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

KIMBERLY A. KRAUTKRAMER, RASHPAL S. DHILLON, JOHN M. DENU, and HANNAH V. CAREY

MADISON, WIS

The mammalian gut microbiota has been linked to host developmental, immunologic, and metabolic outcomes. This collection of trillions of microbes inhabits the gut and produces a myriad of metabolites, which are measurable in host circulation and contribute to the pathogenesis of human diseases. The link between endogenous metabolite availability and chromatin regulation is a well-established and active area of investigation; however, whether microbial metabolites can elicit similar effects is less understood. In this review, we focus on seminal and recent research that establishes chromatin regulatory roles for both endogenous and microbial metabolites. We also highlight key physiologic and disease settings where microbial metabolite-host chromatin interactions have been established and/or may be pertinent. (Translational Research 2017;189:30–50)

Abbreviations: α-KG = alpha-ketoglutarate; acetyl-CoA = acetyl coenzyme A; BBB = blood brain barrier; bSCFA = branched short chain fatty acid; CoA = coenzyme A; ConvD = conventionalized; ConvR = conventionally raised; CRC = colorectal cancer; DNMT = DNA methyltransferase; GF = germ-free; HAT = histone acetyltransferase; HDAC = histone deacetylase; HDACi = histone deacetylase inhibitor; HMT = histone methyltransferase; IBA = interbout arousal; LC-MS/MS = liquid chromatography coupled to tandem mass spectrometry; MACs = microbial accessible carbohydrates; NAFLD = nonalcoholic fatty liver disease; PTMs = post-translational modifications; SCFA = short chain fatty acid; T2DM = type 2 diabetes mellitus; TPN = total parenteral nutrition

INTRODUCTION

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

These epigenetic factors allow eukaryotes to sense and respond to environmental cues. Intermediary metabolites, such as acetyl coenzyme A (acetyl-CoA) and alpha-ketoglutarate (α-KG; also known as

From the Department of Biomolecular Chemistry, University of Wisconsin - Madison, Madison, Wis; Wisconsin Institute for Discovery, Madison, Wis; Morgridge Institute for Research, Madison, Wis; Department of Comparative Biosciences, University of Wisconsin - Madison, Madison, Wis.

Submitted for publication May 29, 2017; revision submitted August 14, 2017; accepted for publication August 22, 2017.

Reprint requests: Kimberly A. Krautkramer, Department of Biomolecular Chemistry, University of Wisconsin - Madison, Wisconsin Institute for Discovery, Madison, WI 53715; e-mail: kkrautkramer@wisc.edu.

1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2017.08.005

2-oxoglutarate, 2-OG) are key messengers to the epigenome of stimuli and stressors. In addition to intermediates of macronutrient metabolism, micronutrients and minerals (eg, B-vitamins and iron) also regulate the activity of chromatin-modulating enzymes. While the interplay between chromatin and endogenous metabolites has been a subject of intense investigation for nearly two decades, recent findings have revealed the mammalian gut microbiota as a major producer of metabolites, many of which have been demonstrated to play regulatory roles on host physiology (reviewed in[4]). Analogous to endogenous metabolites, gut microbial metabolites may signal to host chromatin to alter host genetic responses to environmental signals.

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

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

Thus, the interactions between mammalian hosts and their gut microbiota are myriad and complex, affected by environmental factors such as diet and lifestyle, and are dynamic throughout the lifespan. While many associations have been made between host phenotypes and microbial community composition and metabolite production, the molecular mechanisms underlying these phenotypes remain largely unexplored. Understanding how the microbiota communicate environmental cues to the host epigenome provides an additional avenue for mechanistic exploration. Here, we review seminal and recent literature focused on the regulation of chromatin states by endogenous and gut microbial metabolite availability. In addition, we highlight clinically relevant settings in which these interactions occur.

CHROMATIN DYNAMICS

Genomic DNA in eukaryotes is packaged into chromatin, a highly structured nucleoprotein complex that compresses DNA by a factor of approximately 1000 to 10,000-fold in interphase and mitotic chromosomes, respectively.[59] The fundamental unit of chromatin is the nucleosome core particle, which is comprised of an octamer of core histone proteins (2 copies each of histone H2A, H2B, H3, and H4) wrapped by 146 bp of genomic DNA.[60] Nucleosome core particles are separated from each other by linker DNA that varies in length from ~10-80 bp. Roughly 75%–90% of the genomic DNA interacts with nucleosomes, which are spaced, on average, every 200 bp. Nucleosome positioning is dictated, in part, by the underlying DNA sequence. The numerous salt bridges, hydrogen bonds, and ionic interactions that occur between histone residues and the DNA phosphate backbone induce significant bending of the DNA as it wraps around the histone core 1.65 times, and sequence-dependent DNA flexibility pays a key role in this process.[60] About 50% of the nucleosome positioning in yeast can be explained by the intrinsic DNA sequence, wherein nucleosome occupancy can be predicted based on nucleosome affinity for a particular sequence of genomic DNA.[61] Packaging of DNA into nucleosomes generally inhibits binding of other nonhistone proteins with DNA-binding motifs. In support