MJMHS 2021 1562

by Mjmhs 2021 1562 Mjmhs 2021 1562

Submission date: 10-Jan-2022 05:19PM (UTC+0800)
Submission ID: 1739491334
File name: MJMHS_2021_1562_7_1_2022_EPIGENETICS_OF_METABOLIC_SYNDROME.docx (37.41K)
Word count: 6008
Character count: 35992

EPIGENETICS OF METABOLIC SYNDROME

Abstract

Prevalence of metabolic syndrome varies depending on ethnicity and gender, indicating that it is associated with genetic factors. The occurrence of this disease is influenced not only by gene variations but also by gene promoters that can be activated or deactivated by environmental factors through epigenetic mechanisms. Epigenetics involves environmental factors that influence specific cells through DNA changes that modify gene expression in promoters. Through this mechanism, DNA methylation can alter metabolism and lead to the development of chronic metabolic diseases, such as metabolic syndrome. Certain dietary components and physical activity can increase DNA methylation or demethylation in gene promoters, which affect the risk of disease or inhibit the disease. Understanding environmental risks for the development of metabolic syndrome through DNA methylation and demethylation is crucial for the therapy, diagnosis and prognosis of this disease through the selection of appropriate nutrition.

Keywords: Diet, DNA Methylation, Epigenetic, Histone, Metabolic Syndrome

Introduction

Metabolic syndrome is a group of metabolic disorders (e.g., central obesity, glucose intolerance, insulin resistance (IR), high blood pressure, and dyslipidemia) that increase the risk of chronic diseases, such as type II diabetes mellitus (T2DM), cardiovascular disease, and some types of cancer. A recent study by the Centers for Disease Control has reported that the prevalence of metabolic syndrome varies depending on ethnicity and gender, indicating that it is associated with genetic factors. Epigenetics involves environmental factors that influence specific cells by chemical changes in DNA that modify gene expression (1).

DNA methylation occurs at the site of cytosine nucleotides followed by guanine nucleotides (CpG sites) and produces 5-methylcytocin, which affects gene expression. CpG sites are located in promoter areas or beyond. Certain gene promoters are easily hypomethylated in the presence of an environment or diet, whereas other areas of DNA are easily hypermethylated (2). Hypermethylation is associated with transcriptional repression, and hypomethylation with

activation (3). Alterations in candidate gene methylation are associated with obesity, appetite control and metabolism, insulin signaling, lipid metabolism, immunity, inflammation, growth, high blood pressure, and regulation of the circadian clock (4). The leptin (LEP), pro-opiomelanocortin (POMC), and neuropeptide Y (NPY) genes, which participate in weight regulation, have CpG islands, where methylation can affect the expression of these genes. Some obesity-associated genes, including adiponectin (ADIPOQ), peroxisome proliferator-activated receptor coactivator 1 (PGC1α), insulin-like growth factor 2 (IGF2), insulin receptor substrate 1 (IRS1), and lymphocyte antigen 86, are associated with DNA hypermethylation and T2DM 104. Meanwhile, lipoprotein lipase (LPL), adrenergic receptor B3 (ADRB3), ATP-binding Cassette G1 (ABCG1), tumor necrosis factor (TNF)-α, methylene tetrahydrofolate reductase (MTHFR), and some other methylation of these genes are correlated with lipid metabolism, IR, and hypertension. Post-translation modification of the core histone processes, including acetylation, methylation, ubiquitination, phosphorylation, and histone tail sumoylation, is an important mechanism in epigenetic regulation. Histone acetylation is associated with gene transcription activity. Histone deacetylation can cause interactions between DNA and histone tails, leading to chromatin compression and silencing transcription (5). DNA methylation and histone modification are interrelated. DNA methylation affects histone modification, and vice versa, by affecting chromatin in RNA polymerase and transcription factors (6).

The epigenetic system becomes sensitive to nutritional factors during developmental transition, the period when epigenetic markers are critically modified. Thus, nutritional deficiencies during pregnancy and lactation have long-term consequences in health. Studies in the Netherlands and Gambia provided examples of nutritional deficiencies leading to metabolic dysregulation in later life, which have been linked to cardiovascular disease, obesity, or hyperglycemia (7).

Macronutrients (carbohydrates, proteins, and fats) and micronutrients (vitamins, minerals, and some bioactive components) alter the repressor and/or activator complexes at the promoter, modulating gene expression/repression. Nutritional intake and dietary habits influence the predisposition of certain diseases due to this epigenetic mechanism (8).

Malnutrition caused by overnutrition also induces epigenetic changes in gene promoters in the metabolic pathway, which can influence gene expression and metabolic changes. High-fat diets with saturated and trans-fatty acids induce promoter hypermethylation, which is associated with

impaired intestinal permeability, obesity, cardiovascular disorders, impaired insulin secretion, and increased T2DM risk (9).

Exercise is an environmental factor that influences DNA methylation and the risk of metabolic syndrome disease. Research related to exercise shows that DNA methylation of genes in retinol metabolism, calcium signaling pathways, and those associated with T2D decreases after exercise. Some of these exercise-associated methylation changes accompany differential gene expression (10). Exercise induces genome-wide changes in DNA methylation in human adipose tissue, influencing adipocyte metabolism.

This review discusses that methylation on promoter DNA can cause metabolic syndrome, which is composed of obesity, IR, dyslipidemia, and hypertension, and that diet affects DNA methylation and further modifies gene expression.

1. DNA methylation and metabolic syndrome

The prevalence of metabolic syndrome is increasing rapidly in many countries, affecting 20% of the adult population globally. In 2010, 38.37% of Spanish people and 29.62% of women showed indications of metabolic syndrome, and this trend has increased with age (7).

Human studies analyzed the relationship between DNA methylation and metabolic syndrome in visceral adipose, IR, hypertension, high-density lipoprotein cholesterol (HDL-C) level, and hypertriglyceridemia. A genome-wide association study (GWAS) with 8165 participants found associations between adipose and changes in DNA methylation in blood cells and adipose tissue. These data relate to changes in DNA methylation, mediated by visceral adiposity (11). Another study with 64 subjects found a correlation between methylation in the promoter genes of lipoprotein lipase in individual hypertriglyceridemia and the development of metabolic syndrome (12). Another GWAS study with 483 children identified differentially methylated regions (DMRs) that are associated with insulin sensitivity (13). Some genes are also involved in the dysregulation of glucose metabolism, hypertriglyceridemia, and decreased levels of HDL-C, which participate in the development of IR and cardiovascular disease (14,15). Other studies found a correlation between the methylation of genes that cause changes in blood pressure and vascular endothelial function, which are associated with hypertriglyceridemia (7).

2. DNA methylation and obesity

The prevalence of obesity has increased since 2016, with more than 1.9 billion adults overweight and 650 million obese (16). Obesity is defined as the accumulation of excess fat that contributes

to the development of comorbid diseases, such as T2DM, cardiovascular disease, dyslipidemia, hypertension, or metabolic syndrome (17). Obesity is associated with an energy imbalance between input and expenditure calories. This balance is influenced by several factors, such as lifestyle (diet, exercise, and sleep patterns), economic factors (level of education and economic status), endocrine disease (hypothyroidism), or medications (corticosteroid administration). In addition to environmental factors, genetic factors also influence the development of obesity (7,18).

Adipocyte hypertrophy and hyperplasia in obesity reduce oxygen availability and cause hypoxic stress, which is associated with inflammation, IR, and mitochondrial dysfunction. Hypoxic conditions increase reactive oxygen species generation and oxidative stress as mediators of inflammation (19). Obesity is almost always associated with IR, and poor glycemic control is associated with epigenetic changes involved in the development of diabetes-related comorbidities. Some genes, such as POMC, NPY, melanocortin, leptin, hypoxia-inducible factor 3 subunit alpha (HIF3A) (20), insulin-like growth factor binding protein 3, sterol regulatory element-binding transcription factor 1 (SREBF1) (21), TNF (22), and clock circadian regulator (23), are affected by epigenetic changes because of environmental factors that suppress their expression. Glycolysis-related HIF system control genes, such as pyruvate dehydrogenase kinase 1, lactate dehydrogenase-A, and glycogen phosphorylase L, stimulate glucose uptake or increase glucose production by activating phosphoenolpyruvate carboxykinase in the liver (24).

Some GWASs identified more than 500 locus genes that affect obesity incidence. Genetic, environmental, and lifestyle factors can affect DNA methylation and contribute to the pathogenesis of obesity. Research on the DNA methylation of peripheral blood leukocytes found CpG sites in people with obesity (25). Variations in DNA methylation occur in subjects with obesity compared with those without, and methylation differences could predict obesity to reach 70%. Research on white blood identified five CpG sites in HIF3A and found that increased levels of methylation are correlated with increased body mass index (BMI) (Figure 1). Other studies investigated CD4+T cells and identified eight CpG sites associated with BMI and waist circumference. These include four CpG sites on *CPT1A, CD38,* and *PHGDH*. *CPT1A* encodes the carnitine palmoyltransferase 1A enzyme that plays a role in the transport of carnitine-dependent lipids through mitochondrial membranes to carry long-chain fatty acids into the mitochondria. *CD38* is associated with metabolic diseases, and research with mice lacking CD38 showed a rapid metabolic rate and

resistance to obesity during the administration of a high-fat diet. In patients with obesity, proteins encoded by ABCG1 are associated with macrophage cholesterol and phospholipid transport (26).

Another research found that 87 CpG sites associated with BMI affect changes in the *ABCG1*, *SREBF1*, and *CPT1A* genes, which play a role in lipid metabolism pathways (27) (Figure 2). *SREBF1* encodes transcription factors that participate in lipid metabolism and serve as a target for the prevention of arterial coronary disease. The increase in the number of CpG sites is significantly related to BMI and waist circumference. Other studies on *MS12* and *LARS2* have been related to the expression of *ABCG1*, *SREBF1*, and *CPT1A*. *MSI2* encodes the Musashi RNA binding protein 2 gene, which influences the post-translational regulation of genes related to eating habits (28). Other studies found a direct correlation among DNA methylation, gene expression, and obesity in the *SOCS3* gene, where obesity is associated with decreased methylation and increased gene expression. *SOCS3* expression is upregulated in individuals with obesity and induces insulin and leptin resistance, which increase glucose level and disturb energy homeostasis (29). Interactions between stress and DNA methylation at one CpG site in *SOCS3* are associated with BMI (30).

Figure 1. Correlation of obesity genes and DNA methylation influences appetite regulation. adipose tissue, blood, skeletal muscle, energy expenditure, and inflammation

DNA methylation and obesity are related to adipose tissue, the endocrine organ that is the main energy source in the human body. Thousands of CpG sites on the subcutaneous adipose tissues are associated with BMI. In addition, 2825 genes successfully identified from DNA methylation and gene expression are associated with BMI; these genes include *FTO*, *Leptin*, *UCP2*, and *IRS1*. A previous study with female subjects reported three CpG *HIF3A* sites that are significantly associated with BMI, whereas a research on male subjects found only 1 *HIF3A* CpG site that is significantly associated with BMI. In subcutaneous adipose tissue, CpG *KCNQ1* sites involve low DNA methylation, which is also related to obesity. DNA-methyltransferase (DNMT3A and 3L) shows decreased methylation due to weight loss, as observed in Methyl-CpG-binding domain protein 4 (MBD4), the gene that encodes proteins and is specifically bound to methylated cytosine that influencee signal methylation . Studies involving subjects who underwent gastric by-pass surgery found 8504 CpG sites, of which 27% are associated with adipogenesis (31).

Methylation of CpG 147,161 sites occurs in the differentiation phase from myoblast to myotube in individuals with obesity. This phenomenon is due to genetic changes found in *MECP2*, *IL18*, *ENHO*, and *PLCB1*, which are involved in immune response, explaining how obesity can interfere myogenesis and affect muscle regeneration and function (Figure 1) (32).

3. DNA methylation and diabetes mellitus

Diabetes mellitus is a common condition worldwide. More than 500 million people have diabetes, with a global prevalence of 8.5% in adults. High blood glucose caused 3.7 million deaths in 2012 alone (33).

T2DM, with the highest frequency in all DM diseases, is characterized by decreased insulin production or IR in which the body does not respond to insulin. Genetic and environmental factors influencing T2DM risk include age, gender, ethnicity, smoking, obesity, poor physical activity, family history, gestational diabetes mellitus history, and some treatments, and these factors can be associated with epigenetic modifications that affect the occurrence of T2DM (34).

DNA methylation in the pancreas, adipose tissue, skeletal muscle, and liver tissue changes during T2DM pathogenesis (35). Studies on epigenetic conditions have been conducted on several T2DM-related organs, such as the pancreas gland, skeletal muscle, adipose tissue, and liver tissue. Results from a number of human epigenetic studies on T2DM disease are shown in Figure 2.

Figure 2. Epigenetics in organs influenced by Type 2 diabetes mellitus

Methylation of the Ins2 promoter influences protein binding, which inhibits the activation of the insulin-synthesizing gene (36). On T2D, the expression of GLUT4 is decreased in adipose tissue (37). Experiments in animals have shown increased tyrosine or serine phosphorylation of IRS1 due to the hyperactivity of c-Jun N- terminal kinase, and endoplasmic reticulum X-box binding protein-1 causes IR (38). Excess free fatty acids due to lipolysis from triglyceride are stored in adipose tissue under the mediation of hormone-sensitive LPL, will release fatty acid and these fatty acids contribute to the occurrence of IR because of impaired insulin secretion pathway. High-fat accumulation causes monocyte infiltration, which triggers the release of proinflammatory cytokines. This phenomenon further inhibits insulin antilipolytic activity and ultimately causes impaired insulin sensitivity. Proliferator-activated receptor gamma (PPARc) is a nuclear hormone receptor that targets many genes involved in inflammation and insulin sensitivity (39).

Studies on DNA methylation , including *PDX1, PPARGC1A* (encode PGC1a), and *GLP1R* (encodes GLP-1 receptors) in the pancreas glands of patients with T2DM; increased DNA methylation and decreased expression of these genes are associated with impaired insulin secretion. High levels of glucose and glycated hemoglobin (HbA1c) can directly increase DNA methylation in this gene (40). DNA methylation that influence the expression of *CDKN1A*, *PDE7B*, and *SEPT9*, causes increased gene expression in the pancreas (Figure 3). Research on *CDKN1A* and *PDE7B* genes showed that the promoter methylation during transcription causes overexpression and decreases insulin secretion. Overexpression of *CDKN1A* that encodes cyclin-dependent kinase inhibitors and regulates cell cycles toward G1 can decrease cell proliferation DNA methylation also occurs in CpG sites of several T2D and obesity gene candidates, such as *ADCY5*, *FTO*, *HHEX*, *IRS1*, *KCNQ1*, *PPARG*, and *TCF7L2* (41).

Previous research used Illumina arrays to analyze DNA methylation in adipose tissue, liver tissue, and skeletal muscle from subjects with T2DM compared with non-diabetic controls (42). The results identified a number of CpG sites with DNA methylation changes in the target tissue of patients with T2DM, which support epigenetic patterns. Another study used whole-genome bisulfite sequencing to analyze ~2.4 × 107 CpG sites (83% CpG site in human genome) on the pancreatic glands of patients with T2DM and controls (43). This analysis identified 25,820 DMRs in the pancreatic gland of patients with T2DM. Significant DMRs are present in PDX1, which is a key transcription factor in glands that regulate insulin expression. About 159 other DMRs related to T2DM are in *ADCY5*, *TCF7L2*, and *KCNQ1*. In addition, some genes, including *NR4A3*, *PARK2*, *PID1*, and *SOCS2*, occur in DMRs and correlate with changes in expression in the pancreatic glands of patients with T2DM. When the candidate gene is overexpressed or silenced in beta cell culture, insulin secretion disorders occur correlated with epigenetic mechanisms to islet cell dysfunction (43). Methylation level in the pancreatic islet is associated with the disruption of histones and affects the control of gene activity and chromatin structure. A previous study used methylated DNA immunoprecipitation-seq to analyze the blood of monozygotic twin pairs and found strong replication signals in *MALT1*, which encodes insulin proteins and glycemic pathways and is correlated with taurocholic levels in the blood (31).

Epigenetic changes in patients with diabetes contribute to vascular complications. In addition, epigenetic modification can result in diabetic complications, such as retinopathy, neuropathy, diabetic kidney disease, stroke, and myocardial infarction (44,45).

4. DNA methylation and hypertension

Hypertension is a global health challenge and a major risk factor of cardiovascular disease, especially stroke. Genetic variation contributes to the risk of high blood pressure with the variability of genetic factors between 30%–70% that affect blood pressure (46). Systemic hypertension is a condition of high blood pressure in systemic arteries with a blood pressure exceeding 140/90 mm Hg in adults. A recent report in 2017 from the American College of Cardiology/American Heart Association (ACC/AHA) updated guidelines that modified the classification of high blood pressure as over 130/80 mm Hg (47). Hypertension is a risk factor for myocardial infarction, heart failure, end-stage kidney disease, and stroke. According to the ACC/AHA report, men have a higher risk of developing hypertension than women in pre- menopausal age, indicating that hormonal signaling participates in the regulation of blood pressure. Chronic conditions that increase the risk of hypertension include age, smoking, low socioeconomic and educational conditions, overweight/obesity, unhealthy diet, infrequent exercise, and other secondary disorders, such as chronic kidney disease, family genetic history, diabetes mellitus, and stress conditions (47). Many signaling pathways correlated with the development of hypertension, such as molecular mechanisms, are associated with epigenomic regulation. This regulation relates to genotypes and phenotypes that are important for normal function and can affect the cellular function of tissues or organs in disease development. Epigenetic regulations that have been identified in hypertension include methylation, acetylation, phosphorylation, ubiquitination, and sumoylation (48).

Global DNA methylation in DNA repetitive elements, such as *ALU* and *LINE*-1, is a genomic methylation that occurs up to 50%. Methylation events occur consistently in *LINE*-1 and *ALU*. Demethylation occurs consistently in *LINE*-1 and *ALU*. A recent study of the *LINE*-1 gene has found that decreased methylation levels affect high systole hypertension and diastolic blood pressure. DNA hypermethylation in *LINE*-1 is related to inflammatory responses due to endothelial damage and causes increased deaths because of chronic kidney disease (49).

Several studies focused on hypertension- or cardiovascular disease-related genes, such as *ADRB3*, *ABCG1*, *GALNT2*, and *HMGCR*. Other studies analyzed proinflammatory genes and biomarkers, such as TRI2, IFNγ, F3, GCR, ICAM-1, TLR-4, NFKB1, PPARγ, and IL-6, or other genes involved in inflammation responses, such as renin–angiotensin–aldosterone system (RAAS), a hormone system that regulates physiological responses of hypertension (50). RAAS genes include promoter

angiotensin I- converting enzyme (*ACE*) and angiotensin II receptor type I (48). The RAAS system plays an important role in fluid retention that maintains blood pressure and is involved in hypertensive pathogenesis (Figure 3) (51).

Figure 3. Methylation of DNA causes hypertension through the renin–angiotensin–aldosterone system. Hormones and inflammation cause impaired blood vessels

Angiotensin receptors include type-1 (AT1) and type-2 (AT2), which are G-class protein receptors with angiotensin as their ligand. AT1 receptors consist of the AT1a and AT1b subunits. Excess activation of AT1 receptors leads to the development of hypertensive disease through its effect on angiotensin II in renal blood vessels. A previous research showed greater expression of AT1a mRNA and protein in mice that cause hypertension spontaneously compared with control mice. This hypertensive response is related to the hypomethylation in AT1aR promoters. ACE is a key enzyme in RAAS that helps regulate blood pressure. The identification of two CpG islands in the proximal promoter region of the *ACE-1* gene affects the ACE expression modulated by CpG methylation and histone deacetylation inhibition. Methylation promoters in ACE may play an important role in the expression of *ACE- 1* and the development of hypertension (52).

RAAS is correlated with the endothelin system, especially endothelin converting enzyme-1 (ECE-1), a key enzyme in endothelin biosynthesis and is mainly distributed in vascular endothelial cells. ECE-1 is responsible for the production of endothelin-1, a vasoconstriction peptide that helps regulate blood pressure. In Caucasian populations, promoter haplotype of the ECE-1b 839G/-338A gene is associated with high systolic and diastolic blood pressures (52).

Adducin (ADD) is a heterodimeric cytoskeleton protein consisting of subunit a combined with subunit b or c. Subunit a is encoded by *ADD1*, which is one of the angiotensin RAAS sub-components. *ADD1* is a strong candidate gene in the development of hypertension. It not only increases renal sodium reabsorption but also participates in the pathophysiology of hypertension. Research on a Chinese population found a correlation between rs4963 of the *ADD1* gene and the risk of hypertension (52).

5. DNA methylation and lipid profile (triglycerides, HDL, low-density lipoprotein (LDL), and cholesterol)

Dyslipidemia is characterized by a decrease in HDL-C and increase in LDL-C and/or increased concentration of triacylglycerol (TAG) and total cholesterol, which are risk factors for cardiovascular disease. Dyslipidemia is caused by environmental factors, such as unhealthy diet, lack of exercise, or excess weight (53).

Genetic factors strongly influence lipid concentration and lipid metabolism. Some GWASs identified genetic variants that influence lipid plasma, reaching 12% between different individuals. Epigenetic influences also play a role because of concurrent environmental factors that affect the expression of genes, especially the presence of methylation that affects transcription factors. Several studies reported that DNA methylation in specific genes is related to blood lipid concentrations, including methylation in the *ApoE, LPL,* and *ABCG1* genes (54). A positive correlation exists between blood TAG and methylation in *NPC1* and *IGF2*, as well as between blood TAG and methylation in some areas of CpG FIAM. In addition, a positive correlation exists between DNA methylation in PLA2G7 and BCL11A in female subjects but not in males (55). Another study identified two DNA methylations (i.e., *ABCG1* and *PHGDH*) that are associated with triglyceride levels. Methylation in *PHGDH* (cg14476101) affects triglyceride levels (56). Some methylations of DNA correlated with lipid profile are depicted in Figure 4.

Figure 4. Methylation of DNA correlated with high levels of triglycerides, cholesterol, and LDL and low DNA level in the blood

The relationship between DNA methylation and candidate genes in blood HDL-C concentrations was studied. Results showed low DNA methylation in *FIAM, ABCA1, NPC1, MTHFR, LEP,* and *ADIPOQ* and high levels of gene methylation in LPL and DPP4 peripheral blood associated with high HDL-C plasma. No correlation exists between HDL-C levels and DNA methylation in *CD14, Et-1, HERV-W, iNOS, TNF-α, TCF7L2, IGF2, MCP-1, APOE, ABCG1, GALNT2,* or *HMGCR*. Other studies have found a gender influence between HDL-C and DNA methylation in *PLTP, CETP,* and *LIPC-CpGA2*, showing a significant correlation in males but not in females (55).

Other studies on methylation in candidate genes correlated with total cholesterol showed that DNA methylation occurs in blood and adipose tissue. Results showed that high methylation in *FIAM, ABCG1, PLA2G7, NPC1*, and *MTHFR* and low methylation levels in DPP4 in peripheral blood result in high levels of total plasma cholesterol. In addition, high methylation levels in *ApoE-CpG-7, COL14A1-CpG2, LEP*, and *ADIPOQ* and low methylation levels in *ApoE- CpG1, 2, 10, 12, 13, ABCG1-CpGC3*, and *TCF7L2-CpG27* are associated with high levels of total cholesterol. No correlation exists between total cholesterol and DNA methylation in *IGF2, ABCA1, MCP-1, GALNT2, HMGCR*, and *BCL11A* (55).

Research on DNA methylation in candidate genes found that DNA methylation is correlated with LDL-C in visceral and placental adipose tissues. Results showed that high methylation levels in *ABCA1, TNF-α, LEP, ADIPOQ,* and *MTHFR* and in some areas of CpG in *FIAM* and low methylation levels in *ADRB3* and *NPC1* are associated with high LDL-C concentrations. LDL-C concentrations are also positively correlated with methylation in *MMP9-CpG1, APOE-CpG9,* and *GCK-CpG3* and negatively correlated with methylation in *MMP9-CpG4* and *TCF7L2-CpG27*. No association was found between LDL-C concentrations with methylation in *CD14, Et-1, HERV-W, iNOS, IGF2, MCP-1, ABCG1, GALNT2, HMGCR,* or *DPP4* (55,57).

Other studies in the CpG area in *ABCG1, SRBF1,* and *LINC00263* found that methylation is positively correlated with lipoprotein ApoB concentrations, total serum triglycerides, and mono unsaturated fatty acid (MUFA). Other groups in the CpG area in *CPT1A* and *TXNIP* are negatively correlated with lipoprotein ApoB, HDL-C, total serum triglycerides, and MUFA levels (58).

6. Environments influence DNA methylation

Physical activity is a therapeutic strategy to increase lipid metabolism. In adipose tissue, healthy adult males with 6 months of physical exercise show increased DNA methylation. Research on DNA methylation and mRNA expression in genes including histone deacetylase 4 (*HDAC4*) and nuclear receptor corepressor 2 (*NCOR2*) demonstrated that silencing these genes in adiposity promotes lipogenesis. PGAC1a is a key regulator during physical exercise. Hypomethylation of the PGC1a promoter area upregulates mRNA expression in skeletal muscles. In addition, low methylation levels occur in the CpG coagulation factor II receptor like 3 (*F2RL3*) area of smoking subjects. Methylation in this gene is also associated with coronary heart disease (59).

In a study using adipose tissue, 21 gen show differential methylation in the CpG locus in response to exercise. This study suggests that exercise induces genome-wide changes in DNA methylation in human adipose tissue, potentially affecting adipocyte metabolism.

Non-nutritional diets, such as genistein and polyphenols, can also modify epigenetic signs and induce persistent changes in gene expression. The expression of altered genes induced by diet has a very low intensity and is difficult to distinguish. Some nutrients serve as ligands and bind to certain receptors, thus directly regulating the expression of the target gene (60). Unsaturated fatty acids influence PPARG gene expression, thereby affecting fatty acid metabolism and oxidation. The vitamin biotin is also involved in chromatin modification and gene silencing by causing the biotinylation of histone H4, green tea, cadmium, and zinc, which inhibit DNMT activity. Alcohol consumption affects DNMT expression, leading to altered methylation patterns.

In general, a limitation of DNA methylation studies is their case–control design. The occurrence of diseases is specific to a certain period, and the mechanism by which DNA methylation affects the pathogenesis of the disease remains unclear.

Conclusion

Environmental factors influence the expression or suppression of genes through epigenetic mechanism, especially by methylation in DNA promoter. Changes in the expression of these genes alter metabolism, leading to metabolic syndrome. The onset of metabolic syndrome can be inhibited by making lifestyle changes, such as regular exercise and consumption of food that inhibits DNA methylation.

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