Personalized microbiome-based approaches to metabolic syndrome management and prevention

Running title: Microbiome and metabolic syndrome

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Abstract

Personalized or precision medicine is a novel clinical approach targeted to the individual patient and based on integration of clinical, genetic and environmental factors that define a patient uniquely from other individuals featuring similar clinical symptoms. Such personalized medicine approach is increasingly applied for diagnosis, clinical stratification and treatment of the metabolic syndrome (MetS) associated risks and diseases, including obesity, type II diabetes, non-alcoholic fatty liver disease and their complications. One emerging factor that governs MetS manifestations is the microbiome, whose composition, function, growth dynamics, associated metabolite profile and diverse effects on the host immune and metabolic systems can all

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significantly affect metabolic homeostasis. The inter-individuality differences in the microbiome composition and function as well as personal variations in microbial-derived products pave the way towards microbiome based personalized medicine in treating MetS-related diseases.

Keywords: microbiome; metabolic syndrome; personalized medicine

Highlights: The microbiome plays pivotal roles in the pathogenesis of multiple manifestations of the metabolic syndrome. Understanding the molecular mechanisms driving these effects will constitute an exciting challenge of microbiome research in the coming decade. As such, decoding how altered host-microbiome interactions influence the metabolic syndrome will enable the development of microbiome-targeting approaches as means of personalized treatment of the metabolic syndrome.

Introduction: The metabolic syndrome and personalized medicine

In recent years modern medicine is rapidly shifting from classical approaches focusing on disease-centered diagnosis and treatment paradigms, to a more individually tailored approach termed personalized medicine. Personalized or precision medicine is defined as treatment targeted to the individual patient on the basis of genetic, phenotypic, biomarker-based and possibly environmental and psychological factors that distinguish one patient from others with similar clinical characteristics[1]. One example for conditions in which precision medicine has been proposed as a therapeutic approach is the metabolic syndrome. The metabolic syndrome (MetS) is a group of co-associated diseases including obesity, insulin resistance, type 2 diabetes, cardiovascular disease and non-alcoholic fatty liver disease (NAFLD)[2]. Common risk factors predispose to these diseases, and in fact each of these metabolic syndrome diseases is considered a risk factor for the others. Common risk factors for features of the metabolic syndrome include abdominal obesity, hyperglycemia, hypertension, elevated triglyceride levels and low HDL levels[2]. The prevalence of the MetS is globally increasing and estimated to encompass around 25-35% of the adult population worldwide[2], highlighting the need for controlling the risk factors, development and progression of MetS-linked diseases.

Limited efficacy of global dietary recommendations in the metabolic syndrome

In obese individuals, weight loss can improve glycemic control, lower blood pressure and normalize cholesterol levels[3]. Consequently, a change of dietary habits (mostly reduction in caloric intake) is probably the most commonly prescribed strategy for prevention and treatment of the MetS. Nevertheless, obese individuals who successfully complete weight-loss diets often regain weight[4-6], rendering the

long-term efficacy of current recommended diet regimes questionable and disappointing.

In addition to facilitating weight loss, diet plays an important role in maintaining healthy glucose homeostasis[7,8]. Diets aimed at prevention and treatment of hyperglycemia often take into account the meal carbohydrates content[9] and the glycemic index (GI)[10], which estimates the post-prandial glycemic response (PPGR) to specific food items. Nevertheless, the ability of such diets to aid in controlling glucose levels showed mixed results in several randomized trials[11]. Several caveats of the glycemic index may contribute to this inconsistency, including the difficulty to determine the glycemic index of real-life meals containing multiple food items with different GIs, and poor predictive accuracy of GI in diabetic individuals.

An important limitation of global dietary recommendation is the sole consideration of food-intrinsic properties, such as the GI. For example, Vega-Lopez *et al.*[12] reported significant inter-individual variation in the PPGR to white bread. Such person-to-person variation in the PPGR to an identical food, as well as to several other test foods, was also reported by Vrolix & Mensink[13]. A recent cohort of 800 participants demonstrated remarkable differences in PPGRs to standardized as well as to real-life meals, with many participants featuring different responses to the same food in contrast to the previously expected and reported GI values[14]. These findings question the applicability of global dietary recommendations, based solely on the properties of food, as dietary guidelines to the individual and may explain the limited efficacy of such approaches in reducing or maintaining weight across human populations. Thus, understanding the factors that drive inter-individual differences in response to food is crucial for improving personalized dietary management and prevention of MetS. As is highlighted in the next sections, some of the inter-

individual variability in human MetS manifestations and response to treatment may be associated with inter-individual differences in the gut microbiome. Understanding these microbial variations and how they contribute to disease manifestations may help in developing potential personalized clinical applications for treating the MetS[14].

The microbiome in MetS

Inter-individual differences in the risk for developing MetS, disease manifestations and the response to diet and medical treatment, are often ascribed to the human genetics and lifestyle. In addition to these factors, the microbiome composition also displays considerable variability in the human population[15], stemming from several determinants including diet[16-18], age[19], and host genetics[20]. The composition of the microbiome and its association with the host can influence various physiological functions and play a pivotal role in numerous diseases including metabolic diseases[21,22] (**figure 1**). A seminal study by the group of Jeffrey Gordon showed that the gut microbiome is different in obese compared to lean persons and rodents[23,24] and its interaction with the host can significantly affect the development of obesity[24,25]. Follow up studies have since shown association and contribution of microbial dysbiosis to other MetS-related diseases such as type 2 diabetes[26], NAFLD[27,28] and atherosclerosis[29,30]. Beyond a description of bacterial community composition and disease association, the microbiome research is moving towards mechanistic elucidation of the molecular pathways and metabolites activated and produced by the microbial community and characterization of their effects on host MetS-related manifestations. These studies are performed via a combination of multi-omics next-generation sequencing, metabolomics techniques[14], and experimentation in gnotobiotic mouse models. Together, they are aimed at identifying bacterial

communities and host changes on the level of microbial species, gene, transcript and metabolite abundances. These analyses may help to develop, in coming years, new precision medicine approach for diagnosing and treating MetS related pathologies[31].

Metabolic consequences of inter-individual variations in the microbiome

The gut microbiome features a high inter-individual variability in community composition, function and interaction with the host, all potentially bearing an influence on variable MetS features in different individuals. As such, the microbiome may be considered as a personal trait contributing to the individual susceptibility to develop discrete MetS complications, yet this notion has only been addressed by a limited number of studies. A recent study (highlighted in the above 'limited efficacy of global dietary recommendations' section) aimed at personally tailoring diets that may maintain a normal-ranged PPGR[14]. As described above, a considerable variation in inter-individual PPGR was noted to identical real-life as well as to standardized meals. When dissecting the factors that contributed to this variation, the microbiome composition and function emerged as an important driver, with positive associations noted between levels of multiple commensal members and pathways and inadequate glycemic responses. Considering these findings, it seems unlikely that global dietary recommendations aimed at preventing and treating MetS complications would be useful to the entire population; rather, they may be beneficial to defined human subgroups, ineffective in others, and may even be harmful to some. A computational algorithm based on clinical metadata, PPGR of reported meals and microbiome composition and function produced a suggested personalized diet individually tailored to the study participants. The diets designed by the algorithm were successfully

validated in a cohort of 26 participants, mostly pre-diabetic individuals. Importantly, the 'good' diets of some participants were 'bad' for others[14].

Additional support to the importance of the microbiome when considering diets beneficial for glucose homeostasis can be found in the study of Kovatcheva-Datchary *et al*[32]. The authors reported improvement of the glycemic response following consumption of barley-kernel bread (BKB) in a subset of individuals, which were characterized by high levels of the genus *Prevotella*. The importance of the microbiome in mediating the beneficial effects of BKB was demonstrated by assessing glucose tolerance in germ-free (GF) mice transplanted with microbiome from human responders to BKB or with *Prevotella copri.* Functional analysis of the microbiome suggested that *Prevotella* may exert its beneficial effects by contributing enzymes facilitating metabolism of the dietary fiber in BKB, and increasing glycogen storage[32].

In addition to mediating the beneficial impacts of food choices on human health, certain microbial compositions may exert individualized negative effects on their host in response to dietary stimuli. One such example is consumption of non-caloric artificial sweeteners (NAS), leading to perturbed microbiome composition, thereby promoting MetS in several studies in rodents[33-35]. Some of these perturbations in microbiome composition and function had a causative role in promoting metabolic derangements[34], and in humans the ability of NAS to promote glucose intolerance was influenced by the host microbiome. Validation of these findings in larger human cohorts may enable to determine which individual might benefit from NAS, in contrast to those who should avoid them.

Personalized aspects of the microbiome in MetS expand beyond the scope of glucose homeostasis. In obese and overweight subjects, dietary intervention in obesity

was reported to be more beneficial in subjects who had high microbial gene richness[36]. Adding to the complexity is the finding that not only the composition, function and richness of the microbiome play a role in disease, but also the growth dynamics of the bacteria in the gut associate with the MetS, and dietary changes may exert differential effects on these human dynamics[37].

Another diet-mediated condition, atherosclerosis, is closely associated with multiple risk factors and conditions comprising the metabolic syndrome, and may lead to devastating complications including ischemic heart disease, heart failure, and cerebrovascular disease. Like other manifestations of the metabolic syndrome, atherosclerosis was suggested to be influenced by inter-individual microbiome differences. Microbial metabolism of L-carnitine[29,38] and phosphatidylcholine[39], nutrients abundant in animal products and specifically red meat produces trimethylamine-N-oxide (TMAO), a pro-atherogenic species. The production of TMAO by the microbiome was dependent on the diet (omnivorous vs. vegan/vegetarian) and its associated microbiome configuration. This suggests that recommendations for dietary modification in individuals suffering of atherosclerosis would potentially modulate the microbiome composition, thereby affecting disease pathogenesis.

Mechanisms implicated in gut microbiome influences on the MetS

Despite many association implicating gut microbes as involved in whole body metabolic responses and MetS-related morbidities, the underlying mechanisms are exceptionally complex and currently elusive. Emerging data suggests that inflammation and microbial-derived metabolites, such as short-chain fatty acids and bile acids, may significantly influence MetS-related disorders and disease progression.

Microbial-derived metabolites

Metabolites produced, degraded or modulated by the microbiota serve as 'communication channels' by which the host and its microbiome signal to each other[40,41]. Alterations in bacterial metabolites contribute to several MetS related risks and pathologies[30,42]. While the best-studied metabolites include short chain fatty acids, bile acids and trimethylamines, many other metabolites may come into play and significantly affect host metabolism. Although the existence of inter-individual differences in the microbiome composition is well established, much less is known about person-to-person metabolomics variability, stemming from individual differences in diet, host genetics, and the microbiome[43].

Short chain fatty acids

Short chain fatty acids (SCFA), including acetate, propionate, and butyrate are produced by bacterial fermentation of polysaccharides in the gastrointestinal tract[44]. SCFA may play a role in the maintenance of body weight, intestinal homeostasis and improved lipids and glucose metabolism[42,45-47]. Most of the studies in obese humans and rodents suggest that elevated SCFA levels combined with- enriched pathways for generating SCFA correlate with an increased capacity to harvest energy[25,48,49]. In most animal studies, SCFA dietary supplementation improved MetS manifestations, by reducing weight gain, improving insulin sensitivity and lowering triglycerides[45,50-52].

Colonic epithelial cells utilize SCFA produced by the bacteria as an energy source[53,54].The beneficial effects of propionate and butyrate on energy expenditure and glucose homeostasis may possibly derive from increased secretion of intestinal incretins such as PYY and glucagon-like peptide-1 (GLP1)[55,56]. Chambers *et al.*[55] tested the effect of inulin-propionate ester in over-weight people and found that acute

administration of propionate decreased weight gain, abdominal adiposity, fatty liver and insulin resistance and significantly increased postprandial PYY and GLP1.

SCFA are ligands for the G-protein coupled receptors GPR41, GPR43 and GPR109a expressed in colonic epithelium, pancreatic beta cells, adipose tissues and other tissues. Mice lacking GPR41 were leaner with reduced expression of the gastric incretin PYY[57]. Acetate and propionate are potent ligands for GPR43 and -GPR43-deficient mice fed with high fat diet (HFD) gained more weight with increased MetS-related complications[58]. Antibiotics or GF conditions abrogated the metabolic phenotypes of GPR41 and GPR43 null mice, suggesting that bacterial SCFA induce GPR43 and GPR41 activation controlling whole body energy and glucose homeostasis[58].

The response of the host to SCFA can also be mediated via glucose sensing by the gut-brain axis. De Vadder *et al.*[45] showed that propionate sensing in the colon induced intestinal gluconeogenesis, which was sensed by the gut-brain neural circuit and led to improved glucose and weight control[45]. Perry *et al.*[51] recently found that HFD rats displayed increased incorporation of acetate in the colon, and chronic administration of acetate caused obesity-associated MetS complications. In this study, acetate infusion led to a parasympathetic excitation stimulating β-cells insulin secretion[51]. While most of the above studies indicate a beneficial role for SCFA in energy and glucose homeostasis, larger human studies are necessary to elucidate possible personalization in the SCFA response. Understanding of the personalized responses to SCFA may enable to develop SCFA supplementation as a novel individualized or generalized treatment modality for MetS manifestations.

Bile acids

Bile acids are mainly produced by hepatic cholesterol catabolism, transported

into the gallbladder and into the intestinal lumen by postprandial peristalsis[59-61]. Microbiome-associated at the distal small intestine and colon can transform primary bile acids into secondary bile acids[59-61]. Mice treated with antibiotics or GF mice feature low concentrations of secondary bile acids, with altered expression profile of genes involved in bile acids conjugation and reabsorption indicating that the gut microbiota is responsible for bile acid synthesis, diversity and possibly host epithelial uptake[62-64]. In addition to the role of bile acids in facilitating dietary fat digestion, they are now recognized to participate in regulation of metabolic homeostasis[65,66]. As such, some bile acids show promising initial results in treatment of MetS disorders such as insulin resistance, hypercholesterolemia and NAFLD[66,67].

Most of the physiological effects of bile acids are mediated by the G-protein coupled receptor TGR5 and the nuclear receptor farnesoid X receptor (FXR). FXR is a transcription factor that controls endogenous synthesis and release of bile acids and FXR activation results in inhibition of hepatic bile acids biosynthesis[63,68]. Obese and insulin resistant mice displayed decreased gut microbiota diversity, accompanied by a reduction in secondary bile acids and hepatic enzymes involved in bile acids biosynthesis, with increased FXR and decreased TGR5 expression[69]. Activation of TGR5 by bile acids led to improved insulin sensitivity, while binding of bile acids to FXR resulted in lowered cholesterol, and reduced liver and serum triglycerides[66].

Experiments in GF and antibiotics-treated mice suggest that the microbiome may modulate FXR and FXR-related genes that control bile acid synthesis[62,63,70]. Intestinal FXR deficient mice fed with HFD displayed decreased weight gain, glucose intolerance and insulin resistance and were protected from development of fatty liver[71,72]. Blocking intestinal FXR by administration of FXR antagonist modified bile acids composition and promoted adipose browning, decreased obesity and insulin

resistance[73]. Ryan *et al.*[74] found that the beneficial effects of bariatric surgery on metabolism including improvement in glucose tolerance were associated with changes in gut microbiota and were diminished in FXR null mice[74]. Together, all these animal studies pointed towards a dominant role for the gut microbiota in regulating bile acids diversity and FXR signaling, which in turn regulates MetS complications.

Obese humans followed after bariatric surgery featured long-term changes in their gut microbiome independently of BMI. Yet, the causal connection between gut microbiota, bile acid production and signaling, the pathogenesis of MetS-related disorders, and potential perturbation of these pathways as modes of MetS treatment merit further investigation in prospective human trials.

Trimethylamines

Trimethylamine (TMA) is a metabolite generated by microbial metabolism of L-carnitine derived from red meat and by conversion of phosphatidylcholine derived from cheese and eggs. TMA is carried to the liver by portal circulation where it is converted into TMA N-oxide (TMAO) by flavin monooxygenases (FMOs). The group of Hazan[38] first found that TMAO is pro-atherogenic and associated with development of coronary heart disease[38] and thrombosis[30] in mice and humans. Mice treated with antibiotics or GF mice had undetectable or levels of TMA and TMAO[29] while conventionalized mice featured increased levels of TMAO, indicating an obligatory role of the microbiota in TMAO production. Correspondingly, mice treated with antibiotics or GF mice fed with L-carnitine or phosphatidylcholine diets had lower atherosclerotic lesions, reduced accumulation of foam cells and lower platelet hyperreactivity[29,30]. An essential role for the gut microbiota in generating TMAO was further affirmed in human subjects treated with L-carnitine or phosphatidylcholine and antibiotics showing near complete suppression of TMAO[29,39]. These interesting,

and potentially clinically important direct roles of TMAO in development and progression of cardiovascular diseases merit further prospective studies.

Microbiota modulation of inflammation

Obesity, insulin resistance, atherosclerosis, steatohepatitis are all MetS disorders associated with inflammation. Adipose tissue inflammation is mostly studied in the contexts of obesity and type II diabetes where it contributes to disease pathogenesis and involves both the innate and adaptive immune responses[75]. While microbial derived endotoxins (such as lipopolysaccharide, LPS) were detected in type 2 diabetes patients and in obese and insulin resistant mice leading to augmented adipose and systemic inflammation[76,77], the role of microbiota-driven adipose tissue inflammation in MetS complications remained conflicting[78,79]. Diet may play a major role in determination of the microbiome effects on MetS-associated inflammation. Mice fed with lard diet showed induction of adipose toll-like receptor (TLR) immune signaling and inflammation with increased serum LPS and adiposity. The metabolic effect was transferrable to GF mice, whereas gut microbiota from fish-oil diet given to lard-fed mice counteract the metabolic phenotype, suggesting that diet has a major implication on microbial composition, which in turn modulates adipose tissue inflammation and adiposity[80].

Similarly, a key link was also suggested between intestinal inflammation, gut microbial alterations and NAFLD[81]. In one study, mice deficient in inflammasome signaling displayed changes in their gut microbiota composition which aggravated hepatic steatosis, driven by massive influx into the portal circulation of TLR4 and TLR9 agonists, ultimately leading to increased hepatic TNFα secretion and resultant hepatic damage and inflammation. The metabolic effects were transferable by co-

housing, suggesting an important crosstalk between gut microbes and host in NAFLD progression. Another study[82] shows that the bile acid taurine controls microbiome composition leading to activation of NLRP6 inflammasome. Mice treated with taurine showed amelioration of colitis and the effect depended on the microbiome and inflammasome activation[82]. The effect of taurine on metabolic complications remains to be determined.

Taken together, these observations may point towards the microbiota as potential new therapeutic target, with microbiome alteration, or supplementation or inhibition of microbiome-associated metabolite signaling may be utilized as part of a personalized MetS approach. Such treatment may potentially enable modification of host adipose and mucosal inflammation, thereby impacting metabolic homeostasis and the risk of MetS diseases.

Summary and future perspectives: from personal microbiome to personalized treatments

The potential contribution of the microbiome to MetS pathogenesis and clinical manifestations, coupled with its plasticity, make the microbiome an appealing therapeutic target for diagnosis and treatment of features of the MetS. However, key limitations currently preclude the widespread incorporation of microbiome characterization and modification into the diagnosis and treatment schemes of MetS. First, the microbiome is highly variable between individuals. As such, accurate characterization of the microbiome in an individual is often confounded by compositional changes induced by medications[84], age[85], and even the time of the day in which a sample is collected[86]. Specifically, the importance of considering medication use as a potential confounder in microbiome analysis of MetS patients

was recently demonstrated by Forslund *et al.*[87], reporting a confounding effect of metformin (an anti-diabetic drug) in two reports characterizing the 'diabetic microbiome' in human patients[26,88]. In addition, diet itself is a potent driver of alterations to the microbiome[89,90], a feature that is also observed in personalized nutritional interventions[14,32]. This may compromise long-term microbiome-based nutritional recommendations, and necessitate repeated periodic sampling and adjustment of dietary recommendations based on a patient's updated dietary routine and associated microbiome configuration. Finally, the microbiome is only one factor impacting personalized response to diet, thus requiring its integration into multivariable prediction algorithms that include multiple host and environmental variables, and only a combination of these person-specific measurements may enable to devise adequate personalized dietary recommendations.

Additionally, when developing means of microbiome modulation as modifying treatment of features of the MetS, unrelated microbiome-mediated effects on host health should be taken into consideration. As one example, several studies have demonstrated a beneficial role for a higher microbial bio-diversity (alpha-diversity) in maintaining healthy body weight and glucose homeostasis[91,92], while reduced diversity is associated with a variety of disease states such as inflammatory bowel disease (IBD). Distinct dietary habits, associated with specific microbial configurations[17], may reduce bio-diversity in some individuals. As such, certain dietary recommendations may potentially contribute to reduced microbial diversity, putatively associated with some disease risks. Thus, microbiome-based tailoring of individualized diets should not only consider how the microbiome mediates the effect of food on host metabolism, but also how the diet may affect the microbial bio-diversity and consequently other features of host health.

Nutritional interventions

Dietary modifications are considered key to prevention and treatment of features of the MetS. Recent studies[14,32] indicate that this approach may yield superior long-lasting results if individually tailored. Integration of personalized microbiome parameters in the diagnosis and dietary planning of individuals predisposed or suffering of the MetS is considered an appealing new avenue of clinical research, yet is still at its infancy[83]. Questions remain as to long-term efficacy of this approach, which merit prospective human-based studies.

Fecal microbiome transplantation (FMT)

FMT is based on transferring microbiome purified from the feces of a healthy donor to an individual with a microbiome-associated condition (such as obesity or diabetes), in which the 'transplanted' microbiome may correct or replace the pathological one. One promising proof-of-concept study utilizing FMT in MetS, demonstrated that microbiome transplanted from lean donors to obese individuals improved the recipients' insulin sensitivity, accompanied by alterations in their microbiome including expansion of butyrate producers[93]. The efficiency of this approach in treating the multiple conditions that underlay MetS remains to be validated in additional long- term clinical studies. One potential caveat to this approach is the unclear ability of the transplanted microbiome to alter the existing, pathological microbial composition. It is well possible that factors driving microbial dysbiosis in a given individual, such as host genetics and lifestyle, will persist even after FMT and resist or revert the microbial changes induced by FMT back towards the diseased configuration.

Probiotics and prebiotics

Rather than transplanting an entire microbial community, a more specific microbial-based approach involves supplementation of diet with a limited number of viable bacterial strains (probiotics), or using nutrients such as non-digestible carbohydrates that promote the growth of so-called 'beneficial' endogenous bacteria (prebiotics). Despite great public interest and extensive research, the efficacy of pre- and probiotics in promoting health benefits remains questionable, and there is currently no clinical indication for their consumption. In mice, supplementation with probiotic strains of ***Lactobacillus*** and/or ***Bifidobacteria*** was suggested to have a beneficial effect on the onset and progression of both T1DM and T2DM[94,95]. In humans, some studies demonstrated beneficial effect of probiotics on MetS, however this effect was not uniformly reproducible[96], and in some studies a controversial link was even suggested to exist between probiotics consumption and weight gain[97]. Considering this significant variability in clinical results, it is possible that, like with the response to diets, humans display inter-individual variability in their responses to probiotics. This individualized response, in turn, may be dependent on variations in the microbiome, and the ability of the supplemented bacterial strains or nutrients to positively alter the resident microbial community. Thus, additional studies in healthy individuals, as well as in those with MetS, are required to determine efficacy, if any, of probiotics usage and the role of its potential 'personalization'.

Microbiome-associated metabolites

Analysis of microbial metabolites in combination with metagenomic analysis of the pathways and genes involved in the metabolism to these metabolites will possibly enable designing personal approaches to treat patients with MetS complications

through targeting of their metabolites and their signaling pathways. We have recently demonstrated that certain pathological microbial communities in mice produce metabolites that modify the host immune system to resist colonization by an exogenous microbiome[82]. Given the potential adverse effects of FMT and the substantial inter-individual variability in microbiome composition precluding probiotic and prebiotic approaches, an approach based on administration of a microbial metabolite cocktail may circumvent the inter-individual microbial differences and thus constitute a safer and more efficient mode of therapeutics for the MetS. One such example is supplementation of the diet with SCFA that protected mice from HFD-induced insulin resistance[45,50,52]. It remains to be determined whether SCFA supplementation has a therapeutic potential in humans. Another microbial derived metabolites currently tested in humans are bile acids. In preliminary studies, the microbial derived bile acid obeticholic acid, which is a potent FXR activator that decreases liver fat and fibrosis in mice, improved the histological features of the liver in non-alcoholic steatohepatitis patients[67].

Likewise, microbiome-modulated metabolites may affect plasma lipid levels and atherosclerosis. As described above, microbial production of trimethylamines such as TMAO derived from red meat[29] is directly linked to development of atherosclerosis[29]. Gut microbiota generation of secondary bile acids facilitates dietary fat digestion and improves plasma and liver lipid profile and indeed bile acids have been used for treatment of hypercholesterolemia[66]. Furthermore and as described above, microbiota may modulate the immune system, thereby inducing low-grade inflammation contributing to the development of many MetS-related diseases including atherosclerosis. Identifying small molecules whose access or deficiency drive these immune mediated downstream effects may enable the development of new

'postbiotic' metabolite interventions[31] as treatment of MetS comorbidities.

In summary, the potential microbiome modulatory effects on the development and progression of MetS-related diseases make its manipualtion a promising therapuetic approach in preventing, ameliorating or treating the MetS. Analyzing the microbial configuration at the individual level may provide new insights into the specific microbiome contributions to the person-specific MetS clinical manifestations, enable to boost or predict the individualized resposne to medical intervention and may lead to development of precision medicine approaches for patients suffering of the MetS and its complications.

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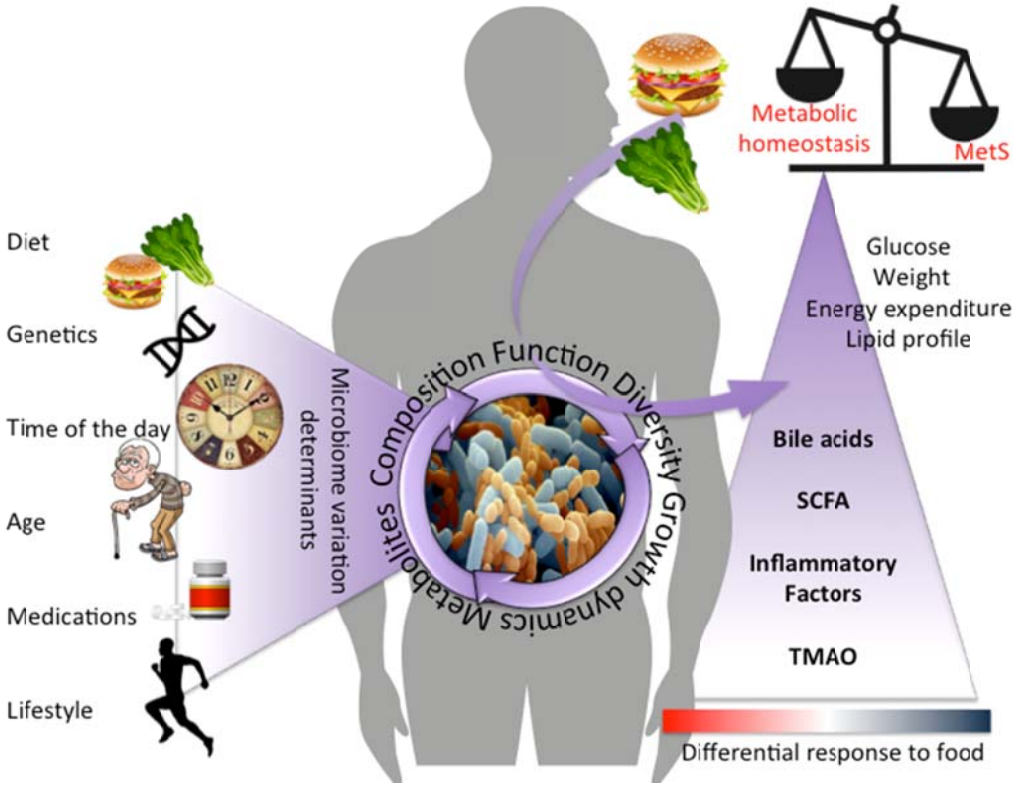
Figure 1 legend: Variations in the microbiome mediate differential effects of the environment on metabolic homeostasis. Multiple host and environmental factors contribute to inter-individual variations in the microbiome. This, in turn, leads to a person-specific microbiome regulation of metabolic homeostasis.



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