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Chromatin dynamics and histone modifications in the intestinal microbiota-host crosstalk

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Abstract

Background

The microbiota in our gut is an important component of normal physiology that has co-evolved with us from the earliest multicellular organisms. It is, therefore, not surprising that there is an intimate crosstalk between the microbial world in the gut and the host. Genome regulation through microbiota-host interactions not only affect the host's immunity, but also metabolic health and resilience against cancer. Chromatin dynamics of the host epithelium involving histone modifications and other facets of the epigenetic machinery play an important role in this process.

Scope of Review

In this review we will discuss recent findings relevant to how chromatin dynamics shape the crosstalk between the microbiota and its host, with special focus on the role of histone modifications.

Major Conclusions

Host-microbiome interactions are important evolutionary drivers and are, thus, expected to be hardwired into and mould the epigenetic machinery in multicellular organisms. Microbial derived short chain fatty acids (SCFA) emerge as a dominant

determinant in microbiome-host interaction and the inhibition of histone deacetylases (HDACs) by SCFA is a key mechanism in this process. The discovery of alternative histone acylations, such as crotonylation, in addition to the canonical histone acetylation reveals a new layer of complexity in this crosstalk.

The epigenome is shaped by the environment

Each cell in the body of a multicellular eukaryotic organism usually has essentially the same genome in its nucleus, packaged into a highly complex superstructure known as chromatin. The basic building block of chromatin is the nucleosome, composed of eight core histones (H2A, H2B, H3, H4) around which DNA winds in almost two turns. An additional linker histone H1 'seals off' this structure. Histone tails, normally unstructured but highly conserved peptide components of the histones, protrude from the core nucleosome body and are subject to a plethora of posttranslational modifications (PTMs). These various histone PTMs are critical components of gene and genome regulatory mechanisms and are thought to constitute something of a 'regulatory language' (the 'histone code'), in part by creating binding sites for effector proteins, often called 'readers' (reviewed in: [1–3]). Histone acetylation is a paradigm histone PTM. This modification occurs on the epsilon amino groups of lysine residues on N-terminal tails of predominantly histones H3 and H4 and is associated with permissive, transcriptionally active chromatin. This modification is mediated by histone acetyltransferases (HATs, 'writers') and reversed by histone deacetylases (HDACs, 'erasers').

Histone lysine methylations are PTMs that have also been well studied, but here the functional context is more complex compared to acetylation. For example, trimethylation of histone H3 at lysine 4 (H3K4me3) is strongly linked to active genes,

whereas trimethylation of histone H3 at lysines 9 (H3K9me3) or 27 (H3K27me3) are part of various gene repressive pathways [4].

The structure of nucleosomes are altered by a plethora of additional proteins of which ATP-dependent nucleosome remodelling factors are an important group (reviewed in [5,6]). These factors can catalyse the eviction or restructuring of nucleosomes, for example by histone dimer eviction or exchange of histone variants. These factors also affect the posttranslational modifications of histones, possibly by facilitating these enzymatic steps in a nucleosomal context.

In addition to histones, DNA itself is modified, most commonly methylation of carbon-5 position of cytosines at CpG dinucleotide sequences. Histone and DNA modifications are important components of epigenetic mechanisms, which not only allow cells to differentiate into many cell types from one genome blueprint, but also form a part of a cellular 'memory' [7]. This 'memory' is not only essential for a cell to 'remember' its identity, but it also constitutes a mechanism by which a cell can integrate external cues, such as environmental influences. Other components of the epigenetic machinery are transcription factor networks and noncoding RNAs, including long noncoding RNAs and micro RNAs. Exactly what constitutes an epigenetic mechanism or what should be called 'epigenetic' has been subject of some debate, but we feel a practical, non-dogmatic approach is useful and we consider everything that moulds the functional output of the genome without changing the underlying DNA sequence to be 'epigenetic', remembering that 'epi' stems from Greek for 'on top of'.

Our microbiota are very dominant environmental factors that our bodies have to deal with, affecting health and disease. In this review we will discuss recent work investigating how the gut microbiota shapes the epigenome. This is a dynamic and

complex field and there have been a number of recent reviews covering various aspects [8–14]. We focus here on how this crosstalk shapes the host's genome function through histone modifications and we discuss very recent papers. As this topic is complex and brings together several fields, we have a 'glossary' box to summarise or explain several critical terms (Table 1).

The microbial world in us

Our world is permeated, if not dominated, by microbes and we find microbes thriving in the most hostile environments on earth. Thus, it is not surprising to find that our bodies are also home to a staggering number and diversity of microbes, including bacteria, archaea, protists, yeasts and viruses. Technological developments, especially next generation sequencing based methods of metagenomics have revolutionised our understanding of the microbial world, including our microbiota. We have learned that complex ecosystems of microbes cover many mucosal surfaces of our body, such as the skin, gut, vagina, lungs, uterus and bladder [15–18].

The microbiota and host have coevolved from the earliest multicellular organisms onwards and it has been argued that pressure on the host to control the microbiota has been an important evolutionary driver [19]. Thus, the host microbiome has been termed 'an ecosystem on a leash' [19]. As Foster *et al*., wrote: "Host control over the microbes (as opposed to microbial control of the host) can be predicted, because there is only one host in the interaction, in contrast to the myriad microbes. Thus, unlike individual microbes, a host can easily influence the entire microbiome, and benefit from doing so" [19]. Therefore, while we will present evidence in this review that the microbiota manipulates the epigenetic machinery for interaction with the

host, we can expect that this interaction also shaped the epigenetic machinery during evolution.

In many mammals, including human, the greatest number of microbes are found in the colon **(Figure 1)**. It is estimated that the number of microbes in the colon at least match the total number of host cells in a human [20]. The microbiota create a complex ecosystem where several species compete with, depend on or influence each other. Importantly, the microbial community in the colon is highly diverse with at least ~ 1000 different species. Despite some redundancy in function between species, this means that the combined microbial 'genome' is more than 100-fold greater than the host's. This has important implications to the host, as the microbiota contain unique genes that are absent in the host's genome. Many of these genes encode enzymes that break down dietary components, such as complex carbohydrates, and make these absorbable and available to the host. In this way, the microbiota make an important contribution to the host's extraction of nutrients and energy from the diet [21]. This can be seen in germ-free mice that are usually leaner then their microbiota containing counterparts [22]. In addition to helping in the digestion of food, bacteria also synthesize essential vitamins and are key in training the immune system. Furthermore, our normal, commensal microbiota protect us from pathogenic microbes, in part by simply competing them out of space and nutrients. Thus, the microbiota exert an important and largely beneficial role in our life. In their role in digesting food and generating vitamins, the microbiota could be considered almost an organ in our body. This notion is strengthened if one considers that structures in the gut, such as the caecum, evolved to house the microbiota. Yet, this would be a highly dynamic organ, not only changing dramatically in size depending on food intake and digestive status, but also in the species composition of microbes.

In fact, the microbial composition differs from person to person because the microbiota composition is strongly affected by nutrition, lifestyle and other factors [23,24].

Furthermore, the microbiome composition evolves during life time, from its acquisition during and after birth, maturing after weaning and changing even into old age [24]. However, the microbiota can turn into the enemy within us. Not only can we ingest harmful bacteria, such as *Salmonella* that invade and poison our body [25], our body can also overreact to the presence of the microbiota in the gut, for example, as a result of genetic predisposition. This can lead to inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis [26]. Furthermore, the microbiota have been identified as contributing factor in cancer processes, especially gastric and colon cancers. The role of *Helicobacter pylori* in gastric cancer is an illustration for this [27].

In summary, the microbiota are a dominant force in our lives and understanding how microbiota-host interactions are regulated is important.

Crosstalk microbiota-host through microbial metabolites

The crosstalk between microbiota and host occurs through a large variety of molecules, such as bacterial structural components and metabolites. Bacterial cell wall components or flagellar proteins are recognized by the host's cells through specific receptors (so called pattern recognition receptors, PRRs) in innate immune responses. Toll-like receptors are well studied PRRs. The microorganism-associated molecular patterns (MAMPs) include lipopolysaccharides, flagellin, and peptidoglycans. These initiate signalling cascades, e.g., leading to an anti-bacterial response through generation of cytokines, chemokines and/ or anti-bacterial peptides (reviewed in [28,29]). Another important mechanism by which the

microbiota interact with the host is through the generation of bioactive molecules that are taken up in the host's cells and affect cellular functions, especially gene regulation [29]. There are several key metabolites that have been studied in this context, which include short chain fatty acids (SCFA), polyamines, vitamins and aryl hydrocarbon receptor (AHR) ligands. **Figure 2** summarises some of these bacterially derived molecules and their impact on the host.

The AHR is a nuclear receptor type of transcription factor that is activated by binding to diverse ligands, including xenobiotics, plant or bacterial metabolites or bacterial pigments [30–32]. AHR function has been shown to be required for intestinal immunity in mice by maintaining intestinal intraepithelial lymphocytes [30].

Bacteria synthesize several vitamins such as B12 (cobalamin), riboflavins and folate [33]. As folate is required for DNA and histone methylation, the commensal bacteria have a potentially broad impact on epigenetic mechanisms [34,35].

Polyamines (PA) such as spermine, spermidine and putrescine are essential for life in eukaryotes and prokaryotes, being involved in many processes, such as gene expression, chromatin structure regulation, stress response, differentiation and proliferation (for review: [36]). Normally, PA are derived from the diet and absorbed by the small intestine, but can also be generated by the microbiota in considerable amounts in the colon, where they are thought to support epithelium health [36]. How microbial PA affect the host's chromatin is poorly understood.

SCFA constitute a major class of bacterial metabolites. They are generated by the microbiota through the fermentation of complex carbohydrates as a metabolic waste product in the colon (and in many animals in the caecum) to large amounts and have a profound impact on the host's physiology (reviewed in: [37]). The major microbial derived SCFA are acetate, propionate and butyrate. Estimates of SCFA

concentration vary between studies and different diets, but Rombeau and associates approximated SCFA concentrations in the content of the human colon to be 75 m*M* for acetate, 30 m*M* for propionate and 20 m*M* for butyrate [38]. These SCFA are generated by several bacterial species and there is cross-feeding between bacterial species, e.g. acetate and lactate producing *Bifidobacterium* species have been shown to feed the butyrate producing *Faecalibacterium prausnitzii* [39].

While acetate and propionate are released into the blood stream through the portal vein, butyrate is mostly absorbed and metabolized by the colon epithelium, which constitutes the preferred energy source in this tissue [21]. In fact, the absence of microbiota in germ-free mice and, therefore, the lack of SCFA causes a complete remodelling of metabolism in the colon epithelium with a dramatic upregulation of autophagy to compensate for the loss of microbial SCFA [21]. Antibiotic treatment to deplete microbiome confirms the importance of the microbiota in energy generation and metabolism [40]. The oxidation of butyrate in the epithelium affects O_2 levels, causing activation of the oxygen sensor HIF1, which in turn affects the response to pathogens [41,42]. Butyrate inhibits cellular proliferation of intestinal stem/progenitor cells at physiologic concentrations and it has been suggested that the epithelial cellular anatomy reflects this influence, protecting the stem and proliferating cells from the effects of butyrate by sequestering them in crypts [43]. Thus, butyrate has different impacts on cells dependent on their location along the crypt axis - with stem cell niche being relatively depleted of butyrate while villus cells use butyrate as a principal carbon source [43].

Butyrate and propionate are effective HDAC inhibitors at the concentrations that are generated in the colon and this constitutes an important mechanism by which these SCFA affect physiology. SCFA also activate G-coupled-receptors (GPCRs, also

called free fatty acid receptors, FFARs). GPR43 and 41 have been studied in this respect. In both capacities, as HDAC inhibitors and activators of GCPRs, the bacterial derived SCFA suppress inflammatory responses (reviewed in [37]). SCFA might also promote histone modifications by metabolic conversion to the acetyl-CoA and other SCFA-CoA precursors to be transferred to histones by HATS such as p300/CBP (see below, [44,45]).

Histone modification in the microbiota-host crosstalk

It has been known for decades that there is a link between fiber content of diet, production of SCFA by the microbiota and histone acetylation in the gut [46] . More recently, a study examined the effect of the microbiota and diet on histone modifications using mass spectrometry analysis [47]. The researchers employed conventionally raised, germ-free and microbiota-re-colonized ("conventionalized") mice to address the role of the microbiota [47]. Since conventionally raised animals exhibit developmental differences versus their germ-free controls (reviewed in: [48]), the use of the conventionalized mice allowed for studying of effects related to the presence or absence of the microbiota directly. This study is important as it showed that the gut microbiota effected histone acetylation and methylation not only in the colon, but also in the liver and white adipose tissue and that generation of SCFA by the microbiota is a dominant driver of this. The researchers found that the presence of microbiota robustly promoted histone acetylation of H3 and H4 at multiple lysine residues in the various tissues, whilst changes in H3 methylation were subtle, but still significant [47]. Some histone PTMs appeared to be similarly regulated across all tissues surveyed, whilst other changes were tissue specific. Interestingly, feeding mice a diet high in fat and sucrose and low in fermentable complex carbohydrates

(HF/HS-diet, “western-style diet”) suppressed microbiota-driven SCFA production and chromatin effects observed in a fiber-rich diet. HF/HS-fed conventionally raised mice displayed higher hepatic total cholesterol and triglycerides versus diet-matched germ-free controls and chow-fed mice, showing that HF/HS feeding impacted the host’s metabolic state in a microbiota-dependent manner. The presence of microbiota and the diets manifested themselves in gene expression in the liver and many affected genes related to metabolism.

Gut microbiota altered expression of genes linked to metabolites that are required for histone PTMs. For example, expression of ATP citrate lyase (*Acly*) an enzyme essential for glucose-driven, but not acetate-driven, histone acetylation in mammalian cells [49], was decreased in conventionally raised versus germ-free mice, under both chow and HF/HS feeding [47]. This suggested that the presence of bacterial SCFA or lipids from HF/HS feeding, may suppress glucose-driven histone modification. The authors did not examine how changes of histone modifications, e.g., over promoters, are linked to changes in gene expression, e.g., by ChIP-seq. Yet, overall, this study highlights the intimate link between diet, the microbiota and genome-regulation in the whole organism.

Alternative histone acylations in the microbiota-host crosstalk

Progress in the analysis of histone PTMs by mass spectrometry has allowed the identification of a range new modifications, many of which can be summarised as alternative acylations. These include histone crotonylation, butyrylation, hydroxybutyrylation and propionylation (reviewed in: [50–52], see **Table 2** for a summary). These modifications are also linked to metabolic pathways. For example, histone crotonylation is promoted by addition of crotonic acid to cell culture media, as

crotonic acid is converted to crotonyl-CoA by the enzyme ASCC2 [53]. Histone crotonylation changes the functionality of nucleosomes compared to histone acetylation as it creates specific binding platforms for YEATS domain containing chromatin remodelling factors. Although both modifications are associated with active chromatin, crotonylation promoted gene expression to a greater extent than acetylation in a cell-free assay [54–56].

We used mass spectrometry to canvas PTMs, including crotonylation, in histones isolated from the intestinal epithelium [57]. We found that histone crotonylation is a relatively abundant modification in the intestinal epithelium (and the brain) with H3K18cr identified as the most prevalent crotonylation. When we acutely depleted microbiota in mice with a 3-day course of a cocktail of antibiotics, this not only reduced luminal SCFA, but significantly affected global histone crotonylation levels in the gut. We could show that butyrate acted as a histone decrotonylase inhibitor and found, consistent with several other studies published around that time [58,59], that class I HDACs are potent histone decrotonylases [57]. Therefore, our study emphasizes inhibition of HDACs through SCFA, especially butyrate, as an important mechanism for the microbiota-host crosstalk. Similar to what has been shown in other cell types, we found H3K18cr ‘peaks’ over promoter regions of many genes and its level seems to correlate with gene expression [53,57]. Interestingly, many of the genes with higher levels of crotonylation over their promoters have been linked to cancer pathways. More recently, we found that promoter chromatin crotonylation reflects gene expression changes dependent on microbiota (Fellows *et al*., in revision). Thus, it appears that promoter crotonylation is an important mechanism for the microbiota-host crosstalk in the gut. Our current model how bacterial derived SCFA affect histone crotonylation is shown in **Figure 3**.

HDACs in microbe-host interactions

The previous sections have already highlighted the importance of HDACs in the microbiota-host crosstalk, mainly because the microbial-derived butyric and propionic acids are HDAC inhibitors. Thus, it is not surprising that HDACs were found to have a critical role in the microbiota-host crosstalk. This is well illustrated with HDAC3 in a study from the Artis lab [60]. Intestinal epithelium specific deletion of HDAC3 ($HDAC3^{\Delta IEC}$) led to gene expression and corresponding H3K9ac level changes at affected genes and a progressive loss of Paneth cells, with evidence of Paneth cell death [60]. Paneth cells are found at the base of the small intestinal crypt, where they play a role in regulating microbiota-host interaction by secreting anti-bacterial peptides (See Fig. 1, [61]). Thus, consistent with the loss of Paneth cells, the $HDAC3^{\Delta IEC}$ mice exhibited increased translocation of bacteria through the epithelium and increased intestinal inflammation, as well as increased susceptibility to oral *Listeria monocytogenes* infection. Remarkably, Paneth cell viability was not affected in $HDAC3^{\Delta IEC}$ mice raised under germ-free conditions and alterations in the majority of HDAC3-dependent transcriptional pathways, including those involved in anti-microbial defence, were not seen. Thus, it appears that HDAC3 is required to respond to bacterial cues and translates this to a gene expression program that protects intestinal integrity. A follow-up study from the Alenghat lab demonstrated that HDAC3 mediates communication between intestinal epithelial cells and resident lymphocytes, thereby promoting resistance against infection by pathogenic microbes [62]. Whether these actions of HDAC3 occur through deacetylation of histones or other factors, or an enzymatic independent role of HDAC3 remains to be discovered.

Furthermore, it will be exciting to find out what are the bacterial cues involved in these pathways.

Sirt1 belongs to the class III group of NAD+ dependent deacetylases, also called sirtuins. Several sirtuins deacetylate histones, but they also have other targets. Epithelial deletion of Sirt1 led to age-dependent enhanced inflammation in one study [63], while another study reported protection against colitis and enhanced anti-bacterial defence in the intestine [64]. Both studies reported changes in the microbiota upon the Sirt1 deletion. If chromatin deacetylation is involved in these observations remains to be elucidated, deacetylation of transcription factor SPDEF was implicated in the observed activity of Sirt1 in the intestine [64].

Another class III deacetylase/ sirtuin is Sirt2. Studies of this enzyme in cultured human cell lines (epithelial cervical adenocarcinoma cell line Hela and colorectal adenocarcinoma cell line Caco2) and mouse spleen tissue showed that this enzyme has a critical role in the pathogenic infection of cells by *Listeria monocytogenes* [65]. Sirt2 is normally predominantly cytosolic, but upon infection by *Listeria monocytogenes,* it translocates to the nucleus to tightly bind to chromatin and to deacetylate H3K18ac. This, in turn, leads to repression of genes normally involved in limiting infection [65,66]. These findings highlight (1) H3K18 as a potentially critical residue in host-pathogen interaction, (2) show that a histone modifier is essential for infection by a pathogen and (3) illustrate how bacteria can subvert the host's biochemistry for their own purposes. Overall, the studies described above highlight the importance of histone deacetylation in host-microbe crosstalk. Future studies will need to address to what extent histone deacylation processes, such as decrotonylation, are important in this crosstalk, as many HDACs can remove other

acyl-groups from histones, such as HDAC1-3 acting as decrotonylases and SIRT3 as a dehydroxybutyrylase (see Table 2, [57–59,67]).

The microbiota affect histone modifications over regulatory elements in conjunction with diet

Several histone modifications are linked to regulatory elements such as promoters and enhancers. For example, H3K27ac in combination with H3K4me1 is often found over active enhancers, while H3K4me1 without H3K27ac marks poised enhancers. Therefore, such histone modification combinations are used to identify candidate enhancer elements [68]. A study from the Wade lab examined how the microbiota in combination with diet affected H3K27ac and H3K4me1 genome wide using ChIP-seq in colon epithelial cells in the mouse model [69]. Consistent with previous work, they found that an obesogenic diet markedly altered the gut microbiota. This, in turn, caused a reduction of microbial derived butyrate and changes in mouse metabolic physiology. Their findings show that the gut microbiota in combination with an obesogenic diet (high fat diet, HFD) changes the enhancer landscape with respect to these modifications and also affected binding of a critical transcription factor in the host-microbiota crosstalk, HFN4alpha, along with concomitant changes in gene expression. Furthermore, they found that many of these changes were similar to those seen in the colon cancer process. Remarkably, transplantation of the bacteria from the HFD-fed, but not from the control diet-fed mice, into germ-free mice led to recapitulation of the HFD-associated epigenetic changes. This work demonstrates how an obesogenic diet, in combination with the microbiota, may impact disease risk, potentially predisposing to cancer by activating pathways similar to those found in cancer cells. The authors speculate that the HFD microbiota is involved in

generating metabolites from the HFD that lead to an epigenetic reprogramming of the enhancer landscape, illustrating the complexity in the microbiota-diet-host interactions [69].

Epigenetics and IBD: histone H3K4me3 changes link IBD to microbiota-host interactions

In general, the causes of IBD are complex, involving triggers from the environment and genetic susceptibility of the host [26]. Aberrant microbiota-host interactions are prime candidates driving IBD and it is important to understand to what extent epigenetic pathways underlie these defective responses. Alterations in DNA methylation have already been linked to IBD [70–74], but what about other epigenetic features? A recent study mapped genes that showed changes in the histone modification H3K4me3 in intestinal epithelial cells from terminal ilea of newly diagnosed pediatric Crohn's disease (CD) patients and compared these findings with changes in gene expression [75]. Remarkably, the changes in H3K4me3 seemed to identify the CD patients more robustly than the changes in gene expression. The researchers compared these changes with those seen in H3K4me3 in ileal epithelial cells between germ-free mice and conventionally housed mice. These global analyses showed that the presence of microbiota in the gut resulted in many changes in H3K4me3 in IECs. This demonstrated furthermore that a significant proportion of the loci identified in the patients exhibited changes in the mice dependent on the presence of the microbiota, identifying an "epigenetic profile of IBD that can be primed by commensal microbes" [75]. The patient sample number in this work was relatively small, and thus, it would be very interesting to see this type of study expanded with more patients, maybe with different forms of IBD. Yet, this

study sheds new light onto pathways by which microbiota might predispose to intestinal inflammation and illustrates how epigenetic analyses can complement other approaches for identification of epithelial abnormalities.

Demethylase KDM5 and the microbiota in the gut-brain axis

There is tantalising evidence that suggests a role of the gut microbiota in intellectual disability (ID) and autism spectrum disorder diseases (ASD). Genome-wide association and family studies have implicated several chromatin remodelling factors and histone modifiers in these diseases, including members of the KDM5 family of demethylases that remove histone H3K4 methyl groups. A group of researchers took advantage of the fact that that *Drosophila* has only one KDM5 paralog (human has four KDM5 paralogues) and that this organism has a relatively simple microbiota, to examine the role of KDM5 in intellectual deficiency and autism spectrum disorder behaviour models in the fly [76]. They found that reduced levels of KDM5 in a fly *kdm5* mutant caused global increase in H3K4me3 in the gut concomitant with intestinal barrier disruption, making the gut permeable to microbes. This was accompanied by a change in the gut microbiota, including reduction of *Lactobacillus plantarum L168,* and impaired fly social behaviour. These changes were not observed in flies reared germ-free or after antibiotics treatment. Probiotic treatment of mutant flies with *Lactobacillus plantarum L168* restored intestinal barrier function and improved social behaviour towards normal. Together, the findings indicate that ablation of KDM5 causes a change in behaviour, at least in part by altering the gut microbiota. Furthermore, the reported activities of KDM5 depended on its demethylase activity and the researchers implicated miss-regulation of innate immunity genes to an aberrant increase in H3K4me3 over their promoters. While this

study does not rule out that a non-histone target is critical in the described functions of KDM5, it is likely that chromatin regulation plays an important role in the process. It is as yet not clear exactly how the miss-regulation of the microbiota on KDM5 mutation affects social behaviour. However, the researchers implicate an increase of the neurotransmitter serotonin, which may be microbiota dependent. Interestingly, another study identified histone serotonylation in combination with methylation (H3K4me3Q5ser) as a new histone PTM linked to active genes [77]. This new modification was found to be most abundant in the brain and gut. Whether there is a link between the microbiota and histone serotonylation remains to be investigated. In summary, the study on KDM5-microbiota interaction is an exciting illustration of how chromatin dynamics links the microbiota to physiology of tissues far from the gut, opening the question if manipulation of the gut microbiota could ameliorate ID and ASD in human.

ATP-dependent chromatin remodelling factor CHD1 and host-microbiome interactions in *Drosophila*

Drosophila with its relatively simple microbiome also provided insights into the role in host-microbiome interaction of a member of another important class of chromatin factors, the ATP-dependent nucleosome remodelling factors: CHD1, which is required for the replication independent incorporation of histone H3 variant H3.3 into chromatin [78]. Following the observation that deletion of this factor led to misregulation of genes involved in immune responses, stress responses and detoxification in larvae, the group of Alexandra Lusser found that loss of CHD1 led to an increased expression of anti-microbial peptides (AMP) in the gut. However, it also rendered flies susceptible to infection by the bacterium *Pseudomonas aeruginosa*

upon ingestion of the bacteria [79]. They found that bacterial load was significantly elevated in the *Chd1* mutant flies in the gut and in the fly body outside the gut after oral infection. This suggested that the gut epithelium was much more permissible to the passage *of P. aeruginosa* and possibly other bacteria into the hemolymph, causing the flies to die. These findings suggest that a misbalance of expressed AMP and other immune factors may have led to dysbiosis and, thus, susceptibility to the *P. aeruginosa* infection. To substantiate this further, the group performed microbiome analysis using 16S rRNA sequencing [80]. This showed a loss of species diversity in the mutant flies. For example, on the family level, the bacterial community in the wildtype flies' guts of *Pseudomonadacea*e, *Enterobacteriaceae*, *Comamonadacea*e and *Staphylococcaceae* together comprised ~19% of the fly microbiota, but these families were nearly absent in the Chd1-mutant flies. Complementary PCR-based assays showed the loss of Chd1 correlated with an accumulation of *Acetobacter* and a decrease of *Lactobacillus* species. These effects were age dependent, being more pronounced in younger flies. Importantly, the authors showed that Chd1$^{-/-}$ flies were unable to sustain *Lactobacillus plantarum* titres after dietary supplementation. Future research needs to determine to what extent gene regulation relevant to microbe-host interaction is the direct result of chromatin remodelling by CHD1 over the genes as opposed to some indirect effects. It will also be very exciting to find out if the role of CHD1 in host-microbe interaction is conserved in mammals.

Outlook

The microbiota affect gene regulation of the intestinal epithelium in various ways, of which the generation of SCFA is a dominant pathway. Inhibition of HDACs by SCFA

is an important mechanism. As SCFA also are an important energy source in the gut, future studies need to unravel to what extent SCFA affect chromatin by providing metabolic precursors in the cell, e.g., butyryl-CoA, for mediating alternative histone acylations.

Microbiota-host interactions are fascinating and important to study. Yet, this field poses many challenges [81]. While we presented several examples in this review, where deletion of chromatin factors affected host-microbiome interactions, the extent to which the microbiome is affected by genetic variation in the general population is an area of debate and intense research [23,82]. A huge problem in studying microbiota-host interactions is the fact that the microbiota is highly dynamic and diverse. Therefore, mice in various facilities, even SOPF (specific or pathogen free), differ markedly in their microbiota, resulting, e.g., in different outcome in experimental colitis outcomes (see for example, [83]). Furthermore, mice in clean, SOPF facilities have a reduced microbiota, with consequences to their immune system and physiology [84–86]. Therefore, future studies should consider the normal rich 'healthy' microbiota of wild mice. These problems are even more challenging considering the human microbiome where greater diversity in genetic background, lifestyle and other factors further complicate studies of the interaction between host and microbiota.

While we focused here on the gut microbiota, mucosal surfaces in other tissues are covered with their specific microbiota. For example, the uterus has a microbiota that affects pregnancy outcomes [87]. The inter-kingdom crosstalk is important in all these compartments and regulation through chromatin dynamics is likely going to be an important facet here, too. We are only at the start of unravelling the mechanism of microbiota-host interactions, many of which have been 'hard-wired' into our genome

through billion years of co-evolution. In the future, more aspects of chromatin dynamics are likely to be revealed as being essential in this process.

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Table 1: Glossary

Term	Definition and explanation
Acylation	A group of post-translational modifications made by covalently adding functional groups to amino acid residues on proteins through acyl linkages. One main type is fatty acylation, the addition of fatty acyl chains to proteins. Acylations include formylation, acetylation, propionylation, crotonylation, butyrylation, hydroxybutyrylation, malonylation, glycosylation, succinylation, benzoylation and palmitoylation.
AhR	Aryl hydrocarbon receptor is a ligand activated transcription factor which regulates a variety of cellular processes. Ligand activation causes dissociation from its chaperone HSP90 and binding to aryl hydrocarbon receptor nuclear translocator (ARNT). AhR is an important regulator of immune responses.

Anti-microbial peptides (AMPs)	A diverse group of peptides expressed as part of the innate immune host defence (therefore, also called host defence peptides, HDPs). The peptides are usually small (12-50 amino acids) and function, for example, by destabilizing the bacterial cell membrane. A group of these peptides are called defensins which are cysteine-rich cationic peptides. Some defensins are expressed by Paneth cells at the base of the crypts of the small intestine.
Bromodomain	The bromodomain is a protein motif that is conserved in eukaryotes and found in over 100 proteins. It preferentially binds acetylated lysine residues such as those found on histones.
Commensal bacteria	These bacteria are part of the microbiota, e.g., in the gut. They do not hurt the host, but also do not provide significant benefits.
Conventionalized mouse	A mouse that was initially germ-free (see below) but has been re-colonized with normal microbiota.
Epigenetics	The study of heritable phenotypic changes in gene expression without changing the underlying DNA sequence. Deriving from the Greek ‘epi’ meaning on or above. This term is often used to describe many DNA and chromatin associated modifications.
Gastrointestinal tract	An organ system which takes in, digests and absorbs nutrients along with removal of waste products. It comprises the mouth, esophagus, stomach, small intestine (duodenum, ileum and jejunum), caecum (and attached appendix), colon, rectum and

	anal canal.
Germ-free mouse	Germ-free animals have no microorganisms living in or on them. Generation and maintenance of germ-free mice is a challenging task. Germ-free mice are bred in isolators that block exposure to microorganisms, keeping them free of detectable bacteria, viruses, and eukaryotic microbes. Re-colonising these mice with defined microorganisms generates gnotobiotic mice. An alternative to using germ-free mice is treating mice with a cocktail of antibiotics to get rid of a majority of bacteria [22].
GPCRs	G protein coupled receptors are a large family of membrane proteins that bind a specific molecule on the extracellular side and couple to a signalling response on the intracellular side. Ligand binding triggers a conformational change that activates the alpha subunit of the G protein which releases the gamma and beta subunits to generate further signalling reactions in the cell to elicit a response.
HDAC	Histone deacetylase. HDACs should really be called lysine deacetylases (KDACs) as they also deacetylate proteins other than histones. Based on sequence homology, 18 human HDACs are grouped into four classes. Class I enzymes are comprised of HDAC1, 2, 3, and 8. Class II enzymes are HDAC4, 5, 6, 7, 9 and 10. Class III enzymes consist of seven sirtuins, which are NAD-dependent protein deacetylases and/or ADP ribosylases. Class IV contains only HDAC11, which

	shares sequences similarity to both class I and II proteins. Several inhibitors against HDACs have been developed with promise in cancer therapy [88].
Hemolymph	The equivalent of blood in vertebrates, the hemolymph is a fluid that circulates around the interior of arthropod bodies as part of the open circulatory system to exchange materials with tissues. Arthropods include *Drosophila melanogaster*, used frequently as a model organism in biological research.
Histone code	The histone code hypothesis was formulated to express the idea that histone modifications, including combinations of these modifications, regulate DNA templated processes, such as transcription [89]. Furthermore, histone modifications are thought to act, at least in part, by creating binding platforms for effector proteins, such as nucleosome remodelling factors.
IECs	Intestinal epithelial cells line the gut lumen and form the first line of defence after the barrier of mucus layer (see Figure 1). Stem cells in the crypt base generate Paneth cells, label retaining cells, transit amplifying cells, enterocytes, enteroendocrine cells, tuft cells and goblet cells required for maintaining the epithelial niche. IECs are supported by the lamina propria.
IELs	Intestinal epithelial lymphocytes are T lymphocytes derived from naïve T cells in the thymus and are present in the epithelial and lamina propria layers of the intestine. Upon detection of antigens they release cytokines to kill infected

	cells.
Inflammatory bowel diseases	Chronic disorders of the digestive tract associated with prolonged inflammation. Two main types are ulcerative colitis, which occurs in the colon, and Crohn's disease which can occur anywhere along the gastrointestinal tract.
MAMPs	Microbial (or pathogen) associated molecular patterns are motifs of microbial specific structures that elicit a host response. They include flagellin, lipopolysaccharide, xylanase elongation factor Tu, peptidoglycan and viral single stranded RNA.
Microbial dysbiosis	An imbalance in the microbiota associated with overrepresentation of certain bacterial species. Caused by antibiotic use, poor diet or chronic stress. There is insufficient evidence as to whether microbial dysbiosis is a direct cause of inflammatory diseases or a result of it. As the microbial species are highly variable between individuals, determining when the microbiota is in dysbiosis can be difficult. A more narrow definition describes microbial imbalance which causes disease, in line with Koch's postulates (criteria for establishing a causal relationship between a microbe and disease).
Microbiome	This term is sometimes used synonymously to microbiota. However, the narrower definition is 'the collective genomes of the microbiota in or on an organism'. The microbial genome has typically 100 times more genes than the host genome. Major phyla of the human bacterial gut microbiome are:

	Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria.
Microbiota	The community of microorganisms (bacteria, archaea, fungi such as yeasts, protozoa, viruses and phages) found in and on a multicellular organism. These microorganisms may be symbionts, commensal or pathogenic. The word microbiota is a plural term (singular would be 'microbiotum') similar to the term 'people'.
Nucleosome	The basic unit of DNA packaging consisting of an octamer of H2A, H2B, H3 and H4 histones which coil approximately 146 base pairs of DNA.
Obesogenic diet	A high fat diet given to mice to induce obesity.
PRRs	Pattern recognition receptors are a key element of the innate immune system. Receptors identify bacterial signals to enable responses to pathogenic bacteria. PRRs include Toll-like and nucleotide binding oligomerisation domain (NOD)-like, C type lectin and RIG-1 like receptors.
PTM	Post-translational modification. Chemical modification of amino acid residues after their assembly into a protein during translation by the ribosome using an mRNA template. This can alter the chemical properties of the protein or change interactions with other proteins. PTMs include acetylation, phosphorylation, hydroxylation, glycosylation, lipidation, ubiquitination, or deamidation.
SCFA	Short chain fatty acid(s). A carboxylic acid less than six carbons in length. The predominant SCFA in the intestine are

	acetate (C2), propionate (C3) and butyrate (C4). Other SCFA include formate (C1), crotonate (C4), isobutyrate (C4), valerate (C5) and isovalerate (C5).
SOPF	Specific or pathogen free. Laboratory organisms free from certain infectious agents that are capable of pathogenicity or may interfere with an experiment.
Westernised diet	A high fat, high salt diet given to laboratory mice to replicate a 'typical' diet consumed in developed countries.
Xenobiotics	A chemical compound not normally produced or consumed by an organism. These foreign compounds can be drugs, carcinogens or pesticides.
YEATS domain	Named after the domain containing Yaf9, ENL, AF9, Taf14 and Sas5 proteins, the YEATS domain is a protein motif that preferentially binds crotonylated lysine residues. This domain has been linked to chromatin structure and gene expression.

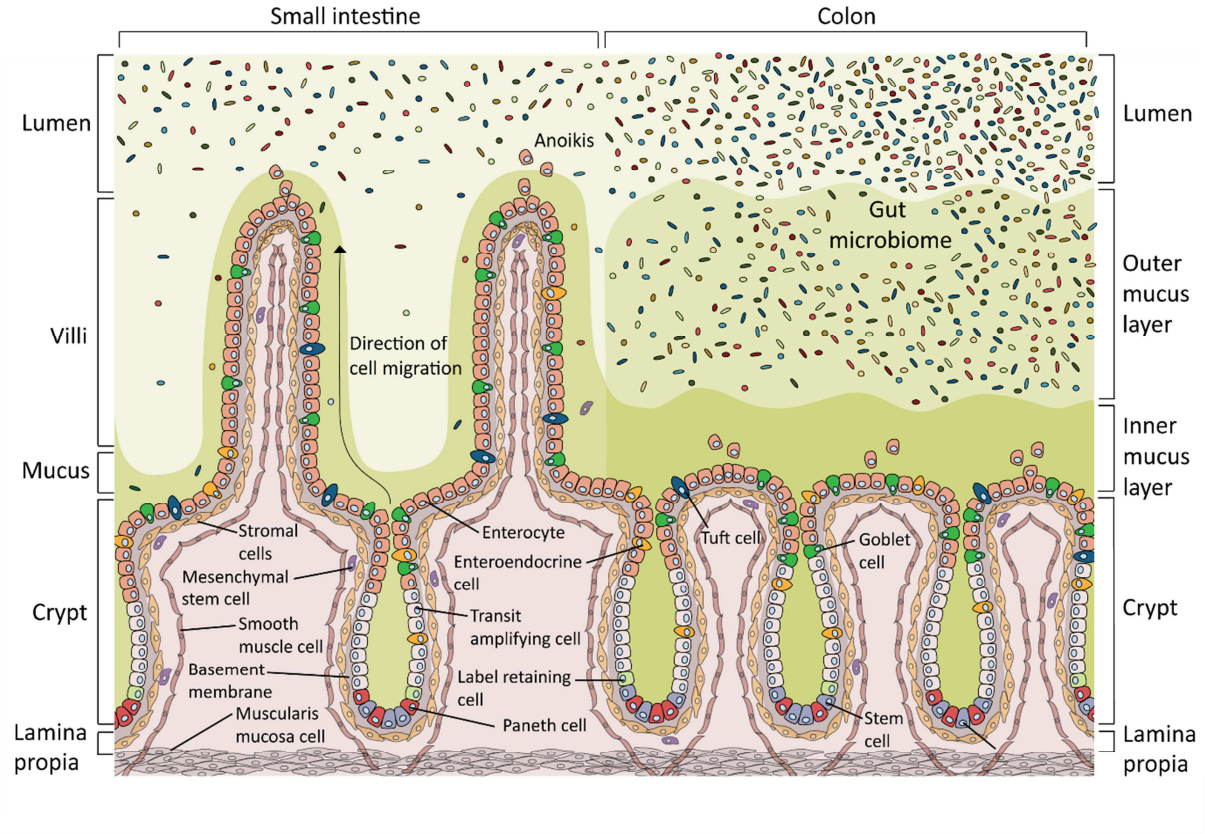

Figure 1. The structure of the small intestine and colon epithelium

The intestine has a large surface area to enable efficient absorption of nutrients from the diet. This is comprised of pocket-like crypts, containing stem cells which generate all of the necessary cell types for the intestinal epithelium. Cells develop as they move up the crypt walls before being lost by anoikis (apoptosis induced by loss of cell contact) into the gut lumen. In the small intestine, cells are lost at the top of villi which are finger like projections that further increase surface area. There are many cell types in the intestine, the absorptive enterocytes and the mucus secreting goblet cells are the most abundant. Transit amplifying cells are proliferative and lineage committed to become enterocytes. Enteroendocrine cells secrete hormones, tuft cells secrete prostanoids and opioids, and Paneth cells secrete antimicrobial peptides and support the stem cells. Label retaining cells are quiescent Paneth cell precursors [90]. The small intestine contains a single diffuse layer of mucus which is not attached to the epithelium and contains some bacteria. The colon contains inner and outer mucus layers. The inner mucus layer is compact and attached to the epithelium and is normally free from bacteria. The outer mucus layer is diffuse with an undefined border and

provides a habitat for intestinal bacteria. The colon microbiota is larger and more diverse than that of the small intestine [91]. The lamina propria is a thin layer of connective tissue which supports the epithelial cell niche. Intestinal associated immune cells, lymphatic vessels and capillaries are not shown. The muscularis mucosae, a thin layer of muscle, separates the lamina propria from the underlying submucosa (not shown). The epithelium, lamina propria and muscularis mucosa together make the mucosal layer [92]

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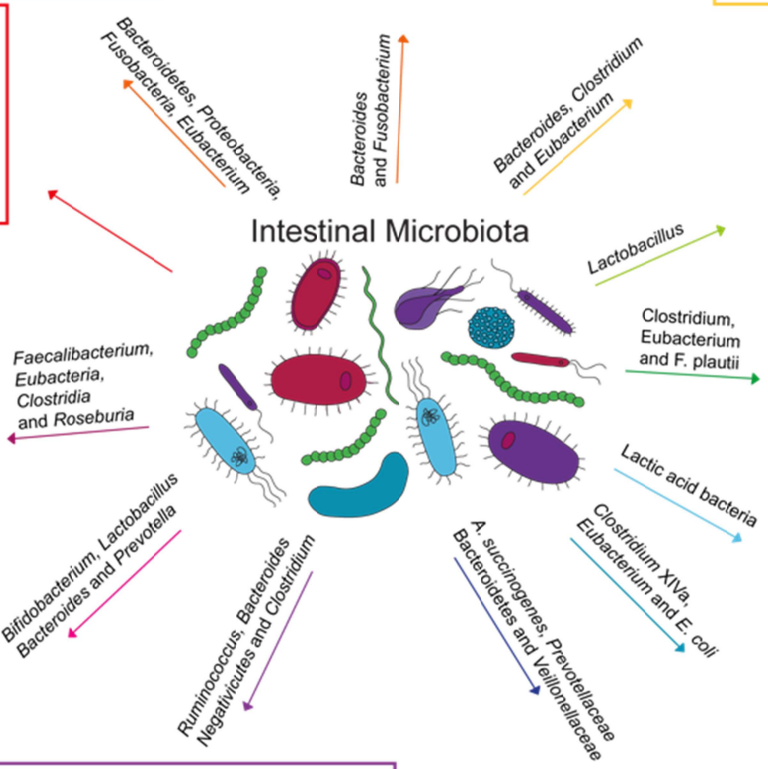
Vitamins
- Vitamin K and certain B vitamins (B12, biotin and folate) required by many germ-free animals
- Bacterial B vitamins mainly absorbed in colon
- B vitamins are important cofactors in metabolic processes and maintain immune homeostasis
- Folate required for DNA and histone methylation
- Vitamin D receptor potential driver of microbial control (A)

Polyamines
- E.g. Spermine, spermidine and putrescine
- Maintenance of IEC turnover and proliferation
- Barrier integrity and gut homeostasis
- Involved in chromatin structure regulation
- Modulates systemic and mucosal adaptive immunity
- High polyamine concentration related to cell growth
- Dysregulation linked to ageing and diseases such as metabolic disorders, cancer and neurodegeneration (B)

Secondary bile acids
- Host bile acids regulate gut microbiota
- Use of conjugated, hydrophilic bile acid pool by microbiota to produce unconjugated hydrophobic bile acid pool
- Degree of hydrophobicity of bile acid pool associated with disease states
- Reduces bile acid hepatotoxicity
- Influences liver gene expression and metabolism (C)

Microorganism associated molecular patterns
- E.g. lipopolysaccharides, flagellin and peptideglycans.
- Initiate signalling cascades through Toll-like and NOD-like receptors
- Generation of cytokines, chemokines and antibacterial peptides (L)

Aryl hydrocarbon receptor activators
- Ligands derived from dietary compounds e.g. through tryptophan metabolism
- Nuclear transcription factor
- Required for intraepithelial lymphocyte maintenance
- Epithelial cell turnover
- Control of microbial load and composition
- Impaired AhR signalling linked to IBD and metabolic disorders (D)



Butyrate
- HIF1 activation through aerobic metabolism of butyrate and oxygen depletion
- HDAC inhibition
- GPCR activator (FFAR2/Gpr43 and FFAR3/Gpr41)
- Metabolism generates energy and can prevent autophagy
- Reduces colon pH
- Cellular proliferation
- Modulates inflammation
- Anti-carcinogenic
- Regulates intestinal macrophage function
- Prevents reactive oxygen and nitrogen species generation
- Activation of Gpr41 to regulate energy homeostasis and host adiposity
- Increases tight junction protein expression (K)

Polyphenols
- E.g. Ellagitannins, phenolic acids and flavonoids
- Diet derived e.g. fruit, cereals and tea
- Processed by microbiome to increase bioavailability
- May inhibit pathogenic and stimulate beneficial bacteria
- Many suggested health benefits e.g. anti-carcinogenic and anti-inflammatory
- Some polyphenols reduce DNMT, HAT or HDAC activity (E)

Trans- and conjugated-fatty acids
- Metabolism of polyunsaturated fatty acids (PUFAs) e.g. into conjugated linoleic acids
- Omega-3 PUFAs are anti-oncogenic mediated by epigenetic down regulation of polycomb group protein EZH2
- Detoxifying metabolism by anaerobic bacteria
- Trans- and conjugated fatty acids have proposed anti-obesity and anti-inflammatory effects (F)

Acetate
- Metabolised in liver and muscle
- Suppression of appetite
- Substrate for cholesterol and lipid synthesis
- Activates Gpr41 to modulate host adiposity
- Activates parasympathetic nervous system to stimulate ghrelin and insulin secretion
- Chronic increases in serum acetate associated with obesity and metabolic syndrome
- Promotes defense response of IECs to protect against enteropathogens (J)

Propionate
- HDAC inhibition
- GPRC activation e.g. Gpr41 and 43
- Substrate for hepatic gluconeogenesis
- Improves glucose tolerance and insulin sensitivity
- Suppression of appetite
- Activation of Gpr41 to modulate host adiposity (I)

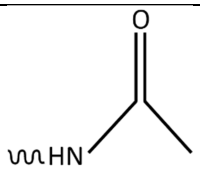
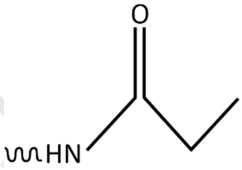
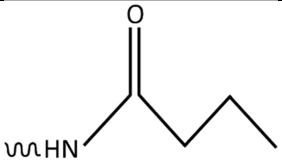
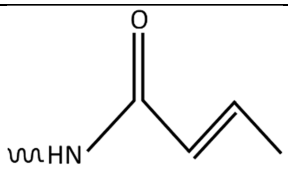
Succinate
- Produced by fibre fermentation
- Accumulates during microbiota disturbances and IBD
- Pro-inflammatory depending on context
- Activates HIF1α in pseudohypoxia
- Inhibits JmjC histone and TET family DNA demethylases (H)

Choline metabolites
- Microbial conversion of dietary choline to trimethylamine which is metabolised in the liver
- Linked to liver and cardiovascular diseases e.g. non-alcoholic fatty liver
- Contributes to one-carbon metabolism to influence histone and DNA methylation (G)

Figure 2. Microbial metabolites influence host function

A non-exhaustive list of microbial generated molecules and their effects on cellular and organismal function. Some of the bacteria species that generate the specified metabolites are listed on the arrows. References for **(A**) [34,35,93–98] **(B)** [36,99] **(C)** [100,101] **(D**) [30,102] **(E)** [103–108] **(F)** [109–114] **(G)** [115,116] **(H)** [99,117–121] **(I)** [122–125] **(J)** [122,123,126–128] **(K)** [37,38,40–42,122–124,129,129–133] **(L)** [28,29,134]

Table 2: Histone acylations and their 'writers', 'readers' and 'erasers'.

Modification	Structure	Writer	Reader	Eraser
Acetylation		p300 (CBP, p300), MYST (Tip60, MOF, MOZ, HBO1), GCN5 (GCN5, PCAF) (a)	Bromodomain (BRD2, BRD9, TAF1, CECR2), PHD (MOZ, DPF2) and YEATS (AF9, YEATS2) (b)	Zn^{2+} dependent (HDAC1-11), NAD^{+} dependent (SIRT1-7) (c)
Propionylation		p300/CBP, PCAF, GCN5, MOF, HBO1, MOZ (d)	Most BRDs (CECR2, BRD2-4,7,9, TAF1), MOZ, DPF2, AF9 YEATS2 (e)	SIRT1/2/3 (f)
Butyrylation		p300/CBP, PCAF, GCN5 (g)	TAF1(2), BRD7, BRD9, CECR2, MOZ, DPF2, AF9 YEATS2 (h)	SIRT1/2/3 (i)
Crotonylation		p300/CBP, MOF (j)	TAF1(2), AF9, YEATS2, MOZ, DPF2 (k)	HDAC1-3, SIRT1/2/3 (l)

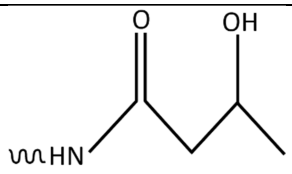
β- Hydroxybutyrylation		p300/CBP (m)	MOZ, DPF2 (n)	HDAC1-3, SIRT3 (o)

Table 2. Histone acylations and their modifying enzymes

Histone acylations are set down by 'writers', acyl-transferases, bound by 'readers' for downstream events and removed by 'erasers', de-acylases. References: (a) [135] (b) [136–138] (c) [139] (d) [51,140–144] (e) [145,146] (f) [147] (g) [51,140,141] (h) [50,55,56,145,146] (i) [147] (j) [148,149] (k) [50,54–56,58,145,146,150] (l) [57–59,151,152] (m) [144] (n) [146] (o) [52,56,67].

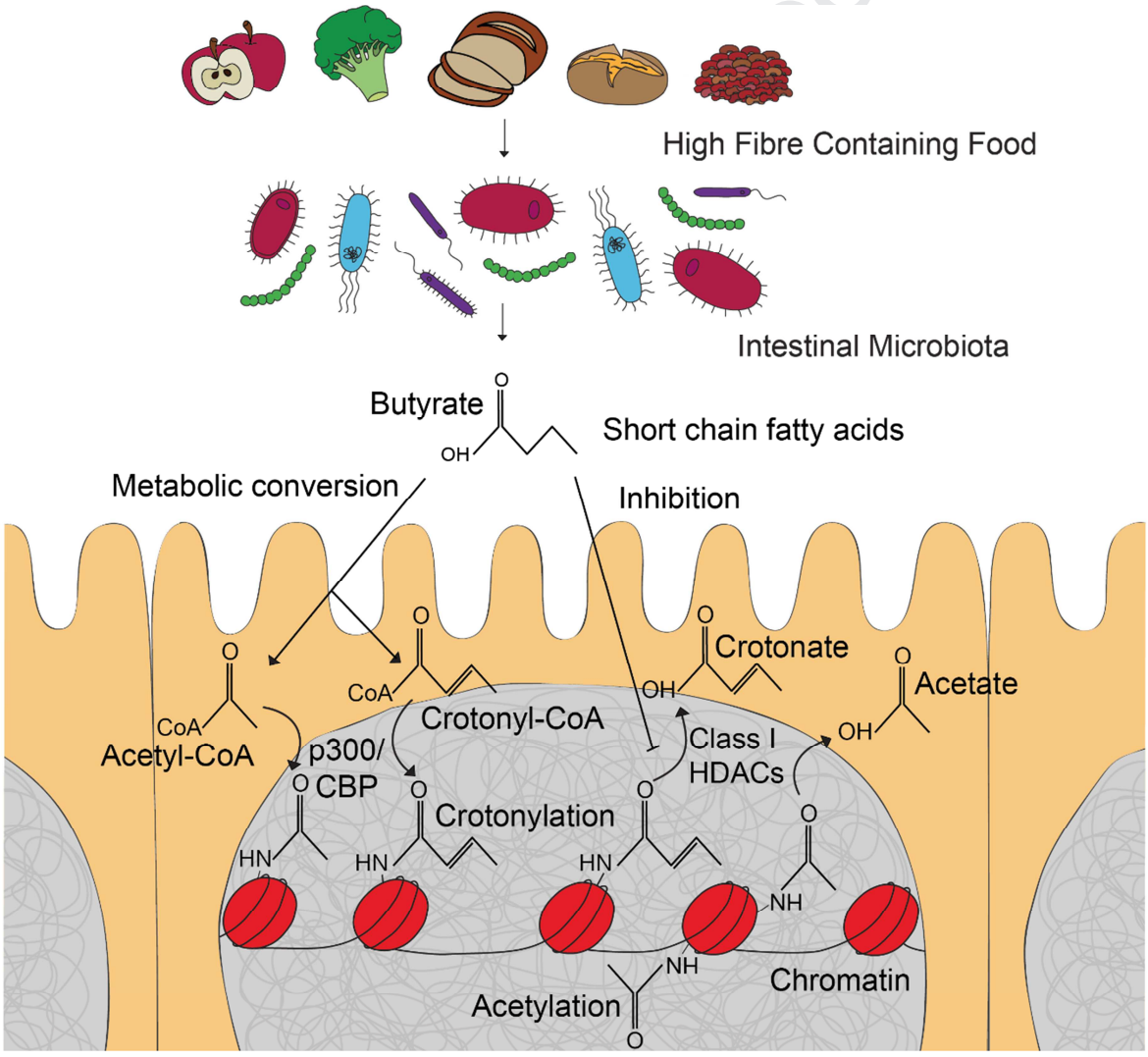


Figure 3. Current model of how microbial derived SCFA affect histone acetylation and crotonylation

The intestinal microbiota digests fibre present in dietary components, such as apples and brown bread, into SCFA. Butyrate is the main SCFA taken up by intestinal epithelial cells. Butyrate inhibits class I HDACs to reduce the removal of acetylation and crotonylation from the histone. It might also promote histone crotonylation and acetylation by metabolic conversion to the acetyl-CoA and crotonyl-CoA precursors to be transferred to histones by p300/CBP.

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Highlights

Chromatin dynamics and histone modifications in the intestinal microbiota-host crosstalk

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- Chromatin dynamics of the host epithelium involving histone modifications play an important role in host-microbiota crosstalk

- Microbiota-derived short chain fatty acids (SCFA) are a dominant determinant in microbiome-host interaction and the inhibition of histone deacetylases (HDACs) by SCFA is a key mechanism in this process.

- Alternative histone acylations, such as crotonylation, reveal a new layer of complexity in host-microbiota crosstalk.