The role of diet in inflammatory bowel disease

Impact paragraph

Inflammatory bowel disease (IBD) is a chronic relapsing-remitting inflammatory disease of the gastrointestinal tract, with ulcerative colitis (UC) and Crohn's disease (CD) as the two main forms. IBD is characterized by periods of active disease alternated with remission. It can be very painful and debilitating, and can sometimes lead to serious complications. The burden of IBD is rising globally with over 1 million residents in the USA and 2.5 million in Europe are estimated to have IBD [1]. According to a study by researchers from the Crohn's and Colitis Foundation updated in 2020, people with IBD in the United States have more than triple the total healthcare cost and twice as high out-of-pocket healthcare expenses as compared with people without IBD [2]. The costs of care for IBD have been increasing over the last several decades, driven by specific therapeutics and disease features [2, 3]. Especially, the costs can escalate because of the chronic nature of the disease and the ongoing clinical monitoring and treatments needed during patient's life. Moreover, IBD incidence has emerged in newly industrialized countries in Asia, South America, and Middle East, which might be due to two underlying factors: first, the unmasking of incidence in which economic progress improves awareness of IBD and access to healthcare; and second, a true rise in incidence due to Westernization of society, such as diets containing higher levels of fat and refined sugar [4, 5]. Evidence suggests that dietary factors might act as environmental triggers in the development of IBD, as well as in the progression and treatment of IBD [6]. Therefore, it is important to gain further insight into the role of dietary factors in IBD onset and disease course, in order to optimize intervention strategies and reduce costs and improve disease outcome and quality of life.

In current thesis, different kinds of *in vitro* cellular models combined with observational human studies were applied to explore the various dietary effects in IBD. We identified the dietary factors that were associated with the genotoxicity of fecal water derived from IBD patients and healthy individuals (Chapter 2). In Chapter 3, we compared the effects of fermentation products from three high protein diets on gut health, and found that protein source is an important factor that affects microbial metabolism and hence modulates barrier function and immune response, key processes associated with IBD. In chapter 4, we

identified perturbations of intestinal tryptophan metabolism in IBD. Tryptophan is an important precursor of aryl hydrocarbon receptor (AhR) ligands. We showed that the fecal levels of tryptophan and its metabolites were associated with AhR activation ability of fecal water, and intestinal inflammation as indicated by fecal calprotectin level. We further summarized previously published transcriptome and metabolome data to gain a complete understanding of changes in three intestinal tryptophan metabolic pathways in IBD patients with varying inflammatory status and phenotypes (Chapter 5). In Chapter 6, we reviewed so far reported dietary AhR modulators which could be present in the gut, and summarized the role of intestinal AhR activity in intestinal inflammation and discussed the challenges of dietary AhR modulators as targets for IBD management. Our studies gain more knowledge concerning the dietary effects on the development and/or management of IBD, and further elucidate the possible underlying mechanisms through regulating AhR signaling. Our findings within this thesis might have implications for researchers, clinical professionals and IBD patients, and whole society.

Implications for researchers

Further dietary intervention studies with improved study design are required in the future to assess the efficacy of dietary factors (such as dietary protein, tryptophan metabolites and dietary AhR ligands) in IBD management. Additionally, large variations were observed in individual responses to dietary factors in our studies. For example, there was a large variation in genotoxicity of fecal water derived from IBD patients with similar dietary patterns. Moreover, the fecal concentrations of tryptophan metabolites varied between IBD patients with comparable dietary intake of tryptophan. This might result from the dynamic heterogenous presentation and pathophysiology within the different IBD patients. Therefore, personalized nutrition approaches are required to answer IBD patients' key question "what foods may contribute to IBD and what should I eat?". More patient-based studies in the future will be needed to identify those that respond more favorably to certain dietary factors or dietary interventions than other, and find individual genetic, epigenetic, microbial and/or metabolic signatures that can predict these responses.

With regard to the research in AhR, we showed that the fecal concentrations of tryptophan metabolites were associated with the ability of fecal water to activate the AhR, and intestinal inflammatory status (Chapter 4). However, the tryptophan metabolites were not the main AhR agonists in the fecal samples. AhR ligands in the feces mostly come from various dietary ligands and microbial metabolites. Therefore, AhR ligands characterization of fecal samples might be an important step to reveal the AhR biology in the gastrointestinal tract, as well as the interaction between food intake, gut microbiota, and host cellular function. Furthermore, when compared to fecal water from healthy individuals, fecal water from IBD patients induced lower AhR activation, which aid in understanding the mechanisms of IBD pathogenesis. Identification of AhR ligands in the feces can be linked to their food precursors and potential involved gut microorganisms. Consequently, modulating intestinal AhR activity by recommending specific food intake and/or modulating gut microbiota by prebiotics/probiotics may have preventive and therapeutic potential for IBD patients to induce and/or maintain remission, without or with less pharmacological interventions.

Lines of evidences have identified the role of AhR in modulating immune/inflammatory process. In addition to IBD, AhR were found to be involved in many other diseases including major depressive disorders, multiple sclerosis, rheumatoid arthritis, asthma, and allergic responses, among others [7]. The preventive and therapeutic targets based on AhR activation might also be interesting for these diseases.

Implications for clinical professionals and IBD patients

It is crucial for patients with IBD to consult with clinical professionals, such as gastroenterologists and/or dietitians, who can provide personalized advices based on the latest research and clinical guidelines. They can help monitoring the disease, guiding dietary modifications, and to ensure nutritional adequacy while managing IBD. The current thesis gains more insight into the role of diet in IBD, which will help gastroenterologists/dietitians to develop more detailed dietary guidance for IBD patients.

In this thesis, we identified some specific food groups, nutrients and dietary patterns that were correlated to the genotoxic potential of fecal water from IBD patients and healthy controls (Chapter 2), which may aid in defining dietary suggestions for IBD patients to reduce

the risk of developing IBD-associated dysplasia. Chapter 3 showed that high protein diet with different protein sources divergently affect gut microbiome metabolism and gut health. It is recommended by European Society for Clinical Nutrition and Metabolism (ESPEN) that IBD patients with active inflammation should increase the intake of dietary protein (more than the Recommended Dietary Allowance for protein), but the protein sources are not indicated. Our study suggests that clinical professionals should consider the influence on colonic health when choosing protein sources for high protein diet. Moreover, we explored the involvement of intestinal tryptophan metabolism and dietary AhR ligands in the pathogenesis of IBD (Chapter 4-6). Our findings can help the clinical professionals to provide more tailored advice on dietary intake and gastrointestinal symptoms or disease course in daily practice. For example, monitoring the tryptophan and its metabolites in feces and blood could be a potential biomarker for clinical professionals to predict inflammatory status of the gut and IBD related psychiatric disorders as indicated by the results from Chapter 5. Furthermore, supplementation of tryptophan metabolites, dietary AhR ligands and/or probiotics that regulate intestinal AhR activity could be potential treatments for IBD symptoms.

Implications for Society

Growing understanding of dietary implications for IBD pathogenesis will result in an emphasis on nutritional education in schools and public health initiatives. The education will increase public knowledge about the importance of dietary choices and promote healthier eating habits for individuals. Moreover, the nutritional education may influence broader lifestyle changes in general population. People may adopt healthier diets and lifestyles, incorporating more anti-inflammatory food, to promote overall gut health and reduced the risk of developing IBD or other gastrointestinal disorders.

In addition, ongoing research on dietary effects on IBD will increase options for therapeutic strategies for IBD patients, such as dietary interventions and/or medications that targeted inflammation and improve gut health. This will help to decrease flare occurrence, hospitalization rates, surgery, and extra-intestinal manifestations, which is of great importance for IBD patients' overall well-being, and may improve work productivity and social participation. This will also beneficial for both direct and indirect healthcare cost. The

decreased incidence and improved long-term outcome of IBD will reduce the burden to healthcare systems and improve the individuals' quality of life.

References

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