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宫腔粘连治疗现状和干细胞疗法的研究进展

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[摘 要] 宫腔粘连(intrauterine adhesions，IUA)是以月经异常和不孕为主要临床表现的妇科疾病。目前，宫腔镜下粘连分离术是IUA的主要治疗手段，但中重度患者术后复发率仍较高。临床上常于术后辅以药物治疗、宫内放置物理屏障等措施，以期促进子宫内膜再生、降低再粘连风险。上述方法对轻度IUA患者具有一定疗效，但对中重度患者的子宫内膜结构恢复及妊娠结局改善效果仍较为有限。近年来，干细胞疗法在修复子宫内膜方面展现出良好的应用前景，其中，间充质干细胞(mesenchymal stem cells，MSCs)被认为是最具临床转化潜力的干细胞类型。MSCs不仅可通过分化为子宫内膜相关细胞参与组织再生，还可通过分泌胞外囊泡(extracellular vesicles，EVs)等发挥抗炎、免疫调节、抗纤维化、促进子宫内膜细胞增殖及血管再生等间接修复作用，从而有效促进子宫内膜再生并改善妊娠结局。然而，现有研究多处于基础或早期临床阶段，相关临床证据尚不充分，其具体作用机制及最佳应用方式仍有待进一步明确。未来需深入挖掘潜在治疗靶点，系统阐明MSCs及其EVs在IUA治疗中的作用机制，并推动相关研究向规范化临床转化，以期为改善子宫内膜环境及女性生殖功能提供更加有效的治疗策略。

[关键词] 宫腔粘连；再生医学；干细胞疗法；间充质干细胞；胞外囊泡；再粘连

Current status of intrauterine adhesion treatment and research progress in stem cell therapy

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ABSTRACT Intrauterine adhesions (IUA) are gynecological disorders mainly characterized by menstrual abnormalities and infertility. At present, hysteroscopic adhesiolysis is the primary treatment for IUA; however, the postoperative recurrence rate remains high in

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patients with moderate to severe disease. In clinical practice, postoperative adjuvant therapies, including pharmacological treatment and intrauterine placement of physical barriers, are commonly applied to promote endometrial regeneration and reduce the risk of re-adhesion. These approaches show certain efficacy in patients with mild IUA, but their effects on restoring endometrial structure and improving pregnancy outcomes in moderate to severe cases remain limited. In recent years, stem cell therapy has demonstrated promising potential in endometrial repair, among which mesenchymal stem cells (MSCs) are considered the stem cell type with the greatest potential for clinical translation. MSCs can not only participate in tissue regeneration through differentiating into endometrial-related cells, but also exert indirect reparative effects through the secretion of extracellular vesicles (EVs), including anti-inflammatory, immunomodulatory, anti-fibrotic, pro-proliferative, and pro-angiogenic activities, thereby effectively promoting endometrial regeneration and improving pregnancy outcomes. However, most existing studies remain at the basic research or early clinical stage, and current clinical evidence is still insufficient. Their precise mechanisms of action and optimal application strategies also require further clarification. Future studies should focus on identifying potential therapeutic targets, systematically elucidating the mechanisms by which MSCs and their EVs contribute to IUA treatment, and promoting the standardized clinical translation of related research, with the ultimate goal of providing more effective therapeutic strategies for improving the endometrial environment and female reproductive function.

KEY WORDS intrauterine adhesions; regenerative medicine; stem cell therapy; mesenchymal stem cells; extracellular vesicles; re-adhesion

宫腔粘连(intrauterine adhesions，IUA)，又称Asherman综合征，是一种由于宫腔操作、感染或其他因素损伤子宫内膜基底层，导致子宫内膜再生修复困难的宫腔疾病。IUA的主要病理表现为子宫内膜瘢痕组织增生和纤维性粘连，引起宫腔狭窄或闭锁，显著减少子宫内膜面积并损害其生理功能[1]。临床上IUA患者主要表现为月经异常和生育功能障碍，包括闭经、反复流产、胚胎着床失败等，严重影响育龄期女性的月经及生殖健康[2]。目前，临床上IUA的主要治疗方式为宫腔镜下宫腔粘连分离术(transcervical resection of adhesions，TCRA)[3]，术后常辅以药物、宫内节育器等预防再粘连的发生[4]。然而，这些疗法在促进子宫内膜再生和改善妊娠结局方面存在明显局限。干细胞不仅具有多向分化能力，还可以通过释放生物活性因子改善子宫内膜局部微环境，在内膜修复方面显示出潜在优势。笔者检索了PubMed、Web of Science及中国知网(China National Knowledge Infrastructure，CNKI)数据库中关于宫腔粘连治疗与干细胞疗法的研究，检索时限为建库至2026年1月。英文检索词包括“intrauterine adhesions”“Asherman syndrome”“hysteroscopic adhesiolysis”“endometrial repair”“stem cells”“mesenchymal stem cells”“extracellular vesicles/exosomes”“hydrogel”“biomaterials”等，中文关键词包括“宫腔粘连”“Asherman综合征”“宫腔镜粘连分离术”“子宫内膜修复”“干细胞”“间充质干细胞”“胞外囊泡/外泌体”“水凝胶”“生物材料”等，重点纳入指南、系统评价、随机对照试验、前瞻性临床研究及代表性基础研究。基于对相关文献的总结，笔者阐述了IUA的病理生理机制、现有治疗手段及其局限性，回顾了干细胞疗法治疗IUA的研究进展，并讨论了该疗法当前面临的挑战与应用前景，以期为推动干细胞治疗IUA的临床转化提供借鉴与参考。

1 IUA的病理生理机制

IUA的形成是子宫内膜基底层损伤后多种病理过程相互作用的结果，主要表现为氧化应激、炎症反应、异常纤维化修复及持续性血管损伤。基底层受

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损后，局部缺氧和炎症反应可诱导活性氧(reactive oxygen species，ROS)过量产生[5-6]，引起内膜上皮及微血管内皮细胞损伤，进一步加重局部缺血缺氧环境[7-9]。同时，持续的炎症微环境可促进成纤维细胞异常活化和细胞外基质过度沉积，最终导致宫腔粘连形成[10-11]。缺氧和粘连进一步抑制内膜及血管再生[12]，形成持续性的“组织损伤-炎症反应-纤维化重塑-血管损伤”恶性循环，最终严重损害子宫内膜的再生修复能力和胚胎着床容受性。

2 当前IUA的临床治疗策略及局限性

目前TCRA的疗效与粘连严重程度密切相关。轻度IUA患者术后通常可获得良好的宫腔形态恢复；但对于中重度IUA患者，由于子宫内膜基底层被广泛破坏、残余功能内膜不足，且局部纤维化和缺血状态持续存在，TCRA后粘连复发率较高[4, 13]，月经恢复及临床结局(包括妊娠率及活产率等)的改善也相对有限。为预防术后再粘连并促进受损子宫内膜再生，药物治疗、物理屏障应用及中医药疗法是目前IUA术后常用的3类辅助治疗策略。然而，这些方法在改善上述临床结局方面均存在一定局限性。

2.1 药物治疗

药物治疗是TCRA后常用的辅助治疗方法，主要包括激素类药物(如雌激素)和血管活性药物，旨在促进子宫内膜再生[14]。动物实验研究[15]结果显示，生长激素联合雌激素可能通过调控大鼠子宫内膜微环境代谢及β-联蛋白(β-catenin)信号通路减轻纤维化，为IUA的药物治疗提供了新的潜在靶点。一项临床研究[16]显示，雌激素与阿司匹林的联合用药方案可在一定程度上促进中重度IUA患者子宫内膜血管生成、抑制纤维化，并改善患者预后；但由于缺乏长期妊娠结局的随访数据，其临床价值仍需在不同给药方案的随机对照研究中进一步验证。此外，现有药物治疗仍面临个体化剂量缺乏统一标准、作用机制尚未完全阐明等问题，且部分研究[17-18]提示高剂量雌激素可能增加血栓等并发症风险。综上所述，术后雌激素可促进子宫内膜厚度增加及月经恢复，但其对中重度IUA患者在降低术后复发率、改善妊娠率及活产率方面的作用，尚缺乏充分且一致的研究证据支持[4, 19]。

2.2 物理屏障应用

TCRA后通过放置宫内节育器、Foley球囊、羊膜移植及透明质酸凝胶等物理或生物材料，可以隔离受损的子宫内膜，防止愈合过程中发生再粘连[20-21]。临床试验(NTR 3120)[22]结果提示，宫内放置透明质酸凝胶可降低既往刮宫患者的粘连复发率。然而，此类疗法存在显著局限性：羊膜制品来源受限，且具有潜在感染及免疫风险[23]；Foley球囊需在7 d内取出[24-25]，过度充盈会压迫子宫内膜血管；宫内节育器在重度粘连患者中易发生嵌顿[23, 26]。总体而言，物理屏障疗法主要通过机械隔离创面来预防粘连，对于轻中度IUA患者具有明确的临床价值；但对于子宫内膜基底层严重损伤的患者，单纯机械隔离促进内膜再生的疗效有限。因此，物理屏障更适合作为TCRA后的辅助措施，而非重建受损子宫内膜的根本手段。

2.3 中医药疗法

中医理论认为，肾虚血瘀是IUA的核心病机，治疗应以补气活血、散瘀通络为主。部分中药复方被报道具有促进子宫内膜修复的潜在作用。例如，菟葜等中草药具有抗炎、抗氧化及活血化瘀等功效[27]。体外实验和动物实验研究[27-28]显示，中药复方的辅助治疗可以有效改善内膜细胞纤维化程度，如调参通络方、菟葜等中药复方可能通过调控转化生长因子(transforming growth factor，TGF)-β/Sma和Mad相关蛋白(Sma- and Mad-related protein，Smad)、磷脂酰肌醇3-激酶(phosphoinositide 3-kinase，PI3K)/蛋白激酶B(protein kinase B，AKT)等信号通路抑制纤维化进程。研究[29]采用自创的“养膜方”治疗中重度IUA患者，可促进子宫内膜恢复并提高妊娠率，其效果可能优于雌激素和孕激素治疗；该作用可能与改善子宫局部血流、上调子宫内膜孕激素受体表达及改善子宫内膜营养状况有关。然而，目前中医药研究仍以单中心、小样本及机制探索为主，结局指标多集中于症状改善或分子标志物变化，针对粘连复发率、妊娠率及活产率等远期预后的证据尚不充分。中药治疗IUA的疗效需通过更大样本量及多中心研究加以验证，其活性成分及具体作用机制亦有待更深入的药理学研究阐明。

综上所述，IUA的现有治疗手段尚难以有效阻断“组织损伤-炎症反应-纤维化重塑-血管损伤/缺氧”这一恶性循环。尤其是中重度IUA患者，术后再粘连仍较为常见，妊娠率和活产率等远期生殖结局的改善亦不理想[13, 30]。因此，具备多途径修复能力、兼具抗炎与抗纤维化等综合调控作用的干细胞再生医学策略，已成为当前IUA治疗领域的重要研究方向。

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3 干细胞治疗IUA的研究进展

3.1 干细胞的概述

干细胞是一类具有自我更新能力和多向分化潜能的细胞，在组织发育及再生修复中发挥关键作用。目前研究较为深入的干细胞主要分为3类：1)胚胎干细胞(embryonic stem cells，ESCs)；2)成体干细胞，如间充质干细胞(mesenchymal stem cells，MSCs)；3)诱导多能干细胞(induced pluripotent stem cells，iPSCs)[31]。基于证据成熟度与临床转化可行性，目前MSCs及其来源的胞外囊泡(extracellular vesicles，EVs)被认为最具应用潜力，因此本文将重点综述其研究进展。

3.2 ESCs和iPSCs

ESCs具有较强的自我更新和多向分化潜能，在子宫内膜再生研究中受到关注[32-33]。体外及动物实验研究[34-35]结果提示，ESCs衍生的免疫和基质调节细胞(immunity-and-matrix-regulatory cells，IMRCs)及其外泌体可促进受损子宫内膜修复，增加子宫壁厚度和腺体数量，并改善大鼠生育结局。一项I期临床试验(NCT04232592)[36]结果初步提示，ESCs-IMRCs治疗难治性IUA具有潜在疗效和一定的安全性，其作用可能与促进血管生成及减轻瘢痕形成有关。然而，ESCs的临床应用受伦理争议、细胞来源及长期安全性等因素限制，距离广泛临床应用仍有较大距离。

iPSCs可通过体细胞重编程技术获取[37]，兼具多向分化潜能和相对较少的伦理限制[38-40]。目前其在IUA中的研究主要处于临床前阶段。体外实验研究[41]表明，人源iPSCs可定向分化为子宫内膜相关细胞；动物实验研究[42]结果提示，iPSCs移植可能减轻子宫损伤后的炎症反应并改善妊娠结局。然而，其应用存在重编程效率较低、分化稳定性不足、致瘤风险及伦理与隐私管理等问题[43]。

总体来看，ESCs和iPSCs在IUA治疗中均显示出一定再生修复潜力，但二者目前更多属于储备性技术路线，短期内在IUA中的临床应用价值有限。

3.3 MSCs

目前用于IUA研究的MSCs主要来源于骨髓、脐带、脂肪及胎盘等组织。骨髓来源MSCs研究起步较早，临床应用经验相对较多，但采集具有侵入性，且细胞产量有限[44]；脐带来源MSCs获取方便，扩增能力较强，免疫原性较低，是目前临床前及早期临床研究中应用较多、转化前景较好的细胞来源[45]；脂肪来源MSCs取材相对便利，但其在IUA中的直接研究证据仍较为有限。基于现有研究趋势，脐带来源MSCs可能是当前治疗IUA综合优势较明显、临床转化潜力较高的候选来源，但不同来源MSCs的优劣尚缺乏头对头比较研究，仍有待进一步验证。现有研究[46]发现，MSCs主要通过直接修复和旁分泌调控2条途径参与受损子宫内膜的修复(图1)。

MSCs的直接修复作用主要源自其多向分化潜能。当MSCs植入损伤区域后，可分化为子宫内膜相关细胞，或激活受损组织内源干细胞的分化潜能，从而在一定程度上促进内膜组织结构的重建[47-48]。动物研究[47]结果提示，人脐带血来源MSCs可迁移至子宫损伤区域分化为子宫内膜细胞，其作用可能与调节核因子κB(nuclear factor kappa-B，NF-κB)相关炎症通路有关。一项自体骨髓来源干细胞宫腔灌注的5年随访研究(CTRI/2013/08/003896)[49]纳入了难治性IUA及子宫内膜萎缩患者，结果显示，23例患者中大部分治疗后月经状况及宫腔形态有所改善，其中3例成功妊娠；另一项I期临床研究(NCT02313415)[50]提示，脐带MSCs联合胶原支架治疗复发性IUA具有一定可行性，26例患者中最终10例妊娠，且内膜组织中Ki67及血管性血友病因子(von Willebrand factor，vWF)等蛋白质表达上调，提示内膜增殖和血管生成可能得到改善。综上，MSCs在IUA治疗中展现出一定的研究价值和应用前景，但其作用机制尚未完全阐明，现有临床研究样本量较小，且多缺乏随机对照设计，仍需进一步系统研究及规范化临床试验加以验证。

MSCs的间接修复作用主要通过其旁分泌途径实现。MSCs分泌的EVs是一类直径为30~1 500 nm，由脂质双层膜包裹的纳米颗粒，富含蛋白质、微RNA(microRNA，miRNA)等生物活性物质[51]。MSCs通过递送EVs介导细胞间通信，调控组织细胞的生物学功能，从而产生调节抗炎免疫、抑制纤维化、促进血管新生及激活细胞增殖等多重协同效应[46, 52]。现有体外与动物实验提示，这些多效作用机制可协同促进受损子宫内膜的结构与功能重建。1)免疫炎症调控作用：MSCs及其EVs可促进巨噬细胞向M2型极化，抑制自然杀伤细胞与T淋巴细胞活化，同时上调白细胞介素-10等抗炎因子表达，减轻子宫内膜炎症损伤[53-55]。动物实验[56]表明，脐带MSCs来源EVs中的miR-223-3p可特异性增强大鼠子宫内膜中巨噬细胞的M2型极化，并降低肿瘤坏死因子-α等促炎因子水平，从而促进子宫内膜再生及生育功能恢复。然而，此类证据主要来源于动物实验，相关效应在IUA患者中的稳定性和可重复性仍有待进一步验证。2)抗纤维化作用：抗纤维化是MSCs治疗IUA最受关注的机制之一。MSCs及其EVs可调控TGF-β/Smad、

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Wnt/β-catenin等纤维化相关信号通路，减少胶原沉积并抑制成纤维细胞异常活化。动物实验[57]结果表明，骨髓MSCs来源EVs可通过抑制IUA模型兔子宫内膜中TGF-β1/Smad信号通路，显著降低胶原沉积并逆转上皮-间质转化；胎盘MSCs来源EVs在IUA模型大鼠子宫内膜中可通过特定miRNA组合(如miR-21-5p)靶向下调TGF-β信号轴，抑制成纤维细胞异常增殖[58]。综上，现有临床前研究支持MSCs及其EVs具有抗纤维化潜力，但不同细胞来源、给药方式及模型构建的差异可能影响结果的一致性。3)促血管生成作用：血管生成障碍是IUA中子宫内膜再生受限的重要因素。多项体外及动物实验[59-60]提示，MSCs及其EVs可通过激活AKT、胞外信号调节激酶(extracellular signal-regulated kinase，ERK)等相关信号通路分子，诱导内皮型一氧化氮合酶(endothelial nitric oxide synthase，eNOS)、血管内皮生长因子A(vascular endothelial growth factor A，VEGF-A)、血管内皮生长因子受体1(vascular endothelial growth factor receptor 1，VEGFR-1)、血管内皮生长因子受体2(vascular endothelial growth factor receptor 2，VEGFR-2)和酪氨酸激酶受体(tyrosine kinase with immunoglobulin-like and EGF-like domains 2，TIE2)的过表达，促进功能性血管网络形成，从而改善子宫内膜微循环。需要指出的是，现有证据主要来自细胞及动物研究，其对临床妊娠结局的实际贡献尚难以单独量化。4)促细胞增殖作用：MSCs分泌的血管内皮生长因子、成纤维细胞生长因子等可激活丝裂原激活的蛋白激酶(mitogen-activated protein kinase，MAPK)/ERK信号通路，上调细胞周期蛋白表达，从而加速细胞增殖[61-63]。体外及动物实验[58]表明，胎盘MSCs来源的EVs可促进子宫内膜细胞增殖。5)氧化应激调控的潜在作用：氧化应激可能是MSCs干预IUA的重要潜在机制之一。已有体外及动物实验[7, 64-66]表明，氧化应激参与IUA的发生、发展，而部分药物及特定miRNA(如miR-27a)可能通过调控沉默信息调节因子3(sirtuin 3，SIRT3)-超氧化物歧化酶(superoxide dismutase，SOD)2-ROS信号通路及磷酸酶与张力蛋白同源物的诱导激酶1的表达，抑制氧化应激并减轻子宫内膜损伤。同时，MSCs及其EVs在其他组织损伤模型中已显示出一定的抗氧化应激潜能。然而，目前在IUA中尚缺乏直接证据支持其通过调控ROS相关通路促进内膜修复，该机制仍有待进一步研究。

综上所述，MSCs及其衍生EVs在IUA治疗中展现出较好的临床前研究基础，早期临床研究证据也支持其可行性。MSCs治疗IUA的疗效可概括为直接作用与间接作用，分别对应上述直接分化机制及“免疫调节-抗纤维化-促血管生成-促细胞增殖”轴的协同调控(图1)。然而，目前多数研究证据仍来源于动物实验及小样本早期临床研究，不同来源MSCs的优劣比较、最佳给药途径及剂量、长期安全性以及对妊娠和活产结局的影响等问题，仍需进一步研究。

综合当前干细胞治疗IUA的研究进展，不同类型干细胞的临床转化进展存在明显差异。ESCs虽具有较强的分化潜能，其在IUA中的研究已由动物实验推进至早期临床试验阶段，但仍受伦理争议及来源限制等因素影响；iPSCs具备个体化治疗优势，但面临重编程效率、遗传稳定性及潜在致瘤风险等关键问题，且研究证据主要来自体外及动物实验，临床转化仍处于储备阶段。相比之下，MSCs因来源广泛、获取相对便利、免疫原性较低，且已积累较多体外、动物及少量早期临床研究证据，是目前IUA再生治疗中最具现实转化价值的细胞类型。然而，干细胞疗法的真实疗效仍需高质量临床研究进一步验证。

3.4 干细胞及其EVs的潜在修复机制

动物实验研究[67-68]发现，在肾脏、椎间盘等其他组织损伤模型中，MSCs及其EVs显示出一定的抗氧化应激作用，可降低脂质过氧化产物丙二醛(malondialdehyde，MDA)水平，升高抗氧化酶SOD1及过氧化氢酶(catalase，CAT)水平，其作用可能通过EVs携带的乳脂肪球表皮生长因子8(milk fat globule-EGF factor 8，MFG-E8)介导。然而，在IUA中，目前尚缺乏直接证据证明MSCs及其EVs可通过调控氧化应激促进子宫内膜修复。因此，氧化应激调控可能是未来阐明MSCs及其EVs治疗IUA机制的重要研究方向。MSCs来源的EVs可上调SOD1等抗氧化酶水平，后续研究可结合IUA模型，围绕EVs携带的miRNA、MFG-E8及沉默信息调节因子3(sirtuin 3，SIRT3)-SOD2-ROS[66]等关键通路开展进一步验证，以完善MSCs治疗IUA的机制体系。

4 干细胞疗法的挑战与前景

4.1 主要挑战

干细胞治疗在IUA修复中的临床转化仍面临多项与疾病特征密切相关的挑战。IUA患者在病因、粘连程度、基底层损伤深度及既往宫腔操作史等方面存在明显异质性，且针对感染性或结核性内膜损伤的相关研究有限，不同类型病变对干细胞疗法的反应可能存在差异。此外，现阶段尚缺乏统一且具有临床针对性的疗效评价体系，各研究所采用的组织

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学指标(如子宫内膜厚度、腺体数量)与临床结局指标(如月经恢复率、妊娠率、活产率等)不一致，增加了证据整合与疗效比较的难度。同时，细胞来源、质量控制、给药剂量与途径、治疗频次、干预时机及是否联合支架或药物等关键因素尚未标准化，均可能影响疗效的稳定性。

IUA的干细胞治疗还应重视患者分层与治疗窗口期。不同病因及病程所致的基底层损伤和纤维化程度各异，可能影响治疗效果，因此需结合病因学特征、宫腔镜分型及内膜状况进行分层评估。目前，TCRA后干细胞干预的最佳时机及其与防粘连措施的联合应用，仍缺乏统一标准。

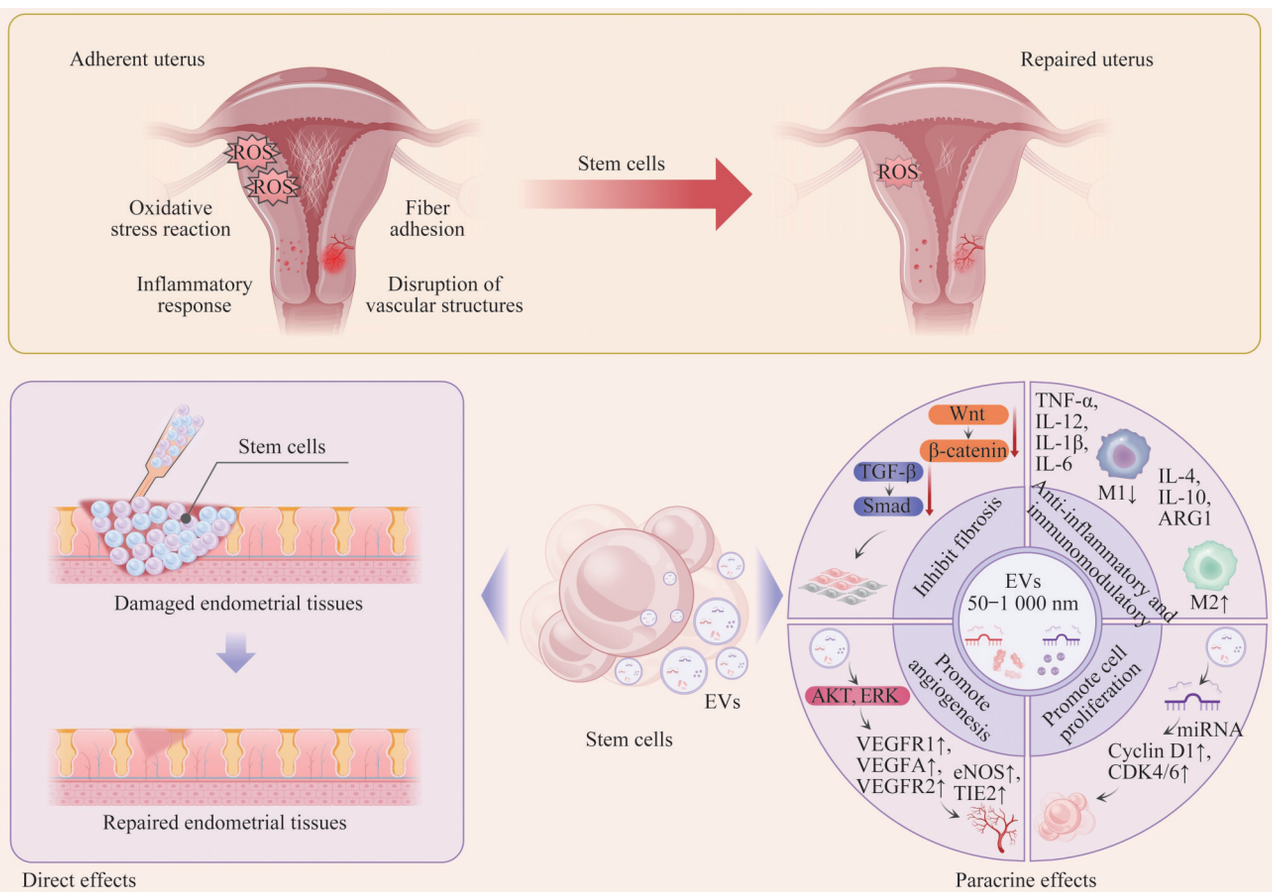


图1 干细胞治疗宫腔粘连的主要作用机制：直接修复与旁分泌调控

Figure 1 Main mechanisms of stem cell therapy for intrauterine adhesions: Direct repair and paracrine regulation

EVs: Extracellular vesicles; ROS: Reactive oxygen species; TNF-α: Tumor necrosis factor-α; IL-1β: Interleukin-1β; IL-4: Interleukin-4; IL-6: Interleukin-6; IL-10: Interleukin-10; IL-12: Interleukin-12; ARG1: Arginase 1; M1: M1 macrophages; M2: M2 macrophages; VEGFR1: Vascular endothelial growth factor receptor 1; VEGFR2: Vascular endothelial growth factor receptor 2; AKT: Protein kinase B; ERK: Extracellular signal-regulated kinase; VEGFA: Vascular endothelial growth factor A; eNOS: Endothelial nitric oxide synthase; TIE2: Tyrosine kinase with immunoglobulin-like and EGF-like domains 2; CDK4/6: Cyclin-dependent kinase 4/6; TGF-β: Transforming growth factor-β; Smad: Sma- and Mad-related protein.

此外，临床试验的安全性评价除需关注短期不良事件外，更应重视长期随访中的复发情况、异常内膜增生风险、妊娠结局及母胎安全性。未来仍需开展设计规范、分层明确、随访充分的临床研究，以推动干细胞治疗IUA的临床转化与规范应用。

干细胞治疗的临床推进还受到费用高昂、可及性不足以及严格伦理与监管要求的限制。相关技术需经过备案、伦理审查及多中心验证，因此多数三级甲等医院在开展临床研究时面临较重的行政与成本压力。此外，由于该技术目前尚未纳入医保，患者自费负担较重，进一步限制了干细胞治疗IUA的临床可及性。

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4.2 前沿策略和优化方向

为进一步提高干细胞或其衍生物在宫腔局部的滞留、存活及功能发挥能力，近年来IUA再生治疗领域逐渐发展出多种基于材料工程、细胞工程及细胞重编程的创新策略，相关研究类型较多、技术路线差异较大，大致可分为水凝胶/支架递送系统和细胞工程、纳米材料及细胞重编程策略2类(表1、2)。

水凝胶/支架递送系统可提供更稳定的局部微环境，同时具备机械支撑、病灶隔离和缓释递送等优势。温敏水凝胶、透明质酸水凝胶、黏附性复合水凝胶及三维培养联合支架系统等相关研究[69-75]表明，这些材料可延长治疗成分在宫腔内的滞留时间，提高细胞存活率及旁分泌效应，从而在抗炎、抗纤维化、促血管生成和促进腺体再生等方面优于单纯细胞输注。在细胞工程、纳米材料及细胞重编程策略方面，ESCs衍生的免疫及基质调节细胞、经炎症因子预处理的MSCs及其EVs、钌(Ru)单原子纳米酶，以及条件性重编程子宫内膜上皮细胞等策略，分别从增强免疫调控能力、改善氧化应激状态及直接补充内膜相关细胞等不同角度修复IUA受损子宫内膜[7, 34, 36, 76-77]。这些策略在机制上具有协同靶向多重病理环节的特点，有望弥补传统单一治疗模式对复杂病灶微环境干预不足的局限。然而，目前相关证据仍以临床前研究为主，其最佳适用人群、给药时机、联合方式及长期安全性仍需进一步研究明确。

基于当前证据，临床医生可将干细胞治疗作为对既往治疗反应欠佳患者的探索性选择，尤其适用于反复TCRA后仍存在中重度宫腔粘连、子宫内膜持续薄化，或常规药物与物理防粘连措施无效者。鉴于疗效稳定性和长期安全性仍待进一步验证，目前干细胞治疗更建议在规范化伦理审查下的临床试验或注册研究中开展，不推荐在试验体系之外常规应用。

表1　基于水凝胶/支架系统的新型联合治疗策略在IUA中的应用

Table 1　Application of the novel combined treatment strategy based on hydrogel/scaffold system in IUA

水凝胶种类	材料特点	递送途径	主要机制/潜在优势	研究阶段
温敏水凝胶[11]	37 ℃下原位凝胶化	局部注射	延长EVs滞留时间；抗炎、抗纤维化；改善内膜修复及生育结局	动物实验
透明质酸水凝胶[72, 75]	生物相容性良好，物理/化学交联成胶	局部注射	提高细胞局部保留与存活；促进内膜再生和血管生成；改善着床率和活产率	动物实验
甲基丙烯酸酯-蜗牛黏液黏附性水凝胶[74]	光固化，黏附性强，增强局部固定，持续释放	局部注射	缓释EVs；抑制炎症级联反应；抗纤维化；提高活产率	动物实验

IUA：宫腔粘连；EVs：胞外囊泡。

表2　基于细胞工程、纳米材料及细胞重编程的新型治疗策略在IUA中的应用

Table 2　Application of novel therapeutic strategies based on cell engineering, nanomaterials and cell reprogramming in IUA

治疗策略	特点	递送方式	主要机制/潜在优势	研究阶段
三维培养MSCs[70-71]	模拟体内的三维生长环境	宫内注射	提高EVs产量；增强抗炎、抗纤维化作用；改善内膜厚度和腺体数量	动物实验
ESCs衍生的IMRCs[34, 36]	体外扩增能力较强，具有免疫与基质调节特征	局部注射	抑制炎症；减轻纤维化；促进血管生成和内膜修复；改善生育力	动物实验/早期临床研究
新型Ru单原子纳米酶[7]	高稳定性，生物安全性较好，类抗氧化酶活性	局部注射	清除ROS；减轻氧化应激和铁死亡相关损伤；抑制纤维化	动物实验
经TNF-α预处理的MSCs及其外泌体[77]	外泌体免疫调节能力增强，galectin-1表达升高	尾静脉注射	促进M2型巨噬细胞极化；增强抗炎和抗纤维化效应	动物实验
条件性重编程子宫内膜上皮细胞[76]	保留组织特异性分化潜能，表达雌孕激素受体	宫内注射	促进腺体再生；减少纤维化面积；改善内膜厚度并提高妊娠率	动物实验

ESCs：胚胎干细胞；MSCs：间充质干细胞；IMRCs：免疫和基质调节细胞；ROS：活性氧；TNF-α：肿瘤坏死因子α；Galectin-1：半乳糖凝集素1。

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5 结 语

IUA的发生和发展涉及复杂的病理生理过程，其临床治疗的核心不仅在于解除粘连组织，更在于实现子宫内膜的功能性再生与结构重建。动物实验及临床研究表明，MSCs及其EVs可通过直接分化、抗炎免疫调节、促血管生成、纤维化抑制及增殖促进等多靶点作用机制协同干预IUA进程，但具体的分子机制(如抑制氧化应激作用)仍有待阐明。同时，当前干细胞治疗在制备标准化、适宜人群筛选、最佳治疗窗口期选择及长期安全性评估等方面仍面临诸多挑战，制约了其临床转化效率。因此，未来干细胞再生医学研究应重点聚焦以下方向：1)深入探索干细胞修复子宫内膜损伤的作用机制；2)根据IUA的病因、病程及损伤程度建立患者分层策略；3)优化干细胞与生物活性支架的联合递送方案，并探索更合理的术后干预时机；4)建立标准化干细胞制剂的质控体系；5)通过严格的临床试验验证其长期疗效及对妊娠、活产和母胎安全性的影响。解决上述问题是实现干细胞治疗从基础研究向临床转化的关键。

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