

The cardiovascular macrophage: a missing link between gut microbiota and cardiovascular diseases?

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Abstract. – The prevalence of cardiovascular diseases is on the rise. Interventions that would aid prevention or treatment of these diseases are essential. The microbes residing in the gut, collectively called “gut microbiota”, produce a plethora of compounds that enter the bloodstream and affect the cardiovascular system. Signals ascending from gut microbiome are believed to modulate differentiation and functional activity of macrophages residing in perivascular tissue, atherosclerotic plaques, and perivascular areas of the brain. Cardiovascular macrophages may be the key players that transform the signals ascending from gut microbiome into increased predisposition to cardiovascular diseases. The present review summarizes the knowledge to date on potential relationships between gut microbiota, cardiovascular macrophages, and cardiovascular diseases.

Key Words:

Cardiovascular disease, Atherosclerosis, Hypertension, Gut microbiota, Macrophage, Differentiation, Cell, Fatty acids, Short-chain.

Introduction

Cardiovascular diseases are characterized by marked prevalence and high negative impact on the quality of life. They still remain the biggest cause of premature mortality in the developed countries. Factors that would help prevent or attenuate the development of cardiovascular diseases are of high interest to clinicians, researchers, and patients.

One of the endogenous factors potentially contributing to development of cardiovascular dis-

eases is the vast community of commensal microorganisms (mostly bacteria, but also archaea and yeast species, and some viruses), present in several organs and cavities of the body. This community is called microbiota. The biggest microbiota is found in the gut. Numerous microorganisms that inhabit the gut produce multiple compounds that can have both beneficial and harmful effects. These effects are exerted both locally and remotely. As a local effect, it was documented that compounds generated by gut microorganisms modulate the cells within the gut associated lymphoid tissues¹. Specifically, lymphoid organs comprise large numbers of T- and B-lymphocytes. As a remote effect, which is of particular interest to this review, gut microbiota may modulate functional activity of another type of immune cells, called macrophages. These cells are found in lesions associated with many cardiovascular diseases.

Given the supposed involvement of macrophages in cardiovascular diseases, the main focus of this review is on potential associations between changes in gut microbiota (also known in the literature as “dysbiosis”), macrophage functional activity, and a cardiovascular disease. As examples of the latter, we paid specific attention to atherosclerosis and hypertension.

Normal Gut Microbiota, and Its Changes Under Physiological and Pathological Conditions

In adults, gut microorganisms include bacteria, archaea, unicellular eukaryotes, yeast, and some viruses. While there are other parts of the

gastrointestinal tract that also contain microorganisms (for example, oral cavity), the gut (that is, the colon), host the majority of gut microbiota. The predominant microorganisms are bacteria, specifically from the species *Firmicutes* and *Bacteroidetes*². These species are presented in different ratios in each individual. Yet their relative amounts seem to remain constant through most of the adulthood³. In contrast to these two bacterial species, *Proteobacteria*, *Verrucomicrobia*, *Actinobacteria*, *Fusobacteria*, and *Cyanobacteria* are present in much lower quantities². For more detailed description of the bacteria that comprise the genera mentioned above we refer the reader to the recently published excellent and comprehensive reviews⁴.

Birth and childhood are accompanied with high fluctuations in the ratio between the two main bacterial inhabitants of the gut³. First microbial colonization of the gut was traditionally thought to occur during the birth, through exposure to vaginal or skin microbiota, depending on the mode of delivery (respectively, vaginal or caesarean routes)⁵ (Figure 1). There were also some reports that gut microbiota may establish prenatally^{6,7}. While this was an interesting hypothesis, the most recent belief returned to the original idea

of perinatal and postnatal establishment of gut microbiota^{8,9}. The previous conflicting reports were considered as confounded by artifacts of insufficiently developed methodology⁹.

The support of the postulate that microbial inhabitation of the gut and establishment of gut microbiota is related to birth and first hours of postnatal life comes from the very fact that initial gut inhabitation by the microorganisms depends on vaginal or caesarean birth. Indeed, there is evidence from human studies supporting this assumption⁵. However, other factors may also contribute to the initial heterogeneity of gut microbiota¹⁰, including gestational age, dietary habits of the mother, genetic predisposition, and so on.

The establishment of gut microbiota in infants and young children is a complex and dynamic process¹¹⁻¹⁵ (Figure 1), which we only now begin to properly understand. Key factors in this process may include the duration of breastfeeding, presence of older siblings and pets in the household, diet, and other factors. Specifically to breastfeeding, it should be mentioned that there seems to be a reinforcement of specific microbiota by human breast milk. In particular, constituents of human breast milk seem to favor the proliferation of specific microorganisms, with

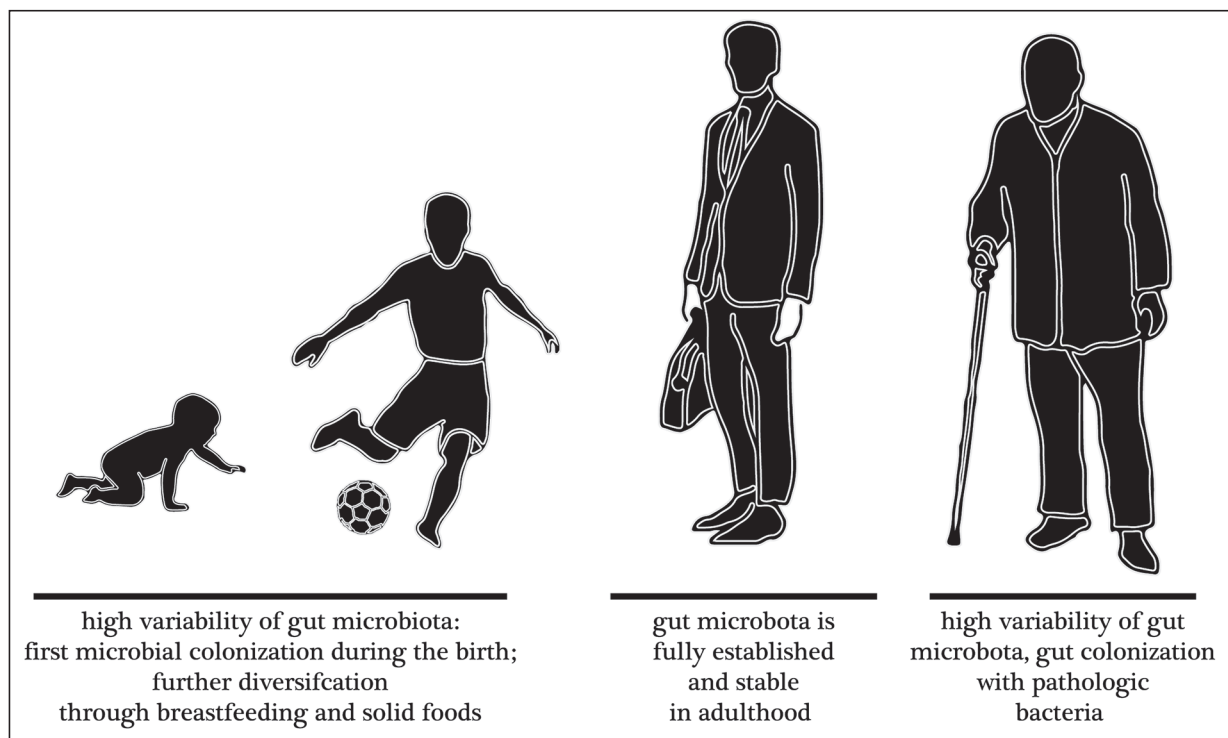


Figure 1. Dynamics of gut microbiota through the life.

many constituents acting as prebiotics. As it will be addressed in subsequent sections, prebiotics are specific carbohydrates¹⁶ that permit proliferation of some, but not the other microbes.

The establishment of gut microbiota in infants is further influenced once breastfeeding is supplemented, and at some later point replaced by consumption of complex carbohydrates. These carbohydrates promote a rise of gut-associated bacteria, as well as their respective adaptation to the new source of food¹⁷. Of importance, these are the bacteria that are associated with adult gut microbiota (e.g., *Bacteroidetes*)¹⁷. As mentioned above, specific bacteria, and in specific relative ratios, seem to dominate the normal gut microbiota in the adulthood. In addition, gut-associated bacteria become functionally active during late infancy and early childhood, which is demonstrated by increased levels of metabolites of their activity (such as short chain fatty acids) in fecal specimens¹⁷.

Interestingly, aging is also known to be associated with the increased variability of gut microbiota (Figure 1). Many factors appear to influence the presence of microorganisms in the colons of older individuals: diet, living in a home or long-term residential institution, dental problems, presence of chronic diseases, and so forth¹⁸. In many older individuals, pathological microorganisms start colonizing the gut, including *Clostridium difficile*. Interestingly, the aging is associated with increased incidence of cardiovascular dis-

eases. Therefore, it is possible that alterations in composition and/or functioning of gut microbiota (that is, dysbiosis) may predispose to increased susceptibility to cardiovascular diseases or other diseases of older age¹⁹.

Macrophages and Their Involvement in Cardiovascular Diseases

Macrophages are immune cells that originate from local embryonic cells, deposited in tissues prenatally, and from circulating monocytes recruited to tissues postnatally. Macrophages exhibit extreme plasticity of their phenotypes. A conventional dogma used to be that there exist extreme macrophage phenotypes, such as classically or alternatively activated macrophages²⁰. Yet the newest data showed the existence of multiple intermediate phenotypes (Table I). Moreover, it is likely that macrophages are present in a continuum of various phenotypes that stretch between the most extreme classically or alternatively activated macrophages²¹. In addition, macrophage phenotypes are believed to be reversible²², which renders extreme plasticity and versatility to macrophages (Figure 2).

Macrophage functions are diverse. Depending on the tissue, macrophages play antimicrobial functions, contribute to or attenuate inflammation, and exert important immunomodulating actions. Macrophage versatility is explained by co-existence of multiple phenotypes²³. For example, classically activated macrophages (dif-

Table I. Examples of systemic and local macrophage phenotypes.

Macrophage phenotype	Growth factors or differentiation stimuli	Location	Assumed function
M (M-CSF)	Macrophage Colony-Stimulating Factor	Systemic	Intermediate phenotype
M (LPS+IFN- γ)	Bacterial endotoxin (LPS) and Interferon- γ	Systemic	Pro-inflammatory
M (IL-4)	Interleukin-4	Systemic	Anti-inflammatory
M (IL-10)	Interleukin-10	Systemic	Anti-inflammatory
M (GC)	Glucocorticoids	Systemic	Anti-inflammatory
M4*	CXCL4	Local (atherosclerotic lesion)	Possibly, An intermediate phenotype
Mox ^{&}	Oxidized phospholipids and lipids	Local (atherosclerotic lesion)	Pro-atherogenic
Mhem [#]	Haem/haemoglobin	Local (atherosclerotic lesion)	Anti-atherogenic, anti-inflammatory
M(Hb)	Haemoglobin	Local (atherosclerotic lesion)	Anti-atherogenic, anti-inflammatory

Footnote: Macrophage phenotypes should be assigned based on nomenclature recommendations 21. *Per nomenclature recommendations, should be named M(CXCL4); [&]per nomenclature recommendations, should be named M(Ox); [#]per nomenclature recommendations, should be named M(hem).

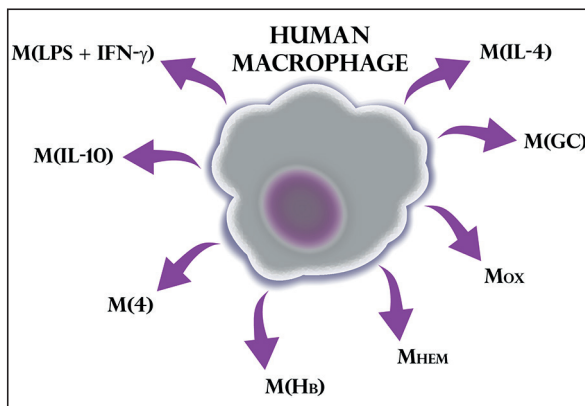


Figure 2. Macrophage phenotypes and plasticity.

ferentiated in the presence of interferon- γ and/or bacterial endotoxin) are believed to be pro-inflammatory, meaning that they produce increased amounts of inflammatory factors (cytokines, leukotrienes, etc.)²². In contrast, alternatively activated macrophages (typical example: macrophages differentiated with interleukin-4 and/or interleukin-13) assume the anti-inflammatory function and aid the resolution of inflammation. The anti-inflammatory functions can be exerted either by secretion of inflammation-resolving factors (anti-inflammatory cytokines or lipoxins), enzymes that “digest” the inflammatory edema, or by phagocytic elimination of apoptotic cells, the process called “efferocytosis”²². All macrophage phenotypes appear to have ability to phagocytose²⁴, that is, engulf and digest macromolecules and small objects, such as bacteria, yeast or cells.

Similar to macrophages, circulating monocytes also exist in different phenotypes. In humans, one distinguishes three phenotypes; the current classification is based on expression of two cell surface receptors, Cluster of Differentiation (CD) 14 and 16. These are, respectively, receptors (or part of receptor complexes) for bacterial endotoxin and immunoglobulins of class G. Specifically, the majority (> 90%) of circulating monocytes are called “classical”. They express high levels of CD14 and no CD16 (CD14⁺⁺/CD16⁻). The remaining two monocyte populations express either intermediate levels of both CD14 and CD16 (“intermediate” phenotype; CD14⁺⁺/CD16⁺), or low levels of CD14 and high levels of CD16 (“nonclassical” phenotype; CD⁺/CD16⁺⁺)²⁵. These phenotypes are believed to respectively execute immune function (e.g., phagocytosis), partake in an inflammatory response, or assume patrolling and wound healing functions²⁶.

Macrophages are present in cardiac and vascular tissue, even under physiological conditions²⁷. Specifically, macrophages are considered as primary immune cells in cardiac tissue and in blood vessels. The majority of evidence comes from animal studies²⁸. These macrophages are tissue-resident macrophages, deposited in the tissues shortly before or after the birth²⁸. It is possible that these macrophages are required for conduction of an electric signal within the heart tissue²⁹, which underlines the importance of these cells for cardiac function. This unexpected macrophage function comes on top of their stereotypical function as scavengers of dead tissue and cells³⁰. In addition, macrophages arise from circulating monocytes during processes associated with inflammation, such as in atherosclerosis.

The macrophage involvement in atherosclerosis is a well-documented fact. Still, many questions remain with regard to their exact role. The pathogenesis of an atherosclerotic plaque is thought to involve a build-up of lipids, lipoproteins (especially low-density lipoproteins), and phospholipids in the wall of a blood vessel (“fatty streak”), and their subsequent oxidation³¹. The presence of oxidized lipoproteins stimulates production of inflammatory and growth factors by the neighboring endothelial cells, including those that stimulate differentiation of circulating monocytes into macrophages³². These macrophages internalize oxidized lipoproteins by phagocytosis. However, unlike with bacteria, macrophages cannot completely digest lipoproteins, essentially becoming lipid-laden, or “foam cells”. This process leads to eventual macrophage apoptosis and death, while lipids and lipoproteins continue to build up. With time, these sites become calcified, eventually turning into an atherosclerotic plaque.

In addition to circulating monocytes as a source of atherosclerotic macrophages, the latter cells also proliferate locally. This local proliferation contributes substantially to macrophage infiltration of atherosclerotic plaques³³. Another potential source of atherosclerotic macrophages is through transdifferentiation of vascular smooth muscle cells into foam-like cells³⁴.

The macrophage phenotypes present in atherosclerotic plaques are not well understood³². It is possible that several phenotypes can be present simultaneously in different layers of the plaque³². It further appears that local differentiation factors exist in addition to classical macrophage differentiation factors (e.g., interferon- γ and endotoxin, or interleukins -4 and -13), which respectively

cause classical or alternative macrophage differentiation. These local differentiation factors, specific for atherosclerosis lesion, govern the rise of lesion-specific macrophage phenotypes. Among those local factors, platelet factor 4 (CXCL4), oxidized phospholipids, heme, and hemoglobin complexes are most commonly described^{35,36}. The atherosclerosis-specific macrophage phenotypes driven by these local factors respectively are M4, Mox, Mhem, and M(Hb) (Table I; Figure 2).

Macrophages are also thought to contribute to the pathophysiology of systemic or pulmonary hypertension. The understanding of their involvement in these pathologies is much less advanced than our knowledge of macrophage contribution to atherosclerosis³⁷. One of the mechanisms of macrophage contribution to hypertension could be associated with production of reactive oxygen species and inflammatory mediators. The latter increase resistance of local vasculature³⁸. In case of systemic hypertension, these processes may occur in the kidney. Then, they will negatively impact sodium excretion, thereby aggravating hypertension³⁸. In addition, perivascular macrophages in the brain could contribute to neuroinflammation by production of reactive oxygen species in response to angiotensin II³⁹.

The great majority of the knowledge on the impact of macrophages on atherosclerosis or hypertension stems from animal (mostly murine) investigations. The relevance of these observations for human situation certainly requires further verification. Nonetheless, it is widely accepted that macrophage functioning can be induced by many metabolic factors ascending from the gut (Figure 3). These metabolic factors will be described in the sections below.

Gut-Derived Bacterial Factors and Small Molecule Metabolites That, Through Macrophages, May Predispose to a Cardiovascular Disease

The gut-associated microorganisms produce a plethora of metabolic and signaling molecules⁴⁰ (Table II). These metabolites arise as constituents of bacterial structure and/or metabolism, or from their functional activity in the gut.

As examples of the former, endotoxins attracted substantial attention (Table II). Under certain circumstances, endotoxins, which are constituents of bacterial walls of Gram-negative bacteria, can leach out in low quantities into the blood stream⁴¹. This condition is referred in the literature as “metabolic endotoxemia”⁴². It was

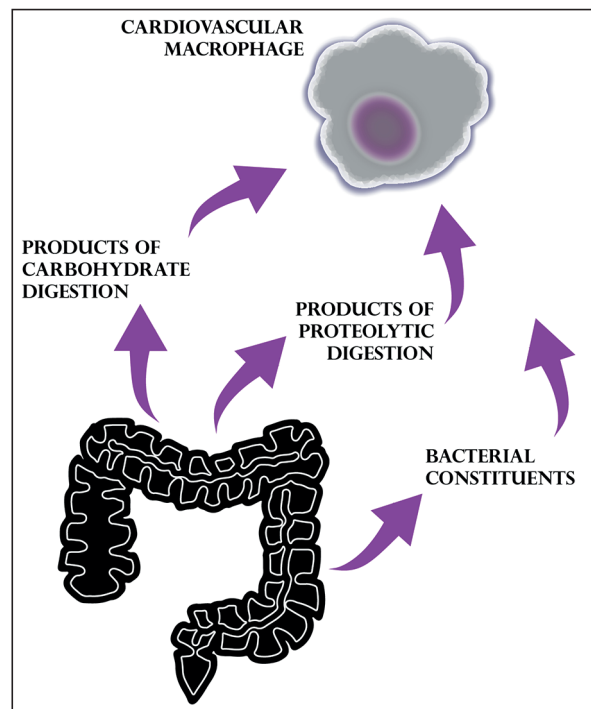


Figure 3. Macrophage functions, and gut-ascending microbial factors and metabolites.

shown to be associated with obesity, which is a risk factor for cardiovascular diseases. Of note, macrophages are known to be modulated by the endotoxin. Specifically, macrophages produce inflammatory factors when exposed to endotoxin, which involves the Toll-Like Receptor 4 pathway⁴³. Moreover, macrophage differentiation is driven toward a pro-inflammatory phenotype when macrophages are chronically exposed to low levels of endotoxin⁴⁴. Importantly, this was shown in conditions that are known to predispose to cardiovascular diseases⁴¹. Furthermore, monocytes, the macrophage precursors, when exposed to low-grade endotoxin, can also change their phenotype and contribute to aggravated atherosclerosis⁴⁵.

Another example of bacterial constituents is peptidoglycans (Table II). Peptidoglycans are present in bacterial walls of both Gram-positive and -negative bacteria, whereas the former bacteria contain higher levels of peptidoglycans. Peptidoglycans stimulate Toll-Like Receptor 1 and 2 pathways, as well as the Nucleotide-binding Oligomerization Domain-containing protein 1 and 2 pathway, also leading to inflammatory responses in macrophages⁴⁶. Peptidoglycans were demonstrated as contributing to pro-inflammatory activity of circulating monocytes⁴⁷.

Table II. Compounds produced by gut microbiota and their potential effects on macrophages.

Classes of compounds	Examples	Effects on macrophage differentiation?	Effects on macrophage function?
Bacterial constituents	Endotoxins (lipopolysaccharides)	Yes (promote pro-inflammatory “classical” macrophage differentiation)	Pro-inflammatory stimulation
	Peptidoglycans	Insufficient data	Pro-inflammatory stimulation
Fermentation of complex carbohydrates	Short-chain fatty acids (acetate, butyrate, propionate)	Insufficient data	Anti-inflammatory stimulation
Proteolytic fermentation	Trimethylamine*, short-chain fatty acids#, branched-chain fatty acids, organic acids, amines, phenols, thiol-containing compounds, ammonia, gases	Insufficient data	Pro-inflammatory stimulation
Other compounds	Vitamins, serotonin	Insufficient data	Insufficient data

Footnote: *Precursor to trimethylamine N-oxide, TMAO; #Minor amounts.

Bacterial functional activity is related to two fermentation processes in the gut. Bacterial fermentation helps our body to digest complex carbohydrates and, to a certain extent, protein. Therefore, these fermentation processes yield short-chain fatty acids and various small molecule metabolites. Short-chain fatty acids are produced predominantly through fermentation of complex carbohydrates, and to a lesser magnitude, through proteolytic fermentation. Short-chain fatty acids are described in detail in the next section of this review. In contrast, proteolytic fermentation yields branched chain fatty acids, gases, organic acids, and other products of peptide and amino acid degradation, including amines, phenols, thiol-containing compounds, and ammonia (Table II).

Belonging to the products of proteolytic fermentation with unfavorable effects on the cardiovascular system, trimethylamine N-oxide (TMAO) is the compound that most commonly appears in epidemiologic studies as a risk factor⁴⁸. In addition, confirmatory evidence on the adverse role of TMAO in a cardiovascular disease (in particular, atherosclerosis) is also provided by experimental studies⁴⁹. TMAO is a product of choline and carnitine metabolism⁵⁰ (Figure 4). TMAO may also be generated from betaine, the oxidation product of choline⁵¹ (Figure 4). The precursor to TMAO is trimethylamine. When the latter is absorbed from the gut and enters the bloodstream, it reaches the liver. In the liver, trimethylamine is oxidized by the enzyme flavin-containing monooxygenase (FMO) 3 to yield

TMAO (Figure 4). The food that gives rise to the highest yield of TMAO is red meat.

Gut bacteria are also involved in the synthesis of many vitamins (e.g., vitamin B, K, folate, etc)⁵². Another example of an important compound whose metabolism involves gut microbiota is serotonin. This compound is a neurotrans-

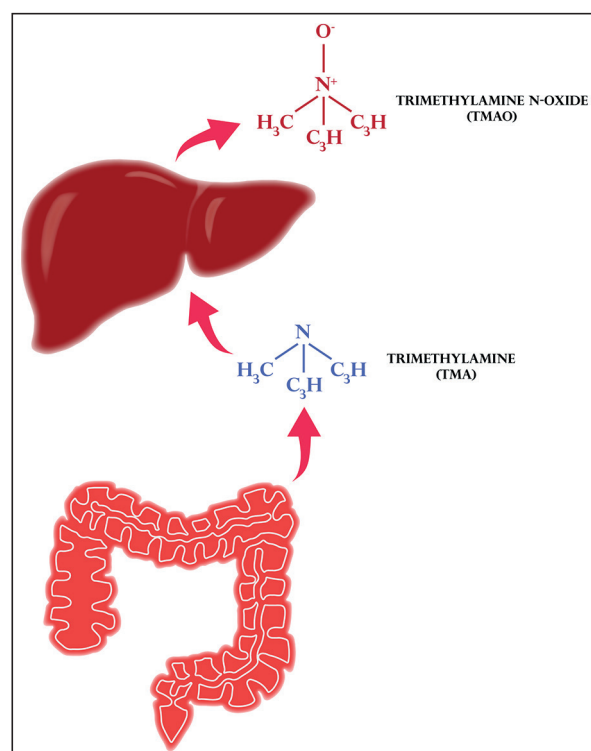


Figure 4. Trimethylamine N-oxide (TMAO) metabolism.

mitter modulating neurophysiological processes. Serotonin is almost exclusively produced in the gastro-intestinal tract⁵³.

Generation of Short-Chain Fatty Acids by Gut Microbiota

The bacteria present in the gut aid fermentation of complex carbohydrates, including dietary fibers. This fermentation yields numerous compounds, such as gases (hydrogen, carbon dioxide, and methane) and low-molecular weight metabolites. The gases can be utilized by the body through appropriate biochemical reactions. The reader is referred to a very recent comprehensive review on this subject⁵⁴. The low-molecular weight metabolites include short-chain fatty acids (Table II). The great majority of the latter are represented by acetate (acetic acid), butyrate (butyric acid), and propionate (propionic acid) (Table II). Acetate is the most abundant of the three aforementioned short-chain fatty acids. These fatty acids have several (ranging from one to six) carbon atoms and are freely absorbed in the gut⁵⁵.

Interestingly, gut bacteria seem to have some specialization in what short-chain fatty acid they produce. For example, butyrate is predominantly produced by bacteria belonging to the *Clostridium* family (specifically, the cluster XIVa) and *Firmicutes*⁵⁴, as well as by several other bacterial families⁵⁶. Interestingly, the metabolic pathways to generate butyrate are different among bacteria⁵⁶. Propionate is generated through activity of bacteria belonging to the family of *Bacteroidetes* and some other bacteria⁵⁴.

Some of the short-chain fatty acids (such as butyrate) provide energy for epithelial cells lining the colon. Furthermore, these short-chain fatty acids exert anti-inflammatory effects on macrophages and their precursors, monocytes⁵⁷⁻⁶³. Specifically, butyrate was shown to downregulate monocyte and macrophage inflammatory responses^{57,61,63}. This could be because of direct anti-inflammatory effects of butyrate^{57,62,63}, either through transcriptional or epigenetic mechanisms^{61,62}, or because of modulation of macrophage differentiation^{58,59}. Confirming the overall beneficial roles of butyrate, its anti-atherosclerotic effects were documented in animal studies⁶⁰.

So far, it seems that the evidence on relationship between the short-chain fatty acids and macrophages is more substantiated with regard to atherosclerosis. In contrast, a similar relationship concerning hypertension is sparse. Alterations of gut microbiota (dysbiosis) may contribute to ele-

vated blood pressure, at least in animal models⁶⁴. Evidence about similar associations in patients has only begun to emerge⁶⁴. One of the earliest publications on this topic demonstrated decreased diversity of gut microbiota of people with hypertension⁶⁵. Other alterations of gut microbiota may exhibit as a decrease in the relative or absolute abundance of butyrate-generating bacteria⁶⁶, or as lower abundance of specific bacterial species⁶⁷. In experimental animals, another potential mechanism of hypertension-inducing effects of dysbiosis has just recently been described. In particular, dysbiosis may elevate blood pressure by acting through sympathetic innervation⁶⁸. We do not know of published data demonstrating the same in humans. Therefore, it remains to be proven how well animal observations are applicable to clinical situations.

Gut Microbiota, Cholesterol Metabolism, and Bile Acid Reabsorption

In addition to metabolic functions based on fermentation of complex carbohydrates and proteins, bacteria aid to metabolize cholesterol and reabsorb bile acids.

Specifically, cholesterol conversion (mostly to coprostanol, insignificantly to coprostanone⁶⁹) in the gut is an important route of cholesterol metabolism and excretion. Cholesterol metabolites are poorly absorbable in the gut; this could be the mechanism to prevent excessive accumulation of cholesterol⁶⁹.

In addition, gut bacteria metabolize side chain of bile acids, in addition to deconjugation, oxidation, and other modifications⁷⁰. Notably, only a few bacterial species in the gut are involved in cholesterol metabolism, whereas many more bacteria contribute to bile acid reabsorption.

Of the aforementioned compounds, circulating cholesterol plays an important role in the genesis of atherosclerotic plaques. Furthermore, cholesterol is internalized by macrophages, driving their transformation into foam cells, with subsequent demise of the latter cells. Thereby, cholesterol is a hazard to the cardiovascular system in general and cardiovascular macrophages in particular.

Other Potential Associations Between Gut Microbiota and Cardiovascular Diseases

The aforementioned pathogenetic factors link abnormal (dysbiotic) gut microbiota and cardiovascular diseases, such as atherosclerosis and

hypertension. Moreover, gut dysbiosis is believed to be associated with other pathologies, such as obesity, diabetes, kidney disease, dysregulated immune system, and chronic systemic inflammation. All of the latter are known risk factors for development of cardiovascular diseases.

For example, pro-inflammatory factors ascending from the gut promote chronic inflammation and obesity⁴¹ (Figure 5). Similarly, abnormal gut microbiota is found in the Type 2 diabetes⁷¹ (Figure 5). Inflammation, obesity and diabetes increase the risk of acquiring cardiovascular diseases (Figure 5).

The current knowledge is mostly limited to animal studies and cross-sectional observations in humans. While highly valuable, these shed little light on potential genetic causes of abnormalities in gut microbiota and susceptibility to cardiovascular diseases⁷².

Another essential question is related to exact relationship between aging, changes in gut microbiota, and development of cardiovascular diseases. As rightfully stated elsewhere⁷², future studies need to demonstrate that this relationship exceeds a mere association and is, indeed, a causal relationship. Changes in gut microbiota were linked to renal abnormalities, and, through them, to cardiovascular status⁷³.

Potential Interventions to Rectify Gut Microbiome

The most obvious potential intervention is altering of one's diet (Table III). Other potential interventions include supplementation with probiotics (that is, bacteria that can beneficially modulate gut microenvironment^{74,75}) or pre-

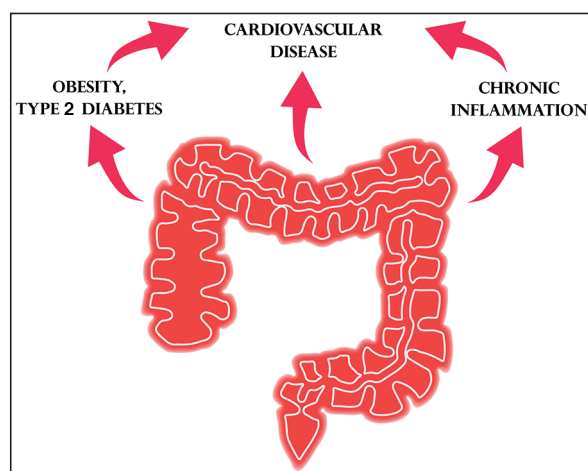


Figure 5. Gut microbiota, and direct and indirect risk factors for cardiovascular diseases.

biotics (Table III). The probiotics are defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host”⁷⁶. The probiotics are exemplified by lactic acid bacteria, specifically those of the following species: *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, and *Streptococcus* species. The prebiotics, as described in the preceding text, are dietary components (for example, specific carbohydrates¹⁶) that promote the growth of specific types of microorganisms in the gut⁷⁷ (Table III).

This shaping of the human gut microbiota with pre- and probiotics can be initiated very early in life⁷⁸ and can continue into advanced age. In addition, beneficial metabolites, such as the short-chain fatty acid, which stem from digestion of prebiotics, can be used in a direct intervention^{60,79}.

A more radical approach to rectification of gut microbiome is the use of bacteriocins (Table III). The latter are substances with antibiotic properties synthesized by bacteria⁸⁰. The use of bacteriocins is favored in the literature as a targeted approach to normalize gut microbiota. Administration of bacteriocins may avoid broad and extensive changes of gut microbiota associated with antibiotics⁸⁰. Furthermore, bacteriocins may help overcome the issue of rising antibiotic resistances of many pathogenic gut-associated microorganisms⁸¹. Indeed bacteriocins, in addition to their direct antibiotic properties, also possess signalling capabilities⁸². This could enhance their microbiota-modulating effects.

The even more radical interventions to normalize gut microbiota are administration of antibiotics and/or faecal transplant (Table III).

Conclusions

Signals ascending from gut microbiome are believed to modulate differentiation and functional activity of macrophages residing in perivascular tissue, atherosclerotic plaques, and perivascular areas of the brain. These macrophages matter for the pathophysiology of cardiovascular diseases. The process of aging is associated with changes in gut microbiome and with increased prevalence of cardiovascular diseases. Macrophages may be key players that transform the signals from the gut microbiome into increased predisposition to cardiovascular diseases. Future interventions may include modulation of gut microbiome to prevent or treat cardiovascular diseases, also by targeting the signals that converge on cardiovascular macrophages.

Table III. Potential interventions to rectify gut microbiome.

Intervention	Example	Mechanism	Specificity of targeting	Potential effects on cardiovascular macrophages
Change of dietary habits	Fibre-rich diet (oat bran or other grain brans, whole grains and brown rice, beans, nuts, fruits and vegetables)	Dietary fibres are digested by gut microbiota, yielding beneficial compounds (eg, short-chain fatty acids)	This intervention targets microbiota in general. No specificity against particular microbial strains	Beneficial modulation, potentially enhancing anti-inflammatory functions of macrophages ^{57-59,83,84}
Probiotics	<i>Bifidobacterium lactis</i> , <i>Lactobacillus acidophilus</i> (microbial components of fermented dairy products)	Normalization of gut microbiota and the overall gastrointestinal health	This intervention targets microbiota in general. No specificity against particular microbial strains	The effects on cardiovascular macrophages are expected to be indirect, through normalization of processes in the gut, or direct (eg, facilitation of cholesterol efflux in macrophages) ^{85,86}
Prebiotics and direct interventions with metabolites of prebiotic digestio (eg, butyrate)	Specific complex carbohydrates, which are digestible only in the gut, giving rise to beneficial substances (eg, short-chain fatty acids). The most studied examples are inulin, fluctooligosaccharides, lactulose, galactooligosaccharides	Favoring the growth of beneficial microorganisms in the gut; potentiation of production of short-chain fatty acids, such as butyrate	This intervention favors particular microbial strains, both serving as a source of food and by modifying the microenvironment in the gut ⁸⁷	Anti-inflammatory effects, attenuation of local production of reactive oxygen species, potential modulation of macrophage differentiation ^{58-62,79,84}
Bacteriocins	Antimicrobial peptides produced in the ribosomes of bacteria as a “weapon” against other bacterial species (eg, nisin from <i>Lactococcus lactis</i> ⁸⁸)	Normalization of gut microbiota by elimination of pathogenic bacteria	This intervention favors particular microbial strains by acting as a targeted antimicrobial agent against pathogenic bacteria	Potential indirect beneficial effects on cardiovascular macrophages by normalization of gut microbiota
Antibiotics	Antimicrobial drugs produced as secondary metabolites by soil bacteria or fungi as a “weapon” against other bacterial species	Broad elimination of classes of pathogenic bacteria	Not specific. Capable of destroying the delicate balance of gut microbiota by eliminating both commensal and pathogenic bacteria	Potential adverse effects because of direct cytotoxicity on cardiovascular macrophages and/or unfavorable manipulation of gut microbiota
Faecal transplant	Transfer of a specimen of healthy gut microbiota into someone’s gut, either via oral capsules or by colonoscopy, usually as means to eliminate resilient pathological bacteria, such as <i>Clostridium difficile</i> ⁸⁹	Normalization of gut microbiota by transplanting donor’s normal microbiota	Not specific. Current medical use is mostly limited to <i>Clostridium difficile</i> infections	Beneficial effects on cardiovascular macrophages are expected because of the overall normalization of gut microbiota

Footnote: *Precursor to trimethylamine N-oxide, TMAO; #Minor amounts.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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