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FIELD OF VISION

Impaired inactivation of digestive proteases: The possible key factor for the high susceptibility of germ-free and antibiotic-treated animals to gut epithelial injury

Xiaofa Qin

Xiaofa Qin, GI Biopharma Inc, Westfield, NJ 07090, United States

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Correspondence to: Xiaofa Qin, MD, PhD, GI Biopharma Inc, 918 Willow Grove Road, Westfield, NJ 07090, United States. xiaofa_qin@yahoo.com
Telephone: +1-908-4637423

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Abstract

Recent study shows that germ-free and antibiotic-treated animals are highly susceptible to gut epithelial injury. This paper addresses that impaired inactivation of digestive proteases may be the key factor for the increased susceptibility.

Key words: Digestive proteases; Germ-free; Antibiotics; Gut microbiota; Gut epithelial injury

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Core tip: This paper addresses that impaired inactivation of digestive proteases may be the possible key factor for the high susceptibility of germ-free and antibiotic-treated animals to gut epithelial injury.

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COMMENTARY ON HOT TOPICS

I read with great interest the paper by Hernández-Chirlaque *et al*[1] regarding the high susceptibility of germ-free and antibiotic-treated mice to epithelial injury. It is found that germ-free mice treated with dextran sulfate sodium (DSS) showed only minimal inflammation (no colonic thickening, lower myeloperoxidase activity, IL-6, IL-17, TNF-alpha and IFN-gamma secretion by splenocytes and mesenteric cell cultures, *etc.)*, but enhanced hemorrhage, epithelial injury and mortality along with weakened intestinal barrier. Animals treated with antibiotics also showed similar but less severe changes with intermediate effects. That paper discussed the interaction among gut bacteria, immune cells, and epithelial cells through inflammatory mediators, cytokines, bioactive molecules, receptors, ligands, tran-

scription factors, and pathways, but failed to provide a coherent mechanistic explanation. Here I suggest that impaired inactivation of digestive proteases may be the key factor for the observed increased susceptibility. Studies have well documented that large amount of digestive proteases can be found in the large intestine of germ-free or antibiotics-treated animals but not in animals raised at conventional condition[2-7]. As we know, the gut is mainly protected by a layer of mucus secreted from goblet cells. Mucin, the structural molecule of mucus, contains a central core of peptide and side carbohydrate branches that can constitute up to 85% of the molecule. These carbohydrate side chains greatly retarded degradation of the protective mucus layer and damage of the underlying gut tissue by the digestive proteases being existed in germ-free or antibiotics-treated animals. However, the great destructive potency of these digestive proteases would be released and manifested once the gut barrier is broken as occurred either shortly after treatment with high concentrations of DSS or prolonged treatment with lower dose of DSS, resulting in the severe damage of epithelial cells at gut surface and then blood vessels in the mucosa, leading to excessive blood loss and enhanced mortality, even in the absence of remarkably inflammation. This would be similar to the so-called tryptic hemorrhagic necrosis of the gut as seen in animals under shock, which can be greatly prevented by previous inactivation of digestive proteases or ligation of pancreatic duct[8]. In fact, evidences I collected during the last fifteen years make me to believe that impaired inactivation of digestive proteases due to reduction in gut bacteria along with the improved hygiene and inhibition by some dietary chemicals such as saccharin and sucralose may have also played critical causative role in the pathogenesis of inflammatory bowel disease (IBD) in human[9-11]. Thus, impaired inactivation of digestive proteases in colitis and IBD would be worthwhile for further study.

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