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Chairman of Chinese Digestive Psychosomatic Union
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Role of duodenal inflammation in functional dyspepsia

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Abstract: Functional dyspepsia (FD) refers to recurrent upper gastrointestinal (GI) symptoms with no structural explanation. As one of the most common functional GI disorders, no cure for FD has been established and thus significantly affects quality of life of patients. The pathophysiology of FD is currently still not fully elucidated. Delayed gastric emptying, visceral hypersensitivity, *Helicobacter pylori* infection, abnormal brain-gut interactions, and environmental factors such as psychological events are considered to contribute to the pathogenesis of FD. A growing body of evidence points towards the duodenum as the pathogenic center for symptom generation in FD. Duodenal inflammation may serve as a major trigger for FD symptoms. Impaired duodenal mucosal integrity and low-grade inflammation have been demonstrated in patients with FD. Of note, it has been shown that they are associated with generation of dyspeptic symptoms. Thus, understanding of mechanisms underlying duodenal pathology will be helpful for the discovery of new therapeutic targets.

Key words: dyspepsia; duodenum; eosinophil; mast cell; immune

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Introduction

Functional dyspepsia (FD) refers to recurrent upper gastrointestinal (GI) symptoms with no structural explanation. According to Rome IV consensus, FD is classified into the following two subgroups: (i) postprandial distress syndrome (PDS) with meal-related symptoms of postprandial fullness and early satiation, and (ii) epigastric pain syndrome (EPS) with meal-unrelated epigastric pain and epigastric burning. All these symptoms exist for at least 6 months. As one of the most common functional gastrointestinal disorders (FGIDs), it affects up to 16% of the general population[1,2]. Currently, no cure for FD has been established; therefore, it greatly affects quality of life and social activities of the sufferers. Current treatment approaches include eradication of *Helicobacter pylori* (*H pylori*) to *H pylori* -positive patients, acid suppression therapy (e.g. proton pump inhibitors (PPIs) and histamine-2 receptor antagonists), prokinetic agents, and central neuromodulators such as tricyclic antidepressants [3].

To date, the pathophysiology of FD is still not fully elucidated. Delayed gastric emptying, visceral hypersensitivity, *H pylori* infection, abnormal brain-gut interactions, and environmental factors such as psychological events are considered to contribute to the pathogenesis of FD[3]. Recently, the role of duodenal pathology associated with abnormal immune activation, especially low-grade inflammation, in the pathophysiology of FD attracts great attention. Low-grade duodenal inflammation has been considered to be an important trigger for the generation of FD-associated symptoms[4-7]. In the current mini-review, we summarize the recent advances about the role of duodenal inflammation in the pathogenesis of FD based on the publications.

Duodenal mucosal inflammation in FD

The duodenum is critical for the coordination of gastro-duodenal function. The passage of partially digested food as chyme to the small intestine from the stomach is regulated by the duodenum. At this intestinal segment, a variety of autocrine and paracrine mechanisms are involved in the mucosal defense against acid and luminal nutrient digestion with bile acid and pancreatic juice secreted into the lumen[8]. Under physiological conditions, the activation of duodeno-gastric feedback reflex by luminal chemicals (such as bile acids or lipids), via inhibition of gastric motility, can protect the duodenum from excess acid or lipid exposure[9]. Accumulating data point towards the duodenum as a key integrator in generation of dyspepsia symptoms associated with FD. For example, a previous study demonstrated that infusion of the duodenum with acid induced gastric motility abnormalities, visceral hypersensitivity, and other physiological abnormalities associated with dyspeptic symptoms[10].

Eosinophils and mast cells are normally distributed in the GI tract (except for the esophagus). Elevated quantity and activation (clustering and degranulation) have been demonstrated in patients with FGIDs, including FD subtypes (PDS and EPS)[11-14]. Increased infiltration of both eosinophils and CCR2-positive macrophages into the duodenal mucosa and focal aggregation of $CD8^+$ T cells have been found in patients with post-infectious FD, indicating persistent activation of cellular immune response after the initial infectious episode[15,16]. Importantly, duodenal immune cells have been shown to be correlated with FD symptoms. It has been shown that increased mucosal eosinophil counts in the duodenum are associated with early satiety, postprandial fullness, and abdominal pain in Australian adults[17]. In another study on children with FD, duodenal eosinophil counts >112/mm^2 was identified as a predictive factor for FD[18]. Moreover, it has been demonstrated that increased serum cytokine (tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and IL-10) levels and elevated circulating "gut homing" T cell ($CD4^+α4β7^+CCR9^+$) counts are correlated with the severity of symptoms (upper abdominal pain, cramps, nausea, vomiting, and delayed gastric emptying) in patients with FD[19]. Therefore, cellular immune activation with increased duodenal mucosal eosinophil and mast cell counts and elevated small bowel homing T cells may be a key factor contributing to the clinical manifestations of FD.

Potential causes of DI

Duodenal barrier defect and immune activation

Besides sensing of acid and nutritional components,

trans-mucosal passage of luminal content such as immune cells, cytokines, and microorganisms occurs in the duodenum. This process is modulated by the apical junction complex (consisting of tight junctions, adherens junctions, and desmosomes), which is critical for gut barrier function[20]. Several groups reported an impairment of barrier function in the duodenum in patients with FD, as reflected by increased duodenal mucosal permeability (in vivo mucosal electrical impedance and ex vivo Ussing chambers), decreased expression of tight junctions, adherens junctions, and desmosomes[13, 21]. Interestingly, these changes may correlate with the duodenal number of mast cells, eosinophils, and macrophages as well as duodenal IL-1β expression[13, 21]. In addition, a study performed by Vanheel et al. on patients with FD (Rome III) suggested that impaired duodenal barrier function may promote the trans-epithelial passage of luminal antigens, leading to low-grade inflammation[13]. These findings indicate that subtle inflammation and increased mucosal permeability in the duodenum could be closely related and that increased permeability of duodenal mucosa may be indicative of the presence of mucosal immune activation in the duodenum.

The cause of the duodenal barrier defect and abnormal immune activation in FD is still unclear. However, several factors have been suggested to be possibly involved in these pathological processes, including bile acids, microbial components, psychological stress, and food antigens[4,5].

Disruption of bile acid-microbiota-epithelial barrier homeostasis

Duodenal luminal factors, including bile salts, are candidate risk factors for FD[1]. In a study on patients with FD (Rome III; *n* =17), Beeckmans et al. found decreased fasting concentration of primary bile salts and increased receptor expression in the duodenum compared with healthy controls (with fewer deconjugated bile salts)[22]. Similarly, another study revealed that bile salt components in the duodenum of patients with FD are different from that in healthy subjects[23]. It has also been reported that the bile salts released into the duodenum may trigger or worsen meal-related dyspeptic symptoms in patients with FD[24,25]. These data suggests that altered bile salt pool may be associated with the pathogenesis of FD.

The duodenal epithelium, in addition to being responsible for the uptake and transport of dietary nutrient components, also acts as a critical physical and biochemical barrier to prevent the passage of harmful bacteria and antigens into the mucosa. For FD, the duodenum is of particular importance due to the observed mucosal immune activation, low-grade inflammation, and exposure to the stomach-derived acid. Recently, Keely & Talley proposed disruption of bile acid-microbiota-epithelial barrier homeostasis as a key pathophysiological process driving FD[26]. A reduction in primary bile salt amounts in the duodenum may influence microbial diversity of this intestinal segment, leading to an overgrowth of pro-inflammatory bacteria and the resultant low-grade mucosal inflammation. These changes could cause epithelial barrier dysfunction in the duodenum.

Dysregulated brain-gut interactions by psychological stress

Psychosocial stress, via activating hypothalamic-pituitary adrenal and/or sympathoadrenal axis, is a major trigger for the development and relapse of FD symptoms[3]. Emerging evidence supports the notion that psychosocial stress, via disrupting brain-gut interactions, may be involved in mucosal inflammation in the intestine, particularly in the proximal segments. Lee reported that chronic restraint stress induces low-grade inflammation of the proximal intestine, manifested as mild lymphocytic infiltration and irregular crypts[27]. In addition, a recent study revealed that peripherally administrated corticotropin releasing hormone (CRH; to induce psychosocial stress) aggravates intestinal inflammation via inducing intestinal macrophage autophagy[28]. Of note, it has been reported that chronic restraint stress induces CRH expression in mucosal eosinophils in the intestine of mice. This effect is mediated by the mast cell mediator substance P and companied with the impaired jejunal permeability upon activation of mast cells by eosinophil-derived CRH[29]. Also, it has been reported that the eosinophil-mast cell signaling axis are implicated in stress-induced increase in mucosal permeability as peripheral administration of CRH, which activates the specific receptors on both

eosinophils and mast cells, increases permeability of the small intestine; this effect can be blocked by pretreatment with disodium cromoglycate, a mast cell stabilizer[30,31]. These findings are in support of the notion that stress-induced intestinal barrier defect may be associated with immune activation. In the study of Vanuytsel et al.[31], there is other evidence suggesting that psychological stress leads to increased intestinal mucosal permeability via mediation of mast cells. In this study, healthy volunteers were subjected to a form of psychological stress (a public speech) and measurement of intestinal mucosal permeability (indicated with the lactulose–mannitol ratio). The authors found that this form of psychological stress caused increased mucosal permeability, which was also abrogated by pre-treatment with disodium cromoglycate. Based on these findings, we suggest that psychological stress, via disrupting brain-gut interactions, may play a critical role in duodenal inflammation and mucosal barrier impairment.

Management of FD via intervening duodenal inflammation

Based on recent advances in the understanding about the role of duodenum inflammation in the pathogenesis of FD, reducing duodenal inflammation is an important strategy for the treatment of FD and thus duodenal eosinophils and mast cells may serve as potential therapeutic targets for FD therapy. Recent clinical studies demonstrate that PPIs alleviate FD symptoms via reducing duodenum inflammation, which may be exerted through reducing duodenal eosinophils and mast cell counts[32,33]. Therefore, except for potent acid suppressant effect, the anti-inflammatory actions of PPIs may also underlie their therapeutic efficacy in FD. Notably, further studies are still urgently needed to unravel the detailed mechanisms underlying duodenal immune activation and barrier defect in search for more efficacious therapeutic strategies for FD therapy.

Conclusion

Recently, the paradigm of FD as a functional gastroduodenal disorder with no evidence of structural abnormality has been challenged. Although the Rome IV criteria potentially admit that microscopic changes such as duodenal eosinophilia could exist[2], many studies have not currently taken duodenal inflammation into consideration. Accumulating data point towards the duodenum as the pathogenic center for symptom generation in FD. Duodenal inflammation may serve as a major trigger for FD symptoms. Thus, understanding of duodenal pathology associated with mucosal immune activation and the resultant low-grade inflammation will be helpful for the discovery of new therapeutic approaches, which may be useful for biologically targeted FD therapy.

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Conflicts of interest statement

None declared.

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