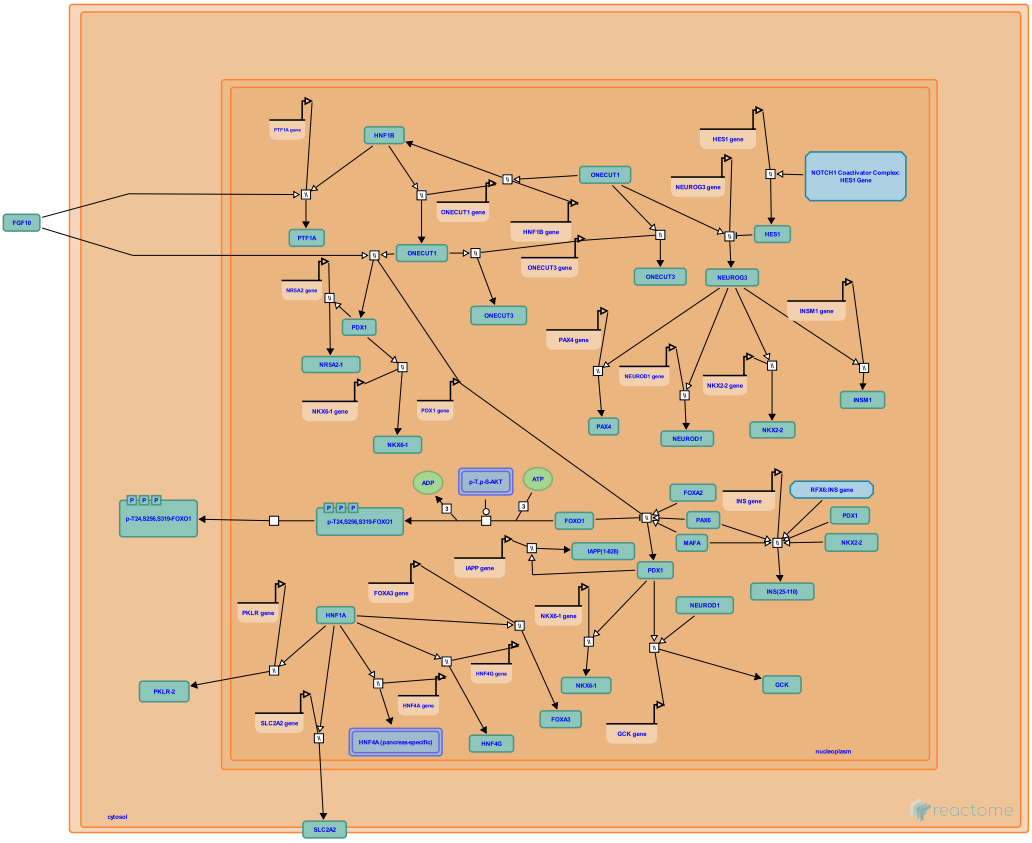
Regulation of beta-cell development



D'Eustachio, P., Ferrer, J., Jensen, J., Tello-Ruiz, MK.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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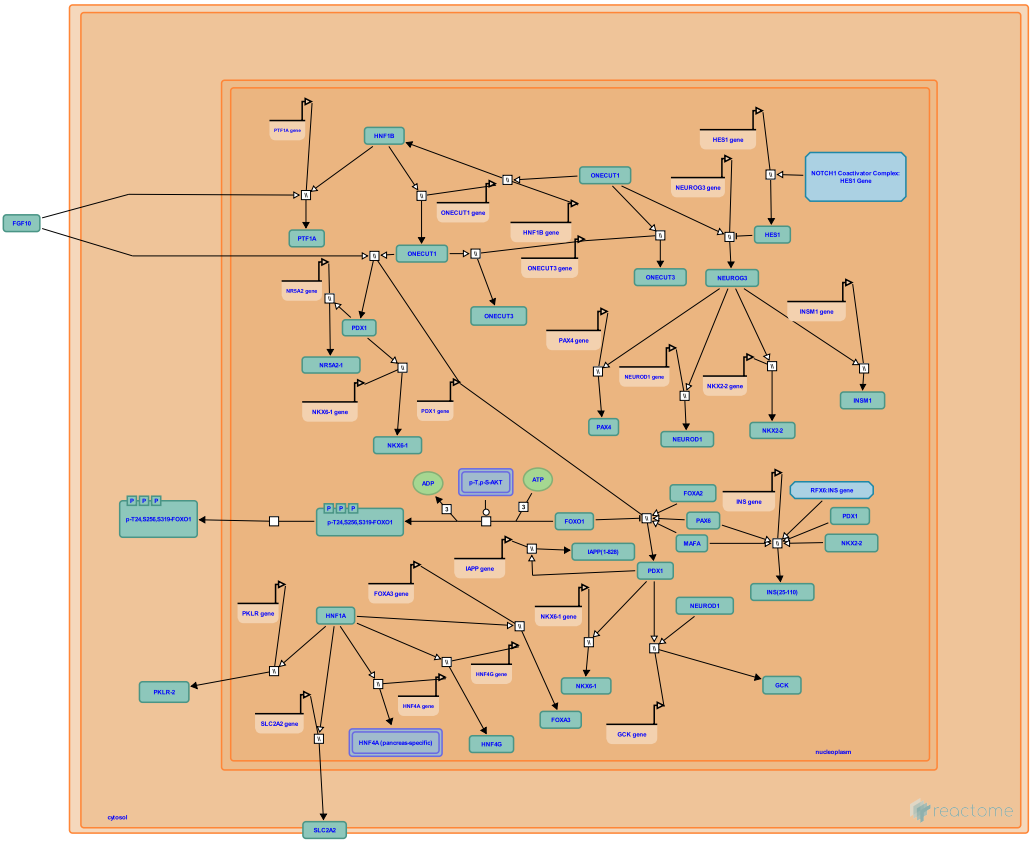
Regulation of beta-cell development ↗

Stable identifier: R-HSA-186712



The normal development of the pancreas during gestation has been intensively investigated over the past decade especially in the mouse (Servitja and Ferrer 2004; Chakrabarti and Mirmira 2003). Studies of genetic defects associated with maturity onset diabetes of the young (MODY) has provided direct insight into these processes as they take place in humans (Fajans et al. 2001). During embryogenesis, committed epithelial cells from the early pancreatic buds differentiate into mature endocrine and exocrine cells. It is helpful to schematize this process into four consecutive cellular stages, to begin to describe the complex interplay of signal transduction pathways and transcriptional networks. The annotations here are by no means complete - factors in addition to the ones described here must be active, and even for the ones that are described, only key examples of their regulatory effects and interactions have been annotated.

It is also important to realize that in the human, unlike the mouse, cells of the different stages can be present simultaneously in the developing pancreas and the linear representation of these developmental events shown here is an over-simplification of the actual developmental process (e.g., Sarkar et al. 2008).

The first stage of this process involves the predifferentiated epithelial cells of the two pancreatic anlagen that arise from the definitive endoderm at approximately somite stages 11-15 and undergo budding from somite stages 20-22. This period corresponds to gestational days 8.75-9.5 in the mouse, and 26 in the human.

Pancreatic buds subsequently coalesce to form a single primitive gland, while concomitantly a ductal tree lined by highly proliferative epithelial cells is formed. A subset of such epithelial cells is thought to differentiate into either endocrine or acinar exocrine cells. A third cellular stage is defined by the endocrine-committed progenitors that selectively express the basic helix-loop-helix transcription factor NEUROG3. NEUROG3 is known to activate a complex transcriptional network that is essential for the specification of endocrine cells. Many transcription factors that are activated by NEUROG3 are also involved

in islet-subtype cellular specification and in subsequent stages of differentiation of endocrine cells. This transient cellular stage thus leads to the generation of all known pancreatic endocrine cells, including insulin-producing beta-cells, and glucagon-producing alpha cells, the final stage of this schematic developmental process.

The diagram below summarizes interactions that take place between transcription factors and transcription factor target genes during these cellular stages, and shows cases where there is both functional evidence that a transcription factor is required for the target gene to be expressed, and biochemical evidence that this interaction is direct. We also describe instances where a signaling pathway is known to regulate a transcription factor gene in this process, even if the intervening signaling pathway is not fully understood.

Literature references

Fajans, SS., Polonsky, KS., Bell, GI. (2001). Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. *N Engl J Med, 345*, 971-80. ↗

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Chakrabarti, SK., Mirmira, RG. (2003). Transcription factors direct the development and function of pancreatic beta cells. *Trends Endocrinol Metab, 14*, 78-84. ↗

Hutton, JC., Still, T., Hayek, A., Sarkar, SA., Kobberup, S., Beattie, GM. et al. (2008). Global gene expression profiling and histochemical analysis of the developing human fetal pancreas. *Diabetologia, 51*, 285-97. ↗

Editions

2008-05-13	Edited	D'Eustachio, P.
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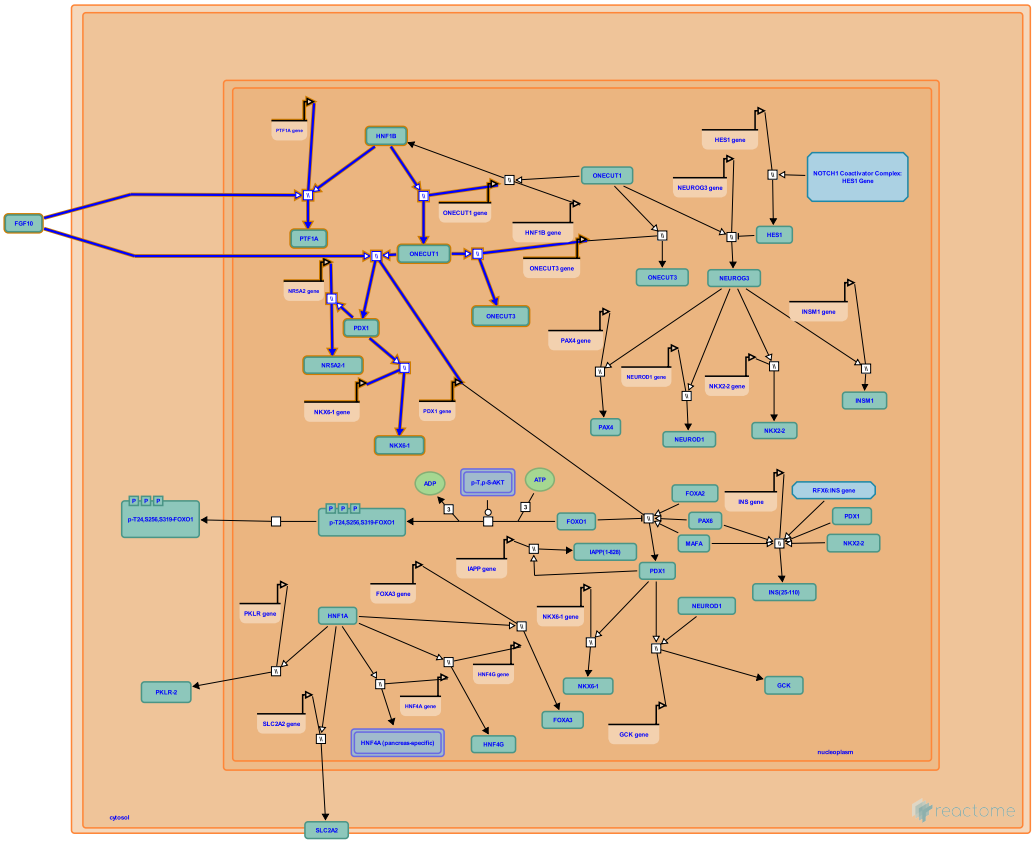
Regulation of gene expression in early pancreatic precursor cells ↗

Location: Regulation of beta-cell development

Stable identifier: R-HSA-210747

Compartments: nucleoplasm



The properties of transcriptional networks early in the differentiation of human pancreatic cells are inferred from the properties of well-studied networks in mouse models. In mice, the first visible sign of pancreatic development is the appearance of pancreatic buds at about embryonic day 9. The cells in these buds are already committed to differentiate into specialized cells of the exocrine and endocrine pancreas. Expression of transcription factors including Hnf1b, Hnf6, and Pdx1, as well as responsiveness to Fgf10 (fibroblast growth factor 10), up-regulates the expression of factors including Ptf1, Onecut3, Lrh1, and Nkx6.1 (Servitja and Ferrer 2004; Chakrabarti and Mirmira 2003).

Literature references

Servitja, JM., Ferrer, J. (2004). Transcriptional networks controlling pancreatic development and beta cell function. *Diabetologia, 47*, 597-613. ↗

Chakrabarti, SK., Mirmira, RG. (2003). Transcription factors direct the development and function of pancreatic beta cells. *Trends Endocrinol Metab, 14*, 78-84. ↗

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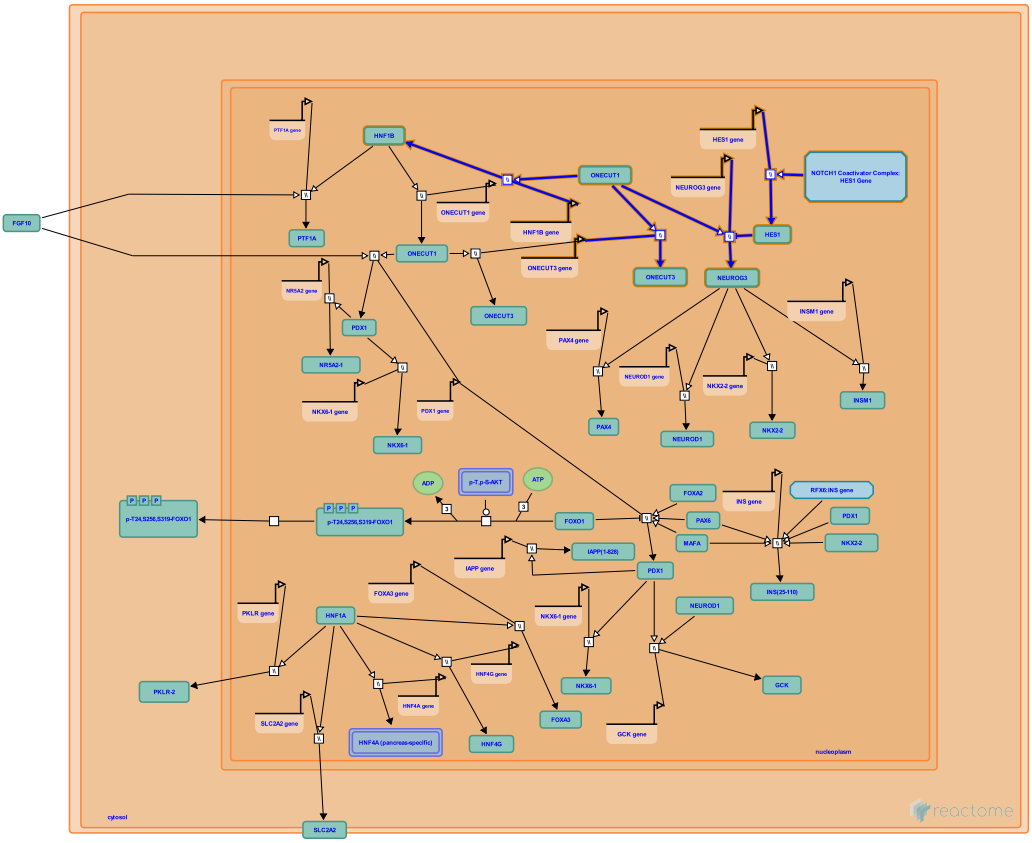
Regulation of gene expression in late stage (branching morphogenesis) pancreatic bud precursor cells ↗

Location: Regulation of beta-cell development

Stable identifier: R-HSA-210744



The properties of transcriptional networks in late stage (branching morphogenesis) pancreatic bud precursor cells are inferred from the properties of well-studied networks in mouse models. In mice, committed but undifferentiated epithelial cells are organized into branching ductal structures. At a molecular level, expression of Pdx1, Nkx2.2, and Nkx6.1 is reduced while Hnf6 expression remains high. Hnf6 mediates the continued expression of Onecut3 and Hnf1 beta and epithelial cell proliferation. As expression of Ngn3 (corresponds to human NEUROG3) rises, endocrine differentiation of the epithelial cells begins (Servitja and Ferrer 2004; Chakrabarti and Mirmira 2003).

Literature references

Servitja, JM., Ferrer, J. (2004). Transcriptional networks controlling pancreatic development and beta cell function. *Diabetologia, 47*, 597-613. ↗

Chakrabarti, SK., Mirmira, RG. (2003). Transcription factors direct the development and function of pancreatic beta cells. *Trends Endocrinol Metab, 14*, 78-84. ↗

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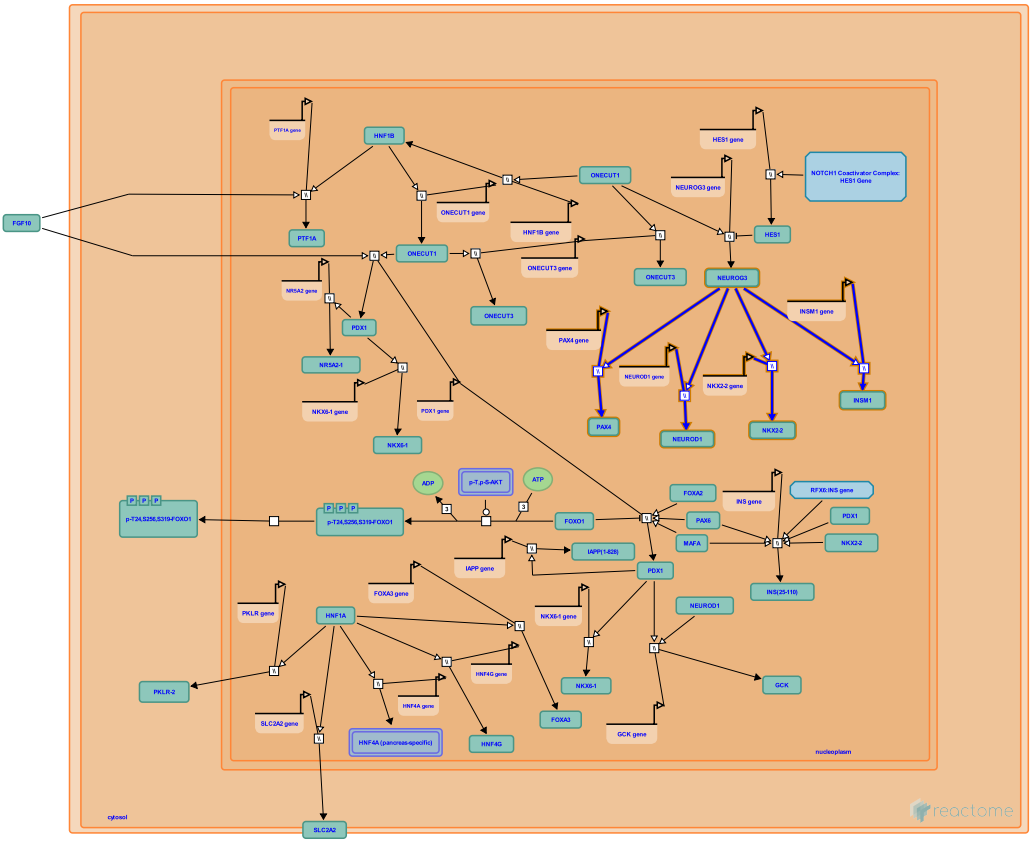
Regulation of gene expression in endocrine-committed (NEUROG3+) progenitor cells ↗

Location: Regulation of beta-cell development

Stable identifier: R-HSA-210746



Studies in mouse model systems indicate that the transcription factor neurogenin 3 plays a central role in the induction of endocrine differentiation in the developing pancreas (Servitja and Ferrer 2004; Chakrabarti and Mirmira 2003). In both mice and humans critical events in this induction process include the neurogenin 3 (NEUROG3)-dependent transcription of PAX4, NEUROD1, NKX2-2, and INSM1.

Literature references

Servitja, JM., Ferrer, J. (2004). Transcriptional networks controlling pancreatic development and beta cell function. *Diabetologia, 47*, 597-613. ↗

Chakrabarti, SK., Mirmira, RG. (2003). Transcription factors direct the development and function of pancreatic beta cells. *Trends Endocrinol Metab, 14*, 78-84. ↗

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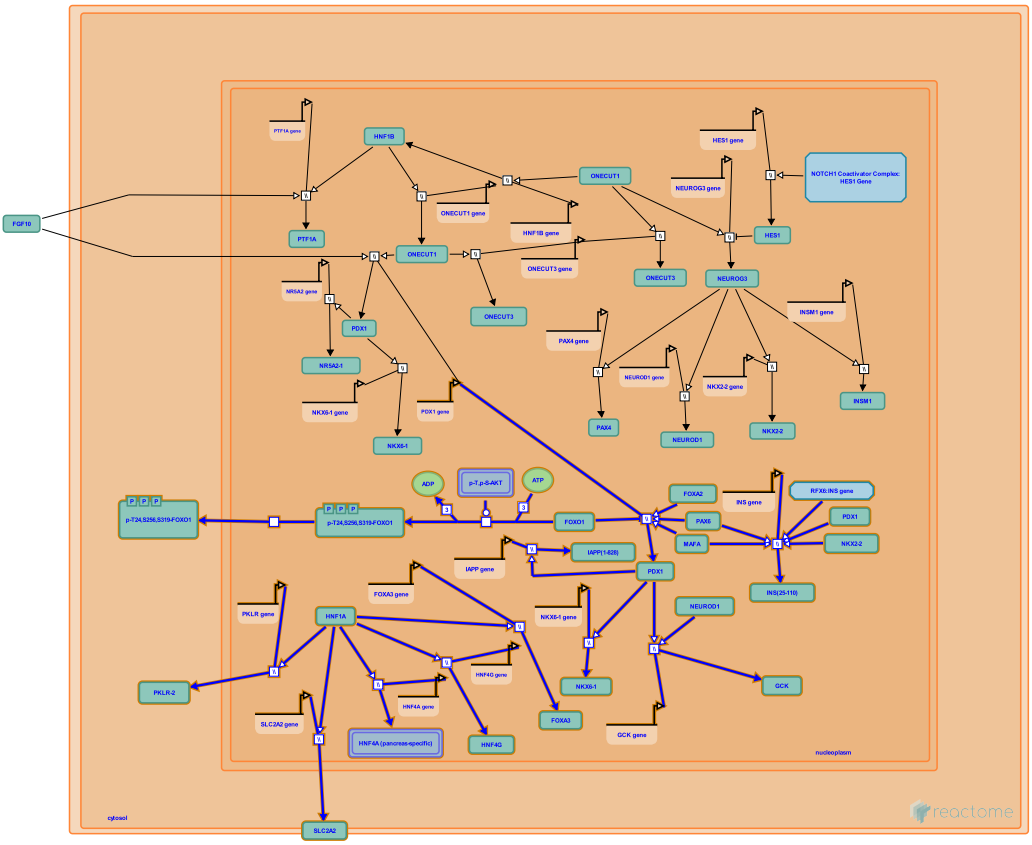
Regulation of gene expression in beta cells ↗

Location: Regulation of beta-cell development

Stable identifier: R-HSA-210745



Two transcription factors, PDX1 and HNF1A, play key roles in maintaining the gene expression pattern characteristic of mature beta cells in the endocrine pancreas. Targets of these regulatory molecules include genes encoding insulin, the GLUT2 glucose transporter, the liver- (and pancreas) specific form of pyruvate kinase and other transcription factors including HNF4A, HNF4G, and FOXA3. PDX1 expression in turn is controlled by the activities of MAFA, FOXA2, and PAX6, and negatively regulated via AKT (Chakrabarti and Mirmira 2003; Servitja and Ferrer 2004).

Literature references

Servitja, JM., Ferrer, J. (2004). Transcriptional networks controlling pancreatic development and beta cell function. *Diabetologia, 47*, 597-613. ↗

Chakrabarti, SK., Mirmira, RG. (2003). Transcription factors direct the development and function of pancreatic beta cells. *Trends Endocrinol Metab, 14*, 78-84. ↗

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Table of Contents