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)

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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 transactivation 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 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, Q22R and R197H) or a reduced transactivity (C18R, P33T, Q59L, D76N, E178G, R197H, G212R, E224K and P239Q) compared to wild-type PDX-1.
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 expressed in hepatic metastasis of colorectal cancer is significantly correlated with lymph node metastasis, TNM grading, pathological grading and tumor cell proliferation.

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. InsCCGG243, 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


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