缺氧条件下中枢神经系统外泌体作用机制

张佳佳[1] 苏刚[2] 陈丽霞[1] 王满侠[1] 周娟平[1] 高娟[1] 张振昶[1]*

([1]兰州大学第二医院神经内科, 兰州 730030; [2]兰州大学基础医学院遗传研究所, 兰州 730000)

摘要 外泌体是来源于细胞内吞噬作用的细胞外囊泡(extracellular vesicles, EVs), 其含有特定的蛋白质、脂质、RNA和DNA, 能将信号传递给受体细胞, 从而介导细胞通讯过程。缺氧作为一种严重的细胞应激, 是脑部疾病的重要特征, 可以诱导外泌体的释放并影响其内容物。越来越多的证据显示, 外泌体携带的生物活性物质可以反映其细胞起源和疾病状态, 成为诊断或预测缺氧性疾病的潜在生物标志物。现对外泌体的一般特性和功能、缺氧条件下外泌体的分泌机制以及缺氧胁迫下正常神经细胞(例如神经元和星形胶质细胞)和胶质瘤细胞释放的外泌体的作用机制作一综述。

关键词 外泌体; 缺氧; 氧和葡萄糖剥夺; 中枢神经系统

The Role of Exosomes in Central Nervous System under Hypoxic Condition

ZHANG Jiajia[1], SU Gang[2], CHEN Lixia[1], WANG Manxia[1], ZHOU Juanping[1], GAO Juan[1], ZHANG Zhenchang[1]*

([1]*Department of Neurology, Lanzhou University Second Hospital, Lanzhou 730030, China*;
[2]*Institute of Genetics, School of Basic Medical Sciences, Lanzhou University, Lanzhou 730000, China*)

Abstract Exosomes are EVs (extracellular vesicles) deriving from the endosomal system, which contain specific proteins, lipids, RNA and DNA. They can transfer signals to recipient cells thus mediating intercellular communication. Hypoxia, as a serious cellular stress, is a vital feature of brain diseases, which can induce the release of exosomes and affect the content of exosomes. Increasingly, studies have indicated that the bioactive substances carried by exosomes can reflect their cellular origin and disease status, which can become potential biomarkers for the diagnosis or prediction of hypoxic diseases. This article reviews the general characteristics of exosomes, functions of exosomes, secretory mechanism of exosomes under hypoxic condition, as well as the mechanism of exosomes released by normal nerve cells (such as neurons and astrocytes) and glioma cells under hypoxia.

Keywords exosomes; hypoxia; oxygen and glucose deprivation; central nervous system

充足的氧气(40~60 mmHg氧压)供应对哺乳动物的正常新陈代谢和生理功能至关重要。缺氧是指氧分压不足, 降至大约10 mmHg时发生的缺氧反应。缺氧是脑部疾病(包括缺血性、创伤性、慢性神经退行性病变以及脑肿瘤等)中常见的病理性应激, 可影响细胞周期、形态结构、代谢、增殖、分化、自噬、

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*通讯作者。Tel: 13893647595, E-mail: 13893647595@163.com

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*Corresponding author. Tel: +86-13893647595, E-mail: 13893647595@163.com

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凋亡等, 成为细胞死亡潜在的环境因子[1-2]。然而最近的实验数据表明, 暴露于特定剂量的缺氧能触发中枢神经系统神经保护作用和缺氧耐受性的内源性机制[3]。但是, 神经肿瘤微环境中的缺氧却与肿瘤预后不良密切相关[4]。外泌体(exosomes)作为神经系统重要调节因子, 微环境的变化可以影响外泌体的组成和释放水平。近年来, 在不同的缺氧实验模型中检测到外泌体释放增加, 且外泌体通过提供缺氧特异性信息广泛参与缺氧损伤机制以及缺氧适应机制[5]。然而, 缺氧对神经系统外泌体的分泌、组成和功能的影响机制尚不清楚。因此, 这篇综述就缺氧对外泌体的影响机制, 以及正常神经细胞和胶质瘤细胞在缺氧条件下释放外泌体的作用机制进行总结。

1 外泌体概述

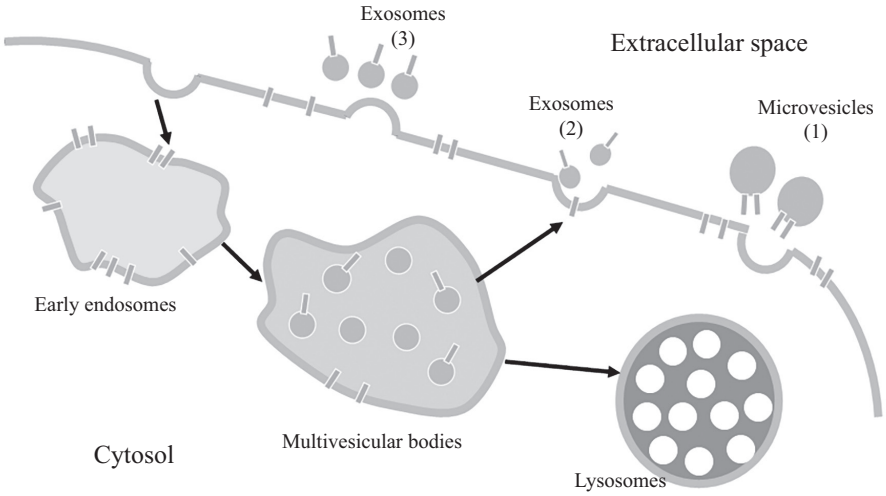
1.1 外泌体的形成及生物学特点

生物体内几乎所有的细胞都分泌细胞外囊泡(extracellular vesicles, EVs), EVs是脂质双层膜包裹性的囊泡。外泌体起始于细胞内吞作用, 是直径为30~100 nm的EVs[6-7]。质膜内陷形成早期核内体(early endosomes), 然后内生出芽形成管腔内囊泡(intraluminal vesicles, ILVs)并在多囊泡体(multivesicular bodies, MVBs)内聚集。一部分MVBs被运送至溶酶体进行降解; 另一部分MVBs可与质膜(plasma membrane, PM)融合, 释放出ILVs到胞外空间, 被释放到细胞外的ILVs即外泌体[8-10](图1)。外泌体的主要内容物包括来自核内体、质膜和胞质溶胶的特定蛋白质亚集、某些脂类、DNA、mRNA、miRNA(microRNA)、lncRNAs(long noncoding RNAs)[11]。虽然现在已经有大量研究专注于外泌体内容物, 但是这些内容物的具体参与方式仍然不清楚, 未来还需要进一步的深入探讨。

1.2 外泌体的功能

外泌体的生物学功能和异质性取决于来源细胞的种类以及释放外泌体时的细胞状态。最开始的研究认为, 外泌体主要负责清除多余或无功能的细胞成分。但现在越来越多的研究表明, 外泌体在各种生物学过程中发挥着重要作用, 如血管生成、抗原呈递、细胞凋亡、凝血、细胞稳态、炎症和细胞间信号传导等。外泌体的这些作用归因于它们能够转运蛋白质、脂质以及RNA和DNA等, 从而影响各种疾病的生理和病理过程, 包括癌症、神经退行性疾病、感染和自身免疫性疾病等[12]。

此外, 外泌体在生物医学应用中具有巨大潜力。外泌体的显著特点是减少炎症反应、穿透血脑屏障以及多次静脉给药而没有任何副作用, 现已成为一种新型的治疗方法[13]。来自骨髓间充质干细胞(mesenchymal stem cell, MSC)的外泌体通过促进细胞外基质重塑来抑制炎症因子的表达, 从而发挥



(1) 微泡(microvesicles, MVs)是EVs的主要类别之一, 由质膜向外出芽形成; (2) MVBs可与质膜融合后释放外泌体; (3) 外泌体可直接通过质膜向外萌芽形成。

(1) Microvesicles (MVs) represent one of the major classes of EVs and are formed by the outward budding of the plasma membrane. (2) The MVBs fuse with plasma membrane and release exosomes. (3) Exosomes are formed directly by outward budding of plasma membrane.

图1 外泌体的生物发生(根据参考文献[9-10]修改)

Fig.1 Biogenesis of exosomes (modified from references [9-10])

抗炎作用和促进组织再生。同样, 诱导多功能干细胞、胚胎干细胞和心脏祖细胞分泌的外泌体具有与MSC来源的外泌体相似的治疗效果[14-15]。肿瘤细胞来源的外泌体可通过促进T细胞凋亡, 抑制树突状细胞分化、NK细胞毒性以及调节性T细胞等抑制肿瘤免疫过程, 从而促进肿瘤进展[16]。与全身给药相比, 当化疗药物被装载于外泌体中时, 观察到细胞内阿霉素(doxorubicin, DOX)浓度更高, 而心脏毒性水平更低[17]。在小鼠异种移植模型中, miR-122在脂肪来源的间充质干细胞外泌体中的过表达增强了对肿瘤生长的抑制和化疗敏感性[18]。同样, 骨髓基质细胞衍生的外泌体富含miR-146b, 能够抑制胶质瘤大鼠模型中肿瘤细胞的增殖[19]。以上这些研究结果说明了外泌体的治疗潜力可以通过用功能分子修饰或miRNA的过表达来挖掘。

2 缺氧条件下的外泌体

外泌体的释放与内容物的变化与周围环境密切相关, 如激活或应激条件。外泌体是细胞调节细胞内应激状态和适应周围环境的一种有效介质[20]。缺氧处理使外泌体组分的改变可以增强外泌体的生物学效应[21-22]。

2.1 缺氧可以促进外泌体的释放和内容物的变化

EVs的释放量和内容物可以根据缺氧刺激而发生显著改变。越来越多的证据表明, 缺氧刺激细胞可以增加EVs的分泌。人乳腺癌细胞[23]、肝癌细胞[24]、胶质瘤细胞[25]以及前列腺癌细胞[26]等在缺氧条件下, 外泌体的释放量增加、直径变小以及外泌体标志蛋白CD63和CD81含量升高。与这些结果一致的是, 肺动脉内皮细胞[27]、脂肪细胞[28]、上皮细胞[29]和心脏祖细胞[30-31]等非肿瘤细胞在缺氧条件下也可以分泌更多的外泌体。

在缺氧条件下, 细胞释放外泌体的丰度显著提升, 且外泌体内容物的组分和含量也不发生变化。缺氧脂肪细胞来源的外泌体中75种蛋白质被上调, 而67种蛋白质被下调[28]。基质金属蛋白酶-13(matrix metalloproteinase-13, MMP-13)在缺氧鼻咽癌细胞来源的外泌体中过度表达[32]。除了分析外泌体蛋白外, 大量研究还专注于外泌体miRNA。黑色素瘤来源的15种miRNA在缺氧条件下含量更高, 促进了黑色素瘤表型的可塑性、耐药性和转移性[33]。研究表明, 缺氧不仅促进细胞外泌体的释放, 而且可以选择性地改变外泌体中内容物的组分, 包括选择性蛋白质和miRNA[5]。

2.2 缺氧条件下外泌体调节的分子机制

缺氧诱导因子(hypoxia-inducible factor, HIF)可以诱导细胞囊泡生成增加, 从而促进细胞间通讯, 而缺氧应激的主要转录反应是由缺氧诱导因子HIF介导的[34]。缺氧条件下, 胶质母细胞瘤(glioblastoma, GBM)细胞来源的EVs富含*HIF-1α*靶基因的mRNA, 包括Bcl-2相互作用蛋白3(Bcl-2 interacting protein 3, *BNIP3*)、赖氨酰氧化酶(lysyl oxidase, *LOX*)、*N*-myc下游调节1(*N*-myc downstream regulated 1, *NDRG1*)[35]。除mRNA外, 这些EVs中还富集了多种HIF-1α诱导蛋白, 包括白细胞介素-8(including interleukin-8, IL-8)、胰岛素样生长因子结合蛋白1(insulin-like growth factor binding protein 1, IGFBP1)、碳酸酐酶9(carbonic anhydrase 9, CAIX)[35-36]。AGA等[37]甚至在鼻咽癌细胞EVs中发现了功能性HIF-1α。HIF被认为通过增加一些细胞表面受体, 如表皮生长因子受体(epidermal growth factor receptor, EGFR)、葡萄糖转运蛋白受体和转铁蛋白受体的表达和活化诱导内吞噬作用, 从而促进外泌体的释放[38]。也有研究表明, HIF通过激活Rab家族小GTP酶的成员Rab22A来增加外泌体的产生和分泌[39]。Rab22A与EVs共定位于乳腺癌细胞的质膜表面。以上这些转录元件和信号通路使细胞能够适应低氧或低氧相关的条件, 如低pH和氧化应激等[39]。

3 缺氧条件下中枢神经细胞的外泌体

在神经系统中, 包括神经元及神经胶质细胞在内的多种细胞可以分泌外泌体。这些外泌体可以通过表面间相互作用和细胞间miRNA的穿梭机制来介导细胞间通讯[40]。来自神经系统的外泌体不仅可以反映中枢神经系统的病理改变作用机制, 而且为神经保护作用提供了新的治疗靶点。

3.1 缺氧条件下神经元的外泌体

在神经系统中, 神经元外泌体通过调节轴突发育、突触可塑性和细胞间通讯发挥保护作用[41]。氧和葡萄糖剥夺(oxygen/glucose deprivation, OGD)是一种被广泛接受的体外中风模型, 用于模拟缺氧导致的细胞凋亡和坏死过程[42]。经OGD处理的皮层神经元来源的外泌体中miR-181c-3p可以降低星形胶质细胞趋化因子(C-X-C基序)配体1(C-X-C motif

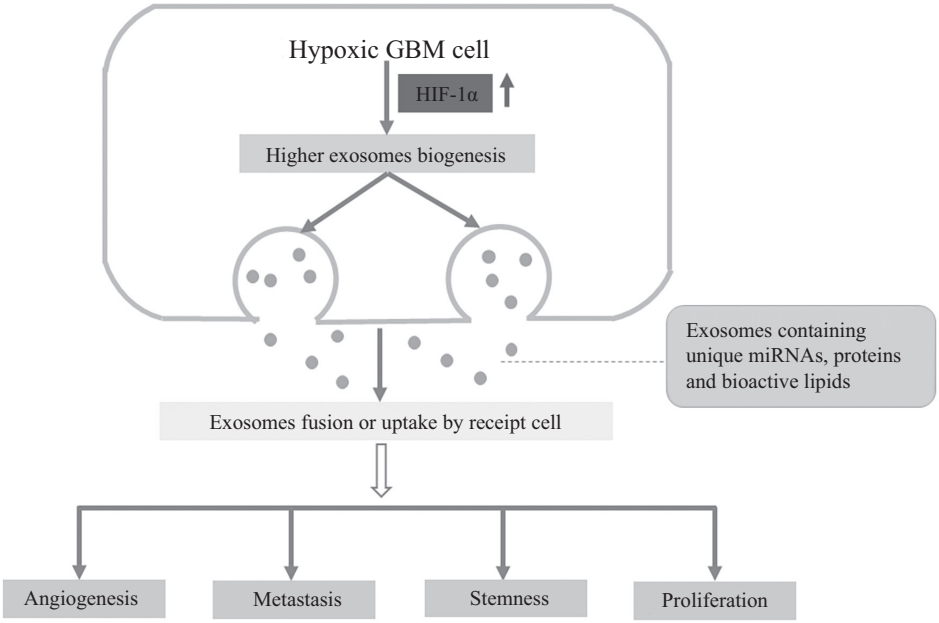
chemokine ligand 1, CXCL1)和炎症因子的表达, 从而阻断中枢神经系统中炎症体的激活[43]。

3.2 缺氧条件下星形胶质细胞的外泌体

尽管在病理状态下反应性星形胶质细胞往往对邻近细胞产生有害影响, 但最新研究表明, 星形胶质细胞也可在脑损伤过程中发挥脑保护作用或促进脑重塑[44]。星形胶质细胞释放的外泌体通过调节哺乳动物雷帕霉素靶蛋白(mammalian/mechanistic target of rapamycin, mTOR)和炎症凋亡信号通路减轻OGD诱导的神经元死亡和功能障碍, 发挥脑保护作用[45]。来源于OGD预处理的星形胶质细胞的外泌体释放量增加, 并且可以被神经元摄取, 通过外泌体介导的miR-92b-3p穿梭机制保护神经元, 免受OGD损伤[46]。朊病毒蛋白(prion protein, PrP)可保护神经细胞免受缺氧损伤, 用OGD处理星形胶质细胞后释放的外泌体中PrP水平升高, 提高了神经元在缺氧条件下的存活率[47]。OGD星形胶质细胞释放的外泌体处理原代皮层神经元后, 显著增加了每个神经元的轴突分枝数量和总轴突长度[48]。与单纯OGD星形胶质细胞释放的外泌体相比, 用过表达miR-133b的MSC释放的外泌体预处理OGD星形胶质细胞后释放的外泌体对原代皮质神经元突起的生长具有更强的促进作用[48]。脑信号蛋白3A(semaphorin 3A, Sema3A)是一种抑制轴突生长的细胞外基质分子, Sema3A抑制剂处理OGD星形胶质细胞后释放的外泌体促进了OGD皮质神经元轴突生长和功能恢复[49]。

4 缺氧条件下GBM细胞的外泌体

肿瘤是低氧微环境作用研究的原型系统, 肿瘤微环境的改变是癌症进展和治疗耐药性的重要因素。GBM是神经系统中最常见、致死率最高的恶性肿瘤, 缺氧是胶质瘤的公认特征。但是, 癌细胞在肿瘤发展过程中的缺氧耐受机制仍是一个需要探讨的问题[50]。越来越多的证据表明, 缺氧肿瘤细胞来源的外泌体通过影响肿瘤血管生成、侵袭、转移和免疫逃逸促进肿瘤进展(图2)。将GBM细胞外泌体进行质谱分析, 发现缺氧胁迫下的外泌体蛋白质组学发生显著改变, 选择性地升高促血管生成因子, 包括蛋白质赖氨酸6-氧化酶(lipoprotein receptor, LOX)、血小板反应蛋白1(thrombospondins 1, TSP1)和血管源性内皮因子(vascular endothelial growth factor, VEGF)等, 从而诱导血管内皮细胞增殖[51]。与常氧条件相比, 缺氧条件可以调节mRNA和蛋白(如LOX、MMP以及IL-8等)在GBM细胞衍生的外泌体中的富集过程。缺氧GBM细胞来源的外泌体可以诱导内皮细胞分泌生长因子和细胞因子, 并激活周



↑: HIF-1α升高。

↑: increase of HIF-1α.

图2 缺氧胶质瘤细胞释放的外泌体对肿瘤微环境的影响

Fig.2 Effects of exosomes released by glioma cells under hypoxic condition on tumor microenvironment

细胞PI3K/AKT信号。外泌体介导的信号通路显著增强了肿瘤血管形成、周细胞血管覆盖和GBM细胞增殖, 是肿瘤发展过程中缺氧耐受性的靶向驱动因素[52]。

ZHAO等[53]发现, VEGF-A在缺氧GBM细胞来源的外泌体中过表达, 并通过阻断claudin-5和occludin的表达来增强血脑屏障通透性。外泌体介导的细胞间通讯与肿瘤免疫抑制微环境的形成密切相关。低氧GBM的外泌体中的miR-1246通过靶向TERF2IP激活STAT3(signal transducer and activator of transcription 3)信号通路, 抑制NF-κB(nuclear factor kappa-B)信号通路, 参与诱导M2巨噬细胞极化, 继而促进了胶质瘤的增殖、迁移和侵袭。因此, 靶向miR-1246的治疗可能有助于抗肿瘤免疫治疗[54]。GBM在脑肿瘤患者中死亡率最高, 放射治疗是其治疗的重要组成部分。关于GBM进展和抗辐射性的机制研究表明, 缺氧GBM特征性表达和分泌外泌体中的miR-301a是Wnt/β-catenin的强效调节因子, 并通过靶向抗癌基因转录延伸因子A样蛋白7(transcription elongation factor a-like 7, TCEAL7)降低辐射敏感性[55-56]。

5 小结与展望

神经系统是一个复杂的网络系统, 外泌体通过其携带的蛋白质和miRNA在神经细胞之间发挥重要的通讯功能。缺氧作为神经系统疾病的重要特征, 通过HIF依赖性调节机制促进外泌体的释放以及影响外泌体内容物的组分和含量。缺氧条件下细胞释放的外泌体可以靶向靠近其供体细胞或者远离其释放部位的细胞, 通过提供缺氧特异性信息广泛参与缺氧相关疾病的病理生理过程。缺氧条件下神经元和星形胶质细胞释放的外泌体对神经系统发挥显著保护作用, 为神经保护的非药物治疗提供新的方向; 而胶质瘤细胞在缺氧条件下释放的外泌体携带多种血管生长相关因子, 在肿瘤血管生成、侵袭、转移和治疗抵抗性中发挥关键作用。虽然缺氧能显著影响外泌体的释放、组成和功能, 但外泌体在缺氧胁迫下释放机制的改变以及如何靶向调控的作用机制仍然不完全清楚。因此, 阐明缺氧条件下释放外泌体的相关信号通路可能有助于未来早期发现和治疗缺氧性疾病(如缺血性疾病和肿瘤), 为脑缺氧性疾病的病理生理学、诊断和治疗提供新的思路。

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