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Effects of Qingli Gandan decoction on IL-23/IL-17 in rats with experimental autoimmune uveitis

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Abstract

In this study, through animal experiments, we investigated the effects of Qingli Gandan decoction on the IL-23/IL-17 signalling pathway and the expression of CD4+/IL-17A+ cells in EAU rats. We then predicted the potential mechanisms of the action. First, Lewis rats were divided using the random number table method into a (1) control group, (2) model group and (3) TCM group. The TCM group was given a Qingli Gandan prescription by gavage after an intervention model. Next, blood, aqueous humour and vitreous were collected from each group on days 4, 8, 12, 16 and 20 after immunisation. An enzyme linked immunosorbent assay (ELISA) was used to detect the protein concentrations of IL-17 and IL-23 in a serum, aqueous humour and vitreous of rats on different immunisation days, and the percentage of CD4+/IL-17A+ cells in rat spleen was detected by flow cytometry. The peak concentration of serum IL-17 protein in group 3 was statistically lower than that in group 2 ($P < 0.05$) on days 4, 8 and 12 of immunisation. However, the peak concentration of serum IL-23 protein in group 3 was statistically lower than in group 2 ($P < 0.05$) on days 8 and 12 of immunisation; in addition, on days 8 and 12, the protein concentrations of IL-23 and IL-17 in the aqueous humour group 3 were all lower than those in group 2. On days 4, 8 and 12, the protein concentrations of IL-23 and IL-17 in vitreous in group 3 were significantly lower than those in group 2. We found that the proportion of CD4+/IL-17A+ cells in the groups 2 and 3 increased on day 8 compared with group 1 ($P < 0.05$). The proportion of CD4+/IL-17A+ cells decreased in group 3 compared with group 2 ($P < 0.05$).At last, we think Qingli Gandan can reduce the onset of EAU in rats and treat it, presumably because of inhibiting the IL-23/IL-17 axis. It may inhibit the expression of CD4+/IL-17A+ cells and play a role in inhibiting the IL-23/IL-17 signalling pathway.

Keywords: experimental autoimmune uveitis; Qingli Gandan decoction; IL-23/IL-17; CD4+/IL-17A+.

Practical Application: Previous studies found that Qingli Gandan decoction affected Th1/Th2 cytokines in the peripheral blood of patients with acute preuveitis, thus inhibit the uveal inflammatory reaction. In this study, the EAU rat model was established to observe the effects of Qingli Gandan decoction on the expression of IL-17 and IL-23 protein in serum, aqueous humour and vitreous and the expression of CD4+/IL-17A+ cells in the spleen in order to explore the potential mechanism of TCM in the treatment of uveitis.

1 Introduction

Uveitis is one of the most common intraocular inflammations. It occurs frequently in young adults. It is often recurring and may lead to serious complications (Yeo et al., 2013). The pathogenesis of uveitis is complex, including infection, autoimmune reaction, endogenous microbiome disorders, oxidative damage and genetic factors. Among non-infectious factors, autoimmune reaction is the most common (Yeung et al., 2015; Horai et al., 2015). Autoimmune uveitis is mediated by CD4+ T cells, and studies have shown that the main cause of uveitis is that the body produces T lymphocytes specific for self-antigen, mainly including Th1, Th2 and Th17 cell subsets (Horai et al., 2015). Recently, IL-17 has been considered to be a very important anti-inflammatory cytokine in vivo. Th17 subsets of cells are important for independently mediating autoimmune diseases (Sun et al., 2015; Li et al., 2019), which secretes IL-6 and IL-17 and is involved in inflammatory responses and autoimmune diseases. In this process, the relevant receptor molecules and transcription molecules in T cells play an important role. Some research indicated that the inhibition of Th17 immune responses in R406-treated mice might be a possible mechanism which causes mitigation of psoriasis-like inflammation,and sulforaphane treatment reverses corticosteroid resistance in a mixed granulocytic mouse model of asthma by attenuation of Th17 immune responses in the airways (Alzahrani et al., 2019; Al-Harbi et al., 2019). Moreover, the survival and reproduction of Th17 cells are closely related to IL-23 (Yasuda et al., 2019).

Due to the complex aetiology and pathogenesis, the treatment of uveitis is difficult (Barfüßer et al., 2021). Glucocorticoids, immunosuppressants and other drugs are often used in the clinical treatment of autoimmune uveitis, but long-term use may lead to many adverse reactions (Cunningham & Wender, 2010; Okada, 2005; Díaz-Llopis et al., 2009). Finding a therapeutic drug may not only ensure a curative effect but also reduce recurrence; toxic side effects have become a focus of clinical

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practice. Traditional Chinese medicine (TCM) has a characteristic effect in the treatment of uveitis by distinguishing its deficiency and reality and by regulating *qi* and blood circulation (National Standard, 1994). The Qingli hepatobiliary prescription medicine is unique. It includes gypsum, forsythia, fried gardenia, *Scutellaria baicalensis*, raw semen coicis, straw kou, *Poria cocos*, rhubarb and licorice, and it has a certain immunomodulatory effect. Our department has screened out the hepatobiliary prescription and achieved results in clinical applications. Previous studies found that this prescription affected Th1/Th2 cytokines in the peripheral blood of patients with acute preuveitis, which can inhibit the secretion of IFN and TNF and thus inhibit the uveal inflammatory reaction (Pang et al., 2010). Therefore, in order to further explore the effect of this prescription on Th17 cell subset, we intend to establish an experimental autoimmune uveitis (EAU) rat model, including rat serum IL-17 and IL-23 detection and rat spleen expression of CD4+/IL-17A+ cells to provide a novel scientific basis for the treatment of EAU.

2 Materials and methods

2.1 Materials

Experimental materials

Forty-five female Lewis rats aged 6-8 weeks and with a mass of 160-180 g were selected and provided by Beijing Vital River Laboratory Animal Technology Co., Ltd. (part of CRL, US). We obtained the interphotoreceptor vitamin A-binding protein from Shanghai Biotechnology Biotechnology Co., Ltd. (Shanghai, China) and total tuberculin adjuvant (complete Freund's adjuvant [CFA]) from Sigma (St. Louis, MO, US). The enzyme-linked immunosorbent test (enzyme-linked immunoadsordent assay, ELISA) kit was purchased from CUSABIO (Wuhan, China). CD4 and IL-17A monoclonal antibody were all obtained from Invitrogen (Carlsbad, CA, US).

The Qingli hepatobiliary prescription medicine is unique and was obtained from the Pharmacy Department of Tianjin Eye Hospital (Tianjin China). The main ingredients of this medicine are as follows: raw gypsum 25 g, rhizoma anemarrhenae 9 g, danpi 12 g, rehmannia glutinosa 9 g, gentian 6 g, forsythia 9 g, fried gardenia 9 g, *scutellaria baicalensis* 9 g, coix chinensis 12 g, alpinia katsumadai hayata 9 g, poria cocos 20 g, rhubarb 6 g and licorice 6 g. In our study, the animals were treated according to the *Regulations on the Management of Laboratory Animals* (2017 revision).

2.2 Animal groupings and establishment of the EAU model

Using the random number table method, the rats were divided into 3 groups: a control group (group 1), model group (group 2) and TCM group (group 3), with each group including 15 animals. Group 1 was not treated and ate as normal; group 2 and group 3 were injected with 100 μL of photoreceptor vitamin A binding protein (1177-1191), complete Freund adjuvant containing tuberculin and sterile PBS to induce EAU (Fang et al., 2013). Following the first day after modelling induction, each rat in group 3 was given 2 mL Qingli Gandan decoction with a concentration of 25.38 mL/kg intragastric administration every day (Using Li Yikui's pharmacological experimental methods, the equivalent dose ratio between humans and animals according to the body surface area was calculated). A corresponding volume of normal saline was added to groups 1 and 2 as a control. All rats were raised in an SPF environment system, with temperature 20-26 °C, humidity 40%-70%, ventilation 15 times/h and a cycle of 12 h light/12 h dark. We next recorded the different indicators on different days.

2.3 The protein expression levels of aqueous humour, vitreous fluid, serum IL-17 and IL-23 were determined by ELISA

On days of 4, 8, 12, 16 and 20 after immunisation, we collected capillary water from the room fluid, vitreous fluid and blood of the abdominal aorta. Next, the standards were made according to the instructions for the ELISA kit. The sample to be examined was added to the microplate reaction hole. We added a 100 μL sample to each well, culturing at 37 °C for 1 h and then washed with PBS. We then added an HRP-labelled antibody and substrate solution horseradish peroxidase to the labelled avidin, culturing at 37 °C for another hour. Last, we added a termination solution. The protein expression levels of IL-17 and IL-23 were detected at different time points.

2.4 CD4+/IL-17A+ cell expressions in rat spleen tissues of each group were analysed by flow cytometry

Three blood samples were taken from each group on days 4, 8, 12, 16 and 20. Rat spleen tissues were then collected, ground, filtered and centrifuged. We then obtained erythrocyte lysate, terminated with PBS and centrifuged. Afterwards, we adjusted the cell density, stained with CD4-PE and IL-17A-FITC, incubated by light and fixed cells. The expression of CD4 and IL-17A cells was detected by flow cytometry after soaking with 0.5% Triton-X for 20 min at room temperature.

2.5 Statistical analysis

SPSS 26.0 was used for the statistical analyses, and the results of IL-23 and IL-17 protein concentrations in serum, aqueous humour and vitreous were expressed as the mean ± standard deviation ($\overline{x}$ ± SD). Expression of CD 4+ and IL-17A+ cells was indicated by Cell proportion (%). The one-way analysis of variance (ANOVA) was used to analyse the statistical differences of IL-23 and IL-17 protein concentrations in serum, aqueous humour and vitreous among these groups, Chi square test was used to to analyse the statistical differences of expression of CD 4+ and IL-17A+ cells among these groups, and $P < 0.05$ was considered significantly different.

3 Results

3.1 Serum protein expression levels of IL-23/IL-17 in each group of rats

ELISA results showed that the serum IL-23 and IL-17 protein concentrations in groups 2 and 3 increased significantly after immunisation, with IL-17 peaking on immunisation day 4 and IL-23 on immunisation day 8. On immunisation days 4, 8 and 12, the peak concentration of IL-17 protein in group 3 was lower than in group 2, and the difference was statistically significant ($P < 0.05$) (Tables 1-2). On immunisation days 8 and 12, the peak

Table 1. Protein expression levels of IL-23 in different sites of each group.

	4 Days	8 days	12 Days	16 Days	20 Days
In Serum (pg/mL)					
Control group	0.12 ± 0.02	0.17 ± 0.05	0.19 ± 0.04	0.16 ± 0.02	0.17 ± 0.06
model group	0.25 ± 0.03*	0.73 ± 0.14*	0.54 ± 0.05*	0.38 ± 0.07*	0.32 ± 0.03*
TCM group	0.23 ± 0.04*	0.65 ± 0.12*#	0.31 ± 0.09*#	0.29 ± 0.07*	0.25 ± 0.10
In aqueous humor (pg/mL)					
Control group	1.17 ± 0.05	1.35 ± 0.07	1.31 ± 0.12	1.47 ± 0.20	1.43 ± 0.32
Model group	1.78 ± 0.12*	3.53 ± 0.44*	5.74 ± 1.41*	3.18 ± 0.12*	2.93 ± 0.06*
TCM group	1.65 ± 0.24*	2.01 ± 0.30*#	3.38 ± 0.22*#	2.95 ± 0.44*	2.43 ± 0.29*
In vitreous (pg/mL)					
Control group	1.02 ± 0.10	1.25 ± 0.13	1.56 ± 0.04	1.48 ± 0.34	1.37 ± 0.11
Model group	1.73 ± 0.35*	3.82 ± 0.86*	2.84 ± 1.34*	2.81 ± 0.16*	2.36 ± 0.1
TCM group	1.34 ± 0.21*#	1.62 ± 0.81*#	2.58 ± 0.86*#	2.38 ± 0.96*	1.77 ± 0.68*

*Compared with the blank group, P < 0.05. #Compared against the model group, P < 0.05.

Table 2. Protein expression levels of IL-17 in different sites of each group.

	4 Days	8 days	12 Days	16 Days	20 Days
In Serum (pg/mL)					
Control group	687.55 ± 46.71	694.25 ± 32.52	731.22 ± 63.96	730.01 ± 62.84	690.95 ± 78.57
Model group	2201.19 ± 53.42*	1320.64 ± 103.57*	981.79 ± 62.34*	772.40 ± 89.43	733.54 ± 45.68
TCM group	1832.73 ± 101.32*#	1197.73 ± 72.35*#	799.71 ± 82.53*#	753.88 ± 69.38	714.44 ± 93.24
In aqueous humor (pg/mL)					
Control group	20.06 ± 2.25	28.74 ± 5.88	25.48 ± 2.56	21.98 ± 3.48	23.67 ± 4.45
Model group	37.54 ± 3.67*	59.57 ± 2.54*	86.53 ± 8.43*	68.97 ± 3.59*	42.69 ± 5.32*
TCM group	36.79 ± 2.52*	43.26 ± 8.31*#	66.64 ± 6.73*#	57.03 ± 7.39*	38.94 ± 6.35*
In vitreous (pg/mL)					
Control group	28.76 ± 4.53	29.56 ± 10.27	29.24 ± 6.17	27.26 ± 12.53	28.62 ± 4.26
Model group	63.24 ± 25.21*	88.25 ± 14.16*	61.22 ± 14.74*	32.91 ± 2.36*	33.42 ± 5.35
TCM group	42.78 ± 9.37*#	50.39 ± 26.33*#	46.65 ± 7.63*#	37.08 ± 3.53*	31.23 ± 8.27

*Compared with the blank group, P < 0.05. #Compared against the model group, P < 0.05.

concentration of IL-23 protein in group 3 was lower than in group 2, and the difference was statistically significant (P < 0.05) (Tables 1-2). By immunisation day 20, there was no significant difference in IL-23 concentration values between groups 1 and 2 (P > 0.05) and the IL-23 concentration values between group 3 and the blank group (P < 0.05); there was no significant difference in the concentration of IL-17 between the three groups (P > 0.05) (Tables 1-2).

3.2 Protein expression levels of IL-23/IL-17 in aqueous humour of each group

The ELISA results showed that the protein concentrations of IL-23 and IL-17 in the aqueous humour were compared on days 4, 8, 12, 16 and 20 with the blank group (P < 0.05). Both had peaked on the 12th day of immunisation. On immunisation days 8 and 12, the protein concentrations of IL-23 and IL-17 in group 3 were lower than those in group 2, and the differences were statistically significant (P < 0.05) (Tables 1-2).

3.3 Protein expression levels of vitreous IL-23/IL-17 in each group of rats

ELISA showed that the concentrations of IL-23 protein in vitreous of groups 2 and 3 were higher than that of the blank group on days 4, 8, 12, 16 and 20. The exception was on day 20, when concentration of the IL-17 protein increased compared with the blank group (P < 0.05). IL-23 peaked on day 12, and IL-17 peaked on day 8. On days 4, 8 and 12, the protein concentrations of IL-23 and IL-17 in group 3 were significantly lower than those in group 2 (P < 0.05) (Tables 1-2).

3.4 Expression of CD 4+ and IL-17A+ cells

The expression level of CD4+/IL-17A+ cells in the spleens of the three groups was detected by flow cytometry. It was found that the proportion of CD4+/IL-17A+ cells in groups 2 and 3 increased on immunisation day 8, compared with group 1 (P < 0.05). The proportion of CD4+/IL-17A+ cells decreased in group 3 compared with group 2 (P < 0.05) (Figure 1).

4 Discussion

In this study, the EAU rat model was established to observe the effects of Qingli Gandan decoction on the expression of IL-17 and IL-23 protein in serum, aqueous humour and vitreous and the expression of CD4+/IL-17A+ cells in the spleen in order to explore the potential mechanism of TCM in the treatment of uveitis.

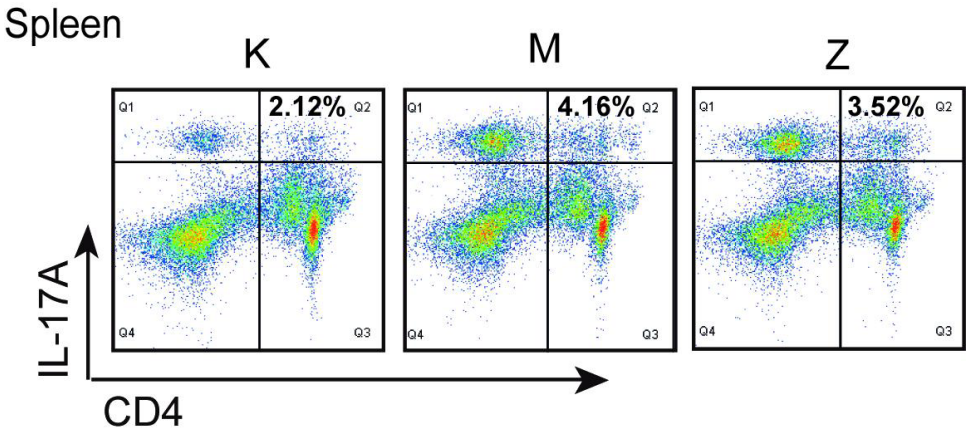

Figure 1. Note: K is control group, M is model group and Z is Chinese medicine group.

In previous studies of TCM, it was found that gypsum and rhizoma anemarrhenae both are antipyretic and inhibit the metabolism, anti-pathogen and anti-inflammatory effects of corticoids in the liver (Yang, 2012). For immune diseases, long-term use of glucocorticoids, gypsum, anemarrhena and other drugs can enhance the adrenal cortex function, assist in hormone reduction and adjust the autoimmune status. Gardenia has the effect of benefiting the gallbladder and reducing yellow, antipyretic, antibacterial and anti-inflammatory effects (Luo et al., 2021), *Scutellaria baicalensis* mainly contains flavonoids, baicalein and other components, and it has anti-inflammatory, anti-allergy, anti-allergic reaction, antipyretic and detoxification effects (Tang et al., 2007). Licorice has a hormone-like action and has a bidirectional regulation of immune functions (Zhang & Shen, 2011). Therefore, Qingli hepatobiliary prescription medicine plays a certain role in immune regulation.

EAU is characterised by infiltration of autoimmune T cells along with increased proinflammatory factors and reactive oxygen species (Choi et al., 2021). Th17 cell subsets have a very important role in defending against extracellular infection and independently mediating autoimmune diseases (Noack & Miossec, 2014). Th17 cells can secrete the cytokine IL-17. Additionally, IL-17 can enhance the initiation of T cell responses and stimulate various types of cells to produce proinflammatory mediators, which mainly functions in the effector phase of the inflammatory response (Weinstein & Pepple, 2018).

IL-23, an IL-12 family member, is a heterodimeric protein composed of p19 and p40 subunits, secreted by dendritic cells, monocytes, macrophages and activated myeloid cells, and it is critical in intestinal inflammatory diseases (e.g. ulcerative colitis and Crohn's disease) (Pepple & Lin, 2018). The key target is a unique memory T cell specifically activated by IL-23 to produce pro-inflammatory mediators IL-17 and IL-6 (Nadeem et al., 2019). The IL-23/IL-17 axis plays a central role in the pathogenesis of immune-mediated diseases, such as psoriasis, ankylosing spondylitis and inflammatory bowel diseases (Pepple & Lin, 2018; Jethwa & Bowness, 2016; Tsukazaki & Kaito, 2020). There is evidence that in the context of autoinflammation and autoimmunity, most uveitis cases may have a common molecular and immunologically pathogenic basis, in which activation of the IL-23/IL-17 pathway may be key (Zhong et al., 2021). Therefore, investigating the IL-23/IL-17 pathway has become the focus of research in multiple autoimmune diseases. Chi et al. (2011) found that IL-23 can promote IL-17 production by CD4+ T cells in Behcet disease (BD) patients, and the upregulated IL-17 levels were associated with the intraocular inflammatory response in BD patients.

In this study, serum IL-23 and IL-17 concentrations in EAU rats were measured. It was found that the expression of IL-17 could be stimulated in the early stage after modelling, and the protein concentration was the highest on day 4 after immunisation. The expression peak of IL-23 was later than that of IL-17, and the concentration was the highest on day 8. The peak of the two-protein concentration in aqueous humour and vitreous was delayed compared with the serum. The concentrations of both reached a peak on day 12. Vitreous IL-23 peaked on day 1, and IL-17 peaked on day 8. CD4+ T cells play a key role in inducing immune responses during host defence and in the pathogenesis of inflammatory diseases. IL-17A and IL-17F in the IL-17 family are both thought to be the most specific to the Th17 response (Park et al., 2005). Both IL-17A and IL-17F exist in homodimer or heterodimers and can show a similar function (Wright et al., 2007). The expression level of CD4+/IL-17A+ cells in spleens of EAU rats was analysed, and it was found that the expression level of CD4+/IL-17A+ cells in groups 2 and 3 increased, but it decreased in group 3 compared with group 2 on the 8th day after immunisation. Qin (2011) found that the inflammatory response of EAU reached its peak at day 14, and the up-regulation of the death receptor 3 (DR3) expression in CD4+ T cells in EAU promoted IL-17 secretion.

Our study has several advantages. First, EAU is an ideal model for evaluating uveitis with drug treatment (Bansal et al., 2015), which is useful for studying human uveitis and even systemic autoimmune diseases. Second, experimental animal model performance is characteristic, reproducible and easy to observe and record. However, the present study exhibits limitations. Only one dose was designed in this study, and further studies are needed concerning the correlation between drug dose and efficacy. Recurrence was not studied in this study.

5 Conclusion

In conclusion, this study showed that the Qingli Gandan decoction can affect the IL-23/IL-17 signalling pathway in EAU, and it may inhibit the IL-23/IL-17 pathway by inhibiting the expression of CD4+/IL-17A cells. The effect provides a novel idea for the mechanism study of the Qingli Gandan decoction in EAU, but the specific intervention target of the therapeutic effect requires further study.

Ethical approval

The experimental protocol was approved by the Animal Experimentation Ethics Committee of Tianjin eye hospital. Experimental animals underwent all procedures under anesthesia, and every effort was made to minimize their pain, suffering, and death.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Conflict of interest

All of the authors had no any personal, financial, commercial, or academic conflicts of interest separately.

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Author contributions

Wang QM and Pang YJ conceived of the study, and Gao J participated in its design and data analysis and statistics and Zhang YL and Wang X and helped to draft the manuscript. All authors read and approved the final manuscript.

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