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Metabolic programming of the epigenome: host and gut microbial metabolite interactions with host chromatin

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Abstract

The mammalian gut microbiota has been linked to host developmental, immunologic, and metabolic outcomes. This collection of trillions of microbes inhabits the gut and produces a myriad of metabolites, which are measurable in host circulation and contribute to the pathogenesis of human diseases. The link between endogenous metabolite availability and chromatin regulation is a well-established and active area of investigation, however, whether microbial metabolites can elicit similar effects is less understood. In this review, we focus on seminal and recent research that establishes chromatin regulatory roles for both endogenous and microbial metabolites. We also highlight key physiologic and disease settings where microbial metabolite-host chromatin interactions have been established and/or may be pertinent.

Introduction

The static information contained in the eukaryotic genome is made remarkably more dynamic and complex via its association with other nuclear proteins and nucleic acids. In eukaryotes, genomic DNA is organized and compacted into what is known as chromatin, which consists of nucleic acids, histone proteins, and other chromatin-associated proteins. Adding to this complexity, these proteins and nucleic acids undergo chemical modification, and small and non-coding RNAs can also exert regulatory effects on the genome (reviewed in (1–3)). This collection of factors, that exists independently of the DNA sequence itself, comprises the epigenome and exerts regulatory control over processes such as transcription and DNA replication and repair.

These epigenetic factors allow eukaryotes to sense and respond to environmental cues. Intermediary metabolites, such as acetyl coenzyme A (acetyl-CoA) and alpha-ketoglutarate (α-KG; also known as 2-oxoglutarate, 2-OG) are key messengers to the epigenome of stimuli and stressors. In addition to intermediates of macronutrient metabolism,

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micronutrients and minerals (e.g., B-vitamins and iron) also regulate the activity of chromatin-modulating enzymes. While the interplay between chromatin and endogenous metabolites has been a subject of intense investigation for nearly two decades, recent findings have revealed the mammalian gut microbiota as a major producer of metabolites, many of which have been demonstrated to play regulatory roles on host physiology (reviewed in (4)). Analogous to endogenous metabolites, gut microbial metabolites may signal to host chromatin to alter host genetic responses to environmental signals.

The mammalian gut microbiota consists of trillions of bacteria that inhabit the mammalian gut. Fungi and viruses are also detectable within the host gut microbiome, however data regarding regulation of host physiology by these organisms are scarce, and there is no evidence, to our knowledge, of commensal fungi (5,6) and viruses (7) directly impacting host epigenetic programming. Thus, this review will primarily focus on gut bacteria. The gut microbiota has been demonstrated to play both protective and contributory roles in the setting of human disease. Several associations have been made between the gut microbiota and host metabolic disease, including obesity and adipose tissue inflammation (8–13), metabolic syndrome and type 2 diabetes mellitus (T2DM) (14–23), cardiovascular disease (24–27), and non-alcoholic fatty liver disease (NAFLD) (28–30). The gut microbiota has also been linked to autoimmune, inflammatory, and allergic disease, including type 1 diabetes mellitus (T1DM) (31,32), inflammatory bowel disease (33–36), allergy and asthma (37–39). In the setting of colon cancer, the gut microbiota has been associated with both therapeutic effects (40,41) and promotion of disease (42). Thus, the gut microbiota exerts effects on a variety of host organ systems and either contributes to or provides protection against metabolic, immunologic, inflammatory, and oncologic disease.

Host diet and environment also affect the functional capacity and composition of the gut microbiota. Both over-nutrition (9,10,12) and malnutrition (43–46) affect the gut microbiome. In humans, an altered diet can affect gut microbial community composition and function within as little as one day after the altered diet reaches the distal gut (47). Common dietary additives such as non-caloric artificial sweeteners and emulsifiers have also been linked with gut dysbiosis (alteration in the gut microbiota associated with pathogenesis) and glucose intolerance and inflammatory bowel disease, respectively (16,34). Additionally, there are known differences in microbiota composition, gene-richness, and metabolite production associated with agrarian or plant-based diets *vs.* “Westernized” diets (47–51). There are also lasting consequences of obesity and a “Western” lifestyle on the microbiome, both in the setting of post-diet weight gain (52) and multigenerational consumption of a diet low in microbial accessible carbohydrates (MACs), which result in a progressive loss of diversity that cannot be replenished by reintroduction of dietary MACs (53). In addition to dietary factors, altered gut anatomy in the setting of gastric bypass surgery influences the gut microbiota and its function (54,55). Finally, the early life environment, including in-utero, has been shown to impact the gut microbiota and metabolic outcomes (32,56–58).

Thus, the interactions between mammalian hosts and their gut microbiota are myriad and complex, affected by environmental factors such as diet and lifestyle, and are dynamic throughout the lifespan. While many associations have been made between host phenotypes and microbial community composition and metabolite production, the molecular

mechanisms underlying these phenotypes remain largely unexplored. Understanding how the microbiota communicate environmental cues to the host epigenome provides an additional avenue for mechanistic exploration. Here, we review seminal and recent literature focused on regulation of chromatin states by endogenous and gut microbial metabolite availability. Additionally, we highlight clinically relevant settings in which these interactions occur.

Chromatin Dynamics

Genomic DNA in eukaryotes is packaged into chromatin, a highly structured nucleo-protein complex that compresses DNA by a factor of approximately 1,000 to 10,000-fold in interphase and mitotic chromosomes, respectively (59). The fundamental unit of chromatin is the nucleosome core particle, which is comprised of an octamer of core histone proteins (2 copies each of histone H2A, H2B, H3, and H4) wrapped by 146bp of genomic DNA (60). Nucleosome core particles are separated from each other by linker DNA that varies in length from ~10–80bp. Roughly 75–90% of genomic DNA interacts with nucleosomes, which are spaced, on average, every 200 bp. Nucleosome positioning is dictated, in part, by the underlying DNA sequence. The numerous salt bridges, hydrogen bonds, and ionic interactions that occur between histone residues and the DNA phosphate backbone induce significant bending of the DNA as it wraps around the histone core 1.65 times, and sequence-dependent DNA flexibility pays a key role in this process (60). About 50% of nucleosome positioning in yeast can be explained by the intrinsic DNA sequence, wherein nucleosome occupancy can be predicted based on nucleosome affinity for a particular sequence of genomic DNA (61). Packaging of DNA into nucleosomes generally inhibits binding of other non-histone proteins with DNA-binding motifs. In support of this, accessibility of DNA bound to a nucleosome core particle has been reported to be 73% that of bare DNA (60). However, nucleosomes can also recruit specific chromatin “readers”, including bromodomain and chromo- and tudor-domain containing proteins, which recognize and bind to acetylated and methylated histone residues, respectively (62,63).

Histones are small, highly basic proteins with flexible N-terminal tails that are subject to a variety of covalent post-translational modifications (PTMs). Although histone methylation, acetylation, and phosphorylation are the most commonly studied modifications, a growing list of other chemical modifications has been identified on histones, including various acylations (propionylation (64), butyrylation (64), 2-hydroxyisobutyrylation (65), malonylation (66), succinylation (66), and crotonylation (67,68)), sumoylation (69), O-linked N-acetylglucosamine (70–72), ubiquitination (70,73), formylation (74), glutathionylation (75), and ADP-ribosylation (76) (reviewed in (77)). These modifications and their functional significance, if known, have been extensively catalogued (78). Briefly, histone PTMs affect chromatin structure (i.e. open vs. closed) and/or recruit other factors that recognize specific histone PTM states, ultimately impacting processes involving interaction with genomic DNA. It is noteworthy that linker DNA can also be bound by the linker histone H1, and that selective incorporation of histone H1 is generally associated with closed chromatin. Finally, there exists extensive crosstalk between histone PTMs, which are thought to collectively comprise a “histone code,” a complex and combinatorial cipher that integrates environmental cues to regulate transcription, replication, and repair processes (3).

The activity of most histone-modifying enzymes is dependent upon sufficient levels of intermediary metabolites, vitamins, and minerals. These small molecules act as necessary co-substrates, activators, or inhibitors, thereby coupling cellular metabolic state to chromatin regulation. Subsequent sections will focus on regulation of chromatin by endogenous and gut microbial metabolites. Given the focus on gut microbiota-mediated regulation of host chromatin here, we cannot exhaustively cover chromatin regulation by endogenous metabolites, but direct readers to high yield reviews on those subjects.

Regulation of Chromatin Modification by Endogenous Metabolite Availability

Histone Acetylation and Central Carbon Metabolism

Histone acetylation was first identified in 1963 (79), and was demonstrated to de-repress histone-mediated inhibition of RNA synthesis in 1964, at which point it was hypothesized not only to regulate transcription, but also to be reversible (80). More than 50 years later, histone acetylation remains an active area of investigation, particularly in relation to cellular metabolism and in the setting of cancer pathogenesis and treatment. Histone acetylation has been reported on lysine, arginine, threonine, and serine residues, and occurs on canonical histone proteins H2A, H2B, H3, and H4 as well as the variant histones H2A.Z and H3.3 and the linker histone H1 (reviewed in (77,78)).

Acetylation of lysine residues neutralizes the positive charge on the lysine epsilon amino group, which decreases the ionic interaction between histones and the negatively charged phosphate backbone of DNA. This results in a relative opening of chromatin, and histone acetylation is broadly associated with activate transcription. Acetylated lysine residues are “read” or recognized by bromodomain-containing proteins, which in addition to a bromodomain, often contain a variety of other functional domains that allow for HAT activity, DNA binding, histone methyltransferase activity, helicase activity, ATPase activity and more (reviewed in (81)).

Histone acetylation most commonly occurs on lysine residues and is catalyzed by histone acetyltransferases (HATs; also known as KATs, lysine acetyltransferases). HATs comprise a superfamily of enzymes that is divided into 5 sub-families, based on sequence and structural similarities. These families include Hat1, Gcn5/PCAF, MYST, p300/CBP, and Rtt109, all of which possess a conserved acetyl-CoA binding region, but their N- and C-terminal regions play roles in substrate binding (reviewed in (82)). All 5 sub-families transfer an acetyl moiety from the thioester of acetyl-CoA to a lysine epsilon amino group on histones, generating a molecule of CoA, but each has a unique catalytic mechanism (reviewed in (83) and (82)). HATs also display rather promiscuous substrate specificity, and the molecular mechanisms underlying this process are not well understood.

In addition to its role in histone acetylation, acetyl-CoA lies at the center of both catabolic and anabolic metabolism. Acetyl-CoA is produced by a number of processes including (1) oxidation of glucose to pyruvate and oxidative decarboxylation of pyruvate to acetyl-CoA via glycolysis and the pyruvate dehydrogenase complex, (2) activation of acetate to acetyl-

CoA via mitochondrial and cytosolic acetyl-CoA synthetase 1 and 2, respectively (ACSS1 and 2), (3) β-oxidation of free fatty acids, and (4) breakdown of amino acids and ketone bodies (Figure 1A). In a fed state, acetyl-CoA production is mostly associated with breakdown of glucose, whereas in a fasted state, the majority of acetyl-CoA comes from fatty acid β-oxidation. Depending on cellular state, acetyl-CoA is either fed into the TCA cycle to support ATP production or is shuttled into biosynthetic pathways, including lipid, cholesterol, and amino acid production.

Given that acetyl-CoA is the acetyl donor for all HATs, availability of this metabolic intermediate also affects HAT activity and functions as a cellular rheostat linking metabolic and chromatin states. Indeed, oscillations in acetyl-CoA availability during the yeast metabolic cycle coincide with enrichment of histone acetylation at key growth genes (84). Mammalian cells have a similar dependence on acetyl-CoA availability for histone acetylation. In contrast to single-celled eukaryotes, which rely upon acetate conversion to acetyl-CoA via ACS2 for histone acetylation (85), metazoans rely on glucose as a primary carbon source. Thus, in mammalian cells, nucleocytosolic acetyl-CoA is produced, in part, from glucose-derived citrate that is shuttled out of mitochondria and converted to acetyl-CoA via ATP-citrate lyase (ACL). Wellen et al. demonstrated that ACL is necessary for glucose-dependent histone acetylation in mammalian cells and that supplementation with acetate can partially rescue histone H3 acetylation in siACL-treated mammalian cells (86). Thus, histone acetylation in both single-celled and metazoan eukaryotes is mediated by acetyl-CoA availability, and although ACL plays a primary role in histone acetylation in mammalian cells, AceCS1-mediated (also known as ACSS2) production of acetyl-CoA may contribute as well. Indeed, both ACL and AceCS1 have been demonstrated to be important for histone acetylation in the setting of mammalian tumorigenesis (87,88).

Interestingly, the cytosolic isoform of acetyl-CoA synthetase in yeast and mammalian cells (ACS2 and AceCS1, respectively) is localized to both the cytosol and nucleus (86,89). ACL is also localized to both the cytosol and nucleus (86). Since both acetate and citrate are small enough to diffuse through nuclear pores (90), this suggests that acetyl-CoA can be produced in both the cytosol and nucleus, possibly supporting localized production for histone acetylation. A number of metabolic enzymes have been reported to “moonlight” in the nucleus, including pyruvate kinase (PK) and the pyruvate dehydrogenase complex (PDC), which can translocate to the nucleus and facilitate local acetyl-CoA production for histone acetylation (91). Further, PK and PDC form a complex with the HAT p300 to promote histone acetylation and activation of transcription (92). This phenomenon of “moonlighting” metabolic enzymes in the nucleus is not limited to those involved in histone acetylation. A number of other mitochondrial enzymes whose products regulate histone-modifying enzymes have also been reported to translocate to the nucleus under various conditions (reviewed in (93)). Therefore, local production of key regulatory metabolites may represent a key mode of communication of metabolic status to the nucleus.

Histone Deacetylation and Intermediary Metabolites

Histone acetylation is a balance between the activity of HATs and histone deacetylases (HDACs). Mammalian HDACs are grouped into four classes, based on their homology to

yeast deacetylases, enzymatic activities, and subcellular localization. Class I, IIa-b, and IV HDACs are Zn^{2+}-dependent, and are inhibited by small molecules that chelate the active-site Zn^{2+}, including trichostatin A (TSA) and the pharmacologic HDAC inhibitor (HDACi) Vorinostat (suberoylanilide hydroxamic acid, SAHA). While Class I HDACs are localized to the nucleus, Class IIa are nucleocytosolic, Class IIb are primarily cytosolic, and Class IV are cytoplasmic (reviewed in (94)). The Class III HDACs, also known as sirtuins, are a family of enzymes that carry out NAD^+-dependent lysine deacetylation, generating nicotinamide and 2'-O-acetyl-ADP-ribose (reviewed in (95) and (96)). Although sirtuins have a conserved NAD^+-binding site and catalytic domain, they diverge based on their subcellular location, tissue-specific expression patterns, and substrate specificity (95). There are 7 mammalian sirtuins, of which Sirt1 and Sirt6 are nuclear, Sirt2 is nucleocytosolic, and Sirt7 is localized to the nucleolus.

Regulation of histone deacetylation by metabolic intermediates is shown in Figure 1B. Sirtuins require NAD^+ as a co-substrate for histone deacetylation. NAD^+ can be synthesized de-novo from tryptophan via the kynurenine pathway, or salvaged from niacin (vitamin B3), which is comprised of nicotinamide (NAM) and nicotinic acid (NA), or nicotinamide riboside (NR). NAD^+ production, salvage, and biology is thoroughly reviewed in (97). NAD^+ functions as a redox cofactor in multiple oxidative pathways, including glycolysis, the TCA cycle, oxidative phosphorylation, and β-oxidation of fatty acids. Therefore, sirtuins can sense cellular metabolic status via NAD^+ availability.

Sirtuin histone deacetylase activity was first linked to nutrient availability in 2000. Imai et al. demonstrated that yeast and mouse Sirt2 (H4 K16 deacetylase), which was already associated with silenced chromatin, required NAD^+ for histone deacetylase activity (98). Sirt1 (H3 K9 and K14 deacetylase) activity is also affected under conditions where NAD^+ salvage is impaired, including aging and diet- and age-induced T2DM. Gomes et al. have identified a PGC1α/β-independent pathway that links the age-related decline in NAD^+ availability to decreased Sirt1 activity, which ultimately stabilizes Hif1α and decreases expression of mitochondrial encoded OXPHOS genes (99). Caloric excess associated with high fat feeding can overwhelm mammalian metabolism. Indeed, mice fed a high fat diet display impaired NAD^+ biosynthesis and develop T2DM. This diet-induced T2DM is rescued by supplementation with an NAD^+ precursor via a mechanism that is partially mediated by Sirt1 (100).

Given that Sirt6 (H3 K9 and K56 deacetylase) has a higher affinity for NAD^+ and can bind it in the absence of a an acetylated substrate, it is less likely that Sirt6 is regulated by availability of this metabolite (101). Interestingly, Sirt6 has very low *in-vitro* histone deacetylase activity but is activated up to 35-fold by select long-chain fatty acids (LCFAs), including myristic, oleic, and linoleic acid (95). Sirt6 plays a role in genome stability and glucose homeostasis, and loss of Sirt6 function plays a role in the metabolic switch that occurs in human tumors (102,103).

Unlike sirtuins, the Zn^{2+}-dependent HDACs do not require NAD^+ as a co-substrate. However, these HDACs are still regulated by small molecule metabolites. The discovery that butyrate inhibits HDACs in Friend erythroleukemic cells was one of the first examples of

metabolite-mediated regulation of epigenetic machinery (104,105). The structural analog and ketone body, β-hydroxybutyrate (β-OHB, also known as 3-hydroxybutyrate), also inhibits these HDACs. During fasting, the liver switches to oxidation of fatty acids rather than glucose. When the acetyl-CoA produced by fatty acid oxidation exceeds the oxidative capacity of the liver, it is channeled into synthesis of ketone bodies, two of which are organic acids: acetoacetate and β-OHB. Interestingly, the ratio of acetoacetate to β-OHB produced is dependent upon the NAD^+/NADH ratio, which is low during fatty acid oxidation, thus favoring production of β-OHB. β-OHB inhibits Class I and IIa HDACs with a median IC_{50} in the range of 2–5 mM (106). Human serum levels are typically ~100 μM, but levels can increase up to 6 mM following a 2–3 day fast or strenuous exercise, up to 25 mM in uncontrolled diabetes mellitus, and up to 2 mM with a ketogenic diet that is almost devoid of carbohydrates (107–109). Thus, physiological fluctuations in serum ketone bodies are sufficient to exert effects on HDAC activity. Though not a primary focus here, the functional effects of ketone body inhibition of HDACs are reviewed in (110).

Histone Methylation and One-Carbon Metabolism

Lysine and/or arginine methylation occurs on all core histone proteins, variant histones H3.3, H2A.Z, and macroH2A; and the linker histone H1 (histone methylation is reviewed in (62)). Lysine residues can be monomethylated (me1), dimethylated (me2), or trimethylated (me3), whereas arginine residues can be either monomethylated or dimethylated, and arginine dimethylation can occur either asymmetrically or symmetrically. Both the site and degree of methylation determine function. For example, methylation of H3K4, H3K36, and H3K79 is associated with active transcription, whereas methylation of H3K9, H3K27, and H4K20 are associated with repressed transcription (78). In contrast to histone acetylation, methylation of histones does not alter the positive charge of lysine and arginine residues, and thus does not have a significant impact on chromatin structure. Rather, histone methylation serves as a docking site for other factors that contain methyl-binding domains, including PhD fingers, WD40 repeats, CW domains, PWWP domains, Ankyrin repeats, and members of the Royal superfamily (includes chromodomains and Tudor domains).

As with acetylation, histone methylation is dynamic and informed by intermediate metabolites (Figure 1C). Histone methylation is carried out by histone methyltransferases (HMTs) and is removed by demethylases. All HMTs utilize the methyl donor, S-adenosylmethionine (SAM), an intermediary metabolite in the one-carbon (1C) cycle. SAM availability is maintained by the folate and 1C cycles, which not only support histone and DNA methylation, but also provide intermediates for nucleic acid synthesis, amino acid homeostasis, and redox homeostasis. Thus, SAM availability connects several metabolic processes to histone methylation.

One-carbon metabolism is reviewed in (111). Although plants and select bacteria and yeast can synthesize folate and methionine, humans cannot and must obtain both via diet. Notably, while a number of dietary nutrients can serve as sources of 1C units, choline, serine, and glycine are the most important sources (111). The folate and 1C cycles converge at re-methylation of homocysteine to form methionine via a vitamin B12-dependent reaction catalyzed by methionine synthase (MTR). Homocysteine can also be re-methylated to

methionine via betaine-homocysteine methyltransferase (BHMT), which uses betaine as a methyl donor. The formation of SAM from methionine is then catalyzed by methionine adenosyltransferase (MAT) in an ATP-dependent reaction that is conserved across all branches of life (112,113). Thus, vitamin and nutrient availability affects SAM levels, which may regulate the activity of HMTs.

Indeed, restriction of either methionine or folate in the growth medium of methionine-dependent Δmet or folate-dependent Δfol yeast strains, respectively, results in decreased H3K4me2 and H4K4me3 (114). Similar evidence is present in higher eukaryotes as well. In mouse embryonic stem cells (mESCs), threonine catabolism provides a significant fraction of cellular glycine, which feeds into production of SAM. Restriction of threonine in the growth medium of mESCs and knockdown of *Tdh* (threonine dehydrogenase) results in decreased SAM availability and H3K4me3, which slowed growth and increased differentiation (115). Methionine restriction in Hct116 cells results in decreased H3K4me3 in select regions of the genome, which corresponded with decreased expression of enzymes involved in 1C metabolism, suggesting direct feedback on 1C metabolism to maintain homeostasis (116). Further, methionine restriction in mice results in decreased plasma methionine and liver SAM levels and a concomitant decrease in liver H3K4me3, demonstrating that dietary restriction of 1C sources affects histone methylation *in-vivo* (116).

Histone Demethylation and TCA cycle intermediates

There are two families of histone demethylases, both of which are regulated by intermediates of the TCA cycle: (1) the FAD-dependent LSD (lysine specific demethylase) family of enzymes, and (2) the alpha-ketoglutarate- (α-KG), iron-, and oxygen-dependent JmjC (Jumonji C) family of enzymes (Figure 1C). These enzymes are reviewed in detail in (117). FAD is produced in the cytoplasm and mitochondria from vitamin B2 (riboflavin), and is involved in the TCA cycle, oxidative phosphorylation, and fatty acid β-oxidation. Loss of the H3K4 and H3K9 demethylase LSD1 in cultured adipocytes, either by small molecule inhibition or by knockdown, leads to increased expression of genes involved in energy expenditure via increased H3K4me3 at promoters (118). α-KG is a TCA cycle intermediate that is produced in mitochondria by IDH2/3 (isocitrate dehydrogenase 2 and 3) and in the cytosol by IDH1. While the role of α-KG levels in regulation of JmjC family histone demethylases has not yet been shown, both oxygen and iron availability mediate the activity of these enzymes. Hypoxia has been reported to increase histone methylation and modulate downstream gene expression in a number of settings and cell types via inhibition of JmjC demethylases (119–121), and pharmacologic iron chelation in mouse myoblast cells results in increased histone methylation at JmjC target sites (122). Notably, although the direct role of α-KG as a regulator of JmjC family members remains to be elucidated, its structural analog 2-hydroxyglutarate (2-HG), which is produced by cancer-associated IDH1 and IDH2 mutants, is a competitive inhibitor of these enzymes, resulting in aberrant histone methylation that contributes to the cancer phenotype (123,124). The role of 2-HG as an oncometabolite is reviewed in (125). A subset of cancers also display mutations in FDH (fumarate dehydrogenase) and SDH (succinate dehydrogenase), which result in

accumulation of fumarate and succinate, respectively, both of which inhibit JmjC demethylases (126,127).

While not a focus of this review, it is also worth noting that DNA methyltransferases (DNMTs) and the Ten Eleven Translocation (TET) methylcytosine dioxygenases, which oxidize 5-methylcytosines to promote DNA demethylation, have similar metabolite dependencies as histone methyltransferases and demethylases (Figure 1C). Dietary restriction of 1C sources results in altered DNA methylation (DNAm) patterns in mice and humans (128,129), and the cancer-associated FDH and SDH mutations induce DNA hypermethylation via inhibition of α-KG-dependent TET enzymes (126,130,131).

Regulation of chromatin by gut microbial metabolites

Given the many roles endogenous metabolites play in chromatin regulation, the question arises whether gut microbial metabolites can exert similar effects. The interaction between microbial metabolites and histone acetylation, histone methylation, and DNA methylation is depicted in Figures 2–4, respectively. Mammalian hosts (and all other coelomates) have coevolved with a collection of trillions of microorganisms that inhabit the gut, known as the gut microbiota (132–134). The gut microbiome, which collectively contains roughly 9.9 million bacterial genes, profoundly expands the genetic capacity and diversity of the human host by a factor of 500-fold (135,136). This collection of symbiotic microorganisms, which is shaped by complex trophic and competitive interactions, provides the host with considerable metabolic flexibility. Complex dietary substrates, including polysaccharides and resistant starches (known as microbial accessible carbohydrates or MACs), are not metabolized by host enzymes in the upper gastrointestinal tract and pass to the distal gut where they are subject to microbial fermentative reactions that produce a wide variety of metabolites, including short chain fatty acids (SCFAs). Acetate (C2), priopionate (C3), and butyrate (C4) comprise ≥95% of SCFAs produced by the gut microbiota, but lactate (C3), valerate (C5), capropate (C6), and branched SCFAs (bSCFAs) such as isobutyrate (C4) and isovalerate (C5) are also produced in lesser quantities (137). The gut bacteria also degrade proteins and amino acids, producing branched-chain fatty acids, amines, volatile sulfur compounds, and phenolic compounds (137). The gut microbiota and its metabolites have been associated with a number of host developmental, immunologic, and metabolic outcomes, including proper nervous and immune system development (138–140), obesity (8,9,13,141), diabetes mellitus (14,15,32) (142), cardiovascular disease (24), non-alcoholic liver disease (28), inflammatory bowel disease (33,34), and colorectal cancer (40–42).

Here we discuss evidence for gut microbial regulation of the host epigenetic machinery via de-novo synthesis, co-metabolism of dietary and host intermediates, direct competition with the host for dietary nutrients, and conversion of dietary substrates to bioactive compounds.

Organic Acids

While direct modification of chromatin states by gut microbial metabolites in vivo has not yet been revealed for the vast majority of microbially produced small molecules, there is direct evidence that SCFAs impact host tissue histone modification (Figure 2) (40,143). In a mouse model of colorectal cancer (CRC), colonization with a minimal core microbiome plus

the butyrate producer *B. fibrisolvens* and high fiber feeding resulted in increased butyrate production by the microbiota and accumulation of butyrate in Warburg-like cancer cells, leading to HDAC inhibition and increased histone H3 acetylation (40,41). These mice also had a lower tumor burden and altered expression of genes involved in apoptosis and proliferation in tumors relative to controls (40). Butyrate and histone acetylation levels were also higher in human CRC tumor samples vs. nearby normal tissue, suggesting that this diet-microbiota-host chromatin interactions occurs in human tissue as well (40). We recently demonstrated that global host histone methylation and acetylation are driven by the gut microbiota in a diet-dependent manner in multiple tissues, including those outside the alimentary tract (143). Further, the microbiota-driven chromatin effects were partially mimicked by supplementation of germ-free mice with a mixture of the three most abundance SCFAs (acetate, propionate, and butyrate) (143).

Treatment of HT-29 human CRC cells with propionate, butyrate, and valerate induces histone H4 acetylation, causes cell cycle arrest, and induces expression of markers of cellular differentiation (144). Notably, although acetate and caproate were tested in this study as well, there were no appreciable effects of these organic acids (144). However, acetate can induce histone acetylation in Hct116 cells (86). Waldecker et al. show that C3–C5 SCFAs and C4–C5 bSCFAs inhibit HDACs in HT-29 cells, but that acetate has no HDACi activity, even at concentrations as high as 20 mM (145). Lactate (C3), another fermentation product, also displays HDACi activity (146). Finally, the gut microbiota produce succinate, which is a known inhibitor of both the JmjC family of histone demethylases and the TET family enzymes that facilitate DNA demethylation (126,130).

B-vitamins

The gut bacteria can synthesize de novo a number of B-vitamins, including riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), folate (B9), and cobalamin (B12) (reviewed in (147)). B-vitamins play a role in histone acetylation (Figure 2), histone methylation (Figure 3), and DNA methylation (Figure 4). Vitamins B6, B9, and B12 are all important components and cofactors of the folate and 1C cycles, and promote availability of the universal methyl donor SAM for HMTs and DNMTs. More specifically, vitamins B6 and B12 are both necessary cofactors in 1C metabolism (Figure 1C). Animals cannot synthesize folate, and thus depend on exogenous sources such as dietary intake. Another potential source, however, is the colonic microbiota, which can synthesize equal or more folate than typical adult dietary intake (148,149). Further, microbially produced folate is readily absorbed across the gut in adult human subjects (149). Vitamin B2 is a precursor for FAD, a necessary cofactor for methylenetetrahydrofolate reductase (MTHFR) in the folate cycle.

Vitamins B3 and B5 affect histone acetylation. Vitamin B3 (niacin) is comprised of nicotinic acid (NA) and nicotinamide (NAM), both of which contribute to the NAD^+ pool via the NAD^+ salvage pathway via distinct enzymes (150). Increasing the NAD^+ pool may impact the activity of the NAD^+-dependent sirtuin family of histone deacetylases. It is also worth noting that NAM is a product inhibitor of sirtuins (151). VItamin B5 is a precursor for coenzyme A (CoA), and is phosphorylated by pantothenate kinase during the first step of CoA synthesis. CoA is necessary for the production of the HAT substrate acetyl-CoA.

Although it is unclear how bacterial production of vitamin B5 affects availability in host circulation, RNAi-mediated silencing of pantothenate kinase in *Drosophila* S2 cells reduces CoA levels and acetylation of histone H3, histone H4, and tubulin (152). This decrease in protein acetylation is associated with impaired DNA damage repair and survival that is partially rescued by supplementation with pantethine or HDACi treatment (152). Thus, gut microbial production of B-vitamins may promote histone and DNA methylation by supporting SAM availability and may impact histone acetylation via regulation of sirtuins and HATs, though direct regulation by the gut microbiota of these processes remains to be demonstrated.

Conversion of Dietary Substrates to Chromatin-Modulatory Compounds

In addition to degradation of complex plant polysaccharides, resistant starches, and proteins, the gut microbiota also chemically transforms plant polyphenol and isothiocyanate metabolites into bioactive compounds. Plant polyphenols are found in various fruits, vegetables, nuts, and teas and undergo extensive transformations by the gut microbiota prior to entering enterohepatic circulation and undergoing further metabolism by the host (153,154). Although these compounds have limited bioavailability and are found at low levels in plasma, in-vitro and cell culture experiments reveal that these compounds affect HATs, HDACs, DNMTs, and even non-coding RNAs. It is also worth noting that a number of polyphenol metabolites are aromatic organic acids, which may account for their weak HDACi activity. Epigallocatechin (ECGC), phenolic acids, stilbenes, and coumarins exert weak HDACi activity (145,155,156). Additionally, the stilbene resveratrol has been demonstrated to target the class III HDAC Sirt1, the HAT p300, and non-coding RNA expression (156–158). Unlike other polyphenol metabolites, ellagic acid does not affect HDAC activity, but rather has been shown to decrease HAT activity in TNF-stimulated THP-1 cells (159). The polyphenol metabolites ECGC and flavonoids (catechin and quercetin) and the isothiocyanate sulforaphane have been demonstrated to inhibit DNMTs (160–162).

Host-microbe Cometabolites

In addition to the myriad of metabolites produced by the gut microbiota, there is also considerable cometabolism of circulating host and microbial metabolites. For example, bile acids are synthesized from cholesterol in the liver, excreted into the gut following a meal, and about 95% are reabsorbed across the gut to circulate back to the liver in a process called enterohepatic circulation. These primary bile acids are metabolized by the gut microbiota in the ileum and colon to generate secondary bile acids, which function as potent signaling molecules and regulate a number of metabolic processes, including synthesis of primary bile acids (reviewed in (163)). Of note, the gut microbiota influences both the bile acid pool size and composition (163). Ursodeoxycholic acid, which is a primary bile acid in mice but a secondary bile acid in humans, induces expression of HDAC6 and subsequent hypoacetylation of histones H2A, H3, and H4 in cultured cells (164). However, it is unclear how ursodeoxycholic acid affects the expression of *HDAC6*, and more investigation is required to better understand how bile acids may affect histone modification.

Microbial metabolites are also metabolized by the host. Trimethylamine (TMA) is a microbial product of dietary choline metabolism (165). There is also evidence that TMA-producing gut microbes compete with the host for dietary choline availability (26). TMA enters host circulation and is metabolized to trimethylamine-N-oxide (TMAO) in the liver by flavin-dependent monooxygenase 3 (FMO3) (166). TMAO has recently been associated with both non-alcoholic fatty liver disease (167) and cardiovascular disease (24). Therefore, gut microbial competition with the host for dietary choline may impact SAM availability and ultimately histone and DNA methylation. Whether this competition contributes to a chromatin-mediated mechanism underlying these diseases remains unclear.

The gut microbiota also participates in metabolism of dietary PUFAs (poly-unsaturated fatty acids). Gut bacteria isolated from humans are able to metabolize PUFAs such as linoleic acid and alpha-linolenic acid into conjugated linoleic acids and conjugated linolenic acids (168). The conjugated PUFAs are detectable in cecal contents of mice supplemented with dietary PUFAs, but not in plasma, suggesting that the effects of these compounds is likely confined to the intestine (168). Given that the gut microbiota can metabolize PUFAs, it is also possible that microbes compete with the host for these compounds. Linoleic acid is a known activator of the nuclear HDAC Sirt6 *in-vitro* (95), therefore, it is possible that bacterial co-metabolism of this PUFA may affect its availability to Sirt6 in mammalian hosts.

Interplay Between Environment, Microbiota, and Chromatin in Disease

The mammalian gut microbiota has emerged as a key mediator of host metabolism and health. A major route of chemical communication between this vast group of microorganisms and the host is via microbial metabolism of dietary nutrients and production of metabolites. Microbial metabolites have been demonstrated to play roles as signaling molecules and metabolic substrates (15,18,19,52,163,169), a topic which has been thoroughly reviewed (4,163,170). There is evidence that exposure to antibiotics (171), cold ambient temperatures (172), natural seasonal variation in food intake and ambient temperature during hibernation (173–175), natural seasonal variation in food sources (176), geographical and cultural differences in dietary habits or dietary scarcity (48–50,177,178), hormonal cues (31,58), alteration in dietary macronutrient composition (10,47,53,179), food additives (16,34), and more can affect gut microbial communities.

This prompts a new framework for investigation of gut microbiota-host interactions, wherein communication between the host and its microbiota occurs not only through ligand:receptor interactions, but also through modification of chromatin via regulation of histone- and DNA-modifying enzymes by small molecule metabolites. Within this model (Figure 5), mammalian hosts encounter any number of environmental exposures throughout life. These exposures are sensed by the gut microbiota, which are in direct contact with the environment given their residence in the alimentary tract. Microbial community composition and activity are altered in response to changes in environment, resulting in altered microbial metabolite profiles. Metabolites are then absorbed across the host gut and serve as effector molecules at the level of host chromatin, where they elicit changes in gene expression programs, ultimately leading to a new developmental and/or metabolic phenotype. Below, we highlight

known relationships between gut microbial metabolites and host chromatin in the setting of host health and disease.

Innate and Adaptive Immunity

Gut microbial metabolites and microbial components signal to the host immune system, regulating both proper immune system development and function. This includes production of SCFAs, aryl hydrocarbon receptor ligands, polyamine metabolites, and activation of host pattern recognition receptors via microbial components such as lipopolysaccharide, flagellin, peptidoglycan, and formyl peptides. This topic is vast and readers are directed to a recent comprehensive review (140) for specific information about microbiota-host immunity interactions. Here, we specifically highlight instances in the literature that associate the gut microbiota with epigenetic control of host immunity.

Blood-brain barrier (BBB) permeability is increased in GF mice relative to specific pathogen free (SPF) control mice (180). GF mice have decreased expression of the tight junction proteins occludin and claudin-5, but colonization of GF mice with SPF fecal microbiota increased expression of these tight junction proteins and decreased BBB permeability (180). Since SCFAs are known to enhance barrier integrity in the intestinal epithelium via proper assembly of tight junctions, Braniste et al. investigated whether the SCFA butyrate could induce similar effects at the BBB, and found increased histone acetylation in brain lysates from GF mice either treated with sodium butyrate (an HDACi) or mono-colonized with the butyrate producer *C.tyrobuticum* (180). Priming of NK cells in the innate immune system has also been shown to be partially affected by differential histone H3K4me3 enrichment at transcriptional start sites of microbiota-mediated inflammatory response genes, and treatment of conventionally raised (ConvR) mice with antibiotics erased H3K4me3 at these genes (181). Differences in chromatin accessibility at enhancers in GF mice relative to their ConvR counterparts have also been identified in purified intraepithelial lymphocytes (IEL), revealing transcription factor circuits that are differentially regulated in GF and ConvR mice (182). Enhancers in IEL populations also stratify by their history of microbial exposure, where IEL enhancers from GF mice clustered separately from those in ConvR mice, which were colonized at birth, and from IELs in conventionalized mice (ConvD), which were colonized at 3 weeks of age (182). Collectively, these studies suggest that the gut microbiota signals to innate and adaptive host defense systems via mechanisms that are at least partly tuned by chromatin responses.

SCFAs in Cancer and Diet-Induced Obesity

Gut microbial butyrate is protective in the setting of colon cancer via its action as an HDACi (40). Conversely, butyrate has also been associated with microbiota-dependent promotion of cancer in a genetic mouse model of CRC ($APC^{Min/+}$, $MSH2^{-/-}$) (42). This genetic mouse model of CRC has a loss of the tumor suppressor gene *APC* (*Adenomatous Polyposis Coli*) and the DNA mismatch repair gene *MSH2* (*MutS Homolog 2*), suggesting that the protective effects of microbial butyrate in the setting of CRC are partly mediated through regulation of these genes or their downstream effects.

We have also recently demonstrated that the gut microbiota alters global histone methylation and acetylation in a diet-dependent manner (143). Mass spectrometry analysis of >50 unique histone PTM states revealed that the gut microbiota drives changes in global histone acetylation and methylation in multiple tissues, including colon, liver, and white adipose tissue (143). Feeding a western-type diet, which is lower in fermentable substrates, attenuated microbiota-driven changes in global histone acetylation and methylation (143). Further, supplementation of GF mice with SCFAs was sufficient to partially recapitulate the colonization-associated chromatin signature. Changes in chromatin state were also associated with altered expression of genes involved in processes such as glucose homeostasis, lipid metabolism, and immunity (143). These results support a role for bacterial SCFAs and other metabolites as key mediators of host phenotype via signaling to host chromatin.

Early Life Environments

There are also interesting parallels between the gut microbiota and host chromatin during early life. Environmental exposures that occur early in life, particularly during key developmental windows for the host and its gut microbiota, can have lasting impacts on host chromatin and microbial communities. For example, both maternal and paternal nutrition and early life adversity have been shown to alter DNA methylation in humans and mice (128,129,183–185). Early host life is also a critical developmental time for the mammalian gut microbiota, which matures over the course of the first several years of life in humans (57,184,186–188).

Maternal prenatal stress, BMI, and weight gain during pregnancy affect offspring microbial community composition and activity (189,190). Recent evidence also suggests that the infant gut microbiome may be established in a stepwise manner that begins *in utero*, challenging the concept of a sterile *in utero* environment (191). There is also evidence that the microbial community composition in human meconium is indicative of maternal diabetes status (192), and that high fat feeding during pregnancy alters the offspring metabolome and microbiome in primates (193,194). Further, maternal high fat feeding in primates induces acetylation of histone H3K14 (195). Although there is no evidence to-date that definitively links the maternal gut microbiota to epigenetic programming in offspring, these studies collectively suggest a possible role for gut microbial mediation of host epigenetic states *in utero*. Notably, Sonnenburg et al. demonstrate that changes in microbial community composition in response to a low-MAC diet over several generations results in progressive loss of diversity that is not recoverable simply by switching to a higher-MAC diet (53). This study provides evidence for transgenerational inheritance of the gut microbiota that is influenced by diet. Although the early life environment was not explicitly examined in this study, it was an implicit part of the study design. While it remains unclear how early life factors and microbiota-host chromatin communication may be involved in this setting, it suggests the possibility that diet-microbiota interactions may program host chromatin responses across generations.

Antibiotics represent an extremely prevalent early-life exposure that can affect both host and microbial community development and metabolic outcomes. Extrapolations from 2010 data

comprised of information on >70% of prescriptions in the United States (US) suggest that an average child in the US has received roughly 3, 10, and 17 courses of antibiotics by the age of 2, 10, and 20 years of life (187). For decades, administration of sub-therapeutic doses of antibiotics has been used to promote growth and fattening in livestock (196,197). Importantly, if antimicrobials are given later in the animal's life the effects on growth are less than if the exposure occurred in early life, and a study of germ-free chickens showed loss of the growth-promoting effects of antibiotics in the absence of a gut microbiota (187,198,199). Similar effects have been reported in murine models, where exposure to subtherapeutic doses of antibiotics either from birth or early in life altered gut microbial community composition and increased host adiposity and susceptibility to metabolic disease (56,200,201). Further, these effects were synergistic when coupled with high fat feeding, and the metabolic impacts on the host persisted even after microbial communities have recovered, suggesting metabolic reprogramming occurs in response to early life exposure to antibiotics (56,200). While there is currently no evidence of epigenetic reprogramming in the setting of early life exposure to antibiotics, it is possible that gut microbiota-mediated reprogramming of the host epigenome may mediate some of the persistent metabolic effects of this transient exposure.

Total Parenteral Nutrition-Induced Gut Dysfunction and Extreme Stress

Total parenteral nutrition (TPN) is a therapeutic intervention that provides nutrients intravenously, allowing for complete bowel rest in patients that cannot be fed enterally (202). Although TPN is critical for the survival of these patients, it is not without sequelae. Enteral deprivation adversely affects the gastrointestinal tract in a number of ways, including the disruption of the epithelial and mucosal immune system; the induction of an inflammatory response to the decrease of lymphocytes (202,203) and an increase in mucosal proinflammatory cytokines (e.g. TNF-α) (204); reduced epithelial barrier function, which in many cases results in sepsis (205); hepatitis due to oxidative stress (206) and hepatobiliary complications (ex: steatosis, cholestasis, and fibrosis) (207); and dysbiosis resulting from changes in the gut microbiota community structure and a loss of microbial diversity. This alteration of the microbiome may play a central role in the deleterious outcomes resulting from TPN. Previous studies have shown that the lack of enteral intake favors phyla such as Proteobacteria and Bacteroidetes, and contributes to a loss of Firmicutes (208). Firmicutes rely heavily on dietary carbohydrates which are absent during prolonged fasting or TPN, whereas Proteobacteria can metabolize a broader range of substrates, including the amino acid leucine, which permeates to the lumen during TPN feeding and causes dysbiosis (209). *Akkermansia muciniphila*, a species in the phylum Verrucomicrobia, also increases markedly in TPN-fed mice (210). Like Proteobateria, *A. muciniphila* demonstrates resistance to fasting by relying on host mucin as a carbon source. The consequences of these alterations in intestinal microbiome communities have been linked to hepatic disease via activation of toll-like receptor 4 (TLR4)-induced inflammation (211). Furthermore, the loss of epithelial barrier function increases the susceptibility of the host to the transport of microbial products (212). To our knowledge, however, no studies to-date have examined the link between TPN-induced changes in gut microbial communities and their significance to the epigenetic architecture of the host.

TPN provides an interesting and clinically relevant setting for investigation of how bypassing the GI tract for nutrient assimilation may affect microbiota-host chromatin interactions. However, the animal adaptation known as hibernation represents a natural, recurring state of chronic enteral nutrient deprivation that occurs over the lifetime of an animal. Hibernation shares a number of similarities with TPN, the foremost being the exclusion of the gastrointestinal tract from nutrient acquisition, yet the lack of enteral nutrient sources is a normal part of a hibernator's annual feeding cycle, and these animals are resistant to maladies associated with prolonged fasting. Hibernation is a circannual suppression of metabolism that facilitates survival during periods in which food resources in the environment are reduced, and maintenance of constant, high body temperature and metabolism are energetically expensive due to low ambient temperatures. In the case of small hibernating mammals such as thirteen-lined ground squirrels (Ictidomys tridecimlineatus), basal metabolic rates fall to less than 5% of summer active rates as body temperatures approach near-freezing temperatures in a state called torpor (213). Bouts of torpor (which last 1–3 weeks) are interspersed with periodic interbout arousals (IBAs) during which metabolic rate rises and body temperatures briefly return to 37°C for less than 24 hours (213), however complete fasting is maintained throughout the hibernation season.

The absence of enteral nutrients causes shifts in microbial community composition, some of which are shared between animals on TPN and hibernators. Firmicutes, which specialize in the processing of plant polysaccharides are reduced in both models, whereas Protobacteria and Verrucomicrobia that can process host-derived mucin in conditions of limiting substrates tend to increase (173,214,215). The natural shifts in microbial communities observed in hibernators may also be driven by the marked changes in body temperature, but the effects of body temperature independent of changes in feeding behavior and metabolic depression on microbial community dynamics remain poorly defined. During torpor when body temperatures are lower than 10ºC, microbes have limited metabolic and proliferative activity while IBAs provide brief periods of rewarming and microbial proliferation, particularly for those species capable of degrading and utilizing host-derived compounds (216). These large shifts in temperature during torpor-arousal cycles do not appear to cause extinction of summer-active populations. Microbial communities associated with enteral feeding remain present in lower abundance, and are available for reseeding as dietary intake shifts the circannual cycle. In hibernating thirteen-lined ground squirrels, the concentrations of SCFAs are 25% of that found in the summer active period (213). Additionally, the relative molar amounts of acetate, propionate, and butyrate change, likely due to differences in substrate availability over the winter hibernation season and relative microbial taxa abundance during different metabolic states (137).

The key distinguishing feature between TPN and hibernation is that the association between hibernating animals and the gut microbiome represents a unique coevolution that has adapted to the extreme dietary and thermal shifts that occur during their annual cycle. For example, the increase in gut permeability that occurs during hibernation is not associated with an increase in the inflammatory response (217,218), reductions in tight junction proteins like occludin, or increased enterocyte apoptosis (see (215) for review). Investigating the effects of parenteral nutrition in conventional laboratory animal models using approaches such as germ-free mice have many advantages and are an essential investigative tool, but

their limitations include the exposure to stressors to which the animal has not evolved that distance these experimental systems from the animal's natural physiology. Hibernators, which represent the most extreme example of fasting in mammals, provide a unique opportunity to investigate the implications of naturally occurring changes in gut microbial populations and metabolite production on chromatin states. Additionally, hibernating mammals exhibit a robust resistance to other extreme stressors that have profound deleterious effects to most mammals, including hemorrhagic shock and ischemia-reperfusion injury (219,220), radiation (221,222), and thermal stress (213) that may be linked to chromatin and the microbiome.

Conclusions

The mammalian gut is a bioreactor that contains a vast population of microbes. These complex communities supply the host with ~10% of the calories harvested from the diet and produce a multitude of metabolites whose roles in signaling and epigenetic regulation are multifaceted and only beginning to be understood. There is a paucity of data that directly link microbial metabolites to host chromatin regulation relative to the rapidly growing body of literature regarding gut microbial mediation of human health and disease. This is partly due to the highly complex nature of gut microbiota-host interactions. Host genetics affect gut microbial community composition and functional capacity (223,224), however environmental factors appear to exert stronger effects (18). The massive genetic and environmental diversity within the human population poses a significant challenge for the study of gut microbial metabolite-host chromatin interactions in human cohorts, and study of these interactions in gnotobiotic mouse models is relatively resource intensive. Nonetheless, the fact that environmental factors have been shown to outweigh host genetics is a harbinger for the role of gut microbial communication of environmental changes to host chromatin, particularly given that chromatin allows for dynamic responses to external stimuli by an otherwise static genome. Given the ever-increasing prevalence of metabolic disease worldwide, understanding how microbial metabolites signal to host chromatin in this setting offers new opportunities to develop preventive and treatment measures for environment- and lifestyle-associated disorders.

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Abbreviations

α-KG	alpha-ketoglutarate
acetyl-CoA	acetyl-coenzyme A
BBB	blood brain barrier
bSCFA	branched short chain fatty acid

CoA	coenzyme A
ConvD	conventionalized
ConvR	conventionally raised
CRC	colorectal cancer
DNMT	DNA methyltransferase
GF	germ-free
HAT	histone acetyltransferase
HDAC	histone deacetylase
HDACi	histone deacetylase inhibitor
HMT	histone methyltransferase
IBA	interbout arousal
LC-MS/MS	liquid chromatography coupled to tandem mass spectrometry
MACs	microbial accessible carbohydrates
NAFLD	non-alcoholic fatty liver disease
PTMs	post-translational modifications
SCFA	short chain fatty acid
T2DM	type 2 diabetes mellitus
TPN	total parenteral nutrition

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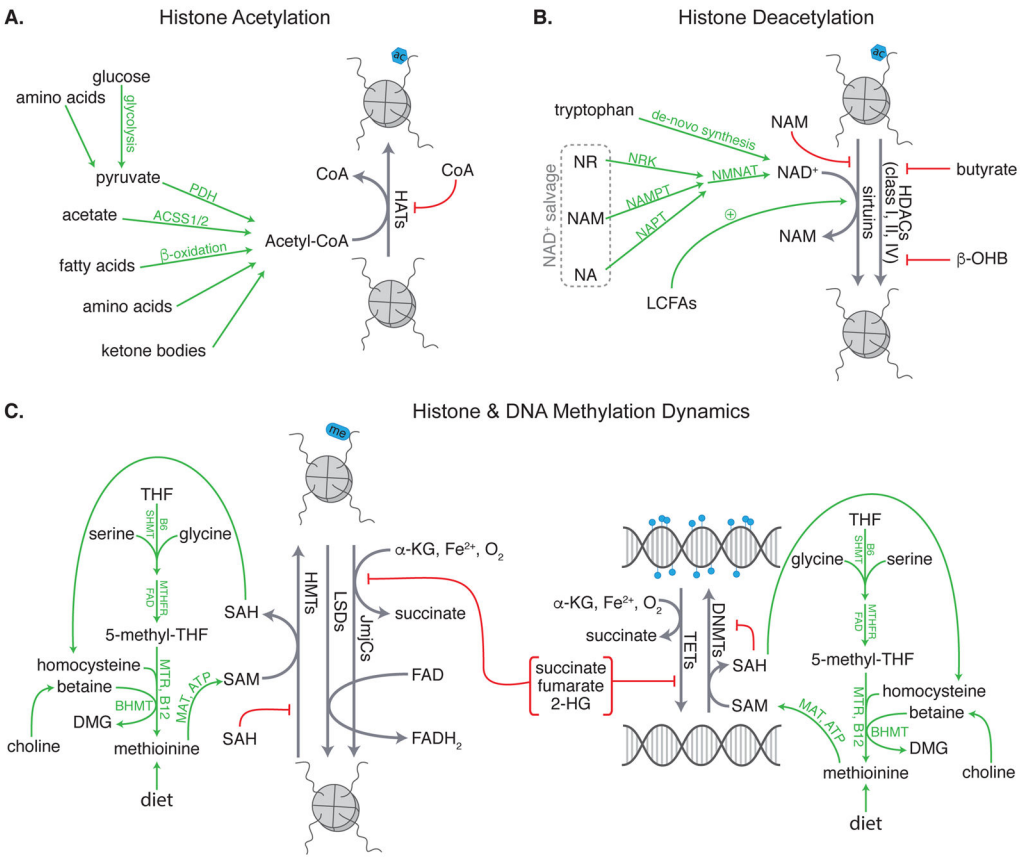

Figure 1.

Endogenous metabolites regulate (A) histone acetylation, (B) histone deacetylation, and (C) histone and DNA methylation and demethylation. PDH = pyruvate dehydrogenase, ACSS1/2 = acetyl-CoA synthetase 1/2, HAT = histone acetyltransferase, NR = nicotinamide riboside, NA = nicotinic acid, NAM = nicotinamide, NMNAT = nicotinamide/nicotinic acid mononucleotide adenylyltransferase, LCFAs = long-chain fatty acids, NAD^+ = nicotinamide adenine dinucleotide, HDACs = histone deacetylases, β-OHB = β-hydroxybutyrate, SHMT = serine hydroxymethyltransferase, MTHFR = methylenetetrahydrofolate reductase, 5-methyl-THF = 5-methyl- tetrahydrofolate, THF = tetrahydrofolate, MTR = methionine synthase, DMG = dimethylglycine, MAT = S-adenosylmethionine synthase, SAH = S-adenosyl homocysteine, SAM = S-adenosylmethionine, HMTs = histone methyltransferases, LSDs = lysine specific demethylases, JmjCs = Jumonji C family histone demethylases, α-KG = α-ketoglutarate, TETs = Ten Eleven Translocation methylcytosine dioxygenases, DNMTs = DNA methyltransferases

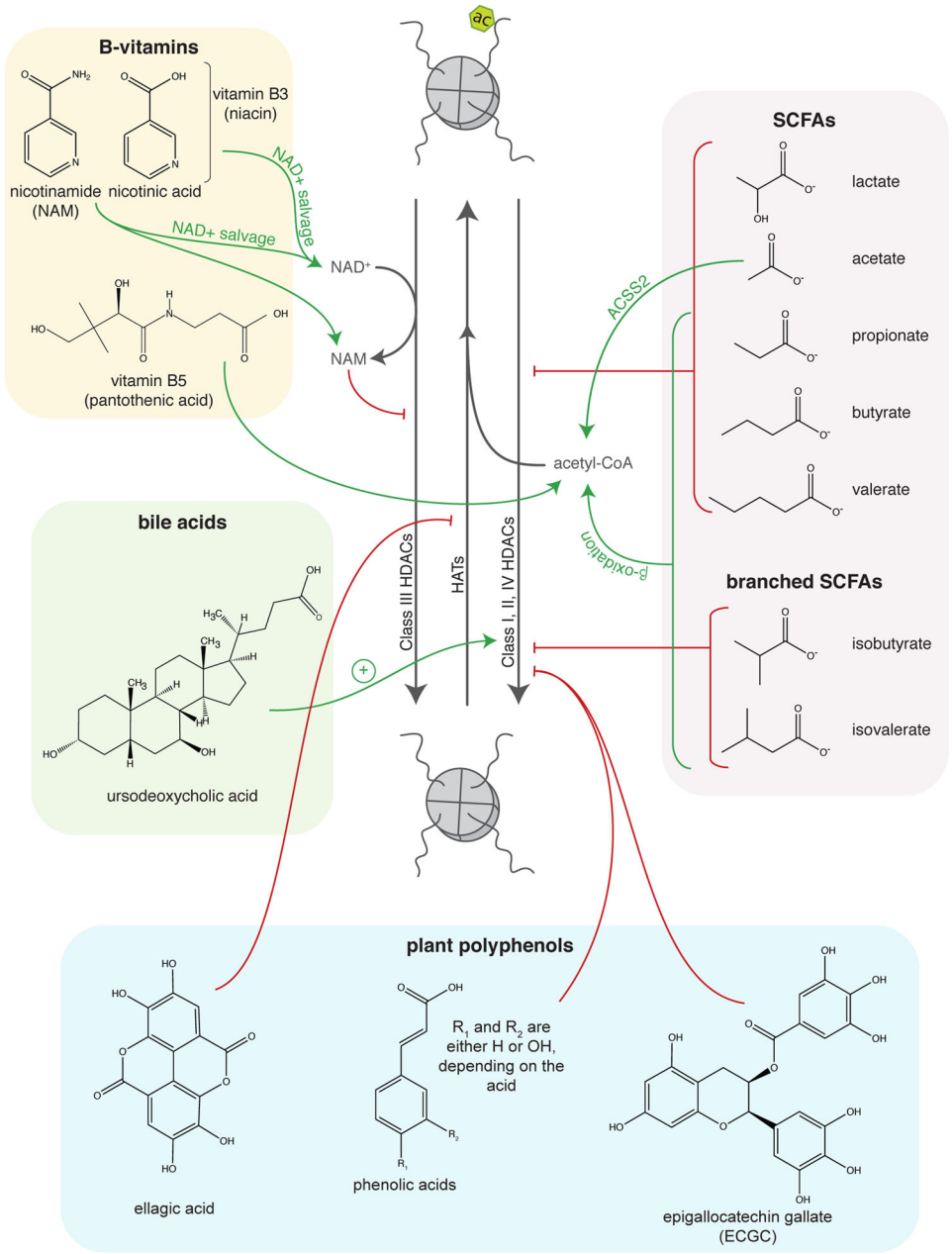

Figure 2.
Regulation of histone acetylation by gut microbial metabolites.

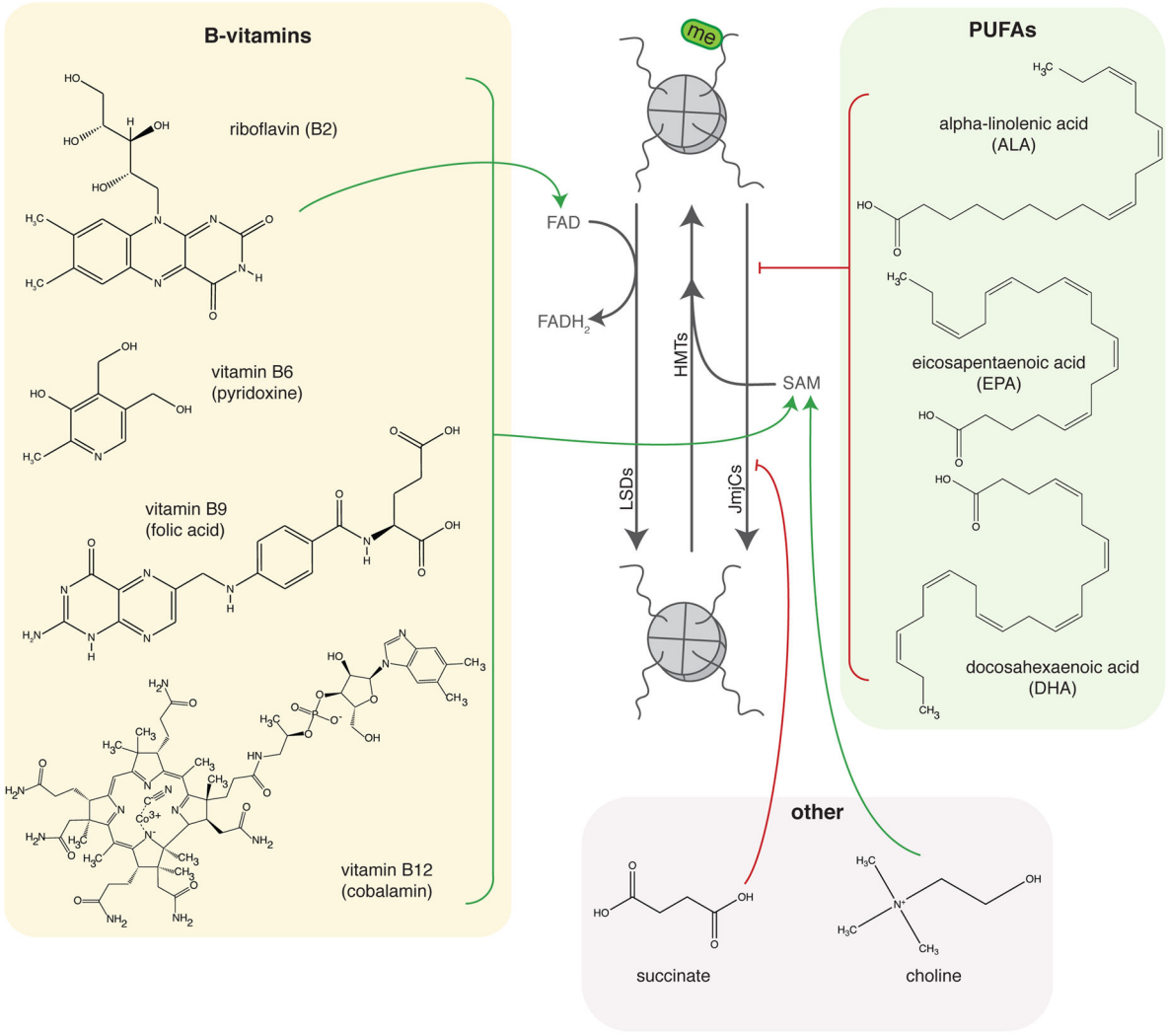

Figure 3.
Regulation of histone methylation by gut microbial metabolites.

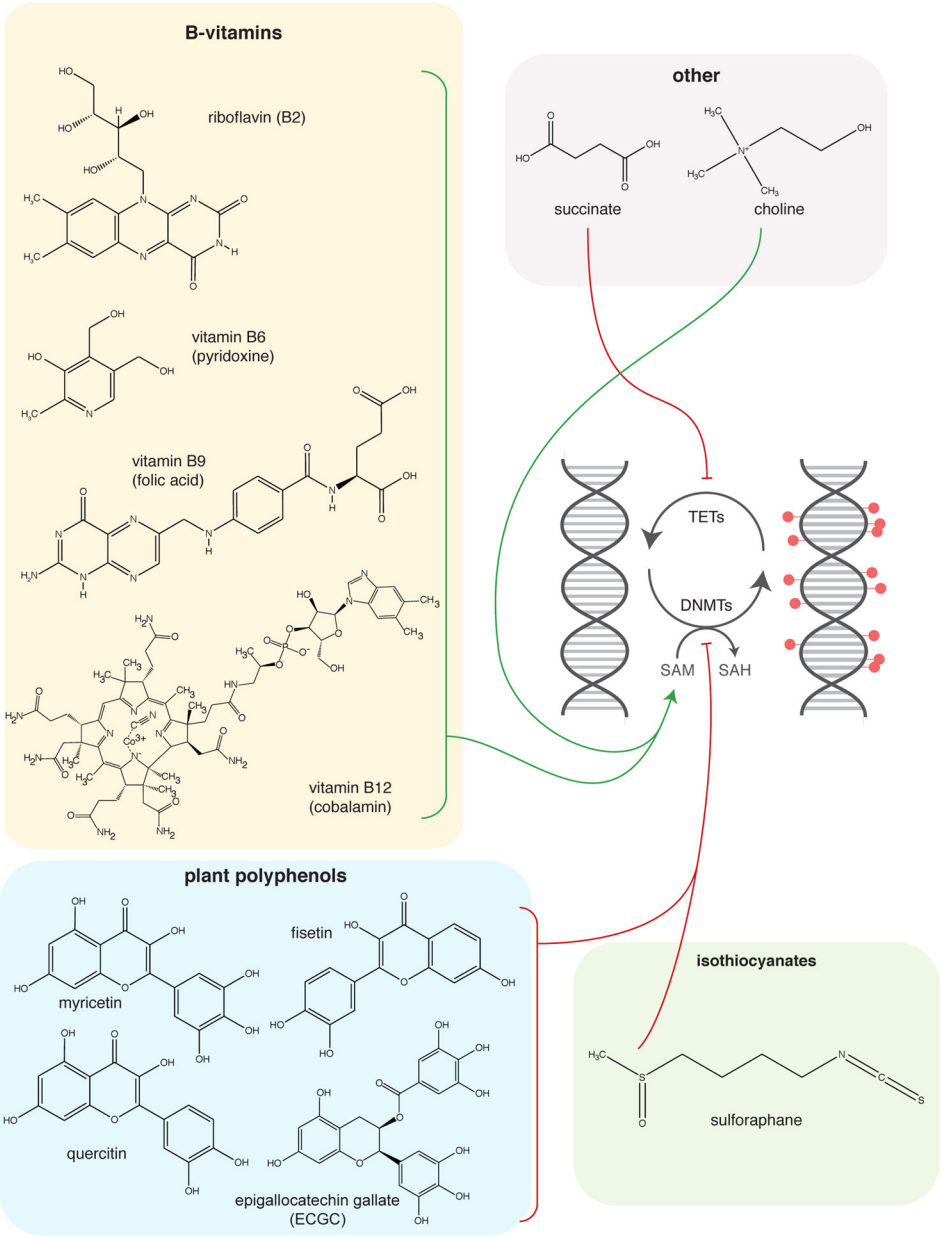

Figure 4.

Regulation of DNA methylation by gut microbial metabolites. PUFAs = polyunsaturated fatty acids

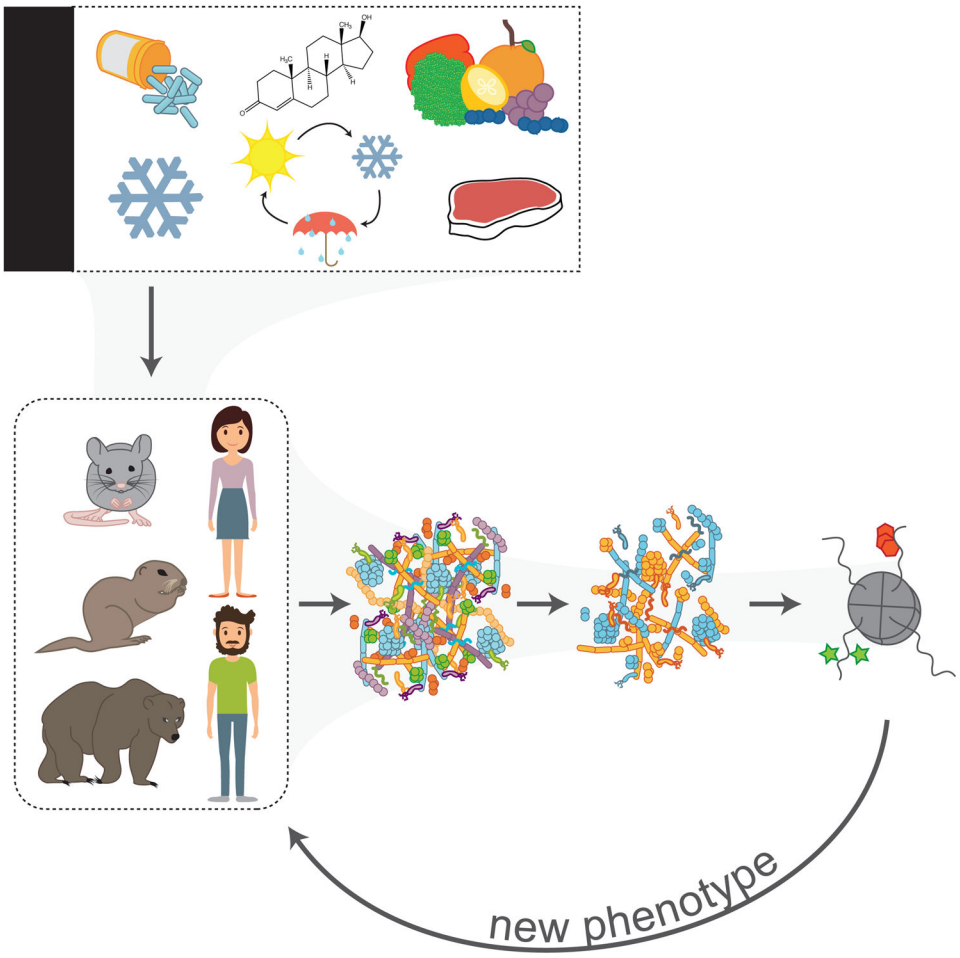

Figure 5.

A model wherein the mammalian gut microbiota mediates communication between environmental exposures and host epigenetic programming of downstream phenotypes. Environmental exposures known to affect mammalian microbiota include: antibiotics, cold exposure, hormones, natural seasonal cycles in ambient temperature and food sources, and dietary composition, excess, and scarcity. The composition of the mammalian gut microbiota, which resides in the host alimentary tract and is in direct contact with the environment, is altered in response to environmental factors. Alteration of microbial community composition leads to differences in microbial metabolite production, and ultimately altered chemical signaling to host chromatin. Modifications to host chromatin then drive new transcriptional programs to produce an adapted phenotype. The proposed cycle may repeat in response to continued exposure to the same environmental factor or in response to a new exposure.