

**ABSTRACT:** Living eukaryotic systems evolve delicate cellular mechanisms for responding to various environmental signals. Among them, epigenetic machinery (DNA methylation, histone modifications, microRNAs, etc.) is the hub in transducing external stimuli into transcriptional response. Emerging evidence reveals the concept that epigenetic signatures are essential for the proper maintenance of cellular metabolism. On the other hand, the metabolite, a main environmental input, can also influence the processing of epigenetic memory. Here, we summarize the recent research progress in the epigenetic regulation of cellular metabolism and discuss how the dysfunction of epigenetic machineries influences the development of metabolic disorders such as diabetes and obesity; then, we focus on discussing the notion that manipulating metabolites, the fuel of cell metabolism, can function as a strategy for interfering epigenetic machinery and its related disease progression as well.

**KEYWORDS:** epigenetics, DNA methylation, histone modifications, microRNA, cellular metabolism, metabolites

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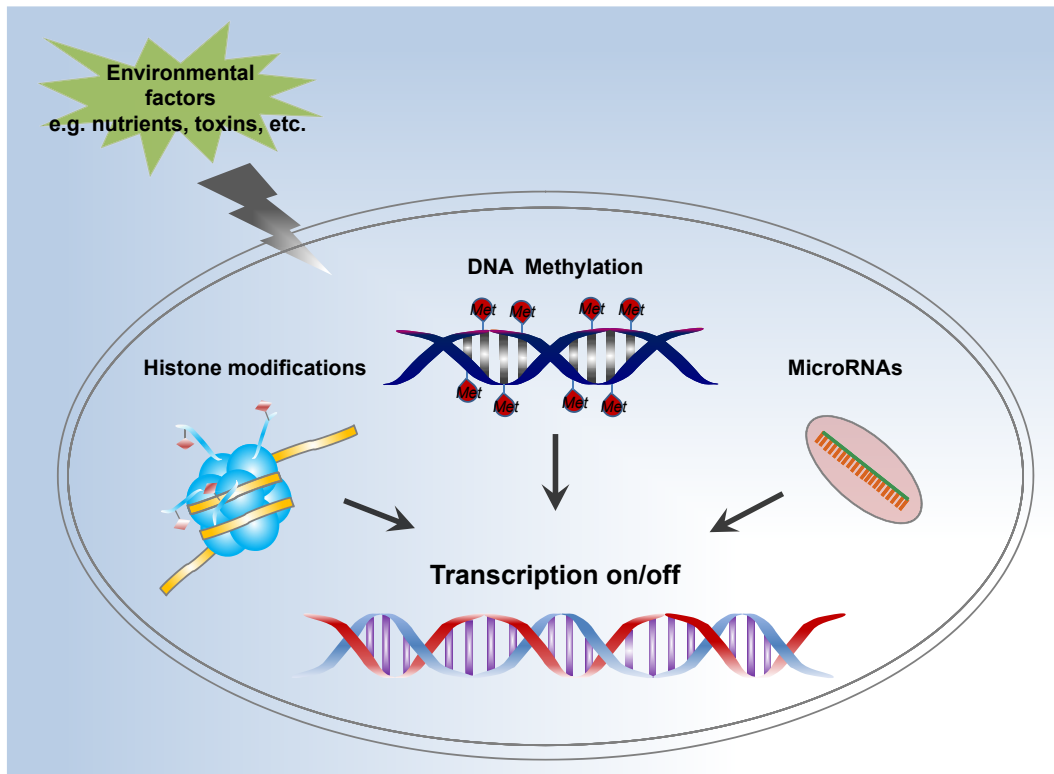
## Epigenetics

In biology, epigenetics is characterized by regulations of gene expression without alteration of the underlying DNA sequence.<sup>1,2</sup> In epigenetic manifestations, external or environmental factors (including nutrition, stress, toxins, and medical history) play an important role in regulating the expression of certain genes.<sup>3</sup> Hence, epigenetic investigations aim to understand how external factors regulate gene expression, and even phenotypic traits. Actually, the term epigenetics, with the prefix “epi” taken from the Greek language (meaning outside of, or around), emerged in the 1990s. Until 2008, the formulated definition of epigenetic traits was present as a stably heritable phenotype without changes in DNA sequences at a Cold Spring Harbor meeting.<sup>4</sup> During the past 15 years, plenty of cases and mechanisms are discovered and studied in the field of epigenetics. Among them, three major mechanisms are categorized by biologists to instruct epigenetic regulations (Fig. 1): DNA methylation, histone posttranslational modifications (PTMs), and noncoding RNAs.<sup>2</sup>

**DNA methylation.** DNA methylation is among the best studied and characterized epigenetic modifications. A methyl group is added to the C-5 position of a cytosine adjacent to a guanine residue (CpG dinucleotides), which normally leads to gene suppression.<sup>2</sup> In mammals, the CpGs are predominately methylated. However, the CpG islands, which locate in the promoter region of housekeeping and developmental regulator genes with dense CG distribution, are largely resistant to DNA methylation. During the progression of diseases, CpGs

of some key genes are reported to be abnormally hyper- or hypomethylated, which further result in transcriptional misregulation.<sup>5</sup> It is well demonstrated that in mammalian cells, DNA methylation is performed by DNA methyltransferases DNMT1, DNMT3A, and DNMT3B. Among them, DNMT1 propagates DNA methylation patterns during DNA replication, while 3A and 3B are involved in establishing de novo patterns of DNA methylation during development and cell fate determination.<sup>6,7</sup> DNA can also be demethylated through several enzymatic reactions. For instance, the 10 to 11 translocation (TET) proteins can mediate the oxidation of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), finally leading to DNA demethylation.<sup>8</sup>

**Histone PTMs.** Chromatin is a macromolecular structure that consists of DNA, protein, and RNA. DNA wraps around histone octamer to form nucleosomes, the fundamental unit of chromatin. Each histone octamer involved in the organization of nucleosomes contains two copies of four histones (H2A, H2B, H3, and H4). The precise structure of a nucleosome has been illustrated, and the functions of these protein–DNA or protein–protein interactions are suggested to be important for many cellular processes.<sup>9,10</sup> Since chromatin is usually packed with nucleosomes, which is believed to be a challenge for transcription accessibility, chromatin should be remodeled to allow the access of transcription machinery to DNA.<sup>11</sup> In the past few decades, compelling evidences suggest that histone modifications are able to change chromatin structure and are associated with both transcriptional



**Figure 1.** Mechanisms of epigenetic modifications. Cell transduces the environmental changes (eg, nutrients, toxins, etc.) into epigenetic modifications including DNA methylation, histone PTMs, and noncoding RNAs (especially the microRNAs), which eventually turn certain genes on or off and regulate the transcription process without changing DNA sequence.

activation and repression.<sup>12</sup> Therefore, the chromatin features are essential for the molecular biologist to analyze the transcriptional regulations and cellular status.<sup>13–17</sup>

In general, histone modifications mainly include acetylation, methylation, phosphorylation, and ubiquitination. Recently, some novel modifications are identified by tandem mass spectrometry (MS/MS), such as histone lysine GlcNAcylation, butyrylation, malonylation, and crotonylation.<sup>18,19</sup> Among them, acetylation is one of the most widely studied epigenetic modifications that commonly occurs on the basic amino acids (lysine and arginine). Basically, acetylation can neutralize the positive charge of basic residues and reduce the affinity between histones and DNA for gene activation.<sup>19</sup> This process is catalyzed by histone acetyltransferases (HATs). HATs are traditionally divided into two different classes (type A and B) based on their subcellular localization. Type A HATs locate in the nucleus and are involved in the regulation of gene expression through acetylation of nucleosomal histones. Type B HATs locate in the cytoplasm and are responsible for acetylating newly synthesized histones prior to their assembly into nucleosomes.<sup>20–22</sup> The acetylation of histones can also be removed by histone deacetyltransferases (HDACs). HDACs are classified into four classes (I, II, III, and IV) according to their functions and DNA sequence similarity. Classes I, II, and IV are considered as “classical” HDACs whose activities are zinc dependent and inhibited by

trichostatin A (TSA). Whereas class III enzymes, known as sirtuins, are NAD<sup>+</sup> dependent and not affected by TSA.<sup>23–25</sup> Histones can also be modified by other acyl moieties, eg, crotonyl, but the mechanisms and the functional consequences of acetylation versus crotonylation are still unclear. Sabari et al<sup>26</sup> indicated that p300, which belongs to the type A HATs, processes both crotonyltransferase and acetyltransferase activities, and the induced transcription by crotonylation is greater than acetylation. These results provide a new clue to clarify the specificities of different histone acylations in regulating metabolic-related gene expressions. Methylation is another widely studied histone modification, which is catalyzed by histone methyltransferases.<sup>27</sup> Methylation can influence gene expression in both positive and negative ways. For example, trimethylation of lysine 4 on H3 (H3K4me3) is strongly associated with gene activation, while trimethylation of lysine 27 on H3 (H3K27me3) is reported to be associated with gene silencing.<sup>28,29</sup> Histone demethylation is performed by two classes of histone demethylases: lysine-specific demethylase (LSD) family proteins (LSD1 and LSD2) and JmjC domain-containing histone demethylase (JHDM).<sup>27</sup> The histone PTMs are not independent of each other, some crosstalks exist among them. Recent studies of Li et al indicated that a Serine-responsive SAM-containing Metabolic Enzyme complex, which consists of pyruvate kinase, serine metabolic enzymes, and SAM synthetases, can interact with a H3K4

methyltransferase Set1 and mediate the crosstalk between H3T11 phosphorylation (H3Tp11) and H3K4me3.<sup>30</sup>

**MicroRNAs.** MicroRNAs (miRNAs), the short non-coding RNAs (approximately 22 nucleotides in length), are able to regulate target gene expression via multiple molecular pathways. Normally, miRNAs can interfere with gene expression through their complementary binding to the target mRNAs, which either inhibit translation or cause mRNA degradation.<sup>31,32</sup> Currently, miRNAs are identified in almost all metazoan genomes and even in some viruses.<sup>33</sup> Bioinformatic analysis of known miRNAs suggests that they can regulate the large majority of mRNAs and that a single miRNA can also target multiple mRNAs. Recent findings implicate that miRNAs participate in either regulating expression of certain genes or RNA degradation in important cellular processes, such as apoptosis, cell proliferation, differentiation, and metabolism.<sup>32,34</sup> Furthermore, enzymes involved in epigenetic modifications can also be governed by miRNAs. It is reported that some miRNAs can directly inhibit the activities of enzymes, which are related to histone acetylation, thereby considered as key regulators during epigenetic cascade. For example, *miR-34a* can directly inhibit the activities of SIRT1 to regulate cholesterol homeostasis (discussed in “miRNAs and cellular metabolism” section).<sup>35,36</sup>

### Epigenetic Regulation on Metabolism

The prevalence of type 2 diabetes (T2D), obesity (OB), and other metabolic diseases has caused wide public attention during past two decades. Increasing studies also reveal that the epigenetic regulation can modulate metabolic dysfunctions in many aspects, which further broadens our understandings about metabolic disease progressions. Here, we discuss the recent research progress about how epigenetic machineries: DNA methylation, histone PTMs, and miRNA regulate the metabolisms.

**DNA methylation and metabolic disorders.** DNA contains the genetic information of a cell, and methylation of DNA bases can be highly influential on regulating gene activity, including some important genes that are involved in metabolic pathways.<sup>37–39</sup> Over the past decade, evidence has been accumulated to define the regulatory role of DNA methylation in metabolic disorders such as diabetes and OB by taking the advantage of molecular genetic dissection and genome-wide association study (GWAS) analysis.<sup>40</sup>

The balance of blood glucose is very important for human health, the pancreatic  $\beta$  cells in islets can secrete insulin (INS) in response to the increased blood glucose level to prevent hyperglycemia and inhibit insulin secretion under fasting conditions to avoid hypoglycemia.<sup>41</sup> Studies by Kuroda et al<sup>42</sup> showed that the CpG sites in mouse *Ins2* and human *INS* promoter are unmethylated compared to other tissues or non-islet fraction. Overall, DNA methylation that occurred at insulin promoter correlates negatively with insulin gene expression in human pancreatic islet samples. Patients with T2D show

an increased level of DNA methylation and a reduction of insulin mRNA expression compared to nondiabetic donors.<sup>43</sup> In mammals, the de novo DNA methylation process is mainly catalyzed by DNMT3A and DNMT3B.<sup>6,7</sup> Interestingly, deletion of *Dnmt3a* in mouse  $\beta$  cell prevents the execution of metabolic switch during  $\beta$ -cell maturation, resulting in a loss of glucose-stimulated insulin secretion (GSIS). Mechanistically, loss of DNMT3A leads to a reduction of DNA methylation at two key metabolic switch genes, namely, hexokinase 1 (HK1) and lactate dehydrogenase A, while their mRNA expressions are upregulated. However, *Ins1* and *Ins2* are not affected in *Dnmt3a-KO* islet cells, which suggest that DNMT3A is not involved in transcriptional regulation of *Ins* genes.<sup>41</sup> Thus, it is still an open question that how INS is regulated by DNA methylation.

The GWAS studies indicate that metabolic diseases (eg, diabetes and OB) are also associated with the alterations of DNA methylation at specific genomic loci such as peroxisome proliferator-activated receptor  $\gamma$  (*PPAR $\gamma$* ) and glucose transporter 4 (*GLUT4*).<sup>44</sup> *PPAR $\gamma$*  is a key regulator of adipocyte differentiation and required for inducing the expression of adipocyte-specific genes.<sup>45</sup> *GLUT4* is a critical regulator in glucose uptake, whose alterations are related to insulin resistance (IR) and OB. It is reported that the promoter of both *PPAR $\gamma$ 2* and *GLUT4* are differentially methylated during the differentiation of 3T3-L1 cells.<sup>46,47</sup> With the treatment of DNA methylation inhibitor (5'-aza-cytidine), the mRNA expressions of both *PPAR $\gamma$*  and *GLUT4* are increased.<sup>48</sup> These studies provide direct evidence that DNA methylation can regulate metabolic gene expression. Thus, the manipulation of DNA methylation provides an ideal target for understanding the metabolic disease progression and the potential therapy.

**PTMs and T2D.** Histone modifications can regulate gene expression by modifying the structure of chromatin as described. Recently, an increasing number of evidence is accumulated to elucidate the roles of histone PTMs in metabolic diseases, especially in T2D.<sup>49,50</sup>

For diabetic patients, metabolic memory means inflammation and vascular complications after controlling the blood glucose level, which presents major challenges to treatment.<sup>51</sup> Recent findings suggest that epigenetic mechanisms may be responsible for metabolic memory. Compared with normal cells, trimethylation on H3 lysine 9 (H3K9me3) was significantly reduced in vascular smooth muscle cells (VSMCs) derived from the *db/db* mice (diabetic mouse, the typical mouse model of T2D). Similarly, the protein level of SUV39H1 (a methyltransferase, which catalyzed H3K9me3 methylation) was also decreased in *db/db* VSMC. Overexpression of SUV39H1 in *db/db* VSMC partially rescued this diabetic phenotype. These studies indicate a protective role of H3K9me3 and SUV39H1 in metabolic memory in cases of diabetes.<sup>52</sup> Vecellio et al analyzed cardiac mesenchymal cells (CMSCs) from volunteers with normal blood glucose level (ND-CMSC) and type 2 diabetic patients (D-CMSC).



Compared with control cells, acetylation on histone H3 lysine 9 (H3K9Ac) and lysine 14 (H3K14Ac) was decreased, as well as phosphorylation at histone H3 serine 10 (H3S10P), whereas the H3K9me3 and H3K27me3 were significantly increased. Remarkably, modification patterns of H3K9Ac and H3K14Ac were restored by treating with HAT activator, pentadecylidenemalonate 1b (SPV-106),<sup>53</sup> and the diabetes-associated decreased histone H3 acetylation could also be restored by treating with HDAC inhibitors (valproic acid).<sup>54,55</sup> These studies provide a novel way for reversing the misregulated epigenetic memory of diabetic patients in cardiac tissue.

**MiRNAs and cellular metabolism.** MiRNAs are found to be responsible for regulating various biological processes and viewed as an emerging and exciting topic of biomedical research. In recent years, it has been increasingly reported that miRNAs are associated with disease development.<sup>56,57</sup> However, the underlining molecular mechanisms are still ambiguous. Here, in order to get a comprehensive understanding of the associations between miRNAs and metabolic disease progression, we collect and summarize the latest progress in miRNA studies (see Table 1).

Rottiers and Naar<sup>58</sup> showed that miRNAs are essential for glucose homeostasis. For example, *miR-223* was upregulated in T2D patients through quantitative analysis of miRNA

expression. Overexpression of *miR-223* via adenovirus-mediated delivery significantly elevated the glucose uptake in rat cardiomyocytes. For the target genes, *miR-223* did not affect the expression of myocyte enhancer factor 2C (MEF2C) and insulin-like growth factor 1 (IGF1) receptor, which were predicted to be related to glucose metabolism. Further studies also indicated that *miR-223*-induced glucose uptake was independent of insulin signaling pathway and AMPK activity, both of which play essential roles during glucose homeostasis. Interestingly, the protein expression level of GLUT4 was 1.3-fold upregulated. Consistently, introduction of a synthetic *miR-223* inhibitor decreased GLUT4 expression. Moreover, the induced glucose uptake by overexpression of *miR-223* can be restored by knocking down of *GLUT4* via siRNA technology. Therefore, *miR-223* regulates glucose metabolism by affecting GLUT4 expression in cardiomyocytes.<sup>59</sup> In obese and aging mice, *miR-34a* was elevated with the decreased level of NAD<sup>+</sup>. *miR-34a* directly targets SIRT1, NAMPT (a rate-limiting enzyme for NAD<sup>+</sup> biosynthesis), and represses the expression of both genes. In addition, the hepatic overexpression of *miR-34a* reduces the levels of NAMPT, SIRT1, and NAD<sup>+</sup>, while it increases the acetylation levels of SIRT1-targeted transcriptional regulators, including peroxisome proliferator-activated receptor  $\gamma$  co-activator 1a (PGC1a),

**Table 1.** Involvement of miRNAs in cellular metabolic pathways.

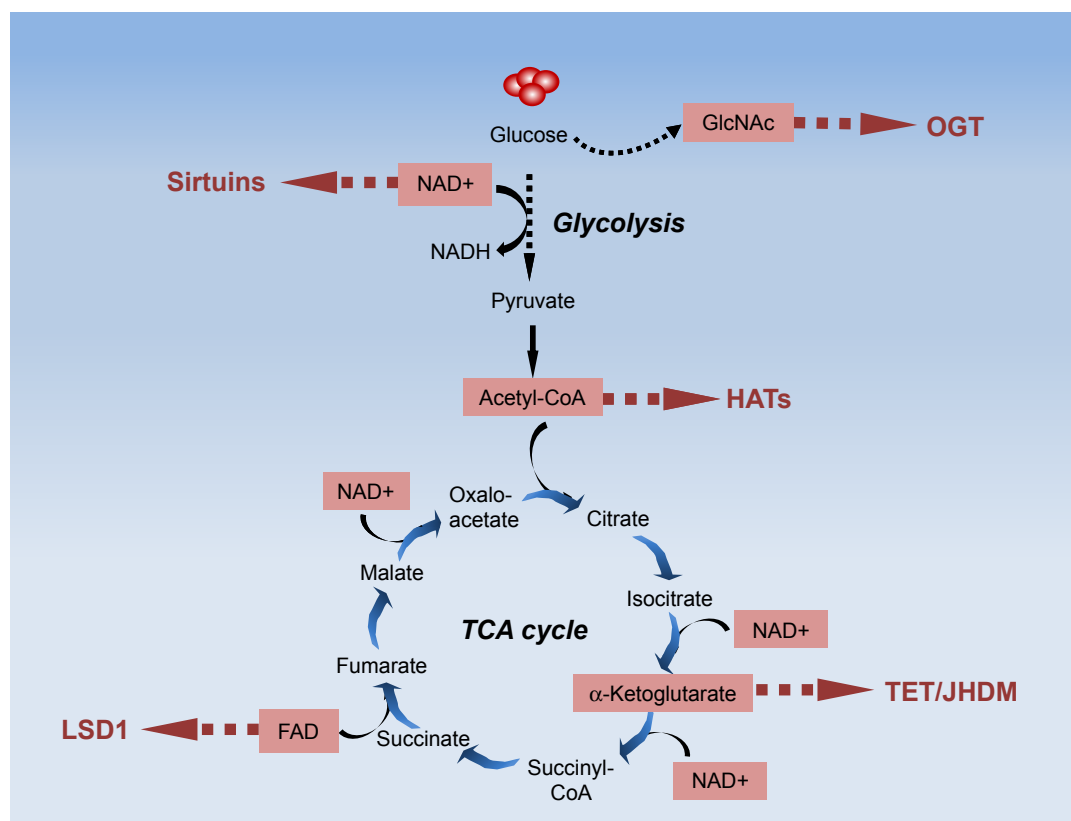
miRNAs	TARGETS	FUNCTIONS	REFERENCES
miR-9	<i>SIRT1</i>	Insulin secretion	35
miR-10b	<i>ABCA1/ABCG1</i>	Cholesterol transport	91
miR-14	<i>Reaper</i>	Fat metabolism	92
miR-24	<i>SOX6, BHLHE22</i>	Insulin biosynthesis	93
miR-26	<i>ADAM17, SOX6, BHLHE23</i>	Adipogenesis	94
miR-27	<i>ANGPTL3, GPAM</i>	Lipid metabolism	95
miR-29b	<i>BCKD complex</i>	Amino acid metabolism	31
miR-33	<i>ABCA1, ABCG1, CPT1A, SREBF1</i>	Cholesterol transport and cholesterol homeostasis	96, 97
miR-34a	<i>SIRT1, NAMPT</i>	Cholesterol and lipid homeostasis	60
miR-96	<i>Granuphilin, Noc2</i>	Insulin secretion	36
miR-103	<i>CAV-1</i>	Insulin signaling and glucose homeostasis	98
miR-107	<i>CAV-1</i>	Insulin signaling and glucose homeostasis	98
miR-122	<i>HMGCR, G6PC, AMPK<math>\alpha</math>1</i>	Triglyceride metabolism; cholesterol biosynthesis	99
miR-124a	<i>SNAP25, Noc2, Rab3A</i>	Insulin secretion	36
miR-130	<i>PPAR<math>\gamma</math></i>	Adipogenesis	100
miR-143	<i>ERK5</i>	Preadipocyte differentiation	101
miR-148	<i>SOX6, BHLHE22</i>	Insulin biosynthesis	93
miR-182	<i>SOX6, BHLHE23</i>	Insulin biosynthesis	102
miR-208	<i>MED13</i>	Insulin signaling and glucose homeostasis	103
miR-223	<i>GLUT4</i>	Glucose metabolism	59
miR-335	<i>PPAR<math>\gamma</math>, AP2, FAS</i>	Lipid metabolism	104
miR-370	<i>CPT1A</i>	Insulin secretion	105
miR-375	<i>PKD, Myotrophin</i>	Insulin secretion	106
miR-378/378*	<i>FABP4, FAS, SCD1, Resistin</i>	Preadipocyte differentiation	107

sterol regulatory element-binding proteins 1c (SREBP1c), farnesoid X receptor, and nuclear factor kappa B (NF- $\kappa$ B), finally mimicking the outcomes of OB.<sup>60</sup> Taken together, these findings reveal the regulatory roles of miRNA in cellular metabolism and suggest that miRNA may be putative therapeutic targets for metabolic diseases.

### Metabolites Modulate Epigenetics

Chromatin-dependent gene modifications interact with the cellular metabolism reciprocally. Metabolic-related genes can be regulated by epigenetic modifications, and many metabolites of cell metabolism can serve as essential cofactors for chromatin-modifying enzymes and control the transcription or translation processes. Therefore, the fluctuation of local metabolites' concentrations is considered as novel signaling cues for regulating gene expressions.<sup>61</sup> Here, we take several metabolites from glycolysis and tricarboxylic acid (TCA) cycle as examples to discuss the regulatory role on epigenetics. Moreover, the supplement or depletion of nutrients (through fasting or calorie restriction [CR]), which can also influence epigenetics via manipulating the concentration of metabolites, is also detailed in this part.

**Metabolic products and epigenetics.** Once glucose enters into cells, the major portion can be converted to acetyl-CoA through glycolytic pathways, along with the decreased NAD<sup>+</sup>/NADH ratio.<sup>61</sup> NAD<sup>+</sup> is a key cofactor in a variety of enzymatic reactions, such as sirtuin-mediated histone deacetylations. Unlike the other HDACs, sirtuins consume NAD<sup>+</sup> and release nicotinamide, *O*-acetyl-ADP-ribose (AADPR), and the deacetylated substrate.<sup>24,25</sup> Additionally, a minor portion of glucose involves into hexosamine biosynthetic pathways to produce GlcNAc, which can act as a substrate for histone GlcNAcylation.<sup>61</sup> It is well known that acetyl-CoA generated from glycolysis and fatty acid  $\beta$ -oxidation enters into TCA cycle to produce cellular energy. Meanwhile, acetyl-CoA is a substrate of HATs and behaves as an essential acetyl group donor in histone lysine acetylation reactions (Fig. 2). Since histone acetylation is tightly associated with chromatin structure and regulates gene expression, acetyl-CoA links energy metabolism with chromatin dynamics and transcription. The study also indicated that the glucose-induced histone acylation is in a dose-dependent manner.<sup>62</sup>  $\alpha$ -Ketoglutarate ( $\alpha$ -KG), an intermediate generated from TCA cycle, can function as a cofactor for DNA demethylation reactions by TET. The TET



**Figure 2.** Crosstalk between cell metabolism and epigenetics. As glucose comes into glycolytic reactions, a minor portion involves in hexosamine biosynthetic pathway to produce GlcNAc, which can act as the substrate for histone GlcNAcylation by *O*-GlcNAc transferase. The majority of glucose is converted to acetyl-CoA and passed into TCA cycle with the alteration of NAD<sup>+</sup>/NADH pair. NAD<sup>+</sup> is a key cofactor for reactions catalyzed by sirtuins. Acetyl-CoA is used as an acetyl group donor for histone acetylation catalyzed by HATs. Other intermediates from TCA cycle, such as  $\alpha$ -KG, can function as cofactors for DNA and histone demethylation reactions by TET proteins and JHDM, respectively. Lysine-specific demethylase 1 (LSD1) is proposed to catalyze demethylation using FAD.

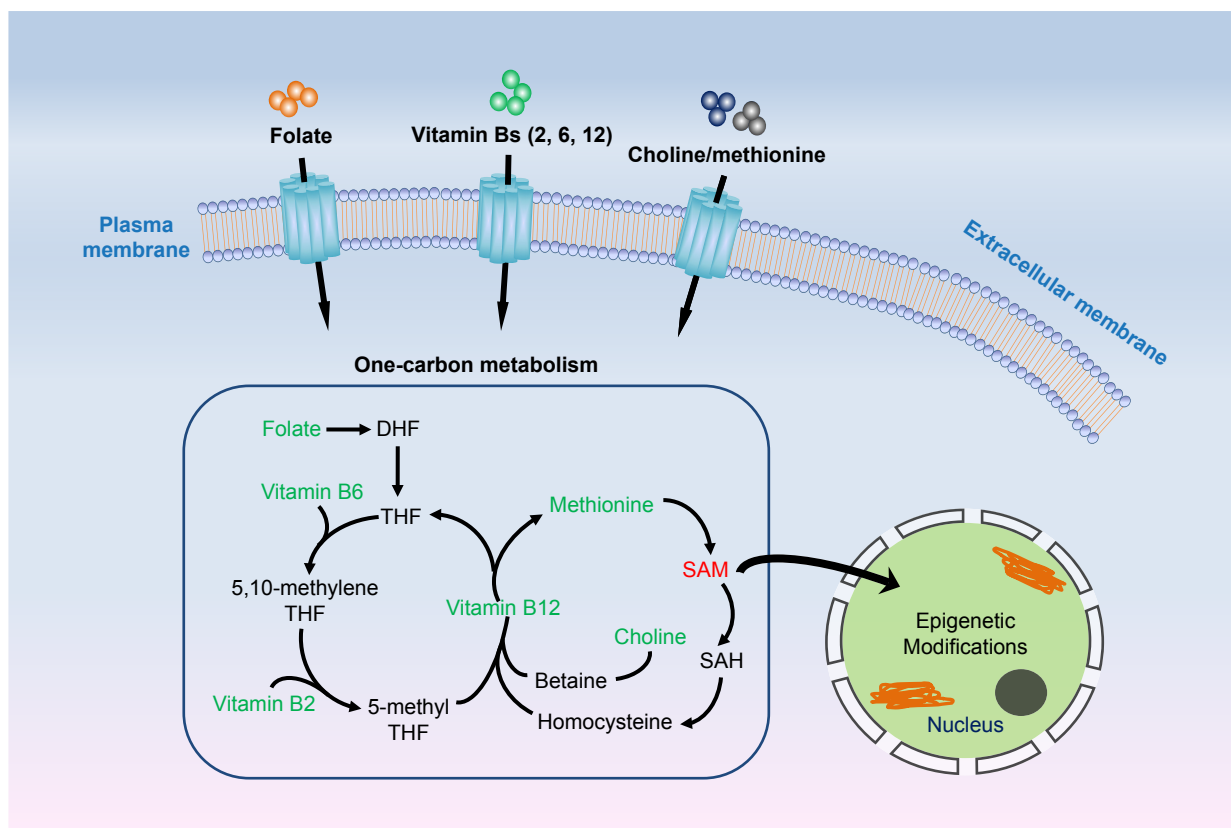


proteins (including TET 1, 2, and 3) utilize oxygen and  $\alpha$ -KG to catalyze multiple oxidation reactions, converting 5mC to 5hmC and finally to 5-carboxylcytosine (5caC).<sup>8,63</sup> Inactivation of other intermediates in the TCA cycle, such as succinate dehydrogenase and fumarate hydratase, leads to accumulation of their substrates and then inhibits TET catalyzing reactions.<sup>64</sup> Regarding histone demethylation, LSD1 is proposed to catalyze demethylation through an amine oxidation reaction that uses flavin adenine dinucleotide (FAD) as a cofactor. JHDM requires Fe(II) and  $\alpha$ -KG as cofactors to demethylate lysine of histones through an oxidative mechanism.<sup>27</sup> Thus, the glycolysis and TCA cycle are able to connect energy pathways with epigenetic modifications to regulate gene transcription.

**Nutrients and epigenetics.** Nutrients are essential components in foods that are used by organisms to survive and grow. Among them, most of the carbohydrates, proteins, and fats are the energy supplier for supporting daily metabolism and body activities. While for other nutrient components like

vitamin, docosahexenoic acid (DHA) and dietary fibers are also indispensable for human health. Here, we discuss how these nutrients affect health and disease progression via the epigenetic regulation.<sup>65-67</sup>

Folate (also called folic acid), a water-soluble vitamin B, is extensively studied for its important function in DNA synthesis, DNA repair, and DNA methylation.<sup>68</sup> Moreover, folate is widely used as food supplementation during pregnancy and infancy to decrease the risk of neural tube defects. Because humans cannot synthesize folates in a de novo manner, folate has to be provided and absorbed from diet to meet demands. Structurally, folate carries a methyl group and can feed into the one-carbon metabolism, in which folate goes through several reactions to generate S-adenosylmethionine (SAM), the universal methyl group donor for DNA and histone methylations (Fig. 3).<sup>68,69</sup> Before and during pregnancy, insufficient folate supplementation for mothers can increase the risk of neural tube defects of infants. One underlying mechanism is that low dietary folate can lead to abnormal DNA methylation



**Figure 3.** Involvement of dietary nutrients in epigenetics. Dietary intake of folate, vitamin B (2, 6, and 12), choline, and methionine (green color) regulate epigenetic modifications through involving one-carbon metabolism where the intermediate SAM is produced (red color) and subsequently be provided as the universal methyl group donor for DNA and histone methylations. One-carbon metabolism is described briefly as follows: folate is first converted to dihydrofolate, then to tetrahydrofolate (THF), which enters the cycle. Vitamin B6 is a cofactor in the conversion of THF to 5,10-methylene THF. The process of 5,10-methylene THF to 5-methyl THF is vitamin B2 dependent. 5-methyl THF serves as a methyl donor in a reaction converting homocysteine to methionine, in which vitamin B12 serves as a precursor to methionine synthase. In turn, methionine generated SAM. S-adenosylhomocysteine (SAH) that is converted from SAM participates in the generation of homocysteine. Choline is also involved in the production of methionine by converting it to betaine. The alteration of dietary methionine can also modulate the histone methylations through regulating SAM and SAH levels; the methionine restriction decreases histone modification, and this phenomenon can be sustained by diet.<sup>108</sup>

via one-carbon metabolism.<sup>70,71</sup> Steegers-Theunissen et al<sup>72</sup> investigated whether periconceptional folate supplementation of the mother was related to methylation at the differentially methylated region (DMR) of the insulin-like growth factor 2 gene (*IGF2*) of the child. Children whose mother used folate 400 µg per day showed about 4.5% higher methylation of the *IGF2* DMR than those who were not exposed to folate (absolute methylation was 0.495 [SE 0.004] and 0.474 [SE 0.007], respectively;  $P = 0.014$ ). Interestingly, an inverse association between *IGF2* DMR methylation and birth weight was observed. Their study indicates that periconceptional folate supplementation is associated with epigenetic changes in *IGF2* in the child affected by intrauterine growth and development as reflected in birth weight.

Components of vitamin B family (eg, 2, 6, and 12) and choline can also function as essential cofactors in one-carbon metabolism, which provides the methyl donor for chromatin methylation (Fig. 3).<sup>66,67</sup> Severe deficiency of vitamin B12 induces promoter hypomethylation of the cystathionine beta-synthase gene and represses its transcription in rats, which cannot be recovered by dietary supplementation of methionine to the B12 deficient rats. The human studies also show a link between vitamin B12 deficiency and the increased risk of various cancers (eg, colon and breast cancers).<sup>73</sup> Choline is essential for fetal neurogenesis such as hippocampal development and memory function throughout life. During mouse embryonic development, choline deprivation caused hypermethylation of CpG3 within the promoter region of *calbindin 1* (*Calb1*) and CpG7 within the repressor element 1 (RE1) binding site, and the binding of transcriptional repressor neuron restrictive silencing factor to RE1 decreased by 45%. These changes led to increasing of both gene and protein expressions of calbindin1, the early marker of neuronal differentiation.<sup>74</sup> These findings suggest that during the early fetal period, a deficiency in methyl donors can alter DNA methylation and thereby affect fetal development.

DHA, an omega-3 fatty acid, is a primary structural component for human brain, cerebral cortex, sperm, and retina, which has a wide range of effects to human health, including against Alzheimer's disease and cancer.<sup>75,76</sup> Sadli et al<sup>77</sup> reported that the addition of DHA to M17 neuroblastoma culture medium showed elevated levels of H3K9ac and reduced levels of HDAC1, 2, and 3, suggesting that DHA promotes gene expression.

Dietary fibers are the indigestible component of food derived from plants, which are helpful for the digestion and absorption of nutrients.<sup>78,79</sup> It has been demonstrated that dietary fibers facilitate the generation of short-chain fatty acids (butyrate), and there is a positive linear correlation between butyrate level and histone acetylation in colon epithelial cell.<sup>80</sup> In the last decade, several effects of butyrate are clarified, including anti-inflammatory effects, effects on OB, IR, and inherited disorders.<sup>81–84</sup> One of the major functions of butyrate that is involved in the epigenetic regulation

of gene expression is inhibiting HDACs.<sup>85,86</sup> Specifically, butyrate treatment of cells results in histone hyperacetylation, and butyrate itself inhibits class I HDAC activity in mammalian cells. These findings suggest that dietary fibers are an effective food component that is able to regulate epigenetic modifications.

**CR and epigenetics.** CR simulates human dieting, which is considered as the most effective environmental manipulation for extending life span so far. This phenomenon has also been experimentally proved in multiple species that range from worm to rodent.<sup>87</sup> CR can induce wide metabolic changes (gluconeogenesis, fat mobilization, etc.) and undergoes weight loss in human subjects. Huang et al found that weight loss is associated with DNA methylation.<sup>88</sup> The DNA methylation pattern in human individuals with normal weight, OB, and successful weight loss maintainers is different, and the pattern in successful weight loss maintainer is more closely resembled than those in normal weight. These findings suggest a relationship between OB, weight loss, and DNA methylation. Moreover, extensive studies reported the crucial role of CR on regulating SIRT1 activities, which is an NAD<sup>+</sup>-dependent deacetylase. Mechanistically, CR increases NAD<sup>+</sup>/NADH ratio and induces SIRT1 expression. The upregulated SIRT1 further suppresses the downstream PPAR $\gamma$ , then downregulates its target gene *aP2*, which encodes an assisting fat storage protein, thereby promoting fat mobilization into the blood.<sup>89,90</sup> Therefore, CR regulation on metabolism through epigenetic mechanisms opens new avenues for related diseases therapy and precision nutrition supply.

## Conclusions

Epigenetics influence gene expression with no alterations of DNA sequence and might be inherited by next generation. The major molecular machinery of epigenetics includes DNA methylation, histone posttranslational modifications, and miRNAs. Modifications of chromatin structure ultimately regulate transcription. Increasing evidence demonstrates that metabolic diseases are highly associated with epigenetic alterations. It is well established that metabolic products from cellular metabolic processes like TCA cycle and glycolysis are involved in the regulation of chromatin methylation and acetylation. Moreover, dietary nutrients (such as folate, vitamin B family, DHA, and dietary fibers) play important roles in DNA methylation and histone modifications by directly inhibiting related enzymes or by changing the availability of substrates for those enzymatic reactions.

In the past two decades, scientists have generated a variety of valuable data and knowledge about the basis of epigenetics and cellular metabolism. Here, we discussed the reciprocal regulation between these two phenomena, which eventually leads us to a better understanding of metabolic-related disease progression and pathogenesis. Nevertheless, due to our incomplete knowledge from current studies, we need to make investigations on two key issues. (1) How



nutrients and environmental factors are sensed and signaled to the epigenetic machinery? Here, we discussed sparse cases and steps of how nutrients are able to direct epigenetic modifications. However, the detailed molecular mechanisms are still missing for several important signaling pathways. (2) How does the cell respond to the metabolic changes at a systematic level? Since the whole cellular network is highly orchestrated and complicated, it is basically impossible to understand the connection between metabolite and epigenetics by focusing on a single pathway. In order to achieve a deeper understanding of these puzzles, there is no doubt that the conventional genetic and cellular analysis should be upgraded and combined with recently developed high-throughput sequencing strategies. In future, we expect more exciting discoveries and methods to thrive and help us understand the molecular regulation of epigenetics and cellular metabolism, which may provide a better way to maintain our health through nutritional modulation besides pharmacotherapies.

### Author Contributions

Wrote the first draft of the manuscript: WX. Contributed to the writing of the manuscript: ZY and FX. Jointly developed the structure and arguments for the paper: FW. Made critical revisions and approved final version: ZY and FX. All authors reviewed and approved of the final manuscript.

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