DOI: 10.53469/jcmp.2025.07(02).09

The Pathogenesis and Treatment of Autoimmune Uveitis

Wang Pan[1], Furong Pan[1], Yanrui Dong[1], Jing'an Tong[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Department of Ophthalmology, Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China
Correspondence Author

Abstract: ***Uveitis is an inflammatory reaction that occurs in intraocular tissues. Among them, non-infectious uveitis is a T cell-mediated autoimmune inflammatory response, but its pathogenesis is not fully understood. This article reviews its pathogenesis and treatment progress.***

Keywords: Uveitis, Immunity, Traditional Chinese medicine, Treatment**.**

1. Introduction

The eye can be considered as a miniature immune system that can undergo any type of immune response. Because of its special structure and function in anatomy, physiology and biochemistry, it is different from the immune response of the whole body, forming a unique immune physiological and pathological process. It is related to the immune response of the whole body and has relatively independent local function.

Uveitis is a common type of blinding eye disease. Although infection, trauma and other factors can cause it, the most common and important type is uveitis caused by autoimmune response. The common causes and types are uveitis associated with rheumatic diseases, Vogt-Koyanagi-Harada syndrome, Fuchs syndrome, Beh-cel disease and uveitis caused by ocular toxoplasmosis [1]. It is generally believed that uveitis is a disease mediated by Th1 cells. Studies have found that T-bet (T box expressed in T cells, T-bet) is a specific transcription factor of Th1 and plays a decisive role in the differentiation of Th1. In the process of inflammatory response, T-bet can induce the production of interferon, inhibit the production of Th2 factors such as interleukin and IL-4, and initiate Th1 response, leading to inflammatory response damage dominated by cellular immunity [2].

2. Immune Response in Uveitis

The important role of genetic factors and immune disorders in the pathogenesis of uveitis has been widely recognized, but the exact mechanism of these factors involved in the occurrence of uveitis is not fully understood. Based on the basic research results of Behcet's syndrome, VKH syndrome and experimental autoimmune uveitis model, Chinese researchers have updated and improved the new theoretical framework of autoimmune diseases [3,4]. In individuals carrying multiple genetic susceptibility mutations such as interleukin 23 receptor, exogenous infection factors activate nucleotide-binding domain-containing and leucine-rich repeat family Pyrin domain protein 3, Notch signaling pathway and other regulatory factors through Toll-like receptors. Under the joint participation of the imbalance of IL23/IL17 pathway (Th17 cells) regulatory network, Th17 cells are over-activated, and a large number of (pro) inflammatory factors and chemokines are produced in retinal pigment epithelial cells, eventually leading to the occurrence, recurrence and chronicity of uveitis. In this theoretical framework, Chinese researchers have done a lot of work in several aspects. Firstly, the important role of IL-23/IL-17 pathway (Th17 cells) in the occurrence of uveitis was found for the first time in the world; Secondly, it was found that the target cells of IL-23/IL-17 pathway were RPE cells. Thirdly, the huge regulatory network of IL23/IL17 pathway was revealed [5].

In recent years, studies have shown that the activation of the complement system is one of the pathogenesis of uveitis. A variety of complement proteins, including CFH, CFB, CFI, MAC, and CD59, regulate complement system-mediated host tissue damage through rigorous mechanisms. Studies have found that complement proteins are involved in the occurrence and development of uveitis at the genetic level and biological functions. In addition, complement components such as C2, C3, C4, and C5 affect the pathogenesis of uveitis in terms of copy number variation, gene polymorphism, and regulation of T cell response-mediated autoimmune development. Therefore, complement inhibition therapy and related gene therapy provide new ideas and targets for the treatment of uveitis.

The complement system maintains a balanced homeostasis under the strict regulation of complement regulatory proteins to protect the body from the damage of ' alien ' components. When the balance is out of balance, it will mediate the development of uveitis. Clinical studies have found that the levels of Ba, Bb, C4d and sC5b-9 in plasma of patients with Behcet 's disease are increased, and the expression of C3aR in peripheral blood mononuclear cells of patients with BD and Koyanagi-Harada syndrome is increased. Studies on experimental autoimmune anterior uveitis have also shown that the activation of the complement system is essential for the occurrence of EAAU. On the contrary, the depletion of the host complement system can lead to complete inhibition of EAAU, confirming that the activation of the complement system is involved in the occurrence of uveitis. At the same time, genetic studies have shown that polymorphisms in the complement system can affect the development of immune-related diseases, such as complement factor H, complement factor I and complement factor B, which are related to the occurrence of uveitis. In summary, the

complement system is closely related to uveitis, and the imbalance of complement system regulation is involved in the occurrence and development of uveitis.

The complement system affects the progression of uveitis by regulating the response of T cells. More evidence shows that the complement system affects the progression of uveitis by regulating the T cell response of the adaptive immune system. The regulatory mechanism of the complement system on T cells is achieved by phosphatidylinositol 3-kinase-mediated AKT phosphorylation: up-regulating the expression of anti-apoptotic gene Bcl-2 in T cells and down-regulating the expression of pro-apoptotic molecule Fas; Activation of APC up-regulates the expression of co-stimulatory factors CD80 (B7-1) and CD86 (B7-2), and promotes the production of inflammatory factors IL-12 and IL-23. In the course of uveitis, antigen induction leads to the production of peripheral cross-reactive T cells, and the activation of effector T cells penetrates the blood retinal barrier into the eye. The new antigen is released and accumulates in the local lymph nodes. Autoreactive T cells are produced and the disease progresses. T cell subsets involved in the pathogenesis of uveitis include Th1, Th2, Th17 and regulatory T cells. Th1 cells secrete IL2 and interferon IFN-γ, Th2 cells secrete IL-4, IL-5, IL-6, IL-9 and IL13, Th17 cells secrete IL-17 A, IL-17 F, IL-21, IL-22, TNF-α and granulocyte-macrophage colony stimulating factor, Tregs secrete TGF-β and IL-10, and various complex cytokine networks mediate autoimmune and inflammatory responses. The interaction and imbalance between cells lead to the occurrence and development of uveitis [6].

Interleukin IL-35 is a new member of the IL-12 family. It is similar to other members in structure but different in function. It is an anti-inflammatory cytokine similar to IL-10 and transforming growth factor-β. IL-35 plays a role in a variety of autoimmune diseases, organ transplantation and tumors, and is an anti-inflammatory cytokine with important therapeutic prospects. Many studies have shown that IL-35 is involved in the occurrence and development of a variety of non-infectious uveitis. IL-35 is an immunosuppressive cytokine that inhibits autoimmune diseases by transforming resting T lymphocytes and B lymphocytes into Tregs and Bregs that express IL-10 and IL-35. Its abnormal high expression will prevent the host 's immune response to microorganisms and promote tumor growth and metastasis. Initial reports have shown that IL-35, mainly produced by T cells, is involved in the inhibitory activity of Tregs. Subsequent studies have shown that IL-35 is also an inducer of IL-10 and IL-35 Bregs [7].

Programmed death 1 (PD-1) has been shown to be associated with many autoimmune diseases. The signaling pathway composed of PD-1 and programmed death ligand 1 (PD-L1) plays a key role in regulating the immune response. The inactivation of PD-1/PD-L1 pathway may lead to abnormal activation of autoimmune T cells, leading to the occurrence and development of autoimmune diseases. In patients with autoimmune uveitis, the mRNA expression of PD-1, PD-L1 and PD-L2 in peripheral blood lymphocytes decreased, and the decrease was greater in active patients [8]. The study of experimental autoimmune uveitis (EAU) mouse model [9] found that PD-1 was expressed in the retina of normal and EAU mice, while in the active stage of inflammation, PD-L1 and PD-L2 were significantly reduced in the inflammatory cells, blood vessels and retinas infiltrated by the eyes. LEE et al. found that inhibition of autoimmune response can improve EAU inflammation [10]. The high expression of PD-1 and its ligands in the eyes is related to the transition of EAU from active to stationary phase : Treg is stimulated by co-stimulatory molecules and cytokines to differentiate into iTreg, iTreg inhibits the autoimmune response of T cells by up-regulating the expression of PD-1 and PD-L1, which in turn leads to a decrease in the production of IFN-γ in effector T cells and an increase in the secretion of transforming growth factor-β, which ultimately stops the progression of EAU [11].

3. Treatment of Autoimmune Uveitis

3.1 Western Medicine Treatment

Intraocular inflammation caused by uveitis is a chronic and recurrent process, which may be unilateral or bilateral. This is not only the main cause of many ocular complications, but also the main reason for long-term treatment. Therefore, anti-inflammatory immunosuppressive agents have become the main drugs for the treatment of non-infectious uveitis. The treatment of non-infectious uveitis focuses on inhibiting excessive autoimmune response. At the same time, attention should be paid to reducing the side effects of drugs, preventing the aggravation of eye tissue damage, and protecting visual function to the greatest extent. Current guidelines for the treatment of non-infectious uveitis require a rapid method of controlling inflammation, usually using local or systemic corticosteroids, represented by glucocorticoids [12]. The immunosuppressive agents used in the treatment include hormones and hormone replacement agents, and hormones are still the main immunosuppressive agents. The traditional treatment is mainly based on glucocorticoids and immunosuppressants, which mainly inhibit the immune response non-specifically. The curative effect is limited and the adverse reactions are large. With the development of modern immunology and molecular biology techniques, some new drugs for the pathogenesis of uveitis, especially biological agents, have been gradually applied in clinical practice.

3.1.1 Glucocorticoid

The anti-inflammatory effect of glucocorticoids is achieved by inhibiting the activation of transcription factors such as NF-KB and AP1, and the administration methods include systemic administration and local administration. However, the systemic use of glucocorticoids is limited due to adverse effects such as elevated blood glucose, systemic hypertension, decreased bone mineral density, depression, and weight gain.

3.1.2 Anti-metabolic drugs

Anti-metabolic drugs inhibit cell proliferation mainly by inhibiting nucleic acid production. Drugs commonly used in the treatment of non-infectious uveitis include methotrexate, azathioprine and mycophenolate mofetil.

3.1.3 T cell inhibitor

cyclosporine: Cyclosporine is an 11-amino acid cyclic peptide

derived from fungi. It can preferentially inhibit the signal transduction of antigen-induced T lymphocytes by forming a complex with cyclophilin, thereby inhibiting the expression of lymphokines and anti-apoptotic proteins. Tacrolimus: a novel macrolide immunosuppressant isolated from the fermentation broth of Streptomyces sp. 9993.

3.1.4 Alkylation agent

Alkylation agent inhibits the synthesis of DNA by alkylation of DNA leading to DNA cross-linking. The commonly used alkylating agents are cyclophosphamide and chlorambucil. Because alkylating agents have serious side effects, they are only used for poorly treated or severe uveitis.

3.1.5 Biological agents

Biological targeting agents can specifically target a certain inflammatory mediator, block the development of the disease, showing good efficacy. Several common biological targeted agents for the treatment of non-infectious uveitis are: anti-tumor necrosis factor biological agents, interferons, and rituximab [13].

3.2 Chinese Medicine Treatment

Traditional Chinese medicine is the treasure of Chinese. Traditional Chinese medicine has the characteristics of multi-component, multi-target and multi-link, and has unique curative effect and advantage for uveitis with complex mechanism [14]. Recent studies have shown that the study of traditional Chinese medicine in the prevention and treatment of uveitis has received more and more attention.

3.2.1 Single Chinese medicine treatment

In the history of medication for the treatment of uveitis, traditional Chinese medicines such as clearing heat, tonifying, purging and tonifying qi can play a good therapeutic role by calming liver and clearing heat, purging fire and detoxification, clearing heat and drying dampness, promoting stagnation and dredging arthralgia, removing blood stasis and dredging meridians, nourishing liver and kidney, and benefiting essence and eyesight. Single medicine is mainly based on effective parts or active ingredients, which has a good therapeutic effect on uveitis, such as berberine of coptis chinensis, matrine of sophora flavescens, and hedysari polysaccharide of hedysari.

Dracocephalum heterophyllum can inhibit the proliferation of CD4+ cells in experimental autoimmune uveitis mice. The occurrence of uveitis is closely related to CD4+ cells [15]. Rhizoma Coptidis are the dry rhizomes of Coptidis Rhizoma. It has been found that berberine can alleviate the symptoms of conjunctival congestion, ciliary congestion, corneal edema and retinal vascular leakage in EAU mice, reduce the proportion of CD4+ IL-17 cells and CD4+ IFN-γ cells, down-regulate the expression levels of multiple immune-related pathway genes, and alleviate the inflammatory infiltration of the fundus, so as to significantly improve the intestinal flora and alleviate EAU [16].

3.2.2 Compound treatment

Shaoyao Gancao Decoction is composed of two traditional Chinese medicines, peony and licorice. This prescription has the effects of benefiting yin and blood, softening liver and soothing tendons, and relieving pain [17]. Studies have shown that when the ratio of Shaoyao Gancao Decoction is 3:1, the improvement of ocular inflammation in EAU rats is the most obvious. It may play an anti-inflammatory role by correcting the Th1/Th2 immune balance in rats, reducing the ratio of IFN-γ/IL-10, and down-regulating the level of IL-17 pro-inflammatory factors [18].

Longdan Xiegan Decoction is a classic prescription composed of gentian, bupleurum, scutellaria, gardenia, alisma, akebia, plantain, angelica, rehmannia, licorice and so on. It has the effects of clearing heat of viscera, clearing heat of liver and gallbladder, clearing heat and dampness of liver meridian. Yin et al. studied the effect of Longdan Xiegan Decoction on Notch signaling pathway in ocular tissue of EAU rats and found that Longdan Xiegan Decoction could effectively reduce the expression levels of Notch1, DLL4, IL-10 and IL-17 mRNA and protein by inhibiting the activation of Notch signaling pathway, regulate the balance of Th17/Treg cells, reduce the infiltration of inflammatory cells in ocular tissue, protect the ocular tissue structure, and regulate the immune status of the eye, thus exerting the therapeutic effect on EAU [19]. Longdan Xiegan Capsule combined with glucocorticoid can effectively regulate the levels of IL-10, IL-23, TNF-α, IFN-γ and other pro-inflammatory factors in patients with HLA-B27-related acute anterior uveitis, improve the immune imbalance of patients, and exert the effect of treating AAU [20].

4. Conclusion

Uveitis has the characteristics of complex condition, long course of disease and high recurrence rate. Its pathogenesis is not completely clear. It is one of the clinically refractory blinding eye diseases and is closely related to the human immune mechanism. Therefore, in-depth study of the immunological mechanism of its pathogenesis is an important part of breaking through the treatment of uveitis. We should explore the immunological problems of eye diseases from multiple angles and levels, advocate multi-center research, strive for a breakthrough in some aspects of ophthalmic immunological research, and promote the development of ophthalmology in China.

References

[1] Yang Peizeng, Zhang Zhen, Wang Hong, et al. Studies on the etiologies and classification of uveitis [J]. Chinese Journal of Ocular Fundus Diseases, 2002(4).

[2] Zhou Qin, Yan Ying, Zhang Yan. Research progress of ophthalmic immunology [J]. International Eye Science, 2010, 10(5): 918-920.

[3] Hou S, Du L, Lei B, et al. Genome-wide association analysis of vogt-koyanagi-harada syndrome identifies two new susceptibility loci at 1p31.2 and 10q21.3 [J]. Nature Genetics, 2014, 46(9): 1007-1011.

[4] Chi W, Yang P, Li B, et al. IL-23 promotes CD4+ T cells to produce IL-17 in vogt-koyanagi-harada disease [J].

Journal of Allergy and Clinical Immunology, 2007, 119(5): 1218-1224.
[5] Yang Peizeng, Du Liping. Research progress of uveitis in China [J]. Chinese Journal of Ophthalmology, 2019, 55(4): 5.
[6] Xiong Hui, Yang Mingming, Yu Xuhui. Role of complement system in the pathogenesis of uveitis [J]. International Eye Science, 2022, 22(8): 1293-1297.
[7] Yang Shufang, You Caiyun. Research advances in interleukin-35 for the treatment of non-infectious uveitis [J]. Recent Advances in Ophthalmology, 2022, 42(3): 249-252.
[8] Meng Q, Yang P, Guo H, et al. Characteristic expression of PD-1 and its ligands mRNAs in patients with noninfectious uveitis [J]. International Journal of Clinical and Experimental Medicine, 2016, 9(1): 323-329.
[9] Chen J, Qian H, Horai R, et al. Mouse models of experimental autoimmune uveitis: comparative analysis of adjuvant-induced vs spontaneous models of uveitis [J]. Current Molecular Medicine, 2015, 15(6): 550-557.
[10] Lee D J, Taylor A W. Recovery from experimental autoimmune uveitis promotes induction of antiuveitic inducible tregs [J]. Journal of Leukocyte Biology, 2015, 97(6): 1101-1109.
[11] YANG Chenling, ZHOU Huifang. Research progress on the role of PD-1/PD-L1 pathway in autoimmune eye diseases [J]. Journal of Shanghai Jiaotong University (Medical Science), 2022, 42(1): 107-112.
[12] Chan Zhao, Meifen Zhang. Immunosuppressive treatment of non-infectious uveitis: history and current choices [J]. Chinese Medical Sciences Journal, 2017, 32(1): 48-61.
[13] Zhang Yuqing, Shao Yi, Zhou Qiong. Progress in systemic treatments of non-infectious uveitis [J]. International Eye Science, 2019, 19(12): 2045-2047.
[14] Xu Xinyue, He Wei. Recent research progress on treatment of traditional Chinese medicine for uveitis [J]. Journal of Practical Traditional Chinese Internal Medicine, 2021, 35 (05): 133-136.
[15] Wang Shanshan, Tang Xiaoting, Li Xueting. Research progress in the mechanism of traditional Chinese medicine in the treatment of uveitis [J]. Asia-Pacific Traditional Medicine, 2021, 17 (11): 213-216.
[16] Yu Jiazhen, Mo Ya. New progress in the treatment of uveitis by extracts of traditional Chinese medicine [J]. Journal of Chinese Ophthalmology and Otorhinolaryngology, 2021, 11 (02): 93-97.
[17] Zou Taoyuan, Ning Yunhong, Guo Chengwei. Mechanism of Shaoyao Gancao Decoction against uveitis: based on network pharmacology and experimental verification [J]. World Chinese Medicine, 2022, 17 (08): 1064-1070.
[18] LYU Lu, Ning Yunhong, Guo Chengwei. Effects of Shaoyao Gancao Decoction on experimental autoimmune uveitis rats guided by translational medicine approach [J]. Journal of Shandong University of Traditional Chinese Medicine, 2018, 42(3): 255-258.
[19] Yin Xuewei, Liu Bin, Wei Huixia, et al. Inhibitory role of longdanxiegan decoction in the activation of notch signaling pathway in treating experimental autoimmune uveitis rats [J]. Recent Advances in Ophthalmology, 2019, 39(7): 615-619.
[20] Xiang Shengjin, Wang Yuqin, Li Yan, et al. Effect of Longdan-xiegan Capsule on the levels of cytokine in patients with positive HLA-B27 acute anterior uveitis. [J]. Journal of Medical Research, 2013, 42(1): 58-61.