

【TRAIL基因修饰MSCs肿瘤治疗专栏】

基因修饰间充质干细胞治疗肿瘤研究进展

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摘要: 间充质干细胞(MSCs)是来源于中胚层的成体干细胞, 体内分布广泛, 可从骨髓、脂肪、牙髓、脐带/胎盘等组织中分离获取, 具有高度的可增殖和分化潜能, 较低的免疫原性, 同时具有向炎症损伤部位微环境的趋向性, 在疾病治疗方面可作为基因药物的载体实现精准治疗。癌症被认为是永远无法愈合的伤口, 其组织微环境在损伤与修复中呈无休止的动态变化, MSCs在其中扮演了重要角色。利用MSCs具有的向肿瘤组织中归巢及定位的特点, 对其进行抗肿瘤药物的基因工程改造可能在癌症的治疗上是一种新的策略。概述MSCs在癌症发生发展中的作用以及基因修饰MSCs治疗癌症的研究进展, 旨在为临床使用基因修饰MSCs治疗癌症提供策略和见解。

关键词: 基因修饰; 间充质干细胞; 肿瘤; 载体; 免疫; 趋向性

中图分类号: R979.1 **文献标志码:** A **文章编号:** 1674-6376 (2021) 10-2049-09

DOI: 10.7501/j.issn.1674-6376.2021.10.001

Research progress of genetically modified mesenchymal stem cells in treatment of tumors

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Abstract: Mesenchymal stem cells (MSCs) is one of the adult stem cells, which is derived from mesoderm tissues. MSCs are widely distributed in tissues and organs, and can be isolated from bone marrow, fat, dental pulp, umbilical cord/placenta and other tissues. MSCs have high potential for proliferation and differentiation, low immunogenicity and a tendency to the microenvironment of inflammatory injury sites. MSCs hold clinical promise for the treatment of many diseases. Cancer is considered as a wound that can never be healed, and its tissue microenvironment changes endlessly during injury and repair, in which mesenchymal stem cells play an important role. Using the characteristics of mesenchymal stem cells to home and locate tumor tissue, genetic modification of MSCs with antitumor drug may be a new strategy in the treatment of cancer. This paper summarizes the role of mesenchymal stem cells in the occurrence and development of cancer and the research progress of gene modified mesenchymal stem cells in the treatment of cancer, in order to provide strategies and insights for the clinical use of gene modified mesenchymal stem cells in the treatment of cancer.

Key words: gene modification; mesenchymal stem cells; tumor; vector; immunity; tendency

间充质干细胞(mesenchymal stem cells, MSCs) 具有自我更新、多向分化、集落形成等能力^[1]。它们来源于分化早期的中胚层, 作为一种成体干细胞, 可以分化为间充质谱系, 包括成骨细胞、软骨细胞、

收稿日期: 2021-08-01

基金项目: 北京市科技计划课题(Z211100002521006)

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脂肪细胞、内皮细胞和心肌细胞等,以及非间充质谱系,如肝细胞和神经元细胞等^[1]。除了分化潜能外,MSCs还具有归巢能力,这意味着它们可以迁移到损伤部位,分泌生长因子、趋化因子、细胞因子等^[2],可增加血管生成,减少细胞凋亡和纤维化,增强神经元存活和分化,刺激细胞外基质重塑,限制局部炎症,调节免疫反应。通过这种方式,MSCs直接或通过旁分泌诱导再生,以拯救受损细胞,减少组织损伤,并最终加速器官修复^[3-4]。在动物模型和人类临床试验中,MSCs在修复各种退行性疾病的受损组织方面显示出富有希望的结果^[5-10],它们可以迁移到损伤部位,分化为损伤部位局部成分,以及分泌趋化因子、细胞因子和生长因子以帮助组织再生^[11-14]。MSCs的多向分化潜力^[15-16]使之成为细胞治疗和组织修复中最常用的干细胞。到目前为止,在临床试验中,MSCs最常见的来源是成人骨髓,其次是废弃的脂肪和脐带/胎盘组织^[17]。Lazarus等^[18]于1995年首次人体中将骨髓来源的MSCs作为细胞药物进行测试,目前已有多款MSCs药品在全球多个国家获得上市批准,间充质干细胞在临床应用的安全性是得到充分验证的。

MSCs可向受损伤的组织微环境趋化,同样也能向发生肿瘤恶变的细胞、组织或器官移动、聚集,其趋化性与免疫细胞相似,但具体机制仍不十分明确。MSCs对肿瘤的作用存在双重性,部分研究显示MSCs抑制肿瘤细胞生长,另有研究却显示MSCs能够促进肿瘤的生长和转移。虽然MSCs在某些情况下可能会促进肿瘤的增长,但不影响将MSCs作为携带细胞毒性或免疫对抗性药物的有效载体进行抗肿瘤研究。目前已有大量研究证实,基因修饰的MSCs在肿瘤治疗的应用研究中获得了积极、正向的评价,本研究就MSCs在癌症发生发展中的作用以及基因修饰MSCs治疗癌症的研究进展进行概述。

1 MSCs与肿瘤

1.1 肿瘤——过度愈合的伤口

正常的创伤愈合主要有3个阶段,包括炎症、组织增殖和重塑,由成人组织细胞相继启动并高度协调^[19]。在没有重大感染的情况下,短期炎症后进入大约2周的增殖期。增殖期伴随着上皮细胞(再上皮化)、间充质细胞(纤维增生)和内皮细胞(再血管化或血管生成)3种主要细胞类型的增殖。通过自分泌和旁分泌机制,大量的细胞因子和营养因子促进上皮组织再生长、胶原和其他细胞外基质蛋白的

产生以及新血管的形成^[20]。在组织重塑过程中,杂乱无章的胶原纤维将沿着张力线重新排列。伤口收缩伴随着巨噬细胞和成纤维细胞数量的减少并通过凋亡导致血管减少,这些程序的高度协调实现了一个成功的愈合过程^[21]。

长期以来,肿瘤被喻为“过度愈合的伤口”^[22]。在肿瘤发生的早期,癌细胞被天然和适应性免疫细胞介导的宿主监视识别并导致凋亡或坏死。死亡的肿瘤细胞继而释放各种废物,如腺苷、高迁移率族蛋白1(HMGB1)、膜联蛋白和钙网蛋白,它们用于启动炎症反应,随后参与伤口愈合过程中的一系列事件^[23]。随着肿瘤的进展,周围血管变得可渗透,进一步触发血小板和纤维蛋白沉积,进而启动炎症、增殖和细胞外基质重塑^[24]。只要肿瘤没有被宿主免疫系统或外部疗法根除,愈合的步骤就会继续下去,直到肿瘤负荷超过宿主的生存能力。正常生理性伤口愈合和肿瘤发生的1个明显区别是后者有1个或多个延长的、未完成的阶段,因此长期以来,肿瘤一直被认为是无法愈合的创伤^[25]。

1.2 MSCs的肿瘤靶向趋化性

当损伤影响组织的结构完整性时,MSCs在恢复组织稳态中起着重要作用^[7]。自体的或外源性MSCs在多种因素的作用下可定向趋化性迁移至靶组织并定植,这种能力被定义为MSCs的归巢。同样,MSCs也能向发生肿瘤恶变的细胞、组织或器官移动、聚集。MSCs向损伤或肿瘤组织趋化归巢的具体机制仍不十分明确,目前认为炎症因子及趋化因子参与了这一过程。肿瘤环境由许多免疫细胞组成,这些免疫细胞与癌细胞一起,分泌可直接调节MSCs趋化性和向受损组织募集的细胞因子。主要的细胞因子有:成纤维细胞生长因子、血管内皮细胞生长因子^[26]、肝细胞生长因子、血小板源性生长因子、表皮生长因子、单核细胞趋化蛋白-1(MCP-1)、转化生长因子- β (TGF- β)^[27]等。最近发现,C-X-C基序趋化因子受体4(CXCR4)也是参与MSCs肿瘤趋化性的主要趋化因子受体之一^[28]。在肿瘤微环境中,肿瘤细胞可局部产生高浓度的细胞因子,有利于MSCs向肿瘤组织趋向转移,参与肿瘤微环境的构建。肿瘤还可以动员来自远处器官的MSCs,包括骨髓和脂肪组织,通过炎症信号驱动它们植入肿瘤微环境^[29-30]。MSCs向肿瘤部位迁移的特性还在其他一些临床前体外迁移实验和肿瘤动物模型实验中得到证实,包括恶性神经胶质瘤^[6,9,31]、乳腺癌^[10,32-34]、卡波西肉瘤、黑色素瘤、结肠癌^[35-36]、卵巢

癌和肺癌^[37-38],以及在肿瘤过程中发生的转移等。

1.3 MSCs与肿瘤组织的相互作用

肿瘤的进展过程被认为是肿瘤内不同类型细胞及其周围宿主组织和器官或肿瘤间质之间不断演变的串扰结果^[39]。大量实验结果表明, MSCs和肿瘤具有复杂的相互作用:肿瘤细胞分泌趋化因子、细胞因子和生长因子,将MSCs招募到肿瘤部位;反过来, MSCs作为肿瘤微环境的组成部分,通过分泌细胞因子和趋化因子作用于MSCs与肿瘤细胞间的信号通路来影响肿瘤的生长和转移,从而实现对肿瘤细胞增殖或凋亡的调控^[33,40]。有研究表明, MSCs通过影响Akt/NF- κ B、Wnt/ β -catenin等信号通路促进肿瘤进展和转移^[41-42], MSCs还可分泌与恶性肿瘤转移有关的细胞因子,如基质金属蛋白酶2/9(MMP-2/9),通过TGF- β 信号通路促进肿瘤的侵袭与转移^[43]。而另一些研究表明, MSCs既能通过影响细胞间信号通路来抑制肿瘤细胞增殖又能促进凋亡^[44-45]。Atsuta等^[46]通过体内外实验证实, MSCs可通过表达凋亡相关因子配体Fas-L作用于Fas/Fas-L信号通路诱导多发性骨髓瘤细胞凋亡。在体外和不同的肿瘤动物模型中, MSCs都具有抗肿瘤作用,这归因于MSCs分泌的因子可以抑制胶质瘤、黑色素瘤、肝癌和乳腺癌细胞的增殖^[47-49]。还有研究表明, MSCs通过抑制胶质瘤细胞中的血管生长而发挥抗胶质瘤作用,这种作用是通过下调血小板衍生生长因子(PDGF)/PDGFR轴^[50]介导的。此外,人类脐带来源的MSCs(hUC-MSCs)已被证明通过诱导肿瘤细胞死亡和抑制血管生成来抑制乳腺癌的进展^[51]。

2 基因修饰MSCs治疗肿瘤

由于MSCs的低免疫原性和对肿瘤组织的趋向性,携带细胞毒性或免疫对抗性基因,表达后并靶向递送至肿瘤部位,使得它成为一种很有前途的抗肿瘤药物载体。从成人组织中分离MSCs的做法回避了胚胎或胎儿干细胞使用中的许多伦理和安全问题^[52-53]。然而, MSCs对肿瘤的作用具有双重性,使得这种治疗策略对癌症患者来说是有风险的,在某些情况下可能会刺激癌症的进展^[54],对于这种风险,还需要进行更为深入的研究和探讨,但不影响将MSCs作为有效的载体进行抗肿瘤的研究。将MSCs作为抗肿瘤基因的载体对肿瘤能够起到抑制作用已经有多篇文献报道^[55-56]。由于细胞因子在体内的半衰期很短,如果直接单独应用细胞因子进行肿瘤治疗,在体内会很快被降解,而且可能也会对

正常细胞产生毒副作用。如果采用细胞因子基因修饰的MSCs进行治疗就可以避免上述情况。MSCs会迁移到肿瘤局部扮演“特洛伊木马”,释放细胞因子,在肿瘤部位提高细胞因子的浓度,通过激活免疫或直接触发肿瘤细胞凋亡,引起肿瘤微环境中细胞级联反应,最终消除肿瘤。在此过程中,由于基因修饰MSCs的靶向性,使得治疗药物的分布是局部的,能够显著地降低对正常细胞的毒副作用。另外,由于MSCs的免疫原性低,异体的MSCs在体内可以逃避免疫系统的清除,能够进行多次给药,使得同种异体MSCs用于肿瘤治疗成为可能。

2.1 基因修饰MSCs治疗肿瘤的临床前研究

对MSCs进行基因修饰的方法通常使用病毒载体,包括逆转录病毒、慢病毒或腺相关病毒载体,以及DNA质粒等^[57]。修饰的基因主要包括:自杀基因、促凋亡或抑制细胞周期基因、免疫刺激基因和抗血管生成基因等。基因修饰的选择是由治疗疾病的目的或机制所驱动的。

2.1.1 自杀基因 通过基因工程方式将催化肿瘤前体药物的酶类基因导入MSCs,其表达的酶可催化无毒的药物前体转变为细胞毒物质,导致携带该基因的受体细胞被杀死,同时诱导邻近肿瘤细胞凋亡,这类酶类基因称为自杀基因。在静脉输注基因修饰的MSCs后, MSCs携带自杀基因酶类归巢至肿瘤组织,系统地给前体药物,从而在肿瘤部位转化为细胞毒性衍生物,可将非靶标毒性降至最低。这种抗癌方法的主要优点是通过“旁观者效应”放大药物的毒性:基因修饰的MSCs凋亡间接释放大量的抗肿瘤药物进而导致邻近靶细胞的死亡。激活的前药所产生的细胞毒作用还会促进有毒物质的释放,从而激活免疫细胞,包括细胞毒性T细胞和巨噬细胞,进而取得更有效的抗肿瘤效果^[58]。半衰期短或全身毒性高的药物,如更昔洛韦(GCV)或5-氟尿嘧啶(5-FU),可能是基因修饰酶前药治疗的理想候选药物^[59]。基因修饰的MSCs用于靶向各种肿瘤的最常见的酶前药复合物是单纯疱疹病毒胸苷激酶/更昔洛韦(HSV-TK/GCV)系统和胞嘧啶脱氨酶/5-氟胞嘧啶(CD/5-FC)系统。以MSCs为基因治疗载体的CD/5-FC自杀基因系统已经在黑色素瘤和前列腺癌小鼠模型中进行有效验证^[60-61]。在这种方法中,归巢至肿瘤组织的MSCs产生CD将前药5-FC转化为化疗药5-FU,然后可以扩散到肿瘤组织中将其杀灭。同样,导入HSV-TK/GCV系统的MSCs趋化至肿瘤组织,通过分泌HSV-TK将无毒性前体药物

GCV单磷酸化,并通过细胞其他激酶进一步转化成一磷酸、二磷酸GCV,最后形成具有细胞毒性的三磷酸化GCV,该系统也在肿瘤抑制的试验中得到积极的效果^[62-64]。

2.1.2 促凋亡或抑制细胞周期基因 肿瘤坏死因子(TNF)相关的凋亡诱导配体(TRAIL)在临床应用上是目前最有前景的促凋亡细胞因子之一,它可以选择性地诱导肿瘤细胞凋亡。在肿瘤细胞中,TRAIL可以通过与其受体死亡受体4(DR4)和DR5结合来诱导caspase介导的细胞凋亡^[65]。TRAIL修饰的MSCs对胶质母细胞瘤、胰腺癌有抗肿瘤作用^[65-68],但尚未发现TRAIL对正常哺乳动物细胞和组织有细胞毒性^[69-70]。然而,一些肿瘤通过过表达抑制caspase 3和9活性的X连锁凋亡抑制蛋白(XIAP)而产生TRAIL耐药机制。这种耐药机制的解除可通过使用MSCs运送和同时表达新的细胞穿透形式的Smac和TRAIL来解决,这种方法的有效性在耐药乳腺癌细胞系MCF-7中得到了证明^[71]。为了提高TRAIL修饰的MSCs的治疗潜力,有人建议可以与化疗药物联合使用^[72]。最近的一项研究表明,组蛋白去乙酰化酶抑制剂(HDACis)能有效地诱导化疗耐药细胞凋亡,如CD123/CD47阳性细胞,它们在肿瘤微环境中是不稳定的;在异种移植急性髓系白血病小鼠模型中,HDACis能有效地靶向并去除了化疗耐药的白血病细胞^[73]。因此,将HDACis基因转染至MSCs可能是治疗肿瘤的新的潜在选择。除此之外,PTEN基因通过细胞周期G1期阻滞来抑制细胞增殖,将PTEN基因导入MSCs后,增强了MSCs在体外向脑胶质母细胞瘤(DBTRG)迁移^[74]。PTEN修饰的MSCs对U251胶质瘤细胞展现出良好的抗癌活性^[75]。

2.1.3 免疫刺激基因 可作为基因修饰的免疫调节相关基因包括干扰素(IFN- α 、IFN- β 、IFN- γ)、白细胞介素(IL-2、IL-12、IL-15、IL-18)等^[76]。IFN- β 能够通过促进机体免疫功能,提高巨噬细胞、自然杀伤细胞(NK)和细胞毒性T淋巴细胞(CTL)的杀伤能力来杀伤肿瘤细胞。在较为早期的研究中,IFN- β 基因修饰的骨髓MSCs在人黑色素瘤小鼠异种移植模型中展现出良好的抗肿瘤作用,可显著提高小鼠存活时间^[77]。此外,在黑色素瘤移植小鼠模型中显示,IFN- γ 基因修饰的犬骨髓MSCs联合化疗药物顺铂显著增加了抗肿瘤治疗的有效性^[78]。

2.1.4 溶瘤病毒 除了通过修饰MSCs靶向运送细胞因子和凋亡基因外,MSCs还可以靶向运送可复

制的溶瘤病毒,这些病毒通过复制直接破坏并溶解肿瘤细胞,进一步产生新的病毒,释放到肿瘤的周围,如此往复。由于宿主免疫防御的清除作用,单独给予的溶瘤病毒又不能高效迁移至肿瘤部位,溶瘤病毒全身直接给药通常无效^[79-80]。而MSCs介导溶瘤病毒的表达后,可以帮助病毒逃避机体的防御清除,同时将病毒直接导向肿瘤,极大的降低了对正常组织的毒性作用。有研究^[81]在免疫缺陷和免疫活性小鼠的人脑黑色素瘤转移模型中使用MSCs作为递送溶瘤单纯疱疹病毒(OHSV)的载体,引入的MSCs-OHSV迁移到肿瘤形成部位,显著延长了小鼠的生存期;在免疫活性模型中,MSCs-OHSV和PD-L1阻断剂(aPD-L1)的组合增加了产生IFN- γ 的CD8⁺肿瘤浸润性T淋巴细胞,并导致治疗动物的中位生存期显著增加。

2.1.5 MSCs的外泌体 MSCs对肿瘤表现出内在的趋向性,但MSCs分泌的外泌体可能更具有优势。正如Smyth等^[82]所证明的,肿瘤细胞外泌体的内化比同等大小的脂质体大10倍,外泌体表现出对癌症靶向的优异特异性。与正常细胞相比,癌细胞内化了更大比例的外泌体。外泌体比它们的亲代细胞更小、更简单、免疫原性更低,因为它们的膜结合蛋白含量更低^[83]。此外,外泌体的产生和储存比它们的亲代细胞更容易。因此,一种基于MSCs外泌体的新疗法可能是一种更好的替代方法,因为它们比MSCs更有益处。有研究证实,用紫杉醇基因修饰的MSCs具有强大的抗肿瘤效果,因为它们有可能获得药物并随后将其包装在外泌体中^[84-85]。除了将药物负载到外泌体中的方法外,还可以采用不同的加载方法将miRNA包埋在外切体中。根据Munoz等^[86]的研究,携带抗miR-9的MSC外泌体逆转了多药转运蛋白在多形性胶质母细胞瘤耐药细胞中的表达,并逆转了对化疗药(替莫唑胺)的耐药性。另1项研究表明,瘤内注射表达miR-146b的MSCs外泌体可以显著减少大鼠脑瘤模型中胶质瘤的异种移植发展,并减少细胞的生长、迁移和侵袭^[87]。最近的1项研究也肯定了牙髓MSCs(DPSCs)衍生的基因修饰外泌体作为载体传递肿瘤抑制因子miR-34a,抑制乳腺癌细胞增殖的能力^[88]。根据这些发现,miRNAs可以包装到MSCs外泌体中来抑制胶质瘤细胞,这表明基因修饰的MSCs分泌富含miRNAs的外泌体可能是治疗恶性胶质瘤的有效策略。

由于基因修饰技术的成熟可靠,在MSCs上实现单基因甚至多基因共表达修饰也相对容易。对

于基因靶点的选择和应用主要取决于不同肿瘤的特性。虽然上述方法已在临床前有了大量研究,但对于多靶点的互补或联合应用还鲜有报道。

2.2 基因修饰MSCs治疗肿瘤的临床研究

目前为止,有多种通过不同途径用于肿瘤治疗的基因转入MSCs参加了临床研究。1项I/II期临床试验目的是评估在趋化因子配体5(CCL5)启动子控制下MSCs传递HSV-TK系统的安全性和有效性。该试验方案包括给10例胰腺癌患者静脉输注HSV-TK基因修饰的MSCs,总剂量为 $3.0 \times 10^6/\text{kg}$,然后重复GCV注射。这项技术基于CCL5,一种由MSCs与肿瘤细胞接触后产生的趋化因子,它允许CCL5启动子的激活,该启动子仅在浸润肿瘤的MSCs中驱动HSV-TK基因,限制前体药物转化酶在肿瘤微环境中的表达,引入这种选择性激活是为了减少全身副作用。作为主要的临床试验目标,研究者证明了基因修饰的MSCs治疗的可接受安全性和耐受性^[89]。

在干扰素基因使用方面,2015年的1个I期临床试验测试IFN- γ 基因修饰的骨髓MSCs在临床使用的安全性,并确定卵巢癌患者可以接受该方法的的最大耐受量为 $1.0 \times 10^5/\text{kg}$ ^[90]。

TRAIL基因修饰的MSCs联合化疗在一项I/II期临床试验中用以评估对转移性非小细胞肺癌(NSCLC)患者的安全性和抗肿瘤活性^[91]。该试验共分为2个阶段,第一阶段,患者在第1天接受顺铂 $75 \text{ mg}/\text{m}^2$ 和培美曲塞 $500 \text{ mg}/\text{m}^2$ 化疗,第2天接受TRAIL基因修饰的MSCs移植,剂量为 $4 \times 10^8/\text{kg}$,每位患者每隔21 d接受3个周期的治疗用以评估安全性,并确定联合化疗时的第二阶段推荐剂量;第二阶段,患者将被随机分配到干预组或对照组,所有入选的患者将在第1天接受化疗,被随机分到干预组的患者第2天将接受TRAIL基因修饰的MSCs移植,其目的是评估TRAIL基因修饰的MSCs联合传统化疗的耐受性和疗效。目前,该临床试验尚在进行中,预计在2023年9月初步完成。

最近的1项I期临床试验正在研究携带溶瘤腺病毒DNX-2401的骨髓MSCs在复发性胶质母细胞瘤(GBM)、胶质肉瘤或异柠檬酸脱氢酶1(IDH1)野生型间变性星形细胞瘤患者中的最佳校准剂量和副作用。DNX-2401是一种肿瘤选择性溶瘤腺病毒,这种病毒已经过基因改造,对患者来说是安全的,并能够特异性地针对脑癌细胞。这项临床试验招募了36名患者,他们将接受监测,以确定最大耐

受量和局部/全身毒性^[92]。给予治疗的36名患者中有20%的生存时间超过3年,有3名患者的增强肿瘤减少95%,复发性高级别胶质瘤的长期生存率显著提高。

近年来,利用基因修饰的MSCs治疗肿瘤的研究数量在不断增加,大多数集中在临床前和临床研究中,尚未有上市的药品获批。利用MSCs作为载体将基因、小分子蛋白质或溶瘤病毒等运送到肿瘤组织中正在成为一个很有前途的选择。

3 展望

目前为止,外科手术、放化疗仍然是癌症治疗的主要手段,治疗效果可圈可点,但存在很多副作用。手术治疗创伤性较大,有些部位手术难度大,在治疗方面存在着一定的局限性,不能彻底的消灭癌细胞,在一定的时间内癌细胞还会再长;化疗药物对杀灭癌细胞并无特异性,杀灭癌细胞的同时也杀死正常细胞,过度化疗会缩短患者生存时间;放射治疗周期长,并发症较多,甚至引起部分功能丧失。MSCs的安全性和有效性在一些其他临床应用上已经得到了充分的证实,即使是来自异体的MSCs,在有效治疗或减轻病症的同时并无严重的不良反应。基因修饰MSCs在肿瘤治疗的研究和应用中展示出良好的作用和前景。但无论是外科手术、放化疗还是目前的基因修饰MSCs对肿瘤的治疗效果都是有限的,要提高其治疗效果不仅要寻找新的和更加有效的基因靶点,还需要结合多种方式加以辅助。比如将MSCs修饰为多种治疗性蛋白的共表达来增强其抗癌能力。研究表明,TRAIL和HSV-TK共修饰的MSCs在GCV存在的情况下就可显著抑制肿瘤生长和提高对高度恶性多形性GBM的杀伤力^[93]。另外,通过外科手术对较大肿瘤病灶加以清除,再结合放化疗对远端和较小肿瘤加以杀伤,同时给予基因修饰的MSCs进一步杀灭,MSCs还能参与修复手术、放化疗带来的创伤或炎症,提高患者的生存期和生活指数。

供体MSCs的排斥是否影响同种异体MSCs治疗效果尚不清楚,迄今为止,自体MSCs相对于同种异体MSCs没有明确的临床优势。虽然MSCs可能通过短暂的“打了就跑”机制发挥治疗作用,但保护MSCs免受免疫检查并延长其在体内的持久性可能会改善临床效果并防止患者对供体抗原的过敏。另外,有效且安全的目标基因也是要考虑的,将目标基因转入MSCs并使其发挥作用。目前MSCs及基因修饰的MSCs移植对肿瘤的治疗效果已得到大

量的临床前和临床试验的正面验证,但进一步提高其治疗效果和安全性还需要继续深入的研究。

利益冲突 所有作者均声明不存在利益冲突

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