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Opinion

Bacterial Postbiotics as Promising Tools to Mitigate Cardiometabolic Diseases

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ABSTRACT

Gut microbes dictate critical features of host immunometabolism. Certain bacterial components and metabolites (termed postbiotics) mitigate cardiometabolic diseases whereas others potentiate pathological processes. In this review, we discuss key aspects related to the usefulness of bacterial-related molecules strategically positioned as promising treatment strategies for cardiometabolic diseases.

Keywords: Obesity; Diabetes mellitus, type 2; *Akkermansia*; Lipopolysaccharides; Peptidoglycan

INTRODUCTION

To this date, *Akkermansia muciniphila* is the only bacterial strain shown to impact markers of human cardiometabolic disease to a high degree of reliability and efficacy. Oral administration of *A. muciniphila* to human individuals with obesity/overweight improved insulin resistance and reduced circulating cholesterol.[1,2] Similar results were reported using pre-clinical models of diet-induced obesity and genetic-induced dyslipidemia, whereby *A. muciniphila* improved blood glucose control,[3,4] facilitated hepatic triglyceride clearance[5] and reduced atherogenesis.[6] Findings from both pre-clinical models and human trials have pointed to pasteurization (i.e. exposure to mild heat) as an effective way to enhance the cardiometabolic benefits of *A. muciniphila*.[2,3] Pasteurization render bacteria non-replicant while retaining the health benefits of certain probiotic strains.[7] Because bioactivity is preserved, it is likely that pasteurization retain the molecular structure of bacterial components needed to elicit immune regulation. These findings are of great importance stressing the utility of bacterial metabolites, cell wall components and bacterial peptides—referred to as *postbiotics*—as promising strategies to treat metabolic complications linked to overweight and obesity. Postbiotics, however, must not be confused with probiotics or prebiotics. Indeed, probiotics define bacteria that, when administered alive, confer health benefits to the host, whereas the latter term refers to dietary compounds that can favor

the expansion of beneficial bacteria in the gut. This article puts into perspective evidence relevant to the usefulness of certain postbiotics against cardiometabolic complications. The impact of short-chain fatty acids (SCFA)—arguably the most studied bacterial postbiotics—on cardiometabolic diseases has been extensively examined elsewhere[8,9] and is not addressed in this review.

MAIN TEXT

Host immunity bridges gut microbial components to host metabolic regulation.[10] Activation of Toll-like receptor (TLR) 4 by bacterial lipopolysaccharides (LPS) is a classic example of this interaction. In the presence of obesity and poor dietary habits, gut microbial LPS can breach the gut barrier and elicit innate immune activation in key insulin-responsive organs, causing a mild and chronic raise in circulating LPS termed metabolic endotoxemia (ME).[11] This moderate, yet persistent, increase in circulating LPS appears to be an important feature of metabolic syndrome as ME is increasingly recognized in the constellation of risk factors involved in cardiovascular diseases (CVD) (**Fig. 1**).[12,13] In agreement, pre-clinical mouse studies have shown that ME is sufficient to initiate and aggravate the low-grade inflammatory state linked to insulin resistance, dysglycemia[11] and atherogenesis.[6]

While the cardiometabolic benefits of *A. muciniphila* are, at least in part, linked to its capacity to strengthen the gut barrier and lower ME,[2-4,14] an isolated component from the cell wall of this bacterium (Amuc_1100) was shown to recapitulate the metabolic benefits reported after administration of pasteurized *A. muciniphila* to diet-induced obese mice.[3] Amuc_1100, which appears to elicit immune activation via TLR2, increased high-density lipoprotein (HDL) cholesterol, improved insulin sensitivity and alleviated ME in diet-induced obese mice (**Fig. 1**).[3] While more mechanistic pre-clinical studies and clinical trials are warranted, Amuc_1100 holds promise as a postbiotic from *A. muciniphila* that may curb several features of metabolic syndrome.

Peptidoglycan is a key constituent of the bacterial cell wall containing specific muropeptide sequences that are detected by nucleotide-binding oligomerization domain-containing (NOD) proteins. NOD1 recognizes meso-diaminopimelic (meso-DAP) acid-containing muropeptides, whereas NOD2 detects muramyl dipeptide (MDP)-containing peptidoglycan. We have demonstrated in murine models that acute activation of NOD1 causes whole-body and hepatic insulin resistance,[15] whereas others have shown that genetic ablation of NOD1 confers protection against diet-induced insulin resistance.[16] Concordantly, microbiota-derived muropeptides act on NOD1, but not NOD2, to augment systemic immunity.[17,18] In contrast, NOD2 attenuates inflammation induced by other bacterial products and protects against inflammatory colitis[19] insulin resistance[20] and nonalcoholic fatty liver disease (NAFLD).[21] This is, at least in part, linked to NOD2-dependent downstream processing of a wealth of host defense peptides (HDPs) improving gut barrier function.[22,23] We have shown that intraperitoneally injected MDP can protect mice from LPS-induced dysglycemia, and that the MDP-based drug mifamurtide can improve glucose tolerance in mice with diet-induced obesity.[24] Not surprisingly, the metabolic impact of NOD activation has cardiovascular implications. While NOD1 activation with the synthetic peptidoglycan FK565 caused major site-specific inflammation in the aortic root,[25] a recent study showed that depletion of NOD1/2 protected low-density lipoprotein (LDL) receptor knockout mice from developing atherosclerosis.[26] Interestingly, both NOD1 and NOD2 signals intracellularly
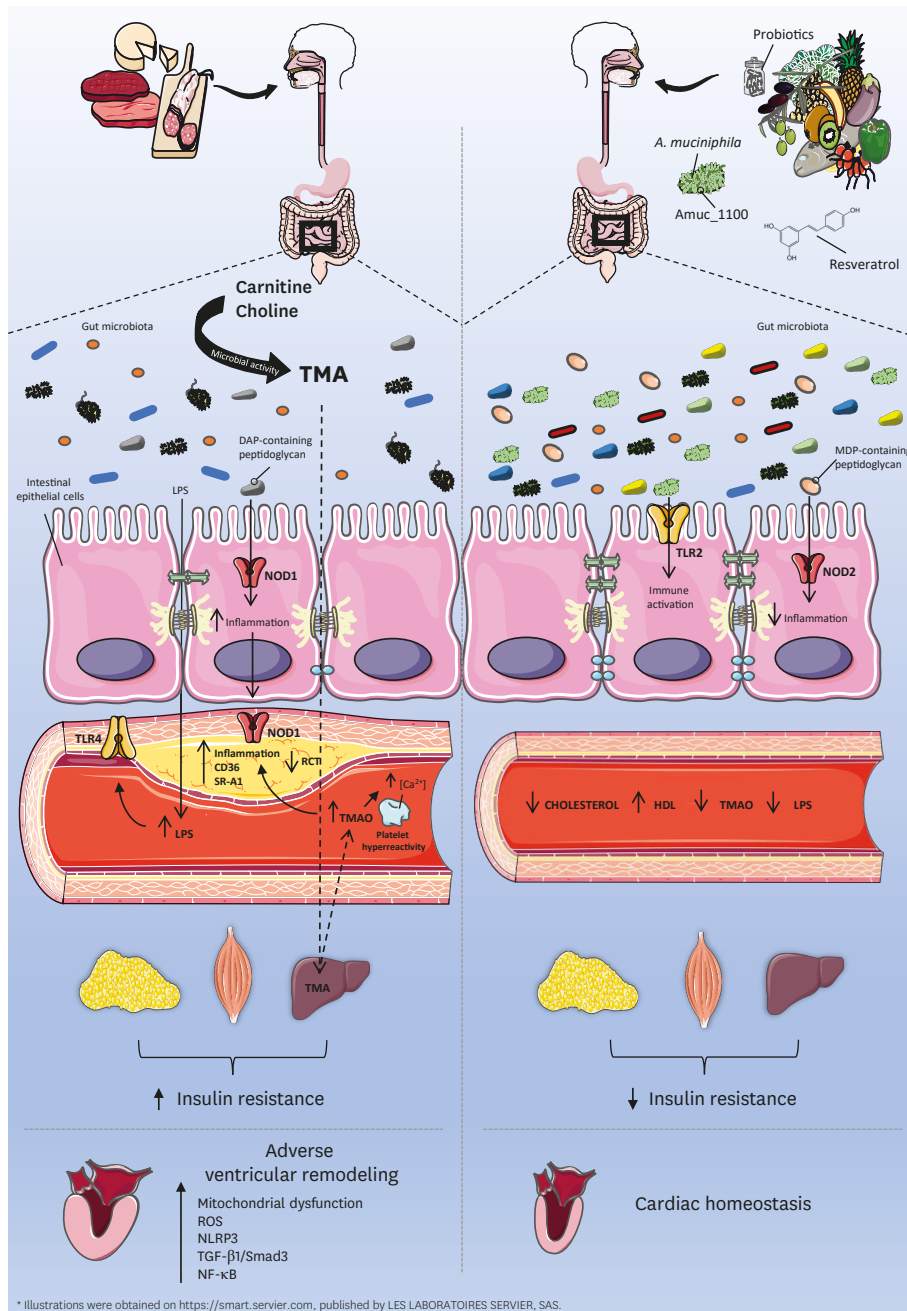
Fig. 1. Bacterial postbiotics influence cardiometabolic disorders. Poor dietary habits (left) contribute to the impairment of gut barrier homeostasis, which favors the leakage of gut microbial LPS into circulation (metabolic endotoxemia). Conversely, healthy dietary habits (right) are linked to preserved gut barrier function. Metabolic endotoxemia is increasingly recognized in the constellation of risk factors involved in cardiometabolic diseases and insulin resistance. Dietary carnitine and choline (left) are metabolized into TMA through microbial activity in the gut. TMA is later converted into proatherogenic TMAO in the liver. Once in circulation, TMAO facilitates atherosclerotic plaque deposition by reducing RCT, increasing inflammation, upregulating scavenger receptors (CD36, SRA1) and promoting platelet hyperreactivity. TMAO further impairs cardiac function by stimulating oxidative stress (mitochondrial dysfunction, ROS), inflammation (NLRP3, NF-kB) and the profibrotic TGF-β1/Smad3 pathway. Consumption of certain probiotics and resveratrol (right) were shown to reduce serum levels of TMAO. Amuc_1100 (right), a cell wall component of *A. muciniphila*, was shown to recapitulate the beneficial metabolic effects of this bacterium in mice. Likewise, the interaction between NOD receptors and some peptidoglycans, key constituents of the bacterial cell wall, also influence host metabolism. Gut microbiota-derived meso-DAP acid-containing muropeptides act via NOD1 to increase inflammation and insulin resistance, whereas NOD-2 interaction with MDP-containing peptidoglycan resulted in protection against inflammation and insulin resistance.

LPS, lipopolysaccharide; TMA, trimethylamine; TMAO, trimethylamine-N-oxide; RCT, reverse cholesterol transport; CD36, cluster of differentiation 36; SR-A1, scavenger receptor-A1; ROS, reactive oxygen species; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3; NF-κB, nuclear factor-κB; TGF-β1, transforming growth factor-β1; NOD, nucleotide-binding oligomerization domain-containing; DAP, diaminopimelic; MDP, muramyl dipeptide; TLR, toll-like receptor; HDL, high-density lipoprotein.

through receptor-interacting serine/threonine-protein kinase 2 (RIPK2). We have shown that nonhematopoietic—but not hematopoietic—RIPK2 mediates the glucose lowering and anti-inflammatory effects of NOD2 activation, whereas LPS and NOD1 synergize in hematopoietic cells to promote insulin resistance.[27] Together, these findings show that postbiotics that target NOD receptors are well-positioned as promising strategies to curb CVD (**Fig. 1**).

The intestinal microbiota metabolizes certain dietary trimethylamines, such as choline and L-carnitine, to produce trimethylamine (TMA). This microbial metabolite crosses the gut barrier and is later oxidized in the liver forming trimethylamine N-oxide (TMAO). Recent epidemiological studies linked TMAO to higher risk of major cardiovascular events.[28,29] Several pieces of evidence suggest that gut microbes are necessary to the detrimental effects of certain atherogenic dietary components. Wang et al. found that dietary supplementation with choline and TMAO upregulated both cluster of differentiation 36 (CD-36) and scavenger receptor type-1 (SR-A1) in macrophages while promoting atherosclerosis in a gut microbiota-dependent manner.[30] Likewise, mice fed with TMAO, carnitine, or choline exhibited reduced reverse cholesterol transport, which accelerated atherosclerosis only when the gut microbiota was intact.[31] TMAO was further reported to directly promote platelet hyperreactivity by enhancing stimulus-dependent release of Ca^{2+} from intracellular stores, and to upregulate clot formation rate *in vivo*, contributing to elevated risk of thrombosis.[32] The choline-related thrombosis potential was transferred to germ-free mice after fecal microbial transplantation, pointing to a causal role of the gut microbiota.[32] The authors further revealed specific gut microbial taxa, such as the SCFA-producing bacteria *Lachnospiraceae*, *Oscilospira* and *Ruminococcus*, to inversely correlate with both TMAO and thrombosis potential.[32]

Inflammation is a keystone of cardiometabolic disease, and reports from different research groups support the pro-inflammatory potential of TMAO. In rodent models of heart failure, TMAO upregulated profibrotic atrial natriuretic peptide (ANP) and beta-myosin heavy chain (β-MHC),[33] as well as nuclear factor-κB (NF-κB) and the transforming growth factor-β1 (TGF-β1)/Smad3 pathway.[34] Further, NF-κB and mitogen-activated protein (MAP) kinase were both shown to mediate the impact of TMAO on vascular inflammation.[35] Moreover, TMAO activated nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome and caspase-1 while increasing mitochondrial-derived reactive oxygen species (ROS) in the aorta.[36] In cardiomyocytes, TMAO-derived mitochondrial dysfunction led to impaired pyruvate and fatty acid oxidation.[37]

Gut microbial modulation might represent an important strategy to alleviate TMAO production and thereby attenuate CVD (**Fig. 1**). Individuals classified within an enterotype dominated by *Prevotella* displayed higher circulating levels of TMAO than subjects with an enterotype enriched in *Bacteroides*.[31] In the same study, omnivorous subjects with enhanced plasma TMAO showed higher abundance of *Peptostreptococcaceae* and *Clostridium* and lower *Lachnospira* as compared to vegan/vegetarian individuals with low circulating TMAO concentration.[31] Heianza and colleagues[38] recently reported that continuous increase in circulating TMAO over a period of 10 years was associated with higher risk of coronary heart disease, which was shown to be alleviated by healthy dietary patterns. Accordingly, consumption of the polyphenol resveratrol remodeled the gut microbiota in mice, including augmented *Lactobacillus* and *Bifidobacterium* abundances, thereby decreasing TMAO levels by mitigating commensal microbial TMA.[39] Similarly, four weeks of daily consumption of certain probiotic strains reduced serum TMAO in healthy adult males.[40] Further, limiting TMA production with choline analogs was shown as a potential therapeutic strategy against atherosclerosis[41] and heart failure.[42]

CONCLUSION

Host-microbe interaction takes place through engagement of immune responses. Postbiotics, such as MDP and Amuc_1100, are promising candidates to promote cardiometabolic benefits via innate immune activation. Other bacteria derived molecules, such as certain LPS and TMAO, are pathognomonic to immunometabolic mechanisms worsening cardiovascular disease risk. TMAO is well-positioned as a biomarker and a possible treatment target to mitigate cardiometabolic complications.

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