The gut microbiota in cardiovascular disease
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CHAPTER 2

The immunity-diet-microbiota axis in the development of metabolic syndrome

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Abstract

Purpose of the review
Recent evidence demonstrates that the gut-microbiota can be considered as one of the major factors causing metabolic and cardiovascular diseases.

Recent findings
Pattern recognition receptors as well as antimicrobial peptides are a key factor in controlling the intestinal microbiota composition. Deficiencies in these genes lead to changes in the composition of the gut-microbiota, causing leakage of endotoxins into the circulation, and the development of low-grade chronic inflammation and insulin resistance. Dietary composition can also affect the microbiota: a diet rich in saturated fats allows the expansion of pathobionts that damage the intestinal epithelial cell layer and compromise its barrier function. In contrast, a diet high in fiber supports the microbiota to produce short chain fatty acids, thereby promoting energy expenditure and protecting against inflammation and insulin resistance.

Summary
The interactions between the microbiota, innate immunity and diet play an important role in controlling metabolic homeostasis. A properly functioning innate immune system, combined with a low fat and high fiber diet, is important in preventing dysbiosis and reducing susceptibility to developing the metabolic syndrome and its associated cardiovascular diseases.
Introduction

Recent evidence points to an important role for the microbiota in the development of the metabolic syndrome. The link between the microbiota and host metabolism was initially discovered by Jeffrey Gordon’s group, which showed that germfree mice are not susceptible to developing diet-induced obesity[1]. Conventionalization of germfree mice by the microbiota of lean mice led to an increase in adiposity and, strikingly, this effect was significantly stronger if the microbiota were derived from obese mice, demonstrating a causal role of microbiota composition on energy metabolism, and eventually leading to obesity. Microbiota analysis has shown that obese mice have a higher ratio of the firmicutes:bacteroidetes phyla and this composition has a greater capacity to harvest energy from the diet[2]. This means that the composition of the microbiota changes during obesity and that this change also contributes to the further development of obesity.

To study whether the microbiota composition also affects host metabolism in man, Ridaura et al performed an elegant study in which they transplanted the gut microbiota of human twins discordant for obesity into germfree mice. The mice that received microbiota from obese human subjects had a significantly increased body mass and adiposity compared to mice receiving microbiota from lean subjects[3], supporting that the microbiota contribute to development of obesity. Differences in microbiota composition and function have also been linked to the more advanced stages of metabolic syndrome, such as type 2 diabetes (T2D), non-alcoholic fatty liver disease (NAFLD), and cardiovascular diseases (CVD) [3,4**,5,6]. A change in microbiota composition is not merely associated with disease, but also appears to play a causal role in the development of the metabolic syndrome in humans, since transplanting the microbiota of healthy individuals into subjects diagnosed with metabolic syndrome led to an increased insulin sensitivity, thereby improving the metabolic phenotype of these patients[7]. Thus, the microbiota are an important factor in the development of the metabolic syndrome, although we are only just starting to understand how the microbiota influences the development of metabolic diseases. Microbiota composition is controlled by the mucosal immune system and is strongly influenced by dietary consumption. If the microbiota is not well maintained, this can lead to leakage of bacterial cell wall components into the circulation, which can
contribute to low-grade systemic inflammation, and consequently to metabolic syndrome. The microbiota can also influence the development of metabolic syndrome through the production of metabolites, such as short chain fatty acids, which can directly affect the host metabolism. In this review we will discuss the importance of the microbiota in the development of metabolic syndrome and how microbiota composition and its function is controlled by the mucosal immune system and affected by dietary intake.

**Microbial control by innate immunity**
The mucosal immune system is delicately balanced between tolerating commensal bacteria and eliminating pathogens. The first line of defense in the mucosal immune system is the physical barrier, consisting of epithelial cells kept together by tight junctions and the mucus layer lying on top of the epithelial cells. Goblet cells produce the mucus overlying the epithelial cells, physically separating the bacteria from the intestinal epithelial layer. The Paneth cells excrete antimicrobial peptides such as RegIIIy and alpha-defensins into this mucus layer. These peptides are important in preventing bacteria that are present naturally in the gut lumen from penetrating the mucus layer and adhering to the intestinal cell wall (Fig. 1).

**Antimicrobial peptides**
It has recently been shown that REGIIIy-/- mice have increased numbers of mucosa-associated-bacteria, which leads to the development of low-grade intestinal inflammation[8*,9]. RegIIIy is secreted by epithelial and Paneth cells under stimulation of the cytokine IL-22, thus IL-22 plays an important role in protecting the mucosal intestinal barrier (Fig. 1). IL-22R knockout mice show aberrant mucosal immunity and develop metabolic syndrome, characterized by an increase in bodyweight, hyperglycemia, insulin resistance, and decreased glucose tolerance. Strikingly, on administration of IL-22-Fc, which stimulates IL-22R, mice on a high fat diet (HFD) show reduced bodyweight, smaller fat pads, and better insulin sensitivity and glucose tolerance. Thus, mucosal protection by IL-22 plays an important role in protecting the host against metabolic syndrome[10**]. Protection by IL-22 can likely be explained by the reduced infiltration of bacteria in the intestinal epithelial cell layer, thus preventing low-
grade inflammation of the intestine and maintaining intestinal integrity. Maintenance of intestinal integrity is important to prevent translocation of bacteria or endotoxins from the gut lumen into the systemic circulation. Translocation of endotoxins (metabolic endotoxemia) into the systemic circulation leads to weight gain, higher insulin resistance and lower glucose tolerance[11]. Endotoxemia has also long been associated with the development of atherosclerosis in humans and increased production of endotoxins has been associated with symptomatic atherosclerosis in humans[5]. Altogether, leakage of endotoxins from the gut lumen into the systemic circulation contributes to the development of metabolic syndrome and atherosclerosis (Fig. 1).

In conclusion, a reduced control of microbiota localization by antimicrobial peptides could lead to more leakage of endotoxins into the circulation leading to inflammation in the liver, adipose tissue, and arteries.

**Pattern recognition receptors**

In addition to the physical features of the immune system preventing the translocation of bacteria, pattern recognition receptors (PRR) play an important role in protecting the human body from bacterial invasion by recognizing pathogen-associated molecular patterns (PAMPS), such as endotoxins. There are two major forms of PRRs: extracellular PRRs mainly consisting of the Toll-like receptor family (TLR) and intracellular PRRs, such as NOD-like receptors. Both types of PRRs have been shown to be important in controlling the microbiota composition and can thus affect the development of metabolic syndrome. TLRs as well as NOD-like receptors are expressed in the intestinal epithelial cells and are important for their proliferation, IgA production, tight junction formation, and the production of the antimicrobial peptides discussed earlier. This means the expression of PRRs in intestinal epithelial cells can play an important role in preventing a leaky gut[12,13]. PRRs are also abundantly expressed on innate immune cells, such as macrophages and dendritic cells, where they trigger phagocytosis of bacteria and the expression of cytokines and co-stimulatory molecules, which trigger the adaptive immunity[14]. Thus, PRRs in the intestine are important in controlling the gut microbiota and preventing translocation of bacteria into the systemic circulation.
Figure 1. Microbiota control by immunity is essential to prevent dysbiosis and endotoxemia
**Extracellular pattern recognition receptors**

Germfree TLR2 knockout mice have been shown to be resistant to diet-induced insulin resistance, but they show a more severe development of metabolic syndrome upon colonization with microbiota. Their microbiota composition is changed showing a three-fold increase in firmicutes and a decrease in bacteroidetes. This change in composition leads to increased translocation of PAMPs, such as lipopolysaccharide into the circulation, causing subclinical inflammation and eventually insulin resistance, glucose intolerance, and obesity (Fig. 1). Strikingly, the metabolic phenotype is transferable to wild-type mice, by microbiota transfer, demonstrating that a lack of microbiota control is responsible for the observed phenotype[15]. Lack of microbial control in TLR5 knockout mice also leads to the metabolic syndrome developing under the influence of a HFD[16]. There are thus several lines of evidence showing that TLRs play an important role in controlling the microbiota composition and preventing metabolic diseases.

1a) The epithelial lining of the intestine is mainly formed by enterocytes, which are linked together by tight junctions. Goblet cells produce the mucus layer physically separating the microbiota, whereas Paneth cells excrete antimicrobial peptides such as RegIIIγ into this layer upon stimulation of the IL22 receptor by IL-22. This prevents bacteria from the microbiota to infiltrate the intestinal epithelial cell layer. Intracellular and extracellular PRRs recognize endotoxins, binding of endotoxins to PRRs on enterocytes stimulates production of antimicrobial peptides and formation of tight junctions. 1b) The intracellular PRR NLRP3 plays an important role in shaping the microbiota composition. Disruption of NLRP3 function leads to dysbiosis, characterized by increased abundance of prevotellaceae and TM7, whereas abundance of Lactobacillus is decreased. 1c) Also extracellular PRRs are important in controlling microbiota composition. Disruption of TLR2 leads to dysbiosis, characterized by an increased firmicutes:bacteroidetes ratio. 1d) Disruption of stimulation of the IL22 receptor by Il-22 leads to decreased production of RegIIIγ. Consequently bacteria from the microbiota can infiltrate the intestinal epithelial cell layer. Disturbance of NLRP3, TLR2 or IL22R function, leads to increased permeability due to disrupted tight junctions. Consequently endotoxins can leak through the intestinal epithelial cell layer into the systemic circulation, causing endotoxemia and contributing to low-grade systemic inflammation, which leads to development of the metabolic syndrome.
**NOD-like receptors**

Inflammasomes belong to the NOD-like receptor (NLR) family and are important intracellular PRRs that play an important role in mucosal defense. Upon recognition of danger signals by an NLR (e.g. NLRP3), a multiprotein complex is formed with ASC and caspase 1, and together these are named inflammasomes. On formation of the inflammasome, caspase 1 is activated and pro-IL-1B and pro-IL-18 are post-translationally processed into their active isoforms IL-1B and IL-18. Disruption of the NLRP3 inflammasome function has been shown to influence the development of NAFLD.

The NLRP3 inflammasome influences the microbiota composition as well as the localization of the microbiota. NLRP3-/- mice have increased numbers of prevotellaceae and the bacterial phylum TM7, while having a reduced abundance of the lactobacillus genus (Fig. 1)[4**]. This change in microbiota composition leads to an increased severity of NAFLD under the influence of a methionine-choline-deficient diet. Increased severity of NAFLD is triggered by translocation of endotoxins into the systemic circulation, which activate TLR2 and TLR9 in the liver and consequently upregulate TNF-α and increase inflammation in the liver. Increased development of NAFLD depends on the inability of NLRP3-/- mice to process pro-IL-18 into IL-18, since IL-18-/- mice also showed a more severe development of NAFLD, which could be transferred to wild-type mice by microbiota transplantation[4**]. It is possible that the more severe development of NAFLD due to the translocation of endotoxins into the systemic circulation could be explained by the protective function that IL-18 exhibits against mucosal challenges or disruption of the intestinal mucosa[17].

NLRP3 does not merely play a role in controlling the microbiota composition but its expression in the intestinal epithelial cells is also important in preventing infiltration of the mucosal barrier by bacteria from the microbiota[13].

In conclusion, intracellular PRRs could have an important function in the protection against NAFLD, as highlighted by the function of NLRP3 in controlling the microbiota composition and localization in the intestine. Consequently, NLRP3 acts in preventing translocation of bacteria and endotoxins that can lead to low-grade systemic inflammation, which contributes to NAFLD development. Whether other intracellular PRRs also
have a protective role against NAFLD and whether they are also important for protection against T2D and CVD still needs to be established.

**Diet-microbiota interactions in the development of metabolic syndrome**

In addition to mucosal immunity, the diet strongly influences microbiota composition and function[18,19*]. Two general changes can be observed on consumption of a high-fat, low-fiber diet. First, pathobionts can expand during consumption of a HFD, and second, the abundance of protective bacteria, such as producers of short chain fatty acids, declines[19*,20,21**] (discussed later).

**Pathobiont expansion under influence of dietary components**

Decreased protection against pathobionts during consumption of a HFD is exemplified by the increased infiltration of adherent-invasive Escherichia Coli into the intestinal epithelial cell layer. This infiltration leads to less mucus thickness, and more intestinal inflammation and permeability (Fig. 2)[22]. Furthermore, expansion of pathobionts has been shown in humans with a diet rich in animal fats leading to expansion of the sulfate-reducing bacterium Bilophila Wadsworthia (Fig. 2)[19*,21**]. Increased abundance of Bilophila Wadsworthia in the microbiota has been associated with overall adiposity, dyslipidemia[6], and T2D and it triggers intestinal inflammation[21**,23]. This inflammation could possibly be explained by the production of H2S by Bilophila Wadsworthia, which is toxic to host cells[24]. In addition, H2S deprives the enterocytes of energy by inhibiting oxidation of the most abundant energy source, butyrate[25]. Hence, increased infiltration of the intestinal epithelial layer, or production of toxic metabolites by pathobionts, can damage the intestinal epithelial layer and provide yet another cause of translocation of endotoxins or bacteria from the gut lumen into the systemic circulation, thereby contributing to the metabolic syndrome.

**Modulation of dietary-derived choline by the microbiota promotes CVD**

Modulation of dietary-derived choline, phosphatidylcholine or L-carnitine by the microbiota directly contributes to development of CVD. The
microbiota converts these dietary components into tri-methyl-amine (TMA) by the CutC gene cluster present in the microbiota[26,27]. TMA is taken up by the host and metabolized into tri-methylamine-N-oxide (TMAO) by flavin mono-oxygenase 3 in the liver. Increased levels of TMAO are associated with major cardiovascular events in humans and a causal role was demonstrated by promoting atherosclerosis in mice upon ingestion of TMAO[26-29**]. Altogether, conversion of dietary components by the gut microbiota leads to production of TMAO, which then promotes CVD.

**Function of short chain fatty acids on host metabolism**

The beneficial effects of “healthy” fiber-rich diets, which influence microbiota composition, are now better understood[30,31]. The microbiota of children consuming a high fiber diet have a lower firmicutes:bacteroidetes ratio. Furthermore the microbiota has an increased capacity to degrade dietary fibers, leading to the production of short chain fatty acids (SCFA), such as acetate, propionate and butyrate[30]. Human studies show a protective role for SCFA against metabolic syndrome, T2D and atherosclerosis[5,6,7].

The capacity of the microbiota to produce butyrate is negatively correlated with C-reactive protein levels in patients with atherosclerosis[5]. In addition, a decrease in butyrate production was found in T2D patients[6]. Causality for butyrate having a protective role against the development of metabolic diseases was demonstrated in a mouse study that showed that administering butyrate to mice on a HFD prevented the development of obesity and insulin resistance[32].

The mode of action for the protective role of SCFA against metabolic syndrome is mainly through binding to GPR41 and GPR43. These G-coupled receptors are widely expressed, including in tissues with an immunological function such as the spleen, lymph nodes, and bone marrow, as well as in metabolic tissues such as the large intestine, adipose tissue, and pancreas[33-36]. Binding of propionate to GPR41 in sympathetic neurons leads to an increased heart rate and oxygen consumption, causing higher energy expenditure (Fig. 3)[37]. Energy uptake is also modulated by SCFA. The SCFA propionate and butyrate stimulate intestinal gluconeogenesis and has beneficial metabolic effects, including the prevention of obesity and improved glucose and insulin tolerance. Butyrate directly stimulates intestinal gluconeogenesis, whereas the effect of propionate
Figure 2. High fat diet induces pathobiont expansion
The intestinal epithelial layer protects against invasion of bacteria or endotoxins into the systemic circulation during consumption of a chow diet (left hand side of the figure). Consumption of a HFD leads to expansion of the pathobionts AIEC and Bilophila Wadsworthia. AIEC infiltrate the intestinal epithelial layer, causing decreased mucus thickness, inflammation and increased permeability. Expansion of Bilophila Wadsworthia leads to increased production of H2S. H2S is toxic to host cells and can possibly cause intestinal inflammation (dotted arrow). H2S can disturb the intestinal epithelial cell layer also by inhibiting the oxidation of butyrate by enterocytes, leading to decreased energy availability (right hand side of the figure).

is dependent on gut-brain neural signaling via GPR41[38*]. Furthermore, SCFA stimulate adipocytes to produce leptin, which is known to improve insulin sensitivity as well as to induce satiety, thereby controlling energy intake as well as uptake[39,40]. Moreover, SCFA also modulate glucose metabolism by stimulating L-cells in the intestine via GPR43, leading to the production of glucagon-like peptide 1 (GLP-1) and thereby improving glucose tolerance (Fig. 3)[41]. The importance of GPR43 in the signaling of SCFA was elegantly demonstrated by Kimura et al, who showed that GPR43/- mice developed increased obesity, adiposity, white adipose
tissue inflammation, and decreased glucose tolerance[42**]. Whereas overexpression of GPR43 restricted to the adipose tissue suppresses insulin signaling in adipocytes, thereby preventing fat accumulation and metabolic dysfunction[42**]. In conclusion, SCFA are protective against metabolic syndrome by their modulation of the host metabolism via GPR41 and GPR43.

Bile acid modulation
A well-established role for the gut microbiota is the metabolism of bile acids [see review by Jones et al][43]. Primary bile salts are deconjugated by bile salt hydrolases, which are present in multiple gram-positive bacteria[44]. Recently the physiological role of bile salt hydrolase (BSH) by bacteria was demonstrated: the expression of bacterial BSH was found to reduce weight gain, and lower plasma cholesterol and hepatic triglycerides levels[45]. In addition, the microbiota affect the composition of the bile acid pool by 7-α/7-β dehydroxylation, desulfation and dehydrogenation, leading to the formation of secondary bile acids, such as deoxycholic acid, lithocholic acid, and tauro-beta-muricholic acid[43]. Bile acids have been shown to be important regulators of metabolic signaling via the Farnesoid X receptor (FXR) and the G-coupled protein receptor, TGR5[46]. Stimulation of FXR improves the glucose and lipid metabolism, leading to increased insulin sensitivity and decreased steatosis in the liver. Activation of TGR5 in the intestine by bile acids leads to secretion of GLP-1, thereby improving glucose tolerance and insulin sensitivity. FXR is activated by bile acids with the following potency: chenodeoxycholic acid > deoxycholic acid > litohocholic acid >> cholic acid, whereas TGR5 is activated as follows: lithocholic acid > deoxycholic acid > chenodeoxycholic acid > cholic acid[46]. Next to the agonistic effect of bile acids on FXR, Tauro β-muricholate (TβMCA) has recently been reported to be an antagonist of FXR. In mice the microbiota reduces TMCA levels, leading to increased activation of FXR in the intestine and excretion of FGF15, which is transported to the liver and inhibits bile acids synthesis[47]. Although the potency of multiple bile acids in stimulating FXR and TGR5 are known, it is not yet fully understood how changes in the composition of the bile acid pool affect the metabolism. It should be noted that bile acid metabolism differs considerably between mice and humans. The human bile acid pool is much more hydrophobic. Hence,
Figure 3. SCFA are protective against development of metabolic syndrome

Fibers are converted by the microbiota to SCFA. Production of SCFA stimulates L-cells in the intestine via GPR43 to produce GLP-1, this leads to increased glucose tolerance. In addition, SCFA can directly stimulate intestinal gluconeogenesis (IGN), either by direct stimulation of IGN via an unknown mechanism or by stimulation of IGN dependent on the gut-brain axis. Increased IGN leads to decreased obesity, increased glucose tolerance and insulin sensitivity. Next to protective effects in the intestine, SCFA are also taken up into the circulation where stimulation of GPR41 or GPR43 in adipose tissue leads to increased production of leptin and thereby increased insulin sensitivity. Furthermore SCFA can also stimulate sympathetic neurons leading to an increased heart rate and consequently increased energy expenditure.

data for mice cannot be translated easily to the human situation. Yet, both in humans and mice the microbiota are important for regulating the bile acid composition, and can thereby regulate the metabolism via FXR and TGR5. Which members of the bacterial community are responsible for the
many different modifications of bile acids, as well as the effect of the bile acid pool composition on metabolism, is not yet well understood and this would be an interesting target for future research.

**Conclusion**

There is no doubt that the intestinal microbiota plays an important role in host metabolism and that dysbiosis is a strong risk factor in the development of metabolic syndrome and CVD. We are just starting to understand how the host’s immune system and dietary intake can influence the microbiota composition and function. Technological advances include lower sequencing costs, which enables the generation of meta-genomic data to identify individual species and specific functions, such as the presence of the CutC gene cluster. The strain-specific information is crucial to gaining a better understanding of the complex interactions between the different members in the microbiota and their cross-talk with the host in relation to metabolic dysfunction. This could lead to the identification of new biomarkers for metabolic and other diseases. There is furthermore an urgent need for meta-genomic data from prospective cohort studies that include multiple layers of information, such as dietary intake and metabolic data (stool, plasma). The causal roles of newly identified pathobionts or the functions of specific members of the microbiota found in mice or human studies need to be validated in germfree and gnotobiotic mouse models, as well as in human intervention studies with individual bacterial strains. Ultimately, better insight into the immunity-diet-microbiota axis is expected to reveal new targets for intervention and an enormous potential for the prevention of cardiovascular disease.

**Key points**

1) The mucosal immune system is essential for microbiota control and prevention of endotoxemia

2) Consumption of high fat diets leads to expansion of pathobionts damaging the intestinal epithelial layer

3) Production of SCFA by the microbiota is protective against development of the metabolic syndrome
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Conflicts of interest
None
References

Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
** of outstanding interest


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This study elegantly shows that a diet rich in animal fat triggers taurine conjugation of bile acids, triggering the expansion of the pathobiont Bilophila Wadsworthia, and consequently promoting intestinal inflammation.


This study elegantly shows that conversion of phosphatidylcholine to trimethylamine by the microbiota leads to increased TMAO production in humans. They correlate TMAO production with major cardiovascular events in a large human cohort study, thereby implying an important role for the microbiota in the development of cardiovascular disease in humans.


This study shows the importance for signaling of short chain fatty acids via GPR43 in the protection against the metabolic syndrome. GPR43⁻/⁻ mice develop obesity and decreased glucose tolerance, whereas overexpression of GPR43 in adipocytes protects against development of the metabolic syndrome by preventing insulin-mediated fat accumulation in the adipose tissue.


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