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多机制协同调控成纤维细胞重编程的瘢痕治疗转化路径

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摘　要

基于成纤维细胞重编程的瘢痕治疗研究已形成从机制解析到临床转化的完整链条。本综述阐明瘢痕形成的核心机制在于TGF-β1信号驱动的肌成纤维细胞转分化与ECM硬化正反馈循环，并受免疫微环境双向调节。在调控层面，表观遗传修饰、代谢重编程(糖酵解/脂质合成)共同决定细胞命运。治疗策略整合靶向干预与创新递送系统：非编码RNA调控、小分子协同药物(TiT/CRFVPTM)及光响应水凝胶等智能载体实现时序控释，联合疗法显著提升抗纤维化效能。当前仍需突破细胞身份认知局限、衰老表观屏障及基因编辑风险，未来融合单细胞解析与智能材料递送将加速转化进程。

关键词

瘢痕治疗，成纤维细胞重编程，TGF-β信号通路，表观遗传调控，智能递送系统，代谢重编程

Translational Pathways for Scar Treatment with Multiple Mechanisms Synergistically Regulating Fibroblast Reprogramming

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Abstract

Research on scar therapy, grounded in the field of fibroblast reprogramming, has established a comprehensive framework encompassing mechanism analysis and clinical translation. This review elucidates that the core mechanism of scar formation lies in a positive feedback loop of myofibroblast transdifferentiation and ECM sclerosis driven by TGF-β1 signaling and regulated by the immune microenvironment in both directions. At the regulatory level, epigenetic modifications and metabolic reprogramming (glycolysis/lipid synthesis) work in concert to determine cell fate. Therapeutic strategies have been developed that integrate targeted interventions with innovative delivery systems, including non-coding RNA modulation, small molecule synergistic drugs (TiT/CRFVPTM), and smart carriers such as light-responsive hydrogels to achieve sequential controlled release. The combination of therapies has been shown to dramatically improve antifibrotic efficacy. Presently, there is an ongoing need to overcome the limitations of cell identity recognition, aging, epigenetic barriers, and gene editing risks. The integration of single-cell analysis and smart material delivery will accelerate the translational process in the future.

Keywords

Scar Treatment, Fibroblast Reprogramming, TGF-β Signaling Pathway, Epigenetic Regulation, Smart Delivery Systems, Metabolic Reprogramming

1. 引言

瘢痕作为多组织损伤后的常见病理结局，不仅存在于皮肤(如创伤后的增生性或萎缩性瘢痕)，还包括心肌梗死后的心肌纤维化瘢痕及脊髓损伤后的胶质瘢痕，这些均可引发功能障碍、美观受损及严重心理负担。传统疗法如手术、激光及药物注射虽能部分改善症状，却难以从根源上干预瘢痕的形成机制，存在复发率高、疗效受限等不足。近年研究发现，表观遗传调控、代谢重编程及多信号通路的协同交互作用是驱动纤维化的关键。

成纤维细胞重编程是指通过特定因子或条件，将已分化的成纤维细胞诱导为其他类型细胞的过程。根据重编程深度与最终产物可分为完全重编程、直接转分化、去分化，三者的核心区别在于是否经过多功能阶段及最终产物类型，如完全重编程产生 iPSC，直接转分化生成终末分化细胞，去分化则获得可扩增的祖细胞状态[1] [2]。本文聚焦成纤维细胞重编程的分子网络与转化应用，系统阐述靶向干预技术、智能递送系统及多机制联合策略如何协同逆转纤维化进程，突破微环境屏障限制。通过整合单细胞解析、抗衰老协同与仿生材料等前沿方向，旨在为瘢痕治疗的临床转化提供创新路径。

2. 瘢痕形成的细胞生物学基础

2.1. 成纤维细胞与瘢痕形成

瘢痕形成的细胞生物学基础核心在于成纤维细胞向肌成纤维细胞(MF)的转分化及其调控网络。如图1所示，该过程主要由 TGF-β1 信号主导，可形成“ECM 硬化→TGF-β1 活化→纤维化”的正反馈循环；且免疫细胞与成纤维细胞的旁分泌互作还可双向调节瘢痕进程[3]-[7]。

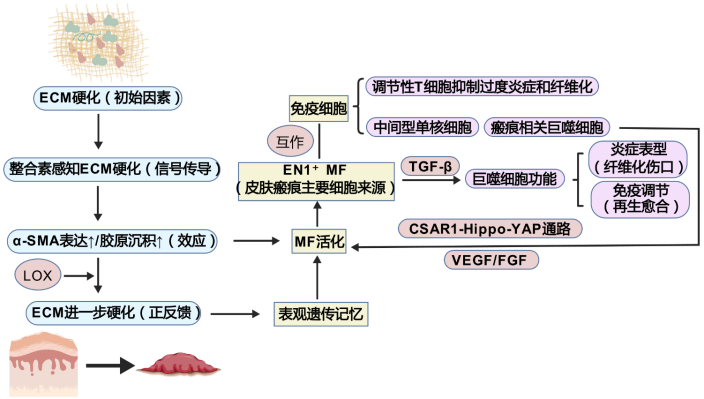
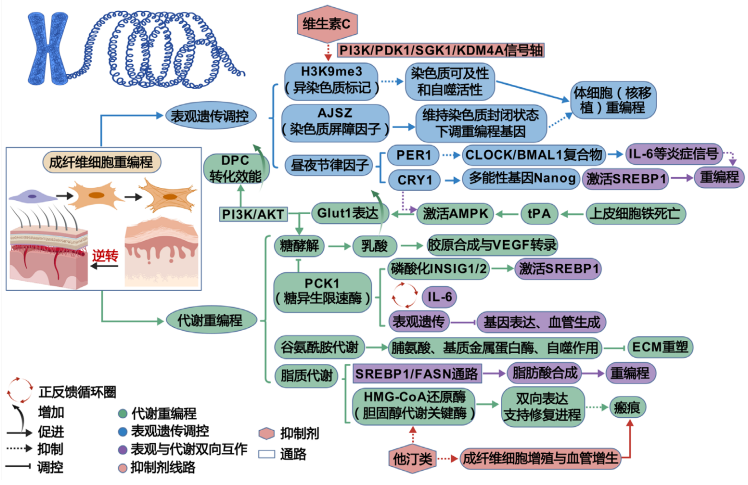


Figure 1. Schematic diagram of the core mechanism of scar formation
图 1. 瘢痕形成的核心机制示意图

2.2. 成纤维细胞的异质性和多能性

成纤维细胞是一个异质性极高的细胞群体，传统标记物为 CD90、Hic1、波形蛋白、TCF21 和 FSP1，而 PDGFRA 和 DPEP1 等可作为新型特异性标记物[8]。真皮细胞类型中 EN1 阳性和阴性肌成纤维细胞是核心细胞群，前者与瘢痕形成相关，被确定为背侧皮肤瘢痕形成的主要细胞来源，而后者则促进再生性愈合，但在机械刺激下可转化为 En1 阳性表型[6] [7]；皮肤最深层的筋膜组织中，CD201+成纤维细胞祖细胞在伤口愈合过程中可分化为 7 种不同的成纤维细胞亚群，核心分化轨迹为“筋膜成纤维细胞→促炎性成纤维细胞→原肌成纤维细胞→肌成纤维细胞”，由两种关键信号通路控制分化方向，视黄酸信号促进向促炎性成纤维细胞分化，缺氧信号促进向肌成纤维细胞分化，以此控制伤口愈合的节奏和进程，确保炎症反应、细胞增殖和组织重塑阶段的适时转换[9]；动脉外膜中，CD55+与血管发育相关、CXCL14+参与抗原呈递、LOX+调控胶原纤维组织，这些亚群的基因集在心血管疾病 GWAS 中显著富集，衰老与高胆固醇等环境刺激可特异性重编程成纤维细胞亚群，驱动纤维化表型[8]。

3. 成纤维细胞重编程的基因与代谢调控



注：AJSZ (ATF7IP、JUNB、SP7、ZNF207)；昼夜节律因子需避免过度积累导致的非振荡性时钟；毛乳头细胞(DPC)。

Figure 2. Schematic diagram of key regulatory network for fibroblast reprogramming
图 2. 成纤维细胞重编程关键调控网络示意图

由图 2 可知，在细胞命运决定中，表观遗传调控靶点如 H3K9me3、昼夜节律因子和染色质屏障因子，通过重塑染色质状态和影响基因表达等显著调控细胞重编程效率；成纤维细胞还可通过糖酵解、PCK1 介导的代谢转换、氨基酸及脂质代谢重编程协同驱动纤维化与修复[10]-[21]。值得注意的是，表观与代谢可通过 CRY1-SREBP1/PCK1-IL-6 轴协同调控成纤维细胞重编程。

4. 基于重编程的瘢痕治疗策略

4.1. 靶向干预机制与表观重编程

成纤维细胞亚群通过 Mmp9/Mmp13 等促纤维化基因和 TGF-β1/Smad、YAP/TAZ、Piezo1/TRPC3-NFAT 信号通路驱动瘢痕形成，靶向抑制这些靶点或上调 Manf、TGF-β3 等抗纤维化基因可逆转纤维化表型[22] [23]。非编码 RNA (ncRNAs)通过调控 TGF-β/Smad 通路实现表观重编程；多种 miRNAs (microRNAs)已被证实能调控成纤维细胞的增殖、迁移和分化，其中 EpiSC-EVs 递送的 miR-203a-3p 靶向抑制 PIK3CA/PI3K/AKT 通路以促进 MF 去分化；而 lncRNAs 通过基因翻译和翻译后修饰调控成纤维细胞命运[24] [25]。动态重编程研究显示，间充质–上皮转化(MET)和以“Klf4/Nanog↑、Cebpb/Sox4↓”为特征的多能性网络激活是避免纤维化命运的关键，分阶段调控 Taf7/Ezh2/Klf2 等因子可诱导再生修复(iPSCs) [26]。实现表明上皮细胞铁死亡与成纤维细胞代谢重编程关系密切，可使用铁死亡抑制剂 Ferrostatin-1、DFO 减轻上皮细胞铁死亡，或 siRNA 沉默抑制 tPA 降低 FN、α-SMA、COL1A1 表达，阻断成纤维细胞的激活[19]。表观遗传修饰通过抑制 DNMTs/HDACs 消除“纤维化记忆”，或利用 BMP2/4 信号将 MF 重编程为脂肪细胞、DNP63a/GRHL2 转化为角质形成细胞，恢复组织稳态；EN1 基因敲除则通过增强迁移能力促进再生；此外，炎症期干预 MF-巨噬细胞相互作用、增殖期靶向成纤维细胞等时空特异性治疗策略可进一步优化干预策略[6] [27]。

4.2. 递送系统与基因编辑技术创新

为突破重编程过程中转录因子/药物的递送瓶颈，近年来基于材料功能化设计和仿生策略的载体系统迅速发展，其核心创新在于靶向精准性提升、时空可控释放以及协同治疗增效。代表性递送系统按其设计原理可分为四类(表 1)，通过安全性优化、再生效能强化及多机制协同，显著提升重编程效率。此外，在成纤维细胞重编程中基因编辑取得突破性发展，第二代 CRISPR 激活系统(SAM)激活内源 Gata4 效率达 150 倍，联合外源 Mef2c/Tbx5 实现高效重编程[28]；间充质干细胞外泌体(MSC-Exo)通过 TNFSF13/HSPG2 通路抑制成纤维细胞活化，双向调控胶原沉积[29]。

Table 1. Fibroblast reprogramming delivery system and its innovative functions
表 1. 成纤维细胞重编程递送系统及其创新功能

类型	代表系统	创新功能
生物材料载体	HA/atelocollagen 海绵	提升转录因子递送安全性[30]
智能响应系统	AHFS 光响应水凝胶微球	结合脂质体纳米药物(TiT 组合)，实现毛囊再生与瘢痕抑制[12]
仿生纳米颗粒	FNLM (tenascin-C 肽 + 中性粒细胞膜)	靶向损伤部位递送 miRNA [27]
协同载体	MPSS@ZIF-90	pH 响应控释 + 促凋亡 + 基因下调 (TGF-β1/VEGF/α-SMA) [31]

注：HA：透明质酸；TiT：Tideglusib + Tamibarotene；MPSS：甲基强的松龙琥珀酸钠。

4.3. 小分子药物与纳米协同策略

小分子化合物库在促进组织再生与逆转病理性纤维化方面展现出重要潜力。在皮肤再生领域，TiT 组

合通过激活 PI3K/AKT 信号通路，有效促进 DPC 功能恢复与毛囊再生，并显著抑制瘢痕形成，为创伤愈合提供了新策略[12]。为提升治疗效果并克服药物递送挑战，纳米载体–药物协同机制的应用至关重要。一方面，通过载体功能化设计，如经聚烯丙基胺盐酸盐(PAH)修饰的 GelMA 光响应水凝胶，可显著增强载体对创面的黏附性，并实现药物的精准时序控释；例如，TiT 药物能在 5 天内实现 95%的缓释，完美覆盖成纤维细胞转分化的关键时间窗，从而优化疗效并减少副作用[12]。另一方面，利用 MSC-Exo 等载体的智能时序调控能力，可在组织愈合的不同阶段发挥双向调节作用，即在愈合早期促进必要的胶原合成以加速伤口闭合，在愈合后期则有效抑制胶原的过度沉积，从而防止病理性瘢痕或纤维化的发生，实现愈合质量与功能的同步优化[29]。

4.4. 联合疗法的协同增效

瘢痕治疗正基于“1 + 1 > 2”的协同增效理念，积极转向联合疗法。“重编程因子 + 抗炎/抗氧化药物”策略通过前者降低细胞炎症敏感性，后者保障因子稳定性与转染效率，协同抑制胶原沉积、肌成纤维分化及血管新生，如 iPSC 源神经干细胞球(高表达 Nrf2/HO-1)联合聚缩醛–姜黄素纳米粒，通过下调 ROS-CTGF 轴实现内/外源抗氧化及双重抗纤维化[32]。药物–抗氧化剂共递送系统(如电纺膜缓释 DEX + GTP)在模型中协同促进胶原降解，使瘢痕体积显著下降 58% [33]。经典三联注射(5-FU 抑制增殖、TAC 抗炎、透明质酸酶促渗透)协同治疗陈旧瘢痕，可使其变平且症状消失，长期随访无复发[34]。此外，依据谷氨酰胺代谢调控/脂肪干细胞特性[18] [35]并联用适当药物，以及基于 HOX 基因位置记忆特性的细胞表型重编程结合 iPSC 技术[3]等策略，均可发挥协同增效，共同促进组织修复。

5. 挑战与未来方向

5.1. 技术瓶颈

细胞身份认知革新挑战了传统“脂肪细胞向肌成纤维细胞转化”的可塑性假说，单细胞转录组与谱系追踪证实，伤口脂肪细胞仅呈现迁移性表型(特异性高表达 Saa3/Orm1/Pdk4 等抗菌/代谢基因)，其核心功能为炎症调控而非瘢痕形成，需针对性靶向成纤维细胞[23]。重编程效率受限于细胞来源异质性及病理微环境，其中肌成纤维细胞需突破表观遗传屏障，而 TGF-β 信号、ECM 硬度、IL-6 及缺氧协同阻碍转化[27] [36]；衰老成纤维细胞通过“信号–表观–微环境”三轴耦合，构筑多道分子刹车，显著削弱诱导重编程效率。具体表现为 TGF-β/Smad 信号显著上调，驱动胶原、纤连蛋白等 ECM 过度沉积，从而强化细胞纤维化身份；其次，HDACs、EZH2、DNMTs 等表观修饰在纤维化中上调，锁定纤维化基因表达；再者，ECM 硬度等机械信号可通过 Hippo/YAP/TAZ 和 Rho/ROCK 通路维持纤维化表型，进一步降低细胞对重编程因子的敏感性；最后，慢性炎症微环境诱导 IL-6、IL-8 等 SASP 因子大量分泌，通过旁分泌作用加固细胞周期阻滞并稳定上述表观遗传锁定，形成“纤维化–衰老–抗重编程”正反馈环[27] [37]。技术风险方面，CRISPRa 的 sgRNA 脱靶可激活 MYH6 等非目标基因，导致功能异常细胞群及 de novo 表观遗传屏障，种属间表观差异进一步放大致瘤性[28]。

5.2. 转化医学突破口

转化医学的核心突破口在于单细胞解析指导个性化重编程，其通过皮肤切口成纤维细胞的单细胞多组学解析，识别 ECM 合成与信号配体驱动基因并解析谱系轨迹，进而设计时空特异性靶向干预方案[38]；抗衰老协同策略则可联合 Senolytics 清除 SASP、抑制屏障因子 AJSZ，经 FNLM 纳米颗粒靶向递送构建多靶点体系以重置表观障碍[13] [27]；纳米纤维/凝胶、微针等仿生材料递送系统通过增强药物穿透与控释能力，精准靶向瘢痕组织并提升抗纤维化疗效[39]-[41]。三者最终融合形成“精准解析–微环境调控–

智能递送”的闭环转化路径。

6. 结论

成纤维细胞重编程为瘢痕治疗开辟了革命性转化前景。其核心在于通过靶向干预 TGF-β/Smad、YAP/TAZ 等信号通路及非编码 RNA 介导的表观重编程，有效逆转肌成纤维细胞活化；而基因调控与代谢重塑的深度协同——尤其是 CRY1-SREBP1/PCK1-IL-6 轴的发现——揭示了阻断纤维化进程的关键节点。技术创新层面，三大协同路径推动临床转化：基于智能材料(如光响应水凝胶、FNLM 仿生纳米粒)的时空控释型递送系统显著提升重编程因子/药物的靶向性与安全性；小分子协同策略(如 TiT 组合)通过调控 PI3K/AKT 等通路实现毛囊再生与瘢痕抑制的双重目标；CRISPRa 等基因编辑技术则大幅提升内源基因激活效率。未来突破需聚焦单细胞解析指导个体化干预、克服衰老微环境建立的抗重编程屏障，并融合“精准解析–微环境调控–智能递送”策略推动临床转化，最终实现瘢痕的再生性修复。

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