

椎间盘微环境重塑的再生策略: 间充质干细胞、细胞外囊泡与水凝胶

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摘要 椎间盘退变(intervertebral disc degeneration, IVDD)是腰椎间盘突出、椎间源性腰痛和退变性腰椎疾病的重要病理基础。现有治疗以减压、镇痛和稳定为主, 难以重建退变椎间盘的细胞、基质和力学稳态。间充质干细胞(mesenchymal stem cell, MSC)以旁分泌、免疫调节和有限软骨样分化为主, 受酸化、低营养、异常负荷和局部滞留限制; 细胞外囊泡(extracellular vesicle, EV)具有无细胞递送和工程化潜力, 但需解决制备标准化、效价评价和持续递送问题; 水凝胶可提供仿生支撑和时空递送平台, 却需兼顾黏弹性、降解、抗挤出和纤维环封闭。复合体系的价值在于按退变阶段实现抗炎保护、基质重建和力学适配, 而非简单成分叠加。该文围绕终板-营养-代谢、炎症-免疫、ECM-细胞命运-力学耦合三条病理轴, 综述MSC、MSC来源EV及水凝胶在椎间盘微环境重塑中的作用边界。

关键词 椎间盘退变; 椎间盘再生; 间充质干细胞; 细胞外囊泡; 水凝胶; 组织工程; 微环境重塑

Regenerative Strategies for Intervertebral Disc Microenvironment Remodeling: Mesenchymal Stem Cells, Extracellular Vesicles and Hydrogels

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Abstract IVDD (intervertebral disc degeneration) is an important pathological basis for lumbar intervertebral disc protrusion, intervertebral source lumbar pain, and degenerative lumbar diseases. Current treatments mainly focus on decompression, pain relief, and stabilization, but they are unable to restore the cellular, matrix, and mechanical homeostasis of the degenerated intervertebral discs. MSC (mesenchymal stem cell) mainly exert paracrine, immunomodulatory, and limited chondrogenic differentiation effects, and are limited by acidification, low nutrition, abnormal loading, and local retention; EV (extracellular vesicle) have the potential for cell-free delivery and engineering, but the issues of standardized preparation, potency evaluation, and continuous delivery need to be addressed; hydrogels can provide a biomimetic support and spatial delivery platform, but they need to balance vis-

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coelasticity, degradation, resistance to extrusion, and annulus fibrosus closure. The value of the composite system lies in achieving anti-inflammatory protection, matrix reconstruction, and mechanical adaptation according to the degeneration stage, rather than simple component stacking. This article focuses on the three pathological axes of endplate-nutrition-metabolism, inflammation-immunity, ECM-cell fate-mechanics coupling, and reviews the roles of MSC, MSC-derived EVs, and hydrogels in the remodeling of the intervertebral disc microenvironment.

Keywords intervertebral disc degeneration; disc regeneration; mesenchymal stem cells; extracellular vesicles; hydrogel; tissue engineering; microenvironment remodeling

椎间盘退变(intervertebral disc degeneration, IVDD)是腰椎间盘突出症、椎间源性腰痛、退变性腰椎管狭窄及节段不稳的重要病理基础^[1]。药物、康复、介入、髓核摘除、神经减压及融合等治疗可缓解症状、解除神经压迫或恢复节段稳定性,但通常难以逆转退变椎间盘的细胞功能衰退、细胞外基质(extracellular matrix, ECM)丢失及生物力学失衡^[2]。因此,椎间盘再生的关键并非单纯补充细胞或材料,而是恢复能够支持细胞存活、信号传递、基质沉积和负荷传导的局部稳态^[3]。

椎间盘低血供、低氧并依赖终板(endplate, EP)弥散供养,终板退变、异常负荷和纤维环(annulus fibrosus, AF)损伤可共同诱发营养障碍、酸化、炎症激活、细胞衰老及ECM降解^[4]。间充质干细胞(mesenchymal stem cell, MSC)、MSC来源细胞外囊泡(extracellular vesicle, EV)和水凝胶分别侧重细胞及旁分泌调控、无细胞信号递送与仿生支撑,但三者的作用层级、适用阶段和证据强度并不相同^[5]。本文以“终板-营养-代谢、炎症-免疫、ECM-细胞命运-力学耦合”三条病理轴为主线(图1),比较三类策略的功能边界,重点辨析两两组合及三元体系产生真实协同所需的时空条件、关键设计变量与转化障碍。

1 椎间盘退变微环境的关键病理轴

1.1 终板-营养-代谢轴

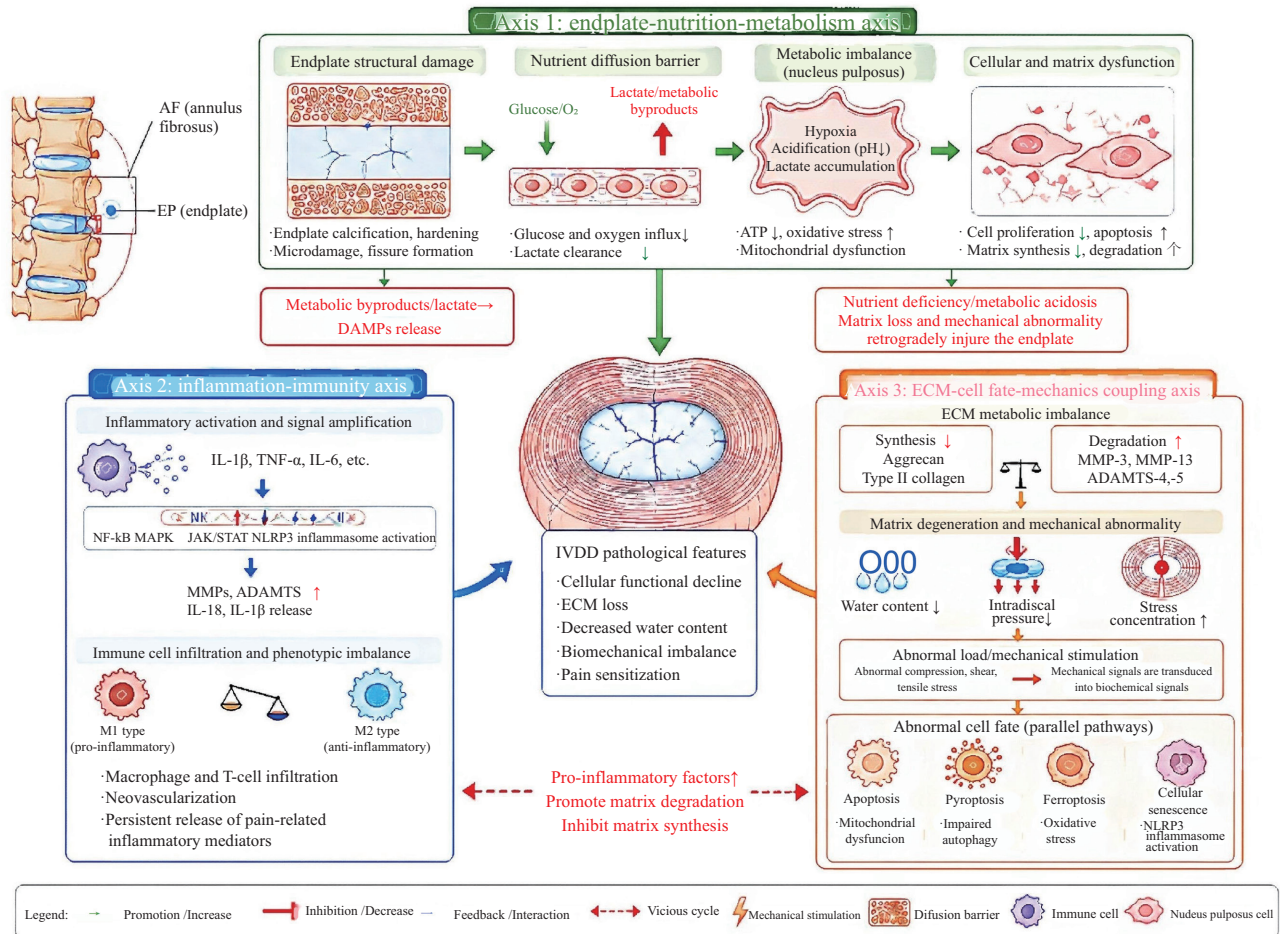
软骨终板是成人椎间盘摄取葡萄糖和氧并排出乳酸等代谢产物的主要通道。终板钙化、硬化及微损伤会降低其通透性,造成营养输入不足和乳酸清除受限^[6]。尽管正常髓核(nucleus pulposus, NP)细胞可通过缺氧诱导因子-1 α (hypoxia-inducible factor-1 α , HIF-1 α)等通路适应生理性低氧,持续的营养匮乏与酸化仍会抑制细胞增殖和ECM合成,并放大氧化应激及炎症反应^[7]。研究发现终板钙化明显的退

变椎间盘常伴随葡萄糖和氧弥散效率下降、髓核区乳酸积聚及pH降低,说明终板功能障碍是代谢失衡的重要上游环节^[8]。

正常髓核依赖较高的蛋白聚糖含量维持固定负电荷密度、渗透压和含水量。蛋白聚糖丢失后,髓核脱水、椎间盘高度下降,负荷进一步向纤维环和终板转移;应力集中又可诱导炎症因子和基质降解酶表达。由此,终板损伤、代谢障碍、ECM丢失和力学异常构成连续的正反馈链,而非彼此独立的病理现象^[9]。这一链条提示,再生干预除促进细胞和基质修复外,还需判断终板通透性与节段力学是否仍具有可逆性。研究发现,椎间盘退变伴随椎间盘高度降低和髓核压力下降,压缩负荷由髓核向纤维环转移并形成局部应力集中;异常机械刺激可进一步诱导炎症因子和基质降解酶表达,从而形成“基质丢失-脱水塌陷-应力异常-进一步退变”的恶性循环^[10]。

1.2 炎症-免疫轴

纤维环裂隙和终板屏障破坏后,退变组织与循环免疫系统的隔离程度下降。白细胞介素-1 β (interleukin-1 β , IL-1 β)、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)和白细胞介素-6(interleukin-6, IL-6)等介质可激活核因子- κ B(nuclear factor- κ B, NF- κ B)、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)、Janus激酶(Janus kinase, JAK)/信号转导及转录激活因子(signal transducer and activator of transcription, STAT)及核苷酸结合寡聚化结构域样受体家族含pyrin结构域蛋白3(nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing protein 3, NLRP3)炎症小体,促进基质金属蛋白酶(matrix metalloproteinase, MMP)和含血小板反应蛋白基序的解整合素金属蛋白酶(a disintegrin and metalloproteinase with thrombospondin motifs, ADAMTS)家族表达,抑制聚集蛋白聚糖和II型胶原合成,使髓核细胞由合成代谢转向分解



↑ 表示增加或增强; ↓ 表示降低或减弱。

↑ indicates an increase or enhancement; ↓ indicates a decrease or reduction.

图1 IVDD微环境三轴病理网络示意图

Fig.1 Schematic diagram of the three-axis pathological network of the IVDD microenvironment

代谢^[11]。研究发现TNF-α、IL-6相关信号与NLRP3炎症小体之间还可相互放大,增加IL-1β、白细胞介素-18(interleukin-18, IL-18)释放量并加剧细胞损伤和ECM降解^[12]。

ECM碎片可作为损伤相关分子模式(damage-associated molecular patterns, DAMPs)进一步激活固有免疫反应;巨噬细胞、T细胞等免疫细胞的浸润可进一步放大大局炎症反应,异常血管长入可促进免疫细胞募集,而感觉神经纤维向椎间盘深部生长则与痛觉敏化和椎间盘源性疼痛密切相关。巨噬细胞状态受低氧、酸化、乳酸积聚和局部细胞因子谱动态调节,具有连续性和可塑性,不宜仅以M1/M2二分法概括^[13]。研究发现在纤维环裂隙、终板损伤及神经血管长入明显的退变椎间盘中,巨噬细胞浸润程度常与疼痛相关炎症介质表达水平升高并存,且其表型可受低氧、酸化、乳酸堆积和局部细胞因子谱

影响而动态变化,提示免疫调控应强调表型重塑而非简单清除炎症细胞^[14]。

1.3 ECM-细胞命运-力学耦合轴

IVDD的组织学核心是ECM合成与降解失衡。聚集蛋白聚糖和II型胶原含量减少,基质金属蛋白酶3(matrix metalloproteinase 3, MMP-3)、基质金属蛋白酶13(matrix metalloproteinase 13, MMP-13)、含血小板反应蛋白基序的解整合素金属蛋白酶4(a disintegrin and metalloproteinase with thrombospondin motifs 4, ADAMTS-4)及含血小板反应蛋白基序的解整合素金属蛋白酶5(a disintegrin and metalloproteinase with thrombospondin motifs 5, ADAMTS-5)等基质降解酶的表达上调,促进ECM降解,导致髓核凝胶样结构丧失并逐渐纤维化。基质破坏降低组织含水量和抗压性能,异常压缩、剪切或过度牵张又可诱导髓核细胞和纤维环细胞表达炎症因子及基质降

解酶,使机械刺激转化为分解代谢信号^[15]。研究发现异常压缩、剪切或过度牵张负荷可诱导髓核细胞和纤维环细胞表达炎症因子及基质降解酶,使机械刺激转化为生物学退变信号,进一步证明IVDD并非单纯结构磨损,而是力学异常与细胞分解代谢相互驱动的过程^[16-17]。

凋亡直接减少功能细胞数量,焦亡和铁死亡放大炎症及氧化损伤,细胞衰老则通过衰老相关分泌表型持续释放IL-6、白细胞介素-8(interleukin-8, IL-8)和MMP等因子^[18]。研究发现退变髓核细胞中细胞周期蛋白依赖性激酶抑制因子2A(cyclin-dependent kinase inhibitor 2A, CDKN2A, 别称p16)、细胞周期蛋白依赖性激酶抑制因子1A(cyclin-dependent kinase inhibitor 1A, CDKN1A, 别称p21)、肿瘤蛋白p53(tumor protein p53, p53)等衰老相关标志物表达水平升高,且常伴随线粒体功能障碍、自噬功能不足和NLRP3炎症小体激活,说明多种异常细胞命运共同削弱内源性修复能力^[19]。研究发现氧化应激可诱导线粒体功能障碍、细胞凋亡和铁死亡,而NLRP3炎症小体激活可促进焦亡及炎症因子释放;同时,自噬功能不足会削弱细胞对应激损伤的清除能力,说明多种异常细胞命运共同构成IVDD内源性修复失败的重要机制^[20]。由此,微环境重塑至少应同时覆盖3个层面:保存或恢复功能细胞池,纠正炎症-代谢失衡,以及重建具有含水和承载能力的ECM;这也构成评价MSC、EV和水凝胶作用的统一框架。

2 MSC介导的微环境调控

2.1 主要作用机制

MSC来源广泛,具有分泌、免疫调节和一定的软骨样分化潜能,但现有证据不支持将其疗效简单归因于长期细胞替代。Khalid等^[21]通过性别决定区Y盒转录因子9(sex-determining region Y-box transcription factor 9, *SOX9*)与转化生长因子- β 1(transforming growth factor- β 1, *TGF- β 1*)共同调控人脐带来源MSC,在体外上调*SOX9*、聚集蛋白聚糖及II型胶原等软骨形成相关标志物的mRNA表达,并在动物模型中改善组织学表现和基质沉积;其另一项*SOX9*/同源盒基因1(sine oculis homeobox homolog 1, *Six1*)调控研究亦显示,人脐带来源MSC可向软骨祖细胞样表型转化,并在移植后维持一定存

活和修复效应^[22]。上述研究表明,经特定转录因子调控的MSC具有软骨样分化及促进椎间盘修复的潜力,但尚不能据此认为未经相应处理的MSC能够在退变椎间盘内长期存活并稳定分化为髓核样细胞。

MSC还可释放生长因子、细胞因子及EV,调节髓核细胞存活、线粒体功能、ECM代谢和炎症反应,并影响巨噬细胞及其他免疫细胞的功能状态。Lehmann等^[23]在人髓核细胞与MSC共培养体系中证实转化生长因子- β (transforming growth factor- β , TGF- β)参与二者的细胞通信和基质相关反应。Teixeira等^[24]在促炎/退变性椎间盘离体模型中观察到MSC的免疫调节性旁分泌效应,但未见明确的ECM重塑。综合来看,MSC的旁分泌、细胞保护和免疫调节证据强于短期内直接恢复组织结构的证据,评价时应将这些作用层级分开。

2.2 微环境依赖性与局限

退变椎间盘中的营养受限、酸化、氧化应激和周期性异常负荷可降低MSC的存活率,并削弱其旁分泌功能;纤维环裂隙和髓核结构破坏还可能导致细胞外漏或分布不均。Wuertz等^[25]发现酸性pH会影响MSC代谢、基质相关基因表达和功能状态,且供者年龄亦可能造成差异;Herger等^[26]在退变椎间盘离体模型中虽观察到免疫调节性旁分泌效应,但未证实明确的ECM重塑。上述结果说明,MSC疗效同时受宿主微环境和细胞产品属性制约。

低氧、抗炎或抗氧化预处理,基因修饰以及三维支架负载虽然可提高MSC对不利环境的耐受性,但这会增加制备复杂度、批间一致性和长期安全评价要求。Peck等^[27]研究显示,低氧预处理可提高骨髓来源MSC在低氧、营养受限三维环境中的存活能力。Zhang等^[28]则发现水凝胶联合MSC可改善动物模型的椎间盘高度指数和组织学表现,提示局部滞留、材料力学、降解行为和营养交换均会影响细胞疗效。从机制上推测,MSC更适合终板尚具一定通透性、纤维环可封闭且节段相对稳定的早中期退变,不宜泛化至终板重度硬化、椎间隙塌陷或明显不稳的晚期病例。

2.3 NP、AF与EP的分区效应及应用边界

椎间盘再生不能以NP改善替代全椎间盘修复。NP、AF与EP在细胞表型、ECM组成以及承担的力学和运输功能方面不同,MSC的作用靶点和评价终点亦应分区界定。NP现有证据主要支持MSC通过

旁分泌和免疫调节减轻炎症反应和氧化应激,抑制异常细胞死亡,并促进聚集蛋白聚糖和Ⅱ型胶原的合成;但酸化、营养匮乏和异常压缩可降低MSC的存活能力并削弱其功能效价。因此, NP内MSC更适用于EP弥散尚存、AF可封闭的早中期退变,评价应同时报告细胞滞留、代谢活性、基质含量和内压恢复,而不宜仅以细胞示踪或单一基因表达推断组织替代。

AF治疗目标是恢复层板连续性、I型胶原主导的纤维软骨表型以及抗拉、抗扭和抗挤出能力。MSC若用于AF修复,应与组织特异性ECM、黏附封闭或具有方向性力学线索的支架联合;单纯液体注射既难以重建层板排列,也可能经裂隙外漏。Peng等^[29]构建京尼平交联的脱细胞AF水凝胶,其可诱导骨髓MSC向AF样表型分化并促进椎间盘修复,提示“组织特异性基质+细胞”较单纯NP内植入更符合AF修复逻辑。

在EP中MSC相关干预的重点由“补充髓核细胞”转向保护终板细胞、抑制炎症/氧化损伤和异常钙化,并维持葡萄糖、氧及乳酸的跨终板运输。终板重度硬化时, NP内移植MSC难以直接纠正已形成的终板营养弥散障碍;伴活动性Modic改变时,还需关注终板炎症及屏障损伤。因此,可考虑EP靶向干预、局部酸化缓冲或必要的结构性修复。Zhan等^[30]报道的EP靶向工程化外泌体的酸中和水凝胶可富集于致密EP并改善局部氧化应激与酸性环境,虽非直接MSC治疗,但为分区靶向和运输轴修复提供了近期证据。

3 MSC来源EV介导的无细胞调控

3.1 生物学效应与工程化潜力

MSC来源EV可携带miRNA、蛋白质和脂质等活性成分,被髓核细胞、纤维环细胞或免疫细胞摄取后,可调节炎症、氧化应激、线粒体功能、凋亡、自噬及ECM代谢^[31]。Cheng等^[32]报道MSC来源外泌体可递送微小核糖核酸21(microRNA-21, miR-21),通过抑制磷酸酶及张力蛋白同源物(phosphatase and tensin homolog, PTEN)并激活磷脂酰肌醇3激酶(phosphoinositide 3-kinase, PI3K)/蛋白激酶B(protein kinase B, Akt)通路减少髓核细胞凋亡; Zhu等^[33]发现骨髓MSC来源外泌体可递送微小核糖核酸142-3p(microRNA-142-3p, miR-142-3p)并靶向混

合谱系激酶3(mixed lineage kinase 3, MLK3),抑制MAPK信号及IL-1 β 诱导的炎症和凋亡。

与活细胞相比, EV不依赖移植细胞长期存活,原则上更便于剂量化、储存和载荷工程化,但其功能组成仍受供体细胞来源、培养条件及预处理方式影响^[34]。Sun等^[35]发现诱导多能干细胞来源MSC释放的小EV富含微小核糖核酸105-5p(microRNA-105-5p, miR-105-5p),可通过磷酸二酯酶4D(phosphodiesterase 4D, PDE4D)/沉默信息调节因子6(sirtuin 6, Sirt6)相关通路改善衰老髓核细胞状态; Duan等^[36]报道MSC来源外泌体可递送微小核糖核酸125b-5p(microRNA-125b-5p, miR-125b-5p)并靶向肿瘤坏死因子受体相关因子6(tumor necrosis factor receptor-associated factor 6, TRAF6),抑制NF- κ B通路及细胞凋亡和炎症。工程化EV能否带来稳定增益,仍取决于载荷稳定性、靶向特异性、剂量-效应关系和批间一致性。

3.2 制备标准化与递送瓶颈

EV研究的首要瓶颈是制剂定义和质量控制不统一。仅凭粒径及少数表面标志物不足以证明制剂纯度或将生物学效应归因于EV;应报告细胞来源与培养条件、分离流程、粒径和浓度、形态、阳性/阴性标志、蛋白与非囊泡颗粒污染、批间变异以及与适应证相关的功能效价^[37]。剂量宜同时说明颗粒数和蛋白量,并将无菌、内毒素、残留试剂及冻融稳定性纳入关键质量属性。椎间盘内高压和纤维环裂隙可导致EV注射后扩散、外漏或快速清除,单次给药难以维持有效暴露。水凝胶缓释可延长EV在局部的滞留时间,但其释放动力学同时受材料孔隙结构、降解行为、EV与材料间相互作用以及囊泡稳定性等因素的影响^[38]。评价EV-水凝胶联合体系时,应设置游离EV组、空白水凝胶组和EV-水凝胶联合组,并根据研究目的设置不同EV剂量,同时测定EV释放动力学。若拟证明EV与水凝胶具有协同作用,还应采用适当的因子设计和交互作用分析,判断联合效应是否超出两者单独效应所预期的可加和效应,而不能仅依据联合组组织学指标改善即推断存在“协同”^[39]。

3.3 NP、AF与EP的分区效应

EV的靶细胞、局部清除和有效剂量受组织分区影响, NP、AF与EP不应共用单一“椎间盘修复”效价指标。NP相关疗效评价的主要终点包括炎症反

应减轻, 凋亡、焦亡和铁死亡等异常细胞死亡减少, 自噬功能改善和线粒体稳态恢复, 以及ECM合成代谢增强。其中, ECM合成代谢可通过聚集蛋白聚糖和II型胶原的表达水平及基质沉积量等指标进行评价。相应效价测定宜覆盖受体细胞摄取、关键信号通路、ECM合成及剂量-效应关系, 而不能仅凭EV粒径或标志物推定功能^[31-39]。AF内EV递送除需关注其生物活性外, 还应兼顾EV在缺损部位的局部滞留与AF裂隙的结构性封闭。Hu等^[40]构建仿纤维环层状结构的线状微针并持续递送工程化外泌体, 通过恢复线粒体自噬、促进AF细胞增殖和迁移以及抑制ECM病理性重塑, 促进AF缺损修复; 同时, 该微针可在缺损部位实现原位固定并减少髓核外漏, 提示AF修复策略应兼顾生物活性信号的持续递送与缺损部位的结构性固定和封闭。EP组织致密、通透性较低且易发生钙化, 常规NP内注射的游离EV可能难以在EP中达到有效浓度。因此, 对靶向EP的EV递送策略, 应评价EV在EP中的靶向富集和局部滞留情况, 并进一步考察终板营养及代谢物运输功能是否得到改善; Zhan等^[30]报道的靶向工程化外泌体的酸中和水凝胶体系同时干预铁负荷、氧化应激及cGAS-STING相关炎症, 为EP定向递送提供了分区证据。因此, NP、AF和EP的EV剂量、载体与效价终点需分别定义。

4 水凝胶介导的仿生支撑与递送

4.1 仿生支撑与时空递送

髓核是富含水分和蛋白聚糖的黏弹性组织。水凝胶可通过高含水三维网络模拟部分ECM特征, 为细胞分布、新生基质沉积和局部药物滞留提供空间^[41]。天然材料通常具有较好的生物相容性和细胞识别能力, 但力学强度及降解可控性有限; 合成材料虽便于调节交联密度、黏弹性和释放行为, 却可能缺乏内在生物活性。因此, 复合设计的目标应是匹配髓核的黏弹性、营养交换和降解过程, 而非单纯追求更高强度^[42]。Jia等^[43]发现具有髓核黏弹性匹配特征的可注射水凝胶可在动物模型中延缓退变进展; Peroglio等^[44]报道透明质酸基热可逆水凝胶可支持MSC维持三维生长并向椎间盘样表型分化。两项研究共同说明, 材料的价值不仅在于填充缺损, 更在于为细胞行为和负荷传导提供适宜的微环境, 但其长期力学稳定性和降解匹配仍需验证。

水凝胶与髓核的力学匹配不能仅依据单一压缩模量或简单的材料刚度进行评价, 还应综合考虑储能模量、损耗模量、应力松弛时间、蠕变特性、渗透性及动态力学响应的频率依赖性等参数。水凝胶过硬或松弛过慢时, 可能在早期承担过多载荷, 造成残余NP/新生ECM的应力遮蔽, 并将负荷转移至AF和EP; 过软或松弛过快则难以维持流体承载和椎间盘内压, 可能增加AF膨出和EP接触应力。Cai等^[45]构建多尺度力学适配水凝胶, 通过调控应力松弛、细胞尺度基质线索及节段稳定性促进NP修复, 支持“材料松弛-细胞机械感受-全椎间盘负荷传导”的协同设计。因此, 材料的力学评价不应仅限于静态模量, 还应分别表征应力松弛和蠕变等黏弹特性; 在生理相关的循环加载条件下, 需进一步评估椎间盘内压、AF环向应变及EP载荷或接触应力分布, 并通过长周期循环加载评价材料及修复节段的疲劳耐久性和力学性能保持能力。

水凝胶还可作为MSC、EV、生长因子或小分子药物的局部储库, 将短时暴露转化为相对持续的作用。理想系统应在早期提供抗炎和细胞保护信号, 在后续阶段允许ECM沉积和组织整合, 并使释放曲线、材料降解与力学变化相互匹配^[46]。Russo等^[47]以透明质酸-富血小板血浆水凝胶递送MSC, 在器官培养模型中为细胞存活和旁分泌提供局部环境; Cunha等^[48]以透明质酸基热可逆水凝胶联合SDF-1构建趋化因子递送系统, 用于细胞募集和局部修复调控。这些研究体现了水凝胶由“被动载体”向时空递送平台的转变。

4.2 可注射与响应性设计

可注射水凝胶可经细针进入髓核, 并通过温度、离子、光或酶等触发原位成胶, 符合微创治疗需求。剪切变稀、自修复和动态交联有助于水凝胶在注射后恢复网络完整性; pH、ROS或炎症相关刺激响应设计则可将病理微环境变化作为触发信号, 调控治疗载荷的释放速率、持续时间及释放时序, 从而实现按需递送^[49]。此类环境响应体系应明确其响应触发阈值, 并验证治疗载荷释放速率、持续时间和释放时序的可预测性与重复性; 体外观察到的响应特征和释放行为仍需在体内条件下进一步验证, 不能直接外推为体内治疗效果。Showalter等^[50]在人离体椎间盘模型中发现, 原位成胶型水凝胶可局部保留, 并在循环载荷和复水条件下帮助维持力

学功能; Varma等^[51]报道热响应、氧化还原聚合的纤维素基水凝胶可原位成胶,并在髓核切除后部分恢复生物力学性能。由此可见,可注射材料除应具备原位成胶能力外,还应具有良好的注射和操作性能,在与注射操作相匹配的时间内完成成胶,并在循环加载条件下保持结构完整性和力学稳定性。

在“响应性”基础上,更值得强调的是智能或程序化降解。理想体系可在早期保持网络完整和抗挤出能力,稳定MSC/EV并优先释放抗炎、抗氧化信号;中期由ROS、酸性pH或MMP等病理刺激触发可控断键,逐步开放孔隙并释放促基质重建载荷;后期阶段,水凝胶的降解和力学性能衰减应尽可能与新生ECM形成及组织整合过程相匹配,使材料提供的力学支撑逐步由新生组织承担。可采用双网络/牺牲键、酶敏肽段、ROS敏感硫缩酮键或动态共价键实现分阶段调控,但应预先界定材料质量损失、模量衰减和载荷释放的时间尺度,并评估个体病理微环境差异是否会导致治疗载荷突释,或水凝胶网络在组织修复完成前过早失去结构完整性和力学支撑。Lu等^[52]构建的ROS/pH双响应性注射水凝胶可响应退变椎间盘微环境中ROS升高和pH降低,发生动态网络变化并调控治疗载荷释放,同时减轻氧化应激和炎症反应,体现了病理微环境触发的按需干预理念。程序化降解的有效性应以体内降解、力学保持、ECM替代和长期安全性共同证明,而不能仅凭体外降解曲线。

注入体积和成胶速度同样关键。成胶过慢会增加外漏,过快则可能妨碍均匀注射;注入量过大可能升高椎间盘内压力并增加终板或纤维环负荷。纤维环缺损明显时,材料滞留往往还依赖针道或纤维环封闭,而不能仅依靠髓核内成胶^[53]。Varden等^[54]发现椎间盘内注射后局部压力不会立即消散,撤针及压力缓慢释放过程中存在注射物外漏风险; Sloan等^[55]发现髓核增强联合纤维环修复较单纯髓核增强更有利于缺损愈合、髓核水合和压缩/扭转刚度维持。这提示递送路径、压力管理和纤维环修复应作为材料设计的一部分。

4.3 NP、AF与EP的分区化材料设计

水凝胶的材料参数应针对不同组织分区设定,不能用单一NP配方同时替代AF和EP功能。NP水凝胶强调高含水、可注射、低摩擦以及与原生NP相近的黏弹性和渗透性,既要恢复流体承载,又应允

许营养弥散和新生ECM进入。Cherif等^[56]在负载人退变椎间盘器官培养模型中观察到可注射水凝胶促进自然退变组织的再生反应,为接近临床组织状态的NP评价提供了近期证据。AF材料则需优先满足组织黏附、抗拉/抗扭、疲劳耐受和缺损封闭,并尽量模拟层板方向性。Li等^[57]开发的复合水凝胶封闭材料可匹配AF结构和力学并提高抗突出能力; Liu等^[58]采用脱细胞AF基质/壳聚糖杂化水凝胶修复AF缺损,进一步支持组织特异性材料与细胞募集/分化相结合。AF评价应包括封闭完整性、爆破/挤出压力、环向应变及扭转疲劳。用于EP修复或靶向递送的材料应合理控制材料层厚度和致密程度,并具有适宜的物质通透性,以避免形成额外的跨终板物质运输屏障,同时兼具抗炎、抗氧化或抗钙化功能;材料层过厚、网络结构过于致密或刚度过高,可能增加物质运输阻力,并影响局部力学环境。Zhan等^[30]构建的软骨终板细胞靶向工程化外泌体的酸中和水凝胶体系具有较长的局部滞留时间,可实现工程化外泌体的持续释放,并促进其被软骨终板细胞特异性摄取。结合EP承担营养运输和力学传递的特点,EP相关材料的评价除应关注葡萄糖、氧和乳酸等物质的跨终板通量及组织通透性外,还应考察终板接触应力、材料局部滞留时间、载荷释放动力学以及靶向递送效率。

4.4 转化限制

水凝胶过软难以维持髓核压力分布,过硬则可能造成应力集中和邻近结构负荷增加。材料降解产物、残留交联剂、灭菌方式、针道损伤及长期疲劳性能均可能影响安全性;不同退变阶段的含水量、椎间隙高度和力学环境又存在明显差异,单一配方难以覆盖全部患者^[59]。因此,水凝胶更适合作为与病理阶段相匹配的支撑和递送平台,而不是可独立逆转退变的“替代髓核”。临床前评价除细胞相容性和短期MRI变化外,还应覆盖循环负荷下的疲劳、外漏、终板应力、降解产物、长期组织整合以及纤维环缺损条件下的抗挤出能力^[60]。在临床转化方面,Beall等^[61]的早期可行性研究表明,椎间盘内水凝胶注射具有技术可行性,并可改善经筛选患者的疼痛和功能指标;但该研究样本量较小、缺乏对照且随访时间有限,尚不能据此判断结构再生及长期疗效。后续研究需重点排除材料移位/挤出、针道损伤、邻近终板负荷变化及不恰当适应证,并将影像、力

学、疼痛和功能结局并列评价。

5 复合体系的协同逻辑与证据边界

5.1 组合路径与功能分工

MSC-水凝胶联合主要用于提高MSC在椎间盘内的局部滞留率、减少注射后外漏,并为细胞提供三维微环境;EV-水凝胶联合主要用于延长EV在局部组织中的有效暴露时间,并调控EV的释放速率和释放时程;将MSC来源EV负载于水凝胶,则构成不含活细胞的递送体系。上述两两组合具有明确的功能互补,但其评价重点不同:前者需同时验证细胞存活、表型和材料力学,后者更应关注EV稳定性、效价和释放动力学^[62]。Frith等^[63]将间充质前体细胞与含戊聚糖多硫酸酯的可注射水凝胶联合,为细胞提供三维递送和基质诱导环境;Smith等^[64]构建干细胞负载的三重互穿网络水凝胶,在体外模拟髓核力学并支持相关基质合成。两项研究表明, MSC-水凝胶联合的核心不是增加注射细胞数量,而是通过“滞留-诱导-力学适配”共同调节细胞行为。

“MSC+外源EV+水凝胶”三元体系更为复杂。MSC本身会持续释放EV,额外加入外源EV是否产生增益,取决于来源、剂量、作用时间和靶点是否互补,也可能出现功能重叠或剂量过度。三元共载不能自动等同于协同;只有在包含各单元、所有两两组合和三元组合的完整对照中,并经交互作用分析证明联合效应超过可加和效应,方可支持协同结论^[65]。Luo等^[66]将工程化软骨终板干细胞负载于软骨基质水凝胶,使细胞持续释放具有调控作用的EV,为“细胞-EV-材料”一体化路径提供了依据,但并未直接证明同时外加MSC、外源EV和水凝胶优于所有两两组合。Lu等^[67]发现MSC来源EV可模拟部分MSC与髓核细胞相互作用所产生的保护效应,进一步提示MSC与外源EV之间可能存在功能重叠。因此,三元体系的首要问题不是成分数量,而是功能互补性。

5.2 时空耦合与修复反馈

复合体系的潜在优势在于按时间和空间组织干预,而不是同时最大化所有生物活性。早期可由EV或MSC旁分泌信号减轻炎症、氧化应激和减少细胞死亡,为内源性细胞及移植细胞保留生存窗口;随后通过持续的合成代谢信号促进聚集蛋白聚糖和II型胶原沉积;水凝胶则提供局部滞留、缓释和有限

的力学支撑^[68]。Xia等^[69]发现MSC来源外泌体可通过抗氧化和抗炎作用减轻髓核细胞损伤,并在动物模型中改善组织学表现;Song等^[70]利用可编程DNA水凝胶组织自噬调控信号,改善细胞应激和基质代谢异常。上述研究支持“先稳定微环境、后促进基质修复”的时序逻辑,但尚不能证明固定的释放顺序适用于所有退变阶段。

新生ECM增加后,组织含水和应力分布可能改善,进而减少机械和炎症刺激,形成修复反馈;但该反馈依赖终板营养通路、纤维环完整性和节段稳定性。若结构破坏已超出材料和生物干预的补偿范围,即使分子指标改善,也未必能够恢复椎间盘整体功能^[71]。Vergroesen等^[72]阐明了力学异常与细胞生物学改变相互驱动的退变机制;Fu等^[73]则报道基质水凝胶负载骨髓MSC可通过抑制氧化应激相关铁死亡改善MRI和组织学表现。二者共同提示,复合体系必须同时评估分子、组织、影像和力学结局,不能以单一分子指标替代功能恢复。

5.3 关键设计变量、验证框架与证据边界

三元体系的关键变量横跨4个层级^[74-75](图2):治疗成分,包括MSC来源、剂量、活性与预处理方式,以及EV来源、剂量和功能效价;材料参数,包括黏弹性、降解、释放、注入体积和抗挤出能力;疾病条件,包括退变分级、终板通透性、纤维环完整性和节段稳定性;结局层级,包括细胞存活、ECM合成、影像学、力学以及疼痛和功能。研究设计应预先界定主要终点,并采用因子设计或等效的交互作用分析区分独立效应、可加和效应与真实协同。

现有证据仍以体外实验和小动物研究为主,模型、退变诱导方式、观察时间及结局指标差异较大。直接比较单用MSC、单用EV、单用水凝胶、两两组合和三元组合的研究很少,因而尚不足以确定最优配方、适用阶段和真实协同程度^[76]。Wei等^[77]系统评价和Meta分析显示,SC-sEVs可提高大鼠针刺IVDD模型的椎间盘高度指数(disc height index, DHI),并降低MRI Pfirrmann分级和组织学评分,但研究间异质性较高,结果仍需谨慎解释。Kumar等^[78]开展的自体脂肪来源MSC联合透明质酸衍生物椎间盘内注射单臂I期试验,初步支持细胞-材料组合的安全性和可行性,但不能证明临床有效性,更不能作为三元协同的临床证据。总体而言,现有研究支持各组成单元的生物合理性及部分两两组合的可行性;从“可

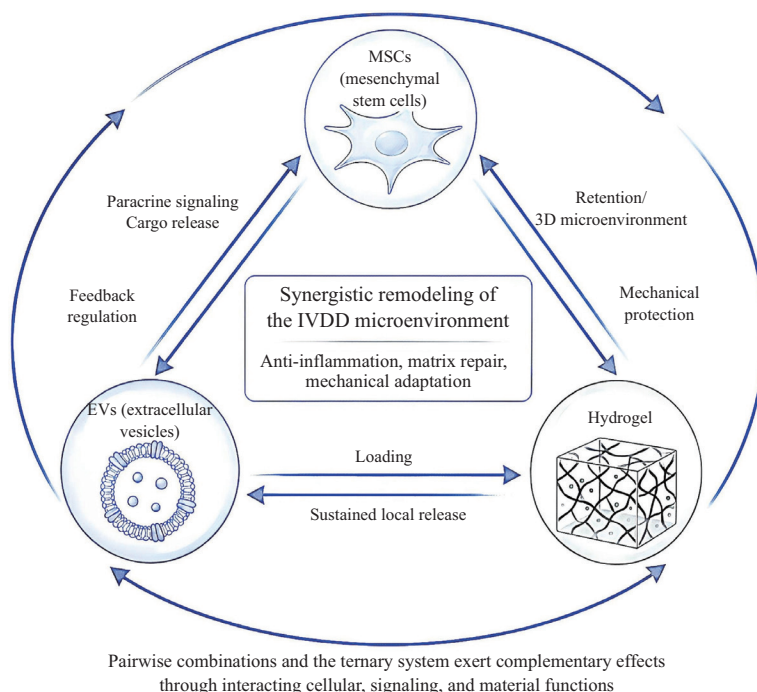


图2 MSC、EV与水凝胶两两组合及三元体系协同逻辑图

Fig.2 Logical diagram of the pairwise combinations of MSC, EV and hydrogel, as well as the synergistic effect of the ternary system

行”到“协同”再到“临床有效”之间仍存在明确的证据台阶。

6 讨论

IVDD再生治疗的核心难点在于退变微环境并非单一损伤因素,而是营养弥散、炎症免疫、细胞命运、ECM代谢和力学负荷长期耦合后的稳态崩解。相较于将MSC、EV或水凝胶分别作为“细胞替代物”“信号药物”或“髓核填充物”,更符合转化逻辑的理解是:三者分别对应功能细胞池调节、无细胞信号递送和局部结构/递送平台。因而,再生策略的评价应从“是否改善某一分子指标”转向“是否能在特定退变阶段重建可持续的细胞-基质-力学闭环”。

从适应证角度看,生物再生策略更可能获益于早中期退变、终板弥散尚未严重受限、纤维环屏障可维持或可修复、节段尚无明显不稳的病例。对于终板重度硬化、椎间隙明显塌陷、纤维环大缺损、Modic改变活动期或合并明显神经压迫和节段不稳的患者,单纯椎间盘内注射MSC、EV或水凝胶难以跨越营养和力学障碍,其临床定位更可能是手术或康复治疗的辅助,而非替代减压、固定或重建稳定性的方案。MSC、EV和水凝胶的组合并不等同于

协同。MSC可持续释放多种旁分泌因子和EV,外源EV可能与MSC功能重叠;水凝胶既可促进局部滞留,又可能因孔径、降解和电荷作用改变EV稳定性或细胞表型。

基于上述分区机制和证据边界,可按退变阶段进行概念性分层(表1)。表中策略用于将组织状态、治疗目标和评价终点对应起来。

转化研究还需建立面向产品的质量控制框架。MSC制剂应报告来源、供者年龄、传代次数、表型、活率、分化/旁分泌效价及批间差异;EV制剂应报告分离方法、粒径、颗粒数、蛋白量、形态、阳性/阴性标志、污染物、内毒素、冻融稳定性和与适应证相关的功能效价;水凝胶则需给出注射剪切、成胶时间、黏弹性、降解产物、灭菌方式、疲劳性能、外漏风险和纤维环缺损条件下的抗挤出性能。只有将这些参数转化为关键质量属性,复合体系才具备从动物实验走向临床试验的可比性。

综上所述,MSC、MSC来源EV和水凝胶为IVDD微环境重塑提供了互补工具,但目前证据仍处于“生物学合理性和临床前可行性”向“机制明确协同和临床有效性”的过渡阶段。而复合再生策略的关键不是成分越多越好,而是以终板营养、纤维环完整性和节段力学为基础,建立分层适应证、标准

表1 不同退变阶段的微环境特征与再生策略选择

退化阶段及其主要特征	NP/AF/EP的主要治疗目标	优先策略组合	不推荐的情况和关键评估
The degeneration stage and its main characteristics	The main therapeutic goals of NP/AF/EP	Priority strategy combination	Unrecommended situations and key evaluations
Early stage: EP dispersion is basically preserved; NP is mainly characterized by inflammatory/metabolic imbalance; AF has only small fissures and can be closed; segments are stable	NP: anti-inflammatory, anti-oxidant and cell preservation functions; AF: prevent crack expansion; EP: maintain nutrient diffusion	Free or hydrogel sustained-release EV; pre-treated MSC; low-dose, short-course responsive hydrogel; minimally invasive AF sealing when necessary	Avoid excessive injection and high modulus materials; evaluate pH/inflammation, cell survival, ECM, leakage and symptoms
Mid-term: NP dehydration and ECM loss; AF fissures can still be repaired; EP permeability decreases; there is no obvious segmental instability	First, stabilize the inflammation/metabolism, then rebuild the ECM and fluid carrying capacity; simultaneously repair AF and protect EP transport	MSC or engineered EV+viscoelastic matching, programmed degradation hydrogel; AF adhesion sealing; when necessary, EP targeting/acid neutralization	Verification of release-degradation-ECM replacement matching; evaluation of MRI/DHI, intra-pleural pressure, circumferential strain of AF, EP flux, pain and function
Advanced stage: severe sclerosis or active Modic changes of the EP; intervertebral space collapse; large defect of the AF; instability or nerve compression	The priority is to relieve nerve compression, control pain and restore stability; regenerative therapy is only used as an auxiliary measure after structural repair	Prioritize pressure reduction, stabilization or reconstruction; consider cell/EV/material assistance only when strict selection is made and the structural barriers can be repaired	It is not recommended to perform simple intervertebral disc injections; instead, evaluate nerve compression, stability, EP load, extrusion risk and long-term safety

化制剂和多维结局体系。只有在严格对照、标准化制备和长期安全评价下, MSC/EV/水凝胶体系才可能由实验性方案转化为可进入临床验证的椎间盘再生策略。

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