

外泌体在骨肉瘤侵袭转移及耐药性中的研究进展

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摘要: 骨肉瘤(osteosarcoma)是一种具有高度侵袭性的恶性肿瘤,已成为青少年人群中导致癌相关死亡的首要疾病。但由于其早期高发的肺转移率以及广泛的对化疗药物耐药性问题,骨肉瘤在临床上的治疗仍存在巨大挑战。目前,骨肉瘤的早期诊断及基因治疗已经在国内外的基础研究和临床应用中取得了一定的进展,其中外泌体(exosomes)在骨肉瘤中的诊断治疗具有极大的应用前景。外泌体是一种可由多种活细胞分泌的纳米级(40~100 nm)微囊泡,它具有传递 mRNA、miRNA、DNA 和蛋白质等各种信息和功能性物质的功能。它可由多种活性细胞产生和分泌,存在于多种体液和细胞间液中。由于其特殊的存在和传递形式以及所搭载的信息和物质,因此,骨肉瘤来源的外泌体可通过多种途径和方式促进骨肉瘤的发生、侵袭转移、耐药性及免疫逃逸。利用这些特点,外泌体可被人为搭载靶向药物或治疗性基因等物质,或通过多种方式对其分泌和释放进行调控来治疗多种肿瘤。近年来,关于外泌体在骨肉瘤方面作用和应用的研究成为热点,但仍停留在基础研究且尚未在临床的诊断及治疗中进行应用。本文旨在对外泌体在骨肉瘤侵袭转移及耐药性上的作用机理、临床诊断、治疗方面的研究进展进行总结,望有助于为利用外泌体诊断、治疗和改善骨肉瘤预后提供参考。

关键词: 外泌体;骨肉瘤;转移;肿瘤免疫;治疗

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Research progress on the role of exosomes in metastases and drug resistance of osteosarcoma

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Abstract: Osteosarcoma is a malignant tumor with a poor prognosis, and it has become the leading cause of cancer-related deaths in adolescents. However, due to its early high rate of lung metastasis and extensive resistance to chemotherapeutic drugs, clinical treatment of osteosarcoma remains a huge challenge. At present, advances in the early diagnosis and gene therapy of osteosarcoma have achieved some progress in fundamental researches and clinical applications worldwide. Among them, exosomes have great research prospects in the diagnosis and treatment of osteosarcoma. Exosomes are nanoscale microvesicles (40–100 nm) that can be secreted by a variety of living cells and have the ability to transmit multiple messages and functional substances such as mRNA, miRNA, DNA, and proteins. It can be produced and secreted by a variety of living cells and is present in a variety of body fluids and intercellular fluids. Because of its special existence and transfer form, as well as the information and substances it carries, osteosarcoma-derived exosomes can promote the tumorigenesis, invasion, metastasis, drug resistance, and immune escape of osteosarcoma in many ways. Using above characteristics, exosomes can be artificially loaded with targeted drugs or therapeutic genes, or they can be regulated in various ways to adjust the secretion and release in multiple tumor cells. In recent years, research on the role and application of exosomes in osteosarcoma has become a hotspot, but it still remains in basic research and has not yet been applied in clinical diagnosis and treatment. This article aims to summarize the functional mechanisms of exosomes on the invasion, metastasis and drug resistance in osteosarcoma, as well as the research progress in clinical diagnosis and treatment, hoping this will contribute to develop novel strategies to diagnose, treat and improve the prognosis in osteosarcoma.

Key words: Exosomes; Osteosarcoma; Metastasis; Tumor immunology; Therapy

骨肉瘤是一种好发于青少年的原发恶性肿瘤,平均发病年龄为16岁^[1],并且在青少年人群中已成为因癌致死的首要疾病^[2]。尽管近年来综合治疗方法如治疗骨肉瘤的新型手术方式、围手术期化疗和基因治疗蓬勃发展,骨肉瘤的疗效有了很大的提高,但骨肉瘤患者在早期阶段,仍有约15%~20%的患者存在肺转

移^[3],且由于骨肉瘤发展到IV期时多伴有对化疗药物耐药性存在^[4],导致患者的生存率依然不高,其预后也较原位癌患者更差。有研究^[5-6]表明,骨肉瘤细胞可以自发地向周围的微环境中释放外泌体,这些外泌体能够发挥如诱导或促进骨肉瘤细胞的免疫逃逸,促进骨肉瘤的血管形成和生长,以及骨肉瘤的侵袭和转移等多重功能。因此,针对外泌体在骨肉瘤的早期转移机制和耐药机制中作用的研究,已成为目前骨肉瘤的研究热点。

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1 外泌体概述

外泌体是一种由哺乳类动物体内的多种活性细胞自发产生并主动分泌的纳米级(直径40~100 nm)碟形多囊泡体^[7-9]。目前研究人员普遍认为,外泌体是源于多泡体(multivesicular bodies)的内腔膜泡(intraluminal vesicles)与细胞质膜融合后向胞外释放形成的产物^[10-11],并且在体内正常或病理状态下均可产生。多泡体能够与溶酶体融合来降解其中的内容物,或能与质膜融合向其周围细胞外间质释放内腔膜泡^[6,12],形成内含有多生物活性物质的外泌体^[12-13]。目前,可从多种体液或分泌液如血清^[12,14]、尿液^[15]、关节液^[16]、恶性胸腔积液^[17]、附睾液^[18]和精液^[19]中分离出外泌体。在鉴别上,除了与其他细胞微泡的直径和功能有所不同外,外泌体还有一个特点即只由活细胞分泌释放^[10,20]。

1.1 外泌体的来源 1983年,JOHNSTONE等首次报道了一种由羊成熟网织红细胞释放的膜性小囊泡,起初研究者认为这种小囊泡是用来排出细胞内的废物和无用蛋白质的载体,如可以运载红细胞成熟过程中进入红细胞内的转铁蛋白受体,并将这种小囊泡命名为外泌体^[21]。然而,越来越多的研究结果表明,外泌体是多种细胞间传递信息的重要介质,如癌细胞和正常细胞之间的信息传递等^[13,22]。目前,已经在多种细胞来源的外泌体中发现了超过4 600种包括蛋白质和核酸等的生物活性物质,如dsDNA、miRNAs^[23-24]、主要组织相容性复合体I(MHC class I, B细胞来源^[25]、T淋巴细胞来源^[26]、树突细胞来源^[27]、肠上皮细胞来源^[28]和肿瘤细胞来源^[29])、网织红细胞来源的 $\alpha 4\beta 1$ 整联蛋白^[30],来源于肿瘤细胞的热休克蛋白HSC7023,和源自树突细胞和T淋巴细胞的类钙调神经磷酸酶B样蛋白(calcineurin B-like protein, CBL)和淋巴细胞特异性蛋白酪氨酸激酶(lymphocyte-specific protein tyrosine kinase, LCK)等^[27,31]。

1.2 外泌体的结构和功能 外泌体的结构和生物学功能使其能够在细胞信息和物质交换过程中发挥各种功能。首先,外泌体可以通过多种配体和胞膜表面受体的结合,从而在细胞不直接接触的情况下发挥生理作用。其次,外泌体能够结合在靶细胞膜上,从而作为媒介使靶细胞获得结合新表面受体的潜能。另外,外泌体在与靶细胞融合的过程中,可与其交换膜蛋白及细胞溶质从而达到2种不同类型细胞的物质和信息交换^[9,25,32]。而且释放到细胞周围,或随体液传递至远端的外泌体,能够携带一系列调节细胞微环境的遗传物质和蛋白质,从而在不同水平和多种方式及途径上实现细胞间信息与物质的交换,并以此完成进一步调控。

2 外泌体在促进骨肉瘤侵袭和转移中的作用

在众多骨肉瘤侵袭转移的研究中认为,骨肉瘤细胞在转移前就有相关因子先到达转移灶进而形成利于肿瘤生长的微环境。研究^[33]表明,外泌体在骨肉瘤这一进程中扮演了重要角色,其可以通过将蛋白(如EGFR蛋白、KRAS蛋白和SRC家族激酶蛋白等)和RNA等可改变细胞微环境的物质传递到靶细胞周围,从而为骨肉瘤的转移提供有利条件。此外,骨肉瘤来源的外泌体中富含有多种基质金属蛋白酶(matrix metalloproteinase, MMPs, 如MMP1、MMP13)和解整合素金属蛋白酶(a disintegrin and metalloproteinase, ADAMs 如ADAM-10、ADAMTS1)。而MMP家族的蛋白酶和ADAMs能够在体内发挥降解细胞外基质并剪切细胞间黏附分子的作用,从而促进骨肉瘤细胞侵袭并为其转移提供条件^[27,34]。同时,外泌体携带的mRNA和miRNA(如miR-675),可通过调控Wnt、TGF- β 及CALN1等信号通路调控并促进骨肉瘤的血管生成,或通过诱导单核细胞分化为M2型巨噬细胞,进而促进骨肉瘤的生长和侵袭转移^[35-37]。

3 外泌体在骨肉瘤化疗耐药和免疫逃逸中的作用

目前在临床对于骨肉瘤的治疗中,仍以手术及围手术期化疗为主^[38]。然而,包括骨肉瘤在内的许多恶性肿瘤,在临床治疗中出现的对化疗药物耐药性的问题变得越来越普遍和严重。有研究^[9]表明,骨肉瘤细胞源性的外泌体中,可分离出能够使骨肉瘤产生对化疗药物耐药性的miR-135b等RNA。同时,这些外泌体也可通过传递糖蛋白发挥作用,使骨肉瘤产生对化疗药物的抵抗性,例如骨肉瘤细胞可以在外泌体递送糖蛋白的过程中,获取来自其他肿瘤细胞的抗肿瘤药物的物质,达到抵抗紫杉醇的作用^[7]。外泌体的产生可以被与溶酶体相关细胞器(lysosome-related organelle)相关的ATP结合盒转运体A3(ATP binding cassette A3, ABCA3)调控,而ABCA3被认为是导致肿瘤产生对化疗药物耐药性的原因之一^[39]。另外有研究发现,由基质细胞转移至乳腺癌的外泌体,可通过抗病毒及NOTCH3通路增强肿瘤对于化疗药物和射线治疗的抵抗性^[7]。

近年来,有许多研究都证实了骨肉瘤介导的外泌体具有广泛促进免疫抑制的作用。有研究^[40]表明,这类外泌体能够通过多种通路和机理抑制T淋巴细胞和NK细胞的活性,甚至诱导T细胞凋亡从而帮助骨肉瘤细胞逃离免疫监视,并同时激发骨髓源性抑制细胞(MDSC)的活性。有研究显示,骨肉瘤释放的外泌体可通过NKG2D可溶性受体下调NK细胞的活性,其机制可能是外泌体所释放或膜表面搭载的可溶性主要组织相容性复合体I链相关蛋白(sMIC),介导了NK细

胞或细胞毒性 T 淋巴细胞功能的下调,从而为肿瘤细胞产生免疫逃逸提供有利环境和条件^[33]。此外,ISLA LARRAIN M T 等^[41]发现,有 36% 的癌症患者体液中可分离出含有吡啶胺双加氧酶 (IDO) 的外泌体,而吡啶胺双加氧酶可通过介导色氨酸耗竭来调节机体抗肿瘤免疫,并参与肿瘤炎症微环境的形成,促进肿瘤血管新生等。

4 外泌体在骨肉瘤诊断和治疗中的应用

SHIMBO K 等^[27]研究发现通过外泌体搭载的合成 miR-143 能够高效地传递到受体细胞,并明显抑制 143B 骨肉瘤细胞的生长及转移。有研究发现外泌体转运的 mRNA 可被受体细胞翻译及表达^[42]。此外,未成熟的树突细胞衍生的外泌体与多柔比星和其他药物的整合可以有效增加肿瘤细胞对药物的摄取,并发挥抑制肿瘤细胞增殖的作用^[43],提示无论在基因治疗还是药物治疗骨肉瘤等恶性肿瘤上,外泌体都可以作为临床治疗的潜在的递送系统。有研究在患者体内的肿瘤细胞中发现了 8 种具有诊断学价值的 microRNA,这些 microRNA 同样存在于患者血液的外泌体中并且与肿瘤细胞中的含量相当,并且在多种体液中均可被分离出来,表明利用外泌体作为标志物来检测和诊断癌症甚至是诊断无症状患者成为可能,同时也可作为癌症患者病情变化及预后的重要指标^[44]。

上文所述的外泌体对促进骨肉瘤等恶性肿瘤发生发展的相关研究已较为完善,因此,抑制或减少骨肉瘤来源外泌体的产生和释放,或者利用外泌体结合药物等其他方式而发挥作用,有望成为治疗骨肉瘤的一种新疗法。外泌体的释放是由调节细胞内 Ca^{2+} 、 H^{+} / Na^{+} 和 Na^{+} / Ca^{2+} 通道引起的^[23-34],研究发现在 CT26 肿瘤小鼠模型中,二甲基氨基吡啶 (DMA) 可阻断上述通道并减少肿瘤来源外泌体的释放^[18,45]。另外,KO-SAKA N 等^[46]发现化学抑制剂 GW4869 通过调控和影响鞘磷脂酶 2 的生成可抑制外泌体介导的肿瘤的生长。而利用外泌体能够呈递骨肉瘤抗原的特点,增强 T 淋巴细胞抗骨肉瘤的免疫能力以此研发相关疫苗,也成为目前骨肉瘤治疗研究的热点。

5 结语

外泌体是一种脂质双分子层结构并因其来源不同,而包裹有多种不同生物活性物质的纳米级微囊泡,可由绝大多数活细胞分泌释放,并存在于细胞间隙及血液等体液中。外泌体可作为细胞间的载体,传递各种信息及生物分子如 DNA、mRNA、miRNA 和蛋白质等,并在骨肉瘤发生发展的各个阶段发挥重要作用,如通过调控 Wnt、TGF- β 及 CALN1 等信号通路调控并促进骨肉瘤的血管新生。此外,骨肉瘤来源的外泌体富含的 MMPs 及 ADAMs 能够促进骨肉瘤的侵袭和转移,

而某些由外泌体传递的 miRNA 和 ATP 结合盒转运体 (ABC) 还可成为肿瘤耐药性增强的调控因素。总之,外泌体能够促进或增强骨肉瘤的发生、侵袭转移、免疫逃逸和耐药性,并在骨肉瘤的诊断和治疗等方面发挥重要作用。未来,可利用外泌体可被加工修饰的潜力及特异性抗原的特点,为研发搭载抗肿瘤药物的递送系统或骨肉瘤的早期检测、诊断和治疗提供新思路。

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