We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Novel Implications of Exosomes and lncRNAs in the Diagnosis and Treatment of Pancreatic Cancer

Jin Wang, Xuan Zhang, Chunxia Ji, Lei Zhang,
Yang Di, Wenhui Lou, Xiaoyan Zhang and
Jianqing Xu

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.69510>

Abstract

Pancreatic cancer remains a leading cause of cancer-related deaths. Most patients are present with advanced stages of the disease at the time of diagnosis; thus, surgery, which is the best curative option for this malignancy, is no longer an effective treatment modality for affected individuals. As a likely source of “liquid biopsies,” exosomes, which are secreted by fusing intracellular multivesicular bodies with cell membranes, have relative stability and composition, allowing them to cover the entire range of cancer-related biomarkers, including cellular proteins, lipids, DNA, RNA, miRNA, and long non-coding RNAs (lncRNAs). To explore the early detection biomarkers of pancreatic cancer and to develop successful therapeutic intervention for this disease, assessing the implications of exosomes in pancreatic cancer patients is essential. In this chapter, we wish to focus on the possibility of using exosomes and lncRNAs in the clinical management of patients with pancreatic cancer. We will discuss the mechanisms of tumor formation under the exosomal action, demonstrate how circulating exosomes and lncRNAs have come into the research spotlight as likely biomarkers of pancreatic cancer, and discuss the applications of exosomes as transfer vectors in tumor therapeutics.

Keywords: exosomes, lncRNA, pancreatic cancer, biomarkers, diagnosis, therapeutic intervention

1. Introduction

1.1. Exosomes, ncRNAs, and lncRNAs

Exosomes are a class of small (40–120 nm) extracellular vesicles (EVs) that originate in multivesicular endosomes [1–3] and can be released from a wide range of cells, including cancer cells [4]. Exosomes differ in size from microvesicles (50–1000 nm) and apoptotic bodies (800–5000 nm) and are secreted directly from the cell membrane in a budding form [5–7]. Late endosomes released from multivesicular bodies (MVBs) are integrated with the cell membrane in the extracellular matrix during the release of exosomes. Exosomes released into the extracellular environment can be utilized by tumor cells to alter the tumor microenvironment or to provide a favorable microenvironment for distant metastases by affecting distant organs [8–10]. Therefore, exosomes serve as efficient vehicles for long- and short-distance intercellular communication by signaling molecules in the form of lipids, proteins, DNA, RNAs, and non-coding RNAs (ncRNAs) [11]. Exosomes play an important role in signal transduction between cells.

In the complicated human genome, approximately 2% of the genomic sequence encodes proteins involved in biological progression [12], of which approximately 90% are ncRNAs. ncRNAs are described as the “noise” of the genome in their primary form, and they can be divided into two subgroups: small ncRNAs (sncRNAs) and long ncRNAs (lncRNAs) [13–16]. If RNA is <200 nt in length, the ncRNAs are defined as sncRNAs, which includes microRNAs (also called miRNAs or miRs). Conversely, long non-coding RNAs (lncRNAs) are >200 nt in length. Previous studies have reported that lncRNAs are involved in numerous physiological and pathological processes.

In recent years, an increasing number of lncRNAs have been investigated, and play a vital role in various major biological processes associated with promoting proliferation, invasion, and migration metabolism [17–19]. Increasing evidence points to important functional or regulatory roles of lncRNAs in cellular processes, including the cell cycle, proliferation, apoptosis [20–22], RNA processing [23], chromatin modification [24, 25], genomic reprogramming [26, 27], and gene imprinting [28]. They also play a role in cancers resulting from aberrant lncRNA expression. Recent findings indicate that lncRNAs are dysregulated in many kinds of cancer, including pancreatic cancer (PaCa), and they are closely related with tumorigenesis, metastasis, prognosis, and diagnosis.

2. The physiological function of exosomes

Exosomes carry a variety of substances from secreted cells, including proteins, lipids, DNA, RNA, and ncRNA [29, 30]. The intercellular communication regulated by exosomes is not only involved in regulating the physiological processes of normal cells but also participates in many pathological processes associated with disease development, including tumors [31–33]. Exosomes regulate biological activity through the rapid reaction of signal

molecules on their surface or by the release of extracellular biologically active substances. Exosomal biological activity is mainly determined by its components (i.e., the exosome cell source) [8–10]. Exosomes, which use autocrine, paracrine, and endocrine signaling to exchange biological information, are involved in the transmission of substances and signals between cells.

In addition, exosomes have immunomodulatory function [34]. Antigen-presenting cell (APC)-derived exosomes can promote the proliferation of T lymphocytes and induce anti-tumor immune responses *in vivo*. Exosomes have the features of their original cells because they bring DNA, RNA, and proteins from the original cell and carry a variety of proteins on their surface. Since exosomes are released from endosomes, they carry certain endosomal-specific proteins, including GTPases, flotillin, Alix, Tsg101, CD81 and CD82, heat shock proteins Hsp70 and Hsp90, and epithelial cell adhesion molecules [35–38] that are involved in exosome formation.

If exosomes are secreted by tumor cells, they can kill the tumor cells by providing information to cytotoxic T lymphocytes by cross-reacting with antigen-presenting cells [39]. However, exosomes from tumor cells have a dual role in that they have antitumor activity and also promote tumor growth. For example, exosomes from colorectal cancer cells contain cell cycle-related mRNAs that promote the proliferation of endothelial cells, which can induce tumor angiogenesis [40]. Exosomes obtained from gastric cancer cells promote tumor progression by activating the NF- κ B pathway in macrophages [41]. In ovarian cancer, epithelial ovarian cancer (EOC) cell-derived exosomes promote ovarian cancer metastasis and deterioration by transferring CD44 to peritoneal cells [42].

3. Exosomes as novel biomarkers of cancer

The identification of cancer-specific exosomes in bodily fluids, such as serum, plasma, and urine, will be useful for the detection of cancer and will allow for the identification of specific DNA, RNA, and protein content in the absence of contamination from non-cancerous exosomes [43]. The proteoglycan glypican-1 (GPC1) is highly expressed in tumor cell-derived exosomes. GPC1 has been shown to be a specific, sensitive marker in serum from pancreatic patients that are in both the early and late stages but not in benign pancreatic diseases [43]. CD24 and EpCAM are tumor-derived exosome markers isolated by immune-affinity techniques involving anti-CD24 and anti-EpCAM magnetic beads [44]. In serum, CD24 and EpCAM serve as early diagnosis biomarkers [44], while fibronectin can serve as an early diagnosis biomarker in plasma. The ELISA method has been used to detect fibronectin [45]. The levels of exosomal EDIL3 from breast cancer patients can be dramatically reduced with surgery, indicating that EDIL3 can also serve as a diagnostic and prognostic biomarker [46]. Survivin expression has been shown to be significantly increased in patients with prostate cancer, but lower survivin expression has been found in benign prostatic hyperplasia (BPH) and healthy subjects. Additionally, the levels of survivin in BPH and healthy subjects are not significantly different. Thus, survivin can be used as a new diagnostic indicator of prostate cancer [47].

Separated and purified exosomes not only contain mRNA and miRNA but also tRNA and some lncRNA [11, 48–50]. Six miRNAs (miR-19b-3p, miR-21-5p, miR-221-3p, miR-409-3p, miR-425-5p, and miR-584-5p) were found to be upregulated in lung adenocarcinoma [51]. Eight miRNAs (miR-21, miR-141, miR-200a, miR-200c, miR-200b, miR-203, miR-205, and miR-214) have served as diagnostic biomarkers for ovarian cancer, and these miRNAs have also been identified in exosomes from ovarian cancer patients [52]. miRNAs can also be diagnostic biomarkers for esophageal squamous cell cancer (ESCC), as the serum levels of exosomal miR-21 from patients with ESCC are significantly higher than those of patients with benign diseases without systemic inflammation and are positively correlated with tumor progression and aggressiveness [53].

4. Exosomes for therapeutic intervention in cancer

The recent contribution by Zhang et al. reviewed the recent advances in cancer immunotherapy, exosome functions, exosome immunoregulation, and immune cell-derived exosomes [34]. As mentioned in Zhang's manuscript, exosomes cannot only transfer messages between cells by carrying RNA and proteins but also can modulate the immune response. After reviewing recent findings regarding exosomes and immunity in cancer, we have highlighted the novel insights into the development of efficient exosome-based cancer vaccines for cancer therapeutic intervention. Specifically, exosomes derived from immune cells, such as APCs, dendritic cells (DCs), and NK cells, play a crucial role in the immunomodulation of cancer, and they may be the best cancer vaccine candidates because they can inhibit the malignant activity of cancer cells and leave healthy cells unaffected [54–56]. Recently, researchers have noted that exosomes may lead to key advances in cancer therapy. Exosomes isolated from DCs have been evaluated in clinical trials as treatment for various kinds of cancers [57–59]. In a phase I clinical trial, exosomes derived from autologous DCs loaded with MAGE 3 peptides were applied as cancer therapy for stage III/IV melanoma patients [58]. Several phase I or phase II clinical trials involving exosome-based regimens have occurred in breast cancer, gastric cancer, malignant glioma, and non-small cell lung cancer patients, which demonstrates that exosomes are effective tools for the transportation of anticancer drugs [59]. Exosomes were employed to form a complex with curcumin and delivered to recipient pancreatic cancer cells, which was found to promote cytotoxicity [60]. Moreover, exosomes have been shown to deliver small, molecular anticancer drugs across the blood-brain barrier and significantly inhibit tumor growth in a brain cancer model [61, 62].

5. Long non-coding RNAs as novel biomarkers in cancer

lncRNAs modulate gene expression, while lncRNA dysregulation is associated with human cancer. lncRNAs could play a significant role in cancer progression by interacting with proteins. Since they are highly specific and easily detectable in tissue, serum, plasma, and urine, interest in exploring lncRNAs in cancer patients continues to increase. Metastasis-associated

lung adenocarcinoma transcript 1 (MALAT-1, also known as NEAT2), a novel lncRNA, is found on chromosome 11q13 and is well conserved among mammalian species. MALAT-1 is a critical regulator of the metastatic phenotype of lung cancer cells [63] and can enhance proliferation, cell motility, invasion, and metastasis in CNE-1 [64], lung adenocarcinoma [65], thyroid cancer [17], cervical cancer [19], and ovarian cancer cells [18]. MALAT-1 has an important role in regulating the metastasis of bladder cancer and can be a potential application in bladder cancer therapy [66]. The MALAT-1-mediated promotion of renal cell carcinoma (RCC) proliferation and metastasis may be due to the upregulation of Livin expression [67]. MALAT-1 promotes the proliferation of chondrosarcoma cells via activating the Notch-1 signaling pathway [68], indicates poor prognosis in non-small cell lung cancer, and induces migration and tumor growth [69]. Upregulation of MALAT-1 has been associated with survival rate, cell cycle, and migration in patients with esophageal squamous cell carcinoma (ESCC) [70]. However, the loss of MALAT1 is compatible with cell viability and normal development [71]. On the other hand, MALAT-1 is downregulated in preeclampsia and regulates the proliferation, apoptosis, migration, and invasion of JEG-3 trophoblast cells [72]. MALAT-1 is also expected to be a potential therapeutic target in prostate cancer [73]. As another critical oncogenic lncRNA in human cancers [74, 75], the lncRNA HOTTIP promotes tumor growth, inhibits cell apoptosis [76], contributes to the progression of prostate cancer [77] and non-small cell lung cancer [78] by regulating HOXA13, and increases the chemoresistance of osteosarcoma cells by activating the Wnt/ β -catenin pathway [79]. HOTTIP is upregulated and associated with poor prognosis in patients with osteosarcoma [80]. Overexpression of HOTTIP can promote tumor invasion and predict poor prognosis in gastric cancer [81]. This accumulating evidence indicates that long non-coding RNAs have immense potential as powerful, non-invasive tumor markers. However, overexpression of HOTTIP inhibits glioma cell growth by brain and reproductive expression [82].

Circulating lncRNAs have shown potential as biomarkers in the diagnosis and prognosis of many cancers, including cervical cancer, colon cancer, hepatocellular carcinoma (HCC), gastric cancer (GC), PaCa, renal cell carcinoma (RCC), ovarian cancer (OC), non-small cell lung cancer (NSCLC), thyroid cancer, and prostate cancer (**Table 1**). Here, we have identified some interesting circulating lncRNAs (also known as exosomal lncRNAs), including MALAT-1, PVT1, HOTAIR, H19, UCA1, and TUG1, as novel biomarkers in various cancers. MALAT-1 in urine may serve as a potential biomarker for predicting prostate cancer risk. The application of the MALAT-1 model can prevent 30.2–46.5% of unnecessary biopsies in high-grade cancers [83]. PVT1 expression has been shown to be significantly elevated in non-small cell lung cancer (NSCLC), and high PVT1 expression has been associated with poor overall survival and disease-free survival in NSCLC patients; therefore, PVT1 could serve as a promising biomarker for the diagnosis and prognosis of NSCLC. PVT1 knockdown could remarkably inhibit NSCLC cell proliferation [84]. HOTAIR has been shown to be significantly higher in breast cancer patients, and circulating HOTAIR DNA levels were 2.15-fold higher in patients compared with those of healthy controls in one study, which demonstrates a moderate correlation between its expressions in tumor tissues. Plasma HOTAIR levels have been found to be significantly reduced after surgery [85, 86], indicating that plasma HOTAIR might serve as a potential biomarker for diagnosing breast cancer. A multivariate survival analysis also

lncRNA	Functions	Detection in cancer	References
MALAT-1	1. Promotes cell proliferation, invasion, and migration	Thyroid cancer, OC, cervical cancer, NSCLC, human nasopharyngeal carcinoma cell lines, bladder cancer, lung adenocarcinoma, JEG-3 trophoblast cells, PaCa, chondrosarcoma cell, RCC, ESCC	[17–19, 66, 67, 71–75, 77, 106]
	2. Regulator of the metastasis	Lung cancer cells, human nasopharyngeal carcinoma cell lines, PaCa	[65, 66, 111]
	3. Diagnostic and prognostic biomarker	Prostate cancer (urine/plasma), osteosarcoma (serum)	[78, 88, 123]
	4. Potential therapeutic target	Prostate cancer	[78]
HOTTIP	1. Inhibits glioma cell growth	Glioma	[87]
	2. Cell growth, apoptosis, migration, and invasion	HCC, PaCa, GC and colorectal cancer, NSCLC, lung cancer	[80, 81, 83, 85, 113, 123]
	3. Increases chemoresistance	Osteosarcoma cell, PaCa	[119]
	4. Progression and prognosis	Prostate cancer, colorectal cancer, osteosarcoma, tongue squamous cell carcinoma, PaCa, HCC	[80, 82, 119, 124–126]
	5. Biomarkers	PaCa (blood)	[121]
PVT1	1. Promotes cell proliferation and invasion	NSCLC, esophageal cancer, bladder cancer, acute promyelocytic leukemia, GC, BC	[127–133]
	2. Progression and prognosis	Cervical cancer, GC, HCC, PaCa	[115, 134–137]
	3. Promotes resistance	OC, GC	[138, 139]
	4. Modulates thyroid cancer cell proliferation	Thyroid cancer	[140]
	5. Apoptosis	Colorectal cancers	[141]
	6. Novel biomarker for diagnosis and prognosis	Cervical cancer, HCC, RCC (Serum); PaCa, NSCLC (tissue)	[89, 114, 142–145]
uc.345	1. Promotes tumorigenesis	PaCa	[122]
LINC-PINT	1. Diagnostic and prognostic biomarkers	PaCa (plasma and tumor tissues)	[127]

lncRNA	Functions	Detection in cancer	References
HOTAIR	1. Enhances cell proliferation, survival and migration	PaCa, HCC, cervical cancer, GC, OC, NSCLC, colorectal cancer, prostate cancer	[113, 146–155]
	2. Enhances its prognostic potential and correlates with disease progression	BC, HCC, cervical cancer, bladder cancer	[156–169]
	3. Relative to resistance	BC, cervical cancer, OC, bladder transitional cell carcinoma	[157, 160–162]
	4. Associated with EMT, cancer stem cells	Epithelial OC, colorectal cancer	[163, 164]
	5. Activates autophagy	HCC	[165]
	6. Modulates HLA-G expression	Cervical cancer, GC	[166, 167]
	7. Potential biomarker for diagnosis	PaCa, BC, colorectal carcinoma (serum/plasma), PaCa (tissue), GC (tissue, blood, and gastric juice)	[90, 91, 114, 149, 168–170]
H19	1. Promotes cell proliferation, migration and invasion	PDAC, lung cancer, BC, glioblastoma	[117, 172–174]
	2. Prognosis and progression and Metastasis	Gastrointestinal, colorectal cancer, NSCLC, gallbladder carcinoma	[175–179]
	3. Regulates angiogenesis	Glioma, glioblastoma	[173, 180]
	4. Contributing to resistance	OC	[181]
	5. Modulates tumorigenicity and stemness	Malignant carcinoma	[182]
	6. Regulatory role in pluripotency and tumorigenesis	Human embryonic carcinoma	[183]
	7. Promotes EMT	Colorectal cancer, esophageal cancer, glioblastoma	[173, 184, 185]
	8. Potential biomarkers for diagnosis	GC (serum/plasma/tissue), BC (tissue), bladder cancer	[91–93, 186–188]
IRAIN	1. Promotes proliferation and suppresses apoptosis	PaCa, NSCLC	[123, 189]
	2. As a novel imprinted gene that is aberrantly regulated in breast cancer	BC (tumors and peripheral blood leucocytes)	[190]

lncRNA	Functions	Detection in cancer	References
UCA1	1. Promotes the tumorigenesis, enhances cell proliferation, migration	PaCa, endometrial cancer, colorectal cancer, RCC, NSCLC, prostate cancer	[118, 191–194]
	2. Contributes to the progression and prognosis	OSCC, ESCC	[195, 196]
	3. Promotes EMT	BC	[197]
	4. Suppress metastasis	Epithelial OC	[198]
	5. Modulates cell growth and apoptosis, and epigenetic regulation	BC	[199, 200]
	6. Enhances drug resistance	BC, bladder cancer, GC, colorectal cancer, prostate cancer	[192, 201–205]
	7. Promotes glutamine metabolism	Bladder cancer	[206]
	8. As diagnostic and prognostic markers	HCC, colon cancer (serum), early gastric cancer, lung cancer (plasma), bladder cancer (urine and blood),	[171, 207–217]
TUG1	1. Promotes cell proliferation, migration	Bladder cancer, BC, osteosarcoma, ESCC, HCC	[218–222]
	2. Poor prognosis and promotes metastasis	Bladder cancer, GC, colorectal cancer, OC	[219, 223–226]
	3. Associated with chemotherapy resistance and poor prognosis	ESCC	[227]
	4. Acts as a tumor suppressor in human glioma	Human glioma	[228]
	5. Affects apoptosis and insulin secretion	PaCa	[124]
	6. As biomarker for poor prognosis	Osteosarcoma (plasma), B-cell neoplasms (plasma)	[229, 230]

Table 1. Long non-coding RNAs (lncRNAs) as potential biomarkers for cancer.

indicated that H19 might serve as a potential biomarker for early detection and prediction of prognosis of breast cancer and gastric cancer. The expression of H19 was remarkably increased in breast cancer and gastric cancer tissues. H19 expression has been shown to be significantly correlated with invasion depth, advanced TNM stage and regional lymph node metastasis in gastric cancer. Additionally, elevated expression levels of H19 have been shown to contribute to the poor overall survival and disease-free survival of gastric cancer patients [87]. This makes H19 closely associated with progressive gastric cancer, and it could be a potential non-invasive diagnostic gastric cancer biomarker for management. Better performance could be achieved

using both carcinoembryonic antigen (CEA) and H19 simultaneously [88]. Plasma H19 levels have been shown to be significantly decreased in postoperative breast cancer samples compared to those in preoperative samples [89]. Urothelial cancer-associated 1 (UCA1), originally identified as a lncRNA in bladder cancer, has been proven to play a pivotal role in bladder cancer progression and embryonic development. Upregulation of the lncRNA UCA1 and the lncRNA WRAP53 has been observed in hepatocellular carcinoma (HCC), and CA1 might serve as a novel serum biomarker for HCC. Moreover, the expression levels of UCA1 and WRAP53 in tissue have been shown to be strongly correlated with their levels in sera. Further, the combination of UCA1 and WRAP53 with serum alpha fetoprotein could improve sensitivity to 100% [90]. Further, meta-analysis also found that higher levels of UCA1 were correlated with shorter progression-free survival (PFS) and overall survival (OS) times in cancer [91], indicating that circulating lncRNAs, such as MALAT-1, PVT1, HOTAIR, H19, UCA1, and WRAP53, could serve as novel biomarkers for the early detection and the prediction of prognosis of cancer.

6. Exosomes and lncRNAs in the diagnosis and treatment of pancreatic cancer

Pancreatic cancer is one of the most lethal tumors, and its main tumor type is that of adenocarcinoma [92–94]. Pancreatic ductal adenocarcinoma (PDAC), the fourth leading cause of cancer-related deaths in both males and females in the USA, is usually asymptomatic [186], and PDAC is one of the most lethal malignant neoplasms worldwide [89, 95, 96]. Statistical analysis indicated that death rates rose from 2001 to 2010 [97]. In America, approximately 53,000 people were diagnosed with pancreatic cancer in 2016, and pancreatic cancer was responsible for 41,750 deaths in the USA [98] in that same year. Additionally, the incidence of pancreatic cancer has shown an increasing trend year-by-year in China, and pancreatic cancer has become one of the top 10 causes of cancer-related deaths [99].

It is well known that pancreatic cancer has a poor prognosis because it is usually diagnosed after the cancer has already spread, leading to poor patient outcomes. Pancreatic ductal adenocarcinoma patients have a 5-year survival rate of ~5% [100]. Survival can be improved if tumors are detected at an early stage, and the 5-year survival rate is 50% if tumors are <2 cm in size [101]. However, there have been no reliable biomarkers to accurately diagnose, image, or predict the tumor classification and biological behavior of pancreatic cancer until now. Thus, it is urgent to screen potential biomarkers and treatment-related biomarkers, such as exosome-derived proteins, DNA (exoDNA), miRNAs (exosomal miRNAs), and lncRNAs (exosomal lncRNAs), for the early detection of pancreatic cancer. Allenson found that KRAS mutations in the exoDNA of control, localized, locally advanced, and metastatic PDAC patients were 7.4, 66.7, 80, and 85%, respectively, which demonstrates that KRAS in exosomes could be applied to diagnose PDAC [102]. Takikawa also confirmed that pancreatic stellate cell (PSC)-derived exosomes stimulate the proliferation and migration of pancreatic cancer cells and upregulate the mRNA expression of the chemokine (C-X-C motif) ligands 1 and 2 in pancreatic cancer cells [103]. Over the last few years, non-coding RNAs, especially

exosomal lncRNAs and exosomal miRNAs, have become a new diagnostic, prognostic, and predictive tool for pancreatic cancer. Exosomal miR-155, miR-196a, miR-17-5p, miR-10b, and miR-21 have good sensitivity and specificity in the serum of PaCa patients and can be useful serum biomarkers for pancreatic cancer [104, 105]. Not only can single exosomes be a diagnosis biomarker, but combined exosomal miRNAs, such as miR-1246, miR-4644, miR-3976, and miR-4306, can also increase sensitivity and specificity for the diagnosis of pancreatic cancer.

Specifically, exosomal lncRNAs have been identified as potential biomarkers of various cancers in recent years, including gastric cancer, breast cancer, and lung cancer. However, few studies have explored the potential use of exosomal lncRNAs in pancreatic cancer detection and prognosis. MALAT-1, HOTTIP, PVT1, and HOTAIR, which are secreted from PDAC cells to bodily fluids, such as blood, pancreatic juice, cystic fluid, and urine, are some of most widely studied lncRNAs in pancreatic cancer (**Figure 1**). As a potential oncogenic lncRNA, MALAT-1 involves in proliferation, migration, and invasion and promotes the undifferentiated phenotype of pancreatic tumor cells [106]. MALAT-1 can also promote the tumorigenicity of pancreatic cancer cells, increase the proportion of pancreatic cancer stem cells, maintain a self-renewing capacity, and decrease chemosensitivity to anticancer drugs. Moreover, MALAT-1 has potential effects on the stem cell-like phenotypes of pancreatic cancer cells, which suggests that MALAT-1 has a novel role in tumor stemness [107]. The lncRNA HOTTIP enhances pancreatic cancer cell proliferation, survival, and migration and has been implicated in pancreatic cancer diagnosis and prognosis [108]. The overexpression of HOTAIR has been described as a poor prognostic factor in PDAC and can also be a novel non-invasive salivary biomarker for the early diagnosis of PaCa with PVT1 expression [109]. Increased expression of the lncRNA PVT1 is associated with poor prognosis in pancreatic cancer patients [110]. PVT1 expression is

Figure 1. Exosomal lncRNAs secreted from PDAC cells as potential biomarkers of pancreatic cancer.

significantly increased in PDAC and is correlated with tumor progression. Moreover, patients with high PVT1 expression levels have been shown to have shorter overall survival times compared to those with low PVT1 expression levels, which implies that PVT1 could be a potential molecular biomarker for predicting the prognosis of patients with PDAC [110]. H19 has been shown to be overexpressed in PDAC tissues and to be correlated with the histological grade of PDAC. Knockdown of H19 can suppress cell viability, proliferation, and tumor growth, while H19 overexpression can enhance cell viability, proliferation, and tumor growth [111]. UCA1 expression has been shown to be significantly upregulated in PaCa tumor tissues and to be significantly correlated with malignant potential factors, such as tumor size, depth of invasion, CA19-9 levels, and tumor stage. Highly expressed UCA1 has been shown to be an independent prognostic biomarker of PaCa, leading to an obviously shorter 5-year overall survival (OS). Downregulation of UCA1 could effectively inhibit cell proliferative activities, which implies that UCA1 could be a potential prognostic biomarker and therapy target of PaCa [112].

In addition, high expression levels of the lncRNA HOXA13 have been shown to be correlated with lymph node metastasis, poor histological differentiation, and decreased overall survival in PDAC patients. The knockdown of HOXA13 resulted in proliferation arrest and impaired cell invasion in pancreatic cancer [113]. Using microarray analysis, HOTTIP was confirmed to be one of the most significantly upregulated lncRNAs in PDAC [113]. HOTTIP has been shown to be overexpressed in pancreatic cancer, and knockdown of HOTTIP in pancreatic cancer cells decreased proliferation, induced apoptosis, and decreased migration [108]. Using an Arraystar Human lncRNA Microarray, HOTTIP-005, XLOC_006390, and RP11-567G11.1 were found to be the most increased lncRNAs in PaCa. Elevated HOTTIP-005 and RP11-567G11.1 expression could serve as poor prognostic markers for patients with PaCa. Plasma HDRF and RDRF (HOTTIP-005- and RP11-567G11.1-derived RNA fragments in plasma/serum) have also shown to be significantly increased in patients with PaCa, which demonstrates that HDRF and RDRF levels could be promising indicators for distinguishing patients with PC [114]. As an oncogenic lncRNA, uc.345 has been shown to promote tumor progression and to serve as a poor predictor for OS in pancreatic cancer patients. uc.345 was found to be upregulated in tumor tissues, and higher uc.345 expression levels have been associated with cancer invasion and metastasis, which could be an independent risk factor for the OS of pancreatic cancer patients [115]. The lncRNA IRAIN plays an important role in many malignancies, and upregulation of IRAIN has been shown to be significantly correlated with tumor size, the TNM classification of malignant tumors (TNM) stage, and lymph node metastasis in PaCa patients. The knockdown of IRAIN significantly induced cell apoptosis and inhibited cell proliferation in PaCa cells [116]. The lncRNA TUG1 has been shown to be highly expressed in pancreatic tissue compared with its expression in other organ tissues, and downregulation of TUG1 has been shown to affect apoptosis and insulin secretion in pancreatic β cells [117]. CCDC26 might be identified as a novel oncogene in PaCa by regulating proliferating cell nuclear antigen (PCNA) and Bcl2 expression. CCDC26 is significantly upregulated in PaCa, and it is correlated with tumor size, tumor number, and reduced OS [118]. Univariate and multivariate analysis showed that CCDC26 expression can be an independent prognostic factor of OS in patients with PaCa; therefore, CCDC26 could serve as a novel biomarker and therapeutic target of PC for cancer in the future [118]. LINC-ROR has been shown to be upregulated in PaCa tissues, and overexpression of LINC-ROR promoted cell proliferation, migration, invasion,

and metastasis both in vitro and in mouse models. LINC-ROR acts as an important regulator of ZEB1 and might represent a novel therapeutic target [119]. The lncRNA LINC-PINT (p53-induced transcript) could also regulate tumor cell viability and proliferation. However, the expression levels of LINC-PINT have been shown to be lower in plasma and tumor tissue samples in PaCa patients. LINC-PINT has been shown to be more sensitive than CA19-9 in detecting PaCa, which suggests that LINC-PINT could be used for distinguishing the cause of malignant obstructive jaundice [120]. The lncRNA HMLincRNA717 has also been shown to be downregulated in pancreatic cancer and associated with overall survival, suggesting that HMLincRNA717 could be a potential prognostic biomarker for pancreatic cancer progression [121]. As a potential tumor suppressor, the long intergenic non-coding RNA (lincRNA) LINC00673 has been associated with pancreatic cancer risk. A G>A mutation at rs11655237 of LINC00673 created a target site for miR-1231 binding, which diminished the effect of LINC00673 in an allele-specific manner and conferred susceptibility to PaCa [122].

All the abovementioned exosomal lncRNAs could serve as diagnostic and prognostic factors to complement clinical and pathological parameters in predicting the outcome of patients with pancreatic cancer. Although there are an increasing number of clinical assays for studying exosomes, determining clinical applications for lncRNAs and exosomes is a long ways off. No matter how exosomes have become the most effective cancer vaccines, future research to investigate exosomal lncRNAs as biomarkers for the early detection of pancreatic cancer and to assess the validity and quality of the exosomes as effective vaccines for pancreatic cancer will be valuable. To achieve this long-term goal, further understanding of exosome biology, especially of the molecular mechanisms of tumor- and immune cell-derived exosomes as cancer vaccines, is required.

Acknowledgement

This research was supported by a grant from the National Natural Science Foundation of China (81672383) and a grant (16PJ1408800) from the Shanghai Pujiang Program in Shanghai, China.

Abbreviations

APC	Antigen-presenting cell
BC	Breast cancer
BPH	Benign prostatic hyperplasia
CEA	Carcinoembryonic antigen
DCs	Dendritic cells
EMT	Epithelial-mesenchymal transition
EOC	Epithelial ovarian cancer
ESCC	Esophageal squamous cell carcinoma
EVs	Extracellular vesicles
GC	Gastric cancer

HCC	Hepatocellular carcinoma
PCNA	Proliferating cell nuclear antigen
PFS	Progression-free survival
lncRNAs	Long non-coding RNAs
MALAT-1	Metastasis-associated lung adenocarcinoma transcript 1
ncRNAs	Non-coding RNAs
NSCLC	Non-small cell lung cancer
OC	Ovarian cancer
OS	Overall survival
OSCC	Oral squamous cell carcinoma
PaCa	Pancreatic cancer
PDAC	Pancreatic ductal adenocarcinoma
RCC	Renal cell carcinoma
sncRNAs	Small ncRNAs
UCA1	Urothelial cancer-associated 1

Author details

Jin Wang^{1*}, Xuan Zhang¹, Chunxia Ji¹, Lei Zhang², Yang Di³, Wenhui Lou², Xiaoyan Zhang¹ and Jianqing Xu¹

*Address all correspondence to: wangjin@shaphc.org

1 Scientific Research Center, Shanghai Public Health Clinical Center, Fudan University, Shanghai, China

2 General Surgery Department, Zhongshan Hospital, Fudan University, Shanghai, China

3 Department of Pancreatic Surgery, Pancreatic Disease Institute, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China

References

- [1] Tkach M, Thery C. Communication by extracellular vesicles: Where we are and where we need to go. *Cell*. 2016;**164**:1226-1232
- [2] Thery C, Zitvogel L, Amigorena S. Exosomes: Composition, biogenesis and function. *Nature Reviews Immunology*. 2002;**2**:569-579
- [3] Keller S, Sanderson MP, Stoeck A, Altevogt P. Exosomes: From biogenesis and secretion to biological function. *Immunology Letters*. 2006;**107**(2):102-108

- [4] Nuzhat Z, Kinhal V, Sharma S, Rice GE, Joshi V, Salomon C. Tumour-derived exosomes as a signature of pancreatic cancer — liquid biopsies as indicators of tumour progression. *Oncotarget*. 2017;**8**(10):17279-17291
- [5] Clombo M, Raposo G, Thery C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. *Annual Review of Cell and Developmental Biology*. 2014;**30**:255-289
- [6] Raposo G, Stoorvogel W. Extracellular vesicles: Exosomes, microvesicles, and friends. *The Journal of Cell Biology*. 2013;**200**(4):373-383
- [7] Brinton LT, Sloane HS, Kester M, Kelly KA. Formation and role of exosomes in cancer. *Cellular and Molecular Life Sciences*. 2015;**72**(4):659-671
- [8] Costa-Silva B, Aiello NM, Ocean AJ, Singh S, Zhang H, Thakur BK, et al. Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver. *Nature Cell Biology*. 2015;**17**(6):816-826
- [9] Hoshino A, Costa-Silva B, Shen TL, Rodrigues G, Hashimoto A, Tesic Mark M, et al. Tumour exosome integrins determine organotropic metastasis. *Nature*. 2015;**527**(7578):329-335
- [10] Peinado H, Aleckovic M, Lavotshkin S, Matei I, Costa-Silva B, Moreno-Bueno G, et al. Melanoma exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype through MET. *Nature Medicine*. 2012;**18**(6):883-891
- [11] Valadi H, Ekstrom 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. *Nature Cell Biology*. 2007;**9**(6):654-659
- [12] Esteller M. Non-coding RNAs in human disease. *Nature Reviews Genetics*. 2011;**12**(12):861-874
- [13] Lee JT. Epigenetic regulation by long noncoding RNAs. *Science*. 2012;**338**(6113):1435-1439
- [14] Wapinski O, Chang HY. Long noncoding RNAs and human disease. *Trends in Cell Biology*. 2011;**21**(6):354-361
- [15] Hung T, Chang HY. Long noncoding RNA in genome regulation: Prospects and mechanisms. *RNA Biology*. 2010;**7**(5):582-585
- [16] Guttman M, Amit I, Garber M, French C, Lin MF, Feldser D, et al. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. *Nature*. 2009;**458**(7235):223-227
- [17] Huang JK, Ma L, Song WH, Lu BY, Huang YB, Dong HM, et al. MALAT1 promotes the proliferation and invasion of thyroid cancer cells via regulating the expression of IQGAP1. *Biomedicine & Pharmacotherapy*. 2016;**83**:1-7
- [18] Zhou Y, Xu X, Lv H, Wen Q, Li J, Tan L, et al. The long noncoding RNA MALAT-1 is highly expressed in ovarian cancer and induces cell growth and migration. *PLoS One*. 2016;**11**(5):e0155250

- [19] Zhang Y, Wang T, Huang HQ, Li W, Cheng XL, Yang J. Human MALAT-1 long non-coding RNA is overexpressed in cervical cancer metastasis and promotes cell proliferation, invasion and migration. *Journal of BUON*. 2015;**20**(6):1497-1503
- [20] Kino T, Hurt DE, Ichijo T, Nader N, Chrousos GP. Noncoding RNA gas5 is a growth arrest- and starvation-associated repressor of the glucocorticoid receptor. *Science Signaling*. 2010;**3**(107):ra8
- [21] Hu W, Yuan B, Flygare J, Lodish HF. Long noncoding RNA-mediated anti-apoptotic activity in murine erythroid terminal differentiation. *Genes and Development*. 2011;**25**(24):2573-2578
- [22] Meola N, Pizzo M, Alfano G, Surace EM, Banfi S. The long noncoding RNA Vax2os1 controls the cell cycle progression of photoreceptor progenitors in the mouse retina. *RNA*. 2012;**18**(1):111-123
- [23] Tripathi V, Ellis JD, Shen Z, Song DY, Pan Q, Watt AT, et al. The nuclear-retained non-coding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation. *Molecular Cell*. 2010;**39**(6):925-938
- [24] Wang KC, Yang YW, Liu B, Sanyal A, Corces-Zimmerman R, Chen Y, et al. A long noncoding RNA maintains active chromatin to coordinate homeotic gene expression. *Nature*. 2011;**472**(7341):120-124
- [25] Tsai MC, Manor O, Wan Y, Mosammaparast N, Wang JK, Lan F, et al. Long noncoding RNA as modular scaffold of histone modification complexes. *Science*. 2010;**329**(5992):689-693
- [26] Loewer S, Cabili MN, Guttman M, Loh YH, Thomas K, Park IH, et al. Large intergenic non-coding RNA-RoR modulates reprogramming of human induced pluripotent stem cells. *Nature Genetics*. 2010;**42**(12):1113-1117
- [27] Guttman M, Donaghey J, Carey BW, Garber M, Grenier JK, Munson G, et al. lincRNAs act in the circuitry controlling pluripotency and differentiation. *Nature*. 2011;**477**(7364):295-300
- [28] Gregg C, Zhang J, Weissbourd B, Luo S, Schroth GP, Haig D, et al. High-resolution analysis of parent-of-origin allelic expression in the mouse brain. *Science*. 2010;**329**(5992):643-648
- [29] EL Andaloussi S, Mäger I, Breakefield XO, Wood MJ. Extracellular vesicles: Biology and emerging therapeutic opportunities. *Nature Reviews Drug Discovery*. 2013;**12**(5):347-357
- [30] De Toro J, Herschlik L, Waldner C, Mongini C. Emerging roles of exosomes in normal and pathological conditions: New insights for diagnosis and therapeutic applications. *Frontiers in Immunology*. 2015;**4**(6):203
- [31] Meckes DG. Exosomal communication goes viral. *Journal of Virology*. 2015;**89**(10):5200-5203
- [32] Barteneva NS, Maltsev N, Vorobjev IA. Microvesicles and intercellular communication in the context of parasitism. *Frontiers in Cellular and Infection Microbiology*. 2013;**6**(3):49

- [33] Kucharzewska P, Belting M. Emerging roles of extracellular vesicles in the adaptive response of tumour cells to microenvironmental stress. *Journal of Extracellular Vesicles*. 2013. DOI: 10.3402/jev.v2i0.20304
- [34] Zhang X, Pei Z, Chen J, Ji C, Xu J, Zhang X, et al. Exosomes for immunoregulation and therapeutic intervention in cancer. *Journal of Cancer*. 2016;**7**(9):1081-1087
- [35] Runz S, Keller S, Rupp C, Stoeck A, Issa Y, Koensgen D, et al. Malignant ascites-derived exosomes of ovarian carcinoma patients contain CD24 and EpCAM. *Gynecologic Oncology*. 2007;**107**(3):563-571
- [36] Simons M, Raposo G. Exosomes—Vesicular carriers for intercellular communication. *Current Opinion in Cell Biology*. 2009;**21**(4):578-581
- [37] Kowal J, Tkach M, Théry C. Biogenesis and secretion of exosomes. *Current Opinion in Cell Biology*. 2014;**29**:116-125
- [38] Mathivana S, Ji H, Simpson RJ. Exosomes: Extracellular organelles important in intercellular communication. *Journal of Proteomics*. 2010;**73**(10):1907-1920
- [39] Wolfers J, Lozier A, Raposo G, Regnault A, Théry C, Masurier C, et al. Tumor-derived exosomes are a source of shared tumor rejection antigens for CTL cross-priming. *Nature Medicine*. 2001;**7**(3):297-303
- [40] 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. *Oncology Reports*. 2012;**28**(5):1551-1558
- [41] Wu L, Zhang X, Zhang B, Shi H, Yuan X, Sun Y, et al. Exosomes derived from gastric cancer cells activate NF- κ B pathway in macrophages to promote cancer progression. *Tumour Biology*. 2016;**37**(9):12169-12180
- [42] Nakamura K, Sawada K, Kinose Y, Yoshimura A, Toda A, Nakatsuka E, et al. Exosomes promote ovarian cancer cell invasion through transfer of CD44 to peritoneal mesothelial cells. *Mol Cancer Res*. 2017;**5**(1):78-92
- [43] Melo SA, Luecke LB, Kahlert C, Fernandez AF, Gammon ST, Kaye J, et al. Glypican-1 identifies cancer exosomes and detects early pancreatic cancer. *Nature*. 2015;**523**(7559):177-182
- [44] Rupp AK, Rupp C, Keller S, Brase JC, Eehalt R, Fogel M, et al. Loss of EpCAM expression in breast cancer derived serum exosomes: Role of proteolytic cleavage. *Gynecologic Oncology*. 2011;**122**(2):437-446
- [45] Moon PG, Lee JE, Cho YE, Lee SJ, Chae YS, Jung JH, et al. Fibronectin on circulating extracellular vesicles as a liquid biopsy to detect breast cancer. *Oncotarget*. 2016;**7**(26):40189-40199
- [46] Moon PG, Lee JE, Cho YE, Lee SJ, Jung JH, Chae YS, et al. Identification of developmental endothelial locus-1 on circulating extracellular vesicles as a novel biomarker for early breast cancer detection. *Clinical Cancer Research*. 2016;**22**(7):1757-1766

- [47] Khan S, Jutzy JMS, Valenzuela MMA, Turay D, Aspe JR, Ashok A, et al. Plasma-derived exosomal survivin, a plausible biomarker for early detection of prostate cancer. *PLoS One*. 2012;7(10):e46737
- [48] Ratajczak J, Wysoczynski M, Hayek F, Janowska-Wieczorek A, Ratajczak MZ. Membranederived microvesicles: Important and underappreciated mediators of cell-to-cell communication. *Leukemia*. 2006;20(9):1487-1495
- [49] Gusachenko ON, Zenkova MA, Vlassov VV. Nucleic acids in exosomes: Disease markers and intercellular communication molecules. *Biochemistry (Moscow)*. 2013;78(1):1-7
- [50] Bullock MD, Silva AM, Kanlikilicer P, Filant J, Rashed MH, Sood AK, et al. Exosomal non-coding RNAs: Diagnostic, prognostic and therapeutic applications in cancer. *Non-Coding RNA*. 2015;1:53-68
- [51] Zhou X, Wen W, Shan X, Zhu W, Xu J, Guo R, et al. A six-microRNA panel in plasma was identified as a potential biomarker for lung adenocarcinoma diagnosis. *Oncotarget*. 2017;8(4):6513-6525
- [52] Taylor DD, Gercel-Taylor C. MicroRNA signatures of tumor-derived exosomes as diagnostic biomarkers of ovarian cancer. *Gynecologic Oncology*. 2008;110(1):13-21
- [53] Tanaka Y, Kamohara H, Kinoshita K, Kurashige J, Ishimoto T, Iwatsuki M, et al. Clinical impact of serum exosomal microRNA-21 as a clinical biomarker in human esophageal squamous cell carcinoma. *Cancer*. 2013;119(6):1159-1167
- [54] Zitvogel L, Regnault A, Lozier A, Wolfers J, Flament C, Tenza D, et al. Eradication of established murine tumors using a novel cell-free vaccine: Dendritic cell derived exosomes. *Nature Medicine*. 1998;4(5):594-600
- [55] Baleeiro RB, Anselmo LB, Soares FA, Pinto CA, Ramos O, Gross JL, et al. High frequency of immature dendritic cells and altered in situ production of interleukin-4 and tumor necrosis factor-alpha in lung cancer. *Cancer Immunology, Immunotherapy*. 2008;57(9):1335-1345
- [56] Thery C, Regnault A, Garin J, Wolfers J, Zitvogel L, Ricciardi-Castagnoli P, et al. Molecular characterization of dendritic cell derived exosomes. Selective accumulation of the heat shock protein hsc73. *The Journal of Cell Biology*. 1999;147(3):599-610
- [57] Viaud S, Thery C, Ploix S. Dendritic cell-derived exosomes for cancer immunotherapy: What's next? *Cancer Research*. 2010;70(4):1281-1285
- [58] Escudier B, Dorval T, Chaput N, André F, Caby MP, Novault S, et al. Vaccination of metastatic melanoma patients with autologous dendritic cell (DC) derived-exosomes: Results of the first phase I clinical trial. *Journal of Translational Medicine*. 2005;3(1):10
- [59] Azmi AS, Bao B, Sarkar FH. Exosomes in cancer development, metastasis, and drug resistance: A comprehensive review. *Cancer Metastasis Reviews*. 2013;32(3-4):623-642
- [60] Osterman CJ, Lynch JC, Leaf P, Gonda A, Ferguson Bennit HR, Griffiths D, et al. Curcumin modulates pancreatic adenocarcinoma cell-derived exosomal function. *PLoS One*. 2015;10(7):e0132845

- [61] Pardridge WM. Drug transport across the blood–brain barrier. *Journal of Cerebral Blood Flow and Metabolism*. 2012;**32**(11):1959-1972
- [62] Yang T, Martin P, Fogarty B, Brown A, Schurman K, Phipps R, et al. Exosome delivered anticancer drugs across the blood-brain barrier for brain cancer therapy in *Danio rerio*. *Pharmaceutical Research*. 2015;**32**(6):2003-2014
- [63] Gutschner T, Hammerle M, Diederichs S. MALAT1—a paradigm for long noncoding RNA function in cancer. *Journal of Molecular Medicine*. 2013;**91**(7):791-801
- [64] Xie L, Hu Z, Wang X, Li Z. Expression of long noncoding RNA MALAT1 gene in human nasopharyngeal carcinoma cell lines and its biological significance. *Nan Fang Yi Ke Da Xue Xue Bao*. 2013;**33**(5):692-697
- [65] Tano K, Mizuno R, Okada T, Rakwal R, Shibato J, Masuo Y, et al. MALAT-1 enhances cell motility of lung adenocarcinoma cells by influencing the expression of motility-related genes. *FEBS Letters*. 2010;**584**(22):4575-4580
- [66] Ying L, Chen Q, Wang Y, Zhou Z, Huang Y, Qiu F. Upregulated MALAT-1 contributes to bladder cancer cell migration by inducing epithelial-to-mesenchymal transition. *Molecular Biosystems*. 2012;**8**(9):2289-2294
- [67] Chen S, Ma P, Zhao Y, Li B, Jiang S, Xiong H, et al. Biological function and mechanism of MALAT-1 in renal cell carcinoma proliferation and apoptosis: Role of the MALAT-1-Livin protein interaction. *The Journal of Physiological Sciences*. 2016. DOI: 10.1007/s12576-016-0486-8.
- [68] Xu F, Zhang ZQ, Fang YC, Li XL, Sun Y, Xiong CZ, et al. Metastasis-associated lung adenocarcinoma transcript 1 promotes the proliferation of chondrosarcoma cell via activating Notch-1 signaling pathway. *OncoTargets and Therapy*. 2016;**9**:2143-2151
- [69] Schmidt LH, Spieker T, Koschmieder S, Schäffers S, Humberg J, Jungen D, et al. The long noncoding MALAT-1 RNA indicates a poor prognosis in non-small cell lung cancer and induces migration and tumor growth. *Journal of Thoracic Oncology*. 2011;**6**(12):1984-1992
- [70] Yao W, Bai Y, Li Y, Guo L, Zeng P, Wang Y, et al. Upregulation of MALAT-1 and its association with survival rate and the effect on cell cycle and migration in patients with esophageal squamous cell carcinoma. *Tumour Biology*. 2016;**37**(4):4305-4312
- [71] Eißmann M, Gutschner T, Hämmerle M, Günther S, Caudron-Herger M, Groß M, et al. Loss of the abundant nuclear non-coding RNA MALAT1 is compatible with life and development. *RNA Biology*. 2012;**9**(8):1076-1087
- [72] Chen H, Meng T, Liu X, Sun M, Tong C, Liu J, et al. Long non-coding RNA MALAT-1 is downregulated in preeclampsia and regulates proliferation, apoptosis, migration and invasion of JEG-3 trophoblast cells. *International Journal of Clinical and Experimental Pathology*. 2015;**8**(10):12718-12727

- [73] Ren S, Liu Y, Xu W, Sun Y, Lu J, Wang F, et al. Long noncoding RNA MALAT-1 is a new potential therapeutic target for castration resistant prostate cancer. *The Journal of Urology*. 2013;**190**(6):2278-2287
- [74] Lian Y, Cai Z, Gong H, Xue S, Wu D, Wang K. HOTTIP: A critical oncogenic long non-coding RNA in human cancers. *Molecular Biosystems*. 2016;**12**(11):3247-3253
- [75] Chang S, Liu J, Guo S, He S, Qiu G, Lu J, et al. HOTTIP and HOXA13 are oncogenes associated with gastric cancer progression. *Oncology Reports*. 2016;**35**(6):3577-3585
- [76] Deng HP, Chen L, Fan T, Zhang B, Xu Y, Geng Q. Long non-coding RNA HOTTIP promotes tumor growth and inhibits cell apoptosis in lung cancer. *Cellular and Molecular Biology (Noisy-le-Grand, France)*. 2015;**61**(4):34-40
- [77] Zhang SR, Yang JK, Xie JK, Zhao LC. Long noncoding RNA HOTTIP contributes to the progression of prostate cancer by regulating HOXA13. *Cellular and Molecular Biology (Noisy-le-Grand, France)*. 2016;**62**(3):84-88
- [78] Sang Y, Zhou F, Wang D, Bi X, Liu X, Hao Z, et al. Up-regulation of long non-coding HOTTIP functions as an oncogene by regulating HOXA13 in non-small cell lung cancer. *American Journal of Translational Research*. 2016;**8**(5):2022-2032
- [79] Li Z, Zhao L, Wang Q. Overexpression of long non-coding RNA HOTTIP increases chemoresistance of osteosarcoma cell by activating the Wnt/ β -catenin pathway. *American Journal of Translational Research*. 2016;**8**(5):2385-2393
- [80] Li F, Cao L, Hang D, Wang F, Wang Q. Long non-coding RNA HOTTIP is up-regulated and associated with poor prognosis in patients with osteosarcoma. *International Journal of Clinical and Experimental Pathology*. 2015;**8**(9):11414-11420
- [81] Ye H, Liu K, Qian K. Overexpression of long noncoding RNA HOTTIP promotes tumor invasion and predicts poor prognosis in gastric cancer. *OncoTargets and Therapy*. 2016;**9**:2081-2088
- [82] Xu LM, Chen L, Li F, Zhang R, Li ZY, Chen FF, et al. Over-expression of the long non-coding RNA HOTTIP inhibits glioma cell growth by BRE. *Journal of Experimental & Clinical Cancer Research*. 2016;**35**(1):162
- [83] Wang F, Ren S, Chen R, Lu J, Shi X, Zhu Y, et al. Development and prospective multi-center evaluation of the long noncoding RNA MALAT-1 as a diagnostic urinary biomarker for prostate cancer. *Oncotarget*. 2014;**5**(22):11091-11102
- [84] Cui D, Yu CH, Liu M, Xia QQ, Zhang YF, Jiang WL. Long non-coding RNA PVT1 as a novel biomarker for diagnosis and prognosis of non-small cell lung cancer. *Tumour Biology*. 2016;**37**(3):4127-4134
- [85] Zhang KJ, Zhang Y, Luo ZL, Liu L, Yang J, Wu LC, et al. Long non-coding RNA HOTAIR in plasma as a potential biomarker for breast cancer diagnosis. *Nan Fang Yi Ke Da Xue Xue Bao*. 2016;**36**(4):488-492

- [86] Zhang L, Song X, Wang X, Xie Y, Wang Z, Xu Y, et al. Circulating DNA of HOTAIR in serum is a novel biomarker for breast cancer. *Breast Cancer Research and Treatment*. 2015;**152**(1):199-208
- [87] Chen JS, Wang YF, Zhang XQ, Lv JM, Li Y, Liu XX, et al. H19 serves as a diagnostic biomarker and up-regulation of H19 expression contributes to poor prognosis in patients with gastric cancer. *Neoplasma*. 2016;**63**(2):223-230
- [88] Hashad D, Elbanna A, Ibrahim A, Khedr G. Evaluation of the role of circulating long non-coding RNA H19 as a promising novel biomarker in plasma of patients with gastric cancer. *Journal of Clinical Laboratory Analysis*. 2016;**30**(6):1100-1105
- [89] Zhang K, Luo Z, Zhang Y, Zhang L, Wu L, Liu L, et al. Circulating lncRNA H19 in plasma as a novel biomarker for breast cancer. *Cancer Biomarkers*. 2016;**17**(2):187-194
- [90] Kamel MM, Matboli M, Sallam M, Montasser IF, Saad AS, El-Tawdi AH. Investigation of long noncoding RNAs expression profile as potential serum biomarkers in patients with hepatocellular carcinoma. *Translational Research*. 2016;**168**:134-145
- [91] Hong HH, Hou LK, Pan X, Wu CY, Huang H, Li B, et al. Long non-coding RNA UCA1 is a predictive biomarker of cancer. *Oncotarget*. 2016;**7**(28):44442-44447
- [92] Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. *Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11*. Lyon, France: International Agency for Research on Cancer; 2013
- [93] Hidalgo M, Cascinu S, Kleeff J, Labianca R, Löhner JM, Neoptolemos J, et al. Addressing the challenges of pancreatic cancer: Future directions for improving outcomes. *Pancreatology*. 2013;**15**(1):8-18
- [94] Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. *Lancet*. 2011;**378**(9791):607-620
- [95] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN. *International Journal of Cancer*. 2015;**136**(5):E359-E386
- [96] Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, et al. *SEER Cancer Statistics Review, 1975-2013*. Bethesda, MD: National Cancer Institute; 2016
- [97] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA: A Cancer Journal for Clinicians*. 2014;**64**(1):9-29
- [98] Hanada K, Okazaki A, Hirano N, Izumi Y, Teraoka Y, Ikemoto J, et al. Diagnostic strategies for early pancreatic cancer. *Journal of Gastroenterology*. 2015;**50**(2):147-154
- [99] Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA: A Cancer Journal for Clinicians*. 2016;**66**(2):115-132
- [100] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin*. 2017 Jan;**67**(1):7-30

- [101] Egawa S, Takeda K, Fukuyama S, Motoi F, Sunamura M, Matsuno S. Clinicopathological aspects of small pancreatic cancer. *Pancreas*. 2004;**28**(3):235-240
- [102] Allenson K, Castillo J, San Lucas FA, Scelo G, Kim DU, Bernard V, et al. High prevalence of mutant KRAS in circulating exosome-derived DNA from early stage pancreatic cancer patients. *Annals of Oncology*. 2017;**28**(4):741-747
- [103] Takikawa T, Masamune A, Yoshida N, Hamada S, Kogure T, Shimosegawa T. Exosomes derived from pancreatic stellate cells: MicroRNA signature and effects on pancreatic cancer cells. *Pancreas*. 2017;**46**(1):19-27
- [104] Que R, Ding G, Chen J, Cao L. Analysis of serum exosomal microRNAs and clinicopathologic features of patients with pancreatic adenocarcinoma. *World Journal of Surgical Oncology*. 2013;**11**:219
- [105] Joshi GK, Deitz-McElyea S, Liyanage T, Lawrence K, Mali S, Sardar R, et al. Label-free nanoplasmonic-based short noncoding RNA sensing at attomolar concentrations allows for quantitative and highly specific assay of microRNA-10b in biological fluids and circulating exosomes. *ACS Nano*. 2015;**9**(11):11075-11089
- [106] Jiao F, Hu H, Yuan C, Wang L, Jiang W, Jin Z, et al. Elevated expression level of long noncoding RNA MALAT-1 facilitates cell growth, migration and invasion in pancreatic cancer. *Oncology Reports*. 2014;**32**(6):2485-2492
- [107] Jiao F, Hu H, Han T, Yuan C, Wang L, Jin Z, et al. Long noncoding RNA MALAT-1 enhances stem cell-like phenotypes in pancreatic cancer cells. *International Journal of Molecular Sciences*. 2015;**16**(4):6677-6693
- [108] Cheng Y, Jutooru I, Chadalapaka G, Corton JC, Safe S. The long non-coding RNA HOTTIP enhances pancreatic cancer cell proliferation, survival and migration. *Oncotarget*. 2015;**6**(13):10840-10852
- [109] Xie Z, Chen X, Li J, Guo Y, Li H, Pan X, et al. Salivary HOTAIR and PVT1 as novel biomarkers for early pancreatic cancer. *Oncotarget*. 2016;**7**(18):25408-25419
- [110] Huang C, Yu W, Wang Q, Cui H, Wang Y, Zhang L, et al. Increased expression of the lncRNA PVT1 is associated with poor prognosis in pancreatic cancer patients. *Minerva Medica*. 2015;**106**(3):143-149
- [111] Ma L, Tian X, Wang F, Zhang Z, Du C, Xie X, et al. The long noncoding RNA H19 promotes cell proliferation via E2F-1 in pancreatic ductal adenocarcinoma. *Cancer Biology and Therapy*. 2016;**17**(10):1051-1061
- [112] Chen P, Wan D, Zheng D, Zheng Q, Wu F, Zhi Q. Long non-coding RNA UCA1 promotes the tumorigenesis in pancreatic cancer. *Biomedicine & Pharmacotherapy*. 2016;**83**:1220-1226
- [113] Li Z, Zhao X, Zhou Y, Liu Y, Zhou Q, Ye H, et al. The long non-coding RNA HOTTIP promotes progression and gemcitabine resistance by regulating HOXA13 in pancreatic cancer. *Journal of Translational Medicine*. 2015;**13**:84

- [114] Wang Y, Li Z, Zheng S, Zhou Y, Zhao L, Ye H, et al. Expression profile of long non-coding RNAs in pancreatic cancer and their clinical significance as biomarkers. *Oncotarget*. 2015;6(34):35684-35698
- [115] Liu C, Wang J, Yuan X, Qian W, Zhang B, Shi M, et al. Long noncoding RNA uc.345 promotes tumorigenesis of pancreatic cancer by upregulation of hnRNPL expression. *Oncotarget*. 2016;7(44):71556-71566
- [116] Lian Y, Wang J, Feng J, Ding J, Ma Z, Li J, et al. Long non-coding RNA IRAIN suppresses apoptosis and promotes proliferation by binding to LSD1 and EZH2 in pancreatic cancer. *Tumour Biology*. 2016;37(11):14929-14937
- [117] Yin DD, Zhang EB, You LH, Wang N, Wang LT, Jin FY, et al. Downregulation of lncRNA TUG1 affects apoptosis and insulin secretion in mouse pancreatic β cells. *Cellular Physiology and Biochemistry*. 2015;35(5):1892-1904
- [118] Peng W, Jiang A. Long noncoding RNA CCDC26 as a potential predictor biomarker contributes to tumorigenesis in pancreatic cancer. *Biomedicine & Pharmacotherapy*. 2016;83:712-717
- [119] Zhan HX, Wang Y, Li C, Xu JW, Zhou B, Zhu JK, et al. LincRNA-ROR promotes invasion, metastasis and tumor growth in pancreatic cancer through activating ZEB1 pathway. *Cancer Letters*. 2016;374(2):261-271
- [120] Li L, Zhang GQ, Chen H, Zhao ZJ, Chen HZ, Liu H, et al. Plasma and tumor levels of Linc-pint are diagnostic and prognostic biomarkers for pancreatic cancer. *Oncotarget*. 2016;7(44):71773-71781
- [121] Sun XL, Cao GH, Cao Y, Jiang X, Li XK, Ye XH, et al. Association of LncRNA HMLincRNA717 with prognosis in pancreatic cancer. *European Review for Medical and Pharmacological Sciences*. 2016;20(11):2230-2234
- [122] Zheng J, Huang X, Tan W, Yu D, Du Z, Chang J, et al. Pancreatic cancer risk variant in LINC00673 creates a miR-1231 binding site and interferes with PTPN11 degradation. *Nature Genetics*. 2016;48(7):747-757
- [123] Fellenberg J, Bernd L, Dellling G, Witte D, Zahlten-Hinguranage A. Prognostic significance of drug-regulated genes in high-grade osteosarcoma. *Modern Pathology*. 2007;20(10):1085-1094
- [124] Ren YK, Xiao Y, Wan XB, Zhao YZ, Li J, Li Y, et al. Association of long non-coding RNA HOTTIP with progression and prognosis in colorectal cancer. *International Journal of Clinical and Experimental Pathology*. 2015;8(9):11458-11463
- [125] Zhang H, Zhao L, Wang YX, Xi M, Liu SL, Luo LL. Long non-coding RNA HOTTIP is correlated with progression and prognosis in tongue squamous cell carcinoma. *Tumour Biology*. 2015;36(11):8805-8809
- [126] Quagliata L, Matter MS, Piscuoglio S, Arabi L, Ruiz C, Procino A, et al. Long noncoding RNA HOTTIP/HOXA13 expression is associated with disease progression and predicts outcome in hepatocellular carcinoma patients. *Hepatology*. 2014;59(3):911-923

- [127] Zheng X, Hu H, Li S. High expression of lncRNA PVT1 promotes invasion by inducing epithelial-to-mesenchymal transition in esophageal cancer. *Oncology Letters*. 2016;**12**(4):2357-2362
- [128] Wan L, Sun M, Liu GJ, Wei CC, Zhang EB, Kong R, et al. Long noncoding RNA PVT1 promotes non-small cell lung cancer cell proliferation through epigenetically regulating LATS2 expression. *Molecular Cancer Therapeutics*. 2016;**15**(5):1082-1094
- [129] Zeng C, Yu X, Lai J, Yang L, Chen S, Li Y. Overexpression of the long non-coding RNA PVT1 is correlated with leukemic cell proliferation in acute promyelocytic leukemia. *Journal of Hematology & Oncology*. 2015;**8**:126
- [130] Zhuang C, Li J, Liu Y, Chen M, Yuan J, Fu X, et al. Tetracycline-inducible shRNA targeting long non-coding RNA PVT1 inhibits cell growth and induces apoptosis in bladder cancer cells. *Oncotarget*. 2015;**6**(38):41194-41203
- [131] Kong R, Zhang EB, Yin DD, You LH, Xu TP, Chen WM, et al. Long noncoding RNA PVT1 indicates a poor prognosis of gastric cancer and promotes cell proliferation through epigenetically regulating p15 and p16. *Molecular Cancer*. 2015;**14**:82
- [132] Yang YR, Zang SZ, Zhong CL, Li YX, Zhao SS, Feng XJ. Increased expression of the lncRNA PVT1 promotes tumorigenesis in non-small cell lung cancer. *International Journal of Clinical and Experimental Pathology*. 2014;**7**(10):6929-6935
- [133] Zhang Z, Zhu Z, Zhang B, Li W, Li X, Wu X, et al. Frequent mutation of rs13281615 and its association with PVT1 expression and cell proliferation in breast cancer. *Journal of Genetics and Genomics*. 2014;**41**(4):187-195
- [134] Zhang S, Zhang G, Liu J. Long noncoding RNA PVT1 promotes cervical cancer progression through epigenetically silencing miR-200b. *APMIS*. 2016;**124**(8):649-658
- [135] Iden M, Fye S, Li K, Chowdhury T, Ramchandran R, Rader JS. The lncRNA PVT1 contributes to the cervical cancer phenotype and associates with poor patient prognosis. *PLoS One*. 2016;**11**(5):e0156274
- [136] Yuan CL, Li H, Zhu L, Liu Z, Zhou J, Shu Y. Aberrant expression of long noncoding RNA PVT1 and its diagnostic and prognostic significance in patients with gastric cancer. *Neoplasma*. 2016;**63**(3):442-449
- [137] Ding J, Li D, Gong M, Wang J, Huang X, Wu T, et al. Expression and clinical significance of the long non-coding RNA PVT1 in human gastric cancer. *OncoTargets and Therapy*. 2014;**7**:1625-1630
- [138] Liu E, Liu Z, Zhou Y, Mi R, Wang D. Overexpression of long non-coding RNA PVT1 in ovarian cancer cells promotes cisplatin resistance by regulating apoptotic pathways. *International Journal of Clinical and Experimental Medicine*. 2015;**8**(11):20565-20572
- [139] Zhang XW, Bu P, Liu L, Zhang XZ, Li J. Overexpression of long non-coding RNA PVT1 in gastric cancer cells promotes the development of multidrug resistance. *Biochemical and Biophysical Research Communications*. 2015;**462**(3):227-232

- [140] Zhou Q, Chen J, Feng J, Wang J. Long noncoding RNA PVT1 modulates thyroid cancer cell proliferation by recruiting EZH2 and regulating thyroid-stimulating hormone receptor (TSHR). *Tumour Biology*. 2016;**37**(3):3105-3113
- [141] Takahashi Y, Sawada G, Kurashige J, Uchi R, Matsumura T, Ueo H, et al. Amplification of PVT-1 is involved in poor prognosis via apoptosis inhibition in colorectal cancers. *British Journal of Cancer*. 2014;**110**(1):164-171
- [142] Yang JP, Yang XJ, Xiao L, Wang Y. Long noncoding RNA PVT1 as a novel serum biomarker for detection of cervical cancer. *European Review for Medical and Pharmacological Sciences*. 2016;**20**(19):3980-3986
- [143] Yu J, Han J, Zhang J, Li G, Liu H, Cui X, et al. The long noncoding RNAs PVT1 and uc002mbe.2 in sera provide a new supplementary method for hepatocellular carcinoma diagnosis. *Medicine (Baltimore)*. 2016;**95**(31):e4436
- [144] Wu Y, Wang YQ, Weng WW, Zhang QY, Yang XQ, Gan HL, et al. A serum-circulating long noncoding RNA signature can discriminate between patients with clear cell renal cell carcinoma and healthy controls. *Oncogenesis*. 2016;**5**:e192
- [145] Ding C, Yang Z, Lv Z, Du C, Xiao H, Peng C, et al. Long non-coding RNA PVT1 is associated with tumor progression and predicts recurrence in hepatocellular carcinoma patients. *Oncology Letters*. 2015;**9**(2):955-963
- [146] Ding C, Cheng S, Yang Z, Lv Z, Xiao H, Du C, et al. Long non-coding RNA HOTAIR promotes cell migration and invasion via down-regulation of RNA binding motif protein 38 in hepatocellular carcinoma cells. *International Journal of Molecular Sciences*. 2014;**15**(3):4060-4076
- [147] Lee M, Kim HJ, Kim SW, Park SA, Chun KH, Cho NH, et al. The long non-coding RNA HOTAIR increases tumour growth and invasion in cervical cancer by targeting the Notch pathway. *Oncotarget*. 2016;**7**(28):44558-44571
- [148] Luo ZF, Zhao D, Li XQ, Cui YX, Ma N, Lu CX, et al. Clinical significance of HOTAIR expression in colon cancer. *World Journal of Gastroenterology*. 2016;**22**(22):5254-5259
- [149] Sun W, Yang Y, Xu C, Xie Y, Guo J. Roles of long noncoding RNAs in gastric cancer and their clinical applications. *Journal of Cancer Research and Clinical Oncology*. 2016;**142**(11):2231-2237
- [150] Dong L, Hui L. HOTAIR promotes proliferation, migration, and invasion of ovarian cancer SKOV3 cells through regulating PIK3R3. *Medical Science Monitor*. 2016;**22**:325-331
- [151] Zhu Y, Yu RK, Ji AF, Yao XL, Fang JJ, Jin XD. Effects of long non-coding RNA-HOTAIR on the cell cycle and invasiveness of prostate cancer. [Article in Chinese] *Zhonghua Nan Ke Xue*. 2015;**21**(9):792-796
- [152] Yang XD, Xu HT, Xu XH, Ru G, Liu W, Zhu JJ, et al. Knockdown of long non-coding RNA HOTAIR inhibits proliferation and invasiveness and improves radiosensitivity in colorectal cancer. *Oncology Reports*. 2016;**35**(1):479-487

- [153] Li H, An J, Wu M, Zheng Q, Gui X, Li T, et al. LncRNA HOTAIR promotes human liver cancer stem cell malignant growth through downregulation of SETD2. *Oncotarget*. 2015;6(29):27847-27864
- [154] Yiwei T, Hua H, Hui G, Mao M, Xiang L. HOTAIR interacting with MAPK1 regulates ovarian cancer skov3 cell proliferation, migration, and invasion. *Medical Science Monitor*. 2015;21:1856-1863
- [155] Zhou C, Ye L, Jiang C, Bai J, Chi Y, Zhang H. Long noncoding RNA HOTAIR, a hypoxia-inducible factor-1 α activated driver of malignancy, enhances hypoxic cancer cell proliferation, migration, and invasion in non-small cell lung cancer. *Tumour Biology*. 2015;36(12):9179-9188
- [156] Milevskiy MJ, Al-Ejeh F, Saunus JM, Northwood KS, Bailey PJ, Betts JA, et al. Longrange regulators of the lncRNA HOTAIR enhance its prognostic potential in breast cancer. *Human Molecular Genetics*. 2016;25(15):3269-3283
- [157] Qiu H, Liu Q, Li J, Wang X, Wang Y, Yuan Z, et al. Analysis of the association of HOTAIR single nucleotide polymorphism (rs920778) and risk of cervical cancer. *APMIS*. 2016;124(7):567-573
- [158] Gao JZ, Li J, Du JL, Li XL. Long non-coding RNA HOTAIR is a marker for hepatocellular carcinoma progression and tumor recurrence. *Oncology Letters*. 2016;11(3):1791-1798
- [159] Berrondo C, Flax J, Kuchеров V, Siebert A, Osinski T, Rosenberg A, et al. Expression of the long non-coding RNA HOTAIR correlates with disease progression in bladder cancer and is contained in bladder cancer patient urinary exosomes. *PLoS One*. 2016;11(1):e0147236
- [160] Shang C, Guo Y, Zhang H, Xue YX. Long noncoding RNA HOTAIR is a prognostic biomarker and inhibits chemosensitivity to doxorubicin in bladder transitional cell carcinoma. *Cancer Chemotherapy and Pharmacology*. 2016;77(3):507-513
- [161] Xue X, Yang YA, Zhang A, Fong KW, Kim J, Song B, et al. LncRNA HOTAIR enhances ER signaling and confers tamoxifen resistance in breast cancer. *Oncogene*. 2016;35(21):2746-2755
- [162] Li J, Yang S, Su N, Wang Y, Yu J, Qiu H, et al. Overexpression of long non-coding RNA HOTAIR leads to chemoresistance by activating the Wnt/ β -catenin pathway in human ovarian cancer. *Tumour Biology*. 2016;37(2):2057-2065
- [163] Wu H, Shang X, Shi Y, Yang Z, Zhao J, Yang M, et al. Genetic variants of lncRNA HOTAIR and risk of epithelial ovarian cancer among Chinese women. *Oncotarget*. 2016;7(27):41047-41052
- [164] Dou J, Ni Y, He X, Wu D, Li M, Wu S, et al. Decreasing lncRNA HOTAIR expression inhibits human colorectal cancer stem cells. *American Journal of Translational Research*. 2016;8(1):98-108

- [165] Yang L, Zhang X, Li H, Liu J. The long noncoding RNA HOTAIR activates autophagy by upregulating ATG3 and ATG7 in hepatocellular carcinoma. *Molecular Biosystems*. 2016;12(8):2605-2612
- [166] Sun J, Chu H, Ji J, Huo G, Song Q, Zhang X. Long non-coding RNA HOTAIR modulates HLA-G expression by absorbing miR-148a in human cervical cancer. *International Journal of Oncology*. 2016;49(3):943-952
- [167] Song B, Guan Z, Liu F, Sun D, Wang K, Qu H. Long non-coding RNA HOTAIR promotes HLA-G expression via inhibiting miR-152 in gastric cancer cells. *Biochemical and Biophysical Research Communications*. 2015;464(3):807-813
- [168] Kishikawa T, Otsuka M, Ohno M, Yoshikawa T, Takata A, Koike K. Circulating RNAs as new biomarkers for detecting pancreatic cancer. *World Journal of Gastroenterology*. 2015;21(28):8527-8540
- [169] Zhang Y, Zhang K, Luo Z, Liu L, Wu L, Liu J. Circulating long non-coding HOX transcript antisense intergenic ribonucleic acid in plasma as a potential biomarker for diagnosis of breast cancer. *Thoracic Cancer*. 2016;7(6):627-632
- [170] Zhao W, Song M, Zhang J, Kuerban M, Wang H. Combined identification of long non-coding RNA CCAT1 and HOTAIR in serum as an effective screening for colorectal carcinoma. *International Journal of Clinical and Experimental Pathology*. 2015;8(11):14131-14140
- [171] Arita T, Ichikawa D, Konishi H, Komatsu S, Shiozaki A, Shoda K, et al. Circulating long non-coding RNAs in plasma of patients with gastric cancer. *Anticancer Research*. 2013;33(8):3185-3193
- [172] Wang L, Sun Y, Yi J, Wang X, Liang J, Pan Z, et al. Targeting H19 by lentivirus-mediated RNA interference increases A549 cell migration and invasion. *Experimental Lung Research*. 2016;42(7):346-353
- [173] Jiang X, Yan Y, Hu M, Chen X, Wang Y, Dai Y, et al. Increased level of H19 long noncoding RNA promotes invasion, angiogenesis, and stemness of glioblastoma cells. *Journal of Neurosurgery*. 2016;124(1):129-136
- [174] Berteaux N, Lottin S, Monté D, Pinte S, Quatannens B, Coll J, et al. H19 mRNA-like noncoding RNA promotes breast cancer cell proliferation through positive control by E2F1. *The Journal of Biological Chemistry*. 2005;280(33):29625-29636
- [175] Jing W, Zhu M, Zhang XW, Pan ZY, Gao SS, Zhou H, et al. The significance of long non-coding RNA H19 in predicting progression and metastasis of cancers: A meta-analysis. *BioMed Research International*. 2016;2016:5902678
- [176] Wang SH, Wu XC, Zhang MD, Weng MZ, Zhou D, Quan ZW. Upregulation of H19 indicates a poor prognosis in gallbladder carcinoma and promotes epithelial-mesenchymal transition. *American Journal of Cancer Research*. 2015;6(1):15-26

- [177] Han D, Gao X, Wang M, Qiao Y, Xu Y, Yang J, et al. Long noncoding RNA H19 indicates a poor prognosis of colorectal cancer and promotes tumor growth by recruiting and binding to eIF4A3. *Oncotarget*. 2016;**7**(16):22159-22173
- [178] Wang SH, Wu XC, Zhang MD, Weng MZ, Zhou D, Quan ZW. Long noncoding RNA H19 contributes to gallbladder cancer cell proliferation by modulated miR-194-5p targeting AKT2. *Tumour Biology*. 2016;**37**(7):9721-9730
- [179] Zhang E, Li W, Yin D, De W, Zhu L, Sun S, et al. c-Myc-regulated long non-coding RNA H19 indicates a poor prognosis and affects cell proliferation in non-small-cell lung cancer. *Tumour Biology*. 2016;**37**(3):4007-4015
- [180] Jia P, Cai H, Liu X, Chen J, Ma J, Wang P, et al. Long non-coding RNA H19 regulates glioma angiogenesis and the biological behavior of glioma-associated endothelial cells by inhibiting microRNA-29a. *Cancer Letters*. 2016;**381**(2):359-369
- [181] Zheng ZG, Xu H, Suo SS, Xu XL, Ni MW, Gu LH, et al. The essential role of H19 contributing to cisplatin resistance by regulating glutathione metabolism in high-grade serous ovarian cancer. *Scientific Reports*. 2016;**6**:26093
- [182] Li W, Jiang P, Sun X, Xu S, Ma X, Zhan R. Suppressing H19 modulates tumorigenicity and stemness in U251 and U87MG glioma cells. *Cellular and Molecular Neurobiology*. 2016;**36**(8):1219-1227
- [183] Zeira E, Abramovitch R, Meir K, Even Ram S, Gil Y, Bulvik B, et al. The knockdown of H19lncRNA reveals its regulatory role in pluripotency and tumorigenesis of human embryonic carcinoma cells. *Oncotarget*. 2015;**6**(33):34691-34703
- [184] Huang C, Cao L, Qiu L, Dai X, Ma L, Zhou Y, et al. Upregulation of H19 promotes invasion and induces epithelial-to-mesenchymal transition in esophageal cancer. *Oncology Letters*. 2015;**10**(1):291-296
- [185] Liang WC, Fu WM, Wong CW, Wang Y, Wang WM, Hu GX, et al. The lncRNA H19 promotes epithelial to mesenchymal transition by functioning as miRNA sponges in colorectal cancer. *Oncotarget*. 2015;**6**(26):22513-22525
- [186] Hidalgo M, Cascinu S, Kleeff J, Labianca R, Löhner JM, Neoptolemos J, et al. Addressing the challenges of pancreatic cancer: Future directions for improving outcomes. *Pancreatology*. 2013;**15**(1):8-18
- [187] Yang T, Zeng H, Chen W, Zheng R, Zhang Y, Li Z, et al. Helicobacter pylori infection, H19 and LINC00152 expression in serum and risk of gastric cancer in a Chinese population. *Cancer Epidemiology*. 2016;**44**:147-153
- [188] Hua Q, Lv X, Gu X, Chen Y, Chu H, Du M, et al. Genetic variants in lncRNA H19 are associated with the risk of bladder cancer in a Chinese population. *Mutagenesis*. 2016;**31**(5):531-538

- [189] Feng J, Sun Y, Zhang EB, Lu XY, Jin SD, Guo RH. A novel long noncoding RNA IRAIN regulates cell proliferation in nonsmall cell lung cancer. *International Journal of Clinical and Experimental Pathology*. 2015;8(10):12268-12275
- [190] Kang L, Sun J, Wen X, Cui J, Wang G, Hoffman AR, et al. Aberrant allele-switch imprinting of a novel IGF1R intragenic antisense non-coding RNA in breast cancers. *European Journal of Cancer*. 2015;51(2):260-270
- [191] Lu L, Shen Y, Tseng KF, Liu W, Duan H, Meng W. Silencing of UCA1, a poor prognostic factor, inhibited the migration of endometrial cancer cell. *Cancer Biomarkers*. 2016;17(2):171-177
- [192] Bian Z, Jin L, Zhang J, Yin Y, Quan C, Hu Y, et al. LncRNA-UCA1 enhances cell proliferation and 5-fluorouracil resistance in colorectal cancer by inhibiting miR-204-5p. *Scientific Reports*. 2016;6:23892
- [193] Nie W, Ge HJ, Yang XQ, Sun X, Huang H, Tao X, et al. LncRNA-UCA1 exerts oncogenic functions in non-small cell lung cancer by targeting miR-193a-3p. *Cancer Letters*. 2016;371(1):99-106
- [194] Na XY, Liu ZY, Ren PP, Yu R, Shang XS. Long non-coding RNA UCA1 contributes to the progression of prostate cancer and regulates proliferation through KLF4-KRT6/13 signaling pathway. *International Journal of Clinical and Experimental Medicine*. 2015;8(8):12609-12616
- [195] Yang YT, Wang YF, Lai JY, Shen SY, Wang F, Kong J, et al. Long non-coding RNA UCA1 contributes to the progression of oral squamous cell carcinoma via regulating WNT/ β -catenin signaling pathway. *Cancer Science*. 2016;107(11):1581-1589
- [196] Li JY, Ma X, Zhang CB. Overexpression of long non-coding RNA UCA1 predicts a poor prognosis in patients with esophageal squamous cell carcinoma. *International Journal of Clinical and Experimental Pathology*. 2014;7(11):7938-7944
- [197] Xiao C, Wu CH, Hu HZ. LncRNA UCA1 promotes epithelial-mesenchymal transition (EMT) of breast cancer cells via enhancing Wnt/beta-catenin signaling pathway. *European Review for Medical and Pharmacological Sciences*. 2016;20(13):2819-2824
- [198] Yang Y, Jiang Y, Wan Y, Zhang L, Qiu J, Zhou S, et al. UCA1 functions as a competing endogenous RNA to suppress epithelial ovarian cancer metastasis. *Tumour Biology*. 2016;37(8):10633-10641
- [199] Lee JJ, Kim M, Kim HP. Epigenetic regulation of long noncoding RNA UCA1 by SATB1 in breast cancer. *BMB Reports*. 2016;49(10):578-583
- [200] Tuo YL, Li XM, Luo J. Long noncoding RNA UCA1 modulates breast cancer cell growth and apoptosis through decreasing tumor suppressive miR-143. *European Review for Medical and Pharmacological Sciences*. 2015;19(18):3403-3411
- [201] Wang X, Yang B, Ma B. The UCA1/miR-204/Sirt1 axis modulates docetaxel sensitivity of prostate cancer cells. *Cancer Chemotherapy and Pharmacology*. 2016;78(5):1025-1031

- [202] Wu C, Luo J. Long non-coding RNA (lncRNA) urothelial carcinoma-associated 1 (UCA1) enhances tamoxifen resistance in breast cancer cells via inhibiting mTOR signaling pathway. *Medical Science Monitor*. 2016;**22**:3860-3867
- [203] Pan J, Li X, Wu W, Xue M, Hou H, Zhai W. Long non-coding RNA UCA1 promotes cisplatin/gemcitabine resistance through CREB modulating miR-196a-5p in bladder cancer cells. *Cancer Letters*. 2016;**382**(1):64-76
- [204] Fang Q, Chen X, Zhi X. Long non-coding RNA (lncRNA) urothelial carcinoma associated 1 (UCA1) increases multi-drug resistance of gastric cancer via downregulating miR-27b. *Medical Science Monitor*. 2016;**22**:3506-3513
- [205] Li X, Wu Y, Liu A, Tang X. Long non-coding RNA UCA1 enhances tamoxifen resistance in breast cancer cells through a miR-18a-HIF1 α feedback regulatory loop. *Tumour Biology*. 2016;**37**(11):14733-14743
- [206] Li HJ, Li X, Pang H, Pan JJ, Xie XJ, Chen W. Long non-coding RNA UCA1 promotes glutamine metabolism by targeting miR-16 in human bladder cancer. *Japanese Journal of Clinical Oncology*. 2015;**45**(11):1055-1063
- [207] Hariharan D, Saied A, Kocher HM. Analysis of mortality rates for pancreatic cancer across the world. *HPB*. 2008;**10**(1):58-62
- [208] El-Tawdi AH, Matboli M, El-Nakeep S, Azazy AE, Abdel-Rahman O. Association of long noncoding RNA and c-JUN expression in hepatocellular carcinoma. *Expert Review of Gastroenterology & Hepatology*. 2016;**10**(7):869-877
- [209] Gao J, Cao R, Mu H. Long non-coding RNA UCA1 may be a novel diagnostic and predictive biomarker in plasma for early gastric cancer.
- [210] Tao K, Yang J, Hu Y, Sun Y, Tan Z, Duan J, et al. Clinical significance of urothelial carcinoma associated 1 in colon cancer. *International Journal of Clinical and Experimental Medicine*. 2015;**8**(11):21854-21860
- [211] Wang HM, Lu JH, Chen WY, Gu AQ. Upregulated lncRNA-UCA1 contributes to progression of lung cancer and is closely related to clinical diagnosis as a predictive biomarker in plasma. *International Journal of Clinical and Experimental Medicine*. 2015;**8**(7):11824-11830
- [212] Milowich D, Le Mercier M, De Neve N, Sandras F, Roumeguere T, Decaestecker C, et al. Diagnostic value of the UCA1 test for bladder cancer detection: A clinical study. *Springerplus*. 2015;**4**:349
- [213] Eissa S, Matboli M, Essawy NO, Shehta M, Kotb YM. Rapid detection of urinary long non-coding RNA urothelial carcinoma associated one using a PCR-free nanoparticle-based assay. *Biomarkers*. 2015;**20**(3):212-217
- [214] Eissa S, Matboli M, Essawy NO, Kotb YM. Integrative functional genetic-epigenetic approach for selecting genes as urine biomarkers for bladder cancer diagnosis. *Tumour Biology*. 2015;**36**(12):9545-9552

- [215] Srivastava AK, Singh PK, Rath SK, Dalela D, Goel MM, Bhatt ML. Appraisal of diagnostic ability of UCA1 as a biomarker of carcinoma of the urinary bladder. *Tumour Biology*. 2014;**35**(11):11435-11442
- [216] Zhang Z, Hao H, Zhang CJ, Yang XY, He Q, Lin J. Evaluation of novel gene UCA1 as a tumor biomarker for the detection of bladder cancer. [Article in Chinese] *Zhonghua Yi Xue Za Zhi*. 2012;**92**(6):384-387
- [217] Wang XS, Zhang Z, Wang HC, Cai JL, Xu QW, Li MQ, et al. Rapid identification of UCA1 as a very sensitive and specific unique marker for human bladder carcinoma. *Clinical Cancer Research*. 2006;**12**(16):4851-4858
- [218] Zhao XB, Ren GS. WITHDRAWN: LncRNA TUG1 promotes breast cancer cell proliferation via inhibiting miR-9. *Cancer Biomarkers*. 2016. DOI: 10.3233/CBM-160669
- [219] Iliev R, Kleinova R, Juracek J, Dolezel J, Ozanova Z, Fedorko M, et al. Overexpression of long non-coding RNA TUG1 predicts poor prognosis and promotes cancer cell proliferation and migration in high-grade muscle-invasive bladder cancer. *Tumour Biology*. 2016;**37**(10):13385-13390
- [220] Huang MD, Chen WM, Qi FZ, Sun M, Xu TP, Ma P, et al. Long non-coding RNA TUG1 is up-regulated in hepatocellular carcinoma and promotes cell growth and apoptosis by epigenetically silencing of KLF2. *Molecular Cancer*. 2015;**14**:165
- [221] Xu Y, Wang J, Qiu M, Xu L, Li M, Jiang F, et al. Upregulation of the long noncoding RNA TUG1 promotes proliferation and migration of esophageal squamous cell carcinoma. *Tumour Biology*. 2015;**36**(3):1643-1651
- [222] Zhang Q, Geng PL, Yin P, Wang XL, Jia JP, Yao J. Down-regulation of long non-coding RNA TUG1 inhibits osteosarcoma cell proliferation and promotes apoptosis. *Asian Pacific Journal of Cancer Prevention*. 2013;**14**(4):2311-2315
- [223] Kuang D, Zhang X, Hua S, Dong W, Li Z. Long non-coding RNA TUG1 regulates ovarian cancer proliferation and metastasis via affecting epithelial-mesenchymal transition. *Experimental and Molecular Pathology*. 2016;**101**(2):267-273
- [224] Zhai HY, Sui MH, Yu X, Qu Z, Hu JC, Sun HQ, et al. Overexpression of long non-coding RNA TUG1 promotes colon cancer progression. *Medical Science Monitor*. 2016;**22**:3281-3287
- [225] Zhang E, He X, Yin D, Han L, Qiu M, Xu T, et al. Increased expression of long noncoding RNA TUG1 predicts a poor prognosis of gastric cancer and regulates cell proliferation by epigenetically silencing of p57. *Cell Death & Disease*. 2016;**7**:e2109
- [226] Sun J, Ding C, Yang Z, Liu T, Zhang X, Zhao C, et al. The long non-coding RNA TUG1 indicates a poor prognosis for colorectal cancer and promotes metastasis by affecting epithelial-mesenchymal transition. *Journal of Translational Medicine*. 2016;**14**:42
- [227] Jiang L, Wang W, Li G, Sun C, Ren Z, Sheng H, et al. High TUG1 expression is associated with chemotherapy resistance and poor prognosis in esophageal squamous cell carcinoma. *Cancer Chemotherapy and Pharmacology*. 2016;**78**(2):333-339

- [228] Li J, Zhang M, An G, Ma Q. LncRNA TUG1 acts as a tumor suppressor in human glioma by promoting cell apoptosis. *Experimental Biology and Medicine* (Maywood, N.J.). 2016;**241**(6):644-649
- [229] Ma B, Li M, Zhang L, Huang M, Lei JB, Fu GH, et al. Upregulation of long non-coding RNA TUG1 correlates with poor Tumour Biology. 2016;**37**(4):4445-4455
- [230] Isin M, Ozgur E, Cetin G, Erten N, Aktan M, Gezer U, et al. Investigation of circulating lncRNAs in B-cell neoplasms. *Clinica Chimica Acta*. 2014;**431**:255-259