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Research Progress of Chinese Medicine in Regulating Relevant Signalling Pathways for the Treatment of Ulcerative Colitis

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Abstract: ***Ulcerative colitis (UC) is a recurrent, chronic inflammatory bowel disease with varying severity and prolonged healing, and Western medicine drug treatment has certain side effects. In recent years, a large number of animal experimental studies have demonstrated that traditional Chinese medicine (TCM) can reduce the inflammatory response and improve intestinal inflammation by interfering with the relevant signalling pathways, effectively improving the symptoms of patients with ulcerative colitis. The purpose of this article is to summarise the relevant articles on the modulation of relevant signalling pathways by TCM for the treatment of ulcerative colitis in recent years, and to provide new ideas for the active exploration of UC drug therapy.***

Keywords: Traditional Chinese medicine, Signalling pathways, Ulcerative colitis, Research progress**.**

1. Introduction

Ulcerative colitis (UC) is a chronic non-specific inflammatory bowel disease with lesions mainly in the rectum and colon, and its main clinical manifestations are diarrhoea, mucopurulent and bloody stools, and abdominal pain, fever, malnutrition and so on, and its basic pathological change is the damage of the intestinal mucosal barrier [1]. The pathogenic mechanism of ulcerative colitis may be mainly related to autoimmunity, infection, psychological and dietary, environmental and other factors [2]. Relevant studies have shown that immune system disorders are one of the important mechanisms for inducing UC. When subjected to external stimuli, autoimmune system disorders activate relevant signalling pathways, such as NF-κβ, JAK/STAT, MAPK and other relevant signalling pathways, leading to the recruitment of inflammatory cells in the mucous membranes and the massive secretion of pro-inflammatory cytokines. When a large number of pathogens invade the organism, the immune response is activated, and the activation of immune cells (e.g., macrophages, neutrophils, T-cells, etc.) releases a large number of cytokines and inflammatory factors, including tumour necrosis factor-α (TNF-α), interleukins (e.g., IL-1β, IL-6, IL-23, etc.) and interferons (e.g., IFN-γ), which result in the persistence and exacerbation of intestinal inflammation. This is usually manifested by a decrease in mucosal cell junction proteins (e.g., adhesins, tight junction proteins, etc.) that disrupts the intestinal mucosal barrier function, which in turn allows pathogenic bacteria and toxins in the intestines to cross the mucosal barrier more easily [3].

In the last decade or so, the incidence of UC has been rapidly increasing in Asia, South America, and the Middle East, while developed countries in Europe and the United States have levelled off, and the trend of youthfulness is obvious, which may be related to the westernisation of lifestyles, dietary shifts, improvements in hygiene, the increase in the application of antibiotics, and changes in the intestinal microbiota [4]. For some UC patients with mild symptoms, medication can effectively control the condition and have less impact on life and work, whereas for patients with obvious UC symptoms and more severe conditions, not only will their mental health and quality of life be affected, but also the risk of complications, transformation into colon cancer, and even death is elevated [5]. Currently, the western medical treatment of UC is based on drug therapy, including 5-aminosalicylic acid drugs, immunosuppressants, glucocorticosteroids, biologics, etc. Although the drugs have a better clinical therapeutic effect, there are still problems such as higher recurrence rate, toxic side effects and drug resistance. Some patients with dysplasia that fails drug therapy or is secondary to long-term colitis require surgery, and the absolute indications for surgery include uncontrollable bleeding, perforation, and colorectal cancer or dysplastic lesions that are not amenable to endoscopic resection. However, 50% of patients have acute flare-ups within 5 years of surgery, so surgery is not the ultimate ideal treatment. Relevant studies have confirmed that TCM can inhibit the release of inflammatory factors, regulate the immune function and repair the intestinal mucosal barrier by regulating the expression of inflammation-related signalling pathways, such as NF-κβ, JAK/STAT, MAPK and other signalling pathways, effectively alleviating the clinical symptoms of patients with UC, and has the advantages of small side effects and significant efficacy, which can improve the survival rate of the patients to a certain extent [6]. Therefore, it is very important to actively explore the signalling pathways and targets of drug therapy for the prevention and treatment of UC.

2. Theoretical Basis of UC treatment in Chinese Medicine

The name of UC in the motherland medicine does not have its detailed records, according to the clinical manifestations of mucus, pus and blood stools and the recurrence of the disease, the characteristics of the prolonged difficult to cure, UC belongs to the category of "long diarrhoea". Its pathology is due to the attack of external evils, dietary disorders, emotional and emotional disorders, spleen deficiency, the disease is

mainly in the large intestine, and the dysfunction of the liver, spleen, kidney and other organs. The basic pathogenesis is dampness-heat stagnation in the intestines, qi and blood disharmony, dysfunction of the intestinal tract, and damage to the lipid complex [7]. The onset of UC is divided into active and remission phases. The active phase of UC is mostly solid, and the pathogenesis is dampness-heat embedded in the intestines, with qi and blood imbalance, and the severity of the disease is mostly dominated by heat toxins and stasis-heat. The remission phase of UC is mostly a mixture of deficiencies and realities, and the pathogenetic mechanism is the spleen's weakness and loss of transport, dysfunction of the transport and transformation, and the phlegm, blood stasis is one of the most important factors in the disease's recurring and difficult to cure. Its evidence type is dominated by spleen and stomach weakness evidence and large intestine damp-heat evidence, and the treatment is to clear the intestines and eliminate dampness, accompanied by strengthening the spleen, with commonly used formulas such as Paeonia lactiflora soup, Ge Ge Ge Baicalin Lian Tang, Sijunzi Tang, etc. Meanwhile, external treatments of traditional Chinese medicine (TCM), such as acupressure, Chinese medicine enema, and Chinese medicine fumigation, etc., also have a certain degree of efficacy in the treatment of ulcerative colitis [8]. In summary, Chinese medicine treatment of ulcerative colitis should be based on its clinical symptoms, analysis of pathological manifestations in order to clarify the mechanism of disease and the prevalence of qi and blood, and accurate identification of evidence in order to achieve the special prescription for specific diseases, and effectively alleviate the patient's pain.

3. Major Signalling Pathways in the Pathogenesis of UC

3.1 NF-κβ Signalling Pathway

Nuclear factor κβ (NF-κβ) is a transcription factor mediated by most members of the tumour necrosis factor receptor (TNFR) and toll-like receptor (TLR) superfamily, as well as inducers of metabolic or genotoxic stress. They are mainly involved in the regulation of inflammatory responses, immune responses and apoptosis [9]. Under normal conditions, NF-κβ binds to Iκβ to form the NF-κβ/κβ complex, which is in a cytoplasmically inactive state. When the intestine is subjected to inflammatory stimuli from cell membrane receptors or intracellular signal transduction pathways delivered to the cell, the NF-κβ signalling pathway is activated, and Iκβ proteins (e.g., Iκβα) are phosphorylated and degraded by specific kinases, resulting in the release of NF-κβ. NF-κβ translocates to the cell nucleus and binds to specific sequences in the DNA to promote transcription of inflammation-related genes, such as TNF-α, IL-1 β, IL-6, and other inflammatory factors, leading to an increased intestinal inflammatory response [10]. In UC patients, NF-κβ is usually in an overactive state, leading to a sustained inflammatory response and intestinal tissue damage. Therefore, regulation of the NF-κβ signalling pathway plays a key role in inflammatory response and immune regulation.

Relevant studies have shown that some traditional Chinese medicines have a variety of active ingredients such as anti-inflammatory, antioxidant and immunomodulatory components, which are able to affect the activation and signalling of NF-κβ through different pathways. Song Yan [11] et al. found that astragalus polysaccharide could inhibit the release of inflammatory factors and activate the activities of TGF and SOD in mice by regulating the lipocalin/TLR/NF-κβ signalling pathway, improve the oxidative stress damage of the tissues, and effectively treat UC. Yang Lingxia [12] et al. found that wu zhu zhou alkaloids could reduce the intestinal MDA content in the intestinal mucosa and increase the MDA content in the intestinal mucosa by inhibiting the HMGBI/TLR-4/NF-κβ signalling pathway. MDA content in the mucosa, increase SOD content to inhibit oxidative stress, reduce the expression of inflammatory factors TNF-α and IL-6, promote the expression of IL-10, and inhibit the inflammatory response of intestinal mucosa. Liu Jinghong [13] et al. found that resveratrol regulates the gene expression of TLR4 and NF-κB proteins through the TLR4-mediated signalling pathway, reduces the release of pro-inflammatory factors, which inhibits the immune response and reduces the inflammatory damage of rat colon tissues.

3.2 JAK/STAT Signalling Pathway

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is a class of non-receptor tyrosine kinase signalling pathways that play a key role in the regulation of cell proliferation, differentiation, apoptosis, and immune response, etc. The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling pathway can be activated by a wide range of inflammatory cytokines (e.g. IL-6, TNF-α, etc.). In UC patients, the pro-inflammatory factor IL-6 binds to the corresponding receptor, which undergoes a conformational change that causes JAK protein kinase to bind to the receptor and phosphorylate each other, thereby activating JAK protein kinase. The activated JAK protein kinase further phosphorylates the targeted STAT protein, dimerises it and transfers it to the nucleus, where it interacts with other transcription factors or coactivators through its signalling domains to regulate the expression of downstream genes, resulting in the abnormal proliferation of immune cells and the over-release of inflammatory factors, which then triggers chronic inflammatory responses in the intestinal mucosa [14]. In addition, abnormalities in the JAK/STAT signalling pathway may also lead to a polarisation imbalance of immune cells in the intestinal mucosa, so that immune cells in the intestinal mucosa of patients with UC may show a tendency to be over-activated, leading to an ever-increasing inflammatory response and forming a vicious circle [15].

In recent years, a large number of experimental studies have shown that some active ingredients of traditional Chinese medicines can reduce the release of corresponding inflammatory factors by regulating the JAK/STAT signalling pathway, effectively alleviating the clinical symptoms of UC patients. For example, Lu Huidong [16] et al. found through animal experiments that atractylenolide III could inhibit the activation of JAK2/STAT3 pathway, reduce the local inflammatory response by lowering the expression of IL-1β, IL-6 and JAK2-related proteins, and effectively alleviate the intestinal injury in mice. Li Chunlin [17] et al. found through experiments that Huanglianin may inhibit JAK and STAT phosphorylation, inhibit apoptosis of colonic epithelial cells

and promote apoptosis of PMN cells in UC mice by regulating the JAK/STAT signalling pathway. Xu [18] et al. found that xianmaooside inhibited the release of pro-inflammatory factors through the expression of proteins related to the JAK/STAT signalling pathway, effectively alleviating colonic mucosal damage in UC mice. Various studies have shown that effective components of traditional Chinese medicine, such as safranin and xianmaooside, have certain clinical efficacy in the treatment of UC by regulating the JAK/STAT signalling pathway, reducing the expression of pro-inflammatory factors through the expression of proteins related to this signalling pathway.

3.3 MAPK Signalling Pathway

The MAPK signalling pathway is an important cell signalling pathway involved in the regulation of cell growth, proliferation, differentiation and apoptosis. In the pathogenesis of ulcerative colitis, inflammatory response and immune system abnormalities play an important role. After being stimulated by pathogens, inflammatory factors, oxidative stress, etc., extracellular growth factors activate tyrosine kinase receptor, the activated RTK binds to the junction protein GRB2 and provides a binding site for the recruitment of SOS, and SOS activates Ras, which is activated and binds to c-Raf, and activated c-Raf activates downstream MEK1/2, which phosphorylates MEK1/2. Downstream extracellular regulation of protein kinase 1/2, ERK1/2 activation will regulate the level of signal transduction and transcription activator 1/3, signal transduction molecule ELK-1 and other transcription factors in the colonic tissue, promote intestinal epithelial cell demodulation, damage to the intestinal mucosa, aggravate the symptoms of UC. p38 The MAPK signalling pathway plays a role in cellular stress response, inflammatory response and apoptosis. In ulcerative colitis, the p38 MAPK signalling pathway is activated to regulate TLR4-mediated ER stress-induced inflammatory effects in IBD. It can promote the production of inflammatory factors and chemokines and exacerbate the inflammatory response [19]. The MAPK signalling pathway affects the immune response of the intestinal mucosa by regulating the activation of inflammatory cells, cytokine release and apoptosis, among other pathways.

Epimedium has the efficacy of warming the kidney and aiding yang, dispelling wind and removing dampness, and it reduces the pro-inflammatory factors TNF-α and IFN-γ by regulating the p38MAPK signalling pathway in the intestinal epithelial cells, as well as inhibiting the abnormal proliferation of colonic tissue cells induced by LPS, improving the oxidative balance imbalance, and attenuating the inflammation and cell apoptosis. At the same time, Epimedium inhibits the activation of T lymphocytes, suppresses Th2 cell-mediated humoral immunity, attenuates hyperimmunity, and exerts a therapeutic effect on UC [20]. Huanglian detoxification soup has the efficacy of clearing heat and detoxification, and relevant studies have shown that quercetin, the active ingredient in Huanglian detoxification soup, can effectively reduce the levels of cytokines such as TNF-α, IL-1β, IL-17 and IL-6, thereby reducing inflammation, improving intestinal flora, and effectively alleviating the clinical symptoms of patients [21]. Cangzhu has the efficacy of drying dampness, strengthening the spleen, dispelling wind and dispersing cold, and its main component, cangzhuol, can inhibit LPS-induced phosphorylation activation of JNK, ERK and p38, inhibit the activation of the MAPK signalling pathway, and inhibit the expression of inflammatory factors in RAW264.7 cells [22].

4. Modulation of Signalling Pathways by Chinese Medicine

4.1 Inhibits the Release of Inflammatory Factors

One of the important pathogenetic mechanisms of UC is the imbalance of pro-inflammatory and anti-inflammatory factors, of which TNF-α, MPO, IL-6, MMP-2, and INOS belong to the pro-inflammatory factors, and IL-10 belongs to the anti-inflammatory factors. Excessive release of pro-inflammatory factors such as tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1), and IL-6 leads to intestinal mucosal destruction, inflammatory cell infiltration, and ulcer formation, which in turn causes clinical symptoms such as abdominal pain, diarrhoea, and haematochezia in patients [23]. A variety of active ingredients in traditional Chinese medicine, such as baicalin and baicalein, can inhibit inflammatory secretion and reduce the release of colonic mediators, such as TNF-α and IL-6, thereby reducing the inflammatory response. It was found that baicalein could dose-dependently inhibit the secretion of inflammatory factors such as TNF-α, IL-8, IL-1, and reduce the expression of colonic COX-2 and NF-κB in UC model rats; reduce the levels of TNF-α, IL-1β, and IL-6 mRNA, and reduce the expression level of Fascin in UC model rats, which could exert an anti-inflammatory effect to alleviate the colonic injury. Baicalein significantly reduced the levels of IL-6, TNF-α, IL-1β and LPS in serum and colon tissues of UC model mice, increased the sIgA content, and lowered the expression of colonic NF-κB, NOD2, SPHK1, S1PR1, and p-STAT3 proteins; it is suggested that baicalein reduces inflammatory responses and alleviates colonic mucosal oedema and inflammatory cell infiltration by inhibiting the S1P-STAT3 signaling pathway [24]. inflammatory cell infiltration [24].

4.2 Modulation of Immunity

Immunological abnormalities are both the initiating factor and the final link in UC. When there is an imbalance of the immune system in the intestinal tract or after the invasion of pathogens, the abnormally activated inflammatory vesicles, as an important branch of the innate immune system, are involved in the development of UC; and the T lymphocytes, as adaptive immune cells, also play an important role in its pathogenesis. Adaptive immune T cells are involved in the process of immune-inflammatory response and control the intensity of the inflammatory response to prevent the body from immune damage. T cell receptor (TCR) forms TCR-peptide-MHC complexes after recognising antigens and binds to antigen-presenting cells on the surface of the co-receptor CD4 or CD8 to determine the differentiation of T cells. The T cell subsets are mainly CD3+, CD4+, CD8+, CD3+, CD4+, CD4+, CD4+, CD4+, CD4+, CD4+ and CD8+. T cell subpopulations include CD3+, CD4+, CD8+, and so on. Inflammatory CD4+ T cells are mainly dependent on Th1 cells and Th17 cells to invade the intestinal mucosal tissues, which contribute to the release of a large number of

characteristic pro-inflammatory factors such as γ-interferon, tumour necrosis factor-α and IL-17 through the expression of the transcription factor T-bet and the expression of the transcription factor class retinol-related orphan receptor γt, aggravating mucosal damage [25]. Ulcerative colitis is triggered by an imbalance of Th cell types 1 and 2, and there is a shift from Th2 to Th1 cytokine balance, which in turn activates signalling pathways such as nuclear factor kappa-B (NF-κB), mitogen-activated protein kinase (MAPK) and other factors, contributing to leukocyte damage [25]. The release of NF-κB, mitogen-activated protein kinase (MAPK), and interleukin (IL)-1β, IL-13, and tumor necrosisfactor-α (TNF-α), which exacerbate the inflammatory progression of colitis, has been found to be a significant factor in the inflammation of colitis. Ginsenoside Rg3 was found to regulate the secretion of Th1/Th2 cytokines, modulate the immune balance, and reduce the inflammatory response in ulcerative colitis [26].

4.3 Protecting and Repairing the Intestinal Mucosal Barrier

The intestinal mucosal barrier includes mechanical, chemical, immune and biological barriers, and the tight junctions between normal epithelial cells are an important structure that constitutes the intestinal mechanical barrier, maintains the permeability of the intestinal mucosal epithelial cell bypass, and prevents the internal invasion of bacteria and endotoxin. In patients with UC, the inflammatory response of the intestinal tract can cause damage to intestinal cup cells and their mucus secretion to decrease, and the intestinal epithelial cell necrotic detachment, which leads to changes in the permeability and decrease in the mucosal barrier function of the intestine [27]. This leads to changes in intestinal permeability and decreased mucosal barrier function [27]. Impairment of the epithelial barrier, such as alterations in intestinal secretory function (antimicrobial peptides, mucus layer, etc.) and structural defects (decreased expression of tight junction proteins such as claudin and occludin, increased mucosal permeability, etc.), is an important causative factor in UC. The absence of desmosomal cadherin desmoglein 2 (DSG2) is considered to be a characteristic alteration in the intestinal epithelium of UC patients [28]. Wang Bo et al. found through experimental studies that Sophora japonica can elevate the expression of ZO-1 and occludin levels in the colon, effectively improve the intestinal mucosal permeability in mice, maintain the integrity of the colonic mucosal tight junctions, and repair the damaged intestinal mucosal barrier, which has an important protective function for the intestinal mucosal barrier [29].

5. Conclusion and Outlook

Ulcerative colitis (UC) is a clinically refractory chronic inflammatory bowel disease with a certain tendency to become cancerous, and the search for efficacious therapeutic agents is of positive significance in improving the prognosis of patients. Traditional Chinese medicine (TCM) has made positive research progress in the treatment of UC by modulating relevant signalling pathways, but still faces some challenges. Research on the specific mechanisms of TCM on signalling pathways, screening of active ingredients and clinical translation still need to be further deepened. In addition, TCM treatment needs to be supported by more high-quality clinical trials and systematic studies to verify its safety and efficacy. In summary, a series of important advances have been made in the study of TCM in the treatment of UC based on the modulation of signalling pathways, which provides strong support for the development of novel therapeutic strategies and drugs, but its clinical application still requires further improvement and in-depth research.

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