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

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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

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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

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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 lose 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 Ecadherin while enhancing the expression of the mesenchymal factors (e.g., Ncadherin, 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 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, SNAI1, 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, MIA/PaCa-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].

Moreover, Gunogor et al. [17] 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 NFκB and increases chemoresistance in PDAC.
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 [13,15]. 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 TWIST1) 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 tumorinitiating 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-
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/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.

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.

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