



Review

MicroRNA-Regulated Signaling Pathways: Potential Biomarkers for Pancreatic Ductal Adenocarcinoma

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) is the most aggressive and invasive type of pancreatic cancer (PCa) and is expected to be the second most common cause of cancer-associated deaths. The high mortality rate is due to the asymptomatic progression of the clinical features until the advanced stages of the disease and the limited effectiveness of the current therapeutics. Aberrant expression of several microRNAs (miRs/miRNAs) has been related to PDAC progression and thus they could be potential early diagnostic, prognostic, and/or therapeutic predictors for PDAC. miRs are small (18 to 24 nucleotides long) non-coding RNAs, which regulate the expression of key genes by targeting their 3'-untranslated mRNA region. Increased evidence has also suggested that the chemoresistance of PDAC cells is associated with metabolic alterations. Metabolic stress and the dysfunctionality of systems to compensate for the altered metabolic status of PDAC cells is the foundation for cellular damage. Current data have implicated multiple systems as hallmarks of PDAC development, such as glutamine redox imbalance, oxidative stress, and mitochondrial dysfunction. Hence, both the aberrant expression of miRs and dysregulation in metabolism can have unfavorable effects in several biological processes, such as apoptosis, cell proliferation, growth, survival, stress response, angiogenesis, chemoresistance, invasion, and migration. Therefore, due to these dismal statistics, it is crucial to develop beneficial therapeutic strategies based on an improved understanding of the biology of both miRs and metabolic mediators. This review focuses on miR-mediated pathways and therapeutic resistance mechanisms in PDAC and evaluates the impact of metabolic alterations in the progression of PDAC.

Keywords: cancer; microRNAs; cell signaling pathways; metabolic stress



Citation: Mortoglou, M.; Wallace, D.; Buha Djordjevic, A.; Djordjevic, V.; Arisan, E.D.; Uysal-Onganer, P. MicroRNA-Regulated Signaling Pathways: Potential Biomarkers for Pancreatic Ductal Adenocarcinoma. *Stresses* **2021**, *1*, 30–47. <https://doi.org/10.3390/stresses1010004>

Received: 10 February 2021

Accepted: 5 March 2021

Published: 10 March 2021

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is highly lethal and a major cause of cancer-associated deaths in Western countries [1]. The poor prognosis of PDAC is the outcome of late diagnosis of the disease when the tumor is locally advanced or has metastasized [2]. PDAC can be characterized as a “silent killer”, since it has the smallest overall survival rate of all human cancers [3]; the median survival rate does not exceed 5 to 8 months [4]. PDAC prognosis is poor due to enhanced cell proliferation, invasion, and metastatic features in combination with the chemo- and radiotherapy resistance of PDAC cells [5]. Consequently, early-stage diagnostic biomarkers and efficient therapeutic strategies are crucial for minimizing PDAC-related deaths [6].

In recent years, numerous important findings have been discovered in relation to the molecular biology of PDAC in diagnosis, staging, and treatment [7]. However, since

PDAC is a highly metastatic malignancy, only a small portion of PDAC patients have benefited from an improvement in overall survival rates [7,8]. Gemcitabine is the first drug treatment that improved median survival, but only by a few weeks [9]. Another commonly used chemotherapy agent, FOLFIRINOX (5-FU, irinotecan, oxaliplatin, and leucovorin), combined with gemcitabine has been suggested to elevate the median survival rate to 11.1 months, in contrast to 6.8 months with gemcitabine alone [10]. Nevertheless, the limitations of the current therapeutic options for PDAC accentuate the importance of a better understanding of the molecular mechanisms and pathways linked to PDAC. Therefore, through a better understanding of the modified molecular signaling, we would have the ability to diagnose PDAC early in the progression of the disease and develop beneficial therapeutic regimens that could abort the aggressiveness of PDAC [11].

PDAC development originates from pre-cancerous lesions to pancreatic intraepithelial neoplasia (PanIN-I, -II, or -III) to more advanced invasion and metastasis, which is associated both with the activation of several oncogenes and the inactivation of tumor suppressors [12]. The most common genetic alterations linked to PDAC development are mutations in Kirsten rat sarcoma viral homolog (*K-RAS*) and the overexpression of human epidermal growth factor receptor (HER-2/neu) [13]. At later stages (PanIN-III or -IV), the inactivation of tumor suppressor genes (TS), including cyclin-dependent kinase inhibitor 2A (*CDKN2A*), tumor protein 53 (*TP53*) and Sma- and Mad-related protein (SMAD) family number 4 (*SMAD4*) [13,14], has been considered as a key regulator of PDAC pathogenesis [15]. Moreover, previous studies have revealed that 12 main signaling pathways, comprising KRAS signaling, Hedgehog signaling, apoptosis, control of G1/S phase transition and transforming growth factor (TGF- β) signaling, are dysregulated in more than 80% of PDAC patients [16,17]. Modifiable risk factors can significantly increase the risk of PDAC development up to 132-fold [18]. Some of these risks include chronic pancreatitis development, diabetes mellitus, and some infectious diseases [19]. Additionally, environmental exposures can induce PDAC development through various mechanisms, such as the inhalation of cigarette smoke, exposure to mutagenic nitrosamines or chlorinated hydrocarbon solvents, and exposure to toxic metals such as arsenic, nickel, and cadmium [20–26].

miRs are small (18 to 28 nucleotides long), endogenous, non-coding, evolutionary conserved, single-stranded RNA molecules that have been shown to moderate gene expression at the posttranscriptional level through binding to the complementary sequences of their target mRNAs at the 3' untranslated region (UTRs) [27]. Based on the interactions between the 3' untranslated region (3' UTR) and mRNAs, miRs can control the expression levels of several genes and also regulate a number of cell signalling pathways related to tumorigenesis [28]. miRs play a significant role not only in cell growth and development, but also in cell survival and lipid/glucose metabolic pathways in numerous carcinomas and autoimmune diseases [29,30]. Consequently, alterations in the expression of miRs can cause apoptosis, angiogenesis, and metastasis [31]. Specifically, epithelial–mesenchymal transition (EMT) can be considered as a key component of the metastatic cascade, which includes the repression of E-cadherin and the activation of genes related to motility and invasion [32]. miRs can act as oncogenes (oncomiR) or tumor suppressor genes (tsmiR) [33]. Recent studies have suggested a correlation between aberrant expression levels of numerous miRs and PDAC, especially in the initiation, proliferation, and chemoresistance of PDAC [34,35]. miRs can be characterized as vital biomarkers not only for the early prognosis and diagnosis of PDAC, but also for better management of therapeutic specimens [36]. Identifying the most commonly expressed miRs and their related signaling pathways is crucial for a better understanding of PDAC pathophysiology. The aim of this review is to explore the signaling pathways that are associated with PDAC prognosis and metastasis via miR signatures.

2. Signaling Pathways Associated with PDAC

2.1. TGF- β and HGF-MET Signaling Pathways

SMADs have been widely associated with PDAC progression and are involved in several biological processes, such as cell proliferation, differentiation, and apoptosis, in PDAC pathogenesis [37] through the transduction of the TGF- β signaling pathway. The TGF- β pathway is regulated by three principal target genes, including *TGFBR2*, *SMAD3* and *SMAD4*, which are involved in cell growth, differentiation, and cell cycle progression in PDAC [38]. Specifically, TGF- β is one of the most critical EMT-inducing factors in several malignancies, including PDAC [39]. Moreover, SMAD4 mutations are common in the TGF- β pathway [40] and are found in 60% of PDAC cases [16], where it is associated with a higher risk of metastasis and poor prognosis [41,42]. SMAD4 inactivation is present in the late stages of PDAC development, while normal expression of SMAD4 is observed in early PanIN lesions [40]. Specifically, TGF- β moderates EMT, metastasis, extravasation of colonization sites, and escape from immune surveillance in advanced and metastatic PDAC cases [43]. A study by Li et al. stated that the loss of SMAD4 can cause elevated levels of forkhead Box M1 (FOXM1), nuclear localization of β -catenin, and decreased levels of miR-494 [44], which results not only in elevated cell proliferation, migration, and invasion, but also in increased resistance to gemcitabine in PDAC patients [45]. Further miRs that are also linked to SMAD4 expression in PDAC are miR-421 and miR-483-3p [46,47]. The mesenchymal-epithelial transition factor gene (MET) can be activated as a response to hepatocyte growth factor (HGF) [45]. Specifically, Src, MEK-ERK1/2, PI3K-AKT, NK- κ B, mTOR, and STAT are common effector molecules of the HGF-MET signaling cascade [48], and are associated with cell proliferation, migration, and survival [49]. In PDAC, elevated MET expression levels have been observed and linked to tumor-node-metastasis (TNM) stage [49]. Furthermore, increased MET expression levels have also been correlated to epithelial-mesenchymal transition (EMT)-like changes and gemcitabine resistance in PDAC [50]. In particular, miR-26a has been associated with the upregulation of MET in PDAC cancer stem cells [51]. A previous study has revealed that miR-424-5p is overexpressed in PDAC, and that it can also regulate the ERK1/2 signaling pathway through the negative modulation of SOCS6 [52].

2.2. JAK-STAT Signaling Pathway

Previous studies have shown that mutations in the JAK-STAT signaling pathway are closely associated with PDAC progression [45]. Specifically, downregulation of let-7 has been determined in PDAC and has been associated not only with the decreased phosphorylation/activation of *STAT3* and its downstream signaling events, but also with the downregulated growth and migration of PDAC cells [53]. The cytoplasmic expression of suppressor of cytokine signaling 3 (*SOCS3*) can be enhanced by let-7 re-expression, which further leads to the blockage of *STAT3* activation by *JAK2* [53]. Further miRs associated with the JAK-STAT pathway in PDAC are miR-216a, miR-130b, and miR-155 [54]. In particular, miR-216a is downregulated in PDAC and is the direct target of *JAK2* [55]. Additionally, miR-130b is overexpressed in PDAC and binds directly to the 3'-UTR of *STAT3* mRNA [56]. Aberrant expression of this miR is linked to poor prognosis, suppression of cell proliferation, and invasion in PDAC by inhibiting *STAT3* [56]. miR-155 is also closely correlated with the JAK-STAT signaling pathway [54] through the inhibition of *SOCS1*, which further promotes PDAC cell invasion and migration [57].

2.3. PI3K-AKT Signaling Pathway

The PI3K-AKT signaling pathway is associated with cell proliferation and the inhibition of apoptosis in PDAC [58]. Specifically, PI3K-AKT-mTOR signaling, which is suppressed by *PTEN*, can be targeted by miR-21, miR-221, and miR-181a [59–62]. miR-21 inhibits cell cycle arrest, apoptosis, and gemcitabine sensitivity [59], and thus the inhibition of miR-221 can result in the uncontrolled proliferation and migration of PDAC cells [60,63]. miR-181a also prompts the migration of PDAC cells [61]. Controversially, miR-375 and

miR-220c are also linked to the PI3K–AKT signaling pathway in PDAC [54]. *PDK1* encodes a kinase downstream of PI3K and is the direct target of miR-375 [64]. Moreover, the upregulation of miR-200c is also linked to both EMT [65] and *MUC4* expression in PDAC [66]. Specifically, *MUC4* expression results not only in the stabilization of HER2, but also in the activation of AKT, which further leads to the activation of N-cadherin [67,68].

2.4. TP53 Signaling Pathway and Apoptosis

The loss of *TP53* is detected in more than 70% of PDAC patients, particularly in advanced cases, with the most common mutations being missense point mutations [40,69]. The inactivation of p53 has consequences for PDAC heterogeneity and chemoresistance [70] and results in the dysregulation of several biological processes, such as cell proliferation, migration, invasion, and apoptosis [71]. Some examples of miRs that can target p53 are miR-222 and miR-203 [72]. Previous studies have shown that *TP53* directly regulates miR-34, which in turn targets NOTCH (which is responsible for the maintenance and survival of PDAC cells) [71]. Moreover, it has been shown that miR-155 downregulates the TP53-induced nuclear protein 1 gene, which promotes PDAC progression [73]. Dysregulation of apoptosis is a common cause of chemoresistance in PDAC and can be caused by several stimulatory and inhibitory factors that are associated with a high number of miRs [74]. For example, oncogenic miR-21 is observed in several cancer types and controls genes that are necessary for apoptosis [75]. Additionally, miR-23a can target *APAF1*, which results in the activation of caspase-9 and prompts apoptosis in several cancer types, including PDAC [76]. Furthermore, in PDAC, a decrease in the expression levels of *BIM* has been observed through the modulation of miR-24, which inhibits apoptosis and the cell cycle [76].

2.5. KRAS Signaling Pathway

K-RAS mutations have been reported not only in more than 90% of PDAC patients, but also in colorectal cancer, lung adenocarcinomas, and urogenital cancers [77,78]. In recent years, numerous miRs have been found to be key regulators of the KRAS signaling pathway in PDAC. Specifically, miR-217 acts as a tumor suppressor in PDAC, which directly targets the *KRAS* oncogene [79]. miR-217 causes a decrease in the constitutive phosphorylation of the downstream signal transducer *AKT* [79]. A study by Yu et al. also suggested that miR-96 not only targets *KRAS*, but also negatively modulates the phosphorylated *AKT* signaling pathway downstream of *KRAS* [80]. Further studies have also observed that miR-126 and let-7d target *KRAS* via post-transcriptional upregulation [81]. Moreover, the miR-21 promoter can be stimulated by activated *KRAS* (G12D) in PDAC cells [82], which has been linked to poor prognosis in PDAC [16]. miR-206 acts as a tumor suppressor in PDAC and was found to inhibit both the *KRAS* and *ANXA2* oncogenes [83]. Hence, miR-206 can be a negative regulator of oncogenic *KRAS*-induced NF- κ B transcriptional activity, which leads to reduced proangiogenic and proinflammatory factors that further result in tumor growth and poor prognosis [84]. miR-27a has been found to be overexpressed in PDAC and has been linked to reduced cell growth and migration [54]. Specifically, miR-27a is the direct target of *Sprouty2*, which controls *KRAS* expression [85]. The overexpression of miR-143/145 is repressed by activated *KRAS*, which promotes the growth of PDAC cells [86]. Additionally, activated *KRAS* can stimulate downstream signaling components, including MAP2K1/MEK and MAPK1/ERK2 [15,87,88]. Collisson et al. have shown that the MAPK signaling pathway is involved in the genesis of PanIN, especially in the early stages of PDAC development [89]. Therefore, further understanding of the oncogenic role of *KRAS* in PDAC could lead to novel strategies for earlier diagnosis and a more effective targeted therapy for this malignancy.

2.6. Epidermal Growth Factor Receptor and HER2/neu Signaling Pathways

The epidermal growth factor receptor (EGFR) family is a group of cytoplasmic receptor tyrosine kinases that contains the human EGF receptor or Her1 (*EGFR* or *ErbB-1*), Her2 (*EGFR2* or *ErbB-2*), Her3 (*EGFR3* or *ErbB-3*), and Her4 (*EGFR4* or *ErbB-4*) [40]. Specifically,

ErbB-2 is commonly upregulated in PDAC, particularly in PanIN lesions and carcinoma in situ lesions [40] and has been linked with invasion [40]. Moreover, two common ligands of EGFR, EGF and TGF- α , are significantly upregulated in PDAC tissues [40]. In particular, TGF- α can activate Notch signaling downstream of EGFR signaling [90]. Similarly, *ErbB-3* has been also found to be overexpressed in PDAC patients with advanced tumor stages and limited survival time [91]. Hence, it has been suggested that targeting EGFR could be an effective therapeutic strategy in PDAC patients [40]. Subsequently, *ErbB-1* has been linked to both aggressiveness and unfavorable prognosis in PDAC cases [92]. Furthermore, EGFR upregulation is observed in more than 95% of PDAC cases and is closely associated with the aberrant expression of numerous miRs in PDAC [93]. A study by Du Rieu et al. indicated that EGFR could promote the overexpression of miR-21 in PDAC cells [94]. A further study by Ali et al. showed a correlation between miR-146a and the upregulation of EGFR in PDAC cells [93]. Another study also demonstrated that miR-200c can directly target the expression levels of mitogen-inducible gene 6 (*MIG6*), which is a negative modulator of EGFR [95]. The HER2/neu signaling pathway plays a key role in PDAC prognosis [96], as 4–50% of PDAC cases show HER2 upregulation [97]. Recent studies have suggested a correlation between miR-150 and the HER2/neu signaling pathway [45]; in particular, miR-150 is upregulated in PDAC and results in a considerable reduction in the expression levels of its target gene, *MUC4* [45].

2.7. Notch and Hedgehog Signaling Pathways

The Notch signaling pathway, which is crucial for tissue proliferation, the development of organs, cell differentiation, and apoptosis, has been linked with poor prognosis in PDAC [73,98]. The oncogenic role of Notch homolog 1 (*Notch*) activation contributes to stem cell self-renewal, cell proliferation, apoptosis, migration, invasion, metastasis, and angiogenesis [99]. Blocking of the Notch signaling pathway is related to the attenuation of NF- κ B activity and upregulation of p21 and p27 [100]. Elevated expression of Notch pathway genes is present in early PanIN lesions [90]. It has been demonstrated that several miRs are associated with the Notch pathway in PDAC [83]. Specifically, miR-34 can be directly regulated by *TP53*, which further leads to the downstream signaling of Notch targets [83]. Moreover, Notch-1/2 can be downregulated through the restoration of miR-34 expression in PDAC cancer stem cells (CSCs) [101]. Furthermore, treatment of PDAC stem cells with chromatin-modulating agents can also lead to the suppression of miR-34 targets such as *Bcl-2*, *CDK6*, and *SIRT1* [71]. A further study by Brabletz and colleagues suggested that miR-200 can inhibit Notch pathway components such as *Jagged1* and the mastermind-like coactivators *Maml2* and *Maml3*, which further prompt the enhancement of Notch activation through EMT and *ZEB1* [102]. Other studies have also remarked that the upregulation of miR-145 and downregulation of let-7a and miR-200 causes not only a decrease in the expression of EMT-related transcription factors, but also the inhibition of Notch1 via miR-144 [103]. The Hedgehog signaling pathway (HH) acts as a regulator of embryonic development but is also responsible for the moderation of CSCs [104]. Specifically, several cases with deregulations in HH signaling have been observed in PDAC [105]. Previous studies have shown that the activity of this pathway is upregulated in PanIN lesions, which suggests that HH could be a regulator of the early and late stages of PDAC pathogenesis [105]. The HH pathway also plays a crucial role in cell cycle progression and apoptosis in PDAC [40]. Hence, the inhibition of several HH pathway components could be a novel therapeutic strategy for PDAC [40]. A study by Dosch et al. has demonstrated that Hedgehog, which is a secreted ligand, can bind to its receptor, Patched1 (*PTCA1*) [106]. In PDAC, *PTCA1* can be downregulated by miR-212, which is overexpressed in this malignancy. This could lead to unfavorable effects on cell growth, migration, and invasion via the HH pathway [107].

2.8. Wnt/ β -Catenin Signaling Pathway

The WNT/ β -catenin signaling pathway plays a crucial role in several biological and cellular processes, such as proliferation, differentiation, invasion, and migration, while it can also affect the PDAC tumor cell compartment [54]. miR-29c, which is downregulated in PDAC, can be suppressed by TGF- β but can also moderate the regulators upstream of WNT, including *FZD4*, *FZD5*, *FRAT2*, and *LRP-6* [108]. Similarly, miR-29a expression levels are associated with both the resistance of PDAC cells to gemcitabine and with the activation of the Wnt/ β -catenin signaling pathway [109]. Moreover, this pathway can be activated when the cell membrane of the WNT receptor is bound to its ligands, which leads to the release of β -catenin into the cytoplasm [40]. The elevated expression of β -catenin is observed in most PDAC cases [110], especially in the later stages of PanIN lesion development [111].

2.9. Cell Cycle Signaling Pathway and p16/CDKN2A Inactivation

The cell cycle is controlled by the activity of Cdk/cyclins, which regulate several mechanisms in normal cells [112]. The overexpression of cyclin D1 and downregulation of p16 have been found in several PDAC cases [113]. Recent studies have shown that a high number of miRs are associated with dysregulations in cell cycle signaling [54]. Specifically, cyclin D1-dependent kinase can be targeted by miR-107 to initiate cell cycle progression [112], whereas, in PDAC, miR-107 can be silenced through the methylation of CpG islands in its 5' promoter region [114]. A study by Zhao et al. has shown that miR-192 results in the promotion of cell proliferation, and it can also moderate cycle progression via the G1 to S-phase transition in PDAC cells [115]. This study revealed that the overexpression of miR-192 led to an elevated expression of cyclin D1, cyclin D2, *CDK4*, and *CDC2* [115]. Further research denoted that miR-301a is responsible for the promotion of PDAC cell proliferation through the inhibition of the *Bim* gene [116], which acts as an initiator of apoptosis through the generation of multidomain pro-apoptotic proteins, including *Bak* and *Bax* [117]. Additionally, miR-193b can deregulate the action of the KRAS pathway in PDAC [83]. miR-193b acts as a cell cycle brake in PDAC, which induces G1-phase arrest and reduces the fraction of cells in the S phase [118]. miR-223 can indirectly target cyclin E2, which further inhibits *FBXW7* [11,119]. Moreover, cyclin E2 can be also targeted by p27 and p57, which negatively regulate G1/S progression via miR-222 [59,120]. Conclusively, a previous study has also indicated that miR-148a can target *CDC25B*, which controls the activation of distinct CDK/cyclin complexes [121]. This can lead to the inhibition of PDAC cell phenotype [122]. The *p16-Ink4A* locus is encoded by the *CDKN2A* tumor suppressor gene [123] and alterations in the expression levels of *Ink4A* have been found in 95% of PDAC cases [124]. Loss of p16 is linked to early PanIN lesions through invasive carcinomas [125]. *P16* is a well-described cyclin-dependent kinase inhibitor which binds to *CDK4* and *CDK6* [126]; it is the product of the *CDKN2A* gene and is connected to PDAC [127]. p16 is involved in the inhibition of the activity of phosphorylated retinoblastoma (*pRb*), which is responsible for G1/S transition [126]. Moreover, specific miRs such as miR-222 can directly target p27 and p57, which are essential cell cycle inhibitors [128]. A further study has also denoted that dysregulated expression levels of both miR-132 and miR-212 can cause G2/M cell cycle arrest and decreased cell proliferation in PDAC [129]. Nevertheless, these mechanisms have not been fully understood in PDAC and therefore the examination of these pathway regulators in PDAC is vital [130].

2.10. Transcription Factors and DNA Methylation

Transcription factors can affect the downstream gene transcription of signal transduction pathways which are targeted not only by genetic alterations, but also through epigenetic alterations, which lead to the aggressiveness of PDAC [131]. Specifically, both DNA methylation and histone tail alterations are associated with epigenetic modulation through chromatin remodeling [132]. Controversially, forkhead members of the class O (FOXO) transcription factors have been characterized as tumor suppressors in numerous biological processes, such as stress resistance, metabolism, cell cycle, apoptosis, oxidative

stress, [133] and DNA repair [134]. miR-21 can target FOXO1, which promotes PDAC growth in vivo [135]. Similarly, FOXO3a can be targeted by miR-155 in PDAC, which further leads to cell proliferation and metastasis through the generation of reactive oxygen species [136]. The FOXM1 transcription factor can be overexpressed through the regulation of miR-200b expression in PDAC [137]. In addition, *NF-κB* is closely related to several cellular processes and its expression is attributed to the aggressiveness of PDAC [138]. *NF-κB* can be downregulated upon the upregulation of miR-146a in PDAC [139]; *NF-κB* activity can be also increased via miR-301a in PDAC, which results in increased tumor growth [140]. Previous studies have also revealed that DNA methylation plays a crucial role during PDAC development [141]. Specifically, DNA methyltransferase 1 (*DNMT1*) is commonly upregulated in several cancer types [142], including PDAC, and can be targeted both by miR-148b and miR-152 [143]. Moreover, in PDAC, miR-141 can directly target Yes-associated protein 1 (*YAP1*), which is a main downstream effector of the protein kinase Hpo (HIPPO) pathway. The HIPPO pathway controls tissue homeostasis, organ size, regeneration, and tumorigenesis [144]. miR-217 can directly target sirtuin 1 (*SIRT1*), which is an NAD-dependent deacetylase that regulates cell proliferation, differentiation, apoptosis, metabolism, DNA damage, stress responses, genome stability, and cell survival [145]. Upregulated *SIRT1* can also generate EMT in PDAC patients [146] (Table 1, Figure 1).

Table 1. MicroRNAs (miRs) and their expression levels and functions in pancreatic ductal adenocarcinoma (PDAC).

miRs	Regulation in PDAC	Signaling Pathways Involved	Target Genes	Functional Involvement in PDAC	References
let-7	Down	JAK-STAT K-RAS	STAT3, SOCS3, N-cadherin, ZEB1	Tumor growth, migration	[53]
let-7a	Up	NOTCH	JAK, STAT	EMT	[103]
let-7d	Up	K-RAS	KRAS	Cell proliferation, migration, invasion, apoptosis	[81]
miR-21	Up	PI3K-AKT K-RAS EGFR Cell cycle Apoptosis	G12D, p27, p57, FOXO1, Bcl-2, FasL, PI3K, AKT, PTEN, RECK, SPRY2	Cell cycle arrest, apoptosis, gemcitabine resistance, aggressiveness	[59,82,94]
miR-23a	Up	Apoptosis	APAF1	Apoptosis	[76]
miR-24	Up	Apoptosis	BIM	Apoptosis, cell cycle	[76]
miR-26a-5p	Down	HGF-MET	ARMTL2, Cyclin E2, MMP12	Cell proliferation, migration, survival, EMT	[51]
miR-27a	Up	K-RAS	Sprouty2	Cell proliferation, migration, invasion, apoptosis	[85]
miR-29a	Up	Wnt	MUC1	Cell proliferation, differentiation, invasion, migration, gemcitabine resistance	[109]
miR-29c	Down	Wnt	ZD4, FZD5, FRAT2, LRP-6	Cell proliferation, differentiation, invasion, migration	[108]
miR-34a	Down	TP53 NOTCH	NOTCH1/2CDK6, SIRT1	Cell proliferation, migration, invasion, apoptosis	[71,83]
miR-96b	Down	K-RAS	KRAS, AKT	Cell proliferation, migration, invasion, apoptosis	[80]

Table 1. Cont.

miRs	Regulation in PDAC	Signaling Pathways Involved	Target Genes	Functional Involvement in PDAC	References
miR-107	Up	Cell cycle	Cyclin D1-dependent kinase	Cell proliferation	[114]
miR-126	Down	K-RAS	KRAS	Cell proliferation, migration, invasion, apoptosis	[81]
miR-130b	Down	JAK-STAT	STAT3	Cell proliferation, invasion	[54,56]
miR-132	Up	P16	Rb1	G2/M cell cycle arrest, cell proliferation	[129]
miR-141	Down	DNA methylation	YAP1, MAP4K4	Tissue homeostasis, organ size, regeneration	[144]
miR-143	Down	K-RAS	KRAS, MMP-2, MMP1	Tumor growth	[86]
miR-144	Down	NOTCH	PRR11	EMT	[103]
miR-145	Down	K-RAS NOTCH	KRAS	Tumor growth, EMT	[86,103]
miR-146a	Down	EGFR	EGFR, NF-κB, IRAK-1	Increased tumor growth	[93]
miR-148a	Down	Cell cycle	CDC25B	Cell proliferation, differentiation, invasion, migration	[121]
miR-148b	Down	DNA methylation	DNMT1, AMPKa1	Cell proliferation, differentiation, invasion, migration	[143]
miR-150	Up	HER-2/neu	MUC4, IGF-1R	Invasion, migration	[45]
miR-152	Down	DNA methylation	DNMT1	Cell proliferation, differentiation, invasion, migration	[143]
miR-155	Up	JAK-STAT Tp53	SOCS1 TP53-induced nuclear protein 1 gene, FOXO3a, RHOA, SMAD1/5, ZNF652	Cell invasion, migration, metastasis, generation of reactive oxygen species	[54,57,73]
miR-181a	Up	PI3K-AKT	PTEN	Migration	[61]
miR-192	Up	Cell Cycle	Cyclin D1, cyclin D2, CDK4	Cell proliferation	[115]
miR-193b	Down	Cell Cycle	KRAS	G1-phase arrest	[118]
miR-200	Up	NOTCH	Jagged1, Maml2, Maml3	EMT	[102]
miR-200c	Down	EGFR	MIG6, EP300	Invasion, migration	[95]
miR-203	Up	TP53	p53	Cell proliferation, migration, invasion, apoptosis	[72]
miR-206	Down	K-RAS	KRAS, ANXA2	Decrease in proangiogenic and proinflammatory mediators, tumor growth, progression	[83,84]

Table 1. Cont.

miRs	Regulation in PDAC	Signaling Pathways Involved	Target Genes	Functional Involvement in PDAC	References
miR-212	Up	P16 Hedgehog	Rb1	G2/M cell cycle arrest, cell proliferation	[107,129]
miR-216a	Down	JAK-STAT	JAK2	Cell proliferation, invasion	[54,55]
miR-217	Down	K-RAS, DNA methylation	KRAS, SIRT1	Cell proliferation, migration, invasion, apoptosis, metabolism, DNA damage, stress responses, genome stability, cell survival	[79,145]
miR-220c	Up	PI3K-AKT	MUC4	EMT	[54]
miR-221	Up	PI3K-AKT	Cdk4, p16, E2F, CDKN1B, MMP-2, MMP-9, PUMA, PTEN, MDM2, ICAM-1, P27, BIM, SOD2, STAT5A	Proliferation, migration	[60]
miR-222	Up	TP53 P16 Cell cycle	p53, p27, p57, MMP2, MMP9, PUMA, PTEN, BIM, MMP1, SOD2, STAT5	Cell proliferation, migration, invasion, apoptosis	[72,120,128]
miR-223	Up	Cell Cycle	FBXW7, Cyclin E2	Cell proliferation, differentiation, invasion, migration	[11,119]
miR-301a	Up	Cell Cycle	Bim, Bak, Bax, NF-κB	Cell proliferation	[116]
miR-375	Down	PI3K-AKT	PDK1	Cell proliferation, invasion, migration	[54,64]
miR-421	Up	TGF-β	SMAD4	Cell proliferation, migration, invasion	[46]
miR-424-5p	Up	HGF-MET	SOCS6	Cell proliferation, migration, survival, EMT	[52]
miR-483-3p	Up	TGF-β	SMAD4	Cell proliferation, migration, invasion	[47]
miR-494	Down	TGF-β	FOXM1	Cell proliferation, migration, invasion, increased resistance to gemcitabine	[44]

JAK: Janus Kinase; STAT: Signal Transducer And Activator Of Transcription 3; ZEB: Zinc Finger E-Box Binding Homeobox 1; PI3K: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase; AKT: AKT Serine/Threonine Kinase; BCL2: Apoptosis Regulator; FasL: Fas Ligand; PTEN: Phosphatase and Tensin Homolog; RECK: Reversion-inducing-cysteine-rich protein with kazal motifs; SPRY2: Sprouty homolog 2; APAF1: Apoptotic Peptidase Activating Factor 1; ARMTL2: Aryl Hydrocarbon Receptor Nuclear Translocator Like; MMP12: Matrix Metalloproteinase 12; FZD5: Frizzled Class Receptor 5; FRAT2: FRAT Regulator Of WNT Signaling Pathway 2; LRP-6: LDL Receptor Related Protein 6; Rb1: RB Transcriptional Corepressor 1; MAP4K4: Mitogen-Activated Protein Kinase Kinase Kinase Kinase 4; PRR11: Proline Rich 11; NF-κB: nuclear factor-kappa B; IRAK-1: Interleukin 1 Receptor Associated Kinase 1; CDC25B: Cell Division Cycle 25B; DNMT1 DNA Methyltransferase 1; RHOA: Ras Homolog Family Member A; ZNF652: Zinc Finger Protein 652; MAML2/3: Mastermind Like Transcriptional Coactivator 2/3; MIG6: Mitogen-inducible gene 6; EP300: E1A Binding Protein P300; ANXA2: Annexin A2; E2F1: E2F Transcription Factor 1; PUMA: p53 upregulated modulator of apoptosis; SOD2: Superoxide Dismutase 2; FBXW7: F-Box And WD Repeat Domain Containing 7; PDK1: Pyruvate Dehydrogenase Kinase 1.

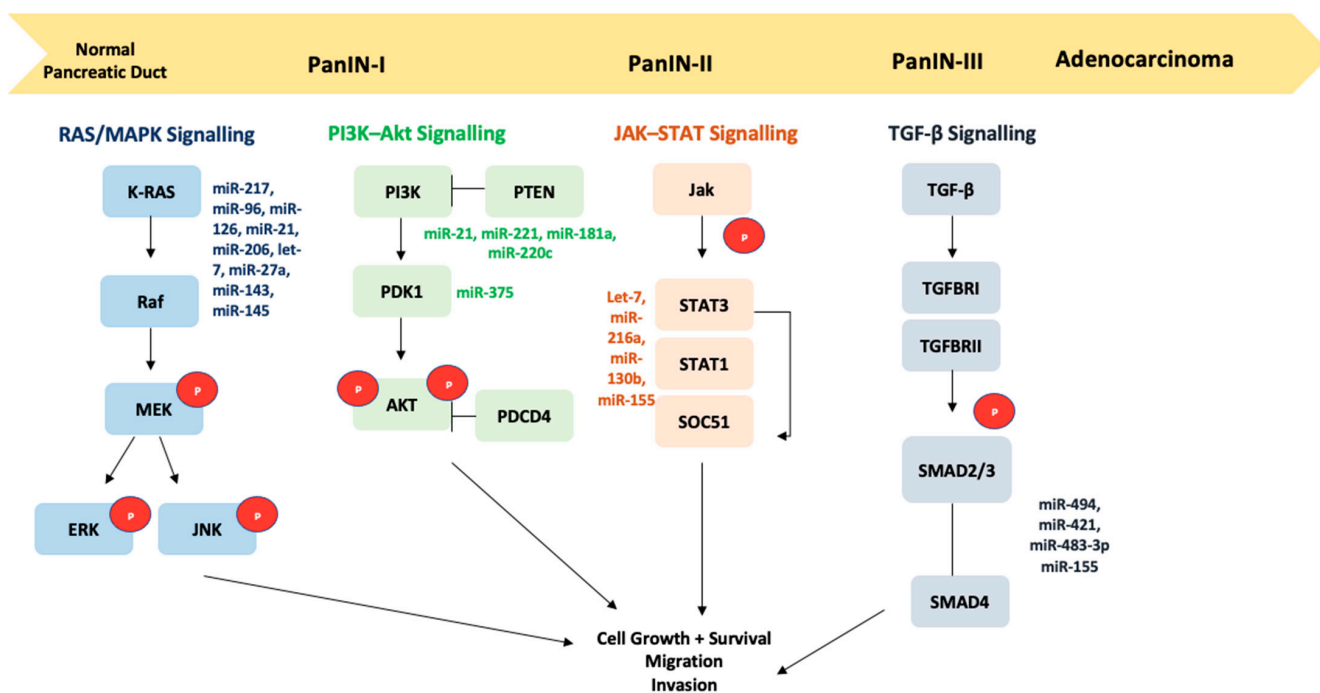


Figure 1. Mechanistic role of miRs in PDAC prognosis. miRs are involved in the main signaling pathways in PDAC. PDCD4: Programmed Cell Death 4.

3. Involvement of Metabolic Stress in PDAC

Reprogramming of the cellular metabolic system occurs to accommodate the changes in cellular energy requirements needed during tumorigenesis. Glutamine is pivotal in regulating energy utilization [147–149]. Modifications that increase glutamine metabolism will attenuate the severity of PDAC. Increased expression and activity of 4-hydroxyphenylpyruvate dioxygenase-like protein (HPDL) promotes tumor formation, whereas reductions in HPDL expression inhibit cell growth [147]. Increased glutamine metabolism also protects cells from elevated oxidative stress. Numerous reports have discussed the potential for metabolic stress leading to increased oxidative stress [147,149–153]. Transcription factor EB (TFEB) has attracted a lot of interest recently for its ability to regulate PDAC growth. Elevated TFEB in PDAC has been shown to suppress both glutamine and mitochondrial metabolism [152]. Suppression of glutamine metabolism will lead to nutrient deprivation-related stress in the cells, increasing oxidative stress and the expression of epidermal growth factor (EGFR) [154]. Glutamine is not only integral to cellular metabolism, but also to metastasis. Reductions in glutamine promote the transition from epithelial to mesenchymal cells in PDAC, which is regulated by *Slug* [155]. The E3 ubiquitin ligase, neural precursor cell-expressed developmentally downregulated gene 4-like (*NEDD4L*), has been shown to reduce mitochondrial metabolism and is negatively correlated with glutamine transporter (ASCT2) expression [154].

The modification of cellular energy metabolism by miRs has been shown for a few select miRs. The involvement of miR-1291 has been shown to reduce cell growth and metastasis, and that there can be an interaction between miR-1291, carnitine palmitoyltransferase, and estrogen receptor α [156]. The involvement of carnitine palmitoyltransferase 1C (*CPT1C*) in the mitochondrial β -oxidation of fatty acids is important for cell survival. Low activity of *CPT1C* results in a negative cellular outcome with increased metabolic and oxidative stress, decreased cell growth, and dysregulated mitochondria [157]. Increasing the expression and activity of *CPT1C* reverses the negative cellular effects.

miR-143 is reported to be differentially expressed in patients following the ketogenic diet and has been identified as a metabolism-related biomarker [158]. miR-143 is downregulated in PDAC and associated with cytokine signaling pathways, nutrient metabolism,

oxidative phosphorylation, and insulin signaling pathways to maintain metabolic homeostasis [86,158]. Additional work is needed to further establish connections between miRs and the metabolic stress process that occurs during tumorigenesis.

4. Angiogenesis and miRs in PDAC

Several previous studies have shown that numerous miRs are correlated to PDAC angiogenesis. Specifically, miR-34 is considerably downregulated in PDAC, while its upregulation can affect various biological processes, including angiogenesis, as well as apoptosis, cell cycle progression, and metastatic potential [101,159]. Guo et al. suggested that the upregulation of the tumor suppressor miR-410 could cause the inhibition of angiogenesis in PDAC [160]. It has also been stated that the inhibition of both miR-21 and miR-210 has been linked to the targeting of migration and invasion of PDAC cells and the suppression of angiogenesis [161]. A further study by Khan et al. reported that hypoxia-related angiogenic miRs, including miR-21, miR-200c, and miR-199, are commonly aberrantly expressed in PDAC [162]. In particular, hypoxia can promote PDAC cell migration, invasion, and angiogenesis in vitro through the induction of miR-21 [163]. Conclusively, miR-221/222 play a crucial role in the migration, invasion, angiogenic potential, and tumorigenicity of PDAC [164].

5. Conclusions

Understanding the relationship between the function and mechanism of miRs in PDAC is important as miRs have the potential to be used as novel biomarkers for the early diagnosis, prognosis, and therapeutic response in PDAC. miR-mediated altered metabolic mediators may play a crucial role in PDAC development through the dysregulation of several cellular functions, including proliferation, apoptosis, metastasis, and chemoresistance. The examination of these molecules can lead to a better understanding of the underlying molecular mechanisms that are responsible for the pathogenesis of PDAC. The clarification of the regulatory role of different miRs may elucidate a functional role in the therapy or diagnosis of PDACs. This review summarized the involvement of miR-mediated metabolic mediators and their affected regulatory pathways through modulating different genes that are responsible for PDAC progression. Further clinical studies are needed to identify the complex mechanisms and associations of miRs in PDAC.

Author Contributions: Writing—original draft preparation, M.M. and P.U.-O.; writing—review and editing, M.M., D.W., A.B.D., V.D., E.D.A. and P.U.-O. All authors have read and agreed to the published version of the manuscript.

Funding: M.M. is supported by University of Westminster SLS PhD Studentship.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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