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Long non-coding RNAs: Emerging regulators of invasion and metastasis in pancreatic cancer

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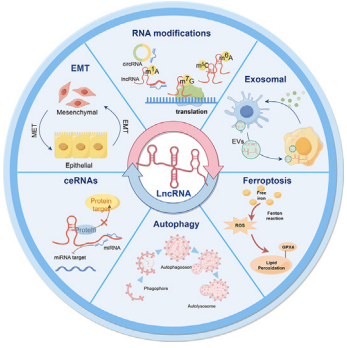
HIGHLIGHTS

- Elucidates how lncRNAs regulate EMT in pancreatic cancer via TGF-β, Wnt, and Notch pathways.
- Summarizes the effects of lncRNAs on autophagy during pancreatic cancer invasion.
- Reviews the impact of lncRNAs on ferroptosis in the invasive progression of pancreatic cancer.
- Explores the role of exosomal lncRNAs in modulating the tumor microenvironment to promote PC spread.
- Discusses RNA modifications (m^6A, m^5C) that enhance lncRNA stability and function in PC.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: The invasion and metastasis of pancreatic cancer (PC) are key factors contributing to disease progression and poor prognosis. This process is primarily driven by EMT, which has been the focus of recent studies highlighting the role of long non-coding RNAs (lncRNAs) as crucial regulators of EMT. However, the mechanisms by which lncRNAs influence invasive metastasis are multifaceted, extending beyond EMT regulation alone.

Aim of review: This review primarily aims to characterize lncRNAs affecting invasion and metastasis in pancreatic cancer. We summarize the regulatory roles of lncRNAs across multiple molecular pathways and highlight their translational potential, considering the implications for clinical applications in diagnostics and therapeutics.

Key scientific concepts of review: The review focuses on three principal scientific themes. First, we primarily summarize lncRNAs orchestrate various signaling pathways, such as TGF-β/Smad, Wnt/β-catenin, and Notch, to regulate molecular changes associated with EMT, thereby enhancing cellular motility and invasivenes. Second, we summarize the effects of lncRNAs on autophagy and ferroptosis and discuss the role of exosomal lncRNAs in the tumor microenvironment to regulate the behavior of neighboring cells and promote cancer cell invasion. Third, we emphasize the effects of RNA modifications (such as m^6A and m^5C methylation) on stabilizing lncRNAs and enhancing their capacity to mediate invasive metastasis in PC. Lastly, we discuss the

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translational potential of these findings, emphasizing the inherent challenges in using lncRNAs as clinical biomarkers and therapeutic targets, while proposing prospective research strategies.

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Introduction

Invasion and metastasis in cancer are complex biological processes involving the tight regulation of various cellular and molecular mechanisms[1]. This process begins with the detachment of cancer cells from the primary tumor, a step that involves the downregulation of cell adhesion molecules (CAMs) such as E-cadherin[1]. The loss of E-cadherin disrupts cell–cell junctions, increasing cellular motility and facilitating the transition to a more invasive phenotype, a process known as epithelial-mesenchymal transition (EMT)[1,2]. During EMT, cancer cells not only lose their epithelial characteristics, such as E-cadherin expression, but also acquire mesenchymal markers, including N-cadherin, vimentin, and fibronectin, which further enhance their ability to invade surrounding tissues[2,3]. Additionally, molecular changes such as the reduced expression of tight junction proteins, increased secretion of matrix metalloproteinases (MMPs), and activation of signaling pathways like TGF-β and Wnt contribute to the breakdown of epithelial architecture, allowing cells to become more migratory and invasive[4]. As tumor cells invade the local stroma, they release MMPs that degrade the basement membrane of neighboring tissues, promoting local invasion[4]. Subsequently, the cancer cells intravasate into blood vessels or the lymphatic system. Once in circulation, these cells must overcome immune surveillance and the physical forces exerted by blood flow, mechanisms that enable the cells to survive even after detachment from the extracellular matrix (ECM)[5]. Ultimately, circulating tumor cells extravasate into distant organs or tissues, where they settle and grow to form metastatic tumors. The ability of cancer cells to successfully complete this metastatic cascade ultimately leads to the formation of secondary tumors, which are typically more resistant to treatment and associated with poorer patient outcomes[6].

Pancreatic cancer (PC), particularly pancreatic ductal adenocarcinoma (PDAC), is recognized for its aggressive nature and dismal prognosis, largely due to its high invasive migration and metastatic potential[7]. In PDAC, the dense desmoplastic stroma creates a physical barrier that obstructs the effective delivery of chemotherapy and immunotherapy[7,8]. The tumor microenvironment (TME), composed of fibroblasts, immune cells, and endothelial cells, further exacerbates this challenge by secreting pro-inflammatory cytokines and growth factors that facilitate tumor invasion[8]. A key process in metastasis, EMT, is critically involved in PDAC progression. However, targeting EMT remains difficult due to the complexity and redundancy of the signaling pathways that regulate it, including TGF-β, Wnt/β-catenin, and Notch[4]. Although PDAC cells initially exhibit sensitivity to various chemotherapeutic agents, the development of intrinsic resistance mechanisms complicates treatment regimens. This resistance is driven by genetic mutations, dysregulated signaling pathways, and adaptive responses of cancer cells to hypoxic and nutrient-deprived conditions, all of which enhance the metastatic capability of the tumor[9,10]. The lack of reliable biomarkers for early detection further compounds therapeutic challenges, as PDAC is typically diagnosed at the metastatic stage, limiting opportunities for early intervention[11,12]. The propensity of PDAC cells to migrate early in the disease further restricts the efficacy of conventional therapies, as tumor cells frequently disseminate to distant organs prior to the detection of the primary tumor[11]. Moreover, the complex network of signaling pathways that drive invasive migration remains poorly understood, hindering the development of effective therapeutic strategies aimed at targeting these metastatic processes.

Dysregulation of long non-coding RNAs (lncRNAs) crucially shifts cellular dynamics toward oncogenesis or tumor suppression, particularly affecting cancer's invasion and metastasis. LncRNAs modulate this shift by regulating gene expression, influencing oncogenic and tumor-suppressive protein activities, and acting as competitive endogenous RNAs (ceRNAs) that sequester and neutralize miRNAs, thus freeing miRNA target genes from repression[13]. Central to this is their role in orchestrating EMT, enabling cancer cells to migrate and invade. Beyond EMT, lncRNAs shape the tumor microenvironment and promote cellular processes such as autophagy and ferroptosis, while also driving the metabolic reprogramming of cancer cells to support invasion and metastasis[14–16].

While significant progress has been made in understanding the role of lncRNAs in pancreatic cancer metastasis[17–19], the clinical application of these insights remains challenging[20]. This review

aims to dissect these challenges, assess the current landscape of lncRNA research in pancreatic cancer metastasis, and propose future directions to unlock their full potential for improving diagnosis and treatment.

Overview of lncRNAs in pancreatic cancer invasion and metastasis

LncRNAs, a diverse class of non-coding transcripts longer than 200 nucleotides, have revolutionized our understanding of gene regulation, highlighting their ability to influence key cellular processes without coding for proteins[21]. Unlike the more familiar microRNAs (miRNAs)[22] and small interfering RNAs (siRNAs), which primarily target mRNA degradation or inhibition, lncRNAs exert complex regulatory effects by modulating chromatin architecture, impacting mRNA stability, and controlling translation [23–25]. These molecular mechanisms make lncRNAs crucial players in numerous pathophysiological processes, including cancer progression. In pancreatic cancer, lncRNAs are known to orchestrate multiple oncogenic pathways, driving invasion, metastasis, and resistance to therapies[26]. Their regulatory actions occur at various levels, including chromatin remodeling, transcriptional regulation, and interaction with other non-coding RNAs, which in turn fine-tune gene expression patterns involved in tumorigenesis[24,27,28]. Fig. 1 illustrates the multifaceted mechanisms by which lncRNAs play a role in the development and progression of pancreatic cancer. It highlights their roles in chromatin modification, transcriptional control, and interaction with key signaling molecules that promote oncogenesis and metastatic behavior.

At the epigenetic level, the ability of lncRNAs such as X-inactive specific transcript (XIST) to modulate chromatin architecture, thereby dictating gene expression patterns, is demonstrated through mechanisms such as the recruitment of chromatin-modifying complexes. XIST, for example, plays a pivotal role in X chromosome inactivation by recruiting Polycomb repressive complex 2 (PRC2) to the X chromosome, leading to histone methylation and subsequent chromatin compaction, a process essential for dosage compensation between males and females[24]. In the realm of chromatin organization and transcriptional regulation, lncRNAs act as dynamic scaffolds that facilitate the assembly of protein complexes at specific genomic loci. HOTAIR exemplifies this by recruiting PRC2 to target genes, leading to altered histone methylation and suppression of gene expression, which impacts genome-wide chromatin states and affects various cellular outcomes, including cancer metastasis[28].

In addition, lncRNAs play a critical role in transcriptional regulation, acting either as enhancers or repressors of gene expression. lncRNA TPT1-AS1 acts as an endogenous sponge for miR-30a-5p, leading to increased integrin β3 (ITGB3) expression in pancreatic cancer cells[29]. Increased ITGB3 levels activate the signal transducer and activator of transcription 3 (STAT3), a key transcription factor. Activated STAT3 binds to the promoter region of TPT1-AS1, thereby influencing its expression. This interaction creates a positive feedback loop in which TPT1-AS1 enhances its own expression through STAT3 activation, further promoting pancreatic cancer cell proliferation, migration, invasion and EMT[29]. In addition, LINC01094 contributes to pancreatic carcinogenesis and metastasis by acting as a ceRNA for miR-577[30]. This interaction suppresses the activity of miR-577, preventing it from targeting its downstream gene, lin-28 homolog B (LIN28B), an RNA binding protein. The resulting upregulation of LIN28B activates the PI3K/AKT signalling pathway, which drives pancreatic cancer growth and metastasis[30].

The interplay between lncRNAs and miRNAs is well established, with lncRNAs acting either as miRNA sponges or as regulators of miRNA expression, thereby influencing gene expression networks that drive cancer progression[31]. However, recent studies suggest that another layer of regulatory complexity exists, involving circular RNAs (circRNAs) in cross-talk with lncRNAs[32]. CircRNAs, characterised by their covalent closed-loop structure, can also act as miRNA sponges, sequestering miRNAs and preventing them from targeting their mRNA targets[33,34]. This creates a regulatory network in which lncRNAs and circRNAs can interact synergistically or competitively to modulate the availability of miRNAs in cancer cells[32]. In the context of pancreatic cancer, this cross-

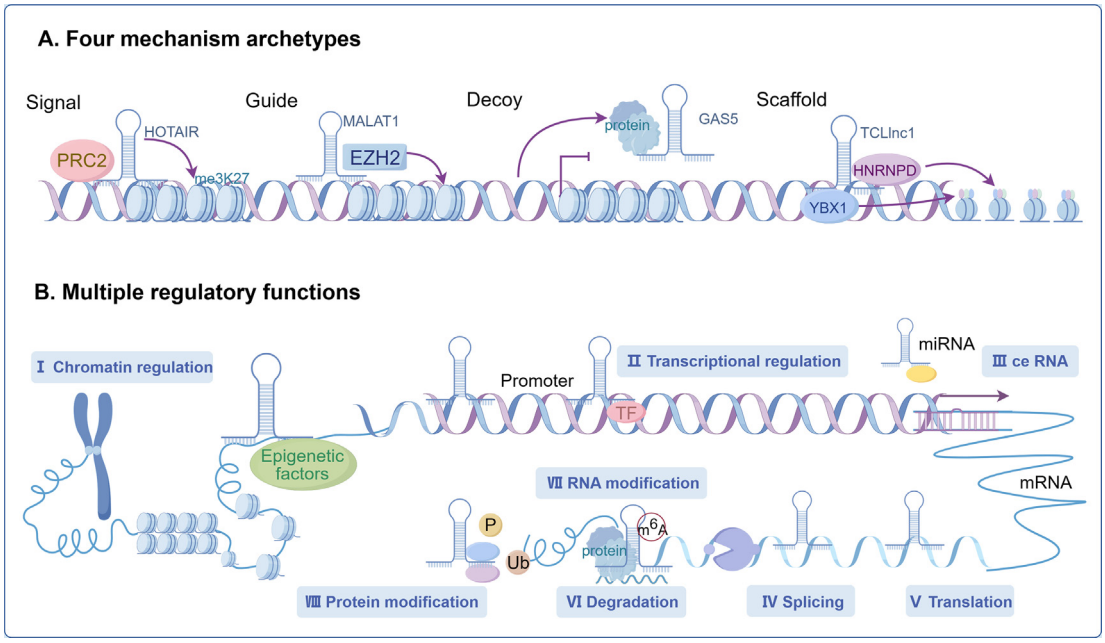

Fig. 1. Mechanisms and regulatory functions of lncRNAs in pancreatic cancer. A illustrates the major mechanisms by which lncRNAs function, including signaling, decoy function, targeting of molecular complexes to specific genomic loci, and scaffolding for macromolecular assembly. These mechanisms are illustrated with examples that highlight the diverse roles of lncRNAs in cellular processes. B provides a comprehensive review of the diverse regulatory functions of lncRNAs, including chromatin remodeling, transcriptional regulation, competitive endogenous RNA activity, modulation of splicing events, control of translation processes, involvement in RNA degradation pathways, RNA modification, and protein modification.

talk between lncRNAs, circRNAs and miRNAs plays a key role in regulating cancer cell invasion and metastasis[35]. For example, CircRTN4 interacts with the oncogenic miRNA miR-497-5p in PC cells[32]. Knockdown of circRTN4 increases miR-497-5p, which inhibits the oncogenic lncRNA HOTTIP. CircRTN4 stabilises the EMT driver protein RAB11FIP1 by preventing its ubiquitination, thereby promoting EMT and facilitating tumour cell invasion and metastasis[32]. In contrast, knockdown of circRTN4 reduced EMT markers such as Slug, Snai1, Twist, Zeb1 and N-cadherin. However, the complex interactions between lncRNAs, circRNAs and miRNAs in PC remain poorly understood[36]. A deeper understanding of these functional interactions is crucial as it may provide new insights into the molecular mechanisms driving PC metastasis.

lncRNAs in EMT-mediated invasive migration of PC

The invasion-metastasis cascade in PC involves a series of sequential steps: local invasion, intravasation into blood vessels, survival in the circulatory system, extravasation into distant tissues, and colonization at secondary sites[37]. EMT is a key process driving these steps, particularly in the early stages of metastasis, where epithelial tumor cells lose their cell–cell adhesion properties and gain mesenchymal traits, allowing them to detach from the primary tumor and invade surrounding tissues[38].

Several signaling pathways are critically involved in the regulation of EMT and subsequent metastasis in PC. Transforming growth factor-beta (TGF-β) is one of the most well-studied pathways and is known to induce EMT through SMAD-dependent and independent mechanisms, leading to the repression of epithelial markers like E-cadherin and the induction of mesenchymal markers such as vimentin[39,40]. The Wnt/β-catenin pathway also plays a significant role by promoting the stabilization and nuclear translocation of β-catenin, which in turn activates EMT-associated transcription factors[41]. Additionally, Notch signaling has been implicated in PC progression, where it contributes to EMT and enhances the invasive capacity of cancer cells[42].

The transcription factors SNAIL, SLUG, TWIST, and the ZEB family are central to the EMT process in PC. These factors orchestrate the transcriptional repression of epithelial genes and the activation of mesenchymal genes, facilitating the transition to a more invasive phenotype[43]. SNAIL and SLUG, for example, directly repress E-cadherin transcription by binding to its promoter region, while TWIST and ZEB1 promote the expression of mesenchymal markers and the remodeling of the extracellular matrix[44,45].

(1) TGF-β/Smad

The TGF-β signaling pathway is instrumental in the regulation of EMT, a process pivotal for cancer metastasis. Upon ligand binding, TGF-β receptors, which are serine/threonine kinase receptors of type I and II, undergo dimerization and phosphorylation. This event activates downstream SMAD transcription factors, notably SMAD2 and SMAD3, which, upon phosphorylation, associate with SMAD4 to form complexes[46]. These complexes translocate into the nucleus to modulate gene expression, targeting not only mesenchymal markers like Vimentin and Fibronectin but also key EMT transcription factors (EMT-TFs) such as SNAIL, SLUG, TWIST, and ZEB1[40]. The action of these factors leads to a reduction in epithelial markers, notably E-cadherin, and an increase in mesenchymal markers, thus driving the EMT process. Additionally, the expression of these EMT-TFs can further induce TGF-β production, creating a positive feedback loop that maintains EMT activation[47].

In the progression of PC, lncRNAs play a pivotal role as regulators of EMT via the TGF-β signaling pathway[30,48–60]. These lncRNAs are capable of directly modulating the components of the TGF-β pathway, including its receptors and SMAD proteins, thereby influencing the cellular processes underlying cancer metastasis. Specifically, PVT1 is known to amplify TGF-β signaling by upregulating the expression of p-Smad2/3 and TGF-β1, effectively promoting EMT[48]. In a similar vein, LINC00462 elevates the levels of TGFβR1 and TGFβR2, leading to enhanced SMAD2/3 pathway activation and further facilitating EMT[49]. Additionally, lncRNAs such as MEG8[50] and TUG1[51] are intricately linked to the activation of the TGF-β pathway; TUG1, for instance, markedly increases the phosphorylation of SMAD2 and SMAD3, which in turn influences calmodulin levels and thereby drives cellular proliferation and metastasis[50].

Moreover, MIR31HG has been recognized as a crucial regulator in pancreatic ductal adenocarcinoma, playing a significant role in facilitating EMT and enhancing cell invasion [52]. This effect is attributed to TGF-β's induction of MIR31HG expression, which competitively inhibits the binding of miR-193b to the mRNA of COL1A1, a marker of mesenchymal cells, thereby mitigating EMT [53]. Additionally, XIST contributes to cellular proliferation and metastasis by downregulating miR-141-3p and elevating levels of TGF-β2[54]. An innovative aspect of lncRNA functionality is observed in their capability for intercellular communication via extracellular vesicles. For instance, miR-622, a microRNA suppressed by TGF-β, when overexpressed, markedly diminishes the expression of HULC[55]. This reduction leads to decreased levels of N-calmodulin and Snail, thus strategically inhibiting EMT and impacting the processes of cellular invasion and metastasis.

In the non-Smad pathway mediated by TGF-β signaling, activation of the PI3K-AKT-mTOR cascade plays a crucial role in transcriptional regulation, with activated AKT further regulating transcription by inhibiting heterogeneous nuclear ribonucleoprotein E1 (hnRNPE1), thereby facilitating the induction of EMT [61,62]. For instance, SNHG1 enhances cell proliferation and tumorigenicity by activating key components of the PI3K/AKT signaling pathway[56]. Conversely, MEG3[57] and LINC00671[58] have been demonstrated to suppress the activity of PI3K, AKT, and ERK pathways, thereby inhibiting the process of EMT. Moreover, LINC00261, through its interaction with the upstream transcription factor KLF13, not only promotes its own transcription but also suppresses the expression of proteins associated with metastasis, such as MMP2 and vimentin, thereby impeding EMT in PC via the mTOR pathway[59]. Additionally, HOXA10-AS[60] and LINC01094[30] function as ceRNAs, sponging miRNAs to potentiate the PI3K-AKT signaling pathway and exacerbate the malignancy of PC.

(2) Wnt/β-catenin

TGF-β and Wnt pathways are pivotal in the regulation of EMT [63,64]. Generally, the Wnt pathway refers to the canonical signaling pathway mediated by β-catenin. β-catenin serves as a critical biomarker for detecting the activation of the Wnt pathway. Wnt signaling is initiated when Wnt ligands bind to Frizzled receptors and co-receptors LRP5/6 (Low-density lipoprotein receptor-related protein 5/6), leading to the stabilization and accumulation of β-catenin in the cytoplasm[63]. In the absence of Wnt signaling, β-catenin is continuously degraded by a destruction complex consisting of Axin, APC (Adenomatous polyposis coli), GSK-3β (Glycogen synthase kinase 3 beta), and CK1α (Casein kinase 1 alpha)[65]. Upon activation of the pathway, this destruction complex is inhibited, allowing β-catenin to translocate into the nucleus where it interacts with TCF/LEF (T-cell factor/Lymphoid enhancer factor) family of transcription factors to activate the transcription of target genes, including those involved in EMT, such as SNAIL, SLUG, TWIST, and ZEB1/2[66,67].

Recent studies have further elucidated the intricate crosstalk between the Wnt/β-catenin signaling pathway and other cellular pathways, as well as lncRNAs, in regulating EMT and cancer metas-

tasis[68,69]. Here, we explore the specific mechanisms by which lncRNAs influence the Wnt/β-catenin pathway to regulate EMT and cancer metastasis. lncRNAs exert a profound impact on the stability and accumulation of β-catenin by influencing the activity of components within the β-catenin degradation complexes, such as GSK-3β and APC. For instance, LINC01614 interacts with GSK-3β, disrupting its interaction with AXIN1[70]. This interference inhibits the assembly of the β-catenin degradation complexes, leading to the accumulation of β-catenin and its translocation to the nucleus, where it activates genes associated with EMT and metastasis. Additionally, exosomal LINC01133 engages in interaction with EZH2 to silence AXIN2 and inhibit GSK3 activity, ultimately activating β-catenin[71].

TSLNC8 enhances the binding of HuR to CTNNB1 mRNA, thus increasing its stability[72]. CTNNB1 acts as a co-activator for the TCF/LEF family of transcription factors, supporting the expression of genes related to the Wnt/β-catenin signaling pathway, such as β-catenin, cyclinD1, c-myc, LEF-1, and c-Jun, as well as the regulation of EMT markers including E-cadherin, N-cadherin, and vimentin. The knockdown of HOTAIR[73] results in reduced expression of these genes and markers, indicating inhibition of the Wnt/β-catenin signaling pathway. Furthermore, certain lncRNAs, including FGD5-AS1[74], BANCR[75], GATA3-AS1[76], and DLX6-AS1 [77], act as ceRNAs or molecular sponges for miRNAs targeting Wnt ligands or receptors. By alleviating miRNA-mediated repression, they facilitate the activation of the Wnt signaling pathway, thereby contributing to the stimulation of EMT.

(3) Notch signaling pathway

The Notch signaling pathway, characterized by its single transmembrane receptors NOTCH1-4, plays a pivotal role in cellular differentiation and proliferation. Activation of these receptors occurs upon ligand binding, initiating a cascade of calcium-dependent cleavage events. This process releases the Notch receptor's outer cytoplasmic domain, subsequently subjected to further cleavage by γ-secretase. This cleavage liberates the Notch intracellular domain (NICD), which then associates with the CSL complex to regulate downstream transcription factors associated with EMT, including SNAIL, SLUG, and TWIST[78].

Recent advancements have illuminated the significant influence of lncRNAs on the Notch pathway, particularly in the regulation of its receptors and ligands, such as Jagged1 and Delta-like 4 (Dll4), at both the transcriptional and post-transcriptional levels. For instance, HOTAIR has been identified to augment Notch signaling by upregulating NOTCH3 expression[79], thereby enhancing EMT and contributing to pancreatic cancer's aggressiveness. Similarly, MIR99AHG activates the Notch signaling pathway by modulating NOTCH2 expression and sequestering miR-3129-5p[80], in conjunction with recruiting the ELAV-like RNA-binding protein 1 (ELAVL1). Additionally, XIST serves as a ceRNA, indirectly upregulating NOTCH1 by inhibiting miR-137[81].

LncRNAs regulate the expression of key EMT markers by modulating Notch signaling. For instance, TUG1 have been found to negatively regulate Notch signaling, leading to a decrease in the expression of mesenchymal markers and suppression of EMT[82], highlighting their potential roles as tumor suppressors in PC. Additionally, lncRNAs can regulate signaling cascades downstream of Notch receptor activation. HCG11 has been identified to interact with components of the Notch pathway[83], enhancing nuclear translocation of the NICD and levels of HES1 protein, and promoting transcription of genes associated with EMT. The Notch pathway, regulated by lncRNAs, is crucial for the maintenance of CSCs, which are implicated in EMT and metastasis. SNHG7 has been shown to interact with NOTCH1[84], enhancing the stem cell characteristics of pancreatic cancer cells by modulating the NOTCH1/Jagged1/HES-1 pathway, thereby increasing the metastatic potential of the cancer.

(4) Other pathways

Beyond the commonly acknowledged pathways, several signaling cascades, including the Hippo[85–92], NF-κB[93–95], hypoxia-inducible[10,96–100], and PTEN pathways[101–103], play pivotal roles in either inhibiting or promoting EMT to various extents. The Hippo signaling pathway, in particular, exerts significant influence over the activities of Yes-associated protein (YAP) and PDZ-binding motif (TAZ)[85]. Activation of this pathway triggers a kinase cascade that results in the phosphorylation and subsequent cytoplasmic retention and degradation of YAP/TAZ, effectively curtailing their function as transcriptional coactivators. Conversely, inactivation of the Hippo pathway facilitates the nuclear translocation of YAP/TAZ, where they engage with TEAD family transcription factors to drive processes conducive to tumor metastasis [85]. LncRNAs, including LINC01559[86], THAP9-AS1[87], and LNC-EPIC1[88], have been shown to promote the invasiveness and metastatic potential of PC cells by modulating YAP activity. Conversely, PWAR6[89] appears to exert a negative regulatory effect on YAP1, diminishing EMT in PC through its interaction with EZH2. Furthermore, RoR[90] has been identified as a promoter of the Hippo/YAP pathway, facilitating the relocation of YAP from the cytoplasm to the nucleus. FAM83A-AS1[91], on the other hand, augments the activity of downstream YAP by impeding the Hippo pathway's core kinases, MST1 and MST2. Additionally, UCA1[92] targets the Hippo pathway's regulatory components, bolstering the interaction between YAP and TEAD, thereby amplifying YAP's transcriptional activity and stimulating the expression of EMT-associated genes.

SPOCK1 activates the NF-κB signaling pathway via direct interaction with IκBα[93], while the E2F1-mediated overexpression of PLACT1[94] promotes EMT and metastasis by establishing a positive feedback loop with IκBα, thereby maintaining the activation of the NF-κB signaling pathway. Additionally, CERS6-AS1 functions as a ceRNA to modulate miRNA-217[95], leading to the upregulation of YWHAG and the phosphorylation of RAF1, further activating the ERK pathway and promoting PC invasion and metastasis. The overexpression of hypoxia-inducible factor (HIF-1α) plays a pivotal role under hypoxic conditions in PC, enhancing invasion and metastasis. The expression of NR2F1-AS1 is transcriptionally regulated by HIF-1α in response to hypoxia, where hypoxia-induced NR2F1-AS1 expression elevates NR2F1 levels, driving cell metastasis and invasion through the activation of the AKT/mTOR signaling pathway[10]. Moreover, HIF-1α influences the response to hypoxia-induced lncRNAs, including LncRNA-BX111[96], RP11-390F4.3[97], PCED1B-AS1[98], FEZF1-AS1[99], ENST00000480739 [100], among others, which promote hypoxia-induced EMT in pancreatic cells by modulating the expression of ZEB1 and its downstream proteins, E-cadherin, and MMP2. Phosphatase and tension protein homologue (PTEN) acts as a tumour suppressor that inhibits EMT by inactivating the PI3K/AKT signalling pathway, thereby preventing the activation of key transcription factors that drive EMT[101–103]. lncRNA FLVCR1-AS1, as a ceRNA, can sequester miR-513c-5p or miR-514b-5p from KLF10 mRNA, alleviating their suppressive effect on KLF10 expression, thereby inhibiting the PTEN/AKT pathway[101]. Additionally, hepatocyte nuclear factor 1A (HNF1A) has been shown to upregulate the expression of lncRNA CASC2. In turn, CASC2 regulates PTEN expression, impacting the downstream activation of the AKT pathway[102]. KCNK15-AS1 recruits the oncogene MDM2, promoting the ubiquitination and degradation of RE1-silencing transcription factor (REST), which leads to the transcriptional upregulation of PTEN, further

inhibiting the AKT pathway and enhancing its tumor-suppressive effects[103].

EMT process, marked by profound alterations in cell morphology, adhesion, motility, and gene expression, necessitates a concerted effort from multiple signaling cascades beyond the capacity of any singular pathway. For instance, while TGF-β signaling is pivotal in initiating EMT through the induction of key transcription factors such as SNAIL and SLUG, achieving the comprehensive state of EMT often demands supplementary inputs from the Wnt/β-catenin pathway, which plays a crucial role in reinforcing the expression and functionality of SNAIL and SLUG [104]. Furthermore, the activation of YAP/TAZ within the Hippo pathway contributes to the regulation of EMT by influencing the TGF-β pathway through gene transcription, thereby establishing a feedback mechanism that dynamically modulates EMT in accordance with cellular density[105]. Fig. 2 demonstrates the complex regulatory mechanisms by which lncRNAs influence EMT in pancreatic cancer.

LncRNAs mediate invasive metastasis as ceRNAs

Competitive endogenous RNAs represent a fascinating class of lncRNAs that play crucial roles in the post-transcriptional regulation of gene expression. The ceRNA activity is predicated on the presence of miRNA response elements (MREs) within the lncRNA sequence that are complementary to the miRNA seed region. When lncRNAs harbor MREs that are common to certain mRNAs, they can competitively bind miRNAs, diminishing miRNA-mediated repression on those mRNAs[31]. This results in an increase in mRNA stability and translation, leading to an upregulation of the protein encoded by the mRNA. This mechanism of action delineates a novel layer of gene regulation, where lncRNAs, by acting as miRNA sponges, indirectly modulate the stability and translation of mRNAs involved in various cellular processes, including development, differentiation, and disease pathogenesis, notably cancer.

In the context of PC, the regulatory network mediated by lncRNAs in collaboration with miRNAs through the ceRNA mechanism can either promote or inhibit tumor invasion and metastasis in various ways. lncRNAs function as miRNA sponges or decoys, effectively sequestering miRNAs, thereby disrupting their normal regulatory functions and leading to the dysregulation of miRNA target gene expression. This dynamic results in the modulation of key signaling pathways critical for cancer progression. For instance, GAS5 positively regulates the expression of PTEN via miR-32-5p, inhibiting the metastasis and invasion of PC[106]. LINC00976 has been identified to promote PC cell proliferation and invasion by upregulating OTUD7B, a direct target of miR-137 [107]. This upregulation facilitates the activation of the epidermal growth factor receptor (EGFR) and the MAPK signaling pathway, pivotal drivers of oncogenic activity. Similarly, LINC01111 elevates DUSP1 levels by capturing miR-3924[108], culminating in the inhibition of PAPK phosphorylation and subsequent inactivation of the SAPK/JNK signaling pathway, thereby attenuating the invasive capabilities of PC cells. Moreover, ZEB1-AS1 enhances TRIB2 expression by targeting miR-505[109], with rescue assays revealing that TRIB2 overexpression can mitigate the suppressive impact of ZEB1-AS1 knockdown on the viability, metastasis, and invasion of PC.

LncRNAs play a critical role in the post-transcriptional regulation of gene expression, often through the negative regulation of miRNA levels. For instance, HOTAIR is notably upregulated in PC tissues and cell lines[73,110], where it functions as a ceRNA to

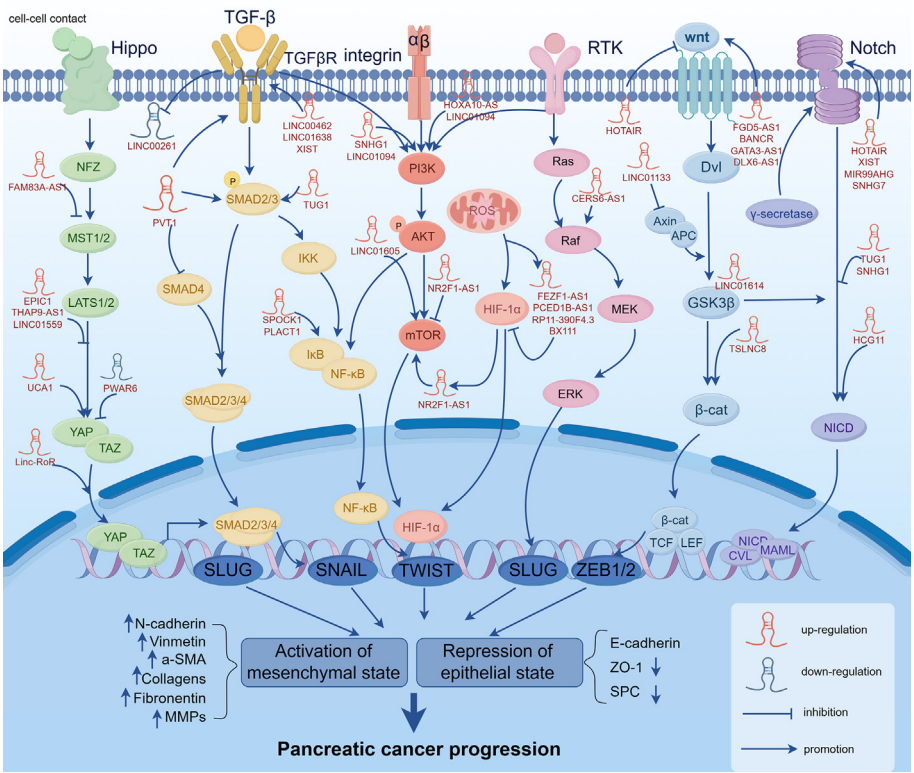

Fig. 2. Complex regulation of EMT by lncRNAs in pancreatic cancer. This diagram illustrates the key signalling pathways associated with EMT, such as Hippo, TGF-β, RTK (receptor tyrosine kinase), Wnt and Notch, each indicated by a different colour for clarity. At the centre of the figure are the key transcription factors involved in EMT regulation: SLUG, SNAIL, TWIST and ZEB1/2, which act as integrators of signals from multiple pathways. Surrounding these transcription factors are arrows symbolising the intricate layers of regulation by lncRNAs. These lncRNAs modulate the expression and activity of key regulators, thereby influencing the invasive and metastatic properties of pancreatic cancer cells.

suppress miR-613 expression[79]. In vivo experiments have demonstrated that the stable overexpression of miR-613 or the knockdown of HOTAIR leads to a reduction in NOTCH3 expression, culminating in the inhibition of tumor growth[79]. Similarly, ZEB2-AS1 serves as a ceRNA to downregulate miR-204 expression, subsequently derepressing the expression of its downstream target HMGB1, thereby facilitating the proliferation and invasion of PC cells[111]. Moreover, DANCR has been shown to reduce HMGB1 levels in both PC tissues and cell lines through its function as a ceRNA, establishing an inhibitory relationship with miR-33b [112]. By acting as a sponge for miR-33b, DANCR upregulates MMP16 expression in PC, thus promoting carcinogenesis. Additionally, other lncRNAs, including PVT1[113], FGD5-AS1[114], XIST[115], and H19[116], engage in interactions with various miRNAs to modulate processes central to PC proliferation. Kindly direct your attention to Table 1, which contains the relevant details.

Understanding the complex molecular mechanisms of pancreatic cancer requires elucidation of the ceRNA network mediated by lncRNAs. However, there is skepticism surrounding the ceRNA hypothesis, particularly regarding the quantitative aspects of ceRNA interactions and the potential impact of changes in the expression of individual lncRNAs on miRNA activity. The ceRNA hypothesis proposes a regulatory network in which various transcripts, such as lncRNAs, pseudogenes, circRNAs, and mRNAs, interact with each other by competing for binding to miRNAs. This interaction affects the expression levels of these transcripts and can dynamically influence gene expression. The ceRNA hypothesis is intriguing because it has the potential to clarify the function of numerous uncharacterized lncRNAs. Although there is empirical support for ceRNA interactions, especially those involving circRNAs and pseudogene-derived transcripts, skepticism remains regarding the physiological significance of these interactions due to the quantitative dynamics of miRNA-target interactions. Critiques emphasize that the effect of individual ceRNAs on miRNA activity is limited by the abundance and expression changes of the ceRNA relative to the entire pool of miRNA targets[117]. However, the hypothesis has led to new research avenues, such as the creation of databases for bioinformatically predicted ceRNA networks. These aim to explore the various roles of non-coding RNAs in gene regulation. However, the practical challenge is to distinguish meaningful interactions within the vast network of competing RNA interactions. This calls for more refined models and experimental validation to elucidate the biological relevance and specificity of ceRNA-mediated regulation.

LncRNA in autophagy

Autophagy plays a dual role in cancer, acting as both a tumor suppressor by degrading oncogenic substrates and a facilitator of tumor survival under stress. Autophagosome formation, a cornerstone of this process, begins with the activation of the ULK1 complex, which is tightly regulated by nutrient availability through AMPK and mTORC1 signaling pathways[118]. The phagophore nucleation stage is orchestrated by the Beclin 1-Vps34-Vps15 complex, generating PI3P crucial for subsequent autophagosome membrane expansion[119]. Two ubiquitin-like systems, the ATG12-ATG5-ATG16L1 complex and the LC3 lipidation pathway, govern the phagophore's elongation into a complete autophagosome[120].

In the context of tumor invasion and metastasis, autophagy modulates EMT, with implications for cancer cell metastasis and invasion[121]. Autophagic degradation of E-cadherin and regulation of EMT-associated transcription factors signify this pathway's influence on cell phenotypic transition[121]. Furthermore, autophagy alters the tumor microenvironment by modulating the secretion of factors that facilitate cancer cell invasion[122]. It also endows metastasizing cells with a survival advantage, allowing them to withstand detachment-induced cell death and establish distant colonies. These insights underscore autophagy's complex involvement in cancer, highlighting its potential as a target for therapeutic intervention.

The interplay between lncRNAs and autophagy is intricate and context-dependent. lncRNAs have been shown to modulate autophagy through various mechanisms, exerting either promotive or inhibitory effects. This variability hinges on the cellular conditions and the specific lncRNAs in question[123]. (Fig. 3) For instance, certain lncRNAs can bind to autophagy-related proteins or mRNAs, influencing the autophagy machinery directly. Others may interact with signal transduction pathways that govern the autophagic process, such as mTOR or AMPK pathways, thereby exerting upstream control[124]. As a critical regulator of autophagy, mTORC1 particularly inhibits autophagy induction in nutrient-rich conditions by phosphorylating and inactivating the ULK1 complex, which is essential for initiating autophagy. At the molecular level, LINC01133 downregulates miR-216a-5p, subsequently influencing TPT1 expression. TPT1 is involved in tumorigenesis and interacts with the mTORC1 pathway, illustrating a complex regulatory network that impacts cellular processes[125].

Furthermore, a significant number of lncRNAs, including LINC01133, can regulate the expression of autophagy-related genes by altering chromatin states or acting as ceRNAs that sequester miRNAs. This, in turn, affects the regulatory roles of miRNAs on autophagy. For instance, LZTS1-AS1 acts as a molecular sponge for miR-532, thereby regulating TWIST1 expression, which in turn inversely modulates miR-532′s autophagic induction and the expression of autophagy markers[126]. This modulation facilitates the metastasis and invasion of PC cells. In a related mechanism, LINC01207 binds to miR-143-5p, influencing its ability to regulate AGR2, a miR-143-5p target gene[127]. The knockdown of LINC01207 has been shown to hinder PC progression by sponging miR-143-5p, thereby reducing AGR2 expression[127]. Moreover, the upregulation of ANRIL in pancreatic cancer tissues is implicated in the competitive inhibition of miR-181a, which targets the 3′UTR of HMGB1[128]. This interaction results in the modulation of autophagic activity, as evidenced by altered LC3 I/II conversion rates and increased Beclin1 expression, indicative of autophagy activation[128].

Clearly, lncRNAs have more complex autophagy regulatory roles, including but not limited to transcriptional regulation, protein–protein interactions, and mitochondrial dynamics. Previous research has demonstrated that the absence of MALAT1 effectively inhibits invasion and metastasis of PC both in vitro and in vivo [129]. Further investigations have clarified that MALAT1 promotes these processes by enhancing the degradation of autophagosomes [130]. Specifically, MALAT1 upregulates the expression of the RNA-binding protein HuR, which in turn enhances the post-transcriptional regulation of TIA-1[130]. This cascade of interactions activates the autophagic pathway, facilitating metastasis in aggressive forms of PC. Additionally, UCA1 has been identified to possess the capability to inhibit mitochondrial autophagy and regulate mitochondrial dynamics in PC. Experimental findings have shown that UCA1 not only activates the MAPK/ERK pathway but also increases the expression of mitochondrial membrane potential, thereby promoting mitochondrial fusion while reducing the expression levels of proteins associated with mitochondrial fragmentation and fission[131]. This regulatory effect of UCA1 on mitochondrial dynamics through the MAPK pathway contributes to the enhancement of the migratory potential of PC[131].

Investigating the role of lncRNA-mediated autophagy in cancer invasion and metastasis presents a multifaceted landscape of both challenges and opportunities. One significant dilemma arises from the dual nature of autophagy in cancer progression; while it can suppress tumor formation in early stages by eliminating damaged

Table 1
Lncrnas function as cernas in pancreatic cancer.

LncRNA	Role in PC	MiRNA	Target gene	pathway	Mechanism of action	Reference
HOTAIR	Oncogenic	miR-613	Notch3	Notch pathway	In pancreatic cancer, HOTAIR acts as a ceRNA by sponging miR-613 to reduce the expression of Notch3.	[79]
GAS5	Tumor suppressor	miR-32-5p	PTEN		GAS5 can positively regulate the PTEN-induced tumor-suppressive pathway via miR-32-5p, thereby inhibiting metastasis in PC.	[106]
LINC00976	Oncogenic	miRNA-137	OTUD7B	EGFR/MAPK pathway	Linc00976 interacts with miRNA-137, preventing OTUD7B degradation and activating the EGFR/MAPK signaling pathway.	[107]
LINC01111	Tumor suppressor	miR-3924	DUSP1	PAPK phosphorylation and the SAPK/JNK pathway	High levels of LINC01111 sequester miR-3924, elevating DUSP1 and consequently inhibiting PAPK phosphorylation and the SAPK/JNK pathway in PC, reducing their invasiveness.	[108]
ZEB1-AS1	Oncogenic	miR-505	TRIB2	miR-505-3p/TRIB2 axis	ZEB1-AS1 upregulates TRIB2 expression by sponging miR-505, promoting tumorigenesis in PC.	[109]
ZEB2-AS1	Oncogenic	miR-204	HMGB1	miR-204/HMGB1	LncRNA ZEB2-AS1 promotes PC growth and invasion through regulating the miR-204/HMGB1 axis.	[111]
DANCR	Oncogenic	miRNA-33b	MMP16	miR-33b/MMP16	DANCR Acts as a miR-33b Sponge to Positively Regulate the Expression of MMP16 in PC.	[112]
PVT1	Oncogenic	miR-448	SERBP1		PVT1 competitively binds miR-448 to regulate the miRNA target SERBP1.	[113]
FGD5-AS1	Oncogenic	miR-520a-3p	KIAA1522	miR-520a-3p/KIAA1522 axis	FGD5-AS1 accelerates cell proliferation and migration by binding miR-520a-3p and upregulating KIAA1522.	[114]
XIST	Oncogenic	miR-133a	EGFR	XIST/miR-133a/EGFR	XIST Serves as a ceRNA for EGFR by Interacting with miRNA-113a, Reducing miRNA-113a's Suppressive Impact on the Downstream Target EGFR.	[115]
H19	Oncogenic	miR-194	PFTK1	Wnt pathway	H19 associates with PFTK1 and inversely relates to miR-194, influencing PC growth and mobility via Wnt pathway downstream of PFTK1.	[116]
H19	Oncogenic	miR-675-3p	SOCS5	STAT3 pathway	H19 interacts with miR-675-3p and triggers the STAT3 pathway by directly engaging SOCS5, facilitating the EMT process.	[199]
PSMB8-AS1	Oncogenic	miR-382-3p	STAT1	PD-L1 pathway	PSMB8-AS1 Regulates PD-L1 through Sponging miR-382-3p and Promotes PC Progression via STAT1.	[200]
XIST	Oncogenic	miR-429	ZEB1	EMT	XIST suppresses miR-429 expression, thus elevating ZEB1 levels, which mediates the tumor-suppressive effect of XIST knockdown in PC.	[201]
SNHG12	Oncogenic	miR-320b		EMT	SNHG12 interacts with miR-320b and enhances cell invasion by upregulating the EMT process.	[202]
LINC00941	Oncogenic	miR-335-5p	ROCK1	LIMK1/Cofilin-1 pathway	LncRNA 00941 binds miRNA-335-5p and activates ROCK1, which in turn triggers the LIMK1/Cofilin-1 signaling pathway, promoting PC invasion and metastasis.	[203]
ABHD11-AS1	Oncogenic	miR-1231	cyclin E1		Knockdown of lncRNA ABHD11-AS1 inhibits PC tumorigenesis through miR-1231 sponging.	[204]
DLX6-AS1	Oncogenic	miR-181b	Zinc finger E-box-binding homeobox 2	EMT	DLX6-AS1 enhances cancer cell proliferation and invasion by weakening miR-181b's control over EMT in PC.	[205]
SNHG14	Oncogenic	miR-613	ANXA2		SNHG14 accelerates PC progression by regulating annexin A2 expression, serving as a ceRNA for miR-613.	[206]
SNHG17	Oncogenic	miR-942			SNHG17 enhances PC proliferation and invasiveness through interaction with miR-942.	[207]
LOXL1-AS1	Oncogenic	miR-28-5p	SEMA7A	lncRNA LOXL1-AS1/miR-28-5p/SEMA7A axis	LOXL1-AS1 sponges miR-28-5p, upregulates SEMA7A expression and promotes PC progression.	[208]
LINC00514	Oncogenic	miR-28-5p	Rap1b		LINC00514 accelerates PC progression by upregulating Rap1b expression through ceRNA acting as miR-28-5p.	[209]
TP73-AS1	Oncogenic	miR-200a	MMP14		TP73-AS1 sponges miRNA –200a which in turn increases MMP14 expression and promotes PC migration and invasion.	[210]
CRNDE	Oncogenic	miR-384	IRS1		CRNDE sponges miR-384 and upregulates IRS1 to promote proliferation and metastasis of PC.	[211]
ADPGK-AS1	Oncogenic	miR-205-5p	ZEB1	EMT	ADPGK-AS1 inhibits miR-205-5p and promotes PC progression by activating ZEB1-induced EMT.	[212]
CYTOR	Oncogenic	miR-205-5p	CDK6	miR-205-5p/CDK6 axis	LncRNA CYTOR promotes PC proliferation and migration by sponging miR-205-5p and upregulating CDK6.	[213]
NUTF2P3-001	Oncogenic	miR-3923	KRAS	miR-3923/KRAS pathway	Hypoxia-induced NUTF2P3-001 promotes PC tumorigenesis by inhibiting the miR-3923/KRAS pathway.	[214]
CASC19	Oncogenic	miR-148b	E2F7	CASC19/miR-148b/E2F7 axis	CASC19 promotes pancreatic carcinogenesis by negatively regulating miR-148b and positively regulating E2F7.	[215]
KTN1-AS1	Oncogenic	miR-23b-3p	HMGB2	miR-23b-3p/HMGB2 axis	KTN1-AS1 promotes PC invasiveness by competitively binding miR-23b-3p and thus upregulating HMGB2.	[216]
CERS6-AS1	Oncogenic	miR-15a-5p miR-6838-5p	HMGA1	miR-15a-5p/miR-6838-5p/HMGA1 axis	CERS6-AS1 enhanced HMGA1 expression to contribute to the progression of PC by sequestering miR-15a-5p and miR-6838-5p.	[217]
LINC00473	Oncogenic	miR-195-5p	PD-L1		LINC00473 sponging miR-195-5p upregulates PD-L1 expression driving PC invasion and migration.	[218]
LINP1	Oncogenic	miR-491-3p			LINP1 enhances PC proliferation and metastasis by regulating miR-491-3p.	[219]
ROR	Oncogenic	let-7 family			ROR regulates microRNA function by acting as a ceRNA to promote cell proliferation and invasion.	[220]
MIAT	Oncogenic	miR-133			MIAT negatively regulates miR-133 to promote PC metastasis.	[221]

Table 1 (*continued*)

LncRNA	Role in PC	MiRNA	Target gene	pathway	Mechanism of action	Reference
OIP5-AS1	Oncogenic	miR-342-3p	AGR2	AKT/ERK pathway	OIP5-AS1 sponges miR-342-3p and activates the AKT/ERK signaling pathway to promote PC cell growth.	[222]
LINC01559	Oncogenic	miR-1343-3p	RAF1	ERK pathway	LINC01559 upregulates RAF1 and activates its downstream ERK pathway by acting as a ceRNA for miR-1343-3p to exert oncogenic effects.	[223]
PTTG3P	Oncogenic	miR-132/212-3p	FoxM1	FoxM1 signaling pathway	PTTG3P sponge miR-132/212-3p upregulates FoxM1 expression, which in turn activates PTTG3P expression, thus creating a feedback loop that promotes the invasiveness of PDAC cells.	[224]
TPT1-AS1	Oncogenic	miR-30a-5p	ITGB3		TPT1-AS1 acts as an endogenous sponge for miR-30a-5p and promotes the EMT process by upregulating integrin β3 (ITGB3) levels.	[29]
ZFAS1	Oncogenic	miR-497-5p	HMGA2	miR-497-5p/HMGA2 axis	ZFAS1 promotes PC proliferation and metastasis by sponging miR-497-5p to regulate HMGA2 expression.	[225]
LINC00152	Oncogenic	miR-150			LINC00152 promotes PC progression by inhibiting miR-150 expression.	[152]
MIR210HG	Oncogenic	miR-125b-5p	HK2 and PKM2	glycolysis	MIR210HG promotes an aggressive phenotype and glycolysis in PC by negatively regulating miR-125b-5p and positively regulating HK2 and PKM2 expression.	[226]
LINC01094	Oncogenic	miR-577	LIN28B	PI3K/AKT pathway	LINC01094 inhibits miR-577 as ceRNA and activates the PI3K/AKT pathway by upregulating LIN28B expression.	[30]
LINC00857	Oncogenic	miR-130b	RHOA	miR-130b/RHOA axis	LINC00857 acts as a sponge for miR-130b and reduces its expression, thereby promoting PC metastasis.	[227]
LUCAT1	Oncogenic	miR-539			LUCAT1 promotes cell proliferation and migration in PC via sponge miR-539.	[228]
SNHG15	Oncogenic	miR-345-5p	RAB27B	miR-345-5p/RAB27B axis	SNHG15 promotes PC invasion migration by sponging miR-345-5p and positively regulating RAB27B.	[229]
LINC00460	Oncogenic	miR-491-5p			LINC00460 accelerates PC by sponging miR-491-5p.	[230]
SNHG7	Oncogenic	miR-146b-5p	Robo1	miR-146b-5p/Robo1 axis	SNHG7 promotes PC genesis by sponging miR-146b-5p and upregulating Robo1 expression.	[231]
TTN-AS1	Oncogenic	miR-589-5p	FOXP1	TTN-AS1/miR-589-5p/FOXP1	TTN-AS1 promotes PC invasive metastasis by sponging miR-589-5p and upregulating FOXP1, which in turn activates TTN-AS1 mRNA expression levels.	[232]
PCAT6	Oncogenic	miR-185-5p	CBX2	miR-185-5p/CBX2 axis	PCAT6 upregulates the expression of the oncogene CBX2 by sponging miR-185-5p, which in turn promotes PC occurrence.	[233]
DUXAP8	Oncogenic	miR-448	WTAP	miR-448/WTAP/Fak Signaling Axis	DUXAP8 promotes PC cell migration and invasion by sponging miR-448.	[234]
NNT-AS1	Oncogenic	miR-889-3p	HIF-1α		CAF-derived exosomal lncRNA NNT-AS1 acts as a molecular sponge for miR-889-3p to promote pancreatic cancer development by targeting HIF-1α.	[144]
LINC00673	Tumor suppressor	miR-504	HNF1A		LINC00673 inhibits PC invasion and migration by inhibiting miR-504 and promoting HNF1A expression.	[235]
PXN-AS1	Tumor suppressor	miR-3064	PIP4K2B		PXN-AS1 inhibits PC progression by sponging miR-3064 and upregulating PIP4K2B expression.	[236]
FLVCR1-AS1	Tumor suppressor	miR-513c-5p/miR-514b-5p	KLF10	PTEN/AKT pathway	FLVCR1-AS1 inhibits the PTEN/AKT pathway by sponging miR-513c-5p or miR-514b-5p and promoting KLF10 expression.	[101]
CASC2	Tumor suppressor	miR-24	MUC6	miR 24/MUC6 axis	CASC2 inhibits pancreatic carcinogenesis by sponging miR-24 and activating its downstream target MUC6.	[237]
LINC01963	Tumor suppressor	miR-641	TMEFF2		LINC01963 inhibits PC proliferation and invasion by negatively regulating miR-641 while upregulating TMEFF2.	[238]
AFAP1-AS1	Tumor suppressor	miR-146b-5p	EGFR		AFAP1-AS1 as ceRNA of miR-146b-5p activates EGFR expression, whereas CuB inhibits PC proliferation by suppressing AFAP1-AS1 expression.	[239]

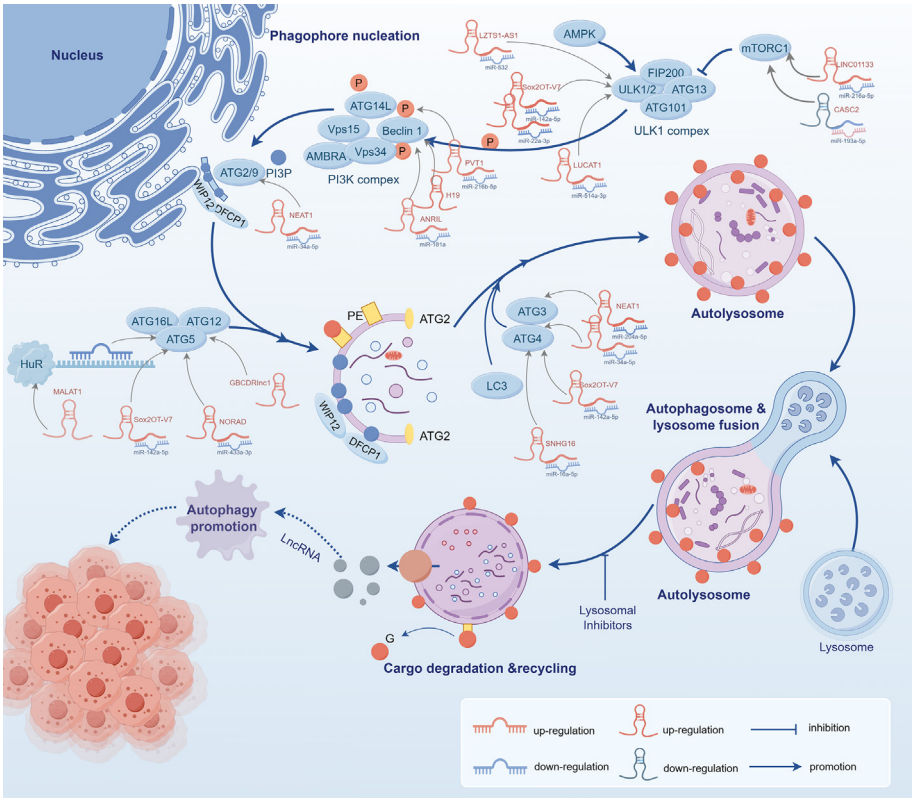

Fig. 3. LncRNA regulation of autophagy affects pancreatic cancer invasion and metastasis. AMPK activation and mTORC1 inhibition trigger the ULK1 complex, which is critical for the stress response. LncRNAs such as CASC2 interact with these regulators and affect autophagy initiation. Phagophore nucleation involves Beclin-1/class III PI3K complex-mediated PI3P generation, with lncRNAs such as PVT1 influencing membrane expansion. During maturation, lncRNAs potentially modulate LC3 lipidation, which affects vesicle completion. Thus, lncRNAs become key regulators in the autophagy process and affect the invasive metastasis of pancreatic cancer cells.

organelles and proteins, autophagy also supports cancer cell survival under stress, facilitating invasion and metastasis. This dichotomy complicates the targeting of lncRNAs involved in autophagy, as their inhibition might unintentionally promote cancer progression in certain contexts. Furthermore, the functional diversity and redundancy of lncRNAs, coupled with their context-dependent effects, add layers of complexity to understanding their precise mechanisms in autophagy regulation and cancer metastasis. Despite the inherent challenges, the exploration of lncRNA-mediated autophagy's role in cancer invasion offers significant potential, particularly when integrated with other therapeutic strategies.

Involvement of lncRNA in ferroptosis

In the rapidly evolving field of ferroptosis research, lncRNAs have emerged as crucial regulators of this unique iron-dependent cell death pathway, significantly impacting the processes of cancer invasion and metastasis. Ferroptosis, distinct from classical cell death mechanisms such as apoptosis, necrosis, and autophagy, is characterized by its reliance on iron metabolism and the consequential lethal accumulation of lipid peroxides facilitated by reactive oxygen species (ROS) [132]. The specific roles of lncRNAs in mediating ferroptosis and thereby influencing the dynamics of PC invasion and metastasis are complex, involving intricate regulatory networks. These lncRNAs modulate various aspects of iron metabolism, antioxidant defense mechanisms, and lipid peroxidation processes, which collectively dictate the susceptibility of cancer cells to ferroptosis.

During the regulation of ferroptosis, lncRNAs intricately collaborate with established signaling pathways crucial for cell survival (including p53, AKT/mTOR, NRF2)[15,133]. Among the regulators of ferroptosis, solute carrier family 7 member 11 (SLC7A11) stands out as a crucial factor, identified as a direct target of the tumor suppressor p53, which acts to suppress its mRNA expression, thereby facilitating ferroptotic cell death[134]. In the context of PC, the oncogenic potential of LINC00578 is manifested through its direct interaction with UBE2K, diminishing the ubiquitination and subsequent degradation of SLC7A11[135]. This interaction leads to enhanced SLC7A11 expression, promoting cellular proliferation and inhibiting ferroptosis, thus contributing to cancer progression. Similarly, PCBP3, functioning as an iron chaperone, is instrumental in the intracellular iron transport, essential for ferroptosis execution. The lncRNA A2M-AS1 leverages this pathway by engaging PCBP3, subsequently activating p38 and repressing AKT/mTOR pathway phosphorylation, thereby promoting ferroptosis in PC [15].

Additionally, lncRNAs exert their influence on ferroptosis through mechanisms such as miRNA sponging. For instance, LINC02086 acts as a ceRNA for miR-342-3p, facilitating upregulation of CA9 expression which leads to elevated levels of Fe^{2+} and ROS, thus mitigating ferroptosis and fostering PC progression [136]. A fascinating aspect of lncRNA function in this context is their ability to form complex molecular structures that confer resistance to ferroptosis. This is exemplified by LINC01133, which not only promotes PC proliferation and metastasis but also enhances resistance to ferroptosis by forming a tripartite complex with FUS protein and FSP1 mRNA[125]. This complex stabilizes FSP1, a known ferroptosis inhibitor, thereby attenuating the cell's susceptibility to ferroptosis. (Fig. 4).

Numerous meta-analyses have underscored the potential of ferroptosis-associated lncRNAs as prognostic biomarkers in PC

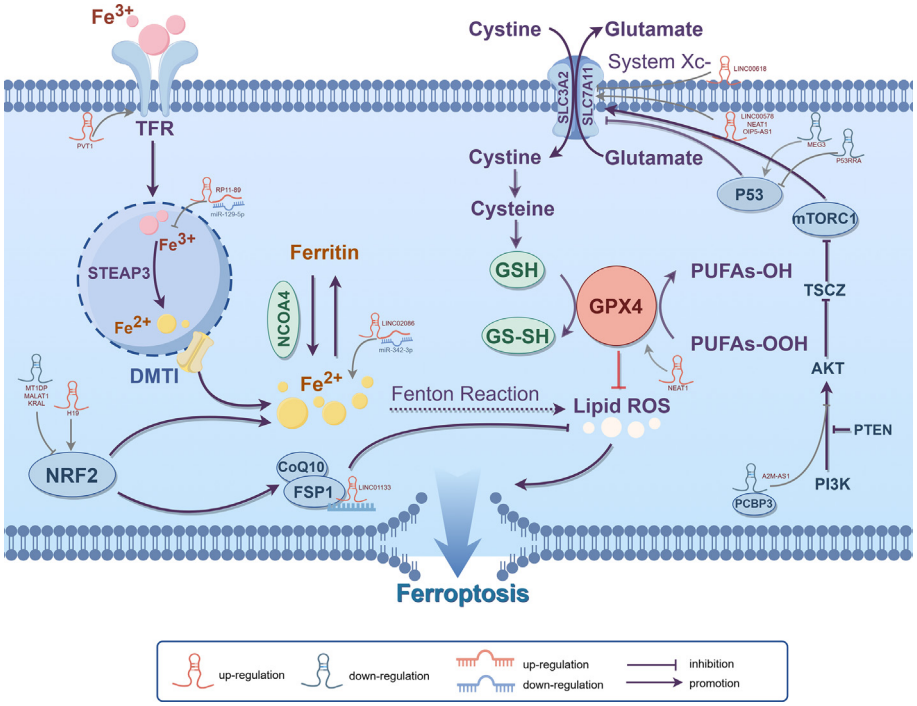

Fig. 4. Involvement of lncRNA in ferroptosis. The transferrin receptor (TFR) mediates the cellular uptake of iron (Fe^{3+}), which is reduced to Fe^{2+} in endosomes by STEAP3. This iron is then translocated to the labile iron pool via DMT1. Iron storage is managed by ferritin, which sequesters Fe^{2+}, and iron release is facilitated by NCOA4-mediated ferritinophagy. Fe^{2+} participates in the Fenton reaction, which generates reactive oxygen species (ROS). In the protective pathway, sufficient GPX4 activity and GSH levels prevent the accumulation of lipid peroxides, thereby protecting the cell from iron-mediated cell death. In contrast, in the injury pathway, inhibition of GPX4 or depletion of GSH results in uncontrolled lipid peroxidation leading to iron-mediated cell death. p53 inhibits SLC7A11 mRNA expression, preventing it from being expressed, leading to cell cycle arrest and iron death. In contrast, activation of mTORC1 promotes iron death resistance and tumour progression by upregulating SLC7A11.

[137]. By targeting specific lncRNAs to either induce or inhibit ferroptosis, it may be possible to enhance the efficacy of existing treatments or overcome resistance mechanisms[138]. However, translating these findings into clinical practice requires a deeper understanding of the complex interactions between lncRNAs, ferroptosis pathways, and the tumor microenvironment, as well as the development of precise methods for measuring lncRNA levels in clinical samples.

Exosome-derived lncRNAs

Exosomal lncRNAs have emerged as key regulators in the TME of several cancers, including pancreatic cancer. These lncRNAs are encapsulated in exosomes – extracellular vesicles secreted by tumour cells – and released into the environment, where they are transferred to both nearby and distant cells[139–142]. In the context of PC, exosomal lncRNAs play an important role in intercellular communication by modulating the gene expression profiles of recipient cells. Through these interactions, exosomal lncRNAs significantly influence cancer-related processes within the TME, including inflammation, immune evasion, apoptosis and metastasis. Specifically, exosomal lncRNAs regulate immune cell functions by promoting macrophage polarisation to a pro-tumour M2 phenotype[139–142], modulating T cell activity to evade immune surveillance, and altering the antigen-presenting capacity of dendritic cells[143]. In addition, exosomal lncRNAs interact with cancer-associated fibroblasts (CAFs) and endothelial cells to promote angiogenesis and extracellular matrix remodelling, thereby supporting tumour growth and invasion[144–146]. Exosomal lncRNAs also influence the secretion of pro-inflammatory cytokines, the activation of inflammatory pathways such as NF-κB [140,142], and the promotion of EMT[55,71,147–150], thereby fostering a microenvironment conducive to tumour invasion, migration and metastasis. By coordinating these complex interactions within the TME, exosomal lncRNAs not only promote tumour cell survival and dissemination, but also establish a dynamic microenvironment that supports cancer progression.

Tumour-derived exosomal lncRNAs, when taken up by recipient cells, regulate key inflammatory pathways such as NF-κB, thereby controlling the production of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-8[142]. Exosomal lncRNAs, such as MALAT1 [151], have been shown to modulate the recruitment and polarisation of immune cells. By influencing the activation of pro-inflammatory pathways such as NF-κB and MAPK, exosomal lncRNAs contribute to a chronic inflammatory state that promotes tumour growth and metastasis[140]. In addition, exosomal lncRNAs can regulate macrophage polarisation to the M2 phenotype, which has immunosuppressive effects that favour PC progression. This alters the immune landscape within the tumour microenvironment, helping the tumour to evade immune surveillance and promote tissue remodelling[139]. For example, exosomes derived from M2 macrophages contain the specific SBF2-AS1, which acts as a competitive endogenous RNA to suppress miR-122-5p and increase XIAP expression, effectively inhibiting PC progression[139]. The transition of macrophages to the M2 phenotype facilitates the metastatic spread of PC. Exosomal FGD5-AS1 interacts with p300 to catalyse the acetylation of STAT3, which promotes M2 macrophage polarisation through activation of the STAT3/NF-κB pathway[140]. In addition, KLHDC7B-DT enhances the malignant properties of PDAC cells by promoting IL-6-induced M2 macrophage polarisation and activating the IL-6-STAT3 pathway[142]. Similarly, exosomal LINC00460 promotes carcinogenesis by inducing M2 macrophage polarisation[141].

Exosomal lncRNAs can also influence apoptotic pathways in recipient cells, promoting pancreatic cell survival or inducing apoptosis. For example, exosomal lncRNAs such as LINC00152 and SNHG1 regulate apoptosis by interacting with apoptotic regulators such as p53, Bcl-2 family proteins or caspases[152]. By

modulating these apoptotic signals, exosomal lncRNAs help tumour cells survive under stressful conditions such as hypoxia or chemotherapy, thereby contributing to chemotherapy resistance and tumour relapse. For example, exosomes derived from hypoxic haematopoietic stem cells (HPSC-EXO) deliver UCA1, which interacts with EZH2 and regulates histone methylation at the SOCS3 gene locus, thereby inhibiting apoptosis and enhancing the invasion and metastatic ability of pancreatic cancer cells[153].

In addition, exosomal lncRNAs have prominent immunoregulatory properties. They carry tumour antigens and present them to immune cells such as dendritic cells, macrophages and T cells, thereby activating T cells or inducing an immunosuppressive environment to help tumours evade immune surveillance[143]. For example, the exosomal lncRNA RP11-161H23.5 derived from CAFs promotes immune escape by downregulating the expression of the antigen-presenting molecule HLA-A, thereby impairing antitumour immune responses[143].

Exosomal lncRNAs promote ECM remodelling by transporting MMPs that degrade ECM components, thereby facilitating tumour cell invasion into adjacent tissues[154]. In addition, tumour-derived exosomal lncRNAs promote angiogenesis by delivering pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), to endothelial cells, thereby supporting the formation of new blood vessels critical for tumour growth[145]. Specifically, the exosomal lncRNA SNHG11 acts as a ceRNA for miR-324-3p, leading to the upregulation of VEGFA expression[145]. This upregulation promotes angiogenesis and metastasis. Similarly, CAF-derived exosomal lncRNA NNT-AS1 serves as a molecular sponge for miR-889-3p and targets HIF-1α, promoting PC development[144]. In addition, perineural invasion (PNI) is considered a key factor in tumour metastasis. In this context, the exosomal lncRNA XIST acts as a ceRNA for miR-211-5p[146]. Through exosomal delivery, it promotes interactions between neurons and tumour cells, thereby promoting the invasion of pancreatic cancer cells[146]. This finding paves the way for the development of novel therapeutic strategies targeting PNI in pancreatic cancer, which promises to significantly improve patient prognosis.

When exosomal lncRNAs are released from PC cells, they can induce EMT in recipient epithelial cells by transferring transcription factors such as SNAIL, TWIST and ZEB1/2, or by regulating miRNAs that suppress E-cadherin expression, thereby promoting a more invasive phenotype[147]. For example, exosomal lnc-Sox2ot regulates Sox2 expression by competitively binding to the miR-200 family, thereby promoting EMT[147]. Similarly, exosomal LINC01268 interacts with miR-217 and positively regulates KIF2A, promoting PC invasiveness and metastasis through EMT[148]. HULC interacts with miR-622 and inhibits EMT via extracellular vesicle trafficking[55]. Exosomal lncRNAs are also involved in regulating cancer cell invasion by directly targeting EMT-related markers and transcription factors. For example, LINC01133 promotes EMT by activating β-catenin, silencing AXIN2 and inhibiting GSK3 activity[71]. In contrast, upregulation of NONHSAT105177 counteracts EMT and disrupts cholesterol biosynthetic pathways [149]. Similarly, exosomal Linc-ROR promotes EMT by activating the HIF1α-ZEB1 axis and enhancing IL-1β-induced adipocyte dedifferentiation[150]. Fig. 5 shows that exosomal lncRNA affects invasive metastasis of pancreatic cancer.

Exosomal lncRNAs have been extensively studied in pancreatic cancer metastasis, but the role of lncRNAs in other extracellular vesicle (EV) subtypes, such as microvesicles and apoptotic bodies, remains largely unexplored. Investigation of these lesser-known EVs may reveal additional regulatory mechanisms involved in invasive migration. For example, Yu et al. identified diagnostic fea-

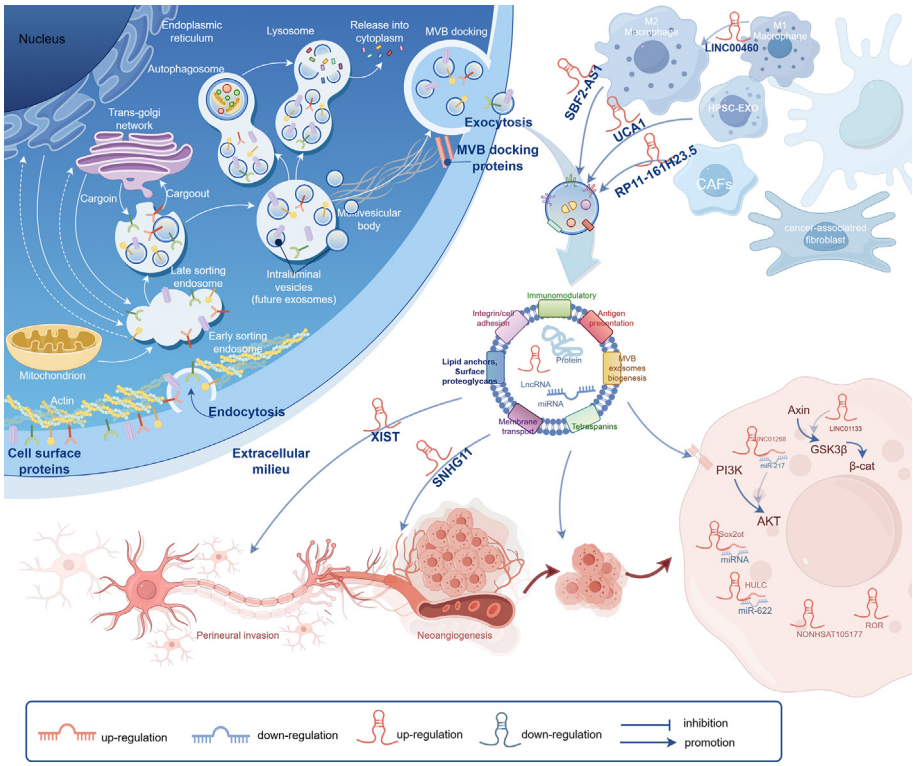

Fig. 5. Exosomal lncRNA affects invasive metastasis in pancreatic cancer. In PC, lncRNAs undergo transcription and complex maturation involving the endoplasmic reticulum and Golgi apparatus, before being packaged into multivesicular bodies (MVBs). These MVBs, guided by the cellular cytoskeleton, merge with the plasma membrane, releasing exosomes containing lncRNAs into the extracellular space. Upon uptake by recipient cells, these exosomal lncRNAs regulate critical signaling pathways, including PI3K/AKT and Wnt/β-catenin, which are pivotal in promoting the invasive and migratory characteristics of cancer cells. Additionally, lncRNA-loaded exosomes enhance PC progression by facilitating angiogenesis and perineural invasion, key factors in tumor growth and metastasis.

tures for PDAC based on plasma EV long RNA analysis, which improved patient outcomes by enabling earlier detection[155]. In addition, exosome-based nanodelivery technologies encapsulating lncRNAs hold great promise for cancer therapy due to their ability to protect molecular cargo from degradation during transport. However, these innovative strategies face critical challenges, including delivery efficiency and specificity, post-delivery stability, and concerns about immune rejection and safety. Overcoming these obstacles is critical to advancing the therapeutic potential of exosome-based applications.

Regulation of lncRNA by RNA modifications

RNA methylation modifications in lncRNAs are increasingly recognized for their critical role in the mechanisms of cancer invasion and metastasis. This chemical modification of RNA molecules encompasses a variety of types, including N6-methyladenosine (m^6A), N1-methyladenosine (m^1A), N6,2′-O-dimethyladenosine (m^6Am), 7-methylguanine (m^7G), 5-methylcytosine (m^5C), 5-hydroxymethylcytosine (hm^5C), pseudouridine (Ψ), and adenosine-to-inosine (A-to-I) editing[156]. Analogous to the regulatory impact of DNA methylation, RNA methylation influences RNA stability, translation, and intermolecular interactions, thus playing a pivotal role in regulating gene expression and cellular functions.

m^6A is the most common internal RNA modification and plays a critical role in the regulation of lncRNAs and their involvement in pancreatic cancer progression[151]. By methylating the nitrogen-6 position of adenosine residues within RNA molecules, the m^6A modification affects various aspects of RNA metabolism, including stability, translation, splicing and degradation[157]. In pancreatic cancer, m^6A alters the interactions and structural dynamics of lncRNAs, which in turn regulate key processes such as cell invasion and migration. Mechanistically, m^6A modification affects the RNA-DNA triple helix structure, thereby regulating the association of lncRNAs with specific genomic loci and controlling gene expression[157]. In addition, m^6A creates binding sites for reader proteins, such as those containing the YTH domain, which can recruit or inhibit RNA-binding proteins (RBPs) and thus determine the downstream fate of m6A-modified lncRNAs[158].

The dynamic interplay between m^6A ‘‘writers,’’ ‘‘erasers,’’ and ‘‘readers’’ plays a crucial role in the oncogenic process. For instance, the methylation of KCNK15-AS1 by m^6A in pancreatic cells and its subsequent demethylation by ALKBH5, a leading m^6A demethylase, illustrate a regulatory mechanism that impedes the motility of PC [103]. The m^6A reader YTHDF3 has been implicated in modulating the invasive and metastatic potential of cancer cells by influencing miRNA stability and function. Remarkably, YTHDF3 is targeted by miR-5586-5p, which establishes a negative feedback loop with DICER1-AS1, thereby enhancing glycolysis, tumor progression, and metastasis in PC[158]. Furthermore, YTHDF3 impacts the expression of lncRNAs, such as LINC00901, which upregulates IGF2BP2, thus augmenting MYC expression and forming the LINC00901/IGF2BP2/MYC signaling axis[159]. In contrast, YTHDF1, through m^6A modification, facilitates the degradation of LINC00901, suggesting that LINC00901 promotes PC progression via an m^6A-dependent mechanism[159]. Intriguingly, IGF2BP2, identified as a novel m^6A reader of the DANCR, stabilizes its RNA, thereby promoting pancreatic carcinogenesis[160].

METTL3 and METTL14 can also be recruited to lncRNAs as ‘‘writers’’ involved in tumor progression and metastasis. Notably, METTL3 has been identified to upregulate the expression of MALAT1 within PC, subsequently influencing cell vitality and contributing to the malignancy’s advancement[151]. Beyond transcriptional regulation, RNA methylation modifications exert profound effects in the post-transcriptional modulation of lncRNAs, altering their stability and functional capacity. For instance, METTL3 targets the 3′ UTR region of LIFR-AS1 for m^6A methylation, thereby augmenting its mRNA stability. This enhancement facilitates LIFR-AS1′s function as a ceRNA targeting miR-150-5p, leading to an indirect upsurge in VEGFA expression[161]. Such modulation activates the VEGFA/Akt/mTOR signaling pathway, intensifying the progression of PC. Similarly, the m^6A-modification of DBH-AS1, acting as a ceRNA for miR-3163, results in the upregulation of USP44, thereby attenuating the pace of cancer metastasis[162].

The discovery of STM2457, an active METTL3 inhibitor with in vivo efficacy, marks a significant advancement, unveiling the therapeutic potential of targeting cellular methylation processes [163]. STM2457 operates by modulating m^6A levels in a METTL3 enzymatic activity-dependent manner, curtailing PC cell invasion and metastasis through the downregulation of BANCR m^6A modifications[164]. This lays a foundational basis for the clinical application of STM2457 in treating PC. Furthermore, METTL14′s role in regulating m^6A levels underscores its contribution to tumor metastasis. By upregulating LINC00941 in an m^6A-dependent manner, METTL14 enhances the affinity of IGF2BP2 for LINC00941[165]. This interaction not only stabilizes LINC00941 but also propels PC metastasis and invasion[165], highlighting a complex regulatory network that influences cancer progression through modifications in RNA methylation. Fig. 6 summarises the major RNA methylation modifications of lncRNAs that affect pancreatic cancer invasion and migration by regulating transcription and binding interactions, thus affecting gene expression.

In the realm of RNA methylation modifications within lncRNAs, m^6A emerges as the most extensively identified modification, whereas investigations into other forms such as m^1A, m^5C, and m^7G are still nascent. Despite the early stage of research, initial discoveries hint at the potential regulatory roles these modifications might play in various pathologies. For example, the modulation of neuro-associated lncRNAs could hinge on their m^1A modifications, which may play a crucial role in the circRNA/lncRNA-miRNA-mRNA ceRNA mechanism, influencing the pathophysiology of neurological disorders[166]. The m^5C methylation of lncRNA NR_033928 has been shown to foster gastric cancer proliferation by stabilizing GLS mRNA[167]. Furthermore, comprehensive transcriptomic analyses of m^7G in the context of hypoxic pulmonary hypertension have pinpointed m^7G-modified lncRNAs as key players in the disease’s etiology[168].

Future research on RNA methylation modifications in lncRNAs, particularly in pancreatic cancer, should focus on several key areas. First, a comprehensive mapping of methylation modifications, such as m^1A, m^5C and m^7G, across lncRNAs in pancreatic cancer is essential to identify their specific roles in tumourigenesis and metastasis. Investigating how these modifications interact with established regulatory networks, such as the circRNA/lncRNA-miRNA-mRNA ceRNA machinery, will deepen our understanding of their contribution to cancer biology. In addition, exploring the functional consequences of these modifications on lncRNA stability, localisation and interaction with RNA-binding proteins will provide insights into their regulatory mechanisms. Another promising avenue of research is the development of targeted therapeutic strategies to manipulate these modifications, such as small molecules or CRISPR-based technologies, to potentially reverse the effects of dysregulated lncRNA methylation.

Therapeutic strategies and applications of lncRNA in PC

Recent advancements in the diagnosis and treatment of pancreatic cancer have been driven by innovations in biomarker discovery[169,170], targeted therapies[171–173], and immunotherapy [174,175]. Liquid biopsy techniques[176], such as the detection of circulating tumor DNA (ctDNA)[176], exosomal RNA[177], and metabolic profiling[172,178], are enabling non-invasive early

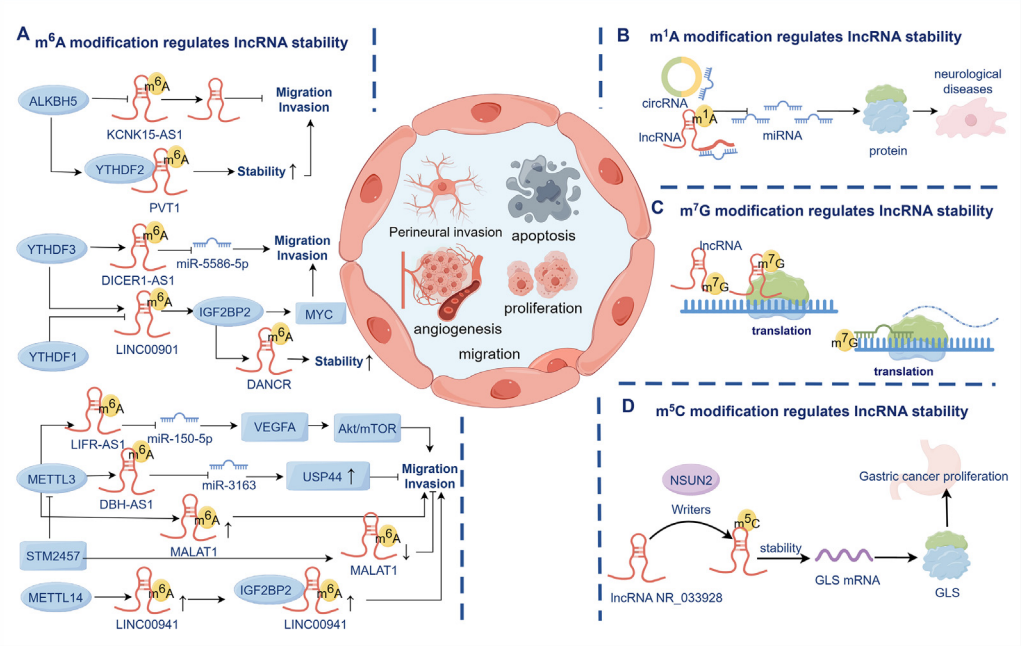

Fig. 6. Effects of RNA modifications on lncRNA stability and function in cancer. Section A focuses on m^{6}A modification, where enzymes like ALKBH5 demethylate and METTL3/METTL14 methylate lncRNAs. The m^{6}A 'readers' YTHDF1-3 recognize these modifications, influencing key cellular processes including metastasis, invasion, and expression of oncogenes such as MYC and VEGFA. Section B discusses the role of m^{1}A modification in neurological diseases, while Section C describes how m^{7}G modifications affect protein synthesis through translation. Section D highlights m^{5}C modifications by NSUN2, stabilizing lncRNAs and regulating gene expression, specifically influencing gastric cancer proliferation via the GLS mRNA-GLS protein axis. Collectively, these modifications are crucial for regulating lncRNA functions and their roles in cancer-related processes such as proliferation, metastasis, angiogenesis, and invasion.

detection. Genomic and transcriptomic technologies, including single-cell sequencing and RNA sequencing[179], are revealing intratumoral heterogeneity and identifying potential therapeutic targets, such as KRAS mutations and specific lncRNAs involved in tumor progression[169]. Targeted therapies, particularly those focusing on KRAS inhibitors[171], BRCA-related therapies and immune checkpoint blockade[174], are being rigorously tested in clinical trials.

Simultaneously, strategies to modulate the TME[180], such as stromal targeting and microbiome-based interventions, are gaining traction to enhance treatment efficacy. Advances in imaging techniques, including molecular imaging and real-time endoscopic ultrasound, are improving diagnostic precision[181]. Drug delivery systems, such as nanoparticles and organoid-based drug testing, are being explored for personalized therapy[173]. Moreover, epigenetic therapies[174] and autophagy modulation[171], particularly targeting autophagy-related proteins and lncRNA-driven autophagy regulation, are emerging as promising approaches. Integration of multi-omics data is providing a holistic view of pancreatic cancer biology, facilitating the identification of novel vulnerabilities and therapeutic strategies. Details of the above are presented in Table 2. These combined efforts are laying the groundwork for more effective, personalized approaches to diagnosing and treating pancreatic cancer.

Targeting lncRNAs has become a promising cancer therapy strategy due to their key role in gene regulation, tumorigenesis, metastasis, and chemoresistance. Several approaches to modulating LncRNA activity have been explored, including RNA interference (RNAi)[79,151,182,183], antisense oligonucleotides (ASOs)[184], CRISPR/Cas9[185,186], small molecule inhibitors[187], and nanoparticle delivery systems[188,189]. RNAi-based methods, particularly siRNAs and shRNAs, effectively silence lncRNAs by promoting their degradation by the RNA-induced silencing complex (RISC) [151,182]. In pancreatic cancer, RNAi has targeted lncRNAs such as lncRNA RP11-161H23.5[143], HOTAIR[79] and MALAT1 [151,182], which are associated with tumour growth and metastasis, and LINC00460[141] and LncRNA-ROR[90,150], which contribute to chemoresistance. However, challenges such as efficient delivery, off-target effects and immune responses hinder their clinical application. Nevertheless, advances in nanoparticle and viral vector delivery systems, along with strategies to minimise immune activation and improve targeting, aim to overcome these barriers [184]. Antisense oligonucleotides (ASOs) inhibit LncRNA function by hybridising to specific lncRNAs, leading to their degradation by RNase H or blocking their interaction with RNA-binding proteins[190]. Preclinical studies show that ASOs effectively suppress lncRNAs such as MALAT1[184], which drive tumour progression, metastasis and chemoresistance. In addition, chemical modifications such as 2′-O-methyl and locked nucleic acids (LNAs) improve ASO stability and cellular uptake[191], while nanoparticle delivery systems enhance their therapeutic efficacy in vivo[184]. The CRISPR/Cas9 genome editing system provides a precise method for targeting lncRNAs at the genetic level. By using guide RNAs (gRNAs) to direct Cas9 to specific LncRNA loci, researchers can knock out LncRNA expression or modify their sequences, deepening our understanding of their role in tumourigenesis and metastasis[185]. In pancreatic cancer, CRISPR/Cas9 has been successfully used to target lncRNAs such as LINC00673[185], all of which contribute to cancer cell proliferation and migration. In addition, CRISPR/Cas9 has been used in large-scale genome-wide screens to identify novel LncRNA targets that drive cancer progression [186].

Small molecule inhibitors are designed to specifically bind and disrupt lncRNA function by interfering with the secondary structure of lncRNAs or blocking their interactions with proteins involved in cancer progression[187]. For example, PVT1 expressed in tumour-associated stromal cells (TASc) and induced by tumour cell interleukin-6, enhances RAF kinase-mediated phosphorylation of tryptophan 2,3-dioxygenase in TASc, promoting the conversion of tryptophan to kynurenine[187]. This pathway promotes an

Table 2
Research methods for the treatment and diagnosis of pancreatic cancer.

Category	Sub-category	New Approaches	Description	Status/Research Phase	Reference
Therapeutics	Molecular Targeting	Targeting KRAS Mutations	Development of KRAS inhibitors (e.g., sotorasib) to inhibit tumor progression.	Early to clinical trial phase	[169]
		Targeting DNA Repair Pathways	Inhibition of DNA damage repair mechanisms (e.g., targeting PARP with olaparib) to sensitize cancer cells to chemotherapy.	Clinical trial phase	[170]
	Immunotherapy	Immune Checkpoint Inhibitors (PD-1/PD-L1)	Use of PD-1/PD-L1 inhibitors (e.g., pembrolizumab) to boost the immune system against pancreatic tumor cells.	Clinical trial phase	[174]
		Cancer Vaccines	Development of vaccines aimed at stimulating immune responses against pancreatic tumor antigens.	Early research phase	[175]
	Autophagy Targeting	Autophagy Inhibition (e.g., ULK1 inhibitors)	Targeting autophagy initiation proteins like ULK1 to sensitize pancreatic cancer cells to stress and chemotherapy.	Pre-clinical to clinical phase	[171]
	Targeting Metabolic Pathways	Glutamine Metabolism Inhibition	Inhibition of glutamine metabolism in pancreatic cancer cells to disrupt energy production.	Early-phase clinical research	[172]
	Nano-Drug Delivery Systems	Targeted Nanoparticles for Chemotherapy Delivery	Using nanoparticles for the targeted delivery of chemotherapeutic agents (e.g., paclitaxel or gemcitabine) to pancreatic cancer cells.	Pre-clinical to clinical phase	[173]
Diagnostics	Genetic Biomarkers	Liquid Biopsy (ctDNA, miRNA)	Detection of circulating tumor DNA (ctDNA) and microRNAs from blood as non-invasive biomarkers for diagnosis and monitoring of pancreatic cancer.	Clinical validation phase	[176]
		Genetic Alterations Detection (KRAS, TP53)	Identification of genetic alterations in blood, especially KRAS and TP53 mutations, to improve early detection and prognostication.	Clinical validation phase	[178]
	Imaging Technologies	Artificial Intelligence in Imaging	Use of machine learning to enhance the detection and interpretation of CT, MRI, and PET scans for early pancreatic cancer detection and monitoring.	Research to clinical phase	[181]
	Exosomal Biomarkers	Exosomal Proteins and RNAs	Analysis of exosomal proteins and RNAs (e.g., miRNAs, lncRNAs) as non-invasive biomarkers for diagnosis and prognosis.	Pre-clinical to clinical phase	[177]
	Single-Cell Analysis	Single-Cell RNA Sequencing	Use of single-cell RNA sequencing to profile tumor heterogeneity and identify novel biomarkers and therapeutic targets in pancreatic cancer.	Research to clinical phase	[179]
	Microbiome and Pancreatic Cancer	Gut Microbiome Profiling	Investigating the role of the gut microbiome in pancreatic cancer progression and identifying microbial signatures for early diagnosis or therapeutic targeting.	Early research phase	[180]

immunosuppressive microenvironment in PC. Depletion of PVT1-expressing TASc inhibits PC tumour growth, while targeting TASc with small molecule inhibitors sensitises PC to immunotherapy, offering a promising treatment approach[187]. In addition, small molecules can inhibit LncRNA-mediated epigenetic silencing, for example by targeting histone methyltransferase EZH2, which is recruited by lncRNAs such as MALAT1[182] and UCA1[153] to promote tumour growth. Nanoparticle-based drug delivery systems show great potential to improve the efficacy of RNA-based therapies, including LncRNA-targeted drugs, in the treatment of pancreatic cancer[188]. These systems, which include liposomes, dendritic polymers and polymeric nanoparticles, improve the stability, bioavailability and tumour-targeting efficiency of RNA-based therapeutics by functionalising the nanoparticles with ligands or antibodies that recognise specific cancer cell markers [188]. In pancreatic cancer, nanoparticles can improve the delivery of LncRNA-targeted drugs such as those targeting lncRNA RP11-161H23.5[143], HOTTIR[188], HOTAIR[188] and PVT1[189], which are involved in tumour growth and metastasis. Moreover, nanoparticles can be used in combination therapy to deliver LncRNA drugs in conjunction with chemotherapeutic agents, improving efficacy while minimising side effects[188,189].

In addition, the scientific literature has increasingly reported on strategies aimed at disrupting the interactions between lncRNAs and proteins, as well as between lncRNAs and DNA[192,193], which are crucial for the regulation of gene expression. Innovative methodologies, such as GRID-seq[194,195], RADICL-Seq[196], and the prediction of lncRNA-protein interactions (LPIs)[197], have been developed, significantly advancing the field of LncRNA research. The therapeutic application of pHLIP-PNA constructs in mice models bearing platinum-resistant ovarian tumor xenografts demonstrates a novel therapeutic strategy[198]. These constructs inhibit the activity of HOTAIR, leading to a reduction in tumor growth and an improvement in survival rates[198].

However, challenges remain, including off-target effects due to sequence homology, delivery difficulties associated with nanoparticle systems or viral vectors, and the complexity of tumour heterogeneity requiring personalised approaches. In addition, the incomplete functional characterisation of many lncRNAs, potential compensatory mechanisms in cancer cells and the risks of immunogenicity or toxicity of delivery systems further complicate therapeutic development. Overcoming these challenges requires improving targeting specificity through advanced delivery systems, integrating lncRNA-targeted therapies with conventional treatments, leveraging personalised medicine, and conducting rigorous preclinical studies. Despite these obstacles, advances in technology and a deeper understanding of lncRNA biology hold promise for overcoming these barriers and unlocking the therapeutic potential of lncRNA-targeted interventions.

Conclusions

In summary, understanding the role of lncRNAs in pancreatic cancer invasion and metastasis is critical for advancing diagnostic and therapeutic strategies. LncRNAs have emerged as key regulators within the complex molecular networks governing pancreatic cancer progression, particularly through their involvement in signalling pathways such as TGF-β/Smad, Wnt/β-catenin and Notch, which are essential for EMT. In addition, their effects on autophagy, ferroptosis and the tumour microenvironment underscore their multifaceted role in promoting cancer cell invasion and metastasis. The effect of lncRNAs on RNA modifications, such as m6A and m^5C

methylation, increases their stability and activity, further enhancing their ability to mediate invasive metastasis in pancreatic cancer. As novel regulatory molecules, lncRNAs have significant potential as biomarkers for early detection and therapeutic targets, offering exciting opportunities for personalised medicine in pancreatic cancer.

However, despite their promise, significant challenges remain in fully understanding their mechanisms of action and translating these findings into clinical practice. Many lncRNAs lack comprehensive functional characterisation, particularly in the context of signalling pathways such as EMT, autophagy and immune evasion. The intricate networks involving lncRNAs, miRNAs and other non-coding RNAs are also underexplored, with limited understanding of their broader regulatory feedback loops. Furthermore, the spatial and temporal dynamics of lncRNAs in the TME, their role in non-tumour cells such as immune or stromal cells, and their involvement in therapy resistance remain poorly defined. Due to the inherent complexity and heterogeneity of PC, the contribution of individual lncRNAs to the disease's invasive and metastatic behavior may not be fully representative, prompting a need for further exploration into the interplay among multiple lncRNAs and their integration with other molecular pathways.

To compensate for the current lack of research on lncRNAs in pancreatic cancer, future studies should focus on the following: (1) In-depth investigation of the molecular mechanisms of lncRNAs in pancreatic cancer invasion and metastasis, including the comprehensive functional characterisation of lncRNAs in key signalling pathways such as EMT, autophagy, and immune evasion, as well as their interactions with other non-coding RNAs (e.g. circRNA, miRNA); (2) To investigate the stage-specific roles of lncRNAs during cancer progression (from early tumourigenesis to metastasis) and to study their spatiotemporal dynamics in the TME, especially in non-oncogenic cells. (3) Applying cutting-edge technologies such as gene editing and RNA interference to further understand the functional roles and mechanisms of lncRNAs in pancreatic cancer; and (4) Integrating multi-omics approaches and developing preclinical models of lncRNA-targeted therapies will improve our ability to translate lncRNA research into effective clinical applications and provide new opportunities for the treatment and early detection of pancreatic cancer. In conclusion, the study of lncRNAs in pancreatic cancer invasion and metastasis has important clinical significance and potential, but further rigorous studies and clinical trials are needed to validate it.

Author contributions

JT, XC and CZ provided financial support for the publication of this review. MS drafted the manuscript, prepared the figure and edited the manuscript. JT, CZ, RZ, HL, SX, DG, QZ and XC helped revise the review and modify the contents of the initial draft. JT, XC and CZ conceptualized and reviewed the manuscript. All authors approved the final version of the manuscript.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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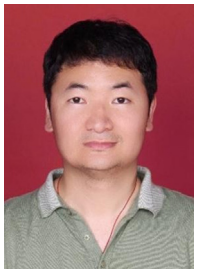

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