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Epigenetic reprogramming in metabolic disorders: nutritional factors and beyond

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Abstract

Environmental factors (e.g., malnutrition and physical inactivity) contribute largely to metabolic disorders including obesity, type 2 diabetes, cardiometabolic disease, and nonalcoholic fatty liver diseases. The abnormalities in metabolic activity and pathways have been increasingly associated with altered DNA methylation, histone modification, and noncoding RNAs, whereas lifestyle interventions targeting diet and physical activity can reverse the epigenetic and metabolic changes. Here we review recent evidence primarily from human studies that links DNA methylation reprogramming to metabolic derangements or improvements, with a focus on cross-tissue (e.g., the liver, skeletal muscle, pancreas, adipose tissue, and blood samples) epigenetic markers, mechanistic mediators of the epigenetic reprogramming, and the potential of using epigenetic traits to predict disease risk and intervention response. The challenges in epigenetic studies addressing the mechanisms of metabolic diseases and future directions are also discussed and prospected.

Keywords

epigenetic marker; DNA methylation; reprogramming; metabolic disorders; intervention

1. Introduction

Epigenetic changes induced by environmental factors have been increasingly associated with metabolic disorders including obesity, type 2 diabetes (T2D), and cardiovascular diseases (CVD) [1–4]. Importantly, the epigenetic differences may reflect metabolic health disparity

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in monozygotic twins who are considered genetically identical [5–10]. It is now recognized that genetic variants account poorly for the observed heritability of disease risk (less than 2% for obesity and 5–10% for T2D) [11–14], and the missing heritability is being revealed in epigenetic studies that target the impacts of prenatal and postnatal environment on the epigenome and metabolic disease risks [15, 16]. For instance, nutritional deficiency or excess (either prenatally or postnatally) leads to epigenetic reprogramming that is significantly correlated with increased obesity incidence [15–17]. Thus, understanding metabolic disorders from an epigenetic perspective may offer new strategies to prevent or treat these diseases.

Epigenetic mechanisms identified in metabolic disorders include DNA modification (e.g., methylation and hydroxymethylation), histone modification (e.g., methylation, acetylation, ubiquitylation, SUMOylation, citrullination and ADP-ribosylation), and altered expression of noncoding RNAs [17–19]. The epigenetic variants can stimulate or suppress gene expression depending on the individual mechanism, e.g., the type of modification and location it affects [17–19]. In general DNA methylation at gene promoters and enhancers tends to silence the gene, while DNA methylation in the gene body promotes gene expression [20, 21]. DNA wraps around a histone protein core (i.e., an octamer composed of two copies of H2A, H2B, H3, and H4) to form a nucleosome, and modifications of histone may increase the exposure of DNA to modification or transcription factors in the regulation of gene expression [19, 22]. Methylation of H3 histone may harbor a repressive mark (e.g., H3K27me3) or an active mark (e.g., H3K4me3) near genes with poised transcription [23]. Noncoding RNAs such as long noncoding RNAs (lncRNA) and small noncoding RNAs (e.g., microRNAs) represent the third epigenetic mechanism that can interact with chromatin or directly regulate gene expression in metabolic disorders [17–19]. The coordinated epigenetic changes not only control gene expression, but in some case may regulate DNA repair and replication [17–19, 22, 24].

The epidemics of obesity and its comorbidities (e.g., T2D and CVD) have been attributed largely to positive energy balance [4, 25–27]. As one of the major contributors, malnutrition can alter epigenetic profile in obese or diabetic patients, and the impact can be passed on to their offspring for generations [15–17]. It was shown that high fat diet caused unique variations in chromatin and epigenome trans-generationally, and low-birthweight subjects had lower DNA methylation plasticity [28–32]. Interestingly, undernutrition during pregnancy or lactation (e.g., famine) also imposes epigenetic influence that increases the risks of the offspring developing obesity and T2D [15–17]. By contrast, physical activity has been effective to prevent obesity and T2D by boosting energy expenditure or balance [33–38], and is associated with robust epigenetic reprogramming [4, 16, 17, 39–42]. In this article, we will summarize the evidence of epigenetic reprogramming in metabolic disorders, primarily from human studies of the plasticity of DNA methylation (the best-studied epigenetic mechanism). We also discuss the mechanistic mediators of epigenetic reprogramming and the potential of DNA methylation marker in disease risk and intervention assessment.

2. Epigenetic reprogramming in metabolic disorders

DNA methylation traits are discovered increasingly in the tissues that undergo metabolic alteration in obese and diabetic patients, including adipose tissue, liver, skeletal muscle, and pancreas (Table 1). The epigenetic reprogramming involves critical pathways or regulatory processes such as: (1) insulin signaling (e.g., IRS1, IRS2, SORBS2) [10, 43–45]; (2) insulin secretion (e.g., PPARGC1A, CCND2, CILP2, FHL2, CDKN1A, PDE7B, SEPT9 and EXOC3L2) [21, 46–48]; (3) adipocyte differentiation, transdifferentiation, and function (e.g., PPARG, PPARGC1A, PRDM16, LEP, ADIPOQ, HIF3A) [10, 49–55]; (4) mitochondrial function and redox regulation (e.g., PPARGC1A, TFAM, MT-ND6, CPT1A, TXNIP, SOD3) [46, 48, 49, 56–63]; (5) lipid and glucose homeostasis (e.g., SREBF1, ABCG1, CPT1A, SORBS2) [45, 48, 64]; (6) cytokine signaling and inflammation (e.g., SOCS3, ADIPOQ, ABCG1) [48, 53, 54, 64]; and (7) cell cycle, apoptosis and autophagy (e.g., DAPK3 and CDKN1A) [21, 65]. These pathways have been implicated in the pathogenesis of obesity and type 2 diabetes. For instance, adipocyte differentiation or expansion may contribute to increased adiposity and dysregulate cytokine secretion and signaling pathways, which is associated with chronic inflammation and insulin resistance [66, 67]. On the other hand, browning of white adipose tissue, where adipocyte transdifferentiation take places, may boost energy balance, prevent obesity and improve insulin sensitivity [68–71].

DNA methylation controls gene activity in cell differentiation, embryogenesis, and development, and unique DNA methylation patterns may distinguish one type of cell (or tissue) from other types [72]. Intriguingly, DNA methylation reprogramming in PPARGC1A (the gene encoding PGC1α, a key regulator of mitochondrial biogenesis and function) has been identified in different tissues from obese and diabetic patients (Table 1) [46, 49, 56] [57, 59–62]. Thus, epigenetic regulation of mitochondria may represent a common mechanism in metabolic changes across tissues. Indeed, functional alterations of mitochondria have been observed across tissues in obesity, T2D, cardiometabolic diseases, and nonalcoholic fatty liver diseases [4, 73–77]. In the adipose tissue mitochondrial malfunction dysregulates adipocyte differentiation, trans-differentiation, cytokine secretion [68, 78, 79]. In the liver and skeletal muscle, mitochondrial impairment leads to incomplete fatty acid oxidation, ectopic fat accumulation, and insulin resistance [80, 81]. In pancreatic beta-cells, mitochondrial dysfunction dampens ATP-dependent insulin secretion [82]. Consistently, PPARGC1A shows increased methylation but reduced gene expression in diabetic islets [46], skeletal muscle from sedentary individuals [60], nonalcoholic fatty liver [56, 57], and adipose tissues from subjects with high T2D risk [49]. The downregulated PPARGC1A gene expression is associated with reduced mitochondrial content in the target tissues [57, 60]. Furthermore, PPARGC1A hypermethylation was found to cause gene downregulation and lower mitochondrial content, where DNA methyltransferase 3B (DNMT3B) is induced to promote PPARGC1A methylation [60].

In addition to mitochondrial alteration, obese and T2D patients also show impairment in glucose and lipid metabolism [83]. Recent studies identified DNA methylation changes in the genes of ATP-binding cassette (ABC) protein family, particularly in *ABCG1* across tissues [48, 84]. The ABCG1 protein can remove excess cholesterol from peripheral tissues

and transporting it to the liver [85], and ablation of ABCG1 in mice leads to sterol accumulation, impaired glucose tolerance and insulin secretion, and inflammation of pancreatic β-cells [86]. Cross-tissue dysregulation of DNA methylation was also identified in *SREBF1*, the gene encodes for sterol regulatory element-binding transcription factor 1 (or sterol regulatory element-binding protein 1 (SREBP1), a key regulator of lipid homeostasis [48, 84, 87, 88]. The altered DNA methylation in *ABCG1* and *SREBF1* genes is associated with downregulation of mRNA levels in the skeletal muscle and liver from T2D individuals compared with health controls [48].

Noteworthy is tissue-dependent epigenetic reprogramming, nevertheless, which may also play important roles in tissue and systemic metabolic changes. As an endocrine organ and energy reservoir, adipose tissues in obese and diabetic patients show altered DNA methylation in adipose *PPARG* [10], *LEP* and *ADIPOQ* [53, 54], and *HIF3A* [44, 50–52]. Functionally, *PPARG* encodes for adipogenic regulator PPARγ that underpins adipocyte differentiation and lipid droplet growth [89–91]. *LEP* encodes leptin that is anorexigenic and proinflammatory, and its action can be counteracted by *ADIPOQ*-encoded hormone adiponectin [92]. In obese individuals, leptin is elevated and adiponectin reduced, which contributes to chronic inflammation, insulin resistance, impaired glucose and lipid metabolism [53, 66, 92, 93]. Epigenetic studies suggested that DNA methylation in *LEP* was correlated negatively with body mass index (BMI), suggesting a trend of hypomethylation of *LEP* in obesity; however, DNA methylation in *ADIPOQ* were correlated positively with BMI, suggesting a trend of hypermethylation of *ADIPOQ* in obesity [54]. Indeed, hypermethylation in *ADIPOQ* suppresses adiponectin expression in obesity, where DNA methyltransferase 1 (DNMT1) is induced by proinflammatory cytokines tumour necrosis factor (TNFα) and interleukin (IL)-1β to stimulate *ADIPOQ* methylation [53]. By contrast, *LEP* DNA methylation level is reduced in obese individuals, which tends to upregulate leptin expression [54, 94]. The reciprocal regulation of DNA methylation and gene expression of *LEP* and *ADIPOQ* accounts, at least in part, for the chronic inflammation and metabolic changes in obesity.

Differing from other tissues, white adipose tissue undergo rapid expansion in obesity, which induces hypoxic stress, adipocyte dysfunction, and dysregulated adipokines secretion [66, 95–97]. Activation of hypoxia inducible factor HIF1α promotes macrophage recruitment to adipose tissues and increases adipocyte-derived pro-inflammatory cytokines [51, 52, 95]. However, the role of HIF3α is unsettled. In line with HIF3α counteracting HIF1α [98–100], HIF3A (HIF3α encoding gene) expression in adipose tissue is inversely associated with serum level of inflammation marker C-reactive protein [51]. By contrast, ablation of adipose HIF3α protects mice from weight gain, improving glucose tolerance and insulin sensitivity, indicative of a pro-obesity role of HIF3α [101]. The complexity of HIF3α role in obesity is further demonstrated by epigenetic studies that reveal positive associations between HIF3A DNA methylation and BMI, whereas HIF3A mRNA is associated negatively with BMI and positively with insulin sensitivity [44, 50, 52]. Although HIF3A DNA methylation was inversely correlated with HIF3A mRNA [50], the relationship was not that straightforward in other studies [51, 52]. The discrepancy may arise from heterogeneity of adipose tissues and fat depot specific difference in angiogenesis and cell population [51, 102, 103].

Methylated DNA can be oxidized into hydroxymethylated DNA, which is known as an intermediate for DNA demethylation [104]. However, recent studies have revealed roles of DNA hydroxymethylation in DNA repair [105], epigenomic remodeling of enhancers to activate transcription [106, 107], and lineage commitment [108]. Dynamic hydroxymethylation of DNA has been identified in different human tissues such as brain, heart, skeletal muscle, and spleen [109, 110]. Acute exercise may elicit robust hydroxymethylation of DNA, which is associated with DNA demethylation and induction of exercise-responsive gene (e.g., nuclear receptor subfamily 4 group A member 3) in skeletal muscle or myotubes [109]. In human adipose tissues, hydroxymethylation of DNA shows depot-dependent differences, with higher level of hydroxymethylated DNA in visceral fat than in subcutaneous fat [111]. Importantly, the DNA hydroxymethylation in human adipose tissue was correlated with clinical variables (e.g., lipid parameters) [111], which was also observed in human blood samples [112]. The responses to physiological and pathophysiological cues reported in these studies suggest that DNA hydroxymethylation may play a role in metabolic regulation.

3. Mechanistic mediators of epigenetic reprogramming

Cross-sectional studies have provided solid evidence linking obesity or BMI to epigenetic reprogramming and altered expression of related genes [24, 44, 113–115]. Until recently was a cause-effect relationship revealed between BMI and DNA methylation by emerging longitudinal studies that were coupled with genetic association analyses or Mendelian randomization (MR) analysis, i.e., BMI and adiposity per se causal to altered DNA methylation [113, 114]. Employing a weighted genetic risk score that combined effects of single-nucleotide polymorphism (SNP) on BMI, Wahl et al. suggested that the predicted effects of BMI genetic risk score on DNA methylation at certain loci (e.g., ABCG1) were significantly correlated with observed effects, and the effect of BMI on DNA methylation was further corroborated by longitudinal follow-up analyses of the participants [114]. In another longitudinal analysis, childhood BMI was correlated with HIF3A DNA methylation in adolescence but HIF3A DNA methylation in childhood was not associated with BMI in adolescence, suggesting that childhood BMI may precede or determine the altered DNA methylation in adolescence [113]. These findings suggest a causal role for adiposity or obesity in altered DNA methylation (Figure 1).

At molecular level, obesity may mediate DNA methylation reprogramming by dysregulating insulin signaling [24, 65, 115], glucose [65, 116], fatty acids or lipid [60, 117–121], and inflammatory cytokines [53, 60]. Insulin was reported to increase DNA methylation in the gene body of DAPK3 (a gene involved in cell proliferation, apoptosis, and autophagy), and in T2D patients who are insulin resistant, DAPK3 methylation was downregulated [65]. Consistently, DNA methylation profile in the liver from non-alcoholic fatty liver disease (NAFLD) patients is correlated with insulin action [57, 122]. Additional evidence shows that insulin resistance is associated with reprogramming of mitochondrial DNA methylation (e.g., ND6, and D-loop) in obese individuals as well as of PPARGC1A DNA methylation in NAFLD patients, concomitant with reduced mitochondrial DNA copy number [24, 57, 115]. In a reciprocal manner, however, an increased glucose dampens DNA methylation in DAPK3 gene body, which might constitute a feedback loop with insulin resistance in the

control of the epigenome [65]. During pregnancy, fetal exposure to increased glucose (i.e., maternal hyperglycemia) leads to altered PPARGC1A DNA methylation in placenta samples and leptin level in cord blood [116]. Dysregulated leptin may arise from altered LEP promoter methylation in the adipose tissue in the offspring who had fetal exposure to hyperglycemia [123]. Currently, the molecular pathways by which insulin (or insulin resistance) and glucose induces DNA methylation reprogramming remains elusive, and it would be interesting to examine whether DNMT1 and DNMT3 are involved (Figure 1).

In addition to insulin and glucose, blood lipids were shown to potentially alter DNA methylation in circulating cells according to a stepwise MR analysis, which suggests that triglyceride induced differential methylation at three CpGs, LDL at one CpG, and HDL at two CpGs [117]. Furthermore, the differential methylation was associated with altered expression of genes that regulate triglycerides (e.g., CPT1A and SREBF1), LDL (e.g., DHCR24) and HDL (e.g., ABCG1) [117]. Experimental evidence from THP-1 monocyte cell culture shows that treatment with fatty acids (arachidonic and oleic acid) induces drastic changes in DNA methylation in monocytes [118]. It was found that circulating level of arachidonic acid was positively associated with global and PDK4-specific DNA methylation in adult men, while it is inversely associated HDAC4 methylation [119]. Importantly, arachidonic acid-induced DNA methylation phenotype was similar to that induced by palmitic acid in metabolic disorders (e.g., atherosclerosis, diabetes, obesity) [118]. However, the diets rich in linoleic acid or palmitic acid were found to affect DNA methylation differently in human adipose tissue [121]. In human pancreatic islets, palmitate treatment leads to drastic epigenetic reprogramming, including global DNA methylation profile, DNA methylation at CpG island shelves and shores, 5′UTR, 3′UTR and gene body regions, and accounting for differential expression of 290 genes [120]. Together, the MR analyses and experimental evidence reveal a causal role for lipid or fatty acids in DNA methylation reprogramming.

The enzymes that regulate DNA methylation include DNA methyltransferases (DNMT1, DNMT3A and DNMT3B) and ‘demethylating’ proteins, i.e., the ten-eleven translocation (TET) family of DNA dioxygenases (TET1, TET2 and TET3) [124, 125]. DNMT3A and DNMT3B catalyze *de novo* methylation of DNA, which is maintained by a DNMT1-mediated copying mechanism, or is removed by TET-mediated reductive reactions [125]. The pathophysiological role of theses enzymes was demonstrated by PPARGC1A methylation reprogramming in metabolic disorders. Genetic variation in TET2 has been associated with altered PPARGC1A-methylation and transcript level in the liver from patients with nonalcoholic fatty liver disease [56]. Further, DNMT3B promotes DNA methylation of PPARGC1A, which underlies fatty acid- or proinflammation cytokine (TNFα)-induced hypermethylation of PPARGC1A, transcript downregulation, and reduced mitochondrial density in human skeletal muscle cells [60]. Proinflammatory cytokines (e.g., TNFα and IL1-β) can also induce hypermethylation in ADIPQ via DNMT1, which downregulates adiponectin secretion from adipocytes and contributes to systemic metabolic changes in mice [53]. Given that obese and T2D subjects have chronic inflammation and elevated fatty acids and glucose in the circulation, DNMT1 and DNMT3B may account largely for the observed reprogramming in DNA methylation [53, 60, 120]. Indeed, skeletal muscle from T2D individuals showed hypermethylation in PPARGC1A and reduced

PPARGC1A mRNA and mitochondrial DNA content compared with normal glucose-tolerant counterparts [60].

Overall, the mechanism of epigenetic reprogramming and its role in metabolic disorders (e.g., obesity, T2D, and NAFLD) remains largely undefined. However, DNMT1 and DNMT3 may serve as the key mediators. Figure 1 summarizes the potential connections among the identified mediators in the induction of DNA methylation reprogramming, with critical questions to be addressed: (1) what is the molecular pathway leading glucose and insulin to DNA methylation [65, 116]? It is interesting to note that insulin and glucose can alter DNA methylation in muscle DAPK3 [65] but not muscle PPARGC1A [60], and it is unknown what constitutes the gene- or locus-specific mechanism regulating muscle DNA methylation. (2) What are the receptors or molecular targets by which pro-inflammatory cytokines or fatty acids regulate DNMT1 and DNMT3 [53, 60]? TNFα induces DNMT3B but not DNMT1 or DNMT3A in skeletal muscle DNA methylation reprogramming [60]; by contrast, TNFα tends to induces DNMT1 other than DNMT3A or DNMT3B in adipose DNA methylation reprogramming [53]. It will be important to define the determinant(s) of tissue-dependent induction of DNMTs by TNFα. (3) Is DNA methylation reprogramming the cause or result of metabolic disorders? Although adiposity was shown to cause DNA methylation alteration, the other way around was also true because DNA methylation in certain locus may predict adiposity [114, 126]. For instance, the DNA methylation profiles of both NFATC2IP and PPARGC1A have been found to predict adiposity [114, 126]. Therefore, it is tempting to speculate that a feedback loop may exist between adiposity and DNA methylation reprogramming (Figure 1).

4. Epigenetic markers in disease risk and intervention assessment

The recognition of epigenetic reprogramming in metabolic diseases has stimulated the interest in identifying epigenetic markers for diagnosis and intervention assessment [24, 39, 115, 127, 128]. To this end, blood samples are being widely tested because it is more accessible than other tissues (Table 2). Cross-tissue examination of epigenetic changes in recent studies demonstrated considerable tissue equivalence between blood and other tissues, and suggested that epigenetic reprogramming in the blood might serve as a surrogate marker for metabolic disorders [44, 48, 52, 54.Bacos, 2016 #1023, 64, 114, 129–131].

In patients with metabolic disorders, altered DNA methylation profiles have been identified in whole blood and sub-type of blood cells (e.g., leukocytes, mononuclear cells, and CD4+ T cells) (Table 2). Of pathophysiological significance, the genes involved in lipid metabolism (e.g., CPT1A, SREBF1, and ABCG1) and inflammation (e.g., SOCS3) consistently show DNA methylation reprogramming (see the details and references in Table 2). These findings cast epigenetic light on the pathogenesis of metabolic diseases because such medical conditions (e.g., obesity, T2DM, and cardio-metabolic diseases) are characterized by dyslipidemia and chronic inflammation [53, 66, 67, 92, 93, 95–97]. In addition, the epigenetic changes appear to be systemic, as altered DNA methylation profiles in these genes (SREBF1, ABCG1, and SOCS3) were identified in adipose tissue [48, 63, 64], liver [48], skeletal muscle [48], and pancreatic islets [48]. In support of the link of mitochondrial dysfunction to metabolic disorders[74, 83, 132], DNA methylation reprogramming has been

observed in mitochondrial genome (e.g., D-loop and ND6) or mitochondrially related genes (e.g., PPARGC1A) in blood samples from obese and prediabetic individuals [24, 115, 126].

The potential of DNA methylation marker in identifying high-risk individuals and predicting metabolic disease incidence has been tested in several population studies. In a recent report, 187 DNA methylation markers in the blood were examined, 62 of which (including ABCG1 gene) were significantly associated with T2D incidence [114]. In addition, the DNA methylation risk score can predict incident T2D in two cohort studies, indicating a relative risk of 2.29 per 1 standard deviation change in methylation risk score ($p = 4.2 \times 10^{-52}$) in the LOLIPOP study, and 2.51 ($p = 5.7 \times 10^{-4}$) in the KORA study [114]. By examining the DNA methylation at specific loci in the LOLIPOP study, Chambers et al. found that the relative risk for future T2D incidence was 1·09 ($p=1.3 \times 10^{-17}$) per 1 percent increase in DNA methylation of ABCG1, 0.94 ($p=4.2 \times 10^{-11}$) of PHOSPHO1, 0.94 ($p=1·4 \times 10^{-9}$) of SOCS3, 1.07 ($p=2·1 \times 10^{-10}$) of SREBF1, and 0·92 ($p=1·2 \times 10^{-17}$) of TXNIP [84]. In the Botnia prospective study, blood DNA methylation at the ABCG1 locus also indicated an increased risk of future T2D, although smaller sample size and differences in study design did not allow the authors to replicate the associations with other loci as observed in the LOLIPOP study [48, 84]. Of note, the DNA methylation risk score predicted the risk of future T2D beyond traditional risk factors (e.g., BMI and waist–hip ratio), suggesting that DNA-methylation marker might be used to identify high-T2D-risk individuals who have normal adiposity or metabolically unfavourable adiposity [84, 114]. Indeed, it was shown that DNA methylation changes in the mitochondria may reflect early stage of prediabetes programming and have the potential to distinguish metabolically unhealthy obesity (MUO) from metabolically healthy obesity (MHO) [115, 133].

Another promising perspective of epigenetic marker resides in the potential to predict the response to interventions. In an 8-week obesity intervention using low calorie diet, the responders had lower DNA methylation levels (by 47%, $p<0.05$) in the promoter of LEP than the non-responders at baseline, suggesting that DNA methylation in LEP might predict the susceptibility to weight loss by dietary intervention [134]. The epigenetic predictors were also discovered in a 10-week lifestyle and nutritional educational weight loss program, where high and low responders among the overweight and obese adolescents showed differential methylation in 5 regions located in/near AQP9, DUSP22, HIPK3, TNNT1, and TNNI3 genes [135]. In fact, weight loss interventions through diets, exercise, and bariatric surgery can also induce robust reprogramming of DNA methylation [134, 136]; [41, 42, 59, 137–141]. The post-intervention methylation score was significantly associated with body fat mass loss, weight loss, and body mass index-standard deviation score [135]. Successful weight loss maintainers for up to 3 years after intervention have DNA methylation patterns that are similar to normal weight individuals but different from obese counterparts [128].

As the well-recognized epigenetic marker across tissues (Table 1, Table 2), PPARGC1A methylation is highly responsive to exercise and bariatric surgery [59, 138]. In individuals with a sedentary lifestyle, acute exercise can induce a marked hypomethylation in the promoter of PPARGC1A, which is concomitant with an exercise dose-dependent upregulation of PPARGC1A transcript [138]. A beneficial effect was also documented for maternal exercise, which reverses high fat diet (HFD)-induced PPARGC1A

hypermethylation and downregulation of PPARGC1A transcript in the offspring [61]. In addition, dysregulated DNA methylation in PPARGC1A promoter in obese patients can be normalized 6 months after Roux-en-Y gastric bypass (RYGB) surgery, to a similar level observed in healthy individuals [59]. Consistently, dysregulated PPARGC1A gene expression was restored to the level of healthy controls [59]. Thus, PPARGC1A methylation is a sensitive epigenetic marker in response to weight loss interventions.

5. Conclusions

DNA methylation reprogramming is generally associated with transcript expression in metabolic disorders, which has revealed an epigenetic link to insulin secretion and signaling, glucose and lipid metabolism, adipocyte differentiation and trans-differentiation, mitochondrial function, inflammation, cell death and autophagy. Although certain epigenetic traits show tissue dependence (e.g., DNA methylation changes in adipocytokine genes LEP and ADIPOQ), mounting evidence has established tissue equivalence for epigenetic markers that regulate mitochondrial homeostasis (e.g., PPARGC1A) among adipose tissue, liver, skeletal muscle, pancreas and the blood samples (Tables 1 and 2). Tissue equivalence is also being revealed for epigenetic changes in genes that mediate lipid metabolism (e.g., ABCG1 and SREBF1) [48], hypoxia response (HIF3A) during obesity [50–52, 64, 142], and mitochondrial function (e.g., ND6) [58, 115] between blood and other tissues. As such, the epigenetic changes (e.g., ABCG1 and SREBF1) in the blood have been tested and shown promising potential as surrogate markers for metabolic diseases [48, 84]. In addition, the epigenetic traits (e.g., DNA methylation in PPARGC1A) respond robustly to lifestyle and surgical interventions [59, 61, 138], underscoring the potential of using epigenetic markers to assess disease risk and intervention efficacy [128, 134, 135].

The mechanism underlying epigenetic changes in metabolic disorders remains largely undefined. The literature suggests that DNA methylation reprogramming can be induced by insulin, glucose, fatty acids or lipids, and inflammatory cytokines [53, 60, 65, 116–120]. In particular, DNMT1 and DNMT3 mediate fatty acid- or inflammatory cytokine-induced DNA methylation changes [53, 60]. Further studies are warranted to dissect the pathways by which DNMT1 and DNMT3 are induced, and whether it is the mechanism shared by insulin- and glucose-induced epigenetic reprogramming. As TET proteins are responsible for DNA demethylation, it would be of interest to examine whether and how TET proteins are involved in the epigenetic reprogramming in metabolic disorders. Regardless of the well-established association between epigenetic changes and metabolic disorders, the evidence examining a cause-effect relationship has just emerged [53, 60, 114, 126]. Therefore, large-scale longitudinal studies of human subjects and functional characterization of epigenetic changes through post-developmental modulation in cell or animal models are critical to address these questions.

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Abbreviations

ABCG1	ATP-binding cassette sub-family G member 1
ADIPOQ	adiponectin encoding gene
CPT1A	Carnitine palmitoyltransferase 1 A
CCND2	Cyclin D2
CDKN1A	cyclin-dependent kinase inhibitor 1
CILP2	Cartilage Intermediate Layer Protein 2
CVD	cardiovascular diseases
DAPK3	Death-associated protein kinase 3
D-loop	displacement loop
DNMT1	DNA methyltransferase 1
DNMT3B	DNA methyltransferase 3B
EXOC3L2	exocyst complex component 3 like 2
FHL2	four and a half LIM Domains 2
HFD	high fat diet
HIF1α	hypoxia inducible factor 1α
HIF3a	hypoxia inducible factor 3α
IL1β	interleukin (IL)-1β
lncRNA	long noncoding RNAs
IRS1	insulin receptor substrate 1
IRS2	insulin receptor substrate 2
LEP	Leptin encoding gene
NAFLD	non-alcoholic fatty liver disease
ND6	NADH:ubiquinone oxidoreductase core subunit 6
PDE7B	phosphodiesterase 7B
PPARG	peroxisome proliferator-activated receptor gamma
PPARGC1A	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PRDM16	PR domain containing 16
RYGB	Roux-en-Y gastric bypass

SEPT9	septin 9
SNP	single-nucleotide polymorphism
SOCS3	suppressor of cytokine signaling 3
SOD3	superoxide dismutase 3
SORBS2	sorbin and SH3 domain containing 2
SREBP1	sterol regulatory element-binding protein 1, also known as SREBF1
SREBF1	Sterol regulatory element-binding transcription factor 1, also known as SREBP1
T2D	type 2 diabetes
TET	ten-eleven translocation family of DNA dioxygenases
TNFα	tumour necrosis factor α
TXNIP	Thioredoxin-interacting Protein.

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Highlights

- Abnormalities in metabolic activity and pathways are associated with DNA methylation reprogramming.
- Metabolic disorders have shown cross-tissue epigenetic changes among the liver, skeletal muscle, pancreas, adipose tissue, and blood samples.
- Adiposity, fatty acids or lipids, pro-inflammatory cytokines (e.g., TNFα and IL-1β), insulin, and glucose may induce DNA methylation reprogramming, with DNMT1 and DNMT3 as the key mediators in certain cases.
- DNA methylation changes (e.g., PPARGC1A and ADIPOQ) may serve as sensitive epigenetic markers to predict metabolic disease risk and intervention responses.

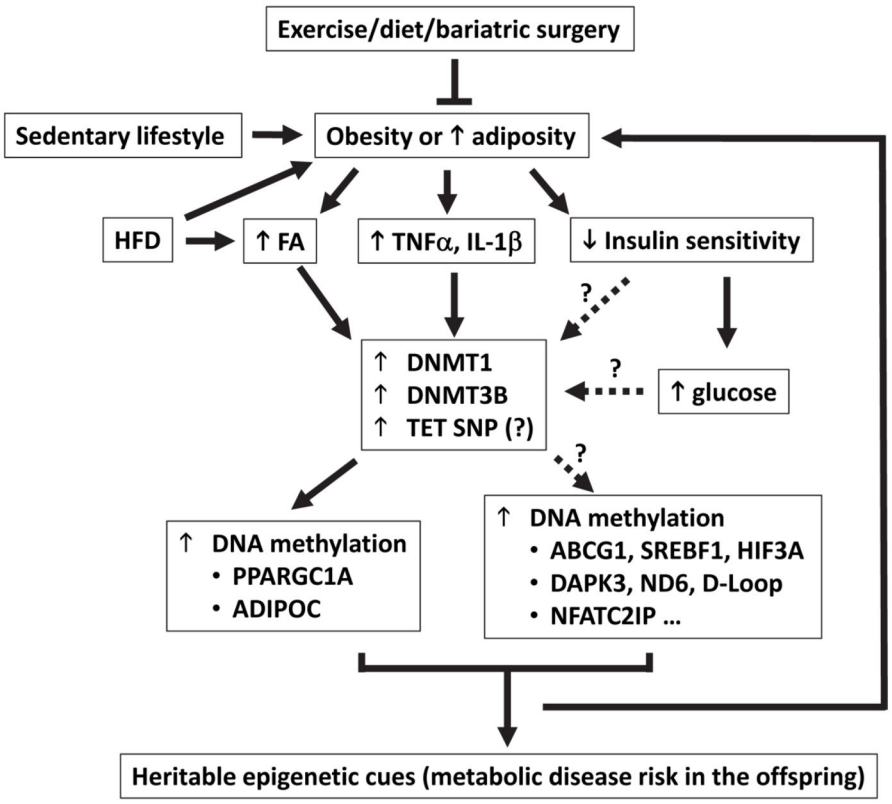

Figure 1.

The potential pathways that link the identified mediators to altered DNA methylation in metabolic disorders. Obesity due to sedentary lifestyle and energy overconsumption (e.g., HFD) is characterized by elevated fatty acids (FA), glucose, pro-inflammatory cytokines (TNFa, IL-1b), insulin resistance (or reduced insulin sensitivity), and resultant hyperglycemia (increased blood glucose). DNMT1 and DNMT3 were shown to account for DNA methylation reprogramming induced by FA, TNFa, and IL-1b in certain genes such as PPARGC1A and ADIPOC. However, it is largely unknown whether this represents a common mechanism for altered DNA methylation in other genes. In fact, TNFα induces DNMT3B in the regulation of skeletal muscle DNA methylation, whereas TNFα induces DNMT1 in adipose DNA methylation reprogramming, suggestive of a tissue-dependent selective induction of DNMTs by TNFα. Insulin and glucose alters DNA methylation of DAPK3 but not PPARGC1A in the muscle; whether and how DNMT1 or DNMT3 is involved and what accounts for the gene- or locus-specific DNA methylation reprogramming remains unknown. Genetic variant in TET2 is associated with altered PPARGC1A DNA methylation in fatty liver disease, and studies are need to examine whether TET2 SNP is related to dysregulated FA, pro-inflammatory cytokines, insulin signaling, and glucose. Longitudinal studies and MR analysis suggest that adiposity may cause DNA methylation reprogramming (e.g., in ABCG1 and HIF3A), while DNA methylation profiles (e.g., in PPARGC1A and NFATC2IP) can also predict adiposity. Maternal obesity confers epigenetic impacts on metabolic disease risk in the offspring, but maternal exercise may normalize DNA methylation (e.g., PPARGC1A hypermethylation) in the offspring. To this end, weigh

loss intervention through exercise, diets or bariatric surgery have been shown to reverse the dysregulation of DNA methylation in subjects with metabolic disorders.

Table 1

DNA methylation reprogramming in metabolically critical tissues

Tissue type*	Medical conditions	Genes that undergo DNA methylation reprogramming	Physiological or pathophysiological relevance	References
Adipose tissue	Obesity	5529 differentially methylated DNA sites for 2223 differentially expressed genes	25 % genes linked to adipogenesis, 19 % to insulin signaling, 27 % to lipolysis	[143]
	T2D	15627 differentially methylated DNA sites covers 7046 genes including PPARG, KCNQ1, TCF7L2, and IRS1	Insulin signaling, adipogenesis, and metabolism.	[10]
	Obesity	ADAMST4, ANGPT2/4, AOC3, AQP7, CETP, DOCK9, LIPE, SOD3, and TIMP4.	Adipogenesis/adiposity, redox, angiogenesis, glycaemia control, and lipolysis	[63]
	Obesity, insulin resistance	COL5A1, GAB1, IRS2, PFKFB3 and PTPRJ	Integrin cell surface interactions and insulin signaling	[43]
	Overweight, obesity, T2D, and aging	FHL2, NOX4, PLG, ELOVL2, KLF14, GLRA1, FTO, ITIH5, CCL18, MTCH2, IRS1, and SPP1, HIF3A	Glucose and fatty acid metabolism, mitochondrial function, oxidative stress, insulin signaling, chemokine signaling, adipocyte differentiation	[44]
	Obesity, T2D, and first-degree relatives of T2D	HIF3A	Glucose and amino acid metabolism, apoptosis, proteolysis, p53 and PPAR signaling, and adipocyte differentiation/adiposity	[50–52]
	High-T2D risk due to low birth weight	PPARGC1A	Mitochondrial biogenesis, energy expenditure and balance, browning of white adipose tissue	[49]
	Obesity	SORBS2 and ETV6	Insulin mediated translocation of GLUT4	[45]
	T2D	ABCG1, and SREBF1	Lipogenesis, dyslipidemia, cytokine signaling, redox and insulin resistance	[48]
	Overweight, and obesity	CPT1A, ABCG1, LYS6GE, KDM2B, RALB, PRRL5, LGALS3BP, C7orf50, PBX1, EPB49 and BBS2	Mitochondrial uptake of long-chain fatty acids and triglyceride metabolism; macrophage cholesterol and phospholipids transport, and lipid homeostasis; immune function and inflammatory pathways	[64]
	Severe obesity, diet induced obesity	LEP and ADIPOQ	Food intake, inflammation, insulin sensitivity, glucose and lipid homeostasis, energy balance	[53, 54]
Liver	Overweigh, obesity, and T2D	ABCG1, PHOSPHO1, SOCS3, SREBF1, and TXNIP	glucose and lipid homeostasis, redox, HDL-mediated increase in insulin secretion	[48]
	T2D	251 differentially methylated sites covering	Inflammatory response, insulin sensitivity in liver,	[55]

Tissue type*	Medical conditions	Genes that undergo DNA methylation reprogramming	Physiological or pathophysiological relevance	References
		GRB10, ABCC3, MOGAT1, and PRDM16, and 29 genes showing differential gene expression besides DNA methylation, including PPP1R1A, RIPK4, H19, TICAM1, MYH10, and RAD50	growth and metabolism, hepatic glycogen synthesis and glucose homoeostasis, fatty acid oxidation, energy homeostasis	
	Hepatosteatosis, nonalcoholic steatohepatitis	DPP4	Signal transduction, glucose and lipid homeostasis	[144]
	Obesity, nonalcoholic fatty Liver disease	DNA methylation ages	Mitochondrial function, insulin resistance, nonalcoholic fatty Liver disease activity score and liver cancer	[145]
	Obese and T2D	PRKCE, ABR, PDGFA, ARHGEF16, ADCY6, RPS6KA1, CTBP1, CCND1, WNT11, and ATF-motifs	Insulin signaling, hepatic glycolysis, de novo lipogenesis	[146]
	Nonalcoholic Fatty Liver Disease	TET, PPARGC1A, TFAM, and MT-ND6	Mitochondrial biogenesis and function, oxidative stress, apoptosis, insulin resistance, lipid metabolism	[56–58].
	Obesity, T2D, non-alcoholic steatohepatitis	LDHB	Glycolysis, cancer development and metastasis	[122]
Skeletal muscle	Obesity, T2D, or low birth weight	PPARGC1A and PDK4	Mitochondrial function, age-associated metabolic dysfunction, inflammation, and dyslipidemia	[59–62]
	T2D	DAPK3	Cell proliferation, apoptosis, and autophagy, responding to insulin and glucose in a reciprocal manner	[65]
	Overweigh, obesity, and T2D	ABCG1, PHOSPHO1, SOCS3, SREBF1, and TXNIP	glucose and lipid homeostasis, redox, HDL-mediated increase in insulin secretion	[48]
Pancreas	T2D	PPARGC1A	Mitochondrial biogenesis and function, reduced in insulin secretion	[46]
	Aging, genetic risk for T2D, pre-diabetes	CCND2, CILP2, FHL2, GNPNAT1, HLTF, KLF14, PBX4, SH2B3, SLC6A4, TCF7, and ZNF518B	Mitochondrial function, altered insulin secretion and glucose homeostasis	[47]
	T2D	Differential DNA methylation in 853 genes, 102 of which were differentially expressed in T2D islets: e.g., CDKN1A, PDE7B, SEPT9 and EXOC3L2	Cell cycle, β-cell mass expansion β-cells and α-cells function, glucagon and insulin secretion, glucose homeostasis	[21]
	Overweigh, obesity, and T2D	ABCG1, SOCS3, SREBF1, and TXNIP	glucose and lipid homeostasis, redox, HDL-	[48]

Tissue type*	Medical conditions	Genes that undergo DNA methylation reprogramming	Physiological or pathophysiological relevance	References
			mediated increase in insulin secretion	
	T2D	PDX1, TCF7L2, ADCY5, NR4A3, PARK2, PID1, SLC2A2, SOCS2, and more	β-cell proliferation, mitochondrial function, and insulin secretion	[147]

*It also include the major cell type, such as adipocytes from adipose tissues, hepatocytes from liver, myotubes from skeletal muscle, and β-cells from pancreas.

Table 2

DNA methylation reprogramming in blood samples

Samples	Medical conditions	Genes that undergo DNA methylation reprogramming	Physiological or pathophysiological relevance	References
Whole blood	Childhood obesity and cardiometabolic disease risk	PPARGC1A	Mitochondrial biogenesis and function, adiposity prediction	[126]
	Overweight, T2D, and first-degree relatives of T2D	HIF3A	Glucose and amino acid metabolism, apoptosis, proteolysis, p53 and PPAR signaling, and adipocyte differentiation/ adiposity	[50, 52]
	Overweight, Obesity	LEP and ADIPOQ	Food intake, inflammation, insulin sensitivity, glucose and lipid homeostasis, energy balance	[54, 148]
	Overweight, obesity, T2D, and aging	FHL2, NOX4, ELOVL2, FHL2, KLF14 and GLRA1	Fatty acid metabolism, mitochondrial function, oxidative stress, chemokine signaling	[44]
	Overweigh, obesity, and T2D	ABCG1, PHOSPHO1, SOCS3, SREBF1, TXNIP	Nutrient sensing/ metabolism, redox regulation, insulin secretion, mitochondrial function, oxidative stress, lipid homeostasis	[48, 84]
	Obesity	FYN, PIWIL4, and TAOK3	Adipocyte proliferation, differentiation, and senescence, insulin signaling or resistance, inflammation, JNK-MAPK signaling, energy expenditure	[149]
	T2D	IGFBP-1	Interaction with insulin-like growth factor, insulin resistance	[150]
	Overweight, obesity, siblings of breast cancer patients	ANGPT4, RORC, SOCS3, FSD2, XYLT1, ABCG1, STK39, ASB2 and CRHR2	Inflammatory and cytokine signaling, angiogenesis, lipid metabolism, leptin resistance, cellular stress	[151]
	Overweight, obesity, Cardiometabolic Disease	BCG1, CPT1A, LGALS3BP, DHCR24, PHGDH, SARS, NOD2, CACNA2D3, HIF3A, SLC1A5, and SREBF1	Energy homeostasis (glycolysis, lipogenesis, mitochondrial fatty acid oxidation), adipogenesis, immune response, amino acid synthesis, cardiac conduction	[152]
	Cardiometabolic disease	HIF3A, CPT1A and ABCG1	Adipogenesis, response to hypoxia, macrophage cholesterol and phospholipids transport, glucose, insulin, lipid homeostasis	[64]
	T2D	TXNIP, ABCG1 and SAMD12	Redox regulation, glucose metabolism, lipid homeostasis	[153, 154]
	T2D and Cardio-metabolic disease	CPT1A and ABCG1	Mitochondrial fatty acid oxidation, macrophage cholesterol and	[155]

Samples	Medical conditions	Genes that undergo DNA methylation reprogramming	Physiological or pathophysiological relevance	References
			phospholipids transport, and lipid homeostasis	
	T2D	CPT1A, DQX1, SREBF1, SBNO2, PRR5L, LY6G6E, TXNIP	Mitochondrial uptake of fatty acids, triglyceride metabolism, cholesterol homeostasis, redox regulation.	[156]
	Obesity and pre-diabetes	MT-ND6 and D-loop	Mitochondrial replication and function	[24, 115, 133]
	Adiposity-related metabolic traits and T2D	ABCG1, LPIN1, HOXA5, LMNA, CPT1A, SOCS3, SREBF1, and PHGDH	Mitochondrial uptake of fatty acids, triglyceride metabolism, cholesterol homeostasis, Inflammatory and cytokine signaling	[114]
	Obesity	HIF3A	Responses to hypoxia, adipose differentiation, liver diseases	[142]
Peripheral blood leukocytes	Obesity	CPT1A, SREBF1, ABCG1, ARID1B, TOP1	Mitochondrial fatty acid oxidation, triglyceride metabolism, macrophage cholesterol and phospholipids transport	[157]
	Obesity	SOCS3	Regulation of cytokine signaling (insulin, leptin, growth hormone, IL-6, prolactin, and interferon), inflammation, energy balance	[158]
Peripheral blood mononuclear cells	Obesity	ADAMTS2, FIP1L1, SAMD4A,	Procollagen processing, connective tissue disease	[43]
	Cardiometabolic disease	HIF3A, CPT1A and ABCG1	Adipogenesis, response to hypoxia, macrophage cholesterol and phospholipids transport, glucose, insulin, lipid homeostasis	[64]
CD4+ T cells	Cardiometabolic disease	CPT1A, PHGDH, CD38	Mitochondrial uptake of fatty acids, serine biosynthesis, cellular growth, immunology	[159, 160]