脂肪干细胞外泌体功能研究进展

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摘 要: 脂肪干细胞外泌体(ADSCs-Exos)不含活细胞,抗原性低,性质稳定,在血管生成、组织再生、免疫调节等方面发挥了重要作用。作为一种无细胞疗法,ADSCs-Exos在组织修复与再生等方面具有广阔的应用前景。该文就ADSCs-Exos功能研究进展作一综述。

关键词: 脂肪干细胞; 外泌体; miRNA
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Progress on function of adipose-derived stem cell exosomes

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Abstract: Adipose-derived stem cell exosomes (ADSC-Exos) are cell-free and stable with low antigenicity, which plays an important role in angiogenesis, tissue regeneration, immune regulation, and so on. As a cell-free therapy, ADSCs-Exos have broad prospects in tissue repair and regeneration. This article reviewed the progress on functional of ADSCs-Exos.

Key words: adipose-derived stem cell; exosome; miRNA

脂肪干细胞(ADSCs)具有分化成不同细胞系的能力,还具有促进内皮细胞、纤维细胞迁移和增殖等功能[1]。研究表明,ADSCs主要通过其外泌体发挥作用[2]。外泌体是一种直径小于150 nm的细胞外囊泡结构,将蛋白质或核酸运输到需要修复的靶细胞,介导局部和系统的细胞间通信和信号转导,调节受损组织细胞的多种生物学行为[3]。相比于ADSCs,脂肪干细胞外泌体(ADSCs-Exos)具有性质更稳定、便于管理和运输、不含活细胞、生物学功能不随时间延长而衰减、低抗原性等优点[1,4]。因此ADSCs-Exos作为一种无细胞疗法,在组织修复与再生等方面具有广阔的应用前景。本文就ADSCs-Exos的研究成果及现状作一综述。

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1 促进伤口愈合和血管新生

1.1 促进成纤维细胞增殖、迁移及分化

Hu[5]和Zhang[6]等发现ADSCs-Exos通过增加N-钙粘蛋白、cyclin-1、增殖细胞核抗原和Ⅰ、Ⅲ型胶原蛋白基因的表达,或通过PI3K/Akt信号通路促进胶原的合成,刺激成纤维细胞增殖与迁移,促进皮肤无瘢痕修复。Ren等[7]研究报道ADSCs-Exos可显著上调成纤维细胞增殖标志物(cyclin D1、cyclin D2、cyclin A1、cyclin A2)的表达,能够显著促进成纤维细胞以及过氧化氢诱导的表皮角质细胞、人皮肤成纤维细胞的增殖与迁移。进一步研究发现透明质酸结合ADSCs-Exos能够明显促进急性皮肤伤口的愈合[8]。

1.2 促进血管内皮细胞增殖、迁移和分化

研究表明ADSCs-Exos可上调生长因子(VEGFA、PDGFA、EGF、FGF2)的表达,在体内外显著促进人脐静脉血管内皮细胞的增殖、迁移及血管形成[1,7],且低氧情况下效果更加显著[9]。同样在缺氧[10]或缺糖

损伤情况下[11]，ADSCs-Exos的miR-181b、miR-126可促进内皮祖细胞的迁移和血管生成，且在过氧化氢存在的情况下更有利于血管的生成[12]。ADSCs-Exos富含的miR-125a和miR-31，可转移到血管内皮细胞中刺激细胞增殖以及促进血管生成[13]。此外，ADSC-Exos还能促进皮瓣的血管化[14]。ADSCs-Exos促进血管新生的作用为缺血再灌注损伤、人工皮肤中皮瓣新生血管不足、愈合不良的治疗提供了新策略。

1.3 调节胶原合成，减少疤痕形成

Yang等[15]发现，ADSCs-Exos高表达的miRNA-21可以增强胶原合成，优化胶原沉积，显著改善小鼠全层皮肤伤口的愈合效果。ADSCs-Exos早期通过Ⅰ、Ⅲ型胶原的合成促进胶原重塑，晚期则通过抑制胶原形成减少瘢痕形成[5]。Wang等[16]发现具有ADSCs-Exos的水凝胶和水凝胶支架载体材料释放的ADSCs-Exos可以显著增加皮肤附件的再生，减少疤痕组织的形成。

2 协调成骨与破骨作用

ADSCs-Exos具有显著的成骨诱导能力[17]。体外研究证实ADSCs-Exos可通过减少核因子κb配体受体激活剂的表达从而拮抗缺血、缺氧引起的骨细胞凋亡，减少破骨细胞生成[18]。研究表明多巴胺的羟基乙酸共聚物（PLGA）/聚多巴胺（PDA）[19]、β-磷酸三钙支架[20]与ADSC-Exos组合，可增强ADSC-Exos促进人骨髓来源干细胞成骨、增殖和迁移的能力。此外，ADSCs-Exos高表达的miR-375可以促进骨再生，且50 mg/L的Exos（miR-375）可促进人骨髓间充质干细胞的成骨分化[21]。

3 双向调节作用

3.1 细胞凋亡中的抑制与激活

ADSCs-Exos在心脏、神经系统、骨组织、肾脏等损伤以及血清饥饿处理或化疗药物5-氟尿嘧啶诱导的乳腺癌中具有抑制细胞凋亡的作用，而其在转移性前列腺癌、A2780和SKOV-3卵巢癌细胞中则起到激活细胞凋亡的作用。ADSCs-Exos可抑制缺血再灌注损伤[12]、氧化应激[22]、缺氧[23]情况下的心肌细胞凋亡。在缺血再灌注损伤情况下，Bai等[12]研究中指出，在过氧化氢刺激下可促进ADSCs-Exos抑制心肌细胞凋亡的作用。在小鼠肾脏缺血再灌注损伤中，ADSCs-Exos抑制肾脏细胞凋亡，促进肾脏细胞增殖[24]。ADSCs-Exos可通过上调Bcl-2/Bax抑制坐骨神经损伤部位的施旺细胞（SCs）[25]、血清剥夺诱导的骨样细胞系MLO-Y4细胞[18]的凋亡。在各类癌细胞中，Wang等[26]指出ADSCs-Exos可激活Hippo信号通路的两个关键下游效应蛋白YAP和TAZ，在体外促进乳腺癌细胞的增殖和迁移，并保护其免受血清饥饿处理或化疗药物5-氟尿嘧啶诱导的早、晚期癌细胞的凋亡。但ADSCs-Exos对不同类型癌细胞的效果不同。如ADSCs-Exos分泌的miR-145可通过caspase-3/7途径抑制转移性前列腺癌细胞增殖，诱导癌细胞凋亡[27]。Reza等[28]则证明了ADSCs-Exos通过诱导细胞周期S、G2期阻滞，从而抑制A2780和SKOV-3卵巢癌细胞的增殖与集落形成能力，促进其凋亡。

3.2 细胞自噬中的抑制与激活

ADSCs-Exos在细胞自噬中具有双向作用，如在肝受损细胞和糖尿病、肾病的足细胞中起到激活自噬的作用，而在坐骨神经损伤的SCs中起到抑制自噬的作用。Qu等[29]指出ADSCs-Exos能选择性转移miR-181-5p到受损的肝细胞，通过抑制其STAT3/Bcl-2/Beclin 1途径增加自噬，有效治疗肝病。也有研究表明ADSCs-Exos携带的miR-486可以抑制足细胞中Smad1/mTOR信号通路的激活，导致自噬增加以及足细胞凋亡减少[30]。相反，ADSCs-Exos通过减轻坐骨神经损伤部位的SCs自噬作用，还可以加速周围神经损伤的修复[31]。

4 免疫反应中的作用

4.1 抗炎

ADSCs-Exos可介导miR-21-3p、miR-17、miR-223等抑制炎症反应。其中ADSCs-Exos通过miR-21-3p抑制缺氧/再氧化处理细胞的凋亡，还可通过miR-21-3p上调MAT2B，进而抑制脑组织的凋亡和炎症反应[32-33]。ADSC-Exos也可介导miR-17和miR-223发挥作用，通过靶向硫氧还原蛋白互作蛋白（TXNIP）和抑制肝巨噬细胞炎症小体激活，减少炎症的发生[34]。另有研究报道ADSCs-Exos可通过抑制NF-κB和MAPK信号通路，抑制BV2小胶质细胞的活化，从而抑制TNF-α、IL-6、IL-1β、iNOs等炎症因子的基因表达和蛋白分泌，保护细胞免受损伤[35-36]。在IL-1β刺激的关节炎软骨细胞中，ADSCs-Exos使核因子-κB和激活蛋白1活化降低，增强抗炎细胞因子IL-10的产生和膜联蛋白A1的表达，减少炎症反应[37]。此外ADSCs-Exos可诱导巨噬细胞向抗炎M2细胞极化[38]，并促使其表达高水平的酪氨酸羟化酶、精氨酸酶-1和IL-10[39]。ADSCs-Exos还可以通过调节Treg细胞数量、降低血脂和炎症因子，缓解葡聚糖硫酸钠

诱导的急性结肠炎模型小鼠的症状[40]。

4.2　免疫调节

ADSCs-Exos具有免疫调节作用，可降低体内的IFN-γ、IL-1β、TNF等的水平，抑制体外刺激下T细胞的增殖、分化及活化，调节机体的免疫功能，促进组织修复[41-42]。此外，ADSCs-Exos携带的miR-223可诱导巨噬细胞极化，具有免疫调节的作用，且低氧条件下作用更显著[43]。在血管复合异体移植术中，ADSCs-Exos处理后的供体细胞嵌合性、Tr1、Treg明显增加，CD4T、Th1细胞明显减少，抑制同种异体免疫反应[44]。

5　作为靶向治疗的转运载体

研究表明含有聚吡咯钛的ADSCs-Exos可以显著促进体内成骨[45]。Li等[46]以ADSCs-Exos为载体，将CD63-血管内皮生长因子靶向输送到淋巴内皮细胞，显著促进了淋巴内皮细胞的增殖、迁移和淋巴管形成，从而治疗淋巴水肿。此外Zhang等[47]研究发现，ADSCs-Exos是miRNAs或circRNAs的重要载体，在非小细胞肺癌中，circ-100395过表达的ADSCs-Exos可以抑制非小细胞肺癌细胞的生物活性，从而抑制非小细胞肺癌的恶性转化。而载有miR-381的ADSCs-Exos可在体外抑制人乳腺细胞系MDA-MB-231的增殖、迁移和侵袭能力[48]。研究表明，对奥沙利铂耐药的结直肠癌细胞Exos可将circ-0005963（即ciRS-122）传递给敏感细胞，促进糖酵解和耐药性，而Exos转运的si-ciRS-122在体内可通过调控ciRS-122-miR-122-PKM2通路抑制糖酵解，逆转对奥沙利铂的耐药[49]。同样，ADSCs-Exos是否可以通过某些机制参与调控细胞的耐药性也值得我们探讨，这将为癌症耐药性治疗提供新思路。

6　其他作用

除上述的功能外，ADSCs-Exos在调节肥胖、调控胰岛素抵抗、促进组织再生等方面也具有一定功能。ADSCs-Exos可以转移到巨噬细胞中诱导抗炎M2表型，增加解偶联蛋白1的表达，促进白色脂肪组织的形成，从而改善肥胖相关的炎症和代谢。在肥胖小鼠模型中，ADSCs-Exos可以降低肥胖引起的全身胰岛素抵抗和肝脏脂肪变性[39]。ADSCs-Exos可以通过刺激PI3K-Akt、Jak-STAT和Wnt等与神经再生相关的信号通路，促进SCs的增殖、迁移、分化，进而促进神经再生[50-51]。ADSCs-Exos还可以通过激活内皮细胞中PI3K/AKT信号通路减轻组蛋白诱导的内皮损伤，从而改善急性肺损伤[52]。此外，Wu等[53]研究发现ADSCs-Exos可以促进毛囊的发育与再生，促进头发的再生。

7　小结与展望

本文通过总结ADSCs-Exos的功能和研究现状，发现ADSCs-Exos在血管重建、组织修复与再生、抑制肿瘤生长、靶向治疗等领域有较大的发展空间，其活性和生物学功能受环境影响。如在低氧环境或过氧化氢刺激下，ADSCs-Exos促血管新生和免疫调节的效果更加显著。此外，ADSCs-Exos可作为靶向治疗的转运载体，利于定向治疗，减少副作用。其联合治疗效果较为明显，如透明质酸、多巴胺的PLGA、β-磷酸三钙和水凝胶支架等与ADSCs-Exos结合，可以更好地发挥作用，这些都为ADSCs-Exos的功能优化提供了策略。

ADSCs-Exos具有双向调节作用，如促进或抑制细胞凋亡及自噬、对炎症反应和免疫调节的正负调控等。在损伤情况下，为实现组织修复再生，ADSCs-Exos往往起到抑制细胞凋亡的作用；但在癌细胞中，ADSCs-Exos既可抑制细胞凋亡，也可促进凋亡，这一作用可能取决于癌症的类型或ADSCs-Exos中miRNAs的种类。如前所述，ADSCs-Exos抑制乳腺癌细胞凋亡时，伴随有Hippo信号通路的两个关键下游效应蛋白YAP和TAZ的激活，而miR-151等家族成员被证实具有促癌功能[26]。那么ADSCs-Exos是否通过介导miR-151抑制乳腺癌细胞凋亡，ADSCs-Exos与miR-151之间与Hippo信号通路效应蛋白YAP和TAZ是否存在联系，如何利用好ADSCs-Exos这把“双刃剑”调节肿瘤生长，还有待进一步研究。

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