Insulin/Glucose-Responsive Cells Derived from Induced Pluripotent Stem Cells: Disease Modeling and Treatment of Diabetes

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Supplementary Table 1. Transcription factors associated with development of the pancreas.

Gene	Aliases	Developmental Stage	Function	Ref.
SOX17	SRY-Box Transcription Factor 17	DE, PFE, PSE	Directs the primitive endoderm specification.	[1]
FOXA2	Forkhead Box A2; Hepatocyte Nuclear Factor 3-β	DE, PFE, PSE, PMPs, EPs, Mature β-cells	Establishes lineage-specific transcriptional programs which leads to proper differentiation of stem cells into pancreatic progenitors. Regulates expression of *PDX1* gene and aids in maturation of β-cells	[2]
SHH	Sonic Hedgehog Signaling Molecule	DE	A pleiotropic developmental gene which regulates growth, and differentiation of several organs. Repression of S*HH* expression is vital for pancreas differentiation and development	[3]
CXCR4	C-X-C Motif Chemokine Receptor 4; Stromal Cell-Derived Factor 1 Receptor; Neuropeptide Y3 Receptor	DE	Promotes cell differentiation, proliferation, and survival. Controls the spatiotemporal migration of the angioblasts towards pre-pancreatic endodermal region which aids the induction of *PDX1* expression giving rise to common pancreatic progenitors	[4]
HNF1B	HNF1 Homeobox B Hepatocyte Nuclear Factor 1-β	PFE, PSE, PMPs	Crucial for generation of pancreatic multipotent progenitor cells and $NGN3^{+}$ endocrine progenitors	[5]
PDX1	Pancreatic and Duodenal Homeobox 1; Insulin Promoter Factor 1; Homeodomain Transcription Factor	PSE, PMPs, EPs, Mature β-cells	Master regulator of pancreatic organogenesis. Induces differentiation from definitive endoderm to pancreatic progenitors. Regulates expression of *Foxa2*, *Gata4*, *Hnf1β*, *Ptf1a*, *Neurog3*, *Nkx6.1*, *Pax6* etc. Activates several key β-cell genes, including *Ins1*, *MafA*, *Glut-2*, *Gck*, and *Iapp*	[6]
GATA4	GATA Binding Protein 4	PSE, PMPs	Expressed in the pancreatic progenitors whereby at later stages of development its expression becomes restricted to mature acinar cells	[7]

SOX9	SRY-Box Transcription Factor 9	PSE, PMPs, EPs	All pancreatic cell lineages are derived from SOX9^{+}. Protects MPCs from apoptosis. Regulates expression of *Hnf1b*, *Hnf6*, *Onecut1* and *Foxa2*. Participates in activating *Ngn3* and *Pdx1* expression	[8]
NEUROG3	Neurogenin 3; NGN3; Class A Basic Helix-Loop-Helix Protein 7; Atoh5; Relax	PMPs, EPs	Activates downstream targets such as *Nkx2.2*, *Nkx6.1*, *Arx*, *Pax4*, *Isl1* and *Neurod1;* is a master switch required for the development of pancreatic endocrine progenitors and successive generation of mono-hormonal endocrine cells	[6,9]
NKX6.1	NK6 Homeobox 1	PMPs, EPs, Mature β-cells	Necessary for generation of mature β-cells and maintaining insulin secretion process. Specific to the pancreas and becomes restricted to β-cells later in the development process	[10–12]
PTF1A	Pancreas Associated Transcription Factor 1a	PMPs	Required for pancreas specification from the foregut endoderm and regulates the expansion of MPCs. Activates exocrine/acinar cell compartment of the pancreas.	[13,14]
GLIS3	GLIS Family Zinc Finger 3	PMPs, EPs, Mature β-cells	Is mainly expressed in preductal and Neurog3^{+} endocrine progenitors. Regulates expression of *Neurog3*. Participates in insulin gene transcription as well as insulin secretion process	[15,16]
RFX6	Regulatory Factor X6	PMPs, EPs, Mature α- and β-cells	Functions in both endoderm development and islet cell differentiation. Directs differentiation of four out of the five islet cells types excluding PP cells. Regulates genes crucial for maturation and function of β-cells	[17–19]
NEUROD1	Neuronal Differentiation 1; Neurogenic Helix-Loop-Helix Protein NEUROD; β-Cell E-Box Transactivator 2	EPs, Mature α- and β-cells	Acts as a transactivator of genes crucial for β-cell function and maturation, like insulin gene transcription	[20,21]
NKX2.2	NK2 Homeobox 2	EPs, Mature α- and β-cells	Crucial for α- and β-cell fate specification and also for maintenance of mature β-cell function by regulating expression of *MAFA* and *GLUT2*	[22,23]
PAX4	Paired Box Protein Pax-4	EPs, Mature β-cells	Required to maintain expression of *PDX1*, *MNX1*, and *INS* in β-cell precursors. Mis-expression of *PAX4* in α-cells transdifferentiates them into β-like cells	[24–26]
PAX6	Paired Box Protein Pax-6	EPs, Mature α- and β-cells	Critical for α-cell development and regulates transcription of key genes such as *MAFB*, *cMAF* and *NEUROD1*. Regulates glucose-regulated ATP synthesis, $Ca2^{+}$ dynamics, and β-cell genes	[27–29]

ISL1	ISL LIM Homeobox 1; ISLET1; Insulin Gene Enhancer Protein ISL-1	EPs, Mature α- and β-cells	Crucial for early pancreas morphogenesis, induction of hormone production, survival, and maintenance of physiological responses in endocrine cells. Regulates expression of *Ins*, *Gcg*, *Glut2*, *Pdx1*, *MafA*, and *Arx* etc	[30–32]
ARX	Aristaless Related Homeobox; Homeobox Protein ARX; Cancer/Testis Antigen 121	EPs, Mature α-cells	Crucial for formation of α, PP and β-cells, but later during development it is restricted in specifying α-cell. *Arx* inhibition in mouse α-cells generates β-like cells or its misexpression in β-cells transdifferentiate them into cells exhibiting α or PP-like cells characteristics	[33–35]
RFX3	Regulatory Factor X3	EPs, Mature α- and β-cells	Aids in development and maturation of endocrine cells. Regulates expression of insulin, *Glut2*, and *Gck.*	[36,37]
MAFB	MAF BZIP Transcription Factor B; V-Maf Avian Musculoaponeurotic Fibrosarcoma Oncogene Homolog B	Embryonic and Mature α- & β-cells	Expressed in both embryonic and adult α- and β-cells. Crucial for induction of hormone genes during terminal differentiation and further provides functional maturation to both the cell types	[38–41]
MAFA	MAF BZIP Transcription Factor A; V-Maf Avian Musculoaponeurotic Fibrosarcoma Oncogene Homolog A; RIPE3b1	Mature β-cells	β-cell specific transcription factor. Acts as a transactivator of *Ins* gene transcription in cooperation with Pdx1 and NeuroD1. Regulates genes critical for β-cell function such as *Pdx1*, *Glut2*, *Neurod1*, *Nkx6.1*, *Slc30a8*, and *G6pc2*	[6,40,42–47]
MNX1	Motor Neuron And Pancreas Homeobox 1; HLXB9	Mature β-cells	Crucial for dorsal pancreas specification, β-cell fate determination, maintenance of β-cell identity and inhibition of other endocrine-lineage programs	[48–51]
LDB1	LIM Domain Binding 1	Mature β-cells	Acts as a scaffold to interact with LIM domain factors like ISL1 to form complexes at promotor/enhancer regions to regulate gene expression for successful β-cell terminal differentiation and maturation processes. Regulates expression of *MafA*, *Glp1R*, *Arx*, *Mnx1* and *Glut2*	[32,52,53]

DE, Definitive Endoderm; PFE, Posterior Foregut Endoderm; PSE, Pancreatic-specified endoderm; PMPs, Pancreatic multipotent progenitors; EPs, Endocrine Progenitors.

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