Pancreatic and duodenal homeobox-1 in pancreatic ductal adenocarcinoma and diabetes mellitus

Zhen-Chu Tang¹, Yi Chu², Yu-Yong Tan², Jing Li³, Shan Gao²

¹Department of Neurology, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China; ²Department of Gastroenterology, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China; ³Department of Forensic Science, School of Basic Medical Sciences, Central South University, Changsha, Hunan 410013, China.

Abstract
Diabetes mellitus and pancreatic ductal adenocarcinoma are two common diseases worldwide which are both derived from different components of pancreas. The pancreatic and duodenal homeobox-1 (PDX1) is an essential transcription factor for the early development of pancreas that is required for the differentiation of all pancreatic cell lineages. Current evidence suggests an important role of PDX1 in both the origin and progression of pancreatic diseases. In this review, we discussed recent studies of PDX1 in diabetes mellitus and pancreatic cancer, and the therapeutic strategies derived from this transcription factor.

Keywords: Pancreatic and duodenal homeobox-1; Diabetes mellitus; Pancreatic cancer

Introduction
The pancreas is a glandular organ that has both exocrine and endocrine functions and is located in the abdominal cavity behind the stomach. Around 90% of the pancreas is an exocrine gland consisting of acinar and ductal cells, whose primary role is nutrient digestion. The rest of the pancreas is its endocrine part, scattered throughout the organ, and possessing the islets of Langerhans as its functional units. Instead of secreting digestive enzymes into the digestive tract, the islets are responsible for regulating glucose homeostasis by releasing hormones into the blood stream.

The pancreatic and duodenal homeobox-1 (PDX1) gene is located at the chromosomal locus 13q12.1.¹ The protein encoded by this gene can transcriptionally activate several genes, such as insulin, glucokinase (GK), somatostatin, and islet amyloid polypeptide (IAPP), which are all essential for regulating glucose metabolism. It is also an essential transcription factor (TF) for pancreas development, which is required for the differentiation of all pancreatic cell lineages [Figure 1].²⁻⁵ In mouse embryos, PDX1 is first detected at embryonic day 8.5 (E8.5) in the dorsal endoderm of the gut while it is still an open tube, and later at E9.5, its expression marks the dorsal and ventral pancreatic buds and the intervening endoderm of the presumptive duodenum.³ Null mutation of this gene prevents the pancreatic bud from expanding, resulting in extreme hyperglycemia and perinatal death.²⁻⁵ In adults, PDX1 is maintained at high levels in beta cells, where it is required for efficient insulin gene transcription,⁶⁻⁸ but its low expression in exocrine cells has not been thoroughly investigated.³,¹⁰

Disorders that affect the pancreas can occur in both the exocrine and endocrine glands. Diabetes mellitus (“diabetes”) is the most common disease associated with the endocrine pancreas, closely related to both genetic and environmental factors. Pancreatitis is an inflammation in the exocrine gland but can secondarily affect endocrine pancreas survival and function. Another notorious disease of the exocrine pancreas is pancreatic ductal adenocarcinoma (PDA), the most common form of pancreatic cancer, which is the fourth leading cause of cancer-related mortality in the United States.¹¹,¹² Further, diabetes is a predisposing factor of PDA; hence, they act as cause and effect, respectively. This review summarizes the current findings of the involvement of PDX1 in pancreatic diseases, with emphasis on diabetes and PDA, and discusses how PDX1 could assist the pursuit of therapeutics for the treatment of these diseases.

Correspondence to: Dr. Shan Gao, Department of Gastroenterology, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China E-Mail: gshan@csu.edu.cn

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PDX1 and diabetes mellitus

Diabetes mellitus is a complex metabolic disorder whose main clinical and diagnostic feature is hyperglycemia, along with the progressive loss or dysfunction of the β cells in the pancreas.\textsuperscript{[13,14]} It has reached epidemic proportions, affecting around 425 million people worldwide (as estimated in 2017). China has the highest number of adults with diabetes, approximately 109.6 million, ranking second in diabetes-related health expenditure among the world, followed by the United States.\textsuperscript{[15]} Thus, efficient control of this disease is needed to both alleviate the patient’s pain and ease the burden placed on healthcare.

There are four main types of diabetes: type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes, and maturity-onset diabetes of the young. Out of these, the most common forms of diabetes are T1D and T2D. T1D is a metabolic disorder caused by autoimmune-mediated destruction of pancreatic β cells, leading to a complete or near-total loss of the hormone insulin.\textsuperscript{[16]} Whereas, the pathogenesis of T2D begins with lifestyle-induced insulin resistance, which gradually increases the demand on β cells to secrete insulin, resulting in the failure of β cells to deliver sufficient amount of insulin.\textsuperscript{[17,18]} When considered together, the main reasons behind diabetes is loss of β cell mass, function, and identity.\textsuperscript{[19]}

**PDX1 maintains β cell mass, function, and identity**

The major treatment methods for diabetes are focused on the pancreatic β cells, since they are the central players in glycemic homeostasis, due to their ability to produce insulin — the only hormone capable of lowering high blood glucose level. The function of β cells is controlled at the transcriptional level, in which PDX1 plays an important role. PDX1 regulates a number of genes involved in maintaining the identity and function of β cells, such as insulin, IAPP (amylin), GK, and glucose transporter 2.\textsuperscript{[20]} Avrahami et al\textsuperscript{[21]} summarized the DNA methylation patterns observed in β cells during diabetes progression, and found that major methylation regulations occurred in functional genes including PDX1, which further emphasized its importance in this disease. Moreover, the inactivation of insulin promoter Cre (cyclization recombinase enzyme) recombinase, which utilizes PDX1, leads to pancreatic agenesis. In addition, the heterozygous PDX1 mutant showed elevated blood glucose level at birth and decreased β cell mass later, indicating that PDX1 levels influence not only β cell function, but also their mass.\textsuperscript{[22]}

Furthermore, Gao et al\textsuperscript{[23]} generated rat insulin promoter-CreER; PDX1\textsuperscript{[24]}; ROSA\textsuperscript{YYFP} mice to specifically knock-down PDX1 in adult β cells. They found that PDX1 deletion mice displayed overt diabetes, while heterozygous ones who still carried one allele of PDX1 exhibited a normal basal glucose level and normal glucose tolerance rates. It suggests that mature β cells could live without PDX1 existence, and changes in glucose tolerance were not due to the incomplete insufficiency of PDX1. The complete removal of PDX1 led to a transcriptional shift in the insulin-positive cell population to an α-like cell phenotype, attributed to the binding of PDX1 to glucagon and MAF BZIP transcription factor B, two α-cell-specific gene targets, resulting in their repression. However, this α-like phenotype was not stable; after 30 days, the proportion of

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**Figure 1:** Lineage decisions during pancreas development. Transcription factors such as PDX1, Ptf1a, and Ngn3 regulate the series of events during the development of the pancreas, leading to the transition of progenitor cells (foregut endoderm) into fully differentiated cells (∞ cells, β cells, duct cells, acinar cells). And the gallbladder cells and bile duct cells arise from PDX1-expressing foregut endoderm cells in early embryo. PDX1 in blue print marks its low expression in duct cells and acinar cells. E8.5: Embryonic day 8.5; E9.5: Embryonic day 9.5; PDX1: Pancreatic and duodenal homeobox-1; Ptf1a: Pancreas associated transcription factor 1a; Ngn3: Neurogenin-3; SOX9: SRY-box 9.
cells expressing glucagon decreased from 35% to less than 15%, indicating that losing PDX1 alone is not enough for the shift, but more mechanisms are involved in the cell maintenance.

In humans, PDX1 expression is detected around E28 of embryonic development. Similar to rodents, human PDX1 with human homozygous mutations in the PDX1 gene were born with pancreatic agenesis. These individuals had permanent neonatal diabetes, with exocrine pancreas insufficiency. A case in 2019 reported an (Persian) 65-day-old Iranian patient with PDX1 homozygous mutation was diagnosed with neonatal diabetes. Additionally, their parents, possessing heterozygous PDX1 mutations, had high susceptibility to diabetes with diagnosis reported as early as 2.5 years old. Later, Guo et al found the levels of PDX1 and a few other key islet-enriched TFs were dramatically reduced in human T2D islet β cells. The Kyoto Encyclopedia of Genes and Genomes database also shows that PDX1 is highly disordered and inactivated in human T2D islets β cells and mouse models of T2D.

In summary, PDX1 is not only an essential TF for adult β cell survival, but also a “master factor” in regulating genes that maintain β cell function and identity, closely related to the progress of diabetes. Knowing more about the epigenetic mechanisms of PDX1 in β cells could provide a valuable approach for the treatment of diabetes.

**PDX1 is essential in β cell reprogramming**

At present, exogenous insulin and ancillary drugs are the major treatments for diabetes. But the burden on patients, with constant treatment and disease monitoring, leads us to pursue alternate therapies. The most definitive treatment for the disease is allogenic pancreas/islet transplantation, which provides a self-regulating insulin source. However, like any organ transplantations, all the recipients need to receive immunosuppressive drug therapy to prevent rejection after operations, which increases the risk of infection and certain types of cancer. In addition, 5-year follow-up data revealed that only a minority of the recipients still maintained insulin independence; though more than half of them were free from exogenous insulin after 1 year from the operation. Therefore, the limitations of pancreatic islet transplantation lead researchers to investigate autologous insulin-producing cells for β cell replacement therapy.

Potentially, the two general approaches to generate β cell replacement are the differentiation of pluripotent stem cells (PSCs) and the reprogramming of adult cells from endoderm-derived tissues. To produce functional and mature β cells for cell-replacement therapy of diabetes, Wang et al used PDX1 and H3K27AC chromatin immunoprecipitation (ChIP-seq) to further study PDX1 target genes. They produced a novel induced pluripotent stem cell (iPSC) line with human pancreatic progenitors (PPs), and compared the PDX1 binding profiles obtained from them. They found that PDX1 regions include important pancreatic TFs, such as PDX1 itself, regulatory factor X6, hepatocyte nuclear factor 1 homeobox B, and Meis homeobox 1, which were activated and required for the differentiation and function of mature β cells. Additionally, they proved that the molecular programs that the PDX1 target sites activated were changed during the developmental stage. Recent studies in developing β cells differentiation protocols have shown that human PSCs (hPSCs)-derived β-like cells are functionally immature, and the efficiencies of differentiation can be variable depending on the hPSC lines used. Wang et al derived a Pdx1-monomeric red fluorescent protein/insulin-humanized renilla reniformis green fluorescent protein (Pdx1-mRFP/insulin-hrGFp) dual-reporter cell line from hPSCs and monitored the expression of PDX1 and insulin, to provide a better method for the development and refinement of β cell differentiation protocols from hPSCs. Thus, significant progress has been made in the differentiation of hPSCs to mature β cells, in clinical applications the practicality of this is hampered by the risk of teratoma formation, immunogenicity, and epigenetic abnormalities. Thus, due to the important role of PDX1 in pancreatic fate, studies have attempted to use ectopic PDX1 to reprogram “permissive” tissues and assorted cell lines into functional β cells.

Pancratic α and β cells are closely lineage-related cells. When ablating β cells, large fractions of regenerated β cells are derived from α cells, which implies that the two types of cells might be easily transformed into one another. However, exogenous PDX1 in glucagon (Gcg)-positive embryonic or adult α cells could suppress Gcg expression but did not induce α/β switching. On the contrary, the neurogenin-3 (Ngn3)-positive endocrine progenitor cells enforced by PDX1 readily transformed to cells indistinguishable from normal β cells, suggesting that the plausibility of exogenous PDX1 alone inducing β cells depends on differentiation evaluation stage of endocrine maturation. Finally, transgenic mice were generated to express both PDX1 and MAF BZIP transcription factor A (MafA) in embryonic endocrine Ngn3-positive and committed glucagon-positive progenitors, and data showed that MafA could potentiate the ability of PDX1 in both Ngn3-positive and glucagon-positive progenitor reprogramming activities.

In fact, multiple other adult cell types have been reprogrammed to undergo same the same fate as β cells. Among them, one promising attempt is to convert the antral stomach cells into functional insulin-secreting cells by expressing the hallmark pancreatic endocrine TFs PDX1, Ngn3, and MafA (NPM). Previously, the transformation of intestine cells to insulin-positive cells by providing NPM factors has been reported. However, this results in incomplete β cell conversion, due to blocking of the intestine-specific caudal type homeobox 2 gene. In comparison, antral stomach endocrine cells and β cells have closer transcriptional similarity, and antral stomach endocrine cells have been proven to reprogram more effectively under NPM condition, with steady expression of key β cell genes and substantially improved glucose responsiveness. Besides, based on the published protocols of bioengineering stomach, researchers embedded insulin-positive cells into “stomach mini-organ” and transplanted it into diabetes mice. This bioengineering technique proved to be effective, regulating blood glucose...
by resealing insulin directly into the circulation.\[47\] With this approach, patients might get long-term treatment with fewer side effects. Furthermore, besides NPM, paired box 4 was introduced by Zhang et al\[48\] as another TF that synergistically acts to promote functional β cells transformation process, which may better serve for further investigation.

Murine gallbladder can be another choice for β cell replacement. It is a dispensable organ easily acquired by invasive laparoscopic procedure without serious sequelae. Also, it shows close developmental proximity to β cells – they are both derived from pancreatobiliary progenitors. Grompe et al\[49\] found that overexpressing NPM factors in mouse gallbladder cells in vitro led to limited amount of insulin production and immature cell types. Moreover, the reprogrammed cells did not display glucose-responsiveness. But when they improved the protocol by adding paired box 6 (Pax6), another key TF for pancreatic endocrine progenitors, the reprogramming was seen to become more efficient in increasing not only β-like cells numbers, but also secret insulin expression. This second-generation reprogrammed β-like cells (rGBC2) could synthesis, process, and secret insulin in response to glucose stimulation, and survived for at least 5 months in vitro.\[50\] Later, the team combined adenoviral-mediated transduction of NPM factors and Pax6 with small molecule-dependent transdifferentiation into the human GBCs and achieved insulin-producing pancreatic β-like cells which could be transiently engrafted in immunodeficient mice.\[50\]

If future studies can uncover how to apply patient-derived GBCs to the patients themselves, it will essentially solve the problems raised by reprogramming PSCs mentioned above. However, other complications related to the reliability and robustness of the reprogrammed GBCs, the risk of transducing TFs like PDX1 into individuals, and the efficiency of reprogramming will need to be further evaluated.

Utilizing human cells for the treatment of diseases is not an unfamiliar concept. Hematopoietic stem cell transplanation for treating hematologic malignancies is a successful and well-developed medical procedure. Prevalent focus is still on multifunctional cells, such as PSCs and mesenchymal stromal cells. If different types of mature cells derived from the same progenitors can be successfully reprogrammed into each other, under stable and well-functioning conditions, it may provide us more resources for the development of improved therapeutic approaches.

**PDX1 and PDA**

PDA accounts for >85% of all pancreatic cancers and is one of the most lethal malignancies worldwide. Despite immense progress in the diagnosis and treatment of pancreatic cancer, its 5-year overall survival is only 8.2% in the United States.\[51\] Kirsten rat sarcoma gene (KRAS) mutations are found in >90% of PDA patients, and are required for tumor initiation and maintenance.\[52\] Studies have shown that mouse models with oncogenic KRAS throughout the pancreatic parenchyma mimic the human PDA progression to maximum extent.\[53-55\] PDA got its name from its histological similarity with ductal structures. However, studies reveal that ductal cells are actually refractory to oncogenic transformation. On the contrary, acinar cells can easily form acinar-to-ductal metaplasia (ADM), the PDA precursor lesions with ductal features, indicating the cellular origin of PDA.\[56\]

**PDX1 in pancreatic injury and ADM formation**

During the development of the pancreas, PDX1 and other TFs regulate the cascade of events which leads the transition of progenitor cells into fully differentiated cells. For instance, the increased expression of SRY-box 9 and PDX1 in PPs induces the differentiation into pancreatic lineages, at the same time inhibiting the formation of intestinal and hepatic lineages. Later, the TFs required for the active maintenance of adult acinar cell differentiation, such as pancreas associated transcription factor 1a (Ptf1a) and nuclear receptor subfamily 5 group a member 2 (Nr5a2), are maintained at high levels but the expression of PDX1 conversely becomes low. However, PDX1 is found to be up-regulated in ADM induced by the constitutive overexpression of transforming growth factor alpha (TGFα).\[57\]

Likewise, the abnormally increased expression of PDX1 is also detected in mouse PDA models with mutant KRAS.

In effect, elevated PDX1 expression in adult exocrine pancreas has been observed in many pathological conditions, including pancreatic injury and pancreatitis. Cerulean is a cholecystokinin analog that stimulates transient ADM in wild-type pancreatitis. Studies have reported abnormally high PDX1 expression in non-islet pancreas, after pancreactectomy or cerulean treatment.\[58\]

Well-differentiated cells tend to dedifferentiate to an earlier stage when they get injured, so that they have more potential to recover from the impairment. Since all pancreatic lineages come from PDX1-positive progenitors, the elevation of it is reasonable in these damages. In addition, when the wild-type and PDX1 ablation pancreas (Ptf1α CreERTM−/−; PDX1−/−) are treated with cerulean, the wild-type cells recovered from the stimulation around 7 days later, but acinar cells with null PDX1 displayed severe reduction in the pancreas-to-body-mass ratio and did not recover, indicating that ADM derived from acinar cells requires PDX1 for regenerating the damaged organ.\[59\]

However, PDX1 overexpression in exocrine precursors marked dysmorphogenesis in the exocrine pancreas.\[60\]

Additionally, its overexpression in benign HEK293 cells and human pancreatic duct epithelial cells results in increased cell proliferation, invasion, and colony formation in vitro.\[61\] Collectively, PDX1 takes the responsibility to maintain and re-establish acinar differentiation when damage happens to the pancreas. Its expression needs to be tightly controlled to properly maintain adult acinar tissue functionality.

In accordance with injury, PDX1 deficiency in KRAS-induced PDA mouse model (KrasL/S; Ptf1α CreERTM−/−; PDX1−/−) displays a widespread loss of acinar cells, accompanied by extensive formation of ductal lesions. This is due to erosion of acinar differentiation, rather than its expansion through increased cell proliferation, based on 5-bromo-2-deoxyuridine incorporation. Genome-wide
Multiple roles of PDX1 in tumorigenesis

Unlike the role of PDX1 in diabetes, this master gene behaves differently at different tumor stages. PDX1 function as a tumor suppressor in maintaining acinar cell identity and preventing ADM formation. Whereas, further data shows that knocking down PDX1 in mouse PDA-derived cell lines can block cell growth and increase apoptosis, which is consistent with human PDA cell lines,[61] and this is not affected by the different malignant cell origins.[62] Hence, PDX1 changes its role from tumor suppressor to oncogene during the process of tumorigenicity.

Interestingly, recent next-generation sequencing analysis has revealed that PDA is a mixture of four different subtypes with distinct histopathological features and prognosis.[63,64] Among them, the PDX1 promoter is highly methylated in the worst sub-type, the squamous one, indicating epigenetic silencing of PDX1. The squamous sub-type displays higher metastatic potential compared to others, which is the reason PDA patients usually die from distant metastasis. Considering this, later studies suggest that epithelial cells need to reduce PDX1 expression to undergo the epithelial-to-mesenchymal transition (EMT) process, where epithelial cells lose their epithelial marks to undergo easier dissemination into a vascular or lymphatic system, thereby enhancing metastasis. Furthermore, Kondratyeva et al.[65] proposed the possibility of PDX1 delivering into this aggressive PDAC cells to stop cancer metastasis. Thus, in this stage, PDX1 reduction appears to enhance tumor aggressiveness, hence increasing PDX1 levels may be a novel method for gene therapy.[66]

According to PDX1 ChIP-seq (chromatin immunoprecipitation combined with high-throughput sequencing) done on primary mouse acinar cells and mouse PDA-derived cell lines, there is minimal overlap of PDX1 binding regions between acinar and PDA cells, indicating the shift of gene sets that PDX1 regulates in primary and transformed cells. Further investigation shows that in acinar cells, PDX1 interacts with genes maintaining acinar differentiation state (Cela1, Cela2, and Amy1), embryonic development, and epithelial cell differentiation (Nr5a2, Foxa2, and Onect1). On the contrary, in tumor cells, PDX1 binds to genes important for tumorigenesis, including EMT and cellular response to TGFβ signal. Its enrichment of different regions affects active transcription of associated genes, which is also thoroughly proved in the RNA-seq data. PDX1 tends to bind acinar-specifying genome regions in acinar cells (Hnf4a, Nkx6.1, Hnf1α, and Hnf1β), but binds to the motifs of oncogenic TFs in PDA cells (Gsc2, Prrx2, Stat5, c-Jun, and c-Fos).[59] The dynamic shift of PDX1 explains its multi-functionality in tumorigenesis, but detailed analysis about this process is needed to further elucidate how PDX1 regulates tumor formation by changing targets.

As for the role of PDX1 in metastasis, it is hard to give an accurate explanation. A hypothesis is that tumor cells use mechanisms to compensate for PDX1 loss. Due to the fact that MYC is up-regulated in PDX1-absent PDA cells,[63] and well-differentiated tumors are PDX1-high and MYC-low, while undifferentiated invasive tumors are MYC-high and PDX1-low, the MYC regulatory network becomes a potential candidate.[59] However, more evidence and a deeper understanding about this replacement mechanism are needed.

Tons of discovered cancer genes are classified into oncogenes or tumor suppressor genes, according to their function in a cancer cell. However, PDX1 sheds light on another group of genes whose characteristics rely on the genetic network, in context of the whole genome. The multi-functionality of those “chameleons” may elucidate the mechanisms of tumor initiation and progression, highlighting the reasons of chemotherapy failure.

PDX1 is also closely associated with other pancreatic diseases, such as insulinoma, a rare tumor derived from islet β cells within the pancreas. The incidence of this disease is approximately 3 to 4 per 1,000,000 in general population.[67] These patients suffer from uncontrolled hypoglycemia due to the expanded β cell mass continues to secret insulin. Studies have found that PDX1 is significantly overexpressed in human insulinoma specimens, as well as in mouse insulinoma cell lines. Further, using RNA interference therapy to knock down PDX1 exhibits decrease in insulin expression and secretion; this may be harnessed as a novel therapeutic strategy in alleviating the patient’s pain in the future.

Summary

In summary, knowing how PDX1, as an essential TF in pancreas, functions in pancreatic diseases could give us important insights into the epigenetic mechanisms of disease occurrence and development, and also provide a chance to develop new therapeutic strategies.

Conflicts of interest

None.

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