Mini Review

Current Status and Challenges of Inflammatory Bowel Disease in China

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Abstract

Inflammatory bowel disease (IBD) is characterized by two major disorders, ulcerative colitis (UC) and Crohn's disease (CD). The incidence and prevalence of IBD are increasing in past few years in China, although the etiology and pathogenesis of IBD is not fully understood. It is considered that persistent intestinal infection, dysregulation of immune responses, damage of mucosal barrier, environmental and genetic factors contribute to these disorders. In this mini-review, we discuss the current status of IBD in China with characteristics in epidemiology, approaches in the pathogenesis, and advances in diagnosis and treatment. Moreover, we also analyze the modern challenge on IBD research and clinical study.

Keywords: Inflammatory bowel disease; Epidemiology; Pathogenesis; Diagnosis; Treatment

Introduction

Crohn's disease (CD) and ulcerative colitis (UC), two common forms of inflammatory bowel diseases (IBD), are chronic and relapsing inflammatory disorders of the gastrointestinal tract. Although the etiology and pathogenesis of IBD remain uncertain, it is believed that persistent intestinal infection, dysregulation of immune responses, damage of mucosal barrier, environmental and genetic factors contribute to these disorders. IBD patients often suffer from diarrhea, abdominal pain, malnutrition, weight loss, intestinal stenosis, intra-abdominal abscess and fistula formation, additionally, varying degrees of extraintestinal manifestations, even cancer. However, many patients need surgery unfortunately because of the failure of medication and severe complications. Recent years, with novel approaches of immunology, pathology, microbiology, and molecular biology, understanding on the pathogenesis of IBD has greatly improved. Although great achievements on IBD research have been made in China recent years, there is still much challenge in managing these diseases. In this review, we discuss current status and challenge of IBD in China, and put forward more potential approaches in understanding and management of the disease.

Epidemiology of IBD

With the change of lifestyles and environmental factors (such as industrialization, urbanization), as well as the improvement of health care system in China, the incidence and prevalence of IBD have been improving rapidly. Currently, IBD is no longer considered to be a rare disease in China. The national hospital-based studies have revealed that the incidences of CD and UC are $0.848/10^5$ and $1.0-2.0/10^5$, respectively, which are significantly lower than those in Caucasians in Europe, being $14.6-17.4/10^5$ and $7.6-14.3/10^5$, respectively. The prevalence of CD and UC is $2.29/10^5$ and $11.4/10^5$, respectively, in China, which is also significantly lower than in Western countries, being $155.2-279.2/10^5$ and $145-238/10^5$, respectively [1,2]. The data of population-based studies are rare in China. Recent epidemiological survey in Wuhan City (Hubei Province, Central China) was conducted

and demonstrated that the incidences of CD and UC are $0.51/10^5$ and $1.45/10^5$, respectively [3]. Another work demonstrated that the incidences of CD and UC are $1.09/10^5$ and $2.05/10^5$, respectively, in Zhongshan city (Guangdong province, southern China) [4]. The current challenge of epidemiological studies is that research data cannot really reveal the exact numbers of IBD in China, because the majority of patient files are from individual referral centers. The results from local areas are not enough to represent true incidence of IBD at national level.

To date, there is a lack of large population-based epidemiological study in China. Various factors are being taken into consideration in the clinic, such as the high incidence of intestinal infectious diseases, poor understanding on the disease, the unstandardized criteria for intestinal histological, endoscopic and radiologic diagnoses, the inconvenient follow-up because of population migration, and the lack of an advanced level (e.g., national level) for population-based registries, thus, the research on epidemiology of IBD is markedly limited in China.

Approaches in the pathogenesis of IBD

Genome-wide association studies (GWSA) have identified some mutation of IBD susceptibility gene loci in Caucasian patients, such as NOD2/ARD15 (e.g., R702W, G908R, 3020insC), ATG16L1 (rs2241880 A/G), and IL-23R polymorphism (e.g., rs1004819, rs10889677, rs2201841, rs11465804, rs11209026). However, these susceptibility gene loci have been found not to be mutated in Chinese IBD patients. Recent work has demonstrated that gene polymorphisms of rs7530511 and rs11805303 of IL23R, rs60872763 of CTLA-4 are associated with Chinese IBD patients, suggesting that there are huge difference between Chinese and Caucasian IBD patients in the susceptibility genes [5,6]. This may attribute to quite small samples of IBD patients, inadequate research funding and weaker research teams, leading to slow progress in study of susceptibility genes in Chinese IBD patients.

It is well known that gut microbiota plays an important role in

human health and energy balance, which provides protection against diseases in the gut, such as infectious diseases. The concentrations of bacteria in the intestinal lumen and levels of microbial antigens are significantly higher in IBD patients compared with healthy controls. Bacterial dysbiosis, the reduction of mucosal barrier and immune dysregulation have been found to contribute to the occurrence of intestinal mucosal inflammation among susceptibility populations [7]. However, the mechanism whereby intestinal microbial antigens are absorbed and degraded by the intestinal epithelial cells causing an abnormal immune response in the intestinal mucosa remains unclear. Nucleotide-binding oligomerization domain 2 (NOD2), expressed in intestinal epithelial cells and Paneth cells, is an important innate immune sensor of bacterial pathogens. It recognizes muramyl dipeptide (MDP) and presents on most types of peptidoglycan (PGN) produced by Gram-negative and some Gram-positive bacteria in the gut through C-terminal series of leucine-rich repeats (LRRs) to regulate the innate immune response in intestinal mucosa and maintain the integrity of intestinal barrier. Intestinal intraepithelial lymphocytes (IEL) play an important role in the homeostasis of intestinal mucosa, and loss of them results in impaired intestinal barrier function and higher bacterial penetration of the intestinal mucosa, suggesting the protective role of IELs in IBD. Recent study [8] reported that the numbers of IELs are significantly reduced in Nod2$^{-/-}$ mice and that the mucosal adaptive immunity is dysregulated, leading to the disorder of intestinal mucosal environment and intestinal inflammation. The intestinal epithelial barrier consists of epithelial cells and intercellular junctions. Tight junction (TJ) is the apical-most intercellular structure in epithelial cells and plays a crucial protective role in intestinal barrier. Once the intestinal barrier is breached, the submucosa is exposed to a vast pool of luminal antigens, including diets and bacteria, and the innate immune responses are engaged to produce large amounts of cytokines such as IL-12, IFN-γ, and IL-10. This event results in the development of mucosal inflammation. Long isoform of myosin light chain kinase (MLCK) upregulation, myosin II light chain phosphorylation, barrier loss, and weight loss were attenuated in TNFR$^{-/-}$, but not TNFR1$^{-/-}$ in the colitis model of Rag1$^{-/-}$ mice transferred of CD45RB^{high} CD4$^+$ T cells. Therefore, in immune-mediated IBD models, TNFR2 signaling promotes long MLCK expression, resulting in TJ dysregulation, barrier loss, and induction of colitis. At advanced stages, colitis progresses by intestinal epithelial cell apoptosis and mucosal damage, which result in TJ- and MLCK-independent barrier loss [9]. A20 is a kind of anti-inflammatory protein that utilizes deubiquitinating, E3 ligase and ubiquitin binding functions to regulate NF-κB signaling. Single nucleotide polymorphism (SNPs) study demonstrates that the human A20 locus (also known as TNFAIP3) is associated with several human autoimmune diseases including IBD. A20 is an important molecule in the maintenance of the homeostasis in the body via suppressing the NF-κB pathway. Lack of A20 induces severe inflammation in the intestine due to the invalid microbial antigen transferring in enterocytes. We have found that A20 locates in the enterocytes involved in the absorption or transportation of intestinal bacterial antigen and plays a critical role in the innate immunity and adaptive immunity [10].

A large number of activated leukocyte infiltration, expression of adhesion molecule, and high secretion of proinflammatory cytokines (e.g., TNF, IFN-γ, IL-12, IL-15, IL-21, IL-23) are found in inflamed mucosa of IBD patients. IL-16 has been found to induce intestinal inflammation by upregulating the expression of oligopeptide transporter member 1 (PepT1) in a Tetraodon nigroviridis fish model [11]. Intestinal inflammation could be dramatically attenuated by IL-16 depletion using anti-IL-16 Ab, suggesting that IL-16 plays a crucial proinflammation role in IBD. We have reported that IL-23 is markedly increased in inflamed mucosa of IBD and induces the differentiation of IBD CD4$^+$ T cells into Th1 and Th17 cells and activation of mucosal CD4$^+$ T cells [12,13]. Moreover, we also found that IL-25, a negative regulator of inflammatory response in the intestinal mucosa, is significantly decreased in the sera and inflamed mucosa from patients with active IBD [14]. The noticeable decrease of IL-25 contributes to the intestinal mucosa immune system dysfunction, thus leading to the amplification of intestinal immune response.

miRNAs (miR) are small (18-24 nucleotides) non-coding RNAs, which bind the 3'UTRs of their target genes and act as post-transcriptional gene regulators. Current studies reveals that some miR (e.g., miR-21, miR-150, miR192-192, miR-200b) are involved in the regulation of innate and adaptive immune system of intestinal mucosa, and involve in the process of IBD [15,16]. Recent study [17] demonstrates that miR-141, which is significantly higher in patients in the active phase of CD, directly regulates CXCL12 expression and CXCL12-mediated leukocyte migration. Inhibiting colonic CXCL12 expression by using miR precursors could cause the reduction of leukocyte infiltration in the intestinal mucosa and alleviation of experimental colitis. Our recent study has shown that the expression of miR-10a, which mainly expresses in macrophages and dendritic cells of intestinal tissue and could down-regulate intestinal IL-12/23p40 and NOD2 expression in the mice with colitis, decreases in peripheral blood and intestinal mucosa in patients with IBD [18]. Furthermore, we found that microbiota and proinflammatory cytokines (such as LPS, TNF, IFN-γ) could down-regulate miR-10a expression. Together, these data indicate that some miRs are involved in intestinal inflammation and lay an important theoretical basis for prevention or treatment of patients with IBD.

In recent years, the basic research of IBD in China, as well as the development of immunology, genetics, molecular biology and bacteriology, has progressed markedly. However, the research levels of IBD in China still cannot compete with those in developed countries. Currently, the experimental colitis models induced by chemical reagents are mostly utilized in the laboratory, while a few IBD animal models are established through the induction by gene knockout, transgene, or abnormal immune responses, these animal models impede basic research and target immune therapy in IBD.

Advances in diagnosis and treatment

Differential diagnosis plays an important role before the final diagnosis of IBD. Since the incidence and prevalence of IBD are low, and the diagnosis in the etiology and pathology seems to be difficult in China. The infectious diseases are mostly considered to rule out when the diagnosis of IBD is generated. Most of infectious diseases are caused by bacteria (e.g., Escherichia coli, Staphylococcus aureus, Salmonella, Shigella, Clostridium difficile, Mycobacterium tuberculosis), virus (e.g., Cytomegalovirus, Rotavirus), and parasite protozoa (e.g., amebic protozoa, Schistosome). The differential

diagnosis between CD and intestinal tuberculosis is particularly important in China, since the high infection rate of Mycobacterium tuberculosis is still existed in local areas. Several autoimmune disease involved in intestine are also considered to differentiate from IBD, such as Behcet's disease, celiac disease, systemic lupus erythematosus, Sjogren's syndrome, and amyloidosis. Other diseases (e.g., irritable bowel syndrome, intestinal lymphoma, ischemic colitis, diverticulum-associated enteritis, portal hypertensive enteropathy, bypass enteritis, endometriosis, radiation-associated enteritis, drug-associated enteritis) are also needed to differentiate from IBD in the symptoms, signs and endoscopic findings.

Biomarkers (e.g., pANCA, ASCA, CRP, ESR, fecal calprotectin, lactoferrin, new Butterfly Ridge, pyruvate kinase M2 isoenzyme, S100 calcium binding protein A12, matrix metalloproteinase protease 9) in the sera or stool samples will provide the most practical diagnosis tool for the diagnosis of IBD, but there is still a huge difference in the specificity and sensitivity among these biomarkers. Unfortunately, these indicators are still not available in some laboratories, leading to unsatisfactory results in the diagnosis of IBD. Up to date, although the combination of endoscopy with pathological diagnosis is the gold standard to assess intestinal inflammation of IBD, the intestinal CTE, MRI, B ultrasound or X-ray could also detect intestinal lesions in patients with IBD and provide further information in severity and activity. Actually, this imaging examination may serve as important complementary tools to endoscopy for evaluation of the intestinal inflammation [19,20]. Collectively, the best diagnostic tools should be based on comprehensive analysis including the condition of patients, physician's experience, laboratory parameters, histopathology and X-ray or CT examinations.

Apart from the improvement of clinical symptoms and biochemical parameters to assess the clinical efficacy of IBD patients, the degree of disease activity can be evaluated by Crohn's disease activity index (CDAI), the Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD), Lemann and Rutgeert scoring system, which are practical instruments and used by clinicians for the objective assessment of mucosa lesions in CD patients. Similarly, ulcerative colitis activity index (UCAI), Mayo disease activity index and Baron scoring system are currently used for the disease severity of UC patients. However, these systems are time-consuming and complicated, leading to inconvenience in clinical treatment.

Most of the cases of IBD are mild to moderate in China, and the proportion of extraintestinal manifestations and complications is also low. Such clinical characteristics may be associated with genetic or environmental difference, therefore the appropriate individualized treatment plans are currently implemented in the management of IBD patients. Currently, various drugs (e.g., 5-ASA, corticosteroids, immunosuppressants, antibiotics, biological agents) appear to be different effects on IBD. The selection of drug should be based on characteristics of the disease, such as the location of disease, the severity of disease, time point of the onset, complications, the section of bowel, and postoperative prevention of recurrence. In patients with mild to moderate IBD, 5-ASA is generally used to induce remission and maintenance therapy. In the case of moderate to severe diseases, corticosteroids, cyclosporine, and surgical intervention are required, and azathioprine is routinely used for the maintenance treatment.

However, the best timing of operation is difficultly determined leading to a missed best opportunity for surgical therapy and an increase of the disability. Traditional medicines have been successfully used for a long time and still exert a beneficial effect in early or mild-activity IBD patients [21]. Recently, biologic therapies (e.g., anti-TNF monoclonal antibody or infliximab) have been shown to have benefit in the treatment of CD, especially for those young patients of early intestinal lesions (less than 2 years of medical history, age less than 40 years old, type B1 according to the Montreal classification). This kind of therapy is used for induction and maintenance of remission in adult and pediatric CD, promoting mucosal healing, tissue repairing and fistula closure. Thus, the lower rates of surgery and postoperative recurrence of intestinal inflammation as well as the improvement quality of life are achieved. However, the clinical efficacy is poor for those patients suffering for long time, or structuring disease (which causes narrowing of the bowel) and penetrating disease (which causes fistulae or abnormal connections of the bowel, e.g., B2, B3 type, such as stenosis, obstruction, fistula, perforation). Consequently, choosing for best clinical indications by anti-TNF mAb treatment is warranted.

The use of infliximab has changed the treatment by improving both short- and long-term outcomes in patients. Its function lies in neutralizing the biological activity of TNF in body fluids and tissues effectively, promoting the repair of mucosal barrier, inducing apoptosis of leukocytes in the mucosal, inhibiting leukocyte infiltration, regulating the local immune response and inhibiting the angiogenesis in mucosa. The combination of azathioprine and infliximab is the most potent therapy in IBD. The purpose is to enhance the clinical efficacy and reduce the appearance of antibody to infliximab.

Although the satisfactory outcome has achieved by anti-TNF agents, there are still about one-third of the patients unresponsive to therapy. Novel biological agents (e.g., anti-IL-6R, IL-13, IL-12/23p40, IL-23p19, α4β4 integrin, mucosal vascular address in MAdCAM-1 antibody, Treg cells, Smad7 antisense oligonucleotide, Jak inhibitor, TLR9 agonist, Pig whip eggs) are being conducted in the treatment of IBD and demonstrated to be effective in some patients. While, the long-term efficacy and safety of these drugs still need further observation in clinical trial. Because of the weakness of basic research and biotechnology, the development of new biological agents used in clinic is rare and there is still a big challenge compared with western countries in the treatment of IBD.

Currently, several issues need to be addressed in the treatment of patients of IBD, e.g., the assessment of efficacy of 5-ASA in the treatment of CD patients and route of administration (single or multiple doses), medical therapy for steroid-dependent or independent cases, the optimal choice of immunosuppressants, the timing for selecting biological agents related to the disease severity, location, duration, complications, and how to determine whether the use of antibiotics is necessary and the remedy if patients do not response to these drugs. In addition, there are other issues like surgical treatment (e.g., surgical timing, procedure, and follow-up, the treatment of complications), the choice of enteral nutrition and the treatment under special disease conditions (e.g., childhood, pregnancy). Collectively, once these problems are solved rightly, the treatment of IBD patients will be effectively improved and controlled.

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