Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

PDX1 (pancreatic and duodenal homeobox 1)

Guisheng Zhou, F Charles Brunicardi

Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, Texas 77030, USA (GZ, FCB)

Published in Atlas Database: October 2010

Online updated version : http://AtlasGeneticsOncology.org/Genes/PDX1ID43921ch13q12.html
DOI: 10.4267/2042/45037

Identity

Other names: GSF, IDX-1, IPF1, IUF1, MODY4, PDX-1, STF-1

HGNC (Hugo): PDX1

Location: 13q12.2

DNA/RNA

Description

PDX-1 gene is located at human chromosome 13q12.1, mouse chromosome 5qG3 and rat chromosome 12, respectively.

PDX-1 gene consists of two exons spanning a region of about 6 kb. In the promoter region of PDX-1, there are three highly conserved regions, termed "Area I-II-III" which are located between -2800 and -1600 base pairs (bp), and a forth distal enhancer element, termed "Area IV" which is located between -6500 and -6045 bp. These enhancer elements harbor binding sites for multiple transcription factors and transcriptional regulators such as HNF-1alpha, HNF-3beta, HNF-6, Foxa1, Foxa2, Pax6, MafA and PDX-1 itself. Areas I and II impart endocrine expression, while Area III confers beta-cell specificity. Area IV is capable of independently directing pancreatic beta-cell-specific reporter gene expression and potentiating the proximal enhancer activity.

Transcription

PDX-1 mRNA has an open reading frame of 849 bp.

Protein

Description

Human PDX-1 is a protein of 283 amino acids with a calculated molecular weight of 30.64 kDa. However, endogenous PDX-1 is usually detected as a protein with molecular mass of 46 kDa, likely due to posttranslational modifications such as phosphorylation and sumoylation. The N-terminus of PDX-1 contains a transactivation domain. The middle region contains a homeodomain, which is essential for DNA binding and protein-protein interactions. Within the homeodomain, there is an antennapedia-like protein transduction domain (PTD) which allows PDX-1 to permeate into cells and a nuclear localization signal (NLS) motif, RRMKWKK(197-203aa), which is sufficient for the nuclear import of PDX-1. There is a conserved motif in the C-terminus of PDX-1 that mediates the

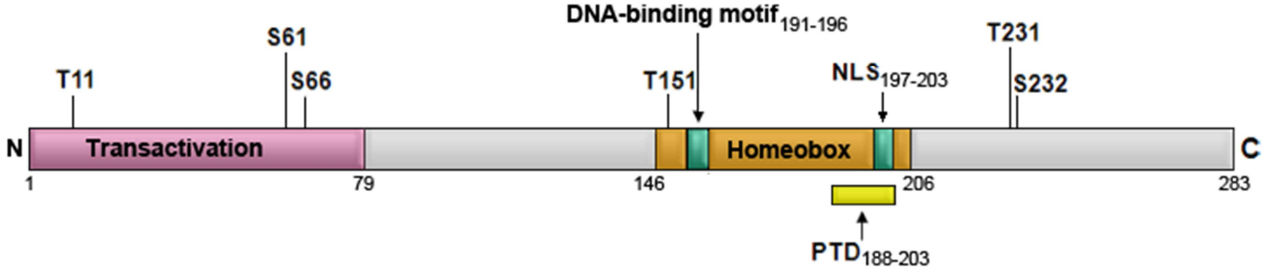

Figure 1. Schematic representation of functional domains and phosphorylation sites of PDX-1. The numbers indicate the positions of phosphorylation sites and functional domains on the polypeptide chain of human PDX-1. NLS: Nuclear localization signal; PTD: Protein transduction domain; S: Serine; T: Threonine.

PDX-1-PCIF1 interaction resulting in the inhibition of PDX-1 transcriptional activity. Several C-terminal residues such as Gly 212, Glu 224 and Pro 239 are essential for full transactivation of PDX-1 as evidenced by the association of their missense mutations with diabetes (Fig. 2). Several potential phosphorylation sites within PDX-1 have been identified, such as Thr 11 by DNA-PK, Ser 61 and 66 by GSK3beta, Thr 152 by PASK, Thr 231 and Ser 232 by CK2 and Ser 268 by AKT-GSK and HIPK2.

Expression

PDX-1 is expressed as early as embryonic day 8.5 (E8.5) in the dorsal and ventral endoderm regions that give rise to pancreatic buds, as well as in the common bile duct, distal stomach, Brunner's glands, and duodenal epithelium. During pancreas development, PDX-1 is expressed in all pancreatic precursor cells. PDX-1 expression becomes restricted to beta cells and a small subpopulation of delta and PP cells in adult. Low levels of PDX-1 are also detected in the nuclei of acinar cells. PDX-1 is also expressed in the gastric antrum and duodenum in adult.

The compartmentalization of PDX-1 is lost under pathological conditions. Aberrant overexpression of PDX-1 is observed in a number of human cancers such as pancreatic, gastric, colon, breast, prostate, colorectal, kidney cancer and paediatric solid pseudopapillary tumors. Up-regulated PDX-1 expression is also observed in premalignant metaplastic ductal epithelium during transforming growth factor (TGF)-alpha-induced pancreatic ductal metaplasia and neoplasia.

PDX-1 expression is subject to regulation by glucose, glucagon-like peptide 1 (GLP-1), palmitic acid, peroxisome proliferator-activated receptor-alpha (PPARalpha) and PPARgamma, epidermal growth factor (EGF) and high fat diet.

Localisation

PDX-1 is localized in the Nucleus of the cells. In solid pseudopapillary tumors (SPT), however, PDX-1 only exists in the cytoplasm, but not in the nucleus.

Function

Pancreatic and duodenal homeobox-1 (PDX-1) is a homeodomain-containing transcription factor essential for pancreatic development, beta-cell differentiation and the maintenance of mature beta cell function through regulating the expression of key endocrine beta-cell-specific genes such as insulin, glucokinase, islet amyloid polypeptide and the glucose transporter type 2. PDX-1 also regulates the expression of elastase I in pancreatic ductal and acinar cells. PDX-1 is functionally involved in mitochondrial signal generation in the moment-to-moment control of insulin release by regulating mitochondrial transcription factor A (TFAM).

Homology

Human PDX-1 shares a 90% amino acid homology with hamster, 88% with rat, 87% with mouse and 68% with Xenopus. Zebrafish PDX-1 shares a 95% amino acid identity to mammalian PDX-1 in the homeodomain.

Mutations

Somatic

Pro63fsdelC: a frameshift mutation resulting from a single nucleotide deletion within codon 63 in exon 1 of the coding sequence of PDX-1. The point deletion causes a frame shift resulting in the translation of 59 novel codons before termination and the production of a prematurely terminated truncated protein of 16 kDa.

InsCCG243: an in-frame proline insertion mutation at codon 243 of PDX-1.

Missense mutations: C18R, P33T, Q59L, D76N, E178G, R197H, G212R, E224K and P239Q. These missense mutants show either a decreased binding activity to the insulin gene promoter (C18R, P33T, D76N and R197H) or a reduced transactivity (C18R, P33T, Q59L, D76N, E178G, R197H, G212R, E224K and P239Q) compared to wild-type PDX-1.

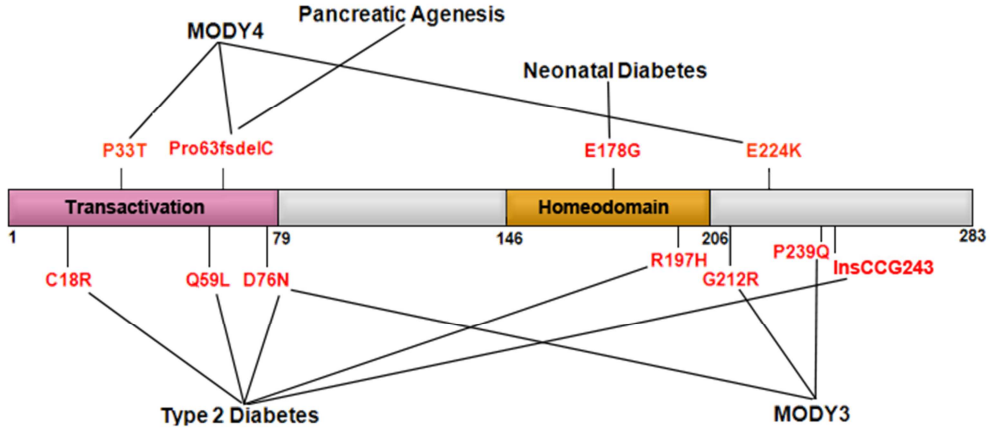

Figure 2. Diabetes-associated genetic mutations of PDX-1. MODY4/3: maturity-onset diabetes of young 43; P: proline; C: cysteine; E: glutamic acid; K: lysine; R: arginine; Q: glutamine; L: leucine; D: aspartic acid; N: asparagine; G: glycine; H: histidine.

Implicated in

Various cancers

Prognosis

Elevated expression of PDX-1 is found in a number of human cancers, including pancreatic, breast, prostate cancer, colorectal cancer, colon cancer, kidney, gastric, paediatric solid pseudopapillary tumors (SPT) and intestinal-type ovarian mucinous neoplasm (OMN). Elevated expression level of PDX-1 in pancreatic cancer is significantly correlated with lymph node metastasis, TNM grading, pathological grading and tumor cell proliferation. PDX-1 expression in pancreatic cancer is an independent survival factor since the patients with positive PDX-1 have a significantly worse prognosis than those patients with negative PDX-1. In colorectal cancer, PDX-1 is highly expressed in hepatic metastasis of colorectal cancer, while lower expression of PDX-1 is found in primary colorectal tumor. Metastatic colorectal adenocarcinoma in the ovarian is also positive for PDX-1. PDX-1 expression also correlates with histological type and depth of invasion of gastric carcinomas.

Diabetes

Prognosis

Maturity-onset diabetes of young 4 (MODY4) is a form of early-onset type-II diabetes mellitus in which expression of diabetes occurs later than that observed for MODY1, MODY2 and MODY3. Pro63fsdelC of PDX-1 contributes to the development of MODY4 when the mutation is heterozygous. InsCCG243, PDX-1 P33T and PDX-1 E224K mutations also contribute to the development of MODY4. Two missense mutations (D76N and P239Q) in PDX-1 are found in MODY3 families. Five missense mutations (C18R, Q59L, D76N, E178G and R197H) in PDX-1 are found in patients with Non-MODY type 2 diabetes.

References

Stoffers DA, Ferrer J, Clarke WL, Habener JF. Early-onset type-II diabetes mellitus (MODY4) linked to IPF1. Nat Genet. 1997 Oct;17(2):138-9

Stoffers DA, Zinkin NT, Stanojevic V, Clarke WL, Habener JF. Pancreatic agenesis attributable to a single nucleotide deletion in the human IPF1 gene coding sequence. Nat Genet. 1997 Jan;15(1):106-10

Stoffers DA, Stanojevic V, Habener JF. Insulin promoter factor-1 gene mutation linked to early-onset type 2 diabetes mellitus directs expression of a dominant negative isoprotein. J Clin Invest. 1998 Jul 1;102(1):232-41

Hani EH, Stoffers DA, Chèvre JC, Durand E, Stanojevic V, Dina C, Habener JF, Froguel P. Defective mutations in the insulin promoter factor-1 (IPF-1) gene in late-onset type 2 diabetes mellitus. J Clin Invest. 1999 Nov;104(9):R41-8

Moede T, Leibiger B, Pour HG, Berggren P, Leibiger IB. Identification of a nuclear localization signal, RRMKWKK, in the homeodomain transcription factor PDX-1. FEBS Lett. 1999 Nov 19;461(3):229-34

Macfarlane WM, Frayling TM, Ellard S, Evans JC, Allen LI, Bulman MP, Ayers S, Shepherd M, Clark P, Millward A, Demaine A, Wilken T, Docherty K, Hattersley AT. Missense mutations in the insulin promoter factor-1 gene predispose to type 2 diabetes J Clin Invest. 2000 Sep;106(5):717

Weng J, Macfarlane WM, Lehto M, Gu HF, Shepherd LM, Ivarsson SA, Wibell L, Smith T, Groop LC. Functional consequences of mutations in the MODY4 gene (IPF1) and coexistence with MODY3 mutations. Diabetologia. 2001 Feb;44(2):249-58

Noguchi H, Kaneto H, Weir GC, Bonner-Weir S. PDX-1 protein containing its own antennapedia-like protein transduction domain can transduce pancreatic duct and islet cells. Diabetes. 2003 Jul;52(7):1732-7

Ashizawa S, Brunicardi FC, Wang XP. PDX-1 and the pancreas. Pancreas. 2004 Mar;28(2):109-20

Cockburn BN, Bermano G, Boodram LL, Teelucksingh S, Tsuchiya T, Mahabir D, Allan AB, Stein R, Docherty K, Bell GI. Insulin promoter factor-1 mutations and diabetes in Trinidad: identification of a novel diabetes-associated mutation (E224K) in an Indo-Trinidadian family. J Clin Endocrinol Metab. 2004 Feb;89(2):971-8

Sakai H, Eishi Y, Li XL, Akiyama Y, Miyake S, Takizawa T, Konishi N, Tatematsu M, Koike M, Yuasa Y. PDX1 homeobox protein expression in pseudopyloric glands and gastric carcinomas. Gut. 2004 Mar;53(3):323-30

Gragnoli C, Stanojevic V, Gorini A, Von Preussenthal GM, Thomas MK, Habener JF. IPF-1/MODY4 gene missense mutation in an Italian family with type 2 and gestational diabetes. Metabolism. 2005 Aug;54(8):983-8

Wang XP, Li ZJ, Magnusson J, Brunicardi FC. Tissue MicroArray analyses of pancreatic duodenal homeobox-1 in human cancers. World J Surg. 2005 Mar;29(3):334-8

Leys CM, Nomura S, Rudzinski E, Kaminishi M, Montgomery E, Washington MK, Goldenring JR. Expression of Pdx-1 in human gastric metaplasia and gastric adenocarcinoma. Hum Pathol. 2006 Sep;37(9):1162-8

Kaneto H, Miyatsuka T, Shiraiwa T, Yamamoto K, Kato K, Fujitani Y, Matsuoka TA. Crucial role of PDX-1 in pancreas development, beta-cell differentiation, and induction of surrogate beta-cells. Curr Med Chem. 2007;14(16):1745-52

Al-Quobaili F, Montenarh M. Pancreatic duodenal homeobox factor-1 and diabetes mellitus type 2 (review). Int J Mol Med. 2008 Apr;21(4):399-404

Ballian N, Liu SH, Brunicardi FC. Transcription factor PDX-1 in human colorectal adenocarcinoma: a potential tumor marker? World J Gastroenterol. 2008 Oct 14;14(38):5823-6

Galmiche L, Sarnacki S, Verkarre V, Boizet B, Duvillie B, Fabre M, Jaubert F. Transcription factors involved in pancreas development are expressed in paediatric solid pseudopapillary tumours. Histopathology. 2008 Sep;53(3):318-24

Jonmarker S, Glaessgen A, Culp WD, Pisa P, Lewensohn R, Ekman P, Valdman A, Egevad L. Expression of PDX-1 in prostate cancer, prostatic intraepithelial neoplasia and benign prostatic tissue. APMIS. 2008 Jun;116(6):491-8

Lin X, Lindner JL, Silverman JF, Liu Y. Intestinal type and endocervical-like ovarian mucinous neoplasms are immunophenotypically distinct entities. Appl Immunohistochem Mol Morphol. 2008 Oct;16(5):453-8

Ma J, Chen M, Wang J, Xia HH, Zhu S, Liang Y, Gu Q, Qiao L, Dai Y, Zou B, Li Z, Zhang Y, Lan H, Wong BC. Pancreatic duodenal homeobox-1 (PDX1) functions as a tumor suppressor in gastric cancer. Carcinogenesis. 2008 Jul;29(7):1327-33

Gauthier BR, Wiederkehr A, Baquié M, Dai C, Powers AC, Kerr-Conte J, Pattou F, MacDonald RJ, Ferrer J, Wollheim CB. PDX1 deficiency causes mitochondrial dysfunction and defective insulin secretion through TFAM suppression. Cell Metab. 2009 Aug;10(2):110-8

Quint K, Stintzing S, Alinger B, Hauser-Kronberger C, Dietze O, Gahr S, Hahn EG, Ocker M, Neureiter D. The expression pattern of PDX-1, SHH, Patched and Gli-1 is associated with pathological and clinical features in human pancreatic cancer. Pancreatology. 2009;9(1-2):116-26

An R, da Silva Xavier G, Semplici F, Vakhshouri S, Hao HX, Rutter J, Pagano MA, Meggio F, Pinna LA, Rutter GA. Pancreatic and duodenal homeobox 1 (PDX1) phosphorylation at serine-269 is HIPK2-dependent and affects PDX1 subnuclear localization. Biochem Biophys Res Commun. 2010 Aug 20;399(2):155-61

Humphrey RK, Yu SM, Flores LE, Jhala US. Glucose regulates steady-state levels of PDX1 via the reciprocal actions of GSK3 and AKT kinases. J Biol Chem. 2010 Jan 29;285(5):3406-16

Liu SH, Patel S, Gingras MC, Nemunaitis J, Zhou G, Chen C, Li M, Fisher W, Gibbs R, Brunicardi FC. PDX-1: demonstration of oncogenic properties in pancreatic cancer. Cancer. 2010 Sep 30;

Nicolino M, Claiborn KC, Senée V, Boland A, Stoffers DA, Julier C. A novel hypomorphic PDX1 mutation responsible for permanent neonatal diabetes with subclinical exocrine deficiency. Diabetes. 2010 Mar;59(3):733-40

This article should be referenced as such:

Zhou G, Brunicardi FC. PDX1 (pancreatic and duodenal homeobox 1). Atlas Genet Cytogenet Oncol Haematol. 2011; 15(6):507-510.