REPLY

Probiotics, bile acids and gastrointestinal carcinogenesis

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We thank Borja Sánchez (Bile acid–microbiota crosstalk in gastrointestinal inflammation and carcinogenesis: a role for bifidobacteria and lactobacilli? *Nat. Rev. Gastroenterol. Hepatol.* <https://doi.org/10.1038/nrgastro.2018.23> (2018))¹ for his interest in our recent Review (Bile acid–microbiota crosstalk in gastrointestinal inflammation and carcinogenesis. *Nat. Rev. Gastroenterol. Hepatol.* **15**, 111–128 (2018))².

In his Correspondence, Sánchez pointed out that probiotic bacteria, bifidobacteria and lactobacilli, could accumulate primary unconjugated bile acids (BAs) such as cholic acid (CA) and probably secondary unconjugated BAs such as deoxycholic acid (DCA) in their cytoplasm either spontaneously or following intracellular BA deconjugation^{3,4}. The primary BAs sequestered in the cytoplasm of these bacteria might escape from the portal circulation and the action of other microorganisms to produce secondary BAs. Thus, a BA depletion strategy using probiotics could be a useful means of reducing colonic DCA levels, leading to decreased inflammation and gastrointestinal cancer risk. This concept is certainly an interesting topic for discussion.

However, we believe that it is premature to have included results from an *in vitro* study⁵ in our Review. First, BAs are reabsorbed primarily in the small intestine (terminal ileum), whereas intestinal BA depletion by bacteria is likely to occur in the large intestine

where bacteria such as bifidobacteria and lactobacilli are present in sufficient amounts to demonstrate the effect of lowering intestinal BA concentrations. Probiotics such as *Lactobacillus* and *Bifidobacterium* spp. are primarily located in the large intestine, which contains the highest bacterial density, about 10¹¹–10¹² bacteria per gram of intestinal content^{6,7}. In other words, BA binding by probiotics that occurs predominantly in the large intestine will probably not affect the apical sodium-dependent BA transporter-mediated BA reabsorption that takes place in the upper intestine. Thus, the proposed BA removal strategy via probiotics might not be practically achievable *in vivo*. Secondly, the ability of a given probiotic to bind and release BAs has not been well studied *in vivo*. Unlike the action of a BA sequestrant resin such as cholestyramine, the probiotic strains must grow to achieve a sufficient amount in the intestine for the binding to become substantial and have notable effects. Although BAs are absorbed by some of the intestinal bacteria, for example, CA is accumulated spontaneously in energized probiotic bacteria^{3,4}, BAs in the cytoplasm of intestinal bacteria will be partially released into the intestinal lumen. *Lactococcus lactis* has been reported to actively release CA via a multispecific organic anion transporter⁸. Thus, well-characterized probiotic strains with a strong ability for BA uptake but not BA excretion into the gastrointestinal tract

could potentially be useful in this application. Additionally, oral administration of BA-binding probiotics with high bile salt hydrolase activity could increase BA deconjugation in the small intestine and, therefore, facilitate greater reabsorption of deconjugated BAs from the distal ileum. Taken together, it is not clear, at this point, how probiotics interact with BAs *in vivo* and whether they have a beneficial effect in depleting cytotoxic secondary BAs in the gastrointestinal tract. We will have the answers to these questions only after in-depth mechanistic studies have been performed, particularly *in vivo*.

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[doi:10.1038/nrgastro.2018.24](https://doi.org/10.1038/nrgastro.2018.24)

Published online 7 Mar 2018

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Competing interests

The authors declare no competing interests.