**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 63450

**Manuscript Type:** MINIREVIEWS

**Role of epithelial-mesenchymal transition in chemoresistance in pancreatic ductal adenocarcinoma**

Hu X *et al*. EMT in chemoresistance in PDAC

Xiu Hu, Wei Chen

**Xiu Hu,** Department of Pharmacy, Affiliated Hangzhou Cancer Hospital, Zhejiang University School of Medicine, Hangzhou 310002, Zhejiang Province, China

**Wei Chen,** Cancer Institute of Integrated Traditional Chinese and Western Medicine, Key Laboratory of Cancer Prevention and Therapy Combining Traditional Chinese and Western Medicine of Zhejiang Province, Zhejiang Academy of Traditional Chinese Medicine, Tongde Hospital of Zhejiang Province, Hangzhou 310012, Zhejiang Province, China

**Author contributions:** Chen W initiated the manuscript concept and approved the final version of the manuscript; Hu X drafted the review and wrote the manuscript.

**Supported by** Zhejiang Provincial Nature Science Foundation of China, No. LR20H160001; Key R&D projects of Zhejiang Province, No. 2020C03G5263593; Zhejiang Provincial Ten Thousand Plan for Young Top Talents (2018); Training Objects of Health Innovative Talents of Zhejiang Health (2018); Key Project Co-constructed by Zhejiang Province and Ministry, No. WKJ-ZJ-1916; Natural Science Foundation of China, No. 81972693, No. 81802383, No. 81972674, No. 81673809 and No. 31900543; Zhejiang Provincial Traditional Chinese Medicine Science and Technology Project, No. 2020ZZ004.

**Corresponding author: Wei Chen, PhD, Chief Doctor,** Cancer Institute of Integrated Traditional Chinese and Western Medicine, Key laboratory of cancer prevention and therapy combining traditional Chinese and Western Medicine of Zhejiang Province, Zhejiang Academy of Traditional Chinese Medicine, Tongde Hospital of Zhejiang Province, No. 234 Gucui Road, Hangzhou 310012, Zhejiang Province, China. wei\_chen@zju.edu.cn

**Received:** January 28, 2021

**Revised:** March 11, 2021

**Accepted:** May 15, 2021

**Published online:**

**Abstract**

Pancreatic cancer (PC) is the seventh leading cause of cancer death worldwide. The vast majority of patients who have PC develop metastases, resulting in poor treatment effects. Although great progress in therapeutic approaches has been achieved in recent decades, extensive drug resistance still persists, representing a major hurdle to effective anticancer therapy for pancreatic ductal adenocarcinoma (PDAC). Therefore, there is an urgent need to better understand the drug resistance mechanisms and develop novel treatment strategies to improve patient outcomes. Numerous studies suggest that chemoresistance is closely related to epithelial-mesenchymal transition (EMT) of PDAC cells. Thus, this article summarizes the impact of EMT on PDAC from the perspective of chemotherapy resistance and discusses the possible novel applications of EMT inhibition to develop more effective drugs against PDAC.

**Key Words:** Epithelial-mesenchymal transition; Drug resistance; Carcinoma; Pancreatic ductal; Transcription factors; MicroRNAs

Hu X, Chen W. Role of epithelial-mesenchymal transition in chemoresistance in pancreatic ductal adenocarcinoma. *World J Clin Cases* 2021; In press

**Core Tip:** This article reviews the role of epithelial-mesenchymal transition in the emergence of chemotherapy resistance in pancreatic ductal adenocarcinoma and summarizes the potential epithelial-mesenchymal transition targets to overcome chemoresistance.

**INTRODUCTION**

Pancreatic ductal adenocarcinoma (PDAC), the most common form of pancreatic cancer (PC), is projected to be the second leading cause of cancer‑related death after lung cancer before 2030[1]. According to GLOBOCAN estimates, in 2018, there were 458918 new cases of PC, resulting in 432242 deaths[2]. PDAC is a complex and heterogeneous disease, involving a multitude of genetic, epigenetic, and other risk factors, such as smoking[3]. Currently, surgical resection followed by adjuvant chemotherapy remains the only potentially curative treatment for PDAC; however, only 20% patients are diagnosed early with locally resectable, non-metastatic disease[4,5]. Chemotherapy is available for the majority of patients who are diagnosed late with advanced disease and gives them hope. Despite the great progress made in the detection and treatment of PDAC, its prognosis remains dismal, with a five-year survival rate of approximately 9%[6]. These poor clinical outcomes are likely caused by the development of chemoresistance and invasive behavior. Therefore, it is essential for researchers to obtain a better understanding of this disease to develop more effective pharmacological therapy and improve patient survival.

Chemoresistance, defined as cancer cells showing no or less response to drugs at the effective inhibitory concentration, is classified into primary and acquired resistance. Currently, folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin or nab-paclitaxel plus gemcitabine are considered first-line therapies, because they provide patients with a 4.3-mo and 1.8-mo increase, respectively, in median survival when compared with gemcitabine alone[7,8]. However, not all patients benefit from first-line therapy owing to chemoresistance. The mechanisms of drug resistance are complex, including the activities of drug transporters, the tumor microenvironment, epithelial-mesenchymal transition (EMT), and the effects of microRNAs (miRNAs), enzymes, and their targets[9]. The EMT process is a major contributor to the development of resistance in multiple cancer types[10]. To this end, we will mainly discuss the effect of EMT on PDAC chemoresistance.

Classical EMT involves a phenotypic change in cells, in which cells loss their epithelial phenotype, such as tight cell-to-cell adhesion and apical-basal polarity, and acquire a highly invasive, mesenchymal phenotype[11]. Molecularly, EMT results in downregulation of the epithelial marker E‑cadherin while enhancing the expression of the mesenchymal factors (*e.g.*, N‑cadherin, fibronectin, SNAIL2, and vimentin)[12]. Initially, EMT was described as being essential for many stages in embryonic development, and was found subsequently to play a crucial role in adult tissue, such as organ fibrosis, wound healing, and metastasis[13,14]. In the past decades, extensive research has been conducted to investigate the role and regulation of EMT in tumor progression[15,16]. Accumulating evidence suggests that EMT plays an important role in the pathogenesis, invasion, metastasis, and drug resistance in PDAC[17-19].

In this review, we summarize the results of published studies on the role of EMT and the proposed EMT targets in drug-resistant PDAC, including a focus on the molecular mechanism of EMT in chemoresistance. Moreover, we also discuss EMT targeted therapy, and review the advantages and disadvantages of each approach.

**EMT involvement in PDAC therapy resistance**

EMT plays an important role in metastasis and is involved in several kinds of cancer, including PDAC[20]. Recently, studies have highlighted the importance of EMT in conferring chemoresistance in diverse cancers[17,21,22]. Although some studies showed that EMT makes a limited contribution to metastases, the role of EMT in conferring chemoresistance is clear in breast and pancreatic tumors[23,24].

Gemcitabine resistance is closely associated with EMT in PDAC. In 1996, gemcitabine was approved by the Food and Drug Administration to treat all stages of advanced PC, and it is still an important drug for the treatment of PC until now[25]. However, gemcitabine treatment provides limited survival benefit because of intrinsic or acquired resistance[26]. PDAC cell lines (BxPC3 and PANC-1) have different intrinsic gemcitabine resistance profiles: BxPC3 cells with an epithelial-like phenotype are more chemosensitive to gemcitabine than PANC‑1 cells with a mesenchymal-like phenotype[27]. El Amrani *et al*[28] reported that gemcitabine treatment induces EMT-like changes that are mediated by the extracellular regulated kinase (ERK)-zinc finger E-box binding homeobox 1 (ZEB1) pathway, and inhibition of ERK1/2 phosphorylation or ZEB1 expression resulted in a decrease in chemoresistance and invasion of gemcitabine-resistant (GR) Panc-1 and MiaPaca-2 cells[28]. This is in line with the results of a previous study showing that ZEB1 might maintain drug resistance of PC cells[17]. SLUG was also reported to contribute to gemcitabine resistance, and *SLUG* knockdown sensitized a CD133-positive PC cell line to gemcitabine[29]. Gemcitabine causes cells to undergo EMT, and GR cells overexpress CD44, CD24, and CD326 compared with sensitive PDAC cells[30]. Other studies showed that AMPK-related kinase 5 and upregulation of glycolysis enhance gemcitabine resistance in pancreatic carcinoma *via* EMT[31,32]. Moreover, emerging evidence suggested that miRNAs are linked to EMT in GR PDAC cells, and targeting miRNAs might represent a therapeutic strategy to treat PDAC[33-35]. Zhao *et al*[36]found that interleukin-37 expression was remarkably decreased in PDAC tissues, which induced gemcitabine resistance in PDAC by suppressing hypoxia-inducible factor-1 alpha (HIF-1α) expression through STAT3 inhibition. Numerous other studies revealed that the tumor microenvironment plays a pivotal role in EMT-driven drug resistance (reviewed in reference 21)[21]. Tumor microenvironment such as cancer-associated fibroblasts, pancreatic stellate cells, and hypoxia facilitate PC cells to undergo EMT and acquire chemoresistance.

EMT causes resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) in PC (Figure 1). Erlotinib (a first-generation EGFR-TKI) in combination with gemcitabine has been approved to treat PC in the USA and Europe[37]. Pancreatic cell lines that have higher expression of ZEB1, SNAIL1, and TWIST and have undergone EMT show a reduced sensitivity to erlotinib[38]. Epithelial tumor cells are significantly more sensitive to EGFR inhibitors than tumor cells with mesenchymal-like characteristics in pancreatic carcinomas[37]. In addition, a study demonstrated that the TGFβ-miR200-MIG6 pathway orchestrates the EMT-associated kinase switch that induces resistance to EGFR inhibitors[39]. Brexpiprazole reverses osimertinib (a third-generation EGFR-TKI) resistance in lung cancer and PC by suppressing survivin, which could activate transforming growth factor-β (TGF-β)/SMAD signaling, thus causing EMT[40,41].

EMT is involved in resistance to other chemotherapeutic agents in PC. According to Arumugam *et al*[17], ZEB1 regulates E-cadherin expression and the sensitivity to 5-fluorouracil (5-FU) and cisplatin treatment negatively, and *ZEB1* silencing upregulated epithelial markers (E-cadherin, EVA1, and MAL2) and restored 5-FU and cisplatin sensitivity in several drug-resistant cell lines (PANC-1, MIAPaCa-2, and Hs766T). EMT inhibition sensitized PDAC cells to 5-FU, and *CHL1* overexpression rescued 5-FU chemoresistance *via* the Hedgehog (Hh) pathway[42]. Mocetinostat, a histone deacetylase (HDAC) inhibitor, inhibited ZEB1 by restoring miR-203 expression, reversing the EMT process in GR PC cells, and sensitizing the cells to docetaxel[43].

**Signaling pathways inducing EMT in PDAC**

EMT is induced by several pathways, mainly including the TGF-β, Notch, Wnt/β catenin, Hh, tumor necrosis factor-α (TNF-α), HIF-1α, nuclear factor kappa B (NF-κB), and receptor tyrosine kinase signaling pathways[44]. Notch receptor-1 (Notch-1) is overexpressed in GR PC cells and plays an important role in GR-induced EMT[45]. Notch-2 activation was shown to mediate a chemoresistant phenotype (EMT phenotype) in GR PDAC cells, and downregulation of Notch signaling reversed the EMT phenotype partially to induce mesenchymal-epithelial transition (MET)[46]. Furthermore, Gungor *et al*[47] reported that gemcitabine induced Midkine (MK), a heparin-binding growth factor that is widely overexpressed in several types of cancers, the depletion of which was linked to increased sensitivity to gemcitabine treatment. Taken together, Notch signaling is activated by MK-derived EMT, which upregulates NF‑κB and increases chemoresistance in PDAC.

The expression pattern of hMENA isoforms, which was regulated by TGF-β1, played a crucial role in TGF-β1-induced EMT, and might represent promising targets to develop new prognostic and therapeutic tools in PDAC[48]. Zhan *et al*[49] found that in gemcitabine-treated PC cells, miR-331-3p was upregulated, which activated Wnt/β-catenin signaling *via* ST7L, while miR-331-3p inhibition and *ST7L* overexpression restored the activation of Wnt/β-catenin signaling and decreased drug resistance.

**EMT-activating transcription factors in PDAC resistance**

EMT is regulated at the cellular level by certain zinc finger transcription factors, mainly of the SNAIL, TWIST, and ZEB families[13,50]. These EMT-activating transcription factors (EMT-TFs) play pleiotropic roles in tumor progression and have been associated with poor clinical outcome in human cancers. Although the EMT process is reactivated in cancers, the end-stage markers, such as vimentin, are usually not expressed[13]. In addition, cancer cells often undergo partial EMT, and both epithelial and mesenchymal markers are expressed in the same cell. Therefore, attention must be paid to EMT-TFs, and not just to the prototypical EMT markers, such as E-cadherin and vimentin. As inhibitors of the epithelial phenotype, ZEB1, ZEB2, SNAIL1, SNAIL2, and TWIST1 are not expressed in normal epithelial cells, but are highly expressed in invading dedifferentiated cancer cells of pancreatic carcinomas[50,51]. Silencing of EMT‑TFs (SNAIL1, SNAIL2, and TWIST) expression using short hairpin RNA or small molecule inhibitors of EMT, such as CX4945 and SD208, reduced EMT metastasis, stem cell properties, and drug resistance (5-FU and Mitomycin C) of PC cell lines[52]. Namba *et al*[53] reported that the AKT-GSK3β-SNAIL pathway was inhibited using Zidovudine, an anti-viral drug, which could reverse EMT and overcome gemcitabine resistance of PC cells.

Wellner *et al*[54] reported that ZEB1 not only activated EMT *via* a stemness‑inhibiting miRNA, but was also necessary for the tumor‑initiating capacity of PC cells, and targeting the ZEB1-miR-200 feedback loop might be a promising treatment for PC. This finding suggested that in addition to directly targeting EF-TFs, miRNAs are also a good target for indirect inhibition of EMT-TFs.

**MiRNA in PDAC resistance**

MiRNAs are a class of small non-coding RNAs shorter than 22 nucleotides, which play a crucial role in the progression and chemoresistance of PDAC[55]. For example, Song *et al*[56] reported that miRNA-21 was overexpressed in patients with GR PDAC compared with that in patients with gemcitabine-sensitive PDAC, and inhibition of miRNA-21 could reverse invasion and metastasis *via* the PTEN/AKT pathway. Moreover, Liu *et al*[57] found that miR-125a-3p was downregulated in a time-dependent manner after treatment with gemcitabine, and upregulation of miR-125a-3p increased chemosensitivity to gemcitabine significantly and inhibited the EMT by targeting *FYN* in PDAC cells. A number of miRNAs that regulate EMT and PDAC drug resistance have been identified, and some of them are summarized in Table 1. It is clear that miRNAs could be promising targets to inhibit EMT to overcome chemoresistance in PDAC.

**Strategies to overcome chemoresistance by targeting EMT**

Given the pivotal role that EMT plays in tumor progression, EMT is considered a target for cancer therapy. Although there are many problems that remain to be resolved, marked progress has been made in the development of anti-EMT agents to overcome chemoresistance in cancer. Recently, several screening strategies have been proposed to identify EMT inhibitors, which were summarized by Marcucci *et al*[58]. Screening strategies to inhibit the EMT pathway to overcome chemoresistance mainly include inhibiting EMT induction, promoting MET, and targeting mesenchymal tumor cells. Inhibitors of EMT induction might be effective to prevent chemoresistance, and cancer cells that have already undergone EMT might benefit from compounds promoting MET[59].

It is clear that targeting a single receptor, enzyme, or transporter protein involved in EMT has limitations, because EMT is not a uniform process defined by a single pathway. Targeting EMT-TFs or miRNAs with pleiotropic function might be an effective approach to inhibit metastasis while overcoming chemoresistance. In addition, EMT-TFs and miRNAs can form a feedback loop to regulate each other, depending on environmental triggers. For example, ZEB1 directly suppresses the expression of miR-200 family members (miR-141 and miR-200c) and *ZEB1* is the predominant target downregulated by these miRNAs. Triggering the ZEB1-miR-200 feedback loop promotes EMT and invasion in PDAC[54,60]. However, there is still a long way to go to achieve targeting of EMT-TFs and miRNAs because of inefficient intracellular delivery *in vivo*. As an alternative approach, small molecule inhibitors (such as Mocetinostat, as mentioned above) are waiting to be discovered.

The composition of the tumor microenvironment is also an attractive target because it makes an important contribution to EMT-driven drug resistance in PDAC[9,21]. Inﬂammation is an important factor in the tumor microenvironment and contributes to the chemoresistance of PDAC cells indirectly *via* EMT induction, resulting in poor survival rates[61]. In addition, inhibitors of HIF-1α, a hypoxia-induced transcription factor, might be promising drugs to inhibit chemoresistance stimuli[58].

**CONCLUSION**

In summary, resistance to several chemotherapies, including gemcitabine, erlotinib, 5-FU, and cisplatin, in PDAC is mediated by EMT. Therefore, the EMT pathway has great therapeutic significance to overcome chemoresistance in PDAC. EMT is regulated by several pathways, such as TGF-β, Notch, and Wnt/β catenin signaling pathways. Although many studies have explored the role of EMT in chemotherapy-resistant PDAC, the mechanism is unclear and further studies are required. The EMT process is executed *via* EMT-TFs; therefore, it can be inhibited by targeting EMT-TFs in its initial stage. In addition, targeting EMT-TFs and miRNAs, and inhibiting stimuli of chemoresistance might be effective to ameliorate EMT-driven drug resistance in PDAC. Despite certain limitations, we can be optimistic about the efficacy of anti-EMT compounds, which might overcome chemoresistance of PDAC cells in the near future.

**REFERENCES**

1 **Rahib L**, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 2014; **74**: 2913-2921 [PMID: 24840647 DOI: 10.1158/0008-5472.CAN-14-0155]

2 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

3 **Collisson EA**, Bailey P, Chang DK, Biankin AV. Molecular subtypes of pancreatic cancer. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 207-220 [PMID: 30718832 DOI: 10.1038/s41575-019-0109-y]

4 **Khomiak A**, Brunner M, Kordes M, Lindblad S, Miksch RC, Öhlund D, Regel I. Recent Discoveries of Diagnostic, Prognostic and Predictive Biomarkers for Pancreatic Cancer. *Cancers (Basel)* 2020; **12** [PMID: 33147766 DOI: 10.3390/cancers12113234]

5 **Löhr M**. Is it possible to survive pancreatic cancer? *Nat Clin Pract Gastroenterol Hepatol* 2006; **3**: 236-237 [PMID: 16672986 DOI: 10.1038/ncpgasthep0469]

6 **Rawla P**, Sunkara T, Gaduputi V. Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. *World J Oncol* 2019; **10**: 10-27 [PMID: 30834048 DOI: 10.14740/wjon1166]

7 **Aroldi F**, Bertocchi P, Savelli G, Rosso E, Zaniboni A. Pancreatic cancer: New hopes after first line treatment. *World J Gastrointest Oncol* 2016; **8**: 682-687 [PMID: 27672426 DOI: 10.4251/wjgo.v8.i9.682]

8 **Passero FC Jr**, Saif MW. Second line treatment options for pancreatic cancer. *Expert Opin Pharmacother* 2017; **18**: 1607-1617 [PMID: 28820270 DOI: 10.1080/14656566.2017.1369955]

9 **Zeng S**, Pöttler M, Lan B, Grützmann R, Pilarsky C, Yang H. Chemoresistance in Pancreatic Cancer. *Int J Mol Sci* 2019; **20** [PMID: 31514451 DOI: 10.3390/ijms20184504]

10 **Shibue T**, Weinberg RA. EMT, CSCs, and drug resistance: the mechanistic link and clinical implications. *Nat Rev Clin Oncol* 2017; **14**: 611-629 [PMID: 28397828 DOI: 10.1038/nrclinonc.2017.44]

11 **Rodriguez-Aznar E**, Wiesmüller L, Sainz B Jr, Hermann PC. EMT and Stemness-Key Players in Pancreatic Cancer Stem Cells. *Cancers (Basel)* 2019; **11** [PMID: 31398893 DOI: 10.3390/cancers11081136]

12 **Krantz SB**, Shields MA, Dangi-Garimella S, Bentrem DJ, Munshi HG. Contribution of epithelial-mesenchymal transition to pancreatic cancer progression. *Cancers (Basel)* 2010; **2**: 2084-2097 [PMID: 24281219 DOI: 10.3390/cancers2042084]

13 **Brabletz T**, Kalluri R, Nieto MA, Weinberg RA. EMT in cancer. *Nat Rev Cancer* 2018; **18**: 128-134 [PMID: 29326430 DOI: 10.1038/nrc.2017.118]

14 **Hay ED**. An overview of epithelio-mesenchymal transformation. *Acta Anat (Basel)* 1995; **154**: 8-20 [PMID: 8714286 DOI: 10.1159/000147748]

15 **Recondo G**, Mezquita L, Facchinetti F, Planchard D, Gazzah A, Bigot L, Rizvi AZ, Frias RL, Thiery JP, Scoazec JY, Sourisseau T, Howarth K, Deas O, Samofalova D, Galissant J, Tesson P, Braye F, Naltet C, Lavaud P, Mahjoubi L, Abou Lovergne A, Vassal G, Bahleda R, Hollebecque A, Nicotra C, Ngo-Camus M, Michiels S, Lacroix L, Richon C, Auger N, De Baere T, Tselikas L, Solary E, Angevin E, Eggermont AM, Andre F, Massard C, Olaussen KA, Soria JC, Besse B, Friboulet L. Diverse Resistance Mechanisms to the Third-Generation ALK Inhibitor Lorlatinib in ALK-Rearranged Lung Cancer. *Clin Cancer Res* 2020; **26**: 242-255 [PMID: 31585938 DOI: 10.1158/1078-0432.CCR-19-1104]

16 **Yang J**, Antin P, Berx G, Blanpain C, Brabletz T, Bronner M, Campbell K, Cano A, Casanova J, Christofori G, Dedhar S, Derynck R, Ford HL, Fuxe J, García de Herreros A, Goodall GJ, Hadjantonakis AK, Huang RJY, Kalcheim C, Kalluri R, Kang Y, Khew-Goodall Y, Levine H, Liu J, Longmore GD, Mani SA, Massagué J, Mayor R, McClay D, Mostov KE, Newgreen DF, Nieto MA, Puisieux A, Runyan R, Savagner P, Stanger B, Stemmler MP, Takahashi Y, Takeichi M, Theveneau E, Thiery JP, Thompson EW, Weinberg RA, Williams ED, Xing J, Zhou BP, Sheng G; EMT International Association (TEMTIA). Guidelines and definitions for research on epithelial-mesenchymal transition. *Nat Rev Mol Cell Biol* 2020; **21**: 341-352 [PMID: 32300252 DOI: 10.1038/s41580-020-0237-9]

17 **Arumugam T**, Ramachandran V, Fournier KF, Wang H, Marquis L, Abbruzzese JL, Gallick GE, Logsdon CD, McConkey DJ, Choi W. Epithelial to mesenchymal transition contributes to drug resistance in pancreatic cancer. *Cancer Res* 2009; **69**: 5820-5828 [PMID: 19584296 DOI: 10.1158/0008-5472.CAN-08-2819]

18 **Rhim AD**, Mirek ET, Aiello NM, Maitra A, Bailey JM, McAllister F, Reichert M, Beatty GL, Rustgi AK, Vonderheide RH, Leach SD, Stanger BZ. EMT and dissemination precede pancreatic tumor formation. *Cell* 2012; **148**: 349-361 [PMID: 22265420 DOI: 10.1016/j.cell.2011.11.025]

19 **Alvarez MA**, Freitas JP, Mazher Hussain S, Glazer ES. TGF-β Inhibitors in Metastatic Pancreatic Ductal Adenocarcinoma. *J Gastrointest Cancer* 2019; **50**: 207-213 [PMID: 30891677 DOI: 10.1007/s12029-018-00195-5]

20 **Mittal V**. Epithelial Mesenchymal Transition in Tumor Metastasis. *Annu Rev Pathol* 2018; **13**: 395-412 [PMID: 29414248 DOI: 10.1146/annurev-pathol-020117-043854]

21 **Du B**, Shim JS. Targeting Epithelial-Mesenchymal Transition (EMT) to Overcome Drug Resistance in Cancer. *Molecules* 2016; **21** [PMID: 27455225 DOI: 10.3390/molecules21070965]

22 **Huang J**, Li H, Ren G. Epithelial-mesenchymal transition and drug resistance in breast cancer (Review). *Int J Oncol* 2015; **47**: 840-848 [PMID: 26202679 DOI: 10.3892/ijo.2015.3084]

23 **Fischer KR**, Durrans A, Lee S, Sheng J, Li F, Wong ST, Choi H, El Rayes T, Ryu S, Troeger J, Schwabe RF, Vahdat LT, Altorki NK, Mittal V, Gao D. Epithelial-to-mesenchymal transition is not required for lung metastasis but contributes to chemoresistance. *Nature* 2015; **527**: 472-476 [PMID: 26560033 DOI: 10.1038/nature15748]

24 **Zheng X**, Carstens JL, Kim J, Scheible M, Kaye J, Sugimoto H, Wu CC, LeBleu VS, Kalluri R. Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer. *Nature* 2015; **527**: 525-530 [PMID: 26560028 DOI: 10.1038/nature16064]

25 **Barton-Burke M**. Gemcitabine: a pharmacologic and clinical overview. *Cancer Nurs* 1999; **22**: 176-183 [PMID: 10217035 DOI: 10.1097/00002820-199904000-00011]

26 **Cao H**, LE D, Yang LX. Current status in chemotherapy for advanced pancreatic adenocarcinoma. *Anticancer Res* 2013; **33**: 1785-1791 [PMID: 23645722]

27 **Kim Y**, Han D, Min H, Jin J, Yi EC, Kim Y. Comparative proteomic profiling of pancreatic ductal adenocarcinoma cell lines. *Mol Cells* 2014; **37**: 888-898 [PMID: 25518923 DOI: 10.14348/molcells.2014.0207]

28 **El Amrani M**, Corfiotti F, Corvaisier M, Vasseur R, Fulbert M, Skrzypczyk C, Deshorgues AC, Gnemmi V, Tulasne D, Lahdaoui F, Vincent A, Pruvot FR, Van Seuningen I, Huet G, Truant S. Gemcitabine-induced epithelial-mesenchymal transition-like changes sustain chemoresistance of pancreatic cancer cells of mesenchymal-like phenotype. *Mol Carcinog* 2019; **58**: 1985-1997 [PMID: 31373074 DOI: 10.1002/mc.23090]

29 **Tsukasa K**, Ding Q, Yoshimitsu M, Miyazaki Y, Matsubara S, Takao S. Slug contributes to gemcitabine resistance through epithelial-mesenchymal transition in CD133(+) pancreatic cancer cells. *Hum Cell* 2015; **28**: 167-174 [PMID: 25997702 DOI: 10.1007/s13577-015-0117-3]

30 **Barati Bagherabad M**, Afzaljavan F, ShahidSales S, Hassanian SM, Avan A. Targeted therapies in pancreatic cancer: Promises and failures. *J Cell Biochem* 2019; **120**: 2726-2741 [PMID: 28703890 DOI: 10.1002/jcb.26284]

31 **Zhao H**, Duan Q, Zhang Z, Li H, Wu H, Shen Q, Wang C, Yin T. Up-regulation of glycolysis promotes the stemness and EMT phenotypes in gemcitabine-resistant pancreatic cancer cells. *J Cell Mol Med* 2017; **21**: 2055-2067 [PMID: 28244691 DOI: 10.1111/jcmm.13126]

32 **Wang X**, Song Z, Chen F, Yang X, Wu B, Xie S, Zheng X, Cai Y, Chen W, Zhong Z. AMPK-related kinase 5 (ARK5) enhances gemcitabine resistance in pancreatic carcinoma by inducing epithelial-mesenchymal transition. *Am J Transl Res* 2018; **10**: 4095-4106 [PMID: 30662653]

33 **Wang S**, Li MY, Liu Y, Vlantis AC, Chan JY, Xue L, Hu BG, Yang S, Chen MX, Zhou S, Guo W, Zeng X, Qiu S, van Hasselt CA, Tong MC, Chen GG. The role of microRNA in cisplatin resistance or sensitivity. *Expert Opin Ther Targets* 2020; **24**: 885-897 [PMID: 32559147 DOI: 10.1080/14728222.2020.1785431]

34 **Li Y**, VandenBoom TG 2nd, Kong D, Wang Z, Ali S, Philip PA, Sarkar FH. Up-regulation of miR-200 and let-7 by natural agents leads to the reversal of epithelial-to-mesenchymal transition in gemcitabine-resistant pancreatic cancer cells. *Cancer Res* 2009; **69**: 6704-6712 [PMID: 19654291 DOI: 10.1158/0008-5472.CAN-09-1298]

35 **Xu D**, Yang F, Wu K, Xu X, Zeng K, An Y, Xu F, Xun J, Lv X, Zhang X, Yang X, Xu L. Lost miR-141 and upregulated TM4SF1 expressions associate with poor prognosis of pancreatic cancer: regulation of EMT and angiogenesis by miR-141 and TM4SF1 *via* AKT. *Cancer Biol Ther* 2020; **21**: 354-363 [PMID: 31906774 DOI: 10.1080/15384047.2019.1702401]

36 **Zhao T**, Jin F, Xiao D, Wang H, Huang C, Wang X, Gao S, Liu J, Yang S, Hao J. IL-37/ STAT3/ HIF-1α negative feedback signaling drives gemcitabine resistance in pancreatic cancer. *Theranostics* 2020; **10**: 4088-4100 [PMID: 32226541 DOI: 10.7150/thno.42416]

37 **Barr S**, Thomson S, Buck E, Russo S, Petti F, Sujka-Kwok I, Eyzaguirre A, Rosenfeld-Franklin M, Gibson NW, Miglarese M, Epstein D, Iwata KK, Haley JD. Bypassing cellular EGF receptor dependence through epithelial-to-mesenchymal-like transitions. *Clin Exp Metastasis* 2008; **25**: 685-693 [PMID: 18236164 DOI: 10.1007/s10585-007-9121-7]

38 **Buck E**, Eyzaguirre A, Barr S, Thompson S, Sennello R, Young D, Iwata KK, Gibson NW, Cagnoni P, Haley JD. Loss of homotypic cell adhesion by epithelial-mesenchymal transition or mutation limits sensitivity to epidermal growth factor receptor inhibition. *Mol Cancer Ther* 2007; **6**: 532-541 [PMID: 17308052 DOI: 10.1158/1535-7163.MCT-06-0462]

39 **Izumchenko E**, Chang X, Michailidi C, Kagohara L, Ravi R, Paz K, Brait M, Hoque MO, Ling S, Bedi A, Sidransky D. The TGFβ-miR200-MIG6 pathway orchestrates the EMT-associated kinase switch that induces resistance to EGFR inhibitors. *Cancer Res* 2014; **74**: 3995-4005 [PMID: 24830724 DOI: 10.1158/0008-5472.CAN-14-0110]

40 **Sanomachi T**, Suzuki S, Togashi K, Seino S, Yoshioka T, Kitanaka C, Okada M, Yamamoto M. Brexpiprazole Reduces Survivin and Reverses EGFR Tyrosine Kinase Inhibitor Resistance in Lung and Pancreatic Cancer. *Anticancer Res* 2019; **39**: 4817-4828 [PMID: 31519584 DOI: 10.21873/anticanres.13667]

41 **Zhao X**, Yang Y, Yu H, Wu W, Sun Y, Pan Y, Kong L. Polydatin inhibits ZEB1-invoked epithelial-mesenchymal transition in fructose-induced liver fibrosis. *J Cell Mol Med* 2020; **24**: 13208-13222 [PMID: 33058500 DOI: 10.1111/jcmm.15933]

42 **Li H**, Jiang W, Liu XN, Yuan LY, Li TJ, Li S, Xu SS, Zhang WH, Gao HL, Han X, Wang WQ, Wu CT, Yu XJ, Xu HX, Liu L. TET1 downregulates epithelial-mesenchymal transition and chemoresistance in PDAC by demethylating CHL1 to inhibit the Hedgehog signaling pathway. *Oncogene* 2020; **39**: 5825-5838 [PMID: 32753651 DOI: 10.1038/s41388-020-01407-8]

43 **Meidhof S**, Brabletz S, Lehmann W, Preca BT, Mock K, Ruh M, Schüler J, Berthold M, Weber A, Burk U, Lübbert M, Puhr M, Culig Z, Wellner U, Keck T, Bronsert P, Küsters S, Hopt UT, Stemmler MP, Brabletz T. ZEB1-associated drug resistance in cancer cells is reversed by the class I HDAC inhibitor mocetinostat. *EMBO Mol Med* 2015; **7**: 831-847 [PMID: 25872941 DOI: 10.15252/emmm.201404396]

44 **Garg M**. Epithelial-mesenchymal transition - activating transcription factors - multifunctional regulators in cancer. *World J Stem Cells* 2013; **5**: 188-195 [PMID: 24179606 DOI: 10.4252/wjsc.v5.i4.188]

45 **Ma J**, Fang B, Zeng F, Ma C, Pang H, Cheng L, Shi Y, Wang H, Yin B, Xia J, Wang Z. Down-regulation of miR-223 reverses epithelial-mesenchymal transition in gemcitabine-resistant pancreatic cancer cells. *Oncotarget* 2015; **6**: 1740-1749 [PMID: 25638153 DOI: 10.18632/oncotarget.2714]

46 **Wang Z**, Li Y, Kong D, Banerjee S, Ahmad A, Azmi AS, Ali S, Abbruzzese JL, Gallick GE, Sarkar FH. Acquisition of epithelial-mesenchymal transition phenotype of gemcitabine-resistant pancreatic cancer cells is linked with activation of the notch signaling pathway. *Cancer Res* 2009; **69**: 2400-2407 [PMID: 19276344 DOI: 10.1158/0008-5472.CAN-08-4312]

47 **Güngör C**, Zander H, Effenberger KE, Vashist YK, Kalinina T, Izbicki JR, Yekebas E, Bockhorn M. Notch signaling activated by replication stress-induced expression of midkine drives epithelial-mesenchymal transition and chemoresistance in pancreatic cancer. *Cancer Res* 2011; **71**: 5009-5019 [PMID: 21632553 DOI: 10.1158/0008-5472.CAN-11-0036]

48 **Melchionna R**, Iapicca P, Di Modugno F, Trono P, Sperduti I, Fassan M, Cataldo I, Rusev BC, Lawlor RT, Diodoro MG, Milella M, Grazi GL, Bissell MJ, Scarpa A, Nisticò P. The pattern of hMENA isoforms is regulated by TGF-β1 in pancreatic cancer and may predict patient outcome. *Oncoimmunology* 2016; **5**: e1221556 [PMID: 28123868 DOI: 10.1080/2162402X.2016.1221556]

49 **Zhan T**, Chen X, Tian X, Han Z, Liu M, Zou Y, Huang S, Chen A, Cheng X, Deng J, Tan J, Huang X. MiR-331-3p Links to Drug Resistance of Pancreatic Cancer Cells by Activating WNT/β-Catenin Signal *via* ST7L. *Technol Cancer Res Treat* 2020; **19**: 1533033820945801 [PMID: 32924881 DOI: 10.1177/1533033820945801]

50 **Sánchez-Tilló E**, Liu Y, de Barrios O, Siles L, Fanlo L, Cuatrecasas M, Darling DS, Dean DC, Castells A, Postigo A. EMT-activating transcription factors in cancer: beyond EMT and tumor invasiveness. *Cell Mol Life Sci* 2012; **69**: 3429-3456 [PMID: 22945800 DOI: 10.1007/s00018-012-1122-2]

51 **Hotz B**, Arndt M, Dullat S, Bhargava S, Buhr HJ, Hotz HG. Epithelial to mesenchymal transition: expression of the regulators snail, slug, and twist in pancreatic cancer. *Clin Cancer Res* 2007; **13**: 4769-4776 [PMID: 17699854 DOI: 10.1158/1078-0432.CCR-06-2926]

52 **Kaşıkcı E**, Aydemir E, Bayrak ÖF, Şahin F. Inhibition of Migration, Invasion and Drug Resistance of Pancreatic Adenocarcinoma Cells - Role of Snail, Slug and Twist and Small Molecule Inhibitors. *Onco Targets Ther* 2020; **13**: 5763-5777 [PMID: 32606788 DOI: 10.2147/OTT.S253418]

53 **Namba T**, Kodama R, Moritomo S, Hoshino T, Mizushima T. Zidovudine, an anti-viral drug, resensitizes gemcitabine-resistant pancreatic cancer cells to gemcitabine by inhibition of the Akt-GSK3β-Snail pathway. *Cell Death Dis* 2015; **6**: e1795 [PMID: 26111057 DOI: 10.1038/cddis.2015.172]

54 **Wellner U**, Schubert J, Burk UC, Schmalhofer O, Zhu F, Sonntag A, Waldvogel B, Vannier C, Darling D, zur Hausen A, Brunton VG, Morton J, Sansom O, Schüler J, Stemmler MP, Herzberger C, Hopt U, Keck T, Brabletz S, Brabletz T. The EMT-activator ZEB1 promotes tumorigenicity by repressing stemness-inhibiting microRNAs. *Nat Cell Biol* 2009; **11**: 1487-1495 [PMID: 19935649 DOI: 10.1038/ncb1998]

55 **Duguang L**, Jin H, Xiaowei Q, Peng X, Xiaodong W, Zhennan L, Jianjun Q, Jie Y. The involvement of lncRNAs in the development and progression of pancreatic cancer. *Cancer Biol Ther* 2017; **18**: 927-936 [PMID: 29053398 DOI: 10.1080/15384047.2017.1385682]

56 **Song WF**, Wang L, Huang WY, Cai X, Cui JJ, Wang LW. MiR-21 upregulation induced by promoter zone histone acetylation is associated with chemoresistance to gemcitabine and enhanced malignancy of pancreatic cancer cells. *Asian Pac J Cancer Prev* 2013; **14**: 7529-7536 [PMID: 24460329 DOI: 10.7314/apjcp.2013.14.12.7529]

57 **Liu G**, Ji L, Ke M, Ou Z, Tang N, Li Y. miR-125a-3p is responsible for chemosensitivity in PDAC by inhibiting epithelial-mesenchymal transition *via* Fyn. *Biomed Pharmacother* 2018; **106**: 523-531 [PMID: 29990840 DOI: 10.1016/j.biopha.2018.06.114]

58 **Marcucci F**, Stassi G, De Maria R. Epithelial-mesenchymal transition: a new target in anticancer drug discovery. *Nat Rev Drug Discov* 2016; **15**: 311-325 [PMID: 26822829 DOI: 10.1038/nrd.2015.13]

59 **Davis FM**, Stewart TA, Thompson EW, Monteith GR. Targeting EMT in cancer: opportunities for pharmacological intervention. *Trends Pharmacol Sci* 2014; **35**: 479-488 [PMID: 25042456 DOI: 10.1016/j.tips.2014.06.006]

60 **Burk U**, Schubert J, Wellner U, Schmalhofer O, Vincan E, Spaderna S, Brabletz T. A reciprocal repression between ZEB1 and members of the miR-200 family promotes EMT and invasion in cancer cells. *EMBO Rep* 2008; **9**: 582-589 [PMID: 18483486 DOI: 10.1038/embor.2008.74]

61 **Khalafalla FG**, Khan MW. Inflammation and Epithelial-Mesenchymal Transition in Pancreatic Ductal Adenocarcinoma: Fighting Against Multiple Opponents. *Cancer Growth Metastasis* 2017; **10**: 1179064417709287 [PMID: 28579826 DOI: 10.1177/1179064417709287]

62 **Gao Y**, Zhang Z, Li K, Gong L, Yang Q, Huang X, Hong C, Ding M, Yang H. Linc-DYNC2H1-4 promotes EMT and CSC phenotypes by acting as a sponge of miR-145 in pancreatic cancer cells. *Cell Death Dis* 2017; **8**: e2924 [PMID: 28703793 DOI: 10.1038/cddis.2017.311]

**Footnotes**

**Conflict-of-interest statement:** The authors declare that they have no conflict of interests for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** January 28, 2021

**First decision:** February 24, 2021

**Article in press:**

**Specialty type:** Gastroenterology and Hepatology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Carloni R **S-Editor:** Wang JL **L-Editor:** Wang TQ **P-Editor:**

**Figure Legends**



**Figure 1 Involvement of epithelial-mesenchymal transition in therapy resistance in pancreatic ductal adenocarcinoma.** Epithelial-mesenchymal transition (EMT) is induced by various factors including signaling pathways, EMT-activating transcription factors (EMT-TFs), microRNAs, or microenvironment. Promotion of the EMT program enhances the chemoresistance in pancreatic ductal adenocarcinoma. EMT: Epithelial-mesenchymal transition; PDAC: Pancreatic ductal adenocarcinoma; EMT-TFs: Epithelial-mesenchymal transition-activating transcription factors; CAFs: Cancer-associated fibroblasts; PSCs: Pancreatic stellate cells.

**Table 1 Involvement of diverse miRNAs associated with epithelial-mesenchymal transition-mediated resistance in pancreatic ductal adenocarcinoma**

|  |  |  |  |
| --- | --- | --- | --- |
| **miRNA** | **Signaling axis** | **Function** | **Ref.** |
| miR-200 | MiR-200/ZEB1/EMT | MiR-200 inhibited EMT and increased the sensitivity of GR PC cells to gemcitabine | [34] |
| miR-141 | MiR-141/TM4SF1/AKT/EMT | MiR-141 inhibited EMT and reduced TM4SF1 expression by suppressing AKT signaling pathway | [35] |
| miR-203 | MiR203-ZEB1-EMT | MiR-203 inhibited EMT and increased the sensitivity to gemcitabine | [43] |
| miR-223 | MiR-223/Fbw7/Notch-1/EMT | MiR-223 induced EMT and conferred gemcitabine-resistance by downregulation of Fbw7 and subsequent upregulation of Notch-1 | [45] |
| miR-331-3p | miR-331-3p/ST7L/Wnt/β-catenin/EMT | MiR-331-3p induced EMT and conferred gemcitabine-resistance by activating the Wnt/β-catenin signaling pathway via ST7L | [49] |
| miR-21 | miR-21/PTEN/Akt | MiR-21 induced invasion, and metastasis, and conferred gemcitabine-resistance by miR-21/PTEN/Akt | [56] |
| miR-125a-3p | miR-125a-3p/Fyn/EMT | MiR-125a-3p inhibited EMT and increased chemosensitivity to gemcitabine by directly targeting Fyn | [57] |
| miR-145 | miR-145/ ZEB1/EMT | MiR-145 inhibited EMT and reversed acquired gemcitabine resistance | [62] |

EMT: Epithelial-mesenchymal transition; ZEB1: E-box binding homeobox 1; GR: Gemcitabine-resistant; PC: Pancreatic cancer.