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Review

The microbial epigenome in metabolic syndrome

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ABSTRACT

Dietary habits, lifestyle, medication, and food additives affect the composition and functions of the GI microbiota. Metabolic syndrome is already known to be associated with an aberrant gut microbiota affecting systemic low-grade inflammation, which is also outlined by differing epigenetic patterns. Thus, structural changes and compositional evaluation of gut microbial differences affecting epigenetic patterns in metabolic syndrome are of research interest. In the present review we focus on the disparities in the gut microbiota composition of metabolic syndrome and the resulting aberrant profile of bioactive microbial metabolites known to affect epigenetic modifications such as G-protein coupled receptors and inflammatory pathways.

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1. Introduction

Metabolic syndrome, a multifactorial disorder, results from a long-term imbalance of diet and physical activity, genetic predisposition, and an imbalanced gut microbiota influencing several metabolic pathways including epigenetic regulation. In 2004, the prevalence of metabolic syndrome was observed to be 13.4% in women and 20.5% in men (Rieder et al., 2004). In 2008, a prevalence of obesity (BMI $\geq$ 30 kg/m^2 (body mass index)) was shown to be 10% in men and 14% in women worldwide (World Health Statistics, 2015, 2015). Thus, this high incidence of overweight (abnormal fat accumulation; BMI $\geq$ 25 kg/m^2) and associated diseases like type 2 diabetes (hyperglycemia on basis of an insulin resistance) are a challenge and financial burden for the national health care system.

It is known that gut microbiota differs between humans according to lifestyle, nutrition and different diseases. Analysis of gut microbiota diversity and composition of gut microbiota subpopulations are of special research interest. For analysis of gut microbiota, usually, qPCR (quantitative real-time polymerase chain

Abbreviations: BHB, beta-hydroxybutyrate; BMI, body mass index; CNS, central nervous system; GF, germ-free; GPRs, G-protein coupled receptors; HDAC, histone deacetylases; IECs, intestinal epithelial cells; IFN-γ, interferon γ; IL, interleukin; iNOS, nitric oxide synthases; JAK, Janus kinase; LDL, low density lipoprotein; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositol-3 kinase; PPARγ, peroxisome proliferator-activated receptor γ; PSA, polysaccharide A; SCFAs, short-chain fatty acids; SNS, sympathetic nervous system; TLR, toll like receptors; TNF-α, tumor necrosis factor α; Tregs, regulatory T cells; VLDL, very low density lipoprotein.

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reaction) is used for compositional evaluation, regarding diversity analysis, DGGE (denaturing gradient gel electrophoresis) is still the method of choice although microbial whole-genome sequencing facilitates mapping and comparing of genomes across multiple samples to generate reference genomes, microbial identification or comparative genomic studies. In accordance with current research, establishment of a balanced relationship between the intestinal tract and a complex microbial ecosystem has been shown as essential for host physiology, metabolism, and immune homeostasis as the gut microbiota is substantial for nutrient utilization, maintenance of the gut barrier, and stimulation of immune development in neonates (development of the gut-associated lymphoid tissue and of the regulation of the intestinal physiology) (Louis et al., 2007a; Sommer and Bäckhed, 2013). In particular, studies in germ-free (GF) mice disclose the interaction of gut microbiota and host metabolism and provide insights into the role of the gut microbiota in the harvest and storage of energy (Berg, 1996). Colonization of GF mice with gut microbiota of conventionally raised mice induced an increase in body fat and insulin resistance independent from diet (Backhed et al., 2004). A gut microbiota implantation of obese humans showed even more profound results indicating differences between diseased and non-diseased, healthy individuals (Ridaura et al., 2013). The symbiosis between host and commensals is required for intestinal homeostasis, with failures in the system leading to an increased risk for various diseases (Gill et al., 2006; Louis et al., 2007b; Takahashi et al., 2011). Metabolic syndrome is associated with less bacterial diversity and altered abundance, gene-representation, and metabolic pathways (Tremaroli and Bäckhed, 2012). These differences involve the representation of members of *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Verromicrobia* (Tremaroli and Bäckhed, 2012) but also archaeal microorganisms.

Changes in gut microbial composition affect various epigenetic patterns (Remely et al., 2013a, 2014a) comprising DNA methylation, histone modifications, and chromatinremodeling (Choi and Friso, 2010), which orchestrate a seemingly infinite variety of molecular and cellular processes essential for higher nervous system functions and evolutionary innovations (Klose and Bird, 2006; Kondo, 2006; Mehler and Mattick, 2007; Tsankova et al., 2007). As these modifications are reversible, they are potential targets for therapies. However, they are also potential biomarkers for diseases. Thus, modulation of these processes through diet or specific nutrients may prevent diseases and maintain health (Louis and Flint, 2007; Tammen et al., 2013).

Alterations in gut microbiota due to obese phenotype induce metabolic changes (Conterno et al., 2011) (Table 1). Possible mechanisms are signaling mediated by bacterial components via pattern-recognition receptors: Toll-like receptor 2 (TLR2) and TLR4 (Remely et al., 2014a) including NF-κB or the signaling of SCFAs (short-chain fatty acids) produced by the microbiota via GPRs (G-protein coupled receptors) (Remely et al., 2013a) (Fig. 1) and via HDAC (histone deacetylases) (Liu et al., 2012; Vinolo et al., 2011).

2. Microbiota regulating epigenetic patterns

The ratio of *Firmicutes* to *Bacteroidetes* is mentioned as a marker for human health, with an imbalance leading to various diseases (Mariat et al., 2009). Several studies have shown a shift of the

Table 1
Gut microbiota modulation and their metabolic effects/mechanisms of action.

Model	Microbiota/ metabolism	Metabolic effect/outcome	Reference
GF mice	Gut microbiota transplantation	Increase in body fat and insulin resistance	(Backhed et al., 2004)
Newborn infants	*L. acidophilus*	Weight gain	(Robinson et al., 1952)
Chicken	*L. fermentum*, *L. ingluviei*	Weight gain	(Khan et al., 2007)
Human gut	*L. planatarum*	Lower retroperitoneal adipose tissue and lower plasma leptin resulting in lower body weight	(Karlsson et al., 2011)
Human and animals	*L. gasserii*	Weight loss	(Million et al., 2012)
Gnotobiotic rats	*B. thetaiotaomicron*	Increase the differentiation of goblet cells with a higher mucin gene expression in the colon	(Wrzosek et al., 2013)
Human obese	*Higher Firmicutes/ Bacteroidetes ratio*	Lower methylation in the first exon of TLR 4, lower methylation in the promoter region of TLR 2	(Remely et al., 2014a)
Mice	CD 14 knock-out or LPS due to high fat diet	Induced metabolic endotoxemia, hypersensitivity to insulin	(Cani et al., 2007; Kim and Sears, 2010)
Mice	Loss-of function of TLR 4 receptor	Protected against diet-induced obesity: decreased adiposity, improved insulin sensitivity, enhanced insulin-signaling	(Tsukumo et al., 2007)
C57BL/6 mice	TLR $2^{-/-}$ knock-out mice	Resistance to high-fat and carbohydrate induced obesity, lower body weight, lower serum glucose, improved insulin sensitivity, increased total serum cholesterol, VLDL, LDL, cholesterol	(Himes and Smith, 2010)
Mice	TLR $2^{-/-}$ knock-out	Gut microbiota impairment	(Kellermayer et al., 2011)
Human	Type 2 diabetes	Lower methylation in TNF-α promoter region, IL-6 promoter and first exon	(Aumueller et al., 2015)
Human monocyte-derived dendritic cells	SCFAs	Inhibit HDACs	(Liu et al., 2012)
RAW 264.7 cells, murine macrophages	Sodium butyrate	Inhibit the production of TNF-α, NF-κB activity, iNOS and IL-6, and enhanced IFN-γ-induced production of IL-10	(Park et al., 2007)
Mouse intestinal and colonic tissues, human colonic cells	beta-hydroxybutyrate, butyrate	Promote via GPR 109A anti-lipolysis in adipocytes, apoptotic effect in colon cancer cells	(Thangaraju et al., 2009)
Gpr43$^{-/-}$ mice, *Gpr109A*$^{-/-}$ mice, *Nlrp3*$^{-/-}$ mice on a C57Bl/6 background.	Dietary fibers	Influence via GPR43 and GPR109A the activation of the NLRP3 inflammasome and the production of IL-18	(Macia et al., 2015)
Epididymal Fat, C57B/6_J male mice	SCFA	Influence via GPR41 leptin production, secretion of serotonin, PYY, and insulin	(Xiong et al., 2004)