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**Therapeutic potential of targeting acinar cell reprogramming in pancreatic cancer**

Wong CH *et al*. Targeting acinar cell reprogramming

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**Abstract**

Pancreatic ductal adenocarcinoma (PDAC) is a common pancreatic cancer contributing to the fourth leading cause of cancer death in the United States. Treating this life-threatening disease remains challenging due to the lack of effective prognosis, diagnosis, and therapy. Apart from pancreatic duct cells, acinar cells may also be the origin of PDAC. During pancreatitis or combined with activating KRasG12D mutation, acinar cells lose their cellular identity and undergo a transdifferentiation process called acinar-to-ductal-metaplasia (ADM) forming duct cells which may then transformed into pancreatic intraepithelial neoplasia (PanIN) and eventually PDAC. During ADM, the activation of mitogen-activated protein kinases, Wnt, Notch, and phosphatidylinositide 3-kinases/Akt signaling inhibits the transcription of acinar-specific genes including Mist and amylase but promotes the expression of ductal genes such as cytokeratin-19. Inhibition of this transdifferentiation process hinders the development of PanIN and PDAC. In addition, the transdifferentiated cells regain acinar identity indicating ADM may be a reversible process. This provides a new therapeutic direction in treating PDAC through cancer reprogramming. Many studies have already demonstrated the success of switching PanIN/ PDAC back to normal cells through the use of PD325901, the expression of E47, and the knockdown of Dickkopf-3. In this review, we discuss the signaling pathways involved in ADM and the therapeutic potential of targeting reprogramming in order to treat PDAC.

**Key words:** Acinar cells; Pancreatic ductal adenocarcinoma; Acinar-to-ductal metaplasia; Signal transduction; Reprogramming

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**Core tip:** Treating pancreatic ductal adenocarcinoma (PDAC) remains challenging due to the lack of effective therapeutics. Apart from pancreatic duct cells, acinar cells may also be the origin of PDAC. During pancreatitis or combined with activating KRasG12D mutation, acinar cells undergo a transdifferentiation process called acinar-to-ductal-metaplasia (ADM) forming duct cells which may then be transformed into PanIN and eventually PDAC. This process involves MAPK, Wnt, Notch, and PI3K/Akt signaling. Since ADM may be a reversible process, switching PDAC back to normal cells may also be achieved and developed as a novel therapy.

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**INTRODUCTION**

Pancreatic cancer is still the fourth leading cause of cancer death in the United States and Europe, although the incidence rate and death rate are stable starting from 1970s (in United States but keep increasing in European countries)[1,2]. Most (96%) of the pancreatic cancer is from exocrine pancreas including pancreatic ductal adenocarcinoma (PDAC)[1]. Due to the lack of reliable diagnostics, over half of patients are usually diagnosed with pancreatic cancer at a distant stage. This also contributes to the low 5-year survival rate (7%) with median survival around 4 mo[1,3]. Surgery, chemotherapy and radiotherapy are commonly used to treat pancreatic cancer although they can only extend survival for several months or can be used as an alleviative instead of curing the patient[3,4]. Also, since many patients already have cancer metastasis when they are diagnosed, only a few patients can receive surgery. Chemotherapy drug gemcitabine is usually used together with surgery or targeted anti-cancer drug erlotinib. In addition, combining gemcitabine with other chemotherapy drug such as nab-paclitaxel or human monoclonal antibody such as AGS-1C4D4 can only provide a limited extension of survival by months in exchange of developing adverse effects including abdominal pain, peripheral neuropathy, and myelosuppression[5,6]. Therefore, a novel therapy is urgently needed. Here, we briefly introduce transdifferentiation of acinar cells to ductal cells with tumorigenic potential under the activation of cellular signaling pathways. Also, we discuss the therapeutic potential of reprogramming PDAC back to normal pancreatic cell such as acinar cell in order to treat cancer.

**ROLE OF ACINAR-TO-DUCTAL METAPLASIA IN THE INITIATION AND DEVELOPMENT OF PANCREATIC DUCTAL ADENOCARCINOMA**

Pancreas is composed of endocrine and exocrine compartment that is responsible for maintaining body homeostasis and digesting food respectively[7]. The endocrine pancreas is formed by islets cells which secrete hormones such as insulin and glucagon regulating the glucose level in the body. The exocrine pancreas consists of acinar cells which synthesize digestive enzymes such as amylase and duct cells which are responsible for transportation of digestive enzymes to duodenum for digestion. Studies show that PDAC may be originated from pancreatic duct cells through the development of pancreatic intraepithelial neoplasia (PanIN) after the first activating gene mutation in KRas[8]. KRasG12D mutation alone is insufficient to drive the development of PDAC[8]. Further genetic changes such as p16, p53 and SMAD4, and overexpression of epidermal growth factor receptor (EGFR), EGF and transforming growth factorα (TGFα) are required for the development to a higher-grade PanIN and eventually PDAC[9-12].

Apart from pancreatic duct cells, pancreatic acinar cells which are the source of acinar cell carcinoma may also contribute to the development of PDAC through acinar-to-ductal metaplasia (ADM)[13]. ADM is a type of transdifferentiation that a mature and differentiated cell type changes its identity to another differentiated cell type[14]. During ADM, acinar cells leave quiescent state and transdifferentiate to duct cells with losing their grape-like morphology and changing the transcriptome from acinar-like such as the expression of Mist, amylase, carboxypeptidase and elastase to duct-like including expression of cytokeratin-19 (CK-19), cytokeratin-20 (CK-20), and carbonic anhydrase II[13,15]. This transdifferentiation process involves a nestin-positive intermediate[15]. Also, studies using *in vivo* model showed that pancreatitis, both acute and chronic can result in ADM[16, 17]. These observations are consistent with the suggestion that chronic pancreatitis may be one of the causes of pancreatic cancer[18].

***MAPK signaling is involved in ADM***

It has been reported that more than 90% PDAC are with KRas activating mutation[10]. In addition, comparing with normal acinar cells, acinar cells with KRas mutation fail to regenerate during pancreatitis and undergo ADM forming PanIN. These indicate the importance of activing mutation of KRas in acinar reprogramming and PDAC development. KRas is involved in many signaling pathway such as mitogen-activated protein kinases (MAPK) signaling pathway, therefore, the importance of MAPK signaling pathway have been studied by the three- dimensional culture of mice acinar cells with activating mutation of KRasG12D after pancreatitis induction[16]. Inhibiting MAPK signaling pathway after pancreatitis maintains cells in grape-like acinar morphology and expressing amylase without undergoing ADM. In contrast, ADM is observed for acinar cell without MAPK signaling pathway inhibition after pancreatitis.

Upon the activation of EGFR by EGF family such as EGF and TGFα, growth factor receptor-bound protein 2 (GRB2) binds to the tyrosine kinase on the cytoplasmic side of EGFR through its SH2 domain[19]. This binding recruits guanine nucleotide exchange factors son of sevenless (SOS) to interact with the SH3 domain of GRB2 resulting in SOS activation. The activated SOS exchanges the GDP in resting Ras with GTP. Therefore, Ras is activated which then activates the protein kinase activity of serine/ threonine kinase Raf. Raf phosphorylates and activates mitogen-activated protein kinase kinase1/2 (MEK1/2). MEK1/2 phosphorylates and activates MAPK.

Nuclear factor of activated T-cells (NFAT) transcription factor family actively participates in the immune system including T-cell, B-cell, and dendritic cell[20]. Apart from immune system, NFAT is also involved in proliferation, invasion, angiogenesis, and drug-resistance in various cancer cells such as prostate, breast, and lung cancer[20-24]. In addition, it has been discovered that two family members NFATc1 and NFATc4 (NFATc1/4) may be the downstream target of MAPK signaling pathway and may correlate with ADM and PanIN development[25,26]. NFATc1 is expressed, activated, and accumulated in the nucleus of pancreatic cancer cells[27]. In addition, after the activation of MAPK signaling by TGFα, both NFATc1/4 are upregulated but not for other NFAT family members such as NFATc2 and NFATc3[25]. Furthermore, acinar to ductal morphological transdifferentiation is observed in NFATc1/4 expressing acinar cells. It has been demonstrated that during ADM, NFATc1 interacts with c-Jun which is activated by MAPK family member c-Jun N-terminal kinases (JNK) after activation of MAPK signaling as indicated by co-immunoprecipitation assay[26]. NFATc1-c-Jun complex is also observed in T-cells mediating immune response[28,29]. It binds to the promoter of *sex determining region Y-box 9* (Sox9) resulting in activation through histone3 lysine4 tri-methylation[26]. Hessmann also reported similar c-Jun complex formation and *Sox9* activation involving NFATc4[25]. Disrupting NFATc1/4-c-Jun complex results in failure in inducing *Sox9*. These observations consistently indicate the involvement of Sox9 in ADM.

Although Sox9 transcription factor is involved in ductal, acinar, and endocrine development, it is not expressed in acinar cells[30]. However, it is induced during chronic pancreatitis and ADM[25,26,31]. In addition, it is expressed in ductal cells, PanINs, and PDAC indicating its association in acinar reprogramming, cancer initiation and development[25,26]. On the other hand, acinar cells with *Sox9* deletion can still undergoes ADM upon pancreatic injury. Kopp suggested that another pancreatic development-related transcription factor hepatocyte nuclear factor 6 (Hnf6) can replace Sox9 with lower ADM-promoting efficiency[31]. Like Sox9, hepatocyte nuclear factor 1β (Hnf1β) and Hnf6 are expressed in normal ductal cells but not in acinar cells[32]. However, contrasting to the suggestion by Herbrok and colleagues that Hnf1β is upregulated during acinar dedifferentiation, the expression of Hnf1β is not observed during ADM in both human and mice tissue samples[32,33].

On the other hand, overexpression of Hnf6 triggers ADM which is indicated by the increase in CK-19 level and decrease in amylase and acinar transcription factor Mist level. Although how Hnf6 is regulated still needs further studies, Prévot demonstrated that Hnf6 can induce the expression of Sox9 while knockdown of *HNF6* alleles cannot fully deplete Sox9[32]. This indicates that Hnf6 is not the sole regulator of Sox9. In addition, Prrx1b isoform of another transcription factor Prrx1 which is also upregulated during acinar transdifferentiation and positively regulates the expression of *Sox9* through binding to its promotor and induces ADM[34]. Therefore, this may suggest that Sox9 is regulated by at least NFATc1/4-c-Jun, Hnf6, and Prrx1. Although depleting *Sox9* can still drive the reprogramming of acinar cells to ductal cells, no progression to PanIN is observed[31]. In addition, *Sox9* is expressed in PanIN and PDAC, but not for Hnf6[32]. This may suggest Sox although can be replaced partially by Hnf6 during ADM, it may still be required for PanIN progression.

Current evidence suggests that there may be a functional correlation between Sox9 and protein kinase D1 (PKD1)[35]. Similar to Sox9, PKD1 which is upregulated under the activation of MAPK signaling by either EGFR or KRasG12D promotes acinar cell reprogramming. Also, knockdown of *PKD1* or inhibiting PKD1 significantly suppress ADM. PKD1 bridges the MAPK and Notch signaling pathway and promotes the PanIN and adenocarcinoma formation[35]. When PKD1 is actively expressed in acinar cells, matrix metalloproteinases7 (MMP7), a disintegrin and metalloproteinase7 (Adam7), and Adam10 which are regulators of Notch are significantly upregulated, while Notch-suppressor suppressor enhancer lin12/Notch 1 like and casitas B-lineage lymphoma are downregulated[35, 36]. Sawey also reported similar findings that MMP7 is involved in ADM via MAPK signaling[36]. In addition, target of Notch signaling pathway such as hairy and enhancer of split-1 (Hes-1), Hairy/enhancer-of-split related with YRPW motif protein-1 (Hey-1), and p21 are significantly upregulated when PKD1 is activated[32, 33]. These results indicate that Notch signaling is involved in ADM.

***Wnt signaling is involved in ADM***

Wnt signaling is directly and indirectly involved in development and repair of various organs including pancreas, bone, kidney, and heart[37-40]. Wnt signaling pathway is complex and the three well-studied pathways are canonical pathway (or Wnt/β-catenin pathway), noncanonical planar cell polarity pathway, and noncanonical Wnt/calcium pathway[41]. Canonical pathway which is different from the other two in the involvement of β-catenin is required for ADM. When there is no Wnt signaling activation, β-catenin is originally degraded by phosphorylation and then ubiquitination involving β-catenin destruction complex (formed by protein phosphatase 2A, glycogen synthase kinase3, casein kinase 1α, adenomatosis polyposis coli, and Axin). Wnt signaling can be activated by the binding of Wnt protein to the Frizzled family receptor complex Fz/LRP5/6. This results in membrane translocation and binding of Axin to LRP5/6 through microtubule actin-linking factor 1. In addition, Dsh is activated and binds to the receptor complex inhibiting glycogen synthase kinase3. As a result, β-catenin destruction complex is disrupted and β-catenin accumulates. β-catenin then translocates to the nucleus activating its target genes.

 A growing numbers of studies suggest the role of canonical pathway in ADM. However, its role whether as a promotor or inhibitor depends on the progression of the reprogramming. Since canonical pathway is involved in many organ regeneration, it may also actively participate in pancreatic regeneration. During pancreatitis, canonical pathway is activated within one week indicated by the accumulation of β-catenin and Axin[42, 43]. Recovered pancreas with normal grape-like morphology and amylase expression is observed after one week. In addition, activation of canonical pathway blocks KRasG12D-driven ADM during pancreatitis resulting in normal recovery process. Similarly, overexpressing β-catenin does not results in PDAC but an uncommon intraductal tubular tumor[44,45].

On the other hand, gradual accumulation of β-catenin is observed after 1 month of pancreatitis in acinar cells with KRasG12D[42]. However, normal acinar morphology and acinar maker expression are not observed. Instead, mice with functional β-catenin and active mutation of KRasG12D express CK-19 and mucin indicating the progression of ADM and PanIN development respectively[44]. Also, inhibition of Frizzled receptor which is the starting point of Wnt signaling pathway by monoclonal antibody OMP-18R5 hinders the progression of ADM. The decrease in Wnt target genes Axin2, Lymphoid enhancer-binding factor-1, and MMP7 after treatment with OMP-18R5 in mice confirm the inhibition of Wnt signaling. Therefore, canonical Wnt signaling functions as an inhibitor during the initiation of ADM but promotes the formation of PanIN in the late process.

Sirtuin-1 (Sirt-1) functions as a protein deacetylase controlling the development of heart, brain, and spinal cord[46]. It is also found in both exocrine and endocrine pancreas. In endocrine pancreas, especially β-cell, Sirt-1 regulates the secretion of insulin[47]. While in injured exocrine pancreas, it promotes acinar transdifferentiation. During pancreatitis, Sirt-1 is transiently translocated from nucleus to cytoplasm, which is important for ADM[48]. Blocking Sirt-1 translocation significantly interferes with the expression of ductal genes. In addition, inhibiting Sirt-1 expression in nucleus by non-functional gene mutation significantly accelerates and prolongs the progression of acinar reprogramming. These results indicate that Sirt-1 functions as an ADM suppressor in nucleus. On the other hand, similar to suppressing MAPK signaling, the use of nicotinamide which is an end-product inhibitor of Sirt-1 in protein acetylation inhibits ADM after cytoplasmic shift of Sirt-1[48, 49]. The cytoplasmic Sirt-1 deacetylates β-catenin and acinar-specific transcription factors inhibiting the acinar regeneration.

***Notch signaling is involved in ADM***

Notch signaling is required for regulating the development of various vital organs including pancreas, bones, and blood[50-53]. Notch protein is composed of Notch extracellular domain (NECD), Notch transmembrane fragment (NTF), and Notch intracellular domain (NICD). Maturation of Notch receptor involves the cleavage of NECD from non-NECD and the integration of NECD heterodimer to the cell membrane. During organs development especially pancreas, Notch receptor is activated by type I transmembrane ligands including jagged-1 resulting in activation of membrane-bound protease which cleaves non-NECD into NTF and NICD. The released NICD translocates to the nucleus resulting in expression of target genes such as Hes-1 and nuclear factor-κB involving Rbp-J, Mastermind-like, and DEAD-box helicase.

Notch signaling is activated in PDAC and its precursor. Comparing with normal pancreatic tissues, Notch ligands jagged1, Notch receptors Notch2 and Notch3, and its target genes Hes-1 and Hey-1 are upregulated during pancreatitis, ADM and cancer development[13,43,54]. In addition, PDK1 which is upregulated during ADM activates Notch signaling pathway through at least MMP7[35]. Also, MMP7 is the downstream target in Wnt signaling during ADM since inhibition of Wnt signaling decreases the level of MMP7. MMP7 is one of main metalloproteinase responsible for activating cleavage of Notch receptor[55]. Therefore, the increase in MMP7 level indicates the involvement of Notch signaling in acinar cells reprogramming[36,56].

The downstream effector Hes-1 in Notch signaling pathway negatively regulates the basic helix-loop-helix (bHLH) transcription factor family which is involved in pancreatic development. One of the members neurgenin3 is involved in endocrine differentiation whereas acinar cell development requires Mist[57]. During development of exocrine pancreas in embryo, Notch signaling is activated in exocrine precursor but it is repressed in normal differentiated acinar cells. Since the downstream target Hes-1 in Notch signaling inhibits the transcription of acinar transcription factors, the inactivation of Notch signaling promotes the development of pancreatic acinar cells[58]. During acinar differentiation, Mist activates the genes involved in producing digestive enzymes such as amylase and carboxypeptidase, exocytosis, and maintaining acinar cell homeostasis[57, 59]. Inhibition of Mist in pancreatic acinar cells results in ADM as indicated by the loss of cell organization, the decrease in acinar gene expression, and the expression of ductal marker CK-19[60].

***PI3K/Akt signaling involved in ADM***

Although many studies focus on the loss of digestive enzymes in acinar cells, little emphasis have been put on the morphological changes during ADM. It has been suggested that the activation of Akt signaling is responsible for the morphogenesis in mammary acinar during malignant transformation[61]. Similarly, phosphatidylinositide 3-kinases (PI3K)/Akt signaling is also involved in structural changes from acinar to ductal through actin remodeling[62, 63]. Under KRas mutation, PI3Kα but not other isoforms (β, γ or δ) induces the morphological changes in acinar cells[63]. The activation of PI3Kα phosphorylates phosphatidylinositol 4, 5-bisphosphate (PIP2) forming phosphatidylinositol-3, 4, 5-trisphosphate (PIP3) which activates phosphoinositide-dependent kinase 1 (PDK1) through binding to pleckstrin homology (PH) domain and eventually activates Akt[64]. In addition, Rho GTPase especially RAC subfamily can be activated by PIP3 via RAC-GEFs (RAC- guanine nucleotide exchange factors) such as Vav-1 and Tiam-1 with PH-domain[65]. These downstream effectors RAC and Akt are important for the dynamic changes in actin structure[61,63-66]. The arranagement of actin *via* polymerization results in the morphological changes during ADM[63]. Inhibition or knockdown of PI3K, RAC or PDK1 not only maintains acinar morphology, but also inhibits the development of PanIN and PDAC[62-64].

Mutation in p53 which is also a downstream effectors in PI3K/Akt signaling can be found in more than 75% PDAC patients[10]. It have demonstrated the importance of p53 inactivation in cancer metastasis[67,68]. However, whether p53 is involved in the early stage of PDAC development is still poorly understood. It may not participate in ADM but is involved in the development of higher grades PanINs and PDAC[63].

***Inactivation of acinar transcription factors in ADM***

In addition to Mist, down-regulation of other acinar-specific transcription factors including Gata6, pancreas transcription factor 1 complex (PTF1), nuclear receptor subfamily 5 group A member 2 (Nr5a2), and Hnf1α are also observed during ADM. During pancreas development, Gata4 and Gata6 are expressed in developing pancreas but not for other Gata, *i.e.,* Gata1-3, 5[69]. In the later stage of development, there is a linage preference of Gata4 and Gate6 expression. Gata4 mRNA and protein can be found only in exocrine pancreas together with amylase but not glycogen whereas Gata6 is in endocrine pancreas[69,70]. However, in the adult pancreas, Gata4 is also expressed in islet cells such as β-cell[69]. Gata6 expression is also observed in both acinar and islet cells in adult pancreas[71]. Gata6 regulates the expression of other acinar transcription factors such as Mist and PTF1 through binding to their promotors[71,72]. The knockdown of *Gata6* hinders the expression of *Mist*, *pancreas specific transcription factor1a* (*Ptf1a)*, and *recombination signal binding protein for immunoglobulin kappa J region1 (Rbpj1)*, and also their downstream acinar genes such as amylase, while expression of CK-19 is promoted. In addition, further activation of MAPK signaling upon Gata6 silencing emphases the role of Gata6 down-regulation in promoting ADM[72].

 PTF1 which is composed of Ptf1**α** and Rbpj1 is involved in exocrine pancreas development and maintain correct spatial orientation under the regulation of Notch signaling[73-75]. Nr5a2, under the regulation of Gata6 and PTF1, is important in acinar development, maintaining acinar identity, and acinar regeneration during pancreatitis[76,77]. During KRasG12D-driven ADM, PTF1 and Nr5a2 are down-regulated and their low expressions are maintained in PanIN and PDAC[76,78]. The loss of these acinar transcription factors sensitize the cells to KRas mutation promoting ADM and PDAC development.

***Targeting PDAC Reprogramming***

Under the stimulation of KRasG12D mutation or combined with pancreatitis, normal acinar cells can be transdifferentiated into ductal cells followed by the formation of PanIN and PDAC. This process involves the activation of MAPK, Wnt, Notch, and PI3K/Akt signaling (Figure 1). Inhibition of these pathways keeps cells in their acinar state. Importantly, treating the transdifferentiated duct cells with nicotinamide reprograms back to acinar cells with re-expression of amylase and repression of CK-20 indicating that ADM may be a reversible process[49]. Therefore, PDAC development from its progenitor acinar cells may also be reversed upon the inhibition of cancer-related signaling (Figure 2).

A growing number of studies proof the concept of reprogramming PanIN or PDAC to normal pancreatic cell types such as acinar cells and endocrine cells (Table 1). Since MAPK signaling pathway is upregulated and is required during ADM and carcinogenesis, attenuation of this pathway may promote cancer transdifferentiation back to quiescent acinar cells. MEK1/2 inhibitor PD325901 has been proved its effectiveness in treating colon cancer, breast cancer, and melanoma and has entered phase II clinical trial[79]. In addition, PD325901 can enhance the anti-cancer ability of PI3K/mTOR inhibitor PF-04691502 in lung cancer and gemcitabine in pancreatic cancer[80]. A recent report suggests that through inhibiting MAPK signaling pathway, PD325901 may re-differentiate PanIN back to acinar state in addition to the reduction of the proliferation rate of cancer cells both *in vitro* and *in vivo*[16]. However, whether PD325901 also reprogram cancer cells to acinar cells is still questioned since more genetic alternations are accumulated in PDAC. Apart from PD325901, exendin-4 in which its synthetic version exenatide is used in treating type II diabetes may reprogram PDAC[81]. It has been reported that exendin-4 induces cell cycle arrest via p27 and pancreatic cancer reprogramming as indicated by expression of digestive enzyme such as amylase and chymotrypsinogen B1[82]. However, the detailed mechanism on how exendin-4 which is glucagon-like peptide-1 receptor agonist initiates cancer reprogramming is not fully understood[83]. In prostate cancer, exendin-4 inhibits cancer proliferation through suppressing MAPK signaling indicated by the decrease in phosphorylated ERK1/2 level[84]. On the other hand, ERK1/2 phosphorylation is observed during liver transdifferentiation to pancreas involving exendin-4[85].

Dickkopf-3 (DKK-3) belongs to DKK family which regulates Wnt signaling pathway. Unlike other DKK members DKK-1, DKK-2 and DKK-4 that bind to LRP5/6 and Kremem1/2 (Krm1/2) receptors on cell surface forming a trimer which inhibits Wnt signaling through receptor internalization, DKK-3 interacts with Krm1/2 receptors but not LRP5/6 intracellularly probably on the membranes of endoplasmic reticulum or Golgi apparatus before transporting to the cell surface[86,87]. The expression of DKK-3 is regulated by Pax6 which is one of the paired box transcription factors for the development of pancreas. DKK-3 can be activated or repressed by Pax6 depending on cancer type while in pancreatic cancer, DKK-3 is positively regulated in pancreatic cells[88]. Pax6 is the downstream target of MAPK signaling pathway through interaction with Erk1/2 and p38 MAPK[89]. Therefore, DKK-3 links MAPK and Wnt signaling pathway controlling the development of pancreas. Although it has been reported that DKK-1 functions as a Wnt signaling inhibitor, the role of DKK-3 may depends on cell type, for example, DKK-3 positively regulates Wnt signaling in embryonic kidney HEK293 cell line but functions as an inhibitor in lung and bone cancer[90-92]. Since it is reported that Wnt signaling pathway contributes to cancer development, DKK-3 may function as a tumor suppressor through inhibiting Wnt signaling pathway. Consistently, DKK-3 is down-regulated in various cancer types such as lung and papillary thyroid cancer, although it promotes cancer invasion in oral squamous cancer[90,93-95]. Also, its expression is significantly decreased or even lost in some pancreatic cancer cell lines and pancreatic cancer tissues probably by *DKK-3* promotor hypermethylation[82,96,97]. However, overexpression of DKK-3 does not inhibit the proliferation of pancreatic cancer cells significantly although Uchida and colleagues reported inhibition in cancer cells proliferation and induction of apoptosis[82,97,98]. Interestingly, knockdown of this tumor suppressor DKK-3 also inhibit cell growth but without apoptosis[82]. In addition, cell cycle arrest, morphological changes to endocrine cell like, and expression of endocrine proteins insulin and glucagon, and acinar proteins amylase, chymotrypsinogen B1 and elastase are observed when DKK-3 is knocked-down. However, these changes in expression of acinar proteins or endocrine proteins have only been studied in mRNA level but not in protein level. In addition, DKK-3 level is upregulated during exendin-4- induced cancer reprogramming. Therefore, whether inhibiting DKK-3 can transdifferentiate pancreatic cancer cells to normal pancreatic endocrine cells or acinar cells is still questioned.

During differentiation of exocrine pancreas, bHLH transcription factor Mist and PTF1 are expressed resulting in the development of acinar identity[57]. Since Mist and PTF1 are involved in acinar development, inhibiting Mist and PTF1 on gene level results in losing acinar identity and promoting ADM[60, 78]. In addition, sustained Mist expression hinders the progression of ADM and the development of PanIN[99]. Therefore, targeting acinar transcription factors can be used in cancer reprogramming. One representative example suggested by Kim and colleagues is the use of another bHLH transcription factor E47[100]. Since bHLH family usually forms dimer either homodimer or heterodimer which then binds to target genes, it has been reported that E47 interacts with Mist or PTF1 facilitating the their entry into nucleus which is followed by acinar genes activation[101]. This bHLH dimer formation can be disrupted by inhibitor of DNA (ID) family member ID3 which is mediated by MAPK signaling. This disruption can be resulted from the interaction between ID3 and bHLH transcription factors forming non-functional ID3/bHLH dimer or resulting in the decrease in E47 expression[101]. Apart from regulating acinar gene expression, E47 also inhibits the progression from G1 phase to S phase in cell cycle through binding to p21 promotor[100]. In PDAC, the elevated protein level of ID3 results in decrease in E47 activity and cell cycle entry. Because of its role in normal acinar cells and its decreased protein level in PDAC, it has been reported that overexpression of E47 induces growth arrest[100,101]. In addition, Kim demonstrated that E47 may reprogram PDAC back to acinar cells as indicated by the expression of Mist and its target genes such as trypsinogen, connexin32 and ZO.1 which is responsible for protein digestion, gap junctions, and tight junctions respectively[100]. The role of overexpressing E47 in suppressing tumor growth and cancer reprogramming is also confirmed by *in vivo* study. Therefore, overexpression of bHLH transcription factors that directly target acinar genes may reprograms PDAC to acinar cells.

In addition to pancreatic acinar cells, normal endocrine cells such as β-cell may also be another goal in cancer reprogramming. During pancreatic development, retinoic acid (RA) stimulates the development of endocrine progenitor cells and the differentiation into β-cell[102]. Also, RA can be used in treating diabetes through regenerating functional endocrine cells or human embryonic stem cells differentiation to β-cell[103, 104]. In addition, RA which has already been approved in treating acute promyelocytic leukemia may inhibit the growth or promote differentiation of pancreatic cancer stem cells[105, 106]. Since pancreatic duct cells and endocrine cells are originated from the same bipotent progenitor, the close developmental relationship favors the transdifferentiation between these two cell types[33]. Metwally demonstrated the use of RA in reprogramming PDAC back to normal quiescent endocrine cells secreting insulin, glucagon and somatostatin although detailed mechanism needs further studies[107]. In addition, induction of insulin production by glucose indicates the expression of insulin receptor gene. This further confirms the formation of functional endocrine cells. Interestingly, apoptosis is observed after cancer transdifferentiation which contrasts to other reprogramming methods that suggest the formation of quiescent acinar cells without undergoing apoptosis[107]. Increasing attention has been paid on the role of mitochondrion during cancer reprogramming. Increase in mitochondrial activity and mass is observed during cancer transdifferentiation which is followed by apoptosis[108]. It has been suggested that apoptosis occurs after cancer transdifferentiation to normal endocrine cells may be due to uncorrectable genetic alternation during cancer development.

**CONCLUSION**

It is generally believed that pancreatic duct cells are the origin of PDAC. However, during pancreatitis, acinar cells can undergo ADM forming duct cells and subsequently PanIN and PDAC under the activation mutation of KRasG12D. Therefore, acinar cells may also be the origin of PDAC through ADM. This acinar transdifferentiation process at least involves MAPK, Wnt, Notch, and PI3K/Akt signaling. Inhibition of ADM in transdifferentiated cells can regain the acinar identity indicating ADM may be a reversible process and can be used as a chemoprevention. In addition, PanIN or even PDAC may be reprogrammed back to normal cells. The use of PD325901, exendin-4, and RA, overexpression of E47, and knockdown of DKK-3 have demonstrated the potential of cancer reprogramming. However, more evidence is needed to confirm the success of reprogramming. Future studies are needed to explore other therapeutic targets in regaining normal identity of PDAC.

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**Figure 1 MAPK, Wnt, Notch, and PI3K/Akt signaling involved in acinar-to-ductal-metaplasia.** The potential therapy are shown in red (retinoic acid is not shown).



**Figure 2 Development of PanINs/** **Pancreatic ductal adenocarcinoma from acinar cells through acinar-to-ductal-metaplasia.** During ADM, cells in each state have their own morphology and protein expression pattern.

|  |
| --- |
| **Table 1 Therapeutic approach in reprogramming Pancreatic ductal adenocarcinoma** |
| **Therapeutic approach** | **Product** | **Mechanism** | **Model studied** | **Ref.** |
| Chemical | PD325901 | Inhibits MEK1/2 in MAPK signaling | 1. Block ADM in *in vitro* experiment
2. Reprogram pancreatitis- induced PanIN back to acinar cells in *in vivo* experiment
 | [16] |
| Exendin-4 | May inhibit ERK1/2 in MAPK signaling | 1. Reprogram PANC-1 cells back to acinar cells and endocrine cells
 | [82] |
| RA | Detailed study is needed | 1. Reprogram HPAF cells to endocrine cells
 | [107] |
| Genetic | DKK3 knockdown | Detailed study is needed | 1. Reprogram PANC-1 cells back to acinar cells and endocrine cells
 | [82] |
| E47 overexpression | Functions as a sponge of ID3 to remove the inhibition of acinar transcription factors | 1. Reprogram PDAC cell lines back to acinar cells using both *in vitro* and *in vivo* model
 | [100] |