ADDENDUM

Triggering Akkermansia with dietary polyphenols: A new weapon to combat the metabolic syndrome?

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ABSTRACT
The gut and its bacterial colonizers are now well characterized as key players in whole-body metabolism, opening new avenues of research and generating great expectation for new treatments against obesity and its cardiometabolic complications. As diet is the main environmental factor affecting the gut microbiota, it has been suggested that fruits and vegetables, whose consumption is strongly associated with a healthy lifestyle, may carry phytochemicals that could help maintain intestinal homeostasis and metabolic health. We recently demonstrated that oral administration of a cranberry extract rich in polyphenols prevented diet-induced obesity and several detrimental features of the metabolic syndrome in association with a remarkable increase in the abundance of the mucin-degrading bacterium Akkermansia in the gut microbiota of mice. This addendum provides an extended discussion in light of recent discoveries suggesting a mechanistic link between polyphenols and Akkermansia, also contemplating how this unique microorganism may be exploited to fight the metabolic syndrome.

KEYWORDS
Akkermansia; cranberry; polyphenols

Introduction

One third of the top 20 most prescribed drugs are plant-derived.1 To name a few examples, Metformin (the most widely prescribed antidiabetic drug) and Aspirin (the prototypical nonsteroidal anti-inflammatory agent), are derived from French lilac (Galega officinalis) and the willow tree (Silax spp) bark, respectively. It has been known for centuries that plants make substances that aid human health, but the obvious question is why plants would produce compounds that provide health benefits to other organisms, especially to those so far apart on the evolutionary scale? Howitz & Sinclair addressed this matter from an evolutionary perspective and formulated the xenohormesis hypothesis, whereby species co-evolved in ways that environmentally stressed plants produce bioactive compounds (eg, polyphenols) capable of providing stress resistance and survival benefits to animals that consume them.1 Thus, animals can take advantage of consuming plant-based foods by perceiving chemical cues in order to anticipate a deteriorating environment while stimulating their own adaptive survival responses.

As our understanding of how the gut and its colonizing microbes modulate whole-body metabolism builds up, new perspectives for treating metabolic diseases arise and novel targets for known drugs are unveiled. For example, the antidiabetic effects of metformin have been related to an increased abundance of Akkermansia muciniphila in the gut microbiota of diet-induced obese (DIO)-mice.2 On the other hand, the local gut anti-inflammatory compound 5-amino-salicylic acid (5-ASA) has been reported to alleviate metabolic alterations in DIO-mice,3 providing further evidence that strategies aiming at exploiting the gut microbiota may help to alleviate obesity and its related dysmetabolic conditions.

Since the intestinal mucosa and its residing microbiota constitute the first site of interaction between diet and the host, it is likely that fruits and vegetables,
whose consumption is consistently associated with lower incidence of metabolic diseases,4–6 possess bioactive compounds capable of exerting beneficial effects even prior to absorption, which positively impacts on whole-body metabolism. Plant-derived foods are important sources of phenolic phytochemicals, the secondary metabolites produced in response to biotic and abiotic stress in plants.7 In fact, there are ample evidences demonstrating the beneficial role of polyphenols in health (for a review see ref. 8). Interestingly, several types of polyphenols have low bioavailability,9–11 remaining in close contact with the gut mucosa and microbiota, leading us and others to hypothesize that such an interaction could play a major role in the positive health effects of polyphenol-rich fruits.8,12

**Prebiotic effect of polyphenol-rich extracts on Akkermansia**

In a recent report we have shown that daily oral administration of a polyphenol-rich cranberry extract (CE) for 8 weeks prevented weight gain and ameliorated several features of the metabolic syndrome in association with a strong increase in the abundance of *Akkermansia* in the gut microbiota of DIO-mice.12 To the best of our knowledge, this was the first evidence of a polyphenol-rich extract from berries improving the metabolic syndrome through a prebiotic effect on *Akkermansia*. These findings were confirmed by a more recent study using a concord grape extract to improve metabolic features in DIO-mice, which was also associated with a prebiotic effect on *Akkermansia*.13 In line with these findings, mice fed a butter fat-based diet supplemented with powdered California table grapes displayed reduced adiposity and hepatic lipogenesis in parallel to an upward trend in the presence of *Akkermansia* in the gut microbiota of DIO-mice.14 Because cranberries and grapes both contain considerable amounts of proanthocyanidins (PACs, also known as condensed tannins), it is reasonable to hypothesize that this particular class of polyphenols plays a special role in this prebiotic activity. Moreover, cranberry PACs have been previously associated with an increase in mucus production in mice,15 which could provide ample trophic resources for *Akkermansia* to thrive.

PACs are polyphenols formed by oligomers and polymers of flavanols (eg, catechin and epicatechin). While monomers and dimers of PAC are relatively absorbable, oligomers (ie, trimers, tetramers and pentamers) and polymers (ie, degree of polymerization higher than 5) have high molecular weight, which hampers their absorption and favors their accumulation in the gut, where they can interact with intestinal microbes and the gut epithelium.9,16 When comparing the polyphenolic profiles of our cranberry extract12 and that of the concord grape extract tested by Roopchand et al.,13,17 we see a marked predominance of PACs and flavonols in the former and a strong presence of anthocyanins, catechins and hydroxycinnamic acids in the latter extract. This observation suggests that distinct polyphenolic mixtures may act redundantly to favor the presence of *Akkermansia* in the gut microbiota, which parallels to improved metabolic outcomes in DIO-mice. Two recent reports further support this idea: one showing that administration of the flavonol quercetin to obese rats was associated with a trend toward increased *Akkermansia* in the gut microbiota18 and the other showing that healthy volunteers drinking a pomegranate extract (a rich source of ellagitannins) displayed increased presence of *Akkermansia* in stool samples.19 This last report is of particular interest because it not only shows that the human gut microbiota also responds with a major shift in *Akkermansia* when challenged with high polyphenol intake, as it also suggests that healthy individuals may also take advantage of the prebiotic effects of polyphenols on *Akkermansia*.

**Is there a specific role for cranberry PACs in the gut microbiota?**

The well-known anti-adhesion effect of cranberries on *P*-fimbriated *E. coli*, which underlies their classical use to prevent urogenital tract infections,20 is particularly associated with A-type PACs,21 which predominate over B-type PACs in this berry.22 We reported that CE-treated DIO-mice expressed more mucin 2 (Muc2) mRNA in the proximal colon than vehicle-treated controls.12 As mentioned above, this prompted us to hypothesize that cranberry PACs could increase mucus secretion thus creating a favorable environment for *Akkermansia* to thrive. This is in line with the fact that cranberry-PACs ameliorate the integrity of the intestinal barrier by increasing mucus secretion in a murine model of elemental enteral nutrition.15 Moreover, Taira et al. recently reported that dietary polyphenols were associated with an increased...
presence of mucin in the faeces of DIO-rats.23 Interestingly, Roopchand et al. reported that a concord grape extract supplementation, which is a source of B-type PACs and other polyphenols, did not affect colonic or jejunal Muc2 mRNA expression, therefore suggesting a direct effect on Akkermansia rather than a modulation of Akkermansia’s niche. This hypothesis is corroborated by the finding that grape juice/red wine polyphenols increased the abundance of Akkermansia when added to an in vitro gut model.24 It is, however, important to consider that using the intestinal mRNA expression of Muc2 as the only read out of mucus layer thickness is limited. Still, taken together these data indicate that several polyphenolic mixtures are able to affect the gut ecosystem in order to favor the presence of Akkermansia, reinforcing the relevance of this bacterium as a biomarker of healthy states. While some polyphenols, such as cranberry-PACs, are able to improve mucus layer integrity by increasing Muc2 expression of PAC) was found to exert more pronounced effects, often present in whole-extracts, this approach will aid to identify the most bioactive molecules. In this regard, our group recently reported the effect of 3 different cranberry phenolic fractions on intestinal inflammation, oxidative stress and mitochondrial dysfunction using intestinal Caco2/15 cells.27 Whereas all 3 fractions had positive effects on iron/ascorbate-induced oxidative stress and LPS-induced inflammation in intestinal cells, the high molecular weight fraction (composed of flavonols and oligomers/polymers of PAC) was found to exert more pronounced effects, in particular by improving mitochondrial function.27 Moreover, recent reports have evidenced the role of the innate immune system through inflammasome-mediated processes in colonic auto-inflammation, which also impacts on nonalcoholic fatty liver disease (NAFLD) and inflammation-induced cancer.28-30 Wlodarska et al. have demonstrated that mice lacking the inflammasome component NOD-like receptor pyrin domain containing 6 (NLRP6) display colonic goblet cells with impaired mucus secretory capacity, which is mechanistically linked with impaired autophagy and accumulating degenerating mitochondria in goblet cells.31 Taken together, these observations raise the hypothesis that cranberry PACs may enhance mucus secretion by acting on goblet cells to maintain mitochondrial function. This effect may also be linked to the modulation of the intestinal innate immune system by triggering the assembly of the NLRP6-associated inflammasome. Since inflammation is a required response to ensure an adequate protection by goblet cells,32,33 this hypothesis is in good alignment with the xenohormetic theory as cranberry PACs, by eliciting a minor stress to goblet cells, would boost mucus secretion to therefore enhance the intestinal barrier, which positively impacts on whole-body metabolism.

**Is Akkermansia a new bacterial weapon to fight chronic inflammatory diseases?**

Administration of Akkermansia as a probiotic was shown to alleviate obesity-related metabolic disturbances while increasing Muc2 production in DIO-mice, thus improving mucus layer thickness and intestinal barrier.34 This study not only showed a beneficial role for Akkermansia against the metabolic syndrome but also that the treatment with this mucin-degrading bacterium actually stimulated mucin production by

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the host. Consistently, while several reports support a causal relevance for *Akkermansia* in improving metabolic phenotypes, molecules of microbial origin were shown to stimulate mucus release and the composition of the gut microbiota plays a key role in the development of an impenetrable mucus layer. In addition, *Akkermansia* has been shown to fortify *in vitro* the integrity of the epithelial cell layer, suggesting that the positive role of this bacterium in the gut barrier is not exclusively associated with mucus layer physiology.

An important question is whether administration of *Akkermansia* should be regarded as a safe approach to prevent or even reverse metabolic diseases. Several studies have shown that raising the presence of *Akkermansia* in the gut microbiota is related to improved metabolic outcomes in animal models and also in human subjects. However, one study reported a positive correlation between *Akkermansia* and type 2 diabetes in a Chinese cohort. Moreover, the hiperproliferative effect of dietary-heme in the gut was associated with the mucolytic activity of *Akkermansia*. More importantly, there seems to be no consensus on the role of *Akkermansia* in other chronic inflammatory settings such as inflammatory bowel diseases (IBD)-related gut dysbiosis. Indeed, while some groups have reported a depletion of *Akkermansia* together with enriched *Fusobacterium spp* and other mucolytic bacteria in the gut microbiota of both humans and animals models of IBD, others have observed an increased presence of *Akkermansia* in relation with these diseases.

One possible explanation for the observation of increased presence of *Akkermansia* in the gut microbiota of IBD models may rely on the fact that *Akkermansia*, besides being strictly anaerobe, can tolerate some exposure to oxygen, which probably confers resistance against highly oxidative environments as that found in the gut microbiota of IBD models. *Akkermansia* may thus find a favorable environment to thrive, which can be further sustained by a wide availability of energetic substrate (ie, mucins). Moreover, such an opportunistic overgrowth of *Akkermansia* takes place in an intestinal environment where several mucin-degraders are also blooming, which may act conjointly in order to reduce mucus layer thickness. It should also be mentioned that overabundance of *Akkermansia* in the gut is not always associated with benefits: oral administration of *Akkermansia* to germ-free mice prior to *Salmonella typhimurium* infection was found to worsen the intestinal pro-inflammatory response, therefore suggesting that exogenously promoting *Akkermansia*’s abundance is not advantageous for the host in some infectious settings. Furthermore, host’s immune response to *Akkermansia* may be compromised in some inflammatory conditions. For instance, IL10−/− mice display an abnormal intestinal inflammatory response that can possibly overwhelm the intestinal immune response to *Akkermansia*. Mucus secretion by goblet cells is closely associated with a tightly controlled activation of the immune system, which is probably one mechanism that *Akkermansia* can recruit in order to increase mucus secretion. However, in IL10−/− mice, *Akkermansia* may trigger an exaggerated immune response, which undermines mucus secretion and results in impaired gut barrier. In addition, the existence of strains other than *MucT* (ATCC BAA-835) may also explain why *Akkermansia* was found to be positively correlated with some but not all gut inflammatory settings. Indeed, the possibility that at least 8 different species of *Akkermansia* exist has been previously reported, and Guo et al. recently identified 12 distinct subtypes of *Akkermansia muciniphila* in stool samples from a southern Chinese population.

The resulting effect of *Akkermansia* on host’s physiology clearly depends on complex interactions with other intestinal microorganisms. Thus, the ratio between *Akkermansia* and other mucin-degrading species may be of relevance when investigating the role of *Akkermansia* in the modulation of metabolic phenotypes. Indeed, Le Chatelier et al. have demonstrated that while individuals harboring high gut microbial diversity (high gene count, HGC) were metabolically healthier than subjects harboring low gut microbial diversity (low gene count, LGC), HGC individuals had higher *Akkermansia* to *Ruminococcus torques/gnavus* ratio in comparison with LGC subjects.

Thus we have to remain cautious about using *Akkermansia* as a probiotic treatment of obesity and associated inflammatory disorders and we feel that a safer approach is the use of alternative strategies, such as polyphenol-rich extracts, to thrive *Akkermansia* abundance in the gut. Moreover, while the administration of *Akkermansia* to IBD patients may impose some risks, further studies are necessary to investigate the response of these subjects to cranberry PACs and...
other polyphenols. Interestingly, the intake of fruits has been inversely correlated with the incidence of Crohn’s disease and PAC-rich diets have been proposed to lower the incidence of colorectal cancer, a common complication of IBD.

Conclusions
In summary, the current state of knowledge suggests that distinct polyphenolic mixtures promote the presence of Akkermansia in the gut microbiota, which is associated with improved metabolic outcomes in DIO mice. Moreover, while there are evidences supporting that cranberry-PACs exert a unique effect on mucus layer integrity by increasing Muc2 production, which may therefore boost the growth of Akkermansia by creating a favorable niche, quercetin and other polyphenols seem to resort on other mechanisms than those of A-type PACs, but that also culminates in an enhanced presence of Akkermansia in the gut microbiota. In light of recent publications, we hypothesized that cranberry PACs may enhance mucus secretion by acting on goblet cells, which may be linked to the modulation of the intestinal innate immune system by triggering the NLRP6 inflammasome assembly, which in turn enhances mitochondrial autophagy and collaborates to maintain mitochondrial function. Furthermore, we conclude that Akkermansia represents a new biomarker of a coupled intestinal-metabolic health, responding similarly to a variety of dietary treatments but also contributing per se to the improved phenotype, as supported by its ability to ameliorate markers of metabolic health when given orally to DIO mice. Finally, as the potential risks related to the use of Akkermansia as a probiotic are not completely ruled out, especially in severe inflammatory bowel diseases, we propose that polyphenols represent a safer alternative to favor the presence of Akkermansia in the gut microbiota in order to alleviate intestinal inflammation and consequently bring metabolic benefits to the host.

Disclosure of potential conflicts of interest
No potential conflicts of interest were disclosed.

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