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May bacterial or pancreatic proteases play a critical role in inflammatory bowel disease?

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Abstract

In a recent review paper, Carroll and Maharshak discussed a critical role of enteric bacterial proteases in the pathogenesis of inflammatory bowel disease (IBD). I take a great interest in this paper as I also suspected proteases, not from the bacteria, but those originated from the pancreas that failed to be inactivated in the lower gut due to a reduction in gut bacteria, may have played a critical role in the pathogenesis of IBD, which was first published more than a decade ago and discussed again in more detail in a recent paper published in this journal. Antibiotics may result in a big reduction in gut bacteria and bacterial proteases, but multiple studies demonstrated dramatic increased of pancreatic proteases like trypsin and chymotrypsin in the feces of animals or patients treated with antibiotics. Multiple large-scale studies also demonstrated use of antibiotics caused an increase but not decrease in the risk of developing IBD, suggesting impaired inactivation and degradation of pancreatic proteases may have played a more critical role in the pathogenesis of IBD.

Key words: Inflammatory bowel diseases; Ulcerative colitis; Crohn's disease; Proteases; Bacteria; Pancreas

Core tip: This is letter commenting on the paper by Carroll and Maharshak recently published in this journal regarding the role of enteric bacterial proteases in the pathogenesis of inflammatory bowel disease (IBD). Here I provide some evidence suggesting that the proteases originated from the pancreas rather than gut bacteria may have played a more critical role in the development of IBD.

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TO THE EDITOR

I read with great interest the paper by Carroll and Maharshak[1] regarding the role of enteric bacterial proteases in the pathogenesis of inflammatory bowel disease (IBD), which succeeded another review on the similar topic[2]. I take a special interest in this paper as I also suspected proteases, not from the bacteria, but rather originated from the pancreas that failed to be inactivated in the lower gut due to a reduction in gut bacteria, may have played a critical role in the pathogenesis of IBD, which was first published more than a decade ago[3] and discussed again in more detail in a paper published in this journal in 2012[4]. It would be necessary to differentiate the proteases from these two sources, as in situations such as after treatment with antibiotics, the gut bacteria and bacterial proteases activity may be reduced as discussed in the paper by Carroll and Maharshak[1], but multiple studies demonstrated that treatment with antibiotics in animals or human results in dramatic increase of pancreatic proteases like trypsin and chymotrypsin in feces and luminal contents of the lower intestine[5-8]. At conventional condition, the activity of pancreatic digestive proteases like trypsin and chymotrypsin in the lower intestine is very low, but large amounts of these digestive proteases

emerged in animals raised in germ-free condition[9-12], suggesting impaired degradation of these enzymes along with the reduction in gut bacteria. A study by Bohe *et al*[7] showed 100-fold increase in trypsin in fecal extracts of normal individuals treated with antibiotics. The paper by Carroll and Maharshak[1] mentioned the increased activity of proteases in stools from IBD patients, but multiple studies demonstrated increased activities of pancreatic proteases like trypsin and chymotrypsin in the feces of patients with IBD[13-15]. According to the study by Macfarlane *et al*[16], protease activities in human ileal effluent, while would be mainly digestive proteases originated from the pancreas, were approximately 20-fold greater than in normal faeces, which may be mainly from bacteria under conventional condition. Another study by Gibson *et al*[17] showed even big differences between the protease activity of the ileal effluent *vs* feces, being 1214 *vs* 20 when casein used as the substrate and 319 *vs* 11 when azocasein used as the substrate, respectively. Thus impaired inactivation of digestive proteases would be capable of causing a more detrimental impact on the lower gut. Multiple large-scale studies also revealed that use of antibiotics increases the risk of IBD[18-21], suggesting impaired inactivation of pancreatic proteases in the lower gut may have played a more critical role in the development of IBD.

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