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The Role of EMT in Pancreatic Cancer Progression

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Pancreatic Cancer (PCa) is one of the most common malignancies in the United States. According to American Cancer Society surveys, it is estimated that 44,030 new PCa cases have been occurred and 37,660 patients diagnosed with PCa died in 2011 [1]. The causes of PCa development are largely unclear even though multiple studies indicated that many factors such as family history, smoking, obesity, diet, diabetes mellitus, and chronic pancreatitis are correlated with increased incidence of PCa [2]. The current treatments for PCa patients include surgery, radiation and chemotherapy. Although the treatments have been improved during past decades, the five-year survival rate is only approximately 6% [1]. One of the reasons is due to fact that about 80% of all PCa patients have locoregional spread and/or distant metastasis [1]. Therefore, understanding the molecular mechanisms underlying the metastasis of PCa is required to improve the survival in patients diagnosed with this deadly disease.

In recent years, many genes and cellular signaling pathways have been found to be involved in the invasion and metastasis in PCa. For example, our studies have demonstrated that Notch signaling pathway promotes migration and invasion through upregulation of NF-κB (Nuclear Factor-Kappa b) and its target gene such as MMP-9 (Matrix Metallopeptidase-9) and VFGF (Vascular Endothelial Growth Factor) in PCa [3]. Moreover, we found that PDGF-D (Platelet-Derived Growth Factor-D) promoted cell invasion through Notch-1 and NF-κB signaling in PCa [4]. One group led by Batra reported that MUC4 potentiates invasion and metastasis of PCa cells through stabilization of FGFR-1 (Fibroblast Growth Factor Receptor-1) [5]. Recently, it has been shown that concurrent inhibition of c-Met and VEGF signaling suppresses the tumor invasion and metastasis in pancreatic neuroendocrine tumors [6].

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Recently, it has been indicated that EMT (Epithelial to Mesenchymal Transition) plays a crucial role in the invasion and metastasis of PCa. It is well known that EMT occurs normally during embryonal development, which is characterized by loss of epithelial cell-cell contacts through inhibition of E-cadherin, ZO-1, occludin, claudin-1, and claudin-7 [7]. In parallel, cells acquire mesenchymal features such as upregulation of Slug, Snail, ZEB1 (Zinc-Finger E-Box Binding Homeobox 1), ZEB2, Twist as well as Vimentin, and production of matrix proteins, leading to cell migration and invasion [7]. Multiple studies have indicated that EMT occurred in the progression of human cancers; however, it has no direct evidence to approve this concept due to the fact that EMT is transient and lacks the specific markers. In addition, the molecular mechanisms by which EMT occurs are not fully elucidated so far.

Accumulating evidence has revealed that many growth factors and cytokines as well as cellular signaling pathways could trigger EMT program such as TGFβ transforming growth factor beta, Wnt, Notch, NF-κB, EGF (Epidermal Growth Factor), HGF (Hepatocyte Growth Factor), and PDGF in PCa cells [8–11]. For example, our studies have shown that the activation of Notch signaling is mechanistically associated with EMT phenotype of PCa cells [12]. To support the role of Notch signaling pathway in EMT, we observed that over-expression of Notch-1 led to the induction of EMT phenotype through activation of mesenchymal cell markers including ZEB1 and EpCAM, suggesting that the activation of Notch-1 signaling contributes to the acquisition of EMT phenotype in PCa cells [9]. Similarly, we found that over-expression of FoxM1 caused the acquisition of EMT phenotype via up regulating mesenchymal cell markers including ZEB1, ZEB2, Snail 2 and Vimentin in PCa cells [13]. Consistent with this notion, Thiery et al. [7] found that FoxM1-Caveolin1 promoted EMT in both mouse and human PCa cells [14]. Additionally, hypoxia has been reported to induce EMT, resulting in promoting metastasis of PCa cells, demonstrating that antioxidants may be useful therapeutic agents for treatment of PCa [15]. Interestingly, Joost et al. [16] reported that inhibition of Hedgehog pathway effector transcription factor Gli1 promotes EMT in PCa cells [16]. These results suggest that further investigation is necessary to explore the mechanisms underlying EMT progression.

Since micorRNAs (miRNAs), 21–25 nucleotide RNA molecules that govern the translation and stability of mRNAs, have been found to be involved in tumor invasion and metastasis in PCa, research scientists hypothesize that miRNAs might play a critical role in regulation of EMT. Indeed, one study from Brabletz group showed that ZEB1 triggers the miR-200 family-mediated feedforward loop that promotes EMT and invasion of PCa cells [17]. Moreover, this group demonstrated that ZEB1 promotes tumorigenicity by repressing stemness-inhibiting microRNAs including miR-203, miR-183 and miR-200 family in PCa cells [18]. Consistent with these results, the abundance of miR-200 family was correlated positively with E-cadherin expression and negatively with the expression of EMT-associated transfactor [19]. To further support the role of miR-200 in regulating EMT, Yu et al. [20] also found a remarkably strong correlation between the levels of miR-200c and E-cadherin expression in PCa cells [20]. Recently, one study revealed that DCAMKL-1 controls EMT via a miR-200-dependent mechanism in PCa, indicating that it has a direct regulatory links between DCAMKL-1, miRNAs, and EMT in PCa [21]. More recently, miR-126 was found to regulate ADAM9 and induce E-cadherin, suggesting that miR-126/ADAM9 axis inhibits the cell invasion partly through regulation of EMT in PCa cells [22]. Taken together, miRNAs play pivotal roles in governing EMT in PCa.

Interestingly, a growing body of evidence suggests that EMT-type cells have CSCs (Cancer Stem Cells) characteristics in a variety of human malignancies including PCa. It is accepted that CSCs, which have been identified using different sets of stem cell surface markers in various types of human cancers, possess the ability to self-renew and generate the diverse

cell population [23]. The cell surface markers for pancreas-specific CSCs are CD44, CD24, ESA (Epithelial Specific Antigen), and CD133 [23]. To support the link between EMT and CSCs in PCa, Shah et al. [24] found that EMT-type cells have increased expression of the stem cell markers CD24, CD44, and ESA [24]. In line with this notion, our previous studies have revealed that PCa cells with EMT phenotype have increased sphere-forming capacity and high expression of CSC surface markers such as CD44 and EpCAM [13]. To this end, targeting EMT could reduce the population of CSCs that have been implicated in tumor metastasis and drug resistance. Without a doubt, further studies are required to explore the molecular mechanisms of how EMT-type cells acquire the CSCs features.

Strikingly, EMT-type cells have been shown to contribute to drug resistance in PCa. For example, the study led by Choi showed that EMT-type cells are resistant to gemcitabine, 5-FU (5-fluorouracil) and cisplatin, while non-EMT-type cells are sensitive to these chemotherapeutic drugs [25]. Furthermore, they found that ZEB1 and other regulators of EMT could maintain drug resistance in human PCa cells [25]. Similarly, the study from our group showed that E-cadherin was down-regulated and Vimentin was up-regulated in Gemcitabine-Resistant (GR) PCa cells [26]. Consistent with this concept that EMT plays a critical role in drug resistance, generated GR PCa cells from gemcitabine sensitive PCa cells are also associated with EMT [24]. Specifically, GR cells have down-regulation of E-cadherin and up-regulation of Vimentin [24]. Moreover, we found that acquisition of EMT phenotype of GR cells is correlated with over-expression of the Notch signaling pathway [12]. In parallel, another group reported that activation of Notch signaling increased chemoresistance in part due to induction of EMT in PCa cells [27]. Additionally, PCa cells resistant to chemoradiotherapy showed phenotypic and molecular changes consistent with EMT, including increased Vimentin and decreased E-cadherin. [28]. Furthermore, these resistant cells expressed high levels of stem cell markers Oct4, CD24, and CD133, indicating that chemoradiation resistance-induced EMT is associated with CSCs generation [28]. More recently, Carbone et al. [29] discovered that anti-VEGF treatment-resistant PCa cells secrete proinflammatory factors to induce EMT [29]. Altogether, EMT plays an important role in regulation of drug resistance in PCa, suggesting that targeting EMT could contribute to increased sensitivity to chemotherapy.

In summary, EMT has been found to play critical roles in the control of tumor invasion, metastasis and drug resistance in PCa. Several factors, cytokines and cellular signaling pathways such as Notch, FoxM1, and Hedgehog could trigger EMT. Moreover, miRNAs have been reported to govern the induction of EMT through regulating its target mRNAs. More importantly, specific natural compounds could partially reverse the EMT phenotype to MET, resulting in the reversal of drug resistance. Therefore, targeting EMT-type cells by non-toxic natural agents could be a novel potential therapeutic strategy for treatment of metastatic PCa.

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