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**Alcohol-related diseases and liver metastasis: Role of cell-free network communication**

Muro M *et al*. Alcohol-related diseases and liver metastasis

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**Abstract**

Alcohol intake is a risk factor for cancer development and metastatic disease progression. Extracellular vesicle (EV)-mediated interorgan communication is assumed to be significant in boosting tumorigenic pathways and disease progression. Recent research indicates that exosomes have a variety of roles in the development of cancer during pathophysiological conditions. The involvement of EV signaling during cancer progression in the alcohol environment is unknown. Therefore, understanding communication networks and the role of EVs as biomarkers can contribute significantly to developing strategies to address the serious public health problems associated with alcohol consumption and cancer.

**Key Words:** Exosomes; Liver metastasis; Alcohol-associated liver disease; Cancer

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**Core Tip:** In this letter to the editor, we discussed the reality that alcohol consumption is a risk factor that acts by itself to favor the appearance of the carcinogenic process and its harmful evolution towards metastatic pathology. One of the hypotheses that have been suggested as important in metastasis and communication between cells and/or organs is the traffic of extracellular vesicles/exosomes that can play or promote tumorigenesis locally and even at a distance from the primary tumor. Unraveling these communication mechanisms and therapeutic possibilities may lead to new ways to combat cancer’s worsening, as metastasis, in the future.

**TO THE EDITOR**

We have read with great attention and particular interest the review by Kuracha *et al*[1] entitled: “Role of cell-free network communication in alcohol-associated disorders and liver metastasis”. The authors highlight the many implications of extracellular vesicle (EV) (exosome) communications across organs in this review, focusing on the role of EVs in alcohol-related illnesses and cancer metastasis. It is crucial to consider the impact of EV cargo and release along a multi-organ axis on tumorigenic pathways and metastatic disease.

Alcohol consumption negatively impacts people’s health and quality of life, contributing to more than 5% of the global disease burden and early death[2,3]. Alcohol intake has been linked to several neoplastic diseases, including colorectal, head and neck, esophageal, liver, breast, and pancreatic cancers[4,5]. On the other hand, recent research suggests that exosomes have different functions in disease progression during pathophysiological circumstances. Exosomes from tumors have been found to operate as regulatory factors in cancer development, promoting cell migration and proliferation and creating a pre-metastatic niche for cells resistant to treatment[6,7].

Hepatocytes and non-parenchymal cells produce and release EVs at higher rates in response to alcohol-mediated stress[8]. The EVs produced can alter gene expression and target cell function, prolonging liver damage[8]. Bidirectional exosomal communication between organs, including the liver, brain, intestine, and lungs, can also happen in addition to intra-organ transmission mediated by EVs. The gut-liver axis maintains bilateral interactions in an environment where alcohol is present, which results in gut dysbiosis and the progression of liver impairment[9,10].

In addition to persistent alcoholism, endotoxin transfer during sepsis and brain inflammation are caused by loss of intestinal barrier integrity. Alcohol dependency and its regulatory consequences, such as altered immunological function and neurological and endocrine signaling, are hypothesized to be influenced by alcohol-induced gut dysbiosis[11,12]. Acute respiratory distress syndrome, bacterial infection, and hepatopulmonary syndrome are also linked to persistent alcohol exposure on the liver-lung axis (ARDS)[[13,14].](https://www.uptodate.com/contents/acute-respiratory-distress-syndrome-prognosis-and-outcomes-in-adults#:~:text=Mortality%20increases%20with%20disease%20severity,with%20severe%20ARDS%20%5B4%5D.)

The significance of alcohol-induced EV communication in cancer initiation and progression is unknown until now because of the high prevalence of alcohol drinking and cancer-related risk. The therapeutic significance of the function of these exosomes has been highlighted by identifying EVs as critical mediators of communication networks within and across organ systems[7,15,16]. Clinical evaluation of EVs in body fluids provides another measure for understanding exosomes as valid and valuable diagnostic biomarkers and therapeutic targets.

Communication between malignant and non-cancerous cells, mediated by nanometric vesicles, is thought to be an essential part of tumor growth and its subsequent spread through the body. By promoting oncogene overexpression, stromal cell remodeling, immune system regulation, and angiogenesis, tumor-derived exosomes may control the course of cancer[17]. Cancer cells’ ability to grow anchorage-independently is thought to be enhanced, and their morphological changes may be modulated by the transfer of tumor-causing material through EVs[18].

Additionally, miRNA-enriched EVs have also been demonstrated in cell-cell communications and the conversion of cells into populations with enhanced motility[19]. The involvement of EV signaling during cancer progression in the alcohol environment is unknown. Recent studies have shown that the exosomal content (proteins, miRNA, non-coding RNA) can help diagnose and treat cancer[20–22]. Therefore, comprehending EVs and communication networks as biomarkers can considerably aid in developing methods to deal with the serious public health issues brought on by alcohol intake and cancer.

**REFERENCES**

1 **Kuracha MR**, Thomas P, Tobi M, McVicker BL. Role of cell-free network communication in alcohol-associated disorders and liver metastasis. *World J Gastroenterol* 2021; **27**: 7080-7099 [PMID: 34887629 DOI: 10.3748/wjg.v27.i41.7080]

2 **Wallace AE**, Weeks WB. Substance abuse intensive outpatient treatment: does program graduation matter? *J Subst Abuse Treat* 2004; **27**: 27-30 [PMID: 15223090 DOI: 10.1016/j.jsat.2004.03.006]

3 **World Health Organization**. Global status report on alcohol and health 2018. July 12, 2019. [cited 3 May 2022]. Available from: https://www.who.int/publications/i/item/9789241565639

4 **Bagnardi V**, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, Scotti L, Jenab M, Turati F, Pasquali E, Pelucchi C, Galeone C, Bellocco R, Negri E, Corrao G, Boffetta P, La Vecchia C. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer* 2015; **112**: 580-593 [PMID: 25422909 DOI: 10.1038/bjc.2014.579]

5 **IARC Working Group on the Evaluation of Carcinogenic Risks to Humans**. Alcohol consumption and ethyl carbamate. *IARC Monogr Eval Carcinog Risks Hum* 2010; **96**: 3-1383 [PMID: 21735939]

6 **Becker A**, Thakur BK, Weiss JM, Kim HS, Peinado H, Lyden D. Extracellular Vesicles in Cancer: Cell-to-Cell Mediators of Metastasis. *Cancer Cell* 2016; **30**: 836-848 [PMID: 27960084 DOI: 10.1016/j.ccell.2016.10.009]

7 **Raposo G**, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. *J Cell Biol* 2013; **200**: 373-383 [PMID: 23420871 DOI: 10.1083/jcb.201211138]

8 **Shim YR**, Jeong WI. Recent advances of sterile inflammation and inter-organ cross-talk in alcoholic liver disease. *Exp Mol Med* 2020; **52**: 772-780 [PMID: 32457490 DOI: 10.1038/s12276-020-0438-5]

9 **Dasarathy S**, Brown JM. Alcoholic Liver Disease on the Rise: Interorgan Cross Talk Driving Liver Injury. *Alcohol Clin Exp Res* 2017; **41**: 880-882 [PMID: 28295407 DOI: 10.1111/acer.13370]

10 **Stärkel P**, Schnabl B. Bidirectional Communication between Liver and Gut during Alcoholic Liver Disease. *Semin Liver Dis* 2016; **36**: 331-339 [PMID: 27997973 DOI: 10.1055/s-0036-1593882]

11 **Leclercq S**, Matamoros S, Cani PD, Neyrinck AM, Jamar F, Stärkel P, Windey K, Tremaroli V, Bäckhed F, Verbeke K, de Timary P, Delzenne NM. Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity. *Proc Natl Acad Sci U S A* 2014; **111**: E4485-E4493 [PMID: 25288760 DOI: 10.1073/pnas.1415174111]

12 **Mutlu EA**, Gillevet PM, Rangwala H, Sikaroodi M, Naqvi A, Engen PA, Kwasny M, Lau CK, Keshavarzian A. Colonic microbiome is altered in alcoholism. *Am J Physiol Gastrointest Liver Physiol* 2012; **302**: G966-G978 [PMID: 22241860 DOI: 10.1152/ajpgi.00380.2011]

13 **Afshar M**, Smith GS, Terrin ML, Barrett M, Lissauer ME, Mansoor S, Jeudy J, Netzer G. Blood alcohol content, injury severity, and adult respiratory distress syndrome. *J Trauma Acute Care Surg* 2014; **76**: 1447-1455 [PMID: 24854314 DOI: 10.1097/TA.0000000000000238]

14 **Moss M**, Parsons PE, Steinberg KP, Hudson LD, Guidot DM, Burnham EL, Eaton S, Cotsonis GA. Chronic alcohol abuse is associated with an increased incidence of acute respiratory distress syndrome and severity of multiple organ dysfunction in patients with septic shock. *Crit Care Med* 2003; **31**: 869-877 [PMID: 12626999 DOI: 10.1097/01.CCM.0000055389.64497.11]

15 **Mathivanan S**, Ji H, Simpson RJ. Exosomes: extracellular organelles important in intercellular communication. *J Proteomics* 2010; **73**: 1907-1920 [PMID: 20601276 DOI: 10.1016/j.jprot.2010.06.006]

16 **Record M**, Carayon K, Poirot M, Silvente-Poirot S. Exosomes as new vesicular lipid transporters involved in cell-cell communication and various pathophysiologies. *Biochim Biophys Acta* 2014; **1841**: 108-120 [PMID: 24140720 DOI: 10.1016/j.bbalip.2013.10.004]

17 **Maia J**, Caja S, Strano Moraes MC, Couto N, Costa-Silva B. Exosome-Based Cell-Cell Communication in the Tumor Microenvironment. *Front Cell Dev Biol* 2018; **6**: 18 [PMID: 29515996 DOI: 10.3389/fcell.2018.00018]

18 **Quaglia F**, Krishn SR, Daaboul GG, Sarker S, Pippa R, Domingo-Domenech J, Kumar G, Fortina P, McCue P, Kelly WK, Beltran H, Liu Q, Languino LR. Small extracellular vesicles modulated by αVβ3 integrin induce neuroendocrine differentiation in recipient cancer cells. *J Extracell Vesicles* 2020; **9**: 1761072 [PMID: 32922691 DOI: 10.1080/20013078.2020.1761072]

19 **Baroni S**, Romero-Cordoba S, Plantamura I, Dugo M, D'Ippolito E, Cataldo A, Cosentino G, Angeloni V, Rossini A, Daidone MG, Iorio MV. Exosome-mediated delivery of miR-9 induces cancer-associated fibroblast-like properties in human breast fibroblasts. *Cell Death Dis* 2016; **7**: e2312 [PMID: 27468688 DOI: 10.1038/cddis.2016.224]

20 **Xu Z**, Chen Y, Ma L, Chen Y, Liu J, Guo Y, Yu T, Zhang L, Zhu L, Shu Y. Role of exosomal non-coding RNAs from tumor cells and tumor-associated macrophages in the tumor microenvironment. *Mol Ther* 2022 [PMID: 35405312 DOI: 10.1016/j.ymthe.2022.01.046]

21 **Jiang J**, Li J, Zhou X, Zhao X, Huang B, Qin Y. Exosomes Regulate the Epithelial-Mesenchymal Transition in Cancer. *Front Oncol* 2022; **12**: 864980 [PMID: 35359397 DOI: 10.3389/fonc.2022.864980]

22 **Zhang K**, Erkan EP, Jamalzadeh S, Dai J, Andersson N, Kaipio K, Lamminen T, Mansuri N, Huhtinen K, Carpén O, Hietanen S, Oikkonen J, Hynninen J, Virtanen A, Häkkinen A, Hautaniemi S, Vähärautio A. Longitudinal single-cell RNA-seq analysis reveals stress-promoted chemoresistance in metastatic ovarian cancer. *Sci Adv* 2022; **8**: eabm1831 [PMID: 35196078 DOI: 10.1126/sciadv.abm1831]

**Footnotes**

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