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Review Article

Tumor Markers Involved in Invasion of Pancreatic Cancer

Fatemeh Tajik[1,2], Sara Kamali Zonouzi[2,3], Sepideh Razi[2,4*]

[1] *Oncopathology Research Center, Iran University of Medical Sciences, Tehran, Iran*
[2] *Cancer Immunology Project (CIP), Universal Scientific Education and Research Network (USERN), Tehran, Iran*
[3] *School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*
[4] *Research Center for Immunodeficiencies, Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran*

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Abstract

Pancreatic cancer is still one of the most lethal malignancies across the world, and hence exploring new biomarkers related to the progression and invasive nature of this cancer is important to overcome its resistance to various types of treatments through the design of new therapeutic strategies. Several markers have been shown to play a role in pancreatic cancer invasion, but CA19-9, CA125, and noncoding RNAs, including microRNAs, long noncoding RNAs, and circular RNAs, are the most common ones. In the current review, the role of these markers in pancreatic cancer progression, invasion, and metastasis, as well as related mechanisms, has been provided, and their potential to be utilized in pancreatic cancer diagnosis and treatment has been discussed.

Keywords: Pancreatic Cancer (PC); Invasion; microRNAs; Long Noncoding RNAs; Circular RNAs; CA19-9; CA125

***Corresponding Author:** Sepideh Razi

Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran

E-mail: sepidrazi1994@gmail.com

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Introduction

The mortality rate of pancreatic cancer (PC) is the highest among other gastrointestinal malignancies since most patients are diagnosed with advanced stage and metastasis (1, 2). It has been predicted that PC will become the second leading cause of cancer-related deaths by 2030 (3). According to the estimations, there will be 62,210 new cases diagnosed with PC and 49,830 deaths during 2022, indicating a high fatality rate (4). The 5-year survival rate is roughly 10 percent worldwide, which is the lowest survival rate among all cancers (1, 4, 5). It is supported that 80 to 90 percent of patients have an unresectable tumor at the time of diagnosis (6). Hence, early detection and treatment of this cancer are critical in preserving patients' lives and boosting survival.

One of the most significant concerns in the pro-

gression of PC is identifying the molecular mechanisms contributing to the invasion and metastasis, which are responsible for about 90 percent of cause deaths in patients (7). Tumor invasion leads to the penetration of tumor cells into adjacent normal tissues, which results in metastasis (8). Invasion is a complex process, and its biochemical, biological, and biomarkers are not completely elucidated. Therefore, it is critical to recognize the underlying actions of tumor markers involved in cancer development and invasion.

Currently, many experimental studies are working on the tumor markers of PC. Tumor markers are biochemicals that can be measured in cancerous patients' blood and can be either tumor-derived or tumor-associated (9, 10). Several tumor markers comprising carbohydrate antigens (CA19-9, CA125, CA50, CA242), glycoproteins like carcinoembryonic antigen (CEA) and pancreatic oncofetal antigen (POA), microRNAs, and others have been considered for the screening and diagnosing of the PC; however, their clinical utility remains obscure (11-13). Of these, CA19-9, the most widely used serum marker in detecting PC, is overexpressed in PC tissues and correlates with perineural invasion and advanced grades of disease (14). It was found that long non-coding ribonucleic acids (RNAs) can act on migration and invasion of PC (15). Specifically, upregulation of LINC00675, LINC01963, and MEG3 are correlated with perineural invasion, inhibition of proliferation and invasion, and decreased rate of metastasis and vascular invasion of PC, respectively (16). LncRNA XIST promotes invasion through the increased expression of TGF-β2 by preventing miR-141-3p expression (17). Besides, stanniocalcin 2, a marker of tumor progression, is overexpressed in PC cells, leading to increased invasion and migration (18).

Overall, multiple biomarkers have played an important role in PC invasion. In the current review, we comprehensively examined tumor markers involved in PC invasion for the first time and described the functions of these markers in the invasion.

Tumor Markers Related to PC Invasion

A wide variety of tumor markers have been associated with pancreatic cancer invasion. Among them, tumor-associated antigens such as CA19-9 and CA125 and noncoding RNAs, including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs), are the most investigated markers related to the invasion of pancreatic cancer. Understanding the role of invasion-associated markers is crucial due to their role in cancer progression and patients' survival rates, making them potential candidates for exploring new therapeutic strategies in the future. Here, we review the role of these markers in the progression and invasion of PC.

CA19-9

Carbohydrate antigen 19-9 (CA19-9), a tetrasaccharide (5-Acetylneuraminyl-2-3-Galactosyl-1-3-(Fucopyranosyl-1-4)-N-Acetylglucosamine), also known as antigen sialyl-Lewis a (sLea), is the most extensively used and the foremost validated biomarker for both diagnosis and therapy monitoring in patients with pancreatic adenocarcinoma (19, 20). CA19-9 elevation can be seen not only in pancreatic cancer but also in multiple pathologic conditions such as obstructive jaundice, acute or chronic pancreatitis, and malignancies originating from the breast, liver, colorectum, and stomach (19). In contrast, Lewis negative individuals cannot synthesize CA19-9, resulting in normal CA19-9 levels even in the advanced pancreatic cancer (21). The alteration of surface glycosylation during the malignant transformation of pancreatic cells results in the overexpression of CA19-9 (22, 23). An altered glycosylation pattern can have an important role in cancer invasion and metastasis (24-26). Several studies have demonstrated the correlation between a high CA19-9 level and a poor prognosis or invasive manner of pancreatic cancer. In an in vivo study conducted by Engle *et al.*, CA19-9 was shown to promote pancreatitis, which led to the development of pancreatic ductal adenocarcinoma (27). The higher ratio of CA19-9 to total tumor volume correlates with lower survival and poor prognosis (28). Persistent elevation of the CA19-9 level after surgical resection serves as a significant negative predictor of survival (29). CA 19-9 level correlates with perineural invasion and advanced grade of disease (14). Pancreatic cancer patients with a normal CA19-9 level significantly have a lower invasion of the surrounding tissues, intrapancreatic neural invasion, angiolymphatic

invasion, anterior serosal invasion, and lymph node metastasis (30). Similarly, it was shown that elevated preoperative CA19-9 was associated with lymphovascular space invasion as well as the pancreatic extension (31).

CA125

Cancer antigen 125 (CA125), also known as mucin 16 (MUC16), is one of the transmembrane glycoproteins belonging to the mucin family, which is used as a screening and diagnostic tumor marker most commonly used for ovarian cancer and less commonly used for some other malignancies like pancreatic cancer (32, 33). CA125 has been reported as a potential prognostic biomarker in many studies. Liu *et al.*. revealed that patients with metastatic pancreatic cancer to either lymph nodes or distant organs had higher levels of CA125 compared to the patients without metastasis, and baseline CA125 serum levels reflected the extent of pancreatic cancer dissemination to the metastatic sites like the liver and lymph nodes. Moreover, higher CA125 levels were associated with earlier distant metastasis in patients following pancreatectomy (34). Chen *et al.* found that Mesothelin binding to MUC16 could promote pancreatic cancer cell migration and invasion through activating MMP-7 and regulating the p38 MAPK-dependent pathway (35). Similarly, Shimizu *et al.* showed that co-expression of mesothelin and MUC16 promoted invasion in pancreatic ductal adenocarcinoma (36).

MicroRNAs

MicroRNAs (miRNAs) are small noncoding RNAs (ncRNAs) with about 22 nucleotides that can target 3'-untranslated regions to express a variety of genes and can cause the breakdown of mRNA by inhibiting the translation (37). Stability in serum, simplicity of non-invasive detection in circulation, and a practical screening procedure are all considered to be the benefits of utilizing miRNAs (38). Previous studies have revealed that the dysregulation of miRNAs has been linked to changes in the genes that control the development of cancer (39). Many oncogenic and tumor suppressor miRNAs have been shown to be involved in the invasion of pancreatic cancer. For example, the study of Pengcheng *et al.* showed that miR-573 was significantly downregulated in pancreatic cancer tissues and cell lines. miR-573 inhibited cell proliferation, migration, and invasion in vitro and inhibited tumor growth in vivo through regulating E2F3. In addition, the expression of miR-573 was associated with the tumor–node–metastasis (TNM) stage, tumor size, and lymph node metastasis (40). MiR 7515 is another tumor suppressor miRNA that is downregulated in pancreatic cancer tissues and cell lines. Downregulated miR 7515 promotes cell proliferation, migration, and invasion both in vitro and in vivo by downregulating insulin-like growth factor 1 (IGF 1) and subsequent Ras/Raf/MEK/ERK signaling pathways. Moreover, miR 7515 negatively correlates with tumor size, TNM stage, distant and lymph node metastasis, and perineural and blood vessel invasion (41). Low expression of miR-1252-5p, which is seen in pancreatic cancer tissue samples and cell lines, is correlated with node invasion and high histologic grade. In vitro, overexpression of miR-1252-5p inhibits cell proliferation, migration, and invasion as well as an epithelial-mesenchymal transition by targeting neural precursor cell expressed, developmentally downregulated 9 (NEDD9), and in vivo, it causes suppression in tumor growth (42). MiR-203-3p is downregulated in pancreatic cancer cell lines. A high level of miR-203-3p suppresses cell proliferation, migration, and invasion. In addition, it induces apoptosis via the downregulation of fibroblast growth factor 2 (43). MiR-1469-5p, as an oncogenic miRNA, is upregulated in pancreatic cancer tissues and cell lines. The expression of miR-1469-5p is associated with the TNM stage and lymph node metastasis. Besides, upregulated miR-1469-5p promotes pancreatic cancer cell proliferation and invasion by regulating the NDRG1/NF-κB/E-cadherin axis (44). MiR-301a is another oncogenic miRNA that is upregulated in pancreatic cancer tissues and cell lines. High expression of miR-301a is related to advanced TNM staging and poor survival. Moreover, MiR-301a has an important role in cell migration, invasion, and angiogenesis in vitro, as well as cell invasion and metastasis in vivo by targeting suppressor of cytokine signaling 5 (SOCS5) and Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signaling pathways (45). **Figure 1** and **Table 1** describe the important miRNAs that play a role in pancreatic cancer invasion.

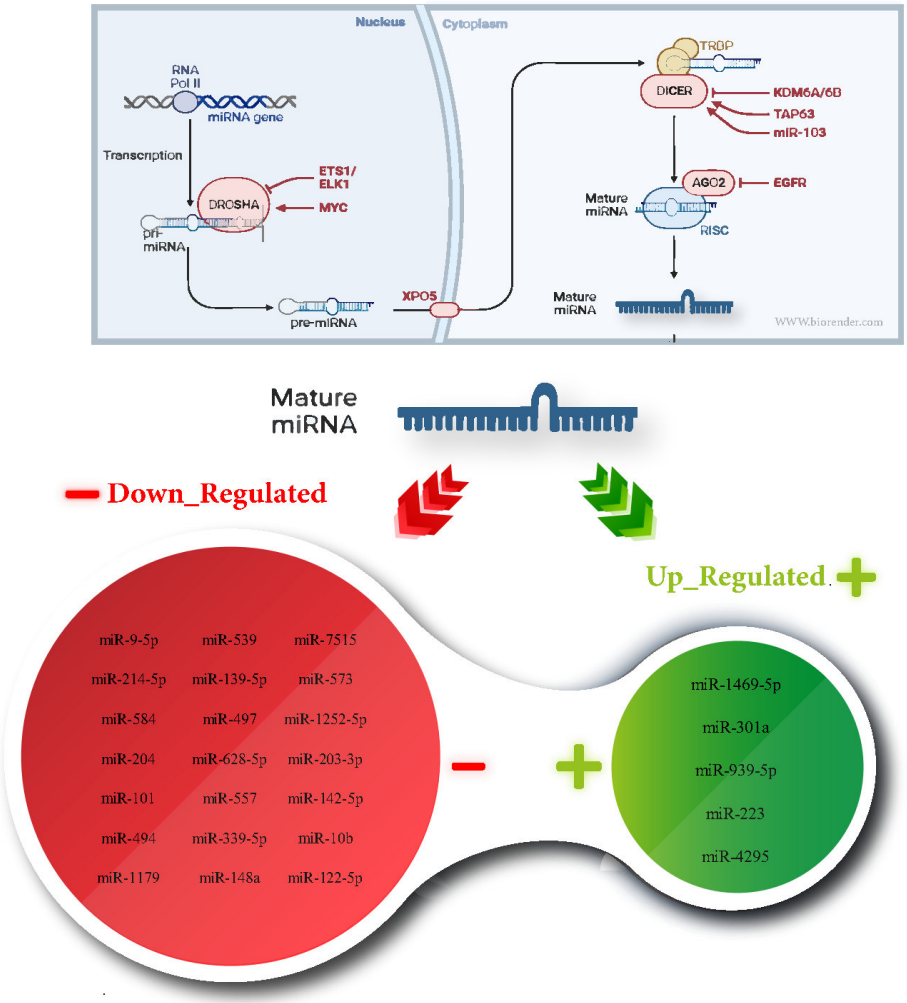

Figure 1. Dysregulated miRNAs involved in pancreatic cancer invasion

Table 1. List of some miRNAs associated with pancreatic cancer invasion

miRNA	Cell line/Animal	Model	Main effect	References
Upregulation				
miR-1469-5p	PANC-1, AsPC-1, and SW1990 cells	*In vitro*	Promoted cell proliferation and invasion	(44)
miR-301a	PANC-1, Mia-PaCa-2, AsPC-1, BxPC-3, and SW1990 cells female BALB/c nude mice	*In vitro* *In vivo*	Promoted cell invasion, angiogenesis, and migration Promoted tumor invasion and metastasis	(45)
miR-939-5p	BxPC-3, Capan-1, PANC-1, MIA PaCa-2, and SW1990 cells	*In vitro*	Promoted cell migration and invasion	(46)
miR-223	AsPC-1, PaTu-8988, and PANC-1 cells Nude mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, and invasion Inhibited apoptosis Promoted tumor growth	(47)
miR-4295	AsPC-1, Panc-1, BxPC-3, and SW1990 cells	*In vitro*	Promoted cell proliferation and invasion	(48)
Downregulation				
miR-7515	AsPC-1, BXPC-3, SW1990, and PANC-1 cells BALB/c nude mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, and invasion Promoted cell proliferation and metastasis	(41)

Table 1. Continued

miR-573	PANC-1, CFPAC-1, and MIAPaCa-2 cells BALB/c nude mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, and invasion Promoted tumor growth	(40)
miR-1252-5p	ASPC-1, CAPAN-2, Panc-1, SW1990, and BxPC-3 cells Mouse	*In vitro* *In vivo*	Promoted cell proliferation, invasion, and epithelial-mesenchymal transition Promoted tumor growth	(42)
miR-203-3p	PANC-1, AsPC-1, BxPC-3, HPAC, and HPNE cells	*In vitro*	Promoted cell proliferation, migration, and invasion Inhibited apoptosis	(43)
miR-142-5p	PanC1, BxPC3, SW1990, and CAPAN-1 cells	*In vitro*	Promoted cell proliferation, migration, and invasion	(49)
miR-10b	ASPC-1, T3M4, BxPc-3, Panc-1, and Miapaca-2 cells	*In vitro*	Promoted cell migration and invasion	(50)
miR-122-5p	PANC-1 and PL-45 cells BALB/c nude mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, and invasion Promoted tumor growth	(51)
miR-539	CAPAN-2, BxPC3, CFPAC1, SW1990, and PANC1 cells	*In vitro*	Promoted cell proliferation, migration, invasion, and epithelial-mesenchymal transition Inhibited apoptosis	(52)
miR-139-5p	PANC-1 and Bx-PC3 cells Nude mice	*In vitro* *In vivo*	Promoted cell proliferation, invasion, and metastasis Promoted tumor growth	(53)
miR-497	Panc1, AsPC1, and Panc28 cells	*In vitro*	Promoted cell proliferation, migration, and invasion	(54)
miR-628-5p	PATU8988T, ASPC-1, CFPAC-1, CAPAN2, SW1990, Panc-1, and BxPC-3 cells	*In vitro*	Promoted cell proliferation, migration, and invasion Inhibited apoptosis	(55)
miR-557	PANC1 cells	*In vitro*	Promoted cell proliferation, migration, and invasion Inhibited apoptosis	(56)
miR-339-5p	PANC02 and PANC02-H7 cells	*In vitro*	Promoted cell migration and invasion	(57)
miR-148a	PANC-1 and Aspc-1 cells BALB/c nude mice	*In vitro* *In vivo*	Promoted cell proliferation and epithelial-mesenchymal transition Promoted tumor growth and invasion	(58)
miR-9-5p	BxPC3, Panc1, Miapaca2, AsPC1, and CFPAC1 cells	*In vitro*	Promoted cell proliferation and invasion Inhibited apoptosis	(59)
miR-214-5p	PANC-1 cells	*In vitro*	Promoted cell proliferation, migration, invasion, and epithelial-mesenchymal transition	(60)
miR-584	Panc-1, Sw1990, and Bxpc-3 cells	*In vitro*	Promoted cell proliferation and invasion	(61)
miR-204	Capan-2, ASPC-1, SW-1990, and Panc-1 cells Male BALB/c nude mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, invasion, and epithelial-mesenchymal transition Promoted tumor growth	(62)
miR-101	PANC-1, AsPC-1, BxPC-3, and SW1990 cells	*In vitro*	Promoted cell proliferation and invasion	(63)
miR-494	ASPC-1, SW1990, BXPC-3, CFPAC-1, and PANC-1 cells BALB/C female nude mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, and invasion Inhibited apoptosis Promoted tumor growth	(64)
miR-1179	CAPAN-2, BxPC3, CFPAC1, HPAFII, and SW 1990 cells Male BALB/c nude mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, and invasion Promoted tumor growth	(65)

Long non-coding RNAs

Long non-coding RNAs (lncRNAs) are a group of RNA transcripts with a length longer than 200 nucleotides that are not capable of encoding proteins. It has been shown that circulating lncRNAs are relatively stable in body fluids and

can be noninvasively obtained from patients with cancer (66). At various levels, including epigenetic, transcriptional, and translational, as well as post-translational levels, LncRNAs are recognized as regulators of gene expression (67). Dysregulated lncRNA profiles have a significant role in the pathogenesis of malignancies with regard to cell proliferation, migration, invasion, epithelial-to-mesenchymal transition (EMT), and apoptosis, as well as resistance to anti-tumor pharmaceutical treatment (68, 69). In many studies, numerous lncRNAs, either tumor suppressor or oncogenic, have been shown to be dysregulated in association with the progression of pancreatic cancer. For instance, in a recent study, Zhao *et al.* demonstrated that the upregulation of lncRNA titin antisense RNA 1 (TTN-AS1) promoted proliferation, migration, and invasion of PC cell lines (70). LncRNA SNHG15 expression level is increased in PC. Silencing of SNHG15 suppresses the proliferation, migration, and invasion of PC cells in vitro by regulating the miR-345-5p/RAB27B axis and reduces the tumor growth in vivo (71). LncRNA LINC00657 is upregulated in PC tissues and cell lines, leading to increased cell proliferation, migration, and invasion via regulating the miR-520h/CKS1B axis (72). The expression level of lncRNA LINC00460 is significantly upregulated in pancreatic ductal adenocarcinoma, and its knockdown results in the inhibition of cell proliferation, migration, and invasion, as well as promoting apoptosis in vitro through regulating the miR-320b/ARF1 axis (73). LncRNA prostate cancer-associated transcript 6 (PCAT6) is upregulated in pancreatic ductal adenocarcinoma. Overexpression of PCAT6 is significantly correlated with advanced TNM stage, advanced lymph node invasion, and worse overall survival. Furthermore, upregulated PCAT6 promotes cell proliferation, migration, and invasion in vitro by suppressing miR-185-5p expression and increasing chromobox 2 (CBX2) expression (74). LncRNA MVIH is upregulated in PC tissues and cell lines. In vitro, overexpressed MVIH promotes cell proliferation and migration, as well as invasion. Also, it inhibits apoptosis. In addition, it reduces both Gemcitabine and 5-FU chemosensitivity. In patients suffering from pancreatic ductal adenocarcinoma, upregulated MVIH in tumor tissue is correlated with advanced TNM stage, tumor size, lymph node invasion, and poor overall survival (75). **Figure 2** and **Table 2** summarize the available data on some lncRNAs that have a role in pancreatic cancer invasion.

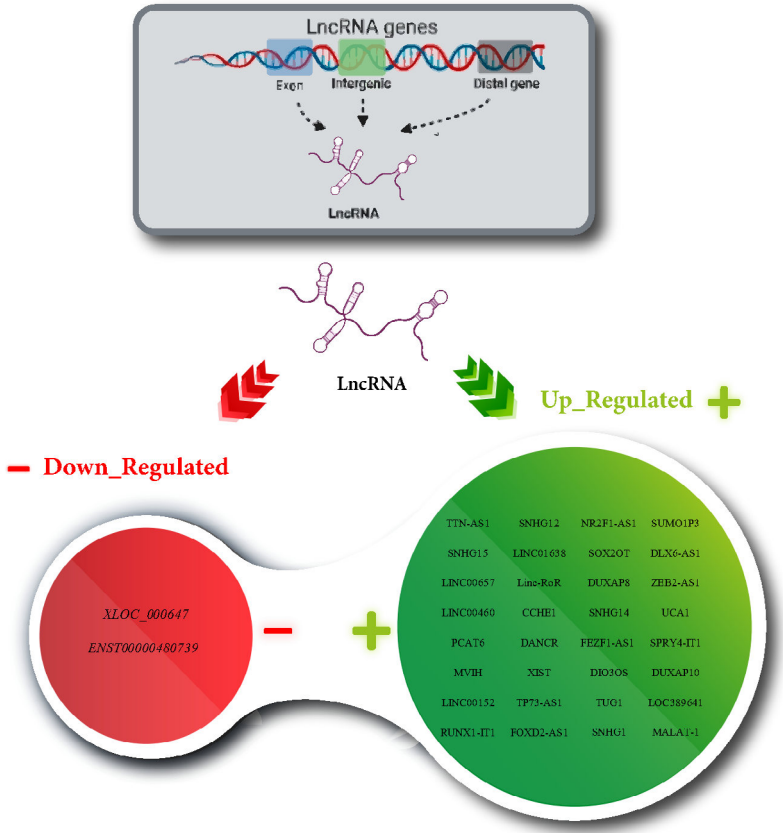

Figure 2. Dysregulated LncRNAs involved in pancreatic cancer invasion

Table 2. List of some lncRNAs associated with pancreatic cancer invasion

LncRNA	Cell line/Animal	Model	Main effect	References
Upregulation				
TTN-AS1	BxPC-3 and AsPC-1 cells	*In vitro*	Promoted cell proliferation, migration, and invasion	(70)
SNHG15	PANC-1 and BXPC-3 cells female BALB/c nude mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, and invasion Promoted tumor growth	(71)
LINC00657	SW1990, PACA-2, and BXPC-3 cells	*In vitro*	Promoted cell proliferation, migration, and invasion	(72)
LINC00460	SW1990 cells	*In vitro*	Promoted cell proliferation, migration, and invasion Inhibited apoptosis	(73)
PCAT6	Capan-2, AsPC-1, PANC1, and BxPC-3 cells	*In vitro*	Promoted cell proliferation, migration, and invasion	(74)
MVIH	PSN-1, AsPC-1, PANC-1, and BxPC-3 cells	*In vitro*	Promoted cell proliferation, migration, and invasion Inhibited apoptosis	(75)
LINC00152	BxPC3, Panc1, AsPC1, and SW1990 cells BALB/c female athymic nude mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, and invasion Promoted tumor growth	(76)
RUNX1-IT1	AsPC-1, BxPC-3, CFPAC-1, PANC-1, and SW1990 cells male nude mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, invasion, and metastasis	(77)
SNHG12	BXPC3, CAPAN1, PANC1, and SW1990 cells	*In vitro*	Promoted cell proliferation, invasion, and epithelial-mesenchymal transition Inhibited apoptosis	(78)
LINC01638	PL45 cells	*In vitro*	Promoted cell migration and invasion	(79)
Linc-RoR	BxPC-3, SW1990, and PaTu8988 cells	*In vitro*	Promoted cell proliferation, migration, invasion, and epithelial-mesenchymal transition	(80)
CCHE1	Capan-2 and HPAF-II cells	*In vitro*	Promoted cell migration and invasion	(81)
DANCR	BxPC-3, MIA-PaCa-2, CFPAC-1, PANC-1, and SW1990 BALB/c mice	*In vitro* *In vivo*	Promoted cell proliferation and invasion Promoted tumor growth	(82)
XIST	PANC-1 and HEK293T cells	*In vitro*	Promoted cell proliferation, migration, and invasion	(17)
TP73-AS1	SW1990, CAPAN-1, JF305, PANC-1, and BxPC-3 cells	*In vitro*	Promoted cell migration, invasion, and metastasis	(83)
FOXD2-AS1	Capan-2 cells	*In vitro*	Promoted cell migration and invasion	(84)
NR2F1-AS1	MIA PaCa-2 and PANC-1 cells female nude BALB/c mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, and invasion Promoted tumor growth and metastasis	(85)
SOX2OT	PANC-1 cells female nude BALB/c mice	*In vitro* *In vivo*	Promoted cell migration and invasion Promoted tumor growth and metastasis	(86)
DUXAP8	BxPC-3, PANC-1, AsPC-1, and Capan-1 cells	*In vitro*	Promoted cell proliferation, migration, and invasion	(87)
SNHG14	Panc1, Panc28, AsPC1, and BxPC3 cells	*In vitro*	Promoted cell proliferation, colony formation, and invasion	(88)

Table 2. Continued

FEZF1-AS1	PANC-1, SW1990, Hup, and CFPAC-1 cells	*In vitro*	Promoted cell proliferation and invasion	(89)
DIO3OS	AsPC-1, MIA PaCa-2, PANC-1, and BxPC-1 cells Female BALB/c nude mice	*In vitro* *In vivo*	Promoted cell proliferation and invasion Promoted tumor growth	(90)
TUG1	SW1990, AsPC-1, BxPC-3, and PANC-1 cells Male nude mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, and invasion Promoted tumor growth	(91)
SNHG1	AsPC-1, PANC1, BxPC-3, and SW1990 cells	*In vitro*	Promoted cell proliferation, migration, invasion, and metastasis	(92)
SUMO1P3	BxPC-3, PANC-1, MiaPaCa-2, and ASPC-1 cells	*In vitro*	Promoted cell proliferation, migration, invasion, and epithelial-mesenchymal transition	(93)
DLX6-AS1	CAPAN-1, BxPC-3, SW 1990, and PANC-1 female BABL/c athymic nude mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, and invasion Promoted tumor growth	(94)
ZEB2-AS1	AsPC-1, HPAC, Cfpac-1, and Panc-1 cells mice	*In vitro* *In vivo*	Promoted cell proliferation and invasion Promoted tumor growth	(95)
UCA1	BxPC-3, SW1990, PaTu8988, and PANC-1 cells	*In vitro*	Promoted cell migration and invasion	(96)
SPRY4-IT1	BxPC-3 and PANC-1 cells	*In vitro*	Promoted cell proliferation and invasion Inhibited apoptosis	(97)
DUXAP10	AsPC-1, BxPC-3, and PANC-1 cells athymic BALB/c mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, and invasion Inhibited apoptosis Promoted tumor growth	(98)
LOC389641	SW1990, AsPC-1, PANC-1, MIAPaCa-2, BxPC-3, and Capan-2 cells athymic BALB/c nude mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, and invasion Inhibited apoptosis Promoted tumor growth	(99)
MALAT-1	BxPC-3, CFPAC-1, CAPAN-1, SW1990, AsPC-1, PANC-1, and HS-766T cells	*In vitro*	Promoted cell proliferation, migration, and invasion	(100)
		Downregulation		
XLOC_000647	MIA-PaCa-2, BxPC-3, and PANC-1 cells Male athymic BALB/c nude mice	*In vitro* *In vivo*	promoted cell proliferation, invasion, and epithelial-mesenchymal transition promoted tumor growth	(101)
ENST00000480739	ASPC-1, BXPC-3, CFPAC-1, PANC-1, and SW1990 BALB/c-nu/nu mice	*In vitro* *In vivo*	Promoted cell invasion and metastasis	(102)

Circular RNAs

Circular RNAs (circRNAs) are endogenous, non-coding RNAs that are just as efficiently transcribed by RNA polymerase II as linear RNAs. They can be developed between an upstream 5' splice site and a downstream 3' splice site in a linear precursor mRNA (pre-mRNA). The main functions of circRNAs include acting as miRNA sponges, acting as modulators of transcription, and acting as protein sponges. CircRNAs are considered to be useful biomarkers for cancer risk prediction due to their high level of stability in blood and other body fluids (103, 104). In many studies, circRNAs have been shown to have an important role in both the initiation and progression of different tumors like pancreatic cancer, and they can be used as a diagnostic and prognostic biomarker (105). Li *et al.* demonstrated that circ-PDE8A (hsa_circ_0036627) was overexpressed in pancreatic ductal adenocarcinoma cells and tissues, and high levels of circ-PDE8A were correlated with advanced TNM stage, ad-

vanced lymphatic invasion, and a poor survival rate of patients with pancreatic ductal adenocarcinoma. Moreover, Circ-PDE8A acted as a competing endogenous RNA (ceRNA) for miR-338 in order to regulate MACC1 and promoted the invasion of pancreatic ductal adenocarcinoma cells through the MACC/MET/ERK or AKT signaling pathways (106). In another study by Huang *et al.*, it was reported that circRNA_000864 is downregulated in pancreatic cancer tissues and cell lines. In addition, upregulated circRNA_000864 was shown to have anti-proliferative, anti-invasive, and anti-migratory effects in vitro and could inhibit tumor growth in vivo by upregulating BTG2 and binding to miR-361-3p (107). CircRHOT1 is an oncogenic circRNA that is upregulated in pancreatic cancer and causes tumor progression and invasion through sponging miR-26b, miR-330, miR-125a, and miR-382 (108). Exosomal circ_0030167, derived from bone marrow mesenchymal stem cells (BM-MSCs), is downregulated in pancreatic cancer cell lines. Hence, it causes cell proliferation, invasion, metastasis, and stemness of these cells through sponging miR-338-5p and targeting the wif1/Wnt 8/β-catenin pathway (109). The information that is currently available on some circRNAs involved in pancreatic cancer invasion is exhibited in **Figure 3** and **Table 3**.

Stanniocalcin 2

Stanniocalcin 2 (STC2), an ortholog of fish stanniocalcins, is a glycosylated peptide hormone that regulates phosphate and calcium homeostasis (113). STC2 is broadly expressed in various tissues and has been shown to have an important role in tumorigenesis and cancer progression in different organs (114). Lin *et al.* revealed that STC2 was highly overexpressed in pancreatic cancer. The increased expression level of STC2 was correlated with bigger tumor sizes and lower 5-year survival rates of patients with pancreatic cancer. Moreover, its expression was positively

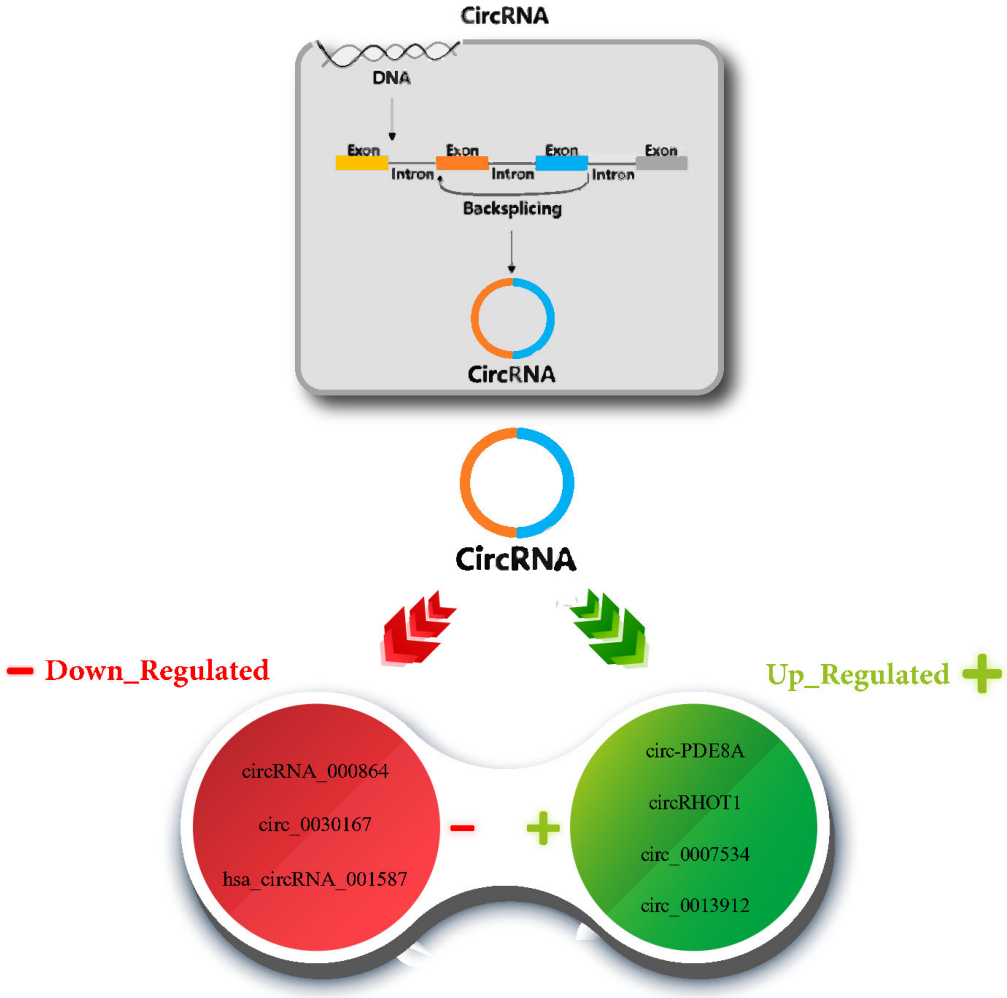

Figure 3. Dysregulated circRNAs involved in pancreatic cancer invasion

Table 3. List of some circRNAs associated with pancreatic cancer invasion

CircRNA	Cell line/Animal	Model	Main effect	References
Upregulation				
circ-PDE8A	BxPC-3, Capan-1, Hs 766T, Hs 766T, Aspc-1, and HEK-293 cells	*In vitro*	Promoted cell invasion	(106)
circRHOT1	PANC-1, Capan-2, Capan-1, SW1990, BxPC-3, and AsPC-1 cells	*In vitro*	Promoted cell proliferation and invasion	(108)
circ_0007534	(BxPC3, Capan-2, AsPC-1, PANC1, and SW1990 cells female BALB/c nude mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, and invasion Inhibited apoptosis Promoted tumor growth	(110)
circ_0013912	PANC-1 and AsPC-1 cells female BALB/c nude mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, and invasion Inhibited apoptosis Promoted tumor growth	(111)
Downregulation				
circRNA_000864	AsPC-1, MiaPaCa-2, PANC-1, and HPAC cells BALB/C nude mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, and invasion Inhibited apoptosis Promoted tumor growth	(107)
circ_0030167	PANC-1 and MIA-PaCa-2 cells female BALB/c nu/nu mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, invasion, and stemness Promoted tumor growth	(109)
hsa_circRNA_001587	AsPC-1, PANC-1, COLO357, and PC-3 cells female BALB/C nude mice	*In vitro* *In vivo*	Promoted cell proliferation, migration, invasion, angiogenesis	(112)

correlated with in vitro proliferation, migration, and invasion (115).

Conclusion and Future Perspectives

Several biomarkers related to pancreatic cancer invasion have been introduced. Among them, CA19-9, CA125, and noncoding RNAs, including microRNAs, long noncoding RNAs, and circular RNAs, are the most common ones and have been shown in many studies to have important roles in PC invasion and metastasis. Stanniocalcin 2 also promotes the invasion in pancreatic cancer. Because of their roles in the pancreatic cancer progression and poorer prognosis, targeting these markers in a clinical context may alleviate patients' condition, improve their quality of life, and increase their survival rate in the future. Thus, more investigations are required to explore the mechanisms related to these markers in order to use them as novel therapeutic targets.

Conflict of Interests

There is no conflict of interest

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