REVIEW ARTICLE

Nutritional Influences on Epigenetics, Aging and Disease

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Received date: March 14, 2019; Revised date: April 30, 2019; Accepted date: April 30, 2019

Abstract

BACKGROUND: Altered epigenetics is regarded to play quite a role in many chronic diseases including cancer, diabetes, obesity, dyslipidemia, hypertension and neurodegeneration, hence nutrition suggested to contribute in epigenetics and disease.

CONTENT: Histone modifications, as a part of epigenetics mechanisms, depend on metabolites which acts as cofactors or substrates. Fluctuating levels of specific metabolites become the direct and rapid mechanisms to influence gene activity. Therefore, these metabolites may have a role as gatekeepers of chromatin, in chromatin landscape modulation as a response to key nutritional cues. Chemical modifications of histones and DNA have a critical role in epigenetic gene regulation including histone acetylation, and DNA methylation. Any mutations from chemical modifications affecting on metabolic enzymes such as succinate dehydrogenase (SDH), fumarate hydratase (FH) and isocitrate dehydrogenase (IDH) can modify the epigenetic and drive tumorigenesis via epigenetic regulation.

SUMMARY: As a response to their nutrient environment, organisms tend to rapidly alter their gene expression. Many evidences showed an epigenetic regulation of chromatin is coupled to the changes on metabolites levels due to this kind of response. These metabolites will lead the recruitment of transcriptional regulatory complexes to DNA, thus clearly influencing the dynamic chromatin landscape.

KEYWORDS: metabolites, enzymes, epigenetics, chromatin, nutrition

Indones Biomed J. 2019; 11(1): 16-29

Introduction

The term 'epigenetic' was first coined as changes in phenotype without changes in genotype in 1942 by Waddington, a British developmental biologist, paleontologist, geneticist, embryologist and philosopher, but the mechanism was little understood.(1,2) Almost three-quarters of a century after, then we know that epigenetic mechanisms do change the genotype patterns, and also be inherited, but the alteration is not specifically underlying DNA sequence but by adapting chromatin as the physiological form of our genetic information. Epigenetics aim to stabilize gene expression programs by modifying the DNA template, and thereby canalize cell-type identities. Researchers have been aware about the importance of epigenetic control since long, but they still cannot define the enzymatic of distinct chromatin states that stimulate or repress gene activity.(3)

A chromatin was built basically from nucleosome core particle, which consist of approximately 147 base pairs of DNA wrapped around a histone octamer and each contains two copies of histones H2A, H2B, H3 and H4. Histone acetylation could be performed on a more open chromatin configuration (euchromatin), so it is permissive for transcription, while histone deacetylation eager to occur on condensed, compacted chromatin (heterochromatin) and transcriptional repression. On chromatin, a variety of post-translational modifications are expected on the tails

of histones H3 and H4 including acetylation, methylation, phosphorylation, sumoylation, and ubiquitylation. Determining which genes capable of being transcribed is influenced by the positions of nucleosomes relative to the DNA strand, which are regulated by chromatin remodeling complexes such as Switch/Sucrose Non-Fermentable (SWI/SNF) complexes. Cellular metabolism generates many co-substrates that regulate the enzymes needed in epigenetic gene regulation, thus become a potential link between nutrition, metabolism, and gene regulation.(4)

Chromatin structure can be modified by epigenetic mechanisms through DNA methylation, RNA interference, histone variants, and post-translational modifications. The progressive combination of these four may lock the epigenome in specific states, and change the fate and physiology of a given cell determination.(5,6) Histone-modifying enzymes need key metabolites, so the metabolic state of a given cell can be interpreted by changing chromatin modification patterns. Therefore, a global reduction of nuclear acetyl coenzyme A (acetyl-CoA) levels decreases histone acetylation, while reduced levels of nicotinamide adenine dinucleotide $(NAD)^+$ give the opposite effect, which is inhibiting histone deacetylation. (7,8) Chromatin-modifying enzymes along with this was proposed to be the authors of an epigenetic language, but we had to explore deeper about what is the real meaning in this chromatin written messages. Current studies suggested that the nutritional influences on epigenetic can be passed to the offspring, adding the idea that histones act as metabolic sensors, and these metabolism changes converted into stable patterns of gene expression.(6)

Dietary Control of Chromatin

Studies on budding yeast about nutritional influence on chromatin and gene regulation frequently encounter a wide variety of growth environments, give ideas that changes in nutrient affect the expression of genes that regulate cell growth or survival. One example, glucose repletion to a starved yeast culture was found to rapidly induce massive changes in gene expression on a global scale.(9,10)

Histones are acetylated by a group of enzymes called histone acetyltransferases (HATs), it is controlled by transcription factor-mediated recruitment of HATs to gene promoters and regulatory regions. The process use acetyl-CoA as the acetyl donor, means the fluctuation concentration of acetyl-CoA also affect the histone acetylation. These enzymes can also modify other (non-histone) proteins, known as lysine acetyltransferases (KATs).(11-15)

Histones and other proteins are deacetylated by enzymes known as histone deacetylases (HDACs) or lysine deacetylases (KDACs). Opposite from acetylation, the histone deacetylation typically results in a more condensed chromatin structure that correlates with repressed transcription. Due to the catalytic mechanisms, HDACs fall into two general groups.(16) Most HDACs (classes I, II and IV) use activated water as the nucleophile, whereas class III HDACs (also known as sirtuins) use a cofactor, NAD^+, to catalyze deacetylation.(17) The oxidation of hydrocarbon fuels needs NAD^+ as a key electron carrier. The discovery of sirtuins as NAD^+-dependent deacylases suggested a link between cellular levels of NAD^+ and the regulation of chromatin and gene expression.(18) As we know that sirtuin could be activated by dietary restriction thus it is proposed to promote health and longevity.(19,20) In fasting condition, the ketone body β-hydroxybutryate (βOHB) in blood can reach low millimolar. βOHB functions to βOHB inhibits HDAC1 and HDAC3 (both class 1) and HDAC4 (class II) *in vitro*, suggesting HDAC activity may be physiologically inhibited by βOHB during fasting.(21-23) Butyrate knows as a product of bacterial fermentation, then this may extend the mechanism of gut microbiome to inhibit HDAC activity in colonocytes.(24)

Histones are so abundant in the chromatin so that their acetylation and deacetylation may impact. Each histone octamer, occupying around 146 bp of DNA, represents nearly 20 acetylatable lysines. These acetyl moieties have very short half-lives, only about 2-3 min.(25,26) suggested that substantial amounts of acetate might be stored on histones and liberated by deacetylation.(27,28) When released, acetate will be re-captured by acetyl-CoA synthetase enzymes, and convert acetate to acetyl-CoA in an adenosine triphosphate (ATP)-dependent reaction. Acetate then become an important carbon source for cancer cells, and is used to synthesize acetyl-CoA in challenging growth environments.(28,29)

Another modification of histone that affect chromatin is methylation, where specific methylation marks can correlate with either active or repressed chromatin and this is also linked to nutrition. All four core histones can be methylated, and in some cases, individual residues can be either mono-methylated, di-methylated, or tri-methylated.(30-34) Methylation is catalyzed by histone methyltransferase enzymes (HMTs), which use S-adenosylmethionine (SAM) as the methyl donor. Since HMTs also target proteins other than histones, they also

known as lysine methyltransferases (KMTs). SAM is synthesized from methionine by methionine adenosyl transferase (MAT), called as SAM synthase. SAM donates its methyl group during methylation, and converted to S-adenosylhomocysteine (SAH). SAH is then hydrolyzed to homocysteine, and in a reaction that requires folate and cobalamin (*i.e.*, vitamin B12) converted back to methionine.(35) Therefore, the status of histone methylation might be influenced by fluctuations in SAM or regulators of SAM synthesis. Moreover, SAM levels also influenced by the methylation of arginine residues and DNA itself.(36)

Histones have apparently similar half-lives with this modification, so it was seems impossible for histone methylation to be reversed, but in 2004, first of several histone demethylases (HDMs) was identified.(37-39) These enzymes also modify non-histone lysines, so they also called as lysine demethylases (KDMs). Two main classes of HDMs are the JmjC (Jumonji C domain)-containing HDMs, which depend on Fe(II) and α-ketoglutarate, and the lysine-specific amine oxidases, which are depend on flavin adenine dinucleotide (FAD). This finding suggested the dynamic character of methylation, estimating the half-lives of methyl modifications on histones range from 0.3 to 4 days (40,41), significantly longer than acetylation modifications, which are on the order of minutes (25,26).

Demethylation of histones needs both α-ketoglutarate (a tricarboxylic acid cycle (TCA) cycle intermediate) and iron, Fe(II), and yielding succinate, formaldehyde, and carbon dioxide.(39) So, the fluctuations level of α-ketoglutarate might influence histone methylation status. A manipulation experimental on mouse embryonic stem cells proposed a mechanism to maintain pluripotency using both glucose and glutamine to maintain high levels of intracellular α-ketoglutarate thus promoting both histone demethylation and DNA demethylation, affected multiple chromatin modifications, including H3K27me3 and ten–eleven translocation (Tet)-dependent DNA demethylation, important for pluripotency-associated genes.(42)

The fluctuations in the level of SAM appear to also influence pluripotency by affecting H3K4 trimethylation. (43) Another metabolite that influences histone methylation status and gene expression is FAD, which was required as a cofactor for lysine-specific amine oxidase class of histone demethylases (KDMs), so FAD availability is crucial for this regulation.(37) High-fat diet mice's adipose tissue have high FAD levels while the lysergic acid diethylamide (LSD)1-targeted genes were repressed, and otherwise it will increased when FAD synthesis was inhibited.(44)

Nutritional or dietary control has not been fully considered in fundamental regulatory mechanism directly linked to human physiology or its role in epigenetic, while they may have functions beyond the gene transcription regulation, including pH regulation and as carbon sources in cancer cells.(36)

Bridging Epigenetics and Metabolism

Cells sense changes in the environment and respond by ordering specific modulations to the genome over a variety of signaling components, including proteins with histone- and DNA-modifying enzymatic activity.(45) Metabolites as a respond of nutrient sensing recently found to surpass these where metabolites may serve as indicators of the metabolic status of the cell and, through metabolite-sensitive protein modifications, can modulate the activities of signaling proteins, metabolic enzymes and transcriptional regulators, generating modifications such as acetylation, methylation, glycosylation and phosphorylation.(46) Particular metabolites such as cytosolic or nuclear acetyl-CoA, even can impact on a bigger and meaningful modifications to the biology of the cell such as signal transduction and gene expression, as well as cellular metabolism itself.(46-49)

Epigenetic control is close connected with metabolism, as proved by findings on the fat mass and obesity-associated (FTO) gene. The gene encodes an N6-methyladenosine (m6A) demethylase, an enzyme that controls the levels of RNA methylation.(50) Single-nucleotide polymorphisms of this gene will alter its response to food intake affecting in the development of obesity. Some chromosome experiments showed the epigenetic impact on this gene where certain variants of FTO can physically loop to and interact with iroquois homeobox 3 (IRX3), a homeobox gene located megabases away from FTO. Thus, manifestation of one gene impact in metabolic dysfunction, will affect influences the function of a distant gene that implicated in controlling body mass.(51,52) Chromatin regulation requires enzymes as cofactors for the reactions either attach small chemical units (*i.e.*, posttranslational modifications or PTMs) or alter nucleosome positioning or composition (*i.e.*, of histone variants), to modify DNA or histones. Here, the variable levels of cellular metabolites acts as enzyme cofactors (Figure 1).(45)

Metabolism can be simply defined as the set of life-sustaining chemical reactions in organisms. In metabolism process, cell interacts with energy sources, coordinating the

energy intake with its use and storage that supports growth and cell division.(27) different enzymes and a variety of cofactors of which ATP, NAD, FAD, nicotinamide adenine dinucleotide phosphate (NADP), heme, coenzyme a, Uridine diphosphate N-acetylglucosamine (UDP-Glc-Nac), SAM, and many more were included to drive a highly interconnected network of chemical reactions in order to maintain metabolic homeostasis (53), enable rapid sense and react yielding an adaptation of physiological processes to the external stimuli.(54-57) Chromatin serves as a platform for epigenetic process, which including receive extra and intracellular stimuli and converts them in transient or stable transcriptional changes. These performed through modifications of both DNA and histone proteins as well as gene transcription.(58,59)

Since acetylation as an epigenetic mechanism was known to be reversible, histone and nonhistone acetylation rise as the integrating key for physiological processes such as metabolism, circadian rhythm and cell cycle, along with gene regulation in various organisms.(60) Methylation and acetylation of DNA and histone proteins are the chemical basis for epigenetics. They are sensitive to cellular metabolic in any models from bacteria to humans. The rate of modification depends on the availability of one-carbon and two-carbon substrates (SAM, acetyl-CoA, and in bacteria also acetyl-phosphate). In addition, they are also sensitive to demodification enzyme cofactors (α-ketoglutarate, NAD^+) and structural analog metabolites that function as epigenetic enzyme inhibitors (*e.g.*, SAM, 2- hydroxyglutarate). In microbes, methylation and acetylation evolved to tailor proteins activities to their metabolic environtment, not in mammals where the extracellular environment is more tightly controlled, the incorporate impact of nutrient and metabolic enzyme expression drive the biological outcomes such as stem cell fate and cancer.(61)

Methylation and acetylation can be affected by the metabolic environment, for example acetyl-CoA can be made from each major category of mammalian nutrients (carbohydrates, fats, protein). In mouse liver, fasting will impact in a higher free CoA while acetyl-CoA is relatively stable (62), suggested a link between dietary nutrient consumption, acetyl-CoA levels, and *in vivo* acetylation rates. Deacetylation by sirtuins, however, was influenced by levels of their co-substrate NAD^+ (relative to competitive inhibitors). Even when deacetylases use only water as the sole substrate, still regulated by circulating β-hydroxybutyrate.

Calorie restriction and high-fat diet may promote histone deacetylation by potentially promoting high NAD^+/NADH.(63-65) Nicotinamide phosphoribosyltransferase

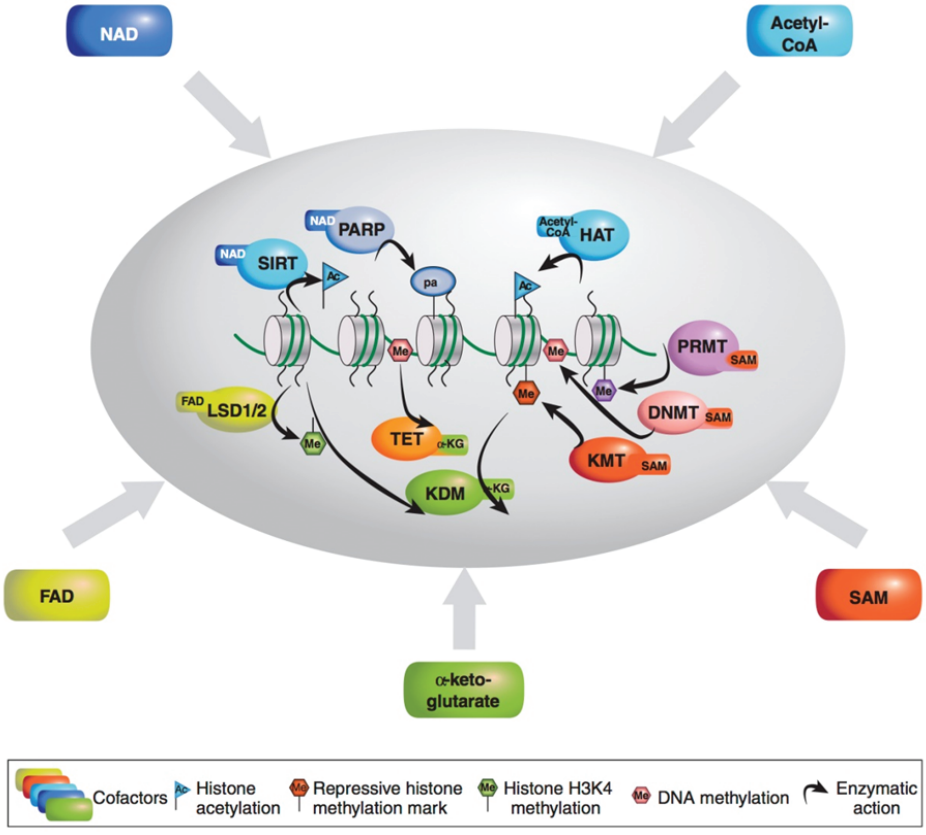

Figure 1. The major cofactors involved in enzyme-mediated DNA or histone post-translational modification (PTM).(45) (Adapted with permission from Cold Spring Harbour Laboratory Press).

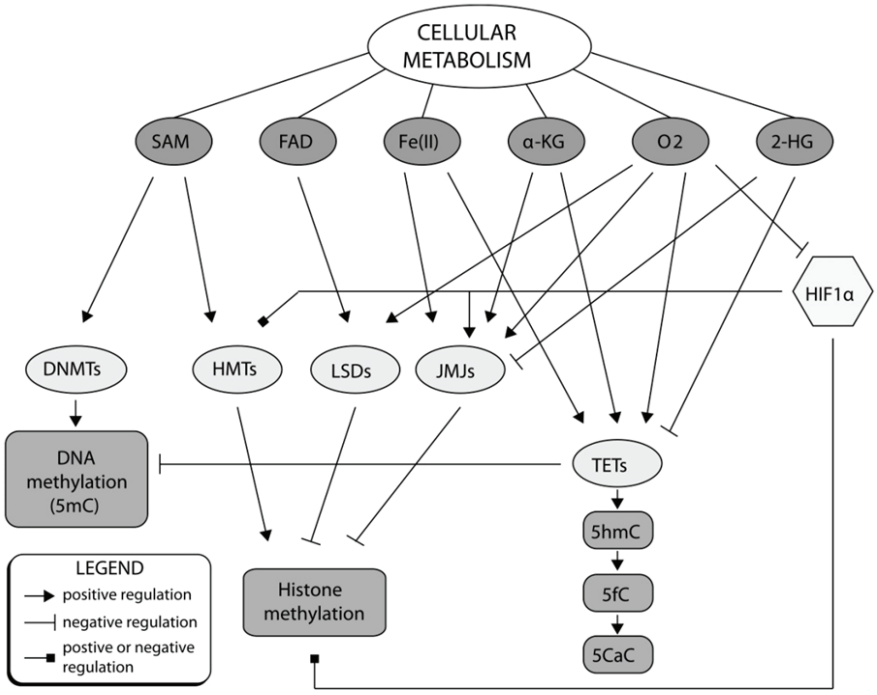

Figure 2. Schematic representation of the role of some products of cell metabolism. the gure highlights their connections in regulating different epigenetic processes. (59) (Adapted with permission from Springer).

(NAMPT), a key enzyme in mammalian NAD^+ synthesis was low in high-fat diet-induced diabetic mice. Administration of this enzyme restores NAD^+, activates SIRT1 and SIRT3, and enhances insulin sensitivity (66,67) N-methyltransferase (NNMT), the enzyme that consuming NAD^+ is up-regulated in mouse models of obesity and insulin resistance (68) and is overexpressed in many tumors (69). NNMT performing dual epigenetic effects, simultaneously depleting SAM and NAD^+, and thereby impairing methylation and deacetylation (68). When fasting, the liver increase in fatty acid oxidation and circulating D-β-hydroxybutyrate levels can rise to above 1 mM. β- hydroxybutyrate increases H3K9 acetylation at the promoter of forkhead Box O3A (FOXO3A), a transcription factor for oxidative stress resistance genes (21). Low carbohydrate diets can promote ketogenesis in order to protect neurons from oxidative damage.(70,71)

Cells can adapt to the new environmental condition due to a regulated cross-talk between metabolic pathways in the mitochondria and epigenetic mechanisms in the nucleus. Harmonized gene expression was accommodated by dynamically changes in chromatin, including methylation of DNA and posttranslational modifications of histones: Acetyl, methyl, and phosphate groups can be added by acetyltransferases, methyltransferases, and kinases, respectively, to different residues on histones. The metabolism and epigenetics crosstalk be held in two-way. Any defects in chromatin modulators will affect the availability of intermediate metabolites, in turn influencing energy metabolism (27), and finally affect epigenetic regulation, such as altered nutrient availability regulating histone and DNA modifications, circadian biological rhythms and cellular replicative aging and senescence.(45)

Regulation of Chromatin and Gene Expression by Metabolic Enzymes and Metabolites

The knowledge of epigenetic have changed from a series of biological phenomena to a functionally dissected study field because of the new discoveries regarding chromatin-modifying enzymes and associated mechanisms that changed chromatin in response to physiological or pathological signals.(3) Chromatin plays a key role in the changes of epigenome function (Figure 3).

In eukaryotic cells, the genomic DNA is packed into chromatin by formation of nucleosomes, where each nucleosome core particle is consist of a histone octamer wrapped by around 146 base pairs.(72) Eight core histones which consist of two copies each of H2A, H2B, H3 and H4 are grouped together into one histone octamer. Histone amino-terminal tails and the globular histone cores are susceptive to a wide array of covalent modifications (73), such as acetylation, methylation, phosphorylation, sumoylation, ubiquitylation, succinylation, glutarylation, propionylation, butyrylation, crotonylation, 2-hydroxy-

isobutyrylation, β-hydroxybutyrylation, malonylation, formylation, citrullination, hydroxylation, O-GlcNAcylation and ADP ribosylation. These modifications could lead to more than 600 post-translational modification sites of eukaryotic histones.(74-76) In addition to histones, modifications of DNA is also possible, such as methylation of the 5-carbon on cytosine residues, which yields 5-methylcytosine (5mC) in CpG dinucleotides; 5mC is oxidized to 5-hydroxymethylcytosine (5hmC), which is further oxidized to 5-formylcytosine (5fC) and eventually to 5-carboxylcytosine (5caC).(77,78) These various chromatin modifications alter chromatin structure, which eventually regulate the binding process of binding protein to DNA and histone. This phenomena will affect the regulation of all DNA-based processes in cell, including gene expression, DNA replication and DNA damage response.(76,79-81)

Methylation is the main chromatin modification which is strongly connected to metabolism. Some methyltransferases are involved in epigenetic gene regulation, such as DNA methyltransferases (DNMTs), KMTs and peptidyl-arginine methyltransferases (PRMTs).(82) These enzymes deposit methyl groups on DNA and histones, which end up to complex alterations in chromatin accessibility, transcription factor binding and gene expression.(83) Methylation is caused by SAM abundance, whereby SAM serves as a methyl donor and is synthesized from methionine and ATP by MATs.(84) Once SAM donor its methyl to the DNA, another metabolite is produced, namely SAH, which is a potent inhibitor of all methyltransferases. Hence, the methyltransferase activity is dynamically regulated by the intracellular ratio of SAM:SAH.(85-87) Therefore, the consumption of food which is rich in methyl-donating nutrients, such as folic acid and vitamin B, could induces DNA and histone methylation and influences gene expression.(88)

External influences including food consumption will globally change the cofactor concentration in cell, hence have a global effect on histone modifications. However, collected evidence shows that histone-modifying enzymes could also make use of local alterations in metabolite concentration to obtain a domain-specific chromatin remodeling.(8,89) The landmark finding established that histone deacetylation is related to transcriptional repression. Taken together, the 1996 HAT and HDAC work provided a compelling one–two punch that histone acetylation and deacetylation are directly coupled to take turn in turning on and turning off the states of gene regulation.(90) Figure 4 shows molecular hallmarks of epigenetic control and other examples for their medical relevance.

Sir1, a NAD-requiring HDAC is a key protein that is necessary of the gene silencing in yeast. Up to now, there are seven Sir-2-like enzymes that were identified in mammals

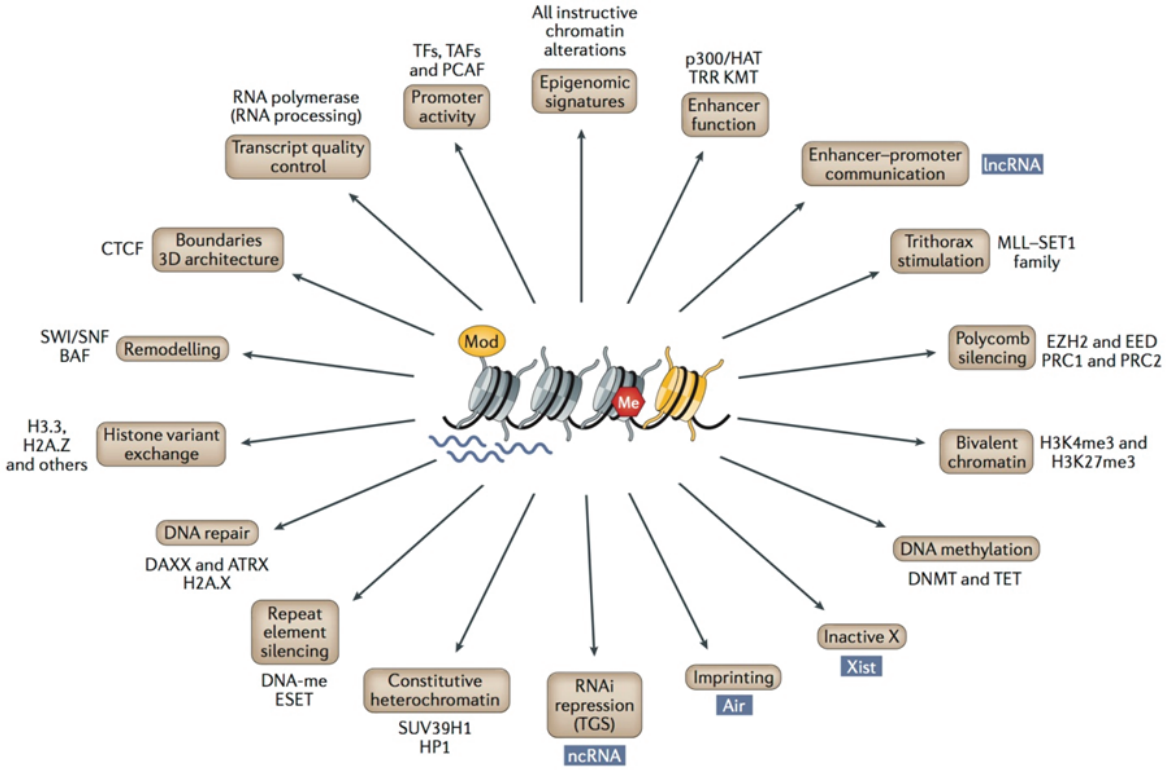

Figure 3. Key examples of chromatin contribution to epigenome function.(3) (Adapted with permission from Springer Nature).

cells. They are now known as Sirtuin protein family. Not only having distinct cofactor and catalytic requirements to the other HDACs, but the Sir2-related HDACs motivate more researchers in investigating their functions in metabolism and ageing.(45) A great number of enzymes depend on the coenzyme NAD^+, including two groups of chromatin regulators, the class III HDACs (sirtuins) and the PARPs (poly-ADP ribose polymerases). The shifting levels of a single metabolite may impact independent groups of enzymes with different functions. Other enzymes, such as HATs, may also be indirectly affected by the changing concentrations of NAD^+.(6) Levels of NAD^+ are regulated in a circadian manner, establishing a direct relationship between cyclic rhythms and energy metabolism in the cell. (7,91)

Both histone and DNA methylation are reversibly regulated by dynamic modulation of methyltransferase and demethylase activities, and these modulations are directed by various metabolites. The production of these metabolites is subject to regulation by cell signaling, meanwhile the producing enzymes can be subject to mutagenesis, thereby determining the biological outcomes. Metabolism and DNA-based processes are thightly integrated to manage physiological responses to extracellular stimuli, and deregulation of these interconnected pathways can have profound consequences, which could end up in a disease development.(92)

Exploratory research into more complex human disease (such as metabolic and neurodegenerative diseases) and habitual functions (such as learning and memory) reveals that the responsiveness to combinatorial epigenetic therapies as more precise inhibitors, for example HDAC inhibitor (HDACi), DNMT Inhibitors (DNMTi), inhibitor of bromodomain and extra-termina (iBET) and sirtuin inhibitors, are currently being developed. New experimental systems are also being used to start analyzing the contribution of epigenetics to behavior and phenotypic polymorphism in social insects.(93) For metabolic disorders and environment-driven adaptations, chromatin is shown to be the physiological template to integrate changing inputs. (45,94,95)

It is still a great challenge to determine how plastic the epigenome is to nutritional challenges and whether epigenetic changes triggered by altered metabolic states can be reversed. Main metabolic alternations are frequently found in cancers, in which cells switch to an anaerobic metabolism even in the presence of oxygen. This Warburg Effect is accompanied by major changes in gene expression profile whose causes are likely to be related to specific chromatin-remodeling events. Lately, the genes encoding isoforms of the enzyme isocitrate dehydrogenase (IDH)1 and IDH2 have been found to be mutated in a wide variety of tumors.

Therefore, an impaired in genes encoding metabolic enzymes could directly affect the enzymatic function of epigenetic regulators, inducing an increase in histone and DNA methylation. The causal relations between IDH mutations, alterations in epigenetic modifications, and the altered patterns of gene expression observed when cancer cells switch to an anaerobic metabolism have not yet been demonstrated. However, it is intriguing to speculate that the epigenetic reprogramming induced by an aberrant metabolite has an important role in this process.(6)

It is known that histone and DNA-modifying enzymes have essential roles in regulating chromatin structure, contributing to both genome integrity and to transcriptional regulation. Yet their connection with different metabolic pathways is still not being investigated enough. The basic role of chromatin-modifying enzymes is also highlighted by their connection with several pathologies. For instance, several of the discussed enzymes harbor mutations that led to a deregulated activity in cancer cells. Similarly, metabolism and metabolic pathways also emerge as significant regulators of cell homeostasis, playing important roles not only in metabolic syndromes but also in the cancer biology. The development of cancer or neurodegenerative disorders as happens in patients suffering from obesity or hyperglycemia is an example on how metabolic syndromes are favored by abnormal epigenetic modifications and how metabolic changes affect epigenetic mechanisms predisposing. This will also be beneficial in predicting the effects of pharmacological manipulation of these two important cellular processes and in defining specific approaches for different pathologies.(59)

Sirtuins As Regulators of Metabolism and Healthspan

The balance among energy intake, utilization and storage are necessary for metabolic control. When there is sufficient food, the excess energy will stored, so that it can be used in times of scarcity. A carefully tuned regulatory and evolutionarily conserved program controls these switches in nutrient intake, use and storage, involving classical food excess signaling pathways, such as insulin growth factor 1 (IGF1) and target of rapamycin (TOR; mTOR in mammals),

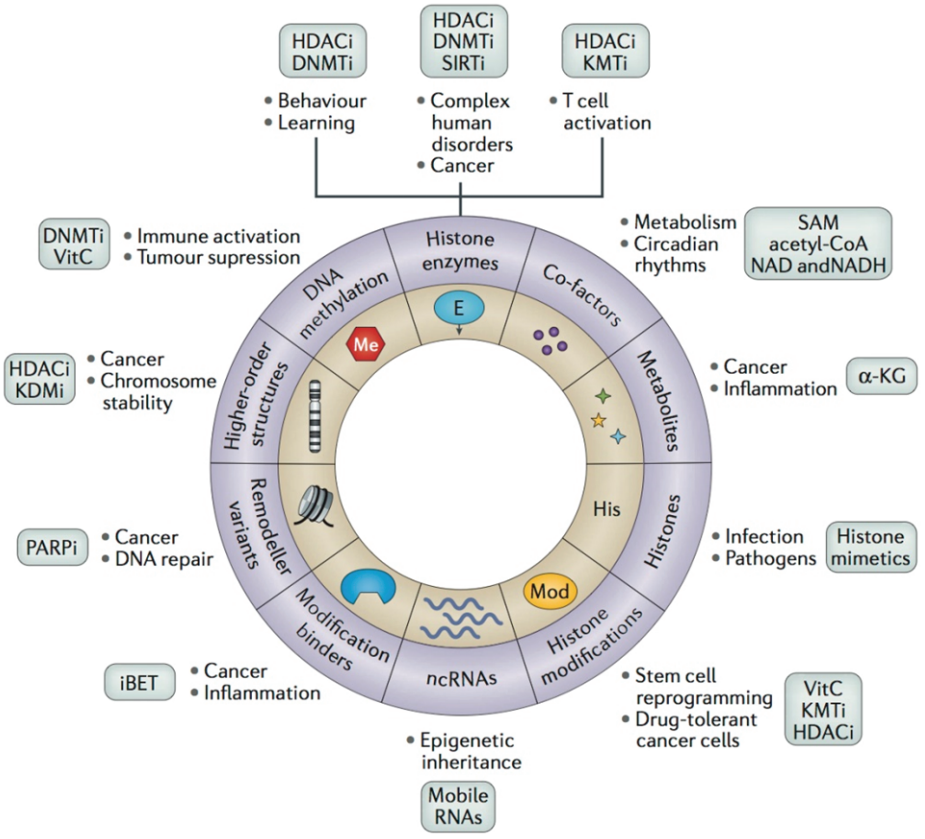

Figure 4. Molecular hallmarks of epigenetic control and examples for their medical relevance.(3) (Adapted with permission from Springer Nature).

and food restriction pathways involving AMP-activated protein kinase (AMPK) and sirtuins.(96-99)

As Sir2 was found to be an NAD-dependent HDAC (100), it became clear that sirtuins work both as energy sensors and as transcriptional effectors by controlling the histone acetylation state. Beside that, sirtuins not only deacetylate histones, but also a broad range of trascriptional regulators, and then controlling their activity. Sirtuins, notably SIRT1, have been known for their role in caloric restriction, prevention of ageing-related diseases and also maintenance of metabolic homeostasis. As a consequence, the search for nutriceutical or pharmaceutical sirtuin activators was intense and drove to the identification of several sirtuin activators. Resveratrol, a polyphenol found in red grapes, berries and peanuts received a lot of attention.(101) Activation of sirtuins is assumed to be beneficial not only for metabolism-related diseases, such as type 2 diabetes and obesity, but also for neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease. This is in part because sirtuins stimulate the activity of mitochondria and of mitochondrial proteins.

An analysis on sequence-based phylogenetic divided mammalian sirtuins into four classes. SIRT1, SIRT 2 and SIRT3 are belong to class II, SIRT4 belongs to class II, SIRT5 belongs to class III, meanwhile SIRT6 and SIRT7 are belong to class IV.(102) In the beginning, sirtuins were known as NAD-dependent type III HDACs, as the founding member, Sir2 in yeast, silenced specific genomic loci by deacetylating histones H3 and H4.(103) Interestingly, mammalian sirtuins, notably those in class I, beside targeting histones, they also deacetylate a broad range of proteins in different subcellular compartments. Moreover, SIRT4 and SIRT6 were reported to function as ADP-ribosyltransferases, even though SIRT6 also can act as a deacetylase.(104-107) SIRT5 was originally reported to deacetylate the urea cycle enzyme carbamoyl phosphate synthetase 1 (CPS1) but was lately shown to primarily demalonylate and desuccinylate proteins, including CPS.(108-110)

To catalyzed an enzymatic reaction, sirtuins needs NAD^+ as a substrate, the concentration of which is determined by the nutritional state of the cell.(111) For example, NAD^+ is well positioned to manage the adaptive responses to energy stress by modulating the activity of sirtuins and their downstream effectors. Sirtuins change NAD^+ to nicotinamide, which at higher concentrations can non-competitively bind and thereby feedback-inhibit the sirtuin activity.(112,113) The other by-product of the sirtuin deacetylase reaction, O-acetyl-adenosine diphosphate

(ADP)-ribose, was also reported to be a signalling molecule (114,115), but similarly to nicotinamide, its exact role in metabolic control is still unclear.(111,116)

SIRT3, SIRT4 and SIRT5 localize primarily to mitochondria.(117,118) SIRT3 is the major mitochondrial deacetylase (119), and some of its targets have been have been known to have important roles in metabolic homeostasis. For example, the long-chain acyl CoA dehydrogenase (LCAD), a protein involved in fatty acid oxidation, is targeted by SIRT3 during prolonged fasting, which results in the activation of fatty acid breakdown. (120) Deletion of SIRT3 in mice bothers fat breakdown, exacerbating diet-induced obesity and rendering them sensitive to cold upon fasting.(121) SIRT3 deacetylation sites have also been identified in 3-hydroxy-3-methylglutaryl CoA synthase 2 (HMGCS2), that regulates the production of ketone bodies, an important energy source for the brain during the low blood glucose levels.(122) In response to caloric restriction, SIRT3 deacetylates and thereby activates IDH2, which is relevant in the TCA cycle.(123) SIRT3 also activates the TCA cycle enzyme glutamate dehydrogenase (GDH) (119), even though the physiological relevance of GDH deacetylation is still unknown. Besides that, SIRT3 deacetylates components of complex I (124), complex II (125) and complex III (126), which are involved in oxidative phosphorylation (OXPHOS), the final stage of mitochondrial aerobic respiration.

There are some natural compounds that have been identified as a SIRT1 activator, this provides further insights into sirtuin regulation.(127) Resveratrol also increases SIRT1 activity and enhances mitochondrial function in mice (128,129), protecting them from put on a high-fat diet, resveratrol-treated mice also live longer compared to those aren't.(129,130) Resveratrol also improves mitochondrial activity and metabolic control in humans, significantly lower resveratrol doses (around 200-fold lower than the doses given in mice) resulted in resembling plasma resveratrol levels, AMPK activation and physiological effects to those observed following resveratrol treatment in mice.(131) Some synthetic compounds have also been known could activate SIRT1. The most potent of these is SRT1720 (132), which is similar to resveratrol in protecting against diet-induced obesity by improving mitochondrial function (133) and extending the lifespan of obese mice (134).

Sirtuins deacetylate not only histones and several transcriptional regulators in the nucleus, but also specific proteins in other cellular compartments, such as in the cytoplasm and in mitochondria, making them known to have roles in different cellular compartments. As a results, sirtuins regulate fat and glucose metabolism in response to physiological alterations in energy levels, therefore acting as crucial regulators of the network which controls energy homeostasis and determines the healthspan.(135)

Epigenetic and Metabolism in Aging Stem Cells

Along with aging, there will also be a decline in tissue function, regeneration and repair, which are caused by the deterioration of tissue stem cell function. Knowing the mechanisms driving stem cell aging and how to counteract them is a critical process to enhance tissue repair and maintenance during aging. Emerging proof indicates that epigenetic modifiers and metabolism regulators interact to affect lifespan, suggesting that this mechanism may also works with stem cell function with age.(136) Tissue-specific stem cells are present in virtually every adult tissue in mammals and are important for tissue homeostasis and repair after injury. The prominent decline in the function of stem cell during aging, coupled with a bias in the type of differentiated cells they generate, could lead to the deterioration in tissue function and diminished capacity for tissue repair in elderly. Stem cell function is regulated in response to variety of external stimuli, including nutrient stress (*e.g.*, starvation or caloric restriction, or high fat diets).(137)

The complexity of stem cell compared to other somatic cells, might be complicate people's understanding on the interaction between cellular metabolism and chromatin features in stem cells. Stem cells naturally give raise to progeny which are vastly different in terms of virtually every biological parameter. For instance, quiescent stem cells show minimal metabolic activity, have few mitochondria and other organelles, and also have a minuscule cytoplasmic volume. Meanwhile in contrast, proliferating progeny manifest dramatic energetic changes, increases in biosynthetic activity, and cell growth. As these progeny differentiate into mature, tissue-specific cells, there are dramatic structural and functional changes. The dynamic interaction between the cellular metabolism and the epigenome is important to the control of stem cell transitions and function.(136)

Epigenetic alteration related to somatic stem cell aging have been reported for multiple stem cell populations, notably hematopoietic stem cells (HSCs) and muscle stem cells (MuSCs)/satellite cells.(138,139) In both HSCs and MuSCs, there is an age-dependent increase in the

repressive histone modification H3K27me3, whereas H3K4me3, a mark associated with active genes, displays breadth increase in HSCs but in slight intensity decreases in quiescent MuSCs along with age. Shifts in a number of other chromatin features, most of which are also altered with age, have been known to regulate stem cell function.(140) For instance, a change in DNA methylation affect the differentiation potential of HSC.(141,142) One mediator of heterochromatin formation, namely H3K9 methylation, is important for HSC differentiation.(143) Meanwhile H4K20 methylation controls MuSC quiescence by promoting the formation of facultative heterochromatin.(144) At last, exceptionally wide H3K4me3 domains form a signature for cell function, and these extended domains mark genes which are crucial for the ability of neural stem cells (NSCs) to self-renew and to differentiate into neurons.(145)

Thus, selected metabolites could promote long-lasting changes in gene expression and stem cell state changes in response to environmental stimuli. Given the epigenetic alternations associated with stem cell aging, it will be interesting to know how the shifting in metabolic regulation associated with aging explain these age-related changes in chromatin.(136)

Different metabolites can alter or maintain certain epigenetic states, thereby driving long-lasting changes in gene expression and modulating stem cell states. Metabolites (Acetyl Co-A, NAD, FAD, SAM, etc) serve as cofactor for epigenetic enzymes such as sirtuin deacetylases which is function as an important modulator for maintaining the somatic stem cells homeostasis. During aging process, NAD becomes limiting during the aging process, subsequently changing global levels of histone acetylation. This will activate the stress-responsive genes such as Nrf2 who is responsible for modulating redox homeostasis during the aging process and stem cells senescence.(146)

Another example, α-ketoglutarate play its role in histone demethylation by functions as a cofactor for both Ten-eleven Translocation (TET) enzymes which implicated in DNA demethylation and Jumonji family proteins applied in histone demethylases, potentially regulating various chromatin events in different types of stem cells.(146)

Whilst several main regulators of lifespan and healthspan, such as sirtuins, are directly influenced by metabolites, other crucial regulators, including the insulin-FOXO and the mTOR signaling pathways, are global integrators of cellular nutrient and metabolic status. The role of these pathways in the control of stem cell fate has been widely studied.(147) The mechanisms of rejuvenation of old stem cells could be mediated at least in part by the interaction between metabolites and epigenetic regulators. Cellular reprogramming has also been known to reset some age-dependent phenotypes including the metabolic and epigenetic features.(148) Hence, a targeted modification of specific metabolic and epigenetic pathways, especially those that happen in the early the reprogramming process, could be sufficient to promote rejuvenation without inducing dedifferentiation. Collectively, the knowledge of the interaction between metabolism and epigenetics will be crucial to identify the new strategies for preserving youthful cellular function as organisms age or to counteract age-related dysfunction of stem cells in old tissues.(136)

Conclusion

The intimate and reciprocal regulation between gene expression outputs and cellular metabolic state is undoubtedly very useful for the cell. There has been found enough proof to suggest that chromatin play a role as a metabolic gatekeeper of the genome. The wrapping of DNA around histones in a default repressive state might enable a cell to closely gather nutrient availability by controlling access to the DNA via the requirement of metabolites as histone modifiers and the regulation of a variety of cellular outputs by controlling the expression of particular modules of genes. Several researches that has been done in the past few years have placed this complex network of metabolism, chromatin architecture, and gene expression at center stage. Studies discussed in this review highlight the possibility that histone acetylation, deacetylation, methylation and demethylation are under the control of several main metabolic regulators, namely Acetyl-CoA, NAD+, SAM, and α-KG. It is likely more than coincidence that cells have chosen to regulate access to their DNA via histone modifications which are dependent on key intermediates of metabolism.

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