Novel opportunities for next-generation probiotics targeting metabolic syndrome
Patrice D Cani and Matthias Van Hul

Various studies have described the beneficial effects of specific bacteria on the characteristics of metabolic syndrome. Intestinal microbiota might therefore represent a modifiable trait for translational intervention to improve the metabolic profiles of obese and type 2 diabetic patients. However, identifying potential probiotic strains that can effectively colonize the gastrointestinal tract and significantly affect host metabolism has been challenging. This review aims to summarize the notable advances and contributions in the field that may prove useful for identifying next-generation probiotics that target metabolic syndrome and its related disorders.

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Introduction
The prevalence of obesity and type 2 diabetes is increasing worldwide, resulting in a plethora of adverse health consequences. In the 1920s, Kylin suggested the concept of an overarching metabolic syndrome by describing for the first time a constellation of metabolic disturbances, including hyperglycemia, hypertension and gout, as risk factors of cardiovascular disease [1]. Since then, different names and definitions have been proposed for this high-risk combination, such as ‘deadly quartet’, ‘insulin resistance syndrome’, and ‘syndrome X’ [2–4]. In 2010, the International Diabetes Federation (IDF), in collaboration with the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI), the World Heart Federation, the International Atherosclerosis Society (IAS), and the International Association for the Study of Obesity (IASO) [5], created a consensus that defined a person as having metabolic syndrome when he/she develops central obesity plus any two of the following factors: elevated triglycerides, reduced HDL cholesterol, elevated blood pressure or blood glucose abnormalities (elevated fasting plasma glucose, previously diagnosed type 2 diabetes, or glucose intolerance). The IDF consensus also acknowledged numerous other parameters that appear to be related to metabolic syndrome and should be included in research studies as additional criteria for predicting cardiovascular disease and/or diabetes. Along with these parameters, which include abnormal fat distribution, elevated plasma proinflammatory markers, prothrombic state, and vascular dysfunction, it has now become clear from both clinical and epidemiological evidence that low-grade inflammation contributes causally to the development of metabolic disorders associated with obesity [6]. However, the origins of this chronic low-grade inflammation remain controversial.

Although lifestyle interventions remain the primary therapy for obesity and the related metabolic syndrome, novel therapies targeting one or more of the underlying etiological factors are desirable. The mechanisms by which these metabolic abnormalities develop have been the subject of intense research, and novel insights into the etiology and pathogenesis of metabolic syndrome have been gained.

Increasing evidence suggests that the gut microbiota is a key component. However, the mechanisms linking gut microbiota to metabolic disorders, and therefore to the onset of metabolic inflammation and obesity, remain elusive. In 2007, we proposed that the gut microbiota plays a key role in the onset of low-grade inflammation associated with obesity and type 2 diabetes [7]. We discovered that in these pathological situations, the gut microbiota sends specific proinflammatory signals to the host in the form of lipopolysaccharides (LPS) originating from Gram-negative bacteria, a phenomenon that we termed ‘metabolic endotoxemia’ [7]. For the first time, gut microbiota, metabolic endotoxemia, insulin resistance and the innate immune system were causally linked to the etiology of obesity and its associated disorders. Later, in 2012, a study by De Vrieze et al. demonstrated the possibility to improve insulin sensitivity in patients with metabolic syndrome by small intestine infusion of microbiota from lean donors [8].

Harnessing the gut microbiota to treat metabolic syndrome
The gut microbiota is now considered a fully fledged organ that is involved in the regulation of numerous physiological pathways and impacts different host
functions [9]. Intestinal microbes have developed a mutualistic relationship with their host and can influence physiological systems by modulating gut motility, intestinal barrier homeostasis, nutrient absorption and fat distribution [10,11,12,13]. Interestingly, the gut microbiota influences the regulation of energy metabolism and fat storage; the gut microbiota is believed to be a driving force in the pathogenesis of metabolic disorders associated with obesity. Indeed, numerous studies have observed differences in the gut microbiota composition between healthy subjects and obese, overweight and/or type 2 diabetic subjects [14–18]. The exact composition of the gut microbiota that facilitates these disorders remains debatable. In the present review, we focus on the role of specific microbes and their potential utility in improving metabolic disorders associated with obesity.

Recent advances regarding Lactobacillus and Bifidobacterium as probiotics that target metabolic syndrome

Numerous reports have demonstrated that manipulating the gut microbiota with prebiotics or probiotics affects host metabolism [19–22]. Notably, the term probiotic is often misused, which has led to the marketing of products that exploit this term without meeting the required criteria. In 2014, the International Scientific Association for Probiotics and Prebiotics published a consensus statement clarifying the scope of and appropriate use for the term ‘probiotic’ (for a review, see [23]).

In particular, various strains of Lactobacillus and Bifidobacterium have beneficial effects, most likely by affecting glucose homeostasis and reducing inflammation and hepatic steatosis. Some of these strains also affect body weight and fat mass development, whereas others do not [19–21]. A comprehensive search of the literature published in the last two years (2013–July 2014) using the key words ‘probiotic(s) and obesity’ revealed that more than 20 publications have reported the impact of specific Lactobacillus or Bifidobacterium strains on obesity and associated disorders in rodents. At least 15 different strains of Lactobacillus and three strains of Bifidobacterium have been studied using different protocols and models [24–46]. Different strains are not equally potent in terms of the impact on body weight, fat mass, glucose metabolism, inflammatory markers, plasma and hepatic lipids or plasma cholesterol levels (Table 1). This is most likely due to different putative mechanisms of action (Figure 1), thereby emphasizing the need to consider the effects as strain-specific. Remarkably, 12 strains decreased hepatic and/or adipose tissue inflammation when given as a single treatment (i.e., not mixed with other bacteria) (Table 1). Interestingly, 11 single strains reduced the hepatic triglyceride content (Table 1), and a decrease in body weight and/or fat mass was observed coincident with the treatment of eight of these strains. Of the 18 single strains studied, only 10 decreased the body weight and/or fat mass. Therefore, although several outcomes may be observed in a single strain, no individual strains are expected to have all of the effects listed in Table 1.

Among the probiotics, the yeast Saccharomyces cerevisiae var. boulardii has been widely studied in the context of intestinal inflammation and diarrhea in rodents. Its beneficial effects have been predominantly associated with specific antitoxin effects, antimicrobial activities, and a trophic effect on the gut mucosa [47]. We recently demonstrated that S. boulardii treatment may be effective in the context of obesity and type 2 diabetes. We found that S. boulardii altered the gut microbiota and reduced the fat mass, hepatic steatosis, systemic inflammation, and hepatic inflammation in genetic obese and type 2 diabetic mice [48*]. Whether these impacts of S. boulardii are also possible in obese and type 2 diabetic humans warrants further investigation.

Bile salt hydrolase (BSH) activity

Numerous studies have shown that bile acids act as signaling molecules in the host and thereby regulate energy, glucose and lipid metabolism [49,50]. In addition, several recent studies in mice have demonstrated that the gut microbiota regulates the expression of fibroblast growth factor 15 (FGF15) in the ileum and cholesterol 7α-hydroxylase (CYP7A1) in the liver via Farnesoid X Receptor (FXR)-dependent mechanisms [51,*52,*53*] (Figure 1). In an elegant study, Joyce et al. showed that targeting a single, widely distributed function but not ubiquitous of the gut microbiota, such as BSH activity, impacts body weight and fat mass development [54*] (Figure 1). This study demonstrated that the colonization of the gastrointestinal tract by a transformed bacterium (i.e., Escherichia coli) that increases BSH activity resulted in decreased body weight gain, plasma cholesterol levels and liver triglycerides. Because numerous well-known probiotics exhibit BSH activity [55], this may partially account for their metabolic effects. Although the influence of gut microbiota on energy metabolism is certainly multifactorial, this type of study emphasizes the importance of the rational selection of probiotics based on key features, such as their ability to hydrolyze bile salts.

Next generation probiotics: Akkermansia muciniphila as a putative candidate?

Currently, only one study has provided evidence for a causal link between a single bacterial genus and the onset of obesity, type 2 diabetes and metabolic dysfunctions. Fei and Zhao reported that the Enterobacter cloacae B29 strain isolated from the gut microbiota of an obese human induced obesity in germ-free mice [56*]. Conversely, we and others have shown that A. muciniphila, a mucin-degrading bacterium that resides in the mucus layer, is present at lower levels in obese and type 2 diabetic subjects [14,16,57–59]. We also demonstrated that prebiotic treatment (i.e., oligofructose) increased the
Table 1

Metabolic effects of different probiotic strains in rodents.

<table>
<thead>
<tr>
<th>Strains</th>
<th>BW</th>
<th>FM</th>
<th>Glucose</th>
<th>Inflammation</th>
<th>TG</th>
<th>Chol.</th>
<th>Fatty liver</th>
<th>Model</th>
<th>Animal group size</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactobacillus plantarum OLL2712</td>
<td>ND</td>
<td>ND</td>
<td>(=)</td>
<td>(=)</td>
<td>ND</td>
<td>ND</td>
<td>(=)</td>
<td>DIO mice, 12 weeks</td>
<td>9-10</td>
<td>[32]</td>
</tr>
<tr>
<td>Lactobacillus plantarum LG42</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>DIO mice, 12 weeks</td>
<td>10</td>
<td>[40]</td>
</tr>
<tr>
<td>Lactobacillus plantarum TN8</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>Rats</td>
<td>5-6</td>
<td>[24]</td>
</tr>
<tr>
<td>Lactobacillus plantarum KY1032 + Lactobacillus curvatus HY7601</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow) (fat: TNF(\alpha), IL1(\beta), IL6, MCP-1)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>DIO mice, 8 weeks</td>
<td>9</td>
<td>[30]</td>
</tr>
<tr>
<td>Lactobacillus plantarum KY1032</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow) (liver: TNF(\alpha), IL1(\beta))</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>DIO mice, high-cholesterol diet, 9 weeks</td>
<td>10</td>
<td>[34]</td>
</tr>
<tr>
<td>Lactobacillus curvatus HY7601</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>DIO mice, high-cholesterol diet, 9 weeks</td>
<td>10</td>
<td>[34]</td>
</tr>
<tr>
<td>Lactobacillus plantarum KY1032 + Lactobacillus curvatus HY7601</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow) (liver: TNF(\alpha))</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>DIO mice, high-cholesterol diet, 9 weeks</td>
<td>10</td>
<td>[34]</td>
</tr>
<tr>
<td>Lactobacillus plantarum No. 14</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow) (fat: TNF(\alpha), IL6, MCP-1)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>KK/T mice, 10 weeks</td>
<td>5-6</td>
<td>[29]</td>
</tr>
<tr>
<td>Lactobacillus plantarum WCSF1</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow) (liver: TNF(\alpha), IL1(\beta))</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>DIO mice, 12 weeks</td>
<td>8</td>
<td>[46]</td>
</tr>
<tr>
<td>Lactobacillus rhamnosus GG</td>
<td>(\downarrow) (8%)</td>
<td>(\downarrow) (mesenteric only)</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>DIO mice, 13 weeks</td>
<td>7-8</td>
<td>[53]</td>
</tr>
<tr>
<td>Lactobacillus rhamnosus GG</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow) (liver: TNF(\alpha), IL1(\beta), IL8R)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>Mice, high-fructose diet, 8 weeks</td>
<td>6</td>
<td>[43]</td>
</tr>
<tr>
<td>Lactobacillus paracasei CNCM I-4270</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow) (liver TNF(\alpha) and adipose tissue macrophages)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>DIO mice, 12 weeks</td>
<td>8</td>
<td>[46]</td>
</tr>
<tr>
<td>Lactobacillus. rhamnosus CNCM I-3690</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow) (liver TNF(\alpha) and adipose tissue macrophages)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>DIO mice, 12 weeks</td>
<td>8</td>
<td>[46]</td>
</tr>
<tr>
<td>Bifidobacterium animalis subsp. lactis CNCM I-2494</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>DIO mice, 12 weeks</td>
<td>8</td>
<td>[46]</td>
</tr>
<tr>
<td>Lactobacillus paracasei CNCM I-4034</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>Zuckert fa/fa rats, 4 weeks</td>
<td>8</td>
<td>[41]</td>
</tr>
<tr>
<td>Bifidobacteria breve CNCM I-4035</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>Zuckert fa/fa rats, 4 weeks</td>
<td>8</td>
<td>[41]</td>
</tr>
<tr>
<td>Lactobacillus rhamnosus CNCM I-4036</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>Zuckert fa/fa rats, 4 weeks</td>
<td>8</td>
<td>[41]</td>
</tr>
<tr>
<td>A mix of the above three strains</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>Zuckert fa/fa rats, 4 weeks</td>
<td>8</td>
<td>[41]</td>
</tr>
<tr>
<td>Lactobacillus gasseri ATCC 6475</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>Mice, 10% fat diet, 24 weeks</td>
<td>10</td>
<td>[37]</td>
</tr>
<tr>
<td>Lactobacillus gasseri BNR17</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>Zuckert fa/fa rats, 4 weeks</td>
<td>8</td>
<td>[41]</td>
</tr>
<tr>
<td>Lactobacillus coryniformis CECT7511</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>ND</td>
<td>ND</td>
<td>(\downarrow)</td>
<td>High-sucrose DIO mice, 10 weeks</td>
<td>8</td>
<td>[27]</td>
</tr>
</tbody>
</table>

BW, body weight; FM, fat mass; TG, blood triglycerides; Chol., blood cholesterol; \(=\), no change compared with the appropriate control (i.e., pathological situation); \(\downarrow\), significantly decreased; \(\uparrow\), significantly increased; ND, not determined; DIO, diet-induced obesity; inflammation, the targeted organ is mentioned in parentheses.
abundance of *A. muciniphila* in obese mice [60] and that this resulted in an improved metabolic profile. Strikingly, we also found that the abundance of *A. muciniphila* was associated with L cell number and secretory capacity [60].

On the basis of these observations, we investigated the impact of administering *A. muciniphila* daily for 4 weeks to diet-induced obese and diabetic mice and discovered that *A. muciniphila* treatment reversed high-fat diet-induced obesity, insulin resistance and type 2 diabetes [58*]. The abundance of this bacterium negatively correlated with the levels of gut permeability markers and inflammatory markers. More specifically, *A. muciniphila* treatment decreased metabolic endotoxemia and adipose tissue inflammation by improving intestinal mucosal barrier function at different levels (Figure 1) [58*]. First, *A. muciniphila* increased and subsequently restored the mucus layer thickness to a level similar to that found in healthy lean mice (Figure 1). Second, *A. muciniphila* restored the abundance of specific antimicrobial peptides, such as regenerating islet-derived 3-gamma (RegIIIγ), that are markedly down-regulated during obesity and diabetes. This finding suggests that *A. muciniphila* interacts with the host mucosal defense via different specific targets. In addition to the cross-talk between this bacterium and the innate immune system, we demonstrated that *A. muciniphila* significantly increased the intestinal levels of 2-oleoylglycerol (2-OG), a bioactive lipid that is present in the endocannabinoid system [58*]. Interestingly, 2-OG stimulates the secretion of glucagon-like
peptides through the activation of GPR119, which is localized on intestinal L cells [61], suggesting that A. muciniphila interacts with the host endocrine system involved in both gut barrier function and energy homeostasis. Indeed, in addition to affecting gut barrier function, A. muciniphila reduces fat mass development without affecting total energy intake. This is associated with an increase in adipose tissue fatty acid oxidation and a normalization of adipogenic processes [58]. However, a mechanistic understanding of the relationship between these observations and the presence of A. muciniphila in the intestine remains to be clarified. A potential explanation involves the increase in the production of short chain fatty acids (SCFAs), such as propionate, which may act on G protein coupled receptors (GPR43) and thereby control energy homeostasis and fat accumulation (Figure 1) [62*] (for a review, please see [63*]).

Recently, Shin et al. confirmed the protective effect of A. muciniphila on body weight gain, fat mass development and glucose homeostasis and extended our findings on the mucus layer thickness by showing that A. muciniphila increased the number of Goblet cells and Foxp3 regulatory T cells (Tregs) in visceral adipose tissue [64*].

Taken together, the data indicate that A. muciniphila improves numerous biological processes. However, it is important to note that the key mechanisms involved in these effects remain to be elucidated.

Conclusion
Recently, it has become clear that specific bacteria positively influence the characteristic parameters of metabolic syndrome. However, the microbiome is a complex ecosystem, and it is challenging to unravel the underlying mechanisms governing the cross-talk between individual bacterial strains and a host. As discussed in the present review, the Lactobacillus and Bifidobacterium strains cannot individually account for all of the effects attributed to different probiotics (Table 1). Interestingly, certain probiotics share common beneficial properties, such as improved gut barrier function and subsequent reduced hepatic inflammation. It is worth noting that this effect may be completely distinct from those that decrease body weight and fat mass or improve glucose tolerance. The possibility that convergent mechanisms of action (e.g., BSH activity) may be responsible merits further investigation. It should also be kept in mind that different bacteria may affect different sections of the intestines. Indeed, the small and large intestines are distinctive ecosystems with specific characteristics. For example, in humans it may be expected that probiotic action of Lactobacillus strains is primarily targeting the small intestine, while that of Bifidobacterium strains is directed more towards the colon, however we may not exclude that both intestinal site respond differently to the type of bacteria and specific metabolite produced. It is therefore possible that their underlying modes of actions are also different.

We recently reported that A. muciniphila may be a novel candidate that acts on several targets and thereby improves key components of metabolic syndrome, such as reducing fat mass, plasma glucose, gut permeability and metabolic inflammation. Whether this microbe will ultimately be suitable for human consumption in food, dietary supplements or drugs will depend on its stability and efficacy in humans.

In conclusion, the concept of manipulating the gut microbiota by using specific microbes to improve host metabolism has gained considerable interest in recent years. Currently, several potential bacterial candidates have been identified, and novel mechanisms of action governing their beneficial effects have been elucidated. This knowledge will prove useful in the search for next generation probiotics that target metabolic syndrome and its related disorders.

Acknowledgements
PDC is a research associate at the FRS-FNRS (Fonds de la Recherche Scientifique), Belgium. PDC is a recipient of an ERC starting Grant 2013 (European Research Council, starting Grant 336452-ENIGMO), PDR subsidies (Projet de recherches ‘T0.138.14; Fonds de la recherche scientifique, Belgium) and ARC (Concerted Research Activities-French Community of Belgium convention: 12/17-047).

References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest


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   ● Saccharomyces boulardii administration changes gut microbiota and reduces hepatic steatosis, low-grade inflammation, and fat mass in obese and type 2 diabetic db/db mice. MBio 2014, 6:e01011-e01014.
   This is the first study showing a comprehensive analysis of the gut microbiota following Saccharomyces boulardii treatment, and its impact on hepatic steatosis and inflammation in obese and type 2 diabetic mice.


   ● Mitchell JB, Patterson AD, Gonzalez FJ: Microbiome remodelling leads to inhibition of intestinal farnesoid X receptor signalling and decreased obesity. Nat Commun 2013, 4:2384. A elegant study showing how temporal alters the gut microbiome and changes host metabolism via altering tauro-β-muricholic acid and FXR activity.

   A very interesting study showing how gut microbiota can regulate metabolism via intestinal tauro-β-muricholic acid.

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   A very interesting series of experiments showing the mechanisms by which a mix of probiotics (i.e., VSL3#) modulates hepatic bile acid synthesis and metabolism including a convincing description of the FXR-FGF15 axis in this crosstalk.

54. Joyce SA, MacSharry J, Casey PG, Kinsella M, Murphy EF.
   A very interesting study showing that bacterial bile acids modification via BSH activity contribute to regulate host metabolism.


   A very interesting study showing the causal relationship between one specific pathogen and the onset of obesity in a murine model.


   This is the first study showing the role of Akkermansia muciniphila on host metabolism, mucus layer thickness, glucose and lipid metabolism as well as gut barrier function.


   An elegant study investigating the role of GPR43 and mechanisms linking the gut microbiota with fat accumulation.

   This review outlines different mechanisms involving SCFA and GPR43 on energy metabolism.

   The study highlight that metformin treatment increases the abundance of Akkermansia muciniphila. The study also confirms that Akkermansia muciniphila contributes to improve energy and glucose metabolism.