Review

Long Non-Coding RNAs in Pancreatic Cancer: Biologic Functions, Mechanisms, and Clinical Significance

Jiajia Li 1,†, Sicong Hou 1,2,†, Ziping Ye 3, Wujun Wang 4, Xiaolin Hu 2 and Qinglei Hang 5,*

1 Department of Gastroenterology, The Affiliated Hospital of Yangzhou University, Yangzhou 225009, China; nylijiajia@126.com (J.L.); shou@yzu.edu.cn (S.H.)
2 Department of Clinical Medicine, Medical College, Yangzhou University, Yangzhou 225001, China; hxl15722563995@163.com
3 Department of Gastroenterology, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China; yzp1998@126.com
4 Nanjing Hospital of Chinese Medicine Affiliated to Nanjing University of Chinese Medicine, Nanjing 210023, China; wangwujunnzy@outlook.com
5 Department of Experimental Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
* Correspondence: hql219@hotmail.com; Tel.: +86-138-1458-888
† These authors contributed equally to this work.

Simple Summary: Pancreatic cancer (PC) is a highly aggressive malignant tumor with a high mortality rate. Growing evidence shows that long non-coding RNAs (lncRNAs) might participate in the pathogenesis of PC. This review presents the biogenesis mechanism, classifications, and modes of action of lncRNAs, especially the functions and mechanisms of lncRNAs in PC. It also discusses the clinical significance of lncRNAs in PC.

Abstract: Despite tremendous efforts devoted to research in pancreatic cancer (PC), the mechanism underlying the tumorigenesis and progression of PC is still not completely clear. Additionally, ideal biomarkers and satisfactory therapeutic strategies for clinical application in PC are still lacking. Accumulating evidence suggests that long non-coding RNAs (lncRNAs) might participate in the pathogenesis of diverse cancers, including PC. The abnormal expression of lncRNAs in PC is considered a vital factor during tumorigenesis that affects tumor cell proliferation, migration, invasion, apoptosis, angiogenesis, and drug resistance. With this review of relevant articles published in recent years, we aimed to summarize the biogenesis mechanism, classifications, and modes of action of lncRNAs and to review the functions and mechanisms of lncRNAs in PC. Additionally, the clinical significance of lncRNAs in PC was discussed. Finally, we pointed out the questions remaining from recent studies and anticipated that further investigations would address these gaps in knowledge in this field.

Keywords: LncRNAs; pancreatic cancer; biomarker; cancer diagnosis and therapy

1. Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death in the United States and ranks seventh in terms of cancer-related death worldwide. Globally, nearly 5 million new cases are diagnosed each year, almost equal to the number of deaths caused by PC, and the five-year survival rate is approximately 10% [1,2]. Currently, surgical resection is the only curative treatment option available for PC patients [3]. However, only 10–20% of patients have the option of surgery when diagnosed, and the 5-year survival rate remains relatively low [4]. Although efforts in recent years have partially improved the efficacy of surgery and chemoradiotherapy, as exemplified by the application of the adjuvant chemotherapy regimens referred to as Folfirinox, the overall prognosis of PC...
patients is still unoptimistic. The key to improving the prognosis of PC is early diagnosis and precision treatment, making it critical to find ideal biological biomarkers for PC. Unfortunately, there is still a lack of credible biomarkers and effective therapeutic strategies for clinical application in PC [5].

In recent years, genetic and transcriptional sequencing have revealed the extensive heterogeneity of cancers. Many studies target molecular substrates such as long non-coding RNAs (IncRNAs) as biomarkers for early diagnosis and targeted therapy strategies for tumors. Despite the countless barriers, great progress has been made. IncRNAs are a type of noncoding RNAs (ncRNAs) with a size from 200 to more than one hundred thousand nucleotides [6]. Accounting for the majority (80 to 90%) of all ncRNAs with limited or no protein-coding properties, they are mainly responsible for gene regulation and are implicated in a plethora of biological processes [7]. The abnormal expression of IncRNAs in various cancers has been considered a vital factor during tumorigenesis that affects tumor cell proliferation, migration, invasion, apoptosis, angiogenesis drug resistance, etc. [8,9]. Recently, many studies have reported the important role of IncRNAs in the carcinogenesis of PC. Herein, we reviewed relevant articles published in recent years to summarize the biogenesis mechanisms, classifications, and modes of action of IncRNAs and review the functions and mechanisms of IncRNAs in PC. Additionally, we highlighted the questions remaining from recent studies and anticipate that further investigations will address these gaps in knowledge in this field.

2. Biogenesis and Localization of LncRNAs

Similar to mRNAs, the transcription of most lncRNA species is dependent on RNA polymerase II (Pol II) and involves the addition of 5′-end m7G caps and 3′-end poly(A) tails. However, compared with mRNAs, many Pol II-transcribed IncRNAs are inefficiently processed and retained in the nucleus [10–12]. Briefly, the mechanism of lncRNA retention in the nucleus can be summarized as follows: (a) Some IncRNAs are transcribed by an aberrant phosphorylated form of Pol II, which leads to splicing defects and polyadenylation signal-independent transcription termination during lncRNA transcription. These IncRNAs tend to be tethered to chromatin and are often degraded by nuclear exosomes [13]. (b) Many IncRNAs contain U1 small nuclear RNA (U1 snRNA) binding sites, which assist in the recruitment of U1 small nuclear ribonucleoprotein (U1 snRNP) to Pol II. This recruitment could further enhance the association of IncRNAs with chromatin [14]. (c) The splicing signals in some lncRNAs are relatively weak, and the distance between the 3′ splice site and the branch point is long. These features endow these IncRNAs with relatively low splicing activity and support their nuclear retention [12,15–17]. (d) Specific sequence motifs in cis and factors in trans could lead to nuclear retention [18–20]. In summary, the localization of IncRNAs in the nucleus is sophisticatedly controlled from the transcription level to the RNA processing level and involves the cooperation of diverse sequence motifs in cis and factors in trans. Nevertheless, despite the numerous patterns discussed above, more investigations into the underlying mechanism that determines the different retention modes of IncRNAs in the nucleus are needed.

While some IncRNAs are retained in the nucleus, a large number of IncRNAs are exported to and localized in the cytosol. Due to the limited number of exons contained in the sequences, the export of IncRNAs mainly relies on the nuclear RNA export factor 1 (NXF1) pathway [21]. After reaching the cytoplasm, IncRNAs can exist in diverse forms and interact with various RNA binding proteins (RBPs) in the cytoplasm, associate with ribosomes, and associate with the mitochondria [22–26]. A majority of cytoplasmic IncRNAs are reported to associate with ribosomes. This process has been further proved to be partially dependent on cis-elements such as long ‘pseudo’ 5′ untranslated regions. However, whether the IncRNAs found in polysome fractions take part in translation is unknown [23]. Apart from ribosomes, the mitochondria are also a destination of cytoplasmic IncRNAs. Many mitochondrial IncRNAs exist in the form of mitochondrial RNA-processing endoribonuclease (RMRP) and bind with G-rich RNA sequence-binding factor 1 (GRSF1), which facilitates the further
accumulation of lncRNAs in the mitochondria [26]. Emerging evidence has identified many lncRNAs in other organelles, especially exosomes. It remains unclear how lncRNAs are guided to exosomes, but the possible mechanism might involve them binding with RBPs via specific sequence motifs [27–29]. Given their tremendous diagnostic and predictive potential in various clinical settings, more in-depth research into the localization mechanism of lncRNAs in exosomes is imperative.

3. Classifications of LncRNAs

According to different characteristics, lncRNAs can be sorted into corresponding types: (a) Based on genome location, lncRNAs can be divided into intergenic lncRNAs, intronic lncRNAs, and exonic lncRNAs. Intergenic lncRNAs refer to lncRNAs transcribed from genomic regions between coding genes; intronic lncRNAs derive totally from introns, while exonic lncRNAs share some sequences with exons [30,31]. (b) Compared with protein-coding genes, lncRNAs can be classified as sense or antisense lncRNAs according to the transcriptional orientation [32]. (c) According to the subcellular localization, lncRNAs can be categorized as nuclear or cytoplasmic, categories which are closely related to the mechanism by which they exert their biological functions [33]. (d) Concerning the mode of action, lncRNAs can function in cis or in trans, which depends on the relative position of lncRNAs and the target genes [30,34] (Table 1).

Table 1. Classifications of lncRNAs.

| Criterial                | Classification                  |
|--------------------------|---------------------------------|
| genome location          | intergenic lncRNAs              |
|                          | intronic lncRNAs                |
|                          | exonic lncRNAs                  |
| transcriptional orientation | sense lncRNAs                  |
|                          | antisense lncRNAs               |
| subcellular localization | nuclear lncRNAs                |
|                          | cytoplasmic lncRNAs             |
| mode of action           | cis-acting lncRNAs              |
|                          | trans-acting lncRNAs            |

4. Roles of LncRNAs in PC

LncRNAs delicately regulate gene expression at multiple levels. LncRNAs interact with DNA and proteins to regulate diverse biological processes, including histone modification, DNA methylation, hydroxymethylation, and chromatin remodeling. In contrast, the interaction of lncRNAs with RNAs (including miRNAs) could regulate RNA splicing, stability maintenance, and translation, thereby exerting a posttranscriptional modulation function [35,36]. In addition, lncRNAs can contribute to regulating protein activity, stability, and protein–protein interactions through diverse interactions with proteins [37] (Figure 1). Hereafter, we reviewed the roles of lncRNAs in PC tumorigenesis and progression and highlighted the involved molecular mechanisms (Tables 2, 3, S1 and S2).
Figure 1. Mechanisms underlying long noncoding RNA (lncRNA)-mediated regulation of gene expression. (1) Transcription regulation by lncRNAs. (a) LncRNAs can promote histone H3 Lys27 trimethylation (H3K27me3) of the promoter region of chromatin via the recruitment of histone complexes such as polycomb repressive complex 2 (PRC2), thereby leading to the silencing of gene transcription; (b) lncRNAs can also catalyze DNA methylation to modulate transcriptive activity; (c) lncRNAs can enhance the expression of protein coding genes (PCGs) by remodeling chromatin (for example, by forming chromatin loops). (2) LncRNAs interact with RNAs. (d) Together with alternative splicing factors, lncRNAs are engaged in the processing and maturation of mRNAs; (e) lncRNAs facilitate mRNA translation; (f) lncRNAs help to stabilize some mRNAs by binding to them; (g) lncRNAs can competitively bind to miRNAs by acting as ceRNAs, thereby blocking the inhibition of the target gene. (3) LncRNAs interact with proteins. (h) Through protein modulation (for example, phosphorylation), lncRNAs regulate protein activity; (i) lncRNAs mediate the interactions between proteins; (j) lncRNAs regulate the localization of proteins.
Table 2. Overview of cellular functions of tumor-suppressive lncRNAs in pancreatic cancer.

| No | Lnc          | Vitro Functions | Specimen | Expression | Reference |
|----|--------------|-----------------|----------|------------|----------|
|    |              | Prolife a | Cycle b | Apopt c | Migra d | Invas e | Angio f | CSC g | Drug Resistance | Other | PMID         |
| 1  | GAS5         | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 240/2436 |
| 2  | ENST000003404073 | +     | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 25314504 |
| 3  | linc00673    | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 27213920 |
| 4  | EN5G00000318510 | +     | +       |          |     |     |     |     | ASPC1/CAPAN1/ASPC1 |     | down 27628540 |
| 5  | F11A5I      | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 28320685 |
| 6  | MEG3        | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 28520934 |
| 7  | CASC2       | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 28862512 |
| 8  | DAPK3       | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 31966799 |
| 9  | GAS5        | +        | +       |          |     |     |     | GEM/5-FU | BXP3/CAPAN1/ASPC1 |     | down 29112934 |
| 10 | DGCR5       | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 29207689 |
| 11 | CASC2       | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 29255722 |
| 12 | MEG3        | +        | +       |          |     |     |     | GEM | BXP3/CAPAN1/ASPC1 |     | down 29352854 |
| 13 | XLOC_000047 | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 29386302 |
| 14 | AB289830    | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 29386434 |
| 15 | BC320200    | +        | +       |          |     |     |     | GEM | BXP3/CAPAN1/ASPC1 |     | down 29522885 |
| 16 | PCTST       | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 29578472 |
| 17 | KCNK15A5S1  | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 30021145 |
| 18 | linc00071/00261/SNHFC3 | + | + | + | + | + | + | GEM | BPX3/HPAC | down 30210701 |
| 19 | NONHSAT105177 | +     | +       |          |     |     |     |     | BXP3/HPAC | down 30373797 |
| 20 | GAS5        | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 30386623 |
| 21 | GDS5        | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 30386888 |
| 22 | CASC2       | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 30672129 |
| 23 | linc00552   | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 30712321 |
| 24 | TUSC7       | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 30714313 |
| 25 | linc00197   | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 30946652 |
| 26 | linc00197   | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 31072497 |
| 27 | PANX1       | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 31488713 |
| 28 | GAS5        | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 31740660 |
| 29 | linc00111   | +        | +       |          |     |     |     | GEM | BXP3/CAPAN1/ASPC1 |     | down 31768733 |
| 30 | CASP2       | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 31894271 |
| 31 | linc00073   | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 31949497 |
| 32 | linc00261   | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 32020223 |
| 33 | linc285194  | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 32303144 |
| 34 | linc00261   | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 32414225 |
| 35 | linc00261   | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 32590069 |
| 36 | DGCR5       | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 32630953 |
| 37 | linc00071   | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 32630328 |
| 38 | MTS3-AS     | +        | +       |          |     |     |     |     | BXP3/CAPAN1/ASPC1 |     | down 32593338 |

a. Prolife: proliferation; b. Cycle: cell cycle; c. Apopt: apoptosis; d. Migra: migration; e. Invas: invasion; f. Angio: angiogenesis; g. CSC: cancer stem cell; h. GEM: gemcitabine. “+” means that the lncRNA plays a role in related cancer cell biological functions.
Table 3. Overview of mechanisms and animal studies of tumor-suppressive lncRNAs in pancreatic cancer.

| No | Lnc     | Position | Location | Mechanism | miRNA  | Target | RBPs | Pathways | Upstream | Animal Model    | Vivo Functions | Pheno  | Reference                  |
|----|---------|----------|----------|-----------|---------|--------|------|----------|----------|-----------------|----------------|--------|--------------------------|
| 1  | GAS5    | 17q24.3  | miR-101a | CDK6      |         |        |      |          |          | subcutaneous xenograft | +              |        | 24026436                  |
| 2  | ENST0000048077 |        |          |           |         |        |      |          |          | subcutaneous xenograft | +              |        | 25314054                  |
| 3  | linc00673 |        |          |           |         |        |      |          |          | subcutaneous xenograft | +              |        | 27123920                  |
| 4  | ENSG00000218510 |        |          |           |         |        |      |          |          | subcutaneous xenograft | +              |        | 27628540                  |
| 5  | F11-AS1 |         |          |           |         |        |      |          |          | subcutaneous xenograft | +              |        | 28206855                  |
| 6  | MEG3    |         |          |           |         |        |      |          |          | subcutaneous xenograft | +              |        | 28320094                  |
| 7  | CASC2   |         |          |           |         |        |      |          |          | subcutaneous xenograft | +              |        | 28985212                  |
| 8  | DAPK1   |         |          |           |         |        |      |          |          | subcutaneous xenograft | +              |        | 29112924                  |
| 9  | GAS5    |         | miR-17   |           |         |        |      |          |          | subcutaneous xenograft | +              |        | 29207699                  |
| 10 | DGC85   | 14q32.3  | miR-812  |           |         |        |      |          |          | subcutaneous xenograft | +              |        | 29254810                  |
| 11 | MEG3    |         |          |           |         |        |      |          |          | subcutaneous xenograft | +              |        | 29386037                  |
| 12 | XLOC_000647 |        |          |           |         |        |      |          |          | subcutaneous xenograft | +              |        | 29328835                  |
| 13 | ARB89330 |         |          |           |         |        |      |          |          | subcutaneous xenograft | +              |        | 29978472                  |
| 14 | BC032020 |         |          |           |         |        |      |          |          | subcutaneous xenograft | +              |        | 30032148                  |
| 15 | PCTST   |         |          |           |         |        |      |          |          | subcutaneous xenograft | +              |        | 30210701                  |
| 16 | KCNK35-AS1 |        |          |           |         |        |      |          |          | subcutaneous xenograft | +              |        | 30273797                  |
| 17 | linc00871/00251/SNH829 |        |          |           |         |        |      |          |          | subcutaneous xenograft | +              |        | 30386623                  |
| 18 | NONFSAT105177 |        |          |           |         |        |      |          |          | subcutaneous xenograft | +              |        | 30567129                  |
| 19 | CASC3   |         | miR-221  | SOCS3    |         |        |      |          |          | subcutaneous xenograft | +              |        | 30714151                  |
| 20 | GLS-AS  |         |         | EMT      |         |        |      |          |          | subcutaneous xenograft | +              |        | 30944632                  |
| 21 | CASC2   | 10k26   | miR-101a |         |         |        |      |          |          | subcutaneous xenograft | +              |        | 31027497                  |
| 22 | line00052 |         |         | miR-350p |         |        |      |          |          | subcutaneous xenograft | +              |        | 31898171                  |
| 23 | TUC7    |         | miR-571a |         |         |        |      |          |          | subcutaneous xenograft | +              |        | 32176833                  |
| 24 | TUSC7   | line/plast |         |         | miR-3046| PTP4K2B |        |          |          | subcutaneous xenograft | +              |        | 32176833                  |
| 25 | PXN-A5I |         |         |         |         |        |      |          |          | subcutaneous xenograft | +              |        | 32176833                  |
| 26 | linc01197 |         |         |         |         |        |      |          |          | subcutaneous xenograft | +              |        | 32176833                  |
| 27 | GAS5    |         | miR-23a |         |         |        |      |          |          | subcutaneous xenograft | +              |        | 32176833                  |
| 28 | linc01111 |         |         |         |         |        |      |          |          | subcutaneous xenograft | +              |        | 32176833                  |
| 29 | GAS5    |         |         |         |         |        |      |          |          | subcutaneous xenograft | +              |        | 32176833                  |
| 30 | CASC2   |         |         |         |         |        |      |          |          | subcutaneous xenograft | +              |        | 32176833                  |
| 31 | linc00673 |         |         |         |         |        |      |          |          | subcutaneous xenograft | +              |        | 32176833                  |
| 32 | line00261 |         |         |         |         |        |      |          |          | subcutaneous xenograft | +              |        | 32176833                  |
| 33 | linc00671 |         |         |         |         |        |      |          |          | subcutaneous xenograft | +              |        | 32176833                  |
| 34 | linc00261 |         |         |         |         |        |      |          |          | subcutaneous xenograft | +              |        | 32176833                  |
| 35 | DGCR5   |         |         |         |         |        |      |          |          | subcutaneous xenograft | +              |        | 32176833                  |
| 36 | MEG3    |         |         |         |         |        |      |          |          | subcutaneous xenograft | +              |        | 32176833                  |
| 37 | linc00671 |         |         |         |         |        |      |          |          | subcutaneous xenograft | +              |        | 32176833                  |
| 38 | MTSS1-AS1 |         |         |         |         |        |      |          |          | subcutaneous xenograft | +              |        | 32176833                  |

a. nucl: nucleus; b. cyto: cytoplasm; c. miRNAs: microRNA; d. RBPs: RNA binding proteins; e. Meta: metastasis; f. Pheno: phenomenon; g. suppr: suppressor. “+” means that the lncRNA plays a role in related cancer cell biological functions.
4.1. LncRNAs Act as Histone Modulators

Numerous studies have reported that lncRNAs could facilitate histone modification in PC, thereby engaging in regulating the expression of target genes. In this process, polycomb repressive complex 2 (PRC2), consisting of an enhancer of zeste homolog 2 (EZH2), a suppressor of zeste 12 homolog (SUZ12), and embryonic ectoderm development (EED), acts as a vital mediator [38,39]. By forming complexes with various lncRNAs, PRC2 could enhance histone H3 Lys27 trimethylation (H3K27me3) to repress the expression of various genes [40,41]. The role of PRC2 components, especially EZH2, has been proven in a wide range of tumors, including breast cancer, prostate cancer, and lung cancer [40,42,43]. The interaction of PRC2 with lncRNAs in PC has also been reported by many investigators.

LncRNA Hox transcript antisense RNA (HOTAIR) is a negative prognostic factor for overall survival (OS) in patients with breast and colon cancer, and its high expression is implicated in the metastasis of breast and colon cancer [44–47]. Similar results were found by Kim et al. in PC. Gene array studies revealed the minimal overlap of genes regulated by HOTAIR between PC and breast cancer cells, and further research using EZH2 knockdown and chromatin immunoprecipitation demonstrated that gene repression mediated by HOTAIR was both PRC2-dependent and PRC2-independent [48]. Several miRNAs were reported to be regulated by HOTAIR through interaction with PRC2. In PC, Cai et al. found that HOTAIR suppressed the expression of miR-663b via the H3K4me3 and H3K27me3 histone modification of the miR-663b promoter. This epigenetic modification-mediated decrease in miR-663b further led to upregulation of its target insulin-like growth factor 2 (IGF2), a previously verified oncogenic factor in PC [49–51]. Another miRNA, miR-34a, was also reported to be regulated by HOTAIR via histone modification. In this study, the overexpression of EZH2 in human pancreatic ductal epithelial (HPDE) cells repressed miR-34a expression. Mechanistically, HOTAIR physically interacted with EZH2, which induced the occupancy of EZH2 at the miR-34a promoter, thereby repressing miR-34a transcription through the induction of heterochromatin formation [52]. In addition to the miRNAs which are transcriptionally dependent on EZH2, HOTAIR also participates in regulating many protein-coding genes. In PANC-1 and AsPC-1 cells, HOTAIR expression can be induced by radiation and its knockdown restored radiosensitivity by modulating ATG7-mediated autophagy [53]. In addition, by stimulating hexokinase-2 (HK2) expression, HOTAIR may be engaged in the processes of cancer cell energy metabolism, including glucose uptake, lactate production, and ATP production [54] (Figure 2).

**Figure 2.** LncRNA Hox transcript antisense RNA (HOTAIR) regulates PC development in diverse pathways. LncRNA HOTAIR acts through histone modification, miRNA sponging, and protein interaction to regulate proliferation, apoptosis, migration, invasion, the cell cycle, drug resistance, and cell metabolism in PC. IGF2: insulin-like growth factor 2; DR5: death receptor 5; hexokinase-2 (HK2).
LncRNA HOXA distal transcript antisense RNA (HOTTIP) is a HOX-associated lncRNA transcribed from the 5′ tip of the HOXA locus. By interacting with PRC2 and WD repeat-containing protein 5 (WDR5)/mixed lineage leukemia 1 (MLL1) chromatin modifying complexes, HOTTIP is involved in the enhancement of the transcription of multiple genes associated with the HOXA locus by promoting H3K27me3 histone modification [55,56]. In a study focusing on HOTTIP single-nucleotide polymorphisms (SNPs), the researchers found that HOTTIP rs1859168 A > C is significantly associated with a reduced PC risk, indicating the potential role of HOTTIP in PC [57]. In 2015, Li et al. described upregulated HOTTIP expression in PC tissues and cell lines and demonstrated that HOTTIP could promote proliferation, invasion, and GEM resistance both in vivo and in vitro. In addition, this research found that HOTTIP was positively correlated with HOXA13, and it was speculated that HOTTIP could play a cancer-promoting role in PC through HOXA13 [58]. Interestingly, Cheng et al. reached a different conclusion. They pointed out that HOTTIP in PC cells did not regulate HOXA13 but participated in regulating several other HOX genes, including HOXA10, HOXB2, HOXA11, HOXA9, and HOXA1 [59]. The cause of the inconsistency of HOTTIP-regulated genes between the two studies is still unknown, but the differences in the cell lines applied could be a possible reason. A recent study uncovered that the HOTTIP-mediated promotion of PC progression occurs in both HOXA13-dependent and HOXA13-independent manners and that HOTTIP expression is negatively regulated by miR-497 [60]. In addition to its role in cell proliferation, invasion, and chemoresistance, the function of HOTTIP in PC stem cells (CSCs) was also investigated. The authors analyzed the expression of HOTTIP in pancreatic CSCs and nonpancreatic CSCs in PC tissues by laser capture microdissection (LCM) and found that HOTTIP was highly expressed in pancreatic CSCs. Further functional assays showed that HOTTIP alterations affected pancreatic CSC stemness features, including tumorigenesis, sphericity, and stem factor (Lin28, Nanog, Oct4 and SRY-box transcription factor 2, Sox2) and marker (ALDH1, CD44 and CD133) expression. By binding to WDR5, HOTTIP promoted HOXA9 expression, which further activated the Wnt/β-catenin pathway [61].

LncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is also called nuclear-enriched abundant transcript 2 (NEAT2) and is located on chromosome 11q13; it is a highly evolutionarily conserved, 8.7-kb long non-coding transcript [62,63]. MALAT1 mainly acts as a molecular scaffold for various ribonuclear complexes and functions as a transcriptional and epigenetic regulator [64–66]. To verify whether MALAT1 is dysregulated in PC, Liu et al. first detected MALAT1 expression in 45 PC tissues by qPCR. The results showed that MALAT1 was significantly higher in tumor tissues than in adjacent normal tissues. Higher MALAT1 expression was significantly correlated with an advanced tumor stage, a deeper invasion, and a shorter disease-free survival (DFS) time. Moreover, MALAT1 was found to be an independent predictor of DFS in PC patients [67]. These findings were further confirmed by subsequent studies [68,69]. Functional analysis clarified that MALAT1 is involved in promoting cell proliferation, migration, and invasion in vitro. After MALAT1 knockdown, G2/M cell cycle arrest and cell apoptosis were induced. Additionally, the suppression of epithelial-mesenchymal transition (EMT) and CSC-like properties were implicated [68]. In terms of the underlying mechanism, EZH2 was observed to be recruited to the E-cadherin promoter by MALAT1, where it prompted H3K27me3 at the E-cadherin promoter to repress its expression [70]. This mechanism is also responsible for the regulation of MALAT1-suppressed N-myc downregulated gene-1 (NDRG-1), which is a tumor suppressor in PC that is also co-inhibited by EZH2 [71]. MALAT1 could also aid in increasing the proportion of pancreatic CSCs, maintaining the self-renewal abilities of cells, inducing chemoresistance, and promoting tumor angiogenesis. The internal mechanism may involve the self-renewal-related factor Sox2, but the detailed mechanism awaits further investigation [69]. In addition, the Hippo-YAP signaling pathway was also implicated in MALAT1-mediated PC progression [72].
4.2. LncRNAs Function as ceRNAs

Various lncRNAs engaged in PC progression exert their functions through competing endogenous RNAs (ceRNAs), forming an interconnected lncRNA–miRNA–mRNA network. The following are several examples of lncRNAs acting as ceRNAs in PC (Figure 3).

Figure 3. Overview of the role of lncRNAs with miRNAs in PC cells. By functioning as ceRNAs, lncRNAs can competitively bind to miRNAs, thereby blocking the inhibition of the target gene. PTBP1: polypyrimidine tract-binding protein 1; IRS1: insulin substrate receptor; CBX2: chromobox2; IGF1R: insulin-like growth factor 1 receptor; PTEN: phosphatase and tensin homolog deleted on chromosome ten; EGFR: epidermal growth factor receptor; FOXD1: forkhead box D1; BNIP3: Bel2/adenovirus E1B 19 kDa interacting protein 3; HDGF: hepatoma-derived growth factor; FOXO3: forkhead box O3; ITGA2: integrin subunit α2; Muc6: mucin 6; STAT1: signal transducer and activator of transcription 1.

Apart from its role in histone modification, MALAT1 also acts as a miRNA sponge. In liver fibrosis, MALAT1 regulates Rac1 expression by sponging miR-101b [73]. Luo et al. pointed out that TGFA-targeting miR-376A was sequestered by MALAT1 to promote osteosarcoma development [74]. It was found that miR-217 can bind MALAT1 and regulate its expression in PC cell lines. MALAT1 knockdown attenuated the protein expression of KRAS, a known target of miR-217. After MALAT1 deletion, the downregulation of KRAS expression could be attenuated by inhibiting miR-217. More importantly, MALAT1 knockdown did not directly affect cellular miR-217 expression but decreased the miR-217 nucleus/cytoplasm ratio, suggesting that MALAT1 inhibits the translocation of miR-217 from the nucleus to the cytoplasm [75]. Another study revealed that miR-200c-3p is also a target of MALAT1. By sponging miR-200c-3p, MALAT1 promoted the expression of the miR-200c-3p target zinc finger E-box-binding protein 1 (ZEB1), a known oncogenic factor. In turn, miR-200c-3p could suppress MALAT1 expression, thus uncovering a feedback loop between MALAT1 and miR-200c-3p expression [76]. In PC, researchers confirmed direct binding between miR-216a and MALAT1, and miR-216a was found to suppress MALAT1 expression. MiR-216a overexpression had a similar effect to MALAT1 siRNA in restoring
p21 and p27 expression and inhibiting B-MYB, RAF1, and PCNA1 expression in PC cells. MiR-216a overexpression and MALAT1 knockdown induced cell cycle arrest at the G2/M phase. In addition, miR-216a also reduced cell viability and increased cell apoptosis in response to GEM in cancer cells. Based on these findings, we infer that miR-216a induces apoptosis in both the presence and absence of GEM in PC cells by silencing MALAT1 expression [77].

LncRNA H19 (H19) is located on human chromosome 11p15.5, and its role in cancer progression is still controversial. Considering the absence of H19 in embryonic rhabdomyosarcoma and Wilms’ tumor, H19 is thought to function as a tumor suppressor [78–81]. However, opposite findings were reported in other cancers, including bladder cancer, colon cancer, and gastric cancer, rendering H19 an oncogenic gene [82–84]. Ma et al. isolated pure malignant cells from frozen sections of PC tissues by LCM and detected that H19 was overexpressed in PC tissues and correlated with the histological grade of PC. The knockdown of H19 in T3M4 and PANC1 cells with high endogenous H19 levels suppressed cell viability, proliferation, and tumor growth. This led to G0/G1 arrest, accompanied by decreases in the levels of E2F transcription factor 1 (E2F1) and its downstream targets [85]. Additional studies revealed that H19 could facilitate PC cell invasion and migration by promoting high mobility group AT-hook 2 (HMG2A)-mediated EMT through antagonizing let-7 [86]. The H19/miR-194/CDK14 axis was also indicated to modulate PC proliferation and migration [87]. In addition to acting as an miRNA sponge, H19 could also influence PC by generating miRNAs embedded in its transcript. Researchers found that miR-675-5p, a miRNA transcribed simultaneously with H19, could contribute to PC progression by targeting E2F1 [88]. Interestingly, a recent study reported that, like miR-675-5p, miR-675-3p plays a role in H19-induced PC growth. By targeting STAT3, H19-derived miR-675-3p could activate SOCS5, thereby exerting an oncogenic effect [89].

LncRNA urothelial cancer-associated 1 (UCA1) is a noncoding RNA first identified to be associated with the tumorigenesis of bladder cancer [90]. Numerous studies have proven that UCA1 plays an oncogenic role in gastric cancer, breast cancer, and colorectal cancer [91–94]. One bioinformatic study focusing on PC in patients with diabetes pointed out that UCA1 was especially tied up with the prognosis of PC in patients with diabetes and could serve as a diagnostic marker [95]. By analyzing the lncRNA expression profiles in two public PC microarray datasets, researchers found that UCA1 might be involved in PC progression and was significantly associated with OS in PC [96]. Further functional experiments demonstrated that the downregulation of UCA1 could effectively suppress PC cell proliferative activities, increase the apoptotic rate and cause cell cycle arrest [97]. Regarding the mechanism, previous studies found that the overexpression of UCA1 could lead to the suppression of p27 protein and its downstream targets, thereby contributing to cell growth inhibition and apoptosis induction [92,98]. Subsequent studies reported that many miRNAs are tightly related to UCA1 in PC progression. A negative correlation was first identified between the expression of UCA1 and miR-107 by Gong et al., and then the luciferase reporter assay verified that miR-107 was targeted by UCA1. Further experiments confirmed that integrin subunit α 2 (ITGA2) was a target of miR-107. In downstream pathways, UCA1 and ITGA2 accelerate PC tumorigenesis via focal adhesion pathway-related proteins, including ITGA3 and protein tyrosine kinase 2 [99]. In addition, Zhou et al. observed the downregulation of miR-96 and further upregulation of its target FOXO3 by UCA1, and another UCA1-miR-590-3p-KRAS axis was identified by Liu et al. [100,101].

As a newly discovered lncRNA, lncRNA CYTOR (linc00152), was found to be aberrantly expressed in several malignant tumors [102,103]. Using next-generation sequencing and an extensive analysis of cDNA ends (MACE), the researchers found that CYTOR was differentially expressed between PC tissues and nontumor tissues [104]. Yu et al. analyzed the lncRNA expression profile in human PC tissues and nontumor tissues using four independent public microarray datasets from the Gene Expression Omnibus (GEO); this study confirmed that CYTOR presented a different expression pattern in PC tissues compared with normal tissues, which was further validated in PC cell lines and normal cells. Cell
experiments showed that CYTOR could regulate PC cell proliferation and invasion [105]. This effect was later confirmed to be mediated by miR-205-5p, which directly targets CDK6 to control the proliferation and migration of PC cells [106]. A luciferase reporter assay also verified that miR-150 was a target of CYTOR. Moreover, the inhibition of miR-150 could significantly attenuate the suppression of cell proliferation, migration, and invasion induced by downregulating CYTOR [107]. Collectively, these findings suggest that CYTOR contributes to PC tumorigenesis by functioning as a sponge for multiple miRNAs.

4.3. LncRNAs Bind to Proteins

Several lncRNAs have been found to bind to specific proteins to exert their biological functions. By interacting with proteins, lncRNAs can modulate protein activity and stability and facilitate protein–protein interactions, thereby participating in cellular processes in PC [37].

As a novel lncRNA, lncRNA of metastasis suppressor 1 (MTSS1-AS) was downregulated in PC tissues and correlated with PC clinicopathology, including vascular infiltration, lymphatic invasion, and distant metastasis. Additionally, MTSS1-AS was inversely associated with OS in PC patients and could predict prognosis with an area under the curve (AUC) of 0.691 [108]. MTSS1-AS could scaffold the interaction between E3 ubiquitin-protein ligase STIP1 homology and U-box containing protein 1 (STUB1) and transcription regulator myeloid zinc finger 1 (MZF1), leading to MZF1 degradation by ubiquitination. Under acidic conditions, MTSS1-AS was downregulated, and this downregulation caused an increase in MZF1. MZF1 further suppressed MTSS1 expression, which was validated to be downregulated in PC and inversely correlated with disease progression [108]. Moreover, it was found that MTSS1-AS was transcriptionally repressed by binding the MYC proto-oncogene (Myc) with initiator (Inr) elements of the MTSS1-AS promoter. Reciprocally, MTSS1-AS blocked the expression of Myc by inhibiting MZF1-mediated Myc transcription, thereby forming a negative feedback loop between MTSS1-AS and Myc in acidic PC cells. This study provided us with a possible pathway responsible for the metastasis of PC cells under an acidic microenvironment [109].

Linc00673, reported in thyroid and tongue squamous cell carcinoma, is regarded as a tumor suppressor that inhibits the invasion and metastasis of tumor cells [110,111]. Utilizing a genome-wide association study (GWAS), researchers found that variation in linc00673 was correlated with PC risk. For example, a G > A change at rs11655237 in exon 4 of linc00673 creates a target site for miR-1231 binding, which reduces the effect of linc00673 in an allele-specific manner and thus confers susceptibility to tumorigenesis [112]. Further studies illustrated that linc00673 could suppress PC cell viability and migration by regulating hepatocyte nuclear factor 1 (HNF1A) via competitively binding to miR-504 [113]. Specifically, researchers found that linc00673 could promote the interaction between protein tyrosine phosphatase nonreceptor type 11 (PTPN11) and pre-mRNA-processing factor 19 (PRPF19), an E3 ubiquitin ligase, thereby promoting PTPN11 degradation through ubiquitination. PTPN11 degradation ultimately suppressed SRC-ERK oncogenic signaling and activated the signal transducer and activator of the transcription 1 (STAT1)-dependent antitumor pathway [112].

LncRNA nuclear-enriched abundant transcript 1 (NEAT1) is a lncRNA restricted to the nucleus. It functions as a transcriptional regulator of multiple genes, and its dysregulation is implicated in many human cancers [114–119]. Studies on PC showed that NEAT1 was highly expressed in PC and was associated with poor survival. Functional experiments revealed that NEAT1 remarkably suppressed cell proliferation and metastasis by regulating miR-506-3p and miR-302a-3p [120,121]. According to previous studies, E74-like ETS transcription factor 3 (ELF3) accelerates hepatocellular carcinoma progression by promoting EMT and metastasis [122]. In PC, NEAT1 was found to bind with ELF3 mRNA and enhance the interaction between insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) and ELF3 mRNA, thereby suppressing ELF3 mRNA degradation. Then, increased ELF3 was identified to promote PC cell migration and invasion [123].
A previous study reported that linc00346 was upregulated and served as a prognostic marker in PC [124]. Linc00346 could promote PC growth and GEM resistance by antagonizing miR-188-3p and inducing RD4 expression [125]. Another study using RNA precipitation assays together with mass spectrometry analysis revealed that linc00346 could promote the transcription of c-Myc via interaction with the CCCTC-binding factor (CTCF). This interaction between linc00346 and CTCF prevented CTCF from binding to the c-Myc promoter, blocking the CTCF-mediated inhibition of c-Myc. Thus, these results clarified that linc00346 contributes to PC pathogenesis by stimulating c-Myc expression [126].

4.4. LncRNAs Regulate the EMT Pathway in PC

EMT is the cellular process by which cells lose epithelial features and adopt a mesenchymal phenotype. This process endows the cells with properties of migration and metastasis. Accumulating studies have proven that EMT plays a critical role in the progression of malignant tumors and involves many transcription factors, including Snail, Twist-1, ZEB1/2, and Sna2. This process is accompanied by the increased expression of mesenchymal markers N-cadherin and vimentin and the decreased expression of epithelial markers E-cadherin [127,128]. Multiple lncRNAs have been verified to promote PC development via the EMT process in PC.

Studies have reported that lncRNA taurine-upregulated gene 1 (TUG1) mediates the progression of osteosarcoma and bladder cancer by stimulating cell proliferation [129,130]. TUG1 was expressed at higher levels in PC tissues than in paracarcinoma tissues and could enhance viability, migration, and GEM resistance-processes often facilitated by EZH2-in PC cells [131–133]. Significantly, the protein levels of matrix metalloproteinase 2 (MMP2) and MMP9 were increased, and the protein level of E-cadherin was decreased, indicating the enhancement of the EMT process. Mechanistically, overexpressed TUG1 could promote Smad2 and Smad3 phosphorylation. The expression of TGF-β and TGF-β receptors was higher in the TUG1 overexpression group than in the control group, indicating that the TGF-β/Smad pathway might participate in the TUG1-induced effect on PC cell EMT [134]. Another study found that TUG1 suppression could significantly increase miR-29c expression and thereby downregulate the expression of mesenchymal markers such as N-cadherin and vimentin but upregulate E-cadherin expression. The inhibition of miR-29c reversed tumor growth inhibition resulting from TUG1 knockdown both in vitro and in vivo, whereas miR-29c overexpression exhibited the opposite effects. Taken together, these findings indicate that TUG1 could modulate EMT by targeting the tumor suppressor miR-29c [135].

LncRNA, which is highly upregulated in liver cancer (HULC), is highly expressed in the tissues and serum of PC patients and is useful when distinguishing PC patients from patients with benign pancreatic diseases and healthy individuals [136]. By regulating the expression of proteins involved in the Wnt/β-catenin signaling pathway, including c-Myc, β-catenin, and CKD1, HULC is engaged in the proliferation, apoptosis, and invasion of PC cells [136]. Additionally, miR-15a-mediated activation of the PI3K/AKT signaling pathway was verified to be involved in the effects of HULC on PC cells [137]. Regarding the involvement of EMT, Takahashi et al. revealed that circulating extracellular vesicle (EV)-encapsulated HULC may act as a potent biomarker for detecting human PC and that lncRNA HULC could contribute to the invasion and migration of PC cells by inducing the EMT pathway [138]. In addition, HULC could be targeted by miR-133b in PC cells, which provides insight into the regulation of HULC biogenesis [138]. They further uncovered that during TGF-β induced EMT in PC cells, miR-622 was downregulated, which led to the HULC-mediated promotion of the invasion, migration and suppression of EMT. Moreover, miR-622-overexpressing EVs could transfer miR-622 to recipient PC cells, thus repressing the expression of HULC and inhibiting PC invasion and migration [139]. These results open up the possibility to develop treatment strategies targeting lncRNA-regulating miRNAs for PC.
The lncRNA plasmacytoma variant translocation 1 (PVT1) oncogene, located at chromosome 8q24.21, is upregulated in various cancers, including PC [140–145]. Interestingly, You et al., using a piggyBac transposon-based genome-wide mutagenesis strategy, identified that the PVT1 gene was associated with increased sensitivity to GEM in human PC cells [146]. The high expression of PVT1 could contribute to tumor progression in PC, and it could act as a potential biomarker to predict PC prognosis [141]. In PC, PVT1 upregulation significantly promoted ZEB1/Snail expression but inhibited p21 expression, and p21 downregulation further enhanced ZEB1/Snail expression and cell proliferation in PANc-1 cells. Therefore, PVT1 promoted EMT and cell proliferation and migration by downregulating p21 in PC cells [147]. Another study suggested that PVT1-regulated EMT was mediated through the TGF-β/Smad pathway [148]. Additionally, multiple miRNAs were implicated in PVT1 and PC, including miR-448, miR-519d-3p, and miR-20a-5p [149–151].

4.5. LncRNAs Modulate CSC Properties

CSCs are a subset of tumor cells with self-renew and differentiation abilities [152]. CSCs are engaged in tumor growth, metastasis, and drug resistance processes and are critical to the progression of many cancers [152–156]. The identification of CSCs is often dependent on the detection of stemness markers, mainly CD24, CD44, CD133, Nanog, Sox2, Sox9, OCT1/2/4, c-Myc, Kruppel-like factor 4 (KLF4), and essential specific antigen (ESA) [157–159]. LncRNAs have been illustrated to modulate CSC properties in diverse human cancers, including PC.

LincRNA-regulator of reprogramming (linc-RoR) is highly expressed in embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) and was initially confirmed to be a factor engaged in reprogramming differentiated cells to iPSCs, which is controlled by pluripotency transcription factors such as Sox2, Oct4, and Nanog [160–162]. In 2016, Zhan et al. first reported that linc-RoR was significantly upregulated in PC tissues and cell lines and contributed to cell proliferation, migration, invasion, and metastasis both in vitro and in vivo [163]. Mechanistically, they confirmed that linc-RoR could upregulate ZEB1, a factor shown to regulate EMT in many tumor cells, and this process is partially mediated by p53 [163–166]. Another study indicated that the activation of the Hippo/YAP pathway also played a role in linc-RoR-mediated EMT [167]. Additionally, linc-RoR could contribute to GEM resistance by inducing autophagy, a mechanism dependent on the targeting of PTB1 by miR-124 [168]. In PC, knockdown of linc-RoR in CSCs inhibited proliferation, induced apoptosis, decreased migration in vitro, and suppressed tumorigenicity in vivo. In this process, linc-RoR may act as a ceRNA to compete for miR-145 binding, thereby activating the derepression of the core transcription factor Nanog, which has previously been shown to play critical roles in maintaining stem cell pluripotency and iPSC reprogramming [169]. Fu et al. also observed that linc-RoR expression increased in cancer stem-like cells (CSCs) and that linc-RoR knockdown impaired the properties and tumorigenesis of pancreatic CSCs in vivo. They found that linc-RoR functioned as a ceRNA for several tumor suppressor miRNAs, particularly some members of the let-7 family [170].

Ultra-conserved RNAs (ucRNAs) are a group of lncRNAs with highly conserved sequences that are engaged in multiple biological functions [171–174]. In PC, a lncRNA termed ultraconserved element 345 (uc.345) was reported to be upregulated in tumor tissues, especially in tissues with an increased depth of invasion and advanced TNM stage, indicating that uc.345 could be an independent risk factor for the OS of PC patients. The authors employed soft agar assays and tumor xenograft models to show that uc.345 could accelerate tumor growth. Regarding the mechanism, they found that the ratio of CD44+/CD24+ cells (which are recognized as CSCs) was upregulated by uc.345 overexpression. At the same time, pluripotency-related transcription factors such as Sox2, Oct4, Nanog, and CD133 were remarkably increased. These findings suggest that uc.345 promotes PC pathogenesis by increasing the proportion of CSCs [175]. Further exploration illustrated that this effect was attributed to the upregulated expression of hnRNPL, which is an RNA binding protein involved in tumorigenesis via multiple mRNA processing steps [176,177].
LncRNA AFAP1-AS1 is an antisense transcript of the actin filament-associated protein (AFAP1) gene, the sense strand of which encodes the AFAP1 protein. Using next-generation sequencing and MACE, researchers identified AFAP1-AS1 to be differentially expressed between PC tissues and control tissues [104]. The high expression of AFAP1-AS1 in PC tissues and cell lines was associated with lymph node and perineural invasion and poor survival, making it a promising prognostic factor for predicting tumor progression [178]. Functional experiments further suggested that the high expression of AFAP1-AS1 and activin receptor A type I (ACVR1) was accompanied by the low expression of miR-384, and AFAP1-AS1 silencing or miR-384 overexpression could impair PC cell self-renewal ability and stemness. Further research uncovered that the inhibitory effect of AFAP1-AS1 on PC cell stemness was exerted through binding to miR-384 to regulate ACVR1 expression [179]. Apart from miR-384, several other miRNAs were also involved in AFAP1-AS1-mediated PC progression, including miR-133a, miR-146b-5p, and miR-384. These findings provide additional valuable targets for investigating the role of AFAP1-AS1 in the CSC pathway in PC [96,179–183].

Human maternally expressed gene 3 (MEG3) is a lncRNA located at 14q32 with a nucleotide length greater than 1.6 kb [184]. An increasing number of studies have revealed that MEG3 functions as a tumor suppressor and the possible mechanism involves the modulation of cell growth and apoptosis [185–188]. In PC, MEG3 is downregulated and negatively correlated with tumor size, metastasis, and vascular invasion [189]. The involvement of the PI3K/AKT/Bcl-2/Bax/CKD1/P53 and PI3K/AKT/MMP2/MMP9 signaling pathways was implicated in the effect of MEG3 on PC progression [189]. Notably, the absence of MEG3 increased the sphere-forming ability and CSC properties of PC cells, whereas MEG3 overexpression led to the opposite effect. Snail activation was indicated as a component of the detailed mechanism [190].

The lncRNA Sox2 overlapping transcript (Sox2ot) gene is mapped to the human chromosome 3q26.3 locus and consists of highly conserved sequences of over 700 kb [191]. Containing a critic regulator of pluripotency, Sox2, in its intronic region, lncRNA Sox2ot has been explored in diverse somatic cancers, including esophageal squamous cell carcinoma, breast cancer, lung squamous cell carcinoma, and hepatocellular carcinoma [192–195]. The expression of Sox2ot in PC tissues and cell lines is strongly elevated, and functional experiments suggest that Sox2ot could act as a tumor promoter in PC by physically binding to FUS, thereby regulating its downstream proteins CCND1 and p27, which are regarded as cell cycle-associated factors [196]. More importantly, Li et al. identified that lncRNA Sox2ot could be derived from the exosomes of PC cells, and a positive association was revealed between Sox2ot expression in plasma exosomes and TNM stage and OS rate in PC patients. Further experiments discovered that by modulating Sox2 expression, Sox2ot promoted EMT and CSC-like properties in PC cells. Mechanistically, Sox2ot competitively binds to miR-200 family members, which further target Sox2 expression, thus enhancing the invasive and metastatic properties of PC. Moreover, the researchers found that tumor-derived exosomes could be transmitted to tumor cells or blood circulation in vivo, thereby translating the effect of Sox2ot from that of producer cells to that of recipient cells. In postoperative PC patients, decreased exosomal Sox2ot expression was also observed in blood samples, suggesting a promising role for exosomal Sox2ot as a marker for PC prognosis [197].

5. Clinical Significance of LncRNAs in PC

A large number of lncRNAs are aberrantly expressed in diverse cancers, and some have been verified to be cancer-specific. LncRNAs are usually detected in pancreatic tissues or body fluids such as plasma or saliva, and their expression is often related to disease severity. Thus, lncRNAs have the potential to serve as noninvasive biomarkers for cancer diagnosis and prognosis evaluation [198–200]. The following section lists several representative lncRNAs that could be applied as feasible diagnostic and prognostic biomarkers in PC (Tables 4, 5, S3 and S4).
Table 4. Overview of clinicopathological significance of tumor-suppressive lncRNAs in pancreatic cancer.

| No | Lnc     | Source | No. of Patients | Express | Cut-Off | Size | Differentiation T | Lymphatic (N) | Distance (M) | TNM | Vessel Invasion | Other                  | Reference PMID |
|----|---------|--------|-----------------|---------|---------|------|-------------------|----------------|--------------|-----|----------------|------------------------|----------------|
| 1  | GAS5    | tissue | 23              | down    |         |      |                   |                |              |     |                |                        | 24026436       |
| 2  | BC008363| tissue | 30              | down    |         |      |                   |                |              |     |                |                        | 25206694       |
| 3  | ENST00000480739 | tissue | 35              | down    |         |      |                   |                |              |     |                |                        | 25314054       |
| 4  | LOC285194| tissue | 85              | down    | +       |      |                   |                |              |     |                |                        | 2550852        |
| 5  | linc00673| tissue | 74              | down    | +       |      |                   |                |              |     |                |                        | 27213290       |
| 6  | HMlinRvNA717| tissue | 150             | down    | +       |      |                   |                |              |     |                |                        | 27338046       |
| 7  | ENSG0000210510 | tissue | 80              | down    | +       |      |                   |                |              |     |                |                        | 27628540       |
| 8  | linc-pint| tissue | 59              | down    |         |      |                   |                |              |     |                |                        | 27708234       |
| 9  | MEG3    | tissue | 30              | down    | +       |      |                   |                |              |     |                |                        | 28320094       |
| 10 | CASC2   | tissue | 110             | down    | +       |      |                   |                |              |     |                |                        | 2865121        |
| 11 | DGCR5   | tissue | 30              | down    | MEL a  |      |                   |                |              |     |                |                        | 29207609       |
| 12 | GAS5    | tissue | 22              | down    |         |      |                   |                |              |     |                |                        | 29225772       |
| 13 | MEG3    | tissue | 25              | down    |         |      |                   |                |              |     |                |                        | 29329401       |
| 14 | XLOC_000647| tissue | 48              | down    | MEL    |      |                   |                |              |     |                |                        | 29386037       |
| 15 | AB209630| tissue | 53              | down    |         |      |                   |                |              |     |                |                        | 29526843       |
| 16 | BC032020| tissue | 20              | down    |         |      |                   |                |              |     |                |                        | 29532883       |
| 17 | PCTST   | tissue | 48              | down    | MEL    |      |                   |                |              |     |                |                        | 29978472       |
| 18 | KCNK15-AS1| tissue | 69              | down    |         |      |                   |                |              |     |                |                        | 30032148       |
| 19 | linc00261| tissue | 229             | down    | +       |      |                   |                |              |     |                |                        | 30217071       |
| 20 | linc00671| tissue | 229             | down    | +       |      |                   |                |              |     |                |                        | 30217071       |
| 21 | linc00671/00261/SNHG9| plasma | 229             | down    |         |      |                   |                |              |     |                |                        | 30217071       |
| 22 | SNHG9   | tissue | 229             | down    | +       |      |                   |                |              |     |                |                        | 30217071       |
| 23 | NONHSAT105177| tissue | N/A b           | down    |         |      |                   |                |              |     |                |                        | 30237397       |
| 24 | GAS5    | tissue | 60              | down    | MEL    |      |                   |                |              |     |                |                        | 30388621       |
| 25 | GLS-AS  | tissue | 30              | down    | +       |      |                   |                |              |     |                |                        | 30563888       |
| 26 | TUSC7   | tissue | 94              | down    | +       |      |                   |                |              |     |                |                        | 30714151       |
| 27 | linc-pint| plasma | 46              | down    | +       |      |                   |                |              |     |                |                        | 30944652       |
| 28 | linc01197| tissue | 18              | down    |         |      |                   |                |              |     |                |                        | 31027497       |
| 29 | PXN-AS1 | tissue | 50              | down    | +       |      |                   |                |              |     |                |                        | 31488171       |
| 30 | line01111| tissue | 60              | down    | +       |      |                   |                |              |     |                |                        | 31767833       |
| 31 | line01111| plasma  | 57              | down    | +       |      |                   |                |              |     |                |                        | 31767833       |
| 32 | CASC2   | tissue | 20              | down    |         |      |                   |                |              |     |                |                        | 31894271       |
| 33 | linc00673| tissue | 30              | down    | MEL    |      |                   |                |              |     |                |                        | 31949497       |
| 34 | DAPK1   | tissue | 60              | down    | +       |      |                   |                |              |     |                |                        | 31966799       |
| 35 | linc00261| tissue | 54              | down    | MEL    |      |                   |                |              |     |                |                        | 32020223       |
| 36 | linc00261| tissue | 42              | down    | +       |      |                   |                |              |     |                |                        | 32414223       |
| 37 | linc00671| tissue | 60              | down    | 17.66  |      |                   |                |              |     |                |                        | 32801328       |
| 38 | MTSS1-AS| tissue | 132             | down    |         |      |                   |                |              |     |                |                        | 32929338       |

a. MEL: median expression level; b. N/A: not available. "+" means that the lncRNA plays a role in related PC clinicopathological features.
Table 5. Overview of prognostic and diagnostic significance of tumor-suppressive lncRNAs in pancreatic cancer.

| No. | Lnc   | Source | No. of Patients | Expression | Detection Method | AUC a | Survival | Prognostic Biomarker | Reference PMID |
|-----|-------|--------|-----------------|------------|-----------------|------|----------|---------------------|----------------|
| 1   | GAS5  | tissue | 23              | down       | qRT-PCR         |      |          |         | 24026436         |
| 2   | BC008363 | tissue | 30              | down       | qRT-PCR         |      | OS b     | +                  | 25200694       |
| 3   | ENST00000480739 | tissue | 35              | down       | qRT-PCR         | 0.735 | OS       | +                  | 25314054       |
| 4   | LOC285194 | tissue | 85              | down       | qRT-PCR         | 0.931 | OS +     | +                  | 25550052       |
| 5   | linc00873 | tissue | 74              | down       | qRT-PCR         | 0.87 | OS +     | +                  | 27213290       |
| 6   | HMLincRNA717 | tissue | 150             | down       | qRT-PCR         |      | OS +     | +                  | 27380346       |
| 7   | ENSG00000218510 | tissue | 80              | down       | qRT-PCR         |      | OS +     | +                  | 27628540       |
| 8   | linc-pint | tissue | 61              | down       | qRT-PCR         |      | OS +     | +                  | 27708234       |
| 9   | MEG3   | tissue | 30              | down       | qRT-PCR         |      | OS +     | +                  | 28320094       |
| 10  | CASC2  | tissue | 110             | down       | qRT-PCR         | 0.735 | OS       | +                  | 28865121       |
| 11  | DDX5   | tissue | 30              | down       | qRT-PCR         |      | OS +     | +                  | 29207609       |
| 12  | GAS5   | tissue | 22              | down       | qRT-PCR         |      | OS +     | +                  | 29225772       |
| 13  | MEG3   | tissue | 25              | down       | qRT-PCR         |      | OS +     | +                  | 29328401       |
| 14  | XLOC_000647 | tissue | 48             | down       | qRT-PCR         |      | OS       | +                  | 29386037       |
| 15  | AB209630 | tissue | 53              | down       | qRT-PCR         |      | OS +     | +                  | 29532883       |
| 16  | BC032020 | tissue | 20             | down       | qRT-PCR         |      | OS +     | +                  | 29984724       |
| 17  | PCTST  | tissue | 48              | down       | qRT-PCR         |      | OS +     | +                  | 30021478       |
| 18  | KCNN15-AS1 | tissue | 69             | down       | qRT-PCR         |      | OS +     | +                  | 30021478       |
| 19  | 00261  | tissue | 229             | down       | qRT-PCR         | 0.5712 | OS       | +                  | 30210701       |
| 20  | 00671  | tissue | 229             | down       | qRT-PCR         | 0.6057 | OS       | +                  | 30210701       |
| 21  | 00671/00261/SNHG9 | plasma | 229            | down       | qRT-PCR         | 0.5983 | OS       | +                  | 30210701       |
| 22  | SNHG9  | tissue | 229             | down       | qRT-PCR         |      | OS +     | +                  | 30210701       |
| 23  | NONHSAT105177 | tissue | N/A             | down       | RNA-FISH        |      |          | +                  | 30237397       |
| 24  | GAS5   | tissue | 60              | down       | IHC and qRT-PCR |      | OS       | +                  | 30388621       |
| 25  | GLS-AS | tissue | 30              | down       | qRT-PCR         |      | OS +     | +                  | 30563888       |
| 26  | TUSC7  | tissue | 94              | down       | qRT-PCR         |      | OS +     | +                  | 30714151       |
| 27  | pint   | plasma | 46              | down       | qRT-PCR         | 0.8934 | OS       | +                  | 30944652       |
| 28  | 01197  | tissue | 18              | down       | qRT-PCR         |      | OS       | +                  | 31027407       |
| 29  | PXN-AS1 | tissue | 50              | down       | qRT-PCR         |      | OS       | +                  | 31488171       |
| 30  | 01111  | tissue | 60              | down       | ISH and qRT-PCR |      | OS       | +                  | 31767333       |
| 31  | 01111  | tissue | 57              | down       | qRT-PCR         |      | OS       | +                  | 31767333       |
| 32  | CASC2  | tissue | 20              | down       | qRT-PCR         |      | OS       | +                  | 31894271       |
| 33  | 00673  | tissue | 30              | down       | qRT-PCR         |      | OS       | +                  | 31949497       |
| 34  | DAPK1  | tissue | 60              | down       | qRT-PCR         |      | OS       | +                  | 31966799       |
| 35  | 00261  | tissue | 54              | down       | qRT-PCR         |      | OS       | +                  | 32020223       |
| 36  | 00261  | tissue | 42              | down       | qRT-PCR         |      | OS       | +                  | 32142223       |
| 37  | linc00873 | tissue | 60             | down       | qRT-PCR         |      | OS       | +                  | 32603123       |
| 38  | MTSS1-AS | tissue | 132            | down       | qRT-PCR         |      | OS       | +                  | 32959338       |

a. AUC: area under the curve; b. OS: overall survival; c. DFS: disease-free survival; d. N/A: not available. “+” means that the lncRNA could be used as a prognostic biomarker in PC.
5.1. Diagnostic Biomarkers for PC

Xie et al. conducted the first study to investigate the clinical value of salivary lncRNA in the detection of PC [201]. Five well-documented lncRNAs, H19, HOTAIR, HOTTIP, MALAT1, and PVT1, which are most closely associated with PC from previous studies, were selected as putative lncRNA biomarkers. Compared with benign pancreatic tumor (BPT) and normal pancreatic tissues (NPT), HOTAIR, HOTTIP, and PVT1 were significantly upregulated in PC tissues. Compared to the BPT or healthy groups, the salivary levels of HOTAIR and PVT1 were substantially higher in the PC group. After curative pancreatectomy, the salivary levels of HOTAIR and PVT1 were reduced considerably. ROC analysis showed that both salivary lncRNAs could distinguish PC patients from healthy controls and BPT patients with sensitivities and specificities ranging from 60–97%. The expression of salivary HOTAIR and PVT1 did not differ significantly between healthy controls in any one of eight leading cancers worldwide. In addition, the two lncRNAs in saliva showed better discriminatory power in detecting PC with serum CA19-9 < 37 U/mL from healthy controls. Collectively, these findings indicate that salivary HOTAIR and PVT1 have the potential to become novel noninvasive biomarkers for detecting PC [201]. A more recent study explored the diagnostic value of plasma HOTAIR in PC and reported an AUC of 0.9329, suggesting that plasma HOTAIR could serve as an ideal biomarker for detecting PC [54]. Studies on MALAT1 illustrated that MALAT1 expressed in the tissue could distinguish PC tissues from normal tissues with an AUC of 0.69 (95% CI 0.561–0.829, p = 0.009), and the sensitivity and specificity values reached 77.8% and 60%, respectively [67]. Moreover, data from the Oncomine, the GEO, and The Cancer Genome Atlas databases revealed a moderate diagnostic value of MALAT1 in PC (AUC = 0.75, sensitivity = 0.66, specificity = 0.72) [202].

GWAS showed that rs6971499 at 7q32.3 (linc-pint) was significantly differentially expressed at the genome level between PC patients and normal controls [203]. Researchers used qRT-PCR and RNA FISH analysis to evaluate linc-pint levels in the plasma and tumor tissues of PC patients and found that linc-pint expression was lower in the plasma samples from PC patients than in those of healthy individuals, and plasma linc-pint levels could detect PC with higher sensitivity than CA19-9. The data also showed that plasma linc-pint levels were lower in PC patients than in a patient with carcinoma of the ampulla of Vater (CAV) and cholangiocarcinoma (CCA) and therefore could be used to distinguish the cause of malignant obstructive jaundice. In addition, low plasma linc-pint levels were correlated with tumor recurrence. The levels of linc-pint were lower in PC tissues than in adjacent tissues and CAV and CCA tissues and were associated with a poor prognosis for PC patients after pancreatectomy [204]. Similar results were also reported in studies conducted by Lu et al., supporting linc-pint as a diagnostic parameter in PC [205].

LncRNA CCDC26 (CCDC26), located on chromosome 8q24, has been reported to have a tumorigenic role of in many malignant tumors [206–208]. CCDC26 is highly expressed in PC tissues compared with normal tissues, and its expression is correlated with tumor size, tumor number, and reduced OS. Additionally, CCDC26 expression was identified as an independent prognostic factor in terms of OS in PC patients. Importantly, ROC analysis showed that the AUC of CCDC26 was as high as 0.663, indicating that CCDC26 could be a diagnostic marker for distinguishing PC tissues from healthy tissues.

5.2. Prognostic Biomarkers for PC

LncRNA opa-interacting protein 5 antisense RNA 1 (OIP5-AS1) has been demonstrated to play an oncogenic role in the tumorigenesis of many cancer types [209–212]. Wu et al. used 110 pairs of PC tissues and adjacent normal tissues collected from PC patients after surgery and revealed that OIP5-AS1 is upregulated in tumor tissues and is positively correlated with tumor size, distant metastasis, and TNM stage. Kaplan–Meier survival analysis showed that patients with a high expression of OIP5-AS1 had poorer OS. Moreover, multivariate Cox regression analysis validated OIP5-AS1 expression and TNM stage as independent prognostic factors for PC patients [213]. Another study revealed higher OIP5-AS1 expression in metastatic and advanced-stage tumors [214].
According to previous studies, lncRNA X-inactive specific transcript (XIST) is involved in the development and progression of many malignant tumors [215–218]. Numerous studies have reported that lncRNA-XIST is upregulated in PC tissues and cell lines, and high XIST expression in PC is related to poorer prognosis (larger tumor size, perineural invasion, lymph node micrometastases, and shorter OS) [219].

LncRNA cancer susceptibility candidate 2 (CASC2) has been widely defined as a tumor suppressor in various cancers [220–225]. Yu et al. found that lncRNA-CASC2 was specifically downregulated in PC tissues and cell lines, and lower CASC2 expression in PC was related to a poorer prognosis [226]. This relationship was later confirmed by subsequent studies [227,228]. Linc00671 is an 1844-bp lncRNA and is located on chromosome 17q21.31. Compared with normal tissues, PC tissues had decreased linc00671 expression. Correlation analysis revealed a negative association between linc00671 expression and tumor differentiation, clinical stage, and a poor prognosis [229]. ROC curve analysis showed that the AUC of linc00671 in detecting PC was 0.6057, and high linc00671 expression was related to a significantly higher survival rate than low expression [124].

Due to the late diagnosis and low resection rate of PC, chemotherapy remains a critical strategy in PC treatment. Among various chemotherapy agents, GEM is the first-line therapeutic choice approved for advanced PC treatment, and it can be used both alone and in combination with other chemotherapeutic drugs [230]. Because of acquired and/or inherent resistance, the efficacy of GEM in improving the OS rates of PC is not gratifying [231,232]. Therefore, it is imperative to understand the internal mechanism of GEM resistance to achieve better benefits from cancer therapy [178]. Numerous reports have shown that lncRNAs could contribute to GEM resistance in PC.

Previous studies have revealed that PVT1 is involved in the processes of carcinogenesis and chemoresistance [233]. Further studies revealed that knockdown of PVT1 could sensitize cancer cells to GEM, while the overexpression of PVT1 blocked this effect in PC cells [146]. Regarding the detailed mechanism, researchers found that GEM could increase the expression of drosha ribonuclease III (drosha) and DGCR8 microprocessor complex subunit (DGCR8) to promote the generation of the miR-1207 pair from the PVT1 transcript, thereby disrupting oncogenic signaling in PC cells by targeting ras homolog family member A (RhoA) and the SRC proto-oncogene (nonreceptor tyrosine kinase) [234]. More recently, a study elaborated that PVT1-mediated drug resistance could be attributed to the activation of Wnt/β-catenin signaling and autophagic activity [235]. They found that by decoying miR-619-5p, PVT1 could upregulate the expression of Pygo2 and ATG14, which are responsible for activating both Wnt/β-catenin signaling and the autophagic pathway. In return, elevated Wnt/β-catenin signaling activates PVT1 expression by directly binding to the PVT1 promoter, thereby forming a positive feedback loop between PVT1 expression and Wnt/β-catenin signaling [235]. Moreover, through the interaction with ATG14, PVT1 facilitates the assembly of autophagy-specific complex I (PtdIns3K-C1) and the activation of ATG14-dependent class III PtdIns3K, thereby mediating GEM resistance in PC [235].

LncRNA human histocompatibility leukocyte antigen complex P5 (HCP5), initially identified to be expressed in immune system cells, has been explored in diverse human cancers [236–240]. In PC, by utilizing the GSE15471 and GSE16515 datasets and the Database for Annotation, Visualization, and Integrated Discovery (DAVID), Wang et al. conducted a functional enrichment analysis which demonstrated that the MMP9/ITGB1-miR-29b-3p-lncRNA HCP5 network was associated with the prognosis of PC [241]. A recent study found that lncRNA HCP5 was highly expressed in PC tissues and prompted PC cell proliferation, migration, and invasion by targeting miR-140-5p and upregulating CDK8 expression [242]. Moreover, lncRNA HCP5 was prominently increased in GEM-resistant PC tissues and cells, indicating the critical role of HCP5 in GEM resistance. Cytological experiments revealed that suppressed lncRNA HCP5 could affect the proliferation, invasion, apoptosis, and autophagy properties of GEM-resistant PC cells. This was further confirmed to be fulfilled
by inhibiting HDGF expression through sponging miR-214-3p. Therefore, lncRNA HCP5 may represent a potential treatment target for GEM-resistant PC [243].

LncRNA growth arrest-specific 5 (GAS5) is a newly discovered lncRNA that facilitates cell proliferation, the cell cycle, and chemoresistance [244–246]. It has been reported that GAS5 is downregulated in PC tissues and cell lines [247]. In vitro experiments illustrated that GAS5 modulates the expression of CDK6, which is responsible for the regulation of cell proliferation and the cell cycle [248]. Another study showed that upon inhibiting GAS5, CD133+ cells, responsible for tumor recurrence, were released from growth arrest and exhibited accelerated nucleic acid biosynthesis and proliferation [249]. Regarding chemoresistance, researchers have reported that GAS5 negatively regulates miR-181c-5p and that miR-181c-5p can remarkably enhance PC cell chemoresistance by inhibiting the Hippo signaling pathway [250]. Another study conducted by Liu et al. clarified that GAS5 could directly bind to miR-221 and downregulate miR-221 expression in GEM-resistant PC cells. Gemcitabine resistance induced by miR-221 overexpression could be successfully attenuated by SOCS3 overexpression [251]. Taken together, these findings indicate that lncRNA GAS5 functions as a ceRNA for miR-181c-5p and miR-221 to suppress the development of chemoresistance in PC progression.

In addition to gemcitabine, the role of lncRNA in other forms of drug resistance during PC treatment has also been reported. A recent study uncovered that lncRNA UPK1A-AS1 expression was associated with a poor oxaliplatin-based chemotherapeutic response and a shorter PFS time in advanced PC patients. Mechanistically, IL8 secreted by cancer-associated fibroblasts (CAFs) could induce the expression of UPK1A-AS1, which further strengthened the interaction between Ku70 and Ku80 to facilitate nonhomologous end-joining (NHEJ), thereby enhancing DNA double-strand break (DSB) repair. Therefore, UPK1A-AS1 mediated CAF-derived paracrine IL8-dependent oxaliplatin resistance implicates a potential therapeutic target [252].

6. Future Expectations

Considering that lncRNAs play indispensable roles in tumor pathogenesis, it is of great significance to design potential diagnostic and therapeutic strategies targeting lncRNAs to gain control of malignant tumors. One feasible method is to interfere with lncRNA expression with siRNAs or DNA plasmids, which is the most widely used method in basic research to regulate lncRNAs [35,253]. In 2009, Mizrahi A et al. designed a DNA plasmid called H19-DTA, which contains the diphtheria toxin-A gene to target H19 expression. In vivo experiments showed that H19-DTA could suppress the growth of multiple cancer types [254]. Later, two clinical trials were conducted to verify the efficacy of H19-DTA in cancer patients, where both studies observed suppressed tumor growth and prolonged survival times [255,256]. However, to date, no clinical trials of H19-DTA focusing on PC have explicitly been documented, so whether H19-DTA could exert similar effects is PC still awaits further exploration.

Recently, the development of clustered regulatory interspaced short palindromic repeats (CRISPR)/Cas9 technology and its use in a variety of diseases have drawn much attention [257,258]. Despite the limitations in this field, ncRNA editing using CRISPR-Cas9 technology has been explored in various cancer types [259]. Zhen et al. found that silencing lncRNA UCA1 via the CRISPR/Cas9 method could effectively block bladder cancer progression [260]. It is worth noting that lncRNA UCA1 is also highly expressed in PC, and the downregulation of UCA1 could effectively suppress PC cell proliferation, promote apoptosis, and induce cell cycle arrest [97]. These clues prompted us to reflect on the possibility of inhibiting UCA1 expression with CRISPR/Cas9 technology to treat PC. To date, no investigation on CRISPR-Cas9 editing lncRNA in PC has been reported, but it is foreseeable that this approach could become a promising strategy for PC treatment in the near future.

Strategies for safely, efficiently, and continuously transporting stably altered lncRNAs to target cells or organs are also needed for the future application of lncRNAs. In recent
years, exogenous nanoparticles, which can act as carriers for novel genes and drugs, have attracted wide attention [261]. Compared with traditional treatments, nanoparticles can reduce the concentration of a drug needed for effects that are otherwise only achieved with a high drug or radiation dose while increasing their distribution in target organs and avoiding systemic damage [262]. Another emerging approach for targeting IncRNAs is exosomes, which are defined as microvesicles with diameters of 30-100 nm that can be released from cells to exert intercellular communication functions [263]. Many studies have shown that exosomes containing IncRNAs can regulate the proliferation, migration, and invasion of PC cells [197]. Despite the tremendous progress made in these areas, these findings are still theoretical, and no treatment based on nanoparticles or exosomes has yet been approved in the clinic.

The early diagnosis of PC is crucial for improving the 5-year survival rate [264]. A large number of studies have shown that IncRNAs can serve as ideal noninvasive biomarkers for the diagnosis and prognosis of PC. In the future, a gold standard IncRNA detection method should first be identified to standardize the detection of IncRNAs in different laboratories. Additionally, multicenter, multipopulation trials with large sample sizes should be carried out to obtain more clinically significant thresholds. In practice, it should also be noted that PC development is a long-term and chronic process. The role of IncRNAs in the early diagnosis of precancerous lesions, including pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystadenoma (MCN), should be emphasized. Finally, noninvasive or minimally invasive detection methods are the ultimate goal. Trials related to IncRNA detection in peripheral blood and endoscopic biopsy samples (pancreatic juice or tissue) should be carried out in the early stages of clinical research.

7. Conclusions

Despite extensive efforts made in recent years to treat PC based on surgery, radiation, and chemotherapy, PC remains the seventh most deadly cancer worldwide; thus, the clinical practice of PC requires better biomarkers and treatment strategies. With the help of new detection technologies, studies focusing on IncRNAs have become a hotspot in the field of biological science, especially in the study of diverse cancers. This review summarizes the biogenesis, classification, and mode of action of IncRNAs, as well as the functions and mechanisms of IncRNAs in PC. Additionally, the clinical significance of ncRNAs in PC was discussed. However, what we have uncovered is only the tip of the iceberg, and there are still some obstacles on the way to a deeper understanding of the role of IncRNAs in PC. For example, recent studies have mainly focused on the ceRNA functions of IncRNAs. In contrast, the interactions between IncRNAs and other molecules, especially between IncRNAs themselves, have been rarely reported. Furthermore, to date, no IncRNA has been approved for the diagnosis or treatment of PC. Therefore, there is still a long way to go before these findings can be translated from the bench to the bedside. Nevertheless, with the continued emergence of more gratifying investigations, we believe that this will happen in the near future.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers14092115/s1, Table S1: Overview of cellular functions of oncogenic IncRNAs in pancreatic cancer; Table S2: Overview of mechanisms and animal studies of oncogenic IncRNAs in pancreatic cancer; Table S3: Overview of clinicopathological significance of oncogenic IncRNAs in pancreatic cancer; Table S4: Overview of prognostic and diagnostic significance of oncogenic IncRNAs in pancreatic cancer.

Author Contributions: Conceptualization, Q.H., J.L. and S.H.; original draft preparation and review, Z.Y., W.W. and X.H.; writing and editing, Q.H., J.L. and S.H. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported in part by grant from National Natural Science Foundation of China (No. 31800675 to S.H.).
Cancers 2022, 20, 1113.

21. Zuckerman, B.; Ron, M.; Mikl, M.; Segal, E.; Ullitsky, I. Gene Architecture and Sequence Composition Underpin Selective
22. Carlevaro-Fita, J.; Rahim, A.; Guig
18. Azam, S.; Hou, S.; Zhu, B.; Wang, W.; Hao, T.; Bu, X.; Khan, M.; Lei, H. Nuclear retention element recruits U1 snRNP components
16. Zuckerman, B.; Ulitsky, I. Predictive models of subcellular localization of long RNAs.
14. Yin, Y.; Lu, J.Y.; Zhang, X.; Shao, W.; Xu, Y.; Li, P.; Hong, Y.; Cui, L.; Shan, G.; Tian, B.; et al. U1 snRNP regulates chromatin
13. Schlackow, M.; Nojima, T.; Gomes, T.; Dhir, A.; Carmo-Fonseca, M.; Proudfoot, N.J. Distinctive Patterns of Transcription and RNA
11. Tian, B.; Manley, J.L. Alternative polyadenylation of mRNA precursors. Nat. Rev. Mol. Cell Biol. 2017, 18, 18–30. [CrossRef]
10. Derrien, T.; Johnson, R.; Bussotti, G.; Tanzer, A.; Djebali, S.; Tilgner, H.; Guernec, G.; Martin, D.; Merkel, A.; Knowles, D.G.; et al. The GENCODE v7 catalog of human long noncoding RNAs: Analysis of their gene structure, evolution, and expression. Genome Res. 2012, 22, 1775–1789. [CrossRef]
9. Wang, K.; Liu, C.Y.; Zhou, L.Y.; Wang, J.X.; Wang, M.; Zhao, B.; Zhao, W.K.; Xu, J.S.; Fan, L.H.; Zhang, X.J.; et al. APF lncRNA regulates autophagy and myocardial infarction by targeting miR-188-3p. Nat. Commun. 2015, 6, 6779. [CrossRef]
8. Wang, K.; Liu, C.Y.; Zhou, L.Y.; Wang, J.X.; Wang, M.; Zhao, B.; Zhao, W.K.; Xu, J.S.; Fan, L.H.; Zhang, X.J.; et al. APF lncRNA regulates autophagy and myocardial infarction by targeting miR-188-3p. Nat. Commun. 2015, 6, 6779. [CrossRef]
7. Gutschner, T.; Diederichs, S. The hallmarks of cancer: A long non-coding RNA point of view. RNA Biol. 2012, 9, 703–719. [CrossRef]
6. Noh, J.H.; Kim, K.M.; Abdelmohsen, K.; Yoon, J.H.; Panda, A.C.; Munk, R.; Kim, J.; Curtis, J.; Moad, C.A.; Wohler, C.M.; et al. HuR and GRSF1 modulate the nuclear export and mitochondrial localization of the lncRNA RMRP. Genes Dev. 2016, 30, 1224–1239. [CrossRef]
5. Conroy, T.; Hammel, P.; Hebbar, M.; Ben Abdelghani, M.; Wei, A.C.; Raoul, J.L.; Chone, L.; Francois, E.; Artru, P.; Biagi, J.J.; et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. N. Engl. J. Med. 2018, 379, 2395–2406. [CrossRef]
4. Neoptolemos, J.P.; Stocken, D.D.; Friess, H.; Bassi, C.; Dunn, J.A.; Hickey, H.; Beger, H.; Fernandez-Cruz, L.; Dervenis, C.; Lacaine, F.; et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N. Engl. J. Med. 2004, 350, 1200–1210. [CrossRef]
3. Mercer, T.R.; Neph, S.; Dinger, M.E.; Crawford, J.; Smith, M.A.; Shearwood, A.M.; Haugen, E.; Bracken, C.P.; Rackham, O.; Stamatoyannopoulos, J.A.; et al. The human mitochondrial transcriptome. Cell 2011, 146, 645–658. [CrossRef]
2. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J. Clin. 2021, 71, 209–249. [CrossRef]
1. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer Statistics, 2021. CA Cancer J. Clin. 2021, 71, 7–33. [CrossRef]
27. Li, S.; Li, Y.; Chen, B.; Zhao, J.; Yu, S.; Tang, Y.; Zheng, Q.; Li, Y.; Wang, P.; He, X.; et al. exoRBase: A database of circRNA, lncRNA and mRNA in human blood exosomes. *Nucleic Acids Res.* 2018, 46, D106–D112. [CrossRef]

28. Gudenas, B.L.; Wang, L. Prediction of LncRNA Subcellular Localization with Deep Learning from Sequence Features. *Sci. Rep.* 2018, 8, 16385. [CrossRef]

29. Statello, L.; Maugeri, M.; Garre, E.; Nawaz, M.; Wahlgren, J.; Papadimitriou, A.; Lundqvist, C.; Lindfors, L.; Collén, A.; Sunnerhagen, P.; et al. Identification of RNA-binding proteins in exosomes capable of interacting with different types of RNA: RBP-facilitated transport of RNAs into exosomes. *PloS ONE* 2018, 13, e0195969. [CrossRef]

30. Ma, L.; Bajic, V.B.; Zhang, Z. On the classification of long non-coding RNAs. *RNAS Biol.* 2013, 10, 925–933. [CrossRef]

31. Alessio, E.; Bonadio, R.S.; Buson, L.; Chemello, F.; Cagnin, S. A Single Cell but Many Different Transcripts: A Journey into the World of Long Non-Coding RNAs. *Int. J. Mol. Sci.* 2020, 21, 302. [CrossRef]

32. Mondal, T.; Juvvuna, P.K.; Kirby, A.; Mitra, S.; Kosalai, S.T.; Traxler, L.; Hertwig, F.; Wernig-Zorc, S.; Miranda, C.; Deland, L.; et al. Sense-Antisense IncRNA Pair Encoded by Locus 6p22.3 Determines Neuroblastoma Susceptibility via the USP36-CHD7-SOX9 Regulatory Axis. *Cancer Cell* 2018, 33, 417–434.e417. [CrossRef]

33. Kapranov, P.; Cheng, J.; Dike, S.; Nix, D.A.; Dettaygupta, R.; Willingham, A.T.; Stadler, P.F.; Hertel, J.; Hackermüller, J.; Hofacker, I.L.; et al. RNA maps reveal new RNA classes and a possible function for pervasive transcription. *Science* 2007, 316, 1484–1488. [CrossRef]

34. Ning, S.; Zhang, J.; Wang, P.; Zhi, H.; Wang, J.; Liu, Y.; Gao, Y.; Guo, M.; Yue, M.; Wang, L.; et al. Lnc2Cancer: A manually curated database of experimentally supported lncRNAs associated with various human cancers. *Nucleic Acids Res.* 2016, 44, D980–D985. [CrossRef]

35. Statello, L.; Guo, C.J.; Chen, L.L.; Huarte, M. Gene regulation by long non-coding RNAs and its biological functions. *Nat. Rev. Mol. Cell Biol.* 2021, 22, 96–118. [CrossRef]

36. Bayoumi, A.S.; Sayed, A.; Broskova, Z.; Teoh, J.P.; Wilson, J.; Su, H.; Tang, Y.L.; Kim, I.M. Crossstalk between Long Noncoding RNAs and MicroRNAs in Health and Disease. *Int. J. Mol. Sci.* 2016, 17, 356. [CrossRef]

37. Schmitt, A.M.; Chang, H.Y. Long Noncoding RNAs in Cancer Pathways. *Cancer Cell* 2016, 29, 452–463. [CrossRef]

38. Wang, Y.; Xie, Y.; Li, L.; He, Y.; Zheng, D.; Yu, P.; Yu, L.; Tang, L.; Wang, Y.; Wang, Z. EZH2 RIP-seq Identifies Tissue-specific Long Non-coding RNAs. *Curr. Gene Ther.* 2018, 18, 275–285. [CrossRef]

39. Bhan, A.; Mandal, S.S. LncRNA HOTAIR: A master regulator of chromatin dynamics and cancer. *Biochim. Biophys. Acta* 2015, 1856, 151–164. [CrossRef]

40. Sun, X.; Du, P.; Yuan, W.; Du, Z.; Yu, M.; Yu, X.; Hu, T. Long non-coding RNA HOTAIR regulates cyclin J via inhibition of microRNA-205 expression in bladder cancer. *Cell Death Dis.* 2015, 6, e1907. [CrossRef]

41. Abbosh, P.H.; Montgomery, J.S.; Starkey, J.A.; Novotny, M.; Zuhowskki, E.G.; Egorin, M.J.; Moseman, A.P.; Golas, A.; Brannon, K.M.; Balch, C.; et al. Dominant-negative histone H3 lysine 27 mutant derepresses silenced tumor suppressor genes and reverses the drug-resistant phenotype in cancer cells. *Cancer Res.* 2006, 66, 5582–5591. [CrossRef] [PubMed]

42. Wang, H.F.; Yang, H.; Hu, L.B.; Lei, Y.H.; Qin, Y.; Li, J.; Bi, C.W.; Wang, J.S.; Huo, Q. Effect of siRNA targeting EZH2 on cell viability and apoptosis of bladder cancer T24 cells. *Genet. Mol. Res.* 2014, 13, 9939–9950. [CrossRef] [PubMed]

43. Geng, J.; Li, X.; Zhou, Z.; Wu, C.L.; Dai, M.; Bai, X. EZH2 promotes tumor progression via regulating VEGF-A/AKT signaling in non-small cell lung cancer. *Cancer Lett.* 2015, 359, 275–287. [CrossRef] [PubMed]

44. Rinn, J.L.; Kertesz, M.; Wang, J.K.; Squazzo, S.L.; Xu, X.; Brugmann, S.A.; Goodnough, L.H.; Helms, J.A.; Farnham, P.J.; Segal, E.; et al. Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. *Cell* 2007, 129, 1311–1323. [CrossRef] [PubMed]

45. Gupta, R.A.; Shah, N.; Wang, K.C.; Kim, J.; Horlings, H.M.; Wong, D.J.; Tsai, M.C.; Hung, T.; Argani, P.; Rinn, J.L.; et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature* 2010, 464, 1071–1076. [CrossRef]

46. Tsai, M.C.; Manor, O.; Wan, Y.; Mosammaparast, N.; Wang, J.K.; Lan, F.; Shi, Y.; Segal, E.; Chang, H.Y. Long noncoding RNA as modular scaffold of histone modification complexes. *Science* 2010, 329, 689–693. [CrossRef]

47. Kogo, R.; Shimamura, T.; Mimori, K.; Kawahara, K.; Imoto, S.; Sudo, T.; Tanaka, F.; Shibata, K.; Suzuki, A.; Komune, S.; et al. LncRNA HOTAIR regulates polycomb-dependent chromatin modification and is associated with poor prognosis in colorectal cancers. *Cancer Res.* 2011, 71, 6320–6326. [CrossRef]

48. Kim, K.; Jutooru, I.; Chadalapaka, G.; Johnson, G.; Frank, J.; Burghardt, R.; Kim, S.; Safe, S. HOTAIR is a negative prognostic factor and exhibits pro-angiogenic activity in pancreatic cancer. *Oncogene* 2013, 32, 1616–1625. [CrossRef]

49. Rogers, M.A.; Kalter, V.; Strowitzki, M.; Schneider, M.; Lichter, P. IGF2 knockdown in two colorectal cancer cell lines decreases survival, adhesion and modulates survival-associated genes. *Tumour Biol.* 2016, 37, 12485–12495. [CrossRef]

50. Dong, Y.; Li, J.; Han, F.; Chen, H.; Zhao, X.; Qin, Q.; Shi, R.; Liu, J. High IGF2 expression is associated with poor clinical outcome in human ovarian cancer. *Oncol. Rep.* 2015, 34, 936–942. [CrossRef]

51. Cai, H.; An, Y.; Chen, X.; Sun, D.; Chen, T.; Peng; Y.; Zhi, F.; Jiang, Y.; He, X. Epigenetic inhibition of miR-663b by long non-coding RNA HOTAIR promotes pancreatic cancer cell proliferation via up-regulation of insulin-like growth factor 2. *Oncotarget* 2016, 7, 86857–86870. [CrossRef] [PubMed]

52. Li, C.H.; Xiao, Z.; Tong, J.H.; To, K.F.; Fang, X.; Cheng, A.S.; Chen, Y. EZH2 coupled with HOTAIR to silence MicroRNA-34a by the induction of heterochromatin formation in human pancreatic ductal adenocarcinoma. *Int. J. Cancer* 2017, 140, 120–129. [CrossRef] [PubMed]
53. Wu, C.; Yang, L.; Qi, X.; Wang, T.; Li, M.; Xu, K. Inhibition of long non-coding RNA HOTAIR enhances radiosensitivity via regulating autophagy in pancreatic cancer. *Cancer Manag. Res.* 2018, 10, 5261–5271. [CrossRef] [PubMed]

54. Ma, Y.; Hu, M.; Zhou, L.; Ling, S.; Li, Y.; Kong, B.; Huang, P. Long non-coding RNA HOTAIR promotes cancer cell energy metabolism in pancreatic adenocarcinoma by upregulating hexokinase-2. *Oncol. Lett.* 2019, 18, 2212–2219. [CrossRef] [PubMed]

55. Wang, K.C.; Yang, Y.W.; Liu, B.; Sanyal, A.; Corces-Zimmerman, R.; Chen, Y.; Lajolie, B.R.; Protacio, A.; Flynn, R.A.; Gupta, R.A.; et al. A long noncoding RNA maintains active chromatin to coordinate homeotic gene expression. *Nature 2011*, 472, 120–124. [CrossRef]

56. Schuelke, M.; Delaga, W.; Leumann, J.; Gotz, S.; Urbanek, M.; Wenzel, A.; et al. Long noncoding RNA HOTTIP/HOXA13 expression is associated with disease progression and predicts outcome in pancreatic cancer patients. *Hepatology* 2014, 59, 911–923. [CrossRef]

57. Hu, P.; Qiao, O.; Wang, J.; Li, J.; Jin, H.; Li, Z.; Jin, Y. rs1859168 A > C polymorphism regulates HOTTIP expression and reduces risk of pancreatic cancer in a Chinese population. *World J. Surg. Oncol.* 2017, 15, 155. [CrossRef]

58. Li, Z.; Zhao, X.; Zhou, Y.; Liu, Y.; Zhou, Q.; Ye, H.; Wang, Y.; Zeng, J.; Song, Y.; Gao, W.; et al. The long non-coding RNA HOTTIP promotes progression and gemcitabine resistance by regulating HOXA13 in pancreatic cancer. *J. Transl. Med.* 2015, 13, 84. [CrossRef]

59. Cheng, Y.; Jutooru, I.; Chadalapaka, G.; Corton, J.C.; Safe, S. The long non-coding RNA HOTTIP enhances pancreatic cancer cell proliferation, survival and migration. *Oncotarget* 2015, 6, 10840–10852. [CrossRef]

60. Wong, C.H.; Li, C.H.; He, Q.; Chan, S.L.; Tong, J.H.; To, K.F.; Lin, L.Z.; Chen, Y. Ectopic HOTTIP expression induces noncanonical transactivation pathways to promote growth and invasiveness in pancreatic ductal adenocarcinoma. *Cancer Lett.* 2020, 477, 1–9. [CrossRef]

61. Fu, Z.; Chen, C.; Zhou, Q.; Wang, Y.; Zhao, Y.; Zhao, X.; Li, W.; Zheng, S.; Ye, H.; Wang, L.; et al. LncRNA HOTTIP modulates cancer stem cell properties in human pancreatic cancer by regulating HOXA9. *Cancer Lett.* 2017, 410, 68–81. [CrossRef] [PubMed]

62. Ji, P.; Diederichs, S.; Wang, W.; Böing, S.; Metzger, R.; Schneider, P.M.; Tidow, N.; Brandt, B.; Buerger, H.; Bulk, E.; et al. MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. *Oncogene* 2003, 22, 8031–8041. [CrossRef] [PubMed]

63. Gutschner, T.; Hämmerle, M.; Diederichs, S. MALAT1—a paradigm for long noncoding RNA function in cancer. *J. Mol. Med.* 2013, 91, 791–801. [CrossRef] [PubMed]

64. Zhang, X.; Hamblin, M.H.; Yin, K. The long noncoding RNA Malat1: its physiological and pathophysiological functions. *RNA Biol.* 2017, 14, 1705–1714. [CrossRef]

65. Hirata, H.; Hinoda, Y.; Shahryari, V.; Deng, G.; Nakajima, K.; Tabatabai, Z.L.; Ishii, N.; Dahiya, R. Long Noncoding RNA MALAT1 Promotes Aggressive Renal Cell Carcinoma through Ezh2 and Interacts with miR-205. *Cancer Res.* 2015, 75, 1322–1331. [CrossRef]

66. Li, P.; Zhang, X.; Wang, H.; Wang, L.; Liu, T.; Du, L.; Yang, W.; Wang, C. MALAT1 Is Associated with Poor Response to Oxaliplatin-Based Chemotherapy in Colorectal Cancer Patients and Promotes Chemosensitivity through EZH2. *Mol. Cancer Ther.* 2017, 16, 739–751. [CrossRef] [PubMed]

67. Liu, J.H.; Chen, G.; Dang, Y.W.; Li, C.J.; Luo, D.Z. Expression and prognostic significance of IncRNA MALAT1 in pancreatic cancer tissues. *Asian Pac. J. Cancer Prev.* 2014, 15, 2971–2977. [CrossRef]

68. Jiao, F.; Hu, H.; Yuan, C.; Wang, L.; Jiang, W.; Jin, Z.; Guo, Z.; Wang, L. Elevated expression level of long noncoding RNA MALAT-1 facilitates cell growth, migration and invasion in pancreatic cancer. *Oncol. Rep.* 2014, 32, 2485–2492. [CrossRef]

69. Jiao, F.; Hu, H.; Han, T.; Yuan, C.; Wang, L.; Jin, Z.; Guo, Z.; Wang, L. Long noncoding RNA MALAT-1 enhances stem cell-like phenotypes in pancreatic cancer cells. *Int. J. Mol. Sci.* 2015, 16, 6677–6693. [CrossRef]

70. Han, T.; Jiao, F.; Hu, H.; Yuan, C.; Wang, L.; Jin, Z.L.; Song, W.F.; Wang, L.W. EZH2 promotes cell migration and invasion but not alters cell proliferation by suppressing E-cadherin, partly through association with MALAT-1 in pancreatic cancer. *Oncotarget* 2016, 7, 11194–11207. [CrossRef]

71. Cheng, Y.; Imanriad, P.; Jutooru, I.; Hedrick, E.; Jin, U.H.; Rodrigues Hoffman, A.; Leal de Araujo, J.; Morpurgo, B.; Golovko, A.; Safe, S. Role of metastasis-associated lung adenocarcinoma transcript-1 (MALAT-1) in pancreatic cancer. *PloS ONE* 2018, 13, e0192264. [CrossRef]

72. Zhou, Y.; Shan, T.; Ding, W.; Hua, Z.; Shen, Y.; Lu, Z.; Chen, B.; Dai, T. Study on mechanism about long noncoding RNA MALAT1 affecting pancreatic cancer by regulating Hippo-YAP signaling. *J. Cell. Physiol.* 2018, 233, 5805–5814. [CrossRef] [PubMed]

73. Yu, F.; Lu, Z.; Cai, J.; Huang, K.; Chen, B.; Li, G.; Dong, P.; Zheng, J. MALAT1 functions as a competing endogenous RNA to mediate Rac1 expression by sequestering miR-101b in liver fibrosis. *Cell Cycle* 2015, 14, 3885–3896. [CrossRef] [PubMed]

74. Luo, W.; He, H.; Xiao, W.; Liu, Q.; Deng, Z.; Lu, Y.; Wang, Q.; Zheng, Q.; Li, Y. MALAT1 promotes osteosarcoma development by targeting TGFA via MiR376A. *Oncotarget* 2016, 7, 54733–54743. [CrossRef]

75. Liu, P.; Yang, H.; Zhang, J.; Peng, X.; Lu, Z.; Tong, W.; Chen, J. The IncRNA MALAT1 acts as a competing endogenous RNA to regulate KRAS expression by sponging miR-217 in pancreatic ductal adenocarcinoma. *Sci. Rep.* 2017, 7, 5186. [CrossRef]

76. Zhuo, M.; Yuan, C.; Han, T.; Cui, J.; Jiao, F.; Wang, L. A novel feedback loop between high MALAT-1 and low miR-200c-3p promotes cell migration and invasion in pancreatic ductal adenocarcinoma and is predictive of poor prognosis. *BMC Cancer* 2018, 18, 1032. [CrossRef]

77. Zhang, Y.; Tang, X.; Shi, M.; Wen, C.; Shen, B. MiR-216a decreases MALAT1 expression, induces G2/M arrest and apoptosis in pancreatic cancer cells. *Biochem. Biophys. Res. Commun.* 2017, 483, 816–822. [CrossRef]
81. Yoshimizu, T.; Miroglio, A.; Ripoche, M.A.; Gabory, A.; Vernucci, M.; Riccio, A.; Colnot, S.; Godard, C.; Terris, B.; Jammes, H.; et al. The H19 locus acts in vivo as a tumor suppressor. *Proc. Natl. Acad. Sci. USA* 2008, 105, 12417–12422. [CrossRef] [PubMed]

82. Ariel, I.; Sugbayer, M.; Fellig, Y.; Pizov, G.; Ayesh, S.; Podeh, D.; Libdeh, B.A.; Levy, C.; Birman, T.; Tykocinski, M.L.; et al. The imprint H19 is a marker of early recurrence in human bladder carcinoma. *Mol. Pathol.* 2000, 53, 320–323. [CrossRef] [PubMed]

83. Li, H.; Yu, B.; Li, J.; Su, L.; Yan, M.; Zhu, Z.; Liu, B. Overexpression of IncRNA H19 enhances carcinogenesis and metastasis of gastric cancer. *Oncotarget* 2014, 5, 2318–2329. [CrossRef] [PubMed]

84. Tsang, W.P.; Ng, E.K.; Ng, S.S.; Jin, H.; Yu, J.; Sung, J.J.; Kwok, T.T. Oncofetal H19-derived miR-675 regulates tumor suppressor RB in human colorectal cancer. *Carcinogenesis* 2010, 31, 350–358. [CrossRef]

85. Ma, C.; Nong, K.; Zhu, H.; Wang, W.; Huang, X.; Yuan, Z.; Ai, K. H19 promotes pancreatic cancer metastasis by derepressing let-7's suppression on its target HMG2-mediated EMT. *Tumour Biol.* 2014, 35, 9163–9169. [CrossRef]

86. Ma, C.; Tian, X.; Wang, F.; Zhang, Z.; Guo, H.; Zhang, Z.; Du, C.; Xie, X.; Zou, D.; Hua, Z.; Wang, L.; Zhu, Y.; Qian, H.; Dai, T. LncRNA UCA1 impacts cell proliferation, invasion, and apoptosis by suppression of p27(Kip1). *Cell Death Dis.* 2014, 5, e1008. [CrossRef] [PubMed]

87. Han, Y.; Yang, Y.N.; Yuan, H.H.; Zhang, T.T.; Sui, H.; Wei, X.L.; Liu, L.; Huang, P.; Zhang, W.J.; Bai, Y.X. UCA1, a long non-coding RNA up-regulated in colorectal cancer influences cell proliferation, apoptosis and cell cycle distribution. *Pathology* 2014, 46, 396–401. [CrossRef] [PubMed]

88. Wang, F.; Rong, L.; Zhang, Z.; Li, M.; Ma, L.; Ma, Y.; Tian, X.; Yang, Y. LncRNA H19-Derived miR-675-3p Promotes Epithelial-Mesenchymal Transition and Stemness in Human Pancreatic Cancer Cells by targeting the STAT3 Pathway. *J. Cancer* 2020, 11, 4771–4782. [CrossRef]

89. Wang, F.; Li, X.; Xie, X.; Zhao, L.; Chen, W. UCA1a (CUDR) promotes proliferation and migration of pancreatic cancer through regulating miR-96/FOXO3. *Cell. Physiol. Biochem.* 2018, 58, 22–33. [CrossRef]

90. Wang, Y.; Chen, W.; Yang, C.; Wu, W.; Wu, S.; Qin, X.; Li, Y. Long non-coding RNA UCA1a (CUDR) promotes proliferation and migration of pancreatic cancer cells. *Cell Death Dis.* 2014, 5, 1220–1226. [CrossRef] [PubMed]

91. Chen, P.; Wan, D.; Zheng, Q.; Fu, W.; Zhi, Q. Long non-coding RNA UCA1 promotes breast tumor growth by down-regulating E2F-1 in human pancreatic ductal adenocarcinoma. *J. Cancer* 2018, 9, 389–399. [CrossRef]

92. Liu, Y.; Zhou, D.; Li, G.; Ming, X.; Tu, Y.; Tian, J.; Lu, H.; Yu, B. Long non coding RNA UCA1 contributes to cardiomyocyte apoptosis by suppression of p27 expression. *Cell. Physiol. Biochem.* 2015, 35, 1986–1998. [CrossRef]

93. Yao, K.; Wang, Q.; Jia, J.; Zhao, H. A competing endogenous RNA network identifies novel mRNA, miRNA and IncRNA markers for the prognosis of diabetic pancreatic cancer. *Tumour Biol.* 2017, 39, 1010428317707882. [CrossRef]

94. Fu, X.L.; Liu, D.J.; Yan, T.T.; Yang, J.Y.; Yang, M.W.; Li, J.; Hua, Z.; Liu, W.; Zhang, J.F.; Hong, J.; et al. Analysis of long non-coding RNA expression profiles in pancreatic ductal adenocarcinoma. *Sci. Rep.* 2016, 6, 33535. [CrossRef] [PubMed]

95. Chen, P.; Wang, D.; Zheng, D.; Zheng, Q.; Fu, W.; Zhi, Q. Long non-coding RNA UCA1 promotes the tumorigenesis in pancreatic cancer. *Biomed. Pharmacother.* 2016, 83, 1220–1226. [CrossRef] [PubMed]

96. Liu, Y.; Zhou, D.; Li, G.; Ming, X.; Tu, Y.; Tian, J.; Lu, H.; Yu, B. Long non coding RNA-UCA1 promotes colorectal cancer progression by interacting with NCL and Sam68. *Mol. Cancer* 2018, 17, 110. [CrossRef] [PubMed]

97. Müller, S.; Raulefs, S.; Bruns, P.; Afonso-Grunz, F.; Pöther, A.; Lin, C.; Schüttler, A.; Kong, B.; Regel, I.; et al. Next-generation sequencing reveals novel differentially regulated mRNAs, IncRNAs, miRNAs, sdRNAs and a piRNA in pancreatic cancer. *Mol. Cancer* 2015, 14, 94. [CrossRef] [PubMed]
Cancers 2022, 14, 2115

25 of 31

105. Yu, X.; Lin, Y.; Sui, W.; Zhou, Y.; Ly, Z. Analysis of distinct long noncoding RNA transcriptional fingerprints in pancreatic ductal adenocarcinoma. *Cancer Med.* 2017, 6, 673–680. [CrossRef]

106. Zhu, H.; Shan, Y.; Ge, K.; Lu, J.; Kong, W.; Jia, C. LncRNA CYTOR promotes pancreatic cancer cell proliferation and migration by sponging miR-205-5p. *Pancreatology* 2020, 20, 1139–1148. [CrossRef]

107. Yuan, Z.J.; Yu, C.; Hu, X.F.; He, Y.; Chen, P.; Ouyang, S.X. LINC00152 promotes pancreatic cancer cell proliferation and invasion via targeting miR-150. *Am. J. Transl. Res.* 2020, 12, 2241–2256.

108. Zhou, L.; Li, J.; Shao, Q.Q.; Guo, J.C.; Liang, Z.Y.; Zhou, W.X.; Zhang, T.P.; You, L.; Zhao, Y.P. Expression and Significances of MTS1 in Pancreatic Cancer. *Pathol. Oncol. Res.* 2016, 22, 7–14. [CrossRef]

109. Hu, Y.; Wang, F.; Xu, F.; Fang, K.; Fang, Z.; Shuai, X.; Cai, K.; Chen, J.; Hu, P.; Chen, D.; et al. A reciprocal feedback of Myc and LncRNA MTS1-AS contributes to extracellular acidity-promoted metastasis of pancreatic cancer. *Theranostics* 2020, 10, 10120–10140. [CrossRef]

110. Xia, E.; Bhandari, A.; Shen, Y.; Zhou, X.; Wang, O. LncRNA LINC00673 induces proliferation, metastasis and epithelial-mesenchymal transition in thyroid carcinoma via Kruppel-like factor 2. *Int. J. Oncol.* 2018, 53, 1927–1938. [CrossRef]

111. Yu, J.; Liu, Y.; Gong, Z.; Zhang, S.; Guo, C.; Li, X.; Tang, Y.; Yang, L.; He, Y.; Wei, F.; et al. Overexpression long non-coding RNA LINC00673 is associated with poor prognosis and promotes invasion and metastasis in tongue squamous cell carcinoma. *Oncotarget* 2017, 8, 16621–16632. [CrossRef] [PubMed]

112. Zheng, J.; Huang, X.; Tan, W.; Yu, D.; Du, Z.; Chang, J.; Wei, L.; Han, Y.; Wang, C.; Che, X.; et al. Pancreatic cancer risk variant in LINC00673 creates a miR-1231 binding site and interferes with PTPN11 degradation. *Nat. Genet.* 2016, 48, 747–757. [CrossRef] [PubMed]

113. Gong, Y.; Dai, H.S.; Shu, J.J.; Liu, W.; Bie, P.; Zhang, L.D. LNC00673 suppresses proliferation and metastasis of pancreatic cancer via target miR-504/HNF1A. *J. Cancer* 2020, 11, 940–948. [CrossRef] [PubMed]

114. Clemson, C.M.; Hutchinson, J.N.; Sara, S.A.; Ensminger, A.W.; Fox, A.H.; Chess, A.; Lawrence, J.B. An architectural role for a nuclear noncoding RNA: NEAT1 RNA is essential for the structure of paraspeckles. *Mol. Cell* 2009, 33, 717–726. [CrossRef] [PubMed]

115. Yuan, Z.J.; Yu, C.; Hu, X.F.; He, Y.; Chen, P.; Ouyang, S.X. LINC00152 promotes pancreatic cancer cell proliferation, migration and lncRNA CYTOR promotes pancreatic cancer cell proliferation and migration by sponging miR-188-3p to derepress BRD4 expression. *J. Cancer* 2019, 10, 2099–2108. [CrossRef] [PubMed]

116. Fu, J.W.; Kong, Y.; Sun, X. Long noncoding RNA NEAT1 is an unfavorable prognostic factor and regulates migration and invasion in gastric cancer. *J. Cancer Res. Clin. Oncol.* 2016, 142, 1571–1579. [CrossRef]

117. Wu, Y.; Yang, L.; Zhao, J.; Li, C.; Nie, J.; Liu, F.; Zhuo, C.; Zheng, Y.; Li, B.; Wang, Z.; et al. Nuclear-enriched abundant transcript 1 (NEAT1) facilitates pancreatic cancer growth and gemcitabine resistance by sponging miR-188-3p to derepress BRD4 expression. *J. Exp. Clin. Cancer Res.* 2015, 14, 191. [CrossRef]

118. Chen, X.; Kong, J.; Ma, Z.; Gao, S.; Feng, X. Up regulation of the long non-coding RNA NEAT1 promotes esophageal squamous cell carcinoma cell migration and correlates with poor prognosis. *Am. J. Cancer Res.* 2015, 5, 2808–2815.

119. Fu, J.W.; Kong, Y.; Sun, X. Long noncoding RNA NEAT1 is an unfavorable prognostic factor and regulates migration and invasion in gastric cancer. *J. Cancer Res. Clin. Oncol.* 2016, 142, 1571–1579. [CrossRef]

120. Huang, B.; Liu, C.; Sun, Z. Long noncoding RNA NEAT1 is an unfavorable prognostic factor and regulates migration and invasion in pancreatic ductal adenocarcinoma cell proliferation and migration. *Mol. Cancer* 2019, 18, 3583–3597. [CrossRef] [PubMed]

121. Hu, Y.; Wang, F.; Xu, F.; Fang, K.; Fang, Z.; Shuai, X.; Cai, K.; Chen, J.; Hu, P.; Chen, D.; et al. A reciprocal feedback of Myc and LncRNA MTS1-AS contributes to extracellular acidity-promoted metastasis of pancreatic cancer. *Theranostics* 2020, 10, 10120–10140. [CrossRef]

122. Feng, Y.; Gao, L.; Cui, G.; Cao, Y. LncRNA NEAT1 facilitates pancreatic cancer cell proliferation and metastasis through stabilizing ELF3 mRNA. *Am. J. Cancer Res.* 2020, 10, 237–248. [PubMed]

123. Zhang, B.; Li, C.; Sun, Z. Long non-coding RNA LINC00346, LINC00578, LINC00673, LINC00671, LINC00261, and SNHG9 are novel prognostic markers for pancreatic cancer. *Am. J. Transl. Res.* 2018, 10, 2648–2658. [PubMed]

124. Wang, W.; Zhang, C.; Ning, Z.; Hua, Y.; Li, Y.; Chen, L.; Liu, L.; Chen, Z.; Meng, Z. Long non-coding RNA LINC00346 promotes pancreatic cancer growth and gemcitabine resistance by sponging miR-188-3p to derepress BRD4 expression. *J. Exp. Clin. Cancer Res.* 2019, 38, 60. [CrossRef] [PubMed]

125. Peng, W.X.; He, R.Z.; Zhang, Z.; Yang, L.; Mo, Y.Y. LINC00346 promotes pancreatic cancer progression through the CTGF-mediated Myc transcription. *Oncogene* 2019, 38, 6770–6780. [CrossRef]

126. Mitra, A.; Mishra, L.; Li, S. EMT, CTCs and CSCs in tumor relapse and drug-resistance. *Oncotarget* 2015, 6, 10697–10711. [CrossRef]

127. Karamitopoulou, E. Tumor budding cells, cancer stem cells and epithelial-mesenchymal transition-type cells in pancreatic cancer. *Front. Oncol.* 2012, 2, 209. [CrossRef]

128. Zhang, Q.; Geng, P.L.; Yin, P.; Wang, X.L.; Jia, J.P.; Yao, J. Down-regulation of long non-coding RNA TUG1 inhibits osteosarcoma cell proliferation and promotes apoptosis. *Asian Pac. J. Cancer Prev.* 2013, 14, 2311–2315. [CrossRef]

129. Han, Y.; Liu, Y.; Gui, Y.; Cai, Z. Long intergenic non-coding RNA TUG1 is overexpressed in urothelial carcinoma of the bladder. *J. Surg. Oncol.* 2013, 107, 555–559. [CrossRef]
131. Yang, F.; Li, X.; Zhang, L.; Cheng, L.; Li, X. LncRNA TUG1 promotes viability and associated with gemcitabine resistant in pancreatic ductal adenocarcinoma. *J. Pharmacol. Sci.* 2018, 137, 116–121. [CrossRef] [PubMed]

132. Zhao, L.; Sun, H.; Kong, H.; Chen, Z.; Chen, B.; Zhou, M. The Lncrna-TUG1/EZH2 Axis Promotes Pancreatic Cancer Cell Proliferation, Migration and EMT Phenotype Formation Through Sponging Mir-382. *Cell. Physiol. Biochem.* 2017, 42, 2145–2158. [CrossRef] [PubMed]

133. Huang, C.; Liu, S.; Wang, H.; Zhang, Z.; Yang, Q.; Gao, F. LncRNA PVT1 overexpression is a poor prognostic biomarker and regulates migration and invasion in small cell lung cancer. *Front. Oncol.* 2020, 10, 1013. [CrossRef]

134. Lu, Y.; Tang, L.; Zhang, Z.; Li, S.; Liang, S.; Ji, L.; Yang, B.; Liu, Y.; Wei, W. Long Noncoding RNA TUG1/miR-29c Axis Affects Cell Proliferation, Invasion, and Migration in Human Pancreatic Cancer. *Dis. Markers* 2018, 2018, 6887042. [CrossRef]

135. Lu, Y.; Tang, L.; Zhang, Z.; Li, S.; Liang, S.; Ji, L.; Yang, B.; Liu, Y.; Wei, W. Long Noncoding RNA TUG1/miR-29c Axis Affects Cell Proliferation, Invasion, and Migration in Human Pancreatic Cancer. *Dis. Markers* 2018, 2018, 6887042. [CrossRef]

136. Ou, Z.L.; Luo, Z.; Lu, Y.B. Long non-coding RNA HULC as a diagnostic and prognostic marker of pancreatic cancer. *World J. Gastroenterol.* 2019, 25, 6728–6742. [CrossRef]

137. Feng, H.; Wei, B.; Zhang, Y. Long non-coding RNA HULC promotes proliferation, migration and invasion of pancreatic cancer cells by down-regulating microRNA-15a. *Int. J. Biol. Macromol.* 2019, 126, 891–898. [CrossRef]

138. Takahashi, K.; Ota, Y.; Kogure, T.; Suzuki, Y.; Iwamoto, H.; Fujii, S.; Kitano, Y. The Interaction Between Long Non-coding RNA HULC and MicroRNA-622 via Transfer by Extracellular Vesicles Regulates Cell Invasion and Migration in Human Pancreatic Cancer. *Front. Oncol.* 2020, 10, 1013. [CrossRef]

139. Zhang, Y.; Yan, W.; Jung, Y.S.; Chen, X. PUMA Cooperates with p21 to Regulate Mammary Epithelial Morphogenesis and Epithelial-To-Mesenchymal Transition. *PLoS ONE* 2013, 8, e66464. [CrossRef]

140. Huang, C.; Yu, W.; Wang, Q.; Cui, H.; Wang, Y.; Zhang, L.; Han, F.; Huang, T. Increased expression of the IncRNA PVT1 is associated with poor prognosis in pancreatic cancer patients. *Minerva Med.* 2015, 106, 143–149. [PubMed]

141. Zhou, Q.; Chen, F.; Zhao, J.; Li, B.; Liang, Y.; Pan, W.; Zhang, S.; Wang, X.; Zheng, D. Long non-coding RNA PVT1 promotes osteosarcoma development by acting as a molecular sponge to regulate miR-195. *Oncotarget* 2016, 7, 82620–82633. [CrossRef] [PubMed]

142. Zhou, Q.; Chen, F.; Zhao, J.; Li, B.; Liang, Y.; Pan, W.; Zhang, S.; Wang, X.; Zheng, D. Long non-coding RNA PVT1 promotes osteosarcoma development by acting as a molecular sponge to regulate miR-195. *Oncotarget* 2016, 7, 82620–82633. [CrossRef] [PubMed]

143. Hui, B.; Xu, Y.; Zhao, B.; Ji, H.; Ma, Z.; Xu, S.; He, Z.; Wang, K.; Lu, J. Overexpressed long noncoding RNA TUG1 affects the cell cycle, proliferation, and apoptosis of pancreatic cancer partly through suppressing RND3 and MT2A. *Onco Targets Ther.* 2019, 12, 1043–1057. [CrossRef] [PubMed]

144. Xu, M.D.; Wang, Y.; Weng, W.; Wei, P.; Qi, P.; Zhang, Q.; Tan, C.; Ni, S.J.; Dong, L.; Yang, Y.; et al. A Positive Feedback Loop of lncRNA-PVT1 and FOXM1 Facilitates Gastric Cancer Growth and Invasion. *Cancer Sci.* 2020, 111, 98–111. [CrossRef]

145. Wan, L.; Sun, M.; Liu, G.J.; Wei, C.C.; Zhang, E.B.; Kong, R.; Xu, T.P.; Huang, M.D.; Wang, Z.X. Long Noncoding RNA PVT1 promotes proliferation and migration of pancreatic cancer cells through acting as a molecular sponge to regulate miR-448. *Int. J. Biol. Macromol.* 2019, 125, 165–176. [CrossRef] [PubMed]

146. Qin, C.F.; Zhao, F.L. Long non-coding RNA TUG1 can promote proliferation and migration of pancreatic cancer via EMT pathway. *Mol. Cancer* 2015, 14, 63. [CrossRef] [PubMed]

147. Wu, B.Q.; Jiang, Y.; Zhu, F.; Sun, D.L.; He, X.Z. Long Noncoding RNA PVT1 Promotes EMT and Cell Proliferation and Migration in Human Pancreatic Cancer. *Dis. Markers* 2018, 2018, 6887042. [CrossRef]

148. Zhang, X.; Feng, W.; Zhang, Y.; Zhang, J.; Ge, L.; Zhang, Y.; Jiang, X.; Peng, W.; Wang, D.; Gong, A.; Xu, M. Long non-coding RNA PVT1 promotes epithelial-mesenchymal transition via the TGF-β/Smad pathway in pancreatic cancer cells. *Onco. Rep.* 2018, 40, 1093–1102. [CrossRef]

149. Zhao, L.; Kong, H.; Sun, H.; Chen, Z.; Chen, B.; Zhou, M. LncRNA-PVT1 promotes pancreatic cancer cells proliferation and migration through acting as a molecular sponge to regulate miR-448. *J. Cell. Physiol.* 2018, 233, 4044–4055. [CrossRef]

150. Sun, J.; Zhang, P.; Yin, T.; Zhang, F.; Wang, W. Upregulation of LncRNA PVT1 Facilitates Pancreatic Ductal Adenocarcinoma Cell Progression and Glycosylation by Regulating MiR-519d-3p and HIF-1A. *J. Cancer* 2020, 11, 2572–2579. [CrossRef]

151. Huang, F.; Chen, W.; Peng, J.; Li, Y.; Zhuang, Y.; Zhu, Z.; Shao, C.; Yang, W.; Yao, H.; Zhang, S. LncRNA PVT1 triggers Cytoprotective autophagy and promotes pancreatic ductal adenocarcinoma development via the miR-20a-5p/ULK1 Axis. *Mol. Cancer* 2018, 17, 98. [CrossRef] [PubMed]

152. Yadav, A.K.; Desai, N.S. Cancer Stem Cells: Acquisition, Characteristics, Therapeutic Implications, Targeting Strategies and Future Prospects. *Stem Cell Rev. Rep.* 2019, 15, 331–355. [CrossRef] [PubMed]

153. Dalerba, P.; Clarke, M.F. Cancer stem cells and tumor metastasis: First steps into uncharted territory. *Cell Stem Cell* 2007, 1, 241–242. [CrossRef] [PubMed]

154. Dean, M.; Fojo, T.; Bates, S. Tumour stem cells and drug resistance. *Nat. Rev. Cancer* 2005, 5, 275–284. [CrossRef] [PubMed]

155. Islam, F.; Gopalan, V.; Lam, A.K. Identification of Cancer Stem Cells in Esophageal Adenocarcinoma. *Methods Mol. Biol.* 2018, 1756, 165–176. [CrossRef] [PubMed]
156. Huang, X.; Xiao, R.; Pan, S.; Yang, X.; Yuan, W.; Tu, Z.; Xu, M.; Zhu, Y.; Yin, Q.; Wu, Y.; et al. Uncovering the roles of long non-coding RNAs in cancer stem cells. *J. Hematol. Oncol.* 2017, 10, 62. [CrossRef]

157. Lathia, J.; Liu, H.; Matei, D. The Clinical Impact of Cancer Stem Cells. *OncoFocal 2019*, 25, 123–131. [CrossRef]

158. Najafi, M.; Farhood, B.; Mortezaee, K. Cancer stem cells (CSCs) in cancer progression and therapy. *J. Cell. Physiol.* 2019, 234, 8381–8395. [CrossRef]

159. Prasad, S.; Ramachandran, S.; Gupta, N.; Kaushik, I.; Srivastava, S.K. Cancer cells stemness: A doorstep to targeted therapy. *Biochim. Biophys. Acta Mol. Basis Dis.* 2020, 1866, 165424. [CrossRef]

160. Loewer, S.; Cabili, M.N.; Guttman, M.; Loh, Y.H.; Thomas, K.; Park, I.H.; Garber, M.; Curran, M.; Onder, T.; Agarwal, S.; et al. Large intergenic non-coding RNA-RoR modulates reprogramming of human induced pluripotent stem cells. *Nat. Genet.* 2010, 42, 1113–1117. [CrossRef]

161. Wang, Y.; Xu, Z.; Jiang, J.; Xu, C.; Kang, J.; Xiao, L.; Wu, M.; Xiong, J.; Guo, X.; Liu, H. Endogenous miRNA sponge lincRNA-RoR regulates Oct4, Nanog, and Sox2 in human embryonic stem cell self-renewal. *Dev. Cell* 2013, 25, 69–80. [CrossRef] [PubMed]

162. Cheng, E.C.; Lin, H. Repressing the repressor: A lincRNA as a MicroRNA sponge in embryonic stem cell self-renewal. *Dev. Cell* 2013, 25, 1–2. [CrossRef] [PubMed]

163. Zhan, H.X.; Wang, Y.; Li, C.; Xu, J.W.; Zhou, B.; Zhu, J.K.; Xu, J.W.; Zhou, B.; Zhu, J.K.; Han, H.F.; Wang, L.; Wang, Y.S.; Hu, S.Y. LincRNA-ROR promotes invasion, metastasis and tumor growth in pancreatic cancer through activating ZEB1 pathway. *Cancer Lett.* 2016, 374, 261–271. [CrossRef] [PubMed]

164. Wellner, U.; Schubert, J.; Burk, U.C.; Schmalhofer, O.; Zhu, F.; Sonntag, A.; Waldvogel, B.; Vannier, C.; Darling, D.; zur Hausen, A.; et al. The EMT-activator ZEB1 promotes tumorigenicity by repressing stemness-inhibiting microRNAs. *Nat. Cell Biol.* 2009, 11, 1487–1495. [CrossRef] [PubMed]

165. Zhang, P.; Sun, Y.; Ma, L. ZEB1: At the crossroads of epithelial-mesenchymal transition, metastasis and therapy resistance. *Cell Cycle* 2015, 14, 481–487. [CrossRef] [PubMed]

166. Hill, L.; Browne, G.; Tulchinsky, E. ZEB/miR-200 feedback loop: At the crossroads of signal transduction in cancer. *Int. J. Cancer* 2013, 132, 745–754. [CrossRef]

167. Chen, W.; Wang, H.; Liu, Y.; Xu, W.; Ling, C.; Li, Y.; Liu, J.; Chen, M.; Zhang, Y.; Chen, B.; et al. Linc-RoR promotes proliferation, migration, and invasion via the Hippo/YAP pathway in pancreatic cancer cells. *J. Cell. Biochem.* 2020, 121, 632–641. [CrossRef]

168. Zhulina, Y.; Cao, Y.; Amcoff, K.; Carlson, M.; Tysk, C.; Halfvarson, J. The prognostic significance of faecal calprotectin in patients with inactive inflammatory bowel disease. *Aliment. Pharmacol. Ther.* 2016, 44, 495–504. [CrossRef]

169. Gao, S.; Wang, P.; Hua, Y.; Xi, H.; Meng, Z.; Liu, T.; Chen, Z.; Liu, L. ROR functions as a ceRNA to regulate Nanog expression by sponging miR-145 and predicts poor prognosis in pancreatic cancer. *Oncotarget* 2016, 7, 1608–1618. [CrossRef]

170. Fu, Z.; Li, G.; Li, Z.; Wang, Y.; Zhao, Y.; Zheng, S.; Ye, H.; Luo, Y.; Zhao, X.; Wei, L.; et al. Endogenous miRNA Sponge LincRNA-ROR promotes proliferation, invasion and stem cell-like phenotype of pancreatic cancer cells. *Cell Death Discov.* 2017, 3, 17004. [CrossRef]

171. Bejerano, G.; Lowe, C.B.; Ahituv, N.; King, B.; Siepel, A.; Salama, S.R.; Rubin, E.M.; Kent, W.J.; Haussler, D. A distal enhancer and an ultraconserved exon are derived from a novel retroposon. *Nature* 2006, 441, 87–90. [CrossRef] [PubMed]

172. Katzman, S.; Kern, A.D.; Bejerano, G.; Fewell, G.; Fulton, L.; Wilson, R.K.; Salama, S.R.; Haussler, D. Human genome ultraconserved elements are ultralselected. *Science* 2007, 317, 915. [CrossRef] [PubMed]

173. Sana, J.; Hankeova, S.; Svoboda, M.; Kiss, I.; Vyzula, R.; Slaby, O. Expression levels of transcribed ultraconserved regions uc.73 and uc.388 are altered in colorectal cancer. *Oncology* 2012, 82, 114–118. [CrossRef] [PubMed]

174. Ferdin, J.; Nishida, N.; Wu, X.; Nicoloso, M.S.; Shah, M.Y.; Devlin, C.; Ling, H.; Shimizu, M.; Kumar, K.; Corteza, M.A.; et al. HINCut in cancer: Hypoxia-induced noncoding ultraconserved transcripts. *Cell Death Differ.* 2013, 20, 1675–1687. [CrossRef]

175. Liu, C.; Wang, J.; Yuan, X.; Qian, W.; Zhang, B.; Shi, M.; Xie, J.; Shen, B.; Xu, H.; Hou, Z.; et al. Long noncoding RNA uc.345 promotes tumorigenesis of pancreatic cancer by upregulation of hnRNPL expression. *Oncotarget* 2016, 7, 71556–71566. [CrossRef] [PubMed]

176. Dery, K.J.; Gaur, S.; Gencheva, M.; Yen, Y.; Shively, J.E.; Gaur, R.K. Mechanistic control of carcinomaembryonic antigen-related cell adhesion molecule-1 (CEACAM1) splice isoforms by the heterogeneous nuclear ribonuclear proteins hnRNPL, hnRNPA1, and hnRNPM. *J. Biol. Chem.* 2011, 286, 16039–16051. [CrossRef]

177. Goeh, R.W.; Shultz, J.C.; Murudkar, C.; Usanovic, S.; Lamour, N.F.; Massey, D.H.; Zhang, L.; Camidge, D.R.; Shroyer, J.W.; Minna, J.D.; et al. hnRNP L regulates the tumorigenic capacity of lung cancer xenografts in mice via caspase-9 pre-mRNA processing. *J. Clin. Invest.* 2010, 120, 3923–3939. [CrossRef]

178. Shivapurkar, N.; Weiner, L.M.; Marshall, J.L.; Madhavan, S.; Deslattes Mays, A.; Juhl, H.; Weilstein, A. Recurrence of early stage colon cancer predicted by expression pattern of circulating microRNAs. *PLoS ONE* 2014, 9, e84686. [CrossRef]

179. Wu, X.B.; Feng, X.; Chang, Q.M.; Zhang, C.W.; Wang, Z.P.; Liu, J.; Hu, Z.Q.; Liu, J.Z.; Wu, W.D.; Zhang, Z.P.; et al. Cross-talk among AFAP1-AS1, ACVR1 and microRNA-384 regulates the stemness of pancreatic cancer stem cells and tumorigenicity in nude mice. *J. Exp. Clin. Cancer Res.* 2019, 38, 107. [CrossRef]

180. Ye, Y.; Chen, J.; Zhou, Y.; Fu, Z.; Zhou, Q.; Wang, Y.; Gao, W.; Zheng, S.; Zhao, X.; Chen, T.; et al. High expression of AFAP1-AS1 is associated with poor survival and short-term recurrence in pancreatic ductal adenocarcinoma. *J. Transl. Med.* 2015, 13, 137. [CrossRef]
181. Lou, S.; Xu, J.; Wang, B.; Li, S.; Ren, J.; Hu, Z.; Xu, B.; Luo, F. Downregulation of IncRNA AFAP1-AS1 by oridonin inhibits the epithelial-to-mesenchymal transition and proliferation of pancreatic cancer cells. Acta Biochim. Biophys. Sin. 2019, 51, 814–825. [CrossRef] [PubMed]

182. Chen, B.; Li, Q.; Zhou, Y.; Wang, X.; Zhang, Q.; Wang, Y.; Zhuang, H.; Jiang, X.; Xiong, W. The long coding RNA AFAP1-AS1 promotes tumor cell growth and invasion in pancreatic cancer through upregulating the IGFI1 oncogene via sequestration of miR-133a. CellCycle 2018, 17, 1949–1966. [CrossRef] [PubMed]

183. Zhou, J.; Liu, M.; Chen, Y.; Xu, S.; Guo, Y.; Zhao, L. Curcubitacin B suppresses proliferation of pancreatic cancer cells by ceRNA: Effect of miR-146b-5p and IncRNA-AFAP1-AS1. J. Cell. Physiol. 2019, 234, 4655–4667. [CrossRef] [PubMed]

184. Zhou, Y.; Zhang, X.; Klibanski, A. MEG3 noncoding RNA: A tumor suppressor. J. Mol. Endocrinol. 2012, 48, R45–R53. [CrossRef] [PubMed]

185. Sun, M.; Xia, R.; Jin, F.; Xu, T.; Liu, Z.; De, W.; Liu, X. Downregulated long noncoding RNA MEG3 is associated with poor prognosis and promotes cell proliferation in gastric cancer. Tumour Biol. 2014, 35, 1065–1073. [CrossRef] [PubMed]

186. Krue, T.J.; Dougherty, S.M.; Reynolds, L.; Long, E.; de Silva, T.; Lockwood, W.W.; Clem, B.F. Expression of the lncRNA Maternally Expressed 3 (MEG3) Contributes to the Control of Lung Cancer Cell Proliferation by the Rdh Pathway. PLoS ONE 2016, 11, e0166363. [CrossRef]

187. Xiong, Y.; Liu, T.; Wang, S.; Chi, H.; Chen, C.; Zheng, J. Cyclophosphamide promotes the proliferation inhibition of mouse ovarian granulosa cells and premature ovarian failure by activating the IncRNA-Meg3-p53-p66Shc pathway. Gene 2017, 596, 1–8. [CrossRef]

188. Chak, W.P.; Lung, R.W.; Tong, J.H.; Chan, S.Y.; Lun, S.W.; Tsao, S.W.; Lo, K.W.; To, K.F. Downregulation of long non-coding RNA MEG3 in nasopharyngeal carcinoma. Mol. Carcinog. 2017, 56, 1041–1054. [CrossRef]

189. Gu, L.; Zhang, J.; Shi, M.; Zhan, Q.; Shen, B.; Peng, C. IncRNA MEG3 had anti-cancer effects to suppress pancreatic cancer activity. Biomed. Pharmacother. 2017, 89, 1269–1276. [CrossRef]

190. Ma, L.; Wang, F.; Du, C.; Zhang, Z.; Guo, H.; Xie, X.; Gao, H.; Zhuang, Y.; Kornmann, M.; Gao, H.; et al. Long non-coding RNA MEG3 functions as a tumour suppressor and has prognostic predictive value in human pancreatic cancer. Oncol. Rep. 2018, 39, 1132–1140.[CrossRef]

191. Fantes, J.; Ragge, N.K.; Lynch, S.A.; McGill, N.I.; Collin, J.R.; Howard-Peebles, P.N.; Hayward, C.; Vivian, A.J.; Williamson, K.; van Heyningen, V.; et al. Mutations in SOX2 cause anophthalmia. Nat. Genet. 2003, 33, 461–463. [CrossRef] [PubMed]

192. Shahryari, A.; Rafiee, M.R.; Fouani, Y.; Oliae, N.A.; Samaei, N.M.; Shafiee, M.; Semnani, S.; Vasei, M.; Mowla, S.J. Two novel splice variants of SOX2OT, SOX2OT-S1, and SOX2OT-S2 are co-upregulated with SOX2 and OCT4 in esophageal squamous cell carcinoma. Stem Cells 2014, 32, 126–134. [CrossRef] [PubMed]

193. Askarian-Amiri, M.E.; Seyfoddin, V.; Smart, C.E.; Wang, J.; Kim, J.E.; Hansjii, H.; Baguley, B.C.; Finlay, G.J.; Leung, E.Y. Emerging role of long non-coding RNA SOX2OT in SOX2 regulation in breast cancer. PLoS ONE 2014, 9, e102140. [CrossRef] [PubMed]

194. Hou, Z.; Zhao, W.; Zhou, J.; Shen, L.; Zhan, P.; Xu, C.; Chang, C.; Bi, H.; Zou, J.; Yao, X.; et al. A long noncoding RNA Sox2ot regulates lung cancer cell proliferation and is a prognostic indicator of poor survival. Int. J. Biochem. Cell Biol. 2014, 53, 380–388. [CrossRef] [PubMed]

195. Shi, X.M.; Teng, F. Up-regulation of long non-coding RNA Sox2ot promotes hepatocellular carcinoma cell metastasis and correlates with poor prognosis. Int. J. Clin. Exp. Pathol. 2015, 8, 4008–4014. [CrossRef]

196. Chen, L.; Zhang, J.; Chen, Q.; Ge, W.; Meng, L.; Huang, X.; Shen, P.; Yuan, H.; Shi, G.; Miao, Y.; et al. Long noncoding RNA SOX2OT promotes the proliferation of pancreatic cancer by binding to FUS. Int. J. Cancer 2020, 147, 175–188. [CrossRef]

197. Li, Z.; Jiang, P.; Li, J.; Peng, M.; Zhao, X.; Zhang, X.; Chen, K.; Zhang, Y.; Liu, H.; Gan, L.; et al. Tumor-derived exosomal Inc-Sox2ot promotes EMT and stemness by acting as a ceRNA in pancreatic ductal adenocarcinoma. Oncogene 2018, 37, 3822–3838. [CrossRef]

198. Amaral, P.P.; Dinger, M.E.; Mattick, J.S. Non-coding RNAs in homeostasis, disease and stress responses: An evolutionary perspective. Brief Funct. Genom. 2013, 12, 254–278. [CrossRef]

199. Su, X.; Malouf, G.G.; Chen, Y.; Zhang, J.; Yao, H.; Valero, V.; Weinstein, J.N.; Spano, J.P.; Meric-Bernstam, F.; Khayat, D.; et al. Comprehensive analysis of long non-coding RNAs in human breast cancer clinical subtypes. Oncotarget 2014, 5, 9864–9876. [CrossRef]

200. Melo, C.P.; Campos, C.B.; Rodrigues Jde, O.; Aguirre-Neto, J.C.; Atalla, Â.; Pianovski, M.A.; Carbone, E.K.; Lares, L.B.; Moraes-Souza, H.; Octacílio-Silva, S.; et al. Long non-coding RNAs: Biomarkers for acute leukaemia subtypes. Br. J. Haematol. 2016, 173, 318–320. [CrossRef]

201. Xie, Z.; Chen, X.; Li, J.; Guo, Y.; Li, H.; Pan, X.; Jiang, J.; Liu, H.; Wu, B. Salivary HOTAIR and PVT1 as novel biomarkers for early pancreatic cancer. Oncotarget 2016, 7, 25408–25419. [CrossRef] [PubMed]

202. Xie, Z.C.; Dang, Y.W.; Wei, D.M.; Chen, P.; Tang, R.X.; Huang, Q.; Liu, J.H.; Luo, D.Z. Clinical significance and prospective molecular mechanism of MALAT1 in pancreatic cancer exploration: A comprehensive study based on the GeneChip, GEO, Oncomine, and TCGA databases. Onco Targets Ther. 2017, 10, 3991–4005. [CrossRef] [PubMed]

203. Wolpin, B.M.; Rizzato, C.; Kraft, P.; Kooperberg, C.; Petersen, G.M.; Wang, Z.; Arslan, A.A.; Beane-Freeman, L.; Bracci, P.M.; Buring, J.; et al. Genome-wide association study identifies multiple susceptibility loci for pancreatic cancer. Nat. Genet. 2014, 46, 994–1000. [CrossRef] [PubMed]

204. Li, L.; Zhang, G.Q.; Chen, H.; Zhao, Z.J.; Chen, H.Z.; Liu, H.; Wang, G.; Jia, Y.H.; Pan, S.H.; Kong, R.; et al. Plasma and tumor levels of Linc-pint are diagnostic and prognostic biomarkers for pancreatic cancer. Oncotarget 2016, 7, 71773–71781. [CrossRef]
205. Lu, H.; Yang, D.; Zhang, L.; Lu, S.; Ye, J.; Li, M.; Hu, W. Linc-pint inhibits early stage pancreatic ductal adenocarcinoma growth through TGF-β pathway activation. Oncol. Lett. 2019, 17, 4633–4639. [CrossRef]

206. Moldovan, G.L.; Pfander, B.; Jentsch, S. PCNA, the maestro of the replication fork. Cell 2007, 129, 665–679. [CrossRef]

207. Cory, S.; Adams, J.M. The Bcl2 family: Regulators of the cellular life-or-death switch. Nat. Rev. Cancer 2002, 2, 647–656. [CrossRef]

208. Johnson, N.A.; Savage, K.J.; Ludkovski, O.; Ben-Neriah, S.; Woods, R.; Steidl, C.; Dyer, M.J.; Siebert, R.; Kuruvilla, J.; Klasa, R.; et al. Lymphomas with concurrent BCL2 and MYC translocations: The critical factors associated with survival. Blood 2009, 114, 2273–2279. [CrossRef]

209. Yang, J.; Jiang, B.; Hai, J.; Duan, S.; Dong, X.; Chen, C. Long noncoding RNA opa-interacting protein 5 antisense transcript 1 promotes proliferation and invasion through elevating integrin α6 expression by sponging miR-143-3p in cervical cancer. J. Cell. Biochem. 2019, 120, 907–916. [CrossRef]

210. Wang, M.; Sun, X.; Yang, Y.; Jiao, W. Long non-coding RNA OIP5-AS1 promotes proliferation of lung cancer cells and leads to poor prognosis by targeting miR-378a-3p. Thorac. Cancer 2018, 9, 939–949. [CrossRef]

211. Zou, Y.; Yao, S.; Chen, X.; Liu, D.; Wang, J.; Yuan, X.; Rao, J.; Xiong, H.; Yu, S.; Yuan, X.; et al. LncRNA OIP5-AS1 regulates radioresistance by targeting DRYRK1A through miR-369-3p in colorectal cancer cells. Eur. J. Cell Biol. 2018, 97, 369–378. [CrossRef]

212. Zhang, Z.; Li; F.; Yang, F.; Liu, Y. Kockdown of OIP5-AS1 expression inhibits proliferation, metastasis and EMT progress in hepatoblastoma cells through up-regulating miR-186a-5p and down-regulating ZEB1. Biomed. Pharmacother. 2018, 101, 14–23. [CrossRef] [PubMed]

213. Wu, L.; Liu, Y.; Guo, C.; Shao, Y. LncRNA OIP5-AS1 promotes the malignancy of pancreatic ductal adenocarcinoma via regulating miR-429/FOXO1A/ERK pathway. Cancer Cell Int. 2020, 20, 296. [CrossRef] [PubMed]

214. Meng, X.; Ma, J.; Wang, B.; Wu, X.; Liu, Z. Long non-coding RNA OIP5-AS1 promotes pancreatic cancer cell growth through sponging miR-342-3p via AKT/ERK signaling pathway. J. Physiol. Biochem. 2020, 76, 301–315. [CrossRef] [PubMed]

215. Song, P.; Ye, L.F.; Zhang, C.; Peng, T.; Zhou, X.H. Long non-coding RNA XIST exerts oncogenic functions in human nasopharyngeal carcinoma by targeting miR-34a-5p. Gene 2016, 552, 8–14. [CrossRef] [PubMed]

216. Chen, D.L.; Ju, H.Q.; Lu, Y.X.; Chen, L.Z.; Zeng, Z.L.; Zhang, D.S.; Luo, H.Y.; Wang, F.; Qiu, M.Z.; Wang, D.S.; et al. Long non-coding RNA XIST regulates gastric cancer progression by acting as a molecular sponge of miR-101 to modulate EZH2 expression. J. Exp. Clin. Cancer Res. 2016, 35, 142. [CrossRef]

217. Qin, Y.; Dang, X.; Li, W.; Ma, Q. miR-133a functions as a tumor suppressor and directly targets FSCN1 in pancreatic cancer. Oncol. Res. 2015, 23, 353–363. [CrossRef]

218. Gong, Y.; Ren, J.; Liu, K.; Tang, L.M. Tumor suppressor role of miR-133a in gastric cancer by repressing IGF1R. World J. Gastroenterol. 2015, 21, 2949–2958. [CrossRef]

219. Wei, W.; Liu, Y.; Lu, Y.; Yang, B.; Tang, L. LncRNA XIST Promotes Pancreatic Cancer Proliferation Through miR-133a/EGFR. J. Cell. Biochem. 2017, 118, 3349–3358. [CrossRef]

220. Palmieri, G.; Paliotianni, P.; Sini, M.C.; Manca, A.; Palomba, G.; Doneddu, V.; Tanda, F.; Pascale, M.R.; Cosso, A. Long non-coding RNA CASC2 in human cancer. Crit. Rev. Oncol. Hematol. 2017, 111, 31–38. [CrossRef]

221. He, X.; Liu, Z.; Su, J.; Yang, J.; Yin, D.; Han, L.; De, W.; Guo, R. Low expression of long noncoding RNA CASC2 indicates a poor prognosis and regulates cell proliferation in non-small cell lung cancer. Tumour Biol. 2016, 37, 9503–9510. [CrossRef] [PubMed]

222. Huang, G.; Wu, X.; Li, S.; Xu, X.; Zhu, H.; Chen, X. The long noncoding RNA CASC2 functions as a competing endogenous RNA by sponging miR-18a in colorectal cancer. Sci. Rep. 2016, 6, 26524. [CrossRef] [PubMed]

223. Baldini, P.; Cosso, A.; Manca, A.; Satta, M.P.; Sini, M.C.; Rozzo, C.; Desole, S.; Cherchi, P.; Gianfrancesco, F.; Pintus, A.; et al. Identification of a novel candidate gene, CASC2, in a region of common allelic loss at chromosome 10q26 in human endometrial cancer. Hum. Mutat. 2004, 23, 318–326. [CrossRef] [PubMed]

224. Wang, P.; Liu, Y.H.; Yao, Y.L.; Li, Z.; Li, Z.Q.; Ma, J.; Xue, Y.X. Long non-coding RNA CASC2 suppresses malignancy in human gliomas by miR-21. Cell. Signal. 2015, 27, 275–282. [CrossRef]

225. Cao, Y.; Xu, R.; Xu, X.; Zhou, Y.; Cui, L.; He, X. Downregulation of IncRNA CASC2 by microRNA-21 increases the proliferation and migration of renal cell carcinoma cells. Mol. Med. Rep. 2016, 14, 1019–1025. [CrossRef]

226. Yu, Y.; Liang, S.; Zhou, Y.; Li, S.; Li, Y.; Liao, W. HNF1A/CASC2 regulates pancreatic cancer cell proliferation through PTEN/Akt signaling. J. Cell. Biochem. 2019, 120, 2816–2827. [CrossRef]

227. Xu, D.F.; Wang, L.S.; Zhou, J.H. Long non-coding RNA CASC2 suppresses pancreatic cancer cell growth and progression by regulating the miR-24/SMAD6 axis. Int. J. Oncol. 2020, 56, 494–507. [CrossRef]

228. Zhang, H.; Feng, X.; Zhang, M.; Liu, A.; Tian, L.; Bo, W.; Wang, H.; Hu, Y. Long non-coding RNA CASC2 upregulates PTEN to suppress pancreatic carcinoma cell metastasis by downregulating miR-21. Cancer Cell Int. 2019, 19, 18. [CrossRef]

229. Qu, S.; Niu, K.; Wang, J.; Dai, J.; Ganguly, A.; Gao, C.; Tian, Y.; Lin, Z.; Yang, X.; Zhang, X.; et al. LINCO0671 suppresses cell proliferation and metastasis in pancreatic cancer by inhibiting AKT and ERK signaling pathway. Cancer Gene Ther. 2020, 28, 221–233. [CrossRef]

230. Kleger, A.; Perkhofer, L.; Seufferlein, T. Smarter drugs emerging in pancreatic cancer therapy. Ann. Oncol. 2014, 25, 1260–1270. [CrossRef]

231. Uccello, M.; Moschetta, M.; Mak, G.; Alam, T.; Henriquez, C.M.; Arkenau, H.T. Towards an optimal treatment algorithm for metastatic pancreatic ductal adenocarcinoma (PDAC). Curr. Oncol. 2018, 25, e90–e94. [CrossRef] [PubMed]
232. Binenbaum, Y.; Na’ara, S.; Gil, Z. Gemcitabine resistance in pancreatic ductal adenocarcinoma. Drug Resist. Updat. 2015, 23, 55–68. [CrossRef]

233. Zhang, X.W.; Bu, P.; Liu, L.; Zhang, X.Z.; Li, J. Overexpression of long non-coding RNA PVT1 in gastric cancer cells promotes the development of multidrug resistance. Biochem. Biophys. Res. Commun. 2015, 462, 227–232. [CrossRef]

234. You, L.; Wang, H.; Yang, G.; Zhao, F.; Zhang, J.; Liu, Z.; Zhang, T.; Liang, Z.; Liu, C.; Zhao, Y. Gemcitabine exhibits a suppressive effect on pancreatic cancer cell growth by regulating processing of PVT1 to miR1207. Mol. Oncol. 2018, 12, 2147–2164. [CrossRef]

235. Zhou, C.; Yi, C.; Yi, Y.; Qin, W.; Yan, Y.; Dong, X.; Zhang, X.; Huang, Y.; Zhang, R.; Wei, J.; et al. LncRNA PVT1 promotes gemcitabine resistance of pancreatic cancer via activating Wnt/β-catenin and autophagy pathway through modulating the miR-619-5p/Pgyo2 and miR-619-5p/ATG14 axes. Mol. Cancer 2020, 19, 118. [CrossRef][PubMed]

236. Liu, Y.; Helms, C.; Liao, W.; Zaba, L.; Duan, S.; Gardner, J.; Wise, C.; Minis, A.; Malloy, M.J.; Pullinger, C.R.; et al. A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. PLoS Genet. 2008, 4, e1000401. [CrossRef]

237. Cheng, J.; Zhao, D.; Meng, K. Knockdown of HCP5 exerts tumor-suppressive functions by up-regulating tumor suppressor miR-128-3p in anaplastic thyroid cancer. Biomed. Pharmacother. 2019, 116, 108966. [CrossRef]

238. Wang, L.; Luan, T.; Zhou, S.; Lin, J.; Yang, Y.; Liu, W.; Tong, X.; Jiang, W. LncRNA HCP5 promotes triple negative breast cancer progression as a ceRNA to regulate BIRC3 by sponging miR-219a-5p. Cancer Med. 2019, 8, 4389–4403. [CrossRef]

239. Yang, C.; Sun, J.; Liu, W.; Yang, Y.; Chu, Z.; Yang, T.; Gou, Y.; Wang, D. Long noncoding RNA HCP5 contributes to epithelial-mesenchymal transition in colorectal cancer through ZEB1 activation and interacting with miR-139-5p. Am. J. Transl. Res. 2019, 11, 953–963. [PubMed]

240. Yu, Y.; Shen, H.M.; Fang, D.M.; Meng, Q.J.; Xin, Y.H. LncRNA HCP5 promotes the development of cervical cancer by regulating MACC1 via suppression of microRNA-15a-35. Eur. Rev. Med. Pharmacol. Sci. 2018, 22, 4812–4819. [CrossRef]

241. Wang, W.; Lou, W.; Ding, B.; Yang, B.; Lu, H.; Kong, Q.; Fan, W. A novel mRNA-miRNA-lncRNA competing endogenous RNA triple sub-network associated with prognosis of pancreatic cancer. Aging 2019, 11, 2610–2627. [CrossRef][PubMed]

242. Yuan, B.; Guan, Q.; Yan, T.; Zhang, X.; Xu, W.; Li, J. LncRNA HCP5 Regulates Pancreatic Cancer Progression by miR-140-5p/CDK8 Axis. Cancer Biol. Therapeut. 2020, 35, 711–719. [CrossRef][PubMed]

243. Liu, Y.; Wang, J.; Dong, L.; Xia, L.; Zhu, H.; Li, Z.; Yu, X. Long Noncoding RNA HCP5 Regulates Pancreatic Cancer Gemicitabine (GEM) Resistance By Sponging Hsa-miR-214-3p To Target HDGF. Onco Targets Ther. 2019, 12, 8207–8216. [CrossRef]

244. Mourtada-Maarabouni, M.; Pickard, M.R.; Hedge, V.L.; Farzaneh, F.; Williams, G.T. GAS5, a non-protein-coding RNA, controls gemcitabine resistance in pancreatic cancer mediated by Sponging Hsa-miR-214-3p To Target HDGF. Cell Biosci. 2019, 9, 66. [CrossRef][PubMed]

245. Kino, T.; Hurt, D.E.; Ichijo, T.; Nader, N.; Chrousos, G.P. Noncoding RNA gas5 is a growth arrest- and starvation-associated repressor of the glucocorticoid receptor. Sci. Signal. 2010, 3, ra8. [CrossRef]

246. Tani, H.; Torimura, M.; Akimitsu, N. The RNA degradation pathway regulates the function of GAS5 a non-coding RNA in mammalian cells. PLoS ONE 2013, 8, e55684. [CrossRef]

247. Gao, Z.Q.; Wang, J.F.; Chen, D.H.; Ma, X.S.; Wu, Y.; Yang, B.; Lu, H.; Kong, Q.; Fan, W. A novel mRNA-miRNA-lncRNA competing endogenous RNA triple sub-network associated with prognosis of pancreatic cancer. Aging 2019, 11, 2610–2627. [CrossRef][PubMed]

248. Yuan, B.; Guan, Q.; Yan, T.; Zhang, X.; Xu, W.; Li, J. LncRNA HCP5 Regulates Pancreatic Cancer Progression by miR-140-5p/CDK8 Axis. Cancer Biol. Therapeut. 2020, 35, 711–719. [CrossRef][PubMed]

249. Liu, Y.; Wang, J.; Dong, L.; Xia, L.; Zhu, H.; Li, Z.; Yu, X. Long Noncoding RNA HCP5 Regulates Pancreatic Cancer Gemicitabine (GEM) Resistance By Sponging Hsa-miR-214-3p To Target HDGF. Onco Targets Ther. 2019, 12, 8207–8216. [CrossRef]

250. Gao, Z.Q.; Wang, J.F.; Chen, D.H.; Ma, X.S.; Wu, Y.; Tang, Z.; Dang, X.W. Long non-coding RNA GAS5 suppresses pancreatic cancer cell proliferation by regulating CDK6. Am. J. Transl. Res. 2019, 11, 953–963. [PubMed]

251. Liu, B.; Wu, S.; Ma, J.; Yang, T.; Ye, Y.; He, R.; Li, Z.; Lin, Q.; et al. Downregulation of gas5 increases pancreatic cancer cell proliferation by regulating CDK6. Cell Biosci. 2017, 66. [CrossRef]

252. Zhang, X.; Zheng, S.; Hu, C.; Li, G.; Lin, H.; Xia, R.; Ye, Y.; He, R.; Li, Z.; Lin, Q.; et al. Cancer-associated fibroblast-induced lncRNA UPK1A-AS1 confers platinum resistance in pancreatic cancer via efficient double-strand break repair. Oncogene 2022, 41, 2372–2389. [CrossRef][PubMed]

253. Kristensen, L.; Andersen, M.; Stagsted, L.; Ebbesen, K.; Hansen, T.; Kjems, J. The biogenesis, biology and characterization of circular RNAs. Nat. Rev. Genet. 2019, 20, 675–691. [CrossRef]

254. Mizrachi, A.; Czerwinski, A.; Levy, T.; Amir, S.; Gallula, J.; Matouk, I.; Abu-lail, R.; Sorin, V.; Birman, T.; de Groot, N.; et al. Development of targeted therapy for ovarian cancer mediated by a plasmid expressing dihydropteroxin under the control of H19 regulatory sequences. J. Transl. Med. 2009, 7, 69. [CrossRef]

255. Mizrachi, A.; Czerwinski, A.; Levy, T.; Amir, S.; Gallula, J.; Matouk, I.; Abu-lail, R.; Sorin, V.; Birman, T.; de Groot, N.; et al. Development of targeted therapy for ovarian cancer mediated by a plasmid expressing dihydropteroxin under the control of H19 regulatory sequences. J. Transl. Med. 2009, 7, 69. [CrossRef]

256. Lavin, O.; Edelman, D.; Levy, T.; Fishman, A.; Hubert, A.; Segev, Y.; Raveh, E.; Gilon, M.; Hochberg, A. A phase 1/2a, dose-escalation, safety, pharmacokinetic, and preliminary efficacy study of intraperitoneal administration of BC-819 (H19-DTA) in subjects with recurrent ovarian/peritoneal cancer. Arch. Gynecol. Obstet. 2017, 295, 751–761. [CrossRef][PubMed]

257. Gofrit, O.; Benjamini, S.; Halachmi, S.; Leibovitch, I.; Dotan, L.; Lamm, D.; Ehrlich, N.; Yutkin, V.; Ben-Am, M.; Hochberg, A. DNA based therapy with dihydropteroxin-A BC-819: A phase 2b marker lesion trial in patients with intermediate risk nonmuscle invasive bladder cancer. J. Urol. 2014, 191, 1697–1702. [CrossRef][PubMed]

258. Jiang, F.; Doudna, J. CRISPR-Cas9 Structures and Mechanisms. Annu. Rev. Biophys. 2017, 46, 505–529. [CrossRef]
258. Zhuo, C.; Hou, W.; Hu, L.; Lin, C.; Chen, C.; Lin, X. Genomic Editing of Non-Coding RNA Genes with CRISPR/Cas9 Ushers in a Potential Novel Approach to Study and Treat Schizophrenia. *Front. Mol. Neurosci.* 2017, 10, 28. [CrossRef]

259. Yang, J.; Meng, X.; Pan, J.; Jiang, N.; Zhou, C.; Wu, Z.; Gong, Z. CRISPR/Cas9-mediated noncoding RNA editing in human cancers. *RNA Biol.* 2018, 15, 35–43. [CrossRef]

260. Zhen, S.; Hua, L.; Liu, Y.; Sun, X.; Jiang, M.; Chen, W.; Zhao, L.; Li, X. Inhibition of long non-coding RNA UCA1 by CRISPR/Cas9 attenuated malignant phenotypes of bladder cancer. *Oncotarget* 2017, 8, 9634–9646. [CrossRef]

261. Wolfbeis, O. An overview of nanoparticles commonly used in fluorescent bioimaging. *Chem. Soc. Rev.* 2015, 44, 4743–4768. [CrossRef] [PubMed]

262. Ezzat, K.; Aoki, Y.; Koo, T.; McClorey, G.; Benner, L.; Coenen-Stass, A.; O’Donovan, L.; Lehto, T.; Garcia-Guerra, A.; Nordin, J.; et al. Self-Assembly into Nanoparticles Is Essential for Receptor Mediated Uptake of Therapeutic Antisense Oligonucleotides. *Nano Lett.* 2015, 15, 4364–4373. [CrossRef] [PubMed]

263. Ruivo, C.; Adem, B.; Silva, M.; Melo, S. The Biology of Cancer Exosomes: Insights and New Perspectives. *Cancer Res.* 2017, 77, 6480–6488. [CrossRef] [PubMed]

264. Al-Shaheri, F.; Alhamdani, M.; Bauer, A.; Giese, N.; Büchler, M.; Hackert, T.; Hoheisel, J. Blood biomarkers for differential diagnosis and early detection of pancreatic cancer. *Cancer Treat. Rev.* 2021, 96, 102193. [CrossRef] [PubMed]