Editorial Commentary

Extracellular vesicles in hepatocellular cancer and cholangiocarcinoma

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Submitted Dec 20, 2018. Accepted for publication Jan 02, 2019.
doi: 10.21037/atm.2019.01.12
View this article at: http://dx.doi.org/10.21037/atm.2019.01.12

Introduction

Extracellular vesicles (EVs) are subcellular components produced by a variety of cells, which are microscopic spherical particles containing specific lipids, RNA species, DNA and proteins (1). These small particles of 40 to 5,000 nm in diameter are released by several cells into the extracellular matrix. While they were previously considered as a means to discard cellular metabolic waste, recently emerging evidence suggest that they are essential players in cell-to-cell communication (2,3). Based on their cellular biogenesis and characteristics, EVs are classified into three categories: exosomes, microvesicles, and apoptotic bodies. Exosomes, small vesicles (40–100 nm) synthesized and matured inside multivesicular bodies, are the most studied EVs (4). Also, atypically large (1–10 μm diameter) vesicles, termed large oncosomes, can be secreted by specific cancer cells (5). Given the fact that EVs and their cargo represent the physiopathological state of the cells by which they are emitted, and cancer cells produce a relatively large amount of EVs, recent studies have suggested that EVs and their cargo have a significant impact on the tumor microenvironment, tumor growth and differentiation (6). There is an increasing amount of research suggesting that EVs and their cargo serve as promising biomarker candidates in the diagnosis and prognosis of cancers (7,8). Furthermore, these particles wrapped in lipid bilayer represent a potential target for therapeutic use, and *ex vivo* modified or synthesized EVs can be engineered as therapeutic shuttles in treating cancerous diseases (9).

Hepatocellular carcinoma (HCC) is the most common primary liver cancer which is identified as the second leading cause of all cancer-related deaths (10,11). Due to the absence of typical early clinical manifestations and insufficiency of public surveillance (serum AFP test and abdominal ultrasound), many patients with liver cancer have lost the chance of radical surgical resection by the time of diagnosis (12). Localized interventional chemoembolization, systemic therapy, and chemotherapy can only prolong the survival time of patients with advanced liver cancer for a rather short period (10,12). The same dilemma goes with cholangiocarcinoma (CCA), let alone the worse prognosis of CCA is another problem we have to cope with (12-14). Studies have found that EVs play a critical role in HCC and CCA carcinogenesis and metastasis. Altered EVs in serum and bile as well as their cargo may serve as diagnostic biomarkers and therapeutic target for HCC and CCA and engineered EVs may be a brand-new therapeutic approach (15-17). Here we reviewed the research progress of EVs and their cargo in the diagnosis and treatment of HCC and CCA.

Liver-derived EVs and their physiological characteristics

The liver is a multicellular substantive organ composed of hepatocytes, bile duct epitheliums, hepatic stellate cells (HSCs), sinusoidal endothelial cells, and various immune cells (18). To perform a normal liver function, cells within the liver need to collaborate according to intercellular exchanges of substances and information. In addition to

direct contact between liver cells, liver cell-derived EVs are essential carriers of intrahepatic signal transduction (4). EVs released from different cells function distinctively. For example, EVs released by hepatocytes can regulate their proliferation, while HSCs-derived EVs are involved in liver fibrosis formation (19). When the liver is under stress or pathological conditions, EVs secreted by liver cells undergo significant changes in both quantity and quality, the concentration of EVs and the composition of EVs cargo, namely proteins, lipids, and nucleic acids, and etc., changes dramatically (20).

Bile synthesized by hepatocytes runs through biliary tract. It is a non-circulating fluid that contacts with the tumors directly, and it collects EVs released from hepatocytes, bile duct epitheliums, and cancerous cells, and etc. (1,21). EVs in bile are rich in microRNA (mi-RNA), long noncoding RNA (lncRNA) and proteins. They participate in the regulation of the biliary tract microenvironment and biliary cells proliferation (22). Masyuk *et al.* studied the physiological function of EVs in bile and argued that bile EVs could adhere to cholangiocyte cilia to inhibit the proliferation of bile duct epitheliums by decreasing the phosphorylated-to-total ERK1/2 ratio and promoting the expression of miR-15A (21). Wang *et al.* found that chicken bile EVs can enhance the proliferation of CD4+ and CD8+ T cells and activate intrahepatic monocytes in immune responses (23).

Liver-derived EVs participate in cirrhosis formation. In the process of liver cirrhosis, HSCs are the primary effector cells that secrete a large amount of insoluble collagen to facilitate fibrogenesis. Activation of HSC is the crucial step of liver cirrhosis. Chen *et al.* illustrated that during the activation of HSC, the concentration of TWIST1, a basic helix-loop-helix transcription factor, in HSC-derived EVs decreased, which suppressed the expression of miR-214 and indirectly accelerated the synthesis of connective tissue growth factor 2 (CCN2), which takes the key role in the CCN2-dependent fibrogenesis (24). Charrier *et al.* stated that activated HSCs could wrap CCN2 into secreted EVs, and those EVs transport CCN2 to other quiescent or activated HSCs to further promote hepatic fibrosis (25).

EVs and their cargo as potential biomarkers in HCC and CCA

The concentration and content of EVs released from cancer cells are significantly different from those released from non-cancerous cells (6), making EVs a new source of cancer biomarkers lately. Studies have demonstrated that the mi-RNA components in ovarian cancer and lung cancer cell-derived EVs are distinct from the mi-RNA in non-cancerous cell-derived EVs respectively, enabling them to be used as diagnostic biomarkers for ovarian cancer and lung cancer (26,27). In another study, serum glypican-1 (GPC-1) positive EVs can be used as biomarkers in discriminating between pancreatic cancer and benign pancreatic lesions with absolute sensitivity and specificity, and the concentration of serum GPC-1 positive EVs is correlated with the tumor burden and prognosis of pancreatic cancer patients (28).

EVs as biomarkers for HCC

The study of potential biomarkers of HCC has always been a heated issue in the field of cancer research (29,30). In 2007, Valadi *et al.* found that exosomes can carry abundant mRNAs and mi-RNAs to target cells and express corresponding proteins in target cells (31). Since then, a growing number of evidence shows that cancer cells-derived EVs contain multiple types of RNA with cancer specificity and can serve as potential biomarkers (*Table 1*).

The predominant nucleotide content of HCC-derived EVs is various RNA species (17). Sohn *et al.* stated that the serum level of multiple EVs mi-RNAs in HCC patients was considerably higher than those in hepatitis B and liver cirrhosis patients, including miR-18a, miR-221, miR-222 and miR-224, yet miR-101, miR-106b, miR-122, and miR-195 were significantly lower (36). Sugimachi *et al.* found that compared with HCC patients who did not have cancer recurrence after liver transplantation, the patients suffering from cancer recurrence have a decreased expression of circulating miR-718 in serum EVs. The declining level of miR-718 was associated with HCC aggressiveness (33). Wang *et al.* claimed that the appearance of serum exosomal miR-21 in patients with HCC was significantly higher than that in healthy people and patients with hepatitis B. The expression of EVs miR-21 was correlated with the degree of liver cirrhosis and tumor stage (37).

The proportion of lnc-RNA in EVs RNA is rather small, accounting for about 3% of total EVs RNA (42). However, growing evidence has proven that EVs lnc-RNA is involved in proliferation, recurrence, metastasis, and resistance to hypoxia and chemotherapy in liver cancer. Kogure *et al.* indicated that 1198-bp lnc-RNA, termed as TUC339, was significantly upregulated in HCC cells. The

Table 1 EVs cargo as diagnostic biomarkers for HCC and CCA

Cargo type	Content	EVs specimen	Disease	Control	SEN (%)	SPE (%)	References
mRNA	hnRNPH1	Serum	HCC	CHB	85.2	76.5	Xu *et al.* [2018] (32)
miRNA	miR-718	Serum	HCC recurrence after LT	HCC without recurrence	–	–	Sugimachi *et al.* [2015] (33)
	miR-203, miR-373	Serum	Advanced stage of HCC	The early stage of HCC	–	–	Jang *et al.* [2017] (34)
	miR-125b	Serum	HCC	CHB	–	–	Liu *et al.* [2017] (35)
	miR-18a, miR-221, miR-222, miR-224	Serum	HCC	CHB & LC	–	–	Sohn *et al.* [2015] (36)
	miR-101, miR-106b, miR-122, miR-195			CHB			
	miR-21	Serum	HCC	Normal, CHB	–	–	Wang *et al.* [2014] (37)
lnc-RNA	ENSG00000258332.1	Serum	HCC	CHB	71.6	83.4	Xu *et al.* [2018] (38)
	LINC00635				76.2	77.7	
	ENSG00000258332.1, LINC00635, serum AFP				83.6	87.7	
	HEIH	Serum	HCC	CHC	–	–	Zhang *et al.* [2018] (39)
Protein	AnnexinV$^+$, EpCAM$^+$	Serum	HCC	Normal	78.5	63.3	Julich-Haertel *et al.* [2017] (40)
	AnnexinV$^+$, EpCAM$^+$, CD147$^+$				64.6	82.4	
	AnnexinV$^+$, EpCAM$^+$, CD133$^+$				73.4	50.0	
	AnnexinV$^+$, EpCAM$^+$, ASGPR1$^+$, CD133$^+$				82.6	50.0	
	LG3BP	Serum	HCC	Control	96.6	71.8	Arbelaiz *et al.* [2017] (41)
	PIGR				82.8	71.8	
	A2MG				92.9	56.2	
	FIBG				78.6	75.0	
	AMPN				72.4	71.8	
miRNA	miR-1274b, miR-16, miR-484, miR-486-3p	Bile	CCA	PSC, biliary obstruction, bile leak syndromes	67	96	Li *et al.* [2014] (16)

Table 1 (*continued*)

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Cargo type	Content	EVs specimen	Disease	Control	SEN (%)	SPE (%)	References
Protein	AnnexinV$^+$, EpCAM$^+$	Serum	CCA	Normal	78.5	63.3	Julich-Haertel *et al.* [2017] (40)
	AnnexinV$^+$, EpCAM$^+$, CD133$^+$				73.4	50.0	
	AnnexinV$^+$, EpCAM$^+$, ASGPR1$^+$, CD133$^+$				82.6	50.0	
	AMPN	Serum	CCA	Normal	90.7	65.6	Arbelaiz *et al.* [2017] (41)
	VNN1				72.1	87.5	
	PIGR				83.7	71.8	
	IGHA1				81.4	75.0	
	CRP				79.1	68.7	
	FIBG				79.1	75.0	
	FIBG			PSC	88.	63.3	
	FIBB				74.4	66.0	
	IGHA1				74.4	70.1	

HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma; LT, liver transplantation; LC, liver cirrhosis; CHB, chronic hepatitis B; hnRNPH1, heterogeneous nuclear ribonucleoprotein H1; A1AG1, alpha-1-acid glycoprotein 1; A2MG, alpha-2-macroglobulin; AMPN, aminopeptidase N; ASPGPR1, asialoglycoprotein receptor 1; CRP, c-reaction protein; EpCAM, epithelial cell adhesion molecule; FCN2, ficolin-2; FIBG, fibrinogen gamma chain; ITIH4, inter-alpha-trypsin inhibitor heavy chain H4; LG3BP, galectin-3-binding protein; lnc-RNA, long non-coding RNA; PIGR, polymeric immunoglobulin receptor; PSC, primary sclerosing cholangitis; SEN, sensitivity; SPE, specificity; TAMP, tumor-associated microparticle; VNN1, pantetheinase; IGHA1, Immunoglobulin heavy constant alpha 1.

proliferation and adhesion of HCC cells could be promoted with increasing expression of TUC339or inhibited with decreasing expression of TUC339 (43). Another study demonstrated that lnc-RNA H19 was enriched in EVs released from CD90+ liver cancer stem cells. lncRNA H19 induces an early recurrence of HCC and promotes metastasis of circulating CD90+ liver cancer stem cells by modulating endothelial cell, promoting cell-to-cell adhesion and angiogenesis (44). Takahashi *et al.* found that when HCC cells were exposed to antitumor drugs such as sorafenib, the stress-responsive lncVLDLR was highly expressed in HCC cells as well as within EVs. lnc-VLDLR in EVs can reduce chemotherapy-induced cell death. The expression of ATP-binding cassette, subfamily G member 2 (ABCG2) is suppressed, and the viability of cancer cells is reduced by silencing lnc-VLDLR (45). Also, lnc-ROR is also related to the resistance of liver cancer cells. The expression level of lnc-ROR in normal hepatocytes is considerably low, while it is notably enriched within EVs of HCC cells, resulting in resistance to chemotherapy. Silencing the lnc-ROR could improve the sensitivity of HCC cells to chemotherapy. Besides, lnc-ROR could also serve as a potential biomarker for HCC (46).

EVs as potential biomarkers for CCA

In CCA, Severino *et al.* found that bile EVs were significantly elevated in patients with CCA and pancreatic cancer. The median concentration of bile EVs from malignant patients was more than ten times higher than that from nonmalignant patients. It correctly classified malignant stenosis verse cholelithiasis and chronic pancreatitis (diagnostic accuracy, 100%). Results suggested that the diagnostic ability of bile EVs concentration was more superior when compared to the traditional serum carbohydrate antigen 19-9 (47).

Interestingly, there was no significant difference in serum EVs concentrations in patients with CCA, primary sclerosing cholangitis and HCC. However, several proteins with differential degrees of abundance were found in

serum EV of CCA versus controls, some of which present significant diagnostic potential. In a comparison of patients with primary sclerosing cholangitis and HCC, patients with CCA suffered from higher levels of C-reactive protein, ficolins-2, fibrinogen γ chain, and plasma protease C1 inhibitors in serum EVs. Ficolin-2 and plasma protease C1 inhibitors were significantly elevated in the serum of patients with early staged CCA (I–II), indicating a higher diagnostic value than serum CA19-9 (41). Furthermore, a panel of mi-RNAs (191, 486-3p, 1274b, 16, 484) was found upregulated in bile EVs of patients with CCA comparing to patients with primary sclerosing cholangitis, biliary obstruction, and bile leak syndrome (16). Two lnc-RNAs (i.e., ENST00000588480.1 and ENST00000517758) were identified upregulated in the analysis of the bile EVs lnc-RNA profile in CCA patients versus patients with biliary obstruction (48) (*Table 1*).

EVs-based treatment

EVs can serve as therapeutic compounds carriers, such as chemicals, RNAs or proteins, and protect those compounds from enzymatic degradation. As a result, it bears ideal potential in the new drug-delivery system. Recent studies show that specific RNAs or chemotherapeutic drugs can be effectively delivered to tumor sites once they are packaged into EVs, leading to better pharmacokinetic efficiency and therapeutic efficacy of the drugs (49).

EVs-based treatment for HCC

On the one hand, EVs can be used as miRNAs delivery media in treating liver cancer. Stellate cell-derived EVs carrying miR-335-5p, a tumor suppressor miRNA downregulated in HCC, inhibit HCC cell viability *in vitro* and induce tumor shrinkage *in vivo* by suppressing proliferation and promote apoptosis (50). Moreover, miR-122 loaded EVs released from adipose tissue-derived mesenchymal stem cells (ADMSCs) increases HCC cell sensitivity to the chemotherapeutic agents, sorafenib and 5-FU, by inducing G0/G1 arrest and cell apoptosis in HCC cell cycle. Furthermore, intratumor injection of those loaded EVs in an HCC xenograft mouse model can strengthen the anti-tumor efficacy of sorafenib and reduce tumor size.

On the other hand, EVs are also used as toxic drugs delivery media in treating HCC. The same dosage of methotrexate via direct administration and microparticles-delivered administration causes 2% and 23% cell death respectively (51). Toxicated H22 cells-derived drug-encapsulating microparticles are also cytotoxic, triggering a domino-like cancer-killing effect. Methotrexate carried by microparticles is more effective than dissociative methotrexate in inhibiting tumor growth and prolonging survival time in xenograft mice (51).

EVs-based treatments of CCA

In CCA, fibroblast-derived EVs, carrying miR-195, inhibit CCA growth and invasiveness in vitro. miR-195 is an inhibitor of cancer growth and is generally downregulated in the CCA cells (9). Possible mechanisms of the anti-neoplastic effect of EVs carried miR-195 are downregulating VEGF, cell division control (CDC) proteins 25 and 42, as well as cyclin-dependent kinases (CDK) 1, 4, and 6.

Discussion

To date, the problem of lacking accurate early diagnosis and correct management for staged HCC and CCA is still seeking solutions. The carcinogenesis, development, and metastasis of HCC and CCA are somewhat complicated. Thus, the discovery of methods, as well as treatment for patients, remains a significant challenge. The presence of EVs, their tumor-associated cargo and their unique lipid bilayer characteristics in biological fluids make EVs excellent candidates for clinical application. Consequently, a growing number of studies have been conducted focusing on potential diagnostic use and innovative anti-tumor therapy via EVs. However, certain limitations remain to be unsolved: (I) the molecular mechanism of EVs synthesis, secretion, and participation in information exchange is not crystal clear; (II) although the International Society of Extracellular Vesicles (ISEV) provided official definition and subpopulation categories in 2012, recent literature suggested otherwise, such as large oncosomes. Types and characteristics of subpopulations of EVs need more in-depth study, not until then shall we have the terminology unified; (III) there is no universally recognized procedure in preparation, separation, purification, and reservation of the EVs, especially for each subpopulation.

In conclusion, EVs represent a rather appealing and promising field of research in HCC and CCA with multiple potential applications, including being diagnostic and prognostic biomarkers and new approaches for cancer

treatment. However, more research and data are still needed to learn about EVs and their possible role in cancerous disease.

Acknowledgements

Funding: This study was supported by grants from the CAMS Innovation Fund for Medical Sciences (CIFMS) (No. 2016-I2M-1–001) and the National Natural Science Foundation of China (31500818).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Xie F, Feng S, Yang H, Mao Y. Extracellular vesicles in hepatocellular cancer and cholangiocarcinoma. Ann Transl Med 2019;7(5):86. doi: 10.21037/atm.2019.01.12

