Published in final edited form as:

Diabetes Obes Metab. 2016 September ; 18(Suppl 1): 123–127. doi:10.1111/dom.12730.

Impact of Pdx1-associated chromatin modifiers on islet β -cells

Jason M. Spaeth, Emily Walker, and Roland Stein¹

Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, TN 37232

Abstract

Diabetes mellitus arises from insufficient insulin secretion from pancreatic islet β -cells. In type 2 diabetes (T2D), β -cell dysfunction is associated with inactivation and/or loss of transcription factor activity, including Pdx1. Notably, this particular transcription factor is viewed as a master regulator of pancreas development and islet β -cell formation, identity and function. Transcription factors, like Pdx1, recruit coregulators to transduce activating and/or repressing signals to the general transcriptional machinery for controlling gene expression, including modifiers of DNA, histones, and nucleosome architecture. These coregulators impart a secondary layer of control that can be exploited to modulate transcription factor activity. In this review, we describe Pdx1-recruited coregulators that impact chromatin structure, consequently influencing normal β -cell function and likely Pdx1 activity in pathophysiological settings.

Keywords

coregulators; diabetes mellitus; islet enriched transcription factors; Pdx1; type 2 diabetes; β -cell dysfunction

Introduction

The pancreatic islet consists of several different endocrine, hormone-producing cell types including insulin-producing β -, glucagon-producing α -, somatostatin-producing δ -, ghrelin-producing ϵ -, and pancreatic polypeptide-producing PP-cells. Insulin is secreted under high blood glucose conditions to allow peripheral tissues such as liver, muscle, and fat to take up glucose and reduce blood glucose levels. Glucagon stimulates liver glycogenolysis, increasing blood glucose levels under conditions of hypoglycaemia during extended fasting or exercise. Consequently, glucagon and insulin oppose the action of one another and must be in perfect balance to maintain euglycaemia [1]. Diabetes mellitus arises when this balance is disrupted and improper insulin and/or glucagon release leads to impaired glucose homeostasis.

The most common forms of diabetes are type 1 diabetes (T1D), and T2D. T1D arises from autoimmune destruction of β -cells, while peripheral tissue insulin resistance contributes to compromised T2D β -cell function. Both forms prevent the release of adequate amounts of

¹Corresponding author. roland.stein@vanderbilt.edu.

Conflict of Interest

The authors have no conflict of interest to declare.

insulin to control blood glucose levels. The mechanisms underlying β -cell function are controlled at the transcriptional level, and are mediated by the recruitment of sequence-specific DNA-bound transcription factors (TFs) like Pdx1. In this regard, heterozygous mutations in many islet-enriched TFs associated with the development, differentiation, function and maintenance of β -cells cause an additional form of diabetes, termed maturity onset diabetes of the young (*e.g.* HNF4 α , HNF1 α , PDX1, HNF1 β , PAX4, NEUROD1) [2]. Moreover, mutations in other islet-enriched TFs reduce β -cell function in transgenic mouse models (MafA, Pax6, Nkx6.1) [3–5].

The homeodomain-containing TF Pdx1 is a unique marker of the developing pancreas, and is critical for pancreas specification in both humans and mice [6–9]. The expression of Pdx1 is dynamic, with high expression levels in the developing pancreatic epithelium and low levels in postnatal acini, duct, α -, δ - and PP-cells. High levels of Pdx1 are restricted to islet β -cells. Conditional inactivation of *Pdx1* using *insulin* enhancer/promoter driven Cre recombinase in developing β -cells leads to hyperglycaemia even when only one copy of *Pdx1* is removed [10,11]. Importantly, reduced levels of human PDX1 are associated with and thought to contribute to the T2D β -cell dysfunction [12]. Complete removal of Pdx1 specifically from mature β -cells resulted in severe hyperglycaemia coupled with a transcriptional shift of the insulin⁺ cell population to a α -like cell phenotype. This phenotype was attributed to Pdx1 binding to and repressing α -cell-specific gene targets *Glucagon* and *MafB* [13]. Moreover, forced Pdx1 expression in Neurogenin3⁺ endocrine progenitor cells *in vivo*, but not embryonic or postnatal glucagon⁺ cells, converts α -cells to β -like cells [14]. Collectively, these results illustrate the importance of Pdx1-regulated positive- and negative-control mechanisms in controlling β -cell identity.

Pdx1, like most TFs, cannot impact gene transcription without the aid of recruited coregulators, which modulate activity in numerous ways. For example, several classes of coregulators function to bridge DNA-bound activators to the general transcription machinery (*e.g.* Ldb1, Mediator) [15,16]. Others modify DNA-wrapped histone tails to enhance or restrict chromatin enhancer availability through post-translational modification mechanisms, including acetylation, methylation and ubiquitination [17]. Furthermore, with the energy derived from ATP hydrolysis, nucleosomes can be shuttled or removed by remodeling complexes to allow DNA to be more or less accessible to other TFs, coregulators and the general transcription machinery. Strikingly, while there are hundreds of coregulators (www.nursa.org), relatively little is known about how these impact TF activity in the developing or adult pancreas. Here we describe the effect of various Pdx1-bound coregulators on the chromatin landscape (Figure 1), and speculate how affecting recruitment could modulate TFs like Pdx1 in pathophysiological settings. While the focus for this review is on Pdx1-recruited chromatin modifiers, there are many other important and functionally distinct coregulators, including Pcif1, that impact Pdx1 stability [18].

Pdx1-recruited p300 and HDAC1/2 impact Pdx1 transactivation potential

The N-terminal region of histone proteins is a frequent site of post-translational modifications. For example, histone acetyltransferase (HAT) enzymes relax the interactions between histones and DNA, thereby allowing TF:coregulator binding and gene activation.

Conversely, histone deacetylases (HDACs) remove histone acetylation marks and produce a more highly condensed chromatin structure, restricting gene expression. Many HATs and HDACs have been discovered and implicated in gene regulation, including p300, CREB-binding protein (CBP), p300/CBP associated factor (PCAF), Gcn5-related N-acetyltransferase (GNAT), and HDAC1-8 [19,20]. HATs and HDACs catalyze reactions not only on histones, but also directly modify TFs [21]. Here we will only describe the influence of recruited proteins with acetylation activity on Pdx1 control.

The temporal recruitment of p300 and CBP results in a hyperacetylated chromatin landscape around Pdx1-bound enhancers that promotes gene transcription (Figure 2). This was first demonstrated in the context of the *insulin* gene using an *in vitro* candidate approach [22]. Glucose-stimulated *insulin* gene transcription paralleled the increase in lysine acetylation within the N-terminal tails of Histone H4. Such acetylated histones can recognize bromodomain-containing proteins, including chromatin remodeling components, HDACs, and p300-related CBP. It is likely that p300 and CBP serve as docking sites for other TFs and coregulators to enhance gene transcription in β -cells [23].

Low glucose levels reduce *insulin* gene transcription, promoting a switch in Pdx1:coregulator association. Now Pdx1 recruits HDAC1 and HDAC2 which produce a condensed chromatin structure that leads to reduced target gene expression (Figure 2). HDAC inhibitors (HDACi) have emerged as a potential therapeutic to improve T2D outcomes. Thus, pharmacological approaches that target the HDAC1/2 enzymes in rodents improve insulin sensitivity and mitochondrial function in peripheral tissues [24]. Notably, the ITF2357 HDAC inhibitor improved insulin secretion by reducing nitric oxide synthase production, which contributes to β -cell dysfunction in T1D and T2D rodent islets [25]. Moreover, treatment of a rodent β -cell line with the HDAC inhibitor Trichostatin A increased histone H4 acetylation and *insulin* transcription [26]. However, whether Pdx1 activity is directly modified by these HDAC inhibitors is unclear.

The Swi/Snf chromatin remodeling complex impacts Pdx1 transcriptional activity

Of the many coregulators identified in metazoans, only a few have been linked to modulation of islet-enriched TF activity [26–33]. To begin to address this significant gap in our knowledge, an un-biased biochemical-mass spectrometry approach was recently performed to identify Pdx1-interacting partners in mouse β -cell lines [34]. In addition to previously known Pdx1-interacting proteins (e.g. Set7/9 and HDAC1/2 whose activities are described herein), many novel regulatory activities were identified, including the ATP-dependent nucleosome remodeling deacetylase NuRD [35] and Swi/Snf complexes [36], and the Tif1 β corepressor [37].

Nucleosome shuffling and ejection by remodeling complexes facilitates the recruitment of TFs, coregulators, and the general transcription machinery to gene enhancers [38]. Swi/Snf is a large multi-protein complex containing 8–10 subunits [36]. Nucleosome remodeling requires the hydrolysis of ATP, which is catalyzed by one of two mutually exclusive ATPase subunits, Brg1 or Brm. It has been suggested that Swi/Snf containing Brg1 complexes have

more diverse functionality than Brm [39]. In this regard, Pdx1 binding to Brg1:Swi/Snf was increased in mouse β -cells upon high glucose stimulation, whereas Pdx1 and Brm:Swi/Snf interactions were unaltered. This suggests that Brg1-associated Swi/Snf activity is important for high glucose-mediated Pdx1 activity. Consistent with this, Pdx1:Brg1 interactions were significantly decreased in T2D islet β -cells, while Pdx1:Brm binding was unchanged [34]. Moreover, Pdx1 target gene expression following siRNA mediated depletion of Brg1 or Brm in mouse β -cell lines have opposite effects, with Brg1 loss reducing and Brm loss increasing Pdx1-mediated target gene expression (Figure 2). Interestingly, conditional removal of Brg1 from very early developing Ptf1a⁺ pancreatic progenitor cells results in a hypoplastic pancreas, ~50% reduced in size than control mouse littermates [40]. The pancreatic progenitor cells in which Brg1 is removed co-express Pdx1 and give rise to all pancreatic cell types (acini, duct and endocrine). Whether Pdx1 transcriptional activity is impacting pancreatic progenitor cell formation remains to be investigated.

Depletion of Pdx1 from mature β -cells *in vivo* induces a rapid shift in the transcriptional programs of importance to maintain normal β -cell function and identity. Hence, there is a loss of β -cell identity markers (*Glut2*, *insulin*, *MafA*) and acquisition of α -cell markers (*MafB*, *Glucagon*) in Pdx1-deficient β -cells [13]. The NuRD complex contains both histone deacetylase and ATP-dependent chromatin remodeling activities, and consequently functions as a transcriptional corepressor. Immunoprecipitation and Western blot analysis has shown that the Mi-2 β component of NuRD binds to Pdx1 [34]. The role of this complex in Pdx1-mediated repression in the β -cell, potentially of α -cell markers, is still undefined.

Link between DNA methylation enzymes and Pdx1 in the β -cell

Early developmental loss of the DNA methyltransferase-1 (e.g. Dnmt1) leads to a severe deficiency in pancreas size [41], which is even more profound than Brg1 deficiency [40]. This Pdx1-interacting DNA methyltransferase is required for replication-dependent propagation of repressive methylation marks in dividing cells [42]. Following Dnmt1 elimination from pancreatic progenitor cells, the expression of many TFs required for lineage specification is decreased and there are severe reductions in all mature endocrine and exocrine cell types (e.g. TFs like *Neurogenin3*, *Nkx6.1*, *Nkx2.2*, and *Ptf1a*). This halt in differentiation resulted in accumulation of cells in the G2 phase of the cell cycle and ultimately led to p53-mediated apoptosis. Dnmt1 bound within the *p53* transcription regulatory region, indicating that this methyltransferase directly represses its expression. Indeed, p53 haploinsufficiency restored TF expression, differentiation, and pancreas size in *Dnmt1* conditional knockout animals [41].

Conditional Dnmt1 knockout specifically in β -cells (*RIP-Cre*) led to their conversion to α -like cells [43]. This was attributed to de-repression of the important α -cell-defining aristaless-related homeobox (*Arx*) TF in β -cells. Supportive evidence was provided upon showing that siRNA-mediated knockdown of Dnmt1 in a β -cell line upregulated *Arx*, *MafB*, and *Glucagon* expression, all α -cell-enriched markers. These phenotypes are reminiscent of conditional Pdx1 loss in β -cells [13], although *Arx* levels were not expressed in the α -like cells produced under these conditions. Interestingly, β -cell-specific deletion of related

Dnmt3a, which is associated with the islet-cell-enriched Nkx2.2 TF, causes Arx-dependent β -to- α -cell reprogramming [44].

Pdx1-recruited coregulators are also important in regulating the histone methylation state in β -cells. Histone H3-Lys-4 (H3-K4) dimethylation was identified as a mediator of transcriptional activation through recruitment of RNA Polymerase II [27]. Significantly, H3-K4 methylation of the *insulin* gene leads to transcriptional activation and is facilitated by the methyltransferase Set7/9 in mouse β -cells [45]. Furthermore, this was shown in immunoprecipitation and knockdown experiments to result from binding to Pdx1. Recruitment of Set7/9 by Pdx1 was found to also regulate the H3-K4 dimethylation state of the *insulin*, *Slc2a2* and *MafA* promoters in islets, β -cell Ca^{2+} stimulation and insulin secretion [46]. Interestingly, Set7/9 can methylate N-terminal residues of Pdx1 to augment its transcriptional activity. Moreover, β -cell-specific Set7/9 knockout mice have decreased glucose-stimulated insulin secretion and Pdx1-regulated gene expression [46]. Collectively, these data provide mechanisms by which Pdx1-binding chromatin modifiers can impact β -cell development and function.

Concluding Remarks

T2D results from the combination of peripheral insulin resistance and dysfunctional β -cells, the latter of which can be the consequence of decreased cell function, identity and/or mass. Reduced expression of islet-enriched TFs, MafA, Nkx6.1 and Pdx1, in rodent models significantly compromises β -cell function and identity [3,4,13,32]. Moreover, decreased levels of this same TF subset are observed in dysfunctional human T2D islet α - and/or β -cells [12]. Existing evidence from cultured human islets suggests that human β -cells are capable of dedifferentiating to a hormone-negative cell [47]. This phenomenon is provocative, and dedifferentiation has been proposed to be a major source of β -cell dysfunction in T2D [48,49].

In light of the importance of coregulators in TF action, it is possible that inactivity in pathophysiological settings results from reduced recruitment ability, potentially influenced by the post-translational modification state [12,50]. In this regard, it will be of significant interest to determine how coregulator recruitment to PDX1 (and other islet-enriched TFs) is affected in obese, prediabetic, and T2D islets, with the prediction that PDX1:coregulator association is impacted prior to overt TF loss (Figure 3). Future studies should also be directed towards providing greater insight into how transcriptional coregulators impact β -cell development and function. Furthermore, TF:coregulator binding could also be used as a diagnostic tool in evaluating the integrity of the β -like cells being developed from *e.g.* human embryonic cells, rather than evaluating merely the expression of particular islet-enriched TFs.

Acknowledgments

This review was supported by grants from the National Institute of Diabetes and Digestive Kidney Disease (R01DK050203, R01DK090570) to R.S., and the American Diabetes Association (1-16-PDF-109) to J.M.S. We thank the lab members and colleagues who participated in our cited research.

References

1. Unger RH, Cherrington AD. Glucagonocentric restructuring of diabetes: a pathophysiologic and therapeutic makeover. *J Clin Invest.* 2012; 122:4–12. [PubMed: 22214853]
2. Gardner DS, Tai ES. Clinical features and treatment of maturity onset diabetes of the young (MODY). *Diabetes Metab Syndr Obes Targets Ther.* 2012; 5:101–108.
3. Hang Y, Yamamoto T, Benninger RKP, et al. The MafA transcription factor becomes essential to islet β -cells soon after birth. *Diabetes.* 2014; 63:1994–2005. [PubMed: 24520122]
4. Schaffer AE, Taylor BL, Benthuyzen JR, et al. Nkx6. 1 controls a gene regulatory network required for establishing and maintaining pancreatic beta cell identity. *PLoS Genet.* 2013; 9:e1003274. [PubMed: 23382704]
5. Ashery-Padan R, Zhou X, Marquardt T, et al. Conditional inactivation of Pax6 in the pancreas causes early onset of diabetes. *Dev Biol.* 2004; 269:479–488. [PubMed: 15110714]
6. Jonsson J, Carlsson L, Edlund T, Edlund H. Insulin-promoter-factor 1 is required for pancreas development in mice. *Nature.* 1994; 371:606–609. [PubMed: 7935793]
7. Ahlgren U, Jonsson J, Edlund H. The morphogenesis of the pancreatic mesenchyme is uncoupled from that of the pancreatic epithelium in IPF1/PDX1-deficient mice. *Development.* 1996; 122:1409–1416. [PubMed: 8625829]
8. Offield MF, Jetton TL, Labosky PA, et al. PDX-1 is required for pancreatic outgrowth and differentiation of the rostral duodenum. *Development.* 1996; 122:983–995. [PubMed: 8631275]
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; 15:106–110. [PubMed: 8988180]
10. Ahlgren U, Jonsson J, Jonsson L, Simu K, Edlund H. β -Cell-specific inactivation of the mouse *Ipfl/Pdx1* gene results in loss of the β -cell phenotype and maturity onset diabetes. *Genes Dev.* 1998; 12:1763–1768. [PubMed: 9637677]
11. Gannon M, Ables ET, Crawford L, et al. *pdx-1* function is specifically required in embryonic β cells to generate appropriate numbers of endocrine cell types and maintain glucose homeostasis. *Dev Biol.* 2007; 314:406–417. [PubMed: 18155690]
12. Guo S, Dai C, Guo M, et al. Inactivation of specific β cell transcription factors in type 2 diabetes. *J Clin Invest.* 2013; 123:3305–3316. [PubMed: 23863625]
13. Gao T, McKenna B, Li C, et al. *Pdx1* maintains β cell identity and function by repressing an α cell program. *Cell Metab.* 2014; 19:259–271. [PubMed: 24506867]
14. Yang Y-P, Thorel F, Boyer DF, Herrera PL, Wright CVE. Context-specific α -to- β -cell reprogramming by forced *Pdx1* expression. *Genes Dev.* 2011; 25:1680–1685. [PubMed: 21852533]
15. Love PE, Warzecha C, Li L. Ldb1 complexes: the new master regulators of erythroid gene transcription. *Trends Genet.* 2014; 30:1–9. [PubMed: 24290192]
16. Kornberg RD. Mediator and the mechanism of transcriptional activation. *Trends Biochem Sci.* 2005; 30:235–239. [PubMed: 15896740]
17. Bannister AJ, Kouzarides T. Regulation of chromatin by histone modifications. *Cell Res.* 2011; 21:381–395. [PubMed: 21321607]
18. Claiborn KC, Sachdeva MM, Cannon CE, Groff DN, Singer JD, Stoffers DA. *Pcif1* modulates *Pdx1* protein stability and pancreatic β cell function and survival in mice. *J Clin Invest.* 2010; 120:3713–3721. [PubMed: 20811152]
19. Roth SY, Denu JM, Allis CD. Histone acetyltransferases. *Annu Rev Biochem.* 2001; 70:81–120. [PubMed: 11395403]
20. de Ruijter AJ, Van Gennip AH, Caron HN, Stephan K, Van Kuilenburg AB. Histone deacetylases (HDACs): characterization of the classical HDAC family. *Biochem J.* 2003; 370:737–749. [PubMed: 12429021]
21. Kouzarides T. Acetylation: a regulatory modification to rival phosphorylation? *EMBO J.* 2000; 19:1176–1179. [PubMed: 10716917]

22. Mosley AL, Corbett JA, Özcan S. Glucose regulation of insulin gene expression requires the recruitment of p300 by the β -cell-specific transcription factor Pdx-1. *Mol Endocrinol.* 2004; 18:2279–2290. [PubMed: 15166251]
23. Vo N, Goodman RH. CREB-binding protein and p300 in transcriptional regulation. *J Biol Chem.* 2001; 276:13505–13508. [PubMed: 11279224]
24. Ye J. Improving insulin sensitivity with HDAC inhibitor. *Diabetes.* 2013; 62:685–687. [PubMed: 23431009]
25. Muhammed SJ, Lundquist I, Salehi A. Pancreatic β -cell dysfunction, expression of iNOS and the effect of phosphodiesterase inhibitors in human pancreatic islets of type 2 diabetes. *Diabetes Obes Metab.* 2012; 14:1010–1019. [PubMed: 22687049]
26. Mosley AL, Ozcan S. The pancreatic duodenal homeobox-1 protein (Pdx-1) interacts with histone deacetylases Hdac-1 and Hdac-2 on low levels of glucose. *J Biol Chem.* 2004; 279:54241–54247. [PubMed: 15496408]
27. Francis J. Pdx-1 links histone H3-Lys-4 methylation to RNA polymerase II elongation during activation of insulin transcription. *J Biol Chem.* 2005; 280:36244–36253. [PubMed: 16141209]
28. Liu A, Desai BM, Stoffers DA. Identification of PCIF1, a POZ domain protein that inhibits PDX-1 (MODY4) transcriptional activity. *Mol Cell Biol.* 2004; 24:4372–4383. [PubMed: 15121856]
29. Qiu Y, Guo M, Huang S, Stein R. Insulin gene transcription is mediated by interactions between the p300 coactivator and PDX-1, BETA2, and E47. *Mol Cell Biol.* 2002; 22:412–420. [PubMed: 11756538]
30. Stanojevic V, Yao K-M, Thomas MK. The coactivator Bridge-1 increases transcriptional activation by pancreas duodenum homeobox-1 (PDX-1). *Mol Cell Endocrinol.* 2005; 237:67–74. [PubMed: 15885879]
31. Barbacci E. HNF1 /TCF2 mutations impair transactivation potential through altered co-regulator recruitment. *Hum Mol Genet.* 2004; 13:3139–3149. [PubMed: 15509593]
32. Scoville DW, Cyphert HA, Liao L, Xu J, Reynolds A, Guo S, et al. MLL3 and MLL4 methyltransferases bind to the MAFA and MAFB transcription factors to regulate islet β -cell function. *Diabetes.* 2015; 64:3772–3783. [PubMed: 26180087]
33. Hunter CS, Dixit S, Cohen T, et al. Islet α -, β -, and δ -cell development is controlled by the Ldb1 coregulator, acting primarily with the Islet-1 transcription factor. *Diabetes.* 2013; 62:875–886. [PubMed: 23193182]
34. McKenna B, Guo M, Reynolds A, Hara M, Stein R. Dynamic recruitment of functionally distinct Swi/Snf chromatin remodeling complexes modulates Pdx1 activity in islet β cells. *Cell Rep.* 2015; 10:2032–2042. [PubMed: 25801033]
35. Denslow SA, Wade PA. The human Mi-2/NuRD complex and gene regulation. *Oncogene.* 2007; 26:5433–5438. [PubMed: 17694084]
36. Masliah-Planchon J, Bièche I, Guinebretière J-M, Bourdeaut F, Delattre O. SWI/SNF chromatin remodeling and human malignancies. *Annu Rev Pathol Mech Dis.* 2015; 10:145–171.
37. Friedman JR, Fredericks WJ, Jensen DE, et al. KAP-1, a novel corepressor for the highly conserved KRAB repression domain. *Genes Dev.* 1996; 10:2067–2078. [PubMed: 8769649]
38. Narlikar GJ, Sundaramoorthy R, Owen-Hughes T. Mechanisms and functions of ATP-dependent chromatin-remodeling enzymes. *Cell.* 2013; 154:490–503. [PubMed: 23911317]
39. Kadam S, Emerson BM. Transcriptional specificity of human SWI/SNF BRG1 and BRM chromatin remodeling complexes. *Mol Cell.* 2003; 11:377–389. [PubMed: 12620226]
40. von Figura G, Fukuda A, Roy N, et al. The chromatin regulator Brg1 suppresses formation of intraductal papillary mucinous neoplasm and pancreatic ductal adenocarcinoma. *Nat Cell Biol.* 2014; 16:255–267. [PubMed: 24561622]
41. Georgia S, Kanji M, Bhushan A. DNMT1 represses p53 to maintain progenitor cell survival during pancreatic organogenesis. *Genes Dev.* 2013; 27:372–377. [PubMed: 23431054]
42. Reik W. Stability and flexibility of epigenetic gene regulation in mammalian development. *Nature.* 2007; 447:425–432. [PubMed: 17522676]
43. Dhawan S, Georgia S, Tschen S, Fan G, Bhushan A. Pancreatic β cell identity is maintained by DNA methylation-mediated repression of Arx. *Dev Cell.* 2011; 20:419–429. [PubMed: 21497756]

44. Papizan JB, Singer RA, Tschen S-I, et al. Nkx2. 2 repressor complex regulates islet β -cell specification and prevents β -to- α -cell reprogramming. *Genes Dev.* 2011; 25:2291–2305. [PubMed: 22056672]
45. Deering TG, Ogiwara T, Trace AP, Maier B, Mirmira RG. Methyltransferase Set7/9 maintains transcription and euchromatin structure at islet-enriched genes. *Diabetes.* 2009; 58:185–193. [PubMed: 18984737]
46. Maganti AV, Maier B, Tersey SA, et al. Transcriptional activity of the islet β cell factor Pdx1 is augmented by lysine methylation catalyzed by the methyltransferase Set7/9. *J Biol Chem.* 2015; 290:9812–9822. [PubMed: 25713082]
47. Russ HA, Sintov E, Anker-Kitai L, et al. Insulin-producing cells generated from dedifferentiated human pancreatic beta cells expanded in vitro. *PLoS ONE.* 2011; 6:e25566. [PubMed: 21984932]
48. Talchai C, Xuan S, Lin HV, Sussel L, Accili D. Pancreatic β cell dedifferentiation as a mechanism of diabetic β cell failure. *Cell.* 2012; 150:1223–1234. [PubMed: 22980982]
49. Cinti F, Bouchi R, Kim-Muller JY, et al. Evidence of β -cell dedifferentiation in human type 2 diabetes. *J Clin Endocrinol Metab.* 2016; 101:1044–1054. [PubMed: 26713822]
50. Boucher M-J, Selander L, Carlsson L, Edlund H. Phosphorylation marks IPF1/PDX1 protein for degradation by glycogen synthase kinase 3-dependent mechanisms. *J Biol Chem.* 2006; 281:6395–6403. [PubMed: 16407209]

Figure 1. Pdx1-recruited chromatin modifiers influence transcriptional activity in a context specific manner

For example, p300, CBP, Brg1:Swi/Snf stimulate Pdx1 under high glucose conditions [29,34], while HDAC1/2 and Brm:Swi/Snf constrain activity at low glucose concentrations [26,34].

Low glucose: Deacetylated histones, condensed chromatin, reduced gene expression

High glucose: Acetylated histones, relaxed chromatin, increased gene expression

Figure 2. Regulation of glucose-responsive gene expression by Pdx1-recruited HATs, HDACs, and chromatin remodelers

Under low glucose conditions, Pdx1 recruits HDAC1/2 (possibly in complex with the NuRD corepressor) and Brm:Swi/Snf to deacetylate histones (26,34), condense the chromatin landscape, and reduce target gene expression. Upon stimulating high glucose concentrations, the recruitment and activities of Brg1:Swi/Snf and HATs, such as p300 and CBP, are increased [29, 34]. Acetylated histones and chromatin remodeling promotes active gene transcription. Ac = Acetyl.

Figure 3. Model linking compromised PDX1 activity with changes in T2D β-cell function and identity

PDX1-recruited coactivators (left panel) (e.g. BRG1:SWI/SNF, p300 and CBP) and corepressors (right panel) (e.g. NuRD, HDAC1/2 and BRM:SWI/SNF) regulate β-cell and non-β-cell gene targets in normal β-cells, respectively. Loss of PDX1:coregulator association reduces (coactivators) or de-represses (corepressors) PDX1 target genes in the dysfunctional β-cell prior to overt PDX1 loss.