Not so Splendid for the Gut Microbiota

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A critically important new study by leading inflammatory bowel disease (IBD) researcher Fabio Cominelli and colleagues reveals that, in mice, the artificial sweetener *SPLENDA* deleteriously impacts the intestinal microbiota in a manner that promotes Crohn's-type disease in genetically susceptible hosts. These results suggest that consumption of this product may be a risk factor for IBD.

Key Words: inflammatory bowel, disease, artificial sweetener, microbiota

Susceptibility to developing inflammatory bowel disease (IBD) is influenced by more than 150 genetic variants, wherein many risk alleles are present in a small minority of cases of disease. Such multigenic influence on IBD development is in accord with the notion that this disease does not have a single molecular cause, but rather results from a general breakdown in the normally mutually beneficial relationship between the intestine and the complex microbial community it harbors, referred to as the gut microbiota. However, the importance of genetic factors notwithstanding, the large post–mid–20th century increase in the incidence of IBD highlights the pivotal role of nongenetic factors in determining whether individuals who are genetically prone to IBD actually develop the disease or not. Epidemiologic studies have yet to reveal a "smoking gun" type of environmental factor that triggers disease, but rather suggest that a range of factors that can influence the immune system and/or the gut microbiota may moderately, but collectively, result in disease development. Among the myriad of environmental factors that could influence host-microbiota interactions, those whose usage has paralleled incidence of IBD and might directly interact with the gut microbiota seem particularly good candidates to be contributing to at least some cases of IBD and, consequently, to the increased incidence of this disease. New findings in this issue of the Journal that *SPLENDA* promotes microbiota dysbiosis in mice and exacerbates a hallmark of inflammation in ileitis-prone SAMP mice suggest that consumption of this synthetic sweetener may be a specific factor that contributes to development of IBD in persons genetically prone to this disorder.

The active sweetener in *SPLENDA* is a synthetic chlorinated sugar sucralose, whereas the most abundant (filler) component of *SPLENDA* is maltodextrin (MDX). Similar to many other US Food and Drug Administration (FDA)–approved products, sucralose was approved for human consumption based on its lack of overt toxic and carcinogenic effects in rodents. MDX, which is widely incorporated into many processed foods at levels that would result in greater exposure than that attained from consuming *SPLENDA*, was approved on its GRAS status (generally regarded as safe), in part based on the notion that it is very readily metabolized to glucose. However, it is increasingly appreciated that such screening protocols are not effective at discerning the extent to which a compound might promote low-grade and/or chronic inflammation, and thus may not be appropriate to protect the public from some of the most prevalent diseases that are associated with this state. Moreover, such testing is not sufficient to detect compounds that promote disease only in hosts with a genetic predisposition for a particular disease. Indeed, recent studies have questioned the safety of both sucralose and MDX in animal models, suggesting that these compounds can impact the microbiota and promote gut inflammation.[1,2] Cominelli and colleagues chose to test the combination of sucralose and MDX using *SPLENDA* in the clinically relevant SAMP model. They observed that, when tested at maximal FDA-approved levels, *SPLENDA* did not impact inflammatory markers in control mice, but rather only increased such parameters in SAMP mice, suggesting that such deleterious impacts of *SPLENDA* are unique to the genetics of SAMP mice. However, in both SAMP and control mice, *SPLENDA*

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consumption resulted in a dysbiotic microbiota, particularly enrichment of gamma Proteobacteria, which are broadly associated with gut inflammatory diseases. This suggests that, more likely, *SPLENDA* may promote and/or exacerbate inflammation in general, although it will not, by itself, cause inflammation in most hosts. Hence, like many other food additives/sweeteners, *SPLENDA* may be relatively safe for the majority of the population but still represents a serious risk factor for those prone to developing IBD or other chronic inflammatory diseases.

In addition of testing for overt toxicity, safety of proposed food additives has also, in part, been based on studying how such products are metabolized by the host. In general, synthetic compounds that are absorbed into systemic circulation have been considered to be of greater risk than those that, like sucralose, were primarily excreted in feces and were thus viewed as likely harmless. However, appreciation of the pivotal role of the microbiota in health questions the latter assumption in that such nonabsorbed compounds will, in fact, directly interact with the microbiota.

While the advent of testing food additives for acute toxicity and carcinogenesis by the FDA and other government agencies was a great public health advance over the largely unregulated era of food production that preceded it, such testing modalities seem woefully insufficient to protect society against metabolic and inflammatory diseases that threaten health care systems and economies in the 21st century. Rather, this report, and others, lead us to submit that FDA testing of food additives designed to detect chronic and low-grade inflammation and consider impacts on the gut microbiota should be performed in models including disease-prone and -resistant hosts.

REFERENCES

1. Bian X, Chi L, Gao B, et al. Gut microbiome response to sucralose and its potential role in inducing liver inflammation in mice. *Front Physiol*. 2017;8:487.
2. Nickerson KP, Chanin R, McDonald C. Deregulation of intestinal anti-microbial defense by the dietary additive, maltodextrin. *Gut Microbes*. 2015;6:78–83.