Network Pharmacology-Based Investigation into the Mechanism of Action of Budesonide in IgA Nephropathy: Postprint

Authors: Zhang Kang, Zhao Tingting, Zhang Bo, Gao Mengqi, Li Yuxi, Wang Shaopeng, Zhao Wenjing, Zhao Wenjing

Date: 2023-07-28T00:00:00+00:00

Abstract

Background: IgA nephropathy is the most common primary glomerulonephritis in China and worldwide, with 25%~30% of patients progressing to end-stage renal disease within 20 years of diagnosis. Currently, there is no effective and safe treatment regimen specifically for IgA nephropathy. In recent years, research on new drugs for IgA nephropathy has advanced rapidly, among which targeted delayed-release budesonide capsules represent the world's first etiological treatment drug for IgA nephropathy.

Objective: To investigate the mechanism of action of corticosteroid budesonide enteric-coated capsules in the treatment of IgA nephropathy based on network pharmacology.

Methods: The targets of budesonide were screened through the Chemical Book platform; and the targets related to IgA nephropathy were obtained using the GeneCards and CTD databases. The common budesonide-IgAN targets were obtained by intersection using a Venn diagram. A protein-protein interaction (PPI) network was constructed, and Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed on the intersection targets.

Results: A total of 242 budesonide action targets, 1,443 IgA nephropathy candidate targets, and 146 intersection targets were screened. The PPI network identified 15 core targets: interleukin-6 (IL-6), tumor necrosis factor (TNF), interleukin-10 (IL-10), vascular endothelial growth factor A (VEGFA), epidermal growth factor receptor (EGFR), interleukin-1B (IL-1B), interleukin-4 (IL-4), interleukin-8 (CXCL8), Jun proto-oncogene (JUN), interleukin-13 (IL-13), interleukin-2 (IL-2), C-C motif chemokine ligand 2 (CCL2), Toll-like receptor 4 (TLR4), colony stimulating factor 2 (CSF2), and albumin (ALB). Enrichment

analysis yielded 1,646 GO enrichment results and 174 KEGG signaling pathways. Biological process (BP) mainly involved positive regulation of phosphorylation, inflammatory response, positive regulation of cell motility, etc.; cellular component (CC) mainly involved cytoplasmic vesicle lumen, vesicle lumen, secretory granule lumen, etc.; molecular function (MF) mainly involved signaling receptor activator activity, signaling receptor regulator activity, receptor ligand activity, etc. KEGG signaling pathways mainly involved the interleukin-17 signaling pathway, cytokine-cytokine receptor interaction, pathways in cancer, tumor necrosis factor signaling pathway, etc.

Conclusion: This study preliminarily validates that budesonide can treat IgA nephropathy through multiple signaling pathways, including the cytokine-cytokine receptor interaction pathway, interleukin-17 signaling pathway, pathways in cancer, and tumor necrosis factor signaling pathway, via targets such as IL-6, TNF, IL-10, VEGFA, and EGFR, providing a theoretical basis for further research and clinical practice of budesonide.

Full Text

Study on the Mechanism of Budesonide in the Treatment of IgA Nephropathy Based on Network Pharmacology

Kang Zhang[1], Tingting Zhao[2], Bo Zhang[2], Mengqi Gao[3], Yuxi Li[2], Shaopeng Wang[4], Wenjing Zhao[1]*

[1]Department of Nephrology, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing 100010, China
[2]Institute of Clinical Medical Sciences, China-Japan Friendship Hospital, Beijing 100029, China
[3]Department of Nephrology and Endocrinology, Wangjing Hospital, China Academy of Chinese Medical Sciences, Beijing 100102, China
[4]College of Pharmacy, Weifang Medical University, Weifang 261053, China

Corresponding author: Wenjing Zhao, Chief Physician; E-mail: wenjingz@263.net

---

Abstract

Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis in China and worldwide, with approximately 25%-30% of patients progressing to end-stage renal disease within 20 years after diagnosis. Currently, there is no effective and safe treatment specifically for IgAN. In recent years, research on new drugs for IgAN has progressed rapidly, among which the targeted delayed-release budesonide capsule represents the first etiologic treatment drug for IgAN globally.

Objective: To investigate the mechanism of corticosteroid budesonide enteric-coated capsules in the treatment of IgAN based on network pharmacology.

Methods: The Chemical Book platform was used to screen the targets of budesonide, while GeneCards and CTD databases were utilized to obtain IgAN-related targets. The intersection of budesonide and IgAN targets was identified through a Venn diagram. A protein-protein interaction (PPI) network was constructed, and gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed on the intersecting targets.

Results: A total of 242 targets for budesonide, 1,443 candidate targets for IgAN, and 146 intersecting targets were identified. The PPI network revealed 15 core targets: interleukin-6 (IL-6), tumor necrosis factor (TNF), interleukin-10 (IL-10), vascular endothelial growth factor A (VEGFA), epidermal growth factor receptor (EGFR), interleukin-1B (IL-1B), interleukin-4 (IL-4), interleukin-8 (CXCL8), Jun proto-oncogene (JUN), interleukin-13 (IL-13), interleukin-2 (IL-2), chemokine ligand 2 (CCL2), toll-like receptor 4 (TLR4), colony-stimulating factor 2 (CSF2), and albumin (ALB). Enrichment analysis revealed 1,646 GO enrichment results and 174 KEGG signaling pathways. Biological processes (BP) mainly involved positive regulation of phosphorylation, inflammatory response, and positive regulation of cell movement. Cellular components (CC) primarily involved cytoplasmic vesicle lumen, vesicle lumen, and secretory granule lumen. Molecular functions (MF) mainly involved signaling receptor activator activity, signaling receptor regulator activity, and receptor ligand activity. KEGG signaling pathways primarily included the interleukin-17 signaling pathway, cytokine-cytokine receptor interaction, pathways in cancer, and tumor necrosis factor signaling pathway.

Conclusion: This study provides preliminary verification that budesonide can treat IgAN by targeting IL-6, TNF, IL-10, VEGFA, EGFR, and other molecules through multiple signaling pathways including cytokine-cytokine receptor interaction, interleukin-17 signaling pathway, pathways in cancer, and tumor necrosis factor signaling pathway, providing a theoretical basis for further research and clinical practice of budesonide.

Keywords: Budesonide; Glomerulonephritis, IgA; IgA nephropathy; Network pharmacology; Signaling pathway

Introduction

IgA nephropathy (IgAN) is a common primary glomerulonephritis worldwide, accounting for 52.66% of primary glomerulonephritis cases in China. Approximately 25%-30% of IgAN patients progress to end-stage renal disease within 20 years of diagnosis, imposing a heavy burden on families and national healthcare systems. Currently, there is no effective and safe treatment specifically for IgAN.

The 2021 KDIGO guidelines recommend that the treatment of IgAN should focus on optimized supportive therapy, including blood pressure management, use of maximum tolerated doses of renin-angiotensin system inhibitors (RASI), and lifestyle modifications. For patients who remain at risk of disease progression after at least 90 days of optimized supportive therapy, a 6-month course of corticosteroid therapy may be considered. However, the long-term efficacy and safety of glucocorticoids remain controversial. The STOP-IgAN study demonstrated that intensified immunosuppressive therapy did not slow the decline in estimated glomerular filtration rate (eGFR) in high-risk IgAN patients and was associated with significantly increased adverse effects. The TESTING study showed that full-dose steroid therapy significantly reduced proteinuria and decreased renal failure events by 63% in IgAN patients, but the risk of serious adverse events increased 4.63-fold.

In recent years, research on new drugs for IgAN has progressed rapidly, with targeted delayed-release budesonide capsules emerging as the world's first etiologic treatment for IgAN. In October 2022, the Phase III NefIgArd clinical trial of budesonide enteric-coated capsules published results demonstrating significant advantages in reducing proteinuria, stable renal function, and no serious adverse events, although the mechanism of action in IgAN remains incompletely understood. This study employs network pharmacology methods to explore the therapeutic targets of budesonide in IgAN, conducting drug-disease target interaction analysis and gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses to provide a theoretical basis for the clinical application of budesonide in IgAN treatment.

Methods

1.1 Acquisition of Basic Budesonide Information

Basic information about budesonide, including its molecular formula and structural formula, was obtained from the Chemical Book platform (https://www.ChemicalBook.com/).

1.2 Screening and Standardization of Budesonide Targets

Budesonide-related genes were retrieved from the GeneCards human gene database (https://www.genecards.org/) using the keyword "Budesonide" with data updated until March 2023. Relevant targets were further supplemented using the DrugBank database (https://www.drugbank.ca) and the Therapeutic Target Database (TTD, https://db.idrblab.net/ttd/). The predicted drug target information was standardized against the UniProt database (https://www.uniprot.org/) to identify the primary targets of budesonide.

1.3 Acquisition of IgAN-Related Target Genes

IgAN-related genes were obtained from GeneCards and the Comparative Toxicogenomics Database (CTD, http://ctdbase.org/) using the keyword "IgA nephropathy." In GeneCards, when the number of target genes is large, those with Score values greater than the median can be considered potential disease targets. In this study, the median Score values obtained from GeneCards were 34.0 and 810.67, respectively. Since the number of targets was moderate, no screening was performed and all targets were included. The maximum Score was 73.96 and the minimum was 0.26. Relevant targets from the CTD database were used to supplement the dataset, and the results from both databases were intersected using a Venn diagram to obtain the final IgAN target list.

1.4 Identification of Budesonide-IgAN Intersection Targets

Budesonide-related targets and IgAN targets were imported into the Venny 2.1.0 website (https://bioinfogp.cnb.csic.es/tools/venny/index.html) to identify common targets through Venn diagram intersection analysis.

1.5 Construction of Drug-Disease Target Network

Budesonide and the budesonide-IgAN common target genes were imported into Cytoscape 3.9.1 software to construct a drug-disease target network diagram. In this network, "nodes" represented drug components and their targets, while "edges" represented interactions between nodes.

1.6 Protein-Protein Interaction (PPI) Network Construction

The intersecting target genes were input into the STRING database (https://string-db.org/) to construct a PPI network. The results were imported into Cytoscape 3.9.1 software, and the CytoNCA plugin was used to calculate the degree and betweenness centrality of each node. Targets with degree values greater than or equal to the median were defined as key targets.

1.7 GO and KEGG Pathway Enrichment Analysis

The common target genes were subjected to GO and KEGG enrichment analysis using the Metascape database (https://metascape.org). GO enrichment analysis included three components: biological process (BP), cellular component (CC), and molecular function (MF). The screening parameters were set as follows: Min Overlap = 3, P Value Cutoff = 0.01, and Min Enrichment = 1.5. The visualization of analysis results was performed using the Bioinformatics platform (http://www.bioinformatics.com.cn/).

Results

2.1 Screening of Budesonide and IgAN-Related Targets

The basic information of budesonide is shown in Figure 1 [Figure 1: see original paper]. A total of 242 budesonide targets and 1,443 IgAN-related genes were obtained. Through Venn diagram intersection analysis, 146 common budesonide-IgAN target genes were identified, accounting for approximately 9.5% of the total targets (Figure 2 [Figure 2: see original paper]).

2.2 Network Analysis of Budesonide-IgAN Common Target Genes

A "drug-disease target" network diagram was constructed using budesonide and the 146 common budesonide-IgAN target genes. The central orange node represented budesonide, while the 146 surrounding green nodes represented potential therapeutic targets of budesonide for IgAN, with 146 edges indicating interactions between budesonide and IgAN (Figure 3 [Figure 3: see original paper]).

2.3 PPI Network Analysis

The 146 common budesonide-IgAN target genes were input into the STRING database to construct a PPI network. After applying screening criteria, the network contained 143 nodes and 1,022 edges (Figure 4 [Figure 4: see original paper]). The results were imported into Cytoscape 3.9.1 software, and the CytoNCA plugin was used to calculate the degree and betweenness centrality of each node. Targets with degree values greater than or equal to the median were screened, yielding 15 key target genes: interleukin-6 (IL-6), tumor necrosis factor (TNF), interleukin-10 (IL-10), vascular endothelial growth factor A (VEGFA), epidermal growth factor receptor (EGFR), interleukin-1B (IL-1B), interleukin-4 (IL-4), interleukin-8 (CXCL8), Jun proto-oncogene (JUN), interleukin-13 (IL-13), interleukin-2 (IL-2), chemokine ligand 2 (CCL2), toll-like receptor 4 (TLR4), colony-stimulating factor 2 (CSF2), and albumin (ALB) (Figure 5 [Figure 5: see original paper], Table 1).

2.4 GO Enrichment Analysis

The 146 intersecting target genes were subjected to GO functional enrichment analysis using the Metascape database, yielding 1,646 biological processes (BP), 62 cellular components (CC), and 127 molecular functions (MF). The BP terms mainly involved inflammatory response, positive regulation of phosphorylation, and positive regulation of cell motility. The CC terms primarily involved vesicle lumen, cytoplasmic vesicle lumen, and secretory granule lumen. The MF terms mainly involved signaling receptor activator activity, signaling receptor regulator activity, and receptor ligand activity. The top 20 enrichment results were visualized as bubble plots using the Bioinformatics platform, where dot size represented gene count and color corresponded to P-value (Figures 6-8 [Figure 6: see original paper][Figure 7: see original paper][Figure 8: see original paper]).

2.5 KEGG Signaling Pathway Enrichment Analysis

The 146 intersecting target genes were analyzed for KEGG pathway enrichment using the Metascape database, identifying 174 signaling pathways. A histogram of the top 20 signaling pathways was generated (Figure 9 [Figure 9: see original paper]), with the y-axis showing pathway names and the x-axis showing the number of genes enriched in each pathway. Different colors represented different P-values, with redder colors indicating smaller P-values and more significant enrichment, suggesting stronger association with the disease. The pathways with prominent enrichment included cytokine-cytokine receptor interaction, interleukin-17 signaling pathway, pathways in cancer, and tumor necrosis factor signaling pathway.

Discussion

The production of galactose-deficient IgA1 (Gd-IgA1) molecules due to mucosal immune deficiency plays a crucial role in the pathogenesis of IgAN. Therefore, identifying novel therapeutic strategies targeting the underlying cause represents a current research priority in IgAN. In recent years, the intestinal mucosal immune system, as the most extensive and important component of the mucosal immune system, has received increasing attention for its role in the development and progression of IgAN. The intestinal mucosal immune system possesses the body's most extensive mucosa-associated lymphoid tissue—gut-associated lymphoid tissue (GALT)—which influences both local intestinal and systemic immunity. Peyer's patches serve as the primary sites for antigen sampling and immune induction in GALT and represent the main source of IgA1 molecules in humans, providing a microenvironment that promotes B cell differentiation into IgA-secreting plasma cells. The mislocalization and migration of B cells that have differentiated into IgA plasma cells to systemic sites may lead to excessive circulating Gd-IgA1, potentially representing the fundamental basis and origin of IgAN. Budesonide enteric-coated capsules, as a targeted intestinal-release glucocorticoid, have demonstrated unique advantages in IgAN treatment by delivering the drug specifically to mucosal B cells in the terminal ileum, thereby reducing upstream production of Gd-IgA1 that triggers IgAN.

This study employed network pharmacology methods to explore the mechanism of budesonide in IgAN treatment. The results indicate that IL-6, TNF, IL-10, VEGFA, and EGFR occupy central positions among the key therapeutic targets. IL-6, tumor necrosis factor-α (TNF-α), and IL-10 are all inflammatory cytokines, with serum levels significantly elevated in IgAN patients. As a pro-inflammatory cytokine, IL-6 is one of the primary molecules mediating IgA1 overproduction through adrenal TLR9 activation. IL-6 not only induces excessive production of Gd-IgA1 but also mediates mesangial cell proliferation and matrix expansion while promoting inflammatory cell infiltration in the kidneys, thereby triggering disease development. Furthermore, clinical studies have

shown that urinary IL-6 levels are abnormally elevated in IgAN patients and correlate positively with renal pathological damage, suggesting that IL-6 may serve as a non-invasive biomarker reflecting renal injury in IgAN. TNF-α can induce podocyte apoptosis by binding to TNF-α receptor 1 (TNFR1) on IgAN podocytes, thereby triggering proteinuria. IL-10 expression in IgAN kidneys occurs primarily in tubular regions, and as an anti-inflammatory cytokine, IL-10 can inhibit inflammatory responses by reducing IL-1β synthesis and downregulating TNF synthesis. Additionally, a study in Northwestern Chinese populations demonstrated that IL-10 is a susceptibility gene for IgAN patients, and the IL-10 gene G-1082A polymorphism is associated with IgAN progression.

VEGFA is a crucial vascular endothelial growth factor essential for maintaining the survival, differentiation, and structure of glomerular endothelial cells, mesangial cells, podocytes, and parietal epithelial cells. Increased renal tubular VEGFA production leads to fibrosis and glomerular lesions. VEGFA is strongly expressed in parietal epithelial cells, tubular epithelial cells, podocytes, and mesangial cells of IgAN patients, with urinary VEGFA levels significantly correlating with tubular atrophy/interstitial fibrosis and serving as an independent prognostic factor for IgAN. EGFR is a multifunctional signal transducer, and excessive EGFR can activate the PI3K/Akt pathway, increase TGF-$ $1 levels, promote renal fibrosis, and enhance inflammatory cytokine production.

GO enrichment analysis of key targets revealed that biological processes mainly involve positive regulation of phosphorylation, inflammatory response, and positive regulation of cell movement. Cellular components primarily involve cytoplasmic vesicle lumen, vesicle lumen, and secretory granule lumen. Molecular functions mainly involve signaling receptor activator activity, signaling receptor regulator activity, and receptor ligand activity. KEGG enrichment analysis demonstrated that budesonide can regulate IgAN through multiple signaling pathways, among which the cytokine-cytokine receptor interaction pathway plays a crucial role. Cytokines, as the most active soluble polypeptides in the body, participate in physiological and pathological states through various mechanisms including enzymatic activity, cell membrane permeability, cytoskeletal protein function, and gene expression. The cytokine-cytokine receptor network constitutes an essential component of signal transduction and represents a key target for drug intervention. IgAN is associated with mucosal infections and often presents with elevated cytokine levels. The cytokine-cytokine receptor interaction pathway in IgAN patients plays an important regulatory role in the inflammatory process during bacterial infection. IL-6, as a pro-inflammatory factor, transmits inflammatory signals during infection and promotes immune cell proliferation and differentiation. In IgAN patients, IL-6 can upregulate galactose deficiency in IgA1 molecules by regulating ST6GALNAC2 and C1GALT1 gene expression and enzyme activity, thereby increasing immune complex formation and promoting disease progression. Therefore, budesonide's regulation of the cytokine-cytokine receptor interaction pathway to inhibit Gd-IgA1 synthesis represents an important therapeutic mechanism in IgAN.

In summary, this study preliminarily explored the pharmacological mechanism of budesonide in IgAN treatment. Budesonide may exert therapeutic effects in IgAN through IL-6, TNF, IL-10, VEGFA, EGFR, and other targets, acting on multiple pathways including cytokine-cytokine receptor interaction, interleukin-17 signaling pathway, pathways in cancer, and tumor necrosis factor signaling pathway. These findings provide a theoretical basis for further research and clinical application of budesonide in IgAN, with subsequent validation through basic experiments warranted.

References

[1] SCHENA FP, NISTOR I. Epidemiology of IgA nephropathy: a global perspective. Semin Nephrol. 2018;38(5):435-442. DOI:10.1016/j.semnephrol.2018.05.013.

[2] HOU JH, ZHU HX, ZHOU ML, et al. Changes in the spectrum of kidney diseases: an analysis of 40,759 biopsy-proven cases from 2003 to 2014 in China. Kidney Dis. 2018;4(1):10-19. DOI:10.1159/000484717.

[3] RODRIGUES JC, HAAS M, REICH HN. IgA nephropathy. Clin J Am Soc Nephrol. 2017;12(4):677-686. DOI:10.2215/cjn.07420716.

[4] Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. Kidney Int. 2021;100(4S):S1-S276. DOI:10.1016/j.kint.2021.05.021.

[5] RAUEN T, EITNER F, FITZNER C, et al. Intensive supportive care plus immunosuppression in IgA nephropathy. N Engl J Med. 2015;373(23):2225-2236. DOI:10.1056/NEJMoa1415463.

[6] LV JC, ZHANG H, WONG MG, et al. Effect of oral methylprednisolone on clinical outcomes in patients with IgA nephropathy: the TESTING randomized clinical trial. JAMA. 2017;318(5):432-442. DOI:10.1001/jama.2017.9362.

[7] BARRATT J, LAFAYETTE R, KRISTENSEN J, et al. Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy. Kidney Int. 2023;103(2):391-402. DOI:10.1016/j.kint.2022.09.017.

[8] MAKITA Y, SUZUKI H, NAKANO D, et al. Glomerular deposition of galactose-deficient IgA1-containing immune complexes via glomerular endothelial cell injuries. Nephrol Dial Transplant. 2022;37(9):1629-1636. DOI:10.1093/ndt/gfac204.

[9] HE JW, ZHOU XJ, LV JC, et al. Perspectives on how mucosal immune responses, infections and gut microbiome shape IgA nephropathy and future therapies. Theranostics. 2020;10(25):11462-11478. DOI:10.7150/thno.49778.

[10] BARRATT J, ROVIN BH, CATTRAN D, et al. Why target the gut to treat IgA nephropathy? Kidney Int Rep. 2020;5(10):1620-1624. DOI:10.1016/j.ekir.2020.08.009.

[11] BOYD JK, CHEUNG CK, MOLYNEUX K, et al. An update on the pathogenesis and treatment of IgA nephropathy. Kidney Int. 2012;81(9):833-843. DOI:10.1038/ki.2011.501.

[12] TANG YY, ZHU YF, HE HD, et al. Gut dysbiosis and intestinal barrier dysfunction promotes IgA nephropathy by increasing the production of Gd-IgA1. Front Med. 2022;9:944027. DOI:10.3389/fmed.2022.944027.

[13] HOU J, ZHANG L, WU H, et al. Increased Tim-3+ monocytes/macrophages are associated with disease severity in patients with IgA nephropathy. Int Immunopharmacol. 2021;97:107666. DOI:10.1016/j.intimp.2021.107666.

[14] GROZA Y, JEMELKOVA J, KAFKOVA LR, et al. IL-6 and its role in IgA nephropathy development. Cytokine Growth Factor Rev. 2022;66:1-14. DOI:10.1016/j.cytogfr.2022.04.001.

[15] MAKITA Y, SUZUKI H, KANO T, et al. TLR9 activation induces aberrant IgA glycosylation via APRIL- and IL-6-mediated pathways in IgA nephropathy. Kidney Int. 2020;97(2):340-349. DOI:10.1016/j.kint.2019.08.022.

[16] CHENG J, XU PP, WANG WW, et al. Correlation between urinary IL-6, KIM-1, TGF-$ $1 levels and renal pathology and clinical indicators in IgA nephropathy patients. Chin J Integr Tradit West Nephrol. 2017;18(5):433-435.

[17] LEUNG JCK, LAI KN, TANG SCW. Role of mesangial-podocytic-tubular cross-talk in IgA nephropathy. Semin Nephrol. 2018;38(5):485-495. DOI:10.1016/j.semnephrol.2018.05.018.

[18] WAN Q, ZHOU JB, WU YS, et al. TNF-α-mediated podocyte injury via the apoptotic death receptor pathway in a mouse model of IgA nephropathy. Ren Fail. 2022;44(1):1216-1226. DOI:10.1080/0886022X.2022.2079527.

[19] MYLLYMÄKI JM, HONKANEN TT, SYRJÄNEN JT, et al. Severity of tubulointerstitial inflammation and prognosis in immunoglobulin A nephropathy. Kidney Int. 2007;71(4):343-348. DOI:10.1038/sj.ki.5002046.

[20] ROMAGNANI S. T-cell subsets (Th1 versus Th2). Ann Allergy Asthma Immunol. 2000;85(1):9-18. DOI:10.1016/S1081-1206(10)62426-X.

[21] GAO J, WEI LT, FU RG, et al. Association of interleukin-10 polymorphisms (rs1800872, rs1800871, and rs1800896) with predisposition to IgA nephropathy in a Chinese Han population: a case-control study. Kidney Blood Press Res. 2017;42(1):89-98. DOI:10.1159/000471899.

[22] BANTIS C, HEERING PJ, AKER S, et al. Association of interleukin-10 gene G-1082A polymorphism with the progression of primary glomerulonephritis. Kidney Int. 2004;66(1):288-294. DOI:10.1111/j.1523-1755.2004.00730.x.

[23] GNUDI L, BENEDETTI S, WOOLF AS, et al. Vascular growth factors play critical roles in kidney glomeruli. Clin Sci. 2015;129(12):1225-1236. DOI:10.1042/CS20150403.

[24] KIKUCHI R, STEVENS M, HARADA K, et al. Anti-angiogenic isoform of vascular endothelial growth factor-a in cardiovascular and renal disease. Adv Clin Chem. 2019;88:1-33. DOI:10.1016/bs.acc.2018.10.001.

[25] FENG SZ, HUANG NY, XUE MR, et al. Association between urinary VEGFA and renal pathology of IgA nephropathy patients. J Clin Lab Anal. 2021;35(10):e23995. DOI:10.1002/jcla.23995.

[26] SONG J, WANG XD, LIU HB, et al. Effects of Shen'an Formula on EGFR-mediated PI3K/Akt pathway in rats with chronic kidney disease. Guid J Tradit Chin Med Pharm. 2022;28(8):22-26. DOI:10.13862/j.cn43-1446/r.2022.08.005.

[27] KHAN A, ALI A, JUNAID M, et al. Identification of novel drug targets for diamond-blackfan anemia based on RPS19 gene mutation using protein-protein interaction network. BMC Syst Biol. 2018;12(Suppl 4):39. DOI:10.1186/s12918-018-0563-0.

[28] HUANG H, LIE CH, LIANG LQ, et al. Effect of cytokines on IgA1 O-glycosylation in IgA nephropathy patients and related mechanisms. Southeast Natl Def Med. 2019;21(1):44-48. DOI:10.3969/j.issn.1672-271X.2019.01.010.

Author Contributions: Kang Zhang conceived and designed the study framework, prepared figures and tables, and drafted the manuscript; Bo Zhang and Mengqi Gao conducted literature collection, organization, and synthesis; Yuxi Li and Shaopeng Wang revised the manuscript; Wenjing Zhao and Tingting Zhao approved the final manuscript, supervised quality control, and provided critical review; Kang Zhang and Wenjing Zhao take overall responsibility for the article and its supervision.

Conflict of Interest: The authors declare no conflicts of interest.

Funding: Capital Health Development Scientific Research Special Project (2020-3-2235)

Citation: ZHANG K, ZHAO TT, ZHANG B, et al. Study on the mechanism of budesonide in the treatment of IgA nephropathy based on network pharmacology. Chin Gen Pract. 2023. [Epub ahead of print]. DOI:10.12114/j.issn.1007-9572.2023.0299.

Digital Publication Date: July 28, 2023

Note: Figure translations are in progress. See original paper for figures.