Epigenetic regulation of glucose metabolism

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Purpose of review
Glucose metabolism is a central process in mammalian energy homeostasis. Its deregulation is a key factor in development of metabolic disease like diabetes and cancer. In recent decades, our understanding of gene regulation at the signaling, chromatin and posttranscriptional levels has seen dramatic developments.

Recent findings
A number of epigenetic mechanisms that do not affect the genetic code can be assessed with new technologies. However, increasing complexity becomes a major challenge for translation into clinical application.

Summary
The current review provides an update of transcriptional control of glucose metabolism, focusing on epigenetic regulators, DNA-methylation, histone modifications and noncoding RNAs. Recent studies heavily support the importance of those mechanisms for future therapeutics and preventive efforts for metabolic diseases.

Keywords
DNA methylation, epigenetics, glucose metabolism, histone modification, noncoding RNA

INTRODUCTION

Regulation of glucose metabolism, one of the fundamental biochemical processes in mammals, is a central focus of health research aiming to keep the epidemic of obesity and diabetes in bay. Obesity and diabetes are a consequence of both genetic and environmental factors that can be assessed, which include an enormous deregulation of glucose metabolism. Although candidate gene and genome-wide association studies have identified approximately 153 single-nucleotide polymorphisms (SNPs) across human genome that explain only a minor fraction of the interindividual variation in the susceptibility for type 2 diabetes (T2D) and glycemic traits [1▪▪,2], predictive value or unraveling underlying biological mechanism remains restricted. Therefore, role of epigenetic determinants is increasingly being recognized as a potential important link between environmental exposure and disease risk and thus may be a benchmark to capture both their influences. Epigenetics is the study of heritable changes in gene function without any change in the nucleotide sequence [3]. Thus, epigenetic gene regulation itself is a complex concert of several molecular mechanisms. As epigenetic factors are reversible in most cases, they seem also to be a potential target for future drugs. Another focus of research is epigenetic reprograming of glucose metabolism in cancer. Most of the genes known to be involved in glucose pathways are directly affected by epigenetic mechanisms to cover the high energy demand of cancer cells [4].

Recent advances in omics technologies, especially bead chip-based approaches and next-generation sequencing, improve our possibilities to get deeper insights into more and more parts of the epigenetic puzzle in larger approaches. DNA methylation, histone acetylation and methylation and noncoding RNA got most attraction in larger human studies so far. Techniques to evaluate the role of further epigenetic mechanisms remain to be developed or improved for large-scale studies. Epigenetic mechanisms affecting glucose metabolism can be categorized into defects in the secretion, transport

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KEY POINTS

- Glucose metabolism is a central process in mammalian energy homeostasis.
- The current review provides an update from September 2015 until December 2016 of transcriptional control of glucose metabolism, focusing on epigenetic regulators, DNA-methylation, histone modifications and noncoding RNAs.
- Recent studies heavily support the importance of epigenetic mechanisms for future therapeutics and preventive efforts for metabolic diseases.

or action of insulin; defects in glucose transport into tissues by the glucose transporters and abnormalities in enzymes associated with glucose metabolism caused by gene mutations or metabolic disturbances [5]. The aim of this review is to give an update on the current body of evidence on the role of epigenetic factors in regulation of glucose metabolism including mainly human studies on glucose levels, insulin levels and Homeostasis model assessment index for insulin resistance (HOMA-IR) [6▪▪] in the time frame September 2015 until December 2016. Studies investigating the association between major types of epigenetic signatures including global DNA methylation, site-specific or genome-wide DNA methylation and histone modification with T2D and glycemic traits are summarized and further discussed.

DNA METHYLATION

DNA methylation, involved in regulation of gene expression and genome stability, is commonly found as 5′-methylcytosine in CpG dinucleotides, catalyzed by DNA methyl transferases [7]. Intermediate forms of DNA demethylation process are 5′-hydroxymethylationcytosine, 5′-formylcytosine and 5′-carboxycytosine [8]. Among a wide range of methods for determination of DNA methylation [5,9], especially hypothesis-free approaches, using oligonucleotide chips contributed insights in epigenetic regulation of glucose metabolism recently.

Genome-wide studies

Several genome-wide studies with different ethnicities point out an association between DNA methylation degrees of CpG sites located within *TXNIP* (thioredoxin-interacting protein) and *ABCG1* (ATP binding cassette subfamily G member 1) and parameters of glucose metabolism (fasting glucose, HbA1c and HOMA-IR) [10,11▪,12,13▪]. In addition, Dayeh *et al.* demonstrate a positive association of DNA methylation level of cg06500161 (*ABCG1*) and HbA1c as well as fasting insulin beside other phenotypes in whole blood. Furthermore, also cg11024682 [annotated to *SREBF1* (sterol regulatory element binding transcription factor 1)] was associated with these phenotypes in adipose tissue and blood from diabetic twins comparing monozygotic twins discordant for T2D [14]. In Mexican-Americans, DNA methylation degree of 19 CpG sites could be associated with fasting glucose and 24 with HOMA-IR [12]. In addition to other phenotypes, glucose transport as well as insulin signaling pathway were correlated with hypermethylation in individuals with diabetes or prediabetes, analyzing peripheral blood of women with mixed ancestry from South Africa [15]. Especially in subcutaneous adipose tissue, loci involved in insulin signaling showed differently methylated sites as well as altered expression in insulin resistance in obese women [16]. Also among CpG sites associated with BMI, several loci with a role in glucose metabolism, strongly overlapping with hits from the studies mentioned above, seem to be influenced by obesity, which have potential predictive value for T2D [17▪]. Aging was also associated with specific changes of DNA methylation in human pancreatic islets including loci associated with diabetes risk and islet function [18]. In contrast to DNA methylation effects widely independent of genetic variation, genetically determined *cis*-mQTLs and *trans*-mQTLs have been shown to influence loci involved in glucose metabolism as well as obesity and T2D [19]. In a Korean study, OR10A4 was postulated as epigenetic target of postprandial hyperglycemia, suggesting a potential biomarker in peripheral hyperglycemia and diabetic conversion [20].

Candidate gene studies in animals and humans

Although the transferability of methylation associations between animals and humans remain limited, they still give hints, and some findings could already be replicated in humans. In juvenile rainbow trouts, carbohydrate-rich diet had an influence on DNA methylation levels of CpG sites of *g6pcb1a/b* and *g6pcb2a/b* (glucose-6-phosphatase b, catalytic subunit) in liver tissue, which are involved in gluconeogenesis [21]. Another animal study could show enrichment of genes with altered DNA methylation in glucose homeostasis apart from other pathways performing investigations in cell culture and islets of rats [22]. Comparing the DNA methylation degree of *INS* (insulin) locus in lamb females versus lamb males, Carr *et al.* [23] found out that it

was higher in males and that methylation of these genes correlates negatively with baseline insulin. In mice, liver tissue susceptibility to diet-induced obesity and insulin resistance was associated with increased *Igfbp2* (insulin-like growth factor binding protein 2) methylation [24]. Replicated in humans, methylation at CpG2965 (CpG site within *IGFBP2*) increases in whole blood of men with impaired glucose tolerance and BMI more than 30, and this correlates with fasting blood glucose levels [24].

Different studies including individuals with Asian ancestry demonstrate an association between DNA methylation and glycemic traits. Higher methylation level within the *HGK* (HPK/GCK-like kinase) promoter was associated with glucose tolerance in peripheral blood mononuclear cells of T2D patients compared with normal glucose tolerant individuals [25▪]. Hypermethylation of *BDNF* (brain-derived neurotrophic factor) CpG-6 was found in diabetic patients with higher fasting insulin levels compared with those with lower fasting insulin levels [26]. Furthermore, Su *et al.* [27] show an association of DNA methylation status of different CpG sites within the *IGF2* (insulin-like growth factor 2) and *H19* (H19, imprinted maternally expressed transcript) genes and fasting glucose as well as glucose at 1 and 2 hours in a glucose tolerance test. In addition, several studies including women analyze the association of DNA methylation and glycemic traits. Maternal glucose levels during pregnancy seem to have an influence on DNA-methylation in brown adipose tissue-related genes analyzing placenta samples from nondiabetic women [28]. Analyzing DNA methylation in normoglycemic women, glucose levels were associated with changes in DNA methylation at loci within *LRP1B* (LDL receptor-related protein 1B) and *BRD2* (bromodomain containing 2) in placenta as well as loci within *CACNA1D* (calcium voltage-gated channel subunit alpha1 D) and *LRP1B* gene in cord blood [29▪]. Furthermore, it was demonstrated that LINE-1 methylation was correlated with serum glucose levels in women, investigating the effect of two weight-loss strategies [30]. DNA methylation of *PPARGGC1A* (PPARG coactivator 1 alpha) in muscle and subcutaneuos fat were similar in women with gestational diabetes mellitus and type 1 diabetes and women from the background population. But the mean *PPARGC1A* DNA methylation was associated with HOMA-IR in adult offsprings [31].

HISTONE POSTTRANSLATIONAL MODIFICATIONS

As gene function is primarily regulated by chromatin accessibility, modifications of histone proteins that are responsible for chromatin structure play a major role in epigenetic regulation [32]. N-terminal tails of histone proteins are largely modifiable through, for example acetylation, methylation, phosphorylation and ubiquitination to change the histone structure [33,34]. Histone acetylation process loses the chromosomal DNA and activates the transcription, on the other hand deacetylation of histones results in chromatin compression and hence repressing the transcriptional activity [35]. Histone methylation is more complex with relationship to transcription primarily dependent on the site of histone tail methylation [3]. Histone acetylation and methylation play an active role in tuning the glucose metabolism [33].

Histone acetylation and deacetylation

Previous studies have shown the role of TXNIP in regulating glucose metabolism, especially in diabetes-related traits [36▪]. However, the underlying epigenetic mechanisms that regulate the *TXNIP* gene apart from DNA-methylation was not clear until recently. Bompada *et al.* showed how glucose influenced its effect on *TXNIP* gene expression through modulation of histone acetylation marks. The study showed series of experiments observing elevation of *EP300* and *TXNIP* gene expression in human diabetic islets, followed by the knockout experiment in which reduced glucose-stimulated *TXNIP* genes expression was observed after restraining *ep300* and p300 in rat pancreatic beta cell and human islet, respectively.

Histone methylation and demethylation

It has been shown that Lys methylation affects several aspects of transcription factors including protein decay and DNA coupling/DNA-binding affinity. The study by Maganti *et al.* [37] reveals the role of Lys methylation – mediates the transcription of *PDX1*. Set7/9 is a Lys methyltransferase that influences the role of *PDX1* and islet-enriched genes. MLL3 and MLL4 methyltransferases bind to the MAFA and MAFB transcription factors to regulate islet beta-cell function proposing that MLL3 and MLL4 are broadly required for controlling MAFA and MAFB transactivation during development and postnatally [38]. Histone acylation seems to be directly sensed by glucose flux in a titratable, dose-dependent manner that is modulated by glycolytic flux [39].

NONCODING RNA

Apart from classical epigenetic mechanism such as DNA methylation and histone modification,

microRNA (miRNA) is also linked with the epigenetic mechanisms. Wider class of nonprotein-coding RNAs are known as miRNA, they are capable of large-scale endogenous silencing and its impacts. As regulatory proteins are important in gene regulation, likewise argonaute proteins are required for miRNA regulation. MiRNA are 22-nucleotide long sequence-specific gene regulators involved in endogenous silencing. Majority of miRNAs are found intercellular but few of those are found in extracellular environment, also known as circulating miRNAs, they are also found in tissues and in wide range of bio-fluids such as blood, urine, saliva and tears [40]. In addition to miRNA, the role of long noncoding RNAs (lncRNAs) in regulation of glucose metabolism is increasingly coming to the fore [41].

MicroRNA

O'Connell and Markunas [42▪▪] provide review on a current state of miRNA and methylation-related genetic biomarkers of T2D susceptibility. In a meta-analysis on control studies retrieved from PubMed, Zhu and Leung [43] compare miRNA expression profiles of T2D and people without diabetes, aiming to identify potential miRNA biomarkers of T2D. The meta-analysis confirms existence of 40 miRNAs, which are significantly dysregulated in T2D. The study highlights miR-29a, miR-34a, miR-375, miR-103, miR-107, miR-132, miR-142–3p and miR-144 as potential biomarkers and miR-199a-3p and miR-223 as tissue biomarkers of T2D. Pheiffer *et al.* [44▪] showed genome-wide DNA methylation pattern (in the promoter, intergenic and intragenic regions) varying as per glucose tolerance status in smaller group of patients consisting of three people with diabetes, three people with prediabetes and three controls from South Africa. The differential analysis between the study groups characterizes hypomethylated/hypermethylated differentially methylated regions (DMRs) across genomic regions. They also evaluate miRNAs associated with DMRs and obtain the distribution of miRNA–DMRs amongst disease and non-diseased groups and found that the number of miRNA–DMRs is highest between people with diabetes and controls followed by people with diabetes and people with prediabetes and lastly people with prediabetes and control. Overall, the study brings out the relation shared between methylation and miRNA within intergenic regions. Ghaedi *et al.* [45] analyzed functionally validated miRNA binding sites to find variants that might be associated in type 1 and type 2 diabetes. Using bioinformatics approach, the SNP information was extracted from SNP database excluding insertion and deletion polymorphisms. Genes related to T1DM and T2DM KEGG pathways were screened for the number of SNPs in the target genes and number of polymorphic miRNA. Two variants, rs12158121 and rs13306464, from *MAPK1* and *IRSI* genes, respectively, were obtained that might regulate an impairment of mRNA–miRNA binding, which ultimately leads to the posttranscriptional deregulation of genes strictly related to diabetes.

Long noncoding RNA

Pancreatic beta-cell lncRNAs seem to control cell-specific regulatory networks including *PDX1* [46]. Arnes *et al.* [47] postulate βlinc1 as a novel islet-specific transcriptional regulator supporting lncRNAs as novel therapeutic targets for the treatment of diabetes.

CONCLUSION AND FUTURE DIRECTIONS

Studies on relevant tissues such as adipose tissue and skeletal muscle pancreatic beta-cells, which seem to be represented in part in blood cells, gave evidence that changes in DNA methylation play a role in regulation of glucose metabolism. This supports the use of DNA methylation, histone modification and noncoding RNA for therapeutically approaches to influence glucose metabolism and therefore the risk of T2D. However, the exact mechanisms remain to be clarified in most cases. DNA methylation remains the easiest to access in larger populations. Increasing study numbers reveal validated loci deregulated by methylation like *ABCG1*, *TXNIP*, *SREBPF1*, *SOCS3* and *PHOSPHO1* that are involved in development of T2D by diverse mechanisms. The deregulation through methylation seems to turn out widely as a consequence of other risk factors like obesity. Assessment of histone modifications and noncoding RNAs is still in an infant stage in larger human studies. However, all studies published to date support their importance in the complex regulation of glucose metabolism. In addition, some of these genes have been shown to be regulated by more than one epigenetic mechanism, among them *PDX1*. The interactions between these have to be assessed in more detail in the future. Changes in lifestyle that lower the risk of T2D and those that reduce known risk factors for the disease may affect gene expression through modification of DNA methylation and other epigenetic mechanisms. Therefore, intervention studies to determine whether long-term lifestyle changes such as regular physical activity, weight reduction and maintenance of a healthy diet (individually or in combination) have effects on the epigenome, especially on

genes related to T2D development, are important. Profiling of epigenetic mechanisms could help in the assessment of epigenetic dysregulation of potential candidate sites. Such profiling might deepen investigation of epigenetic effects on the response to antidiabetic treatments, a potential application of pharmacoepigenetics in T2D. For most of these novel modes of transcriptional regulation, it is too early to identify the extent of their roles in the regulation of metabolic physiology. Consortium-wide efforts, such as the Encyclopedia of DNA Elements, the US National Institutes of Health's Roadmap Epigenomics Project, the International Human Epigenome Consortium and the German Epigenome Programme have to find the answers that we cannot give with single-candidate or even genome-wide studies, redefining our understanding of transcriptional programing [33]. With the emergence of single-cell, single-molecule and the massive parallelization of next-generation sequencing technologies, these efforts will be driven forward. Thus, building the basis for functional studies to establish how epigenetic modifications of genes crucial to glucose metabolism and T2D development are induced by environmental factors and how such modifications can be protected from epigenetic reprograming.

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Conflicts of interest

There are no conflicts of interest.

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