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Advances in Cytokine Research and Therapeutic Strategies for Ulcerative Colitis

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Abstract: Ulcerative colitis (UC) is a chronic intestinal inflammatory disease with complex causes that are closely associated with environmental, genetic, and immune factors. However, the precise etiology and pathogenesis remain under investigation in clinical practice. Extensive research has demonstrated that cytokines play a pivotal role in the development, occurrence, and prognosis of UC, with an imbalance between pro-inflammatory cytokines and anti-inflammatory factors being a significant contributor. Given that UC is challenging to cure, therapeutic options such as hormones and aminosalicylic acid are commonly employed. While treatments including Western medicine, traditional Chinese medicine, and other approaches have shown some efficacy, substantial breakthroughs are still lacking. Cytokines, therefore, represent a critical focus in understanding the pathogenesis of UC. This review explores the therapeutic pathways of cytokines and their antagonists.

Keywords: Cytokines; Ulcerative colitis; Research progress

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1. Introduction

Ulcerative colitis (UC) is an autoimmune-mediated inflammatory disease whose causes and mechanisms are not yet fully understood in the clinical setting. Current research suggests that environmental factors and intestinal flora can activate the immune system in genetically predisposed individuals, leading to an excessive release of cytokines. This disrupts the balance between pro-inflammatory and anti-inflammatory cytokines, ultimately resulting in intestinal mucosal damage. Clinically, UC presents with symptoms such as diarrhea, abdominal pain, and the presence of mucus, pus, or blood in the stool [1].

Epidemiological surveys indicate a higher prevalence of UC in Western countries. In China, the incidence of UC has been increasing, with an overall rate of approximately 1/10,000 compared to 10–20/10,000 in Europe and the United States. Differences in incidence rates between countries may be linked to variations in dietary habits and environmental factors. Further studies have shown that UC is more common in economically developed

regions, with the southeast coastal areas of China exhibiting a higher prevalence compared to the inland northwest. This disparity is likely attributable to differences in living conditions and dietary practices [2].

As UC progresses, it may lead to severe complications such as toxic megacolon or an elevated risk of colon cancer, posing significant threats to patients' lives. Prompt and effective treatment is thus essential to control disease progression and improve patient prognosis [3].

Research has consistently highlighted the critical role of cytokines in the pathogenesis and resolution of UC. Cytokines, small molecule peptides or glycoproteins with diverse biological functions, are integral to the inflammatory immune response in the intestine. They are categorized into inflammatory cytokines and anti-inflammatory cytokines. An imbalance or dysfunction within these cytokine groups is a key driver of UC. Emerging cytokine-related therapies have shown encouraging results in clinical settings [4].

While certain cytokines have been identified as influential in UC activity and prognosis, consensus in this area remains limited. This review aims to explore the association between cytokines and UC prognosis, providing insights into their role in disease progression and therapeutic potential.

2. Cytokines in the pathogenesis of ulcerative colitis

Cytokines are small molecular polypeptides secreted by both immune and non-immune cells, playing a pivotal role in immune and inflammatory activities. They can be broadly categorized into inflammatory cytokines and anti-inflammatory cytokines. Inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-2 (IL-2), and interleukin-12 (IL-12), are essential for mediating cellular immune responses. These cytokines regulate receptors and functions on the surface of intestinal epithelial cells, contributing to impaired cellular functionality [5]. Anti-inflammatory cytokines, including IL-4 and IL-1Ra, are vital for humoral immunity. They exert a strong inhibitory effect on Th1 cells, which is effective in preventing intestinal inflammation.

With the advancement of clinical research on UC, it has been established that the disease's pathogenesis is multifactorial, involving genetics, environmental factors, mucosal barrier dysfunction, and immune dysregulation. These factors are increasingly recognized as critical contributors to the disease process. In recent years, the rising prevalence of UC in China has posed significant risks to physical and mental health. Studies have confirmed that cytokines play a crucial role in the intestinal immune response. When the balance between inflammatory and anti-inflammatory factors is disrupted, conditions favorable for the onset of UC are created [6].

In inflammatory bowel disease, including UC, a close correlation has been observed between tissue inflammation and the high expression of pro-inflammatory cytokines. Research indicates that during intestinal mucosal inflammation, the release of pro-inflammatory factors significantly increases, and their levels consistently rise. Conversely, anti-inflammatory factors demonstrate a notable decrease in their levels, further exacerbating the inflammatory response.

2.1. Inflammatory cytokines

2.1.1. IL-1

IL-1 consists of IL-1β, IL-1α, and the IL-1 receptor antagonist (IL-1Ra), each with distinct functions. While IL-1 serves immunomodulatory and pro-inflammatory roles, it does not directly cause tissue damage. Instead, it activates other cytokines, such as IL-6 and IL-8, inducing them to participate in inflammatory responses, which in turn results in tissue damage. IL-1β is the primary active form of IL-1. Research indicates that IL-1β is highly

expressed in the intestinal lesions of UC patients, with levels varying across different disease phases. It exhibits significantly accelerated secretion during the acute phase compared to the remission phase [7].

2.1.2. IL-6

The biological effects of IL-6 are similar to those of IL-1β. In UC patients, serum and intestinal mucosal levels of IL-6 increase significantly during the acute phase. This elevation is closely associated with the severity and extent of the lesions. The IL-6/STAT3 pathway is particularly critical in UC development. IL-6 activates nuclear factor kappa B (NF-kB) through the STAT3 pathway, which promotes intercellular adhesion and NF-kB activation. Moreover, STAT3 strongly inhibits T-cell apoptosis and enhances the polarized expression of intercellular adhesion molecule-1 (ICAM-1). These actions contribute to the prevention of chronic inflammation. Clinically, blocking the IL-6/STAT3 signaling pathway in mucosal T cells has been shown to delay disease progression in UC [8].

2.1.3. TNF-α

TNF-α is an immune mediator and a key inflammatory factor involved in immune and inflammatory responses. It plays an essential role in the intestinal mucosal inflammatory response. TNF-α measurement provides valuable insight into the extent of UC lesions. Intestinal epithelial cells (IECs) are critical to the immune response of the intestinal mucosa. However, TNF-α can damage IECs, impairing the barrier function of the intestinal mucosa, which exacerbates inflammation and triggers further immune responses. Studies have shown that TNF-α-induced damage to IECs is closely associated with the upregulation of tumor necrosis factor receptor 2 (TNFR2) expression. However, TNF-α alone cannot induce TNFR2 expression; it requires the involvement of other inflammatory factors, such as IL-6, to achieve this [9].

2.2. Anti-inflammatory cytokines

2.2.1. IL-1Ra

Interleukin-1 receptor antagonist (IL-1Ra) shares significant molecular mass and structural similarity with mature IL-1. It specifically inhibits the binding of IL-1 to its receptor (IL-1R) on the surface of T cells, thereby exerting a strong inhibitory effect on IL-1 activity. The progression of UC is closely associated with an imbalance between IL-1Ra and IL-1. When IL-1Ra levels decrease, the unchecked activity of IL-1 can result in pronounced inflammatory effects, contributing to disease progression by enhancing inflammation [10].

2.2.2. IL-4

IL-4 is mainly produced by the Th2 subpopulation of $CD4^+$ cells, and is capable of exerting a strong inhibitory effect on macrophage and T cell production, as well as an immunomodulatory effect. In the differentiation of Th2 cells, IL-4 plays an important role, not only can effectively inhibit the production of IFN-γ by Th1 cells, but also promotes the production of IL-1α, which can promote the IL-1α/IL-1 ratio; and it can also inhibit the production of prostaglandin E2 (PGE2), which can play a good anti-inflammatory effect, and plays an important role in maintaining the intestinal immunity [10].

3. Cytokines and UC treatment

The clinical treatment of UC currently relies primarily on drug therapy. Commonly used medications include

aminosalicylic acid and corticosteroids. These drugs can achieve relatively satisfactory outcomes in the early stages of the disease. However, within 5–10 years, approximately 30% of patients develop drug resistance or experience severe complications. Clinical studies have confirmed that cytokines play a key role in the pathogenesis of UC and exhibit a strong correlation with disease severity and recurrence. Based on the role of cytokines in UC, targeting specific cytokine networks and implementing effective blocking measures can help control inflammation and promote recovery.

3.1. TNF-α targeted therapy

TNF-α is typically produced by mononuclear macrophages. It upregulates endocytic adhesion molecules and promotes neutrophil aggregation, mediating mucosal damage in the intestine. During the active phase of UC, plasma and fecal TNF-α levels are significantly elevated. The TNF-α monoclonal antibody infliximab (cA2), a chimeric antibody, demonstrates a high affinity for both soluble and transmembrane TNF-α.

In a study by Dai [11], patients with refractory inflammatory bowel disease treated with infliximab and azathioprine achieved intestinal mucosal healing rates of 55.0% and 52.5%, respectively, showing similar efficacy. Another study by Deji *et al.* [12] compared UC treatment outcomes across three groups: infliximab (IFX), cyclosporine (CsA), and sequential treatment (IFX-CsA or CsA-IFX). After three months, the IFX group demonstrated the highest efficacy (63.3%), followed by the CsA group (45.5%), while the sequential group had the lowest efficacy (37.5%). The short-term colectomy rate was highest in the sequential group, moderate in the CsA group, and lowest in the IFX group, confirming comparable effectiveness among these treatments. A meta-analysis further indicated that infliximab treatment resulted in favorable clinical outcomes, offering better clinical relief and mucosal healing compared to placebo [13].

3.2. Drugs that inhibit IL-6 production

IL-6, primarily produced by mononuclear macrophages, is significantly elevated in UC patients and plays a crucial role in disease activity. IL-6 interacts with TNF-α, and drug treatment in UC patients has been shown to decrease IL-6 levels, restoring them to normal. This suggests that IL-6 has diagnostic and therapeutic relevance in UC management [14]. The chronic inflammatory response mediated by IL-6 can potentially be blocked using IL-6 antibodies. However, IL-6 antibody drugs are still under development and have not yet been applied clinically.

3.3. Methods to inhibit IL-1Ra production

In UC patients, IL-1 secretion levels show a significant upward trend, while IL-1Ra or the IL-1Ra/IL-1 ratio does not demonstrate a similar increase. Research indicates that IL-1Ra can effectively inhibit IL-1 activity only when IL-1 levels are substantially elevated [15]. Animal experiments have shown that IL-1Ra can effectively block IL-1, reducing the degree of inflammation. Currently, IL-1Ra is being gradually introduced in clinical trials for UC treatment [16].

3.4. Treatment targeting IL-1

Studies have indicated that in the intestinal mucosa at sites of inflammatory bowel disease (IBD) inflammation, the levels of IL-1β and IL-1α tend to increase significantly. However, the ratio of IL-1β to IL-1α demonstrates a decreasing trend, creating conditions conducive to the chronicity of mucosal inflammation and correlating closely with disease severity [17,18]. Clinical investigations have revealed that IL-1β mRNA expression is significantly

enhanced in intestinal mucosal biopsies of UC patients, particularly in those with long-term recurrent UC. Using reverse transcription polymerase chain reaction (RT-PCR) to detect IL-1ra mRNA in small intestinal biopsies, it has been observed that IL-1ra mRNA expression varies across different disease stages. Expression levels are notably lower during the acute phase compared to periods of inflammation remission. IL-1ra has demonstrated the ability to ameliorate acetic acid-induced colitis in rats, effectively reducing their inflammatory response.

3.5. Treatment against IL-4

IL-4, an anti-inflammatory cytokine, is produced by activated Th2 cells and mast cells. It can effectively inhibit the secretion of oxygen free radicals by monocyte macrophages and suppress the secretion of IL-8. Additionally, IL-4 induces the production of IL-1β, leading to an increase in the IL-1α/IL-1β ratio. Research has shown that in UC patients, both the number of IL-4-producing cells and the expression of IL-4 mRNA are reduced, suggesting a strong correlation between this reduction and UC pathogenesis. This finding underscores the potential of IL-4 as a marker for disease assessment [19]. Furthermore, studies have demonstrated that using recombinant human type 5 adenoviral vectors expressing IL-4 can be effective in treating trinitrobenzene sulfonic acid-induced colitis. However, the practical clinical application of this approach requires further exploration and refinement [20].

3.6. Cytokine-related gene therapy

Intravenous administration of recombinant cytokines is often cleared from the body within a short timeframe, leading to low bioavailability and limiting its clinical application. Viral vectors expressing immunomodulatory cytokines offer a distinct advantage in the treatment of UC. An optimal approach involves introducing the therapeutic gene directly into the intestinal mucosa. Despite this potential, challenges remain, particularly in devising effective methods to promote the sustained expression of cytokines like IL-10 in the inflamed intestinal mucosa to maximize therapeutic outcomes. Addressing these challenges represents an urgent clinical need.

4. Prospect

Current clinical research on the etiology and pathogenesis of UC predominantly aligns with international research priorities. Simultaneously, the number of UC patients in China continues to increase. To advance understanding of UC pathogenesis, it is crucial to consider the specific characteristics of the Chinese population, providing new avenues for research.

The treatment of UC remains a significant challenge. Both traditional Chinese medicine and Western medicine have demonstrated the ability to achieve satisfactory outcomes; however, neither approach has resulted in groundbreaking advances. While international efforts have initiated extensive research on cytokines and their antagonists to mitigate intestinal inflammatory lesions, research in this area within China remains limited.

Nevertheless, ongoing studies into the biological properties of cytokines, coupled with advancements in the synthesis and clinical application of related therapeutic agents, offer new hope for improving the clinical management of UC. These developments suggest the potential for innovative treatments that could address the current limitations and improve outcomes for UC patients.

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Disclosure statement

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