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Host–microbiota interactions: epigenomic regulation

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The coevolution of mammalian hosts and their commensal microbiota has led to the development of complex symbiotic relationships between resident microbes and mammalian cells. Epigenomic modifications enable host cells to alter gene expression without modifying the genetic code, and therefore represent potent mechanisms by which mammalian cells can transcriptionally respond, transiently or stably, to environmental cues. Advances in genome-wide approaches are accelerating our appreciation of microbial influences on host physiology, and increasing evidence highlights that epigenomics represent a level of regulation by which the host integrates and responds to microbial signals. In particular, bacterial-derived short chain fatty acids have emerged as one clear link between how the microbiota intersects with host epigenomic pathways. Here we review recent findings describing crosstalk between the microbiota and epigenomic pathways in multiple mammalian cell populations. Further, we discuss interesting links that suggest that the scope of our understanding of epigenomic regulation in the host-microbiota relationship is still in its infancy.

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Introduction

Environmental factors have been implicated in driving development and pathogenesis of many chronic human diseases with complex multifactorial etiologies, such as asthma, allergy, inflammatory bowel disease, diabetes and cancer [1–3]. Alterations in the diversity of the microbiota (dysbiosis) have been widely associated with many of these chronic human conditions, highlighting that the microbiota and microbiota-derived signals act as environmental cues that influence host physiology. Trillions of commensal microbes reside in the intestinal tract and are critical in modulating local and systemic immune responses [4,5]. Close association between the microbiota and the single layer of intestinal epithelial cells (IECs) that line the intestine are also necessary to regulate essential biological processes such as metabolism, nutrient uptake, neuronal development and angiogenesis [6–8]. Epigenomic modifications are central mechanisms involved in directing transcriptional response to environmental cues, and thus represent a potentially significant interface by which the microbiota can dynamically interact with the host genome. Further, understanding how underlying epigenomic pathways are regulated by the intestinal microbiota could aid in identifying potential therapeutic targets to prevent and treat health conditions associated with an altered host–microbiota relationship. Here, we review recent advances in our understanding of host–microbiota interactions, focusing on epigenomics as a key mechanism guiding microbe-dependent mammalian physiology.

Basics of epigenomics

Epigenomics is the study of molecular mechanisms that dynamically and reversibly modify a cell's transcriptional potential without altering the underlying genetic sequence. Epigenomic regulation is often associated with development and facilitating tissue/cellular plasticity [9–11], but recently, changes in a mammalian cell's epigenome have been highlighted in the context of transcriptional control by external environmental signals. Within the nucleus of eukaryotic cells, DNA is condensed into a higher order structure termed chromatin. Nucleosomes, the basic repeating units within chromatin, contain DNA wound around a histone octamer (H2A, H2B, H3, and H4), followed by a linker histone H1 that joins adjacent nucleosomes together. Changes in chromatin state through condensation and relaxation allow for DNA replication and repair [12,13]. In addition, gene accessibility based on chromatin conformation and modifications has a substantial influence on a cell's transcriptional program. In general, condensed chromatin (heterochromatin) limits the recruitment of the transcriptional machinery to the DNA and results in decreased expression of associated genes, while open chromatin (euchromatin) is more commonly enriched with actively transcribed genes [14].

Structural reorganization of the chromatin is mediated by ATP-dependent remodeling enzymes and covalent epigenomic modifications in response to endogenous and environmentally derived signals [15]. The most well characterized examples of covalent epigenomic modifications are DNA methylation and histone modifications such as acetylation, methylation, phosphorylation, SUMOylation and ubiquitination. These modifications

are put in place by DNA or histone modifying enzymes such as DNA methyltranferases (DNMTs) and histone methyltransferases, and are maintained by the balanced activity of opposing enzymes (*i.e.* histone acetyltransferases *versus* histone deacetylases (HDACs)). HDACs have recently been examined as targets of microbiota-derived metabolites and therefore these epigenome-modifying enzymes are discussed in more detail below. Collectively referred to as the 'histone code', the pattern of epigenomic modifications can direct chromatin restructuring and transcription factor recruitment and, thus, epigenomics is thought to represent a central mechanism by which the environment impacts mammalian gene expression in health and disease [16,17].

Microbiota-derived metabolites: Short-chain fatty acids (SCFAs)

Mammalian cells can sense microbes through pattern recognition receptors such as toll-like receptors (TLRs) that recognize lipopolysaccharide (LPS). Recently, the microbial-derived short chain fatty acids (SFCAs) that are produced by commensal bacteria, such as *Clostridia* and *Bifidobacteria*, from fermentation of carbohydrates and fiber have emerged as central players mediating crosstalk between the microbiota and host [18,19]. In particular, propionate, acetate and butyrate, the three most abundant SCFAs in the intestinal lumen, have received increasing attention in the field due to their potential beneficial impact on host physiology including reduced inflammation and enhanced epithelial barrier function, although these effects have varied between studies [3,20–24]. Germ-free mice express little to no SCFAs, indicating that production of these metabolites is dependent on the microbiota [25]. Although their mechanism of action is not fully understood, SCFAs are thought to modulate host cellular processes through (1) direct inhibition of HDAC activity and/or (2) activation of G-protein-coupled-receptors (GPCRs) [25–27]. HDACs remove acetyl residues from histone or non-histone proteins and the eighteen known mammalian HDACs are classified into four classes based on sequence homology. These epigenomic-modifying enzymes are often present in large protein complexes that are guided to target chromatin through transcription factor interactions. Given that SCFAs, and particularly butyrate, have long been known to broadly inhibit the HDAC epigenomic family of enzymes, several recent studies have demonstrated or suggested that SCFAs mediate host–microbiota interactions through epigenomic regulation. Therefore, studies related to SCFAs will be discussed in more detail below.

Epigenomic mechanisms regulate microbiota-dependent immune homeostasis

Interactions between the host and microbiota through epigenomic regulation are best characterized in the hematopoietic immune system and reviewed extensively elsewhere [28,29] (Figure 1). Macrophages and dendritic cells (DCs) are critical in innate barrier defense against invading pathogens, and rapidly alter their transcriptional profile in response to bacterial colonization. Histone H3 lysine 4 trimethylation (H3K4me3) is an epigenetic mark associated with enhanced gene expression, and non-mucosal mononuclear phagocytes isolated from conventionally-housed mice displayed increased H3K4me3 levels at the transcriptional start site of pro-inflammatory genes such as interleukin 6 (*IL-6*) and interferon beta 1 (*Ifnb1*). These epigenomic changes corresponded with increased expression of IL-6 and Ifnb1 and enhanced priming of natural killer cells in conventionally housed mice relative to germ-free mice [30]. Microbiota-induced increase in colonic HDAC3 expression and increased histone deacetylation on the *Il12b* promoter in intestinal macrophages were found to be important in the IL-10-mediated inhibition of IL-12 expression and intestinal inflammation [31]. Global histone acetylation was also shown to be increased in intestinal macrophages in response to microbial-derived butyrate, corresponding with decreased expression of *IL-6* and *IL-12* [32•]. These genes, among others, were also downregulated in macrophages from antibiotic-treated mice, and exhibited impaired interferon signaling and anti-viral function compared to conventionally housed mice [33]. Recent work also demonstrated a novel role for butyrate in facilitating colitis-protective M2 macrophage polarization *in vivo*, as well as reducing TNF-α and IL-1β production to suppress inflammation [34]. Moreover, *in vitro* experiments on bone marrow-derived macrophages indicated that M0 to M2 differentiation was induced by butyrate, potentially through inhibition of HDACs and enhanced histone H3K9 acetylation and Il-4/STAT4 signaling [34]. Importantly, decreased gene expression in response to butyrate is not consistent with the generally expected outcome of HDAC inhibition and increased histone acetylation, indicating that butyrate is possibly functioning through other mechanisms in addition to HDACs or that butyrate-induced increased histone acetylation at specific genes mediates decreased gene expression. Nonetheless, these studies collectively support that transcription of critical macrophage-derived factors is induced through microbiota-triggered histone modifications.

DCs are also epigenetically responsive to microbial signals, displaying increased global H3 acetylation and reduced expression of *IL-6*, *IL-12* and transcription factor *Relb* following exposure to butyrate [35] (Figure 1). This pathway was also found to mediate regulatory T cell (Treg) differentiation, discussed in more detail below. Butyrate activation of GPR109A and CpG oligodeoxynucleotide/TLR9 stimulation were found to modulate retinoic acid signaling in DCs [36]. Activation of retinoic acid signaling in DCs was later shown to increase enrichment of active enhancer histone marks, H3K4me1 and H3K27Ac, at the avb8 integrin (Itgb8) locus in DCs,