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Research progress on the correlation between aqueous humor components and pathogenesis and postoperative complications in patients with different types of cataracts

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不同类型白内障患者房水成分与发病机制及术后并发症相关性的研究进展

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摘要

房水为晶状体提供必要的营养,并在眼中运输代谢物。它是一种能直接反映眼内微环境的液体,在手术过程中很容易获得。文章旨在分析不同类型白内障患者的房水成分,以反映疾病的发病机制和发展过程,评估术后并发症的发生率,为后续白内障手术的手术设计提供参考价值。不同类型白内障的房水成分体现了不同程度的炎症、氧化应激和细胞外基质重塑。糖尿病性白内障早期神经病变的生物标志物是 NCAM1。转化生长因子(TGF)-β 是假性剥脱综合征患者疾病发展的评估因子。不同类型白内障术后并发症与房水成分的关系如下:糖尿病性白内障术后黄斑水肿与肿瘤坏死因子-α(TNF-α)相关;高度近视白内障术后囊袋收缩与单核细胞趋化蛋白-1(MCP-1)和 TGF-β2相关;Klotho 和 GSTP1 与原发性开角型青光眼并发白内障手术后高眼压相关;视网膜色素变性并发白内障手术后囊膜收缩与 MMPs 相关;先天性白内障房水中的促炎细胞因子和 FGF4 与后发性白内障相关。G-CSF3 和 MCP-1 是双眼序贯白内障手术短间隔(1 wk)中介导第二眼疼痛的主要细胞因子,而 MCP-1 在长间隔(6 wk)中介导疼痛。双眼序贯白内障术后的第二眼具有更高水平的促炎因子。不同类型白内障患者的房水成分与疾病的发病机制和术后并发症有关。监测房水成分有助于更好了解不同类型白内障的眼内微环境,为预测疾病发展和实施相关靶向治疗提供参考。

关键词:房水;白内障;手术;并发症;细胞因子

Abstract

• Aqueous humor provides the necessary nutrition for the lens and transports the metabolites in the eye. It was a liquid that can directly reflect the microenvironment in the eye, and it can be easily obtained during the operation. This review intended to analyze the components of aqueous humor in patients with different types of cataracts, so as to reflect the pathogenesis and development of the disease, evaluate the incidence of postoperative complications and provide reference value for the surgical design of sequential cataract surgery. The aqueous humor components of different types of cataracts showed different degrees of inflammation, oxidative stress and extracellular matrix remodeling. The biomarker of early neuropathy in diabetic cataract was neural cell adhesion molecule-1 (NCAM1). Transforming growth factor-β (TGF-β) was the evaluation factor of disease development in patients with pseudoexfoliation syndrome. The relationships between postoperative

complications of different types of cataracts and aqueous humor components were as follows: Macular edema after diabetic cataract surgery was associated with tumor necrosis factor-alpha; capsular contraction after high myopic cataract surgery was related to monocyte chemoattractant protein-1 (MCP-1) and TGF-β2; Klotho and glutathione S-transferase P 1 (GSTP1) were associated with high intraocular pressure after primary open-angle glaucoma complicated by cataract surgery; capsular contraction after retinitis pigmentosa complicated by cataract surgery was associated with matrix metalloproteinases; pro-inflammatory cytokines and fibroblast growth factor 4 in the aqueous humor of congenital cataracts were associated with posterior capsular opacification after surgery. Granulocyte colony stimulating factor 3 and MCP-1 were the main cytokines mediating the pain of the second eye in the binocular sequential cataract surgery short interval (1 wk), while MCP-1 mediated pain in the long interval (6 wk). The second eye after binocular sequential cataract surgery had a higher level of proinflammatory factors. The components of aqueous humor in patients with different types of cataracts were related to the pathogenesis and postoperative complications of the disease. Monitoring the components of the aqueous humor could help better understand the intraocular microenvironment of different types of cataracts and provide a reference for predicting the development of the disease and implementing relevant targeted therapy.

• KEYWORDS: aqueous humor; cataract; surgery; complications; cytokine
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INTRODUCTION

Cataract is an ophthalmic disease in which opacity of the lens reduces its transparency, resulting in vision loss and even blindness. Although cataract is one of the primary causes of blindness worldwide, no effective drug for the prevention and reversal of lens opacity has been developed to date. Surgical treatment remains the most important and effective modality[1], and phacoemulsification is the most advanced and commonly used method for cataract surgery. A variety of eye or systemic diseases can be accompanied by cataracts, including diabetes, high myopia (HM), glaucoma, uveitis, retinitis pigmentosa (RP), pseudoexfoliation syndrome (PEX), Fuch's endocorneal dystrophy and hepatitis B virus (HBV) infection. To better study the pathogenesis of these diseases, predict the development of the disease, and diagnose and treat the disease early, accurate biological markers are essential. The common complications after cataract surgery include posterior capsular opacification (PCO), elevated intraocular pressure, macular edema, vitreous hemorrhage, posterior iris adhesion, and retinal detachment[2]. These complications are closely related to other preoperative ocular or systemic complications. For example, diabetes is a risk factor for macular edema after cataract surgery[2]. Patients with HM are more likely to develop capsular contraction syndrome (CCS), PCO, and posterior vitreous detachment after cataract surgery[3]. These complications are largely related to abnormalities in intraocular microenvironments. Unfortunately, the relationship between postoperative complications of cataract surgery and initial state of eyes remains unclear owing to the difficultly of obtaining suitable eye tissues[4]. Binocular sequential cataract surgery is becoming increasingly common, and this approach mainly considers the recovery of binocular vision function in patients. Clinically, it has been observed that patients complain of more severe pain during the second eye surgery[5], which is related to their anxiety, subclinical sympathetic inflammatory reaction[6-7], and even the interval between eye surgeries[8]. The evaluation of pain using more objective indicators remains a problem that needs to be solved clinically.

It is accessible to collect aqueous humor (AH) during cataract surgery. AH is secreted by the ciliary body, circulates into the anterior chamber, and finally flows into the blood circulation through the trabecular meshwork at the corner of the chamber[9]. AH is mainly responsible for providing nutrients, removing metabolic waste, and maintaining the balance of intraocular pressure. AH contains glucose, electrolytes, cytokines, and other proteins. The components of the AH can reflect the pathophysiological conditions of the eyes. For example, cytokines in the AH can prompt the development of intraocular inflammation[10], and an increase in sodium concentration and magnesium deficiency can accelerate cataract formation[11]. Importantly, AH samples can be conveniently obtained during cataract surgery.

This article reviews the role of AH components in different types of cataract complications, discusses the changes in AH components and the significance of these changes in binocular sequential cataract surgery, in order to provide reference for the pathogenesis of various cataract eye diseases and provide biological basis for predicting the occurrence of complications after cataract surgery and the discomfort after the second eye surgery.

ROLE OF AQUEOUS HUMOR COMPONENTS IN DIFFERENT TYPES OF CATARACT AND CATARACT COMPLICATIONS The AH components indicated varying levels of oxidative stress and inflammation in different complicated cataracts (Table 1). The role of AH components in different types of cataracts were complicated.

Table 1 Expression of aqueous humor components in different types of cataract

Number of patients	Age ($\bar{x}\pm s$, years)	Detection method of aqueous humor components	Upregulation of aqueous humor classification and composition (relative to ARC)	Downregulation of aqueous humor classification and composition (relative to ARC)	Year of publication
DC					
10	67.90±11.10	Luminex-multiplex immunoassay	Inflammation promotion (IL-5, TNF-α, IL-2, MCP-1, IL-8, IL-7, IL-17a, IL-9); Inflammation inhibition (IL-4, IL-10); Fibrosis promotion (bFGF)	—	2022[27]
22	63.86±0.90	Chemical assay kit	Oxidative stress (AOPP, MDA, CD, 8-IPG-F2α)	Oxidative stress (SOD, GPx)	2022[19]
33	75.20±7.35	Inductively coupled plasma; optical emission spectrometry	Trace element (P/Ca)	—	2021[29]
18	71.80±6.95	ELISA	Inflammation promotion (IL-23); Extracellular scleral remodelling (TGF-β2)	Inflammation inhibition (IL-10)	2020[20]
49	59-80	Electrochemiluminescence assay	Inflammatory and fibrosis inhibition (25-Hydroxyvitamin D)	—	2020[23]
59	49.60±4.80	ELISA	Fibrosis promotion (IGF-1, bFGF); Inflammation promotion (IL-6)	—	2019[15]
29	67.90±6.60	Quantitative multiplexed antibody assay; ELISA; Western blot	Inflammation promotion (IL-6, sIL-6R)	—	2023[25]
20	65.10±11.20	TMT; HPLC-MS/MS; Western blot	Proliferation and migration (TTR)	Inflammatory and fibrosis inhibition (DBP)	2023[17]
HMC					
15	53.90±8.90	Luminex-multiplex immunoassay	Extracellular scleral remodelling (TGF-β2)	—	2022[94]
10	66.00±7.71	Luminex-multiplex immunoassay	Inflammation inhibition (IL-13)	Inflammation promotion (IL-15)	2022[27]
32	66.40±12.50	ELISA	Inflammation inhibition (CFH)	—	2021[33]
35	68.70±8.00	ELISA	Inflammation inhibition (Irisin); Inflammation promotion (LIF)	Neuronutrition (BDNF); Inflammation inhibition (IL-1ra)	2021[41]
14	67.70±8.50	ELISA	Extracellular scleral remodelling (PLG)	—	2021[35]
20	66.80±4.60	ELISA	Lipid metabolism (ApoA1)	—	2021[42]
8	64.20±12.20	ELISA	Fibrosis promotion (HGF); Oxidative stress (total nitrites/nitrate)	Angiogenesis (VEGF)	2020[30]
34	62.65±12.59	Quantibody custom array	Angiogenesis (ANG-1); Extracellular scleral remodelling (MMP-2)	—	2020[36]
45	62.69±10.43	Suspension cytokine array	Inflammation promotion (MCP-1)	Inflammation inhibition (IL-1ra)	2016[44]

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Table 1 Expression of aqueous humor components in different types of cataract (continued)

Number of patients	Age ($\bar{x}\pm s$, years)	Detection method of aqueous humor components	Upregulation of aqueous humor classification and composition (relative to ARC)	Downregulation of aqueous humor classification and composition (relative to ARC)	Year of publication
PACGC					
10	66.50±8.07	Luminex-multiplex immunoassay	Inflammation inhibition (IL-1ra, IL-13); Inflammation promotion (TNF-α)	—	2022[27]
40	62.30±8.80	Atomic absorption spectrophotometer; Amplex Red assay; Sirius red assay	Oxidative stress (Cu); Extracellular matrix remodelling (Lysyl Oxidase, Collagen)	—	2023[103]
POAGC					
36	64.36±11.77	Electrochemiluminescence assay	—	Inflammatory and fibrosis inhibition (25Hydroxyvitamin D)	2021[53]
18	69.27±7.29	ELISA	—	Oxidative stress inhibition (Klotho)	2021[50]
10	72.80±2.60	ELISA	—	Oxidative stress inhibition (GSTP1)	2021[51]
38	57.80±8.00	ELISA	Inflammation promotion (TNF-α); Extracellular scleral remodelling (TGF-β2)	—	2023[55]
40	60.70±10.40	Atomic absorption spectrophotometer; Amplex Red assay; Sirius red assay	Oxidative stress (Cu); Extracellular matrix remodelling (Lysyl Oxidase, Collagen)	—	2023[103]
27	>40	Bio-Plex Pro Human Cytokine 27-Plex Immunoassay	Inflammation promotion (IL-5, IL-12, IL-15, IFN-γ, MIP-1α)	—	2020[104]
UC					
58	40.80±13.80	Cytometric bead array	Inflammation promotion (MCP-1, IL-8, MIP-1); Angiogenesis (sVCAM, sICAM)	—	2019[58]
75	30-100	Multiplex immunoassay	Inflammation promotion (IL-1Rα, IL-5, IL-6, IL-8, IL-9, IL-12, Eotaxin, G-CSF, IP-10, MCP-1, MIP-1α, MIP-1β, TNF-α); Angiogenesis (VEGF)	Inflammation inhibition (IL-4); Inflammation promotion (IL-15, IL-17); Angiogenesis (PDGF-bb)	2022[60]
16	30	BD™ Cytometric Bead Array Kit; ELISA	Angiogenesis (VEGF); Fibrosis promotion (bFGF); Inflammation promotion (IL-6, IL-8); Inflammation inhibition (IL-10); Angiogenesis (VCAM)	—	2021[63]
RPC					
4	52.75±6.34	Immunohistochemistry staining	Serotransferrin, tenascin-C	—	2021[70]
20	57.60±11.98	Multiplex fluorescent bead immunoassay	IL-8, MCP-1, IP-10, HGF, PDGF-AA, MMP-2, MMP-3, MMP-7, MMP-8, PAI-1, TSP-2	BMP-4	2020[65]

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Table 1 Expression of aqueous humor components in different types of cataract (continued)

Number of patients	Age ($\bar{x}\pm s$, years)	Detection method of aqueous humor components	Upregulation of aqueous humor classification and composition (relative to ARC)	Downregulation of aqueous humor classification and composition (relative to ARC)	Year of publication
FECD					
26	71.77±7.59	Bio-Rad	Inflammation promotion (RANTES, eotaxin, IxP-10)	—	2024[72]
CC					
55	3.61±2.18	ELISA	FGF4	—	2020[76]
18	3.8 months	Multiplex immunoassay	IL-1β, IL-15, IFN-γ, IL-12, IL-6, IL-5, IL-9, MIP-1α, MCP-1, IP-10	—	2016[75]
145	53.39±36.98 months	ELISA	TGM2	—	2023[37]
PEX					
73	81.60±2.47	Bio-Plex multiplex system	Extracellular matrix remodelling (TGF-β1, TGF-β2, TGF-β3)	—	2016[105]
15	80.50±5.70	Liquid chromatography coupled to a Quadrupole Time-of Flight mass spectrometer	Inflammation and oxidation inhibition (Indoleacetaldehyde)	Oxidative stress (L-serine, 3-hydroxy anthranilic acid, L-arginine, Ascorbic acid, Homo-L-arginine, Hydroxybutyrylcarnitine, Decatrienoylcarnitine, S-adenosyl-L-methioninate); Oculointestinal axis (2-hydroxycinnamic acid/m-coumaric acid (co-elution), Ergothioneine)	2021[80]
31	69.19±8.01	ELISA	Inflammation inhibition (HSP-70, irisin); Inflammation promotion (periostin)	—	2020[81]
30	72.73±9.43	Inductively coupled plasma-optical emission spectrometry	Oxidative stress (Cu, Zn)	—	2021[82]
HBV					
40	64.78±13.07	RayBio Human Quantibody Cutom Array	Inflammation promotion (MCP-1, TNF-α)	—	2020[89]
OSRC					
29	58.52±12.15	Ion selective electrode method	Electrolytic (Na^+, Cl^-)	—	2020[91]

ARC: Age-related cataract; DC: Diabetic cataract; IL: Interleukin; TNF-α: Tumor necrosis factor-alpha; bFGF: Basic fibroblast growth factor; MCP-1: Monocyte chemoattractant protein-1; AOPP: Advanced oxidation protein products; MDA: Malondialdehyde; CD: Conjugated diene; 8-IPG-F2α: 8-isoprostaglandin-f2α; ELISA: Enzyme linked immunosorbent assay; SOD: Superoxide dismutase; GPx: Glutathione peroxidase; P/Ca: Phosphorus/calcium; TGF: Transforming growth factor; sIL-6R: IL-6 receptor; TMT: Tandem mass tag; HPLC-MS/MS: High-performance liquid chromatography-mass spectrometry; TTR: Transthyretin; DBP: Vitamin D binding protein; HMC: High myopic cataract; IGF: Insulin-like growth factor; CFH: Complement factors H; LIF: Leukemia inhibitory factor; BDNF: Brain-derived neurotrophic factor; PLG: Plasminogen; ApoA1: Apolipoprotein A-I; HGF: Hepatocyte growth factor; VEGF: Vascular endothelial growth factor; ANG-1: Angiopoietin-1; MMP: Matrix metalloproteinases; IL-1ra: Interleukin 1 receptor antagonist; GC: Glaucoma complicated with cataract; PACGC: Primary angle-closure glaucoma with cataract; POAGC: Primary open angle glaucoma complicated with cataract; GSTP1: Glutathione S-transferase P 1; RPC: Retinitis pigmentosa complicated with cataract; IP-10: Interferon gamma-induced protein 10; PDGF-AA: Platelet-derived growth factor-AA; PAI-1: Plasminogen activator inhibitor-1; TSP-2: Thrombospondin-2; CC: Congenital cataract; FGF4: Fibroblast growth factor 4; IFN-γ: Interferon-γ; MIP-1α: Macrophage inflammatory protein 1-alpha; TGM2: Transglutaminase 2; sVCAM: Soluble vascular cell adhesion molecule; sICAM: Soluble intercellular adhesion molecule; RANTES: Regulated on Activation Normal T-cell Expressed and Secreted; UC: Uveitic cataract; FECD: Fuchs' endothelial corneal dystrophy; PEX: Pseudoexfoliation syndrome; HSP-70: Heat-shock protein 70; HBV: Hepatitis B virus; OSRC: Ophthalmic surgery-related cataract.

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Diabetic Cataract Neurodegenerative diseases in patients with diabetic cataract (DC) were earlier than vascular diseases (such as diabetic retinopathy, DR)[12]. The detection of AH before cataract surgery may screen out the risk factors of DR early, but its related biological markers are not clear. Sachdeva *et al*[13] studied the protein omics of AH, and found that cell adhesion and synaptic proteins decreased in AH of DC patients without retinopathy, and further confirmed the significant decrease of neurexin, neural cell adhesion molecule 1 (NCAM1) and secreted protein acidic and rich in cysteine-like 1 (SPARCL1) by Western blot. Among them, the decrease of polysialylated NCAM had been found to be related to retinal ganglion degeneration.

The osmotic pressure of the lens increased with an increase in the blood sugar level in the body. For DC patients, the fluctuation of blood sugar (such as glycosylated hemoglobin) would affect the permeability of glucose in anterior chamber and thus affect the opacity of cataract[14]. When blood glucose increased, the function of the blood-aqueous barrier was impaired, resulting in an increase in insulin-like growth factor 1, basic fibroblast growth factor, and interleukin (IL)-6 in the anterior chamber[15]. These cytokines further acted on lens epithelial cells, participating in cell proliferation and apoptosis, and thus aggravating cataract[15]. In addition, under hypoxic conditions, the increase of transthyretin (TTR) in AH would affect the proliferation and migration of retinal microvascular endothelial cells in diabetic patients[16]. Therefore, the increase of TTR may further indicate the severity of fundus complications after DC[17].

Oxidative stress levels and inflammatory reactions in the AH were worse in DC than in age-related cataract (ARC). This intense microenvironment in the AH may aggravate vascular complications after DC surgery, such as DR[18]. For example, the activity of antioxidant enzymes (superoxide dismutase and glutathione peroxidase) in AH of DC patients were significantly decreased, whereas the levels of advanced oxidized protein and lipid per oxidation products (malondialdehyde, conjugated diene, and 8-isoprostaglandin-f2α) were significantly increased[19]. In addition, the level of the proinflammatory factor IL-23 in the AH was significantly higher in DC than in ARC, whereas the IL-10 level was significantly lower[20]. IL-23 was an important pro-inflammatory factor that can stimulate the secretion of IL-17, further aggravating the retinal inflammatory reaction and eventually leading to macular degeneration and DR[21]. Meanwhile, IL-10 had immunosuppressive properties[22], and its decrease in the AH of DC further confirmed the severity of oxidative stress. Vitamin D contributed to balance the homeostasis of the microenvironment in the AH[23]. Vitamin D was an effective antioxidant by reducing the proliferation of immune cells and inhibiting the secretion of pro-inflammatory factors[24]. Chen *et al*[25] screened inflammatory factors in AH of DC patients and ARC patients by quantitative multiplexed assays, and then confirmed by enzyme-linked immunosorbent assay (ELISA) and Western blot that the expression levels of sIL-6R and IL-6 in DC patients were significantly higher than those in ARC patients. IL-6 may amplify the inflammatory response by activating the trans-signaling pathway mediated by SIL-6R[26], which may further regulate the activity of immune cells to promote the occurrence of posterior subcapsular cataract.

The incidence of postoperative macular edemawas higher in DC than in ARC[18], and the change in cytokine concentration in the AH can partly explain this phenomenon. In a study by Tang *et al*[27], the levels of tumor necrosis factor-alpha (TNF-α) in the second eye AH was significantly higher in the DC group than in the ARC group 11 days after the first eye surgery. High levels of TNF-α were closely related to the degree of diabetic macular edema[28].

The incidence of PCO after cataract surgery was higher in DC than in ARC[18], which may be related to changes in trace elements in the AH. Flieger *et al*[29] found that the P/Ca ratio in the AH was significantly higher in the DC group than in the non-diabetes group, and this accelerated the deposition of calcium phosphate on the surface of the intraocular lens and promoted PCO formation.

High Myopia Complicated with Cataract The oxidative stress in AH microenvironment of high myopia complicated with cataract (HMC) was obviously increased, which may be related to the pathogenesis of HM. Mérida *et al*[30] found that total antioxidant capacity (TAC) was significantly decreased, while total nitrite/nitrate was significantly increased in the AH of HMC. Furthermore, hypoxia induced the upregulation of hepatocyte growth factor (HGF)[31], which was related to the degradation of the extracellular matrix (ECM) and elongation of AL[32]. To resist the strong oxidative stress level in the eyes, complement factor H (CFH) in the AH was significantly increased in HMC[33]. CFH mainly protected cells by preventing activation of the complement substitution pathway[34].

In eyes with HMC, axial length (AL) needed to be closely monitored. Changes in AL played an important role in the choice of intraocular lens power. In addition, pathological HM caused scleral thinning and posterior scleral staphyloma. The levels of plasminogen (PLG) protein[35], matrix metalloproteinase (MMP)-2[36] and trans glutaminase (TGM2) protein[37] in the AH were significantly higher in HMC than in ARC. After PLG was activated as a fibrinolytic enzyme, it could not only directly degrade fibrin, but also further destroyed the ECM by activating MMPs[38], thus affecting the stiffness, strength, and elasticity of the sclera. TGM2 also played an important role in the remodeling and stability of ECM[39], and the remodeling of ECM may lead to the growth of AL and the occurrence of posterior scleral staphyloma[40]. In addition, the researchers also found that the protein expression level of TGM2 was positively correlated with the AL, suggesting that it was a potential index to evaluate the AL change after HMC[37]. In contrast, leukemia inhibitory factor (LIF) and apolipoprotein A-I (ApoA1) in the AH of HMC were negative regulators of the ocular axis

increase. Studies had shown that LIF and ApoA1 levels in the AH of HMC were significantly higher than those of controls[41-42]. LIF had protective effects against the progression of axial myopia[41], and vitreous injection of an upstream agonist of ApoA1 inhibited eye growth[43].

Patients with HMC were at high risk of postoperative CCS, which was related to the inflammatory microenvironment in the AH. Zhu *et al*[44] found that compared with the ARC group, the HMC group had lower expression of interleukin 1 receptor antagonist (IL-1ra) in the AH and higher expression of monocyte chemoattractant protein-1 (MCP-1). IL-1ra could increase the inhibition of the inflammatory factor IL-1, while MCP-1 was mainly involved in the recruitment and fibrosis of macrophages[45]. In addition, high concentrations of transforming growth factor beta 2 (TGF-β2) in the AH of HMC may increase the risk of CCS by participating in the transdifferentiation of lens epithelial cells into myofibroblasts[46].

Glaucoma Complicated with Cataract The microenvironment was significantly inflamed in AH of primary angle-closure glaucoma complicated with cataract (PACGC), with levels of IL-1ra, TNF-alpha, and IL-13 in the AH being significantly higher relative to ARC. This was related to the course of glaucoma and degeneration of retinal ganglion cells[27]. Patients with acute primary angle closure had a high risk of glaucoma after cataract surgery. Chen *et al*[47] previously showed that the levels of TGF-β1, TGF-β2, MMP-2, and tissue inhibitor of MMP-1 in the AH of these patients were significantly higher than those of ARC patients. These cytokines were all known to affect the composition of ECM in the trabecular meshwork[48], especially the accumulation of type I collagen fibers that eventually leaded to increased intraocular pressure and even glaucoma.

The high intraocular pressure after primary open-angle glaucoma cataract (POAGC) surgery may be related to the pathological state of the trabecular meshwork, in which oxidative stress played an important role[49]. Results had shown that the concentrations of Klotho and glutathione S-transferase P1 (GSTP1) in the AH of the POAGC group were significantly lower than those in the control group[50-51]. Klotho was a neuroprotective protein that protected cells from oxidative stress[52]. GSTP1 could catalyze the combination of reduced glutathione and hydrophobic and electrophilic compounds to exert its antioxidant capacity. Therefore, when the concentrations of Klotho and GSTP1 in the AH were decreased, the trabecular meshwork sensitive to oxidative stress may be damaged, eventually leading to an increase in intraocular pressure. In addition, studies had shown that compared with POAGC, ARC had significantly higher vitamin D concentration in the AH[53]. Vitamin D could prevent fibrosis in trabecular meshwork cells[54]. Compared with ARC, TNF-α and TGF-β2 in AH of POAGC patients were significantly higher[55], which may be related to the preoperative ocular hypertension of patients and may be used as a predictor of intraocular pressure reduction degree after trabeculectomy. However, whether these two cytokines were related to the occurrence and development of ocular hypertension after ARC cataract surgery still needed further study.

Uveitis Cataract Uveitis referred to the inflammation of the uvea (iris, ciliary body and choroid). Recurrence of inflammation accounts for about 41% in 6 mo after uveitis cataract (UC) surgery, which was a major interference factor for postoperative visual quality of patients[56]. Chemokines and adhesion molecules played an important role in the recruitment of immune cells[57], and their changes preceded the recurrence of inflammation. After half a year's follow-up of UC, Pei *et al*[58] found that MCP-1 in patients with recurrent inflammation was significantly higher than that in patients without recurrent inflammation, and MCP-1 was determined as an independent risk factor. MCP-1 could recruit and activate mononuclear macrophages in uveitis eyes, and the infiltration of macrophages would further destroy the tissue damage in related parts[59]. MCP-1 also increased by 76% in AH of patients with idiopathic uveitis[60]. The researchers also found that the inflammatory mechanism of idiopathic uveitis may be mediated by Th17 pathway, because increased IL-17 was found in AH[60]. Further classifying uveitis, Xu *et al*[61] found that IL-8 in AH of patients with acute anterior uveitis, Vogt-Koyanagi-Harada disease, Behcet's disease and Fuchs' syndrome was significantly higher than that of cataract group, suggesting that inflammatory microenvironment was the common feature of four common uveitis, because IL-8, a pro-inflammatory chemokine, could recruit neutrophils to the eyes. The high level of macrophage inflammatory protein (MIP)-1β in Fuchs' syndrome AH was a characteristic cytokine which was different from the other three kinds of uveitis. This discovery may indicated that the pathogenesis of Fuchs' syndrome was related to virus infection, because MIP-1β was related to viral shedding[62].

The inflammatory microenvironment of AH may explain the causes of posterior subcapsular cataract in patients with UC. Wang and Tao[63] found that the highest complication after cataract surgery in Fuchs' syndrome patients was posterior subcapsular cataract, and the severity was positively correlated with inflammatory factors IL-6 and IL-8 in patients' AH.

Retinitis Pigmentosa Complicated with Cataract RP was a hereditary retinal disease characterized by the progressive loss of photoreceptors. Compared to healthy eyes, RP complicated with cataract (RPC) was more prone to PCO, CCS, and intraocular lens displacement after cataract surgery[64]. This was mainly related to the pathophysiological changes in residual lens epithelial cells after surgery, and the cytokines in the AH drove this process. Lu *et al*[65] analyzed cytokines in the AH of 20 eyes with RP and 29 eyes with cataracts and found that levels of platelet-derived growth factor (PDGF)-AA, MMP-2, MMP-3, MMP-7, MMP-8, plasminogen activator inhibitor-1 (PAI-1), and thrombospondin-2 (TSP-2) were significantly higher in RP

eyes, while levels of bone morphogenetic protein - 4 (BMP-4) were significantly lower. PDGF - AA had been shown to promote the proliferation of lens epithelial cells in animal models[66]. The MMP family was mainly involved in the negative regulation of fibrosis, and thus, high levels of MMP in RP eyes had protective effects. PAI-1 could assist in activating plasminogen[67], and TSP-2 was a glycoprotein that secreted ECM[68]. A decrease in BMP4 increased the production of ECM by TGF-β2[69]. Therefore, these cytokines jointly participated in the excessive accumulation of ECM in eyes with RP, leading to the occurrence of CCS. One study analyzed the AH of RP patients with cataracts through proteomics[70] and found high expressions of serotransferrin (TF) and tenascin - C (TNC) by detecting their corresponding receptors. TF could enhance the proliferative ability of lens epithelial cells. Studies had verified the migration-promoting effect of TNC on lens epithelial cells at the cell and tissue levels[70].

Fuchs' Endothelial Corneal Dystrophy Fuchs' endothelial corneal dystrophy (FECD) was a degenerative disease with corneal endothelial cell decompensation, and its disease development experienced corneal interstitial and epithelial edema, bullous keratopathy to blindness. FECD was usually accompanied by cataract[71], and its AH biomarker was helpful to predict its development stage. Fiolka *et al*[72] found that Regulated on Activation Normal T-cell Expressed and Secreted (RANTES), eotaxin and Interferon-gamma (IFN-gamma)-inducible protein-10 (IP-10) were significantly increased in the experimental group by comparing the AH components of FECD with ARC. These chemokines were mainly responsible for recruiting eosinophils and monocytes[73], which would accelerate the formation of cataract and the damage of corneal endothelium.

Congenital Cataract Congenital cataract (CC) was an important cause of visual impairment in children. Owing to the inevitable inflammatory reaction, CC patients often had postoperative complications, such as posterior synechia of the iris, CCS, PCO, and secondary glaucoma[74]. Postoperative complications of CC were associated with increased intraocular inflammatory factors. Sauer *et al*[75] found that the levels of pro-inflammatory cytokines (IL-1β, IL-15, IL-12, IL-6, IL-5, IL-9, MCP-1, and IP-10) in the AH of the CC group were significantly higher than those in the ARC group; among these, IL-1β, TNF-α, and IL-6 had the greatest correlation with PCO at 3 mo postoperative. Growth factors in the AH of the CC also participate in the pathophysiological processes of postoperative complications. Zhang *et al*[76] found that fibroblast growth factor 4 (FGF4) levels in the AH in CC was approximately five times that in ARC. Researchers have further proven that FGF4 can stimulate the proliferation and migration of lens epithelial cells *in vitro*, and thus, it may be one of the key factors in PCO formation[76].

The increase in AL after CC surgery was another major challenge for physicians. Owing to the younger age of CC patients, the increase in the AL after cataract surgery would not only lead to a change in refractive power and affect the surgical outcomes, but also aggravate the risk of retinal detachment[77]. PDGF-BB levels in the AH of CC patients was found to be negatively correlated with changes in AL one year after surgery[78]. This indicated that PDGF-BB may play a role in regulating AL during the stress response after CC surgery. PDGF-BB was a protein related to hypoxia, which contributed to the formation of ocular neovascularization and participated in tissue repair and fibrotic diseases[79].

Cataract with Systemic Diseases

Pseudoexfoliation syndrome The manifestations of PEX in the eyes were generally the deposition of extracellular fibrillary protein material visible in the anterior segment of the eyes mediated by inflammation and oxidative stress. Dmuchowska *et al*[80] showed that the decrease of ascorbic acid and carnitines in AH metabonomics reflected the decrease of antioxidant level. The increase of indole acetaldehyde suggested that PEX may be related to oculo-intestinal axis. Güler *et al*[81] also found that the anti-inflammatory factors heat-shock protein 70 (HSP-70) and irisin increased protectively in PEX, while the increase of inflammatory factor periostin was the result of inflammatory reaction. The trace elements involved in oxidation/antioxidation balance were further studied in AH. The results showed that the high content of Cu and Zn in AH explained the relationship between oxidative stress and PEX[82].

Because glaucoma in the late stage of PEX would seriously damage the optic nerve, it was particularly important to detect early biomarkers in AH. Can Demirdöğen *et al*[83] found that clusterin could be used as a differential protein between early and middle-late PEX (complicated with glaucoma). Clusterin was mainly induced by the level of oxidative stress[84]. Park *et al*[85] found that inflammatory factors and chemokines (IL-8, MIP-1α, fractalkine and FMS-related tyrosine kinase-3 ligand) in AH of PEX complicated with glaucoma were significantly increased compared with PEX. These biomarkers jointly participated in the oxidative stress reaction and increased the resistance of AH drainage by regulating the ECM of trabecular meshwork, thus increasing intraocular pressure. Postoperative complications of PEX with cataract were related to the progressive stage of the disease. In the late stage of the disease, the incidence of long-term postoperative complications (anterior capsule contraction and intraocular lens eccentricity) increased[86]. Garweg *et al*[87] found that TGF-β1 in PEX with cataract in early (no complications), middle (glaucoma) and late (capsular dislocation) stage was significantly higher than that in ARC, and TGF-β1 concentration reached pathological level (100 pg/mL) in the late stage of PEX with cataract. TGF-β1 could promote the proliferation of myofibroblasts and transdifferentiate them into Tenon's capsule fibroblasts[88], which further promoted the development of fibrosis and the contraction of capsular bag.

Hepatitis B virus with cataract Liver dysfunction was one of the risk factors of cataract, and studies had shown that HBV infection was related to ARC. Patients with HBV may

feel more pain during cataract surgery. The study of AH components may contribute to reveal the mechanism that HBV patients were more sensitive to surgical pain. Zhang *et al*[89] found that MCP-1 and TNF-α in AH of HBV patients with cataract were significantly higher than those of the control group. These two inflammatory factors of pain had been widely studied in neuropathic pain, but their specific functions in the eyes needed to be further explored.

Ophthalmic Surgery-related Cataract Silicone oil, a commonly used filler after vitrectomy, would lead to cataract after long-term emulsification[90]. The change of electrolyte in AH may explain this phenomenon. Kars *et al*[91] showed that the concentration of sodium ion in AH of silicone oil eyes was higher than that of non-silicone oil eyes. This may further increase the concentration of sodium ions in the lens, thus accelerating the occurrence of cataract.

CHANGES AND SIGNIFICANCE OF AQUEOUS HUMOR COMPONENTS IN BINOCULAR SEQUENTIAL CATARACT SURGERY In binocular sequential cataract surgery, the first eye after cataract surgery affected the AH microenvironment of the opposite eye (Table 2). Therefore, it was helpful to dynamically observe changes in the intraocular microenvironment by comparing the components in the AH of the first and second eyes to better explain the occurrence and development of postoperative complications. Gong *et al*[92] found that there were no differences in the concentrations of MCP-1 and substance P (SP) between eyes of patients with ARC, but they were significantly increased in the second eye of DC patients. This may be due to the increase in MCP-1 and SP expression caused by hyperglycemia, which partly explained why DC patients felt pain more easily during the second eye surgery than did ARC patients. However, unlike ARC, PACGC, and HMC patients, DC patients did not show fluctuating levels of pro-inflammatory factors in the first and second eyes[27]. In addition, Zhao *et al*[93] reported that the levels of proinflammatory factors (IL-6, IP-10, MCP-1, and IL-2) fluctuated in the AH of the second eye one year after the first eye surgery. However, they found no correlation between these pro-inflammatory factors and iris adhesion, PCO, and CCS. Yan *et al*[94] previous showed that the level of TGF-β2 in the second eye was 17.27% higher than that in the first eye in patients with HMC. A high TGF-β2 level possibly increased the risk of CCS and PCO after cataract surgery[95].

In binocular sequential cataract surgery, pain in the second eye at different intervals was related to different types of cytokines in the AH (Table 3; Figure 1). For example, the level of granulocyte colony stimulating factor 3 (G-CSF3) reached the peak when the interval between surgery was 7 days[96]. G-CSF3 could stimulate the production and maturation of granulocytes and was related to sympathetic nerve excitement and hypernociception[97]. When the surgical interval between eyes was 10 d, the pain score and the concentrations of TNF-α and IL-1β in the second eye were the highest and were significantly higher than those in the first eye[98]. TNF-α could stimulate the cascade release of a large number of pro-inflammatory factors (*e.g.*, IL-1β), which eventually leaded to sensitization of prostaglandin E2 and sympathetic amines to pain receptors[99]. It was previously found that TGF-β2 levels in the AH of the second eye was significantly increased when the interval between binocular surgeries was 23 d. TGF-β2 was involved in sympathetic immune reactions related to pain[8, 100]. Interestingly, when the interval time between surgeries was 1 wk and 4 to 6 wk, the concentration of MCP-1 in the AH of the second eye was higher than that in the first eye[101], and this was strongly correlated with the pain score[101]. MCP-1 mainly recruited leukocytes to participate in inflammatory reactions when tissue was damaged[102].

CONCLUSION

To sum up, the study of AH components can provide biomarkers for different types of cataracts, help to understand the pathogenesis of the disease, predict the outcome of the disease, evaluate the incidence of postoperative complications of cataract, and guide the design of binocular sequential cataract surgery.

AH acquisition is an invasive detection process, which is generally obtained in cataract surgery, and the volume of AH samples obtained each time is about 50-100 μL. The AH comes from blood, which makes its chemical composition complicated. Therefore, the ideal technical means of AH detection should be sensitive and accurate. Tables 1-3 show the common methods of AH detection. The classical detection method is ELISA, which can be used to quantify cytokines, but it is time-consuming to detect only a single analyte at a time. The high-throughput method for detecting AH components includes luminex-multiplex immunoassay and electrochemiluminescence immunoassay (ECLIA), ECLIA can also detect nucleic acids. The advantages of mass spectrometry are that it can analyze the metabonomics of AH and enrich the functions of AH components, which is helpful to understand the mechanism of diseases, although Western blot or polymerase chain reaction is often needed to verify the AH components in the end. In addition, inductively coupled plasma optical emission spectrometry and atomic absorption spectroscopy are generally used for the detection of elements in AH, and ion selective electrode method is used for the detection of ions.

The components of AH are helpful to understand the pathogenesis of the disease. We further classified the AH components in the literature and found that almost all the AH components of cataract types had changes related to inflammation, oxidative stress, ECM/scleral remodelling. DC, glaucoma complicated with cataract, RPC and UC showed changes of fibrosis in AH. In addition, HMC and UC had changes in AH related to angiogenesis. Some special changes need to be further explored by researchers. For example, the components of AH in HMC suggested that the disease was related to neuronutrition and lipid metabolism, and the pathogenesis of PEX was related to oculointestinal axis.

Table 2 Influence of the first eye on the aqueous humor components of the second eye in binocular sequential cataract surgery

Type	Number of patients	Age ($\bar{x}\pm s$, years)	Detection method of aqueous humor components	Upregulation of aqueous humor composition (relative to the first eye)	Upregulation of aqueous humor composition (relative to the first eye)	Average binocular interval time ($\bar{x}\pm s$)	Year of publication
ARC	10	70.30±9.74	Luminex-multiplex immunoassay	GM-CSF, IL-2, IL-13	TNF-α	10.90±6.28 days	2022[27]
HMC	15	53.90±8.90	Luminex-multiplex immunoassay	TGF-β2	—	—	2022[94]
	10	66.00±7.71	Luminex-multiplex immunoassay	IL-2, VEGF, PDGF-BB, GM-CSF, bFGF	—	13.30±5.48 days	2022[27]
PACGC	10	66.50±8.07	Luminex-multiplex immunoassay	IL-2, VEGF, PDGF-BB, GM-CSF	TNF-α	12.90±8.02 days	2022[27]
DC	10	67.90±11.10	Luminex-multiplex immunoassay	IL-2, VEGF, PDGF-BB	—	11.20±4.42 days	2022[27]
CC	37	33 months	Multiplex technology and ELISA	MCP-1, IP-10, IL-6, IL-2	—	24.85±13.72 months	2020[93]

ARC: Age-related cataract; GM-CSF: Granulocyte macrophage colony-stimulating factor; IL: Interleukin; TNF-α: Tumor necrosis factor-alpha; HMC: High myopia complicated with cataract; TGF: Transforming growth factor; VEGF: Vascular endothelial growth factor; PDGF-BB: Platelet-derived growth factor-BB; bFGF: Basic fibroblast growth factor; PACGC: Primary angle-closure glaucoma with cataract; DC: Diabetic cataract; CC: Congenital cataract; MCP-1: Monocyte chemoattractant protein-1; IP-10: Interferon gamma-induced protein 10; ELISA: Enzyme linked immunosorbent assay.

Table 3 Expression of aqueous humor components under pain in second eye after binocular sequential cataract surgery

Number of patients	Age ($\bar{x}\pm s$, years)	Detection method of aqueous humor components	Aqueous humor components	Pain assessment method	Average binocular interval time (days)	Year of publication
ARC						
80	66.90±10.10	Mass spectrometry and PCR array	CSF3	Pain score questionnaire, corneal sensitivity assessment, electrophysiological signature of trigeminal ganglion neurons	3-30	2022[96]
30	72.20±8.40	ELISA	IL-1β, TNF-α	Pain score questionnaire, corneal sensitivity assessment	1-21	2021[98]
54	69	ELISA	MCP-1	State-trait anxiety inventory	25	2021[101]
26	66.00±11.00	Multiplex system	TGF-β2	—	23±4	2020[100]
DC						
22	68.46±9.94	Magnetic Luminex assay and ELISA	MCP-1, SP	—	1-7	2020[92]

ARC: Age-related cataract; PCR: Polymerase chain reaction; CSF3: Colony-stimulating factor 3; IL: Interleukin; TNF-α: Tumor necrosis factor-alpha; MCP-1: Monocyte chemoattractant protein-1; TGF: Transforming growth factor; DC: Diabetic cataract; MCP-1: Monocyte chemoattractant protein-1; SP: Substance P; ELISA: Enzyme linked immunosorbent assay.

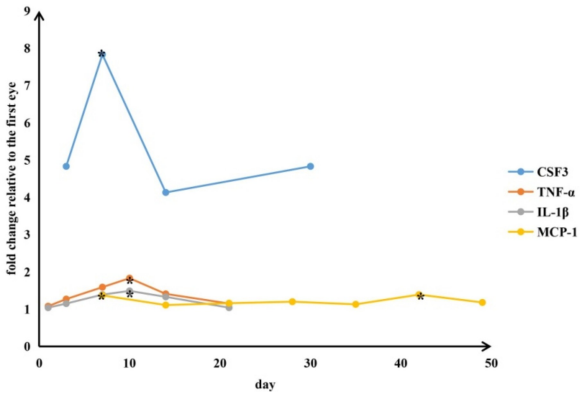

Figure 1 The relationship between the time interval of binocular surgery for senile cataract and the level of pain-related cytokines in the second eye.

* Levels of cytokines and subjective pain scores are significant at the same time. CSF3: Colony stimulating factor 3; TNF-α: Tumor necrosis factor-alpha; IL-1β: Interleukin-1 beta; MCP-1: Monocyte chemoattractant protein-1.

The components of AH are also helpful to predict or identify the development stage of the disease. For example, DC may have had neuropathy before retinopathy, and the increase of NCAM1 in AH may indicate the occurrence of early neuropathy. In addition, the concentration of TGF-β1 in patients' AH can be monitored during the development of PEX, because in the late stage of PEX, TGF-β1 can reach the pathological standard (100 pg/mL). Compared with three common uveitis (acute anterior uveitis, Vogt-Koyanagi-Harada disease and Behcet's disease), the identification protein of AH of Fuchs' syndrome uveitis is MIP-1β.

The relationships between postoperative complications and preoperative AH components are as follows: the predilection for macular edema after DC is related to TNF-α; the predilection of PCO after DC surgery is related to the P/Ca ratio; CCS after HMC is related to MCP-1 and TGF-β2; Vitamin D, Klotho, and GSTP1 are associated with high intraocular pressure after POAGC; postoperative CCS levels in patients with RPC are associated with PDGF-AA, MMPs, PAI-1, and TSP-2 expression in the AH; postoperative high intraocular pressure in patients with RPC is associated with TF and TNC; postoperative PCO in the CC is associated with the pro-inflammatory cytokines and FGF4.

With respect to the influence of the first eye surgery on the aqueous microenvironment of the second eye, the inflammatory response under surgical stimulation is weaker in DC than in ARC, PACGC, and HMC. The predilection of PCO and CCS after HMC may be related to the high level of TGF-β2 in the second eye after the first eye operation. G-CSF3, TNF-α, IL-1β, TGF-β2, and MCP-1 are cytokines related to pain in the second eye during sequential cataract surgery. Among them, G-CSF3 plays a role in the early stage (1 wk), while MCP-1 plays a role in the late stage (6 wk) of the binocular interval.

A limitation of the previous research is that it is impossible to analyze AH samples from the same eye before and after surgery. The development of AH detection technology may gradually overcome this shortcoming and expand the detection range of AH components. In addition, ethical issues still need attention when taking AH before operation. With an in-depth study of AH components, researchers can not only explore the pathogenesis of different types of cataracts, but also better predict the occurrence of postoperative complications and implement more accurate targeted therapy.

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