Review Article

Immunoinflammation and Functional Gastrointestinal Disorders

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ABSTRACT

Functional gastrointestinal disorders (FGIDs) are a group of conditions characterized by the dysfunction of the gastrointestinal (GI) tract. Although the specific pathogenesis of FGIDs is unclear, several theories have been proposed to explain the symptoms. Abnormal GI motility and visceral hypersensitivity have always been considered to be the main physiopathologic basis of FGIDs, and FGIDs related to psychomental disorders have also caused a major social concern. In recent years, a growing number of researches have proved that cytokines have a significant influence on GI motility, and the role of cytokines in FGIDs has aroused more and more attention. In this article, we discuss the interaction between immunoinflammation and FGIDs, and make an overview of current studies.

Key Words: Cytokine, depression, functional gastrointestinal disorders, psychomental disorders

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Functional gastrointestinal disorders (FGIDs), including functional dyspepsia (FD) and irritable bowel syndrome (IBS), are defined as a variable combination of chronic or recurrent gastrointestinal (GI) symptoms that do not have an identified underlying pathophysiology.[1] In Asia, the prevalence of FD has already reached 8–23%, with a 23.5% point prevalence reported for China, and prevalence of IBS in Chinese adults was between 5–10%.[2,3] The specific pathogenesis of FGIDs remains unclear. Several pathogenetic factors, including gastrointestinal dysmotility, visceral hypersensitivity, immune activation, psychomental factors, and dysfunctional brain–gut axis, were considered to be important in the development and progression of FGIDs.[3-5] In this article, we will review the evidence on the role of inflammation and immunity in FGIDs, which may be useful in understanding the pathogenesis of FGIDs.

FGIDS AND PSYCHOMENTAL DISORDERS

With the conversion of biomedical pattern into bio–psycho–social pattern, growing attention is attracted to the role of psychomental factors in the function of GI motor and the progression of FGIDs. IBS is a typical representative of FGIDs and the most frequent psychomental disorder is depression.[6] Relative data[7,8] have indicated that 94% of IBS patients had lifetime mental disorders and general anxiety disorders, and major depressive disorders can occur in up to 90% of patients.

Various social factors, such as mental stress, depression, and anxiety neurosis, are associated with the pathogenesis of FD and IBS. Substantial studies showed that GI symptoms were significantly relieved in these patients with the use of psychotherapies, thus indicating a close relationship between the GI system and the psychomental status.[9,10] A systematic review of 1717 FD patients studied the medication of axiomatic agents and/or antidepressants, concluding that the use of axiomatic agents and/or antidepressants appear to be obviously beneficial compared with placebo.[11] This suggests that the treatment with axiomatic agents and particularly anti-depressants are usually helpful to FD patients, and is thus considerably important.

Depression is characterized by a common mental pathologic status, with main clinical symptoms of continuous low mood or sadness. Studies in recent years tend to regard depression associated with changes of central nervous system function due to immune activation.[12] Cytokines are important components of inflammatory mediators secreted by immune cells and their expression is usually abnormal in many psychologic disorders.[13,14] According to the different

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roles in inflammatory reactions, cytokines can be classified as proinflammatory cytokines and anti-inflammatory cytokines. The former mainly include IL-1, IL-2, IL-6, IL-12, IFN-α, IFN-γ, TNF-α, TNF-β, and so on; the latter include IL-4, IL-10, IL-13, and so on.

In recent years, a series of researches have shown that the level of IL-6 *in vivo* is an important biological marker, which reflects the severity of depression.[15-17] The study by Blume *et al*[15] indicated that in patients with depression, the immune system may not only be inhibited, such as the decrease of natural killer cell cytotoxicity, but also be overactivated, such as the increase of C-reactive proteins (CRPs), IL-6, and TNF-α; Howren *et al*[16] originally conducted a large meta-analysis about the relationship between depression and inflammatory factors and they have found that CRP, IL-1, and IL-6 clearly have a strong dose–response relationship; Yildirim *et al*[17] have suggested that the immune system may perceive various mental or physical stresses, leading to increased secretion of many inflammatory cytokines, including IL-6. IL-6 is a powerful regulator of corticotropin releasing hormone (CRH), and the increase of CRH may also promote the pathogenesis of depression. This positive feedback pathway between IL-6 and the hypothalamic-pituitary-adrenal axis (HPA axis) may result in their reciprocal activation and maintain the symptoms of depression.

IMMUNOINFLAMMATION AND FGIDs

Immunoinflammation and GI motility

In recent years, a number of studies have found the important effect of inflammatory factors on GI motility. GI motility disorder is closely related with various diseases, such as acute enteritis, inflammatory bowel disease, intestinal pseudo-obstruction, and IBS. Nowadays, emerging evidence is found to prove the close relationship between immunoinflammation and GI motility. Immunocyte infiltration of the GI tract is the main histologic change occurring in some of the GI motility disorders. Inflammatory mediators released by the infiltration may induce the alteration of GI motility.[18] An elevation of inflammatory factors, including IL-1β, TNF-α, and IL-6, was found in both IBD and postoperative ileus patients and it should be noted that in IBS patients, no pathomorphologic changes were observed, whereas the elevation of IL-6 was found in the region with gastrointestinal dyskinesis.[19] A study on gastroesophageal reflux disease showed that when the esophageal epithelial cells come in contact with the gastric juice, a great deal of IL-1β and IL-6 could be produced to reduce esophageal muscle contractility.[20] In a murine model of entericnematode parasite infection, Th2 type of immune response was found to be predominantly associated with protective immunity. Th2 cytokines, including IL-4 and IL-13, increased significantly during the acute stage of infection and they could promote the development of T cells, reinforce intestinal muscle contractility and in turn contribute to the worm expulsion process.[21]

FGIDs and immunoinflammation

It has already been shown that a low-grade mucosal inflammation and immune alteration could be found in IBS patients.[22] The persistent low-grade mucosal inflammation could destroy the function of intestinal mucosal barrier, increase its permeability, reduce the absorption of water and sodium, and finally result in diarrhea. Meanwhile, the inflammation might induce the overexposure of antigens, the absence of brush border, and the activation of the mucosal immune system, which might result in the increase of inflammatory cells and immunocytes, such as mast cell, mononuclear macrophage, and endocrine cell.[22-24]

Besides the variation of inflammatory cells and immunocytes, cytokines released by these cells also changed. Ohman *et al*[25] indicated various kinds of proinflammatory cytokines, including IL-1β, TNF-α, and IL-6, played an important role in the development of IBS. In contrast, Kindt *et al*,[26] found that the inflammatory reaction in FGIDs patients was mainly associated with anti-inflammatory cytokines, such as IL-5 and IL-13, whereas there was no obvious change in the proinflammatory cytokines. The abnormality of immunoinflammation could present in both IBS and depression patients.[19] Therefore, we presume that, similar to depression, immune system may not only be inhibited but also be overactivated. This hypothesis may further show the daedal relationship between depression and FGIDs.

MECHANISM OF MEDIATORS OF INFLAMMATION ON THE PROGRESSION OF FGIDs

The mechanism of FGIDs induced by inflammatory mediators is still unclear. Many studies suggested that although the activation of intestinal immune system could only be found in the intestinal mucosa, inflammatory cells, such as macrophages and mast cells, could release a large amount of inflammatory factors by acting on interstitial cells of Cajal (ICC), GI smooth muscles, and enteric nervous system, which might influence the GI motor and sensory function.[27,28]

ICC and immunoinflammation

The ICC are the pacemaker cells in GI tract and serve as a basis for the generation of slow-wave activity. In recent years, a series of researches have indicated that ICC play an important role in the mechanism of generating electric activity and the regulation of motility in the GI tract. More and more concerns have been aroused in injury of ICC induced by GI immunoinflammation, and ICC is closely

related to mast cells (MC) and macrophages. A relevant study indicated that MC could synthesize various kinds of cytokines, such as ILs, IFNs, and TNFs, which might connect MC with leukocytes and induce the local infiltration of inflammatory cells.[29] Inflammation of ICC might also induce the abnormal changes of ultrastructure and the loss of synchronism in electric activity.[27,30] In a well-described model of inflammation (infection by *Trichinella spiralis*) to the mouse jejunum, the protuberant parts of ICC were injured, and the contacts between ICC and smooth muscle cells, as well as ICC and neuron cells, were disturbed and decreased.[31] Macrophages were found to infiltrate into the myenteric nervous plexus and, lymphocytes entered the musculature and formed close contacts with ICC. Based on our earlier research, morphologic changes of ICC could be found in the chronic stress depression model rats, which might result in the abnormal connection with enteric nervous system and impaired contractile function of intestinal smooth muscles mediated by ICC.[32] The alteration of ICC may be responsible for the change of pathophysiology in abnormal GI motility induced by FGIDs. Stress might also increase the amount of inflammatory factors. Therefore, we presume that inflammatory cytokines may induce the FGIDs by impairing the function of ICC.

GI smooth muscles and immunoinflammation

Wehner *et al*[33] indicated that abdominal surgery could result in an inflammatory response in the intestine, which might lead to postoperative ileus, and resident macrophages within the intestinal muscularis had an important role in this local inflammation. They also proved that inflammatory mediators and adhesion molecules, including IL-1β and IL-6, had a close relationship with the contractile function of the intestine.

Recently, investigators have demonstrated in rodents that preoperative glycine treatment inhibit the occurrence of postoperative ileus.[34] In addition, they also found that preoperative glycine injection significantly reduced the induction of IL-6, TNF-α, and infiltration of mast cells on the intestinal wall compared with that in the controls. To our knowledge, glycine treatment was first used for protection against ischemia-reperfusion injury of mucosa by inhibiting the activity of Kupffer cells and reducing the release of cytokines. Similarly, preoperative glycine reduced postoperative ileus principally because it could significantly inhibit the release of inflammatory mediators in myenteron. Furthermore, their animal experiment proved that glycine could downregulate the expression of TNF-α mRNA and IL-6 mRNA, and reduce the protein synthesis and the expression of IL-6 mRNA.[35] These results further showed that inflammatory mediators play an important role in the contraction of GI smooth muscles.

Electrogastrography (EGG) is a noninvasive method used to detect the myoelectric activity of GI smooth muscles by placing surface electrodes on abdomen, particularly for the examination of stomach. Maruna *et al*[36] examined patients with open cholecystectomy and laparoscopic cholecystectomy by EGG, respectively, and they found that disorders of GI motility were related to the systemic inflammatory response. Further observation indicated that the concentration of IL-6 correlated positively with the degree of GI dysfunction. The maximal concentration of plasma IL-6 could be as high as 464 ng/L (371–576 ng/L), and with the level of IL-6 decreased, GI motility recovered gradually. However, another study revealed that IL-6 may arouse the contraction of *in vitro* proximate colonal smooth muscles of guinea pig; the amplitude and frequency of contraction would be increased with a pattern of concentration-dependent IL 6 (20, 40, 80 μg/L); it also demonstrated that the effect of IL-6 on smooth muscles is mainly mediated by intestinal neuron.[37] These contradictive results may be attributed to the different concentrations of IL-6 acting on intestinal smooth muscles.

Recently, some found that the response to neuron, the open duration of Ca^{2+} channel and the amplitude of smooth muscle tissue exposed to IL-1β showed a pattern of concentration-dependent.[18] As the concentration of IL-1β in smooth muscle (*in vitro*) perfusion groove was elevated from 10^{-9}mol/L to 10^{-8}mol/L, the open rate of Ca^{2+} was increased from 17.3% to 24.7%; the result has indicated that IL-1β may directly act on Ca^{2+} channel on GI smooth muscle cell membrane, thus affecting on the intestinal motility function.

VISCERAL HYPERSENSITIVITY AND INFLAMMATION

Some investigators have considered that the infiltration of mast cells into the surrounding of mucosal nerves might lead to abdominal pain in IBS patients.[25] The succedent animal experiment also proved that mast cells could stimulate the hypersensitive neurons and produce relevant symptoms. The specific mechanism is considered to be explained by a recently identified adhesion molecule, cell adhesion molecule-1 (CADM1). CADM1 can be expressed by various cell types and promotes communication between nerves or smooth muscles and mast cells. The result of interactions among mast cells, nerves, and smooth muscles is a hypersensitivity of nerves to stimulation, resulting in elevated smooth muscle contractility. Therefore, the effect is thought to contribute to the symptoms of IBS.[38] Recently, Yan *et al*[39] studied the interaction between visceral hypersensitivity and inflammation. The results indicate that the expression levels of IL-1β and TNF-α in colon are significantly higher in the rats of chronic visceral hypersensitivity than in controls. The proinflammatory

cytokines sensitize the peripheral nociceptors, so that the increased level of these cytokines may be an important contributory factor that causes visceral hypersensitivity.

CONCLUSION

Increasing importance has been attached to the FGIDs caused by psychomental disorders. The most frequent psychiatric disorder in FGIDs patients is depression. Infiltration of inflammatory cells can be identified in the alimentary canal of FGIDs patients and they release a great quantity of inflammatory factors to act on GI smooth muscles, enteric nervous system, and ICC. Release of these inflammatory factors may eventually influence the GI motility and sensory function. A succession of immunoinflammatory changes occur in depression patients and may be relevant to the functional disturbances of the GI tract, however, the specific mechanisms remain to be investigated.

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