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Impaired Inactivation of Digestive Proteases and Increased Degradation of Mucus: The Possible Primary Cause of Translocation of Native Commensal Colonic Bacteria and Inflammation by Antibiotics

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I read with great interest a paper published recently in Gut regarding increased inflammation and translocation of native commensal colonic bacteria by antibiotics[1]. It demonstrated the potential pathological change of the gut and body after alterations of native commensal gut microbes by antibiotics. The study found that translocation of live native commensal bacteria across the colonic epithelium played a critical role in increased inflammation and coincident injury by antibiotics. It is further revealed that the translocation of bacteria crossing the epithelium depends on goblet cells, as evidenced by the fact that increased translocation of gut bacteria by antibiotics needs the presence of goblet cells and bacteria were shown to be associated with goblet cells but no other intestinal epithelial cells. The increased translocation of bacteria was explained by the authors of the paper as decreased microbial sensing by goblet cells, as increased bacterial translocation also occurred in the deficiency of Myd88, the key component of the TLR/MyD88/NF-κB signal pathway. The translocation was further explained as the formation of goblet cell-associated antigen passages (GAPs) in the colon. However, it seems these explanations generated more puzzles and questions than answers. As stated by the author, the specific mechanism and pathways by which commensal gut bacteria traverse the colonic epithelial layer remain to be explored. Here I would like to share my simple explanation that impaired inactivation of digestive proteases could be the primary cause for the increased translocation of native commensal bacteria.

Studies showed that under conventional condition digestive pancreatic proteases are hardly detectable in the lower gut, while large amount of digestive proteases appeared in the large intestine of animal raised under germfree condition, or animals or people treated with antibiotics[2-5]. Evidences I collected during the last fifteen years made me to believe that impaired inactivation of digestive proteases due to reduction in gut bacteria along with improved hygiene and inhibition by antibiotics or dietary chemicals such as saccharin and sucralose in modern society may have played critical causative role in the pathogenesis of Inflammatory Bowel Disease (IBD)[6] and probably multiple autoimmune, allergic, metabolic, neurologic, and other diseases that are dramatically increasing and found by more and more studies to be intimately connected with dysbiosis of gut microbiota[7]. Thus, the increased translocation of gut bacteria through goblet cells would be just the result of increased degradation of the mucus in the gut lumen and within the goblet cells by the poorly inactivated digestive proteases. Yet, mucin, the main component of the mucus, is composed of 85% carbohydrate side branches and 15% core peptide, thus its effective degradation needs the presence of both glycosidases enriched in gut bacteria and digestive proteases mainly originated from the pancreas[8]. This may explain the remarkable bacterial translocation by low dose antibiotics, but not at conventional condition when the digestive proteases are effectively inactivated or germfree or high dose antibiotics when both the bacteria load and the bacterial

glycosidases are low.

Importantly, I believe dietary chemicals such as saccharin and sucralose may just act as low dose antibiotics and may have an even big impact on the general population because of the wide use. As for the increased translocation of gut bacteria in myd88 deficiency, my explanation is that it may be caused by a totally different mechanism such as the failure in effective killing of the invaded bacteria that needs the existence of an intact TLR/MyD88/NF-κB pathway to generate free radicals, etc. The finding of this study that the predisposition for increased inflammation was only associated with antibiotics inducing bacterial translocation provided another critical piece of evidence in supporting the notion I proposed about a decade ago that the increases in autoimmune, allergic, and other diseases in modern society are the result of increased exposure of luminal microbial components due to damage of gut barrier by poorly inactivated digestive proteases[7] rather than decreased microbial exposure as suggested by the "Hygiene Hypothesis" cherished by the mainstream of research. Here I recommended again that the role of impaired inactivation of digestive proteases in pathogenesis of the multiple diseases associated with changes of gut microbiota is worthwhile for further study.

Conflict of Interest: None.

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