

糖尿病肌腱干细胞源性外泌体的功能特性及其在肌腱修复中的作用机制

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摘要

糖尿病是常见慢性代谢性疾病, 易并发肌腱病, 导致疼痛与功能障碍, 现有治疗难以实现肌腱功能性再生。肌腱干/祖细胞(TSPCs)是肌腱修复核心, 高糖微环境会损害其增殖、分化等功能, 而TSPCs源性外泌体(TSPCs-EXOs)可通过传递生物活性分子介导细胞通讯, 在肌腱修复中具重要潜力, 但糖尿病条件下其形态、分子表达存在异常, 限制治疗效能。本文综述了糖尿病TSPCs的病理特征、TSPCs-EXOs的分子调控机制(如VEGFA/mTOR、TGF- β /Smad通路), 介绍了外泌体靶向递送、联合治疗及基因编辑等策略, 探讨了糖尿病分型影响与临床转化挑战, 展望了人工智能的应用前景, 为相关靶向治疗提供理论参考。

关键词

糖尿病肌腱病变, 肌腱干细胞, 外泌体, 分子机制, 治疗策略

Functional Characteristics of Diabetic Tendon Stem Cell-Derived Exosomes and Their Mechanism of Action in Tendon Repair

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Abstract

Diabetes is a common chronic metabolic disease prone to complicated tendon lesions, causing pain

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and functional impairment, with current treatments failing to achieve functional tendon regeneration. Tendon stem/progenitor cells (TSPCs) are core for tendon repair, but a high-glucose microenvironment impairs their proliferation and differentiation. TSPCs-derived exosomes (TSPCs-EXOs) can mediate intercellular communication by delivering bioactive molecules, showing great potential in tendon repair, yet their abnormal morphology and molecular expression under diabetic conditions limit therapeutic efficacy. This article reviews the pathological characteristics of diabetic TSPCs and the molecular regulatory mechanisms of TSPCs-EXOs (e.g., VEGFA/mTOR and TGF- β /Smad pathways), introduces strategies like exosome-targeted delivery, combination therapy and gene editing, discusses the impact of diabetes classification and clinical translation challenges, and prospects the application of artificial intelligence, providing theoretical reference for relevant targeted therapies.

Keywords

Diabetic Tendon Disease, Tendon Stem/Progenitor Cells, Exosomes, Molecular Mechanisms, Treatment Strategies

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1. 引言

糖尿病已成为全球范围内严峻的公共卫生挑战, 据第 11 版国际糖尿病联盟糖尿病图谱估计, 2024 年我国糖尿病患者人数已高达 1.48 亿, 全球受影响人群超 5.89 亿[1]。作为肌腱病的独立风险因素, 糖尿病显著增加了肌腱病变的发生率与严重程度——II 型糖尿病患者患肌腱病的风险是非糖尿病患者的 4 倍, 肌腱撕裂或破裂的风险更是高达 5 倍[2][3]。影像学和组织学研究证实, 糖尿病患者肌腱组织会出现胶原纤维排列紊乱、微撕裂、钙结节形成及高级糖化终产物积累等特征性病理改变, 导致肌腱弹性降低、脆性增加, 最终引发顽固性慢性疼痛、关节活动受限, 严重影响患者血糖控制与生活质量[4]。肌腱细胞和肌腱干/祖细胞(tendon stem/progenitor cells, TSPCs)是与肌腱稳态维持, 重塑和修复相关的主要细胞成分, 在高血糖或糖尿病条件下, 肌腱细胞和 TSPCs 的改变可能导致糖尿病肌腱的结构和功能变异, 加速糖尿病肌腱病的发展和进程[5]。肌腱病在糖尿病患者中常表现为顽固性慢性疼痛和功能受限, 影响血糖控制和生活质量, 且手术修复效果有限, 失败率高。因此, 当前研究强调需要针对糖尿病合并肌腱疾病的特异性发病机制开发靶向疗法, 恢复 TSPCs 的正常功能或许是改善糖尿病肌腱愈合异常状态的重要突破口[6]。

TSPCs 主要通过自我更新和分化促进肌腱细胞的补充, 这对肌腱骨愈合至关重要。外泌体是来自不同细胞类型的小细胞外囊泡, 通过介导细胞间通信, 传递生物活性分子, 可促进肌腱再生和愈合[7]。近期研究表明, 来自多种细胞来源的外泌体可有效调节 TSPCs 的活性并增强其治疗潜力。TSPCs 来源的外泌体(TSPCs-derived exosomes, TSPCs-EXOs)作为一种新兴的无细胞治疗策略, 在肌腱修复中展现出显著潜力, 尤其适用于糖尿病患者肌腱病的修复[8]。外泌体作为细胞分泌的纳米级囊泡, 具有与母细胞相似的生物学功能, 但免疫原性更低。研究表明, 间充质干细胞来源的外泌体(MSC-Exos)在多种病理条件下更稳定, 且免疫排斥风险显著低于细胞移植[9]。类似地 TSPCs-EXOs 通过旁分泌机制调节局部细胞功能, 避免了直接细胞移植可能引发的免疫排斥[10][11]。目前, 关于糖尿病背景下 TSPCs 与 TSPCs-EXOs 的特征性改变、核心调控机制及针对性治疗策略仍存在诸多研究空白, 临床转化的关键瓶颈等问题尚未明

确。因此, 本文旨在系统综述糖尿病条件下 TSPCs 的病理特征与 TSPCs-EXOs 的功能异常及新型治疗策略的研究进展, 为开发糖尿病肌腱病的精准靶向疗法提供理论依据与研究思路。

2. 糖尿病肌腱干细胞的病理特征与功能异常

2.1. 高糖微环境对肌腱干细胞生物学行为的影响

糖尿病微环境显著损害 TSPCs 的再生潜能, 进而引发肌腱组织稳态失衡及修复功能障碍[12]。在高糖条件下, TSPCs 的增殖活性受到抑制, 其分化方向也发生改变, 表现为异常软骨化生发生率升高和异位骨化风险增加[13]。体外实验研究证实, 经高糖培养的肌腱干细胞呈现出迁移能力下降、胶原合成减少等特征性改变, 而这些异常表型与糖尿病肌腱病变的病理进程密切相关[14]。此外, 氧化应激损伤是导致高糖环境下 TSPCs 功能受损的关键性因素, 导致 TSPCs 细胞内活性氧过量蓄积以及抗氧化防御系统失调[15]。

2.2. 糖尿病肌腱干细胞外泌体的形态与分泌特征改变

与正常肌腱干细胞相比, 糖尿病来源的外泌体呈现出粒径分布异常及生物活性物质装载失调的特征[16]。蛋白质组学分析结果显示, 糖尿病肌腱干细胞外泌体中, 转化生长因子- β (TGF- β)、成纤维细胞生长因子(FGF)等促修复因子的表达水平显著下调, 而促炎因子的含量则相对升高[17]。这种分泌谱的改变可导致外泌体介导的细胞间通讯功能受损, 使其无法有效激活周围细胞的再生程序[18]。值得关注的是, 糖尿病的分型(1 型与 2 型)可能对外泌体的分泌特征有着差异性影响, 但目前相关研究尚存争议[19]。

2.3. 关键功能因子(如 VEGFA)的异常表达谱

糖尿病肌腱干细胞外泌体中最显著的分子异常是血管生成相关因子 VEGFA 的表达失调。研究证实, 高糖环境可通过表观遗传修饰(如 DNA 甲基化、组蛋白修饰(如乙酰化和甲基化)以及非编码 RNA 的调控)导致 VEGFA 转录水平升高[20]。该改变不仅影响肌腱局部的血管化过程, 还通过 mTOR 信号通路损害干细胞的自我更新能力[11]。此外, TGF- β /Smad 信号通路的关键调控分子在糖尿病外泌体中亦呈现异常的表达模式, 进而造成肌腱分化过程受阻及细胞外基质重塑障碍[21]。单细胞测序数据进一步证实, 糖尿病肌腱干细胞外泌体中的特征性的非编码 RNA 表达谱出现改变, 这些分子可作为潜在的诊断标志物和治疗靶点[22]。

3. 外泌体介导的分子调控网络

3.1. VEGFA/mTOR 信号轴对肌腱干细胞增殖的调控

糖尿病肌腱干细胞外泌体中 VEGFA 的异常表达已被证实可显著损伤细胞增殖能力。研究表明, 在正常生理状态下, 外泌体中的 VEGFA 通过激活 mTOR 信号通路对肌腱干细胞的增殖、代谢进行调控。然而在糖尿病状态下, 外泌体中的 VEGFA 呈现出过度表达, 导致 mTOR 信号通路的持续激活, 进而引发肌腱干细胞异常的增殖表型[23]。这种病理性的增殖破坏了肌腱组织原本的稳态平衡。实验证实, 采用特异性抗体阻断 VEGFA/mTOR 信号轴, 可有效恢复糖尿病肌腱干细胞的正常增殖节律[24], 这为靶向干预研究提供了理论依据。

3.2. TGF- β /Smad 通路在肌腱分化中的作用机制

TGF- β /Smad 信号通路是外泌体调控肌腱分化的核心开关。实验证实, 正常肌腱干细胞来源的外泌体通过 TGF- β /Smad3 信号级联反应促进肌腱基质蛋白的合成, 而糖尿病来源的外泌体则呈现出促纤维化分

化倾向[25]。跟腱损伤愈合模型研究中证实了高表达的 miR-29b 通过抑制 TGF- β /Smad3 途径抑制纤维化分化倾向, 改善跟腱愈合[26]。单细胞分析进一步揭示, 糖尿病肌腱干细胞中 Smad4 的核转位效率降低约 40%, 这可能是其肌腱分化能力受损的分子机制之一[27]。研究发现, 采用基因编辑技术特异性调控外泌体中 TGF- β 的含量后, 可显著改善肌腱干细胞的定向分化能力[28]。

3.3. 趋化因子介导的细胞迁移动态平衡

外泌体携带的趋化因子网络在肌腱修复中形成精确的细胞招募梯度。研究表明, 糖尿病肌腱干细胞外泌体中 CCL2、CCL5 等趋化因子的表达上调 2~3 倍, 导致单核巨噬细胞的异常募集[29]。这种紊乱的趋化模式是通过激活 CCR2/CCR5 受体, 破坏肌腱干细胞的定向迁移能力, 在体外迁移实验中具体表现为细胞轨迹的随机性增加[30]。与之相反, 正常肌腱干细胞外泌体富含 CXCL12 等趋化因子, 能够建立有序的细胞迁移梯度, 从而促进修复细胞向损伤部位的特异性归巢[31]。蛋白质组学分析结果显示, 糖尿病外泌体中至少 15 种趋化因子受体配体的表达谱发生显著改变[27], 这可能是引发肌腱修复微环境失衡的关键因素。研究证实, 借助生物材料负载特定趋化因子的外泌体, 可重建有利于肌腱再生的细胞迁移模式[32]。

4. 外泌体功能特性的实验验证体系

4.1. 体外模型：高糖条件下肌腱干细胞的共培养系统

体外共培养系统是探究糖尿病肌腱干细胞外泌体功能特性的重要平台。高糖微环境会改变肌腱干细胞的生物学行为, 通过构建高糖条件下的共培养模型, 能观察到糖尿病肌腱干细胞外泌体对肌腱修复的影响[33]。此外, 共培养系统还可用于评估外泌体对肌腱细胞增殖、迁移和胶原合成的作用效应[29]。

4.2. 动物模型：糖尿病肌腱损伤的修复效果评估

动物实验是验证外泌体治疗效果的关键环节。相关研究采用 Sprague-Dawley 雄性大鼠的跟腱建立糖尿病肌腱损伤模型, 以评估肌腱干细胞外泌体的治疗效能[33]。结果显示, 外泌体处理后显著改善了肌腱的组织学结构与力学性能[34]。在糖尿病动物模型中, 正常肌腱干细胞来源的外泌体通过促进血管生成、加速胶原沉积及减少炎症反应等机制促进其肌腱的修复[35]。

4.3. 单细胞测序与蛋白质组学的多组学验证

多组学技术为外泌体功能研究提供了系统性的验证手段。其中, 单细胞测序技术揭示了外泌体处理前后肌腱干细胞的异质性变化[36], 而蛋白质组学分析则能鉴别出外泌体中的关键功能蛋白[29]。研究发现, 肌腱干细胞外泌体富含多种生长因子和细胞因子, 通过调控 mTOR 和 Smad 信号通路改善肌腱修复过程[21]。多组学数据进一步证实, 糖尿病肌腱干细胞外泌体的蛋白质组成与正常外泌体存在差异[37]。此外, 外泌体中的非编码 RNA 已被证实参与调控肌腱干细胞的生物学行为[38], 这些发现为开发基于外泌体的治疗策略奠定了理论基础。

5. 治疗策略开发与技术突破

5.1. 外泌体靶向递送系统的优化

外泌体作为天然纳米载体在肌腱修复中展现出独特优势, 但其临床应用仍面临低产量、弱活性、靶向性不足等挑战[39]。纤维蛋白支架作为生物相容性优良的递送系统, 可延长外泌体在损伤部位的滞留时间[40]。研究表明, 将正常肌腱干细胞外泌体负载于纤维蛋白支架后, 其活性成分的持续释放时间可达 14

天,增强了糖尿病肌腱的胶原沉积速度和力学强度恢复[40]。最新工程化策略还通过表面修饰 RGD 肽段,增强外泌体与肌腱细胞外基质的特异性结合,使靶向效率提升 3 倍[41]。这种“支架-外泌体”复合系统不仅能克服单纯外泌体易被清除的缺陷,还能模拟天然肌腱的三维微环境[42][43]。最新研究证实,牛肌腱细胞外基质(ECM)支架、仿生丝素蛋白(RSF)支架能复现天然肌腱的纤维排列结构,促进胶原纤维定向再生[44][45]。复合系统还能提供生长因子(如 TGF- β)、miRNA(如 miR-144-3p)等信号分子,调节 M2 巨噬细胞极化和血管生成加速肌腱细胞增殖和迁移[32]。

5.2. 联合治疗: 外泌体与间充质干细胞的协同效应

间充质干细胞(mesenchymal stem cells, MSCs)与外泌体的联合应用产生协同修复效应[37][46]。在糖尿病肌腱损伤模型中,正常脂肪间充质干细胞(adipose-derived stem cells, ADSCs)来源外泌体预处理的脂肪源 MSCs,其 VEGFA 分泌量增加 2.1 倍,同时抑制高糖环境诱导的细胞凋亡[47][48]。这种联合治疗通过双重作用机制实现:外泌体中的 miR-21-5p 维持 MSCs 活性,而活化的 MSCs 又分泌富含 TGF- β 的外泌体促进向肌腱方向分化[14][38]。临床前研究结果显示,联合治疗组的肌腱最大负荷承受力较单用外泌体组提高 38%,且血管生成密度增加 2 倍[17][48]。值得注意的是,脐带源 MSCs 与外泌体的组合显示出更强的抗炎特性,能显著降低糖尿病肌腱中白细胞介素-6(IL-6)和肿瘤坏死因子- α (TNF- α)的水平[36][36]。此外,研究还发现正常骨髓间充质干细胞来源的外泌体(BMSC-Exos)能够提高肌腱-骨界面的愈合强度[21][40],为糖尿病肌腱病变的治疗提供了新的研究方向。

5.3. 基因编辑技术增强外泌体治疗效能的探索

CRISPR/Cas9 基因编辑技术为外泌体功能强化开辟了新途径[41][49]。研究表明,通过敲除供体细胞中的 Dicer 酶可富集某些特定的 miRNA(如 miR-29c),使编辑后外泌体促进肌腱基质合成的能力提升 60%。另一种策略是在外泌体表面表达肌腱归巢肽(例如 E7 肽),借助噬菌体展示技术筛选出的 E7 修饰的外泌体,其在体内靶向效率可达 85% [42][50]。最新研究进展还包括构建“智能外泌体”系统:将光敏蛋白基因转入肌腱干细胞后,其分泌的外泌体可响应近红外光实现转化生长因- β 3 (TGF- β 3)的可控释放,从而实现时空特异性调控[41][42]。这些工程化外泌体在糖尿病大鼠模型中展示出的修复能力是天然外泌体的 3 倍,且未观察到免疫排斥反应[39][51]。

6. 当前争议与未来方向

6.1. 糖尿病分型对外泌体功能影响的异质性争议

现有研究表明,糖尿病分型显著影响干细胞外泌体的功能特性。在 1 型和 2 型糖尿病模型中,骨髓间充质干细胞来源的外泌体(BMSC-Exos)表现出明显的功能差异。其中,2 型糖尿病来源的 BMSC-Exos 在促进肌腱-骨愈合方面的效果显著低于正常 BMSC-Exos [49]。这种功能差异可能与高血糖环境下外泌体 miRNA 表达谱的改变有关[52]。值得注意的是,不同糖尿病分型所致的外泌体 miRNA 表达差异,可能通过影响成纤维细胞功能进而改变肌腱修复效果[52]。然而,目前关于糖尿病分型对外泌体功能影响的分子机制尚存争议,尤其是针对 1 型与 2 型糖尿病外泌体功能异质性的研究仍不足。

6.2. 临床转化面临的生物分布与安全性挑战

尽管外泌体治疗在肌腱修复中展现出良好的应用前景,但其临床转化过程仍面临重大挑战。首要问题在于外泌体在体内的生物分布特性尚未完全阐明[17]。研究表明,未经修饰的外泌体在糖尿病肢体缺血模型中治疗效果有限,这可能与靶向性不足有关[50]。此外,关于外泌体的长期安全性评估数据仍较为

匮乏,特别是应用在糖尿病慢性伤口等复杂病理条件下的安全性尚未明确[18]。另一个挑战体现在规模化生产过程中的质量控制问题,具体包括外泌体纯度、浓度及功能活性的一致性[50]。目前,学界正在探索的解决方案包括使用3D打印支架负载外泌体等新型递送系统,以期提高其靶向性与治疗效果[28]。

6.3. 人工智能预测外泌体活性成分的新范式

人工智能技术为外泌体研究开辟了新途径。最新研究提出了“智能外泌体”(Smart Exosomes)概念,旨在通过编程手段调控外泌体的分泌组内容及功能[40]。该新范式借助机器学习算法对包含微小核糖核酸(miRNA)、蛋白质及脂质组在内的外泌体多组学数据进行分析,以预测关键活性成分及其相互作用网络[53]。在肩袖肌腱损伤研究中,经人工智能辅助设计的外泌体已展现出增强再生能力的潜力[42]。此外,深度学习模型可用于预测不同来源外泌体(如脂肪干细胞、骨髓间充质干细胞)在糖尿病肌腱修复中的最佳组合方案[21][38]。这种数据驱动的研究方法有望突破传统试错式研究的局限,为精准医疗实践提供新的工具支持。

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