

间充质干细胞促进肿瘤发生发展的机制研究进展

邵佳康^{1,2}, 李智¹, 刘浩林¹, 秦博宇², 刘茗露², 杨子仲³, 赵卫红², 焦顺昌²

¹解放军医学院, 北京 100853; ²解放军总医院第一医学中心 肿瘤内科, 北京 100853; ³南开大学医学院, 天津 300071

摘要: 间充质干细胞 (mesenchymal stem cells, MSCs) 是一类起源于中胚层的成体干细胞, 因具有良好的增殖能力、低免疫原性、靶向归巢肿瘤等特性, 且易于体外分离培养和基因修饰改造, 已成为肿瘤生物学研究的热点。研究表明 MSCs 具有促进肿瘤生长、增殖、转移和介导化疗耐药等作用, 可以考虑作为抗肿瘤治疗的靶点。本文综述了 MSCs 促进肿瘤发生发展的相关机制, 为寻找潜在的治疗靶点提供参考依据。

关键词: 间充质干细胞; 肿瘤生物学; 抗肿瘤治疗; 肿瘤免疫; 肿瘤标志物

中图分类号: R 730.2 **文献标志码:** A **文章编号:** 2095-5227(2021)03-0358-05 **DOI:** 10.3969/j.issn.2095-5227.2021.03.024

网络出版时间: 2021-03-23 17:11

网络出版地址: <https://kns.cnki.net/kcms/detail/10.1117.R.20210322.0931.004.html>

引用本文: 邵佳康, 李智, 刘浩林, 等. 间充质干细胞促进肿瘤发生发展的机制研究进展 [J]. 解放军医学院学报, 2021, 42 (3): 358-362.

Research advances in mechanisms of mesenchymal stem cells promoting tumor progression

SHAO Jiakang^{1,2}, LI Zhi¹, LIU Haolin¹, QIN Boyu², LIU Minglu², YANG Zizhong³, ZHAO Weihong², JIAO Shunchang²

¹Medical School of Chinese PLA, Beijing 100853, China; ²Department of Oncology, the First Medical Centre, Chinese PLA General Hospital, Beijing 100853, China; ³Medical College of Nankai University, Tianjin 300071, China

Corresponding authors: ZHAO Weihong. Email: zhaowh0818@163.com; JIAO Shunchang. Email: jiaosc@vip.sina.com

Abstract: Mesenchymal stem cells (MSCs) are a kind of adult stem cells originated from mesoderm, which have become a hot spot in tumor biology research because of their characteristics such as excellent proliferative ability, low immunogenicity, homing to the targeted cancerous tissues, etc. Besides, they are easy to be isolated, cultured in vitro and genetically modified. Studies have shown MSCs can promote tumor growth, proliferation, metastasis and mediate chemoresistance, thus they can be considered as a target for anti-tumor therapy. In this paper, the relevant roles of MSCs in promoting tumorigenesis and progression are reviewed to provide references and evidences for the benefit of looking for potential therapeutic targets.

Keywords: mesenchymal stem cell; tumor biology; anti-tumor therapy; tumor immunity; tumor marker

Cited as: Shao JK, Li ZH, Liu HL, et al. Research advances in mechanisms of mesenchymal stem cells promoting tumor progression [J]. Acad J Chin PLA Med Sch, 2021, 42 (3): 358-362.

肿瘤细胞与胞外基质, 包括间充质干细胞 (mesenchymal stem cells, MSCs)、内皮细胞、周细胞、免疫细胞和成纤维样细胞, 构建了一个复杂的细胞生存微环境, 即肿瘤微环境 (tumor micro-environment, TME)^[1]。目前多项研究证实 MSCs 可向肿瘤部位迁移, 促进肿瘤基质形成, 而 MSCs 与肿瘤细胞、肿瘤干细胞亦可在 TME 中通过多种方式相互作用促进肿瘤生长与转移^[2]。本文总结了 MSCs 促进肿瘤发生发展的 6 个相关机

制, 为寻找潜在的治疗靶点、优化现有的抗癌策略提供参考。

1 MSCs 与上皮-间充质转换

上皮-间充质转化 (epithelial-mesenchymal transition, EMT) 的特点是下调上皮细胞相关蛋白的表达, 包括 E-钙黏蛋白、 γ -连环蛋白、斑珠蛋白、紧密连接蛋白; 上调间叶细胞相关蛋白的表达, 包括 N-钙黏蛋白、波形蛋白、纤维连接蛋白和平滑肌肌动蛋白 (smooth muscle actin, SMA)^[3]。在此过程中, 肿瘤组织的上皮细胞层因丧失上皮表型而失去表皮-基底极性后向间质细胞表型转变, 致胞间黏附力降低而细胞运动与迁移能力增强, 历经基质重塑等过程致癌细胞的扩散和侵袭能力增强^[4]。故 EMT 是癌细胞获得侵袭性表型并导致肿瘤转移的重要过程。

在许多肿瘤中, MSCs 分泌的肝细胞生长因

收稿日期: 2020-11-26

基金项目: 国家自然科学基金 (81972681)

Supported by the National Natural Science Foundation of China (81972681)

作者简介: 邵佳康, 男, 硕士, 医师。研究方向: 肿瘤与干细胞。

Email: sjk2622893631@sina.com

通信作者: 赵卫红, 女, 博士, 主任医师, 教授, 硕士生导师。

Email: zhaowh0818@163.com; 焦顺昌, 男, 博士, 主任医师, 教授, 博士生导师, 博士后导师。Email: jiaosc@vip.sina.com

子 (hepatocyte growth factor, HGF)、表皮细胞生长因子 (epidermal growth factor, EGF)、血小板源生长因子 (platelet derived growth factor, PDGF) 和转化生长因子- β (transforming growth factor- β , TGF- β) 等可作为 EMT 的诱导信号, 通过激活一系列促进 EMT 进程的转录因子, 如 Snail、Slug 和 TWIST 等, 调控肿瘤生长、转移及耐药过程^[5]。如 MSCs 可通过传递 gremlin1 诱导食管癌细胞中 EMT 的发生, 并由 TGF- β /骨形态发生蛋白 (bone morphogenetic protein, BMP) 轴调控增强了癌细胞的增殖和侵袭能力^[6]。而 MSCs 分泌的 IL-6、IL-15、 β 2-微球蛋白与 MSCs 表面的整合素- α 5 可分别在 EMT 介导下促进肺癌、胃癌、食管鳞癌和肝癌的生长与转移^[7-10]。

文献报道 MSCs 产生的外泌体也可通过 EMT 途径提高肿瘤的侵袭性。如 MSCs 产生的成纤维细胞生长因子-19 (fibroblast growth factor-19, FGF-19) 外泌体可激活细胞外调节蛋白激酶 (extracellular regulated protein kinases, ERK) 信号通路触发 EMT, 促进鼻咽癌生长和转移^[11]。而最新研究表明 MSCs 产生的外泌体还可以通过自噬方式促进骨肉瘤转移^[12]。此外, MSCs 可与多种肿瘤细胞融合形成杂合体细胞, 并由 EMT 调控诱导新生物学特性的产生, 如恶性程度的增加、侵袭性能的增强和多能耐药性的产生等。相关研究发现 MSCs 与肺癌细胞融合后可使癌细胞获得干细胞的某些特征, 并通过 EMT 机制促进肿瘤生长与转移^[13]。类似现象还在胃癌、肝癌、乳腺癌中得到证实^[14-16]。因此, 阻断肿瘤实质中发生的 EMT 过程, 也许可控制多种肿瘤的生长及转移。

2 介导免疫抑制

MSCs 具有很强的免疫抑制特性, 故可支持肿瘤细胞逃避抗癌免疫攻击而参与肿瘤发生发展过程。有文献报道 MSCs 主要通过分泌细胞因子如 IL-1 α 、IL-4、IL-6、TGF- β 、HGF、HLA-G、IFN- γ 、肿瘤坏死因子- α (tumor necrosis factor, TNF- α) 和吲哚胺 2,3-双加氧酶 (indoleamine 2,3-dioxygenase, IDO) 等, 以及与各类免疫细胞间的相互作用, 包括 T 细胞、B 细胞、树突状细胞 (dendritic cells, DC)、巨噬细胞和 NK 细胞等, 介导 TME 中广泛的免疫抑制过程^[17]。在肿瘤形成的起始过程中, MSCs 可协助肿瘤相关巨噬细胞 (tumor-associated macrophages, TAMs) 发挥重要功能, 而 TAMs 由可杀死病原体的 M1 型细胞和诱导血管生成、组织重塑及介导免疫抑制的 M2 型细胞组成, 后者可通

过分泌 EGF、PDGF、TGF- β 、IL-4、IL-13、血管内皮生长因子 (vascular endothelial growth factor, VEGF) 等促进肿瘤生长^[5,18-19]。目前有观点认为, TAMs 可分为 3 个亚型, 在 TME 中发挥不同作用, 促进肿瘤生长与转移; 其中循环 TAMs 可与癌细胞共同迁移, 促进基质重塑、癌细胞侵袭和局部免疫抑制微环境的形成^[19]。

有研究还证实 MSCs 可诱导 CD4 型 T 细胞由 Th1 向 Th2 转变, 导致 IFN- γ 分泌减少而 IL-4 分泌增多, 抑制了抗癌免疫细胞的激活^[20]。而乳腺癌源 MSCs 除分泌 TGF- β 外, 亦可通过 CCL2 信号通路募集髓源性抑制细胞共同发挥免疫抑制作用^[21]。在促炎的瘤内环境中, 高水平的 IFN- γ 可使 MSCs 的细胞程序性死亡配体-1 (programmed cell death 1 ligand 1, PD-L1) 表达增加以抑制 T 细胞活化^[22]。还有研究表明 MSCs 通过分泌可溶性 PD-L1/PD-L2 介导类似的免疫抑制过程^[23]。值得一提的是, MSCs 分泌的 IL-15 可诱导 T 细胞中程序性死亡受体-1 (programmed cell death protein-1, PD-1) 表达上调发挥免疫抑制功能, 为免疫治疗提供了可能^[8]。此外, 有研究证实, 在常氧和低氧条件下 MSCs 均因表达细胞毒性 T 淋巴细胞相关蛋白 4 (cytotoxic T-lymphocyte-associated protein 4, CTLA4) 发挥免疫抑制功能^[24]。除抑制效应 T 细胞增殖外, MSCs 分泌的 HLA-G 和 IDO 还可抑制 DC 成熟、NK 细胞活化与 B 细胞增殖, 广泛参与了抗癌免疫抑制过程^[5,25]。因此, 巧妙利用 MSCs 的免疫抑制作用, 合理联合其他免疫疗法, 也许会取得令人鼓舞的抗癌效果。

3 MSCs 向癌相关成纤维细胞的转化

与一般成纤维细胞不同, 癌相关成纤维细胞 (cancer associated fibroblasts, CAFs) 高表达促肿瘤生长因子、促血管生成因子和肌成纤维细胞特征性分子。有研究指出, CAFs 在 TME 中具有类似基质合成细胞、基质降解细胞、肌成纤维细胞、血管形成细胞等的功能, 可能对肿瘤的形成具有生物学意义^[1]。此外, 除提供促肿瘤形成的结构与功能支持环境外, 有学者认为 CAFs 还与诱导干细胞壁龛形成、介导免疫抑制、促进肿瘤转移和调控化疗药物耐受等过程相关^[1,26]。在肿瘤组织中, CAFs 调控基质的合成和降解稳态遭到破坏, 导致血管形成异常及胶原纤维过度累积, 为肿瘤的发生发展创造了良好条件^[26]。

目前文献报道 CAFs 来源于循环中招募的 MSCs、成纤维细胞、组织中的原始干细胞及肿瘤

实质中发生的 EMT。且多项研究表明 MSCs 可分化为 CAFs 并促进了肿瘤形成与转移^[26-27]。一项有关结直肠癌的研究证实, CXCR4/TGF- β 1 轴可介导 MSCs 向 CAFs 的分化, 在此过程中 MSCs 分泌的基质细胞衍生因子-1(stromal cell derived factor-1, SDF-1) 及 CAFs 标志物表达明显上调^[28]。后续研究表明 TGF- β 1 是通过激活 JAK/STAT3 信号通路促进了结直肠癌的肝转移^[29-30]。而 Arena 等^[31]表明, 肺癌中的 MSCs 也可分化为 CAFs 并高表达 α -SMA 和多种细胞因子, 如 TGF- β 1、IL-6、TNF- α 、VEGF 和低氧诱导因子-1(hypoxia inducible factor, HIF-1), 协同促进肺癌生长。此外, 骨桥蛋白可通过 MZF1/TGF- β 1 通路诱导 MSCs 向 CAFs 的分化并促进乳腺癌生长与转移^[32]。因此, 若能有效阻断 MSCs 向 CAFs 的转化, 可从多个方面抑制肿瘤生长。

4 介导对抗癌药物的耐受

癌细胞对抗癌药物的耐受不仅涉及基因突变和多耐药蛋白介导的内在耐药机制, 还与 TME 中由 MSCs 调控的外在耐药机制有关。如 MSCs 与髓系白血病细胞密切接触后, 可在整合素- α 4 的介导下激活 ABC 转运体促进药物外排, 进而诱导癌细胞对化疗药物的耐受^[33]。而在慢性淋巴细胞白血病中, MSCs 通过下调 B 细胞表面受体 CD20 的表达降低了对利妥昔单抗的敏感度^[34]。此外, MSCs 与乳腺癌细胞间的物理接触可激活非受体酪氨酸激酶 c-Src 及下调抑癌基因 PTEN 的表达, 并由 PI3K/AKT 通路介导了对曲妥珠单抗的耐药^[35]。而卵巢癌细胞分泌的 Hedgehog(HH) 可诱导 MSCs 中 BMP4 的高表达, 并形成 BMP4/HH 正反馈信号通路, 促进卵巢癌细胞化疗耐药性的产生^[36]。有研究表明 MSCs 分泌的 IL-6 还可诱导癌细胞中 Bcl-2 和 Bcl-XL 的表达, 进而抑制化疗所致的细胞凋亡过程, 与多种化疗耐药的产生有关^[37]。

早前一项研究表明, 暴露于顺铂中的 MSCs 产生的多不饱和脂肪酸具有抵抗化疗所致细胞毒性作用, 而阻断环氧合酶-1 和血栓素合成酶可有效抑制相关耐药性的产生^[38]。值得一提的是, 该研究还发现非肿瘤部位的 MSCs 也能诱导对化疗药物的耐受, 表明 MSCs 本身可能具有对抗化疗药物治疗的作用^[38]。MSCs 还可通过分泌 TGF- β 1 激活 SMAD2/3 通路而诱导胃癌细胞中链非编码 RNA(lncRNA MACC1-AS1) 的表达, 并通过拮抗 miR-145-5p 的功能而促进胃癌细胞脂肪酸氧化依赖途径耐药性的产生^[39]。MSCs 亦可通过分泌

PDGF-c、HGF、NO 和 IL-17a 调节癌细胞对化疗药物的敏感度, 在介导化疗耐药中发挥重要作用^[40]。因此, 以 MSCs 为靶点阻断耐药相关通路, 或许可有效改善多种肿瘤治疗的耐药难题。

5 促进肿瘤血管形成

MSCs 可分化为内皮样细胞或周细胞, 并通过分泌多种促血管生成因子、生长因子、细胞因子和纤溶酶原激活物等, 促进肿瘤血管的形成^[5]。在一项结直肠癌研究模型中, MSCs 分泌的 IL-6 和血管生成素-1 可诱导癌细胞产生内皮素-1, 并通过激活内皮细胞中的 AKT/ERK 信号通路促进肿瘤血管的生成^[41]。而 MSCs 产生的外泌体也可刺激癌细胞分泌 VEGF, 通过激活 ERK1/2 信号通路诱导肿瘤血管的形成^[42]。此外, 有研究证实甲状腺激素可调控 MSCs 与内皮细胞上的整合素 $\alpha\beta$ 3, 通过启动非经典信号通路诱导了新生血管形成、刺激肿瘤生长^[43]。目前, 肿瘤血管形成的新途径——“血管模拟”(vascular mimicry, VM) 方式正成为研究热点。其具体指肿瘤不依赖于典型的血管生成模式, 而是通过创造自身的流体运输通道为肿瘤生长输送营养物质^[44-45]。Vartanian 等^[45]已证实, 黑色素瘤细胞能通过 VM 方式在 VEGF-A 调控下增强 MSCs 的促血管生成潜能, 进而促进黑色素瘤的生长与转移。因此, 通过抑制 MSCs 生长以阻碍肿瘤组织中的血管生成过程, 也许会发挥类似抗血管类药物的作用。

6 介导肿瘤细胞的“永生性”

癌症的标志性特征之一即拥有持续的增殖能力, 而这种复制永生的能力与癌基因激活、抑癌基因失活以及端粒功能障碍等有关。有研究发现大鼠 MSCs 可在体外发生自发转化, 而转化后的 MSCs 含有高水平的 p53 突变体并呈现肿瘤干细胞样特征, 同时伴存活相关基因表达显著上调, 其可能与抑癌基因 p16 介导的表观遗传沉默有关^[46]。Jeon 等^[47]的研究表明, 内源性非端粒酶 RTA 可能是 MSCs 与癌细胞间潜在的生物学标志物及调节因子, 通过与癌细胞共享自我更新和增殖的生物分子标志物, MSCs 可能以“组织驻留干细胞”的身份在肿瘤进展中发挥着重要作用。此外, 肿瘤的进展过程中伴随着营养物质缺乏和炎症状态, 该条件下 MSCs 以自噬方式存活并释放多种抗凋亡及促存活因子, 如 VEGF、FGF-2、PDGF、HGF、SDF-1 α 和 TGF- β 等, 促进肿瘤细胞存活而抑制其凋亡^[5]。因此, 以 MSCs 为靶点间接抑制肿瘤细胞的“永生性”过程, 也许可为抗癌治疗提供更多选择。

7 结语

本文综述了 MSCs 在肿瘤发生发展中的多种作用, 这些作用通过相互影响、混合调节的方式促进了肿瘤形成与转移。更好地理解这些分子机制将为目前的抗癌治疗提供更多选择。如利用 MSCs 本身固有的“归巢”特性, 可将化疗药物精准运送至肿瘤部位进行治疗; 经基因修饰改造的 MSCs 可制成各类肿瘤疫苗, 在癌症的基因治疗领域具有一定潜能。此外, 随着对 MSCs 促进肿瘤发生发展机制的进一步理解, 通过免疫治疗等方式靶向清除肿瘤部位的 MSCs 以抑制肿瘤形成与转移也值得探索。

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