Advances in the study of the pathogenesis of cytokines in inflammatory bowel disease

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Abstract: In recent years, with the continuous development of medical technology, people pay more and more attention to health. From a global perspective, the prevalence of inflammatory bowel disease (IBD) is increasing, and this disease is recurrent and persistent, and may bring physical and psychological harm to patients in the later stage, so the diagnosis and treatment of IBD and its prognostic effect become a clinical. This makes the management and prognosis of IBD a clinical challenge. The cause of IBD is still unclear, but as research continues, it is thought that the pathogenesis of IBD may be related to abnormal immune imbalances in the gut caused by environmental, genetic, immune and intestinal micro-ecological factors. Nowadays, research on the pathogenesis of IBD has been deepened and refined, and it has been found that there are more studies on immune factors and their conclusions are widely accepted, but the mechanisms of interleukin (IL) and tumour necrosis factor (TNF) are more widely studied. This article will mainly review the pathogenesis of IBD from the perspective of cytokines and provide reference for future clinical studies.

1. Introduction

Inflammatory bowel disease (IBD) is a chronic immune inflammatory disease that affects the entire gastrointestinal tract. It includes both types of ulcerative colitis (UC) and Crohn disease (CD). In patients with CD seen in clinical practice, about 30% of patients present with ileal involvement, about one-third present with colonic involvement, and the remaining 30% have ileocolonic disease. In patients diagnosed with UC, about 20% of severe patients may present with intestinal perforation [1]. It is common in the adolescent population in China, with an age of onset roughly around 18-35 years and no significant differences in prevalence between men and women. According to the current data available in China, UC has a high prevalence in the age group 20-49 years; CD has a higher prevalence in the age group 18-35 years. However, early onset of IBD does not allow for timely diagnosis, and it is possible that the peak age of onset of IBD in China may be earlier [2]. Although the etiological mechanism of IBD cannot be fully defined, it involves the interaction between genetic, environmental or microbial factors and the immune response. At the same time, adaptive immune responses play an important role in the pathogenesis of IBD, and immunological

and genetic studies have found that innate immune responses are equally important in the induction of intestinal inflammation [3]. The indeterminate bed manifestations of IBD and the lack of specific direction in endoscopic and pathological findings make its diagnosis very difficult and may even be missed or misdiagnosed. IBD is also known as the "green cancer" [4]. IBD is long-lasting, recurrent and difficult to cure, and in the long run, patients suffer from physical and mental health problems, affecting their normal daily life and even developing depression in severe cases [5].

2. Overview of cytokines

Cytokines are small peptide proteins produced by immune cells that facilitate communication between cells and have important functions in cell development and differentiation [6].Cytokines can be divided into pro-inflammatory and anti-inflammatory cytokines. The main pro-inflammatory cytokines are IL-1, IL-2, IL-6, IL-23, IL-27, TNF-α and IFN-γ, while the main anti-inflammatory cytokines are IL-4, IL-5, IL-10 and IL-13. Ulcerative colitis is characterised by a Th2-type immune response and the main cytokines secreted are TNF-α, IL-5, IL-1β, IL-23, IL-10 and IFN-γ. Th1 and Th17 mainly mediate the immune response in Crohn's disease, which secretes a number of cytokines such as TNF-α, IL-17 and IL-23. Among them, secretion of cytokines such as TNF-α, IL-23, IL-6, IL-17, IFN-γ and TGF-β are significantly increased during the pathogenesis of both. In some studies, IL-4 has been closely associated with the development of ulcerative colitis [7、8]. In addition, a number of toll-like receptor (TLR) polymorphisms/mutations have been identified and directly associated with IBD. Genetic alterations in these receptors may alter the composition of the gut microbiota. The etiology of IBD is multifaceted and includes immune responses, genetics and microbiotaToll-like receptors (TLRs) are central to the gut microbial immune response in the pathogenesis of inflammatory bowel disease (IBD). Abnormal TLR signalling may trigger disease-associated inflammation. TLRs are the key players in the gut that recognise aberrant gut microbes to induce The TLR is a key sensor in the gut for the recognition of abnormal intestinal microbes to induce immune responses and inflammatory diseases [9].

3. Cytokines and IBD

It has been found through numerous studies that inflammatory cytokines in the serum of patients with IBD are expressed at different levels than in normal subjects, and it has been confirmed in numerous experimental animal studies that IBD can cause changes in various cytokines in the serum. It has been found that changes in the number and expression levels of innate and adaptive immune cells and cytokines that affect the production of various cell subpopulations in the mucosa may be the main cause of the pathogenesis of IBD, with alterations in the innate immune system, activation of effector T cells, increased production of B cells and antibodies, and increased production of pro-inflammatory mediators [10]. Although the pathogenesis is complex and varied, it is closely related to the expression levels of T cells, B cells and the cytokines they secrete. B cells originate from pluripotent stem cells in the bone marrow and are stimulated to differentiate and proliferate into plasma cells and synthesise antibodies, which exert the body's immune effects. Bregs cells are a subset of B cells that suppress the immune response and secrete IL-10. The immune effect of Bregs is achieved by contact; its secretion of IL-10 inhibits the differentiation of CD4+ T cells to Th1 and Th17 cells, as well as the activation and differentiation of Th1 and Th17 cells and the conversion of CD4+ T cells to Tregs cells [11-12]. In recent years, several studies have confirmed that the balance between Th17 and Treg cells is one of the important factors affecting the development of IBD. th17 and Treg cells belong to the same class of CD4+ T cell subpopulation cells, and Th17 cells play a bidirectional regulatory role in their pathogenesis, mainly pro-inflammatory, and their protection of the intestinal mucosa is achieved by maintaining the

balance of the immune microenvironment, and can exacerbate intestinal mucosa through the action of TGF-β is a pleiotropic factor that both regulates B-cell function and inhibits Th1 cell function; its reduced activity can lead to autoimmune dysregulation, which can lead to the development of IBD and other diseases. The incidence of IBD is higher in young people than in others, where cytokine IL-10 or IL-10 receptor deficiency is the basis for the development of IBD, which is more difficult to treat and diagnose clinically, with rapid weight loss, more retarded growth and the development of perianal abscesses, fistulas and anal ruptures [13]. Shi Yingqi et al. conducted a correlation analysis of serum TNF-α and IL-6 levels in 65 patients with IBD, and the results showed that the expression levels of TNF-α and IL-6 factors were reduced and their relevance to the inflammatory response of the intestine [14]. In a clinical study of 120 patients with IBD, Zhang Xianming et al. found that the cellular marker expiry levels of serum inflammatory factors IL-13, IL-1Ra and COX-2 increased as the disease progressed. Also, because IL-13 is mainly involved in the humoral immune response of the body, it is a high-potency pleiotropic cytokine secreted by Th2 cells that can both regulate inflammatory factors and stimulate the immune response, so it is important inflammatory cytokine in the development of IBD disease [15]. As research has progressed, IL-36 is now widely studied and is highly expressed in human tissues such as skin, bronchus, lung and intestinal mucosa, all of which are non-specific immune barrier defence structures, suggesting that IL-36 cytokines may have an important role in regulating tissue barrier homeostasis and protecting the body from external environmental influences [16]. Meanwhile, tumour necrosis factor (TNF-α), a variable pro-inflammatory cytokine whose main source is monocytes/macrophages, but other cells such as T cells and B cells can also secrete small amounts of TNF-α, is closely related to IBD. It can induce neutrophil aggregation, regulate the proliferation, maturation and activation of neutrophils and macrophages, and promote their adhesion, migration and degranulation, which in turn stimulates the production of cytokines by monocytes and vascular endothelial cells, resulting in a cascade of responses that lead to inflammatory damage in the intestine and inflammatory bowel disease. The TNF-α-mediated pro-inflammatory transcription factor NF-kB was found to upregulate the expression of genes associated with tumour cell survival, proliferation, invasion, angiogenesis and metastasis, so it was ventured to speculate that there might be some potential link between it and the development of carcinogenesis in inflammatory bowel disease; nowadays, anti-TNF-α analogues are used clinically for the treatment of severe IBD according to this feature, and good results have been achieved in clinical treatment [17, 18]. In the results of several experimental studies, it was found that mice deficient in both TNF and IL-10 induced colitis. Therefore, it is speculated that under certain specific circumstances, TNF plays a protective role in the gastrointestinal tract after inflammation and injury, and may also be a cause of poor outcome after anti-TNF-α treatment in some patients [19]. In summary, the pathogenesis of IBD is not fully understood, but in the present data, cytokines have been found to be associated with the progression of the disease, with inflammatory and anti-inflammatory responses to the gastrointestinal mucosa, and the level of cytokine expression in the immune system is closely associated with the progression and recovery of IBD.

4. Cytokines, environment, genetics, diet and IBD

It is indisputable that environmental factors are equally important in the development of inflammatory bowel disease, for example, aspects such as smoking, diet, medication, geographical factors, social stress, mental health, etc. are all cited as risk factors for the development of IBD [20]. A prospective study of about 10,000 Europeans found that different socio-occupational divisions of labour and different work pressures lead to different prevalence rates of IBD, with people with higher social work status being among the more prevalent groups; in terms of diet is also an

influential factor, for example, the different dietary cultures of Chinese and Western countries, with milk and high-protein diets dominating in Western countries, leading to a generally higher prevalence rate in Western European countries than in China However, in recent years, as the living standard of our people has improved and the dietary structure has changed, the prevalence of UC and CD has also increased [21]. According to relevant studies, the rising prevalence of IBD and the gradual westernisation of diet are associated with commercialised foods, with food additives and a wide variety of processed fast foods constantly appearing in daily life, and the long-term consumption of such foods may be one of the causative factors in the development of inflammatory bowel disease; for example, processed foods containing additives related to polysorbate 80, carboxymethyl cellulose, titanium dioxide and sulphites, etc., have been shown in mice Animal experiments have demonstrated that related foods can induce colitis in mice [22], suggesting that an inappropriate diet or lack of attention to dietary rationality may increase the risk of IBD in humans, and that it is important to consume as few foods with too many additives as possible, eat more fruits and vegetables and establish good lifestyle habits in life. Genetic susceptibility has an important influence in the pathogenesis of IBD, with some studies concluding that approximately 12% of people with IBD have a family history of the disease. Among the current findings, genome-wide association studies (GWAS) have identified more than 230 single nucleotide polymorphisms (SNPs) associated with IBD pathogenesis, and within this chromosome category, more than 100 additional gene targets are closely associated with them, such as the genetic risk point NOD2 that induces activation of NK-κB and MAPK, thereby stimulating transcription of inflammatory cytokines, although it is not possible to fully Although the pathogenesis of IBD has not been demonstrated to be directly related to it, the NOD2 gene polymorphism can regulate the host response to the gut microbiota [23]. The results of a study conducted at Guangzhou Medical University in China among selected IBD patients (99 Zhuang and 113 Han) showed that intestinal mucosal genes were extracted from Zhuang and Han people in China after they had IBD, and the findings showed that differences in gene polymorphisms were found, with significant pathogenetic differences between Han and Zhuang in CD, increased ER4 receptor binding to PGE2 promoting Th1 cell differentiation, Th17 cell proliferation and increased secretion of various pro-inflammatory factors such as IFN -γ, TNF-α and IL-17 are involved in the pathological alterations of CD, hence the relatively higher rate of inflammatory bowel disease among Han Chinese compared to other ethnic groups [24]. Similarly, IBD has a significant family history, with one foreign study indicating that 15-20% of patients, among others, have an effect on their family members, e.g. for patients with paediatric disease manifestations, a positive family history was asked in about 30% of cases, and the risk of disease in monozygotic twins is up to about 30%-50% among twins, while the prevalence of dizygotic twins is extremely low, at only 2%-4%, for which the most common genetic variation in the NOD2 (CARD15) gene, an immunodeficiency that causes differential prevalence in family history [25]. This suggests that geographical differences, changes in dietary habits and family genetic susceptibility are all important reasons for the increasing prevalence of IBD.

5. Cytokines, intestinal flora and IBD

In the normal adult healthy intestine, there are tens of billions of bacteria, 8-10 times the total number of cells in the human body, which are diverse and have different roles, and show various differences in the composition and distribution of the intestinal flora, therefore, it is also called the "second gene pool" or "The importance of the intestinal flora is self-evident [26]. The most common pathogenic bacteria in the intestinal flora are Aspergillus species, mainly represented by Escherichia coli. The increase in pathogenic bacteria destroys the intestinal mucosal barrier and induces an inflammatory response in the intestinal mucosa. Generally speaking, under normal

physiological conditions, the intestinal flora is in a state of mutual influence and mutual restraint, once the balance of the intestinal flora is broken, the mutual restraint between each flora is weakened, the phenomenon of intestinal flora dysbiosis will occur. In addition, the intestinal flora also has a microbial stimulating effect on the body, stimulating the immune system to occur immune cell function, when the pathogenic bacteria invasion, the intestinal mucosa immune system can produce secretory immunoglobulin A (secretory When pathogenic bacteria invade, the intestinal mucosal immune system can produce secretory immunoglobulin A (sIgA), whose main function is to defend the intestinal mucosa against pathogens and their toxins, thus preventing pathogens from attaching to the intestinal mucosa and adding value to it, thus maintaining the stability of the intestinal flora. At the same time, the intestinal flora not only plays an important role in stimulating the activation of immune antigen presentation pathways in the intestinal mucosa, activating immune cytokines and immune response, but also plays a role in regulating the activation of immune cells through SCFAs, promoting cytokine production and T-lymphocyte proliferation [27]. The mechanisms of action of probiotics in the intestinal flora are also diverse. A large number of experimental studies have found that probiotics can promote Th1 cell differentiation through Toll-like receptors, thus improving the immune environment of the intestine and thus enriching the diversity of the intestinal flora, and it can also increase the level of anti-inflammatory cytokines such as TNF-α through immune action, thus playing a role in alleviating intestinal inflammation, and the probiotics Bifidobacterium and Lactobacillus can protect the intestinal mucosa, inhibit the growth of pathogenic bacteria, and play a bi-directional role in regulating the function of the intestinal tract. It has been widely used in the clinical treatment of UC [28]. Yang Wenhong et al. conducted a study on the relationship between intestinal flora and inflammatory cytokines in 120 cases of inflammatory bowel disease. H. pylori and Streptococcus (P<0.05); and positive correlation with Bifidobacterium and Lactobacillus (P<0.05), indicating that cytokines can influence the distribution of intestinal flora [29]. Scientific studies have shown that in healthy humans, intestinal flora and intestinal immunity are in a state of dynamic equilibrium, which is dominated by cytokines such as Treg and TGF-β that act as inhibitors of inflammatory responses. However, under the influence of various factors, when the dynamic balance of the intestinal tract is disrupted, the stability and diversity of the intestinal flora changes, the number of flora changes, etc., after which Toll-like receptors begin to occur in the immune response, the Th17/Treg balance is disrupted and the corresponding inflammatory response is revealed. Similarly, dysregulation of the intestinal flora and its metabolites can lead to an inflammatory response in the intestinal mucosa, dysregulation of cell differentiation and function, cytokine imbalance and oxidative stress throughout the development of IBD disease [30, 31]. In conclusion, there is a complex link between intestinal flora and IBD, and when the intestinal flora is dysregulated, it can affect the development of the disease through a variety of mechanisms, as well as the homeostasis of the intestinal flora, therefore, the treatment of intestinal flora dysregulation has an important place in the treatment of IBD disease.

6. Summary

In recent years, as research into inflammatory bowel disease continues to intensify, the pathogenesis of the disease is still unclear, but with the development of science and technology, research into the pathogenesis of the disease is gradually being refined, research methods are being improved, and clinical understanding, diagnosis and treatment of the disease have all progressed in greater depth, with clinical outcomes improving and patient cure rates making significant progress. Cytokines play an important role in inflammatory bowel disease and can be divided into two categories: pro-inflammatory factors and anti-inflammatory factors. In a healthy body, these two categories of factors regulate and promote each other, thus reaching a dynamic balance, in this paper,

the role of cytokines in inflammatory bowel disease is summarised and reviewed, and it is found that cytokines are only one of the important causes of the pathogenesis of IBD, and that the pathogenesis is multifaceted or caused by a combination of causes. The study of the pathogenesis of IBD needs to be improved to provide a more comprehensive and specific approach to the symptomatic treatment of inflammatory bowel disease.

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