Roles of Epigenetic Modifications in the Differentiation and Function of Pancreatic β-Cells

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Diabetes, a metabolic disease with multiple causes characterized by high blood sugar, has become a public health problem. Hyperglycaemia is caused by deficiencies in insulin secretion, impairment of insulin function, or both. The insulin secreted by pancreatic β cells is the only hormone in the body that lowers blood glucose levels and plays vital roles in maintaining glucose homeostasis. Therefore, investigation of the molecular mechanisms of pancreatic β cell differentiation and function is necessary to elucidate the processes involved in the onset of diabetes. Although numerous studies have shown that transcriptional regulation is essential for the differentiation and function of pancreatic β cells, increasing evidence indicates that epigenetic mechanisms participate in controlling the fate and regulation of these cells. Epigenetics involves heritable alterations in gene expression caused by DNA methylation, histone modification and non-coding RNA activity that does not result in DNA nucleotide sequence alterations. Recent research has revealed that a variety of epigenetic modifications play an important role in the development of diabetes. Here, we review the mechanisms by which epigenetic regulation affects β cell differentiation and function.

Keywords: epigenetics, pancreatic β cells, histone modification, DNA methylation, non-coding RNA

INTRODUCTION

The global incidence of diabetes has risen sharply with societal progress and improvements in living standards, and the disease is showing a trend toward affecting younger individuals. At present, ~1/10th of the world’s medical expenses are used for the treatment of diabetes and its complications, imposing heavy economic burdens on patients’ families and on society as a whole (Hassan et al., 2017). Diabetes and its complications are common and challenging global problems in the twenty-first century. Diabetes, which is a chronic metabolic disease characterized by elevated blood sugar, is caused by the interaction of multiple factors, including genetic, environmental, social, and psychological factors, and among others (Kolb and Martin, 2017). Persistent hyperglycaemia causes chronic damage to various organs, including the eyes, kidneys, heart, blood vessels, and nerves, which can eventually lead to patient death due to organ failure (Zimmet et al., 2016). According to the pathogenesis, diabetes is mainly divided into two types: Type 1 diabetes (T1D) is caused by an autoimmune attack targeting the insulin-producing pancreatic β-cells, while type 2 diabetes (T2D) is associated with aging, early development of insulin resistance, and a deteriorating β cell function. T2DM is a complex disease resulting from the interaction of genetic, epigenetic, environmental, and lifestyle factors. About 90% of diabetic
cases worldwide are accounted to be T2D and predominantly targets adults. Furthermore, T2DM can be complicated with chronic conditions, such as hypertension, coronary heart disease, stroke, macrovascular and microvascular complications, which has greatly challenged the global medical and health system; thus, the prevention and treatment of diabetes and its complications have become popular research topics worldwide (Ueda et al., 2019).

Epigenetics was originally proposed by Waddington in 1942, and its definition was finalized at the 2008 Cold Spring Harbor Conference as “a stable heritable phenotype caused by chromosomal changes without changing the DNA sequence” (Berger et al., 2009; Waddington, 2012). Researches have revealed that the mechanisms of these changes mainly comprise DNA methylation, histone modification and noncoding RNA (ncRNA) activity (Ling and Ronn, 2019). Epigenetic regulation exists throughout the lifetime of an organism and participates in many life activities. Any abnormality in the epigenetic regulatory mechanism will affect chromatin structure and gene expression, leading to the occurrence of a variety of diseases (Nilsson et al., 2018; Li S. et al., 2019; Perez and Lehner, 2019). Epigenetic changes are important regulatory mechanisms of islet β cell function and play irreplaceable roles in the normal physiological function of pancreatic β cells and insulin-secreting cells and apoptosis (Courty et al., 2019; Gong and Jiang, 2020; Makkar et al., 2020). There is no doubt that epigenetics research already becomes the focus of the study of pancreatic β cells in recent years. Epigenetic modifications are closely related to other biological processes in the physiological function of pancreatic β cells. If the epigenetic changes are moderately induced or controlled by drug intervention, it is expected to become a new point to prevent the occurrence and development of diabetes.

**EFFECTS OF DNA METHYLATION ON β CELL DIFFERENTIATION AND FUNCTION**

DNA methylation modification is by far the most thoroughly studied epigenetic modification (Shafabakhsh et al., 2019). DNA methylation modification is mainly controlled by DNA methyltransferase (DNMT) family proteins (Table 1) (Sahin et al., 2010). S-adenosylmethionine is used as the methyl donor to methylate the cytosine on CpG islands. Normally, the CpG island of a gene is in an unmethylated state. Methylation of the cytosines in the CpG island can inhibit the expression of this gene (Figure 1). Increasing evidence shows that the regulation of methylation level is related to diet, physiological activities and glucose level, indicating that methylation is a dynamic process (Wicklow and Sellers, 2015). There is evidence that both the density and methylation level of tissue-specific promoter CpG islands play important roles in the regulation of gene expression (Bansal and Pinney, 2017; Ponnaluri et al., 2017; Zhou et al., 2018).

**DNA Methylation in Diabetic Patients**

Both the environment and diet can lead to apparent changes in the modification of certain imprinted genes and transposable elements in the genome, which in turn affect the development of the disease (Jirtle and Skinner, 2007). Research has shown that glucose metabolism disorders in T2DM patients are related to the hypomethylation of DNA in peripheral blood leukocytes (Toperoff et al., 2015). Another example is in adults exposed to famine during the Dutch Hunger Winter in the late period of World War II. The offspring of these individuals presented a low-birth weight, as well as an increase in the incidence of obesity, T2DM and dyslipidemia (Barres and Zierath, 2016). The DNA methylation level of genes related to cardiovascular disease in peripheral blood leukocytes of diabetic patients was significantly higher than that of normal people, and the DNA methylation level in saliva of diabetic nephropathy patients was significantly higher than that of ordinary people (Babu et al., 2015; Ronn and Ling, 2015). In addition, studies have shown that the long-term exposure of insulin and glucose will seriously change the DNA methylation status of skeletal muscle, indicating that DNA methylation is a rapid adaptation epigenetic marker (Mudry et al., 2017).

The methylation of the CpG island in the insulin promoter region may play a crucial role in the maturation and tissue-specific expression of insulin genes in pancreatic β cells. Research scholars at Malmö University Hospital in Sweden found that in the islets of T2DM patients and those of non-T2DM donors, insulin promoter DNA methylation in human islets was negatively correlated with insulin gene expression and positively correlated with HbA1c (Yang et al., 2011). Relatedly, insulin methylation levels increased and expression decreased in T2DM patients (Yang et al., 2011). Dayeh et al. performed DNA methylation chip array analysis on islets donated by 15 T2DM patients and 34 normal controls and found that 853 genes and 1,649 CpG sites were differentially methylated in the islets of diabetic patients (Dayeh et al., 2014). In vitro

| Name          | Location | Functions                                                                 |
|---------------|----------|---------------------------------------------------------------------------|
| DNMT1         | 19p13.2  | The main enzyme to maintain methylation which ensures the normal replication of DNA methylation mode; and also necessary for de methylation of non CpG sites (Tajima et al., 2016) |
| DNMT2         | 10p15.1  | The methyltransferase of aspartic RNA, which can methylate 38′C of aspartic RNA (Gol et al., 2008) |
| DNMT3A        | 2p23.3   | The main de novo DNA methyltransferase which establishes DNA methylation patterns in gametes and early embryos (Chedin, 2011; de Mendoza et al., 2018) |
| DNMT3B        | 20q11.2  | The main de novo DNA methyltransferase which establishes DNA methylation patterns in gametes and early embryos (Chedin, 2011) |
| DNMT3L        | 21q22.3  | Has no methyltransferase activity by itself, interacts with the DNMT3A and DNMT3B catalytic regions to enhance the activity of DNMT3A and DNMT3B, thus facilitating de novo methylation (Chedin, 2011) |

**TABLE 1 | Members and functions of DNA methylated transferases.**

DNMT1, DNA methyltransferase 1; DNMT2, DNA methyltransferase 2; DNMT3A, DNA methyltransferases 3A; DNMT3B, DNA methyltransferases 3B; DNMT3L, DNA methyltransferases 3L.
The Epigenetic Regulation in Pancreatic β Cell

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FIGURE 1 | Molecular mechanism of DNA methylation (Bansal and Pinney, 2017; Ponnaluri et al., 2017; Zhou et al., 2018; Shafabakhsh et al., 2019). DNA methylation modification is mainly controlled by DNMT proteins. S-adenosylmethionine is used as the methyl donor to methylate the cytosine on CpG islands. Normally, the CpG island of a gene is in an unmethylated state. Methylation of the cytosines in the CpG island can inhibit the expression of this gene.

DNA Methylation in β Cell Differentiation and Function

The role of DNA methylation in early pancreatic development is unclear, and Anderson et al. found in a model of induced pancreatic β cell ablation that DNA methylation in pancreatic progenitor cells plays an important role in the differentiation of pancreatic progenitor cells (Anderson et al., 2009). The specific knockout of DNMT1 in mouse pancreatic progenitor cells showed pancreatic progenitor cell apoptosis and pancreatic hypoplasia (Georgia et al., 2013). In mature β cells, defects in DNMT1 or DNMT3 can cause β cells to lose their “identity” and be reprogrammed into alpha cells, indicating that inhibition of alpha cell programming is necessary to maintain the “identity” of β cells (Dhawan et al., 2011). Currently, research has found that the occurrence of this reprogramming is related to the methylation of the Aristaless-related homeobox (Arx) promoter, causing abnormal Arx expression in β cells (Dhawan et al., 2011). In β cells, the inhibition of this methylation mediator ArxTat occurs through the interaction of NK2 homeobox 2 (Nkx2.2) with an inhibitory complex containing Grg3 (also known as Tle3), HDAC1 and Dnmt3A (Papizan et al., 2011). Therefore, in current cell replacement therapy research, endogenous alpha cells are considered to be important for β cell reprogramming. Recent studies have also shown that inhibiting DNA methylation in pancreatic progenitor cells promotes alpha cell production (Liu et al., 2019). In addition, the hypermethylation of CpG islands can reduce the expression of HNF4α gene and affect the differentiation of pancreatic β cells (Gilbert and Liu, 2012).

PDX1 mutations can cause special types of diabetes, showing that PDX1 silencing can promote pancreatic β cell damage leading to diabetes (Pedica et al., 2014). The DNA methylation of 10 CpG sites in the PDX1 promoter and enhancer regions of pancreatic islets in T2DM patients was increased compared with the control group. Pancreatic β cells exposed to hyperglycaemia showed increased DNA methylation and decreased expression of PDX1 in the islets. Overall, the epigenetic modification of PDX1 may play a role in the development of T2DM.

Peroxisome proliferator-activated receptor γ coactivation 1α (PPARGG1α) is a transcriptional coactivator with high levels of
expression in the human liver, kidneys, pancreas and skeletal muscles. DNA methylation of the PPARGG1α promoter may be an important cause of diabetic cardiopathy (Lacquemant et al., 2000; Waldman et al., 2018). Ling et al. reported that the DNA methylation of the PPARGG1α promoter in the islets of T2DM patients was accompanied by decreased mRNA expression, suggesting that epigenetics can regulate the expression of the PPARGG1α gene and subsequently affect insulin secretion (Ling et al., 2008).

TCF7L2 is a T2DM susceptibility gene that can promote the proliferation and survival of pancreatic β cells, and regulate the function of glucagon-like peptide (GLP-1) synthesis by intestinal L cells. Hu et al. performed high-throughput detection on pancreatic islet cells cultured in high fat and high glucose and found that chronic glycolipid toxicity can induce abnormal DNA methylation of the TCF7L2 gene, which may be one of the mechanisms of glycolipid toxicity leading to the deterioration of diabetic islet cells (Hu et al., 2014).

In addition, DNA methylation is considered to be an important intergenerational genetic mechanism (Sarkies, 2020). DNA methylation markers in paternal and maternal genomes undergo reprogramming during mammalian fertilization and embryonic development; however, some imprinted genes escape the demethylation process during this time and thus change the representative type, resulting in intergenerational inheritance. In 2015, a study of perinatal female rat (F0) exposed to bisphenol A showed that the methylation of the imprinted gene insulin-like growth factor 2 (Igf2) of the F2 generation can be changed and cause intergenerational inheritance to impair insulin secretion and glucose intolerance of the offspring (Mao et al., 2015). Su Rina et al. established a rat model of moderate intrauterine hyperglycemia induced by streptozotocin to detect glucose and lipid metabolism of first-generation (F1) and second-generation (F2) offspring. The results showed that F1 and F2 offspring which were exposed to intrauterine hyperglycemia had impaired insulin secretion from the islets, and both F1 and F2 offspring showed similar hypomethylation level at the −1952 site of the tumor necrosis factor (Tnf) gene (Su et al., 2016). These results confirmed that DNA methylation occurs in offspring exposed to intrauterine hyperglycemia and that the DNA methylation is intergenerational and inherited.

Ten eleven translocation (TET) enzymes and thymine DNA glycosylase (TDG) are implicated in active DNA demethylation (Ito et al., 2010). The three TET family enzymes oxidize 5-methylcytosine (5mC) in DNA to 5-hydroxymethylcytosine (5hmC), and subsequently to 5-formylcytosine (5fC) and 5-carboxycytosine (5caC) (Ito et al., 2010; He et al., 2011). TDG, a base excision repair glycosylase, replaces 5fC and 5caC with an unmodified cytosine via DNA repair (He et al., 2011). Although recent data suggest a role of TET and 5hmC in embryonic stem cells and primordial germ cells, evidence for enzymatic demethylation by TET enzymes during differentiation of cells of later stages, such as the postnatal and adult stem cells of various organs including pancreas, remains very limited (Auclair and Weber, 2012; Tan and Shi, 2012). Interestingly, TET2 and TET3 are highly expressed in the murine adult pancreas, yet the pancreas has lower genomic 5hmC levels than other adult tissues derived from endoderm, including liver and lung (Ito et al., 2010, 2011), suggesting dynamic DNA demethylation during pancreas development. Xianghui Fu et al. found that TETs and TDG are direct targets of miR-26a and the expression of TETs and miR-26a change in opposite directions during in vivo and in vitro pancreatic cell differentiation (Fu et al., 2013). Another study showed that IFN-α exposure causes DNA demethylation by upregulation of the exoribonuclease PNPase old-35 (PNPT1), which mediates degradation of miR-26a leading to overexpression of methylcytosine dioxygenase TET2 and increased 5-hydroxymethylcytosine levels in human islets and β cells. These results provide a mechanistic framework to explain how inflammatory triggers such as viral infections can modify the β cell epigenome and modulate the interactions between the immune system and β cells (Stefan-Lifshitz et al., 2019). Therefore, the role of dynamic DNA demethylation during pancreas development deserves further study.

THE ROLE OF HISTONE MODIFICATION IN β CELL DIFFERENTIATION AND FUNCTION

The core histones in the chromatin structure are subject to a series of covalent modifications with different chemical groups (including acetylation and methylation) that lead to the formation of a modified cascade called a histone code. The histone code can be recognized by a series of protein complexes, is translated into a specific chromatin state, and has a very important gene transcription regulatory function (Sims and Reinberg, 2008). The ease of access to the transcription factor binding site on chromatin is determined by the position and encapsulation of histones, and the degree of nucleosome compression is determined by the activity of a series of enzymes that are responsible for various histone-specific covalent modifications (such as acetylation, methylation, and phosphorylation) (Berger, 2007). The most studied types of histone modifications are acetylation and methylation of specific amino acid residues of histones H3 and H4 (Figure 2). Related research shows that during the differentiation and development of β cells, histone modification plays an important regulatory role and can recruit protein complexes to participate in the regulation of the expression of related genes in β cells (Ahmed et al., 2017; Balaji et al., 2018; Makkar et al., 2020).

Histone Methylation

Histone methylation often occurs at the lysine or arginine residues of histone H3 and H4. Such methylation is cocatalysed by histone methyltransferases (HMTs) and histone demethylase 1 (lysine demethylase 1, LSD1), indicating that the histone methylation process is reversible (Jenuwein, 2006). Histone methylation is more stable and persistent than histone acetylation. Histone methylation of different forms and at different amino acid sites can lead to activation or inhibition of gene transcription (Marmorstein and Trievel, 2009). The forms of histone methylation include monomethylation, dimethylation,
and trimethylation. Histone lysine methylation is relatively stable and often occurs at positions H3K4, HK9, H4K20, H4K27, H3K36, and H3K79 (Table 2).

**Histone Acetylation**

The histone acetylation process consists of histone acetyltransferases (HATs) and histone deacetylases (HDACs) (Ahmed et al., 2017). It is known that HATs can catalyse histone acetylation, resulting in the relaxation of chromatin structure, and makes it easy to recruit transcription factors to combine with them and promote the transcriptional expression of genes. On the contrary, HDACs deacetylate histones to lead to chromatin compression and inhibit gene transcription. HATs and HDACs jointly participate in the dynamic equilibrium processes of histone acetylation to precisely regulate gene transcription, such as for histone H3 at positions 9, 14, 18, and 23. Once the dynamic equilibrium state of acetylation and deacetylation of histones is broken, it may cause disease.

**Histone Deacetylase Inhibitors (HDACis) and Pancreatic β Cells**

HDACis can improve the function of pancreatic β cells, promote insulin synthesis and release, reduce inflammatory response-induced damage to pancreatic β cells, regulate the influence of the systemic immune response on T1DM and T2DM, and ameliorate the complications of diabetes (Sharma and Taliyan, 2016a). Short-chain fatty acids (such as butyric acid) that act as HDACis are intestinal fermentation products that exist in natural foods and may have broad application prospects in the treatment of GDM.

HDACis can be divided into 6 categories, according to their chemical structure (Table 3): ① short-chain fatty acids, such as sodium valproate (VPA) and sodium butyrate (NaB); ② hydroxamic acids, such as trichostatin A (TSA) and suberoylanilide hydroxamic acid (SAHA); ③ cyclic tetrapeptides, such as trapoxin A, (TPX); ④ benzamides, such as entinostat (MS-275); ⑤ epoxy ketones, such as trapoxin B; and ⑥ hybrid molecules, such as peptide hydroxamic acids (cyclic hydroxamic acid-containing peptide 31, CHAP31) (Christensen et al., 2011; Sharma and Taliyan, 2016a). Mosley et al. verified the effect of glucose concentration on the acetylation of the insulin gene promoter in the islet β cell line MIN6. Their study revealed that the histone acetylation level of the glucose promoter was significantly increased when the glucose concentration was 30 mmol/L than when it was 3 mmol/L. After treatment with the
TABLE 2 | Histone-lysine methyltransferase in the differentiation and function of pancreatic β cells.

| Genes       | Action sites | Targets                               | Functions                                      |
|-------------|--------------|---------------------------------------|-----------------------------------------------|
| EHMT2 or G9a| H3K9me3,     | HMGA1                                | Gene silencing (Cao et al., 2019)             |
|             | H3K27        |                                       |                                               |
| SETDB1      | H3K9me3      | PPARγ, CEBPα                         | Gene silencing (Okamura et al., 2010)         |
| SET7/9      | H3K4         | HIF-1α, p21, PDX1, BETα2             | Gene silencing (Saed and Kim, 2016)           |
| SET8        | H4K20        | /                                     | Block ROS accumulation, attenuate vascular inflammation, and restore nitric oxide production (Yao et al., 2014) |
| PRC2        | H3K27        | Insulin gene                          | Inhibit the expression of insulin             |
|             |              |                                       | (Pethe et al., 2014)                          |
|             |              | RAD21                                 | Increased MafA expression (Deering et al., 2009) |
|             |              | PDX1                                  | Inhibit the differentiation of β cells (Chang et al., 2016) |
|             |              | LncRNA ANRIL                          | Increased VEGF expression (Thomas et al., 2017) |
|             |              | miR-200b                              | Increased VEGF expression (Ruiz et al., 2015) |
|             |              |                                       |                                               |
|             |              | SUV39H1                               | Gene silencing (He et al., 2012)              |
|             |              | KMT2D/MLL2                            | Regulate glucose homeostasis                  |
|             |              |                                       | (Scoville et al., 2015)                      |
|             |              | KMT2C/MLL3                            |                                               |
|             |              | KMT2B/MLL4                            |                                               |
|             |              | NSD2                                  | Promote the differentiation of β cells       |
|             |              |                                       | (Poulin et al., 2016)                        |
|             |              | EZH2                                  | Gene silencing (Chen et al., 2009)           |
|             |              |                                       |                                               |

HMGA1, high mobility group at-hook 1; BDNF, brain derived neurotrophic factor; PPARγ, peroxisome-proliferator activated receptor γ; CEBPα, CCAAT-enhancer binding protein α; HIF-1α, hypoxia-inducible factor 1α; PDX1, pancreatic and duodenal homeobox 1; BETα2, beta cell E-box transcription factor 2; SUV39H1, suppressor of variegation 3-9 homolog 1; KMT2D, lysine methyltransferase 2D; KMT2B, lysine methyltransferase 2B; KMT2C, lysine methyltransferase 2C; NSD2, nuclear receptor binding SET domain protein 2; EZH2, enhancer of zeste homolog 2; INK4a/ARF, inhibitor of CDK4/alternative reading frame.

Histone Modification and Pancreatic β Cell Development and Function

Studies have shown that the modification of histones determines whether pluripotent pancreatic progenitor cells produce β cells. Haumaire et al. studied the regulatory role of HDAC expression and activity in the development of rat pancreases and found that HDAC inhibitors can reduce the differentiation of pancreatic exocrine cells and increase the number of ductal cells and Gnas3-negative endoderm progenitor cells (Haumaire et al., 2009). The dynamic changes in histone acetylation on the final different types of endocrine cells (that is, the number of α-, β-, δ-, ε-, and PP cells) have a decisive role. The different types of HDAC have different effects on the development of pancreatic cells. For example, class I HDAC members specifically inhibit the production of α- and PP cells while promoting the differentiation of β- and δ-cells (Haumaire et al., 2008). The genetic deletion of different members of class II HDAC can lead to an increase in β cells and/or δ-cells, and their overexpression can cause the numbers of β- and δ-cells to be reduced (Lenoir et al., 2011). Therefore, histone modification enzymes have a highly specific role during the development and differentiation of different pancreatic cells. In addition, studies have shown that the HDAC inhibitor MC1568 can promote the expression of PDX4 and insulin (Dayeh and Ling, 2015). These results show that HDAC plays a key role in mediating pancreatic β cell differentiation and development.

A series of transcription factors, such as PDX1, require chromatin modification factors to effectively regulate gene transcription, which is essential for maintaining the normal function of β cells. If histone modification changes, it may cause a series of genes in β cells to exhibit high or low expression. This may further cause the occurrence of diabetes. Chakrabarti et al. found that β cells are highly methylated and acetylated at the H3K4 proximal promoter region of the insulin gene, and this modification is highly correlated with the recruitment of the histone methyltransferase Set7/9 and the histone acetyltransferase P300, which suggests that the expression of the insulin gene is regulated by histone modification (Chakrabarti et al., 2003). PDX1 can recruit the histone methyltransferase Set7/9, which in turn methylates H3K4 in the promoter region of the insulin gene, to promote the expression of the insulin gene (Maganti et al., 2015). Another study showed that Set7/9 is necessary for normal β cell function. Set7/9 can regulate insulin secretion-related genes (such as Ins1/2, Glut2, and MafA) with transcription factor PDX1 and RNA polymerase II (Deering et al., 2009). Related studies also show that under high glucose stimulation, p300 and PDX1 cooperate to promote insulin transcription of β cells; on the
The locus Cdkn2a has indeed been linked to reduction in the proliferative capacity of aged β cells (Chang et al., 2016). Studies have also shown that MLL3 and MLL4 bind to the transcription factors MafA and MafB to regulate pancreatic β cell function (Scoville et al., 2015).

The products of the Ink4a/Arf (Cdkn2a) locus, the cyclin-dependent kinase inhibitor p16INK4a and the tumor suppressor p19Arf showed increased expression with age and have been linked to reduction in the proliferative capacity of aged β cells (Krishnamurthy et al., 2006). The locus Cdkn2a has indeed been identified linked to T2DM by genome-wide association analysis (Diabetes Genetics Initiative of Broad Institute of August 2020 | Volume 8 | Article 748). Interestingly, a recent study reported that Bmi-1 dependent modulation of the Ink4a/Arf expression levels is critical to regulate pancreatic β-cell proliferation during aging and regeneration (Dhawan et al., 2009). Loss of Bmi-1 resulted in reduced β-cell proliferation. Decreased Bmi-1 binding to the Ink4a/Arf locus in aged islet led to reduced H2A ubiquitination. This epigenetic modification stimulated the recruitment of MLL1, a trithorax group (TrxG) protein, and increased H3K4me3 that augmented transcriptional activity from the Ink4a/Arf locus. During β-cell regeneration, increased Bmi-1 binding coincided with decreased H3K4me3, resulting in repression of the Ink4a/Arf locus and augmented β-cell proliferation.

The PcG protein Ezh2, functioning as a HMT in PolycombRepressive complex 2 (PRC2), was shown to regulate islet cell growth by influencing the proliferative potential of β cells (Chen et al., 2009). Conditional deletion of Ezh2 in β cells led to decreased H3K27me3 at the Ink4a/Arf locus. This induces a replication failure of β cells in neonatal mice, a reduced β-cell mass and mild diabetes. Ezh2, by regulating histone methylation and repression of the Ink4a/Arf locus in pancreatic islets, permit physiological β-cell expansion in neonatal mice, and adaptive β-cell regeneration after conditional chemical ablation of β cell in adults. This shows the importance of epigenetic mechanisms in the regulation of β-cell proliferation, and suggests that epigenetic manipulation of PcG proteins and their respective histone modification marks in β cells might be a useful tool for promoting β-cell proliferation. Altogether, these studies provide evidence that histone modifications, regulated by complexes containing TrxG and PcG proteins, are required for specific gene repression and permit physiological and adaptive β-cell expansion.

### THE ROLE OF NONCODING RNA IN β CELL DIFFERENTIATION AND FUNCTION

#### The Role of miRNAs in β Cell Differentiation and Function

MicroRNA is a type of endogenous noncoding small, single-stranded RNA of ~22 nucleotides in length. It is complementary to the site of the 3′ untranslated region of the target gene mRNA and binds through sequence-specific base pairing. The latest research shows that microRNA is closely related to pancreatic development, insulin secretion and insulin resistance, and may

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**TABLE 3 | Effects of HDAC inhibitors in preclinical animal models of insulin resistance.**

| HDAC inhibitor | Dosage regimen | Animal model | Potential benefit |
|----------------|----------------|--------------|------------------|
| NaB            | 5% w/w for 16 weeks | HFD-fed mice | Increased insulin sensitivity; Increased energy expenditure (Gao et al., 2009) |
|                | 500 mg/kg, i.p. | HFD-fed mice | Increased energy expenditure (Li et al., 2012); Improved insulin sensitivity (Li et al., 2012) |
|                | 5% w/w for 4 weeks | C57BL/6N mice | Reduced insulin resistance (Khan and Jena, 2016a); Reduced adiposity (Li et al., 2012) |
|                | 400 mg/kg/day for 10 weeks; i.p. | HFD + Low dose | Induction of Fibroblast growth factor-21 (Li et al., 2012) |
| TSA            | 0.6 µg/kg/day for 12 weeks | HFD-fed mice | Increased Energy expenditure; Increased insulin sensitivity (Gaimozzi et al., 2013) |
|                | 0.8 mg/kg, i.p. | HFD-fed mice | Increased Energy expenditure; Increased insulin sensitivity (Gaimozzi et al., 2013) |
| MS-275         | 10 mg/kg i.p. | C57BLKS/ -Leptrdb/db | Increased β-cell proliferation (Khan and Jena, 2016b); Reduced insulin resistance (Khan et al., 2016) |
| SAHA           | 25 mg/kg i.p. every other day for 23 days | C57BLKS/ -Leptrdb/db | Improved insulin resistance (Sharma and Taliyan, 2016b) |
| VPA            | 150–300 mg/kg/day for 3 weeks; orally | STZ (75 mg/kg, i.p.) in SD rats | Reduced insulin resistance (Khan and Jena, 2016b) |
|                | 150–300 mg/kg/day for 10 weeks; orally | HFD + low dose STZ | Reduced insulin resistance (Khan and Jena, 2016b) |
| SAHA           | 25–50 mg/kg i.p. | Swiss albino mice fed with HFD for 8 weeks | Reduced β-cell toxicity; Decreases Serum Nitrite (Lewis et al., 2011) |
| ITF 2357       | 1.25–2.5 mg/kg; orally | Female C57BL/6 mice | Improved insulin resistance (Sharma and Taliyan, 2016b) |
play an essential role in the pathogenesis of diabetes (Table 4) (Gilbert and Liu, 2012).

miR-375 is the first miRNA found to be involved in glucose metabolism and is highly expressed in pancreatic islets. Poy et al. found that inhibiting endogenous miR-375 not only reduces insulin secretion but also affects the proliferation of pancreatic β cells (Joglekar et al., 2007). In mice lacking miR-375 (mi-375 knockout), the number of pancreatic islet alpha cells increased, and the number of pancreatic β cell clusters decreased, leading to increased blood glucose levels (Xu et al., 2009). PDX1 is one of the confirmed target genes of miR-375, and overexpression of miR-375 can downregulate PDX1 in the PI3-K pathway to reduce the expression of insulin genes and inhibit the proliferation of pancreatic β cells (Garikipati et al., 2017). Mir-375 also plays a regulatory role in the differentiation of islet cells. By analyzing the dynamic profile of the miRNA expression during the differentiation of iPSCs from hESCs, it was found that the expression of miR-375 increased at the early stage of iPSC differentiation and then decreased. In addition, miR-375 has a negative regulatory effect on the specific target genes HNF6 and Sox9 in the development of islet embryos to promote the differentiation and maturation of pancreatic β cells (Poy et al., 2004).

Krek et al. found that miR-124a is highly expressed in MIN6 and has a synergistic effect with miR-375, which has been shown to jointly inhibit the myotrophin expression (Krek et al., 2005). FoxA2 is a well-defined miR-124a target gene that has important regulatory effects on pancreatic β cell differentiation and insulin secretion. Baroukh et al. found that miR-124a binds the FoxA2 mRNA 3’ UTR region, which can directly regulate the protein expression level of FoxA2 in pancreatic β cells (Baroukh et al., 2007). As the expression level of the FoxA2 gene decreases, the expression of downstream target genes increases, including PDX1, Kir6.2 and sulfonylurea receptor 1 (SUR1).

miR-7 is the most abundant miRNA expressed in the islets of humans and rats (Correa-Medina et al., 2009). It is highly expressed in the islets of pancreatic humans at 14–18 weeks of gestational age, a time at which the secretion of endocrine hormones by islets increases exponentially. Similar to miR-375, miR-7 is upregulated during the development and differentiation of human islets (Correa-Medina et al., 2009). Nieto et al. established a mouse model in which miR-7 was knocked out at embryonic E10.5. The synthesis of mouse insulin in the embryo was reduced and the number of pancreatic β cells was reduced (Nieto et al., 2012). MIr-7 is an important part of rapamycin complex 1 (miTORC1) and its down-stream effector S6K1 signaling, and the inhibition of mir-7a can activate mTOR signal to promote the proliferation of primary pancreatic β cells in adult mice (Wang et al., 2013).

miR-19 is an important member of the miR-17-92 gene cluster, which is highly enriched in pancreatic precursor cells, while its expression in pancreatic endocrine precursor cells shows a sharp downward trend in differentiated cells. This suggests that miR-19b is involved in the differentiation of pancreatic precursor cells into endocrine precursor cells. Further research shows that NeuroD is the target gene of miR-19b and that miR-19b can

| miRNAs | Targets | Functions |
|--------|---------|-----------|
| miR-7  | GATA6, PDX6 | Regulate development and function of endocrine pancreas (Joglekar et al., 2011; Latreille et al., 2014) |
|        | Fox2, Wip2 | Regulate insulin secretion (Latreille et al., 2014) |
| miR-375 | Mtpn, p38 | Promote the proliferation, differentiation and transdifferentiation of β cells (Ozcan, 2014) |
|        | MAPK, P3K | Regulate pancreatic development (Kloosterman et al., 2007) |
|        | CADM1, CAV1 | Regulate pancreatic development (Joglekar et al., 2007) |
| miR-9  | Onecut-2, SIRT1 | Inhibit insulin secretion (Plaisance et al., 2006) |
| miR-96 | Noc2 | Increase granuphil/Slp4 and decrease Noc2 |
| miR-15b, miR-16, miR-195, miR-106b | Ngn3 | Regulate pancreatic development (Joglekar et al., 2007) |
| miR-21 | PTEN, P3K, AKT | Regulate pancreatic development (Ozcan, 2014) |
| miR-34a | VAMP2, SNARE | Decrease insulin production (Fogli et al., 2010) |
| miR-124a, let-7b | PDX-1, Kir6.2, SUR1, TGF-β / TGF-β-R pathway | Promote the differentiation of β cells (Ozcan, 2014) |
| miR-106b, miR-15a, miR-15b, miR-19b, miR-19 | NeuroD | Promotes the differentiation of pancreatic precursor cells into endocrine precursor cells (Taylor et al., 2011) |
| miR-19b, miR-17-92/217 | Ph1 | Promotes the differentiation of pancreatic precursor cells into endocrine precursor cells (Krapf et al., 1998) |
| miR-18a, miR-145, miR-495 | AIMP2 | Inhibit pancreatic cell proliferation, promote apoptosis and autophagy (Krapf et al., 1998) |
| miR-29 | Pfn2, Wipf2 | Regulate development and function of endocrine pancreas (Joglekar et al., 2011) |
| miR-145, miR-21 | Oct4, Sox2, Klf4 | Promote the differentiation of stem cells into human cells (Xu et al., 2009) |
| miR-290-295, miR-302 | Sox2 | Promote the differentiation of stem cells into human cells (Marson et al., 2008) |
| miR-182 | Rasa1, Grb2 | Maintain the stability of β cells (Melkman-Zehavi et al., 2011) |
| miR-23b | Hes1 | Promote the differentiation of pancreatic endocrine cells (Ozcan, 2014) |
| miR-15a | UCP2 | Regulate the biosynthesis of insulin (Sun et al., 2011) |
| miR-30 | Vimentin, Snail1, Rfx6 | Regulate the proliferation and development of β cells (Liao et al., 2013) |

(Continued)
The Role of lncRNAs in β Cell Differentiation and Function

lncRNA is a type of noncoding RNA with a transcription length greater than 200 nucleotides. Studies have found that lncRNAs are involved in the pathophysiological processes of diabetes, tumors, nervous system diseases and other diseases (Liu et al., 2016; Meng et al., 2017; Qi et al., 2017) LncRNA can combine with proteins to regulate downstream protein functions, or can be used as a structural component to form nucleic acid-protein complexes and bind to the promoter to regulate target gene transcription. Some lncRNAs serve as molecular sponges to bind miRNAs, reducing miRNA bioavailability and regulate the expression of target genes (Table 5) (Guay et al., 2012; Xin et al., 2017).

**TABLE 5 | lncRNAs and circRNAs in the differentiation and function of pancreatic β cells.**

| lncRNAs or circRNAs | Location | Targets | Functions |
|----------------------|----------|---------|-----------|
| KCNQ1                | 11p15.5  | CDKN1C  | Regulate the proliferation and development of β cells (Avrahami et al., 2014) |
| H19                  | 11p15.5  | IGF2    | Regulate insulin secretion (Hark et al., 2000; Schoenher et al., 2003) |
| MEG3                 | 14q32    | DLK1, RTL1 | Regulate the biosynthesis of insulin (Kameswaran et al., 2014) |
| PLUT                 | 13q12.2  | PDX1    | Regulate the development of β cells and insulin secretion (Yin et al., 2015) |
| TUG1                 | 22q12.2  |         | Regulate the biosynthesis and secretion of insulin (Yin et al., 2015) |
| H1-LNC025/ LINC03170 | 20q12    | Gils    | Regulate the development of β cells (Ravassard et al., 2011) |
| CDR1as               | Xq27.1   | miR-7   | Promote development and function of endocrine pancreas; promote insulin secretion (Hansen et al., 2013) |
| circHIPK3            | 11p13    | miR-338-3p, miR-124-3p | Promote the proliferation and development of β cells; promote insulin secretion (Stoil et al., 2018) |

**TABLE 4 | Continued**

| miRNAs | Targets | Functions |
|--------|---------|-----------|
| miR-218 | HNF6, Onecut2 | Regulate pancreatic development (Simon et al., 2010) |
| miR-342 | Foxa2, MafB, GATA4 | Regulate the proliferation and development of β cells (Kloosterman et al., 2007) |
| miR-382 | ISL1 | Regulate the differentiation and function of endocrine cells (Rosero et al., 2010) |
results indicate that the risk allele may be in the islets. In the early stages of development, this study proposed a model in which the risk allele of the rs2237895 SNP led to an increase in KvDMR methylation, which resulted in a decrease in KCNQ1OT1 expression. However, KCNQ1OT1 expression did not differ significantly between the T2DM and control groups. In contrast, the transcription level of KCNQ1OT1 was significantly increased in the islet of the pancreas in T2DM, which was associated with an overall decrease in CpG methylation of the KCNQ1 gene (Moran et al., 2012). Therefore, the pathological interpretation of the variants in this region has always been a contradiction and challenge. However, the regulation of this site and lncRNA KCNQ1OT1 is still closely related to the pathogenesis of β cell biology and T2DM, and the mechanism needs further study.

H19/IGF2 Gene Locus

The H19/IGF2 gene locus is located on chromosome 11p15.5 adjacent to KCNQ1, and includes the IGF2 gene expressed by the male parent and the H19 lncRNA expressed by the female parent (Brannan et al., 1990). The former is essential for early embryonic development, while the latter can inhibit tumors (Hao et al., 1993). The imprinting control region (ICR) is located between these two genes. On the maternal chromosome, the ICR is unmethylated and binds to the transcription factor CCCTC (CTCF). This interaction has an insulator function to block the downstream enhancer from binding to the IGF2 gene promoter so that the downstream enhancer instead acts on the H19 promoter and promotes H19 expression. Because the ICR is methylated on the chromosome, it cannot bind to the CTCF transcription factor and cannot act as an insulator. Therefore, the downstream enhancer cannot bind to the H19 gene promoter, but instead binds only to the IGF2 gene promoter. Thus, the downstream enhancer inhibits the expression of the H19 gene and promotes the expression of IGF2 (Hark et al., 2000; Schoenherr et al., 2003).

Loss of ICR methylation at the H19/IGF2 locus inhibits IGF2 expression, which can cause syndromes of short stature and low birth weight in rodent models and humans; one example is Silver-Russell syndrome, which is a characteristic developmental disorder characterized by retardation of intrauterine and postpartum growth (DeChiara et al., 1990). To ensure the development of important organs, metabolic processes in fat, skeletal muscle and other peripheral tissues can undergo permanent changes and lead to insulin resistance. This observation is called the “thrifty phenotype hypothesis.” However, Ding et al. found that impaired glucose tolerance in the progeny of mice with GDM is accompanied by H19 ICR hypermethylation in islets (Ding et al., 2012). This contradictory finding may be caused by exposure of the developing fetus to different nutritional states or by different exposure times. The above studies show that the H19/IGF2 gene locus can respond to the intrauterine environment and can be used to predict future metabolic complications.

Hypermethylation of the H19/IGF2 ICR can be found in some patients with Beckwith-Wiedemann syndrome (BWS) and focal congenital hyperinsulinaemia (FoCHI); the latter is a glucose metabolism disease characterized by abnormal insulin secretion by pancreatic β cells and hypoglycaemia (Ohlsson et al., 1993). ICR hypermethylation can lead to a decrease in H19 expression and an increase in IGF2 expression. Devedjian and Fournet et al. found that although IGF2 was overexpressed in mouse FoCHI model, expression in the human FoCHI model was different; however, H19 transcription was consistently downregulated, indicating that H19 has a very important regulatory role in inhibiting the proliferation of pancreatic β cells (Devedjian et al., 2000; Fournet et al., 2001). This type of ICR hypermethylation with decreased expression of H19 has also been reported in nephroblastoma. As mentioned previously, the lncRNA H19 regulates β cell function and cell proliferation, and its level can be adjusted independently or indirectly by adjusting the level of IGF2.

DLK1/MEG3 Gene Cluster

DLK1-MEG3 gene cluster is located on chromosome 14q32 in humans (chromosome 12 in mice) and includes paternally expressed protein-coding genes, such as DLK1, RTL1, and DIO3, and maternally expressed non-coding RNAs, such as MEG3, miRNAs, and snoRNAs. DLK1 is expressed in many embryonic tissues and is a negative regulator of adipocyte differentiation. It is highly expressed in human and mouse β cells (Appelbe et al., 2013). This cluster is strictly regulated by the ICR, which consists of two paternal differentially methylated regions (DMR). One region called IG-DMR, which is the primary ICR, is located at 13 kb upstream of the MEG3 transcription start site. The other region overlaps with the MEG3 multi-cis-trans acting transcription site promoter, called the MEG3-DMR. Deletion of this imprinted area can lead to maternal or paternal diploidy of chromosome 14 (uniparental disomy, UPD), thereby causing various severe developmental disorders.

A recent study revealed that the non-coding RNA of the DLK1/MEG3 imprinting site is downregulated in the islets of T2DM patients, but the specific mechanism is unclear (Kameswaran et al., 2014). Increased methylation of the MEG3/DMR and decreased expression of MEG3 can also be observed in some cancers, such as pituitary cancer, renal cell carcinoma, and multiple myeloma. In vitro experiments have further revealed that MEG3 can exert tumor suppressive effects by activating the p53 gene; these functions are partially dependent on the secondary structure of the MEG3 RNA. In addition, the decrease in MEG3 expression in T2DM may be closely related to increased methylation of the MEG3/DMR.

LncRNA PLUT

The lncRNA Pdx1-associated lncRNA upregulator of transcription (PLUT) is abundantly expressed in the nucleus of islet β cells, and its enhancer region can bind to the promoter of the key pancreatic β cell transcription factor PDX1 to participate in regulating pancreatic islet β cell transcription and differentiation processes (Yin et al., 2015). PDX1 can induce endoderm cells to develop and mature into pancreatic cells and can further induce their differentiation into insulin-secreting cells. On the other hand, PDX1 is also involved in mediating insulin transcription factors and glucose transport, which
is important in the development of the pancreas and in the regulation of insulin secretion. Therefore, loss of the lncRNA PLUT, leads to downregulation of PDX1 expression, will lead to abnormal development of the pancreas.

**LncRNA TUG1**

Pancreatic β cells are the main insulin-producing cells, but they are also regulated by insulin and dysfunction of these cells is a key process in the development of T2DM. Studies have shown that lncRNAs are involved in regulating the secretory function of pancreatic β cells. The lncRNA TUG1 is expressed in β cells. Yin et al. silenced the TUG1 gene in adult non-obese diabetic (NOD) mice via siRNA transfection and found that islet β cell synthesis and insulin secretion were significantly reduced, while islet β cell apoptosis was increased (Yin et al., 2015). This pattern suggests that TUG1 may be involved in maintaining islet β cell function and may play an important role in glucose metabolism homeostasis. High-glucose conditions further inhibit the expression of the TUG1 gene in pancreatic β cells, causing a vicious cycle and triggering diabetes.

**LncRNA H1/LNC25**

LncRNA H1/LNC25 is a multifunctional exon transcript cluster that is highly expressed in pancreatic β cells and participates in the regulation of insulin secretion. Studies have shown that the expression of lncRNA H1/LNC25 in pancreatic β cells of diabetic patients is significantly reduced (Ravassard et al., 2011). Moran et al. found that the expression of Glis family zinc finger 3 (Glis3) mRNA was significantly reduced upon the inhibition of lncRNA H1/LNC25 expression in human pancreatic β cells (Moran et al., 2012). Glis3 is a member of the Glis-like zinc finger family and encodes an insulin transcription factor. Loss of Glis3 expression causes the insulin secretion of pancreatic β cells to decrease (Nogueira et al., 2013). Therefore, it can be speculated that the lncRNA H1/LNC25 affects glucose metabolism by affecting the expression of Glis3, which in turn leads to the occurrence of diabetes.

In summary, lncRNAs, which are key factors regulating the homeostasis of glucose metabolism homeostasis, play important roles in the developmental regulation and function of islet β cells development and biological function. A single lncRNA can act through multiple pathways, and multiple lncRNAs can also act together within the same pathway. Although the current understanding of lncRNAs is insufficient, detection and current expression of specific lncRNAs expression in tissues or body fluids may be a new means of approach to predicting the risk of diabetes. The discovery of additional lncRNAs will provide us with more comprehensive ways to improve models for research on glucose metabolism homeostasis research models.

**Roles of Circular RNAs (circRNAs) in β Cell Differentiation and Function**

CircRNAs are closed, circular, non-coding RNAs that do not have 5’ caps or 3’ poly(A) tails, are not easily degraded by exonucleases, and have the characteristics of structural stability, tissue specificity, and evolutionary conservation (Stoll et al., 2018). CircRNAs can be divided into three categories according to their sources: exonic circRNAs (e-circRNAs), intronic circRNAs (i-circRNAs), and exon/intronic circRNAs (EIciRNAs) (Stoll et al., 2018; Li R. et al., 2019). With the rapid development of high-throughput sequencing and other biotechnologies, numerous circRNAs have been found in various organisms, such as nematodes, fruit flies, mice, macaques, and humans. Further studies have revealed that circRNAs play important roles in the occurrence and development of cancer, nervous system diseases, cardiovascular diseases, and metabolic diseases (Wang et al., 2019; Xiao, 2020).

Hansen et al. believed that CDR1as could negatively regulate miR-7 through sponging miR-7, suppress the inhibitory effect of miR-7 on the mTOR signaling pathway, and stimulate pancreatic β cell proliferation and insulin secretion (Hansen et al., 2013). The study showed that circHIPK3 was downregulated in the islets of diabetic model mice which inhibited β cell proliferation and insulin secretion. The mechanism may involve the competitive interaction of circHIPK3 with miR-338-3p and miR-124-3p to regulate the key genes in the development, proliferation and function of pancreatic β cells, such as glucose transporter 2 (Glut2) and protein kinase B1 (PKB1) (Stoll et al., 2018). Zhao et al. found 489 circRNAs differently expressed in the peripheral blood of T2DM patients. They further verified that circRNA-0054633 (hsa_circ_0054633) could be used as a diagnostic marker for T2DM (Zhao et al., 2017). Hsa_circ_0054633 is not only involved in biological processes such as cell cycle and mitotic arrest but is also closely related to the pathogenesis of diabetes mellitus (Werfel et al., 2016; Zhao et al., 2017). By collecting peripheral blood of patients with T2DM, coronary heart disease, T2DM complicated with coronary heart disease and health group, the results of circRNA microarray showed that HAS-circ-11783-2 was closely related to T2DM and coronary artery disease (Salzman et al., 2013).

Although accumulating studies have indicated that circRNAs play key regulatory roles in the occurrence and development of diabetes, the more specific biological functions and molecular mechanisms need to be further revealed.

**CONCLUSION**

Epigenetic regulation of pancreatic islets is of major interest to understand how endocrine cells differentiate, proliferate, establish, and maintain their mature identity and function. The development process of β cells from multipotent progenitors can be successfully recapitulated only partially *in vitro* to generate pancreatic progenitors and functional β cells in cell replacement therapy for treating diabetes. Thus, the epigenomic study of pancreatic islets cells has become a necessity to overcome the barriers that restrict lineage plasticity and is an exciting prospect for the future development of successful β-cell differentiation strategies (Balaji et al., 2018; Lv and Huang, 2019; Scarpa, 2019; Gong and Jiang, 2020). Dissecting the epigenetic components of islet cell-specific transcriptional networks would contribute to induce and maintain appropriate endocrine lineage commitment from embryonic stem cells or induced pluripotent cells. Knowledge and manipulation of the PcG-repression and derepression programs of pancreatic progenitors and β cells would provide benchmarks to direct β cell differentiation protocols. Epigenetic manipulations
demonstrated the importance of DNA methylation and histone modifications in maintaining β-cell identity and driving islet cell differentiation. They have underscored the potential of using reprogramming methods to change identity or regain plasticity of adult endocrine cells and generate novel sources of islet cells. It is also expected that the better understanding of the epigenetic mechanisms leading to enhanced β-cell mass, or to β-cell proliferation and function defects during diabetes, allows identification of novel therapeutic targets. A detailed understanding of the specialized functions of epigenetic regulators in healthy and diabetic islets, together with the generation of specific compounds targeting these components, may accelerate development of strategies for islet replacement or regeneration therapies for prevention and treatment of diabetes.

AUTHOR CONTRIBUTIONS

FX and JL conceived and designed the study. FX and LN performed the data collection and analysis. FX and LC interpreted the data and wrote the manuscript. All authors read and approved the final manuscript.

REFERENCES

Ahmed, M., de Winther, J. M. P., and Van den Bossche, J. (2017). Epigenetic mechanisms of macrophage activation in type 2 diabetes. Immunobiology 222, 937–43. doi: 10.1016/j.imbio.2016.08.011
Anderson, R. M., Bosch, J. A., Goll, M. G., Hesselson, D., Dong, P. D., Shin, D., et al. (2009). Loss of Dnmt1 catalytic activity reveals multiple roles for DNA methylation during pancreas development and regeneration. Dev Biol. 334, 213–223. doi: 10.1016/j.ydbio.2009.07.017
Appelbe, O. K., Yevtodyjenko, A., Muniz-Talavera, H., and Schmidt, J. V. (2013). Conditional deletions refine the embryonic requirement for Dlk1. Mech Dev. 130, 143–159. doi: 10.1016/j.mod.2012.09.010
Auclair, G., and Weber, M. (2012). Mechanisms of DNA methylation and demethylation in mammals. Biochimie 94, 2202–2211. doi: 10.1016/j.biochi.2012.05.016
Avrhami, D., Li, C., Yu, M., Jiao, Y., Zhang, J., Naji, A., et al. (2014). Targeting the cell cycle inhibitor p57Kip2 promotes adult human beta cell replication. J. Clin. Invest. 124, 670–674. doi: 10.1172/JCI69519
Babu, M., Durga Devi, T., Makinen, P., Kaikkonen, M., Lesch, H. P., Junttila, S., et al. (2015). Differential promoter methylation of macrophage genes is associated with impaired vascular growth in ischemic muscles of hyperlipidemic and type 2 diabetic mice: genome-wide promoter methylation study. Circ. Res. 117, 289–299. doi: 10.1161/CIRCRESAHA.115.306424
Baek, S. H., and Kim, K. I. (2016). Regulation of HIF-1alpha stability by lysine methylation. BMB Rep. 49, 245–246. doi: 10.5483/BMRRep.2016.49.5.053
Balaji, S., Napolitano, T., Silvano, S., Friano, M. E., Garrido-Utrilla, A., Atlila, J., et al. (2018). Epigenetic control of pancreatic regeneration in diabetes. Genes. 9:448. doi: 10.3390/genes9040448
Bangal, A., and Pinney, S. E. (2017). DNA methylation and its role in the pathogenesis of diabetes. Pediatr. Diabetes 18, 167–177. doi: 10.1111/pedi.12521
Baroukh, N., Ravier, M. A., Loder, M. K., Hill, E. V., Bounacer, A., Scharffmann, R., et al. (2007). MicroRNA-124a regulates Foxa2 expression and intracellular signaling in pancreatic beta-cell lines. J. Biol. Chem. 282, 19575–19588. doi: 10.1074/jbc.M618412000
Barres, R., and Zierath, J. R. (2016). The role of diet and exercise in the transgenerational epigenetic landscape of T2DM. Nat. Rev. Endocrinol. 12, 441–451. doi: 10.1038/nrendo.2016.87
Berger, S. L. (2007). The complex language of chromatin regulation during transcription. Nature 447, 407–412. doi: 10.1038/nature05915
Berger, S. L., Kouzarides, T., Shiekhattar, R., and Shilatifard A. (2009). An operational definition of epigenetics. Genes Dev. 23, 781–783. doi: 10.1101/gad.178760
Branman, C. I., Dees, E. C., Ingram, R. S., and Tilghman, S. M. (1990). The product of the H19 gene may function as an RNA. Mol. Cell. Biol. 10, 28–36. doi: 10.1128/MCB.10.1.28
Cao, H., Li, L., Yang, D., Zeng, L., Yewei, X., Yu, B., et al. (2019). Recent progress in histone methylation transferase (G9a) inhibitors as anticancer agents. Eur. J. Med. Chem. 179, 537–546. doi: 10.1016/j.ejmech.2019.06.072
Chakraborti, S. K., Francis, J., Ziesmann, S. M., Garvey, J. C., and Mirmira, R. G. (2003). Covalent histone modifications underlie the developmental regulation of insulin gene transcription in pancreatic beta cells. J. Biol. Chem. 278, 23617–23623. doi: 10.1074/jbc.M303423200
Chang, H., Wang, D., Xia, W., Pan, X., Huo, W., Xu, S., et al. (2016). Epigenetic disruption and glucose homeostasis changes following low-dose maternal bisphenol A exposure. Toxicol. Res. 5, 1400–1409. doi: 10.1039/C6TR00047A
Chedini, F. (2011). The DNMT3 family of mammalian de novo DNA methyltransferases. Prog. Mol. Biol. Transl. Sci. 101, 255–285. doi: 10.1016/B978-0-12387685-0.00007-X
Chen, H., Gu, X., Su, I. H., Bottino, R., Contreras, J. L., Tarkhovsky, A., et al. (2009). Polycystic protein Eh2 regulates pancreatic beta-cell Ink4a/Arf expression and regeneration in diabetes mellitus. Genes Dev. 23, 975–985. doi: 10.1101/gad.174250
Christensen, D. P., Dahllof, M., Lundh, M., Rasmussen, D. N., Nielsen, M. D., Billestrup, N., et al. (2011). Histone deacetylase (HDAC) inhibition as a novel treatment for diabetes mellitus. Mol. Med. 17, 378–390. doi: 10.2191/molmed.2011.00021
Correa-Medina, M. V., Bravo-Egana, Rosero, S., Ricordi, C., Edlund, H., Diaz, J., et al. (2009). MicroRNA miR-7 is preferentially expressed in endocrine cells of the developing and adult human pancreas. Gene Expr. Patterns. 9, 193–199. doi: 10.1016/j.gep.2008.12.003
Courty, E., Besseiche, A., Do, T. T. H., Liboz, A., Aguid, F. M., Quilichini, E., et al. (2019). Adaptive beta-cell neogenesis in the adult mouse in response to glucocorticoid-induced insulin resistance. Diabetes 68, 95–108. doi: 10.2337/db17-1314
Daneshpajooh, M., Bacos, K., Bysani, M., Bagge, A., E., Ottosson Laakso, Vikman, P., et al. (2017). HDAC7 is overexpressed in human diabetic islets and impairs insulin secretion in rat islets and clonal beta cells. Diabetologia 60, 116–125. doi: 10.1007/s00125-016-4113-2

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Dayeh, T., and Ling, C. (2015). Does epigenetic dysregulation of pancreatic islets contribute to impaired insulin secretion and type 2 diabetes? Biochem. Cell. Biol. 93, 511–521. doi: 10.1139/bcb-2015-0057

Dayeh, T., Volkov, P., Salo, S., Hall, E., Nilsson, E., Olsson, A. H., et al. (2014). Genome-wide DNA methylation analysis of human pancreatic islets from type 2 diabetic and non-diabetic donors identifies candidate genes that influence insulin secretion. PLoS Genet. 10:e1004160. doi: 10.1371/journal.pgen.1004160

De Mendoza, A., Bonnet, A., D. B., Vargas-Landin, Ji, N., Li, H., Yang, F., et al. (2018). Recurrent acquisition of cytosine methyltransferases into eukaryotic retrotransposons. Nat. Commun. 9:1341. doi: 10.1038/s41467-018-03724-9

DeChiara, T. M., Efstratiadis, A., and Robertson, E. J. (1990). A growth-deficiency cell line from a mouse with a targeted disruption of the Pten gene. Cell 63, 803–815. doi: 10.1016/0092-8674(90)90569-A

Dhawan, S., Georgia, S., Tschen, S. I., Fan, G., and Bhushan, A. (2011). Bmi-1 regulates the Ink4a/Arf tumor suppressor network through a p53-independent mechanism. Proc. Natl. Acad. Sci. U. S. A. 108, 9733–9738. doi: 10.1073/pnas.1102625108

Dhawan, S., Tschen, S. I., and Bhushan, A. (2009). Bmi-1 regulates the Ink4a/Arf tumor suppressor network through a p53-independent mechanism. Proc. Natl. Acad. Sci. U. S. A. 108, 9733–9738. doi: 10.1073/pnas.1102625108

Gilbert, E. R., and Liu, D. (2012). Epigenetics: the missing link to understanding beta-cell dysfunction in the pathogenesis of type 2 diabetes. Epigenetics 7, 841–852. doi: 10.4161/epi.21328

Gong, R., and Jiang, Y. (2020). Non-coding RNAs in pancreatic ductal adenocarcinoma. Front. Oncol. 10:309. doi: 10.3389/fonc.2020.00309

Guay, C., Jacovitti, C., Nesca, V., Motterle, A., Tugay, K., and Regazzi, R. (2012). Emerging roles of non-coding RNAs in pancreatic beta-cell function and dysfunction. Diabetes Obes. Metab. 14(Suppl.3), 12–21. doi: 10.1111/j.1463-1326.2012.01654.x

Hansen, T. B., Jensen, T. L., Clausen, B. H., Bramsen, J. B., Finsen, B., Damgaard, C. K., et al. (2013). Natural RNA circles function as efficient microRNA sponges. Nature 495, 384–388. doi: 10.1038/nature12193

Hao, Y., Crenshaw, T., Moulton, T., Newcomb, E., and Tycko, B. (1993). Tumour-suppressor activity of H19 RNA. Nature 365, 764–767. doi: 10.1038/365764a0

Hark, A. T., Schoenherr, C. J., Katz, D. J., Ingram, R. S., Levere, J. M., and Tilghman, S. M. (2000). CTCF mediates methylation-sensitive enhancer-blocking activity at the H19/IgG2 locus. Nature 405, 486–489. doi: 10.1038/35013106

Hassan, W., Norren, H., Rehm, S., Gal, S., Kamal, M. A., Kamdem, J. P., et al. (2017). Oxidative stress and antioxidant potential of one hundred medicinal plants. Curr. Top. Med. Chem. 17, 1336–1370. doi: 10.2174/15680266176661012125648

Haumairte, C., Lenoir, O., and Scharffmann, R. (2008). Histone deacetylase inhibitors modify pancreatic beta cell fate determination and amplify endocrine progenitors. Mol. Cell. Biol. 28, 6373–6383. doi: 10.1128/MCB.00413-08

Deering, T. G., Ogihara, T., Trace, A. P., Maier, B., and Mirmira, R. G. (2009). Methylation of the p21/WAF1 promoter is correlated with beta-cell dysfunction in Type 1 diabetes. Diabetologia 52, 834–843. doi: 10.1007/s00125-009-1250-4

He, Y., Kornfeld, L., and Huang, J. (2012). Targeting protein lysine methylation and demethylation in cancers. Acta Biochim. Biophys. Sin. 44, 70–79. doi: 10.1093/abbs/gmr109

He, Y. F., Li, B. Z., Li, Z., Liu, P., Wang, Y., Tang, Q., et al. (2011). Tet-mediated formation of 5-carboxylcytosine and its excision by TDG in mammalian DNA. Science 333, 1303–1307. doi: 10.1126/science.1210944

Hassan, W., Norren, H., Rehm, S., Gal, S., Kamal, M. A., Kamdem, J. P., et al. (2017). Oxidative stress and antioxidant potential of one hundred medicinal plants. Curr. Top. Med. Chem. 17, 1336–1370. doi: 10.2174/15680266176661012125648

Hassain, K., Cosgrove, K. E., Shepherd, R. M., Luharia, A., Smith, V. K., Kassem, S., et al. (2005). Hyperinsulinemic hypoglycemia in Beckwith-Wiedemann syndrome due to defects in the function of pancreatic beta-cell adenosine triphosphate-sensitive potassium channels. J. Clin. Endocrinol. Metab. 90, 4376–4382. doi: 10.1210/jc.2005-0158

Ito, S., A. C., D’Alessio, Taranova, O. V., Hong, K., Sowers, L. C., and Zhang, Y. (2010). Role of Tet proteins in 5mC to 5mC conversion, ES-cell self-renewal and inner cell mass specification. Nature 466, 1129–1133. doi: 10.1038/nature09303

Ito, S., Shen, L., Dai, Q., Wu, S. C., Collins, L. B., Swenberg, J. A., et al. (2011). Tet proteins can convert 5-methylcytosine to 5-formylcytosine and 5-carboxylcytosine. Science 333, 1300–1303. doi: 10.1126/science.1210957

Jenuwein, T. (2006). The epigenetic magic of histone lysine methylation. FEBS J. 273, 3121–3135. doi: 10.1111/j.1742-4689.2006.05343.x

Jirtle, R. L., and Skinner, M. K. (2007). Environmental epigenomics and disease susceptibility. Nat. Rev. Genet. 8, 253–262. doi: 10.1038/nrg2045

Joglekar, M. V., Parekh, V. S., and Hardikar, A. A. (2011). Islet-specific microRNAs in pancreas development, regeneration and diabetes. Indian J. Exp. Biol. 49, 401–408

Joglekar, M. V., Parekh, V. S., Mehta, S., Bhonde, R. R., and Hardikar, A. A. (2007). MicroRNA profiling of developing and regenerating pancreas reveal post-transcriptional regulation of neurogenin3. Dev. Biol. 311, 603–612. doi: 10.1016/j.ydbio.2007.09.008

Kameswaran, V., Bramswig, N. C., McKenna, L. B., Penn, M., Schug, J., Hand, N. J., et al. (2014). Epigenetic regulation of the DLK1-MEG3 microRNA cluster in human type 2 diabetic islets. Cell Metab. 19, 135–145. doi: 10.1016/j.cmet.2013.11.016

Kawada, Y., Asahara, S. I., Sugiyama, Y., Sato, A., Furubayashi, A., Kawamura, M., et al. (2017). Histone deacetylase regulates insulin signaling via two pathways in pancreatic beta cells. PLoS ONE 12:e0184435. doi: 10.1371/journal.pone.0184435

Khan, S., and Jena, G. (2016a). Sodium butyrate reduces insulin-resistance, fat accumulation and dyslipidemia in type-2 diabetic rat: a comparative study of...
with metformin. Chem. Biol. Interact. 254, 124–134. doi: 10.1016/j.cbi.2016.06.007

Khan, S., and Jena, G. (2016b). Valproic acid improves glucose homeostasis by increasing beta-cell proliferation, function, and reducing its apoptosis through HDAC inhibition in juvenile diabetic rat. J. Biochem. Mol. Toxicol. 30, 438–446. doi: 10.1002/bmt.21807

Khan, S., Kumar, S., and Jena, G. (2016c). Valproic acid reduces insulin-resistance, fat deposition and FOXO1-mediated gluconeogenesis in type-2 diabetic rat. Biochimie 125, 42–52. doi: 10.1016/j.biochi.2016.02.014

Kim, J. W., You, Y. H., Jung, S., Huh-Kim, Lee, I. K., Cho, J. H., et al. (2013). miRNA-30a-3p-mediated silencing of Beta2/NeuroD expression is a major important initial event of glucotoxicity-induced beta cell dysfunction in rodent models. Diabetologia 56, 847–855. doi: 10.1007/s00125-012-2812-x

Kloosterman, W. P., Lagendijk, A. K., Ketting, R. F., Moulton, J. D., and Plasterk, R. H. (2007). Targeted inhibition of miRNA maturation with morpholinos reveals a role for miR-375 in pancreatic islet development. PLoS Biol. 5:e203. doi: 10.1371/journal.pbio.0050203

Kolb, H., and Martin, S. (2017). Environmental/lifestyle factors in the pathogenesis and prevention of type 2 diabetes. BMC Med. 15:131. doi: 10.1186/s12196-017-0991-x

Krapp, A., Knoffler, M., Ledermann, B., Burki, K., Berney, C., Zeiker, N., et al. (1998). The BHLH protein PTF1-p48 is essential for the formation of the exocrine and the correct spatial organization of the endocrine pancreas. Development 125, 4293–4303. doi: 10.1242/dev.001570

Liao, X., Xue, H., Wang, Y. C., Nazor, K. L., Guo, S., Trivedi, N., et al. (2013). A role for FOXO1-mediated gluconeogenesis in type-2 diabetic rat. J. Cell. Biochem. 114, 42–52. doi: 10.1002/jcb.24493

Lewis, E. C., Blaabjerg, L., Storling, J., Ronn, S. G., Mascagni, P., Dinarello, C. A., et al. (2011). Antisense miR-7 impairs insulin expression in developing beta cells via downregulation of transcriptional repressors. EMBO J. 30, 835–845. doi: 10.1038/emboj.2010.361

Liu, J., Banerjee, A., Herring, C. A., Attalla, J., Ru, R., Xu, Y., et al. (2019). Neurog3-independent myelination is the earliest detectable mark distinguishing pancreatic progenitor identity. Dev. Cell. 48, 49–63 e47. doi: 10.1016/j.devcel.2018.11.048

Liu, X., Hou, L., Huang, W., Gao, Y., Lv, X., and Tang, J. (2016). The mechanism of long non-coding RNA MEG3 for neurons apoptosis caused by hypoxia: mediated by miR-181b-12-15-LOX signaling pathway. Front. Cell. Neurosci. 10.2139/fncell.2016.00201

Lundh, M., Christensen, D. P., Rasmussen, D. N., Mascagni, P., Dinarello, C. A., Billestrup, N., et al. (2010). Lysine deacetylases are produced in pancreatic beta cells and are differentially regulated by proinflammatory cytokines. Diabetologia 53, 2569–2578. doi: 10.1007/s00125-010-1982-8

Lv, Y., and Huang, S. (2019). Role of non-coding RNA in pancreatic cancer. OncoLett. 18, 3963–3973. doi: 10.3974/joal.2019.10758

Maganti, A. V., Maier, B., Tersy, S. A., Sampley, M. L., Mosley, A. L., Ozcan, S., et al. (2015). Transcriptional activity of the islet beta cell factor Pdx1 is augmented by lysine methylation catalyzed by the methyltransferase Set7/9. J. Biol. Chem. 290, 9812–9822. doi: 10.1074/jbc.M114.616219

Makkar, R., Belh, T., and Arora, S. (2020). Role of HDAC inhibitors in diabetes mellitus. Curr. Res. Transl. Med. 68, 45–50. doi: 10.1016/j.retram.2019.08.001

Mao, Z., Xia, W., Chang, H., Huo, W., Li, Y., and Xu, S. (2015). Paternal BPA exposure in early life alters Igf2 epigenetic status in sperm and induces pancreatic impairment in rat offspring. Toxicol. Lett. 238, 30–38. doi: 10.1016/j.toxlet.2015.08.009

Marmorstein, R., and Trievel, R. C. (2009). Histone modifying enzymes: structures, mechanisms, and specificities. Biochim. Biophys. Acta 1789, 58–68. doi: 10.1016/j.bbamcr.2008.07.009

Marson, A., Levine, S. S., Cole, M. F., Frampton, G. M., Brambrink, T., Johnstone, S., et al. (2008). Connecting microRNA genes to the core transcriptional regulatory circuitry of embryonic stem cells. Cell 134, 521–533. doi: 10.1016/j.cell.2008.07.020

Melkman-Zehavi, T., Oren, R., S., Kredo-Russo, Shapira, T., Mandelbaum, A. D., Rivkin, N., et al. (2011). miRNAs control insulin content in pancreatic beta-cells via downregulation of transcriptional repressors. EMBO J. 30, 835–845. doi: 10.1038/emboj.2010.361

Meng, Y. B., He, X., Huang, Y. F., Wu, Q. N., Zhou, Y. C., and Hao, D. J. (2017). Long noncoding RNA CRNDE promotes multiple myeloma cell growth by suppressing miR-451. Oncol. Res. 25, 1207–1214. doi: 10.3727/096360417X714866679715367

Monk, D., Arnaud, P., Apostolidou, S., Hills, F. A., Kelsey, G., Stanier, P., et al. (2006). Limited evolutionary conservation of imprinting in the human placenta. Proc. Natl. Acad. Sci. U. S. A. 103, 6623–6628. doi: 10.1073/pnas.0511301103

Moran, I., Akerman, I. M., van de Bunt, Xie, R., Benazra, M., Nammo, T., et al. (2012). Human beta cell transcriptome analysis uncovers IncRNAs that are tissue-specific, dynamically regulated, and abnormally expressed in type 2 diabetes. Cell Metab. 16, 435–448. doi: 10.1016/j.celmeta.2012.08.010

Mosley, A. L., Corbett, J. A., and Ozcan, S. (2004). Glucose regulation of insulin gene expression requires the recruitment of p500 by the beta-cell-specific transcription factor Pdx1. Mol. Endocrinol. 18, 2279–2290. doi: 10.1210/me.2003-0463

Mosley, A. L., and Ozcan, S. (2004). 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. 279, 54241–54247. doi: 10.1074/jbc.M410379200

Mudry, J. M., Lassiter, D. G., Nylen, C., Garcia-Calzon, S., Naslund, E., Krook, A., et al. (2006). Limited evolutionary conservation of imprinting in the human placenta. Proc. Natl. Acad. Sci. U. S. A. 103, 6623–6628. doi: 10.1073/pnas.0511301103

Mudry, J. M., Lassiter, D. G., Nylen, C., Garcia-Calzon, S., Naslund, E., Krook, A., et al. (2006). Limited evolutionary conservation of imprinting in the human placenta. Proc. Natl. Acad. Sci. U. S. A. 103, 6623–6628. doi: 10.1073/pnas.0511301103

Nilsson, E. E., I., Sadler-Riggleman, and Skinner, M. K. (2018). Environmentally induced epigenetic transgenerational inheritance of disease. Environ. Epigenet. 4:dyv016. doi: 10.1093/eeep/dyv016
Nogueira, T. C., Paula, F. M., Villate, O., Colli, M. L., Moura, R. F., Cunha, D. A., et al. (2013). GLIS3, a susceptibility gene for type 1 and type 2 diabetes, modulates pancreatic beta cell apoptosis via regulation of a splice variant of the B3H-only protein Bim. PLoS Genet. 9:e1003352. doi: 10.1371/journal.pgen.1003352

Ohslos, R., Nyström, A. S., Pfeifer-Ohslos, Tohonen, V., Hedborg, F., Schofield, P., et al. (1993). IGF2 is parentally imprinted during human embryogenesis and in the Beckwith-Wiedemann syndrome. Nat. Genet. 4, 94–97. doi: 10.1038/ng0593-94

Ozcan, S. (2014). Minireview: microRNA function in pancreatic beta cells. Mol. Endocrinol. 28, 1922–1933. doi: 10.1210/me.2014-1306

Papizan, J. B., Singer, R. A., Tschen, S. I., Dhawan, S., Friel, J. M., Hipkens, S. B., Nogueira, T. C., Paula, F. M., Villate, O., Colli, M. L., Moura, R. F., Xu et al. The Epigenetic Regulation in Pancreatic... 815–820. doi: 10.1038/nrm2502

Okamura, M., Inagaki, T., Tanaka, T., and Sakai, J. (2010). Role of histone... 43, 69–83. doi: 10.1007/s12035-016-4565-9

Okamura, M., Inagaki, T., Tanaka, T., and Sakai, J. (2010). Role of histone... 56, 598–611. doi: 10.1186/1471-2164-11-509

Ruiz, M. A., Feng, B., and Chakrabarti, S. (2015). Polycomb repressive complex 2 regulates MiR-200b in retinal endothelial cells: potential relevance in diabetic retinopathy. PLoS ONE 10:e0123987. doi: 10.1371/journal.pone.0123987

Sahin, M., Sahin, E., Gultekin, M. (2010). DNA methylation or histone modification status in metastasis and angiogenesis-related genes: a new hypothesis on usage of DNMT inhibitors and S-adenosylmethionine for genome stability. Cancer Metastasis Rev. 29, 655–676. doi: 10.1007/s10555-010-9253-0

Salzman, J., Chen, R. E., Olsen, M. N., Wang, P. L., and Brown, P. O. (2013). Cell-type specific features of circular RNA expression. PLoS Genet. 9:e1003777. doi: 10.1371/journal.pgen.1003777

Sarkies, P. (2020). Molecular mechanisms of epigenetic inheritance: possible evolutionary implications. Semin. Cell Dev. Biol. 97, 106–115. doi: 10.1016/j.semcdb.2019.06.005

Scarpia, A. (2013). The landscape of molecular alterations in pancreatic and small intestinal neuroendocrine tumours. Ann. Endocrinol. 80, 153–158. doi: 10.1016/j.ando.2019.04.010

Shen, J., Khuri, S., Tsinoremas, N., Klein, D., et al. (2015). PDX-1 (pancreatic/duodenal homeobox-1 protein 1). Pathologica 106, 315–321.

Sharma, S., and Taliyan, R. (2016a). Epigenetic modifications by inhibiting histone deacetylases reverse memory impairment in insulin resistance induced cognitive deficit in mice. Neuropharmacology 105, 285–297. doi: 10.1016/j.neuropharm.2016.01.025

Sharma, S., and Taliyan, R. (2016b). Histone deacetylase inhibitors: future therapeutics for insulin resistance and type 2 diabetes. Pharmacol. Res. 113, 320–326. doi: 10.1016/j.phrs.2016.09.009

Simion, A., Laudadio, I., Prevot, P. P., Raynaud, P., Lemaigre, F. P., and Ascoli, Z. (2019). Role of histone modification and DNA methylation in signaling pathways involved in diabetic retinopathy. J. Cell. Physiol. 234, 7839–7846. doi: 10.1002/jcp.27844

Smale, S. T., and Li, H. (2011). Epigenetic epigenetics: lessons from a transgenerational epigenetic trait. Nature 478, 368–371. doi: 10.1038/nature10339

Su, R., Yan, J., and Yang, H. (2016). Transgenerational glucose intolerance of tumor necrosis factor with epigenetic alteration in rat perirenal adipose tissue induced by intraperitoneal hyperglycemia. J. Diabetes Res. 2016:4952801. doi: 10.1155/2016/4952801

Sun, L. L., Jiang, B. G., Li, W. T., Zou, J. J., Shi, Y. Q., and Liu, Z. M. (2017). Analysis of long non-coding RNA expression of lymphatic endothelial cells in response to high glucose and... 41, 466–474. doi: 10.1159/000456599

Sun, L. L., Jiang, B. G., Li, W. T., Zou, J. J., Shi, Y. Q., and Liu, Z. M. (2017). Analysis of long non-coding RNA expression of lymphatic endothelial cells in response to high glucose and... 56, 978–986. doi: 10.2337/db09-0881
Tajima, S., Suetake, I., Takeshita, K., Nakagawa, A., and Kimura, H. (2016). Domain Structure of the Dnmt1, Dnmt3a, and Dnmt3b DNA Methyltransferases. Adv. Exp. Med. Biol. 945, 63–86. doi: 10.1007/978-3-319-43624-1_4

Tan, L., and Shi, Y. G. (2012). Tet family proteins and 5-hydroxymethylcytosine in development and disease. Development 139, 1895–1902. doi: 10.1242/dev.070771

Tang, X., Gal, J., Zhuang, X., Wang, W., Zhu, H., and Tang, G. (2007). A simple array platform for microRNA analysis and its application in mouse tissues. RNA 13, 1803–1822. doi: 10.1261/rna.498607

Tattikota, S. G., Rathjen, T., McNally, S. J., Wessels, H. H., Akerman, I., M., van de Bunt, M., et al. (2014). Argonaute2 mediates compensatory expansion of the pancreatic beta cell. Cell Metab. 19, 122–134. doi: 10.1016/j.cmet.2013.11.015

Taylor, B. L., Liu, F. F., and Sander, M. (2013). Nkx6.1 is essential for maintaining the functional state of pancreatic beta cells. Cell Rep. 4, 1262–1275. doi: 10.1016/j.celrep.2013.08.010

Thomas, A. A., Feng, B., and Chakrabarti, S. (2017). ANRIL: a regulator of VEGF in diabetic retinopathy. Invest. Ophthalmol. Vis. Sci. 58, 470–480. doi: 10.1167/iovs.16-20569

Toerop, G., Kark, J. D., Aran, D., Nasser, H., Ahmad, W. A., Sinnreich, R., et al. (2015). Premature aging of leukocyte DNA methylation is associated with type 2 diabetes prevalence. Clin. Epigenetics 7:35. doi: 10.1186/s13148-015-0069-1

Travers, M. E., Mackay, D. J., Dekker Nitert, M., Morris, A. P., Lindgren, C. M., Berry, A., et al. (2013). Insights into the molecular mechanism for type 2 diabetes susceptibility at the KCNQ1 locus from temporal changes in imprinting status in human islets. Diabetes 62, 987–992. doi: 10.2337/db12-0819

Ueda, T., Tsurutani, Y., Katsuragawa, S., and Saito, J. (2019). Type 2 diabetes mellitus complicated with idiopathic hypoparathyroidism where poor glycaemic control was associated with low adherence to exercise and medication due to hypocalcaemia. BMJ Case Rep. 2019, 2019. doi: 10.1136/bcr-2019-232553

Unoki, H., Takahashi, A., Kawaguchi, T., Hara, K., Horkoski, M., Andersen, G., et al. (2008). SNPs in KCNQ1 are associated with susceptibility to type 2 diabetes in East Asian and European populations. Nat. Genet. 40, 1098–1102. doi: 10.1038/ng.208

Waddington, C. H. (2012). The epigenotype. 1942. Int. J. Epidemiol. 41, 10–13. doi: 10.1093/ije/dyr184

Walder, M., Nudelman, V., Shainberg, A., Abraham, N. G., Kornwoski, R., Aravot, D., et al. (2018). PARP-1 inhibition protects the diabetic heart through activation of SIRT1-PGC-1alpha axis. Exp. Cell Res. 373, 112–118. doi: 10.1016/j.yexcr.2018.10.003

Wang, H. W., Breslin, M. B., and Lan, M. S. (2007). Pdx-1 regulates histone H4 acetylation and insulin gene expression in terminally differentiated alpha-TC-1 cells. Pancreas 34, 248–253. doi: 10.1097/01.mpa.0000250136.72273.d7

Wang, L., Zheng, Z., Peng, X., Zang, X., Ding, W., Wu, F., et al. (2019). circRNA/miRNA-miRNA-mRNA network in oxidized, low-density, lipoprotein-induced foam cells. DNA Cell Biol. 38, 1499–1511. doi: 10.1089/dna.2019.4865

Wang, Y., Liu, J., Liu, C., Naji, A., and Stoffers, D. A. (2013). MicroRNA-7 regulates the mTOR pathway and proliferation in adult pancreatic beta-cells. Diabetes 62, 887–895. doi: 10.2337/db12-0451

Werfel, S., Nothjunge, S., Schwarzmayr, T., Strom, T. M., Meitinger, T., and Engelhardt, S. (2016). Characterization of circular RNAs in human, mouse and rat hearts. J. Mol. Cell Cardiol. 98, 103–107. doi: 10.1016/j.yjmcc.2016.07.007

Wicklow, B. A., and Sellers, E. A. (2015). Maternal health issues and cardio-metabolic outcomes in the offspring: a focus on Indigenous populations. Best Pract. Res. Clin. Obstet. Gynaecol. 29, 43–53. doi: 10.1016/j.bpobgyn.2014.04.017

Xiao, Y. (2020). Construction of a circRNA-miRNA-mRNA network to explore the pathogenesis and treatment of pancreatic ductal adenocarcinoma. J. Cell. Biochem. 121, 394–406. doi: 10.1002/jcb.29194

Xin, J., Li, J., Feng, Y., Wang, L., Zhang, Y., and Yang, R. (2017). Downregulation of long noncoding RNA HOTAIR1 promotes monocyte/dendritic cell differentiation through competitively binding to endogenous miR-3960. Onco. Targets Ther. 10, 1307–1315. doi: 10.2147/OTT.S124201

Xu, J., Hu, G., Lu, M., Xiong, Y., Li, Q., Chang, C. C., et al. (2013). MiR-9 reduces human acyl-coenzyme A cholesterol acyltransferase-1 to decrease THP-1 macrophage-derived foam cell formation. Acta Biochim. Biophys. Sin. 45, 953–962. doi: 10.1093/abbs/gmt096

Xu, N., Papagiannakopoulos, T., Pan, G., Thomson, J. A., and Kosik, K. S. (2009). MicroRNA-145 regulates OCT4, SOX2, and KLF4 and represses pluripotency in human embryonic stem cells. Cell 137, 647–658. doi: 10.1016/j.cell.2009.02.038

Yanaihara, N., Caplen, N., Bowman, E., Seike, M., Kumamoto, K., Yi, M., et al. (2006). Unique microRNA molecular profiles in lung cancer diagnosis and prognosis. Cancer Cell 9, 189–198. doi: 10.1016/j.ccr.2006.01.025

Yang, B. T., Dayeh, T. A., Kirkpatrick, C. L., Taneera, J., Kumar, R., Groop, L., et al. (2011). Insulin promoter DNA methylation correlates negatively with insulin gene expression and positively with HbA1c levels in human pancreatic islets. Diabetesologia 54, 380–387. doi: 10.1007/s00125-010-1967-6

Yao, L., Li, Y., Du, F., Han, X., Li, X., Niu, Y., et al. (2014). Histone H4 Lys 20 methyltransferase SET8 promotes androgen receptor-mediated transcription activation in prostate cancer. Biochem. Biophys. Res. Commun. 450, 692–696. doi: 10.1016/j.bbrc.2014.06.033

Yin, D. D., Zhang, E. B., You, L. H., Wang, N., Wang, L. T., Jin, F. Y., et al. (2015). Downregulation of IncRNA TUG1 affects apoptosis and insulin secretion in mouse pancreatic beta cells. Cell Physiol. Biochem. 35, 1892–1904. doi: 10.1159/000373999

Zhao, X., Mohan, R., Ozcan, S., and Tang, X. (2012). MicroRNA-30d induces insulin transcription factor Mafa and insulin production by targeting mitogen-activated protein 4 kinase 4 (MAP4K4) in pancreatic beta-cells. J. Biol. Chem. 287, 31155–31164. doi: 10.1074/jbc.M112.362632

Zhao, Z., Li, X., Tian, D., Hao, P., Rao, L., and Li, M. (2017). Hsa_circ_0054633 in peripheral blood can be used as a diagnostic biomarker of pre-diabetes and type 2 diabetes mellitus. Acta Diabetol. 54, 237–245. doi: 10.1007/s00592-016-0943-0

Zhou, Z., Sun, B., Li, X., and Zhu, C. (2018). DNA methylation landscapes in the pathogenesis of type 2 diabetes mellitus. Nutr. Metab. 15:47. doi: 10.1186/s12986-018-0283-x

Zimmet, P., Alberti, K. G., Magliano, D. J., and Bennett, P. H. (2016). Diabetes mellitus statistics on prevalence and mortality: facts and fallacies. Nat. Rev. Endocrinol. 12, 616–622. doi: 10.1038/nrendo.20 16.105

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