Pathogenesis of Ulcerative Colitis Based on Network Pharmacology and New Therapeutic Targets

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\textbf{Abstract.} Ulcerative colitis (ulcerative colitis) is a kind of intestinal inflammatory disease with easy recurrence and long course. Modern medicine does not have a clear understanding of its pathogenesis, and there are no specific drugs to treat it in the world. Therefore, by analyzing, summarizing and summarizing the possible pathogenesis of the disease in existing studies and combining with network pharmacology research, this paper provides references for exploring the pathogenesis of ulcerative colitis and provides ideas for finding new therapeutic targets. While summarizing the literature research on ulcerative colitis in the past five years, combined with the relevant literature and knowledge of network pharmacology, it is believed that ulcerative colitis is mainly related to genetic, immune, microbial, diet, infection, environment and other factors internationally. In the treatment of ulcerative colitis, nf-kappa signaling pathway, tlr4-my8-nf-kappa signaling pathway and pi3k-akt-mtor signaling pathway play a key role. Therefore, in the treatment of ulcerative colitis, IKK, kappa kappa, MyD88, TAK1, and nf-kappa can be regarded as new therapeutic targets, so as to have a significant effect on ulcerative colitis.

\textbf{Introduction}

Ulcerative colitis (UC) is a chronic, non-specific inflammatory disease of the colon. It has the characteristics of easy recurrence, long course of disease, difficult treatment, high acute morbidity and mortality, and high rate of chronic persistent cancer [1]. Currently, there is no specific drug for treatment, so it is listed as one of the modern refractory diseases by WHO. The location of the disease is mostly from the distal end of the intestine, mainly in the sigmoid colon and rectum, in a segmental distribution. Clinically, it is the main symptom of continuous or repeated mucus pus and bloody stool, diarrhea, abdominal pain, urgency and weight, and abdominal distension. Ulcerative colitis, in addition to the intestinal tract itself, will also affect other organs, showing extra intestinal manifestations, such as lesions in the skin mucosa, causing oral ulcers [2].

Network pharmacology is a branch of pharmacology based on systems biology and multi-directional pharmacology. Based on the existing pharmacology [3], the construction of a multi-layer network of "disease-phenotype-gene-drug" is carried out. The biggest advantage is to study the problem from the perspective of mutual connection, break the traditional concept of "one drug, one target, and one disease", systematically observing the intervention and influence of drugs on the disease network [4, 5]. Network pharmacology emphasizes the shift from a “single target” to a “network target” research model [6]. Therefore, it is more suitable for the treatment of complex diseases. Therefore, this article provides a new target for the treatment of ulcerative colitis through network pharmacology analysis, and provides a direction for discovering potential therapeutic drugs.

\textbf{Pathogenesis}

So far, there is no clear understanding of the pathogenesis of UC in the world, and it is currently believed to be mainly related to genetics, immunity, microbes, diet, infection, and environmental factors.
Immunity

Abnormal immune function of the intestinal system plays an important role in the development of ulcerative colitis. When the immune regulation is unbalanced, inflammatory cells and inflammatory mediators will be abnormally secreted, resulting in intestinal mucosal damage. The tumor necrosis factor-a (TNF-a) released by macrophages further stimulates the secretion of (IL)-1β and IL-6, promotes the accumulation of neutrophils to the inflammation site, and destroys the intestinal mucosal barrier, thereby causing a series of intestinal lesions [7]. In addition, under physiological conditions, the number of activation of CD4ten T cells in the intestinal mucosa is closely related to the structure of the mucosa. When the activity of CD4ten T cells is increased, it can promote cell migration and increase cytokine expression. Thereby damage to the intestinal mucosa structure [8].

Genetics

The pathogenesis of ulcerative colitis is closely related to heredity. Statistically, out of 454 patients with UC, 10.1% had a family history. Studies have shown that UC is a genetically related disease with multiple genes involved and genetic susceptibility. Among them, miRNA-target genes play an important role in the pathogenesis of UC. Studies have reported that compared with miRNA in colon tissue of patients with ulcerative colitis and healthy people, the expression of three miRNAs such as mi-192 and mi-375 is significantly reduced in UC patients, mi-21, mi-26, etc. 11 miRNAs were significantly increased [9]. In addition, the polymorphism of the Toll-like receptor 4 (TLR4) 896A>G locus gene is also associated with the pathogenesis of UC [10]. According to studies, the expression of TLR4 is relatively low on the surface of normal intestinal epithelium, but the expression of intestinal epithelial surface in UC patients is significantly increased, which may cause the body's immune system to not properly treat intestinal microbes and cause inflammation. Intensified.

Microorganisms

Some researchers believe that pathogenic bacteria and conditional pathogens in the intestine of patients with ulcerative colitis attack the intestinal mucosa directly or in the form of secreted toxins, which causes the intestinal flora to be dysregulated and the intestinal epithelial cells to be further damaged, which leads to excessive mucosal immune response and chronic inflammation of the intestine induce or aggravate the development of ulcerative colitis [11]. According to reports, in the intestinal tract of patients with ulcerative colitis, the type of bacteria is significantly less than the normal population, while the bacterial diversity of patients with more severe ulcerative colitis is reduced, while the total amount of bacteria is more than normal [12].

Other Factors

In addition to the pathogenesis of a series of ulcerative colitis listed above, it also has a certain correlation with environmental factors, such as smoking, oral contraceptives, dietary factors, breastfeeding and perinatal related events.

New Targets for the Treatment of Ulcerative Colitis Based on Network Pharmacology

Based on the characteristics of multi-component, multi-target and synergistic effects of traditional Chinese medicine prescriptions, it is difficult to study its mechanism of action, which hinders the modernization of traditional Chinese medicine. With the development of science and technology, network pharmacology can not only reveal the relationship between disease-disease, disease phenotype-target protein, but also through network analysis, systematic observation of target protein-drug, drug-drug interaction The influence reveals the principle of synergistic action of multi-molecular drugs, so it has significant advantages for the study of the mechanism of action of traditional Chinese medicine prescriptions and the exploration of new targets for complex diseases. Therapeutic targets for ulcerative colitis are now shown in Fig. 1 by means of network pharmacology.
NF-κB Signal Pathway Target

NF-κB is an important nuclear transcription factor that specifically binds to κB in various gene promoters, thereby regulating a large number of genes involved in cellular emergency responses such as immune response inflammatory responses and cellular anti-apoptotic effects. Transcription [13]. According to experimental reports, NF-κB is highly expressed in the intestinal tissue of UC patients and can promote the transcriptional expression of various inflammatory factors such as IL-1β, IL-2, IL-6, IL-8, TNF-α, etc. In turn, an inflammatory cascade [14] is produced. At the same time, positive feedback can promote the activation of NF-κB, thereby forming a vicious circle, leading to the up-regulation of target gene expression of NF-κB and promoting the occurrence and development of UC[15]. Therefore, NF-κB can be an important therapeutic target in the treatment of ulcerative colitis.

TLR4 - MyD88- NF-κB Signaling Pathway Target

Some stimulatory factors act on TLR4 on the cell membrane, which induces MyD88 and TAK1 to induce TLR4, dissociates TLR4 from the TLR4 complex, activates the NF-κB-dependent cascade, and initiates downstream inflammatory signaling. It causes the release of pro-inflammatory factors IL-1β, IL-6, IL-8, TNF-α, etc., which destroys the intestinal immune homeostasis and ultimately leads to the occurrence of UC [16-17]. Therefore, MyD88 and TAK1 play a vital role in this pathway. Therefore, when studying the treatment of ulcerative colitis, MyD88 and TAK1 in this signaling pathway are the corresponding therapeutic targets, which is an important research direction.

PI3K - AKT- mTOR Signaling Pathway Target

The PI3K-AKT signaling pathway regulates the release of cytokine [18] such as TNF-α, IFN, and IL. Once activated, AKT in this pathway enhances the activity of IKK in the NF-κB pathway and promotes phosphorylation of IκBα. With degradation, it leads to NF-κB activation. Studies have shown that the expression of p-Akt, PI3K, p-Akt/Akt protein in the ulcerative colitis model interfered by Astragalus polysaccharides is significantly decreased, which may indicate inhibition of activation of PI3K-Akt signaling pathway to achieve acute ulcerative colitis. Therapeutic effect [19]. Based on the PI3K-AKT signaling pathway and the combination of network pharmacology for the study of new anti-ulcerative colitis drugs, IKK and IκBα can be used as targets for prevention and treatment.

Discussion

In recent years, with the changes in dietary habits and environment, the incidence of the disease in China has been increasing year by year [20]. Network pharmacology explains the occurrence and development of diseases from the perspective of the balance between systems biology and
biological networks, and from the perspective of improving or restoring the balance of biological networks, to understand the interaction between drugs and organisms and to guide the discovery of new drugs, and to the incidence of complex diseases. Research on mechanisms and therapeutic targets has potential applications. Therefore, this article summarizes the target of treating ulcerative colitis by network pharmacology. At the same time, based on a large number of references to the literature, it is found that the target of treating ulcerative colitis selected by network pharmacology is not difficult to see. Systemic diseases such as ulcerative colitis have more therapeutic targets, but the current research involves relatively few pathways and targets, which is not conducive to the treatment of diseases. Network pharmacology concluded that LTA and TRAF6/TAK1 signaling pathways can be used as new therapeutic targets for ulcerative colitis. LTA, as an activator of TLR2, can specifically activate Toll-like receptors, thereby exerting therapeutic effects; Activation of the TRAF6/TAK1 signaling pathway can further inhibit the expression of related proteins iNOS and COX-2, thereby reducing the occurrence of cellular inflammatory damage. In summary, network pharmacology has significant advantages in the comprehensive treatment of ulcerative colitis, comprehensively analyzing the therapeutic targets of diseases from multiple angles, multiple targets, and multiple levels, and promoting the development of new drugs for ulcerative colitis. The pathogenesis of ulcerative colitis provides a new perspective.

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