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工程化间充质干细胞抗肿瘤研究进展*

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摘要 间充质干细胞(mesenchymal stem cells, MSCs)是一类来源广泛的成体多能干细胞,因其具有低免疫原性、易向受损组织归巢、有旁分泌效应与免疫调节能力以及易于工程化操作等特点,在肿瘤治疗中具有一定优势。尽管目前在肿瘤治疗中应用 MSCs 存在争议,但已观察到过表达抗肿瘤基因(自杀基因、肿瘤坏死因子、白介素和干扰素等)或荷载溶瘤病毒、纳米颗粒、抗癌药物等经工程化改造和修饰的 MSCs 及其胞外囊泡能主动归巢到肿瘤组织,发挥抗肿瘤作用。目前已有工程化 MSCs 应用于复发性多形性胶质母细胞瘤的临床研究。因而概述 MSCs 特性以及工程化 MSCs 靶向肿瘤细胞和/或微环境的治疗研究,以期为 MSCs 临床转化及肿瘤治疗拓展新视野。

关键词 间充质干细胞 肿瘤治疗 工程化修饰 胞外囊泡

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恶性肿瘤是健康细胞在遗传或环境因素影响下发生基因突变,从而获得不受控增殖迁移侵袭、凋亡障碍与代谢异常等不良生物学特性的疾病,是严重危害人民群众健康和生命的主要杀手[1]。放疗、化疗、手术治疗以及近年新兴的针对肿瘤特异性分子靶向设计或调动自身免疫功能的生物疗法是临床上常见的肿瘤治疗手段,然而患者 5 年生存率仍不乐观[2]。因此,急需探索新型肿瘤治疗策略。

间充质干细胞(mesenchymal stem cells, MSCs)作为一类具有组织修复和免疫调节能力的成体干细胞,兼有免疫原性低、向病变组织归巢及易于工程化操作等优势。已有研究表明,荷载内外源性分子、药物或核酸等的工程化 MSCs 主动靶向病灶细胞或组织,发挥抗肿瘤作用,现将工程化 MSCs 靶向肿瘤细胞和/或微环境的优势及其主要应用研究进行概述。

1 MSCs 的定义

MSCs 来源广泛,分布于几乎所有人体组织[3]。但 MSCs 是一类异质细胞群,目前缺乏特异性分子标志物[4-6]。2006 年,国际细胞治疗协会(International Society for Celluar Therapy, ISCT)[7]提出体外培养扩增人 MSCs 的最低标准为:(1)在标准培养体系中具有贴壁特性,能形成成纤维细胞集落形成单位(colony forming unit-fibroblast, CFU-F);(2)表达表面抗原分化簇 105(cluster of differentiation 105, CD105)、CD73、CD90,其阳性细胞≥95%,不表达 CD45、CD34、CD14 或 CD11b、CD79α 或 CD19 和人类白细胞 DR 抗原(human leukocyte antigen DR, HLA-DR)膜表面分子,其阳性细胞≤2%;(3)具有分化为成骨、成软骨和成脂肪样细胞的潜能。

然而上述特点主要来自体外 MSCs 的研究结果,对体内 MSCs 的特点尚不十分清晰[8]。已有研究表明,MSCs 的细胞形态、表面抗原和分化潜能等生物学特性会随着体外培养时间延长而发生变化,且不同组织来源的 MSCs 在共有生物学特征中存在一定差异[4]。例如,脂肪组织来源 MSCs 具有更强成脂能力[9]。因此,

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临床研究使用的 MSCs 应经过更严格的生产工艺、质量控制和管理体系来保障细胞质量。

2　MSCs 在肿瘤治疗方面的潜在优势

2.1　低免疫原性

MSCs 免疫原性低,体外培养扩增的 MSCs 通常表达低水平的主要组织相容性复合体Ⅰ(major histocompatibility complex class Ⅰ,MHCⅠ)类分子,几乎不表达主要组织相容性复合体Ⅱ(major histocompatibility complex class Ⅱ,MHCⅡ)类分子及协同刺激分子(B7-1、B7-2 或 CD40 等)[10-11]。这提示 MSCs 可在同种异体间移植。

2.2　归巢特性

MSCs 在细胞因子、趋化因子等生物活性分子的作用下,通过配体-受体结合方式向受损组织归巢[12]。例如,肿瘤坏死因子α(tumor necrosis factor-α,TNF-α)、白介素-1β(interleukin-1β,IL-1β)和γ干扰素(interferon-γ,IFN-γ)等促炎因子能上调 MSCs 中黏附蛋白的表达;缺氧常导致肿瘤组织高表达缺氧诱导因子(hypoxia inducible factor,HIF),而 HIF 信号通路可通过增加肿瘤自身细胞因子、趋化因子和黏附蛋白的表达,如表皮细胞生长因子(epidermal growth factor,EGF)、血管内皮生长因子 A(vascular endothelial growth factor A,VEGF-A)、血小板衍生生长因子(platelet derived growth factor,PDGF)、成纤维细胞生长因子(fibroblast growth factor,FGF)、粒细胞集落刺激因子(granulocyte colony-stimulating factor,GCSF)、粒细胞巨噬细胞集落刺激因子(granulocyte-macrophage colony-stimulating factor,GM-CSF)、肝细胞生长因子(hepatocyte growth factor,HGF)、转化生长因子β1(transforming growth factor-β1,TGF-β1)、CXC 趋化因子配体 7 型[chemokine(C-X-C motif) ligand 7,CXCL7]、CXCL6、CXCL5、CXCL8、单核细胞趋化蛋白 1(monocyte chemoattractant protein-1,MCP-1/CCL2)、白介素-6(interleukin-6,IL-6)等来招募 MSC 归巢;表达 CXC 趋化因子受体 4 型[chemokine(C-X-C motif) receptor 4,CXCR4]的 MSCs 向着有高浓度基质细胞衍生因子-1(stromal-derived factor-1,SDF-1/CXCL12)的肿瘤部位迁移积聚。因此,可以通过 MSCs 靶向肿瘤组织的归巢能力,避免放疗、化疗对机体正常组织的损伤。

2.3　旁分泌与免疫调节能力

MSCs 主要通过分泌生物活性物质或携带某些信号分子(如蛋白质或 miRNA)的细胞外囊泡(extracellular vesicles,EVs)[13]发挥组织修复和免疫调节作用。MSCs 通过分泌 HGF、TGF-β、吲哚胺 2,3-双加氧酶(indoleamine 2,3-dioxygenase,IDO)、一氧化氮(nitric oxide,NO)、血红素氧合酶 1(heme oxygenase 1,HO-1)、前列腺素 E2(prostaglandin E2,PGE2)、人类白细胞抗原 G5(human leukocyte antigen-G5,HLA-G5)、半乳糖凝集素 1(lectin galactoside-binding soluble 1,Galectin-1)、信号素 3A(semaphorin-3A,Sema-3A)和 Galectin-9 等可溶性因子来抑制效应性 T 淋巴细胞、B 淋巴细胞、自然杀伤细胞、树突状细胞及单核/巨噬细胞的增殖、成熟、分化和分泌,而对调节性 T 细胞(regulatory cells,Tregs)、调节性 B 细胞(regulatory B cell,Breg)有促增殖作用[14-18]。另外,MSCs 分泌的细胞外囊泡携载亲本细胞信息,发挥与 MSCs 相似的免疫调节作用。

正是因为 MSCs 强大的归巢和免疫调节能力使其支持造血和免疫重建,可有效辅助异基因造血干细胞成功植入,减轻或预防移植物抗宿主病(GVHD)发生,从而有助于延长患者生存期[19]。已有临床研究结果表明 MSCs 治疗 GVHD 安全有效,未观察到明显毒副作用,近 5 年发表的 MSCs 治疗异基因造血干细胞移植后 GVHD 的安全性和有效性等信息点见表 1。

表 1　MSCs 治疗异基因造血干细胞移植后 GVHD 的临床研究

Table 1　Clinical trials on mesenchymal stem cell therapy for GVHD after hematopoietic stem cell transplantation

细胞来源	疾病类型	移植方式	病例数	安全性和有效性	注册编号/文献
脐带 MSCs	急性 GVHD	外周血干细胞移植前 4~6 h 静脉输注(1×10^6/kg)	50	无输注细胞相关不良反应 单剂量 MSCs 能促进造血干细胞植入,减少急性 GVHD 的发病率,疾病复发率下降	ChiCTR-INR-16008399[20]
同种异体骨髓 MSCs	激素难治性慢性 GVHD	6~12 月内反复静脉输注(2×10^6/kg)	11	无输注细胞相关不良反应 6 名患者疾病进程和生活质量得到改善;CXCL9 和 CXCL10 可作为 MSCs 治疗的早期生物标志物	NCT01522716[21]

（续表 1）

细胞来源	疾病类型	移植方式	病例数	安全性和有效性	注册编号/文献
脐带 MSCs	激素难治性急性 GVHD	静脉注射低剂量（2×10^6/kg）或高剂量（10×10^6/kg）	10	半年内无输注细胞相关不良反应 低剂量组和高剂量组输注耐受性良好，未观察到异位组织形成，70% 患者的临床症状得到明显改善	NCT03158896[22]
同种异体骨髓 MSCs	急性 GVHD	脐带血移植前 4 h 经骨髓腔内注射（$\geqslant0.2\times10^6$/kg）5 mL	5	一年内无输注细胞相关不良反应 MSCs 能促进脐带血移植植活率，且 1 年内未见疾病复发	UMIN000024291[23]
同种异体骨髓来源 MSCs	激素难治性急性 GVHD	在使用二线药物的 7 天内，静脉注射（1×10^6/kg），每周一次，连续 4 周为一个周期	203	2 年内未观察到输注细胞相关不良反应 MSCs 联合巴利西单抗和钙调磷酸酶抑制剂可以增加激素耐药急性 GVHD 的疗效，减少抗排异药物毒性和 GVHD 复发风险，并且患者的耐受性良好	NCT02241018[24]
自体骨髓 MSCs	难治性急性或慢性 GVHD	静脉输注（2×10^6/kg），按照输注次数分为三组（单剂量、每周 2 次、每周 4 次）	11	3 个月内未观察到输注细胞相关不良反应，未观察到剂量限制性毒性 难治性急性 GVHD 组的病人缓解率较高	NCT02359929[25]
脐带 MSCs	激素耐药性急性 GVHD	静脉输注（1×10^6/kg 或 2×10^6/kg）	7	16 周内未观察到输注细胞相关不良反应 显著抑制 $CD4^+$ 和 $CD8^+$ T 细胞增殖，NK 细胞数明显增加，而 IL-12、IL-17 和 IL-33 水平下降，CCL2 和 CCL11 水平增加	UMIN000032819[26]
同种异体骨髓 MSCs	急性 GVHD	静脉输注（1×10^6/kg）	43	30 天内未观察到输注细胞相关不良反应 输注 MSCs 对异体造血干细胞移植后患者 T 细胞亚群的恢复有积极作用	NCT01941394[27]

然而，MSCs 的免疫调节作用及其在肿瘤微环境中转分化为肿瘤相关成纤维细胞，促进血管形成和耐药，参与肿瘤的发生发展[28-30]。研究表明，不同组织来源的 MSCs 治疗相同肿瘤的疗效不同，可能与 MSCs 移植时机、移植剂量等因素有关，见表 2。正因为未修饰 MSCs 在肿瘤治疗中的“两面性”和复杂性，人们逐渐将目光转移到工程化 MSCs，以期克服 MSCs 潜在的致瘤风险，提高其临床应用的安全性和有效性。

表 2 未修饰 MSCs 在肿瘤治疗中的两面性

Table 2 Double-sided nature of unmodified mesenchymal stem cells in tumor treatment

来源	肿瘤类型	结果	作用机制	参考文献
hBM-MSCs	乳腺癌	抑瘤	分泌细胞外囊泡诱导乳腺癌细胞在骨髓血管周围逐步分化为休眠状态	[31]
hAT-MSCs	乳腺癌	促瘤	吞噬 MSCs 的乳腺癌细胞使 MSR1（CD204）、WNT5A、ELMO1、IL1RL2（IL-36）、ZPLD1 和 SIRPB1（CD172）表达上调，促进癌症侵袭转移	[32]
hUC-MSCs	乳腺癌	促瘤	通过 ERK 途径增加 N-钙黏着蛋白表达，促进乳腺癌细胞的上皮-间质转化，从而提高肿瘤侵袭和迁移潜力	[33]
hCB-MSCs	肺癌	抑瘤	hCB-MSCs 与肺癌细胞自发融合上调 FOXF1 表达，进而诱导肺癌细胞重新编程为非致瘤性的干细胞样状态，逆转肺癌细胞表型以及恢复 p21 信号通路	[34]
hBM-MSCs	肺腺癌	促瘤	MSCs 可激活肿瘤细胞自噬、提高活性氧含量以及上皮-间质转化，从而增强肺腺癌的侵袭迁移	[35]
mBM-MSCs	黑色素瘤	抑瘤	构建黑色素瘤小鼠模型 24 h 后静脉注射 MSCs，可明显增强体内自 NK 细胞和 T 细胞的抗肿瘤能力，进而抑制肿瘤生长，改善实验动物的生存率	[36]
mBM-MSCs	黑色素瘤	促瘤	构建黑色素瘤小鼠模型 14 天后静脉注射 MSCs，可抑制肿瘤浸润性树突状细胞和巨噬细胞的抗原呈递特性，以及降低 NK 细胞和 T 细胞的杀瘤能力，进而促进肿瘤生长	[36]

Note：hBM-MSCs，Human bone marrow mesenchymal stem cells；hAT-MSCs，Human adipose tissue mesenchymal stem cells；hUC-MSCs，Human umbilical cord mesenchymal stem cells；hCB-MSCs，Human umbilical cord blood mesenchymal stem cells；mBM-MSCs，Mice bone marrow mesenchymal stem cells

3　工程化 MSCs 的抗肿瘤作用

MSCs 具有向受损组织归巢的特性,通过工程化改造手段,让 MSCs 携载治疗基因、药物或溶瘤病毒等“生物导弹”,靶向肿瘤细胞和/或肿瘤微环境以发挥精准治疗作用。且修饰后的 MSCs 可维持细胞表型、增殖能力及核型稳定[37-38]。目前,Oraee-Yazdani[39] 及其合作者已完成首个工程化 MSCs 治疗肿瘤的Ⅰ期临床研究(注册号 IRCT20200502047277N2),该研究采用定向瘤内注射携载单纯疱疹病毒胸苷激酶 HSV-TK 的异体脂肪 MSCs 治疗 12 名复发性多形性胶质母细胞瘤患者,结果表明治疗安全可行,未观察到明显副作用或治疗相关并发症,且肿瘤体积在治疗后 12 个月显著缩小,患者抗肿瘤的免疫细胞数量和细胞因子表达量显著上调。

3.1　过表达抗肿瘤基因

3.1.1　*自杀基因*　某些病毒或细菌基因编码的表达产物可催化无毒或毒性低的药物前体转变为细胞毒物质,若将这些基因转染进靶细胞,可诱导受体细胞死亡。因此,自杀基因又称为基因定向酶-前药系统。常见的自杀基因系统有胸苷激酶-更昔洛韦(thymidine kinase-ganciclovir,tk-GCV)、胞嘧啶脱氨酶-5-氟胞嘧啶(cytosine deaminase-5-flucytosine,CD-5-FC)等。研究人员通过构建自杀基因修饰的 MSCs,联合前体药物,可诱导细胞产生毒性代谢物,此时 MSCs 通过间隙连接、凋亡小体、自噬或旁分泌等方式将磷酸化毒性代谢物选择性靶向肿瘤,进一步抑制 DNA 聚合酶活性,并在局部发挥细胞毒作用,从而导致细胞死亡[37-38]。

3.1.2　*肿瘤坏死因子相关凋亡配体*　肿瘤坏死因子相关凋亡配体(tumor necrosis factor-alpha-related apoptosis-inducing ligand,TRAIL/CD253/TNFSF10)可结合肿瘤表面特异性死亡受体 4(death receptor 4,DR4)、DR5,进而诱导肿瘤凋亡。由 TRAIL 修饰的 MSCs 可定向趋化至原发性肿瘤及其转移瘤,从而提高癌症治疗效果[40]。

3.1.3　*白介素*　白介素可作为信号分子调控免疫细胞,在肿瘤发生和发展中发挥一定作用。例如,Bae 等[41]用慢病毒构建可过表达超级 IL-2 突变蛋白的小鼠骨髓 MSCs,该工程化 MSCs 利用天然归巢特性被招募至肿瘤间质,激活浸润的 $CD8^+$ T 细胞,从而引发抗肿瘤免疫以及克服免疫治疗的耐药性;用 IL-10 重组质粒转染的人骨髓 MSCs 通过降低 IL-6、TNF-α 水平以及抑制肿瘤微环境中血管生成,进一步下调胰腺癌细胞的增殖能力[42];携载 *IL-12* 基因的纳米复合物通过磁性转染进 MSCs 诱导乳腺癌细胞凋亡,并使小鼠机体产生长期免疫记忆,抑制肿瘤复发,延长生存期[43];经慢病毒转染 IL-15 的人脐带血来源 MSCs 可抑制胰腺癌负荷小鼠的肿瘤生长[44];经慢病毒转染 IL-18 的人脐带来源 MSCs 可刺激自然杀伤细胞(natural killer cell,NK 细胞)和 T 淋巴细胞以发挥抗乳腺癌作用[45];*IL-28* 基因转染的小鼠骨髓 MSCs 可通过信号转导及转录激活蛋白(signal transducer and activator of transcription,STAT)通路诱导前列腺癌细胞凋亡[46]。

3.1.4　*干扰素*　干扰素作为先天免疫细胞产生的活性物质,可用来调节免疫系统、对抗肿瘤。实验研究发现过表达 α 干扰素的 MSCs 可在肿瘤部位存活 2 周以上,激活自然杀伤细胞和 $CD8^+$ T 细胞发挥抗肿瘤作用[47]。Park 等[48]观察到过表达 β 干扰素的骨髓 MSCs 联合化疗药替莫唑胺治疗胶质瘤比单独用化疗药更好。

3.1.5　*肿瘤浸润免疫细胞激活*　通过改造 MSCs 携载能激活免疫细胞功能的关键抗体来重新启动并维持机体肿瘤-免疫循环以对抗肿瘤。例如,Yin 等[49]通过慢病毒转染方式构建能高表达 CXCL9 和肿瘤坏死因子超家族成员 4 配体(TNF superfamily member 4 ligand,OX40L)的小鼠脂肪来源 MSCs,并将其用于结肠癌小鼠的治疗中。实验结果发现该方法可增加肿瘤组织中 $CD8^+$ T 细胞和 NK 细胞浸润,并且肿瘤微环境中产生了大量抗肿瘤的细胞因子和其他生物活性蛋白。此外,它提高了程序性死亡受体 1(programmed cell death protein 1,PD-1)抗体治疗荷结肠癌小鼠的存活率,并显著抑制了主要组织相容性复合体Ⅰ类抗原缺陷肿瘤的生长。

3.2　荷载溶瘤病毒

溶瘤病毒是一类可自我复制的肿瘤杀伤型病毒,研究最深入的溶瘤病毒包括腺病毒和Ⅰ型单纯疱疹病毒。研究人员通过改造 MSCs 成为高效运输溶瘤病毒的工具细胞,提高肿瘤治疗的有效性和安全性。例如,Ho 等[50]构建可高表达 CXCR4 并且装载腺病毒的人骨髓 MSCs 用于肿瘤治疗,体内外实验结果表明,工程化 MSCs 可特异性靶向 p53 缺陷的结直肠癌细胞,且将前药曲他其卡(tretazicar,CB1954)转化为细胞毒性代谢物,如 4-羟胺和 2-胺,诱导肿瘤溶解和肿瘤生长抑制,而不会对宿主器官产生明显毒性作用。Yuan 等[51]构

建可递送腺病毒的人脐带 MSCs，且腺病毒装载着由人类端粒酶逆转录酶启动子控制的靶向程序性死亡配体 1 的双特异性 T 细胞吞噬因子，用该体系治疗肝癌小鼠模型，发现 T 细胞的浸润和活化明显增强，具有显著抗肿瘤效果。

3.3 携载纳米药物颗粒

单纯利用 MSCs 膜的肿瘤归巢特性，构建生物纳米材料用于肿瘤治疗[52]。第一类是膜包被治疗用纳米颗粒。例如，有研究通过转录反式激活因子（*trans*-activator of transcription，TAT）肽脂质偶联人脐带 MSCs 膜用于制作可包被二氧化锰的递送系统，该递送系统可在肺癌部位显著积聚，有效促进树突状细胞成熟，并将效应 T 细胞募集到肿瘤中以抑制肿瘤生长和转移[53]。第二类是修饰膜表面携载脂质体等治疗药物。例如，通过生物素-亲和素方式修饰小鼠 MSCs 表面，使其能携载阿霉素（doxorubicin，DOX）脂质体，从而高效靶向结肠癌细胞，抑制肿瘤生长[54]；或用 Cas9/sgRNA 的脂质体偶联人骨髓 MSCs 膜包被的纳米纤维，靶向白血病肿瘤的 IL-1 受体辅助蛋白（recombinant interleukin 1 receptor accessory protein，IL1RAP）以延缓疾病进展[55]。第三类是结合物理手段治疗肿瘤。例如，Yun 等[56]制作了一种能用于光热治疗的人脂肪来源 MSCs 的金纳米棒，小鼠静脉注射该纳米材料后，可进入到结肠癌组织深部，显著抑制肿瘤生长。

4 工程化 MSCs 来源细胞外囊泡的抗肿瘤作用

细胞外囊泡是活细胞释放的细胞间信息载体，携带亲本细胞源的核酸（如 DNA、mRNA、miRNA 等）、蛋白质及脂质等生物信息分子。已有研究表明，携载抗肿瘤信息的工程化 MSCs 源囊泡有明确的治疗效果[57-63]。

4.1 携载非编码 RNA

人为构建能高表达靶向沉默肿瘤细胞目的基因的非编码 RNA 的 MSCs 来源的细胞外囊泡，对肿瘤细胞（包含实体瘤和非实体瘤）或肿瘤微环境进行干预发挥抗肿瘤作用（表 3）。

表 3 工程化 MSCs 细胞外囊泡携载非编码 RNA 用于肿瘤治疗

Table 3 Engineered extracellular vesicles carrying non-coding RNA for tumor therapy

来源	转染方式	非编码 RNA	肿瘤类型	靶点	参考文献
hBM-MSC	质粒	miRNA-187	前列腺癌	CD276/B7-H3	[64]
hBM-MSC	质粒	LINC00847	骨尤文肉瘤	ceRNA：GFPT1、HIF1A、NEDD9 和 NOTCH2	[65]
hUC-MSC	质粒	miR-655-3p	食管癌	LMO4/HDAC2-HIF-1α	[66]
mBM-MSC	慢病毒	miR-30C	结肠癌	IL-6	[67]
hMSC	脂质体	miR-744-5p	M2 巨噬细胞	TGFB1	[68]
hUC-MSC	脂质体	miR-15a-5p	胆管癌	CHEK1	[69]
hBM-MSC	质粒	Circ_0006790	胰腺癌	CBX7	[70]
hAT-MSC	慢病毒	miR-199-3p	肝癌	mTOR	[71]
hBM-MSC	质粒	miR-7-5p	急性髓系白血病	OSBPL11	[72]
hBM-MSC	脂质体	ALKBH5-shRNA	三阴性乳腺癌	UBE2C	[73]

Note：hUC-MSC，Umbilical cord mesenchymal stem cells；hBM-MSC，Bone marrow mesenchymal stem cells；hAT-MSC，Adipose tissue mesenchymal stem cells

4.2 携载抗癌药物

通过生物工程方式构建直接携载治疗药物的细胞外囊泡递送系统用于肿瘤治疗。利用超声、电穿孔、孵育、化学偶联等方式将抗癌药物奥沙利铂、紫杉醇、5-氟尿嘧啶、阿霉素等转染进 MSCs 来源的细胞外囊泡，利用其归巢特性靶向肿瘤，诱导肿瘤细胞死亡[74-77]。凋亡的肿瘤细胞会在表面表达钙网蛋白（calreticulin，CRT），随后释放高迁移率组蛋白盒 1（high mobility group protein B1，HMGB1）并分泌三磷酸腺苷（adenosine triphosphate，ATP），这些物质可进一步活化树突状细胞，招募细胞毒性 T 细胞及减少调节性 T 细胞，从而触发一系列免疫原性细胞死亡（immunogenic cell death，ICD）。

4.3 携载细胞凋亡信号

凋亡的 MSCs 可保留其免疫调节能力，并具有与活

体 MSCs 相似的疾病(损伤或炎症)治疗效果[78-79]。有研究发现诱导小鼠骨髓 MSCs 凋亡,可产生较高数量的细胞外囊泡,这些凋亡细胞外囊泡(apoptotic extracellular vesicles, apo-EVs)可以促进多发性骨髓瘤(multiple myeloma,MM)细胞凋亡、抑制肿瘤生长;静脉输注 apo-EVs 可显著延长 MM 小鼠的寿命。从机制上来说,apo-EVs 与 MM 细胞接触,引发 Ca^{2+} 内流和细胞质内 Ca^{2+} 含量升高,进而促进肿瘤细胞内肿瘤坏死因子受体超家族成员 6/凋亡蛋白 1(TNF receptor superfamily member 6,Fas/Apo-1/CD95)从细胞质向细胞膜运输。随后,凋亡 MSCs 来源的细胞外囊泡可利用其膜上的 Fas 配体激活 MM 细胞中的 Fas 信号通路,诱导肿瘤细胞凋亡[80]。

5　结　语

研究人员利用 MSCs 的低免疫原性、归巢特性、旁分泌及免疫调节能力,将 MSCs 改造为高效运输工具,携载抗肿瘤信息分子靶向肿瘤细胞或微环境。此外,MSCs 还可防治或减轻移植物抗宿主病。总而言之,工程化 MSCs 有较好的抗肿瘤作用。然而,未修饰 MSCs 对肿瘤有双重作用,即促瘤或抑瘤。鉴于此,尚不能精准把控未修饰 MSCs 抗肿瘤的安全性和有效性。未来,可多关注取材方便或可批量生产的永生化 MSCs 用于治疗 GVHD;也需要更多、更深入的临床研究支持工程化 MSCs 靶向治疗肿瘤,以拓宽 MSCs 的临床应用前景。

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Advances in Engineered Mesenchymal Stem Cells in Tumor Therapy

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Abstract Mesenchymal stem cells (MSCs) are adult multipotent stem cells possessing the advantages of rich and wide sources, low immunogenicity, homing to the tissue of injury, paracrine activity, immunomodulation capacity, and easiness to be engineered. With the above-mentioned advantages, MSCs may have great application value in the treatment of cancer. Despite the controversial roles of MSC in cancer therapy, engineering MSCs with homing capacity to tumor tissues show great antitumor potential for delivering anticancer agents, suicide genes, and oncolytic viruses to tumors. Current clinical trial utilizing engineered MSCs in GBM treatment was shown to exert anti-GBM activity. Therefore, the following review elaborates on the characteristics of MSCs as well as the effects of engineering MSCs on tumor cells and their microenvironments, in order to provide new insights into MSCs' value in translational medicine and tumor treatment.

Key words Mesenchymal stem cells (MSCs) Tumor treatment Engineered modification Extracellular vesicle