·综　述·

# 脂肪间充质干细胞在纤维化疾病治疗中的作用

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[摘　要]　纤维化疾病由于其广泛性和复杂性带来了重大临床挑战,探究纤维化的发生机制并寻求更有效的治疗方法势在必行。脂肪间充质干细胞(adipose-derived stem cell,ADSC)是适用于再生医学的理想干细胞,可作为许多疾病的替代治疗方案。近年来研究表明,ADSC有显著的抗纤维化潜力。本文就ADSC抗组织纤维化过程中涉及的上皮-间充质转变、成纤维细胞活化、抗炎及免疫调节等潜在干预靶点进行综述,旨在为防治纤维化提供新思路。

[关键词]　脂肪间充质干细胞;纤维化;治疗;机制

[中图分类号]　R329.2　　[文献标志码]　A　　[文章编号]　1007-4368(2024)03-429-06

**doi**:10.7655/NYDXBNSN230190

## The role of adipose-derived stem cells in the treatment of fibrotic diseases

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[**Abstract**]　Fibrotic diseases have brought great clinical challenges due to their extensiveness and complexity. It is imperative to explore the mechanism of fibrosis and seek more effective treatments. Adipose derived stem cells (ADSC) are ideal stem cells for regenerative medicine and can be used as an alternative treatment for many diseases. Recent studies have shown that ADSC has significant anti-fibrosis potential. This article reviews the potential intervention targets involved in the anti-fibrosis process of ADSC, such as epithelial-mesenchymal transition, fibroblast activation, anti-inflammatory and immune regulation, in order to provide new ideas for the prevention and treatment of fibrosis.

[**Key words**]　adipose-derived stem cell;fibrosis;treatment;mechanism

[J Nanjing Med Univ,2024,44(03):429-434]

纤维化是纤维结缔组织在组织器官内广泛沉积的动态过程,其特征为胶原蛋白等细胞外基质(extracellular matrix,ECM)的积累。机体在感染、炎症、自身免疫、退行性病变、肿瘤和损伤等各种触发因素下,启动一系列修复过程[1]。如果组织损伤严重或反复受损,修复过程会演变为进行性不可逆的纤维化反应,成纤维细胞持续激活,ECM过度合成,导致器官组织被结缔组织所取代,功能丧失[2]。肝硬化、肺纤维化、肾间质纤维化、心肌梗死、系统性硬化症、移植物抗宿主病等各种疾病的纤维化重塑可损害器官功能,甚至导致器官衰竭,严重威胁人类生命健康[3]。因此,探寻纤维化的发生机制和抗纤维化的有效治疗方法一直受到关注。

脂肪间充质干细胞(adipose-derived stem cell,ADSC)是一种来源于脂肪组织、具有自我更新及多向分化能力,在体外和体内均具有抗炎、抗凋亡、调节免疫、促进再生等特点的间充质干细胞(mesenchymal stem cell,MSC),在一系列纤维化疾病的治疗中均表现出巨大的潜力[4-8]。本文就近年来ADSC在纤维化疾病中的治疗作用和机制进行综述。

## 1　ADSC概述

ADSC是皮下脂肪组织通过酶促消化获得的、

[基金项目]　国家自然科学基金(82074351);江苏省中医院高峰学术人才项目(y2021rc10);江苏省研究生科研创新计划(KYCX22_1939,KYCX23_2121)

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具有增殖和分化能力的MSC。MSC最早在骨髓中发现，也存在于脐带、脂肪、羊膜、牙髓等多种组织器官[9]。2006年国际细胞治疗学会提出定义MSC的3项基本标准：①塑性黏附；②表达分化簇（cluster of differentiation，CD）73、CD90和CD105，不表达CD11b、CD14、CD19、CD45和人类白细胞抗原DR（human leukocyte antigen DR，HLA-DR）；③有成骨分化、成脂分化和成软骨分化的潜能[10]。MSC分泌多种趋化因子、细胞因子和ECM蛋白，参与多种生物学过程，包括造血、血管生成、白细胞运输、免疫和炎症反应。基于MSC的免疫调节作用及低免疫原性，无需免疫抑制即可进行同种异体移植，其在组织工程和再生医学研究领域受到广泛关注。而脂肪相比胎盘、羊膜、骨髓等组织来源更丰富，便于提取，易于获得较多细胞，且供体创伤小、可自体移植、安全性高，被认为是MSC临床应用的理想来源[11]。与最经典的骨髓来源的MSC相比，ADSC增殖能力更强，且在生物活性因子分泌方面更活跃，能分泌更多的血管内皮生长因子（vascular endothelial growth factor，VEGF）、肝细胞生长因子（hepatocyte growth factor，HGF）、神经生长因子（nerve growth factor，NGF）等，具有更好的促血管生成和再生修复能力[12-13]。

## 2 ADSC对组织纤维化的干预作用与机制

早期研究人员认为纤维化不可逆转，但近年来动物研究和临床试验均表明，纤维化是一个高度动态变化的过程。因此，探索纤维化的发生机制，寻求新型抗纤维化治疗手段具有重要意义。在瘙疮及烧伤瘢痕的临床研究中发现，皮内注射ADSC及其条件培养液（ADSC condition medium，ADSC-CM）可减轻瘢痕严重程度及瘢痕面积占比，改善患者的皮肤弹性[14-15]。慢性阻塞性肺炎患者肱静脉自体输注ADSC，炎症相关C反应蛋白（C-reactive protein，CRP）下降，气道纤维化重塑减轻，肺顺应性提高，肺功能有所改善[16]。一系列临床实验表明ADSC安全且疗效确切，其对组织纤维化的具体干预作用与机制涉及以下几个方面。

### 2.1 阻抑上皮-间充质转化（epithelial-mesenchymal transition，EMT）

EMT参与器官发育与伤口愈合，也是癌症和组织纤维化等疾病发展的重要环节。在EMT过程中，上皮细胞间连接丢失，细胞与基质失去相互作用，上皮标志物如E-钙黏蛋白（E-cadherin）、细胞角蛋白（cytokeratin）、紧密连接蛋白-1（zonula occludens protein-1，ZO-1）减少，进而表达N-钙黏蛋白（N-cadherin）、波形蛋白（vimentin）和α-平滑肌肌动蛋白（α-smooth muscle actin，α-SMA）等间充质标志物[17]。ADSC-CM可改善转化生长因子（transforming growth factor，TGF）-β所致的上皮标志物E-cadherin、ZO-1表达减少，下调N-cadherin[18]，并有效抑制香烟烟雾提取物诱导的人肺上皮细胞死亡，减轻肺纤维化。ADSC还分泌包含微小RNA（microRNA，miR）、长链非编码RNA（long non-coding RNA，lncRNA）的外泌体（exosome，Exo），通过细胞间的物质交换参与调节纤维化进程。在小鼠子宫内膜纤维化模型中，宫腔内注射ADSC-Exo，其包含的lncRNA-MIAT与子宫内膜上皮细胞中的miR-150-5p结合，抑制α-SMA表达，缓解纤维化。此外，在体外角膜上皮重建中，ADSC可以通过间充质-上皮转化（mesenchymal-epithelial transition，MET）衍生出上皮祖细胞[19]。在完全膀胱切除术后植入含ADSC的去细胞化膀胱基质，能够在小鼠体内诱导内源性尿路上皮细胞再生[20]。这些研究表明，ADSC可通过转分化及旁分泌作用，抑制甚至逆转EMT，促进组织器官原有结构和功能的恢复。然而，在肿瘤微环境中，ADSC可能促进癌细胞EMT，参与肿瘤细胞的迁移和侵袭[21]，对癌症患者的治疗安全性还有待探究。

### 2.2 抑制成纤维细胞活化

在慢性炎症或反复组织损伤的环境中，成纤维细胞对ECM合成、降解、重塑的调节失衡，活化为产生ECM的肌成纤维细胞[2]。肌成纤维细胞在纤维化疾病中起重要致病作用，众多抗纤维化研究均通过靶向抑制成纤维细胞活化来发挥效应。TGF-β1是成纤维细胞活化为肌成纤维细胞的关键介质[22]。研究发现，大鼠静脉注射ADSC可降低受损肝脏、肾脏或生殖器海绵体组织中的TGF-β1以及Ⅰ型胶原的表达[23-25]。在人瘢痕疙瘩组织的离体培养中也发现，ADSC-CM抑制TGF-β/Smad及p38丝裂原活化蛋白激酶（p38 mitogen-activated protein kinase，p38 MAPK）信号转导通路，减少成纤维细胞活化，改善胶原沉积[26-28]。ADSC-Exo中的miR-192-5p可直接靶向成纤维细胞中的白介素-17受体A（interleukin-17 receptor A，IL-17RA），通过抑制其下游Smad通路磷酸化，抑制成纤维细胞活化[29]。同时，ADSC-CM还通过环氧合酶-2/前列腺素E2（cyclooxygenase-2/prostaglandin E2，COX-2/PGE2）级联反应，抑制活化

的瘢痕成纤维细胞增殖并促使其凋亡[30]。口腔黏膜纤维化的研究中也发现,过表达ADSC-Exo中miR-375可增强对纤维化颊黏膜成纤维细胞中转录因子活性的抑制,促进细胞凋亡以抑制纤维化进程[31]。ADSC对成纤维细胞存在双向调节作用。在伤口愈合早期,ADSC会促进成纤维细胞的增殖迁移及胶原蛋白的合成,并分泌VEGF等促进血管形成以加速创面愈合[32-33],但在愈合后期或炎症、射线等促纤维化条件下,ADSC能阻止成纤维细胞分化为肌成纤维细胞,抑制肉芽组织形成,调节基质金属蛋白酶(matrix metalloproteinase,MMP)的表达[34-35],抑制胶原沉积[36-37],起到抗纤维化的作用。此外,ADSC升高肿瘤坏死因子α刺激基因-6(tumor necrosis factor α stimulated gene 6,TSG-6)水平,抑制肝星状细胞(hepatic stellate cell,HSC)活化的同时可促使其表达EPCAM、CD133等肝脏谱系标志物,诱导HSC向肝祖细胞转化。

### 2.3 参与抗炎及免疫调节

组织损伤和炎症是再生与纤维化的重要触发因素。随着各种不同类型的炎症细胞如巨噬细胞、T细胞、肥大细胞等的招募和激活,炎症反应被放大,进一步加速纤维化进程。因此,抑制炎症反应是抗纤维重塑,促进损伤后组织结构恢复的重要途径[38]。

#### 2.3.1 巨噬细胞

目前研究认为,巨噬细胞M1型向M2型转化可以改善纤维化。M1型巨噬细胞促炎并产生TGF-β1、IL-1β等促纤维化介质,M2型分泌IL-10和精氨酸酶-1(arginase-1,Arg-1)等促进炎症消退[39-41]。ADSC可通过调节巨噬细胞激活状态,促进巨噬细胞M1型向M2型转化,对抗纤维化相关组织损伤,这在梗死后心肌重塑研究中已有报道[42]。一项人类皮肤光老化的前瞻性研究中发现,ADSC可增加M2型巨噬细胞数量,抑制炎症[43],且这种调节作用在肥胖个体中更加显著。通过抑制Toll样受体4(toll-like receptor 4,TLR4)及其下游信号转导,降低核因子-κB(nuclear factor kappa-B,NF-κB)的DNA结合活性,ADSC抑制M1型相关促炎分子,如细胞因子TNF-α、NO的合成[44]。另有研究比较了脂肪与骨髓来源的MSC对腹膜透析诱导的腹膜纤维化的治疗作用,发现ADSC促M2型巨噬细胞极化作用更显著而具有更好的治疗效果,这基于ADSC在TGF-β1刺激下分泌更多的IL-6[45]。这种MSC来源的IL-6在促调节组织稳态的同时,提高组织的修复活性,促进去分化及再生[46]。此外,ADSC在体内的长期免疫调节作用与巨噬细胞的吞噬清除功能相关,巨噬细胞摄入凋亡的ADSC后产生抗炎介质,而巨噬细胞耗竭和IL-6阻断均抑制ADSC的治疗效果[47]。

#### 2.3.2 T细胞

先天性免疫和获得性免疫都参与了纤维化的形成,调节性T细胞(regulatory T cell,Treg)参与免疫稳态的调节,一般认为Treg抑制纤维化的发生;Th1细胞产生干扰素(interferon,IFN)-γ抑制成纤维细胞诱导的胶原蛋白合成并减轻纤维化,也被认为在很大程度上起着抗纤维化作用[48],而其他表型Th17型与Th2型细胞多被认为对纤维化有促进作用[49]。因此,T细胞的表型转化与平衡也是ADSC抗纤维化的潜在机制。在博莱霉素诱导的小鼠肺损伤模型中,尾静脉注射ADSC可以抑制小鼠Th2型$CD4^+$ T细胞的分化和增殖,促进Treg细胞的分化和增殖,减少肺纤维化面积,改善预后[50]。通过体外共培养人ADSC与外周血单核细胞发现,ADSC通过程序性死亡受体-1(programmed cell death protein 1,PD-1)和T细胞免疫球蛋白黏蛋白-3(T cell immunoglobulin domain and mucin domain-3,TIM-3)途径抑制T细胞中的NF-κB活化,剂量依赖性调节Th1/Th2/Treg细胞亚群转化,起到免疫抑制作用[51-52]。除细胞间接触外,ADSC还通过分泌PGE2、IDO等因子[53],介导哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin,mTOR)抑制,或通过线粒体转移上调下游FoxP3、CTLA4、GITR等mRNA水平,诱导Treg细胞分化,促进Th17/Treg间平衡的恢复[54]。此外,在克罗恩病肛瘘的临床试验中发现ADSC在调节T细胞的同时不增加感染风险,优于免疫抑制剂[55],为炎症相关纤维化的治疗提供了新的思路。

#### 2.3.3 肥大细胞(mast cell,MC)

随着研究深入,MC也被证实与纤维化的发生有关[56]。特发性肺纤维化患者活检标本中,MC数量与纤维化病灶之间呈显著正相关,与患者肺功能呈负相关,因此被视为潜在的治疗靶点[55]。一项关于皮肤瘢痕的临床试验也证实,MC数量与人体皮肤瘢痕形成情况呈正相关[57],阻断MC脱颗粒,可减小瘢痕大小,改善伤口组织的胶原结构及密度。作为皮肤中的免疫哨兵,MC对各种病理和环境刺激的反应与Toll样受体等多个分子通路及其他免疫细胞相关。间质性膀胱炎大鼠黏膜下层注射ADSC,可

下调TNF-α、IFN-γ、MCP、IL-6、TLR2和TLR11等炎症因子水平，抑制MC浸润和上皮细胞凋亡，促进受损膀胱再生[58]。皮下注射ADSC诱导Th17细胞下调IL-17分泌，减少小鼠皮肤中MC浸润，改善炎症反应[59-60]。此外，ADSC还通过COX2依赖性机制抑制B细胞IgE的释放，减少MC富集和激活，并通过上调前列腺素相关受体，减少IgE受体表达，抑制IκB-α降解以降低MC中的NF-κB活性，抑制MC活化[61]。

## 4 结 语

ADSC来源丰富，易于获取，分泌多种细胞因子，参与免疫调节和组织再生，在多项临床试验中显示出治疗优势，在纤维化相关疾病中也具有临床应用前景，已被证实可通过阻抑EMT、抑制成纤维细胞活化、调节免疫等多个途径治疗纤维化。同时，以ADSC-Exo为载体，构建靶向递送系统，也为纤维化疾病的治疗提供了新的方向。然而，ADSC可能促进肿瘤的进展和转移，其是否适合肿瘤微环境下的移植治疗仍然值得讨论。此外，ADSC促血管生成在不同纤维化环境下的影响尚有争议，ADSC抗纤维化作用的时间依赖性及作用间的串扰等也有待进一步探索。

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[收稿日期] 2023-07-19

(本文编辑:陈汐敏)