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Microbial Riboflavin Biosynthesis Associates with Response to Dietary Fiber Consumption: Time to Personalize Adjunct Therapy in Patients with Inflammatory Bowel Disease?

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Conflict of Interest

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Dear Editors:

With great interest I read the study by Armstrong *et al*.[1] who reported on the effects of dietary β-fructan fibers (e.g. inulin and fructo-oligosaccharides [FOS]) in patients with inflammatory bowel diseases (IBD) depending on the abundance and fiber-fermenting capacity of microbiota. They demonstrated that β-fructan fibers like inulin remain intact in select patients with active IBD lacking microbial fermentative activities, with subsequent induction of pro-inflammatory responses mainly through activation of the NLRP3 and TLR2 pathways. Furthermore, microbial cultures revealed that fermentation of β-fructans reduced pro-inflammatory responses only when microbes were derived from patients with quiescent disease. Interestingly, it was shown that fiber-induced immune responses correlated with microbial functions. Riboflavin synthase – the key enzyme involved in microbial riboflavin biosynthesis – was decreased in *ex vivo* biopsy cultures of pediatric patients who displayed pro-inflammatory responses to β-fructans. This observation was further validated through demonstrating that riboflavin was significantly lowered in stool samples collected from ulcerative colitis (UC) patients who relapsed upon β-fructan consumption in a randomized controlled trial (RCT) of UC patients who were in initial remission.[2] In addition, riboflavin was found to negatively correlate with fold-changes in fecal calprotectin. Ultimately, the authors speculated that β-fructan fibers should be administered as adjunct therapy only after medical therapy has induced remission, to ensure other benefits of fibers and their products.

The observed association between microbial biosynthetic capacity of riboflavin and the response to β-fructan consumption is very intriguing, since it suggests a critical link between fiber-degrading microbes, the production of short-chain fatty acids (SCFAs), intestinal availability of riboflavin, and response to dietary fibers. Riboflavin is a redox-active vitamin that plays a pivotal role in human energy metabolism and has anti-inflammatory, antioxidant and microbiota-modulatory properties. As the authors already touched upon themselves, riboflavin is particularly leveraged by the commensal, butyrate-producing and inulin-fermenting microbe *Faecalibacterium prausnitzii*. Previous *in vitro* studies have demonstrated that *F. prausnitzii* employs a specialized form of anaerobic metabolism by using riboflavin and thiols for extracellular electron transfer (EET) through shuttling electrons to oxygen.[3] As such, *F. prausnitzii* reduces its oxygenated micro-environment, thereby preventing oxidative stress and promoting its own growth at the oxic-anoxic interphase of the intestinal barrier. A recent human study also demonstrated an independent association between extracellular antioxidant capacity (reflected by serum free thiols) and fecal abundance of *F. prausnitzii*.[4] Interestingly, we previously uncovered the capacity of *F. prausnitzii* to degrade β-fructans, particularly inulin, with resulting anti-inflammatory and cell viability-promoting effects of inulin-derived fructose.[5] In this study, it was demonstrated that bacterial breakdown of β-fructans to simple monosaccharides in the colon provided constant fuel for epithelial cell viability while suppressing inflammation and oxidative stress. Matching these data with findings reported by Armstrong *et al*.[1], this would suggest a potential role for riboflavin in determining microbial inulin-degrading capacity. In addition, in a prospective clinical study investigating the effects of riboflavin in patients with Crohn's disease, we previously reported that riboflavin supplementation resulted in a reduction of systemic oxidative stress, mixed anti-inflammatory effects, and a reduction in clinical symptoms.[6] All these effects were most prominent in patients with active CD. In line with findings of Armstrong *et al*.[1], another study demonstrated that riboflavin biosynthesis pathways were decreased in patients with CD exacerbations.[7] These findings implied that a difference in microbial riboflavin-producing capacity may determine a disease-specific response to riboflavin and/or fiber supplementation. Moreover, these data raise the possibility that consumption of β-fructan fibers could be improved by concomitant supplementation of riboflavin and, possibly, related compounds. This could especially be targeted to patients with active disease, as exemplified by increased inflammation, oxidative stress, and microbial disturbances, since in the absence of inflammation and/or disease, these effects are usually reported to be only marginal.[4]

Although the precise mechanisms by which microbial functions such as riboflavin biosynthesis contribute to the response to dietary fiber consumption need to be unraveled, the study by Armstrong *et al*.[1] underscores that adjunct therapy with dietary fibers and/or vitamins should be carefully assessed and optimized for patients with IBD – just as we do for existing medical therapy. The combined presence of a reduced microbial fermentative capacity, increased immune cell activity, disrupted barrier integrity, and oxidative stress could

culminate into intestinal inflammation and lead to adverse pro-inflammatory effects of fiber consumption in patients with IBD. Future studies are warranted to determine whether riboflavin (or related compounds) may enhance microbial fermentative capacity, and if this could help to determine which patients would benefit most from fiber consumption or could better avoid it.

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