



## The Close Relationship between Mucosal Healing and Prognoses of Inflammatory Bowel Disease may have just Reflected the Root Mechanism of the Disease

Xiaofa Qin\*

GI Biopharma Inc, USA

\*Corresponding author: Xiaofa Qin, M.D., Ph.D, GI Biopharma Inc, 918 Willow Grove Road, Westfield, NJ 07090, USA, Tel: +1-908-463-7423, E-mail: [xiaofa\\_qin@yahoo.com](mailto:xiaofa_qin@yahoo.com)

More and more studies have shown that mucosal healing on endoscopy has been the key prognostic parameter for inflammatory bowel disease (IBD) that predicts sustained clinical remission and resection-free survival of patients [1-5]. It raised a big question as why the prognosis and long term remission of IBD are most strongly related to mucosal healing as judged by the appearance and integrate of the gut surface under the endoscope, rather than the set of genes the patients being baring, the amount and type of inflammatory cells aggregated in the mucosa, the amounts and type of bacteria found inside the gut and tissue, the type and strength of antibodies in the blood, the feelings and symptoms of the patients, and even those gold standards of clinical remission. Here I suggest this miracle in mucosal healing may actually just reflect the root mechanism of IBD.

About a decade ago, I found that digestive proteases like trypsin and chymotrypsin can be inactivated by free but not conjugated bilirubin. Further pursuit in the literature led me to suspect that impairment in this process as the result of inhibition of gut bacteria (thus the major source of  $\beta$ -glucuronidase that is needed for deconjugation of the mostly conjugated biliary bilirubin) by dietary chemicals like saccharin may have played an important causative role in IBD, by virtue of the damage of the protective mucus layer and the gut barrier by the poorly-inactivated digestive proteases [6]. It provided a simple explanation for many puzzles of IBD such as its emergence around the beginning of last century, its dramatic increase since 1950s, and the leveling off or even decrease of IBD around 1980s as seen in multiple studies. Later, I further found evidence suggesting sucralose, a new generation of artificial sweetener that was first approved in Canada in 1991 followed by many other countries, may also linked to IBD through a similar mechanism as saccharin, which may have contributed to the recent worldwide increase of IBD [7,8]. This led me eventually coming up with a unified hypothesis on the etiology of IBD, including the cause and mechanism of IBD as well as the relationship between ulcerative colitis (UC) and Crohn's disease (CD) [9]. It provided further explanations for the many puzzles in IBD such as the mysterious remarkable increase of IBD in Alberta of Canada since early 1990s, in Brisbane of Australia since middle 1990s, in north California of the United since the end of 1990s, and in South-Eastern Norway since middle 2000s, shortly after the approval of sucralose in Canada in 1991, in Australia in 1993, in the United

States in 1998, and by the European Union in 2004, as well as the especially remarkable recent increase of IBD in children, the shift in the occurrence from UC to CD over time, the increased appearance of CD in the colon, etc [9,10]. This possible link was further demonstrated by multiple more epidemiological studies published thereafter from countries across the world such as the United States [11], Canada [12], Ireland [13], Sweden [14], Singapore [15], Saudi Arabia [16], China [17], etc [18]. More importantly, some peculiar changes in IBD such as the recent decrease in CD but increase in UC in the children in Sweden [14] as well as the shared trend of change of pediatric IBD in Sweden with the general population IBD in Denmark but not pediatric IBD in Norway [19], and even higher incidence of IBD in Guangzhou, China than the adjacent more developed Hong Kong and Macau [18] can also be easily explained by the unified hypothesis through the pattern of consumption of those dietary chemicals.

With evidences accumulating, it suggests that the damage of the gut barrier due to increased degradation of the mucus layer by factors such as the poorly inactivated digestive proteases could be the most primary and fundamental mechanism for IBD, while the inflammatory and immune reaction inside the gut and body are just the natural, secondary response to the increased infiltration of bacterial and dietary components from the gut lumen. It provided a simple explanation for the critical role of mucosal healing in IBD. It suggests the close relationship between the mucosal healing and prognoses of IBD may have just reflected the root mechanism of the disease, an area that would be worthwhile for further study.

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