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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.

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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-aminosalicylic 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,

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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[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 extract[12] 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 microbiota[18] 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* abundance 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 fæces 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 production, which may boost the growth of *Akkermansia* by creating a favorable niche, other polyphenols seem to act through distinct mechanisms that also result in an intestinal environment propitious for *Akkermansia* to thrive. The putative mechanisms involved in the prebiotic effect of polyphenols on *Akkermansia* were recently reviewed by us elsewhere.[25]

Interestingly, a diet rich in omega-3 polyunsaturated fatty acids from fish oil, which are also well known for their health benefits, was recently shown to increase *Akkermansia* population in the gut microbiota in comparison with lard-fed mice.[26] Fæcal transplants from fish oil-fed to lard-fed mice recapitulated the metabolic benefits of fish oil feeding, demonstrating that the "*Akkermansia*-rich" gut microbiota contributed to the phenotypic differences and confirming the causal and beneficial role of *Akkermansia* in host's physiology.[26] Thus, the current state of knowledge suggests that, in the context of an unhealthy diet and obesity, *Akkermansia* seems to represent a new biomarker of metabolic health, responding similarly to a variety of dietary compounds and possibly even contributing *per se* to the improved phenotype.

We believe that future research on the effects of polyphenols on intestinal microbial communities and their impact on host physiology should contemplate the study of fractionated extracts enabling the analysis of isolated groups of polyphenols and/or the use of single phenolic molecules. Besides eliminating potential confounders (eg, fibers, minerals, sugars) 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

the host. Consistently, while several reports support a causal relevance for *Akkermansia* in improving metabolic phenotypes[2,26,35,36], molecules of microbial origin were shown to stimulate mucus release[37] and the composition of the gut microbiota plays a key role in the development of an impenetrable mucus layer.[38] 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.[39]

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[2,12,26,34,36] and also in human subjects.[40,41] However, one study reported a positive correlation between *Akkermansia* and type 2 diabetes in a Chinese cohort.[42] Moreover, the hiperproliferative effect of dietary-heme in the gut was associated with the mucolytic activity of *Akkermansia*.[43] 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, [44-49] others have observed an increased presence of *Akkermansia* in relation with these diseases.[50,51]

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,[39] 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,[52] 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*.[51] Mucus secretion by goblet cells is closely associated with a tightly controlled activation of the immune system,[32] 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 Muc^{T} (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,[53] and Guo et al. recently identified 12 distinct subtypes of *Akkermansia muciniphila* in stool samples from a southern Chinese population.[54]

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.[49,51] 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.[40]

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[55] and PAC-rich diets have been proposed to lower the incidence of colorectal cancer, a common complication of IBD.[56]

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.

References

[1] Howitz KT, Sinclair DA. Xenohormesis: sensing the chemical cues of other species. Cell 2008; 133:387-91; PMID:18455976; http://dx.doi.org/10.1016/j.cell.2008.04.019

[2] Shin NR, Lee JC, Lee HY, Kim MS, Whon TW, Lee MS, Bae JW. An increase in the Akkermansia spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. Gut 2014; 63:727-35; PMID:23804561; http://dx.doi.org/10.1136/gutjnl-2012-303839

[3] Luck H, Tsai S, Chung J, Clemente-Casares X, Ghazarian M, Revelo XS, Lei H, Luk CT, Shi SY, Surendra A, et al. Regulation of obesity-related insulin resistance with gut anti-inflammatory agents. Cell Metab 2015; 21:527-42; PMID:25863246; http://dx.doi.org/10.1016/j.cmet.2015.03.001

[4] Morimoto A, Ohno Y, Tatsumi Y, Mizuno S, Watanabe S. Effects of healthy dietary pattern and other lifestyle factors on incidence of diabetes in a rural Japanese population. Asia Pac J Clin Nutr 2012; 21:601-8; PMID:23017319

[5] Bauer F, Beulens JW, van der AD, Wijmenga C, Grobbee DE, Spijkerman AM, van der Schouw YT, Onland-Moret NC. Dietary patterns and the risk of type 2 diabetes in overweight and obese individuals. Eur J Nutr 2013; 52:1127-34.; PMID:22972436; http://dx.doi.org/10.1007/s00394-012-0423-4

[6] Eshak ES, Iso H, Mizoue T, Inoue M, Noda M, Tsugane S. Soft drink, 100% fruit juice, and vegetable juice intakes and risk of diabetes mellitus. Clin Nutr 2013; 32:300-8; PMID:22917499; http://dx.doi.org/10.1016/j.clnu.2012.08.003

[7] Cushnie TP, Lamb AJ. Recent advances in understanding the antibacterial properties of flavonoids. Int J Antimicro Agents 2011; 38:99-107; PMID:21514796; http://dx.doi.org/10.1016/j.ijantimicag.2011.02.014

[8] Anhê FF, Desjardins Y, Pilon G, Dudonné S, Genovese MI, Lajolo FM, Marette A. Polyphenols and type 2 diabetes: A prospective review. Pharma Nutr 2013; 1:105-14; http://dx.doi.org/10.1016/j.phanu.2013.07.004

[9] Choy YY, Jaggers GK, Oteiza PI, Waterhouse AL. Bioavailability of intact proanthocyanidins in the rat colon after ingestion of grape seed extract. JAgr Food Chem 2013; 61:121-7; PMID:23244439; http://dx.doi.org/10.1021/jf301939e

[10] Felgines C, Krisa S, Mauray A, Besson C, Lamaison JL, Scalbert A, Merillon JM, Texier O. Radiolabelled cyanidin 3-O-glucoside is poorly absorbed in the mouse. Brit J Nutr 2010; 103:1738-45; PMID:20187984; http://dx.doi.org/10.1017/S0007114510000061

[11] Manach C, Williamson G, Morand C, Scalbert A, Remesy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am J Clin Nutr 2005; 81:230S-42S; PMID:15640486

[12] Anhê FF, Roy D, Pilon G, Dudonné S, Matamoros S, Varin TV, Garofalo C, Moine Q, Desjardins Y, Levy E. A polyphenol-rich cranberry extract protects from diet-induced obesity, insulin resistance and intestinal inflammation in association with increased Akkermansia spp. population in the gut microbiota of mice. Gut 2014; 64:872-83;

PMID:25080446; http://dx.doi.org/10.1136/gutjnl-2014-307142

[13] Roopchand DE, Carmody RN, Kuhn P, Moskal K, Rojas-Silva P, Turnbaugh PJ, Raskin I. Dietary polyphenols promote growth of the gut bacterium akkermansia muciniphila and attenuate high fat diet-induced metabolic syndrome. Diabetes 2015; 64:2847-58; PMID:25845659; http://dx.doi.org/10.2337/db14-1916

[14] Baldwin J, Collins B, Wolf PG, Martinez K, Shen W, Chuang C-C, Zhong W, Cooney P, Cockrell C, Chang E, et al. Table grape consumption reduces adiposity and markers of hepatic lipogenesis and alters gut microbiota in butter fat-fed mice. J Nutr Biochem 2016; 27:123-35; PMID:26423887; http://dx.doi.org/10.1016/j.jnutbio.2015.08.027

[15] Pierre JF, Heneghan AF, Feliciano RP, Shanmuganayagam D, Roenneburg DA, Krueger CG, Reed JD, Kudsk KA. Cranberry proanthocyanidins improve the gut mucous layer morphology and function in mice receiving elemental enteral nutrition. JPEN J Parenter Enter Nutr 2013; 37:401-9; PMID:23064255; http://dx.doi.org/10.1177/0148607112463076

[16] Choy YY, Quifer-Rada P, Holstege DM, Frese SA, Calvert CC, Mills DA, Lamuela-Raventos RM, Waterhouse AL. Phenolic metabolites and substantial microbiome changes in pig feces by ingesting grape seed proanthocyanidins. Food Funct 2014; 5:2298-308; PMID:25066634; http://dx.doi.org/10.1039/C4FO00325J

[17] Roopchand DE, Kuhn P, Krueger CG, Moskal K, Lila MA, Raskin I. Concord grape pomace polyphenols complexed to soy protein isolate are stable and hypoglycemic in diabetic mice. J Agr Food Chem 2013; 61:11428-33; PMID:24206100; http://dx.doi.org/10.1021/jf403238e

[18] Etxeberria U, Arias N, Boque N, Macarulla MT, Portillo MP, Martinez JA, Milagro FI. Reshaping faecal gut microbiota composition by the intake of trans-resveratrol and quercetin in high-fat sucrose diet-fed rats. J Nutr Biochem 2015; 26:651-60; PMID:25762527; http://dx.doi.org/10.1016/j.jnutbio.2015.01.002

[19] Li Z, Henning SM, Lee RP, Lu QY, Summanen PH, Thames G, Corbett K, Downes J, Tseng CH, Finegold SM, et al. Pomegranate extract induces ellagitannin metabolite formation and changes stool microbiota in healthy volunteers. Food Funct 2015; 6:2487-95; PMID:26189645; http://dx.doi.org/10.1039/C5FO00669D

[20] Gupta K, Chou MY, Howell A, Wobbe C, Grady R, Stapleton AE. Cranberry products inhibit adherence of p-fimbriated Escherichia coli to primary cultured bladder and vaginal epithelial cells. J Urol 2007; 177:2357-60; PMID:17509358; http://dx.doi.org/10.1016/j.juro.2007.01.114

[21] Foo LY, Lu Y, Howell AB, Vorsa N. A-Type proanthocyanidin trimers from cranberry that inhibit adherence of uropathogenic P-Fimbriated escherichia c oli. J Nat Prod 2000; 63:1225-8; PMID:11000024; http://dx.doi.org/10.1021/np000128u

[22] Feliciano RP, Meudt JJ, Shanmuganayagam D, Krueger CG, Reed JD. Ratio of "A-type" to "B-type" proanthocyanidin interflavan bonds affects extra-intestinal pathogenic Escherichia coli invasion of gut epithelial cells. J Agr Food Chem 2014; 62:3919-25; PMID:24215458; http://dx.doi.org/10.1021/jf403839a

[23] Taira T, Yamaguchi S, Takahashi A, Okazaki Y, Yamaguchi A, Sakaguchi H, Chiji H. Dietary polyphenols increase fecal mucin and immunoglobulin A and ameliorate the disturbance in gut microbiota caused by a high fat diet. J Clin Biochem Nutr 2015; 57:212; PMID:26566306; http://dx.doi.org/10.3164/jcbn.15-15

[24] Kemperman RA, Gross G, Mondot S, Possemiers S, Marzorati M, Van de Wiele T, Doré J, Vaughan EE. Impact of polyphenols from black tea and red wine/grape juice on a gut model microbiome. Food Res Int 2013; 53:659-69; http://dx.doi.org/10.1016/j.foodres.2013.01.034

[25] Anhe FF, Varin TV, Le Barz M, Desjardins Y, Levy E, Roy D, Marette A. Gut microbiota dysbiosis in obesity-linked metabolic diseases and prebiotic potential of polyphenol-rich extracts. Curr Obes Rep 2015; PMID:26343880

[26] Caesar R, Tremaroli V, Kovatcheva-Datchary P, Cani PD, Backhed F. Crosstalk between gut microbiota and dietary lipids aggravates WAT inflammation through TLR signaling. Cell Metab 2015; 22:658-68; PMID:26321659

[27] Denis MC, Desjardins Y, Furtos A, Marcil V, Dudonne S, Montoudis A, Garofalo C, Delvin E, Marette A, Levy E. Prevention of oxidative stress, inflammation and mitochondrial dysfunction in the intestine by different cranberry phenolic fractions. Clin Sci (Lond) 2015; 128:197-212; PMID:25069567; http://dx.doi.org/10.1042/CS20140210

[28] Chen GY, Liu M, Wang F, Bertin J, Nunez G. A functional role for Nlrp6 in intestinal inflammation and tumorigenesis. J Immunol 2011; 186:7187-94; PMID:21543645; http://dx.doi.org/10.4049/jimmunol.1100412

[29] Henao-Mejia J, Elinav E, Jin C, Hao L, Mehal WZ, Strowig T, Thaiss CA, Kau AL, Eisenbarth SC, Jurczak MJ, et al. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. Nature 2012; 482:179-85; PMID:22297845

[30] Normand S, Delanoye-Crespin A, Bressenot A, Huot L, Grandjean T, Peyrin-Biroulet L, Lemoine Y, Hot D, Chamaillard M. Nod-like receptor pyrin domain-containing protein 6 (NLRP6) controls epithelial self-renewal and colorectal carcinogenesis upon injury. Proc Natl Acad Sci U S A 2011; 108:9601-6; PMID:21593405

[31] Wlodarska M, Thaiss CA, Nowarski R, Henao-Mejia J, Zhang JP, Brown EM, Frankel G, Levy M, Katz MN, Philbrick WM, et al. NLRP6 inflammasome orchestrates the colonic host-microbial interface by regulating goblet cell mucus secretion. Cell 2014; 156:1045-59; PMID:24581500; http://dx.doi.org/10.1016/j.cell.2014.01.026

[32] Bhinder G, Stahl M, Sham HP, Crowley SM, Morampudi V, Dalwadi U, Ma C, Jacobson K, Vallance BA. Intestinal epithelium-specific MyD88 signaling impacts host susceptibility to infectious colitis by promoting protective goblet cell and antimicrobial responses. Infect Immun

2014; 82:3753-63; PMID:24958710; http://dx.doi.org/10.1128/IAI.02045-14

[33] Bergstrom KS, Morampudi V, Chan JM, Bhinder G, Lau J, Yang H, Ma C, Huang T, Ryz N, Sham HP, et al. Goblet cell derived RELM-beta recruits CD4+ T cells during infectious colitis to promote protective intestinal epithelial cell proliferation. PLoS Pathogens 2015; 11:e1005108; PMID:26285214; http://dx.doi.org/10.1371/journal.ppat.1005108

[34] Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, Guiot Y, Derrien M, Muccioli GG, Delzenne NM, et al. Cross-talk between akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. Proc Natl Acad Sci U S A 2013; 110:9066-71; PMID:23671105

[35] Schneeberger M, Everard A, Gómez-Valadés A, Matamoros S, Ramírez S, Delzenne N, Gomis R, Claret M, Cani P. Akkermansia muciniphila inversely correlates with the onset of inflammation, altered adipose tissue metabolism and metabolic disorders during obesity in mice. Sci Rep 2014; 5:16643; PMID:26563823; http://dx.doi.org/10.1038/srep16643

[36] Chevalier C, Stojanovic O, Colin DJ, Suarez-Zamorano N, Tarallo V, Veyrat-Durebex C, Rigo D, Fabbiano S, Stevanovic A, Hagemann S, et al. Gut microbiota orchestrates energy homeostasis during cold. Cell 2015; 163:1360-74; PMID:26638070; http://dx.doi.org/10.1016/j.cell.2015.11.004

[37] Petersson J, Schreiber O, Hansson GC, Gendler SJ, Velcich A, Lundberg JO, Roos S, Holm L, Phillipson M. Importance and regulation of the colonic mucus barrier in a mouse model of colitis. Am J Physiol Gastr Liver Physiol 2011; 300:G327-33; PMID:21109593; http://dx.doi.org/10.1152/ajpgi.00422.2010

[38] Rodriguez-Pineiro AM, Johansson ME. The colonic mucus protection depends on the microbiota. Gut Microbes 2015; 6:326-30; PMID:26305453; http://dx.doi.org/10.1080/19490976.2015.1086057

[39] Reunanen J, Kainulainen V, Huuskonen L, Ottman N, Belzer C, Huhtinen H, de Vos WM, Satokari R. Akkermansia muciniphila adheres to enterocytes and strengthens the integrity of the epithelial cell layer. Appl Environ Microbiol 2015; 81:3655-62; PMID:25795669; http://dx.doi.org/10.1128/AEM.04050-14

[40] Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, Almeida M, Arumugam M, Batto JM, Kennedy S, et al. Richness of human gut microbiome correlates with metabolic markers. Nature 2013; 500:541-6; PMID:23985870; http://dx.doi.org/10.1038/nature12506

[41] Dao MC, Everard A, Aron-Wisnewsky J, Sokolovska N, Prifti E, Verger EO, Kayser BD, Levenez F, Chilloux J, Hoyles L, et al. Akkermansia muciniphila and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. Gut 2016; 65:426-36; PMID:26100928; http://dx.doi.org/doi:10.1136/gutjnl-2014-308778

[42] Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature 2012; 490:55-60; PMID:23023125; http://dx.doi.org/10.1038/nature11450

[43] Ijssennagger N, Belzer C, Hooiveld GJ, Dekker J, van Mil SW, Müller M, Kleerebezem M, van der Meer R. Gut microbiota facilitates dietary heme-induced epithelial hyperproliferation by opening the mucus barrier in colon. Proc Natl Acad Sci 2015; 112:10038-43; PMID:26216954

[44] Berry D, Reinisch W. Intestinal microbiota: a source of novel biomarkers in inflammatory bowel diseases? Best Pract Res Clin Gastroenterol 2013; 27:47-58; PMID:23768552; http://dx.doi.org/10.1016/j.bpg.2013.03.005

[45] Vigsnaes LK, Brynskov J, Steenholdt C, Wilcks A, Licht TR. Gram-negative bacteria account for main differences between faecal microbiota from patients with ulcerative colitis and healthy controls. Beneficial Microbes 2012; 3:287-97; PMID:22968374; http://dx.doi.org/10.3920/BM2012.0018

[46] Rajilic-Stojanovic M, Shanahan F, Guarner F, de Vos WM. Phylogenetic analysis of dysbiosis in ulcerative colitis during remission. Inflamm Bowel Dis 2013; 19:481-8; PMID:23385241; http://dx.doi.org/10.1097/MIB.0b013e31827fec6d

[47] Reshef L, Kovacs A, Ofer A, Yahav L, Maharshak N, Keren N, Konikoff FM, Tulchinsky H, Gophna U, Dotan I. Pouch inflammation is associated with a decrease in specific bacterial taxa. Gastroenterol 2015; 149:718-27; PMID:26026389; http://dx.doi.org/10.1053/j.gastro.2015.05.041

[48] Kang CS, Ban M, Choi EJ, Moon HG, Jeon JS, Kim DK, Park SK, Jeon SG, Roh TY, Myung SJ, et al. Extracellular vesicles derived from gut microbiota, especially Akkermansia muciniphila, protect the progression of dextran sulfate sodium-induced colitis. PloS one 2013; 8:e76520; PMID:24204633; http://dx.doi.org/10.1371/journal.pone.0076520

[49] Png CW, Linden SK, Gilshenan KS, Zoetendal EG, McSweeney CS, Sly LI, McGuckin MA, Florin TH. Mucolytic bacteria with increased prevalence in IBD mucosa augment in vitro utilization of mucin by other bacteria. Am J Gastroenterol 2010; 105:2420-8; PMID:20648002; http://dx.doi.org/10.1038/ajg.2010.281

[50] Arthur JC, Perez-Chanona E, Muhlbauer M, Tomkovich S, Uronis JM, Fan TJ, Campbell BJ, Abujamel T, Dogan B, Rogers AB, et al. Intestinal inflammation targets cancer-inducing activity of the microbiota. Science 2012; 338:120-3; PMID:22903521; http://dx.doi.org/10.1126/science.1224820

[51] Chassaing B, Koren O, Goodrich JK, Poole AC, Srinivasan S, Ley RE, Gewirtz AT. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. Nature 2015; 519:92-6; PMID:25731162; http://dx.doi.org/10.1038/nature14232

[52] Ganesh BP, Klopfleisch R, Loh G, Blaut M. Commensal akkermansia muciniphila exacerbates gut inflammation

in salmonella typhimurium-infected gnotobiotic mice. PloS one 2013; 8:e74963; PMID:24040367; http://dx.doi.org/10.1371/journal.pone.0074963

[53] Van den Abbeele P, Gerard P, Rabot S, Bruneau A, El Aidy S, Derrien M, Kleerebezem M, Zoetendal EG, Smidt H, Verstraete W, et al. Arabinoxylans and inulin differentially modulate the mucosal and luminal gut microbiota and mucin-degradation in humanized rats. Environ Microbiol 2011; 13:2667-80; PMID:21883787; http://dx.doi.org/10.1111/j.1462-2920.2011.02533.x

[54] Guo X, Zhang J, Wu F, Zhang M, Yi M, Peng Y. Different sub-type strains of Akkermansia muciniphila abundantly colonize in southern China. J Appl Microbiol 2015; 120:452-459; PMID:26666632; http://dx.doi.org/10.1111/jam.13022

[55] Hou JK, Abraham B, El-Serag H. Dietary intake and risk of developing inflammatory bowel disease: a systematic review of the literature. Am J Gastroenterol 2011; 106:563-73; PMID:21468064; http://dx.doi.org/10.1038/ajg.2011.44

[56] Wang ZJ, Ohnaka K, Morita M, Toyomura K, Kono S, Ueki T, Tanaka M, Kakeji Y, Maehara Y, Okamura T, et al. Dietary polyphenols and colorectal cancer risk: the Fukuoka colorectal cancer study. World J Gastroenterol: WJG 2013; 19:2683-90; PMID:23674876; http://dx.doi.org/10.3748/wjg.v19.i17.2683