中的意义

Table 1 Endoplasmic reticulum stress-related markers and their significance in the progression of intervertebral disc degeneration to herniation

标志物	通路/机制节点	主要机制	主要组织/细胞来源	阶段/应激背景	在退变至突出进程中的意义	参考文献
Marker	Pathway/mechanistic node	Principal mechanism	Main tissue/cell source	Stage/stress context	Significance in the progression from degeneration to herniation	References
GRP78/BiP	Endoplasmic reticulum molecular chaperone; UPR activation	Binds unfolded proteins; dissociates from PERK, IRE1 α , and ATF6 during stress	Nucleus pulposus, annulus fibrosus, cartilaginous endplate, and cells within herniated tissue	Can increase early; often remains elevated in advanced stages	Sensitive indicator of proteostatic burden, but elevation alone does not determine injury severity or herniation subtype	[18,22-25,31-36]
PERK	UPR sensor	Phosphorylates eIF2 α to transiently suppress translation; sustained activation induces ATF4/CHOP and NOXA	Predominantly nucleus pulposus; also annulus fibrosus	Adaptive early; becomes maladaptive with persistent stimulation	Associated with nucleus pulposus cell apoptosis, ECM (extracellular matrix) degradation, and loss of the anabolic phenotype	[22-26,31,34-35]
p-eIF2 α	Downstream effector of PERK	Suppresses global translation while selectively promoting ATF4 expression	Nucleus pulposus and annulus fibrosus	Indicates activation of the PERK branch; should be interpreted together with ATF4/CHOP	Indicates activation of the PERK branch; should be interpreted together with ATF4/CHOP	[25-26,29-31,34]
ATF4	Downstream of PERK/eIF2 α	Regulates amino acid metabolism, antioxidant responses, autophagy, and CHOP expression	Nucleus pulposus and annulus fibrosus	May be protective early; sustained high expression is more common in intermediate/late stages or under high load	Links metabolic adaptation and autophagy to terminal apoptosis	[25-26,29-31,34-35]
CHOP	Transcription factor of maladaptive UPR	Promotes BAX/BCL-2 imbalance, mitochondrial apoptosis, inflammation, and extracellular matrix degradation	Nucleus pulposus, annulus fibrosus, cartilaginous endplate; dorsal root ganglion models	Intermediate/late stages or intense, sustained stress	Marker of terminal injury; associated with cell death but not specific to LDH subtype	[18,22-26,29-36]
IRE1 α	UPR sensor	Mediates unconventional splicing of <i>XBP1</i> mRNA; sustained activation engages JNK, NF- κ B, and RIDD (regulated IRE1-dependent decay)	Prominent in nucleus pulposus; also expressed in annulus fibrosus and immune cells	Adaptive early; shifts to proinflammatory/proapoptotic signaling with persistent inflammation	Associated with inflammation, apoptosis, and ECM catabolism in nucleus pulposus	[22,25,27,30,34]
XBP1s	Spliced downstream product of IRE1 α	Enhances molecular chaperones, endoplasmic reticulum-associated degradation, and secretory protein folding	Nucleus pulposus and annulus fibrosus; dorsal root ganglion nerve-injury models	Predominantly adaptive; either persistent activation or inadequate activity may be maladaptive	IRE1 α /JNK activity should be considered to distinguish protective from damaging effects	[22-25,27,30,34]
ATF6	UPR sensor	Following proteolytic cleavage in the Golgi apparatus, the active ATF6 fragment translocates to the nucleus and induces the expression of molecular chaperone and protein quality-control genes	Evidence is concentrated in cartilaginous endplate; also expressed in nucleus pulposus	Early adaptation; endplate oxidative stress/calcification	The miR-31-5p/ATF6 axis links endplate ERS, apoptosis, and calcification; ATF6 is not the sole dominant branch at all stages	[22,25,28,36]
caspase-12	ERS-associated apoptotic mediator	Mediates the endoplasmic reticulum-associated caspase cascade	Nucleus pulposus and annulus fibrosus	High mechanical load or maladaptive stage	Suggests transition from adaptive UPR to apoptosis; limited extrapolation to human tissue	[24,26,31,33]

续表1

标志物	通路/机制节点	主要机制	主要组织/细胞来源	阶段/应激背景	在退变至突出进程中的意义	参考文献
Marker	Pathway/mechanistic node	Principal mechanism	Main tissue/cell source	Stage/stress context	Significance in the progression from degeneration to herniation	References
NOXA	BH3-only pro-apoptotic protein; component of the PERK/NOXA/MCL-1 axis	Reduces MCL-1 (myeloid cell leukemia-1) stability, linking ERS to mitochondrial apoptosis	Nucleus pulposus cells/degenerative nucleus pulposus	Advanced stages and pharmacologic ERS models	The PERK/NOXA/MCL-1 axis promotes nucleus pulposus cell death and ECM degradation	[35]
NLRP3	ERS/ROS-related inflammasome	Amplifies inflammatory cell death via TXNIP, caspase-1, and GSDMD (gasdermin D)	Mechanically stretched annulus fibrosus, nucleus pulposus, and post-herniation macrophages	High mechanical/inflammatory load; intermediate and late stages; post-herniation	Links ERS, pyroptosis, and inflammatory amplification; not yet a clinical subtype marker	[18,22,32]
MMP-3	ECM-degrading effector	Degrades proteoglycans, collagen, and other ECM components	Nucleus pulposus, annulus fibrosus, and granulation tissue/macrophages in herniated material	Intermediate/late stages and after herniation	Reflects ECM catabolism and structural damage; ERS-associated but nonspecific	[10-11,17-18,22-24,31,34-35]
MMP-13	Collagen-degrading effector	Primarily degrades type II collagen	Nucleus pulposus and annulus fibrosus	Intermediate/late stages	Associated with disruption of the collagen network and reduced compressive capacity	[10-11,17-18,22-24,34-35]
ADAMTS-5	Aggrecanase	Cleaves aggrecan	Nucleus pulposus and annulus fibrosus	Can increase in early/intermediate stages and persist after herniation	Promotes nucleus pulposus dehydration and loss of swelling pressure; not specific to ERS	[10-11,17-18,22,34]
Aggrecan	Core ECM component	Maintains hydration, osmotic pressure, and compressive resistance	Predominantly nucleus pulposus; also expressed in cartilaginous endplate	Declines early and decreases further with degeneration	Readout of anabolic phenotype/function; best interpreted with degradation fragments	[7,10-11,14,22-24,31,34-36]
COL2A1	Type II collagen-encoding gene	Maintains nucleus pulposus and cartilage-like ECM structure	Nucleus pulposus and cartilaginous endplate	Progressively decreases from early to advanced stages	Reflects ECM anabolic capacity; reduction is not specific to ERS	[7,14,22-24,31,34-36]

萄糖和其他营养物质。终板硬化或钙化后, 氧和葡萄糖供应量减少, ATP不足将削弱分子伴侣和蛋白修饰酶功能, 使错误折叠蛋白更易在内质网腔内积聚; 葡萄糖不足还可影响N-糖基化过程, 降低胶原和蛋白聚糖成熟效率^[39]。同时, 椎间盘细胞主要依赖糖酵解供能, 当乳酸清除受限时, 会出现局部乳酸积聚及pH值下降。酸性环境不仅影响代谢酶和基质合成相关酶活性, 还可破坏内质网氧化还原平衡, 干扰二硫键形成及蛋白质正确折叠, 从而持续激活UPR5^[40]。Jackson等^[41]研究发现, 终板钙化和机械负荷可降低椎间盘内葡萄糖浓度, 提示改善终板营养供应可能有助于缓

解椎间盘细胞的代谢应激和内质网应激, 从而延缓退变进展。Zhang等^[42]发现, 乳酸可通过与Akt相互作用促进髓核细胞衰老、氧化应激及相应椎间盘退变, 乳酸积聚不仅可改变细胞外pH, 还可介入细胞内信号转导, 放大氧化损伤和衰老相关分泌表型(senescence-associated secretory phenotype, SASP)。

3.3 氧化应激、线粒体损伤与钙稳态紊乱

ROS水平升高可破坏内质网氧化还原微环境, 干扰二硫键形成及蛋白正确折叠。内质网本身在氧化折叠过程中亦可产生ROS, 使局部氧化压力进一步升高, 形成“氧化应激-内质网应激-ROS再生成”的正反

馈放大环路^[43]。内质网与线粒体之间的 Ca^{2+} 传递、线粒体相关内质网膜(mitochondria-associated endoplasmic reticulum membranes, MAMs)稳定性和线粒体膜电位变化可进一步影响细胞的适应性反应及凋亡或程序性坏死等结局。氧化压力超过细胞抗氧化和蛋白质质量控制阈值时,可促进UPR失代偿和基质代谢紊乱^[44]。Lin等^[45]发现,ROS可调控内质网应激及内质网-线粒体 Ca^{2+} 串扰,并促进受压髓核细胞程序性坏死;Xu等^[46]发现,硫化氢可减轻髓核细胞内质网应激和线粒体损伤并改善椎间盘退变,提示保护线粒体能量代谢和抑制过度内质网应激具有协同意义。

3.4 炎症、代谢异常与细胞衰老

IL-1 β 、TNF- α 、IL-6等炎症因子可通过NF- κ B、MAPK和JNK信号诱导内质网应激;内质网应激又可通过IRE1 α /JNK、PERK/CHOP和NLRP3炎症小体通路进一步放大炎症反应^[47]。该双向环路可促进MMPs、ADAMTSs表达并诱导髓核细胞和纤维环细胞死亡,是退变进展及突出后疼痛微环境形成的重要机制之一。Chen等^[48]发现,IL-1 β /NF- κ B-NLRP3炎症小体正反馈环路可显著促进炎症反应和基质降解,IL-1 β 通过NF- κ B上调NLRP3及相关炎症因子表达,进而促使炎症信号持续放大,阻断NF- κ B/NLRP3轴有助于减轻突出后炎症反应和延缓退变进展。

糖尿病、肥胖、代谢综合征和衰老可分别通过晚期糖基化终末产物(advanced glycation end products, AGEs)积累、慢性低度炎症、微循环障碍和SASP加重椎间盘细胞应激。衰老细胞释放的IL-6、IL-8、TNF- α 、MMPs和ADAMTSs等因子可诱导邻近细胞应激和衰老扩散,使局部微环境由短期适应状态转向慢性损伤状态^[49]。因此,代谢异常和衰老应作为内质网应激上游驱动因素,而非仅作为流行病学风险因素。Luo等^[50]发现,AGEs可呈时间和浓度依赖性诱导内质网应激,破坏细胞内 Ca^{2+} 稳态并促进髓核细胞凋亡;4-苯基丁酸抑制内质网应激后可减轻上述损伤,提示靶向内质网应激可能是糖尿病相关椎间盘退变的潜在干预方向。

4 内质网应激参与退变向突出症演进的机制链条

4.1 髓核细胞凋亡与基质维持能力下降

髓核细胞是维持椎间盘含水量、渗透压和

抗压性能的关键细胞。持续内质网应激可通过PERK/ATF4/CHOP、IRE1 α /JNK、caspase-12及线粒体凋亡相关通路促进髓核细胞凋亡,使细胞数量减少、细胞外基质合成能力降低^[51]。进一步研究发现,PERK/NOXA/MCL-1轴可能参与ERS诱导的线粒体凋亡和ECM降解,是连接髓核细胞死亡与基质破坏的潜在调控节点^[52]。

随着Aggrecan和II型胶原合成量下降,蛋白聚糖丢失使髓核结合水能力减弱,膨胀压降低,轴向负荷分散功能下降,该变化不是单一分子事件,而是将细胞器应激转化为组织力学性能下降的关键环节^[53]。Kang等^[54]研究发现,退变髓核细胞中PERK和IRE1 α 相关内质网应激通路明显激活,并伴有细胞增殖和基质合成能力降低;炎症刺激诱导的UPR持续激活可进一步抑制细胞合成表型并增强基质分解倾向,提示联合调控PERK和IRE1 α 可能有助于恢复髓核细胞的基质合成功能。

4.2 自噬、细胞衰老与程序性细胞死亡

自噬是椎间盘细胞应对内质网应激的重要适应机制。适度自噬可清除错误折叠蛋白和受损细胞器,减轻内质网负荷;持续或过度应激则可导致自噬流阻滞或过度自噬,反而加剧细胞功能衰竭^[55]。因此,自噬在退变不同阶段具有保护与损伤并存的双重作用,治疗策略不宜简单定义为“促进自噬”或“抑制自噬”。Luo等^[56]发现,增强序列相似性家族134成员B(family with sequence similarity 134 member B, FAM134B)介导的内质网自噬可抑制AGEs诱导的髓核细胞凋亡和衰老,提示适度内质网自噬可能减轻持续应激所致的细胞损伤。

长期ERS还可激活p53/p21、p16INK4a和NF- κ B等通路,促进椎间盘细胞衰老及SASP相关因子释放。除凋亡外,焦亡、坏死性凋亡和铁死亡等其他程序性细胞死亡方式也可能参与退变椎间盘细胞损伤。内质网应激可通过ROS积累和 Ca^{2+} 稳态紊乱等上游机制,并通过NLRP3炎症小体相关信号、RIPK1/RIPK3/MLKL信号轴及脂质过氧化等过程,参与焦亡、坏死性凋亡和铁死亡的调控^[57]。这些机制的共同后果是细胞数量下降、炎症信号持续放大和基质降解增强。Xu等^[58]发现,miRNA-141可通过促进ROS生成并激活TXNIP/NLRP3信号诱导髓核细胞焦亡,NLRP3炎症小体介导的焦亡是椎间盘退变中炎症放大的重要机制。

4.3 细胞外基质代谢失衡与纤维环屏障破坏

内质网功能障碍可直接影响胶原和蛋白聚糖的折叠、修饰与分泌, 不仅使基质蛋白数量减少, 而且使其成熟质量下降。在持续应激状态下, Aggrecan和COL2A1表达水平降低, 而MMPs和ADAMTSs表达水平升高, 导致细胞外基质代谢平衡向降解方向偏移^[59]。纤维环细胞在长期机械过载和内质网应激作用下可发生凋亡、衰老及胶原合成异常, 层板间连接逐渐减弱, 内层裂隙在反复应力作用下向外扩展。在纤维环约束能力降低后, 退变髓核组织可沿薄弱区域迁移, 成为突出形成的直接结构基础^[60]。Yang等^[61]发现, 内质网应激与细胞外基质紊乱、氧化应激、钙稳态失衡和炎症反应存在密切联系, UPR持续激活可同时抑制基质合成和促进基质降解酶表达, 内质网应激可作为基质代谢失衡的上游调控节点, 而非单纯的细胞死亡伴随现象。Wang等^[62]研究发现, 基质硬度增加可激活Piezo1并诱导人退变椎间盘细胞氧化应激相关衰老和凋亡, 异常机械微环境可通过机械敏感离子通道、氧化应激及细胞死亡通路破坏椎间盘稳态。

4.4 软骨终板退变与营养障碍闭环

软骨终板退变会降低椎间盘营养扩散能力, 是退变持续进展的重要放大因素。内质网应激可参与终板细胞凋亡、衰老和钙化; 终板硬化又会加重髓核和纤维环细胞的缺氧、低糖及酸性压力, 进一步诱导内质网应激^[63]。间充质干细胞外泌体通过miR-31-5p/ATF6轴保护终板细胞的研究提示, ATF6可能是连接终板细胞应激、凋亡与钙化的重要调控节点, 但靶向该通路的临床转化价值及长期安全性仍需进一步验证^[64]。此外, 外泌体介导的非编码RNA递送可调节髓核细胞内质网应激、凋亡及基质代谢, 为改善椎间盘局部微环境及维持营养稳态提供了间接依据^[65]。

4.5 突出后巨噬细胞反应、组织吸收与痛觉敏化

髓核组织突破纤维环后可激活局部免疫反应。巨噬细胞浸润、炎症因子释放、新生血管形成和神经纤维长入可共同引起神经根水肿、缺血和痛觉敏化^[66]。巨噬细胞既可参与突出组织吸收, 也可在炎症持续时加重疼痛。因此, 应从免疫清除与炎症性疼痛之间的动态平衡理解突出后炎症, 而不宜将其简单界定为有利或有害^[67]。内质网应激可能通过调

控巨噬细胞极化、炎症小体激活和基质降解酶表达参与这一过程, 但目前研究证据仍不足。Ikeda等^[68]研究显示, 巨噬细胞是突出椎间盘组织吸收过程中的关键免疫细胞, 可通过吞噬作用及胶原降解酶参与组织清除, 调控巨噬细胞功能可能同时影响突出物吸收和炎症性疼痛。

在突出物吸收过程中, 巨噬细胞可通过吞噬及MMPs、ADAMTSs等基质降解酶参与组织清除^[69-70]。近年研究发现, 突出髓核周围可发生淋巴管生成, 椎旁淋巴系统参与髓核成分向引流淋巴结的转运及炎症消退; 血管内皮生长因子受体3(vascular endothelial growth factor receptor 3, VEGFR3)条件性缺失可损害突出髓核组织的清除, 并加重局部炎症^[71]。这些研究进一步说明突出后结局由免疫清除、淋巴引流、组织重塑与炎症疼痛之间的动态平衡决定, 脱出/游离型更强的免疫暴露既可能促进吸收, 也可能在早期加重神经根刺激。

痛觉敏化涉及TNF- α 、IL-1 β 、IL-6、神经生长因子(nerve growth factor, NGF)、血管内皮生长因子(vascular endothelial growth factor, VEGF)等介质对神经根、背根神经节(dorsal root ganglion, DRG)神经元及卫星胶质细胞的共同作用^[72]。在脊神经结扎模型中, 结扎后1~3 d损伤侧DRG的GRP78、CHOP和XBP1s表达水平升高; eIF2 α 去磷酸化抑制剂salubrinal可减轻痛觉过敏, 而局部诱导ERS则可产生痛觉过敏^[73], 提示神经元/胶质细胞ERS可能参与神经损伤后痛觉敏化, 但该证据并非LDH特异性证据。LDH临床样本和大鼠模型的近期研究发现, S100钙结合蛋白A9(S100 calcium binding protein A9, S100A9)相关的巨噬细胞M1型极化可伴随DRG神经元瞬时受体电位阳离子通道V亚家族成员1(transient receptor potential cation channel subfamily V member 1, TRPV1)表达及Toll样受体4(Toll-like receptor 4, TLR4)/NF- κ B信号增强; 调控MAPK14/S100A9/Rac1/2轴可减少疼痛相关行为^[74]。目前尚缺乏人LDH中“突出物ERS-巨噬细胞状态-DRG ERS-疼痛表型”的纵向配对证据, 因此该机制链条仍有待进一步验证。

综上, 内质网应激可作为整合异常机械负荷、营养障碍、炎症刺激和代谢异常等多种致病因素的关键枢纽, 通过诱导细胞命运异常和组织力学失稳, 推动腰椎间盘突出退变向突出症演进(图1和表2)。

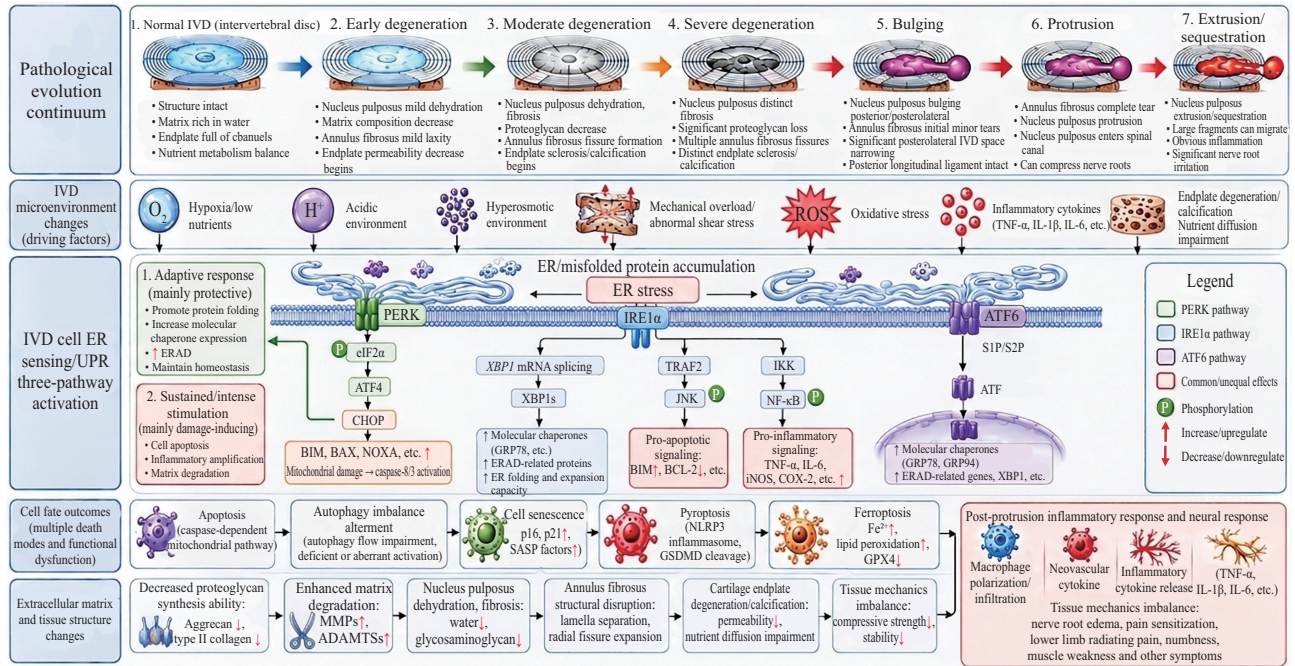


图1 内质网应激介导退变向突出症演进的整合机制图(根据参考文献[22-24,31-36,43-74]修改)

Fig.1 Integrated mechanism diagram of endoplasmic reticulum stress mediating the progression from lumbar intervertebral disc degeneration to herniation (modified from the references [22-24,31-36,43-74])

5 靶向内质网应激的干预进展与转化边界

5.1 上游微环境管理

减少持续机械过载、控制体重、改善代谢状态、维持规律运动和开展规范康复训练,可降低椎间盘细胞所受机械、炎症和代谢压力。此类措施并不直接阻断UPR通路,但可通过减轻机械、炎症和代谢等上游因素的持续刺激,降低内质网应激负荷,并可作为与现有保守治疗体系相衔接的基础策略^[75]。Samartzis等^[76]基于人群影像学和流行病学研究发现,超重和肥胖与椎间盘退变及腰痛风险增加相关,其机制可能涉及轴向负荷增加、脂肪组织介导的慢性低度炎症及代谢异常等多种因素的共同作用,而体重管理可作为降低椎间盘细胞机械和炎症应激负荷的基础措施,而不应被简单理解为单纯减轻症状的生活建议。

5.2 化学伴侣与UPR通路调节剂

4-苯基丁酸和牛磺熊去氧胆酸等化学伴侣可增强蛋白折叠能力、减少未折叠蛋白积聚,并在多种细胞和动物模型中表现出抑制内质网应激相关凋亡和基质降解的作用^[77]。研究发现针对PERK、IRE1α和ATF6等UPR分支进行药理调控,为内质网应激的精准干预提供了可能;但不同UPR分支的效应具有应激强度、持续时间和细胞类型依赖性,非选择性

或过度抑制可能削弱其适应性保护作用^[78]。因此,相关药物需明确最佳干预窗口、剂量范围、细胞类型差异和长期安全性。

5.3 抗氧化、线粒体保护与抗铁死亡策略

由于氧化应激、线粒体损伤和内质网应激之间存在正反馈,Nrf2/HO-1、SIRT1/AMPK、线粒体膜电位保护及ROS清除等策略可能减轻椎间盘细胞的氧化应激和内质网应激负荷^[79]。抗脂质过氧化和调控GPX4、SLC7A11等铁死亡相关分子表达,也被认为是值得关注的基础研究方向^[80]。但现有证据多来自细胞和动物模型,尚不足以支持将抗氧化剂或抗铁死亡药物用于常规临床治疗。

5.4 天然活性物质、外泌体与生物材料递送

小檗碱、槲皮素、姜黄素、红景天苷、Omega-3脂肪酸等天然活性物质具有抗炎、抗氧化和代谢调节等多靶点调控作用,部分研究显示其可影响内质网应激相关通路^[81-82]。该类物质可作为机制研究中的多通路调节工具,但其生物利用度、体内暴露水平、靶组织有效浓度及临床疗效仍需进一步验证。

间充质干细胞、髓核祖细胞或尿源性干细胞来源外泌体可携带miRNA、蛋白质和脂质成分,参与细胞间通信和微环境调节。外泌体携带的miRNA、lncRNA、circRNA等非编码RNA以及m⁶A修饰等表观

表2 内质网应激介导腰椎间盘突出退变向突出症演进的主要机制
Table 2 The major mechanisms by which endoplasmic reticulum stress mediates the progression of lumbar disc degeneration to herniation

病理过程 Pathologic process	细胞类型 Cell type	关键通路 Key pathways	代表性分子 Representative molecules	对退变/突出的影响 Effects on degeneration/herniation	证据来源 Evidence source	参考文献 References
Nucleus pulposus cell apoptosis	Nucleus pulposus cells	PERK/eIF2 α /ATF4/CHOP; IRE1 α /JNK; PERK/NOXA/MCL-1	GRP78, PERK, ATF4, CHOP, BAX, BCL-2, caspase-12, NOXA, MCL-1	Reduced cell number and anabolic activity; nucleus pulposus dehydration and decreased swelling pressure promote mechanical instability	Cells, animals, and patients	[22-24,31,34-35,45-46,50-52,54]
Autophagy dysregulation	Nucleus pulposus and annulus fibrosus cells	PERK/eIF2 α /ATF4; IRE1 α /JNK; AMPK/mTOR	LC3, Beclin-1, p62, ATF4, JNK, mTOR	May be protective early; persistent stress blocks autophagic flux and promotes cellular dysfunction	Cells and animals	[24,39-40,55-56,59]
Cellular senescence and SASP factor secretion	Nucleus pulposus, annulus fibrosus, and cartilaginous endplate cells	CHOP/NF- κ B; p53/p21; p16INK4a	p53, p21, p16, NF- κ B, IL-6, IL-8, MMPs, ADAMTSs	Creates a chronic inflammatory and ECM-degrading microenvironment, propagating degeneration	Cells, animals, and patients	[31,40,42,49,56-57]
Pyroptosis	Nucleus pulposus cells and inflammatory cells in herniated tissue	ERS/ROS/NLRP3/caspase-1/GSDMD	NLRP3, caspase-1, GSDMD, IL-1 β , IL-18	Amplifies inflammation and pain sensitization and may promote the post-herniation inflammatory microenvironment	Cells and animals	[32,45,48,57-59]
Necroptosis	Nucleus pulposus and annulus fibrosus cells	RIPK1/RIPK3/MLKL	RIPK1, RIPK3, MLKL, DAMPs	Cell rupture releases DAMPs (damage-associated molecular patterns), promoting inflammatory degeneration and tissue damage	Cells	[45,51,57]
Ferroptosis	Nucleus pulposus cells and residual nucleus pulposus cells	ERS/ROS/lipid peroxidation; Nrf2/HO-1	Fe ²⁺ , GPX4, SLC7A11, ACSL4, Nrf2, HO-1	Enhanced lipid peroxidation and oxidative injury may contribute to degeneration and postoperative recurrence	Cells and animals	[57,61-62]
ECM metabolic imbalance	Nucleus pulposus and annulus fibrosus cells	CHOP/NF- κ B; MAPK; IRE1 α /JNK	Aggrecan, CO-L2A1, MMP-3, MMP-13, ADAMTS-4/5	Reduced ECM synthesis and enhanced degradation decrease nucleus pulposus water content and compressive capacity	Cells, animals, and patients	[10-11,17-18,22-24,34-35,53-54]
Annulus fibrosus structural disruption	Annulus fibrosus cells	ERS/CHOP/caspase-12; NOX2/ROS-TXNIP/NLRP3	Piezo1, TRPV4, integrins, FAK, CHOP, MMPs, COL1A1	Lamellar separation and fissure propagation in the annulus fibrosus create a pathway for nucleus pulposus migration	Animal/mechanical models	[12,32-33,37-38,60,62]
Cartilaginous endplate degeneration and nutritional impairment	Cartilaginous endplate cells	ATF6/CHOP; inflammation-calcification pathways	ATF6, GRP78, CHOP, RUNX2, MMPs, miR-31-5p	Endplate calcification and reduced permeability create a positive feedback loop between nutritional impairment and ERS	Cells and animals	[14-15,36,63-64]
Post-herniation immune-inflammatory response	Nucleus pulposus cells in herniated tissue, infiltrating macrophages, and dorsal root ganglion neurons/glia cells	Macrophage recruitment/activation; cytokine signaling; S100A9/TLR4/NF- κ B; DRG ERS; lymphatic clearance	CD68, MCP-1, TNF- α , IL-1 β , IL-6, S100A9, TLR4, TRPV1, GRP78, CHOP, VEGF/VEGFR3	May promote resorption of herniated tissue but can also cause nerve-root edema and pain sensitization	Patients and animals	[17-21,65-74]

遗传机制,为内质网应激的精细调控提供了新的研究方向;如miR-31-5p/ATF6轴可参与终板细胞凋亡和钙化的调控^[83-84]。当前,外泌体相关干预的临床转化仍受制于制备标准化、剂量控制、靶向递送、批间一致性及长期安全性等因素。

5.5 与现有临床治疗体系的关系

椎间盘血供缺乏、组织相对封闭且具有特殊的力学与压力环境,系统给药难以在局部维持稳定有效浓度。水凝胶、纳米颗粒、ECM模拟支架和外泌体缓释体系可延长药物在椎间盘内滞留时间,并有望用于早期退变干预、术后髓核腔修复或复发风险控制。但材料力学匹配、降解产物安全性、注射操作风险和长期组织反应仍需系统研究^[85]。目前临床治疗仍以规范保守治疗和必要时手术减压为主。内质网应激靶向策略的潜在价值在于延缓退变、改善局部炎症微环境、降低术后复发风险或促进组织修复,但这些应用场景尚需严格临床研究验证。

5.6 人源类器官、微流控器官芯片与验证路径

传统二维细胞培养难以同时重建椎间盘的低营养、低氧、酸性、高渗及动态力学梯度,穿刺动物模型还存在物种差异,且其损伤多为急性过程,难以完全模拟人类椎间盘的慢性渐进性退变。2017年建立的人源纤维环“spine-on-a-chip”模型可构建炎症因子浓度梯度,并随IL-1 β 及巨噬细胞可溶性因子浓度升高呈现剂量依赖性的炎症、血管生成、疼痛相关和分解代谢表型^[86]。小鼠整椎间盘微流控芯片可通过持续灌流,在21 d内维持髓核和纤维环细胞活性、组织结构以及合成与分解代谢功能,其整体维持效果优于静态培养^[87]。该平台可模拟并调控营养、pH、渗透压及炎症刺激等微环境因素,为研究GRP78、XBP1s、ATF4和CHOP等ERS标志物的动态变化提供条件。

人源机械活性髓核芯片在2% O₂和三维(three-dimension, 3D)微环境中保留髓核表型,生理性10%循环压缩可促进糖胺聚糖沉积,而超生理性30%持续压缩可上调前列腺素内过氧化物合酶2(prostaglandin-endoperoxide synthase 2, PTGS2)和MMP-13表达,诱导基质降解和细胞凋亡;抑制TRPV4可部分恢复基线表型^[88]。因此,微流控器官芯片不仅可用于药物筛选,更适合构建“刺激强度-UPR分支-细胞命运”的时间-剂量曲线,但现阶段尚未界定具有临床外推价值的ERS阈值。

人源类器官可补充细胞谱系和区域结构信息。

已有研究利用人间充质干细胞定向分化构建髓核和纤维环类器官,并结合分层3D打印将其组装为具有中央髓核样区域和同心纤维环样结构的整椎间盘类器官;该整椎间盘类器官在山羊椎间盘切除模型中表现出修复潜力^[89]。未来可将不同分级/分型患者来源的细胞,与巨噬细胞、内皮细胞及DRG神经元共同整合至类器官-芯片联合系统,重建“突出物-免疫-神经”界面并开展剂量、时相和局部递送研究。而供体差异、细胞成熟度不足、免疫/血管/神经成分缺失和材料扩散偏差仍限制其外推,因此类器官和器官芯片应作为人组织队列与动物研究之间的因果验证桥梁,而非临床证据的替代。

6 讨论与展望

ERS是连接椎间盘微环境压力、细胞命运异常、细胞外基质破坏和组织力学失稳的重要细胞器机制。PERK、IRE1 α 和ATF6三条UPR分支与氧化应激、Ca²⁺稳态、线粒体功能、炎症、机械转导及非编码RNA网络交叉,使其在应激早期可维持蛋白质质控,而在持续应激下则可转向促死亡、促炎和促基质降解的损伤性反应。现有证据已支持“微环境输入-ERS/UPR-细胞命运-结构失稳”的总体框架,但不同研究在物种、细胞来源、刺激剂量、退变分级和检测终点等方面差异较大,尚不足以形成可直接指导临床的统一阈值或药物干预方案。

围绕临床转化,尚待解决的核心科学问题可归纳为五点:①如何用时间序列和多标志物组合界定不同退变阶段、不同细胞类型中“适应性UPR-失代偿性ERS”的转换阈值;②髓核、纤维环和软骨终板的PERK、IRE1 α 、ATF6分支特征能否在同一患者的空间配对样本中稳定复现;③GRP78、XBP1s、ATF4、CHOP等ERS标志物是否随膨出、突出、脱出和游离分型而变化,且能否预测突出物吸收情况、症状严重度和保守治疗反应;④ERS如何在因果层面调控巨噬细胞状态、淋巴清除、神经血管长入和DRG敏化;⑤如何利用人源类器官、微流控器官芯片及力学生物学模型确定局部递送的有效剂量、治疗窗口和长期安全性。

后续研究宜建立“前瞻性人组织/影像队列-单细胞与空间组学定位-类器官/器官芯片因果验证-大动物局部递送-早期临床安全性与生物标志物试验”的递进路径。治疗策略应从笼统抑制ERS转向阶段化

和分区化调控: 早期应尽可能维持XBP1s介导的适应性信号、分子伴侣的表达以及ERAD的功能; 中晚期应重点抑制CHOP、JNK/NF- κ B和NLRP3等损伤性通路, 并减轻线粒体损伤与脂质过氧化; 突出后应同时兼顾组织免疫清除和神经炎症控制。只有在明确细胞类型、病程阶段、突出亚型和症状表型后, ERS靶向干预才可能由机制研究转化为LDH预防、保守治疗增效或术后修复策略。后续应发展更接近人类的动物模型和人源类器官/组织模型, 结合单细胞测序、空间组学、力学生物学和长期安全性评价, 建立阶段化、局部化和精准化干预方案, 以推动相关基础研究向临床防治转化。

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