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A preliminary proteomic analysis of tear fluid in patients with high myopia

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Abstract

Background Using liquid chromatography-tandem mass spectrometry (LC-MS/MS) as a protein quantification technique for the analysis of the proteomic profile of myopia patient tear fluid, to clarify the role of dysregulated proteins in high myopia (HM) in order to provide a more thorough understanding of the molecular processes involved in the development of the disease.

Methods Schirmer strips were used to acquire the tear films from 20 subjects (10 high myopia patients and 10 control subjects). LC-MS/MS was utilized to identify the proteome profile of the tears in order to assess protein interrelationships utilizing bioinformatics.

Results The tear preparations from the HM group and the control group included a total of 1544 proteins. The expression of 79 proteins out of the identified ones differed significantly between the two groups. 51 proteins showed overexpression and 28 proteins showed downregulation. 15 differentially expressed proteins (DEPs) were enriched in metabolic pathways, 15 DEPs were enriched in extracellular exomes, and 5 DEPs were enriched in the complement and coagulation cascades pathway. Potentially important proteins and therapeutic targets in human HM include TTR and Antithrombin-III.

Conclusion The proteomic analysis of tear fluid in high myopia patients identifies key proteins and pathways involved in the disease, offering potential biomarkers for its pathogenesis and therapeutic targets.

Keywords High myopia, Tear fluid, Proteomics, LC-MS/MS, Differentially expressed proteins

Background

According to estimates, the most prevalent eye condition in the world is myopia. By 2050, there will be 938 million persons with high myopia (HM) [1]. HM raises the chance of pathologic ocular alterations like cataracts, glaucoma, retinal detachment, and myopic macular degeneration, all of which can result in irreversible vision loss [2]. The molecular mechanisms behind the HM development are mostly unclear at this time. Few research have examined the tear fluid from HM patients, as most investigations have concentrated on examining the sclera, retina, and choroid.

The smooth optical surface of tear fluid reflects light from the atmosphere onto the cornea. It is a significant

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and intricate physiological fluid that covers, nurtures, and protects the ocular surface. There are tens of thousands of molecules in it, including a wide range of proteins with different roles. A thorough examination of its makeup can reveal data that is beneficial for the diagnosis, prognosis, and treatment of systemic diseases in people, such as breast cancer, Parkinson's disease, diabetic retinopathy, and other illnesses [3–5]. The use of tear samples has many benefits. Tear sample collection is simple, quick, safe, and non-invasive, and the protein composition of the samples shows sufficient complexity.

Previous research on tear fluid has been done utilizing a variety of cutting-edge methods [6]. The extremely dynamic nature of the tear proteome and the limited sample size, however, still pose considerable limits to the analysis of tear fluid [7]. With the use of cutting-edge mass spectrometry (MS) methods, the area of proteomics has recently experienced rapid progress, and tear protein properties have been effectively examined using MS. A highly sensitive type of mass spectrometry analysis known as liquid chromatography-tandem mass spectrometry (LC-MS/MS) allows for the identification of thousands of proteins from complex samples like bodily fluids (blood, plasma, saliva, and urine), cell lines, and tissues [8]. To the best of our knowledge, this is the first study to analyze tear samples from patients with HM and compare them to those from control people using LC-MS/MS as a protein quantification method.

Materials & methods

Subjects

At the Fourth Hospital of Hebei Medical University in Shijiazhuang, China, twenty individuals were chosen for this study in 2023. Informed consent was obtained from all patients. They were split into two groups: HM group (10 HM patients) and control group (10 non-myopic volunteers). Patients with axial length ≥ 26 mm were included as high myopia. Axial lengths were measured by Lenstar 900(HAAG-STREIT, USA). Axial lengths of the control cases were found to be between 22.0 mm and 24.0 mm. The inclusion criteria were met by all 20 participants in that they had no history of ocular disease or slit-lamp evidence of ocular trauma, no other ocular diseases outside HM, and no use of systemic antimetabolites, eye drops, or corticosteroids in the three months prior. Age, gender, axial length, non-invasive breakup time (NIBUT), Schirmer test, and Ocular Surface Disease Index (OSDI) scores are gathered on these participants. Oculus Keratograph 5 M (K5M) was used to detect non-invasive breakup time (NIBUT).

Approval for the study was obtained from the Human Research Ethics Committee, The Fourth Hospital of Hebei Medical University (the IRB/ethics number: 2023KS211). The written informed consent was obtained from all patients following the principles of the Declaration of Helsinki.

Sample collection and preparation

To prevent reflex tearing, each subject's ocular health was meticulously examined using a slit lamp before tear samples were taken. The inspection of the cornea with fluorescein was only done after the tears were collected since the administration of fluorescein sodium would have polluted them. The Efron grading system [9] grade 2 (moderate) or higher corneal staining was used to determine eligibility for this investigation. The collection of tear samples took place between 12 and 5 pm.

Schirmer strips (Diagnostic Schirmer Tear Strips, Tianjin Jing Ming New Technological Development Co. China) were used to collect tear samples. They were put in both eyes at the same time and kept there for five minutes without the use of topical anesthesia. Following standard clinical protocols, the Schirmer strips were positioned in the inferior conjunctival membrane's lateral aspect. To reduce the possibility of contamination, the researcher handled the strips while wearing nitrile gloves, and the subjects' eyes remained closed during the collection process. When the Schirmer strips were taken out of the individuals' eyes, their wetted length was measured to the closest millimeter (mm) and kept in storage at -80 °C.

LC-MS/MS analysis

Sample preparation: Schirmer strips were sliced and incubated for one hour at room temperature in 100 µ L of 100 mM ammonium bicarbonate to extract tear proteins. After centrifuging the samples at 13,000 × g for 20 min, the supernatant was moved to a fresh tube. Using the Bradford test, the total protein content of each sample was determined. Membrane-assisted protease digestion in solution and Ziptipc18 extraction were used to get the peptide.

LC-MS/MS analysis was conducted using an Orbitrap Q Exactive HF-X mass spectrometer (Thermo Fisher Scientific, Waltham, MA, USA) in combination with a U3000 system (Waltham, MA, USA). Then, peptide mixtures were separated using a binary solvent system with 99.9% H2O and 0.1% formic acid (phase A) and 80% acetonitrile and 0.1% formic acid (phase B). Linear gradients of 0–6% B for 10 min., 6–10% B for 5 min., 10–0% B for 5 min, 0–30% B for 60 min., 30–40% B for 10 min., 40–95% B for 10 s, 95% B for 4 min and 50 s, 95–6% B for 10 s, and finally 6% B for 4 min and 50 s, with a flow rate of 600nl/min. The eluent was submitted to the Orbitrap Q Exactive HF-X MS system. The full scan MS mode was operated with the following parameters: automatic gain control (AGC) target, 3e6; resolution, 12,000 FWHM; scan range, 350 to 1550 m/z; maximum injection time,

20 mS; and collision energy, 27%. The entire MS scanning range for data-dependent acquisition (DDA)-MS runs was 300–1400 m/z. With a top speed mode of less than 3 s for 15,000 resolution MS/MS scans, the MS possessed a resolution of 60,000. In contrast, HCD had a normalized collision energy of 1.6 m/z and 32%, as well as an isolation window.

The MS data were analyzed using the Max Quant software Proteome Discoverer (version 2.4). The Swiss-Prot Human database (20, 240 entries) was searched using MS data. A 6ppm precursor ion mass tolerance for peptide masses and a 20ppm mass tolerance for fragment ions were the initial search parameters chosen. Trypsin was used as the enzyme specificity for the search, and two missed cleavages were permitted. Protein N-terminal acetylation and methionine oxidation were classified as variable modifications for database searching, whereas carbamidomethylation of cysteines was characterized as a permanent modification. For both protein and peptide identification, the global false discovery rate (FDR) cutoffs were established at 0.01. N1 unique peptides served as the basis for protein identification, with a minimum peptide length of six amino acids.

Based on the differentially expressed proteins (DEPs) (p. adjustment and q-value were both less than 0.05), bioinformatics analysis was carried out using the Kyoto Encyclopedia of Genes and Genomes (KEGG) (http://www.genome.jp/kegg/pathway.html) and the Gene Ontology (GO) database (http://geneontology.org/). Additionally, a protein-protein interaction (PPI) analysis was performed and displayed using the cyto-scape software and the String database (http://string-db.org/).

Results

Clinical features

10 HM patients (5 males, mean age, 22 ± 1.4 years) and 10 control subjects (6 males; mean age, 21.5 ± 1.5 years) had their tear fluid examined in this study. Sex ($p = 0.653$), age ($p = 0.454$), OSDI ($p = 0.288$), tear film break-up time ($p = 0.693$), and Schirmer test findings ($p = 0.192$) did not differ statistically between the two groups. Axial length variations were statistically significant ($p = 0.000$) (Table 1).

Table 1 Patient characteristics

Characteristics	case	controls	*p*-Value
Gender (male/female)	5/5	6/4	0.653
Age (years old)	22(± 1.4)	21.5(± 1.5)	0.454
Axial Length(mm)	26.61(± 0.9)	23.125(± 0.19)	0.000
Schirmer test(mm)	21.00(± 7.7)	15.80(± 9.3)	0.192
NBUT(s)	10.03(± 4.9)	11.03(± 3.8)	0.639
OSDI	2.7(± 1.4)	2.1(± 0.9)	0.288

Sample size: case = 10 participants, 20 eyes; controls = 10 participants, 20 eyes.
NBUT, non-invasive breakup time; OSDI, ocular surface disease index

Proteomic analysis

Identification of DEPs

To detect the DEPs in the tear fluid between groups, a quantitative analysis was conducted after the tear samples were collected and subjected to LC-MS/MS analysis, a total of 1544 proteins were measured in the tear preparations of the HM and control groups. Of the proteins found, 79 had a discernible variation in expression between the groups (Table S1). In the tear fluid samples from the HM group, 51 of the 79 DEPs displayed upregulation, and 28 displayed downregulation. The global quantification of the tear proteins between HM patients and control participants and the dysregulated proteins between groups were represented by a volcano plot (Fig. 1).

GO enrichment analysis

By using GO annotation, DEPs were examined based on "molecular function," "biological process," and "cellular component" to understand better the alterations in protein expression seen in HM tear fluid. The findings show that different biological processes, cellular components, and molecular functions were linked to DEPs in both HM and control participants (Fig. 2(A)、 Fig. 2(B)).

Cellular oxidant detoxification, peptidyl-cysteine S-nitrosylation, the ATP metabolic process, activation of cysteine-type endopeptidase activity involved in the apoptotic process, and acute-phase response by P. Value ranked first through fifth among biological processes. The extracellular exosome, blood microparticle, extracellular space, extracellular region, and platelet alpha granule lumen ranked first through fifth in the cellar component category. The top three in terms of molecular function were protein binding, protein disulfide isomerase activity, and identical protein binding.

KEGG pathway annotation analysis (Table 2)

A review of KEGG pathway annotation was also carried out to determine significant metabolic and signal transduction pathways. The results indicated that there were twenty-five key biological pathways. The complement enhanced five DEPs and the coagulation cascades route, the legionellosis pathway enriched four, and the fructose and mannose metabolism pathway enriched four more DEPs. A total of fifteen DEPs were found to be enriched in metabolic pathways.

Protein networks

Usually, proteins work in concert with one another to carry out a variety of tasks. We utilized the STRING database and Cytoscape software to assess and visualize the PPI analyses to investigate the association between the DEPs further based on the comparison between the samples from the HM group and the control group.

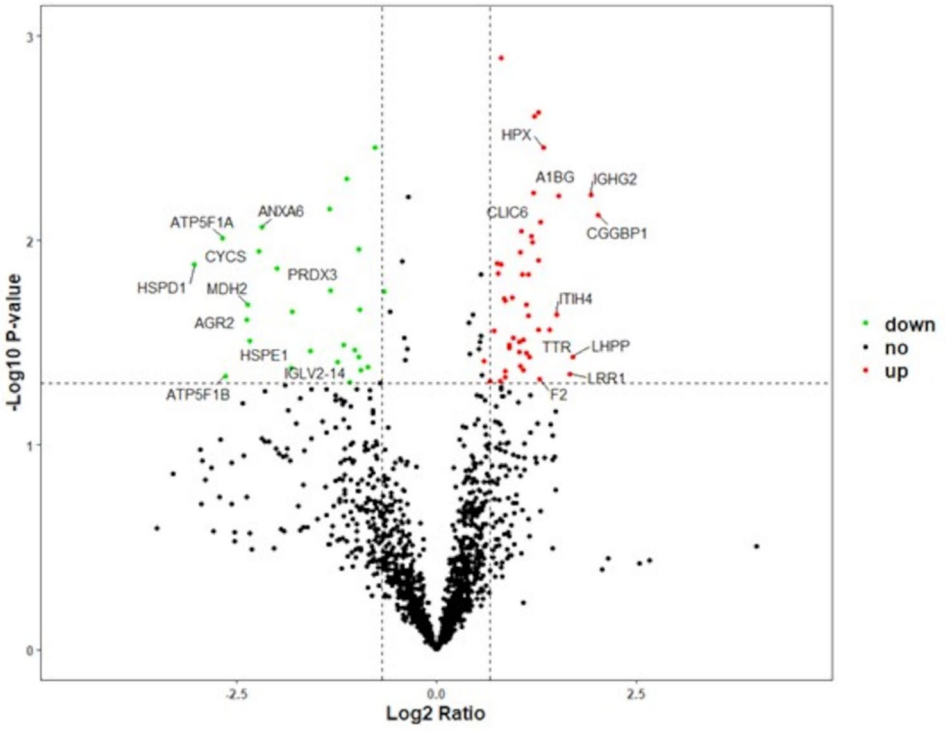

Fig. 1 Volcano plot of tear proteomics quantitative data. two dotted green lines separate the figure into three parts. The rightmost part (red color) shows 51 upregulated proteins and the leftmost part (blue color) shows 28 downregulated proteins. The middle part (black color) shows no significant changes. The gene symbols of the top 10 DEPs are shown

Additionally, it was shown that the most important module contained 16 proteins (Fig. 3). The KEGG functional analysis of the proteins included in this module revealed that they were primarily enriched in the pathways related to coagulation cascades and complement (Fig. 4).

Discussion

The objective of the study was to identify proteins that were either up-regulated or down-regulated between high myopia and controlls, The purpose was to determine the key proteins or singnal pathways in progress of high myopia. To examine the variations in protein profiles between the tear fluid samples from the HM and control groups, this study employed a paired sample technique. A tot.79 DEPS were found, of which 28 had decreased expression and 51 had increased expression in HM patients compared to controls. We discovered that the extracellular exosome, complement and coagulation cascades, and ATP metabolic process pathways can be very important in the pathogenesis of HM utilizing bioinformatics analyses (GO enrichment analysis, KEGG pathway, and PPI). The previous study showed 210 proteins were discovered to have a variable expression in aqueous humor proteomic investigation linked to HM, including 63 upregulated proteins and 38 downregulated proteins [10]. In our study, the majority of these 79 DEPs were found to be accumulated in the complement and coagulation cascades pathway, based on the findings of an examination of KEGG pathway annotation, which is similar to other studies.

The complement and coagulation cascade route is the most statistically significant one, according to the KEGG pathway analysis (*P*-Value, 0.000), including Antithriombin-III, prothrombin, kininogen-1, complement factor D, CD59 glycoprotein. These findings are in line with the findings of the examination of the most important module, it is widely recognized for its role in inducing inflammatory and immune responses. A crucial component of the complement and coagulation cascades is antithrombin-III. With a brief half-life, antithrombin-III is released as an active serine protease inhibitor. However, antithrombin-III is found in both plasma and the extracellular matrix (ECM) and stabilizes its activity. Urokinase plasminogen activator and receptor-mediated cell adhesion and migration have been linked to antithrombin-III. Another important element in the etiology of myopia is scleral ECM remodeling. In comparison to the sclera in healthy eyes, myopic human eyes have been reported to tend to have a thinner sclera and a lower scleral ECM. The complement pathway appears to be involved in hyperopia, according to a meta-analysis of transcriptome datasets from models of myopia and hyperopia in chicks [11]. This meta-analysis provides novel evidence for transcriptional activation of the complement

Fig. 2 Gene Ontology (GO) enrichment analysis of differentially expressed proteins. MF, molecular function; BP, biological processes; CC, cell composition. (**A**) upregulated in high myopia, (**B**) downregulated in high myopia

Table 2 The top 10 signaling pathways pass through KEGG

Term	Description	Count	*p*-Value
hsa04610	Complement and coagulation cascades	5	1.68E-05
hsa05134	Legionellosis	4	0.0001398
hsa00980	Metabolism of xenobiotics by cytochrome P450	4	0.0003878
hsa00051	Fructose and mannose metabolism	3	0.0004503
hsa01100	Metabolic pathways	15	0.0006149
hsa00190	Oxidative phosphorylation	4	0.0025431
hsa04918	Thyroid hormone synthesis	3	0.004172
hsa00982	Drug metabolism - cytochrome P450	3	0.0042725
hsa05204	Chemical carcinogenesis	3	0.005835
hsa04141	Protein processing in endoplasmic reticulum	4	0.0062095

system during both myopia and hyperopia induction and confirms existing literature implicating cell signaling, mitochondrial metabolism, and structural processes in refractive error. Another investigation revealed that the complement system can encourage sclera ECM remodeling [12], Complement activation is a potent immune system defensive mechanism, but it has two sides. It can cause cell lysis or sublytic assault, which can harm host tissue. It can also increase cell survival and facilitate the removal of antigen-antibody complexes.

Animal models of myopia have also shown a thinner sclera and a corresponding decline in the production of collagen, proteoglycan, and other scleral matrix elements [13]. HM development is linked to biochemical changes in the extracellular matrix, which alter biomechanical properties, potentially causing an increase in ocular elongation and development. We found abnormal expression of antithrombin III in tears, which may be due to the secretion of sclera into tears at the same time as the scleral remodeling event in patients with HM.

According to the GO enrichment analysis, the extracellular exosome pathway, which involves 50 DEPs, is enriched. Exosomes are thought to influence intracellular

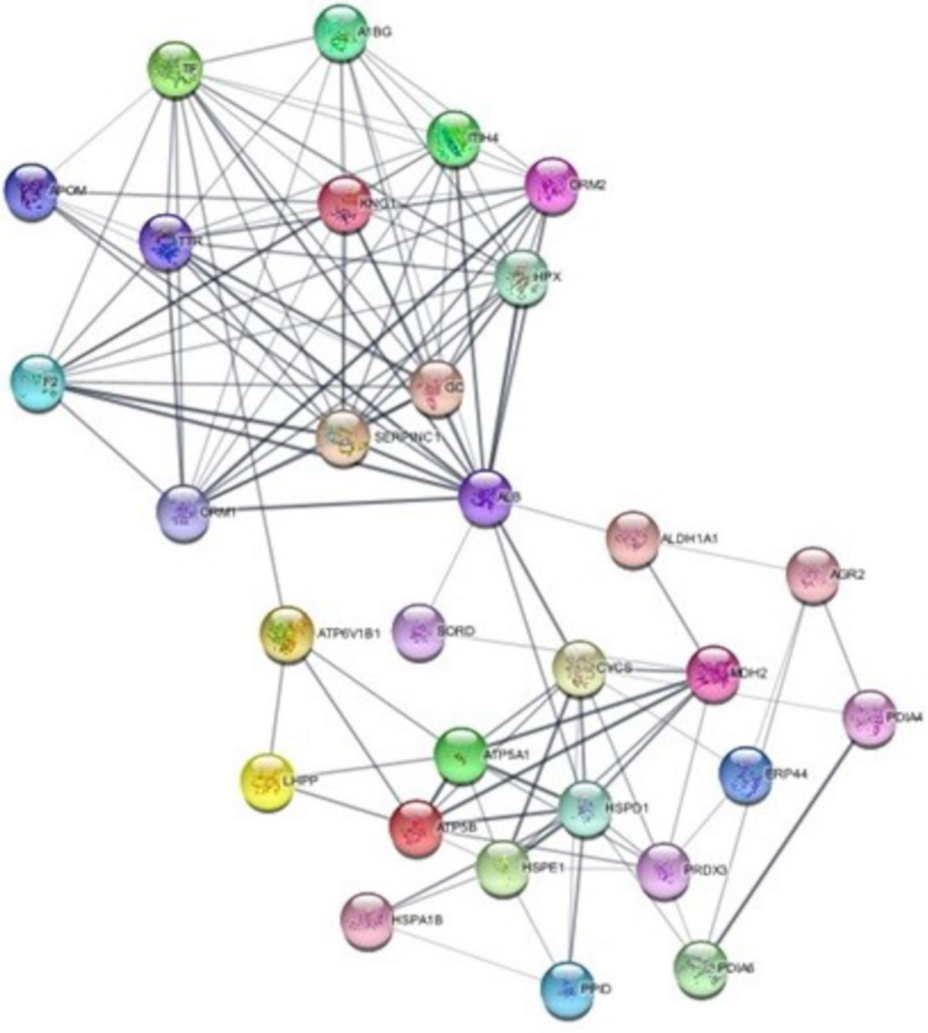

Fig. 3 The biological networks regulated by the identified high myopia tears proteins

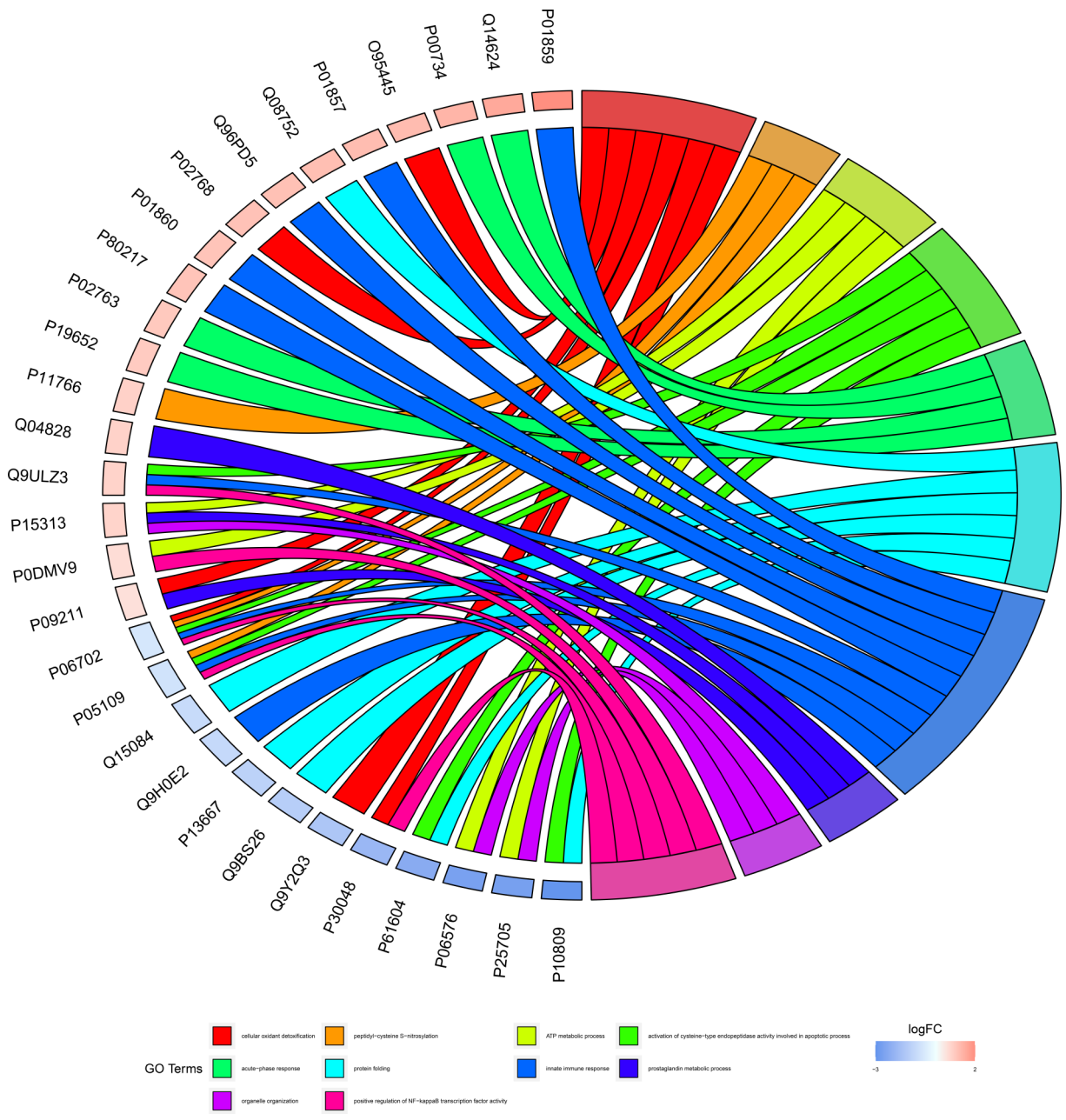

Fig. 4 Gene set enrichment analysis showed that the two classical signaling pathways of complement coagulation cascade and extracellular matrix regulator were enriched and upgregulate

communication between cells by moving exosomes, miRNA, and proteins between them. They are thought to have a crucial role as cell-to-cell messengers and play an important biological role in Physiological and pathological processes [14]. Exosomes generated from the AH may include proteins or miRNAs that are linked to ocular disorders, according to an increasing number of studies [15–18]. For instance, in response to external stimuli, trabecular meshwork cells released exosomes carrying myocilin. Glaucoma and myopia were revealed to be related to different exosome miRNA expression profiles [19, 20]. The tears proteins were enriched exosomes showing exosomes play a role in the development of high myopia through signal transduction, Further research on their role in myopia development is needed.

Previous investigations have consistently shown that numerous major DEPs are found in HM patients. Transthyretin, and retinal dehydrogenase 1 are some of these DEPs [21]. In our study, we found retinal dehydrogenase 1 high expression in tears from high myopia patients. retinal dehydrogenase 1 was most abundant in the choroid, in moderate abundance in the sclera, and substantially

reduced in the retina and RPE, retinal dehydrogenase 1 and 2 may play a role in the regulation of postnatal ocular growth in humans through the synthesis of all-trans-acid [22]. In addition, leucine-rich repeat protein has also been identified as highly expressed in the tears of patients with high myopia, Leucine-rich repeat protein/proteoglycans (SLRP) are a class of extracellular matrix (ECM) molecules that have been linked to several roles, such as controlling cell proliferation, inhibiting transforming growth factor-b, and regulating the diameter and spacing of collagen fibrils. Ocular SLRPs could play a role in regulating eye shape and axial length through a variety of mechanisms.

In our study, Transthyretin (TTR) was one of 50 myopia-specific proteins. TTR was one of 25 myopia-specific proteins that Ching-Yao Tsai1 et al. discovered in the aqueous humor of HM patients [23]. Exosomes can cross the blood-brain barrier [24]. Exosomes from tear fluid that contain TTR may be able to cross the aqueous humor. Additionally, patients with myopia, retinal detachment, and macular holes have high TTR levels in their vitreous humor [25]. Although its physiological function in the eye is not fully understood, TTR may contribute to retinal metabolism. TTR likely plays a significant role in retinal metabolism in the interphotoreceptor matrix since retinal metabolism was changed in TTR mice [26]. Our research demonstrates that large levels of TTR expression are present in patients with high myopia tears, suggesting that TTR is crucial to the progression of myopia.

Conclusions

In conclusion, this study did have certain restrictions, though. The study had a modest sample size and was conducted in a single center. In conclusion, label-free LC-MS/MS quantitative proteome analysis showed that the proteomic profile of tear film from HM patients differed from that of control subjects. The immune system, extracellular exosome-related processes, extracellular matrix remodeling processes, and other HM-related DEPs are where the majority of their involvement lies. For use in future research, we must identify some indicators that are strikingly comparable to the retinal or aqueous humor. Tear contents may be a possible biomarker in research on the pathophysiology of HM. It might be wise to look into this idea further.

Abbreviations

AGC	Automatic gain control
DDA	Data-dependent acquisition
DEPs	Differentially expressed proteins
FDR	False discovery rate
HM	High myopia
K5M	Keratograph 5 M
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
NIBUT	Non-invasive breakup time
NIBUT	Non-invasive breakup time
OSDI	Ocular Surface Disease Index

Supplementary Information

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Supplementary Material 1

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Author contributions

Conceptualization, Zhiyang Jia and Dandan Wang; methodology, Dandan Wang; software, Cunkai Wang; validation, Zhi Hu, Dandan Wang; formal analysis, Cunkai Wang; investigation, Zhi Hu.; resources, Yudan Su.; data curation, Yudan Su; writing—original draft preparation, Dandan Wang; writing—review and editing, Zhiyang Jia; visualization, Dandan Wang, Cunkai Wang; supervision, Zhiyang Jia.; project administration, Zhiyang Jia and Dandan Wang; funding acquisition, Zhiyang Jia. All authors have read and agreed to the published version of the manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent of participate

Approval for the study was obtained from the Human Research Ethics Committee, The Fourth Hospital of Hebei Medical University (the IRB/ethics number: 2023KS211). The written informed consent was obtained from all patients following the principles of the Declaration of Helsinki.

Consent of publication

Not applicable.

Competing interests

The authors declare no competing interests.

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