

World Journal of *Gastroenterology*

World J Gastroenterol 2021 November 7; 27(41): 7005-7209



EDITORIAL

- 7005** Nucleic acid vaccines: A taboo broken and prospect for a hepatitis B virus cure
Tsounis EP, Mouzaki A, Triantos C

FRONTIER

- 7014** Recent insights into the characteristics and role of peritoneal macrophages from ascites of cirrhotic patients
García-Peñarrubia P, Ruiz-Alcaraz AJ, Ruiz-Ballester M, Ramírez-Páez TN, Martínez-Esparza M
- 7025** Involvement of parathyroid hormone-related peptide in the aggressive phenotype of colorectal cancer cells
Novoa Díaz MB, Carriere PM, Martín MJ, Calvo N, Gentili C

REVIEW

- 7041** Over-feeding the gut microbiome: A scoping review on health implications and therapeutic perspectives
Barone M, D'Amico F, Fabbrini M, Rampelli S, Brigidi P, Turrone S
- 7065** Gut microbiota in a population highly affected by obesity and type 2 diabetes and susceptibility to COVID-19
García-Mena J, Corona-Cervantes K, Cuervo-Zanatta D, Benitez-Guerrero T, Vélez-Ixta JM, Zavala-Torres NG, Villalobos-Flores LE, Hernández-Quiroz F, Perez-Cruz C, Murugesan S, Bastida-González FG, Zárate-Segura PB
- 7080** Role of cell-free network communication in alcohol-associated disorders and liver metastasis
Kuracha MR, Thomas P, Tobi M, McVicker BL

MINIREVIEWS

- 7100** DNA diagnostics for reliable and universal identification of *Helicobacter pylori*
Sulo P, Šipková B
- 7113** Non-alcoholic fatty liver disease in patients with intestinal, pulmonary or skin diseases: Inflammatory cross-talk that needs a multidisciplinary approach
Perez-Carreras M, Casis-Herce B, Rivera R, Fernandez I, Martinez-Montiel P, Villena V
- 7125** Current update on molecular cytogenetics, diagnosis and management of gastrointestinal stromal tumors
Wang MX, Devine C, Segaran N, Ganeshan D

ORIGINAL ARTICLE

Basic Study

- 7134** Circulating tumor DNA dynamics analysis in a xenograft mouse model with esophageal squamous cell carcinoma
Terasawa H, Kinugasa H, Nouse K, Yamamoto S, Hirai M, Tanaka T, Takaki A, Okada H

- 7144 Cross-sectional evaluation of circulating hepatitis B virus RNA and DNA: Different quasispecies?

Garcia-Garcia S, Cortese MF, Tabernero D, Gregori J, Vila M, Pacin B, Quer J, Casillas R, Castillo-Ribelles L, Ferrer-Costa R, Rando-Segura A, Trejo-Zahinos J, Pumarola T, Casis E, Esteban R, Riveiro-Barciela M, Buti M, Rodriguez-Frias F

Retrospective Cohort Study

- 7159 Short-term and long-term outcomes of laparoscopic *vs* open ileocolic resection in patients with Crohn's disease: Propensity-score matching analysis

Pak SJ, Kim YI, Yoon YS, Lee JL, Lee JB, Yu CS

Retrospective Study

- 7173 Comprehensive radiomics nomogram for predicting survival of patients with combined hepatocellular carcinoma and cholangiocarcinoma

Tang YY, Zhao YN, Zhang T, Chen ZY, Ma XL

- 7190 Clinical characteristics of gastrointestinal immune-related adverse events of immune checkpoint inhibitors and their association with survival

Yamada K, Sawada T, Nakamura M, Yamamura T, Maeda K, Ishikawa E, Iida T, Mizutani Y, Kakushima N, Ishikawa T, Furukawa K, Ohno E, Honda T, Kawashima H, Ishigami M, Furune S, Hase T, Yokota K, Maeda O, Hashimoto N, Akiyama M, Ando Y, Fujishiro M

LETTER TO THE EDITOR

- 7207 Pancreatic cyst dilemma: Between physical and biochemical markers

Khamayisi I, Zussman E

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Akihiro Tamori, MD, PhD, Professor, Department of Hepatology, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan. atamori@med.osaka-cu.ac.jp

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Report® cites the 2020 impact factor (IF) for WJG as 5.742; Journal Citation Indicator: 0.79; IF without journal self cites: 5.590; 5-year IF: 5.044; Ranking: 28 among 92 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2020 is 6.9 and Scopus CiteScore rank 2020: Gastroenterology is 19/136.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*, Production Department Director: *Xiang Li*, Editorial Office Director: *Ze-Mao Gong*.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

November 7, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Role of cell-free network communication in alcohol-associated disorders and liver metastasis

Murali R Kuracha, Peter Thomas, Martin Tobì, Benita L McVicker

ORCID number: Murali R Kuracha 0000-0002-8475-1412; Peter Thomas 0000-0001-8982-760X; Martin Tobì 0000-0002-3431-6842; Benita L McVicker 0000-0001-7876-149X.

Author contributions: Kuracha MR and McVicker BL wrote the paper; Thomas P and Tobì M made critical revisions; all authors have read and approve the final manuscript.

Supported by Biomedical Laboratory Research and Development, VA Office of Research and Development, No. BX004127 (to McVicker BL and Tobì M).

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/License>

Murali R Kuracha, Benita L McVicker, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE 68198, United States

Peter Thomas, Department of Surgery, Creighton University School of Medicine, Omaha, NE 68178, United States

Martin Tobì, Research and Development Service, Detroit VAMC, Detroit, MI 48201, United States

Martin Tobì, Department of Medicine, Central Michigan University College of Medicine, Detroit, MI 48201, United States

Benita L McVicker, Research Service, Nebraska-Western Iowa Health Care System, Omaha, NE 68105, United States

Corresponding author: Benita L McVicker, PhD, Research Scientist, Research Service, Nebraska-Western Iowa Health Care System, 4101 Woolworth Ave, Omaha, NE 68105, United States. benita.mcvicker@va.gov

Abstract

The aberrant use of alcohol is a major factor in cancer progression and metastasis. Contributing mechanisms include the systemic effects of alcohol and the exchange of bioactive molecules between cancerous and non-cancerous cells along the brain-gut-liver axis. Such interplay leads to changes in molecular, cellular, and biological functions resulting in cancer progression. Recent investigations have examined the role of extracellular vesicles (EVs) in cancer mechanisms in addition to their contribution as diagnostic biomarkers. Also, EVs are emerging as novel cell-free mediators in pathophysiological scenarios including alcohol-mediated gut microbiome dysbiosis and the release of nanosized EVs into the circulatory system. Interestingly, EVs in cancer patients are enriched with oncogenes, miRNA, lipids, and glycoproteins whose delivery into the hepatic microenvironment may be enhanced by the detrimental effects of alcohol. Proof-of-concept studies indicate that alcohol-associated liver disease is impacted by the effects of exosomes, including altered immune responses, reprogramming of stromal cells, and remodeling of the extracellular matrix. Moreover, the culmination of alcohol-related changes in the liver likely contributes to enhanced hepatic metastases and poor outcomes for cancer patients. This review summarizes the numerous aspects of exosome communications between organs with emphasis on the relationship of EVs in alcohol-associated diseases and cancer metastasis. The potential impact of

s/by-nc/4.0/

Specialty type: Biochemistry and Molecular Biology**Country/Territory of origin:** United States**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

Received: May 15, 2021**Peer-review started:** May 15, 2021**First decision:** June 22, 2021**Revised:** July 2, 2021**Accepted:** September 30, 2021**Article in press:** September 30, 2021**Published online:** November 7, 2021**P-Reviewer:** Wang Z**S-Editor:** Chang KL**L-Editor:** A**P-Editor:** Chang KL

EV cargo and release along a multi-organ axis is highly relevant to the promotion of tumorigenic mechanisms and metastatic disease. It is hypothesized that EVs target recipient tissues to initiate the formation of prometastatic niches and cancer progression. The study of alcohol-associated mechanisms in metastatic cancers is expected to reveal a better understanding of factors involved in the growth of secondary malignancies as well as novel approaches for therapeutic interventions.

Key Words: Exosomes; Extracellular vesicles; Alcohol-associated liver disease; Colorectal cancer; Liver metastasis; Interorgan communication

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Alcohol consumption is an independent risk factor for cancer development as well as the promotion of metastatic disease, a major cause of morbidity and mortality in cancer patients. The identification of mechanisms and potential therapeutic targets for metastases remains to be determined for many cancers. Interorgan communication involving extracellular vesicles (EVs) is considered a vital process in the promotion of tumorigenic pathways and the spread of disease. Understanding the role of EVs in organ-organ communication networks will likely contribute to the development of future opportunities to combat cancer metastasis.

Citation: 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(41): 7080-7099

URL: <https://www.wjgnet.com/1007-9327/full/v27/i41/7080.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v27.i41.7080>

INTRODUCTION

The consumption of alcohol in chronic and/or aberrant drinking patterns correlates with a substantial burden of disease worldwide. A recent study conducted by the National Survey on Drug Use and Health stated that in the United States alone, 73.1% of adults regularly use alcohol and nearly 15 million people have an alcohol use disorder[1]. Based on World Health Organization reports, alcohol use has a negative impact on health and quality of life, creating more than 5% of global disease burden and premature deaths[2,3]. The processing of alcohol in the body significantly affects multiple organs including the liver, gut, lungs, heart and brain[4-7]. A prominent alcohol-related disorder is alcohol-associated liver disease (AALD) that is initially facilitated by ethanol metabolism in the liver[8]. However, AALD is a complex disease with factors from other organs also contributing to its development and progression. Notable contributing factors include cells of the innate immune system and bacteria of the alcohol-altered gut microbiota[9,10]. Overall, the interplay between alcohol-affected organs clearly plays a role in the outcomes of AALD as well as additional adverse consequences such as alcohol-related cancer development and metastatic disease.

Alcohol is an identified carcinogenic factor in several cancers including head and neck, esophageal, liver, breast, pancreatic, and colorectal[11,12]. Recent reports indicate that alcohol consumption is the third and fourth largest contributor of all primary cancers in women and men, respectively[3]. Further, studies have shown that alcohol associates with an increased risk of secondary cancers of the upper aerodigestive tract (*i.e.* oral cavity, pharynx and esophagus) as well as metastases of colorectal cancers[13,14]. Multiple mechanisms are attributed to alcohol-induced cancer risk including toxic products and reactive oxygen species generated by ethanol metabolism. Additionally, cellular factors produced in response to injury such as protein, lipids and microRNAs can be packaged and released in extracellular vesicles (EVs)[15]. The EVs can migrate to modulate neighboring cells and/or distant tissues, acting in many cases as tumorigenic signaling molecules. Multiple cell types including endothelial cells, epithelial cells, neuronal cells, immune cells, and cancer cells can secrete nanosized EVs as part of their normal physiology, as well as during the

pathophysiology of disease[16]. Recent studies have suggested that during pathophysiological conditions exosomes have multiple roles in disease progression. Interestingly, tumor-derived exosomes have been implicated as regulatory factors in cancer progression by promoting cancer cell proliferation, migration, and the establishment of a premetastatic niche for drug-resistant cells[17,18]. Overall, EVs have the capability to contribute to the progression of AALD as well as alcohol-related advanced or secondary cancers. A better understanding of the integrated cell-cell communication between cancer cells and normal cells is critical for the development of new therapeutic options. Research into the complex interactions of diverse organs by EVs is a focus of new and clinically relevant areas of study. Here, we review studies on exosome biology and EV communication networks associated with alcohol-related disorders and metastatic cancers.

EXOSOME CHARACTERISTICS

Exosome biogenesis

Exosomes were first identified in 1981 as cell-derived, membrane-bound enzymatic vesicles[19]. Subsequently, it was demonstrated that exosomes are nano-sized (30 to 150 nm) lumen vesicles that originate from the endosomal system[20]. Further, it was elucidated that EV biogenesis is a sequential process in which multivesicular bodies (MVBs) form following membrane invagination of intraluminal vesicles[18,20]. A small fraction of MVBs fuse with the plasma membrane and are released into the extracellular milieu[21]. The regulation of MVB fusion and release can involve cholesterol content as seen in B-lymphocytes where membrane fusion and exosome release were only observed for the high cholesterol pool of MVBs[22]. Additionally, several reports have shown that exosome release depends on the cell polarity and the contribution of specific components of apical or basolateral membranes[23-25]. Overall, existing evidence indicates that different MVB populations exist inside cells and that select pools are involved in extracellular release[25] as well as the scavenging of plasma membrane proteins[26] to maintain cellular homeostasis during the EV maturation process[27,28].

Endosome pathways identified in the regulation of exosome biogenesis include endosomal sorting complex required for transport (ESCRT)-dependent and independent pathways (Figure 1). Studies have eloquently described ESCRT pathways showing the direct control of ESCRT-mediated membrane machinery[29] and ESCRT-independent regulation of EV budding and release by factors such as sphingolipid ceramide[30,31]. It was also demonstrated that vesicle formation and trafficking involve functional proteins such as Rab GTPases, heat shock proteins (HSP70 or HSP90), tetraspanins (CD9, CD63, and CD81), and integrins[18,32]. Further, the role of sphingomyelin, phosphatidylcholine, diacylglycerol, and ceramide as exosome membrane lipids was described[33]. Altogether, these studies suggest that distinct exosome biogenesis pathways, in addition to specific sorting and cargo mechanisms, dictate diverse biological functions and effects of EVs on recipient cells.

Exosome sorting and cargo delivery

A significant feature of exosomes is the morphological and size profile of the vesicles. Based on size, EVs are classified into large exosome vesicles (90-120 nm), small exosome vesicles (60-80 nm), or non-membranous nanoparticles called exomeres (35 nm)[34]. While both large and small size exosomes can respond to signaling pathways such as IL-2/STAT5, density gradient centrifugation studies revealed differences in lipid compositions between various sized EVs[34]. Moreover, subpopulations of low-density and high-density exosomes can have differential effects on gene expression profiles.

In addition to EV size, the characterization of exosome cargo is important to the understanding of EV effects in healthy and pathophysiological scenarios. Exosomes contain distinct ratios of molecular constituents such as nucleic acids, proteins, lipids, and metabolites that vary depending upon their cellular conditions, cells of origin, epigenetic changes, and metabolomic stages[35]. Moreover, studies have described various RNA species that are components of exosome cargo including microRNAs (miRNAs), rRNAs, tRNAs, or long noncoding RNAs (lncRNAs)[36]. The role of miRNAs as EV cargo is an emerging area of study, especially in oncology. In cancer cells, exosomes are highly enriched in miRNAs compared to parent cells indicating that miRNAs are sorting into the exosome cargo[37-39]. Several studies have identified exosomal miRNAs as serum biomarkers for the prediction of cancer progression and

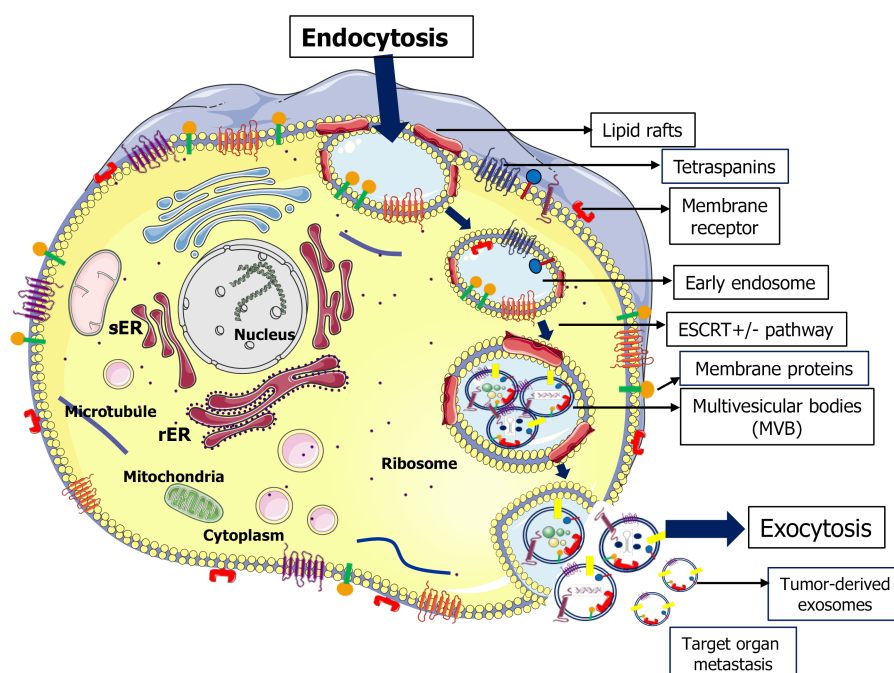


Figure 1 Extracellular vesicle biogenesis. Pathways involved in extracellular vesicle (EV) generation from the endocytosis of cargo components to release of targeting exosomes. EV biogenesis is achieved by endosomal sorting complex required for transport (ESCRT)-dependent or ESCRT-independent pathways. Several cytoplasmic and nuclear molecules can be sorted in the EVs such as ubiquitin-related proteins, heat shock proteins, miRNAs, and cytoskeleton proteins. ESCRT: Endosomal sorting complex required for transport; sER: Smooth endoplasmic reticulum; rER: Rough endoplasmic reticulum.

metastasis[40-42]. Significantly, the differential expression of exosomal miRNA was noted to have a role in the regulation of tumor progression and metastasis in various cancer models[43-45]. However, the mechanisms involved in the loading and sorting of molecules into exosome vesicles remain to be elucidated. Towards those efforts, Villarroja-Beltri *et al*[46], have identified a sequence motif that controls the miRNA loading into exosomes. In addition, Kirsten rat sarcoma (KRAS) oncogene-dependent miRNA sorting into exosomes was found to play a key role in colorectal cancer cell (CRC) since CRC cells expressing mutant KRAS have distinct miRNA profiles compared to wild-type cells[47]. In another study, it was shown that the hyper-activation of mutated KRAS inhibited the localization of the regulatory protein Argonaute 2 into exosomes[48]. The sorting of exosome mRNAs and enrichment of 3' UTR fragments also demonstrates the importance of exosomal RNA effects in recipient cells[49,50]. Also, tumor-derived exosomes can carry double stranded DNA and genomic DNA fragments that reflect the mutational status of oncogene and tumor suppressor genes[51,52]. And finally, ubiquitination has been noted to have a role in the packaging of target proteins into exosomes[53-55].

Another important aspect of exosome cargo and sorting mechanisms is the lipid content of exosome membranes such as cholesterol, sphingomyelin, and glycosphingolipids that have specific roles in protein sorting into exosomes[33,56]. Data indicates that subdomains of the plasma membrane (lipid rafts) enriched with distinct proteins on exosome membranes mediate exosome signaling as well as molecule sorting into exosomes[57,58]. Further, mechanistic studies demonstrated the release of factors such as flotillin-1 and stomatin into the external medium *via* EVs associated with lipid microdomains[59]. Another study showed a positive regulation of sphingosine 1-phosphate (S1P) by sphingosine kinases that enabled S1P receptors to be continuously active on EVs[31]. The continuous activation of S1P has been shown to regulate CD63, CD81, and flotillin-mediated sorting into exosomes through inhibitory G protein-coupled S1P receptors located on MVBs[31]. This suggests that G protein receptor-mediated S1P signaling on MVBs is mainly involved in the ESCRT-independent exosome cargo. Collectively, these studies suggest that distinct molecular constituents such as proteins, lipids, and nucleic acids play an essential role in exosome maturation culminating in effective sorting and extracellular release of EV cargo. The molecular, cellular, and biological functions that result from the released EVs is a critical area of research, especially in the evolving era to understand the mechanisms of alcohol-associated diseases including cancer.

THE EFFECTS OF ALCOHOL ON EXOSOME COMMUNICATION

Alcohol and liver-associated EVs

Clinical manifestations of AALD include steatosis, steatohepatitis, fibrosis, and cirrhosis[8,60]. The liver is sensitized to triggers such as oxidative stress and endotoxins in early phases of AALD resulting in cellular damage and development of advanced disease. Further, consequences of ethanol metabolism lead to alterations in the function of hepatic cells as well as the recruitment of circulating cells and molecules that contribute to organ dysfunction. Previous reviews have comprehensively described the emerging role of EVs during the pathogenesis of alcohol-mediated diseases[61-63]. In brief, alcohol-mediated stresses result in elevated EV generation and release from hepatocytes as well as non-parenchymal cells. The released EVs can modulate gene expression and function of target cells contributing to the perpetuation of liver damage. Examples of the effect of EV cargo (*i.e.* miRNA, proteins, and lipids) include changes in macrophage phenotype and the activation status of hepatic stellate cells. Altogether, EVs generated in the liver are key players in alcohol-mediated liver inflammatory and profibrogenic mechanisms. In addition to EV-mediated intra-organ signaling, communication to extra-hepatic tissues can occur, as well as bidirectional exosome communication between organs such as liver, brain, gut, and lung.

Gut-Liver axis

Alcohol-induced impairments to the intestinal epithelial barrier result in increased gut permeability and release of bacterial products into the circulation[9,64]. The released products can perpetuate gut-barrier dysfunction, as well as contribute to hepatic injury, as the liver is the primary organ to receive and detoxify gut-derived factors. The translocation of intestinal products to the liver is involved in several diseases including obesity, metabolic syndrome, and non-alcoholic and alcoholic liver diseases. In the setting of alcohol, the gut-liver axis sustains bilateral communications between the intestine and the liver leading to gut-dysbiosis and progression of liver injury[65,66]. Notably, the transfer of gut-derived toxins to the liver due to alcohol consumption is considered a pivotal event in the development and severity of AALD. Clinical data indicates that drinking patterns correlate with processes of the gut-liver axis as changes in intestinal permeability increase with the degree of alcohol consumption [64]. Next-generation sequencing data further confirmed the association between chronic alcohol consumption and altered gut microbiome functions in mice and humans[67,68]. Overall, alcohol consumption is linked to multiple changes in the gut including intestinal epithelial barrier dysfunction, alterations in gut epithelial and mucosal cells, and changes to the intestinal microbiota. As a result, bacterial products (*i.e.* endotoxin and other pathogen-associated molecular patterns) translocate to the liver and contribute to the production of proinflammatory pathways. Despite the current understanding of alcohol's effects on the gut microbiome, the role of EVs in the transfer of gut-derived products is not defined. However, emerging data indicates the EVs significantly contribute to alcohol-related liver inflammation.

The effects of alcohol on the intestinal microbiome and the translocation of injurious factors to the liver is an area of extensive research. It is well characterized that alcohol consumption results in the dysbiosis of bacterial and fungal intestinal species and the release of products including lipopolysaccharide (LPS) from the leaky gut[69,70]. In search of contributing mechanisms, studies have described alcohol-induced reductions in the expression of tight junction proteins as well as direct injury to gut epithelial cells [71,72]. The overexpression miRNA has been implicated in tight junction alterations as the knockdown of miRNA-21 prevented ethanol-induced disruption of tight junctions through the restoration of associated transmembrane proteins such as occludin and zonula occludens-1 (ZO-1)[71,73]. Additionally, the blockade of miRNA-122a was found to be protective against tight junction alterations in Caco-2 cells[74]. It is suggested that EVs generated during alcohol-induced changes to the intestinal barrier contain cargo such as miRNAs, LPS, and bacterial products that target the liver and contribute to AALD. Indeed, a recent study by Lamas-Paz *et al*[75] demonstrated that EVs derived from alcohol-affected intestinal epithelial cells contributed to hepatocellular injury. Further, it is likely that ethanol-mediated changes in intestinal barrier and microbiome composition result in the release of bacterial EVs. For example, in addition to its role as a soluble factor, LPS can also be packaged into EVs for transport from the injured gut. This is supported by a recent report indicating the presence and activity of bacterial EVs in patients with intestinal barrier dysfunction[76]. The role of bacterial EVs in alcohol consuming patients remains to be characterized along with the

therapeutic potential of targeting such EVs.

The mechanistic role of bacterial products in the progression of alcohol-associated diseases has led to the study of the gut microbiota as a therapeutic target in patients with alcohol use disorders[77]. Currently, probiotics (living bacterial cultures), prebiotics (promoters of beneficial or commensal bacteria), and antibiotics, all serve as potential therapies for alcohol-associated diseases[78]. For instance, *Lactobacillus rhamnosus* is protective against alcohol-induced liver injury in mice[79]. Further, the administration of prescribed probiotics is promising as a protective barrier against alcohol-induced gut permeability and AALD[80]. The use of prebiotics may also be beneficial as certain diets (*i.e.* oats, flaxseed) protect against alcohol-induced oxidative stress and hepatic inflammation[81,82]. Similarly, antibiotic treatment can attenuate alcohol-induced endotoxemia by preventing the overgrowth of harmful bacteria in the gut[83]. Overall, insight into the mechanistic utility of targeting exosomes generated by the alcohol-altered gut warrants investigation for the development of effective therapeutics against disease progression related to the gut-liver axis.

Liver-Brain axis

It is well described that manifestations of AALD lead to a spectrum of symptoms in the brain such as cerebral edema and hepatic encephalopathy. Of notable involvement, ammonia and other harmful substances produced by the alcohol-injured liver can reach the brain causing injury and neuroinflammation. However, mechanisms related to exosome communication networks of the liver-brain axis remain to be characterized. Reports to date indicate that the coadministration of alcohol and LPS result in altered profiles of cytokines such as TNF- α , MCP-1, IL-1 β in the gut, liver, and brain[84]. Other studies demonstrate that the lack of the tumor necrosis factor receptor 1 results in the accumulation of TNF- α in mouse serum, gut, and liver; and that alcohol intake potentiates long-lasting levels of proinflammatory cytokines in the brain[85]. A recent study demonstrated that TNF- α inhibition reduced systemic inflammation and improved symptoms[86]. Additionally, chronic alcohol consumption not only influences brain inflammation but also interferes with stress-mediated psychiatric behavior through the disruption of the hypothalamic-pituitary-adrenal (HPA) axis [87]. The alcohol-mediated neutralization of the HPA axis could be a potential mechanism by which systemic inflammation continues in individuals who have an addiction to alcohol.

Besides chronic alcohol addiction, the loss of gut barrier integrity is a causative factor of endotoxin transport during sepsis and brain inflammation. Alcohol-induced gut dysbiosis is thought to not only play a role in alcohol dependency but also in the regulation of effects including neuro and endocrine signaling and immune system alterations[64,68]. However, a connective factor such as EVs in the gut-liver-brain axis has yet to be identified. Interestingly, the blood-brain barrier (BBB) serves as a defensive barrier against the extravasation of tumor cells and pathogens[88]. However, cancer cells can destruct the BBB structure to mediate migration during brain metastasis[89]. Overall, it is suggested that EVs facilitate cell network communications through the delivery of their cargo (*i.e.* proteins, mRNA, and miRNAs) to trigger the breakdown of the BBB through EV-induced changes in tight-junction proteins including ZO-1, N-cadherin, and actin.

Liver-Lung axis

Excessive alcohol use is a major factor in the enhanced risk of acute respiratory distress syndrome (ARDS)[90]. Chronic alcohol exposure in the liver-lung axis is linked to hepatopulmonary syndrome, bacterial infection, and increased mortality from ARDS [90,91]. Recently, Siore *et al*[92] reported that pulmonary edema and acute lung damage occur through the activation of inflammatory responses and oxidative stress involving liver-lung axis communications. It was shown that alcohol administration results in elevated levels of the TNF- α responsive chemokines, macrophage inflammatory protein, and keratinocyte chemoattractant. Further, the enhanced chemokine expression is associated with the recruitment of pulmonary neutrophils. Additional studies indicated that the liver-lung axis is bidirectional for the communication and effects involved in alcohol-enhanced hepatopulmonary injury. For instance, ventilator-induced lung injury in a mouse model resulted in significant inflammatory responses produced in cultured hepatic sinusoidal endothelial by perfusate from injured lungs [93]. In relationship to the role of the liver-lung axis in alcohol-related cancers, several studies have investigated the role of metastatic determinants[94,95]. In particular, tumor-derived exosomes may have a significant role in cancer cell metastasis that is mediated by cell adhesion molecules such as integrins, tenascin, and periostin[96-98]. In summary, the role of EVs in the interplay between pulmonary disease, AALD and

alcohol-associated cancers is a needed area of research for the identification of potential therapeutic targets.

EXOSOMES AND CANCER: ROLE OF ALCOHOL-MEDIATED EFFECTS

The interorgan communication mediated by EVs is clearly a factor of pathophysiology in various disease states. The role of alcohol-induced EV communication in the development and progression of cancer is not defined and is an area of clinical importance due to the prevalence of alcohol consumption and associated risk of cancers. Thus, investigations into the role of EVs in the initiation and severity of cancers aims to gain insight into the relationship of comorbid conditions related to the effects of alcohol consumption. Moreover, realization of the importance of EVs in cancer progression and metastasis has increased exponentially, as have their potential application in therapy and diagnosis[99]. The contribution of EVs in pathological processes is far reaching since tumor-secreted exosomes can mediate angiogenesis, modulate the immune system, and facilitate the generation of pre-metastatic niches[96, 100]. Indeed, EVs have been identified as key mediators of communication networks within and between organ systems, highlighting the clinical importance of exosome function[18,101,102]. Existing web-based online bioinformatic tools including high-throughput techniques (*i.e.* ExoCarta, EVpedia, Vesiclepedia catalog, and Ingenuity Pathway Analysis, IPA) are beneficial to the scientific community in EV research[103, 104]. These resources assist in the characterization of EV molecular and pathophysiology mechanisms through the identification of key functional elements. Based on IPA data, EV cargo delivery depends on the content of bioactive molecules such as mRNA, enzymes, proteins, DNA and lipids that can dictate the role of EVs in disease progression and diagnostic functions (Figure 2).

The clinical assessment of EVs in body fluids provides another measure towards the understanding of exosomes as diagnostic biomarkers and therapeutic targets. Biomolecule-loaded EVs from blood are stable for more than 90 days under normal storage conditions making EV analyses more useful compared to other less-stable measures of cell-free DNAs and circulating tumor cells that are used as liquid biopsies [105,106]. Examples of exosome-related identification in serum samples include prostate cancer-derived exosomes[107]; and exosome cargo containing an androgen receptor variant that is a biomarker of metastatic prostate cancer[108]. Several studies have also reported the sensitivity of EV miRNA composition as biomarkers in disease identification that can be isolated from various body fluids including blood, saliva, and urine[109,110]. A noted example is the oncogenic signature of miR-21 as a biomarker for various cancers including colorectal[111], breast[112], brain[113], and liver[114]. Concerning diseases of the liver, it has been shown that the concentration of EVs in the circulation is enhanced in the setting of AALD, nonalcoholic fatty liver disease, viral hepatitis, and hepatocellular carcinoma indicating the clinical significance of EV-mediated communication and subsequent effects[66]. Overall, clinical measures as well as bioinformatic programs are valuable in deciphering EV-mediated mechanisms and are useful tools for the characterization of alcohol-associated EVs in development and progression cancers.

Role of exosomes in cancer progression

Mechanisms of tumor development and progression are dynamic, multi-step processes that occur in response to the accumulation of genetic alterations in damaged cells. An integral component of tumor development is thought to be the communication between cancerous and non-cancerous cells that is mediated by nanosized vesicles [115]. Research to date indicates that cancer cell microvesicles actively transfer oncogenic molecules from primary cancer cells to intercellular populations. Indeed, tumor-derived exosomes can regulate cancer progression by stimulating oncogene overexpression, stromal cell remodeling, immune system modulation, and angiogenesis[115]. The transfer of tumorigenic material *via* EVs is implicated in the modulation of morphological changes and the enhancement of anchorage-independent growth capacity of cancer cells. Similarly, tumor-derived exosomes can act as survival factors that bind to and activate anti-apoptotic pathways[116].

The knowledge that exosomes are potential stimulators in cancer progression indicates that EVs can promote angiogenesis and changes in the microenvironment [117]. In this regard, tumor-derived exosomes can influence mesenchymal stem cell differentiation facilitating cancer cell proliferation and disease progression[118]. Moreover, the exosome-mediated transfer of lncRNAs as tumor-promoting material

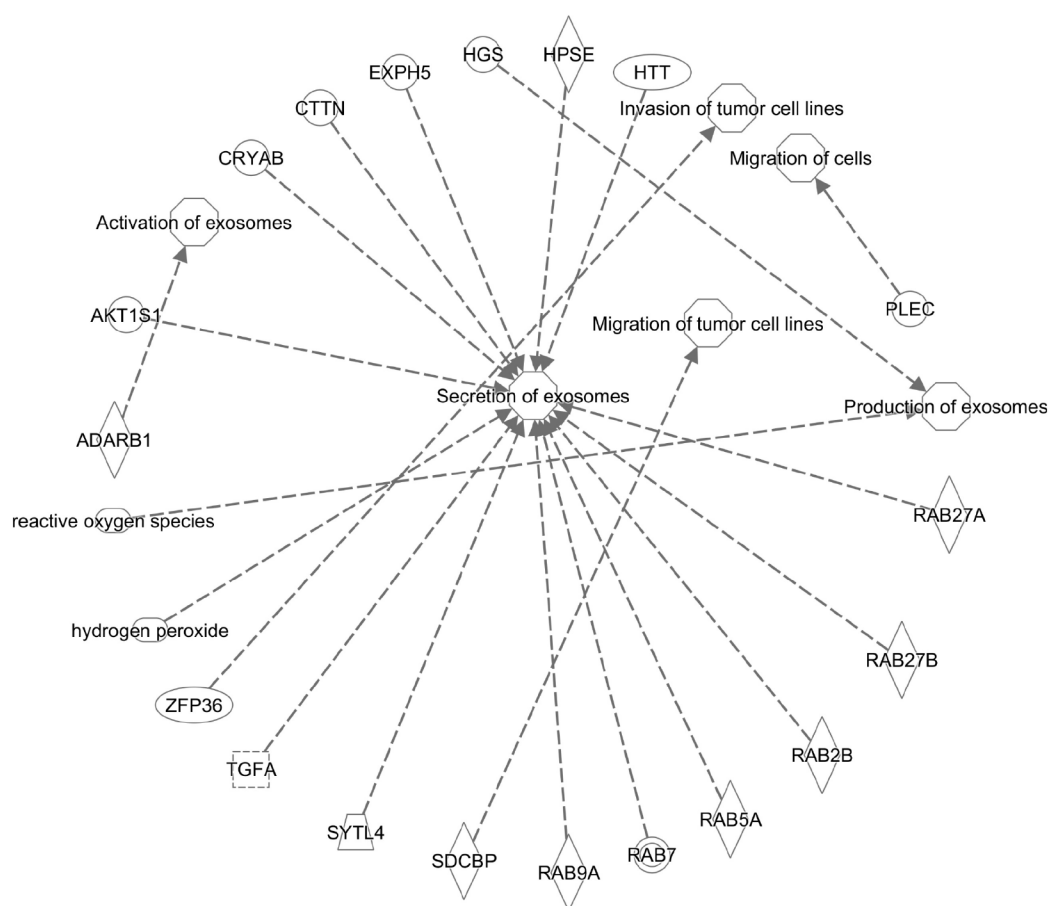


Figure 2 Exosome network analysis. Based on Ingenuity Pathway Analysis, distinct molecules from different tissues and cells can be involved in exosome secretion during cancer progression as well as in diagnostic functions. CRYAB: Chaperone alphaB-crystallin; CTTN: Cortactin; EXPH5: Exophilin 5; HGS: Hepatocyte growth factor; HPSE: Heparinase; HTT: Huntingtin protein; PLEC: Plectin; RAB27A: Ras-related protein Rab-27A; RAB27B: Ras-related protein Rab-27B; RAB2B: Ras-related protein Rab-2B; RAB5A: Ras-related protein Rab-5A; RAB7: Ras-related protein Rab-7; RAB9A: Ras-related protein Rab-9A; SDCBP: Syndecan binding protein; SYTL4: Synaptotagmin like 4; TGFA: Transforming growth factor alpha; ZFP36: Zinc finger protein 36; ADARB1: Adenosine deaminase RNA specific B1; AKT1S1: AKT1 Substrate 1.

has been shown during the transformation of non-malignant cells[119]. The role of EVs enriched with miRNAs has also been shown in cell-cell communications and conversion of cells to populations with enhanced motility[120]. Specific examples include the role of miR-17-92 and miRNA-92a as potent promoters of angiogenesis and oncogenic activity[121]. Likewise, miR-135b-5p[122], miR-30a-5p[40], miR-150-5p [123], miR-183-5p[124], miR-155[125], miR-497[126], miR-181b-5p[127], miR-375[128, 129] and the miR-200 family[110,130,131] have been shown to be effective markers of cancer progression. The clinical evaluation of EV miRNA cargo provides insightful information into processes involved in the various stages of cancer from detection to metastasis as summarized in Table 1.

Another component identified in cancer progression is the release of cancer-associated fibroblasts (CAFs) from exosomes. CAF-derived EVs can play a key role in tumor progression by enabling the transfer of oncogenic molecules such as amino acids, lipids, and TCA-cycle intermediates to confer glycolysis modulation and carboxylation in cancer cells[132]. Tumor-derived exosomes have also been shown to be involved in the stimulation of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 (ICAM-1) enhancing the process of neovascularization in endothelial cells in the microenvironment[133]. Moreover, recent studies suggest that EVs are important in mediating cellular communication between cancer cells and other cells of the microenvironment such as immune cells, neutrophils, natural killer (NK) cells, dendritic cells, T cells, and macrophages. For example, cancer-derived exosomes can alter macrophage polarization[134], induce the recruitment of neutrophils to the tumor site[135], decrease the cytotoxic activity of NK cells[136], or inhibit T-cell proliferation mechanisms[137]. Altogether, it is evident that exosomes can mediate cancer progression through a variety of pathways and cellular communications leading to cancer cell proliferation and spread to distant sites.

Table 1 Summary of exosome miRNA signatures as cancer biomarkers

Exosomal miRNA	Expression profile	Mode of action	Type of cancer	Ref.
miR-320d	Upregulated	Predicts metastasis	CRC	Tang <i>et al</i> [41]
miR-106b-3p	Upregulated	Promotes metastasis	CRC	Liu <i>et al</i> [163]
miR-6803-5p	Upregulated	Prognosis marker	CRC	Yan <i>et al</i> [42]
miR-874	Upregulated	Prognosis marker	GC	Zhang <i>et al</i> [164]
miR-30a-5p	Downregulated	Diagnostic tool	CRC	Sun <i>et al</i> [40]
miR-21	Upregulated	Diagnostic tool	CRC	Bastaminejad <i>et al</i> [111]
miR-135b-5p	Upregulated	Metastatic marker	CRC	Li <i>et al</i> [122]
miR-150-5p	Downregulated	Prognosis, marker	CRC	Zou <i>et al</i> [123]
miR-183-5p	Upregulated	Angiogenesis	CRC	Shang <i>et al</i> [124]
miR-155	Upregulated	Diagnostic tool	CRC	Lv <i>et al</i> [125]
miR-16-5p	Upregulated	Regulation of ITGA2	CRC	Xu <i>et al</i> [165]
miR-497	Downregulated	Prognosis marker	CRC	Zou <i>et al</i> [126]
miR-4461	Downregulated	Regulation of COPB2	CRC	Chen <i>et al</i> [43]
miR-146a	Upregulated	Invasion and metastasis	BC	Yang <i>et al</i> [45]
miR-125a-3p, miR-320c	Upregulated	Stage I marker	CC	Wang <i>et al</i> [166]
miR-4772-3p	Upregulated	Stage II & III marker	CC	Liu <i>et al</i> [167]
miR-21, miR-10b	Upregulated	Metastatic marker	HCC	Tian <i>et al</i> [44]
miR-1290, miR-375	Upregulated	Prognostic marker	CRPC	Huang <i>et al</i> [129]
miR-373, miR-200a, miR-200b, miR-200c	Upregulated	Tumor progression	EOC	Meng <i>et al</i> [131]
mir-181b-5p	Downregulated	Diagnostic tool	GC	Yun <i>et al</i> [127]

CRC: Colorectal cancer; GC: Gastric cancer; ITGA2: Integrin alpha 2; COPB2: COPI coat complex subunit beta 2; BC: Breast cancer; Stage I, II, III: North American Association of Central Cancer Registries Stages I, II, III and IV; CC: Colon cancer; HCC: Hepatocellular carcinoma; CRPC: Castration-resistant prostate cancer; EOC: Epithelial ovarian cancer.

Exosomes role in cancer metastasis

Metastasis is one of the most common causative factors in cancer-related death. Cancer metastasis is a multi-step process for the development of secondary cancers. In 1889, Stephen Paget described the “seed and soil” theory, in which metastasis depends on the interaction between primary cancer cells as the seed and secondary host microenvironments designated as the soil[138]. Involved mechanisms were found to include changes to the extracellular matrix architecture and associated reprogramming of normal cells. Clinically significant interactions between cancer cells and the cells of secondary organ sites have been shown to involve hepatocytes, bone marrow progenitor cells, CAFs, macrophages, and neutrophils. However, regulatory mechanisms of secondary organ-specific metastasis are poorly understood. Towards that understanding, studies have indicated that tumor-derived exosomes assist in the priming of premetastatic niches by delivering prometastatic factors. In particular, the integrin expression profile of tumor derived EVs can act as functional “ZIP codes” during metastatic organotropism to direct metastatic cancer cells to target tissue/organs[96]. Proteomic and clinical data support the role of exosome-sorted integrins as vital players in the development of cancer metastasis. For instance, $\alpha\beta4$ and $\alpha\beta1$ integrins are associated with lung metastasis and $\alpha\beta5$ is involved with liver metastasis[139]. Also, tumor-derived exosomes are involved in the activation of the Src kinase pathway and the upregulation of pro-inflammatory S100 genes during the establishment of premetastatic niches[140]. Thus, cell-cell communication mediated by EVs appears to be a critical element during premetastatic niche formation in cancer development (Figure 3). Review of the literature indicates the variety of cancer types and stromal cell-derived exosome molecules can initiate signals during the reprogramming of the tumor microenvironment (Table 2). Thus, exosome-mediated

Table 2 Extracellular vesicle components in cancer progression and metastasis

EV cargo	Type of molecule	Action on recipient cells/tissue	Type of cancer	Ref.
CEA	Protein	Inflammation	Colorectal	Yokoyama <i>et al</i> [162]
KRAS	Protein	Invasiveness in recipient cells	Colorectal	Beckler <i>et al</i> [152]
ITG	Protein	Metastatic organotropism	Breast	Hoshino <i>et al</i> [96]
TNC	ECM protein	Stem cell niche formation	Breast	Oskarsson <i>et al</i> [97]
MIF	Protein	Liver premetastatic niche formation	Pancreatic	Costa-Silva <i>et al</i> [168]
ZFAS1	lncRNA	Cancer growth/metastasis	Gastric	Pan <i>et al</i> [119]
Amino acids, lipids, TCA-cycle intermediates	Metabolites	Cancer growth	Prostate	Zhao <i>et al</i> [132]

CEA: Carcinoembryonic antigen; KRAS: Kirsten rat sarcoma viral oncogene; ITG: Integrins; TNC: Tenascin C; MIF: Macrophage migration inhibitory factor; ZFAS1: ZNF1 antisense RNA1; lncRNA: Long non-coding RNA; ECM: Extracellular matrix.

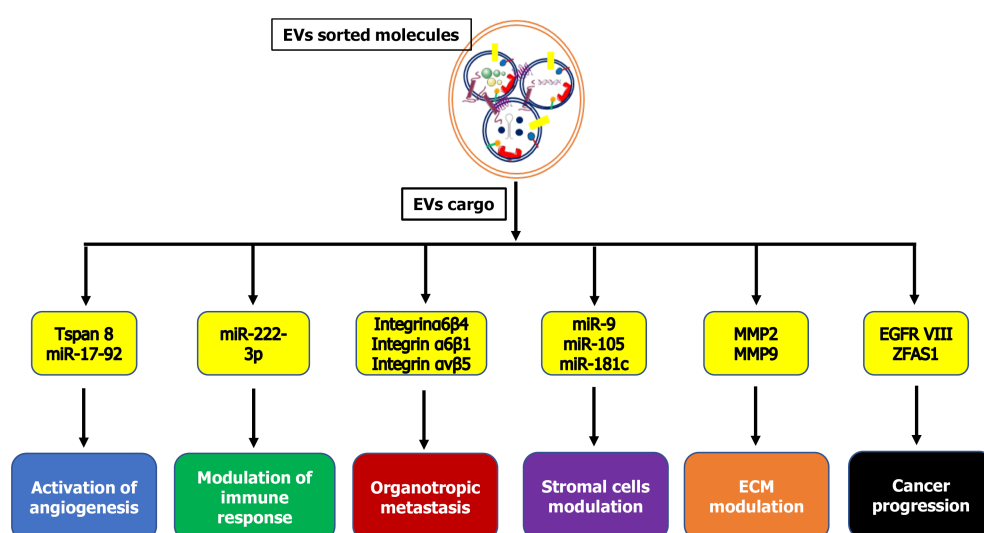


Figure 3 Exosome-mediated functions in the pre-metastatic niche. The role of tumor-derived exosomes along the establishment and progression of metastatic disease. Extracellular vesicle cargo can be involved in the initiation and regulation of cancer by promoting immune responses, angiogenesis, extracellular matrix modulation, stromal cell changes and metastatic organotropism. EVs: Extracellular vesicles; Tspan8: Tetraspanin-8; MMP2: Matrix metalloproteinase 2; MMP9: Matrix metalloproteinase 9; EGFR VIII: Epidermal growth factor receptor variant III; ZFAS1: ZNF1 antisense RNA1; ECM: Extracellular matrix.

intracellular signaling as well as organ-organ communication can influence cancer progression and changes to host and tumor microenvironments to facilitate metastatic disease.

CLINICAL IMPLICATIONS OF EXOSOME COMMUNICATION NETWORKS

Role of EVs in alcohol and colorectal cancer disease

Recent studies indicate an alarming increased rate of morbidity and mortality from alcohol use disorders in the United States[141]. Of particular clinical significance is the disease burden related to alcohol use in colorectal cancer and associated liver metastasis. CRC is a leading cause of cancer mortality with the majority of deaths due to the development of colorectal liver metastasis (CRLM) as the liver is the foremost site of distant metastatic spread in CRC patients[142,143]. Epidemiological studies suggest that chronic alcohol consumption is one of the major causative factors of colorectal cancer mortality in both men and women[144]. Alcohol use correlates with CRLM at colorectal cancer diagnosis as well as hepatic metastases that occur over time. Further, alcohol-associated CRLM requires intensive follow-up and treatment due to poor liver function and unresectable lesions. Despite advancements in surgical interventions and chemotherapeutics, CRLM morbidity and mortality are leading healthcare concerns

emphasizing the significant need to determine contributing mechanisms. The involvement of EV signaling during CRC progression in the setting of alcohol is not known. Thus, understanding EV communication networks and the role of EVs as biomarkers can significantly contribute to the development of strategies to address the serious public health issues associated with alcohol use and cancers.

The development of CRC is a multi-step process involving the malignant transformation of normal cells of the colon. The contribution of ethanol metabolism and related metabolites in colon carcinogenesis has been investigated for some time. A variety of pathways attributed to the effects of alcohol have been identified in the promotion CRC including genetic abnormalities, epigenetic dysregulation, cell signaling, and changes in the tumor microenvironment[13]. However, the role of alcohol during CRC spread to other organs is less understood. In particular, the contribution of alcohol during liver metastasis is emerging as a critical area of study given the substantial mortality associated with CRLM and need to identify targetable mechanisms. Current literature indicates that alcohol creates a hepatic microenvironment susceptible to CRC seeding and growth. Attributable mechanisms include the sensitization of resident macrophages (Kupffer cells, KCs) to endotoxin-induced signaling, the production of inflammatory factors, and the activation of fibroblastic cells that promote disease rather than wound-healing[145]. Moreover, it is likely that targetable mechanisms of CRLM involve communication networks between alcohol-affected macrophages and cancer cell-associated factors. The contribution of EVs in alcohol-associated CRLM is not defined but is clearly considered an important process to characterize.

EVs represent a new form of communication in colorectal cancer progression and liver metastasis. The fact that EVs can deliver cargo (*i.e.* RNAs, lipids, proteins) between cells and organs indicates the potential of playing a key role in metastatic disease[146,147]. CRC proliferation and migration can induce the release of EVs and other tumor-derived factors that can promote prometastatic niche formation, vascular changes, inflammation, and immunosuppression in host microenvironments. Several studies have recently described the contributions of EV cargo as prime mechanisms of CRC metastasis. For example, proteomic data revealed a distinct profile of metastatic factors, signal transduction molecules, and lipid raft-associated components in EVs obtained from metastatic CRC cells[148]. The contribution of mRNA components from CRC-derived EVs in cancer progression has also been shown for miRNAs (*i.e.* miR-21, miR-192 and miR-221) as well as natural antisense RNAs such as Leucine Rich Repeat Containing 24, MDM2 Proto-Oncogene, and Cyclin Dependent Kinase Inhibitor 1A [149]. Moreover, the role of genetic mutations in CRC patients are of interest. In particular, KRAS mutations are frequently associated with CRC metastasis and the regulation of exosome composition and release in CRC cells[150,151]. In addition, many oncogenic proteins (*e.g.* KRAS, Src family kinases, integrins) are highly enriched in mutant KRAS-derived exosomes indicating a role in CRC progression and metastasis[152]. Together, these observations provide novel insight into the role of EVs and the therapeutic potential of targeting the CRC-generated EVs during metastatic disease.

There is a growing body evidence suggesting that tumor-derived exosomes are crucial factors that influence differentiation in the microenvironment through particular signaling pathways[153]. For example, CRC cell-derived EVs have been shown to promote angiogenesis and tumor growth in the host microenvironment through the hyper-activation of Wnt/ β -catenin signaling. As a result, hypoxic metastatic niches provide CRC cells protection from chemotherapy and attack from immune cells[154]. Another signaling pathway implicated in colon tumorigenesis is the activation of proinflammatory cellular kinases. A recent study by Talwar *et al*[155] demonstrated that phosphorylated p38 γ is activated in CRC tumorigenesis. Further, it is suggested that the activation of p38 γ may be associated with immunoglobulin adhesion molecules such as carcinoembryonic antigen (CEA) and biliary glycoprotein (BGP). In support, the expression of CEA and BGP have been linked to hepatic metastasis in various preclinical models and in CRC patients with ongoing efforts to define the mechanistic role of CEA during CRLM[156-158]. Key studies have shown a direct relationship between CEA and the metastatic potential of CRC cells, and that CEA stimulation results in the production of tumorigenic factors by Kupffer cells[159-161]. Current works are evaluating the role of alcohol on KC function to determine if ethanol-sensitized macrophages are more responsive to CEA leading to advanced metastatic disease. To date, studies have shown that the alcohol-injured liver provides a permissive environment for CRLM and that CEA-mediated inflammatory mechanisms may play a key role[157,162]. However, the role of tumor-derived and alcohol-associated EVs in the process of metastatic mechanisms involving MAPK signaling or

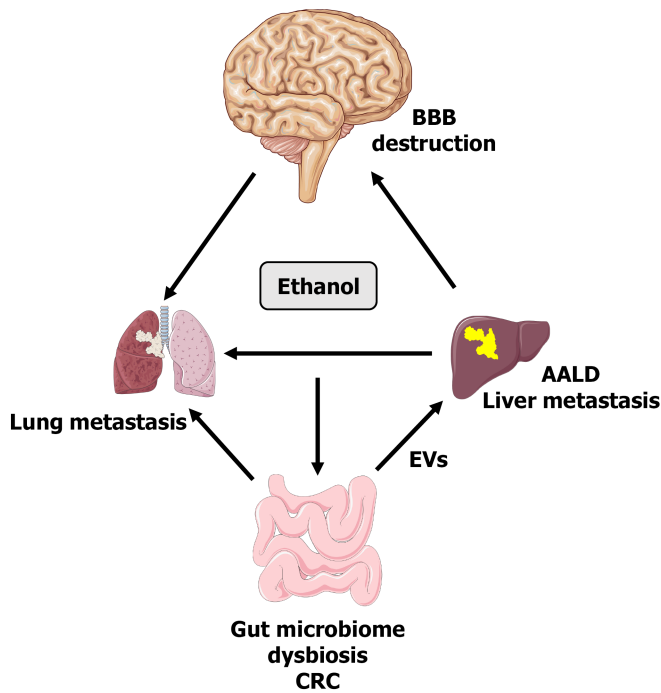


Figure 4 Model of extracellular vesicle interactions along the gut/liver/lung/brain axis during alcohol disorders and cancer progression. Alcohol exposure leads to enhanced gut microbiome dysbiosis, the development of alcohol-associated liver disease, lung inflammation, and neurological manifestations. The potential role of tumor- and alcohol-derived extracellular vesicles (EVs) in advanced malignancies is a potential consequence of EV organ-organ communication during alcohol disorders. BBB: Blood brain barrier; CRC: Colorectal cancer; AALD: Alcohol-associated liver disease.

carcinoembryonic antigen-related cell adhesion molecules is unknown. Further, the effectiveness of blocking EV-mediated communication in the alcohol-injured liver during CRLM also remains to be defined. Overall, the characterization of exosome cargo and communication networks in the transformation of CRC cells and reprogramming of the tumor microenvironment is an important area of translational research, especially in the context of complex comorbidities associated with aberrant alcohol intake.

CONCLUSION

In recent years, investigations into the role of EVs in cancer progression and AALD have increased in a remarkable manner. The elucidation of EV communication networks to date have indicated the powerful role of EVs as metastatic cancer markers and inducers of varied biological effects. Extensive work is ongoing to characterize the biogenesis and effects of distinct EV populations generated from different cell types and diseases. The unique features of EV size and cargo contents can produce hallmark effects on recipient cells. Therefore, the heterogeneity of exosome populations will dictate studies on the role and outcomes of exosome networks during disease states. For example, understanding the diversity of EVs released during gut microbiome dysbiosis, migration, and organ-organ communication aims to reveal the association of AALD and hepatic CRC metastasis. The complexity of interorgan communication and the involvement of mediators such as EVs, cytokines, and chemokines is the ongoing focus of translational research. Related to alcohol-associated diseases, it is proposed that EV-mediated communication affects multi-organ damage as well as cancer metastasis along the liver/gut/lung/brain axis (Figure 4). Future studies will likely focus on the characterization of exosomal components involved in alcohol's effects and cancer cell metastasis to secondary organs. Moreover, further investigation is needed to explore the role of exosome-mediated cell-free networks in the detection of alcohol-related tumors and microenvironment interactions for the development of targeted therapeutics.

REFERENCES

- 1 **Peacock A**, Leung J, Larney S, Colledge S, Hickman M, Rehm J, Giovino GA, West R, Hall W, Griffiths P, Ali R, Gowing L, Marsden J, Ferrari AJ, Grebely J, Farrell M, Degenhardt L. Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. *Addiction* 2018; **113**: 1905-1926 [PMID: 29749059 DOI: 10.1111/add.14234]
- 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. [cited 15 May 2021]. Available from: <https://apps.who.int/iris/handle/10665/274603>
- 4 **Adachi J**, Asano M, Ueno Y, Niemelä O, Ohlendieck K, Peters TJ, Preedy VR. Alcoholic muscle disease and biomembrane perturbations (review). *J Nutr Biochem* 2003; **14**: 616-625 [PMID: 14629892 DOI: 10.1016/s0955-2863(03)00114-1]
- 5 **Barritt AS 4th**, Jiang Y, Schmidt M, Hayashi PH, Bataller R. Charges for Alcoholic Cirrhosis Exceed All Other Etiologies of Cirrhosis Combined: A National and State Inpatient Survey Analysis. *Dig Dis Sci* 2019; **64**: 1460-1469 [PMID: 30673984 DOI: 10.1007/s10620-019-5471-7]
- 6 **Crews FT**, Nixon K. Mechanisms of neurodegeneration and regeneration in alcoholism. *Alcohol Alcohol* 2009; **44**: 115-127 [PMID: 18940959 DOI: 10.1093/alcalc/agn079]
- 7 **Guidot DM**, Roman J. Chronic ethanol ingestion increases susceptibility to acute lung injury: role of oxidative stress and tissue remodeling. *Chest* 2002; **122**: 309S-314S [PMID: 12475807 DOI: 10.1378/chest.122.6_suppl.309s]
- 8 **Seitz HK**, Bataller R, Cortez-Pinto H, Gao B, Gual A, Lackner C, Mathurin P, Mueller S, Szabo G, Tsukamoto H. Alcoholic liver disease. *Nat Rev Dis Primers* 2018; **4**: 16 [PMID: 30115921 DOI: 10.1038/s41572-018-0014-7]
- 9 **Sarin SK**, Pande A, Schnabl B. Microbiome as a therapeutic target in alcohol-related liver disease. *J Hepatol* 2019; **70**: 260-272 [PMID: 30658727 DOI: 10.1016/j.jhep.2018.10.019]
- 10 **Szabo G**, Petrasek J. Inflammasome activation and function in liver disease. *Nat Rev Gastroenterol Hepatol* 2015; **12**: 387-400 [PMID: 26055245 DOI: 10.1038/nrgastro.2015.94]
- 11 **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]
- 12 **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]
- 13 **Rossi M**, Jahanzaib Anwar M, Usman A, Keshavarzian A, Bishehsari F. Colorectal Cancer and Alcohol Consumption-Populations to Molecules. *Cancers (Basel)* 2018; **10** [PMID: 29385712 DOI: 10.3390/cancers10020038]
- 14 **Seitz HK**, Stickel F, Homann N. Pathogenetic mechanisms of upper aerodigestive tract cancer in alcoholics. *Int J Cancer* 2004; **108**: 483-487 [PMID: 14696110 DOI: 10.1002/ijc.11600]
- 15 **Urabe F**, Kosaka N, Ito K, Kimura T, Egawa S, Ochiya T. Extracellular vesicles as biomarkers and therapeutic targets for cancer. *Am J Physiol Cell Physiol* 2020; **318**: C29-C39 [PMID: 31693397 DOI: 10.1152/ajpcell.00280.2019]
- 16 **Kowal J**, Tkach M, Théry C. Biogenesis and secretion of exosomes. *Curr Opin Cell Biol* 2014; **29**: 116-125 [PMID: 24959705 DOI: 10.1016/j.ceb.2014.05.004]
- 17 **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]
- 18 **Raposo G**, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. *J Cell Biol* 2013; **200**: 373-383 [PMID: 23420871 DOI: 10.1083/jcb.201211138]
- 19 **Trams EG**, Lauter CJ, Salem N Jr, Heine U. Exfoliation of membrane ecto-enzymes in the form of micro-vesicles. *Biochim Biophys Acta* 1981; **645**: 63-70 [PMID: 6266476 DOI: 10.1016/0005-2736(81)90512-5]
- 20 **Huotari J**, Helenius A. Endosome maturation. *EMBO J* 2011; **30**: 3481-3500 [PMID: 21878991 DOI: 10.1038/emboj.2011.286]
- 21 **Johnstone RM**, Adam M, Hammond JR, Orr L, Turbide C. Vesicle formation during reticulocyte maturation. Association of plasma membrane activities with released vesicles (exosomes). *J Biol Chem* 1987; **262**: 9412-9420 [PMID: 3597417]
- 22 **Möbius W**, Ohno-Iwashita Y, van Donselaar EG, Oorschot VM, Shimada Y, Fujimoto T, Heijnen HF, Geuze HJ, Slot JW. Immunoelectron microscopic localization of cholesterol using biotinylated and non-cytolytic perfringolysin O. *J Histochem Cytochem* 2002; **50**: 43-55 [PMID: 11748293 DOI: 10.1177/002215540205000105]
- 23 **Chen Q**, Takada R, Noda C, Kobayashi S, Takada S. Different populations of Wnt-containing vesicles are individually released from polarized epithelial cells. *Sci Rep* 2016; **6**: 35562 [PMID: 27765945 DOI: 10.1038/srep35562]
- 24 **van Niel G**, Raposo G, Candalh C, Boussac M, Hershberg R, Cerf-Bensussan N, Heyman M. Intestinal epithelial cells secrete exosome-like vesicles. *Gastroenterology* 2001; **121**: 337-349 [PMID: 11487543 DOI: 10.1053/gast.2001.26263]
- 25 **Tauro BJ**, Greening DW, Mathias RA, Mathivanan S, Ji H, Simpson RJ. Two distinct populations

- of exosomes are released from LIM1863 colon carcinoma cell-derived organoids. *Mol Cell Proteomics* 2013; **12**: 587-598 [PMID: [23230278](#) DOI: [10.1074/mcp.M112.021303](#)]
- 26 **Théry C**, Regnault A, Garin J, Wolfers J, Zitvogel L, Ricciardi-Castagnoli P, Raposo G, Amigorena S. Molecular characterization of dendritic cell-derived exosomes. Selective accumulation of the heat shock protein hsc73. *J Cell Biol* 1999; **147**: 599-610 [PMID: [10545503](#) DOI: [10.1083/jcb.147.3.599](#)]
 - 27 **Baixauli F**, López-Otín C, Mittelbrunn M. Exosomes and autophagy: coordinated mechanisms for the maintenance of cellular fitness. *Front Immunol* 2014; **5**: 403 [PMID: [25191326](#) DOI: [10.3389/fimmu.2014.00403](#)]
 - 28 **Hessvik NP**, Øverbye A, Brech A, Torgersen ML, Jakobsen IS, Sandvig K, Llorente A. PIKfyve inhibition increases exosome release and induces secretory autophagy. *Cell Mol Life Sci* 2016; **73**: 4717-4737 [PMID: [27438886](#) DOI: [10.1007/s00018-016-2309-8](#)]
 - 29 **Henne WM**, Stenmark H, Emr SD. Molecular mechanisms of the membrane sculpting ESCRT pathway. *Cold Spring Harb Perspect Biol* 2013; **5** [PMID: [24003212](#) DOI: [10.1101/cshperspect.a016766](#)]
 - 30 **Trajkovic K**, Hsu C, Chiantia S, Rajendran L, Wenzel D, Wieland F, Schwille P, Brügger B, Simons M. Ceramide triggers budding of exosome vesicles into multivesicular endosomes. *Science* 2008; **319**: 1244-1247 [PMID: [18309083](#) DOI: [10.1126/science.1153124](#)]
 - 31 **Kajimoto T**, Okada T, Miya S, Zhang L, Nakamura S. Ongoing activation of sphingosine 1-phosphate receptors mediates maturation of exosomal multivesicular endosomes. *Nat Commun* 2013; **4**: 2712 [PMID: [24231649](#) DOI: [10.1038/ncomms3712](#)]
 - 32 **Christ L**, Raiborg C, Wenzel EM, Campsteijn C, Stenmark H. Cellular Functions and Molecular Mechanisms of the ESCRT Membrane-Scission Machinery. *Trends Biochem Sci* 2017; **42**: 42-56 [PMID: [27669649](#) DOI: [10.1016/j.tibs.2016.08.016](#)]
 - 33 **Skotland T**, Sandvig K, Llorente A. Lipids in exosomes: Current knowledge and the way forward. *Prog Lipid Res* 2017; **66**: 30-41 [PMID: [28342835](#) DOI: [10.1016/j.plipres.2017.03.001](#)]
 - 34 **Willms E**, Johansson HJ, Mäger I, Lee Y, Blomberg KE, Sadik M, Alaarg A, Smith CI, Lehtio J, El Andaloussi S, Wood MJ, Vader P. Cells release subpopulations of exosomes with distinct molecular and biological properties. *Sci Rep* 2016; **6**: 22519 [PMID: [26931825](#) DOI: [10.1038/srep22519](#)]
 - 35 **Tai YL**, Chen KC, Hsieh JT, Shen TL. Exosomes in cancer development and clinical applications. *Cancer Sci* 2018; **109**: 2364-2374 [PMID: [29908100](#) DOI: [10.1111/cas.13697](#)]
 - 36 **Pefanis E**, Wang J, Rothschild G, Lim J, Kazadi D, Sun J, Federation A, Chao J, Elliott O, Liu ZP, Economides AN, Bradner JE, Rabadan R, Basu U. RNA exosome-regulated long non-coding RNA transcription controls super-enhancer activity. *Cell* 2015; **161**: 774-789 [PMID: [25957685](#) DOI: [10.1016/j.cell.2015.04.034](#)]
 - 37 **Hessvik NP**, Phuyal S, Brech A, Sandvig K, Llorente A. Profiling of microRNAs in exosomes released from PC-3 prostate cancer cells. *Biochim Biophys Acta* 2012; **1819**: 1154-1163 [PMID: [22982408](#) DOI: [10.1016/j.bbagr.2012.08.016](#)]
 - 38 **Mittelbrunn M**, Gutiérrez-Vázquez C, Villarroya-Beltri C, González S, Sánchez-Cabo F, González MÁ, Bernad A, Sánchez-Madrid F. Unidirectional transfer of microRNA-loaded exosomes from T cells to antigen-presenting cells. *Nat Commun* 2011; **2**: 282 [PMID: [21505438](#) DOI: [10.1038/ncomms1285](#)]
 - 39 **Nolte-t Hoen EN**, Buermans HP, Waasdorp M, Stoorvogel W, Wauben MH, 't Hoen PA. Deep sequencing of RNA from immune cell-derived vesicles uncovers the selective incorporation of small non-coding RNA biotypes with potential regulatory functions. *Nucleic Acids Res* 2012; **40**: 9272-9285 [PMID: [22821563](#) DOI: [10.1093/nar/gks658](#)]
 - 40 **Sun Y**, Yang B, Lin M, Yu H, Chen H, Zhang Z. Identification of serum miR-30a-5p as a diagnostic and prognostic biomarker in colorectal cancer. *Cancer Biomark* 2019; **24**: 299-305 [PMID: [30829615](#) DOI: [10.3233/CBM-182129](#)]
 - 41 **Tang Y**, Zhao Y, Song X, Niu L, Xie L. Tumor-derived exosomal miRNA-320d as a biomarker for metastatic colorectal cancer. *J Clin Lab Anal* 2019; **33**: e23004 [PMID: [31420913](#) DOI: [10.1002/jcla.23004](#)]
 - 42 **Yan S**, Jiang Y, Liang C, Cheng M, Jin C, Duan Q, Xu D, Yang L, Zhang X, Ren B, Jin P. Exosomal miR-6803-5p as potential diagnostic and prognostic marker in colorectal cancer. *J Cell Biochem* 2018; **119**: 4113-4119 [PMID: [29240249](#) DOI: [10.1002/jcb.26609](#)]
 - 43 **Chen HL**, Li JJ, Jiang F, Shi WJ, Chang GY. MicroRNA-4461 derived from bone marrow mesenchymal stem cell exosomes inhibits tumorigenesis by downregulating COPB2 expression in colorectal cancer. *Biosci Biotechnol Biochem* 2020; **84**: 338-346 [PMID: [31631786](#) DOI: [10.1080/09168451.2019.1677452](#)]
 - 44 **Tian XP**, Wang CY, Jin XH, Li M, Wang FW, Huang WJ, Yun JP, Xu RH, Cai QQ, Xie D. Acidic Microenvironment Up-Regulates Exosomal miR-21 and miR-10b in Early-Stage Hepatocellular Carcinoma to Promote Cancer Cell Proliferation and Metastasis. *Theranostics* 2019; **9**: 1965-1979 [PMID: [31037150](#) DOI: [10.7150/thno.30958](#)]
 - 45 **Yang SS**, Ma S, Dou H, Liu F, Zhang SY, Jiang C, Xiao M, Huang YX. Breast cancer-derived exosomes regulate cell invasion and metastasis in breast cancer via miR-146a to activate cancer associated fibroblasts in tumor microenvironment. *Exp Cell Res* 2020; **391**: 111983 [PMID: [32268136](#) DOI: [10.1016/j.yexcr.2020.111983](#)]
 - 46 **Villarroya-Beltri C**, Gutiérrez-Vázquez C, Sánchez-Cabo F, Pérez-Hernández D, Vázquez J, Martín-Cofreces N, Martínez-Herrera DJ, Pascual-Montano A, Mittelbrunn M, Sánchez-Madrid F. Sumoylated hnRNP A2B1 controls the sorting of miRNAs into exosomes through binding to specific

- motifs. *Nat Commun* 2013; **4**: 2980 [PMID: [24356509](#) DOI: [10.1038/ncomms3980](#)]
- 47 **Cha DJ**, Franklin JL, Dou Y, Liu Q, Higginbotham JN, Demory Beckler M, Weaver AM, Vickers K, Prasad N, Levy S, Zhang B, Coffey RJ, Patton JG. KRAS-dependent sorting of miRNA to exosomes. *Elife* 2015; **4**: e07197 [PMID: [26132860](#) DOI: [10.7554/eLife.07197](#)]
 - 48 **McKenzie AJ**, Hoshino D, Hong NH, Cha DJ, Franklin JL, Coffey RJ, Patton JG, Weaver AM. KRAS-MEK Signaling Controls Ago2 Sorting into Exosomes. *Cell Rep* 2016; **15**: 978-987 [PMID: [27117408](#) DOI: [10.1016/j.celrep.2016.03.085](#)]
 - 49 **Batagov AO**, Kurochkin IV. Exosomes secreted by human cells transport largely mRNA fragments that are enriched in the 3'-untranslated regions. *Biol Direct* 2013; **8**: 12 [PMID: [23758897](#) DOI: [10.1186/1745-6150-8-12](#)]
 - 50 **Bolukbasi MF**, Mizrak A, Ozdener GB, Madlener S, Ströbel T, Erkan EP, Fan JB, Breakefield XO, Saydam O. miR-1289 and "Zipcode"-like Sequence Enrich mRNAs in Microvesicles. *Mol Ther Nucleic Acids* 2012; **1**: e10 [PMID: [23344721](#) DOI: [10.1038/mtna.2011.2](#)]
 - 51 **Kahlert C**, Melo SA, Protopopov A, Tang J, Seth S, Koch M, Zhang J, Weitz J, Chin L, Futreal A, Kalluri R. Identification of double-stranded genomic DNA spanning all chromosomes with mutated KRAS and p53 DNA in the serum exosomes of patients with pancreatic cancer. *J Biol Chem* 2014; **289**: 3869-3875 [PMID: [24398677](#) DOI: [10.1074/jbc.C113.532267](#)]
 - 52 **Thakur BK**, Zhang H, Becker A, Matei I, Huang Y, Costa-Silva B, Zheng Y, Hoshino A, Brazier H, Xiang J, Williams C, Rodriguez-Barrueco R, Silva JM, Zhang W, Hearn S, Elemento O, Paknejad N, Manova-Todorova K, Welte K, Bromberg J, Peinado H, Lyden D. Double-stranded DNA in exosomes: a novel biomarker in cancer detection. *Cell Res* 2014; **24**: 766-769 [PMID: [24710597](#) DOI: [10.1038/cr.2014.44](#)]
 - 53 **Buschow SI**, Liefhebber JM, Wubbolts R, Stoorvogel W. Exosomes contain ubiquitinated proteins. *Blood Cells Mol Dis* 2005; **35**: 398-403 [PMID: [16203162](#) DOI: [10.1016/j.bcmd.2005.08.005](#)]
 - 54 **Smith VL**, Jackson L, Schorey JS. Ubiquitination as a Mechanism To Transport Soluble Mycobacterial and Eukaryotic Proteins to Exosomes. *J Immunol* 2015; **195**: 2722-2730 [PMID: [26246139](#) DOI: [10.4049/jimmunol.1403186](#)]
 - 55 **Cheng Y**, Schorey JS. Targeting soluble proteins to exosomes using a ubiquitin tag. *Biotechnol Bioeng* 2016; **113**: 1315-1324 [PMID: [26574179](#) DOI: [10.1002/bit.25884](#)]
 - 56 **Record M**, Poirot M, Silvente-Poirot S. Emerging concepts on the role of exosomes in lipid metabolic diseases. *Biochimie* 2014; **96**: 67-74 [PMID: [23827857](#) DOI: [10.1016/j.biochi.2013.06.016](#)]
 - 57 **Pike LJ**. Lipid rafts: bringing order to chaos. *J Lipid Res* 2003; **44**: 655-667 [PMID: [12562849](#) DOI: [10.1194/jlr.R200021-JLR200](#)]
 - 58 **Lingwood D**, Simons K. Lipid rafts as a membrane-organizing principle. *Science* 2010; **327**: 46-50 [PMID: [20044567](#) DOI: [10.1126/science.1174621](#)]
 - 59 **de Gassart A**, Geminard C, Fevrier B, Raposo G, Vidal M. Lipid raft-associated protein sorting in exosomes. *Blood* 2003; **102**: 4336-4344 [PMID: [12881314](#) DOI: [10.1182/blood-2003-03-0871](#)]
 - 60 **Gao B**, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. *Gastroenterology* 2011; **141**: 1572-1585 [PMID: [21920463](#) DOI: [10.1053/j.gastro.2011.09.002](#)]
 - 61 **Eguchi A**, Feldstein AE. Extracellular vesicles in non-alcoholic and alcoholic fatty liver diseases. *Liver Res* 2018; **2**: 30-34 [PMID: [30345152](#) DOI: [10.1016/j.livres.2018.01.001](#)]
 - 62 **Rahman MA**, Patters BJ, Kodidela S, Kumar S. Extracellular Vesicles: Intercellular Mediators in Alcohol-Induced Pathologies. *J Neuroimmune Pharmacol* 2020; **15**: 409-421 [PMID: [30955131](#) DOI: [10.1007/s11481-019-09848-z](#)]
 - 63 **Szabo G**, Momen-Heravi F. Extracellular vesicles in liver disease and potential as biomarkers and therapeutic targets. *Nat Rev Gastroenterol Hepatol* 2017; **14**: 455-466 [PMID: [28634412](#) DOI: [10.1038/nrgastro.2017.71](#)]
 - 64 **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](#)]
 - 65 **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](#)]
 - 66 **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](#)]
 - 67 **Bull-Otterson L**, Feng W, Kirpich I, Wang Y, Qin X, Liu Y, Gobejishvili L, Joshi-Barve S, Ayvaz T, Petrosino J, Kong M, Barker D, McClain C, Barve S. Metagenomic analyses of alcohol induced pathogenic alterations in the intestinal microbiome and the effect of Lactobacillus rhamnosus GG treatment. *PLoS One* 2013; **8**: e53028 [PMID: [23326376](#) DOI: [10.1371/journal.pone.0053028](#)]
 - 68 **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](#)]
 - 69 **Gao B**, Lang S, Duan Y, Wang Y, Shawcross DL, Louvet A, Mathurin P, Ho SB, Stärkel P, Schnabl B. Serum and Fecal Oxylipins in Patients with Alcohol-Related Liver Disease. *Dig Dis Sci* 2019; **64**: 1878-1892 [PMID: [31076986](#) DOI: [10.1007/s10620-019-05638-y](#)]
 - 70 **Zhou R**, Fan X, Schnabl B. Role of the intestinal microbiome in liver fibrosis development and new treatment strategies. *Transl Res* 2019; **209**: 22-38 [PMID: [30853445](#) DOI: [10.1016/j.trsl.2019.02.005](#)]

- 71 **Zhao H**, Zhao C, Dong Y, Zhang M, Wang Y, Li F, Li X, McClain C, Yang S, Feng W. Inhibition of miR122a by *Lactobacillus rhamnosus* GG culture supernatant increases intestinal occludin expression and protects mice from alcoholic liver disease. *Toxicol Lett* 2015; **234**: 194-200 [PMID: 25746479 DOI: 10.1016/j.toxlet.2015.03.002]
- 72 **Tang Y**, Zhang L, Forsyth CB, Shaikh M, Song S, Keshavarzian A. The Role of miR-212 and iNOS in Alcohol-Induced Intestinal Barrier Dysfunction and Steatohepatitis. *Alcohol Clin Exp Res* 2015; **39**: 1632-1641 [PMID: 26207424 DOI: 10.1111/acer.12813]
- 73 **Pettinelli P**, Videla LA. Up-regulation of PPAR- γ mRNA expression in the liver of obese patients: an additional reinforcing lipogenic mechanism to SREBP-1c induction. *J Clin Endocrinol Metab* 2011; **96**: 1424-1430 [PMID: 21325464 DOI: 10.1210/jc.2010-2129]
- 74 **Ye D**, Guo S, Al-Sadi R, Ma TY. MicroRNA regulation of intestinal epithelial tight junction permeability. *Gastroenterology* 2011; **141**: 1323-1333 [PMID: 21763238 DOI: 10.1053/j.gastro.2011.07.005]
- 75 **Lamas-Paz A**, Morán L, Peng J, Salinas B, López-Alcántara N, Sydor S, Vilchez-Vargas R, Asensio I, Hao F, Zheng K, Martín-Adrados B, Moreno L, Cogolludo A, Gómez Del Moral M, Bechmann L, Martínez-Naves E, Vaquero J, Bañares R, Nevzorova YA, Cubero FJ. Intestinal Epithelial Cell-Derived Extracellular Vesicles Modulate Hepatic Injury via the Gut-Liver Axis During Acute Alcohol Injury. *Front Pharmacol* 2020; **11**: 603771 [PMID: 33408632 DOI: 10.3389/fphar.2020.603771]
- 76 **Tulkens J**, Vergauwen G, Van Deun J, Geerickx E, Dhondt B, Lippens L, De Scheerder MA, Miinalainen I, Rappu P, De Geest BG, Vandecasteele K, Laukens D, Vandekerckhove L, Denys H, Vandesompele J, De Wever O, Hendrix A. Increased levels of systemic LPS-positive bacterial extracellular vesicles in patients with intestinal barrier dysfunction. *Gut* 2020; **69**: 191-193 [PMID: 30518529 DOI: 10.1136/gutjnl-2018-317726]
- 77 **Temko JE**, Bouhlal S, Farokhnia M, Lee MR, Cryan JF, Leggio L. The Microbiota, the Gut and the Brain in Eating and Alcohol Use Disorders: A 'Ménage à Trois'? *Alcohol Alcohol* 2017; **52**: 403-413 [PMID: 28482009 DOI: 10.1093/alcalc/agx024]
- 78 **Sung H**, Kim SW, Hong M, Suk KT. Microbiota-based treatments in alcoholic liver disease. *World J Gastroenterol* 2016; **22**: 6673-6682 [PMID: 27547010 DOI: 10.3748/wjg.v22.i29.6673]
- 79 **Tian F**, Chi F, Wang G, Liu X, Zhang Q, Chen Y, Zhang H, Chen W. *Lactobacillus rhamnosus* CCFM1107 treatment ameliorates alcohol-induced liver injury in a mouse model of chronic alcohol feeding. *J Microbiol* 2015; **53**: 856-863 [PMID: 26626356 DOI: 10.1007/s12275-015-5239-5]
- 80 **Kirpich IA**, Solovieva NV, Leikhter SN, Shidakova NA, Lebedeva OV, Sidorov PI, Bazhukova TA, Soloviev AG, Barve SS, McClain CJ, Cave M. Probiotics restore bowel flora and improve liver enzymes in human alcohol-induced liver injury: a pilot study. *Alcohol* 2008; **42**: 675-682 [PMID: 19038698 DOI: 10.1016/j.alcohol.2008.08.006]
- 81 **Tang Y**, Forsyth CB, Banan A, Fields JZ, Keshavarzian A. Oats supplementation prevents alcohol-induced gut leakiness in rats by preventing alcohol-induced oxidative tissue damage. *J Pharmacol Exp Ther* 2009; **329**: 952-958 [PMID: 19276402 DOI: 10.1124/jpet.108.148643]
- 82 **Zhang X**, Wang H, Yin P, Fan H, Sun L, Liu Y. Flaxseed oil ameliorates alcoholic liver disease via anti-inflammation and modulating gut microbiota in mice. *Lipids Health Dis* 2017; **16**: 44 [PMID: 28228158 DOI: 10.1186/s12944-017-0431-8]
- 83 **Kalambokis GN**, Mouzaki A, Rodi M, Tsianos EV. Rifaximin improves thrombocytopenia in patients with alcoholic cirrhosis in association with reduction of endotoxaemia. *Liver Int* 2012; **32**: 467-475 [PMID: 22098272 DOI: 10.1111/j.1478-3231.2011.02650.x]
- 84 **Qin L**, He J, Hanes RN, Pluzarev O, Hong JS, Crews FT. Increased systemic and brain cytokine production and neuroinflammation by endotoxin following ethanol treatment. *J Neuroinflammation* 2008; **5**: 10 [PMID: 18348728 DOI: 10.1186/1742-2094-5-10]
- 85 **Mayfield J**, Ferguson L, Harris RA. Neuroimmune signaling: a key component of alcohol abuse. *Curr Opin Neurobiol* 2013; **23**: 513-520 [PMID: 23434064 DOI: 10.1016/j.conb.2013.01.024]
- 86 **Wang HJ**, Zakhari S, Jung MK. Alcohol, inflammation, and gut-liver-brain interactions in tissue damage and disease development. *World J Gastroenterol* 2010; **16**: 1304-1313 [PMID: 20238396 DOI: 10.3748/wjg.v16.i11.1304]
- 87 **Richardson HN**, Lee SY, O'Dell LE, Koob GF, Rivier CL. Alcohol self-administration acutely stimulates the hypothalamic-pituitary-adrenal axis, but alcohol dependence leads to a dampened neuroendocrine state. *Eur J Neurosci* 2008; **28**: 1641-1653 [PMID: 18979677 DOI: 10.1111/j.1460-9568.2008.06455.x]
- 88 **Lee TH**, Avraham HK, Jiang S, Avraham S. Vascular endothelial growth factor modulates the transendothelial migration of MDA-MB-231 breast cancer cells through regulation of brain microvascular endothelial cell permeability. *J Biol Chem* 2003; **278**: 5277-5284 [PMID: 12446667 DOI: 10.1074/jbc.M210063200]
- 89 **Valadi H**, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat Cell Biol* 2007; **9**: 654-659 [PMID: 17486113 DOI: 10.1038/ncb1596]
- 90 **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]
- 91 **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](#)]
- 92 **Siore AM**, Parker RE, Stecenko AA, Cuppels C, McKean M, Christman BW, Cruz-Gervis R, Brigham KL. Endotoxin-induced acute lung injury requires interaction with the liver. *Am J Physiol Lung Cell Mol Physiol* 2005; **289**: L769-L776 [PMID: [16006484](#) DOI: [10.1152/ajplung.00137.2005](#)]
 - 93 **Patterson EK**, Yao LJ, Ramic N, Lewis JF, Cepinskas G, McCaig L, Veldhuizen RA, Yamashita CM. Lung-derived mediators induce cytokine production in downstream organs via an NF- κ B-dependent mechanism. *Mediators Inflamm* 2013; **2013**: 586895 [PMID: [23606793](#) DOI: [10.1155/2013/586895](#)]
 - 94 **Minn AJ**, Gupta GP, Siegel PM, Bos PD, Shu W, Giri DD, Viale A, Olshen AB, Gerald WL, Massagué J. Genes that mediate breast cancer metastasis to lung. *Nature* 2005; **436**: 518-524 [PMID: [16049480](#) DOI: [10.1038/nature03799](#)]
 - 95 **Minn AJ**, Kang Y, Serganova I, Gupta GP, Giri DD, Doubrovin M, Ponomarev V, Gerald WL, Blasberg R, Massagué J. Distinct organ-specific metastatic potential of individual breast cancer cells and primary tumors. *J Clin Invest* 2005; **115**: 44-55 [PMID: [15630443](#) DOI: [10.1172/jci22320](#)]
 - 96 **Hoshino A**, Costa-Silva B, Shen TL, Rodrigues G, Hashimoto A, Tesic Mark M, Molina H, Kohsaka S, Di Giannatale A, Ceder S, Singh S, Williams C, Soplop N, Uryu K, Pharmed L, King T, Bojmar L, Davies AE, Ararso Y, Zhang T, Zhang H, Hernandez J, Weiss JM, Dumont-Cole VD, Kramer K, Wexler LH, Narendran A, Schwartz GK, Healey JH, Sandstrom P, Labori KJ, Kure EH, Grandgenett PM, Hollingsworth MA, de Sousa M, Kaur S, Jain M, Mallya K, Batra SK, Jarnagin WR, Brady MS, Fodstad O, Muller V, Pantel K, Minn AJ, Bissell MJ, Garcia BA, Kang Y, Rajasekhara VK, Ghajar CM, Matei I, Peinado H, Bromberg J, Lyden D. Tumour exosome integrins determine organotropic metastasis. *Nature* 2015; **527**: 329-335 [PMID: [26524530](#) DOI: [10.1038/nature15756](#)]
 - 97 **Oskarsson T**, Acharyya S, Zhang XH, Vanharanta S, Tavazoie SF, Morris PG, Downey RJ, Manova-Todorova K, Brogi E, Massagué J. Breast cancer cells produce tenascin C as a metastatic niche component to colonize the lungs. *Nat Med* 2011; **17**: 867-874 [PMID: [21706029](#) DOI: [10.1038/nm.2379](#)]
 - 98 **Sousa B**, Pereira J, Paredes J. The Crosstalk Between Cell Adhesion and Cancer Metabolism. *Int J Mol Sci* 2019; **20** [PMID: [31010154](#) DOI: [10.3390/ijms20081933](#)]
 - 99 **Hessvik NP**, Llorente A. Current knowledge on exosome biogenesis and release. *Cell Mol Life Sci* 2018; **75**: 193-208 [PMID: [28733901](#) DOI: [10.1007/s00018-017-2595-9](#)]
 - 100 **Peinado H**, Alečković M, Lavotshkin S, Matei I, Costa-Silva B, Moreno-Bueno G, Hergueta-Redondo M, Williams C, Garcia-Santos G, Ghajar C, Nitoro-Hoshino A, Hoffman C, Badal K, Garcia BA, Callahan MK, Yuan J, Martins VR, Skog J, Kaplan RN, Brady MS, Wolchok JD, Chapman PB, Kang Y, Bromberg J, Lyden D. Melanoma exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype through MET. *Nat Med* 2012; **18**: 883-891 [PMID: [22635005](#) DOI: [10.1038/nm.2753](#)]
 - 101 **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](#)]
 - 102 **Record M**, Carayon K, Poirot M, Silvente-Poirot S. Exosomes as new vesicular lipid transporters involved in cell-cell communication and various pathophysiologicals. *Biochim Biophys Acta* 2014; **1841**: 108-120 [PMID: [24140720](#) DOI: [10.1016/j.bbalip.2013.10.004](#)]
 - 103 **Keerthikumar S**, Gangoda L, Gho YS, Mathivanan S. Bioinformatics Tools for Extracellular Vesicles Research. *Methods Mol Biol* 2017; **1545**: 189-196 [PMID: [27943215](#) DOI: [10.1007/978-1-4939-6728-5_13](#)]
 - 104 **Krämer A**, Green J, Pollard J Jr, Tugendreich S. Causal analysis approaches in Ingenuity Pathway Analysis. *Bioinformatics* 2014; **30**: 523-530 [PMID: [24336805](#) DOI: [10.1093/bioinformatics/btt703](#)]
 - 105 **Kalra H**, Adda CG, Liem M, Ang CS, Mechler A, Simpson RJ, Hulett MD, Mathivanan S. Comparative proteomics evaluation of plasma exosome isolation techniques and assessment of the stability of exosomes in normal human blood plasma. *Proteomics* 2013; **13**: 3354-3364 [PMID: [24115447](#) DOI: [10.1002/pmic.201300282](#)]
 - 106 **Qin Z**, Ljubimov VA, Zhou C, Tong Y, Liang J. Cell-free circulating tumor DNA in cancer. *Chin J Cancer* 2016; **35**: 36 [PMID: [27056366](#) DOI: [10.1186/s40880-016-0092-4](#)]
 - 107 **McKiernan J**, Donovan MJ, O'Neill V, Bentink S, Noerholm M, Belzer S, Skog J, Kattan MW, Partin A, Andriole G, Brown G, Wei JT, Thompson IM Jr, Carroll P. A Novel Urine Exosome Gene Expression Assay to Predict High-grade Prostate Cancer at Initial Biopsy. *JAMA Oncol* 2016; **2**: 882-889 [PMID: [27032035](#) DOI: [10.1001/jamaoncol.2016.0097](#)]
 - 108 **Del Re M**, Biasco E, Crucitta S, Derosa L, Rofi E, Orlandini C, Miccoli M, Galli L, Falcone A, Jenster GW, van Schaik RH, Danesi R. The Detection of Androgen Receptor Splice Variant 7 in Plasma-derived Exosomal RNA Strongly Predicts Resistance to Hormonal Therapy in Metastatic Prostate Cancer Patients. *Eur Urol* 2017; **71**: 680-687 [PMID: [27733296](#) DOI: [10.1016/j.eururo.2016.08.012](#)]
 - 109 **Eguchi A**, Lazaro RG, Wang J, Kim J, Povero D, Williams B, Ho SB, Stärkel P, Schnabl B, Ohno-Machado L, Tsukamoto H, Feldstein AE. Extracellular vesicles released by hepatocytes from gastric infusion model of alcoholic liver disease contain a MicroRNA barcode that can be detected in blood. *Hepatology* 2017; **65**: 475-490 [PMID: [27639178](#) DOI: [10.1002/hep.28838](#)]
 - 110 **Lin J**, Wang Y, Zou YQ, Chen X, Huang B, Liu J, Xu YM, Li J, Zhang J, Yang WM, Min QH, Sun

- F, Li SQ, Gao QF, Wang XZ. Differential miRNA expression in pleural effusions derived from extracellular vesicles of patients with lung cancer, pulmonary tuberculosis, or pneumonia. *Tumour Biol* 2016 [PMID: 27743380 DOI: 10.1007/s13277-016-5410-6]
- 111 **Bastaminejad S**, Taherikalani M, Ghanbari R, Akbari A, Shabab N, Saidijam M. Investigation of MicroRNA-21 Expression Levels in Serum and Stool as a Potential Non-Invasive Biomarker for Diagnosis of Colorectal Cancer. *Iran Biomed J* 2017; **21**: 106-113 [PMID: 27432735 DOI: 10.18869/acadpub.ibj.21.2.106]
 - 112 **Hannafon BN**, Trigos YD, Calloway CL, Zhao YD, Lum DH, Welm AL, Zhao ZJ, Blick KE, Dooley WC, Ding WQ. Plasma exosome microRNAs are indicative of breast cancer. *Breast Cancer Res* 2016; **18**: 90 [PMID: 27608715 DOI: 10.1186/s13058-016-0753-x]
 - 113 **Santangelo A**, Imbrucè P, Gardenghi B, Belli L, Agushi R, Tamanini A, Munari S, Bossi AM, Scambi I, Benati D, Mariotti R, Di Gennaro G, Sbarbati A, Eccher A, Ricciardi GK, Ciceri EM, Sala F, Pinna G, Lippi G, Cabrini G, Dececchi MC. A microRNA signature from serum exosomes of patients with glioma as complementary diagnostic biomarker. *J Neurooncol* 2018; **136**: 51-62 [PMID: 29076001 DOI: 10.1007/s11060-017-2639-x]
 - 114 **Wang H**, Hou L, Li A, Duan Y, Gao H, Song X. Expression of serum exosomal microRNA-21 in human hepatocellular carcinoma. *Biomed Res Int* 2014; **2014**: 864894 [PMID: 24963487 DOI: 10.1155/2014/864894]
 - 115 **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]
 - 116 **Raimondo S**, Saieva L, Corrado C, Fontana S, Fluga A, Rizzo A, De Leo G, Alessandro R. Chronic myeloid leukemia-derived exosomes promote tumor growth through an autocrine mechanism. *Cell Commun Signal* 2015; **13**: 8 [PMID: 25644060 DOI: 10.1186/s12964-015-0086-x]
 - 117 **Hood JL**, Pan H, Lanza GM, Wickline SA; Consortium for Translational Research in Advanced Imaging and Nanomedicine (C-TRAIN). Paracrine induction of endothelium by tumor exosomes. *Lab Invest* 2009; **89**: 1317-1328 [PMID: 19786948 DOI: 10.1038/labinvest.2009.94]
 - 118 **Zhou J**, Tan X, Tan Y, Li Q, Ma J, Wang G. Mesenchymal Stem Cell Derived Exosomes in Cancer Progression, Metastasis and Drug Delivery: A Comprehensive Review. *J Cancer* 2018; **9**: 3129-3137 [PMID: 30210636 DOI: 10.7150/jca.25376]
 - 119 **Pan L**, Liang W, Fu M, Huang ZH, Li X, Zhang W, Zhang P, Qian H, Jiang PC, Xu WR, Zhang X. Exosomes-mediated transfer of long noncoding RNA ZFAS1 promotes gastric cancer progression. *J Cancer Res Clin Oncol* 2017; **143**: 991-1004 [PMID: 28285404 DOI: 10.1007/s00432-017-2361-2]
 - 120 **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]
 - 121 **Umez T**, Ohyashiki K, Kuroda M, Ohyashiki JH. Leukemia cell to endothelial cell communication via exosomal miRNAs. *Oncogene* 2013; **32**: 2747-2755 [PMID: 22797057 DOI: 10.1038/onc.2012.295]
 - 122 **Li L**, Wang A, Cai M, Tong M, Chen F, Huang L. Identification of stool miR-135b-5p as a non-invasive diagnostic biomarker in later tumor stage of colorectal cancer. *Life Sci* 2020; **260**: 118417 [PMID: 32931801 DOI: 10.1016/j.lfs.2020.118417]
 - 123 **Zou SL**, Chen YL, Ge ZZ, Qu YY, Cao Y, Kang ZX. Downregulation of serum exosomal miR-150-5p is associated with poor prognosis in patients with colorectal cancer. *Cancer Biomark* 2019; **26**: 69-77 [PMID: 31306108 DOI: 10.3233/CBM-190156]
 - 124 **Shang A**, Wang X, Gu C, Liu W, Sun J, Zeng B, Chen C, Ji P, Wu J, Quan W, Yao Y, Wang W, Sun Z, Li D. Exosomal miR-183-5p promotes angiogenesis in colorectal cancer by regulation of FOXO1. *Aging (Albany NY)* 2020; **12**: 8352-8371 [PMID: 32364530 DOI: 10.18632/aging.103145]
 - 125 **Lv ZC**, Fan YS, Chen HB, Zhao DW. Investigation of microRNA-155 as a serum diagnostic and prognostic biomarker for colorectal cancer. *Tumour Biol* 2015; **36**: 1619-1625 [PMID: 25528214 DOI: 10.1007/s13277-014-2760-9]
 - 126 **Zou G**, Wang R, Wang M. Clinical response and prognostic significance of serum miR-497 expression in colorectal cancer. *Cancer Biomark* 2019; **25**: 11-18 [PMID: 31006664 DOI: 10.3233/CBM-181902]
 - 127 **Yun J**, Han SB, Kim HJ, Go SI, Lee WS, Bae WK, Cho SH, Song EK, Lee OJ, Kim HK, Yang Y, Kwon J, Chae HB, Lee KH, Han HS. Exosomal miR-181b-5p Downregulation in Ascites Serves as a Potential Diagnostic Biomarker for Gastric Cancer-associated Malignant Ascites. *J Gastric Cancer* 2019; **19**: 301-314 [PMID: 31598373 DOI: 10.5230/jgc.2019.19.e27]
 - 128 **Andreu Z**, Otta Oshiro R, Redruello A, López-Martín S, Gutiérrez-Vázquez C, Morato E, Marina AI, Olivier Gómez C, Yáñez-Mó M. Extracellular vesicles as a source for non-invasive biomarkers in bladder cancer progression. *Eur J Pharm Sci* 2017; **98**: 70-79 [PMID: 27751843 DOI: 10.1016/j.ejps.2016.10.008]
 - 129 **Huang X**, Yuan T, Liang M, Du M, Xia S, Dittmar R, Wang D, See W, Costello BA, Quevedo F, Tan W, Nandy D, Bevan GH, Longenbach S, Sun Z, Lu Y, Wang T, Thibodeau SN, Boardman L, Kohli M, Wang L. Exosomal miR-1290 and miR-375 as prognostic markers in castration-resistant prostate cancer. *Eur Urol* 2015; **67**: 33-41 [PMID: 25129854 DOI: 10.1016/j.eururo.2014.07.035]
 - 130 **Endzeļiņš E**, Berger A, Melne V, Bajo-Santos C, Sobolevska K, Ābols A, Rodríguez M, Šantare D, Rudņickiha A, Lietuviētis V, Llorente A, Linē A. Detection of circulating miRNAs: comparative

- analysis of extracellular vesicle-incorporated miRNAs and cell-free miRNAs in whole plasma of prostate cancer patients. *BMC Cancer* 2017; **17**: 730 [PMID: [29121858](#) DOI: [10.1186/s12885-017-3737-z](#)]
- 131 **Meng X**, Müller V, Milde-Langosch K, Trillsch F, Pantel K, Schwarzenbach H. Diagnostic and prognostic relevance of circulating exosomal miR-373, miR-200a, miR-200b and miR-200c in patients with epithelial ovarian cancer. *Oncotarget* 2016; **7**: 16923-16935 [PMID: [26943577](#) DOI: [10.18632/oncotarget.7850](#)]
 - 132 **Zhao H**, Yang L, Baddour J, Achreja A, Bernard V, Moss T, Marini JC, Tudawe T, Seviour EG, San Lucas FA, Alvarez H, Gupta S, Maiti SN, Cooper L, Peehl D, Ram PT, Maitra A, Nagrath D. Tumor microenvironment derived exosomes pleiotropically modulate cancer cell metabolism. *Elife* 2016; **5**: e10250 [PMID: [26920219](#) DOI: [10.7554/eLife.10250](#)]
 - 133 **Taverna S**, Flugy A, Saieva L, Kohn EC, Santoro A, Meraviglia S, De Leo G, Alessandro R. Role of exosomes released by chronic myelogenous leukemia cells in angiogenesis. *Int J Cancer* 2012; **130**: 2033-2043 [PMID: [21630268](#) DOI: [10.1002/ijc.26217](#)]
 - 134 **Ying X**, Wu Q, Wu X, Zhu Q, Wang X, Jiang L, Chen X. Epithelial ovarian cancer-secreted exosomal miR-222-3p induces polarization of tumor-associated macrophages. *Oncotarget* 2016; **7**: 43076-43087 [PMID: [27172798](#) DOI: [10.18632/oncotarget.9246](#)]
 - 135 **Bobrie A**, Krumeich S, Reyat F, Recchi C, Moita LF, Seabra MC, Ostrowski M, Théry C. Rab27a supports exosome-dependent and -independent mechanisms that modify the tumor microenvironment and can promote tumor progression. *Cancer Res* 2012; **72**: 4920-4930 [PMID: [22865453](#) DOI: [10.1158/0008-5472.CAN-12-0925](#)]
 - 136 **Whiteside TL**. Immune modulation of T-cell and NK (natural killer) cell activities by TEXs (tumour-derived exosomes). *Biochem Soc Trans* 2013; **41**: 245-251 [PMID: [23356291](#) DOI: [10.1042/BST20120265](#)]
 - 137 **Valenti R**, Huber V, Filipazzi P, Pilla L, Sovena G, Villa A, Corbelli A, Fais S, Parmiani G, Rivoltini L. Human tumor-released microvesicles promote the differentiation of myeloid cells with transforming growth factor-beta-mediated suppressive activity on T lymphocytes. *Cancer Res* 2006; **66**: 9290-9298 [PMID: [16982774](#) DOI: [10.1158/0008-5472.CAN-06-1819](#)]
 - 138 **Paget S**. The distribution of secondary growths in cancer of the breast. 1889. *Cancer Metastasis Rev* 1989; **8**: 98-101 [PMID: [2673568](#)]
 - 139 **Hamidi H**, Ivaska J. Every step of the way: integrins in cancer progression and metastasis. *Nat Rev Cancer* 2018; **18**: 533-548 [PMID: [30002479](#) DOI: [10.1038/s41568-018-0038-z](#)]
 - 140 **Guo Y**, Ji X, Liu J, Fan D, Zhou Q, Chen C, Wang W, Wang G, Wang H, Yuan W, Ji Z, Sun Z. Effects of exosomes on pre-metastatic niche formation in tumors. *Mol Cancer* 2019; **18**: 39 [PMID: [30857545](#) DOI: [10.1186/s12943-019-0995-1](#)]
 - 141 **Bataller R**, Arteel GE, Moreno C, Shah V. Alcohol-related liver disease: Time for action. *J Hepatol* 2019; **70**: 221-222 [PMID: [30658723](#) DOI: [10.1016/j.jhep.2018.12.007](#)]
 - 142 **Paschos KA**, Majeed AW, Bird NC. Natural history of hepatic metastases from colorectal cancer--pathobiological pathways with clinical significance. *World J Gastroenterol* 2014; **20**: 3719-3737 [PMID: [24744570](#) DOI: [10.3748/wjg.v20.i14.3719](#)]
 - 143 **Siegel RL**, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**: 145-164 [PMID: [32133645](#) DOI: [10.3322/caac.21601](#)]
 - 144 **Cai S**, Li Y, Ding Y, Chen K, Jin M. Alcohol drinking and the risk of colorectal cancer death: a meta-analysis. *Eur J Cancer Prev* 2014; **23**: 532-539 [PMID: [25170915](#) DOI: [10.1097/CEJ.0000000000000076](#)]
 - 145 **Van den Eynden GG**, Majeed AW, Illemann M, Vermeulen PB, Bird NC, Høyer-Hansen G, Eefsen RL, Reynolds AR, Brodt P. The multifaceted role of the microenvironment in liver metastasis: biology and clinical implications. *Cancer Res* 2013; **73**: 2031-2043 [PMID: [23536564](#) DOI: [10.1158/0008-5472.CAN-12-3931](#)]
 - 146 **Melo SA**, Sugimoto H, O'Connell JT, Kato N, Villanueva A, Vidal A, Qiu L, Vitkin E, Perelman LT, Melo CA, Lucci A, Ivan C, Calin GA, Kalluri R. Cancer exosomes perform cell-independent microRNA biogenesis and promote tumorigenesis. *Cancer Cell* 2014; **26**: 707-721 [PMID: [25446899](#) DOI: [10.1016/j.ccell.2014.09.005](#)]
 - 147 **Skog J**, Würdinger T, van Rijn S, Meijer DH, Gainche L, Sena-Esteves M, Curry WT Jr, Carter BS, Krichevsky AM, Breakefield XO. Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. *Nat Cell Biol* 2008; **10**: 1470-1476 [PMID: [19011622](#) DOI: [10.1038/ncb1800](#)]
 - 148 **Ji H**, Greening DW, Barnes TW, Lim JW, Tauro BJ, Rai A, Xu R, Adda C, Mathivanan S, Zhao W, Xue Y, Xu T, Zhu HJ, Simpson RJ. Proteome profiling of exosomes derived from human primary and metastatic colorectal cancer cells reveal differential expression of key metastatic factors and signal transduction components. *Proteomics* 2013; **13**: 1672-1686 [PMID: [23585443](#) DOI: [10.1002/pmic.201200562](#)]
 - 149 **Chiba M**, Kimura M, Asari S. Exosomes secreted from human colorectal cancer cell lines contain mRNAs, microRNAs and natural antisense RNAs, that can transfer into the human hepatoma HepG2 and lung cancer A549 cell lines. *Oncol Rep* 2012; **28**: 1551-1558 [PMID: [22895844](#) DOI: [10.3892/or.2012.1967](#)]
 - 150 **Camp ER**, Ellis LM. CCR 20th Anniversary Commentary: RAS as a Biomarker for EGFR--Targeted Therapy for Colorectal Cancer-From Concept to Practice. *Clin Cancer Res* 2015; **21**: 3578-

- 3580 [PMID: 26275951 DOI: 10.1158/1078-0432.CCR-14-2900]
- 151 **Kuracha MR**, Thomas P, Loggie BW, Govindarajan V. Bilateral blockade of MEK- and PI3K-mediated pathways downstream of mutant KRAS as a treatment approach for peritoneal mucinous malignancies. *PLoS One* 2017; **12**: e0179510 [PMID: 28640835 DOI: 10.1371/journal.pone.0179510]
 - 152 **Demory Beckler M**, Higginbotham JN, Franklin JL, Ham AJ, Halvey PJ, Imasuen IE, Whitwell C, Li M, Liebler DC, Coffey RJ. Proteomic analysis of exosomes from mutant KRAS colon cancer cells identifies intercellular transfer of mutant KRAS. *Mol Cell Proteomics* 2013; **12**: 343-355 [PMID: 23161513 DOI: 10.1074/mcp.M112.022806]
 - 153 **Webber JP**, Spary LK, Sanders AJ, Chowdhury R, Jiang WG, Steadman R, Wymant J, Jones AT, Kynaston H, Mason MD, Tabi Z, Clayton A. Differentiation of tumour-promoting stromal myofibroblasts by cancer exosomes. *Oncogene* 2015; **34**: 290-302 [PMID: 24441045 DOI: 10.1038/onc.2013.560]
 - 154 **Huang Z**, Feng Y. Exosomes Derived From Hypoxic Colorectal Cancer Cells Promote Angiogenesis Through Wnt4-Induced β -Catenin Signaling in Endothelial Cells. *Oncol Res* 2017; **25**: 651-661 [PMID: 27712599 DOI: 10.3727/096504016X14752792816791]
 - 155 **Talwar H**, McVicker B, Tobi M. p38 γ Activation and BGP (Biliary Glycoprotein) Induction in Primates at Risk for Inflammatory Bowel Disease and Colorectal Cancer-A Comparative Study with Humans. *Vaccines (Basel)* 2020; **8** [PMID: 33276422 DOI: 10.3390/vaccines8040720]
 - 156 **Aldulaymi B**, Byström P, Berglund A, Christensen IJ, Brünner N, Nielsen HJ, Glimelius B. High plasma TIMP-1 and serum CEA levels during combination chemotherapy for metastatic colorectal cancer are significantly associated with poor outcome. *Oncology* 2010; **79**: 144-149 [PMID: 21150229 DOI: 10.1159/000320686]
 - 157 **Mohr AM**, Gould JJ, Kubik JL, Talmon GA, Casey CA, Thomas P, Tuma DJ, McVicker BL. Enhanced colorectal cancer metastases in the alcohol-injured liver. *Clin Exp Metastasis* 2017; **34**: 171-184 [PMID: 28168393 DOI: 10.1007/s10585-017-9838-x]
 - 158 **Tobi M**, Chintalapani S, Kithier K, Clapp N. Carcinoembryonic antigen family of adhesion molecules in the cotton top tamarin (*Saguinus oedipus*). *Cancer Lett* 2000; **157**: 45-50 [PMID: 10893441 DOI: 10.1016/S0304-3835(00)00482-1]
 - 159 **Beauchemin N**, Arabzadeh A. Carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) in cancer progression and metastasis. *Cancer Metastasis Rev* 2013; **32**: 643-671 [PMID: 23903773 DOI: 10.1007/s10555-013-9444-6]
 - 160 **Gangopadhyay A**, Lazure DA, Thomas P. Adhesion of colorectal carcinoma cells to the endothelium is mediated by cytokines from CEA stimulated Kupffer cells. *Clin Exp Metastasis* 1998; **16**: 703-712 [PMID: 10211983 DOI: 10.1023/a:1006576627429]
 - 161 **Thomas P**, Forse RA, Bajenova O. Carcinoembryonic antigen (CEA) and its receptor hnRNP M are mediators of metastasis and the inflammatory response in the liver. *Clin Exp Metastasis* 2011; **28**: 923-932 [PMID: 21901530 DOI: 10.1007/s10585-011-9419-3]
 - 162 **Yokoyama S**, Takeuchi A, Yamaguchi S, Mitani Y, Watanabe T, Matsuda K, Hotta T, Shively JE, Yamaue H. Clinical implications of carcinoembryonic antigen distribution in serum exosomal fraction-Measurement by ELISA. *PLoS One* 2017; **12**: e0183337 [PMID: 28817685 DOI: 10.1371/journal.pone.0183337]
 - 163 **Liu H**, Liu Y, Sun P, Leng K, Xu Y, Mei L, Han P, Zhang B, Yao K, Li C, Bai J, Cui B. Colorectal cancer-derived exosomal miR-106b-3p promotes metastasis by down-regulating DLC-1 expression. *Clin Sci (Lond)* 2020; **134**: 419-434 [PMID: 32065214 DOI: 10.1042/CS20191087]
 - 164 **Zhang N**, Zhang PP, Huang JJ, Wang ZY, Zhang ZH, Yuan JZ, Ma EM, Liu X, Bai J. Reduced serum exosomal miR-874 expression predicts poor prognosis in colorectal cancer. *Eur Rev Med Pharmacol Sci* 2020; **24**: 664-672 [PMID: 32016967 DOI: 10.26355/eurrev_202001_20043]
 - 165 **Xu Y**, Shen L, Li F, Yang J, Wan X, Ouyang M. microRNA-16-5p-containing exosomes derived from bone marrow-derived mesenchymal stem cells inhibit proliferation, migration, and invasion, while promoting apoptosis of colorectal cancer cells by downregulating ITGA2. *J Cell Physiol* 2019; **234**: 21380-21394 [PMID: 31102273 DOI: 10.1002/jcp.28747]
 - 166 **Wang J**, Yan F, Zhao Q, Zhan F, Wang R, Wang L, Zhang Y, Huang X. Circulating exosomal miR-125a-3p as a novel biomarker for early-stage colon cancer. *Sci Rep* 2017; **7**: 4150 [PMID: 28646161 DOI: 10.1038/s41598-017-04386-1]
 - 167 **Liu C**, Eng C, Shen J, Lu Y, Takata Y, Mehdizadeh A, Chang GJ, Rodriguez-Bigas MA, Li Y, Chang P, Mao Y, Hassan MM, Wang F, Li D. Serum exosomal miR-4772-3p is a predictor of tumor recurrence in stage II and III colon cancer. *Oncotarget* 2016; **7**: 76250-76260 [PMID: 27788488 DOI: 10.18632/oncotarget.12841]
 - 168 **Costa-Silva B**, Aiello NM, Ocean AJ, Singh S, Zhang H, Thakur BK, Becker A, Hoshino A, Mark MT, Molina H, Xiang J, Zhang T, Theilen TM, Garcia-Santos G, Williams C, Ararso Y, Huang Y, Rodrigues G, Shen TL, Labori KJ, Lothe IM, Kure EH, Hernandez J, Doussot A, Ebbesen SH, Grandgenett PM, Hollingsworth MA, Jain M, Mallya K, Batra SK, Jarnagin WR, Schwartz RE, Matei I, Peinado H, Stanger BZ, Bromberg J, Lyden D. Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver. *Nat Cell Biol* 2015; **17**: 816-826 [PMID: 25985394 DOI: 10.1038/ncb3169]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

