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EDITORIAL

Proinflammatory Effects of Wheat and Rye in an IBD Model: Give Us Not Our Daily Bread

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The pathogenesis of inflammatory bowel disease (IBD)—Crohn's disease (CD) and ulcerative colitis (UC)—is multifactorial, influenced by genetic, immunologic, and environmental factors, including the intestinal microbiota and the diet. Since diet is a potentially modifiable factor, there is great interest by patients and providers alike to identify potentially useful dietary interventions for the management of IBD.

Gluten is a mixture of gliadins and glutenins, which are complex proteins rich in prolines and glutamines, found in most grains such as wheat, barley, and rye. It is estimated that gluten-related disorders including wheat allergy, celiac disease, and non-celiac gluten sensitivity affect up to 10% of the general population. Wheat allergy is reported in 0.5–9% of the population and can be responsible for many gastrointestinal disorders, such Crohn's disease (CD) and ulcerative colitis (UC), after ingestion of foods containing wheat [1].

IBD treatment is primarily aimed at controlling inflammation rather than just symptomatology, since its symptoms do not always reflect the degree of mucosal inflammation and may be present even when inflammation is quiescent. On the other hand, patients with active inflammation may not report symptoms, potentially leading to under-treatment and increased complications. Thus, the use of inflammatory biomarkers can potentially identify timely and appropriate treatment of IBD patients. [2]. The profiles of these inflammatory markers can be modulated by the diet, highlighting the potential value of food as a therapeutic tool in inflammatory diseases. Though there are still no definitive treatments for IBD, adherence to a specific diet is one of the investigated approaches to control disease progression. Although the associations between dietary patterns and inflammation have already been investigated, comprehensive scientific research of the impact of dietary strategies on inflammatory biomarkers in IBD is lacking [3].

Caspase-mediated apoptosis is important for determining the morphology of the intestinal epithelial cells (IECs) and villi lining the gastrointestinal tract. Moreover, caspase-mediated apoptosis of intestinal epithelial cells (IECs) is implicated in the pathogenesis of IBD [4]. The ($Casp^{8\Delta IEC}$) genotype is associated with gut barrier dysfunction and malabsorption associated with induced colitis [5].

In this issue of *Digestive Diseases and Sciences*, Zimmermann et al. [6] evaluate the effects of different bread types and a gluten-enriched diet on an intestinal inflammation model in mice with an intestinal-specific deletion of caspase-8 ($Casp^{8\Delta IEC}$) bred on a C57BL/6 J genetic background and Cre-negative control littermates with floxed caspase-8 alleles ($Casp^{8fl}$). The authors produced eight different diets: a rice-based gluten-free (GF) control diet, a GF diet based on rice supplemented with 5% wheat gluten, which also served as control, and six different bread-based diets, which consisted of 50% of the corresponding bread and 50% non-cereals to reach the nutritional requirements for mice. During the 28 days of the experimental protocol, the mice were monitored 3 times/week in relation to the evolution of body weight and food intake. At the end of the study, the histopathological damage of the colon and ileum was evaluated, and blood was collected for future analyses. Furthermore, the authors measured intestinal paracellular permeability and gene expression of tumor necrosis factor-α (TNFα), mucin-2 (Muc2), zonula occludens-1 (ZO1), occludin and claudin-2 (CLDN2), and the colitis severity using colonoscopy. Furthermore, the importance of intestinal barrier dysfunction was reported due to an increased hepatic expression of lipopolysaccharide-binding protein (LBP) in ($Casp^{8\Delta IEC}$) mice compared with ($Casp^{8fl}$) mice, and an inverse

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correlation between hepatic LBP and survival, strongly suggesting that LPS translocation from the intestine to the portal vein contributed to the enhanced mortality of ($Casp^{8\Delta IEC}$) mice fed bread. Endoscopy revealed inflammatory injury throughout the mucosa in some ($Casp8^{\Delta IEC}$) mice. Histology revealed neutrophilic infiltration: ($Casp^{8\Delta IEC}$) mice generally had higher inflammation scores than ($Casp^{8fl}$) mice. Moreover, there were significant differences among the six diet groups regarding the extent of colitis. Certain diets worsened colitis, such as yeast-fermented rye and wheat bread as well as sourdough-fermented wheat bread.

The study showed that in healthy mice, a diet containing 50% bread did not affect the weight curve of the animals. On the other hand, in mice with the caspase-8 gene depletion, which developed ulcerative colitis accompanied by epithelial damage and increased intestinal paracellular permeability, inflammation was induced by a 50% bread diet, with further variations dependent on the type of bread consumed. The epithelial barrier is responsible to the intestinal homeostasis and is essential for preserving intestinal functions such as maintaining ionic balance, by acting as a protective layer between the intestinal microbiota and the mucosa, improving the absorption of water and nutrients. Damage to the integrity of the apical tight junctions increases paracellular permeability to electrolytes that can be associated with activation of the mucosal immune system, with consequent mucosal inflammation and diarrheal, and inflammatory symptoms in patients with inflammatory bowel disease.

In this study, Zimmermann et al. [6] did not observe genotype-specific differences regarding ZO1 and CLDN2 expression and mRNA expression of tight junction molecules in $Casp^{8\Delta IEC}$ mice compared with ($Casp^{8fl}$) mice. The authors suggest that epithelial damage can occur independently from changes in tight junction protein expression if inflammation directly induces necroptosis of enterocytes [7]. It is unclear, however, if paracellular permeability is involved in the pathogenesis of inflammation or is merely a marker of mucosal damage [8]. Moreover, this group has shown that colitis in ($Casp8^{\Delta IEC}$) mice is accompanied by changes in the gut microbiome, which again may be primary or secondary.

The authors indicate that though it is not possible to conclude which bread components increase mucosal inflammation in ($Casp^{8\Delta IEC}$) mice, the results of the study indicate that gluten is not the principal trigger. Although animal studies have shown that gluten ingestion can promote intestinal inflammation and increase intestinal paracellular permeability, there have been no prospective studies evaluating the contribution of the GF diet in the induction and maintenance of Crohn's disease and ulcerative colitis [9].

In the current study, rye bread was unexpectedly found to be harmful in ($Casp^{8\Delta IEC}$) mice, with negative effects on weight gain, survival, and colitis. Phytic acid is found in greater amounts in rye compared with wheat and reduces the absorption of minerals such as iron, zinc, and calcium [10]. Furthermore, consumption of wheat or wheat amylase trypsin inhibitors increases intestinal inflammation in mice with colitis, via Toll-like receptor (TLR)4, accompanied by alteration of the composition of the fecal microbiota. Wheat-based, ATI-containing diets, therefore, activate TLR4 signaling and promote intestinal dysbiosis [11].

In conclusion, Zimmermann et al. [6] indicate that bread components, especially those from yeast-fermented bread made from wheat and rye flour, increase the severity of colitis and mortality in ($Casp^{8\Delta IEC}$) mice, which are highly susceptible to intestinal inflammation, whereas control mice can tolerate all types of bread without inflammation.

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