Austin Endocrinology and Diabetes Case Reports

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Austin Publishing Group

Review Article

Genetic and Epigenetic Aspects of Type 2 Diabetes Mellitus: A Review

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Received: November 16, 2016; **Accepted:** December 08, 2016; **Published:** December 09, 2016

Abstract

Diabetes mellitus has become one of the most common chronic diseases across the globe, especially in developing countries. Type 2 Diabetes Mellitus (T2DM) depends on multiple genetic loci as well as environmental factors; it is known as a complex polygenic disorder. Patterns of inheritance suggest that T2DM is both polygenic and heterogeneous; multiple genes are involved and different combinations of genes play a role in different subsets of individuals. Overall, estimates have shown that 30-70% of T2DM risk can be ascribed to genetic factors. With the genetic variations, the environmental changes can lead to a disease phenotype by affecting the gene expression through epigenetic modifications. These changes associated with T2DM are therefore still poorly understood. Further insight into these associations will improve the variety and quality of existing predictive T2DM biomarkers, thereby increasing the possibilities to postpone or prevent T2DM in the individuals at high risk for the disease. Nevertheless, epigenetics may play an important role in the growing incidence of T2DM, and over the next few years, it will be a great challenge to dissect the role of DNA methylation, histone modifications, and non-coding RNAs in the pathogenesis of the disease and its complications.

Keywords: Genetics; Epigenetics; Type 2 diabetes mellitus

Introduction

Diabetes mellitus has become one of the most common chronic diseases in human populations across the globe, especially in the modern societies, with a prevalence of 6.5%, representing 285 million adults in 2010 [1]. In 2015, according to International Diabetes Federation (IDF) Atlas, about 415 million adults worldwide had diabetes. It is estimated that by 2030, the number will be rising to 366 million and shows that diabetes mellitus will become an epidemic, reaching a prevalence of 7.7% [1].

Diabetes mellitus is a syndrome of disordered metabolism with abnormally high blood glucose levels (hyperglycemia) [2]. Two most common forms of diabetes are Type 1 Diabetes (T1D) (absent production of insulin) and Type 2 Diabetes Mellitus (T2DM) (diminished insulin secretion and followed by decline of the beta cell mass). However, other rare forms of diabetes are inherited directly that includes Maturity Onset Diabetes in the Young (MODY) and diabetes due to mutations in mitochondrial DNA. Most diabetes (~90%) is T2DM caused by a combination of impaired insulin secretion from pancreatic β-cells and insulin resistance of the peripheral target tissues, especially muscle and liver. This form of diabetes is most often associated with age, obesity (i.e. increased abdominal fat), family history of diabetes, hypertension, history of gestational diabetes, lack of physical activity, and ethnic background [3].

Type 2 diabetes mellitus depends on multiple genetic loci as well as environmental factors and is known as a complex polygenic disorder (Figure 1). The environmental disorders can lead to a disease phenotype by affecting gene expression through epigenetic modifications [4]. Epigenetic modifications of the genome provide a mechanism that allows the stable proliferation of gene expression from one generation of cells to the next [5]. From the genetic point of view, the genetic risk influenced by the conjoint effects of variation at an undetermined number of genomic sites, some with an affecting and some with a protective effect. Genome-wide studies identified many genetic loci associated with T2DM [6]. However, it is not clear how many genes are involved or how much control each gene exerts over the development of the disease, but several researchers have identified several promising candidates [3,7-14]. In this review, we first consider the evidence in favor of a genetic basis for T2DM, focusing specifically on the specific DNA sequence variants that have been implicated in risk predisposition. Second, we critically review the evidence supporting a role for T2DM epigenetic mechanisms.

Study Criteria

A review of the literature was conducted to identify all English language studies published between 2000-2015 on genetics and epigenetics in T2DM in the databases Medline, Embase, and PubMed. We considered all types of original published studies, reviews, and meta-analysis studies and excluding case reports, clinical trials, and conference abstracts. Duplicate publications were eliminated and eligible records were screened independently, first by title and abstract followed by full text. Overall, 1075 articles were found that 87 eligible articles were selected. Search terms included (diabetes mellitus, type 2 OR diabet*) AND genetics AND/OR epigenetics (DNA methylation, histone modification, microRNA).

Genetics of Type 2 Diabetes Mellitus

With progression in genotyping, sequencing techniques, and

Citation: Zarkesh M, Ehsandar S and Hedayati M. Genetic and Epigenetic Aspects of Type 2 Diabetes Mellitus: A Review. Austin Endocrinol Diabetes Case Rep. 2016; 1(1): 1004.

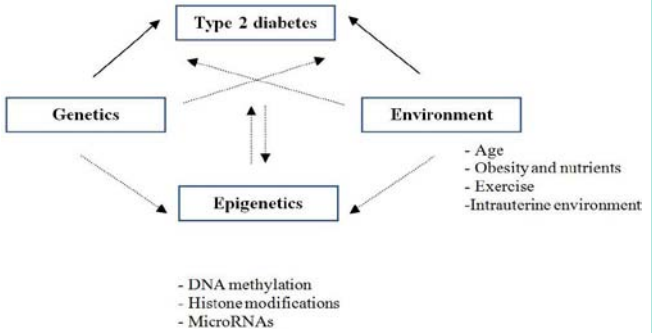

Figure 1: Model proposing a role for epigenetic mechanisms in the pathogenesis of T2DM.

in the statistical handling of data, different approaches have been used to recognize the genetic influences in T2DM. Current methods classify these influences into two main categories include 1) analysis of genomic regions shared by relatives more often than expected (so called linkage analysis using polymorphic markers such as microsatellites or tandem repeats) and 2) candidate gene studies, particularly by attempts to correlate biological variation (phenotype) with variation in DNA sequences (genotype) as a Single Nucleotide Polymorphism (SNP). The first approach (genome-wide studies) includes both Genome-Wide Linkage Studies (GWLS) and Genome-Wide Association Studies (GWAS) [15]. With these methods, 20 common genetic variants have been recognized in association with T2DM in 2009 [16].

Genome-Wide Linkage Analysis Studies (GWLS)

Genome linkage analysis is a genetic method that tests the co-segregation of a chromosomal region by genotyping several hundred microsatellite markers with a disease locus expanded all over the genome on families with two or more affected siblings. Moreover, this method was used to identify genes associated with disorders, and has been very successful for mapping genes with strong penetrance and a known inheritance mode that underlie monogenic 'Mendelian' diseases [17], but it has been less useful for identifying genes that cause complex diseases such as T2DM [18]. Although great efforts have been put into linkage studies of T2DM, only 2 genes have been reported by linkage: Transcription Factor 7-Like 2 (TCF7L2) and Calpain 10 (CAPN10). The association between T2DM and a number of TCF7L2 SNPs has been confirmed in numerous studies in different ethnic groups [19,20]. In 2006, deCODE genetics identified common variation in the TCF7L2 gene to have a substantial effect on T2DM susceptibility. People who carry one copy of a variant TCF7L2 have an approximately 1.5 times increased risk of T2DM, while subjects who carry two copies of a variant have an about 2.4 times increased risk [21].

In 2000, the results of a genome-wide screen for T2DM genes showed that a gene located in the NIDDM1 region had association with the disease which encodes a ubiquitously expressed member of the calpain-like cysteine protease family, CAPN10, with largely unknown functions in glucose metabolism [22]. Despite several negative replication studies, several meta-analyses have shown a consistent association of CAPN10 with T2DM. Nevertheless, CAPN10 has not been confirmed as a candidate gene for T2DM by the large GWAS [19,23].

Genome-Wide Association Analysis Studies (GWAS)

Genome-wide association is a special type of association study that searches the whole genome (or at least most of it) for causal genetic variants and it can be attempted even without persuading evidence regarding the function or location of the candidate causal genes [24]. This approach became possible as a result of the completion of the human genome sequence in 2001 [25,26], the creation of SNP Linkage Disequilibrium (LD) maps by the International HapMap Project [27], and great advancements in microarray-based genotyping technology and statistical tools due to the vast amount of genetic variants [28]. The Diabetes Genetics Replication and Meta-Analysis (DIAGRAM) consortium combined the data from the three GWAS. Through meta-analysis followed by large-scale replication, six additional T2DM susceptibility genes were detected [29]. The results of the first GWAS on T2DM were published in 2007 by Sladek et al [30]. This GWAS was conducted in 661 cases and 614 controls from France and led to identification of two new diabetes loci: 1) Hematopoietically Expressed Homeobox (HHEX) and 2) solute carrier family 30 (zinc transporter that makes zinc available for co-crystallization with and subsequent secretion of insulin) member 8 (SLC30A8). Another gene was Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) which is the first gene reproducibly associated with T2DM [31]. To date, more than 70 susceptibility loci have been detected by GWAS via establishing large research consortia using intermediary diabetes phenotypes (e.g. fasting glucose) and applying study samples of different ethnicities and delivered a whole set of new susceptibility loci for T2DM over the last five years [32-34].

The trans-ethnic meta-analysis comprised from different ethnicity (European, East Asian, South Asian, Mexican, and Mexican-American ancestry) showed excess in the directional consistency of T2DM risk alleles across ancestry groups. Seven new T2DM susceptibility loci were identified by following up the strongest signals of association from the trans-ethnic meta-analysis of European ancestry (rs6813195, rs17106184, rs3132524, rs9502570, rs1727313, rs6808574, and rs702634) [35]. Some validated T2DM susceptibility loci are summarized along with their discovery method, cellular function and putative intermediary mechanism in diabetes (Table 1).

The candidate gene studies

The candidate gene approach to conducting genetic association studies focuses on the known function of the genes. Several candidate genes identified in monogenic forms of diabetes proved to be also involved in the genetics of common forms of T2DM. The rare forms of diabetes include pregnancy, certain medications, or diseases such as MODY characterized by monogenic, autosomal dominant transmission and early age of onset. Although several studies have reported an association between functional and/or positional candidates, only some of them have been consistently associated with T2DM. The most robust candidate variants reported were the E23K variant in the KCNJ11 gene [36,37], the P12A variant in the PPARγ gene [38], and common variants in the HNF1B and the Wolfram Syndrome 1 (WFS1) genes [39,40]. Notably, rare mutations in all four genes cause monogenic forms of diabetes [41,42] and KCNJ11 and PPARγ are targets of anti-diabetic therapies. KCNJ11 encodes a component of the β-cell potassium channel that is a target for the

Table 1: Genetic regions (variants) associated with type 2 diabetes at genome-wide levels of statistical significance ($p< 10^{-8}$) listed by chromosome. Data was adapted from [3,7-9,35]. For many of the loci several SNPs associate with type 2 diabetes, but only one (in some cases two) SNPs are listed.

Chr	Gene region (lead SNP)	Cellular function and putative intermediary mechanism in diabetes
1	**PROX1** (rs340874)	Encodes the prospero-related homeobox 1. Implicated in cell proliferation and development. Associated with elevated FG.
	NOTCH2 (rs10923931)	Transmembrane receptor implicated in pancreatic organogenesis; regulates cell differentiation.
	TMEM154 (rs6813195)	The function of this family of transmembrane proteins has not, as yet, been determined. However, it is thought to decrease Beta Cell Function. Diabetogenic impact of the C-allele of TMEM154-rs6813195 is mediated through reduced beta cell function.
	FAF1 (rs17106184)	Interaction of TNFSF6 with the FAS antigen (TNFRSF6) mediates programmed cell death.
2	**GRB14** (rs3923113)	Adaptor protein binding to insulin receptor and insulin-like growth factor receptors to inhibit kinase signaling. Associated with reduced insulin sensitivity.
	BCL11A (rs243021)	Involved in both B- and T-lymphocyte development and β-cell function. Affects insulin response to glucose.
	RBMS1 (rs7593730)	Encodes RNA-binding motif, single-stranded interacting protein 1. Implicated in DNA replication, gene transcription, cell cycle progression and apoptosis. Unknown diabetogenic mechanism.
	GCKR (rs780094)	Glucokinase regulatory protein. Involved in signal transduction, glucose transport and sensing. Associated with FG, fasting insulin and HOMA-IR.
	IRS1 (rs2943641)	Encodes insulin receptor substrate-1. Associates with reduced adiposity and impaired metabolic profile (e.g. visceral to subcutaneous fat ratio, IR, dyslipidemia, CVD, adiponectin levels).
	THADA (rs7578597)	Thyroid adenoma-associated gene. Associates with PPAR; Involved in apoptosis. Associated with β-cell dysfunction, lower β-cell response to GLP-1 and reduced β-cell mass.
3	**ST6GAL1** (rs16861329)	Enzyme located in Golgi apparatus, involved in post-translational modification of cell-surface components by glycosylation.
	ADCY5 (rs11708067)	Encodes adenylate cyclase 5. Involved in signal transduction. Associated with elevated FG.
	ADAMTS9 (rs4607103)	Proteolytic enzyme. Affects insulin response to glucose. Primary effect on insulin action not driven by obesity.
	IGF2BP2 (rs4402960)	Growth factor (IGF2-mRNA) binding protein. Involved inpancreatic development and stimulation of insulin action.
	PPARG* (rs1801282)	TRF involved in adipocyte development. TRF receptor for TZDs and prostaglandins. Effect on IR.
	LPP (rs6808574)	This protein also shuttles through the nucleus and may function as a transcriptional co-activator.
4	**WFS1*** (rs1801214)	Endoplasmic reticulum transmembrane protein involved in stress and β-cell apoptosis. Insulin response.
5	**ZBED3** (rs4457053)	Encodes an axin-interacting protein activating wnt/beta-catenin signaling. Unknown diabetogenic mechanism.
	ARL15 (rs702634)	The function of ARL15 is not known yet.
6	**CDKAL1** (rs7754840)	Cyklin kinase (CDK5) inhibitor. Involved in cell cycle regulation in the β-cell. Insulin response.
	POUSF1-TCF19 (rs3132524)	The encoded protein is thought to function during the G1/S transition in the cell cycle. Alternate splicing results in multiple transcript variants.
	SSR1-RREB1 (rs9502570)	Relevant to nephropathy susceptibility, *RREB1* polymorphisms reportedly interact with *APOL1* and associate with kidney function. Implicated with fat distribution and fasting glucose, effects potentially related to the observed T2DM associations.
7	**KLF14** (rs972283)	Basic transcription element-binding protein. "Master switch" controlling other genes associated with BMI, insulin, glucose and cholesterol.
	DGKB (rs972283)	Encodes diacylglycerol kinase beta. Implicated in signal transduction. Associated with elevated FG.
	GCK* (rs4607517)	Encodes the enzyme glucokinase. Involved in signal transduction, glucose transport and sensing. Associated with elevated FG and HbA1c.
	JAZF1 (rs864745)	Zinc-finger protein. Function as a transcriptional repressor. Associated with prostate cancer. Insulin response.
8	**TP53INP1** (rs896854)	Encodes the p53-dependent damage-inducible nuclear protein. May regulate p53-dependent apoptosis. Unknown diabetogenic mechanism.
	SLC30A8 (rs13266634)	β-cell zinc transporter ZnT8. Involved in insulin storage and secretion. Associated with fasting proinsulin levels.
9	**TLE4** (rs13292136)	Encodes the transducin-like enhancer of split 4. Unknown diabetogenic mechanism.
	PTPRD (rs17584499)	Encodes the tyrosine phosphatase receptor type D protein. Associated with increased HOMA-IR and may affect insulin signaling on its target cells.
	CDKN2A/B (rs10811661)	Cyclin-dependent kinase inhibitor and p15/16 tumor suppressor. Involved in islet development. Also associated with CVD and several cancers. Insulin response.
10	**VPS26A** (rs1802295)	Multimeric protein involved in transport of proteins from endosomes to the trans-Golgi network. Expressed in pancreatic and adipose tissues.
	CDC123 (rs12779790)	Cell cycle kinase, required for S-phase entry. Affects different aspects of insulin response to glucose.
	HHEX (rs1111875)	TRF involved i pancreatic development. Might influence both insulin release and insulin sensitivity.
	TCF7L2 (rs7903146)	TRF involved in wnt-signaling. Influencing insulin and glucagon secretion. Most important polygene identified for T2DM.

11	**ARAP1** (rs1552224)	Associated with lower proinsulin levels, as well as lower β-cell function (HOMA-B and insulinogenic index).
	HMGA2 (rs1531343)	Oncogene implicated in body size (height). Primary effect on insulin action not driven by obesity.
	MTNR1B (rs10830963)	Receptor for melatonin. Involved in glucose homeostasis. Associated with increased FG and reduced β-cell function.
	KCNQ1 (rs2237892, rs231362)	Encodes the pore-forming alfa subunit of $I_{Ka}K^+$ channel. Insulin response.
	KCNJ11* (rs5219)	Inwardly rectifying potassium channel. Risk allele impairs insulin secretion.
12	**HNF1A*** (rs7957197)	TRF essential for pancreatic β-cell development and function.
	TSPAN8 (rs7961581)	Cell surface glycoprotein implicated in GI cancers. Insulin response.
	SPRY2 (rs1359730)	Inhibitor of tyrosine kinase signaling. Associated with body fat percentage. Homologs inhibit insulin receptor-transduced MAPK signaling. Regulates development of pancreas.
	MPHOSPH9 (rs1727313)	Three MPPS were strikingly localized to interphase structures: MPP7 to centers of DNA replication, MPP9 to the Golgi complex, and MPP10 to nucleoli. No functional information for this protein.
13	**AP3S2** (rs2028299)	Clathrin-associated adaptor complex expressed in adipocytes and pancreatic islets. Involved in vesicle transport and sorting. Unknown diabetogenic mechanism
15	**HMG20A** (rs7178572)	High mobility group non-histone chromosomal protein influencing histone methylation. Involved in neuronal development. Unknown diabetogenic mechanism.
	C2CD4A (rs11071657)	Nuclear calcium-dependent domain-containing protein. Impairs glucose-stimulated insulin response. Associated with levels of fasting glucose and proinsulin.
	ZFAND6 (rs11634397)	Encodes a zinc finger AN1 Domain-containing protein. Unknown diabetogenic mechanism.
	PRC1 (rs8042680)	Protein regulating cytokinesis. Unknown diabetogenic mechanism.
16	**FTO** (rs8050136,rs9939609)	2-oxoglutarate-dependent demethylase. Alters BMI i general population.
17	**SRR** (rs391300)	Encodes a serine racemase protein. May play a role in regulation of insulin and glucagon secretion.
	HNF1B* (rs757210)	TRF involved in development of the kidney, pancreas, liver, and Mullerian duct. Implicated in MODY and renal cyst. Associated with prostate cancer.
20	**HNF4A*** (rs4812829)	Nuclear TRF expressed in liver. Regulates transcription of several genes, e.g. HNF1A. Elevated hepatic glucose production. Defective pancreatic β-cell function and impaired insulin secretion.
X	**DUSP9** (rs5945326)	MAP kinase phosphatase. Decreased insulin release for male risk allele carriers. Up-regulated during adipocyte differentiation. Involved in insulin signaling and stress induced IR.

Abbreviations: Chr: Chromosome; CVD: Cardiovascular Disease; FG: Fasting Glucose; GI: Gastrointestinal; IR: Insulin Resistance; IS: Insulin Secretion; T2DM: Type 2 Diabetes Mellitus; TRF: Transcription Factor; TZD: Thiazolidinediones.

*Genes also implicated in maturity onset diabetes of the young, other monogenic forms of diabetes or rare genetic syndromes.

sulphonylurea class of drugs and PPARγ encodes a transcription factor involved in adipocyte differentiation that is a target for the thiazolidinedione class of drugs [3,43].

Some different studies were considered as known risk factors for T2DM with different combinations. For instance, a correlation has been observed between Catechol-O-Methyl Transferase (COMT) polymorphism (900 I/D C) and the family history of T2DM in Pakistani Punjabi population [44]. Zhang Y.H. et al showed a significant correlation between polymorphism of platelet alloantigen genes HPA-1, -2, -3, and -5 and T2DM complication of carotid atherosclerosis in 99 T2DM patients of Chinese population [45]. A meta-analysis suggested that D allele of G1057D polymorphism in Insulin Receptor Substrate (IRS)-2 gene had a significant effect on reducing risk of T2DM [46]. Moreover, Ninomiya H. et indicated an association between Monocyte Chemoattractant Protein-1 (MCP-1) A-2518G polymorphism and new onset of diabetic retinopathy in 758 T2DM patients in which the new onset of retinopathy increased with the increase of the number of G alleles [47]. Furthermore, in another study, Amle D. et al observed that 18bp insertion/deletion (I/D) polymorphism, at -2549 position of VEGF gene was associated with increased susceptibility to diabetic nephropathy in 40 T2DM patients [48]. Besides, a study by Zhong X. et al showed a significant association between VDR rs2228570 polymorphism with the development of retinopathy in 204 Han Chinese population with T2DM [49]. In another study, Fathi M. et al investigated the combination between Angiotensin Converting Enzyme (ACE) I/D (rs4646994) and Vascular Endothelial Growth Factor (VEGF) polymorphism (+405G/C; rs2010963) with the development of albuminuria in 490 Iranian patients with T2DM [50]. They indicated that ACE-D and VEGF-G alleles could be an independent risk factor for microalbominuria in T2DM.

According to our knowledge, more than 40 genes were recognized increasing susceptibility to diabetes. Except a few functional candidate genes, most of the newly described genes were not suspected to be associated with diabetes. Most identified loci by GWAS appear to affect insulin secretion, but the accurate molecular mechanisms are still incompletely established. The number of loci involved in the development of T2DM has risen from just three in 2006 to almost 20 today. Across all the GWAS completed, TCF7L2 clearly shows the largest effect size with an odd ratio (OR) of 1.37. Up to now, all other confirmed loci display more modest effect sizes (OR 1.1-1.20) [51]. KCNQ1 has been shown to have second largest effect size (OR 1.29) next to TCF7L2 [52,53]. Genetic risk loci identified by standard genetic and genome-wide association approaches account for less than 10% of the observed heritability. These results have led to speculation that epigenetic effects may also play a remarkable role in the development of T2DM [54].

Epigenetic Modifications in Type 2 Diabetes

Epigenetics are described as heritable changes in the gene

expression and function that occurs without a change in the nucleotide sequence. Epigenetic modifications can be passed from one cell generation to the next (mitotic inheritance) or among generations of individuals (meiotic inheritance) [55]. Although data analysis has suggested that the epigenetic variations play a vital role in the initiation and progression of T2DM, there are only a limited number of studies that have examined epigenetic changes in target tissues from patients with T2DM [56,57]. Epigenetic impacts may also affected by the environmental changes making them potentially important pathogenic mechanisms in the complex multifactorial diseases. There are at least three distinct mechanisms through which epigenetic information can be inherited: 1) chromosomal DNA methylations, 2) histone modifications (acetylation, methylation, phosphorylation, ubiquitination, SUMOylation, and ADP ribosylation), and 3) non-coding RNAs (e.g. microRNAs) regulation. They can help to explain how cells with identical DNA can differentiate into different cell types with different phenotypes.

DNA methylation

Patterns of DNA methylation (DNA Methyltransferases (DNMT) catalyzed addition of methyl group to cytosine ring) are often linked to decrease gene expression and in an extreme form of that suppresses it completely. Methylation in a gene promotes region generally correlates with gene silencing [58,59]. DNA methylation is limited to cytosine that follows a guanosine in the DNA sequence (the CpG dinucleotide distributed in the genome asymmetric) in humans and other mammals occurring in small clusters called "CpG islands". The CpG islands are often in promoter regions of genes and are usually un-methylated regardless of the transcriptional state [60]. Zou L. et al indicated that the PRKCZ gene promoter was hyper-methylated and serum level of PRKCZ protein expression was decreased in 152 T2DM subjects. PRKCZ is an important regulatory molecule that affects the signaling pathway of insulin through epigenetic changes. They suggested that the hypermethylation of PRKCZ gene may be involved in the pathogenesis of T2DM [61]. Another study suggested that hypermethylation of the Glucose Transporter Protein 2 (GLUT2) promoter suppresses its gene expression and thus leads to the reduced consumption of glucose [62]. Kuroda A. et al indicated that the expression of the insulin gene is closely related to the level of methylation at its promoter [63].

PPARγC1A encodes PGC1α, which is a transcriptional co-activator that regulates expression of numerous genes with a key role in mitochondrial function. A series of research have revealed that hypermethylation of PPARγ and methylation of PPARγC1A promoter resulting in decreased gene expression in human pancreatic islets whereas DNA methylation of the PPARγ promoter is elevated in patients with T2DM and glucose stimulated insulin secretion [64,65]. Park J.H. et al reported that intrauterine growth retardation has also been associated with increased DNA methylation of the Pancreatic and Duodenal Homeobox 1 (Pdx1) promoter in islets from experimental animals [66]. In a study by Toperoff G. et al, DNA methylation of a regulatory site, located in a region within an intron of the FTO gene, in Peripheral Blood Leukocytes (PBLs) is associated with impaired glucose metabolism and T2DM independent of sex, and BMI [67]. Also, Seman N.A. et al showed that increased DNA methylation of the SLC30A8 gene promoter is associated with T2DM [68]. Besides, Jun Z. et al indicated that increased adiponectin promoter methylation results in decreased mRNA expression, which induces glucose and lipid metabolic disorder [69]. In addition, they found a negative correlation in DNA promoter methylation and mRNA expression of adiponectin gene. The above-mentioned studies demonstrate how epigenetic mechanisms especially DNA methylation might regulate gene expression, such as insulin secretion in human beings.

Histone modifications

Posttranslational variations on the N-terminal histone tails in the chromatin play an essential role in the regulation of gene expression and function. These modifications could affect chromatin structure came from solving the high-resolution X-ray structure of the nucleosome [70]. The most common of these changes include acetylation and methylation of lysine residues in the amino termini of H3 and H4. Increased acetylation induces transcription activation, whereas decreased acetylation usually induces transcription repression. Methylation of histones, by contrast, is associated with both transcription repression and activation [71]. Some studies have been prepared to explore the relationship between chromatin modifications and gene expression. They showed that modification of the chromatin structure could allow or prevent access of proteins to binding with a transcription factor, which has been shown for TCF7L2 intronic variant which is located in islet-selective open chromatin [72]. A genome-wide map of histone modifications has been reported for the human pancreatic islet in which three of them associated with gene activation (H3K4me1, near the start site and the enhancer of the PDX1 gene, H3K4me2, and H3K4me3, at the promoter of GAPDH (a housekeeping gene) and one associated with gene repression (H3K27me3) [73]. The methylation patterns at the highly active promoters of these major islet hormones suggest that epigenetic regulation of these genes in human islets is different from the regulation in mouse pancreatic islets and cell lines, which is dependent on hyper-methylation of histone H3 at the insulin promoter [74]. A study by Vecellio M. et al have been shown that acetylation of histone H3 Lysine 9 and Lysine 14 (H3K9Ac; H3K14Ac) was decreased in histone code profiling of Cardiac Mesenchymal Cells (CMSC) obtained from normoglycaemic (ND-CMSC) while the tri-methylation of histone H3 Lysine 9 and Lysine 27 (H3K9Me3; H3K27Me3) significantly increased [75]. Analyzing the data of methylation at lysine 4 and lysine 9 of histone H3 in primary human adipocytes showed that the level of lysine 9 di-methylation was stable, while adipocytes from T2DM and non-diabetic overweight subjects exhibited about 40% lower levels of lysine 4 di-methylation compared with cells from normal-weight subjects. In contrast, tri-methylation at lysine 4 was 40% higher in adipocytes from overweight diabetic subjects compared with normal-weight and overweight non-diabetic subjects [76].

Both DNA methylation and histone modification are involved in establishing patterns of gene repression during development. Certain forms of histone methylation cause local formation of heterochromatin, which is readily reversible, whereas DNA methylation leads to stable long-term repression. Recent evidence indicates that this two-sided relationship between histone and DNA methylation might be accomplished by direct interactions between histone and DNA methyltransferases [77]. Thus, chromatin modifications induced by adverse stimuli are self-reinforcing and can propagate.

MicroRNAs

Beside biochemical modifications of DNA and histone molecules, gene expression may also be regulated by non-coding RNAs or MicroRNAs (miRNAs), which are 20–30 nucleotides with imperfect sequence complementary to the 3' untranslated region of the target mRNA leading to either posttranscriptional silencing and translational repression or RNA degradation [78]. MiRNAs provide a rapid but reversible means of gene regulation, which also allows the cell/tissue/organism to respond to environmental stimuli without changing the DNA sequence itself. MiRNAs have been identified as negative regulators in various pathways targeting signaling molecules, transcription factors, and numerous other enzymes and proteins. There is also the potential role for miRNAs to target chromatin-modifying enzymes, resulting in epigenetic modifications affecting gene expression [79].

It is estimated that up to 60% of human genes are subject to regulation by miRNAs and that miRNAs are involved in cell proliferation, differentiation, and apoptosis. Recent studies have shown that miRNAs have a vital role in many different gene regulatory pathways. A subset of miRNAs has been shown to be involved in the metabolic regulation of glucose homeostasis and in the epigenetics of T2DM. They are important in X-chromosome inactivation and genomic imprinting [80]. Kameswarn V. et al revealed that a cluster of microRNAs in an imprinted locus on human chromosome 14q32 of β cells expressed specifically and down-regulated dramatically in islets from T2DM organ donors. The down-regulation of this locus strongly correlates with hypermethylation of its promoter. Therefore, disease-relevant targets of the chromosome 14q32 microRNAs, such as Islet Amyloid Polypeptide (IAPP) and Tumor Protein P53-Inducible Nuclear Protein 1 (TP53INP1) that cause increased β cell apoptosis upon overexpression in human islets [81]. Sun K. et al demonstrated that the miR-375 was overexpressed in plasma in patients with T2DM, and this may be used as a novel biomarker to distinguish between patients with T2DM and healthy individuals. Furthermore, hypomethylation of miR-375 promoter was found in patients with T2DM, which may regulate the expression of miR-375 and contribute to the pathogenesis of T2DM [82]. In addition, Rong Y. et al found that circulating miRNA-146a levels were significantly elevated in T2DM patients compared with healthy subjects [83]. Another study by Zhu Y. et al presented a novel network between nutrient overload and genetic diabetes via miR-24 in which a link was observed between this microRNA and MODY gene regulatory pathway to the onset of T2DM. Silencing of two MODY genes (Hnf1a and Neurod1) as direct targets of miR-24 imitated the cellular phenotype caused by miR-24 overexpression, whereas restoring their expression rescued β-cell function [84]. MiR-103 plays a critical role in regulating glucose homeostasis in T2DM. Luo M. et al suggested that platelet-derived miR-103b could negatively regulate the expression of SFRP4 mRNA/protein in pre- T2DM, indicating that miR-103b could be a biomarker for the early diagnosis of T2DM [85]. Higuchi C. et al demonstrated that the circulating miR-101, miR-375 and miR-802 levels are significantly increased in T2DM patients [86]. Decreased GLUT4 expression and impaired GLUT4 cell membrane translocation are involved in T2DM pathogenesis. Yan ST. et al revealed that a high level of miR-199a that reduce GLUT4 expression contributed to the insulin resistance in T2DM patients [87]. They suggested that miR-199a might be a novel biomarker for risk estimation and classification in T2DM patients.

Study of epigenome patterns using numerous advanced technologies such as massively parallel sequencing in combination with bisulfite conversion and RNA or miRNA profiling by microarrays will greatly facilitate a comprehensive understanding of the roles of epigenetic modifications in normal physiology and disease processes. In addition, the advances in comprehension of epigenetic mechanisms implicated in modulating chromatin conformation, gene transcription and diverse cellular signaling pathways have provided the essential basis for the current development of epigenetics-based biomarkers and drugs for the diagnosis and treatment of T2DM. Without detailed characterization of physiological as well as pathological patterns of epigenetic modifications in specific tissues, it would be impossible to identify epigenetic alterations that are causative and specific to disease process, which is essential for developing innovative epigenetics based therapies for diabetes.

Conclusion

Despite of a large volume of published work on the T2DM, no gene(s) has been directly implicated; however, the role of all the variants in increasing susceptibility will be known only by gaining further knowledge of the underlying biology. However, genetic background (personal or family history) of T2DM contributes in estimating the risk of developing of the disease in high-risk subjects. Despite of genetic studies, novel research in the field of epigenetics presents new opportunities for identifying distinguish biomarkers for risk and progression of complex metabolic diseases such as T2DM. Through Epigenome-Wide Association Studies (EWAS) as well as DNA methylation, histone modifications and non-coding RNAs, the most studied in the context of individual gene regulation, may provide important insight into disease pathogenesis which cannot be explained by genetic changes. The flexibility of epigenetic regulation and influencing by nutritional status and environmental changes point to the importance of understanding the effects of lifestyle factors on the molecular changes affect health. Further insight into these associations will improve the variety and quality of existing predictive T2DM biomarkers, thereby increasing the possibilities to postpone or prevent T2DM in the individuals at high risk for the disease.

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