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Diagnostics and therapeutic implications of gut microbiota alterations in cardiometabolic diseases☆

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ABSTRACT

Alterations in gut microbiota composition and its metabolic activity are emerging as one of the most powerful determinants of cardiovascular disease. Although our knowledge of the precise molecular mechanisms by which gut microbiota influences cardiometabolic homeostasis is still limited, a growing body of knowledge has recently been uncovered about the potential modulation of microbiome for cardiovascular diagnostic and therapeutic aspects. The multitude of interactions between the microorganisms inhabiting the digestive tract and the host has been recognized crucial in the development and progression of atherosclerosis, obesity, diabetes and hypertension. Here, we summarize the role of gut microbiota in host physiology as well as in the pathophysiology of the most common cardio-metabolic disorders, discussing the potential therapeutic opportunities offered by interventions aimed at modifying microbiome composition and activity.

Introduction

Despite the tremendous progress achieved in the diagnosis and therapy of cardiovascular diseases (CVDs) in the last twenty years, CVDs remain the leading cause of death and disability in Western countries [1]. Considering the worldwide rising prevalence in obesity, type 2 diabetes (T2D) and metabolic syndrome, it is estimated that in the next two decades the number of people suffering from chronic cardiometabolic illness will continue to grow. It goes along that a critical need exists to identify novel disease-related pathways and therapeutic targets. Although the heart and the arterial tree are the ultimate site of disease, the pathophysiology of CVDs is complex and involves several organs, establishing communications remotely *via* blood circulation.

Recently, a growing body of evidence has emerged regarding the crucial role of gut microbiota in CVDs and in particular in metabolic disorders [2]. Gut microbiota – the entire collection of microbes residing in our gut – can be considered as the largest "endocrine system" of our body. Bacteria and other microbes in the gut produce a number of substances that can be absorbed by the intestinal epithelium in the bloodstream and thus influence the function of several systems and organs. Some of the metabolites produced by gut flora are already biologically active, whereas others can be further metabolized by the host generating secondary mediators that influence the microbiota-host interaction. Given the fact that microbial cells outnumber the cells in human body, it is clear how powerful this interaction can be in determining health and disease.

Here we provide a brief overview of gut microbiota composition in human physiology and present the recent evidence establishing the association between alterations in gut microbiota and in their metabolites and CVDs. Finally, we will discuss the modulation of gut microbiota for diagnostic and therapeutic purposes in CVDs.

Physiological interactions between gut microbiota and host

It has been established that $>10^{14}$ ($>$100-trillion) microorganisms (bacteria, archea, yeast, viruses) inhabit the human intestine

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[3]. Differences in numbers of microbes and microbiota composition have been recognized along the digestive tract, with the highest representation of microbial species founded in colon, where the rich in nutrient and mostly anaerobic environment promotes microbial colonization. Since approximately only one third of gut bacteria species can be identified using conventional culturing methods, a great deal of culture-independent methods have been recently developed to provide a reference catalogue of gut microbiota [4,5]. These methods aim to characterize microbial communities by the analysis of microbe genome (microbiome). Broadly defined as metagenomics, 16S ribosomal RNA(rRNA) pyrosequencing, shot-gun metagenomics and high-throughput sequencing data have indicated the complexity of human gut microbiota (reviewed in [4]).

Food digestion involves the breakdown of macronutrients in the minimal constitutive molecules. In this process, gut microbiota participates in part by its hydrolytic capacity generating short-chain fatty acids (SCFAs) from complex carbohydrates or providing various metabolites from protein fermentation [6]. However, the effect of gut microbiota on host physiology is not limited to process food nutrients otherwise indigestible, but promote host's health in a number of other ways. Intestinal bacteria exert a local protective function regulating mucosal barriers and the immune system preventing the proliferation of pathogens [7,8].

Therefore, the broad effects of gut flora on host metabolism and immunity might be considered as fundamental mechanisms in human physiology.

Microbiota composition

The composition of human microbiota is subjected to a number of changes during health and disease. At the moment, four main bacterial phyla have been identified in human gut: *Firmicutes, Bacteroidetes, Actinobacteria*, and *Proteobacteria* [5] with the phyla *Firmicutes* and *Bacteroidetes* being the most representative in healthy gut (>90%). However, microbiota composition, even in healthy subjects, exhibits both temporal and spatial differences at genus levels. Moving from esophagus to the rectum significant changes in density and diversity of bacteria occur. *Streptococcus* is the most abundant genus in distal esophagus whereas *Helicobacter* dominates in the stomach. Quantitatively, more than 70% of the total numbers of microbes resides in the large intestine and gut flora is the most represented in stool used to obtain metagenomic data. Traditionally, alteration in the *Firmicutes*/*Bacteroidetes* ratio in colon has been implicated in disease states [9]. However, this observation has been challenged given the recognition of the high inter-individual variability among the healthy subjects based on differences in dietary habits, hygiene and lifestyle in general.

More recently, a different classification of gut microbiota has been proposed by the European Metagenomics of the Human Intestinal Tract (MetaHIT) Consortium [10]. This classification introduces the concept of enterotypes, which classifies human beings on the basis of their gut flora identified by fecal metagenomic clusters of bacterial genera, independently of age, body weight, gender or geographical localization. According to this classification, three enterotypes can be identified: enterotype 1, rich in *Bacteroides*; enterotype 2, rich in *Prevotella*; enterotype 3, rich in *Ruminococcus*. Although potentially attractive, the existence and the utility of enterotypes in describing modifications of the gut microbiota has been recently debated, and a new concept has been developed. Instead of isolated enterotypes, a continuum or gradient of bacterial genera based on the similarity in the dependence from resources has been proposed and seems to better segregate patients from healthy subjects [11].

Effects of dietary habits on gut microbiota

A bidirectional influence between food intake habits and gut microbiota diversity exists. As mentioned above, the composition of microbial species in the intestine influences the absorption of fundamental nutrients. However, it is important to note the dietary habits play an important role in shaping gut microbiota. Recently, it has been demonstrated that gut microbiota composition is not significantly associated with the genetic ancestry of the host. In contrast, individuals sharing the same environment, including diet and medications, show significant similarities in the microbiome composition [12].

The potent effect of diet on the collection and diversity of gut microorganisms became evident when gut microbiota was analyzed in populations living in different geographic regions. Differences at phylum level in microbiota composition have been identified between children living in Africa and children living in Western Europe [13]. These differences can be related to different food intake between these two populations. Specifically, a diet rich in fibers, as common in African populations, has been associated with increase in *Bacteroidetes* phylum, resulting in a more efficient breakdown of fibers and greater production of SCFAs [13]. Other studies have not reported differences in microbiota phyla, whereas more discrete differences in general have been shown [14,15]. Collectively, these data strongly suggest a link between microbial richness and dietary habits. Therefore, food intake and diet composition should be taken into consideration and monitored to obtain a better profile of microbiota-host interaction.

Gut microbiota alterations in cardiovascular disease

Virtually any CVDs have been associated with alterations in the composition and metabolic activity of gut microbiota. Cardiovascular risk factors, such as hypertension, diabetes and others modify gut environment and gut flora. However, it is important to note that a pathogenic role of microbiota alterations and of its metabolic activity has also been advocated in CVDs pathophysiology.

Hypertension

Hypertension is the single largest modifiable risk factor for CVDs. Hypertension is a complex, multifactorial disease in which genetic predisposition and environmental factors contribute together to alterations in blood pressure (BP) regulation. Dysbiosis (derangement of gut microbiota composition) has been associated with hypertension in both preclinical and clinical studies [16–19]. Although conclusive human studies specifically recognizing a causative role of microbiota alterations in hypertension are still lacking, several studies in animal models of hypertension have established the important role of gut microbiota in BP control.

Compared to normotensive animals, a reduction in richness and diversity of microbiota composition has been observed in several rodent models of hypertension, including Dhal salt sensitive rats, spontaneously hypertensive rats (SHRs) and chronic infusion of Angiotensin II (Ang II) in mice [16,17,19]. At phylum level, an increase in gut *Firmicutes*/*Bacteroidetes* ratio seems to be a constant feature in experimental hypertensive models and has been observed also in human hypertensive subjects. Depletion of microbial members using the antibiotic minocycline, significantly reduced mean BP in Ang II-infused animals as well as the *Firmicutes*/*Bacteroidetes* ratio [16]. These data collectively suggest an association between gut dysbiosis and hypertension.

Modifications in microbiota composition also change the preponderant microbial metabolic activity. Bacteria with high fermen-

tative activity produce more SCFAs, which have been shown to be implicated in BP modulation [20]. In particular, two G protein-coupled receptors (GPCRs) for SCFAs expressed in kidney, Olfr78 and GRP41, have been shown to modulate renin secretion in response to SCFAs produced by gut microbiota. This notion extends the role of gut microbiota as regulator of BP via its metabolic products, which are assimilated by the host and, at the same time, points out that microbial dysfunction can be associated with hypertension.

Although a potential causal role of microbiome in hypertension pathophysiology has been advocated using antibiotics and probiotics treatments [21,22], the role of microbiota in regulating BP in humans has been poorly understood to date. Only a few human studies [23] have looked into the potential role of gut dysbiosis and its putative mechanisms in hypertension. Further investigations are needed to delineate the shape of this association in humans.

Atherosclerosis, ischemic disease and heart failure

Bacterial DNA has been found within the vessel wall at the site of atherosclerotic plaques with a correlation between the bacteria present in the atherosclerotic plaques and the ones in the gut of the same subjects [24,25]. Some have suggested that the presence of bacteria in the plaques might have a role in their destabilization and the emergence of ischemic heart disease. To this end, using metagenomic sequencing, a different microbiota composition has been found in subjects with stable atherosclerotic plaques versus patients with unstable atherosclerotic plaques. Specifically, a lower fecal abundance of butyrate-producing *Roseburia* genus was present in the latter group, indicative of changes in gut microbiota metabolic activity towards a pro-inflammatory state in subjects with unstable atherosclerotic plaques [26,27].

As mentioned above, alterations in microbiota composition go along with changes in the metabolic production of microbiome. Recently, the identification of Trimethylamine N-oxide (TMAO), a metabolite derived from gut microbes' metabolic activity, as a contributor of atherosclerosis, has shed the light on the potential causative role of gut microbiota alterations in CVDs. TMAO is the product of liver flavin monooxygenases (FMOs), which oxidize the microbial metabolite TMA. TMA is produced in the gut by a variety of microbial species as a waste product of food rich in choline, phosphatidylcholine, and L-carnitine (such as eggs, fish, red meat). In particular, microbial TMA synthesis from choline-rich food requires the presence of a specific enzyme, TMA-lyase (CutC) and its activator CutD. The *CutC/CutD* genes are widely distributed across various taxa belonging to *Firmicutes, Actinobacteria*, and *Proteobacteria* phyla [28]. A closer look to the microbial TMA-producing communities revealed the abundance of microorganisms capable to produce TMA. For example, the genera *Clostridium* and *Sporobacter* has been respectively associated negatively and positively with plasma TMAO concentrations and using the enterotype classification of microbial cells, TMA production has been shown for *Prevotella* genus. Collectively, these results highlight the complexity of TMA production system in microbes. Despite one study providing a comprehensive catalog of TMA-producing microorganisms [29], the identification of the key players and the therapeutic potential of selective inhibition of TMA producers needs to be further explored.

Experimental evidence has delineated the pro-atherogenic role of TMA/TMAO axis. Atherosclerosis-prone apolipoprotein E-knock out ($ApoE^{-/-}$) mice fed with diet rich in choline and intact gut flora have high blood levels of TMAO and develop severe aortic atherosclerotic lesions [30]. In contrast, suppression of gut microbiota using antibiotic treatment or using germ-free mice (which lack of resident microorganisms) abolished TMAO production and reduced the atherosclerotic burden. Interestingly, gut microbial transplantation from high-TMAO producing mouse strain to low-TMAO producing strain, also transfers the atherosclerotic susceptibility to choline-rich diet [31]. These data demonstrate the obligatory role of gut microbiota in TMAO formation and support the importance of TMAO in atherosclerosis development.

On the clinical scenario, a number of observations have been made suggesting the strong association between high TMAO circulatory levels and CVDs [32–35]. In the initial investigation, in a cohort of subjects undergoing elective coronary angiography, TMAO levels showed a positive correlation with the size of atherosclerotic plaque and cardiovascular events [32]. In another larger study, blood TMAO levels were shown to predict the risk to incident major adverse cardio- and cerebro-vascular events (MACCE) over 3 years of follow up [33]. Plasma TMAO levels have also been found increased in patients with heart failure (HF) and correlate with a poor prognosis [30,35]. In a recent meta-analysis pooling the majority of studies that have established the correlation between TMAO plasmatic levels and cardiovascular risk, we were able to show that high levels of circulatory TMAO was associated with increased cardiovascular events, cardiovascular mortality and all-cause mortality in a dose-dependent manner [36].

The potential mechanistic link between TMAO and atherothrombotic events has also been suggested by the preclinical evidence of TMAO-induced prothrombotic effects, mediated by the increase in platelet reactivity [37] as well as TMAO promotion of vascular inflammation [38]. Inflammation and immune cells activation are known to be the initial trigger of atherosclerosis. Despite the important role of gut microbiota in shaping immune response and inflammatory pathways in many chronic diseases [39], the interactions between microbiota and inflammatory mechanisms in CVDs is still poorly understood. Microbiota alterations and, in turn, the modulation of different compartments of immune system (lymphocytes, macrophages etc.), have been shown to influence the atherosclerotic process. TMAO has been recently found capable to activate the inflammasome multiprotein complex in vascular cells promoting reactive oxygen species (ROS) production and lipid deposition [40]. The influence of host microbial status on atherosclerotic progression is also evident by the fact that immune cells infiltration in vascular atherosclerotic plaques depends on the gut microbiota composition. For example, the activation of the pro-atherogenic natural killer T lymphocytes (NKT) is dumped in germ-free mice [41] suggesting that gut microbiota affects NKT function and, in turn, atherosclerotic progression.

Although a great body of evidence recognizes a significant role for TMAO as diagnostic and prognostic biomarker of CVDs, mechanist evidence demonstrating how TMAO might directly or indirectly promote CVDs is still lacking. The availability of specific molecules inhibiting colonic TMA formation and the effects of these compounds on atherosclerotic plaque formation and, ultimately, on cardiovascular risk modification will represent an exciting area of research.

Obesity, diabetes and dyslipidemia

Obesity has reached pandemic proportions [42]. The increase in obesity and associated conditions such as T2D and dyslipidemia will significantly impact on cardiovascular health management. A crosstalk between microbiota and body weight as well as fat mass has been established. Pioneeristic works have shown that germ-free mice fed with high fat diet (HFD) exhibit reduced adiposity and weight gain compared to conventional mice exposed to the same diet. Importantly, fecal transplantation from regular HFD-exposed mice to germ-free mice restored the ability to gain weight of the latter group [43–45]. Interestingly, the transmissibility of metabolic alterations by sharing gut flora has been also demonstrated by transferring feces from obese subjects into germ-free

mice replicating the metabolic phenotype observed with HFD [45]. An increased *Firmicutes*/*Bacteroidetes* ratio has been observed in both animal and human obesity [9,46]. Modifications in gut bacterial composition is evident not only at the phylum levels. The family of hydrogen-producing bacteria *Prevotellaceae* (belonging to the *Bacteroidetes* phylum) has been found much more represented in obese individuals compared to lean subjects. Another example is related to the link established between the abundance of *Clostridium ramosum*, a member of the class *Erysipelotrichi* within the phylum *Firmicutes*, and metabolic syndrome in humans [47]. Collectively, alterations in microbiota compositions in obesity has been associated with the modifications of polysaccharides fermentative capacity which will impact on host intestine absorption as well as on the appetite dysregulation observed in obesity [48].

In dietary intervention, such as caloric restriction, weight loss has been associated with the reduction in the above-mentioned bacterial phyla ratio [26,44,49,50], further strengthening the association between changes in microbiota composition and obesity.

An effect of gut microbiota on whole body metabolic homeostasis is also evident in T2D. The inflammatory and immunity components participating in T2D pathogenesis are influenced by gut dysbiosis. Altered microbial flora might affect the intestinal epithelial barrier permeability altering glucose sensitivity and absorption, promoting insulin resistance [51]. Similarly to what has been found in atherosclerosis, a reduction in the abundance of some butyrate-producing bacteria has been observed in T2D [49]. Reduction in SCFAs (particularly butyrate) in the gut is associated with higher pro-inflammatory state and reduced insulin sensitivity as demonstrated by the treatment with vancomycin in subjects with metabolic syndrome [52]. Accordingly, transplantation of feces from lean subjects to individuals with insulin resistance and metabolic syndrome has been shown to improve insulin sensitivity and increase the number of butyrate-producing bacteria. SCFAs might have a number of effects in regulating metabolic response either locally, via entero-endocrine regulation, or remotely, on adipose tissue, pancreas and skeletal muscle [27,53–55].

Similar to what is observed in physiologic conditions, dietary habits influence gut microbiota composition also in diseases. For example, non-caloric artificial sweeteners (NAS) consumption has been linked with metabolic syndrome [56] and type II diabetes [57]. Recently, a role for microbiota in the determinism of glucose intolerance induced by NAS has been proposed. Despite consumption of NAS, NAS has been shown to induce gut dysbiosis in experimental animals and human subjects [58]. The specific molecular mechanisms by which gut flora composition influences glycemic homeostasis are not yet completely understood. Despite the fact that specific microbial composition predisposing to NAS-induced metabolic detrimental effects can be identified, the microbial bioproducts (e.g. SCFAs) potentially mediating the interaction between host and microbiota in NAS-induced susceptibility to insulin resistance and T2D are lacking and warrant further investigation.

Another important metabolic regulatory pathway modulated by intestinal flora involves bile acids (BAs). BAs facilitate the absorption of nutrient-derived fat and are metabolized by gut microbiota [59]. However, BAs also act as ligands for nuclear receptors that have a powerful effect on metabolic regulation [60]. Farnesoid X receptor (FXR) is a nuclear receptor involved in metabolic inflexibility, which is negatively regulated by the BA tauro-β-muricholic acid. Microorganisms present in the gut metabolize tauro-β-muricholic acid, increasing FXR signaling [61]. The effects of microbiota on lipid metabolism is also evident by the association between circulating lipid levels (triglycerides and high density lipoprotein cholesterol) and gut microbial species [62], and by the fact that some of the proatherogenic effects of TMAO are related to the alterations in cholesterol transport and changes in BAs pool [63]. In addition, modulation of hepatic FMO3, which produces TMAO from microbial TMA, has been shown to regulate blood lipid levels and hepatic lipid metabolism [64,65].

Considering the available evidence, it is possible to conclude that alterations in gut microbiota might affect lipid and glucose metabolism at multiple levels.

Therapeutic modulation of gut microbiota in cardiometabolic disorders

Given the emerging critical importance of gut microbiota functions in cardiometabolic health and the number of alterations in microbiota composition and in its metabolic activity, the possibility of intervention on gut microbiome has been proposed as a potential therapeutic strategy (Fig. 1). Dietary modifications, treatment with pro-, pre- and antibiotics and, more recently, inhibitors of microbial enzymes, are currently tested as interventions aiming to modulate gut microbiota composition and activity in diseases.

Dietary and lifestyle changing interventions

As mentioned previously, changes in dietary habits represent the most powerful stimulus able to modify gut microbial communities. At the same time, nutritional interventions have been proven to significantly reduce cardiovascular risk [66,67]. Therefore, it can be speculated that, at least in part, some of the beneficial effects observed with high-fibers diet might be attributable to a favorable shift of intestinal flora towards a “healthier” composition. One study has demonstrated that a strict vegetarian diet enriched in fibers induced weight loss and improved insulin profile in patients with T2D in association with changes in microbiota phyla composition and modulation in SCFAs production [68]. Experimentally, hypertensive mice fed with high-fibers diet have shown reduced gut dysbiosis and increased microbial production of acetate with amelioration of BP and pathological cardiac remodeling [69]. Therefore, modulation of microbiota composition by dietary intervention might represent a promising therapeutic strategy for a variety of cardiometabolic diseases although the precise molecular mechanisms by which this protection occurs are not yet completely elucidated.

Another potent health-promoting intervention is exercise training (ET). ET has been shown to reduce cardiovascular risk and ameliorate the prognosis of patients with HF and a variety of CVDs [70]. Interestingly, although studies in animals and human subjects have shown that ET potently affects gut microbiota composition [71–73], a mechanist link between exercise-induced modification in microbiota and CVDs has not been established to date.

Modulation of gut microbiota by prebiotics, probiotics and antibiotics

Direct intervention to modify gut microbiota composition using substances that selectively stimulate the growth of specific microorganisms (prebiotics), introducing live bacteria (probiotics) or eliminating part of resident bacteria (antibiotics), have been tested as therapeutic strategies in cardiometabolic diseases.

Prebiotics are food-derived indigestible molecules (such as complex sugars) that will provide a beneficial impact on gut microbiota composition. Favorable effects with the use of prebiotics have been observed in animal studies. Obese mice treated with prebiotics have shown improved metabolic profile, with reduction of fat mass and better glycemic control [74–76]. Despite the encouraging data observed in preclinical studies, prebiotics treatment failed to achieve similar results when tested in obese human subjects, raising questions regarding the real applicability of this type of intervention in humans [77]. Probably more robust evidence in amelioration of human metabolic phenotype has been reached with the use of probiotics. The introduction of live commensal bacteria in

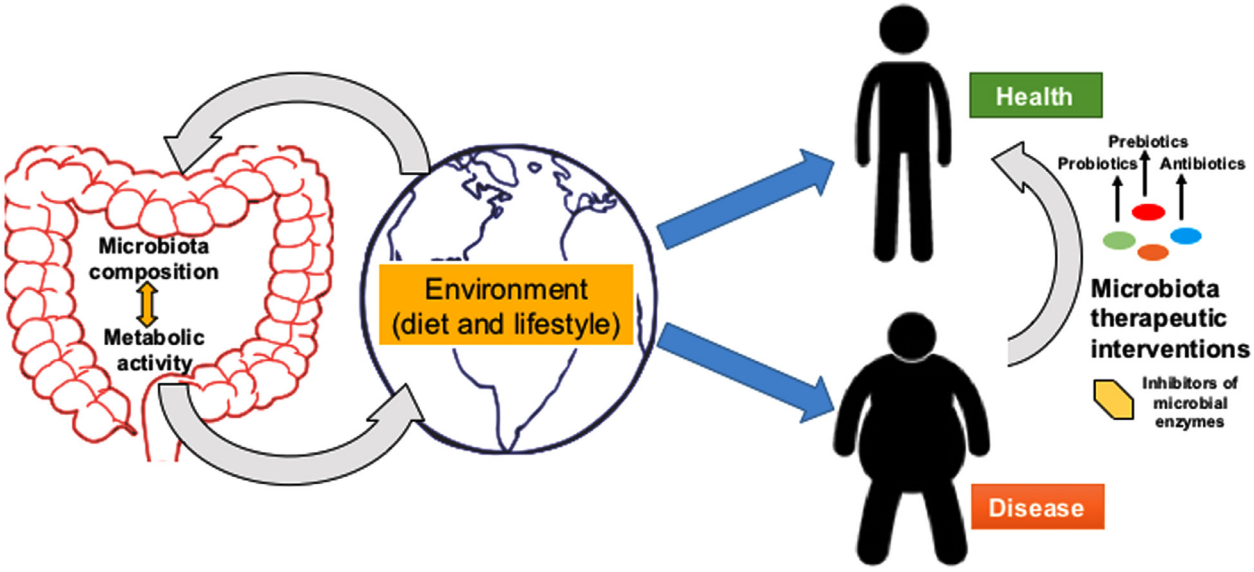

Fig. 1. Interactions between microbiota and environment in human health and disease.

the gut of the host, such as *Lactobacillus* species, has been shown to promote insulin release in obese subjects [78]. The use of probiotics was also associated with reduced dysbiosis, modulation of SCFAs production and less release of toxins in small intestine of subjects with renal disease [79] and atherosclerosis [80]. Finally, although intuitive, the use of antibiotics to selectively eliminate potentially harmful microbial species has not paid off so far. In both animal and human studies, treatment with broad, non-specific antibiotics has been associated with increased fat deposition and a worse metabolic profile [81–83].

These observations point out, once again, the critical role of gut microbiota in metabolic homeostasis and highlight the need for more microbe-personalized therapeutic strategies in cardiometabolic diseases.

Inhibitors of microbial enzymes

Given the recently acquired notion that metabolites produced by gut microbiota exert detrimental cardiometabolic effects on the host increasing the risk of CVDs (e.g. TMA/TMAO pathway), one of the most recent lines of research is focus on the discovery of small molecules capable to selectively target microbial enzymes involved in the production of those metabolites. Therefore, given the microbial source of TMA, the possibility of targeting TMA lyases without influencing microbial composition has emerged as a potentially exciting therapeutic strategy. Recently, an analog of choline, 3,3-dimethyl-1-butanol (DMB), has been used to induced non-lethally inhibition of TMA formation, reducing TMAO circulatory levels and ultimately ameliorating atherosclerotic plaques formation in ApoE$^{-/-}$ mice fed with high choline diet [84]. This study has provided the proof of concept for a strategy – the selective inhibition of microbial functions – that could inform the future research in the field.

Conclusive remarks and future perspective

During the course of CVDs and cardiometabolic disorders, the gut microbiota contributes in the pathophysiology on these conditions. The association observed between alterations in gut microbiota composition and in its metabolism has been reported in several preclinical and clinical studies. Although the understanding of the molecular mechanisms governing microbiota-host interactions is far from being exhaustive, the improvement of genetics and omics technologies has provided the platform to achieve more mechanistic data. A careful phenotypic assessment of patients with CVDs, including dietary and lifestyle habits, coupled with metagenomic sequencing and metabolomic profiling, is warranted to identify new microbiome-related therapeutic strategies (Fig. 2). Further investigations are required to define what a “healthy” microbiota looks like and which – if present – specific alterations in microbiota composition might represent a specific signature in CVDs. Noteworthy, the potential association between alterations in microbiota composition and cardiovascular risk goes beyond just the intestine location and involves the entire digestive tract. For exam-

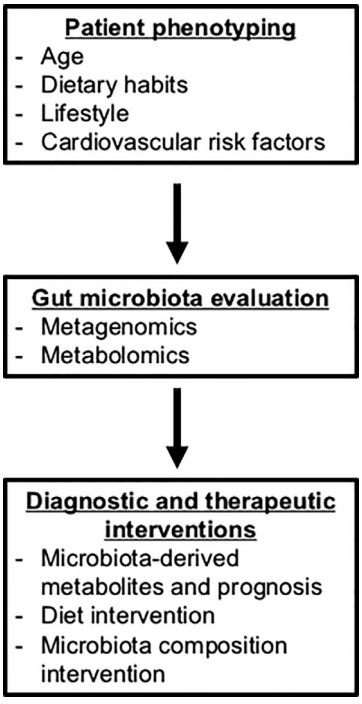

Fig. 2. Simplified flow-chart depicting the relationship between patients' phenotyping and microbiota-directed interventions.

ple, alterations in oral microbiota participate in the chronic inflammation status established in periodontitis contributing to the onset and progression of cardiovascular and metabolic disease [85]. Therefore, challenges and limitations of assessing exclusively gut microbiota status in connection with CVDs exist. In fact, recent evidence has shown how alterations in oral microbiota can affect gut microbiota composition [86] potentially shifting the entire digestive tract microbiota flora towards a pro-inflammatory, disease-prone status.

The discovery of microbial metabolites capable of having an impact on cardiovascular health have also opened a new scenario in biomarkers research. The fact that millions of cells residing in our gut produce specific molecules the levels of which seem to be modulated in diseases, raises the possibility to track those metabolites to assess the natural history of these conditions and evaluate the prognostic impact of specific therapeutic strategies. Since the ultimate goal of therapeutic research is to provide a personalized strategy (precision medicine), a more in depth knowledge of gut metagenomics and pharmacometagenomics might significantly impact on host cardiovascular health.

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