

外泌体在胃癌诊疗中的前景

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摘要

胃癌是人群中常见的消化道恶性肿瘤, 早期胃癌大多无明显特异性的症状, 当症状明显时, 大多已进入晚期, 因此早期做出诊断是胃癌预后的重中之重。外泌体(Exosomes)定义为一种直径在30~100纳米的细胞外囊泡, 几乎所有的细胞都可以分泌。外泌体起初被发现时认为是用来排出细胞代谢产物的“垃圾桶”, 随着近年来研究的不断深入, 发现其还可传输一些生物活性分子(包括蛋白质、脂质和核酸)进行细胞间交流的重要途径。胃癌细胞与其肿瘤微环境通过外泌体建立联系, 影响癌细胞的发展、转移、血管的生成和耐药。在本综述中, 我们总结了目前发现的一些外泌体在胃癌中的作用机制, 并对其诊疗前景做出展望。

关键词

外泌体, 胃癌, 治疗

Prospects of Exosomes in the Diagnosis and Treatment of Gastric Cancer

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Abstract

Gastric cancer is a common gastrointestinal malignancy in the population. Most of the early gastric cancers have no obvious specific symptoms, and when the symptoms are obvious, most of them are

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already in advanced stages, so making early diagnosis is the most important for the prognosis of gastric cancer. Exosomes are defined as extracellular vesicles with a diameter of 30~100 nm, which can be secreted by almost all cells. Exosomes were initially discovered as a “garbage can” for excreting cellular metabolites, but in recent years, they have also been found to be an important means of intercellular communication for transporting some bioactive molecules including proteins, lipids and nucleic acids. Gastric cancer cells are linked to their tumor microenvironment through exosomes, which influence cancer cell development, metastasis, angiogenesis, and drug resistance. In this review, we summarize some of the mechanisms of exosomes' roles in gastric cancer identified so far and provide an outlook on their diagnosis and treatment prospects.

Keywords

Exosomes, Stomach Cancer, Treatment

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1. 背景

胃癌(gastric cancer, GC)包括早期胃癌(early gastric cancer, EGC)和进展期胃癌(advanced gastric cancer, AGC), 与 AGC 相比, EGC 预后良好, 大多数病例可通过手术或内镜切除从而获得根治。根据统计结果显示, 中国每年胃癌新增病例数约为 48 万例, 死亡病例约为 37 万例, 2014~2016 年在国内收集的 88,340 例胃癌病人中早期胃癌仅占比 19.5%, 但在逐年上升[1] [2]。因此, 重视胃癌的早诊早治, 尤其提高早期胃癌的检出率, 是提高远期存活率的根本措施[2]。目前, 内镜下的组织活检依然是确诊胃癌的主要手段, 然而, 提取的小块组织不能很好的代表肿瘤整体性质或者评估肿瘤的远期发展, 而且这种方法可能还会增加肿瘤转移的风险, 最终导致患者预后差, 此外, 在我国开展大规模的内镜筛查手段显然不适用。而外泌体所携带的蛋白质、脂质和核酸正作为一种诊断癌症和评估预后的新兴生物标志物进行测试, 甚至有作为治疗癌症的巨大潜力, 值得深入探究。

2. 外泌体与胃癌的发展

恶性肿瘤通常具有三个特征: 不受控制的生长、转移到其他器官和侵袭临近器官并破坏身体机能, 因此终止肿瘤的继续发展是胃癌治疗中的重要环节。Qu 等人在 2009 年首次报道了胃癌中的外泌体, 他们说, 胃癌细胞衍生的外泌体通过激活 MAPK/ERK 和 PI3K/Akt 途径促进了胃癌细胞的增殖[3]。后续 10 年时间俩越来越多相关的报道揭示了外泌体在胃癌及其它恶性肿瘤中的作用。我们主要探讨其在胃癌中的作用机制。外泌体中的环状 RNA (circRNA)在各类癌症的发展中均有重要的调控作用, 在胃癌中同样也是。胃癌细胞外泌体 circSHKBP1、circ0000654、circUBE2Q2 等均可促进胃癌细胞增殖、迁移和侵袭[4]-[6]。有人做了相关筛选实验, 统计结果显示: circRNA 在正常胃组织细胞和癌变的相同组织细胞中表达有显著不同, Shao 等人共发现 308 个表达有显著差异的 circRNA。其中, 表达水平下降的 circRNA 占 65.26%, 比上升的 circRNA 34.74%更常见。其中, hsa_circ_0014717 表达水平下降最为明显且与肿瘤分期、远处转移、和目前流行的消化道癌胚抗原 CA19-9 的表达有关, 其可以稳定的存在于人的胃液中, 是胃癌患者的独立预后因素, 或许可以作为一种新的筛查高危胃癌患者的生物标志物, circRNA 具有应用于临床诊断胃癌的巨大潜力[7]。另胃癌细胞外泌体 miR-15b-3p 会增加胃粘膜上皮细胞的恶性转化[8], miR-107、LINC01559 通过抑制 PTEN 基因, 从而激活了前文中提到的 PI3K/AKT 途径促进胃癌的进展[3]

[9]。而来自癌症相关成纤维细胞(cancer-associated fibroblasts, CAFs)的外泌体 miRNA-34、miRNA-139 能通过调控下游靶基因从而抑制癌细胞增殖和促进其凋亡来实现抑制胃癌细胞的生长和侵袭的能力[10]。另有一些小分子蛋白,如胃上皮细胞相关的外泌体蛋白 GKN1 和胃癌患者血清中提取到的 TRIM3 蛋白也会抑制胃癌的进展[11][12]。综上所述,胃癌相关的外泌体可通过调控胃癌细胞的凋亡与增殖或促进正常上皮细胞的转化从而影响胃癌的进展,如能通过外泌体影响上述过程,相信会是胃癌患者的一大帮助,但目前缺乏相关药物与临床试验报道。

3. 外泌体与胃癌转移

胃癌是否伴有转移与其预后密切相关,有研究表明, circ-RanGAP1、MiR-301a-3p、FRLnc1 会通过靶向调节下游基因序列促进胃癌侵袭和转移[13]-[15]。胃癌最常见的转移部位有淋巴结、腹膜和肝脏。胃癌细胞衍生的外泌体 miR-21-5p 可以使腹膜间皮细胞(PMC)经历从间皮到间充质的转化(MMT),从而导致 PMCs 的侵袭和对肿瘤细胞的粘着能力增加,最终促进了胃癌的腹膜转移[16]。Wang 等人研究发现胃癌外泌体中 CD44 分子会在胃癌细胞间传递淋巴结转移能力,此或许可作为胃癌淋巴结转移的新型预测指标[17]。淋巴结转移的胃癌细胞(LNM-GCs)也会通过外泌体 Wnt5a 促进淋巴管的生成,进一步增加胃癌淋巴结转移的风险[18]。而胃癌的外源性 miR-519a-3p 则会通过诱导肝内 M2 类巨噬细胞介导的血管再生成促进肝转移的发生[19]。

4. 外泌体与胃癌血管生成

为了支持癌细胞的高增殖率,肿瘤大多倾向于生成更多的血管网络为其提供氧气和营养物质,有学者提出,抗血管生成疗法可以纠正肿瘤血管的结构和功能缺陷,因此能减少其转移倾向[20]。如胃癌的外泌体 miR-155 作为血管生成的驱动因素,可以通过抑制 FOXO3a 蛋白的表达,增强胃癌新血管的生成,从而导致病情进展[21]。而人脐带间充质干细胞相关的外泌体 microRNA-6785-5p 通过 INHBA 抑制胃癌血管生成和转移[22]。

5. 外泌体与胃癌细胞的耐药

在临床上胃癌的耐药一直以来都是一大难题,近年来随着研究的不断深入,外泌体在这方面或许有着很大的潜力。胃癌细胞来源的外泌体可以分别将正常的周围细胞和间充质干细胞诱导为 CAFs [23][24]。CAFs 是肿瘤微环境(Tumor micro-environment, TME)中的最终细胞类型[25]。CAFs 分泌的外泌体 miR-522 可以减少脂质 ROS 的积累从而抑制癌细胞中的铁死亡,而顺铂和紫杉醇会促进 CAFs 分泌 miR-522,最终导致化疗的敏感性降低[26]。另有研究表明,顺铂耐药的胃癌细胞会分泌微囊泡与 TME 进行交流。miR-769-5p 可以整合到其外泌体中,并传递给敏感的细胞,使顺铂的抗性扩散[27]。而用 miR-769-5p 的拮抗剂靶向治疗顺铂耐药的胃癌细胞可以恢复顺铂的反应,此方法可辅助顺铂等药物治疗胃癌[27],但目前缺乏相关试验论证。

6. 外泌体在胃癌治疗中的应用

外泌体被认为是递送药物的天然载体,载药外泌体可用于癌症的治疗[28]。外泌体 PD-L1 相关酶 LSD1 的缺失,降低了 PD-L1 并恢复了胃癌中的 T 细胞反应;为胃癌的免疫治疗提供了一个新的目标[29]。Jiang 等人从 5-FU 敏感胃癌细胞中提取的外泌体 miR-107 明显增强了抗性胃癌细胞对化疗药物的敏感性,外泌体 miR-107 可能是胃癌治疗的一个新靶点[30]。另有研究发现,活化的 CD8T 细胞衍生的细胞外囊泡(EV)可以中断成纤维细胞介导的肿瘤进展[31]。Li 等人提出了一种新型运载体模型 DOX@aiPS-DCexo,其是由多能干细胞(iPSC-exos)外泌体和树突状细胞外泌体(DC-exos)结合修饰后运输化疗药物多柔比星

(DOX)。该载体不仅可以增强抗肿瘤药物的上传应答能力,还可以保留肿瘤组织靶向杀伤、肿瘤抑制和免疫刺激等生物学功能。引起强烈的一系列抗肿瘤免疫应答反应,实现化疗和免疫治疗的协同治疗,该系统具有应用于临床治疗癌症的潜力[32]。外泌体作为一种生物活性物质的集合体,积极参与了胃癌的免疫治疗与靶向治疗。

7. 结语

综上所述,在胃癌的发生发展、转移、耐药与治疗中,外泌体都是一个重要的物质,外泌体因具有良好生物学特性而可作为抗癌药物或生物治疗分子的载体,在胃癌的靶向治疗中展示出潜在的应用前景。随着研究的不断深入,外泌体在胃癌中的作用及其机制有望得到进一步阐明,预期将为胃癌的发生、发展提供更多有价值的信息,进而为胃癌的诊疗提供新的思路 and 手段。其应用在临床面临最大挑战之一就是高效、高纯度的分离,因此,需要积极研发一种易于操作、高灵敏度、高纯度、特异性强的外泌体分离、检测平台。其次在胃癌与血管生成方面,相关研究还需进一步扩展,补充空缺。目前关于外泌体的基础研究大都缺乏相关临床试验验证,需进一步结合临床,为众多胃癌患者带来希望。

参考文献

- [1] Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., et al. (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, **71**, 209-249. <https://doi.org/10.3322/caac.21660>
- [2] 苗儒林 李子禹 武爱文. 中国胃肠肿瘤外科联盟数据报告(2014-2016) [J]. 中国实用外科杂志, 2018, 38(1): 90-93.
- [3] Qu, J.-L., Qu, X.-J., Zhao, M.-F., Teng, Y.-E., Zhang, Y., Hou, K.-Z., et al. (2009) Gastric Cancer Exosomes Promote Tumour Cell Proliferation through PI3K/AKT and MAPK/ERK Activation. *Digestive and Liver Disease*, **41**, 875-880. <https://doi.org/10.1016/j.dld.2009.04.006>
- [4] Xie, M., Yu, T., Jing, X., Ma, L., Fan, Y., Yang, F., et al. (2020) Exosomal circSHKBP1 Promotes Gastric Cancer Progression via Regulating the miR-582-3p/HUR/VEGF Axis and Suppressing HSP90 Degradation. *Molecular Cancer*, **19**, Article No. 112. <https://doi.org/10.1186/s12943-020-01208-3>
- [5] Liu, H. and Dai, W. (2022) Circular RNA 0000654 Facilitates the Growth of Gastric Cancer Cells through Absorbing microRNA-149-5p to up-Regulate Inhibin-Beta A. *Bioengineered*, **13**, 469-480. <https://doi.org/10.1080/21655979.2021.2009414>
- [6] Yang, J., Zhang, X., Cao, J., Xu, P., Chen, Z., Wang, S., et al. (2021) Circular RNA UBE2Q2 Promotes Malignant Progression of Gastric Cancer by Regulating Signal Transducer and Activator of Transcription 3-Mediated Autophagy and Glycolysis. *Cell Death & Disease*, **12**, Article No. 910. <https://doi.org/10.1038/s41419-021-04216-3>
- [7] Shao, Y., Li, J., Lu, R., Li, T., Yang, Y., Xiao, B., et al. (2017) Global Circular RNA Expression Profile of Human Gastric Cancer and Its Clinical Significance. *Cancer Medicine*, **6**, 1173-1180. <https://doi.org/10.1002/cam4.1055>
- [8] Wei, S., Peng, L., Yang, J., Sang, H., Jin, D., Li, X., et al. (2020) Exosomal Transfer of miR-15b-3p Enhances Tumorigenesis and Malignant Transformation through the DYNLT1/Caspase-3/Caspase-9 Signaling Pathway in Gastric Cancer. *Journal of Experimental & Clinical Cancer Research*, **39**, Article No. 32. <https://doi.org/10.1186/s13046-019-1511-6>
- [9] Ren, W., Zhang, X., Li, W., Feng, Q., Feng, H., Tong, Y., et al. (2019) Exosomal miRNA-107 Induces Myeloid-Derived Suppressor Cell Expansion in Gastric Cancer. *Cancer Management and Research*, **11**, 4023-4040. <https://doi.org/10.2147/cmar.s198886>
- [10] Shi, L., Wang, Z., Geng, X., Zhang, Y. and Xue, Z. (2020) Exosomal miRNA-34 from Cancer-Associated Fibroblasts Inhibits Growth and Invasion of Gastric Cancer Cells *in Vitro* and *in Vivo*. *Aging*, **12**, 8549-8564. <https://doi.org/10.18632/aging.103157>
- [11] Yoon, J.H., Ashktorab, H., Smoot, D.T., Nam, S.W., Hur, H. and Park, W.S. (2020) Uptake and Tumor-Suppressive Pathways of Exosome-Associated GKN1 Protein in Gastric Epithelial Cells. *Gastric Cancer*, **23**, 848-862. <https://doi.org/10.1007/s10120-020-01068-2>
- [12] Fu, H., Yang, H., Zhang, X., Wang, B., Mao, J., Li, X., et al. (2018) Exosomal TRIM3 Is a Novel Marker and Therapy Target for Gastric Cancer. *Journal of Experimental & Clinical Cancer Research*, **37**, Article No. 162. <https://doi.org/10.1186/s13046-018-0825-0>
- [13] Lu, J., Wang, Y., Yoon, C., Huang, X., Xu, Y., Xie, J., et al. (2020) Circular RNA Circ-RanGAP1 Regulates VEGFA

- Expression by Targeting miR-877-3p to Facilitate Gastric Cancer Invasion and Metastasis. *Cancer Letters*, **471**, 38-48. <https://doi.org/10.1016/j.canlet.2019.11.038>
- [14] Xia, X., Wang, S., Ni, B., Xing, S., Cao, H., Zhang, Z., *et al.* (2020) Hypoxic Gastric Cancer-Derived Exosomes Promote Progression and Metastasis via MiR-301a-3p/PHD3/HIF-1 α Positive Feedback Loop. *Oncogene*, **39**, 6231-6244. <https://doi.org/10.1038/s41388-020-01425-6>
- [15] Zhang, Y., Chen, L., Ye, X., Wu, Z., Zhang, Z., Sun, B., *et al.* (2021) Expression and Mechanism of Exosome-Mediated A FOXM1 Related Long Noncoding RNA in Gastric Cancer. *Journal of Nanobiotechnology*, **19**, Article No. 133. <https://doi.org/10.1186/s12951-021-00873-w>
- [16] Li, Q., Li, B., Li, Q., Wei, S., He, Z., Huang, X., *et al.* (2018) Exosomal miR-21-5p Derived from Gastric Cancer Promotes Peritoneal Metastasis via Mesothelial-To-Mesenchymal Transition. *Cell Death & Disease*, **9**, Article No. 854. <https://doi.org/10.1038/s41419-018-0928-8>
- [17] Wang, M., Yu, W., Cao, X., Gu, H., Huang, J., Wu, C., *et al.* (2022) Exosomal CD44 Transmits Lymph Node Metastatic Capacity between Gastric Cancer Cells via YAP-CPT1A-Mediated FAO Reprogramming. *Frontiers in Oncology*, **12**, Article 860175. <https://doi.org/10.3389/fonc.2022.860175>
- [18] Wang, M., Zhao, X., Qiu, R., Gong, Z., Huang, F., Yu, W., *et al.* (2021) Lymph Node Metastasis-Derived Gastric Cancer Cells Educate Bone Marrow-Derived Mesenchymal Stem Cells via YAP Signaling Activation by Exosomal Wnt5a. *Oncogene*, **40**, 2296-2308. <https://doi.org/10.1038/s41388-021-01722-8>
- [19] Qiu, S., Xie, L., Lu, C., Gu, C., Xia, Y., Lv, J., *et al.* (2022) Gastric Cancer-Derived Exosomal miR-519a-3p Promotes Liver Metastasis by Inducing Intrahepatic M2-Like Macrophage-Mediated Angiogenesis. *Journal of Experimental & Clinical Cancer Research*, **41**, Article No. 296. <https://doi.org/10.1186/s13046-022-02499-8>
- [20] Jain, R.K. (2001) Normalizing Tumor Vasculature with Anti-Angiogenic Therapy: A New Paradigm for Combination Therapy. *Nature Medicine*, **7**, 987-989. <https://doi.org/10.1038/nm0901-987>
- [21] Zhou, Z., Zhang, H., Deng, T., Ning, T., Liu, R., Liu, D., *et al.* (2019) RETRACTED: Exosomes Carrying MicroRNA-155 Target Forkhead Box O3 of Endothelial Cells and Promote Angiogenesis in Gastric Cancer. *Molecular Therapy-Oncolytics*, **15**, 223-233. <https://doi.org/10.1016/j.omto.2019.10.006>
- [22] Chen, Z., Xie, Y., Chen, W., Li, T., Chen, X. and Liu, B. (2021) RETRACTED: microRNA-6785-5p-Loaded Human Umbilical Cord Mesenchymal Stem Cells-Derived Exosomes Suppress Angiogenesis and Metastasis in Gastric Cancer via INHBA. *Life Sciences*, **284**, Article 119222. <https://doi.org/10.1016/j.lfs.2021.119222>
- [23] Ning, X., Zhang, H., Wang, C. and Song, X. (2018) Exosomes Released by Gastric Cancer Cells Induce Transition of Pericytes into Cancer-Associated Fibroblasts. *Medical Science Monitor*, **24**, 2350-2359. <https://doi.org/10.12659/msm.906641>
- [24] Gu, J., Qian, H., Shen, L., Zhang, X., Zhu, W., Huang, L., *et al.* (2012) Gastric Cancer Exosomes Trigger Differentiation of Umbilical Cord Derived Mesenchymal Stem Cells to Carcinoma-Associated Fibroblasts through TGF- β /Smad Pathway. *PLOS ONE*, **7**, e52465. <https://doi.org/10.1371/journal.pone.0052465>
- [25] Arneth, B. (2019) Tumor Microenvironment. *Medicina*, **56**, Article 15. <https://doi.org/10.3390/medicina56010015>
- [26] Zhang, H., Deng, T., Liu, R., Ning, T., Yang, H., Liu, D., *et al.* (2020) CAF Secreted miR-522 Suppresses Ferroptosis and Promotes Acquired Chemo-Resistance in Gastric Cancer. *Molecular Cancer*, **19**, Article No. 43. <https://doi.org/10.1186/s12943-020-01168-8>
- [27] Jing, X., Xie, M., Ding, K., Xu, T., Fang, Y., Ma, P., *et al.* (2022) Exosome-Transmitted miR-769-5p Confers Cisplatin Resistance and Progression in Gastric Cancer by Targeting CASP9 and Promoting the Ubiquitination Degradation of P53. *Clinical and Translational Medicine*, **12**, e780. <https://doi.org/10.1002/ctm2.780>
- [28] Qi, H., Liu, C., Long, L., Ren, Y., Zhang, S., Chang, X., *et al.* (2016) Blood Exosomes Endowed with Magnetic and Targeting Properties for Cancer Therapy. *ACS Nano*, **10**, 3323-3333. <https://doi.org/10.1021/acs.nano.5b06939>
- [29] Shen, D., Pang, J., Bi, Y., Zhao, L., Li, Y., Zhao, L., *et al.* (2022) LSD1 Deletion Decreases Exosomal PD-L1 and Restores T-Cell Response in Gastric Cancer. *Molecular Cancer*, **21**, Article No. 75. <https://doi.org/10.1186/s12943-022-01557-1>
- [30] Jiang, L., Zhang, Y., Guo, L., Liu, C., Wang, P. and Ren, W. (2021) Exosomal microRNA-107 Reverses Chemotherapeutic Drug Resistance of Gastric Cancer Cells through HMG2A/mTOR/P-gp Pathway. *BMC Cancer*, **21**, Article No. 1290. <https://doi.org/10.1186/s12885-021-09020-y>
- [31] Seo, N., Shirakura, Y., Tahara, Y., Momose, F., Harada, N., Ikeda, H., *et al.* (2018) Activated CD8⁺ T Cell Extracellular Vesicles Prevent Tumour Progression by Targeting of Lesional Mesenchymal Cells. *Nature Communications*, **9**, Article No. 435. <https://doi.org/10.1038/s41467-018-02865-1>
- [32] Li, Y., Tian, L., Zhao, T. and Zhang, J. (2023) A Nanotherapeutic System for Gastric Cancer Suppression by Synergistic Chemotherapy and Immunotherapy Based on iPSCs and DCs Exosomes. *Cancer Immunology, Immunotherapy*, **72**, 1673-1683. <https://doi.org/10.1007/s00262-022-03355-6>