



Histone acylations as a mechanism for regulation of intestinal epithelial cells

Mariane Font Fernandes, Marco Aurélio Ramirez Vinolo

Laboratory of Immunoinflammation, Department of Genetics, Evolution, Microbiology and Immunology, Institute of Biology, University of Campinas, Campinas, Brazil

Contributions: (I) Conception and design: Both authors; (II) Administrative support: None; (III) Provision of study materials or patients: MF Fernandes; (IV) Collection and assembly of data: MF Fernandes; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Marco Aurélio Ramirez Vinolo, PhD. Laboratory of Immunoinflammation, Department of Genetics, Evolution, Microbiology, and Immunology, Institute of Biology, University of Campinas, Rua Monteiro Lobato, 255, Campinas, SP 13083-862, Brazil. Email: mvinolo@unicamp.br.

Abstract: Histone post-translational modifications are reversible epigenetic mechanisms that regulate chromatin structure and gene transcription. In recent years, in addition to the well-characterized histone acetylation, new acylations such as propionylation, crotonylation, butyrylation and beta-hydroxybutyrylation have been described and explored in different cell types at contexts of health and disease. Understanding how histone acylations contribute to gene expression regulation is especially important in intestinal epithelial cells (IECs) because they receive many different signals from other cells and the external environment and must adapt to maintain essential functions such as nutrient and water absorption, maintenance of tolerance and protection against pathogens. In this review, we describe how cells regulate these modifications, how they are recognized by other proteins and impact gene expression. We summarize recent studies that explored the role of these distinct epigenetic marks in the regulation of IECs and discuss their biological importance for the intestinal epithelium's adaptations to changes in metabolism and to respond to environmental signals provided, for example, by the diet, components of the intestinal microbiota and pathogens. Finally, we discuss how the histone acylations are affected by inflammatory signals and how this knowledge may provide new targets for treatment of pathologies such as the inflammatory bowel diseases.

Keywords: Histone acetylation; histone crotonylation; colon; microbiota; inflammation

Received: 26 January 2023; Accepted: 19 May 2023; Published online: 05 June 2023.

doi: 10.21037/dmr-23-3

View this article at: <https://dx.doi.org/10.21037/dmr-23-3>

Introduction

Different biological processes are regulated by epigenetic mechanisms that occur independently of changes in the DNA sequence (1,2), such as DNA methylation in CpG islands, non-coding RNAs (ncRNAs) and histones post-translational modifications (hPTMs) (3), that collectively form a dynamic code, which has an important function in adapting the transcription to different types of signals including from environmental factors such as microbiota, diets and diseases (4).

Histones are nuclear proteins divided into subunits H2A,

H2B, H3 and H4 that form octamers wrapped around by approximately 146 base pairs of DNA (5) in a highly compacted manner, referred as nucleosomes (6). These structures, which are linked by histone H1, form the basic unit of chromatin that constitute the chromosomes of eukaryotic cells (5,7,8).

The N-terminal tails and central globular domains of histones undergo different types of post-translational modifications including methylation, acetylation, propionylation, crotonylation, butyrylation and β -hydroxybutyrylation (*Figure 1*) that are likely to have

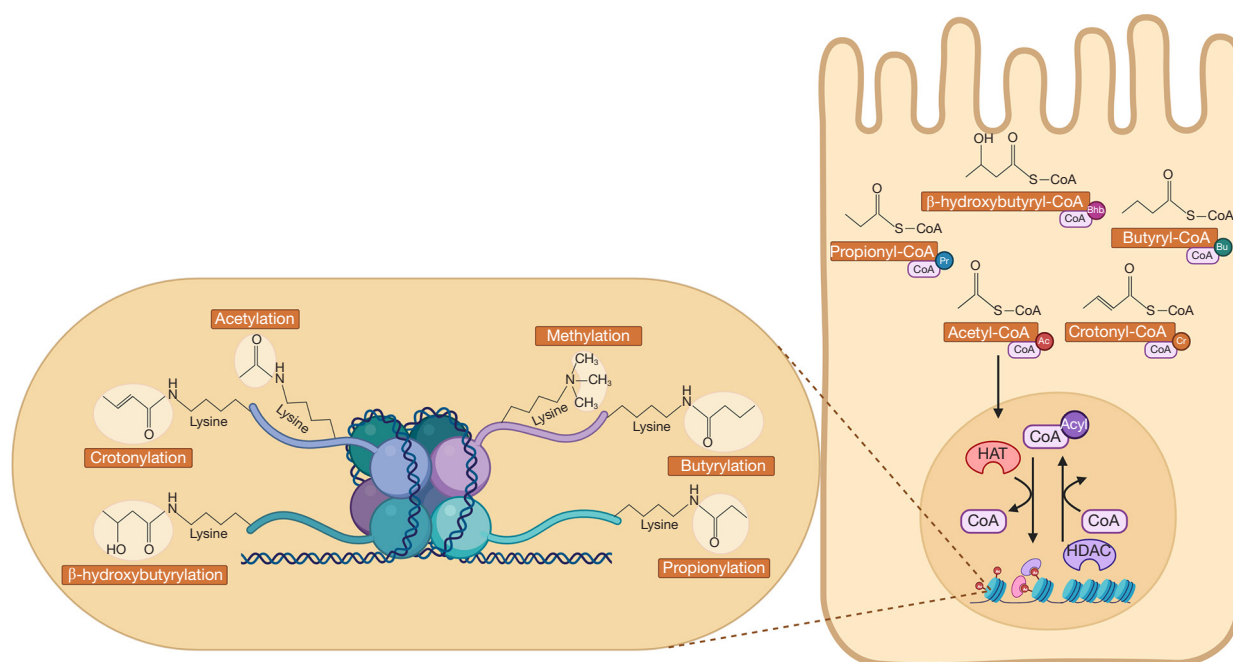


Figure 1 Specific acyl groups and chemical structures of lysine acylations. Original figure created with BioRender.com. CoA, coenzyme A; bbb, β -hydroxybutyrylation; bu, butyrylation; pr, propionylation; ac, acetylation; cr, crotonylation; HAT, histone acyltransferase; HDAC, histone deacetylase.

unique impact on chromatin structure and its interactions with non-histone proteins thus reflecting on gene expression. The effects of hPTMs on gene expression depends on a highly-controlled and reversible process involving proteins and enzymes known as writers, erasers and readers, which add, remove or recognize and bind to acyl groups in lysine residues, respectively. These enzymes can be regulated according to external signals and the availability of exogenous and endogenous metabolites (7,9-11), which also serve as substrate for acyl-coenzyme A (acyl-CoA) production (5).

Acetylation is one of the most studied hPTMs. This hPTM, in most cases associated to a transcriptionally active profile, neutralizes positively charged residues in the N-terminal tails of histones, decreasing the interaction with DNA and leading the chromatin structure to a less condensed conformation, called euchromatin (5,12).

Histone acetyltransferases (HATs), also known as lysine acetyltransferases (KATs), are the writers responsible for adding acetyl groups from acetyl-CoA to lysine residues of histone and non-histone proteins in the nucleus (type A) (Figure 1) or newly synthesized histones in the cytoplasm (type B) (13,14). Nuclear HATs are divided into five main families (Hat1, GNAT, MYST, p300/CBP, and Rtt109)

based on their structure and similarities, with new nuclear families still being explored (15-17). The removal of this histone modification is responsible for chromatin condensation (heterochromatin) (Figure 1), and it is generally associated with increased methylation at certain residues that difficult the binding of transcription factors to DNA [reviewed by others (18,19)]. Histone deacetylases (HDACs), also referred as lysine deacetylases (KDACs), are part of complexes that remove acetyl groups (erasers) from lysine residues (5,10,20) and are subdivided based on their similarities into four main classes: I (HDACs 1–3 and 8), II (HDACs 4–7, 9 and 10), III or sirtuins (SIRT1–7) and IV (HDAC 11), with SIRTs being dependent on nicotinamide adenine dinucleotide (NAD^+), while the other HDACs are zinc-dependent (8,14,16,21,22).

The acetylated lysine residues, as well as other hPTMs, enable the interaction with reader domains present in diverse chromatin-associated proteins (23). Histone readers are divided in three major families and have differing affinities according to their structure. YEATS domain (such as AF9, YEATS2, Taf14) and double PHD finger (DPF) domain (such as MOZ and DPF2) show enhanced affinity for longer acyl chains, such as crotonylated and butyrylated sites. In contrast, bromodomain (with a few exceptions)

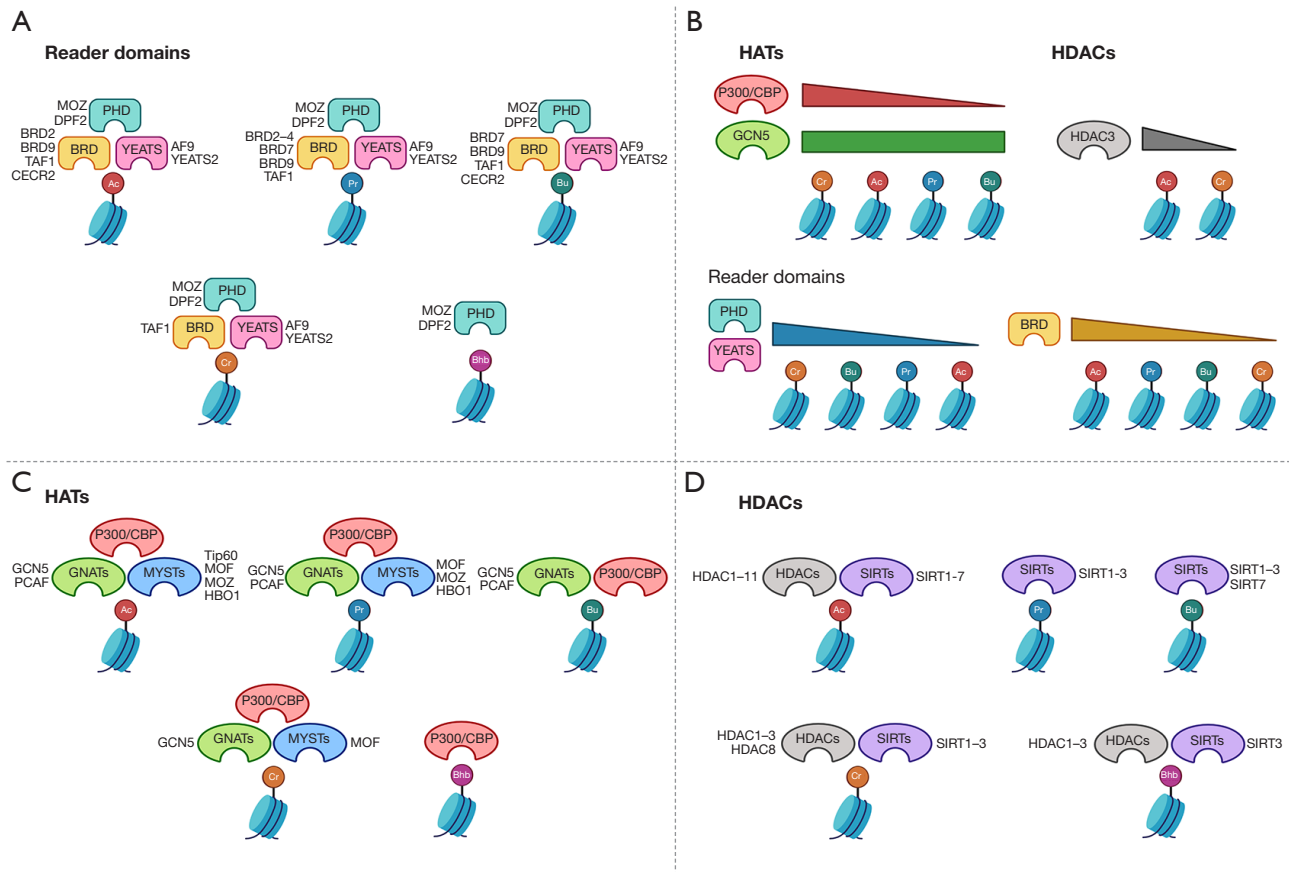


Figure 2 Histone acylations depends on a highly-controlled and reversible process involving proteins and enzymes known as readers (A), writers (HATs) (C) and erasers (HDACs) (D) with differing affinities (B), which recognize and bind, add or remove acyl groups to lysine residues, respectively. Along with the graphical representation of each group, examples of components already explored in the literature were added. Original figure created with BioRender.com. PHD, plant homeodomain; BRD, bromodomain; ac, acetylation; pr, propionylation; bu, butyrylation; cr, crotonylation; bhb, β -hydroxybutyrylation; HATs, histone acyltransferases; HDACs, histone deacetylases; CBP, CREB-binding protein; GNATs, Gcn5-related N-acetyltransferases; MYST, Moz, Ybf2, Sas2 and Tip60; SIRTs, sirtuins.

prefers acetylated and propionylated sites than butyrylated and crotonylated [reviewed by others (9,23-28)] (Figure 2A,2B).

HATs and HDACs display a promiscuous substrate specificity and have different activity for distinct histone acylations, such as histone crotonylation (5,9,25,28-32), butyrylation (10,32-34), propionylation (23) and β -hydroxybutyrylation (Figure 2C,2D) (35,36). These preferences were observed in p300 and HDAC3, for example, which have more ability to modify crotonylated and acetylated histones (Figure 2B).

Histone crotonylation, butyrylation, propionylation and β -hydroxybutyrylation are relevant and non-redundant hPTMs, which are, as described for acetylation, associated with activation of gene transcription (10,12,31,37). One of

the first published works about propionylation in mammalian cells identified decreased levels of H3K23pr during monocytic differentiation, which suggested an association of this histone mark with lineage determination (38). Butyrylation has been explored in the context of spermatogenesis. This acylation competitively inhibits acetylation on H4K5 and H4K8 at gene promoters thus preventing the binding of bromodomain-containing protein, an effect that may affect genome reorganization during spermatogenesis (39). Crotonylation was also identified in male germinal cells following meiosis (37). This latter histone mark was associated with expression of testis-specific genes that escaped sex chromosome inactivation and is likely to regulate spermatogenesis (37). Recent characterization of lysine crotonylation showed

its involvement with biological processes and different diseases, including carcinogenesis and inflammation (40). The unsaturation (also known as C-C π -bond) present on the four-carbon atoms structure of crotonyl-CoA distinguishes the cofactor for crotonylation from the cofactor for butyrylation (butyryl-CoA), and leads to an increased volume and stiffness on the planar conformation, which may be associated with a greater induction of gene transcription compared to acetylated residues (9,23,37). β -hydroxybutyrylation depends on β -hydroxybutyrate (BHB) concentrations, which can be drastically increased during starvation and it has been reported to be relevant in a wide range of conditions including metabolic diseases, depression and cancer, suggesting different functions from other histone acylations (34,36). It is worth mentioning that these hPTMs (crotonylation, butyrylation, propionylation and β -hydroxybutyrylation) are less abundant in cells than acetylation (10,41), but they seem to be relevant for controlling sets of genes or to adapt transcription in some specific conditions, as it will be discussed.

The aim of this review is to present an updated discussion about the participation of hPTMs in regulating gene expression and cellular processes. We focused on intestinal epithelial cells (IECs) because of their direct interactions with diet and microbiota signals to which they have to adapt to keep essential functions such as absorption of nutrients and protection against pathogens and due to their emerging role in inflammatory bowel diseases (IBD), as discussed at the final part of this review.

Regulation of IECs proliferation and differentiation by hPTMs

The gastrointestinal tract is lined by a continuous epithelium monolayer with complex functions and essential roles for the organism including the transport of ions, nutrients and water and defense against pathogenic microorganisms. The intestinal epithelium is rapidly and constantly renewed by cells formed from intestinal stem cells (ISCs), which present high expression of leucine rich repeat containing G protein-coupled receptor 5 (*Lgr5*) and are located in the base of intestinal crypts. These cells give rise to a pool of progenitor transit-amplifying (TA) cells that proliferate and differentiate into absorptive (enterocytes/ colonocytes and M cells) and secretory [Paneth/deep crypt secretory (DCS) *Reg4*⁺, goblet, enteroendocrine and tuft cells] lineages as they migrate in the epithelial layer (4,42). Regulation of proliferation, maturation and differentiation

of IECs is essential to maintain intestinal homeostasis and barrier function, to promote regenerative responses after damage, while preventing premalignant hyperproliferation. Distinct aspects of these complexes processes are modulated by hPTMs and associated enzymes, as exemplified below.

Inhibition or ablation of HDACs, which remove histone acylations, induces expression of intestine-specific markers such as sucrase-isomaltase (43), ion transporter *SLC26A3* (44), intestinal alkaline phosphatase and fatty acid binding protein (11), important for the differentiation of absorptive cells. This phenomenon is in part a consequence of the increase in histone acetylation in the absence of HDAC, as observed by Suzuki *et al.* (43) on the sucrase-isomaltase promoter, suggesting that acetylation in this system is linked with absorptive cell differentiation. Other studies lead by Gonneaud *et al.* (45,46) and Zimmerlin *et al.* (47) demonstrated that HDAC1 and HDAC2 activity are relevant for inducing the differentiation of progenitor intestinal cells to secretory lineages (i.e., Paneth and goblet cells) in part due to the inhibition of Notch pathway signaling (45,46). Together these findings indicate that hPTMs are relevant for intestinal epithelial differentiation. Although, a detailed characterization of the role of specific histone acylations and the mechanisms involved on their effects is still missing.

Marruecos *et al.* (48) described an interesting mechanism regulating intestinal cells differentiation that involves interactions between nuclear factor kappa B (NF- κ B) inhibitor alpha (*I κ B α*) and acetylated histones. The authors found that the phosphorylated-NF- κ B inhibitor alpha (p-*I κ B α*) binds to acetylated histone H4 at lysine 12 and 16 (H4K12ac and H4K16ac) in ISCs and that a subsequent cleavage of the N-terminal tail of H4 between K16 and K20 residues by trypsin and chymotrypsin, also known as histone clipping, favors the dissociation of *I κ B α* from chromatin, an event that impacts on genes transcription and epithelial differentiation (48). The histone H3 N-terminal tail cleavage in small intestinal villi by cathepsin L and trypsins also can shape the nucleosome structure and influences the acetylations of H3, which are more abundant on the clipped forms. *In vitro* inhibition of these proteases has been shown to interfere in intestinal epithelial development (49).

Epigenetic mechanisms are also involved on the dedifferentiation of ISC from the crypt. Jadhav *et al.* (50) described that *Bmi1*⁺ preterminal enteroendocrine cells and *CD69*⁺*CD274*⁺ goblet cell precursors can revert their distinctive chromatin signature, which is rich in H3K4me1, to progenitors and *Lgr5*⁺ stem cell chromatin

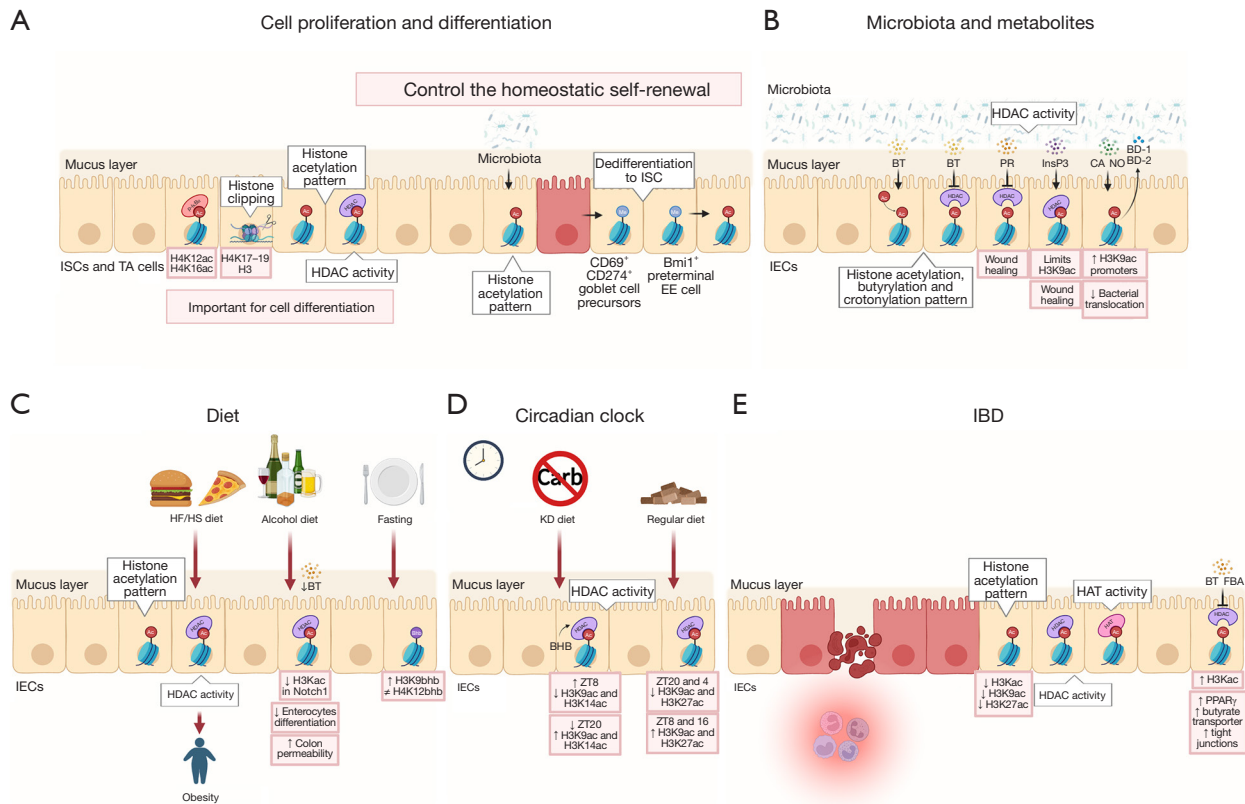


Figure 3 Illustration of intestinal epithelial cell epigenome in different contexts. (A) Cell differentiation and proliferation depends on the dynamic interaction between proteins and chromatin, histone clipping, HDAC activity and histone acetylation pattern. Chromatin signatures of differentiated cells can be reverted upon loss of *Lgr5*⁺ ISCs. (B) Microbiota and its metabolites influence HDAC activity and histone acetylation, crotonylation and butyrylation pattern in intestinal epithelial cells for host protection. (C,D) Acylations of histones also seem to be relevant for adaptation of IECs to different diets and circadian rhythm. (E) Intestinal inflammation is associated with low levels of H3Kac, H3K9ac and H3K27ac possibly due to HAT and HDAC enzymes down-regulation. Original figure created with BioRender.com. ISCs, intestinal stem cells; TA, transit-amplifying; p-IκBα, phosphorylated-NF-κB inhibitor alpha; ac, acetylation; HDAC, histone deacetylase; me, methylation; ISC, intestinal stem cell; EE, enteroendocrine; IECs, intestinal epithelial cells; BT, butyrate; PR, propionate; InsP3, inositol-1,4,5-trisphosphate; CA, caprylic acid; NO, nonanoic acid; BD, β-defensin; HF/HS, high fat and high sucrose diet; KD, ketogenic diet; BHB, β-hydroxybutyrate; ZT, zeitgeber time; IBD, inflammatory bowel disease; HAT, histone acyltransferase; FBA, N-(1-carbamoyl-2-phenylethyl) butyramide; PPARγ, peroxisome proliferator-activated receptor gamma.

with H3K4me2 and/or H3K27ac at enhancers, to restore ISC function after epithelial damage (50). These cells are responsible for the self-renewal of the intestinal epithelium, as mentioned before, and seem to be regulated by histone acetylation. Schell *et al.* (51) demonstrated an important role for the mitochondrial pyruvate carrier (MPC) on intestinal epithelial proliferation. MPC is formed by the assembly of *Mcp1* and *Mcp2* and provides pyruvate from glycolysis to mitochondria. MPC is expressed in low levels at ISCs and increases in differentiating cells. Strategies that affect its expression on ISCs, also impact cell proliferation. The loss

of MPC increases proliferation, while the opposite response is observed in cells overexpressing it (51). Interestingly, the loss of MPC was associated with reduction in histone acetylations (i.e., H3K27ac and H3K4ac), an effect that may be relevant for the observed phenotype (*Figure 3A*) (51).

Collectively, these reports show the importance of histone acetylation for the development and maintenance of epithelium. From the stem cell compartment to the differentiated cells in the intestinal villi, IECs seem to be dependent on the dynamic interaction between proteins and chromatin, histone clipping, and histone acetylation pattern

to regulate important processes, such as proliferation and differentiation. Further work is needed to assess the respective roles of other histone acylations in these cells.

Involvement of hPTMs on the adaptation of IECs functions to environmental and endogenous signals

Microorganisms play an important role in the maintenance of homeostasis and regulation of host metabolism and immunity (11,52-54). Recent experiments demonstrated that histone acylations are sensitive to changes in the commensal microbiota composition. The high levels of histone crotonylation (32), butyrylation and propionylation (55) observed in the colon and cecum of colonized mice are drastically reduced in antibiotic-treated or germ-free (GF) mice (32,55).

This crosstalk between microbial and intestinal cells starts in early life, when the microbiota colonization is essential for the expression of HDAC3 on the epithelial cells and contributes to the establishment of commensal tolerance (56). Additionally, Abo *et al.* found that the initial microbial colonization of the intestinal tract leads to enhanced histone acetylation in IECs thus increasing the expression of a gene called erythroid differentiation regulator-1 (*Erd1*) (57). The protein coded by *Erd1* is relevant for maintenance and regenerative responses of the intestinal epithelium (57).

The host-microbiota crosstalk involves different mechanisms including short-chain fatty acids (SCFAs). These are small molecules produced from bacterial fermentation of non-digestible carbohydrates (58), which are found in high concentrations in the cecum (~130 mM) (59) and proximal colon (~70–140 mM) (54). Acetate (C2), propionate (C3) and butyrate (C4) are the main SCFAs (54) in the intestine, where they exert important effects, even in hPTMs. Histone crotonylation and butyrylation, for example, are influenced by the gut microbiota at least in part via these metabolites, since they act as direct precursor for the generation of intracellular acyl-CoAs (10,32). SCFAs are transported across the apical surface of the cells mainly by monocarboxylate transporters (MCT1, MCT4 and SMCT1) and then converted by acyl-CoA synthetases (ACSs) and other enzymes in compartments of mammalian cells (60). In addition, SCFAs also act as well-known HDAC inhibitors thus contributing to increased histone acylations (60,61).

Butyrate contributes to chromatin modifications as a substrate for acyl-CoA production (60,62) and a class I

HDAC inhibitor in the colon (60,61). Different hPTMs on IECs are affected by butyrate and the other SCFAs, as shown for H3K9 and H3K27 butyrylation (55), acetylation on H4 (62), and crotonylation on multiple lysines of H3 and H4 (32).

Another SCFA, propionate, stimulates IEC migration along the villus and its eventual extrusion into the lumen in homeostatic conditions (63). In experimental colitis, this SCFA promotes wound healing by enhancing cell spreading and polarization through inhibition of class I HDACs and activation of G protein-coupled receptor 43 (GPR43) and signal transducer and activator of transcription 3 (STAT3), without influencing the inflammatory responses. The inhibition of class I HDACs via valproate recapitulated the effects of propionate (63).

Unlike the inhibitory effect of butyrate and propionate described above, inositol-1,4,5-trisphosphate (InsP3) produced by commensal bacteria through the metabolism of phytate, activates HDAC3 and limits histone acetylation, such as H3K9ac, at directly repressed gene-targets in homeostasis, as well as promotes cell proliferation and repair following intestinal damage (64).

The medium chain fatty acids caprylic acid (C8) and nonanoic acid (C9), naturally present in some foods, also have beneficial effects. They reduce bacterial translocation and improve antibacterial activity by inducing gene expression and secretion of the antimicrobial peptides β -defensins 1 (pBD-1) and pBD-2 on intestinal epithelial porcine cells, an effect that involves H3K9ac at promoters when challenged with *Escherichia coli* (65) (Figure 3B).

Different microorganisms can modulate the acylation of histones thus interfering on gene expression by IECs. *Lactobacillus rhamnosus* and *Lactobacillus fermentum*, host beneficial commensal bacteria, decrease H4 and H3 acetylation on human intestinal cells (Caco-2). This effect is observed even in the presence of the opportunistic commensal pathogen *Escherichia coli*, which is known to induce an increase in histones acetylation (66). This response is associated with the capacity of *L. fermentum* to enhance the expression of epigenetic modifiers, such as p300 and HDAC1, in contrast to *Escherichia coli*, which reduces the expression of these genes (67). The oral administration of another probiotic, *Lactobacillus casei* (*L. casei*) LH23, in a mouse model of intestinal inflammation [i.e., ingestion of dextran sodium sulfate (DSS) that induce colonic epithelial disruption] has an anti-inflammatory activity and restores the levels of H3K9ac in colon (68). Pathogens also modify the pattern of post-translational modifications in the

intestinal epithelium, an aspect that may be relevant for the immune responses to them, but that will not be covered in this review (69-74).

Acylation of histones play a role on the adaptation of IECs to different diets, microbiota and circadian rhythm. Experiments with GF mice conventionalized or not with microbiota showed that the microbiota regulates histone acetylation in proximal colon, liver, and the white adipose tissue (WAT), especially in canonical H3, the variant H3.3 and multiple lysines sites of H4 (7). This response was recapitulated with the supplementation of SCFAs in GF mice and was shown to be diet-dependent in liver and WAT, where this epigenetic pattern was reduced in response to a “Western-type” high fat, high sucrose diet (HF/HS) (7). Other experiments performed using high-fat diet demonstrated the participation of epithelial HDAC3 on obesity development. This latter effect was reversed by antibiotic treatment (75) or HDAC3-inhibition by butyrate administration (76), suggesting it happens in a microbiota-dependent manner. Forsyth *et al.* (77) also demonstrated the importance of diet in hPTMs using a diet with 15% alcohol. The authors of this study found a reduction on butyrate production in animals treated with this diet. This effect was associated with H3 deacetylation at the Notch1 locus, thus suppressing Notch1 expression and impacting on intestinal barrier function (i.e., increasing colon permeability) and epithelial differentiation (i.e., decreasing enterocytes and increasing enteroendocrine cells) (77).

Interestingly, the absence of food consumption, as observed during fasting, also influences hPTMs. The lack of glucose induces the overproduction of acetyl-CoA, which can be converted to the ketone bodies acetone, acetoacetic acid, and BHB. This latter ketone body inhibits HDAC and induces H3 and H4 lysine beta-hydroxybutyrylation (Kbhb) on regulatory elements near genes that control lipolytic and ketogenic transcriptional program in intestine. During fasting, H3K9bhb is associated with an active chromatin state and may be co-enriched with H3K27ac, thus inducing gene expression in ISCs and transit amplifying cell populations (4) (Figure 3C).

Intake of a ketogenic diet (high-fat and low-carbohydrate diet) increases serum and intestinal BHB levels in a diurnal rhythmicity. The BHB concentration is associated with a time-of-the-day-dependent modulation of HDAC activity (78). Considering Zeitgeber time as a representation of the diurnal cycle (ZT0 for lights on and ZT12 for lights off), the highest activity of these enzymes happens at ZT8 (daytime), and the lowest at ZT20 (nighttime). This

result is in line with the circadian changes in H3K9ac and H3K14ac levels at specific promoters, which are higher at ZT20 than at ZT8. Part of this ketogenic diet response in IECs at ZT20 involves the activation of the nuclear transcription factor peroxisome proliferator-activated receptor alpha (PPAR α). Its rhythmic activity in the gut is marked by nuclear accumulation and expression of target genes, which are associated with mitochondrial and peroxisomal β -oxidation, at ZT20 (78). In homeostatic conditions, with a regular diet consumption, this circadian clock of the acetylation pattern changes, presenting peaks of H3K9ac and H3K27ac between ZT8 and ZT16, and falls between ZT20 and ZT4 in conventionalized mice (75) (Figure 3D). Other metabolites produced by gut microbiota, such as acetate, butyrate and isovalerate, influence host intestinal epithelial circadian rhythms via HDAC inhibition mechanism (79).

Together, these studies show the importance of epigenetic mechanisms for IECs adaptation to environmental and dietary signals to develop an appropriate response in order to maintain homeostasis.

Histone acylations in the context of IBDs

Crohn's disease (CD) and ulcerative colitis (UC) are the main IBD, characterized by chronic, progressive and relapsing inflammatory conditions associated with body weight loss, abdominal pain, diarrhea with or without blood and some extra intestinal effects (80-82). In recent years, the role of epigenetic modifications in IBD has attracted attention, because environmental factors may increase the risk of disease development by epigenetic mechanisms (83).

In this regard, it has been shown that H3 pan-acetylation and H3K9ac in IECs are negatively associated with UC severity, as these epigenetic markers are reduced in the colon of UC patients and in a mouse model of intestinal inflammation (68) compared to healthy controls (84). The reduction of another hPTM, H3K27ac, was observed in the mucosa of patients with UC and in a murine colitis model compared with controls (73). These findings were associated with an increased HDAC activity that removed H3K27ac in the intestine but maintained hyperacetylation in inflammatory genes promoter. This status was reverted during the resolution of inflammation or by the broad-acting HDAC inhibitor valproic acid (VPA) in biopsies cultured *ex vivo*, inhibiting inflammatory cytokine production (85). A second HDAC inhibitor, suberoylanilide hydroxamic acid (SAHA), also attenuates the inflammation

of DSS-induced colitis by suppressing the secretion of pro-inflammatory cytokines and chemokines as well as the recruitment and accumulation of inflammatory cells, such as macrophages, dendritic cells and monocytes (86). The positive response to treatments with HDAC inhibitors could be partially a compensation of the compromised endogenous HDAC inhibition on IECs due to the intestinal dysbiosis and lower production of butyrate in the gut of UC patients (87-89). This low concentration of butyrate results in fewer anti-inflammatory processes and reduction of autophagy in IECs. Experiments with an IEC line (HT29 cells) showed that butyrate promotes histone acetylation at the promoter region of the heat-shock transcription factor 2 (HSF2) gene (90). This results in increased expression of HSF2 that is positively associated with autophagy on IECs, a process that may contribute to reduce inflammation in the intestine and is altered in UC patients (90). The preventive and therapeutic treatments of a more palatable butyrate-releasing derivative, N-(1-carbamoyl-2-phenylethyl) butyramide (FBA), reproduces the beneficial effects of butyrate in mouse model of colitis, by inhibiting HDAC9 and the proinflammatory NF- κ B activation, while increasing peroxisome proliferator-activated receptor gamma (PPAR γ), butyrate transporter, tight junctions and histone H3 acetylation, thus exerting an anti-inflammatory effect (91).

Class I HDACs attracted attention in this context, since HDAC1 and HDAC2 may play an important role in the regulation of IEC-specific inflammatory responses by controlling, directly or indirectly, the JAK/STAT pathway (45), while the reduced expression of HDAC3 in IECs may be associated with regions of active disease in IBD (92). In this context, the absence of the epithelial HDAC3 in mice promoted T cell-driven intestinal inflammation through the reduction of Tregs, accumulation of Th17 cells and alterations in the composition of commensal bacteria (56).

HDAC1 and HDAC5 have also been linked to intestinal inflammation. These enzymes have opposite effects on intestinal colonization by adherent-invasive *Escherichia coli* (AIEC), which has been associated with CD development. Reduced expression of HDAC1 and high expression of HDAC5 were linked with intestinal colonization by AIEC through hyperacetylation of histone H3 in ileal mucosa. A similar profile was observed in HF-fed mice, but not in chow-fed mice, indicating another mechanism by which the consumption of a western diets impairs the gut homeostasis (93).

The HAT KAT2B is another enzyme down-regulated in inflamed CD and UC tissues, which may contribute to

the disruption of the innate and adaptive inflammatory responses due to the reduction of H4K5ac and suppression of IL-10 expression (1). Other HDACs and HATs were also explored in intestinal injury under inflammatory conditions, such as Sirt6 (70) and EP300 (83), respectively, that may be promising targets for IBD treatment in the future (Figure 3E).

Collectively, this section summarizes recent finds showing alterations of hPTMs in IECs of IBD patients. This information is relevant for the development of new approaches for detecting and/or treating IBD. Changes in the microbiota composition and their products including the SCFAs are associated with alterations in the histone acylation at various residues (e.g., H3K9ac, H3K27ac and H3Kac) in intestinal cells and may contribute to the development of IBD due, for example, to the attenuation of anti-inflammatory processes.

Conclusions

The intestinal epithelium is an essential protective barrier of our body. The cells that form this barrier are in direct contact with the external environment and sense nutrients, microbiota-derived molecules, pathogen or damage signals to which they respond accordingly, in part, through a wide range of histone post-translational modifications, that control the expression of genes that regulate their proliferation, differentiation, metabolism and communication with immune cells.

The hPTMs are key epigenetic regulators that add complexity to the study of chromatin regulatory mechanisms and gene expression. Based on the recent data discussed in this review, we highlight the importance of histone acylations for controlling different processes on IECs. Histone acylations are relevant for proliferation, maturation, differentiation, and adaptation of IECs to diets, microbiota, circadian rhythm and inflammatory signals. The regulation of these modifications occurs through multiple mechanisms since the early life. One example is the inhibition of HDACs by BHB and SCFAs and its activation by InsP3, which depends on the availability of fermentable substrate and the microbiota composition. In a complex bidirectional relationship, the IECs also regulate the composition of the microbiota through the production of cytokines and antimicrobial peptides (AMPs), for example (Figure 4).

Interestingly, one of the most explored sites for histone acylations is H3K9, which was reported to be acetylated under ketogenic diet, pathogen challenges and homeostasis, β -hydroxybutyrylated during fasting, crotonylated and

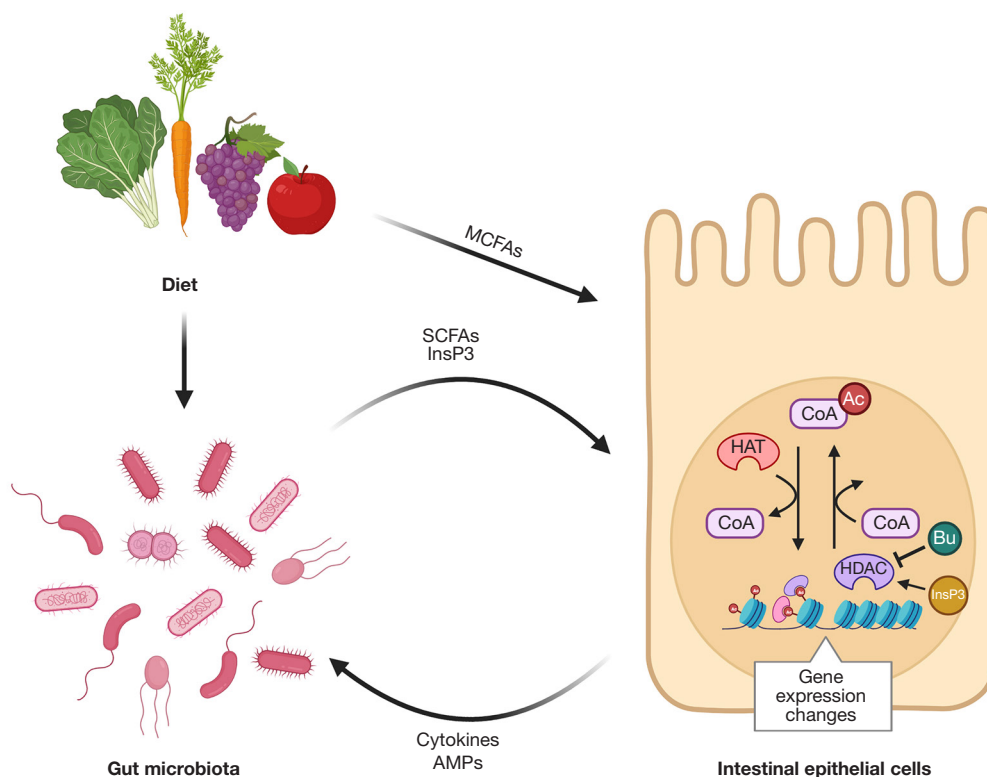


Figure 4 Crosstalk between the gut microbiota and epithelial cells. The epigenome of intestinal epithelial cells can be influenced by diverse environmental factors, such as diet and microbiota, through factors that serve as substrate or regulators of epigenetic modifiers. In a complex bidirectional relationship, the IECs also regulate the composition of the microbiota, through the production of cytokines and AMPs, for example. Original figure created with BioRender.com. MCFAs, medium-chain fatty acids; SCFAs, short-chain fatty acids; InsP3, inositol-1,4,5-trisphosphate; AMPs, antimicrobial peptides; ac, acetylation; CoA, coenzyme A; HAT, histone acyltransferase; bu, butyrylation; HDAC, histone deacetylase; IECs, intestinal epithelial cells.

butyrylated in homeostasis. H3K27 can be butyrylated and acetylated in diverse conditions as well, showing a competition of different and non-redundant hPTMs to the same site. These findings bring us new questions about the specificity of function of each acylation and enzymes responsible for them, that should be considered in future studies.

For the coming years, the characterization of different histone modifications should be encouraged, considering that acetylation was the main hPTM explored in research of the last decade.

Acknowledgments

Funding: This work was supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (Nos. 2018/15313-8 and 2021/10478-1), the National Council for Scientific and Technological Development

(CNPq), the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) (Finance Code 001), and the National Institutes of Health (NIH) (No. 1R01DK126969-01 for M.A.R.V.).

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Patrick Varga-Weisz and Raquel Franco Leal) for the series “Evidence of Epigenetics in Inflammatory Bowel Diseases” published in *Digestive Medicine Research*. The article has undergone external peer review.

Peer Review File: Available at <https://dmr.amegroups.com/article/view/10.21037/dmr-23-3/prf>

Conflicts of Interest: Both authors have completed the

ICMJE uniform disclosure form (available at <https://dmr.amegroups.com/article/view/10.21037/dmr-23-3/coif>). The series “Evidence of Epigenetics in Inflammatory Bowel Diseases” was commissioned by the editorial office without any funding or sponsorship. M.F.F. and M.A.R.V. were supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (Nos. 2018/15313-8 and 2021/10478-1), the National Council for Scientific and Technological Development (CNPq), and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior Brasil (CAPES) (Finance Code 001). M.A.R.V. was also supported by the National Institutes of Health (NIH) (No. 1R01DK126969-01). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

- Bai AH, Wu WK, Xu L, et al. Dysregulated Lysine Acetyltransferase 2B Promotes Inflammatory Bowel Disease Pathogenesis Through Transcriptional Repression of Interleukin-10. *J Crohns Colitis* 2016;10:726-34.
- Stylianou E. Epigenetics: the fine-tuner in inflammatory bowel disease? *Curr Opin Gastroenterol* 2013;29:370-7.
- Handy DE, Castro R, Loscalzo J. Epigenetic modifications: basic mechanisms and role in cardiovascular disease. *Circulation* 2011;123:2145-56.
- Terranova CJ, Stemler KM, Barrodia P, et al. Reprogramming of H3K9bhb at regulatory elements is a key feature of fasting in the small intestine. *Cell Rep* 2021;37:110044.
- Li X, Egervari G, Wang Y, et al. Regulation of chromatin and gene expression by metabolic enzymes and metabolites. *Nat Rev Mol Cell Biol* 2018;19:563-78.
- Allen J, Sears CL. Impact of the gut microbiome on the genome and epigenome of colon epithelial cells: contributions to colorectal cancer development. *Genome Med* 2019;11:11.
- Krautkramer KA, Kreznar JH, Romano KA, et al. Diet-Microbiota Interactions Mediate Global Epigenetic Programming in Multiple Host Tissues. *Mol Cell* 2016;64:982-92.
- Park SY, Kim JS. A short guide to histone deacetylases including recent progress on class II enzymes. *Exp Mol Med* 2020;52:204-12.
- Sabari BR, Tang Z, Huang H, et al. Intracellular crotonyl-CoA stimulates transcription through p300-catalyzed histone crotonylation. *Mol Cell* 2015;58:203-15.
- Simithy J, Sidoli S, Yuan ZF, et al. Characterization of histone acylations links chromatin modifications with metabolism. *Nat Commun* 2017;8:1141.
- Turgeon N, Blais M, Gagné JM, et al. HDAC1 and HDAC2 restrain the intestinal inflammatory response by regulating intestinal epithelial cell differentiation. *PLoS One* 2013;8:e73785.
- Etchegaray JP, Mostoslavsky R. Interplay between Metabolism and Epigenetics: A Nuclear Adaptation to Environmental Changes. *Mol Cell* 2016;62:695-711.
- Fan J, Krautkramer KA, Feldman JL, et al. Metabolic regulation of histone post-translational modifications. *ACS Chem Biol* 2015;10:95-108.
- Chakravarty S, Pathak SS, Maitra S, et al. Epigenetic regulatory mechanisms in stress-induced behavior. *Int Rev Neurobiol* 2014;115:117-54.
- Luan Y, Ngo L, Han Z, et al. Chapter 14 - Histone Acetyltransferases: Enzymes, Assays, and Inhibitors. Vol. 10, Epigenetic Technological Applications. In: Zheng YG, editor. *Epigenetic Technological Applications*. Elsevier Inc.; 2015:291-317.
- van den Bosch T, Leus NGJ, Timmerman T, et al. Chapter 8 - Small molecule inhibitors of histone deacetylases and acetyltransferases as potential therapeutics in oncology. In: Egger G, Arimondo P, editors. *Drug Discovery in Cancer Epigenetics*. Elsevier Inc.; 2015:191-208.
- Krautkramer KA, Dhillon RS, Denu JM, et al. Metabolic programming of the epigenome: host and gut microbial metabolite interactions with host chromatin. *Transl Res* 2017;189:30-50.
- Bayarsaihan D. Epigenetic mechanisms in inflammation. *J Dent Res* 2011;90:9-17.
- Choudhary C, Weinert BT, Nishida Y, et al. The growing landscape of lysine acetylation links metabolism and cell

- signalling. *Nat Rev Mol Cell Biol* 2014;15:536-50.
20. Tsaprouni LG, Ito K, Powell JJ, et al. Differential patterns of histone acetylation in inflammatory bowel diseases. *J Inflamm (Lond)* 2011;8:1.
 21. McClure JJ, Li X, Chou CJ. Advances and Challenges of HDAC Inhibitors in Cancer Therapeutics. *Adv Cancer Res* 2018;138:183-211.
 22. Seto E, Yoshida M. Erasers of histone acetylation: the histone deacetylase enzymes. *Cold Spring Harb Perspect Biol* 2014;6:a018713.
 23. Sabari BR, Zhang D, Allis CD, et al. Metabolic regulation of gene expression through histone acylations. *Nat Rev Mol Cell Biol* 2017;18:90-101.
 24. Xue Q, Yang Y, Li H, et al. Functions and mechanisms of protein lysine butyrylation (Kbu): Therapeutic implications in human diseases. *Genes & Diseases* 2022. doi: 10.1016/j.gendis.2022.10.025.
 25. Li Y, Sabari BR, Panchenko T, et al. Molecular Coupling of Histone Crotonylation and Active Transcription by AF9 YEATS Domain. *Mol Cell* 2016;62:181-93.
 26. Fellows R, Varga-Weisz P. Chromatin dynamics and histone modifications in intestinal microbiota-host crosstalk. *Mol Metab* 2020;38:100925.
 27. Kebede AF, Nieborak A, Shahidian LZ, et al. Histone propionylation is a mark of active chromatin. *Nat Struct Mol Biol* 2017;24:1048-56.
 28. Flynn EM, Huang OW, Poy F, et al. A Subset of Human Bromodomains Recognizes Butyryllysine and Crotonyllysine Histone Peptide Modifications. *Structure* 2015;23:1801-14.
 29. Gowans GJ, Bridgers JB, Zhang J, et al. Recognition of Histone Crotonylation by Taf14 Links Metabolic State to Gene Expression. *Mol Cell* 2019;76:909-921.e3.
 30. Wu Q, Li W, Wang C, et al. Ultra-deep Lysine Crotonylome Reveals the Crotonylation Enhancement on Both Histones and Nonhistone Proteins by SAHA Treatment. *J Proteome Res* 2017;16:3664-71.
 31. Kelly RDW, Chandru A, Watson PJ, et al. Histone deacetylase (HDAC) 1 and 2 complexes regulate both histone acetylation and crotonylation in vivo. *Sci Rep* 2018;8:14690.
 32. Fellows R, Denizot J, Stellato C, et al. Microbiota derived short chain fatty acids promote histone crotonylation in the colon through histone deacetylases. *Nat Commun* 2018;9:105.
 33. Chen Y, Sprung R, Tang Y, et al. Lysine propionylation and butyrylation are novel post-translational modifications in histones. *Mol Cell Proteomics* 2007;6:812-9.
 34. Xu H, Wu M, Ma X, et al. Function and Mechanism of Novel Histone Posttranslational Modifications in Health and Disease. *Biomed Res Int* 2021;2021:6635225.
 35. Huang H, Zhang D, Weng Y, et al. The regulatory enzymes and protein substrates for the lysine β -hydroxybutyrylation pathway. *Sci Adv* 2021;7:eabe2771.
 36. Zhou T, Cheng X, He Y, et al. Function and mechanism of histone β -hydroxybutyrylation in health and disease. *Front Immunol* 2022;13:981285.
 37. Tan M, Luo H, Lee S, et al. Identification of 67 histone marks and histone lysine crotonylation as a new type of histone modification. *Cell* 2011;146:1016-28.
 38. Liu B, Lin Y, Darwanto A, et al. Identification and characterization of propionylation at histone H3 lysine 23 in mammalian cells. *J Biol Chem* 2009;284:32288-95.
 39. Goudarzi A, Zhang D, Huang H, et al. Dynamic Competing Histone H4 K5K8 Acetylation and Butyrylation Are Hallmarks of Highly Active Gene Promoters. *Mol Cell* 2016;62:169-80.
 40. Jiang G, Li C, Lu M, et al. Protein lysine crotonylation: past, present, perspective. *Cell Death Dis* 2021;12:703.
 41. Ntorla A, Burgoyne JR. The Regulation and Function of Histone Crotonylation. *Front Cell Dev Biol* 2021;9:624914.
 42. Gehart H, Clevers H. Tales from the crypt: new insights into intestinal stem cells. *Nat Rev Gastroenterol Hepatol* 2019;16:19-34.
 43. Suzuki T, Mochizuki K, Goda T. Histone H3 modifications and Cdx-2 binding to the sucrase-isomaltase (SI) gene is involved in induction of the gene in the transition from the crypt to villus in the small intestine of rats. *Biochem Biophys Res Commun* 2008;369:788-93.
 44. Roostae A, Guezguez A, Beauséjour M, et al. Histone deacetylase inhibition impairs normal intestinal cell proliferation and promotes specific gene expression. *J Cell Biochem* 2015;116:2695-708.
 45. Gonneaud A, Turgeon N, Boisvert FM, et al. JAK-STAT Pathway Inhibition Partially Restores Intestinal Homeostasis in Hdac1- and Hdac2-Intestinal Epithelial Cell-Deficient Mice. *Cells* 2021;10:224.
 46. Gonneaud A, Turgeon N, Jones C, et al. HDAC1 and HDAC2 independently regulate common and specific intrinsic responses in murine enteroids. *Sci Rep* 2019;9:5363.
 47. Zimmerlin CD, Lancini C, Sno R, et al. HDAC1 and HDAC2 collectively regulate intestinal stem cell homeostasis. *FASEB J* 2015;29:2070-80.
 48. Marruecos L, Bertran J, Álvarez-Villanueva D, et al.

- Dynamic chromatin association of I κ B α is regulated by acetylation and cleavage of histone H4. *EMBO Rep* 2021;22:e52649.
49. Ferrari KJ, Amato S, Noberini R, et al. Intestinal differentiation involves cleavage of histone H3 N-terminal tails by multiple proteases. *Nucleic Acids Res* 2021;49:791-804.
 50. Jadhav U, Saxena M, O'Neill NK, et al. Dynamic Reorganization of Chromatin Accessibility Signatures during Dedifferentiation of Secretory Precursors into Lgr5+ Intestinal Stem Cells. *Cell Stem Cell* 2017;21:65-77.e5.
 51. Schell JC, Wisidagama DR, Bensard C, et al. Control of intestinal stem cell function and proliferation by mitochondrial pyruvate metabolism. *Nat Cell Biol* 2017;19:1027-36.
 52. Bauer E, Thiele I. From metagenomic data to personalized in silico microbiotas: predicting dietary supplements for Crohn's disease. *NPJ Syst Biol Appl* 2018;4:27.
 53. Corrêa-Oliveira R, Fachi JL, Vieira A, et al. Regulation of immune cell function by short-chain fatty acids. *Clin Transl Immunol* 2016;5:e73.
 54. Koh A, De Vadder F, Kovatcheva-Datchary P, et al. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. *Cell* 2016;165:1332-45.
 55. Gates LA, Sgarbi Reis B, Lund PJ, et al. Microbiota-dependent histone butyrylation in the mammalian intestine. *bioRxiv* 2022. doi: <https://doi.org/10.1101/2022.09.29.510184>.
 56. Eshleman EM, Shao TY, Woo V, et al. Intestinal epithelial HDAC3 and MHC class II coordinate microbiota-specific immunity. *J Clin Invest* 2023;133:e162190.
 57. Abo H, Chassaing B, Harusato A, et al. Erythroid differentiation regulator-1 induced by microbiota in early life drives intestinal stem cell proliferation and regeneration. *Nat Commun* 2020;11:513.
 58. Schönfeld P, Wojtczak L. Short- and medium-chain fatty acids in energy metabolism: the cellular perspective. *J Lipid Res* 2016;57:943-54.
 59. Vinolo MA, Rodrigues HG, Nachbar RT, et al. Regulation of inflammation by short chain fatty acids. *Nutrients* 2011;3:858-76.
 60. Trefely S, Lovell CD, Snyder NW, et al. Compartmentalised acyl-CoA metabolism and roles in chromatin regulation. *Mol Metab* 2020;38:100941.
 61. Waldecker M, Kautenburger T, Daumann H, et al. Inhibition of histone-deacetylase activity by short-chain fatty acids and some polyphenol metabolites formed in the colon. *J Nutr Biochem* 2008;19:587-93.
 62. Lund PJ, Gates LA, Leboeuf M, et al. Stable isotope tracing in vivo reveals a metabolic bridge linking the microbiota to host histone acetylation. *Cell Rep* 2022;41:111809.
 63. Bilotta AJ, Ma C, Yang W, et al. Propionate Enhances Cell Speed and Persistence to Promote Intestinal Epithelial Turnover and Repair. *Cell Mol Gastroenterol Hepatol* 2021;11:1023-44.
 64. Wu SE, Hashimoto-Hill S, Woo V, et al. Microbiota-derived metabolite promotes HDAC3 activity in the gut. *Nature* 2020;586:108-12.
 65. Wang J, Huang N, Xiong J, et al. Caprylic acid and nonanoic acid upregulate endogenous host defense peptides to enhance intestinal epithelial immunological barrier function via histone deacetylase inhibition. *Int Immunopharmacol* 2018;65:303-11.
 66. Bhat MI, Kumari A, Kapila S, et al. Probiotic lactobacilli mediated changes in global epigenetic signatures of human intestinal epithelial cells during *Escherichia coli* challenge. *Ann Microbiol* 2019;69:603-12.
 67. Kumari A, Bhawal S, Kapila S, et al. Strain-specific effects of probiotic *Lactobacilli* on mRNA expression of epigenetic modifiers in intestinal epithelial cells. *Arch Microbiol* 2022;204:411.
 68. Liu M, Ding J, Zhang H, et al. *Lactobacillus casei* LH23 modulates the immune response and ameliorates DSS-induced colitis via suppressing JNK/p-38 signal pathways and enhancing histone H3K9 acetylation. *Food Funct* 2020;11:5473-85.
 69. Xiong X, Yang C, He WQ, et al. Sirtuin 6 maintains epithelial STAT6 activity to support intestinal tuft cell development and type 2 immunity. *Nat Commun* 2022;13:5192.
 70. Liu F, Bu HF, Geng H, et al. Sirtuin-6 preserves R-spondin-1 expression and increases resistance of intestinal epithelium to injury in mice. *Mol Med* 2017;23:272-84.
 71. Navabi N, Whitt J, Wu SE, et al. Epithelial Histone Deacetylase 3 Instructs Intestinal Immunity by Coordinating Local Lymphocyte Activation. *Cell Rep* 2017;19:1165-75.
 72. Fischer N, Sechet E, Friedman R, et al. Histone deacetylase inhibition enhances antimicrobial peptide but not inflammatory cytokine expression upon bacterial challenge. *Proc Natl Acad Sci U S A* 2016;113:E2993-3001.
 73. Woo V, Eshleman EM, Whitt J, et al. Commensal

- bacterial-derived retinoic acid primes host defense to intestinal infection. *bioRxiv* 2021. doi: <https://doi.org/10.1101/2021.01.27.428280>.
74. Jeffrey MP, MacPherson CW, Mathieu O, et al. Secretome-Mediated Interactions with Intestinal Epithelial Cells: A Role for Secretome Components from *Lactobacillus rhamnosus* R0011 in the Attenuation of *Salmonella enterica* Serovar Typhimurium Secretome and TNF- α -Induced Proinflammatory Responses. *J Immunol* 2020;204:2523-34.
 75. Kuang Z, Wang Y, Li Y, et al. The intestinal microbiota programs diurnal rhythms in host metabolism through histone deacetylase 3. *Science* 2019;365:1428-34.
 76. Whitt J, Woo V, Lee P, et al. Disruption of Epithelial HDAC3 in Intestine Prevents Diet-Induced Obesity in Mice. *Gastroenterology* 2018;155:501-13.
 77. Forsyth CB, Shaikh M, Bishhearsari F, et al. Alcohol Feeding in Mice Promotes Colonic Hyperpermeability and Changes in Colonic Organoid Stem Cell Fate. *Alcohol Clin Exp Res* 2017;41:2100-13.
 78. Tognini P, Murakami M, Liu Y, et al. Distinct Circadian Signatures in Liver and Gut Clocks Revealed by Ketogenic Diet. *Cell Metab* 2017;26:523-538.e5.
 79. Fawad JA, Luzader DH, Hanson GF, et al. Histone Deacetylase Inhibition by Gut Microbe-Generated Short-Chain Fatty Acids Entrain Intestinal Epithelial Circadian Rhythms. *Gastroenterology* 2022;163:1377-1390.e11.
 80. Wawrzyniak M, Scharl M. Genetics and epigenetics of inflammatory bowel disease. *Swiss Med Wkly* 2018;148:w14671.
 81. Melgar S, Karlsson A, Michaëlsson E. Acute colitis induced by dextran sulfate sodium progresses to chronicity in C57BL/6 but not in BALB/c mice: correlation between symptoms and inflammation. *Am J Physiol Gastrointest Liver Physiol* 2005;288:G1328-38.
 82. van der Beek CM, Dejong CHC, Troost FJ, et al. Role of short-chain fatty acids in colonic inflammation, carcinogenesis, and mucosal protection and healing. *Nutr Rev* 2017;75:286-305.
 83. Yu YL, Chen M, Zhu H, et al. STAT1 epigenetically regulates LCP2 and TNFAIP2 by recruiting EP300 to contribute to the pathogenesis of inflammatory bowel disease. *Clin Epigenetics* 2021;13:127.
 84. Li C, Chen Y, Zhu H, et al. Inhibition of Histone Deacetylation by MS-275 Alleviates Colitis by Activating the Vitamin D Receptor. *J Crohns Colitis* 2020;14:1103-18.
 85. Felice C, Lewis A, Iqbal S, et al. Intestinal Inflammation is Linked to Hypoacetylation of Histone 3 Lysine 27 and can be Reversed by Valproic Acid Treatment in Inflammatory Bowel Disease Patients. *Cell Mol Gastroenterol Hepatol* 2021;11:889-891.e6.
 86. Ali MN, Chojjookhuu N, Takagi H, et al. The HDAC Inhibitor, SAHA, Prevents Colonic Inflammation by Suppressing Pro-inflammatory Cytokines and Chemokines in DSS-induced Colitis. *Acta Histochem Cytochem* 2018;51:33-40.
 87. Lavelle A, Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol* 2020;17:223-37.
 88. Lloyd-Price J, Arze C, Ananthakrishnan AN, et al. Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. *Nature* 2019;569:655-62.
 89. Ni J, Wu GD, Albenberg L, et al. Gut microbiota and IBD: causation or correlation? *Nat Rev Gastroenterol Hepatol* 2017;14:573-84.
 90. Zhang F, Wang W, Niu J, et al. Heat-shock transcription factor 2 promotes sodium butyrate-induced autophagy by inhibiting mTOR in ulcerative colitis. *Exp Cell Res* 2020;388:111820.
 91. Simeoli R, Mattace Raso G, Pirozzi C, et al. An orally administered butyrate-releasing derivative reduces neutrophil recruitment and inflammation in dextran sulphate sodium-induced murine colitis. *Br J Pharmacol* 2017;174:1484-96.
 92. Alenghat T, Osborne LC, Saenz SA, et al. Histone deacetylase 3 coordinates commensal-bacteria-dependent intestinal homeostasis. *Nature* 2013;504:153-7.
 93. Chervy M, Sivignon A, Dambrine F, et al. Epigenetic master regulators HDAC1 and HDAC5 control pathobiont *Enterobacteria* colonization in ileal mucosa of Crohn's disease patients. *Gut Microbes* 2022;14:2127444.

doi: 10.21037/dmr-23-3

Cite this article as: Fernandes MF, Vinolo MAR. Histone acylations as a mechanism for regulation of intestinal epithelial cells. *Dig Med Res* 2024;7:4.