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·专论与综述·

外泌体在淋巴瘤中的研究进展 *

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摘要：病毒感染和环境污染等使得淋巴瘤的发病率逐年升高，早期诊断和精准治疗具有十分重要的临床意义。外泌体是一种脂质双层膜结构的微小囊泡，介导了细胞间交流和信息交换。近几年许多研究证实外泌体是淋巴瘤的发生、进展和耐药的重要机制。外泌体内核酸和小分子可用于淋巴瘤的早期诊断和预测患者预后。材料学修饰可显著增强外泌体治疗的靶向性和治疗效能。本文总结了外泌体生物学特性、分离和鉴定方法、与肿瘤相关性、及其在淋巴瘤中的研究进展，为淋巴瘤的预警和治疗提供参考。

关键词：淋巴瘤；外泌体；早期诊断；精准治疗

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Research Progress of Exosomes in Lymphoma*

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ABSTRACT: Viral infection and environmental pollution make the incidence of lymphoma increase year by year. Early diagnosis and precise treatment are of great clinical significance. Exosomes are tiny vesicles of lipid bilayer membrane structure, which mediate cell to cell communication and information exchange. In recent years, many studies have proved that exosomes are the important mechanism of the occurrence, development and drug resistance of lymphoma. Nucleic acids and small molecules in exosomes can be used for early diagnosis and prognosis of lymphoma. Material modification can significantly enhance the targeting and therapeutic efficacy of exosomes. This paper summarized the biological characteristics of exosomes, the methods of isolation and identification, the relationship between exosomes and tumor, and the research progress of exosomes in lymphoma, to provide references for the early warning and treatment of lymphoma.

Key words: Lymphoma; Exosomes; Early diagnosis; Precise treatment

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前言

近几年淋巴瘤的发病呈快速上升和年轻化趋势，已经成为血液系统最常见的恶性肿瘤，可分为非霍奇金淋巴瘤（non-Hodgkin's lymphoma，NHL）和霍奇金淋巴瘤（Hodgkin's lymphoma，HL）两大类[1]。淋巴瘤症状包括发热、无痛性淋巴结肿大和全身器官组织受累症状等，大部分不具有临床特异性，早期诊断十分困难，很多患者发现时已经进入了晚期[2]。化疗和放疗是淋巴瘤的主要治疗手段，可以获得暂时较好的缓解，但是淋巴瘤的复发率十分高，统计数据显示约有 40%的弥漫性大 B 细胞淋巴瘤在治疗后数月至数年间会复发，且复发后往往是很难治愈的[3]。因此寻找淋巴瘤诊断和治疗的新靶点具有十分重要临床意义。大量研究证实外泌体（exosome）是淋巴瘤发生和进展的重要机制，可用于淋巴瘤的早期诊断和靶向治疗[4]。本文总结了外泌体生物学特征及其在淋巴瘤中的最新进展，为其诊断和治疗提供理论参考。

1 外泌体的生物学特征

外泌体是一种细胞分泌具有脂质双层膜结构的微小囊泡，直径约为 30-120 nm，内含丰富的脂类、核酸和蛋白质等小分子，是细胞间交流和信息交换的重要机制。外泌体表达生物膜特异性标志，包括 CD63、CD9、CD81 和肿瘤敏感基因 101（tumor sensitive gene 101，TSG101）等[5]。此外外泌体还保留着供体细胞特征，高表达相应的表面标志，因此通过检测这些蛋白的表达可以追踪外泌体的来源[6]。

目前认为外泌体生物学功能的发挥主要通过三条途径：

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结合靶细胞细胞膜，融合成为新的细胞表面分子；结合靶细胞表面受体，激活细胞内特定的信号通路；与细胞融合或者被消化后，释放内含蛋白质或者核酸小分子，调控靶细胞功能[7]。

2 外泌体的分离和鉴定

去除细胞碎片或者蛋白质影响，富集到合适的浓度是外泌体分离的关键。目前常用的外泌体分离方法包括差速超速离心法、聚乙二醇（polyethylene glycol，PEG）沉淀法、多孔结构诱捕法、免疫磁珠法和沉淀试剂盒法等。目前应用较多的为沉淀试剂盒法、免疫磁珠法和差速超速离心法[8]。每种分离方法均有各自的优点和不足之处，研究者应该根据自己需求选择最合适的方法。

2006 年，外泌体典型的形态结构图第一次发布，之后科学家逐渐制定了外泌体鉴定的标准和常用方法。透射电镜下呈茶托型或一侧凹陷的半球形的双层囊膜超微结构，直径 30-120 nm[9]；粒径分析仪检测外泌体大小及粒径分布；Western blot 或者流式细胞术检测外泌体特异性表面标志，比如 TSG101、CD9、CD81 和 CD63 等。另外一些指标比如 Alix、Syntenin 和热休克蛋白 70（heat shock protein 70，HSP70）也有一定的辅助鉴定作用[10]。这些监测指标均存在不足之处，比如透射电镜只关注少量外泌体特征，很难检测整个样本的纯度；外泌体特异性表面标志检测缺乏合适的阳性或者阴性对照。

3 外泌体与恶性肿瘤

外泌体的生物学功能与供体细胞紧密相关，因此对肿瘤具有双重作用。T 细胞、树突细胞、自然杀伤细胞（natural killer cell，NK 细胞）和巨噬细胞源性外泌体内含 IL-6 和 IL-1 等免疫活性分子，在肿瘤内可激活免疫反应，抑制肿瘤生长和转移[11-14]。免疫抑制细胞，比如间充质干细胞、调节性 T 细胞（regulatory T cell，Treg 细胞）和 M2 型巨噬细胞源性外泌体则高表达细胞毒性 T 淋巴细胞相关抗原 -4（cytotoxic T lymphocyte associated antigen-4，CTLA-4）、人白细胞抗原 -G（human leucocyte antigen-G，HLA-G）和糖皮质激素诱导的肿瘤坏死因子受体（glucocorticoid-induced tumor necrosis factor receptor，GITR）等免疫抑制分子，能够诱导 T 细胞凋亡，抑制抗肿瘤免疫反应，促进肿瘤增殖、侵袭和转移[15-17]。此外，外泌体还能通过其他方式发挥生物学功能，比如内皮祖细胞（endothelial progenitor cell，EPC）源性外泌体内含血管内皮生长因子（vascular endothelial growth factor，VEGF）、IL-10 和基质金属蛋白酶 9（matrix metalloproteinase 9，MMP9）等，可诱导肿瘤生长、血管生成、周围组织浸润和远处转移等[18-21]。

恶性肿瘤内部缺血缺氧微环境使得肿瘤细胞能够分泌更多的外泌体。肿瘤细胞分泌的外泌体在一定程度上可激活免疫反应，发挥抗肿瘤功能。但是这种效果是十分局限和微弱的，总的来说，肿瘤细胞源性外泌体主要发挥免疫抑制和促肿瘤进展的作用[7,22,23]。胃癌细胞源性外泌体内含大量转化生长因子 -β（transforming growth factor-β，TGF-β）和 IL-10，可增加淋巴细胞分类中 Treg 细胞比例，诱导 T 细胞和 NK 细胞凋亡，抑制抗肿瘤免疫反应。此外，胃癌细胞分泌的外泌体还能激活丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）、细胞外调节蛋白激酶（extracellular regulated protein kinase，ERK）等信号通路，直接诱导胃癌的生长、浸润和转移，CD97 在这些过程中扮演着关键角色[10,24,25]。外泌体与化疗、靶向治疗耐药也具有很大的相关性，许多研究显示耐药癌细胞分泌的外泌体可将一些 microRNA（miR）、LncRNA 和小分子靶向递送给敏感细胞，促进敏感癌细胞对曲妥珠单抗、替莫唑胺、伊马替尼和紫杉醇的耐药[26-28]。

4 外泌体与淋巴瘤

外泌体在淋巴瘤进展、复发和耐药中均发挥着重要的作用。免疫细胞源性外泌体可进入淋巴瘤瘤体内，具有一定抗肿瘤功能。淋巴瘤源性外泌体可被树突细胞摄取，在一定程度上能激活免疫反应[29,30]。但是对于淋巴瘤患者，这些作用往往是十分有限的。很多细胞分泌的外泌体发挥着促进淋巴瘤进展的作用。内皮细胞或者 EPC 源性外泌体可促进淋巴瘤血管生成；Treg 在淋巴瘤患者外周血淋巴细胞分类中比例显著升高，分泌的外泌体可显著抑制抗肿瘤免疫反应。淋巴瘤源性外泌体通过多条途径促进肿瘤发生和进展。BART miRNA 具有免疫抑制功能，诱导巨噬细胞向 M2 型极化。外泌体介导了 BART miRNA 从 Epstein-Barr 病毒（Epstein-Barr virus，EBV）感染细胞向未感染细胞转移，诱导 EBV 相关淋巴瘤的发生[31]。大量研究证实淋巴瘤源性外泌体可促进基质细胞增殖、侵袭和血管新生，诱导 T 淋巴细胞内 PD-1、CTLA-4 和 TGF-β 等免疫抑制性蛋白的上调，抑制抗肿瘤免疫反应[32]。外泌体与淋巴瘤耐药也具有很大的相关性，研究发现外泌体内 Bcl-6 mRNA 水平与利妥昔单克隆抗体的耐药性呈正相关，外泌体介导了这种耐药基因在淋巴瘤细胞之间的交流[33,34]。

早期诊断、精准治疗是淋巴瘤目前研究的主要方向。目前国内外已经研发了数个基于外泌体的疾病诊断试剂盒，Exosome Diagnostics 公司推出全球首个基于外泌体的液态活检产品，可准确检测非小细胞肺癌的 EML4-ALK 突变[35,36]。许多研究表明淋巴瘤源性外泌体表面可表达有肿瘤细胞的特异性表面标志，包括 c-Myc、Mcl-1 和 Bcl-2 等，同时某些标志还能在一定程度上区分淋巴瘤的类型，比如 B 细胞淋巴瘤源性外泌体表达 CD19 和 CD20，T 细胞淋巴瘤表达 CD3 等[37,38]。相对于实体肿瘤，淋巴瘤在发病初期即随血液循环到达全身各个部位，很难进行有效手术切除，同时这也意味着在外周血中淋巴瘤源性外泌体浓度更高，在发病早期即可检测到。因此外泌体在淋巴瘤早期诊断、进展和复发监测中具有广阔的应用前景[4]。Feng 等[37]对弥漫性大 B 细胞淋巴瘤进行基因测序，筛选出了显著上调的 miR 共 37 种，下调的 miR 共 17 种，并进一步分析了其与治疗效果和临床病理的相关性，发现血浆外泌体 miR -125b-5p 和 miR -99a-5p 可有效预测淋巴瘤的化疗效果，且与患者的生存时间紧密相关。Provencio M 等[39]分析了近 100 例淋巴瘤患者的临床标本，发现 c-Myc、Bcl-6、Bcl-xl、AKT 和PTEN 可作为生物标志物监测淋巴瘤的治疗效果，预测患者的预后。

鉴于外泌体在淋巴瘤中的重要作用，细胞实验和动物实验结果均显示抑制外泌体分泌可显著抑制淋巴瘤生长、转移和耐药。然而这种方法基本不可能应用于临床，因为外泌体在维持人体稳态平衡和各系统功能中发挥着至关重要的作用。外泌

体属于双重生物膜构成的纳米囊泡样结构,科学家很容易对其进行材料学修饰[40]。通过改造供体细胞或者在外泌体表面组装靶向分子,可增强外泌体治疗的靶向性。淋巴瘤表面特异性表达 c-Myc、Mc l-1 和 Bcl-2 等分子,通过聚乙烯亚胺(polyethylenimine,PEI)等修饰方法将相应抗体结合到外泌体表面,体内和体外结果均显示修饰后的外泌体特异性结合淋巴瘤细胞的能力显著升高[41,42]。通过电转染或者化学转染的方式将 DNA、RNA 或者小分子递送到外泌体内,增强外泌体治疗的作用效能[43]。研究者将阿霉素包裹到外泌体内,克服了化疗药物无法通过血脑屏障问题,可靶向杀伤脑组织内淋巴瘤细胞,药物作用时间延长,且副作用也显著降低,这为中枢神经系统肿瘤治疗提供了新的手段[44]。

5 结语

淋巴瘤是最常见的血液系统恶性肿瘤,早期诊断和精准治疗具有十分重要的临床意义。外泌体是近几年研究的热点,大量研究证实外泌体与恶性肿瘤的发生、进展和耐药性紧密相关。外泌体上特异性标志和 miRNA 可用于淋巴瘤的早期诊断、复发监测和治疗效果预测。材料学修饰可显著增强外泌体治疗的靶向性和治疗效能。当然这些方法的有效性还需要大规模的临床数据评估。筛选高度特异性生物标志物、构建基于外泌体的靶向治疗体系、外泌体与疾病相关性研究是未来外泌体的主要发展方向。相信随着纳米材料、液体活检和基因技术的发展,在不久的将来外泌体产品将进入临床应用于淋巴瘤诊断和治疗。

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