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Review article

MicroRNAs as the critical regulators of epithelial mesenchymal transition in pancreatic tumor cells

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ABSTRACT

Pancreatic cancer (PC), as one of the main endocrine and digestive systems malignancies has the highest cancer related mortality in the world. Lack of the evident clinical symptoms and appropriate diagnostic markers in the early stages of tumor progression are the main reasons of the high mortality rate among PC patients. Therefore, it is necessary to investigate the molecular pathways involved in the PC progression, in order to introduce novel early diagnostic methods. Epithelial mesenchymal transition (EMT) is a critical cellular process associated with pancreatic tumor cells invasion and distant metastasis. MicroRNAs (miRNAs) are also important regulators of EMT process. In the present review, we discussed the role of miRNAs in regulation of EMT process during PC progression. It has been reported that the miRNAs mainly regulate the EMT process in pancreatic tumor cells through the regulation of EMT-specific transcription factors and several signaling pathways such as WNT, NOTCH, TGF-β, JAK/STAT, and PI3K/AKT. Considering the high stability of miRNAs in body fluids and their role in regulation of EMT process, they can be introduced as the non-invasive diagnostic markers in the early stages of malignant pancreatic tumors. This review paves the way to introduce a non-invasive EMT based panel marker for the early tumor detection among PC patients.

1. Introduction

Pancreatic cancer (PC) ranks as the 4th leading cause of cancer related mortality in the Unites States [1], and its prevalence is expected to rise to the second rank by 2030 [2]. It has a high risk of invasion and metastasis in which around 80 % of patients have tumor metastasis at the time of diagnosis [3–5]. About 95 % of PC tumors are adenocarcinoma that originate from the exocrine pancreas [6]. Despite significant advancements in therapeutic modalities, there is still a low 5-year survival rate (15 %) among PC patients [7,8]. Surgery is the primary treatment approach for pancreatic cancer. However, it is only appropriate for 10–15 % of patients, while 80–85 % of PC patients have metastatic or unresectable tumors [9]. It has been reported that the patients with successful treatment have a five-year survival rate of about 20 % [10]. Because of the lack of evident clinical symptoms and efficient diagnostic

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Table 1
Role of miRNAs in EMT regulation in pancreatic tumor cells.

STUDY	YEAR	GENE	TARGET	SAMPLES	FUNCTION	APPLICATION
an [32]	2020	miR-203a-3p	SLUG	PANC-1, AsPC-1, Capan-1 and SW 1990 cell lines	Inhibited EMT process	Diagnosis
liang [33]	2022	miR-30e-5p	SNAI1	30 patients HCCLM3, MHCC97L, MHCC97H, and Huh7 cell lines	Inhibited EMT process	Diagnosis and Prognosis
zhang [34]	2018	miR-204	ZEB1	63 patients Capan-2, ASPC-1, SW-1990, and Panc-1 cell lines	Inhibited EMT process	Diagnosis
zheng [35]	2022	miR-128- 3p	ZEB1	AsPC-1, BxPC-3, CFPAC-1, and PANC-1 cell lines	Inhibited EMT process	Diagnosis
liu [36]	2016	miR-1271	ZEB1 TWIST1	58 patients SW1990, Bxpc-3, PANC-1 and ASPC-1 cell lines	Inhibited EMT process	Diagnosis and Prognosis
fu [37]	2021	miR-506-3p	ZEB2	SW1990 and PANC-1 cell lines	Inhibited EMT process	Diagnosis
gao [38]	2017	miR-145	MMP3	BxPC-3, AsPC-1 and PANC-1 cell lines	Inhibited EMT process	Diagnosis
zhang [39]	2021	miR-1251	SOX4	50 patients AsPC-1, PANC-1, SW-1990 and PaCa-2 cell lines	Induced EMT process	Diagnosis and Prognosis
lu [40]	2017	miR-142	HIF-1α	42 patients PANC-1, SW1990, Hup, and CFPAC-1 cell lines	Inhibited EMT process	Diagnosis
xue [41]	2020	miR-539	SP1	56 patients CAPAN-2, BxPC3, CFPAC1, SW1990 and PANC1 cell lines	Inhibited EMT process	Diagnosis
zhao [42]	2021	miR-9	c-MYC	53 patients Canpan-2 cell line	Inhibited EMT process	Diagnosis and Prognosis
mody [43]	2017	miR-202	TGFBR1 TGFBR2	PAN 02 cell line	Inhibited EMT process	Diagnosis
zhou [44]	2018	miR-665	TGFBR1TGFBR2	35 patients SW1990, BxPC-3, PANC-1, AsPC-1, and CFPAC-1 cell lines	Inhibited EMT process	Diagnosis
hiramoto [45]	2017	miR-509-5p miR-1243	Snail ZEB1	50 patients Panc1 and KMP3 cell lines	Inhibited EMT process	Diagnosis and Prognosis
zhang [46]	2015	miR-15b	SMURF2	19 patients HPAC, BxPC-3, Colo357, L3.6 pl, ASPC-1, Panc-1 and MiaPaCa-2 cell lines	Induced EMT process	Diagnosis
ma [47]	2019	miR-141	NRP-1	57 patients BxPC-3, AsPC-1, PANC-1, MIA-PaCa-2, Capan-1 and SUIT-2 cell lines	Inhibited EMT process	Diagnosis
zhang [48]	2022	miR-1301-3p	RhoA	72 patients SW1990, AsPC-1, CFPAC-1, PANC-1, Patu-8988, and HPDE6-C7 cell lines	Inhibited EMT process	Diagnosis and Prognosis
kang [49]	2020	miR-181a	RKIP	56 patients PANC-1 cell line	Induced EMT process	Diagnosis
hu [50]	2018	miR-361-3p	DUSP2	65 patients BxPC-3, PANC-1, CFPAC-1 and SW1990 cell lines	Induced EMT process	Diagnosis and Prognosis
sun [51]	2015	miR-29a	TTP	30 patients Panc-1 and BXPC3 cell lines	Induced EMT process	Diagnosis
wu [52]	2020	miR-429	FOXD1	110 patients PANC-1, BxPC-3, AsPC-1 and CFPAC-1 cell lines	Inhibited EMT process	Diagnosis and Prognosis
sun [53]	2021	miR-338-5p	EGFR	84 patients AsPC-1, BxPC-3, PANC-1, MIA PaCa-2, Capan-2 and SW1990 cell lines	Inhibited EMT process	Diagnosis and Prognosis
wan [54]	2020	miR-382	Anxa3	115 patients CFPAC-1, BxPC-3, PANC-1, and SW1990 cell lines	Inhibited EMT process	Diagnosis
xu [55]	2020	miR-141	TM4SF1	90 patients SW1990, PANC-1, BxPC-3, and CFPAC-1 cell lines	Inhibited EMT process	Diagnosis and Prognosis
shen [56]	2021	miR-671	S100P	40 patients AsPC-1, BxPC-3, SW-1990 and PaCa-2 cell lines	Inhibited EMT process	Diagnosis and Prognosis
zhao [57]	2021	miR-374b-5p	KDM5B	78 patients PANC-1, AsPC-1, MIA PaCa-2, and SW1990 cell lines	Inhibited EMT process	Diagnosis and Prognosis
tang [58]	2017	miR-34a	Snail1 Notch1	PANC-1 and SW-1990 cell lines	Inhibited EMT process	Diagnosis
kong [59]	2020	miR-1224-5p	ELF3	20 patients AsPC-1, Capan-2, PANC-1, and SW1990 cell lines	Induced EMT process	Diagnosis and Prognosis
peng [60]	2017	miR-148a	Wnt10b	33 patients BxPC-3, AsPC-1 and Mia PaCa-2 cell lines	Inhibited EMT process	Diagnosis and Prognosis

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Table 1 (*continued*)

STUDY	YEAR	GENE	TARGET	SAMPLES	FUNCTION	APPLICATION
chen [61]	2018	miR-331-3p	ST7L	17 patients PANC-1, MIAPaCa-2, AsPC-1, BxPC-3, and SW1990 cell lines	Induced EMT process	Diagnosis
zhan [62]	2020	miR-455-3p	TAZ	PANC-1 and MIAPaCa-2 cell lines	Inhibited EMT process	Diagnosis
zhang [63]	2020	miR-382-3p	STAT1 PD-L1	90 patients CEPAC, AsPC-1, PANC-1, BxPC-3, Capan-2, and MIAPaCa-2 cell lines	Inhibited EMT process	Diagnosis and Prognosis
wang [64]	2020	miR-675-3p	SOCS5	CAPAN-1 and PANC-1 cell lines	Inhibited EMT process	Diagnosis
liu [65]	2018	miR-221	SOCS3	60 patients PANC-1, AsPC-1, Capan-2, SW1990, and BXPC-3 cell lines	Inhibited EMT process	Diagnosis and Prognosis
zhao [66]	2017	miR-382	EZH2	34 patients PANC-1, AsPC-1, PATU 8988, BxPC-3 and SW 1990 cell lines	Inhibited EMT process	Diagnosis and Prognosis
guo [67]	2014	miR-15a	Bmi-1	188 patients PANC-1 cell line	Inhibited EMT process	Diagnosis
yang [68]	2018	miR-494	SDC1	42 patients ASPC-1, SW1990, BXPC-3, CFPAC-1 and PANC-1 cell lines	Inhibited EMT process	Diagnosis
ma [69]	2021	miR-20a-3p	COL11A1	170 patients BXPC-3, CFPAC-1, MIA PACA-2, PANC-1, and SW1990 cell lines	Inhibited EMT process	Diagnosis and Prognosis
wu [70]	2017	miR-23a	ESRP1	52 patients Aspc-1, Bxpc-3, Cfpac-1, and Panc-1 cell lines	Induced EMT process	Diagnosis and Prognosis
yu [71]	2021	miR-1206	ESRP1	40 patients AsPC-1, BxPC-3, SW-1990, and PaCa-2 cel lines	Inhibited EMT process	Diagnosis and Prognosis
zhong [72]	2022	miR-561-5p	LDHA	48 patients SW1990, AsPC-1, PANC-1, BxPC-3, Capan-2, and MIAPaCa-2 cell lines	Inhibited EMT process	Diagnosis and Prognosis
su [73]	2013	miR-221	TRPS1	AsPC-1 cell line	Induced EMT process	Diagnosis
dai [74]	2020	miR-122-5p	CCNG1	60 patients PANC-1 and PL-45 cell lines	Inhibited EMT process	Diagnosis

markers, the majority of PC patients are diagnosed in advanced tumor stages with poor prognosis [11,12]. Therefore, investigation of the molecular mechanisms involved in PC progression is required to introduce novel markers for the early diagnosis, targeted therapy, and determination of drug response in these patients. The poor prognosis in PC patients is related to the invasion and migration of pancreatic tumor cells [13,14].

Epithelial-mesenchymal transition (EMT) is a process in which the epithelial cells lose their polarity to gain a mesenchymal phenotype [15,16]. EMT is described by the CDH1 down regulation, while CDH2 and Vimentin up regulations [17]. It is orchestrated by a number of transcription factors, such as Twist1, ZEB1, and Snail1, which are also CDH1 transcriptional suppressors. EMT is a critical process in embryogenesis, cell differentiation, tissue regeneration, fibrosis, tumor progression, and chemo-resistance [18,19]. PC cells can spread to distant organs through EMT during the early stages of tumor progression [20]. EMT is a critical phase in the development of PC and is closely associated with drug resistance [21]. Targeting the EMT in PC is also a potential therapeutic method [22].

MicroRNAs (miRNAs) are the pivotal regulators of cell proliferation, migration, metastasis, and apoptosis. They regulate gene expression by mRNA destruction or translational inhibition [23,24]. Deregulation of miRNAs has been reported during tumorigenesis through activating or silencing oncogenes or tumor suppressor genes, respectively [25–27]. Deregulation of miRNA expression profile was reported in PC patients that can be related with the drug resistance, tumor stage, or patient survival. Therefore, targeted therapy for these specific miRNAs, can afford an efficient and appropriate approach for the potential treatment of the PC patients [28]. Additionally, delivery of the synthetic oligonucleotides via nanoparticles or taking profit from natural remedies can regulate miRNA expression, hence hampering PC growth. MiRNA targeting in conjunction with the conventional tumor therapies may be a novel therapeutic method to increase drug response among PC patients [28]. MiRNAs can promote or repress EMT and tumor metastasis [29–31]. To facilitate the establishment of efficient therapeutic approaches for the metastatic PC, it is imperative to clarify the molecular mechanisms of EMT regulation by miRNAs. Therefore, in the present review we discussed the role of miRNAs in regulation of EMT process in pancreatic tumor cells (Table .1). Regarding the importance of signaling pathways and EMT related transcription factors as the main upstream regulators of EMT process during PC progression, we discussed the role of miRNAs in EMT process by regulation of signaling pathways, EMT related transcription factors, and EMT related structural proteins.

2. EMT related transcription factors

EMT process is orchestrated via a series of EMT related transcription factors (EMT-TFs) [75]. MiRNAs have a pivotal role in

regulation of EMT process by EMT-TFs targeting in pancreatic tumor cells (Fig. 1). SLUG is an important transcription factor that promotes metastasis and invasion during tumor progression through initiating EMT by CDH1 down regulation [76]. Snail1 is also a zinc-finger transcription factor that promotes EMT process by up regulation of mesenchymal genes like CDH2 while down regulation of epithelial genes like CDH1 and Occludin [77,78]. MiR-203a-3p inhibited the EMT process by suppressing cell invasion via SLUG targeting [32]. MiR-30e-5p had a tumor suppressor function in regulation of PC cell proliferation, EMT, and migration through SNAI1 suppression. There was also miR-30e-5p down regulation in PC tissues in comparison with normal samples [33]. MiR-199 inhibited self-renewal of gemcitabine (GEM)-treated PC cells. It also repressed the GEM's inhibitory effect on EMT in PC cells by Snail1 targeting [79].

Zinc finger E-box binding (ZEB) family is involved in the EMT process through inhibiting the expression level of epithelial marker E-cadherin in various human cancers, indicating the role of ZEB in metastasis and cancer patients prognosis [80]. The miR-204 expression has been reported to be significantly down regulated in PC tissues that was correlated with invasive tumor characteristics. MiR-204 significantly suppressed PC cell migration and EMT via ZEB1 targeting [34]. ADPGK-AS1 promoted the PC cell migration and EMT, while inhibited apoptosis by miR-205-5p sponging and ZEB1 up regulation [81]. MiR-128-3p also suppressed the EMT and cell migration in PC through ZEB1 targeting [35]. There was miR-1271 down-regulation in PC cells and clinical samples. MiR-1271 enhanced CDH1 expression and inhibited PC cell growth, invasion, and EMT by TWIST1 and ZEB1 targeting [36]. There were significant higher invasion and migration abilities in Gemcitabine-resistant (GR) cells that were associated with CDH1 down regulation, while increased levels of CDH2, Vimentin, Snail1, and ZEB1-2 expressions. NEAT1 down regulation increased the gemcitabine sensitivity via regulating the miR-506-3p/ZEB2 axis and reversing the EMT process in GR cells [37]. Cancer stem cells (CSCs) are a small fraction of cancerous cells that potentially have self-renewal traits and have a critical role in cell division, drug resistance, and tumor relapse [82]. CSC-like characteristics can be provided by virtue EMT process in cancer cells, and CSCs utilize an EMT phenotype for metastasis [83]. Oct4 and Nanog are critical transcription factors that regulate self-renewal in the early stages of PC progression [84]. There was Linc-DYNC2H1-4 up regulation in GEM-resistant PC cells. Linc-DYNC2H1-4 increased the EMT in GEM-sensitive PC cells through miR-145 sponging that resulted in ZEB1, Sox2, Lin28, Nanog, MMP3, and Oct4 up regulations [38]. MiR-200a suppressed EMT and cell migration through down-regulating ZEB1 in PC cells [85].

SOX4 is a transcription factor involved in EMT regulation in several malignancies [86,87]. SOX4 expression is significantly correlated with tumor growth, EMT, and metastasis [88]. EZH2 is a catalytic component of the polycomb complex which is involved in transcriptional inhibition through catalyzing the trimethylation of histone3 lysine27 [89]. SOX4 acts as a direct transcriptional activator of the EZH2 gene in cancer cells [90]. There was circ_0001666 up regulation in PC tissues that was associated with a worse prognosis. Circ_0001666 enhanced PC invasion and EMT through miR-1251/SOX4 axis [39].

Hypoxia is a typical characteristic of middle- and late-stage solid tumors, promoting tumor angiogenesis, migration ability, and drug resistance [91,92]. Hypoxia-inducible factor 1α (HIF-1α) is considered as an important transcription factor that modulates the oxygen homeostasis during hypoxia [93,94]. MiR-142 down regulated HIF-1α, vimentin, and VEGF-C, while up regulated CDH1 that resulted in hypoxia-mediated EMT suppression. HIF-1α and miR-142 expression levels were also shown to be correlated with the stage and lymph node involvement in PC patients [40].

Specificity protein 1 (Sp1) belongs to the Sp1/Krüppel-like protein family that is associated with tumor metastasis [95,96]. There

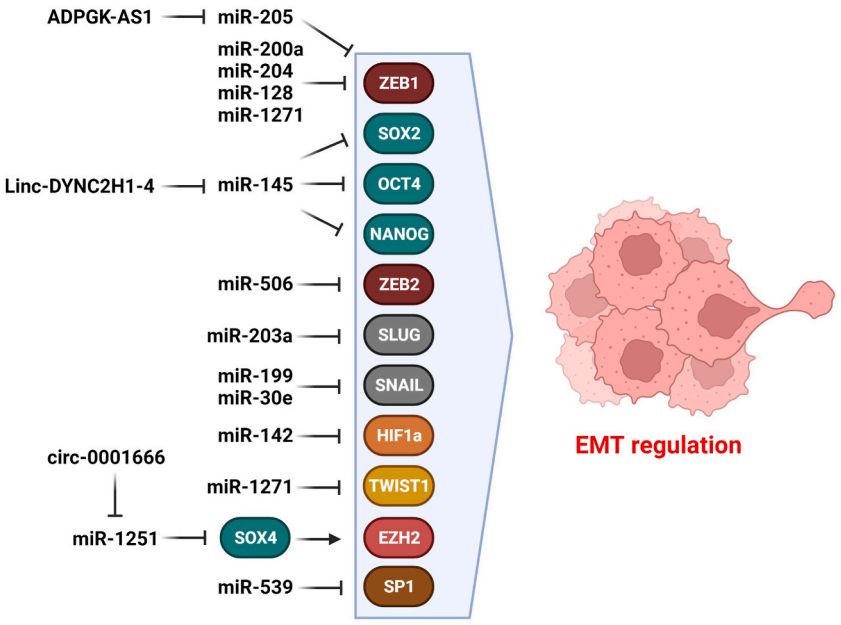

Fig. 1. Role of miRNAs in EMT regulation via EMT-related transcription factors in pancreatic tumor cells. (Created with BioRender.com).

was miR-539 under expression in PC tissues in comparison with normal samples. MiR-539 up regulated the CDH1, while down regulated CDH2 and Snail1. MiR-539 reduced PC cell migration and EMT through SP1 targeting [41]. The c-Myc as a master regulator is responsible for cellular growth and apoptosis [97]. The up regulation of c-Myc leads to the beginning and preservation of a wide range of signal-transduction pathways which induce EMT, invasion, and metastasis in numerous human cancers [98]. The c-MYC oncogene, which is a crucial regulator of EMT and metastasis, plays an important role in the development of several malignancies through stimulating miR-9 expression [99,100]. EIF4A1 is the main isoform of eIF4A, involved in eIF4F assembly in cancer cells. It was observed that eIF4A1 reduced the levels of CDH1 expressions via the c-MYC/miR-9 axis that stimulated EMT and invasion in PC cells [42].

3. TGF-β and MAPK signaling pathways

TGFβ-1 is a critical multifunctional cytokine that regulates the EMT process in tumor microenvironment [101,102]. TGF-β stimulates serine-threonine kinase receptors, which mainly function through canonical Smad-dependent signaling cascades and have often paracrine effects on the pancreatic tumor microenvironment [103,104]. TGF-β signaling pathway is triggered by TGF-β/TGFBR2 interaction that phosphorylates the Smad2 and Smad3 [105]. R-Smads further interact with Smad4 to enter to the nucleus where they up regulate the Snail1, ZEB2, and Twist transcription factors. TGF-β also regulates the EMT process by interaction with PI3K/AKT, MAPK, and WNT signaling pathways [106]. MiRNAs have an important role in EMT regulation by the TGF-β signaling (Fig. 2). TGF-β induces EMT by Snail1 up regulation [107,108]. Snail1 enables PC cells to undergo EMT through CDH2 overexpression and CDH1 under expression [20,109]. MiR-202 reduced TGFβ1-mediated EMT in PC cells via TGFBR1 and TGFBR2 targeting [43]. There was linc00462 up regulation in PC cells and tissues that was associated with tumor size, differentiation, distant metastasis, and TNM stage. Linc00462 promoted cell migration while suppressed cell adhesion and apoptosis through EMT induction. MiR-665 suppressed cell migration and enhanced apoptosis through targeting TGFBR1 and TGFBR2 in PC cells. Linc00462 enhanced PANC progression via regulating the miR-665/TGFBR1-2/SMAD2-3 axis [44]. MiR-509-5p was shown to regulate HMGA2 and VIM, which resulted in induction of the mesenchymal-epithelial transition (MET). MiR-1243 also induced MET by regulating SMAD2 and SMAD4, which mediate the TGF-β signaling. MiR-655 induced the MET process via CDH1 up regulation. MiR-509-5p and miR-1243 promoted the MET phenotype by Snail1 and ZEB1 targeting [45].

SMURF2 is an E3 ubiquitin ligase involved in TGF-β signaling pathway, cell mobility, and chromatin remodeling [110]. It

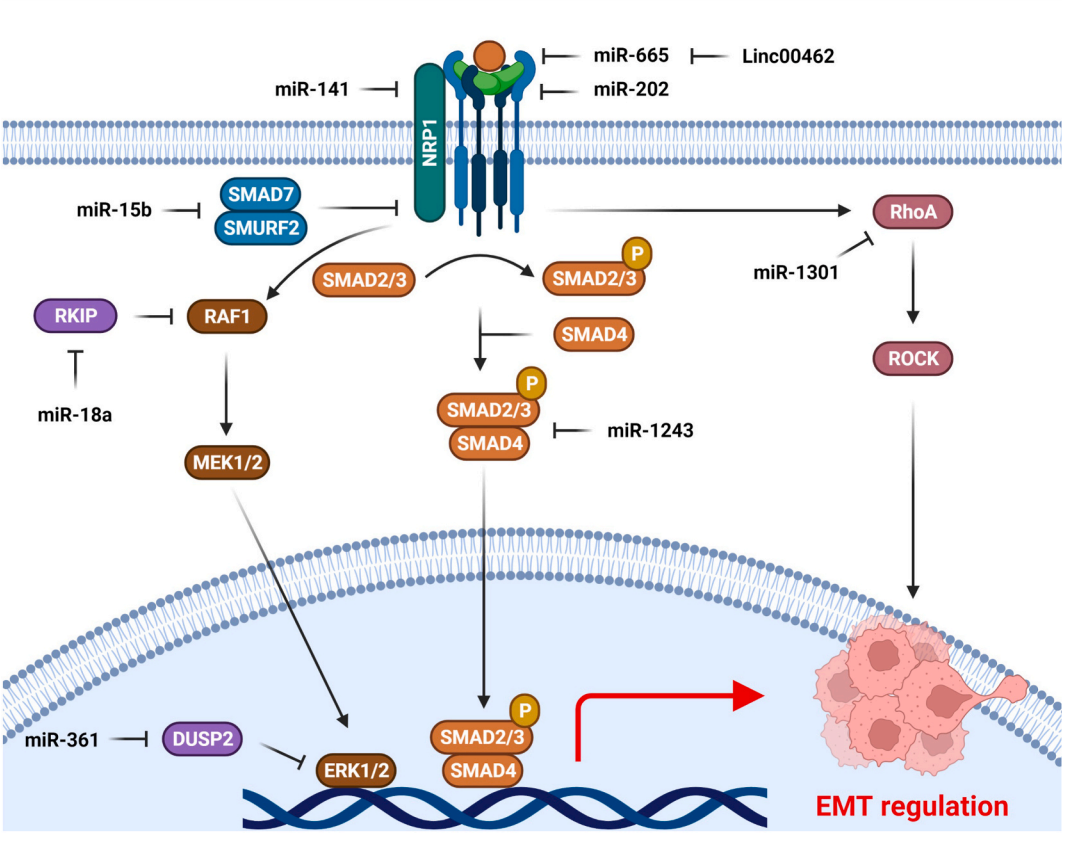

Fig. 2. Role of miRNAs in EMT regulation via TGFβ signaling pathway in pancreatic tumor cells. (Created with BioRender.com).

attenuates the TGF-β cascade through ubiquitin-dependent degradation of Smad2/7 proteins and TGF-β receptors [111]. There was a negative association between the levels of SMURF2 expressions and GEM resistance in PC. MiR-15b enhanced EMT in PC cells via SMURF2 targeting [46]. Neuropilin-1 (NRP-1) acts as a co-receptor for TGF-β [112]. It was observed that NRP-1 depletion suppressed TGF-β that resulted in Snail1, *p*-Smad2/3, and CDH2 down regulations, while CDH1 up regulation. MiR-141 reduced EMT process by NRP-1 targeting in PC cells [47]. RhoA belongs to the GTPase protein family that can stimulate actin cytoskeleton rearrangement to control cell adhesion and motility [113,114]. It regulates gene expression, cell growth, and cell cycle development via downstream effector proteins such as ROCK1 and ROCK2 [115]. Smad signaling regulated RhoA activity and function, especially in EMT and TGF-β-induced actin organization. Consequently, the Smad and RhoA pathways have been shown that mediate TGF-β activity [116]. There was miR-1301-3p down regulation in PC tissues that was correlated with poor survival. MiR-1301-3p suppressed PANC cell migration and RhoA-mediated EMT process [48].

MEK/ERK pathway has a pivotal role in cell proliferation, survival, differentiation, and self-renewal of stem cells through STAT3 inhibition [117]. MiRNAs have a key role in EMT regulation through the modulation of MAPK signaling in pancreatic tumor cells (Fig. 2). Raf-1 kinase inhibitor protein (RKIP) acts as a metastasis suppressor in human malignancies [118]. The Raf/MEK/ERK axis is frequently deregulated in malignancies due to mutation and amplification of receptor tyrosine kinases and Ras as the upstream regulators of Raf-1 [119,120]. It was shown that miR-18a induced EMT and CSC phenotypes in PC cells via RKIP down regulation [49]. TGF-β-mediated EMT can be affected by ERK signaling [121]. TGFβ-1 -induced Snail1, which is known for its role in EMT via binding to the CDH1 promoter, also requires the ERK pathway activation [122,123]. Ago2 participates in endogenous miRNA synthesis and RNA interference [124]. MiR-361-3p activated the ERK pathway by DUSP2 targeting. There were miR-361-3p up regulations in PC tissues that were associated with poor survival and advanced tumor stage. MiR-361-3p modulated ERK1/2-induced EMT in PC by DUSP2 targeting. Ago2 also up regulated the miR-361-3p that subsequently promoted EMT in PC cells through DUSP2 targeting [50]. Tris-tetraprolin (TTP) promotes deadenylation and degradation of target mRNAs [125]. ERK and p38 signaling pathways regulate TTP activity and phosphorylation in which ERK decreases TTP levels through protein degradation [126,127]. MiR-29a increased PC invasion and EMT via TTP targeting [51]. There was OIP5-AS1 up regulation in TCGA-PAAD samples that was correlated with survival. OIP5-AS1 increased the PC malignancy by modulating the miR-429/FOXD1/ERK axis [52]. EGFR has a critical impact on EMT program in a variety of malignancies [128,129]. The increased tyrosine kinase activity of the EGFR receptors resulting from EGFR dimerization with other members of the EGFR family can activate p38 MAPK and PI3K signaling pathways [130,131]. It has been demonstrated that TIP30 targeting by miR-10b promoted EGF-dependent invasion, EGFR phosphorylation, and activation of ERK1/2 in PC, while reduced EGFR degradation [132]. There was miR-338-5p down regulation in PC tissues in comparison with normal specimens that was contributed with higher AJCC stage and lymph node involvement. MiR-338-5p reduced PC cell invasion and EMT process by EGFR targeting [53].

4. PI3K/AKT and Notch signaling pathways

PI3K/Akt signaling pathway is an important regulator of EMT process and tumor cell invasion [133,134]. The activation of PI3K/Akt pathway via a series of EMT-TFs promotes EMT by a positive feedback loop between Akt and Twist and up regulating Snail1 and Slug after GSK-3β degradation [133,135]. Moreover, the up regulation of MMPs leads to the PI3K/Akt activation, E-cadherin down

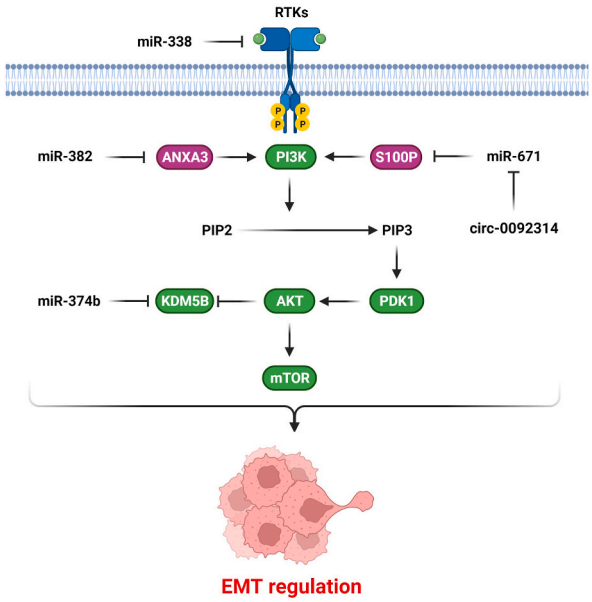

Fig. 3. Role of miRNAs in EMT regulation via PI3K/AKT signaling pathway in pancreatic tumor cells. (Created with BioRender.com).

regulation, and extracellular matrix (ECM) degradation, resulting in EMT process, cell migration, and invasion [136–138]. It has been shown that the miRNAs have a pivotal role in regulation of EMT process by PI3K/AKT targeting in pancreatic tumor cells (Fig. 3). Annexin A3 (Anxa3) belongs to the Annexin protein family which binds to the phospholipids during PC progression [139,140]. It was reported that miR-382 up regulated the CDH1, while down regulated PI3K, AKT, Vimentin, and CDH2. Therefore, miR-382 inhibited EMT and lymph node involvement by suppressing the PI3K/Akt pathway via Anxa3 targeting in PC [54]. Transmembrane-4-L-six-family (TM4SF1) as a cell surface protein plays a critical function in cell proliferation, motility, and EMT [141]. There was an inverse association between the levels of TM4SF1 and miR-141 expressions that was correlated with advanced stage and poor survival. MiR-141 directly targets and blocks the expression of TM4SF1, reducing angiogenesis and EMT in PC cells. TM4SF1 positively and negatively regulated the VEGF-A and CDH1 expressions, respectively in PC cells using the promotion of AKT signaling [55]. S100A4 as an EF-hand Ca^{2+}-binding protein interacts with numerous target proteins to regulate some cellular processes, including proliferation, motility, differentiation, cell cycle regulation, protein phosphorylation, and survival [142]. Calcium-binding protein S100P expression has been shown to enhance tumor development and metastasis in several malignancies [143,144]. S100P is able to induce EMT and invasion in colon cancer cells through AKT activation and S100A4 up regulation [145]. Circ_0092314 promoted the EMT features of PC cells by miR-671/S100P axis. There was circ_0092314 up regulation in PC tissues that was associated with PC aggressiveness [56]. KDM5B is a histone demethylase that is involved in regulation of stem cell differentiation, gene transcription, and genome stability via demethylation of histone 3 lysine 4 [146,147]. KDM5B promotes PI3K-AKT-mTOR signaling via histone modification level of KDM5B and binding to the PIK3CA promoter [148,149]. KDM5B overexpression has been observed in many cancers [150–152]. There was miR-374b-5p down regulation in PC tissues. MiR-374b-5p reduced tumor progression and lung metastasis through suppressing PC cell proliferation and migration by KDM5B targeting and subsequent EMT inhibition [57].

Notch signaling is a pivotal regulator of cell cycle progression and apoptosis that is triggered by binding of Jag or DLL ligands with NOTCH receptors [153,154]. Binding of ligand to its receptor leads to proteolytic cleavages of Notch receptor via metalloproteinase and gamma-secretase, which release and translocate intracellular domain of Notch (Notch-ICD) to the nucleus [155,156]. ICD interacts with CBF1/Su(H)/Lag-1 (CSL) and induces the transcription of several NOTCH target genes such as SLUG, SNAIL1, ZEB1, HEY, HES, and CCND1, while down regulation of CDH1 to promote EMT [155,157,158]. NOTCH signaling can also be activated by the EMT related transcription factors [159,160]. MiR-34a down regulation was correlated with higher PC cell invasion and migration. MiR-34a

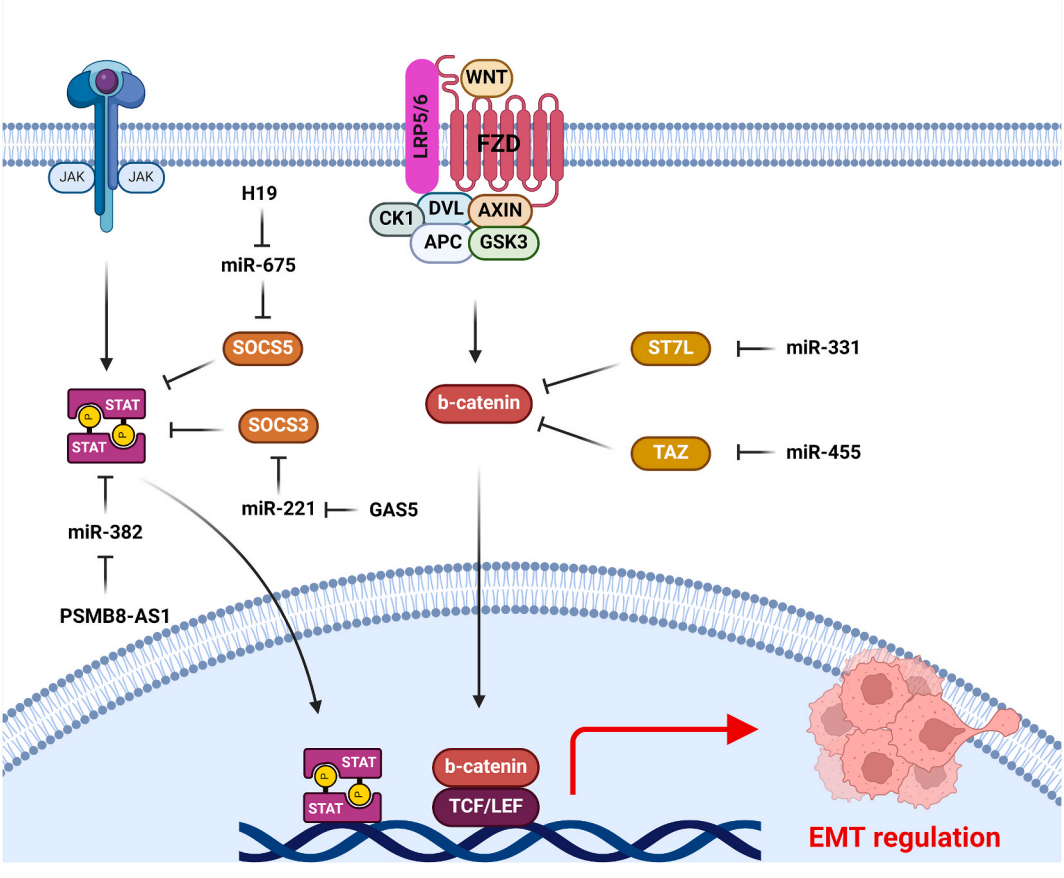

Fig. 4. Role of miRNAs in EMT regulation via WNT and JAK/STAT signaling pathways in pancreatic tumor cells. (Created with BioRender.com).

inhibited the EMT process in PC cells by Notch1 and Snail1 targeting that resulted in CDH1 up regulation [58]. ELF3 belongs to the ETS transcription factor family that promotes or represses tumor progression. ELF3 induced tumor growth in HER2+ breast cancer, liver cancer, and lung cancer [161–163]. However, ELF3 silencing promoted the EMT in ovarian cancer [164]. There was miR-1224-5p down regulation in PC tissues. MiR-1224-5p decreased PC cell invasion by ELF3 targeting. P-PI3K and P-Akt expression levels were found to be significantly reduced when ELF3 was knocked down, suggesting that ELF3 may induce EMT via activating the PI3K/AKT pathways. ELF3 silencing also down regulated the Notch signaling related genes such as Notch-1, C-myc, CCND1, Hes1, and VEGF in pancreatic tumor cells [59].

5. WNT signaling pathway

WNT signaling is a developmental molecular pathway associated with cell differentiation, proliferation, apoptosis, and ontogenesis [165,166]. It can be triggered with WNT stimulation and increased cytoplasmic β-catenin accumulation that enters into the nucleus which induces target genes [167,168]. MiRNAs have a key role in EMT process via the regulation of WNT signaling in pancreatic tumor cells (Fig. 4). Wnt10b belongs to the Wnt ligand protein family that activates the WNT signaling [169,170]. MiR-148a suppressed the EMT process in PC cells via Wnt10b targeting. There was significant miR-148a under expression in PC tissues that was contributed with advanced tumor stage and lymphatic metastasis. There was also CDH1 down regulation while vimentin up regulation in PC tissues. MiR-148a significantly reduced the levels of β-catenin, CCND1, and MMP-9 expressions in pancreatic tumor cells [60]. Wnt1 stimulates the Wnt/β-catenin pathway that influences cell proliferation, EMT, and self-renewal [171]. MiR-148a-3p inhibited cell invasion, self-renewal, and EMT in PANC via Wnt1 targeting. MiR-148a-3p up regulated CDH1 while down regulated the CDH2 and vimentin in PC cells. MiR-148a-3p was considerably down regulated in pancreatic CSCs, while CSC markers were up regulated. There was significant miR-148a-3p down regulation in PC patients that was correlated with poor OS [172]. ST7L functions as a tumor suppressor by interaction with the β-catenin pathway [173,174]. It reduces the expression level of β-catenin and GSK-3β phosphorylation, leading to inhibition of β-catenin transcription. Consequently, knockdown of ST7L promotes growth, invasion, and EMT of tumor cells [175].

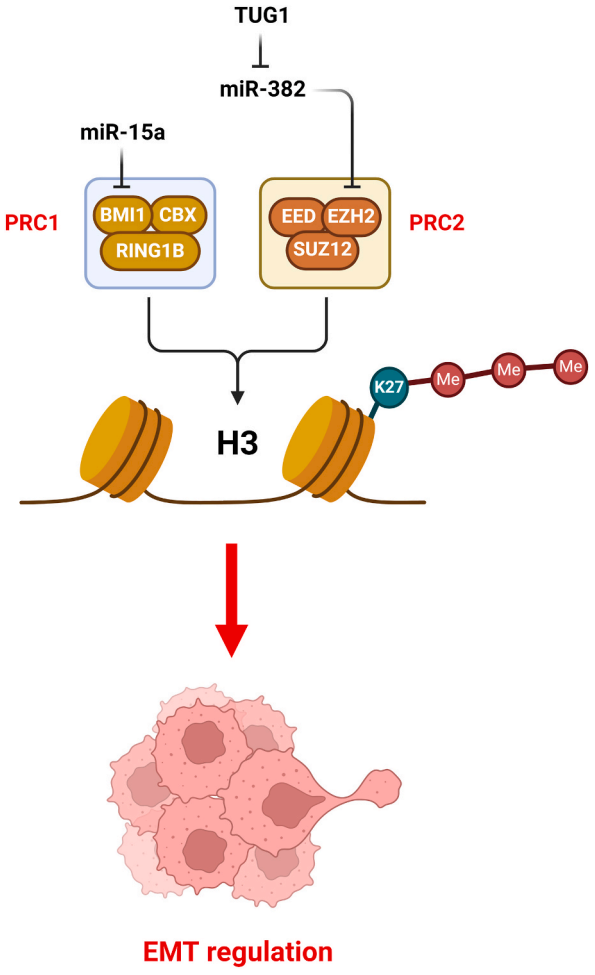

Fig. 5. Role of miRNAs in EMT regulation via polycomb complex in pancreatic tumor cells. (Created with BioRender.com).

There was miR-331-3p up regulations in PC cells and clinical specimens, which was associated with the advanced stage and distant invasion. MiR-331-3p inhibited ST7L and then enhanced proliferation and EMT-mediated metastasis in PC cells [61]. Transcriptional co-activator with PDZ-binding motif (TAZ) is up regulated in many cancers [176]. TAZ was found to be induced by the interaction of β-catenin with TBX5, while inhibited by polymerase activity inhibitors via the WNT pathway [177]. It was found that miR-455-3p inhibited TAZ expression with subsequent WNT/β-catenin signaling inactivation, resulting in apoptosis induction, while cell migration and EMT inhibition in PC. MiR-455-3p enhanced cell death through influencing the Bcl-2, CASP3, and Bax apoptotic proteins. MiR-455-3p inhibited CCND1, β-catenin, and C-myc by TAZ targeting in PC cells [62].

6. JAK/STAT signaling pathway

JAK/STAT signaling pathway is activated via the binding of a ligand (such as interleukins and interferons) to its receptor that leads to phosphorylation of cytoplasmic STAT. The activated STATs translocate to the nucleus, bind to DNA, and induce target gene transcription [167,178]. JAK/STAT pathway is involved in tumor metastasis, EMT, and drug resistance [167,179]. MiRNAs are the critical EMT regulators by affecting the JAK/STAT signaling in pancreatic tumor cells (Fig. 4). STAT1 is a transcription factor involved in tumor immune function that regulates tumorigenesis, and tumor progression through the NF-KB signaling pathway [180,181]. PSMB8-AS1 down-regulation was shown to considerably suppress PC progression and metastasis by regulation of miR-382-3p/STAT1/PD-L1 axis [63]. H19 as an imprinted long noncoding RNA plays a role in cell division, apoptosis, migration, and tumor invasion [182,183]. SOCS3 regulates cytokine signaling through inhibiting receptor-JAK complex [184]. SOCS5 regulates the binding of EGF and IL-4 to the receptor by the JAK/STAT pathway to inhibit cytokine signaling [185]. It has been demonstrated that H19 was correlated with the EMT process, enhanced migration, invasion, and resistance to chemotherapy in PC cells. SOCS5 as an endogenous inhibitor of the STAT3 pathway can be directly targeted by miR-675-3p. H19 induced EMT in PC cells by regulation of miR-675-3p/SOCS5 axis that resulted in STAT3 activation [64]. There were GAS5 and SOCS3 down regulations, while miR-221 up regulation in PC tissues and cell lines. GAS5 promoted SOCS3 expression that resulted in reduced PC growth and gemcitabine resistance through EMT suppression. GAS5 reverses the EMT process in PC cells via miR-221/SOCS3 axis [65].

7. Polycomb repressive complex

Polycomb group proteins (PcG) are the epigenetic regulators involved in transcriptional inhibition through chromatin remodeling. Polycomb complex regulates the EMT related signaling pathways [186]. It has been reported that miRNAs have key roles in EMT process during PC progression by regulation of polycomb complex (Fig. 5). Enhancer of zeste homolog 2 (EZH2) is one of the components of the polycomb repressive complex-2 (PRC2) that is involved in histone methylation [187]. EZH2 inhibits the expression of tumor suppressor genes in a wide spectrum of cancers using epigenetic modifications and trimethylation of H3K27 that results in regulation of cell proliferation, invasion, migration, and apoptosis [188,189]. EZH2 down regulated the miR-139-5p that induced EMT in PC cells. There was miR-139-5p down regulation in PC tissues that was correlated with advanced TNM stages, distant metastases, and poor prognosis [190]. TUG1 knockdown inhibited migration and EMT processes. TUG1 regulated the PC development by miR-382 sponging and subsequent EZH2 up regulation in PC cells [66]. Bmi-1 is also a critical polycomb protein that regulates the hematopoietic and neural stem cells' self-renewal and proliferation [191]. There was miR-15a down regulation in PC tissues in comparison with normal controls. MiR-15a repressed proliferation and EMT in PC cells through Bmi-1 targeting [67].

8. Structural proteins and cell cycle regulators

It has been reported that the EMT process in PC cells can also be affected by the structural proteins and cell cycle regulators (Fig. 6). Syndecan-1 (SDC1) is a crucial cell surface adhesive molecule that plays an essential role in cell morphology and tumor progression

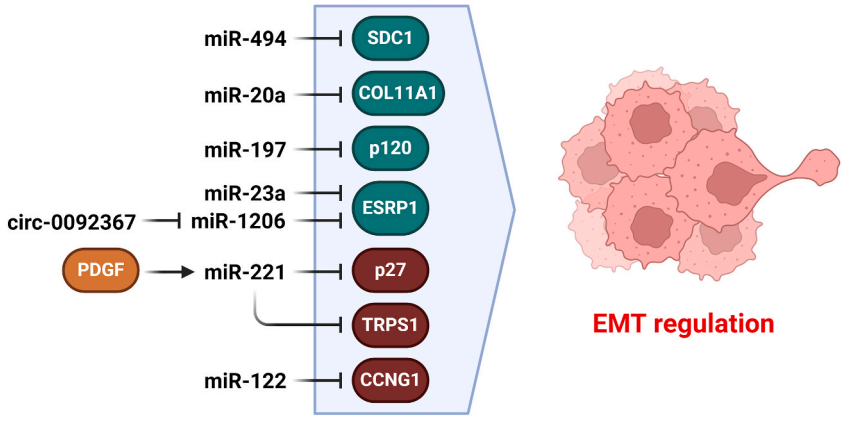

Fig. 6. Role of miRNAs in EMT regulation via structural proteins and cell cycle regulators in pancreatic tumor cells. (Created with BioRender.com).

[192]. Deregulation of SDC1 is implicated in the induction of CSCs formation that leads to drug resistance and tumor relapse [193]. MiR-494 suppressed PC cell migration and EMT by SDC1 inhibition [68]. Collagen type XI alpha 1 (COL11A1) is a critical collagen involved in the regulation of EMT. Several collagens, including collagen type I, III, V, VI, and XI are found to be associated with chemo resistance and tumorigenesis [194,195]. There was circ-0005105 up regulation in PC tissues that was associated with poor prognosis. Circ-0005105 promoted PC cell proliferation, EMT, and invasion by COL11A1 up regulation through miR-20a-3p sponging [69].

P120-catenin acts as a regulator of cadherin stability, cell motility, cellular transformation, and cancer progression [196]. The p120 catenin regulates the CDH1 membrane trafficking through endocytosis [197]. E-cadherin and p120 catenin are the regulators of colon tumor cell migration [198]. MiR-197 promoted the EMT in PC cells through p120 Catenin targeting [199].

CD44 as a cell surface protein is involved in cell migration, angiogenesis, and cell differentiation. CD44s has been associated with the mesenchymal phenotype in tumor cells [200,201]. There was miR-23a up regulation in PC tissues compared with normal margins that was contributed with tumor invasion, lymph node involvement, and lower survival rates. MiR-23a promoted the epithelial cells for the CD44v to CD44s switch and down regulated the ESRP1 [70]. Epithelial splicing regulatory protein 1 (ESRP1) is an inhibitor of EMT in different cancers [202,203]. ESRP1 as a splicing factor modulates alternative splicing of CD44 to promote EMT and metastasis [204,205]. By modulating the miR-1206/ESRP1 axis, circ-0092367 dramatically increased GEM sensitivity in PC cells. There was circ-0092367 down regulation in PC tissues that was inversely correlated with tumor stage and lymph node involvement. ESRP1 not only decreased EMT and cell invasion but also sensitized PC cells toward GEM treatment [71].

Lactate dehydrogenase A (LDHA) enhances tumor progression via elevating lactic acid production, and glucose uptake, as well as modulating several cancer-related chemicals [206–208]. The overexpression of LDHA is positively associated with N-cadherin and negatively with E-cadherin [209]. There was LINC01128 up regulation in PC cells and tissues that enhanced in vivo tumorigenesis and in vitro cell proliferation and EMT through miR-561-5p/LDHA axis. LINC01128 has been linked to a poor prognosis in PC patients [72].

P27Kip1 is a Cip/Kip cyclin-dependent kinase (CDK) inhibitor that binds with RhoA to regulate the cytoskeletal structure and cell motility [210,211]. Platelet-derived growth factor (PDGF) is a receptor tyrosine kinase that regulates cell migration, EMT, angiogenesis, and proliferation [212]. PDGF down regulated the CDH1, while up regulated the ZEB2 that resulted in EMT induction in epithelial-like tumor cells [213]. TRPS1 as a transcriptional factor from the GATA family can control ZEB2 expression [214]. PDGF-BB treatment increased cell migration and EMT in PC cells. PDGF up regulated the miR-221 by recruitment of transcription factors. MiR-221 increased PC cell proliferation by p27Kip1 down regulation. MiR-221 was also regulated by PDGF that induced the EMT via TRPS1 inhibition [73]. Cyclin G1 (CCNG1) belongs to the cyclin protein family, which regulates cell proliferation [215,216]. CCNG1 was found to be associated with cell proliferation, migration, and invasion by enhancing tumorigenesis and the EMT process [217]. There was miR-122-5p down regulation in PC cells and tissues that was inversely associated with tumor size, stage, and lymph node metastasis. MiR-122-5p reduced PC cell proliferation, invasion, and migration via suppressing CCNG1. MiR-122-5p inhibited EMT by CDH1 up regulation while CDH2, Vimentin, and MMP9 down regulations [74].

9. Conclusions

EMT process is a pivotal cellular mechanism during tumor cell invasion, in which the tumor cells obtain the mesenchymal features to separate from the tumor bulk for the distant implantation and metastasis. Therefore, assessment of the molecular biology of EMT process is required to suggest the novel biomarkers for the prediction of metastatic behavior in pancreatic tumors. Since, the PC cells can spread to distant organs through EMT process during the early stages of tumor progression; the regulators of EMT process can be used as the early stage diagnostic markers among these cancer patients. On the other hand, high mortality rate among the PC patients is associated with lack of screening programs that leads to the late diagnosis with poor prognosis. Therefore, it is required to introduce novel non-invasive biomarkers that can be assessed without any invasion in general population for the screening of PC. MiRNAs as the stable molecules in body fluids can be reliable non-invasive biomarkers. In the present review, we discussed the role of miRNAs in regulation of EMT process in pancreatic cancer. It was observed that miRNAs mainly affect the EMT in pancreatic tumor cells by regulating transcription factors and signaling pathways. Considering the importance of miRNAs in EMT regulation, this review can be an effective step in introducing a non-invasive EMT based panel marker for the early tumor diagnosis among PC patients. However, more studies are needed to investigate miRNA levels in the serum of cancer patients so that they can be used as the non-invasive markers to predict the metastatic behavior of tumors in pancreatic cancer patients. EMT related miRNAs can also be used for the targeted tumor therapy. Since, miRNAs inhibit the EMT process in pancreatic tumor cells; therapeutic strategies based on miRNA mimics can be used to inhibit the EMT process in these tumor cells. However, more animal studies and clinical trials are also needed to use miRNAs as the inhibitors of EMT process and tumor cell invasion in pancreatic cancer patients.

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Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Faezeh Tolue Ghasaban: Writing – original draft. **Mahmoud Ghanei:** Writing – original draft. **Reihaneh Alsadat Mahmoudian:** Writing – original draft. **Negin Taghehchian:** Writing – original draft. **Mohammad Reza Abbaszadegan:** Validation. **Meysam Moghbeli:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization.

Declaration of competing interest

none

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