RNA binding proteins in extracellular vesicles and their potential value for cancer diagnosis and treatment (Review)

WEICHAO SUN[1,2*], HANWEI CUI[2,3*], TIANHAO XU[4], JIAJI YUE[1], JIANHUI LIANG[1], WEI YOU[1], WEI SUN[1] and QIAN YI[4]

[1]Department of Bone Joint and Bone Oncology, Shenzhen Second People's Hospital; [2]Central Laboratory, Shenzhen Second People's Hospital, Shenzhen, Guangdong 518035; [3]Central Laboratory, Shenzhen Samii Medical Center, Shenzhen, Guangdong 518118; [4]Department of Physiology, School of Basic Medical Science, Southwest Medical University, Luzhou, Sichuan 646000, P.R. China

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Abstract. Extracellular vesicles (EVs) are spherical bilayer membrane vesicles released by cells into extracellular spaces and body fluids, including plasma and synovial fluid. EV cargo comprises various biomolecules, such as proteins, DNA, mRNAs, non-coding RNAs, lipids and metabolites. By delivering these bioactive molecules to recipient cells, EVs mediate intercellular communications and play a critical role in maintaining cellular homeostasis and promoting pathological progression. Of note, cells can selectively sort these bioactive molecules (particularly RNAs) into EVs for secretion, as well as regulate cell-cell communications. RNA-binding proteins (RBPs) are a large class of proteins capable of binding to RNA molecules and function in regulating RNA metabolism. There is increasing evidence to indicate that RBPs can be delivered to receipt cells to influence their cell biology and play a significant role in the sorting of coding and non-coding RNAs in EVs. The present review summarized the current knowledge on EV-associated RBPs, their functions in tumorigenesis and RBP-related exosome engineering. It is hoped that the present review may provide novel insight into RBPs and targeted cancer treatment.

Correspondence to: Professor Wei Sun, Department of Bone Joint and Bone Oncology, Shenzhen Second People's Hospital, 3002 Sungang West Road, Shenzhen, Guangdong 518035, P.R. China
E-mail: 414464705@qq.com

Dr Qian Yi, Department of Physiology, School of Basic Medical Science, Southwest Medical University, Section 1, Xianglin Road, Luzhou, Sichuan 646000, P.R. China
E-mail: yiqian@swmu.edu.cn

*Contributed equally

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Contents

1. Introduction

Extracellular vesicles (EVs) are spherical bilayer membrane vesicles (1). They can be divided into three subgroups according to their diameter: Exosomes, microvesicles and apoptotic bodies (2,3). Studies have demonstrated that EVs contain various bioactive substances, including functional proteins, RNA molecules, lipids and metabolites (4,5). EVs can be secreted by almost all types of cells, and mediate communications among different types of cells, cell microenvironments, distant organs and tissues by delivering these contents (6,7). For example, cancer cell-derived exosomal NOP16 nucleolar protein has been shown to promote colorectal cancer liver metastasis by reprogramming lipid metabolism in cancer-associated fibroblasts (8). Activated T-cell-derived exosomal programmed cell death protein 1 has been shown to attenuate programmed death-ligand 1-induced immune dysfunction in triple-negative breast cancer (9). It has been proven that 80% of the proteins in EVs are highly conserved among different cells. These proteins, including cytosolic protein ALG-2-interacting protein X and cell surface protein CD63, can also be used as biomarkers for EVs (10,11). However, the proteins or RNA contents of EVs are also markedly altered under pathological conditions. For example, Zhang *et al* (12) reported that exosomes derived from ovarian cancer patient plasma contained tumor-specific proteins associated with tumorigenesis and metastasis. Exosomal circular RNA (circRNA) expression patterns have been shown to differ between patients with cancer and healthy controls (13,14). Furthermore, tumor-originated exosomal lnc-UEGC1 has been shown to be significantly upregulated in gastric cancer, exhibiting an area under the curve of 0.876 in discriminating patients

with early-stage gastric cancer from healthy individuals (15). circRNA Serpin family E member 2 (cSERPINE2) has been found to be upregulated in breast cancer-derived exosomes, and a PLGA-based nanoparticle loaded with si-cSERPINE2 was shown to have a notable efficiency in attenuating breast cancer progression *in vivo* (16). These studies have indicated that the specific contents of exosomes have potential value in tumor diagnosis or treatment; however, the regulatory mechanisms underlying the sorting of these specific contents by exosomes remain unclear.

Recent research has revealed that RNA-binding proteins (RBPs) have a special function in regulating the contents of exosomes. RBPs are a diverse class of proteins capable of binding to RNA molecules, including mRNAs, microRNAs (miRNAs/miRs) and others (4). This family of proteins consists of >2,000 members and plays a critical role in all aspects of RNA-driven processes, ranging from RNA transcription and maturation to translation processes (17,18). RBPs affect these processes by forming single protein-RNA element interactions or recruiting multiple RBPs to form protein-RNA complexes. Critical RBP functions include the regulation of RNA metabolism, including RNA splicing (19), mRNA stability (20), translation process to proteins (21), intracellular localization (22) and co-operation with non-coding RNAs (23,24). The ectopic expression of RBPs contributes to the development of various diseases, particularly in tumorigenesis by stabilizing mRNAs or inducing alternative splicing (25,26). Recently, RBPs were also reported to be localized in EVs and to be associated with disease progression. For example, insulin like growth factor 2 mRNA binding protein (IGF2BP)1 has been reported to be overexpressed in EVs of colorectal cancer and may serve as a biomarker for tumor diagnosis (27). Mancarella *et al* (28) found that IGF2BP3 affected the miRNA cargo profile of EVs in Ewing sarcoma and then contributed to cell migration by regulating the PI3K/Akt pathway in neighboring cells. Furthermore, RBPs have been reported to regulate the sorting process of RNA molecules into EVs. Zhang *et al* (29) reported that hnRNP, heterogeneous nuclear ribonucleoprotein (hnRNP)A1 regulated the transfer of miR-522 to the EVs of cancer-associated fibroblast (CAFs) and promoted the progression of gastric cancer. hnRNPA2B1 mediates the loading of lymph node metastasis-associated transcript 2 (LNMAT2) into bladder cancer cell-secreted EVs and promotes tumor lymphatic metastasis (30). Furthermore, it has been shown that hnRNPH1 is upregulated in castration-resistant prostate cancer cells, and that the inhibition of hnRNPH1 contributes to the reduced EV biogenesis and secretion (31). These results indicate a novel function of EV-associated RBPs in regulating tumorigenesis, and these RBPs may serve as potential targets for cancer diagnosis and treatment.

The present review aimed to provide an overview of the current understanding of the role of EV-associated RBPs in tumorigenesis. Specifically, the EV-transported RBPs and their functions in recipient cells, the function of these EV-associated RBPs in the sorting processes of RNAs into EVs, as well as the specific function of these RBPs in tumorigenesis and their clinical value in cancer diagnosis, are summarized herein. Finally, the potential value of engineered EVs in cancer treatment is discussed. The EVs discussed herein are referred to as exosomes, as they did not involve apoptosis bodies. Information regarding apoptosis bodies has been previously discussed (32-34).

2. RBPs in EVs and their function in recipient cells

Studies have reported that some RBPs can localize in EVs and be transported to recipient cells, and subsequently affect the biological process of recipient cells and contribute to tumorigenesis (35-38). These are summarized in Table I.

First, the EVs deliver some RBPs to recipient cells, which then induce oncogene expression. For example, it has been found that Y-box binding protein 1 (YBX1) can be transferred by gastric cancer exosomes and promote angiogenesis by enhancing the expression of angiogenic factors in receipt vascular endothelial cells (35). Wang *et al* (36) reported that embryonic stem cell-derived EVs containing hnRNPU were transferred into human coronary artery endothelial cells, and hnRNPU promoted VEGF expression in human coronary artery endothelial cells. In addition, Qin *et al* (37) demonstrated that gallbladder cancer cell-derived EVs promoted macrophage M2 polarization, induced the malignant behavior of gallbladder cancer cells by carrying IGF2BP3 and increased the expression level of p-STAT3.

Secondly, EVs transport RBPs to recipient cells and regulate the stability of targeted mRNA. Fang *et al* (38) reported that IGF2BP2 was secreted by lung squamous cell carcinoma cell exosomes and absorbed by endothelial cells, thereby improving the stability of Fms-related receptor tyrosine kinase 4 mRNA, activating the PI3K-Akt signaling pathway, and eventually promoting angiogenesis and metastasis. Furthermore, colon cancer cell-derived EVs containing human antigen R (HuR) have been found to promote the proliferation of lung cells by stabilizing c-Myc mRNA and HuR associated with lung metastasis in patients with colon cancer (39). In addition, serum-derived EVs have been shown to deliver hnRNPC to non-small lung cancer cells, wherein hnRNPC recognizes the m6A modification of DLG associated protein 5 mRNA, ultimately promoting cancer cell growth and metastasis (40). In addition, hnRNPA1 can be SUMOylated, and then packaged and transported to lymphatic endothelial cells, thus stabilizing prospero homeobox 1 mRNA and promoting lymphangiogenesis and lymph node metastasis in pancreatic cancer (41).

Finally, EVs can deliver some RBPs that function as splicing factors to recipient cells and regulate the alterative splicing of target genes. For example, Pavlyukov *et al* (42) found that RBM11 RNA binding motif protein 11 could be transferred by EVs and promoted the malignancy of glioblastoma by switching the splicing of MDM2 homolog MDMX and cyclin D1. Moreover, Zhang *et al* (43) reported that multiple myeloma-derived exosomes delivered splicing factor SWAP homolog (SFRS8) into osteoclasts, and SFRS8 promoted multiple myeloma malignancy and bone lesion by alterative splicing of calcyclin-binding protein.

3. RBPs in EV cargo sorting

RBPs in EVs directly affect the functions of recipient cells to promote tumor progression; however, recent studies have also highlighted that the critical role of RBPs is to determine the enrichment of selected RNA transcripts into EVs (44-48).

Table I. Extracellular vesicle-transported RBPs and their functions in recipient cells.

RBPs	Cancer type	Originated cells	Recipient cells	Function	(Refs.)
Y-box binding protein 1	Gastric cancer	Cancer cells	Vascular endothelial cells	Promoted expression of angiogenic factors, promoted angiogenesis	(35)
hnRNPU	-	Embryonic stem cells	Coronary artery endothelial cells	Regulate VEGF transcription, promoted proliferation and migration	(36)
IGF2BP3	Gallbladder cancer	Cancer cells	Macrophages	Promoted p-STAT3 expression, promoted malignant progression	(37)
IGF2BP2	Lung squamous cell carcinoma	Cancer cells	Endothelial cells	mRNA stability, promoted angiogenesis and metastasis	(38)
Human antigen R	Colon cancer	Cancer cells	Bronchial epithelial cells	mRNA stability, promoted proliferation and metastasis	(39)
hnRNPC	Non-small cell lung cancer	Serum	Cancer cells	mRNA stability, promoted cell growth and metastasis	(40)
hnRNPA1	Pancreatic cancer	Cancer cells	Lymphatic endothelialcells	mRNA stability, promoted lymphan-giogenesis and lymph node metastasis	(41)
RNA binding motif protein 11 (RBM11)	Glioblastoma	Cancer cells	Cancer cells	RNA splicing, promoted malignancy progression	(42)
Splicing factor SWAP homolog	Multiple myeloma	Cancer cells	Osteoclasts	RNA splicing, promoted malignancy progression	(43)

RBPs, RNA-binding proteins; hnRNP, heterogeneous nuclear ribonucleoprotein; IGF2BP3, insulin like growth factor 2 MRNA binding protein 3.

These RBPs include members of the hnRNP family, YBX1, IGF2BPs and HuR. The functions of these EV-localized RBPs in transcript sorting are summarized in Fig. 1 and Table II.

RBPs in in regulating cargo sorting

hnRNP family members in regulating cargo sorting. Human hnRNPs consist of 20 proteins with differential RNA-binding capacities. The RNA recognition motif (RRM) of hnRNPs allows them to bind with RNAs and modulate RNA metabolisms. Several RBPs participate in the sorting process of specific RNA molecules into EVs (44-48).

Firstly, hnRNPA2B1 has been reported to be associated with the recruitment of RNA into EVs and to play a crucial role in herpes simplex virus 1 release from infected cells (44). In addition, Villarroya-Beltri *et al* (45) revealed that hnRNPA2B1 controlled the sorting of miR-198 and miR-601 into EVs by binding to specific GGAG/UGCA motifs. The promotion of the sorting of miR-17 and miR-93 into EVs by hnRNPA2B1 has been shown to be dependent on its binding with AGG/UAG motifs (46,47).

Secondly, hnRNPA1 is another key hnRNP involved in packaging RNAs into EVs. It regulates the transfer of miR-27b-3p to human umbilical vein endothelial cells, increasing blood vessel permeability and generating circulating tumor cells (48). Other hnRNPs have also been reported as a secreted factor in EVs. hnRNPQ has been reported to regulate the exosomal sorting of miRNAs, such as miR-3470a and miR-194-2-3p (49). Hobor *et al* (50) demonstrated that the N-terminal of hnRNPQ may mediate the recognition and exosomal partitioning of miRNA targets. Kim *et al* (51) reported that hnRNPQ also regulated the sorting of miR-137 into EVs in the dorsal striatum. Moreover, Robinson *et al* (52) reported that hnRPNK could recruit AsUGnA motif-containing miRNAs and cause their release within EVs. Gao *et al* (53) revealed a physical interaction between hnRNPK and lncRNA 91H, indicating that hnRNPK may mediate the EV-induced sorting of lncRNA 91H. Leidal *et al* (54) reported the involvement

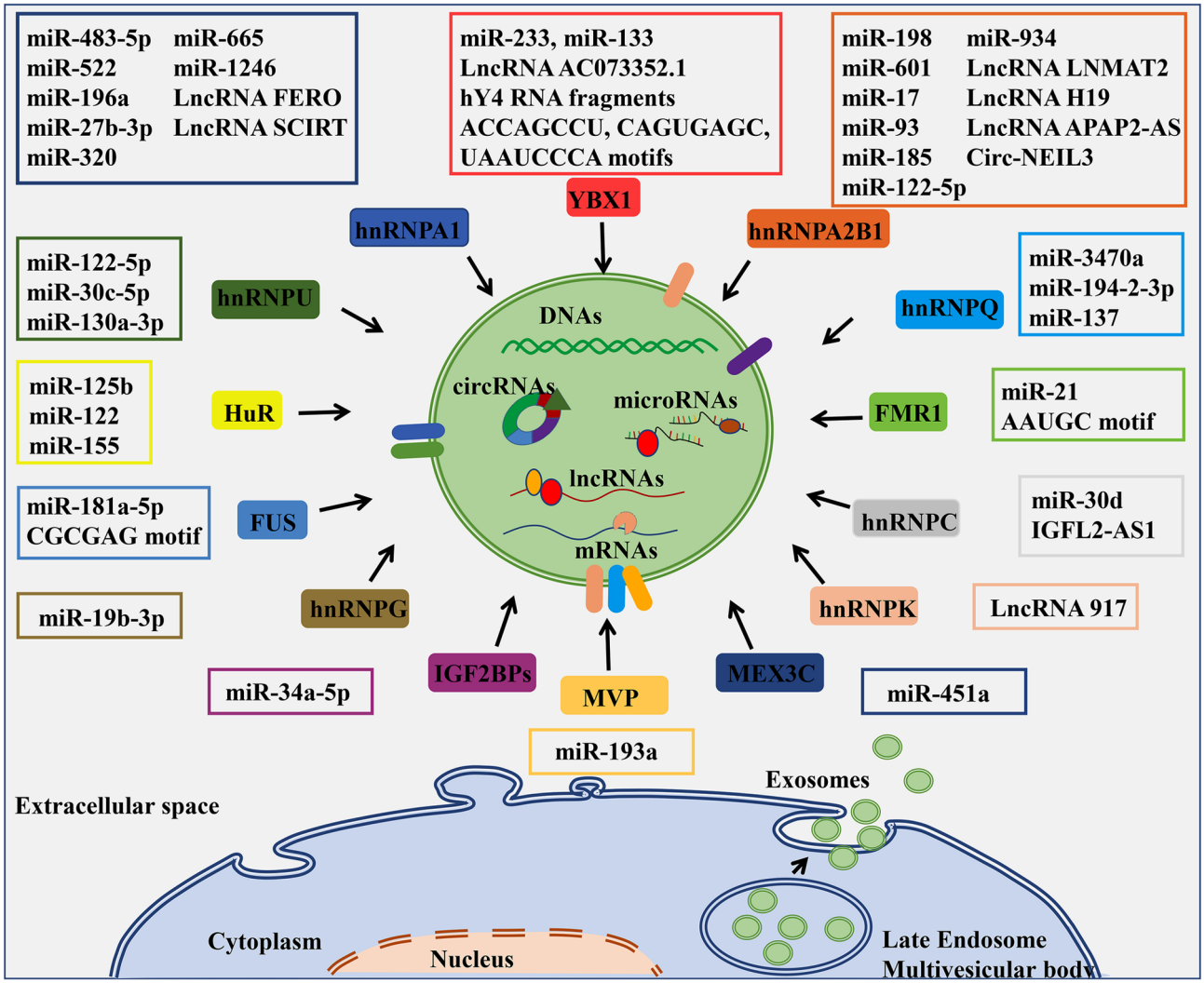

Figure 1. Functions of EV-localized RBPs in transcript sorting. RBPs, including members of the hnRNP family, YBX1, IGF2BPs, HuR and others, have been reported to be associated with the recruitment of RNA into EVs (44-45,58,64,74). Solid rectangles of various colors represent different RBPs; the hollow rectangles of the same color as RBP represent the RNA sorted by this RBP; the green double layer membrane structure circle represents EVs. EVs, extracellular vesicles; RBPs, RNA binding proteins; hnRNP, heterogeneous nuclear ribonucleoprotein; YBX1, Y-box binding protein 1; IGF2BPs, insulin-like growth factor 2 mRNA-binding proteins; HuR, human antigen R; FUS, fused in sarcoma; MVP, major vault protein; MEX3C, muscle excess 3 RNA binding family member C; FMR1, fragile X messenger ribonucleoprotein 1; SCIRT, stem cell inhibitory RNA transcript; lncRNA, long non-coding RNA.

of hnRNPK in the specific LC3-conjugated EV loading and secretion machinery. Furthermore, Statello *et al* (55) reported that hnRNPH1 facilitated the transport of RNAs into EVs and the maintenance of RNAs inside EVs. Hosen *et al* (56) reported that hnRNPU encapsulated miR-122-5p into EVs and then regulated the viability and apoptosis of cardiomyocytes. Balaguer *et al* (57) reported that hnRNPC1 may control miR-30d levels in endometrial exosomes.

YBX1 in tumor cells. YBX1, also known as YB1, is a protein that functions as both a DNA and RBP. Recent studies have revealed that it plays a crucial role in the regulation of mRNA packaging into EVs (58-61). Kossinova *et al* (58) demonstrated that YBX-1 binds specifically to potential RNA sorting motifs, including ACCAGCCU, CAGUGAGC and UAAUCCCA in EVs derived from 293 cells. Furthermore, Shurtleff *et al* (62) found that YBX-1 was required for the sorting of miRNAs into EVs, such as miR-233. They also reported that YBX-1 mediates miRNA sorting in a phase separation-dependent manner, promoting the local enrichment of YBX-1 and its cognate RNAs, enabling their targeting and packaging by vesicles (63).

IGF2BPs in RNA exosomal sorting. IGF2BPs consist of three members: IGF2BP1, IGF2BP2 and IGF2BP3. The RRM domains and hnRNPK homology domains allow them to bind with RNAs (64). Recently, Chen *et al* (65) reported that EVs carry distinct proteo-transcriptomic signatures, including IGF2BP2, that differ from their cancer cell of origin. Mizutani *et al* (66) also revealed the interaction between IGF2BP3 and exosome using co-immunoprecipitation analysis, indicating the potential role of IGF2BPs in sorting of RNAs into EVs. IGF2BP3 is involved in the methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit-mediated m6A modification of pre-miR-34A and the secretion of exosomal miR-34a-5p in mesenchymal stem cells (67).

Fused in sarcoma (FUS) in RNA exosomal sorting. The human FET family of RBPs includes FUS, TATA-box binding protein associated factor 15 and EWS RNA-binding

Table II. RBPs regulating the sorting of RNA molecules into extracellular vesicles.

RBPs	Cancer type	Originated cells	Recipient cells	RNA	Function	(Refs.)
hnRNPA2B1	NSCLC	Cancer cells	Liver cells	miR-122-5p	Promoted tumor progression	(82)
hnRNPA2B1	Colorectal cancer	Cancer cells	Macrophages	miR-934	Promoted tumor metastasis	(83)
hnRNPA2B1	Bladder cancer	Cancer cell	Lymphatic endothelial cells	Lymph node metastasis-associated transcript 2	Promoted tumor lymphatic metastasis	(30)
hnRNPA2B1	Breast cancer	Trastuzumab-resistant cells	Trastuzumab-sensitive cells	lncRNA AGAP2 antisense RNA 1	Inhibited apoptosis	(84)
hnRNPA2B1	NSCLC	Gefitinib-resistant cells	Gefitinib- sensitive cells	lncRNA H19	Induced drug resistance	(85)
hnRNPA2B1	Glioma	Cancer cells	Macrophages	Circ-nei like DNA glycosylase 3	Promoted tumor progression	(86)
hnRNPA2B1	Hepatocellular carcinoma	Cancer cells	$CD8^+$ T-cells	Circ-cell cycle and apoptosis regulator 1	Induced immune evasion	(87)
hnRNPA2B1	Prostate cancer	Cancer cells	Macrophages	miR-378a-3p	Promoted tumor migration	(88)
hnRNPA1	Colorectal cancer	Cancer cells	HUVECs	miR-27b-3p	Promoted tumor metastasis	(48)
hnRNPA1	Gastric cancer	CAFs	Cancer cells	miR-522	Induced drug resistance	(29)
hnRNPA1	Gastric cancer	Cancer cells	Cancer cell	Ferroptosis-associated lncRNA	Induced drug resistance	(89)
hnRNPA1	Bladder cancer	Cancer cells	Lymphatic endothelial cells	Brain cytoplasmic RNA 1	Promoted tumor metastasis	(90)
hnRNPA1	Prostate cancer	DOX-resistant cells	DOX-sensitive cells	Long intergenic non-protein coding RNA, regulator of reprogramming	Regulated drug resistance	(91)
hnRNPA1	Head and neck cancer	CAFs	Cancer cells	miR-196a	Induced drug resistance	(106)
hnRNPA1	Leukemia	Cancer cells	Bone marrow mesenchymal stem cells	miR-320	Promoted tumorigenesis	(107)
hnRNPA1	NSCLC	Cancer cells	Cancer cells	Stem Cell Inhibitory RNA Transcript	Promoted tumor metastasis	(92)
hnRNPA1	Glioma	Cerebrospinal fluid	Myeloid-derived suppressor cells	miR-1246	Regulated tumor progression	(93)
hnRNPK	Prostate cancer	Cancer cells	Osteoblasts	-	Promoted metastasis	(52)
hnRNPU	-	Serum	Human coronary artery endothelial cells	miR-30c-5p	-	(108)
RBMX	Lung squamous cell carcinoma	Cancer cells	Macrophages	miR-19b-3p	Promoted tumor metastasis	(94)
hnRNPC	Renal cell carcinoma	Sunitinib-resistant cells	Sunitinib-sensitive cells	IGFL2 antisense RNA 1	Induced drug resistance	(95)

Table II. Continued.

RBPs	Cancer type	Originated cells	Recipient cells	RNA	Function	(Refs.)
hnRNPC	head and neck squamous cell carcinoma	Cancer cells	Macrophages	Anilin actin binding protein-210	Promoted proliferation and progression	(96)
YBX1	Breast cancer	Cancer cells	HUVECs	AC073352.1	Promoted metastasis and angiogenesis	(97)
YBX1	NSCLC	Cancer cells	-	hY4	Promoted tumor progression	(98)
Insulin-like growth factor 2 mRNA-binding proteins 1	Melanoma	Cancer cells	$CD45^+$ cells	-	Promoted tumor metastasis	(99)
Fused in sarcoma	Colorectal cancer	Cancer cells	Hepatic stellate cells	miR-181a-5p	Promoted tumor metastasis	(101)
Major vault protein	Colon cancer	Cancer cells	Cancer cells	miR-193a	Promoted tumor progression	(103)

RBPs, RNA-binding proteins; NSCLC, non-small cell lung cancer; hnRNP, heterogeneous nuclear ribonucleoprotein; CAF, cancer-associated fibroblast; miR, microRNA; HUVECs, human umbilical vein endothelial cells; lncRNA, long non-coding; DOX, docetaxel; YBX1, Y-box binding protein 1.

protein 1 (68), with FUS containing a Gly-rich domain, an RRM domain, two arginine/glycine-rich domains and a zinc finger motif. It has been reported that FUS is present in amyotrophic lateral sclerosis muscle vesicles and can induce cellular toxicity in recipient cells (69). Additionally, FUS has been found in EVs and can bind to RNAs containing enriched GUGGU or GUU motifs (70,71), suggesting its role in RNA exosomal sorting. Recently, Garcia-Martin *et al* (72) demonstrated that FUS and Aly/REF export factor (ALYREF) were involved in the exporting miRNAs carrying CGGGAG motifs. FUS and ALYREF have been reported to regulate the distribution of miRNAs into EVs, and this regulation is associated with senescence and aging (73).

HuR in RNA exosomal sorting. HuR belongs to the embryonic lethal abnormal vision family of RBPs and has three RRM domains. It increases the stability of target mRNAs by binding to the AU-rich elements. It was recently reported that HuR may have a function in EVs, with diabetic milieu stimulating HuR nuclear-to-cytoplasmic translocation and EV transfer in cardiac- and cultured bone marrow-derived macrophages (74). HuR has also been shown to enhance the exosomal export of miR-125b in response to ultraviolet irradiation (75) and accelerate the EV-mediated export of miR-122 in starved human hepatic cells (76). Furthermore, Li *et al* (77) developed a novel strategy for enhanced RNA cargo encapsulation into engineered EVs using the fused CD-9-HuR to successfully enrich miR-155 into EVs. In addition, lysosome-associated membrane protein 2 (LAMP2)-HuR fusion protein-engineered exosomes have been shown to recruit specific RNA to lysosomes for targeted degradation (78).

Other RBPs in RNA exosomal sorting. Fragile X messenger ribonucleoprotein 1 (FMR1) is an RBP involved in mRNA transport from the nucleus to the cytoplasm. Recently, Wozniak *et al* (79) found that FMR1 controlled the EV loading of miRNAs with the AAUGC motif during inflammation. Muscle excess 3 RNA binding family member C has been found to promote the exosomal sorting of miR-451a (80). Major vault protein (MVP) has been shown to facilitate the transport of RNAs into EVs (55). Luo *et al* (81) found that MVP expression was higher in astrocytes than in neurons and regulated the sorting of miRNAs with a GUAC motif into astrocytic EVs. These data suggest that RBPs play key roles in mediating RNA exosomal sorting and indirectly affect the function of recipient cells.

Role of RBPs from tumor cells in regulating cargo sorting. RBPs in tumor cells regulate the cargo sorting of RNA molecules into tumor derived EVs. For example, Li *et al* (82) found that hnRNPA2B1 mediated the sorting of miR-122-5p into lung cancer cell-derived EVs, promoting tumor progression. hnRNPA2B1 has also been shown to mediate the packaging of miR-934 into EVs of in cancer cells, inducing macrophage M2 polarization and liver metastasis (83). Furthermore, hnRNPA2B1 regulates the loading of LNMAT2 into bladder cancer cell-secreted EVs, promoting lymphatic metastasis (30). Zheng *et al* (84) revealed that hnRNPA2B1 mediated the secretion of lncRNA AGAP2 antisense RNA 1 outside of cells by EVs, inhibiting trastuzumab-induced cell cytotoxicity in breast cancer cells. hnRNPA2B1 has also been found to mediate the packaging process of lncRNA H19 into tumor-derived EVs, inducing gefitinib resistance in non-small

cell lung cancer (NSCLC) (85). Moreover, hnRNPA2B1 has been shown to promote the packaging of circ-nei like DNA glycosylase 3 into EVs, which are then transmitted to infiltrated tumor-associated macrophages, inducing immunosuppressive properties and glioma progression (86). In addition, hnRNPA2B1 mediates the EV secretion of circ-cell cycle and apoptosis regulator 1 of hepatocellular carcinoma cells and promotes $CD8^+$ T-cell dysfunction and anti-PD1 resistance (87). Wang *et al* (88) reported that hnRNPA2B1 regulated the enrichment of miR-378a-3p in tumor-derived EVs and then promoted bone metastasis of prostate cancer by activating the Dyrk1a/Nfatc1/Angptl2 axis in bone marrow macrophages.

It has been demonstrated that hnRNPA1 expression is upregulated by chemotoxicity and is involved in ferroptosis-associated lncRNA packaging into EVs, leading to enhanced stemness and acquired chemoresistance in gastric cancer cells (89). Zheng *et al* (90) found that hnRNPA1 regulated the sorting of lnc-brain cytoplasmic RNA 1 into tumor-derived exosomes and contributed to lymphatic metastasis of bladder cancer by activating the WNT5A/VEGF-C/VEGFR3 axis. Moreover, Jiang *et al* (91) reported that long intergenic non-protein coding RNA, regulator of reprogramming was packaged into EVs in an hnRNPA1-dependent manner and then disseminated the docetaxel resistance phenotype to receipt cells in prostate cancer. Furthermore, Wang *et al* (92) demonstrated that hnRNPA1 assisted the exosomal loading of lncRNA stem cell inhibitory RNA transcript and miR-665 in lung cancer cells, promoting cancer cell metastasis. Moreover, hnRNPA1 has been shown to promote the selective packaging of miR-1246 into glioma-derived EVs, driving the differentiation and activation of myeloid-derived suppressor cells (93).

hnRNPG promotes the packaging of miR-19b-3p into lung adenocarcinoma cell-derived exosomes, facilitating M2 macrophage polarization and tumor metastasis (94). Pan *et al* (95) reported that hnRNPC regulated the packaging of IGFL2 antisense RNA 1 (IGFL2-AS1) into EVs and contributed to the sunitinib resistance in renal cell carcinoma. Moreover, Guo *et al* (96) found that hnRNPC contributed to the exosome transfer of ANL-210 to macrophages, and subsequently promoted macrophage polarization and stimulated the growth of head and neck squamous cell carcinoma. Furthermore, YBX1 has been shown to promote the metastasis and angiogenesis of breast cancer by binding and packaging the lncRNA AC073352.1 into EVs (97). Li *et al* (98) demonstrated that YBX1 promoted the progression of lung cancer by selectively sorting hY4 RNA fragments into EVs. Ghoshal *et al* (99) suggested that IGF2BP1 was intimately involved in regulating the cargo of EVs, affecting the pro-metastatic function of melanoma-derived EVs. Of note, Latifkar *et al* (100) recently reported that IGF2BP2 promoted tumor cell survival and invasiveness by increasing the release of EVs enriched in ubiquitinated protein cargo and soluble hydrolases. Furthermore, FUS has been shown to mediate the packaging of miR-181a-5p into colorectal cancer cell-derived EVs, which in turn persistently activate hepatic stellate cells, remodeling the tumor microenvironment and promoting liver metastasis (101). In addition, Teng *et al* (102) revealed that MVP regulated the exosomal sorting of miR-193a and promoted colon cancer progression.

Role of RBPs from tumor-associated cells in regulating cargo sorting. In the tumor microenvironment, EVs mediate communications among cancer cells, tumor-associated fibroblasts, tumor-associated macrophages, tumor-associated endothelial cells and tumor-associated adipocytes (103). Therefore, in addition to RBPs in tumor cells, RBPs in tumor-associated cells can also affect the functions of tumor cells by regulating RNA sorting into EVs originating from the tumor microenvironment. A previous study demonstrated that the exosomal transfer of miR-185 from vascular smooth muscle cells to endothelial cells was controlled by hnRNPA2B1 (104). Furthermore, hnRNPA1 has been found to mediate the exosomal sorting of miR-483-5p out of renal tubular epithelial cells (105), and to promote the transfer of miR-522 into the EVs of CAFs, suppressing ferroptosis and promoting chemotherapy resistance in gastric cancer (29). Furthermore, hnRNPA1 facilitates the packaging of miR-196a into CAF-derived EVs, conferring cisplatin resistance in head and neck cancer by regulating cyclin dependent kinase inhibitor 1B and inhibitor of growth family member 5 (106). hnRNPA1 has also been found to be involved in the regulation of the exosomal transfer of miR-320 from leukemia cells to bone marrow stromal cells and is a critical mediator of leukemia progression (107). Moreover, hnRNPU has been reported to retain miR-30c-5p, miR-130a-3p and other miRNAs, preventing their export into large EVs in endothelial cells (108,109). YBX-1 mediates the sorting of miR-133 into EVs derived from hypoxia/reoxygenation-induced human endothelial progenitor cells, which increases fibroblast angiogenesis and mesenchymal-endothelial transition (110). Furthermore, Shaban *et al* (111) reported that the expression of miR-21 in EVs from senescent endothelial cells was associated with elevated FMR1 expression. In addition, Brossa *et al* (112) reported that RBP Annexin A2H existed on the surface of EVs isolated from human liver stem cells. Annexin A2H bound to miR-145, protecting it from ribonuclease digestion, and then more effectively inhibited the invasive properties of cancer stem cells (112).

4. Exosome-RBP-based strategies for diagnosis and therapy

As aforementioned, RBPs can be delivered by EVs to recipient cells and can play critical roles in non-coding RNA sorting in EVs, contributing to tumorigenesis. The contained RBPs are derived from tumor cells or other tumor microenvironment-associated cells, and these characteristics suggest the possibility of the development of EV-RBP-based strategies for diagnosis and therapy. Tumor-derived EVs containing specific RBPs could function as novel cancer biomarkers, and targeting the RBP-mediated RNA molecule sorting process may be beneficial for cancer treatment.

Potential of exosomal proteins as novel cancer biomarkers. For a number of years, studies focused on non-coding RNAs of EVs as novel biomarkers for cancer diagnosis. However, the critical function of exosomal proteins has been neglected (113). Melo *et al* (114) identified glypican-1, a cell surface proteoglycan, specifically enriched on cancer cell-derived EVs, which may serve as a potential non-invasive diagnostic marker for the detection of

Table III. Potential clinical applications of extracellular vesicle-associated RBPs in cancer.

RBPs	Cancer type	Role in	Potential application	(Refs.)
Insulin-like growth factor 2 mRNA-binding proteins 1	Colorectal cancer	Poor prognosis	Diagnostic/prognostic biomarker	(27)
Nucleolin	Nasopharyngeal carcinomacancer	Poor prognosis	Diagnostic biomarker	(117)
Human antigen R	Lung cancer	Poor prognosis	Diagnostic biomarker	(39)
hnRNPC	Renal cell carcinoma	Poor prognosis	Prognostic indicator/ Therapeutic target	(95)
hnRNPA1	Colorectal cancer	Poor prognosis	Metastasis biomarker	(48)
hnRNPA1	Glioma	Recurrence rate	Therapeutic target	(93)
hnRNPA2B1	Bladder cancer	Lymphatic metastasis	Therapeutic target	(30)
hnRNPA2B1	Non-small cell lung cancer	Gefitinib resistance	Therapeutic target	(85)
hnRNPA2B1	Breast cancer	Trastuzumab resistance	Therapeutic target	(84)
Y-box binding protein 1	Gastric cancer	Angiogenesis	Diagnostic biomarker/ Therapeutic target	(35)
Major vault protein	Colon cancer	Poor prognosis	Therapeutic target	(103)
Poly(A) binding protein cytoplasmic 1	Esophageal squamous cell carcinoma	Poor prognosis	Therapeutic target	(118)

RBPs, RNA-binding proteins; hnRNP, heterogeneous nuclear ribonucleoprotein.

early stages of pancreatic cancer. Recently, using liquid chromatography-mass spectrometry, Yeung *et al* (115) found that circadian-synchronized tendon fibroblasts release small EVs enriched in RBPs (115). Furthermore, Uzbekova *et al* (116) found numerous RBPs within follicular fluid EVs that originated from follicular and other cells; the different expression patterns of these RBPs may affect oocyte competence. Kuhn *et al* (27) reported that IGF2BP1 could directly enter EVs in a transformation-dependent manner, regulate the progression of colorectal cancer and serve as a diagnostic/prognostic circulating tumor biomarker. Xing *et al* (117) analyzed the proteins of circulating tumor-derived EVs from 50 μl serum and revealed the potential application of nucleolin$^+$ EVs for nasopharyngeal carcinoma cancer diagnosis. Zhang *et al* (118) found that poly(A) binding protein cytoplasmic 1 (PABPC1) bound to miR-21-5p via an ACUGAUG sequence to direct miR-21-5p packaging into EVs, and that an elevated PABPC1 expression was associated with tumor cell differentiation and a poor prognosis of patients. Furthermore, tumor-secreted proteins are often degraded or diluted in the circulating blood. However, these proteins can be well-enriched and protected within tumor-derived EVs, enabling the easy detection and in-depth analysis of relevant tumors (119,120). Proteins in EVs can be more straightforward and representative, and may provide comprehensive information about the distal primary parent tumor cells compared with miRNAs (113,121). These features suggest that proteins in EVs have potential value for use in disease diagnosis. These proteins and their potential clinical applications in cancer diagnosis and target treatments are summarized in Table III.

Engineered EVs for cancer treatment. It has been well-illustrated that EVs can function as novel delivery platforms of RNAs, particularly miRNAs and/or siRNAs for cancer therapy. However, their loading efficiency is limited. Recent studies have reported that the loading efficiency of EVs can be improved by constructing engineered EVs with a fusion protein of exosomal membrane proteins and RBPs that select and sort specific RNAs into EVs. For example, Li *et al* (77) fused the exosomal membrane protein CD9 with the RBP HuR, and successfully enriched miR-155, functional miRNA inhibitor, or CRISPR/dCas9, which transport the AU-rich elements into EVs. They also reported that HuR could be fused to the C-terminus of LAMP2B (77). Another study demonstrated that EVs engineered with LAMP2B-HuR successfully decreased the abundance of RNA targets and significantly reduced liver fibrosis in a mouse model of CCl4-induced liver injury (78). Furthermore, EVs engineered with MS2 bacteriophage coat protein, a fusion protein, have been shown to successfully enrich the low density lipoprotein receptor (LDLR) mRNA into EVs and efficiently deliver LDLR to the liver cells, restore LDLR expression and ameliorate the phenotype of high LDL cholesterol, atherosclerosis and steatosis in the LDLR$^{-/-}$ mouse model (122). Wang *et al* (123) demonstrated that aptamer AS1411-modified EVs could deliver lethal-7 to breast cancer cells and inhibit cell proliferation by targeting binding nucleolin, which is highly expressed on the surface membrane of breast cancer cells. Furthermore, Es-Haghi *et al* (124) developed a fusion protein of the EV membrane protein CD9 and the RBP argonaute RISC catalytic component 2 (AGO2), and revealed that the engineered EVs exhibited significantly higher levels of miRNA or short hairpin RNA (shRNA; miR-466c

or shRNA-451, respectively). These results suggest that RBP-fusion protein-engineered EVs can potentially resolve the issue of the inefficient endogenous loading of cargo and have significant value for the future development of targeted cancer treatment.

RBPs inhibitors or decoy nucleic acids for cancer treatment. As described above, RBPs play a crucial role in the sorting of non-coding RNAs into EVs. It has also been proven that RBPs play a critical role in the formation of circRNAs and maturation of miRNAs, and then these non-coding RNAs are sorted into EVs. Recent studies have demonstrated that some small molecules can inhibit the functions of RBPs, which may serve as a potential strategy for cancer treatment. For example, MO-460 can bind to the C-terminal glycine-rich domain of hnRNPA2B1 and inhibit its binding with targeted transcripts (125). Pérez-Boza *et al* (126) reported that epirubicin disrupted the interaction between hnRNPA2B1 and miR-503, thereby affecting the exosomal sorting of miR-503. In addition, the expression of hnRNPA1 has been shown to be suppressed by the natural compound, quercetin (127), and the ubiquitin-proteasome-dependent degradation of hnRNPK has been found to be accelerated by the natural compound, nujiangexathone A (128). Furthermore, it has been demonstrated that the HuR inhibitor, MS-444, inhibits HuR dimerization and blocks the nucleocytoplasmic transport of targeted mRNA (129,130). Wallis *et al* (131) reported that a small molecule inhibited the binding of IGF2BP1 with the target mRNAs by interacting with the hydrophobic surface at the boundary of IGF2BP1 KH3 and KH4 domains.

On the other hand, certain RNA molecules can competitively bind with RBPs and subsequently suppress their carcinogenic function. Yu *et al* (132) reported that circ-TNPO3 competitively interacted with IGF2BP3; thus, the role of IGF2BP3 in stabilizing MYC mRNA was weakened, which inhibited the expression of MYC and its target snail family transcriptional repressor 1, thereby suppressing the proliferation and metastasis of GC. It has been reported that circ_0000079 decoys FMR1 autosomal homolog 1 (FXR1) to interrupt the formation of the FXR1/protein kinase C, iota complex, and suppresses the cell invasion and drug resistance of NSCLC (133). Wang *et al* (134) found that the administration of RNA decoys specifically targeting YB-1 in a mouse xenograft model of glioblastoma resulted in slower tumor growth and an improved survival. Furthermore, Barbagallo *et al* (135) identified a GAUGAA motif which could function as a decoy for serine and arginine rich splicing factor (SRSF)1, decrease the binding between SRSF2 and tumor suppressor circ-SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 5, and could subsequently regulate the migration and angiogenesis of glioblastoma multiforme. These results indicate that both RBP inhibitors and RBP decoy nucleic acids can suppress the function of RBPs and may be used for targeted cancer treatment.

5. Conclusions and future perspectives

The number of studies on EVs have markedly increased over the last decade since they were identified in the 1980s (1). EVs have been proven to play a crucial role in cellular communication and regulate the phenotype of recipient cells by delivering specific contents. A number of studies have focused on non-coding RNAs in EVs and the regulatory mechanisms whereby cells can selectively control their non-coding RNA cargo. According to current research, there are four potential modes of miRNA sorting into EVs: The neural sphingomyelinase 2-dependent pathway, the miRNA-induced silencing complex-related pathway, the 3' miRNA sequence-dependent pathway, and the miRNA motif-dependent pathway (136,137). However, the specifics of these mechanisms remain largely unclear. Studies have demonstrated that RBPs play a critical role in selectively sorting non-coding RNAs and facilitating their transfer into EVs (45,72). Of note, the selective shuttling of non-coding RNAs into EVs directly influences the pathological process of various diseases. Moreover, the dysregulation of RBPs has been proven to be associated with the development of diseases, particularly cancer (138). These studies have indicated that RBPs may influence the pathological process of disease by regulating the selective sorting of non-coding RNAs into EVs (136-138).

RBPs can be used for cancer diagnosis and targeted cancer treatment due to their specific functions in EVs. First, RBPs in EVs can provide more straightforward, representative and comprehensive information about the distal primary parent tumor cells, as compared with non-coding RNAs. These proteins are enriched and protected in EVs, enabling the easy detection and in-depth analysis of relevant tumors, and thus rendering them ideal biomarkers for cancer diagnosis (65). Hu *et al* (113) reported that exosomal proteins have potential value as novel cancer biomarkers for liquid biopsy. Fuji *et al* (139) revealed that the detection of serum-derived AGO2 exosomes could monitor the tumor dynamics of colorectal cancer patients during chemotherapy. Secondly, the sorting of tumor suppressor non-coding RNAs could be modulated by the overexpression of specific RBPs, and the sorting of oncogenic non-coding RNAs could be suppressed by RBPs inhibitors. Furthermore, a number of RNA motifs have been reported to be recognized by RBPs and sorted into EVs, which can be used for RNA interference-dependent gene therapy. In addition, the loading efficiency could be improved by constructing engineered EVs in which a special RBP is overexpressed.

As aforementioned, the study of EVs began in the 1980s (1), and the sorting mechanisms of non-coding RNAs remain unclear. The function of RBPs in EVs have not been studied in depth, and further studies are required in order to be able to draw stronger conclusions. Although bioengineered EVs for cancer treatment have already been validated in mouse models, additional *in vivo* research is required for more definitive conclusions and the development of these therapies for clinical use.

In conclusion, the present review underlines the current knowledge of RBPs in EVs, and discusses their potential value in cancer diagnosis and target treatment. RBPs have a specific function in regulating the EV sorting of RNA molecules and affecting tumorigenesis, and have notable clinical value for cancer diagnosis and treatment. Specifically, RBPs in EVs have potential applications for liquid biopsy. To the best of our knowledge, this topic is novel, and herein, EVs, RBPs and tumorigenesis were discussed in combination for the first time. However, their

functions and regulatory mechanisms remain complex and are not yet completely understood. Further studies will hopefully enable their clinical use. It is considered that following further research, more accurate conclusions will be drawn.

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Availability of data and materials

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Authors' contributions

WeichaoS was responsible for writing the original draft, writing, reviewing and editing the final manuscript, and funding acquisition. HC was responsible for writing the original draft and funding acquisition. TX revised the manuscript, tables and figure. JY, JL and WY were responsible for editing the manuscript. WeiS was responsible for the conceptualization, writing, reviewing and editing of the manuscript. QY was responsible for the conceptualization, writing, reviewing and editing of the manuscript, and funding acquisition. WeichaoS and HC contributed equally to the study. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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