Chromatin Modifications Associated With Diabetes and Obesity

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Abstract—The incidence of obesity across the globe has doubled over the past several decades, leading to escalating rates of diabetes mellitus, cardiovascular disease, and other complications. Given this dramatic rise in disease incidence, understanding the cause of these diseases is therefore of paramount importance. Metabolic diseases, such as obesity and diabetes mellitus, result from a multitude of genetic and environmental factors. Although the genetic basis of these diseases has been extensively studied, the molecular pathways whereby environmental factors influence disease progression are only beginning to be understood. One manner by which environmental factors can contribute to disease progression is through modifications to chromatin. The highly structured packaging of the genome into the nucleus through chromatin has been shown to be fundamental to tissue-specific gene regulation. Modifications to chromatin can regulate gene expression and are involved in a myriad of biological functions, and hence, disruption of these modifications is central to many human diseases. These modifications can furthermore be epigenetic in nature, thereby contributing to prolonged disease risk. Recent work has demonstrated that modifications to chromatin are associated with the progression of both diabetes mellitus and obesity, which is the subject of this review. (Arterioscler Thromb Vasc Biol. 2015;35:1557-1561. DOI: 10.1161/ATVBAHA.115.305041.)

Key Words: chromatin ■ diabetes mellitus ■ epigenomics ■ gene–environment interaction ■ obesity

Nutritional Factors and Chromatin Modifications

Nutritional factors, such as micronutrients from diet, can affect chromatin modifications by directly providing substrates necessary for modification or by providing cofactors that modulate the enzymatic activities of chromatin-modifying enzymes. For example, S-adenosylmethionine, a universal methyl donor for methyltransferases,9 is synthesized in the methionine cycle from precursors in the diet of an individual. Lack of methyl donors from diet can result in DNA hypomethylation in rodent liver10 and brain,11 and similar effects are supposed in humans. A recent and extensive review12 described many studies of the effect of micronutrients on chromatin modifications. Here, we instead review some of the seminal work exploring the effect that diet can have on chromatin modifications and focus on more recent work describing modifications to chromatin that are associated with type 2 diabetes mellitus (T2D) and obesity that are influenced by nutrients and excess consumption of calories from fats and refined carbohydrates.8 We also discuss the role of epigenetics in the vascular complications that are significantly accelerated in diabetes mellitus and obesity. Furthermore, we highlight the emerging evidence of gene and environmental interaction in these diseases.
The agouti viable yellow mouse (A\(^v\)) is a classic mouse model for studying fetal programming. The A\(^v\) allele contains an intracisternal A particle retrotransposon upstream of the Agouti gene that can be DNA methylated. Interestingly, genetically identical offspring vary in agouti expression depending on developmental availability of methyl donors in the diet,\(^1\) which influences the DNA methylation state of the intracisternal A particle retrotransposon upstream of the Agouti gene.\(^2\) Although the Agouti gene encodes a signaling protein that promotes yellow pigmentation, it is also antagonistic to melanocortin receptors, a regulator of feeding behavior and metabolism.\(^3\) Differential methylation of the intracisternal A particle upstream of the Agouti gene, therefore, results in offspring with varying coat colors, as well as differential susceptibility to diabetes mellitus, obesity, and cancer.\(^4\)

### Chromatin Modifications Associated With Obesity

In addition to the effects of nutrients on chromatin modifications, diet is also a key factor driving metabolic disease. Excess consumption of calories from fats and refined carbohydrates is associated with the development of obesity, nonalcoholic fatty liver, T2D, and other metabolic diseases.\(^5\) Diet-induced obesity is also associated with modifications to chromatin in the brain,\(^6\) although the molecular mechanisms underlying these chromatin modifications are less clear. Primary hepatocytes treated with palmitate and oleate mimicking high-fat (HF) diet express histone demethylase genes at elevated levels.\(^7\) Furthermore, human pancreatic islets treated with palmitate have altered DNA methylation patterns that are associated with gene expression changes for 290 genes, with numerous pathways altered, including insulin signaling and other metabolic pathways.\(^8\)

Rats developing obesity from HF diet show altered histone modifications at p16 and p21 loci.\(^9\) More recently, it has been shown that C57BL/6J mice fed a HF diet to induce obesity display chromatin remodeling in liver tissue across the genome.\(^1\) Furthermore, the greatest degree of remodeling was at regulatory regions bound by transcription factors, such as HNF-4\(\alpha\), CEBP/\(\alpha\), and FOXA1 and marked by histone lysine 4 monomethylation, a chromatin modification associated with regulatory regions (Figure 2).\(^2\) A large number regions displaying chromatin remodeling occurred near genes associated with metabolism and insulin signaling. Intriguingly, DBA/2J mice fed a HF diet for the same time period also displayed chromatin remodeling in the liver, but the regions of the greatest remodeling were largely unique to the DBA/2J genome, further revealing a link between genetic and environmental factor in diet-induced obesity.\(^3\) Interestingly, studies with the Hybrid Mouse Diversity Panel have demonstrated tremendous strain-specific diversity in metabolic responses to HF diet in mice,\(^2,2\) further underscoring the genetic-epigenetic cross-talk and a possible correlation in humans.

### Chromatin Modifications and Diabetes Mellitus

It was recently demonstrated that DNA methylation changes can be induced in adipocytes of mice on a HF diet.\(^2\) It was further shown that homologous loci in the human genome displayed differential methylation before and after gastric bypass, demonstrating cross-species conservation of differential methylation induced by HF diet.\(^2\) These regions of differential methylation overlapped with T2D risk loci that, for the most part, were deemed not significant by genome-wide association analysis alone. However, it was shown that 4 of these genes are involved in insulin resistance, indicating that further integration of epigenetic data with genetic studies can be used to identify molecular pathways of disease.\(^2\)

An additional study evaluating monozygotic twin pairs concordant or discordant for T2D also revealed differentially methylated regions in peripheral blood that overlap with genome-wide association study loci associated with T2D.\(^2\) Interestingly, pancreatic islet cells also display variation in DNA methylation across different individuals.\(^2\) These variable methylation regions are associated not only with gene expression variation in islets but also with secretion of insulin, indicating that DNA methylation may be an important mediator in the development of diabetes mellitus.\(^2\) DNA methylation may also be a key player in the development of diabetic pathologies associated with T2D.

**Figure 1.** Chromatin modifications demonstrated to be associated with diabetes mellitus and obesity. DNA methylation,\(^2,2\) ATP-dependent remodeling,\(^2\) histone post-translational modifications (PTMs),\(^2,2\) and noncoding RNAs (ncRNAs)\(^2,2\) have been demonstrated to be altered in diabetes mellitus and obesity.

**Figure 2.** Diet-induced obesity chromatin remodeling. Diet-induced obesity leads to chromatin remodeling in the liver at regulatory regions across the genome. These regions are pre-marked by H3K4me1 and bound by liver transcription factors (TFs; details are given in the text) and can lead to the expression of metabolic pathway genes, such as Lpin1.
vascular complications, perhaps as a result of the hyperglycemic state.27,28

In addition to DNA methylation, PTMs to histone proteins are also involved in the development of diabetes mellitus and its vascular complications.28 Differences in the levels of histone PTMs, such as histone H3 lysine 9 acetylation and histone H3 lysine 4 methylation (chromatin marks associated with expressed genes) at key fibrotic, inflammatory, and cell cycle genes, are observed in renal mesangial cells treated with transforming growth factor-β1 or high glucose.29,30 PTM changes were also noted in renal glomeruli of diabetic mice compared with glomeruli from nondiabetic control mice.31 These chromatin modifications observed in the kidney can contribute to diabetic nephropathy, although similar chromatin modifications in distinct target organs can contribute to other diabetic micro and macrovascular complications, such as retinopathy and atherosclerosis.27,28,32 Inflammation and monocyte/macrophage activation are associated with the pathology of diabetic complications, such as atherosclerosis and hypertension. Evidence shows that monocytes display changes in key histone lysine modifications at inflammatory genes under diabetic conditions.33 Furthermore, chromatin modifications have been observed in white blood cells from T1D patients compared with normal controls.34 Additional studies have shown changes in post-PTM to histones occur in vascular smooth muscle cells (VSMCs). With increase in angiotensin II (Ang II), a major contributor to vascular dysfunction that occurs frequently with diabetes mellitus and leads to hypertension and atherosclerosis, VSMCs display elevated levels of histone H3 lysine 4 trimethylation and H3K36me3 genome wide at several pathological genes.35 Interestingly, VSMCs cultured from db/db diabetic mice display sustained decreases in levels of the repressive chromatin mark H3K9me3 at promoters of inflammatory genes compared with control mice, despite being maintained under the same conditions, with reciprocal upregulation of these genes.36 In endothelial cells, transient hyperglycemic conditions resulted in sustained changes in active histone modification in vitro and in vivo at inflammatory genes.37 The data indicate that modifications to chromatin occur with disease and may persist after restoration of normoglycemia. They are furthermore potential mediators of metabolic memory, as discussed below.

Another avenue through which diabetes mellitus and its complications can be regulated is through long noncoding RNAs (lncRNAs). These lncRNAs have been shown to be involved in chromatin regulation and gene regulation via epigenetic mechanisms and recent evidence suggests that they may contribute to diabetic complications.38,39 One study evaluating the potential role of lncRNAs in Ang II signaling identified hundreds of lncRNAs that are expressed in VSMCs, with over a hundred of those being regulated by Ang II. One Ang II–regulated IncRNA, Lnc-Ang362, was characterized to be the host transcript of 2 miRNAs, miR-222 and miR-221, which are found at the same genomic locus (Figure 3).39 Furthermore, Lnc-Ang362 knockdown revealed that this lncRNA is important for VSMC proliferation. Presumably, the proliferative function of Lnc-Ang362 occurs through the actions of miR-221 and miR-222, although it is possible the Lnc-Ang362 also has miRNA-independent effects. Future studies may reveal additional Ang II– and other growth factor–regulated lncRNAs that are important for VSMC function and phenotype. These additional lncRNAs may also directly affect chromatin by interacting with chromatin-modifying complexes.39 LncRNAs can also be induced in macrophages by diabetic conditions in mouse models, affecting the macrophage phenotype and inflammation.40 Finally, lncRNAs have been characterized in islet cells, suggesting a direct role in diabetes mellitus development.41

Although studies have implicated DNA methylation, PTMs of histones and lncRNAs in susceptibility and development of diabetes mellitus and its complications, a major challenge remaining is to show the direct effect of these chromatin modifications on disease progression. Although obesity and T2D are tightly linked, it was recently demonstrated that disruption of the bromodomain containing protein 2, which plays a role in chromatin remodeling, leads to metabolically healthy obesity, without T2D.42 Another recent study demonstrated that a bromodomain containing protein 4 inhibitor can inhibit endothelial cell inflammatory genes and also attenuate atherosclerosis development in mouse models.43 These results suggest that chromatin modifications and remodeling are involved in the link between obesity, T2D, and other metabolic diseases.

**Epigenetics as a Mediator of Metabolic Memory**

Clinical studies examining blood glucose control for diabetic patients have demonstrated that complications can continue to develop long after blood glucose normalization, a phenomenon that was originally termed metabolic memory.44,45 Similarly, many obese people find it difficult to maintain weight loss,46,47 with long-term physiological changes contributing to weight regain.48,49 Mice that develop diet-induced obesity develop metabolic dysfunctions, including insulin resistance and impaired glucose tolerance, mimicking dysfunctions observed in many obese patients.50,51 Furthermore, it has been demonstrated that mice transitioning from HF to low-fat diet do not completely revert to the same state as mice only maintained on low-fat
diet. Similarly, reports have indicated that the diabetic condition, including hyperglycemia, can result in persistent histone modification changes in VSMCs and endothelial cells. Although the molecular mechanisms responsible for this metabolic memory remain unclear, epigenetic mechanisms represent attractive potential mediators. A recent epigenomics study with monocyes obtained from patients with T1D who were experiencing metabolic memory of diabetic complications versus those without evidence of metabolic memory supports this concept. This study identified significant variations in histone H3K9ac at several inflammatory genes in the patients experiencing metabolic memory and a strong association of H3K9ac with mean hemoglobin A1c levels.

**Links to Other Diseases**

It is now well established that obesity is associated with additional diseases, including cardiovascular disease and many types of cancer. There is tantalizing evidence that modifications to chromatin might be one manner by which obesity confers susceptibility to the development of other diseases. As an example, obesity is a major risk factor for colorectal cancer, the third most common form of human cancer. Recent work profiling histone modifications to predict enhancer use in the colon in mouse models of diet-induced obesity and genetic obesity revealed that obesity induces an enhancer profile that more closely resembles colorectal cancer than normal cells. Exactly how this happens remains an area of active debate. The chronic inflammation associated with the obesity state is one potential mediator. Indeed, high serum lipid levels are associated with inflammation and other metabolic complications.

**Conclusions**

The dramatic increase in obesity, diabetes mellitus, and related vascular complications is leading to a public health crisis, and it is imperative that we act to curb these trends. Fundamental to this will be a greater understanding in the molecular underpinnings of these diseases. Given that these are complex diseases with multiple genetic and environmental influences, the use of integrative methods will be necessary to fully unravel the pathways involved in disease development. These ventures can exploit the rapidly emerging high-throughput sequencing technologies for profiling modifications to chromatin and the associated bioinformatics tools. Furthermore, there is much discussion about the use of epigenetic therapies, such as those already in use for certain cancers, although several challenges remain. As described above, much progress has been made in the past several years, but there is still a long way to go.

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**Disclosures**

None.

**References**


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