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(编校:李亚东)

间充质干细胞源性外泌体及其在肿瘤治疗中的研究进展

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A comprehensive overview of exosomes derived from mesenchymal stem cells and their function in cancer therapy

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【Abstract】Exosomes denote a family of nanoparticles with a diameter in the range of 40 ~ 100nm that are secreted by most cell types of the body. As the important genetic information carriers and intercellular communicators, they contain a wide variety of bioactive substances, such as proteins and miRNA. They can be isolated from several types of extracellular fluids including blood, urine, amniotic fluid, saliva, and cerebrospinal fluid. To be interesting, exosomes derived from mesenchymal stem cells have the similar character to migrate to inflammation and cancer, which maybe provide a new thought of cancer therapy. In this review, we will describe MSC - exosomes in three parts, biological characteristics, methods of isolation & identification and cancer therapy.

【Key words】mesenchymal stem cells, exosome, cancer therapy, miRNA

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【指示性摘要】外泌体(exosomes)是细胞内多囊泡体(multivesicular bodies, MVBs)与细胞膜融合后释放到细胞外直径为40 ~ 100nm的囊泡样小体。作为一种重要的细胞间信息传递分子及遗传物质传递载体,外泌体内含有蛋白质、RNA等多种活性物质,广泛分布于血液、尿液等体液中。目前发现多种类型细胞均可产生外泌

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体，尤其是间充质干细胞（MSCs）被认为是产生外泌体能力最强的细胞，并且MSCs源性外泌体（MSC-exosomes）与MSCs同样具有向炎症组织及肿瘤组织迁移的特性，为肿瘤治疗提供了一种新思路。由此，本文将从MSC-exosomes生物学特性、分离鉴定方法、肿瘤治疗潜能三方面进行综述。

【关键词】间充质干细胞；外泌体；肿瘤治疗；miRNA
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间充质干细胞（mesenchymal stem cells，MSCs）来源于中胚层，是一类具有自我复制能力和多向分化潜能的细胞，存在于骨髓、肝脏、脾脏、外周血、脂肪、胎盘、脐血、皮肤等多种组织中，因其具有免疫抑制，组织损伤修复，神经保护等多种功能，且不涉及伦理等诸多问题，广泛应用于神经、心血管等多系统疾病的治疗研究，为当今世界自然科学领域研究的热点问题。外泌体（exosomes）最初发现于绵羊网织红细胞[1]，被认为是一种“细胞垃圾”，随后，B细胞通过释放含有功能性MHC1、MHC2分子及T细胞共刺激因子的外泌体来促进T细胞增殖，起到了抑制肿瘤细胞生长作用的发现[2,3]；肿瘤细胞源性外泌体内含有肿瘤细胞分泌的特异成分，具有肿瘤早期诊断及个体化治疗的潜在功能的发现；引起了外泌体抗肿瘤研究的热潮。直至多项研究指出外泌体中含有RNA和miRNA，并且能转导入受体细胞调节蛋白表达[4-6]，开启了外泌体作用的新篇章-外泌体不仅是一种细胞信息传递分子，更是一种遗传物质传递载体。2010年Lai等[7]研究发现MSCs源性外泌体（MSC-exosomes），着眼于MSCs强大的外泌体分泌能力[8]，越来越多的试验研究致力于探讨MSC-exosomes对肿瘤进程的影响，以及MSC-exosomes治疗肿瘤的广泛前景。对此本文对相关文献进行归纳总结，主要从MSC-exosomes生物学特性，分离鉴定方法，肿瘤治疗潜能三方面进行综述。

1 外泌体的生物学特性

外泌体是细胞分泌的直径为40~100nm的囊泡样小体。有别于微泡（microversicle，MV）直接从细胞膜出芽形成，外泌体起源于细胞晚期内体向内出芽形成的多囊泡体（multivesicular bodies，MVBs），由MVBs与细胞膜融合后以胞吐的方式将外泌体释放到细胞外，存在一个“内陷-融合-外排”的过程。在电子显微镜下，可见外泌体由双层磷脂分子包裹，呈杯状或碟样小体，通常可在（1.13~1.19）g/ml蔗糖密度梯度溶液中富集，并在100 000×g离心下分离沉淀[9,10]。外泌体可由多种细胞产生释放，广泛分布于血液、尿液、乳汁、唾液、腹水、胸水等体液中，其表面存在多种相对特异性蛋白质，如四跨膜家族（CD63、CD81、CD9）、热休克蛋白（Hsc70）、溶酶体蛋白（Lamp2b）、融合蛋白（CD9，flotillin，Annexin）等，其中四跨膜蛋白常作为外泌体鉴定的分子标志物，将其与多种细胞外囊泡样结构如MV、凋亡小体等鉴别开来，但是真正的外泌体特异性蛋白还未被发现[11]。外泌体内还含有胆固醇、神经酰胺、前列腺素、mRNA、miRNA、LncRNA等多种活性物质。其中mRNA、miRNA可传递至受体细胞调节其蛋白表达，其可作为标志物用于癌症等疾病的早期诊断[12]。近来研究认为MSCs是产生外泌体能力最强的细胞[8]，并且MSC-exosomes具有与MSCs相似的多种生物学功能，如减轻心机缺血/再灌注损伤[13]、减轻肾脏损伤[14]、调节免疫系统功能[15]、调节肿瘤生长、治疗神经系统疾病[16]等。

2 外泌体的分离保存鉴定方法

2.1 外泌体的分离方法

2.1.1 超速离心法 超速离心法是传统最常用的外泌体分离方法。收集样本后分别于300×g离心10分钟，2 000×g离心20分钟，10 000×g离心30分钟以除去细胞及细胞碎片，最后在4℃条件下100 000×g离心70分钟获得外泌体。该法分离外泌体成本低，不易被分离试剂污染，但耗时较长，纯度低，易聚集成块，但是有报道指出高速离心过程易使外泌体囊泡破裂，导致囊泡内成分丢失[17]。

2.1.2 超滤法 超滤法利用聚醚砜超滤膜截留特定分子量的物质。该法通过压力或离心设备收集外泌体效果差异较大，通常认为离心法较优。近来Richard等指出50~200ml样本更适合采用离心法，当样本量达到400ml以上时更适合采用压力法[18]。该法分离外泌体耗时短，但由于从超滤膜上洗脱外泌体及移除超滤膜截留的大分子蛋白存在困难，该法同样存在纯度和提取率低的问题[17]。

2.1.3 密度梯度离心法 密度梯度离心法利用外泌体通常可在（1.13~1.19）g/ml蔗糖密度梯度溶液中富集这一特性，先将样本2 000×g离心45分钟，取上清转移至30%浓度蔗糖溶液，最后在4℃条件下100 000×g离心70分钟获得外泌体。该法获得的外泌体较传统离心法获得的外泌体纯度高，但耗时长，也有研究指出该法仅适用于细胞培养液中外泌体的提取，用于血清及尿液的提取纯度较低，不利于临床生物标志物的探索研究[19]。

2.1.4 聚合沉淀法 聚合沉淀法由System Biosciences（SBI）研发，可通过ExQuick试剂盒完成。该法在4℃下将聚合物沉淀剂与样本共同孵育30分钟，使外泌体在“聚合物网袋”中聚集，再通过1 500×g离心5分钟，PBS重悬沉淀获得外泌体。用该法分离外泌体提取率高，耗时较短[20]，大分子蛋白含量少，但有报道指出该法可影响外泌体miRNA和蛋白组分，改变外泌体形态[21,22]，使其更易聚集成块，不利于后续以外泌体为基础的治疗研究[20]。

2.1.5 免疫磁珠法 免疫磁珠是指用磁性粉末包被的单克隆抗体微颗粒，其能与外泌体膜表面蛋白特异性结合。该法在4℃下将样本与免疫磁珠共同孵育4小时，再用蒸馏水、PBS溶液相继多次冲洗，在4℃下100 000×g离心1小时得到免疫磁珠-外泌体复合物，最后通过甘氨酸-Tris-HCL溶液（pH=2.8）洗脱获得外泌体。该法较2.1.1和2.1.3提取率高，纯度高[21]，但酸性溶液和低渗溶液的使用对外泌体的形态及活性有一定影响，不利于后续以外泌体为基础的治疗研究。

2.2 外泌体的保存

Sokolova等[23]对脐带血源性MSC-exosomes的研究指出保存环境对维持外泌体直径及完整性至关重要，MSC-exosomes在37℃下保存2天，直径下降60%；在4℃下保存2天，直径无明显变化，但3~4天直径下降25%；在-20℃下直径无明显变化，可长时间保存。

2.3 外泌体的鉴定

鉴定识别外泌体的方法包括：原子力显微术、扫描电子显微术、纳米粒子示踪分析、透射电子显微术、流式细胞检测分析、western - blot、ELISA 等[23,24]。通常采用两到三种方法联合鉴定外泌体，外泌体的一些相对特异性蛋白和脂质相关成分（如磷脂酶类）常被当作标志物，除文章第一部分已经说明与外泌体起源相关的蛋白外，不同来源外泌体有一些来自其母细胞的相对特异性分子，如 B 细胞来源的外泌体含有 CD19[25]，树突状细胞来源外泌体含有 CD80、CD86[26]，恶性胶质瘤细胞来源的外泌体含有磷脂酰乙醇胺[27]等。

3 MSC - exosomes 与肿瘤治疗

MSC - exosomes 对肿瘤的作用尚未达成共识。Krishna 等[28]研究指出 MSC - exosomes 通过向肿瘤细胞运输肿瘤支持因子 *miRNA - 21*、*miRNA - 34a*、*PDGFR - β*、*TIMP - 1*、*TIMP - 2*、代谢支持因子（存活于缺氧微环境）乳酸、谷氨酸等促进肿瘤细胞增殖及转移。Zhu 等[29]的研究也得到了相似的结论，他们认为 MSC - exosomes 通过活化细胞外 ERK1/2 信号调节通路，促进肿瘤细胞 VEGF 表达。但是一些学者提出了相反意见，认为 MSC - exosomes 能够抑制肿瘤生长。Ono 等[30]观察到 MSC - exosomes 富含 miRNA - 23b，并且能被乳腺癌细胞获取。而 miRNA - 23b 通过抑制肿瘤细胞 MARCKS 基因（编码促进细胞周期活动性蛋白）的表达，使肿瘤细胞休眠。同样 Lee 等[31]观察到 MSC - exosomes 能向乳腺癌细胞转运 miRNA - 16，并且 miRNA - 16 的含量与 VEGF 呈负相关，通过抑制新生血管形成抑制肿瘤生长。Roccaro 等[32]对多发性骨髓瘤的研究更具有代表性，他们认为多发性骨髓瘤患者 MSC - exosomes 较正常人 miR - 15a（能抑制肿瘤生长）含量少，致瘤蛋白、细胞因子、黏附因子含量多，并且发现正常人 MSC - exosomes 抑制肿瘤生长，多发性骨髓瘤患者 MSC - exosomes 促进肿瘤生长。此外，还有学者提出 MSC - MV 能抑制肝癌、卡波氏肉瘤、卵巢癌、膀胱癌细胞系细胞周期进程，甚至使细胞周期停滞，从而诱导肿瘤细胞凋亡或坏死[33,34]。

尽管对直接从 MSC 获得的自然存在的外泌体对肿瘤的作用仍存在争议，但毋庸置疑 MSC - exosomes 是一种肿瘤生物靶向治疗的良好载体，与以往的生物靶向治疗材料相比其优点[8,35]主要为：①能被受体细胞吸收；②不引起免疫排斥；③没有致瘤性；④可以用自体细胞人工培育生成；⑤MSC 具有强大的外泌体分泌能力；⑥可以运载多种治疗性 RNA，实现个体化治疗。为了实现以 MSC - exosomes 为载体的肿瘤靶向治疗作用，多项研究对 MSC - exosomes 的供体细胞、装载方法以及运载的治疗性成分进行探讨，其采用的 MSC - exosomes 供体细胞主要为骨髓干细胞，治疗成分主要为 miRNA（详见表 1）。存在不足的是这些研究都未使 MSCs - exosomes 带有靶向多肽片段，实现真正意义的靶向治疗。对此，Ohno 等[41]的研究具有指导意义，他们将 GE11（编码 let - 7a miRNA）和 EFG 基因转染至 HEK293（人胚胎肾细胞系），在小鼠乳腺癌模型成功实现了对 EGFR 表达阳性乳腺癌的治疗。

表 1　MSC - exosome 的供体细胞、装载方法以及运载的治疗性成分总结

Tab. 1　Types of Donor cells, therapeutic cargo and loading methods

Donor cell	Target peptide	Disease model	Cargo	Loading method
BM - MSCs[36]	Not mentioned	Glioblastoma Multiforme	Cy5 - Anti - miR - 9	Transfection
SR4987 BM - MSCs[37]	Not mentioned	CFPAC - 1（human pancreatic adenocarcinoma）	Paclitaxel	Incubation
BM - MSCs[38]	Not mentioned	143B（osteosarcoma）	miR - 143	Transfection
Placenta and cord derived MSCs[39]	Not mentioned	Glioma	miR - 124, miR - 145	Transfection
BM - MSCs[35]	Not mentioned	Glioma	miR - 146b	Transfection
Adipose tissue - derived MSC[40]	Not mentioned	Hepatocellular Carcinoma	miR - 122	Transfection

综上所述，寻找发现肿瘤的某些特异性靶向位点，并针对这一位点实现 MSCs - exosomes 的肿瘤靶向治疗将是未来十年 MSC - exosomes 领域研究的一大热点问题。

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