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The Role of Pyroptosis in Age-Related Cataracts: Insights from Gene Expression Analysis

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ABSTRACT

Background: Understanding cataract development is essential for addressing its impact on global healthcare systems. Pyroptosis has been implicated in cataract formation, but the underlying mechanisms remain poorly understood.

Objectives: While pyroptosis is thought to contribute to cataract development, the exact mechanisms are not fully understood. This study aimed to investigate the role of pyroptosis in the progression of age-related cataract formation.

Methods: The GSE161701 dataset was retrieved from the Gene Expression Omnibus (GEO) database to compare lens tissue samples from 12 distinct chips. These samples were obtained via high-throughput sequencing of human lens epithelial cells, specifically wild-type (WT) HLE-B3 cells and Atg7 knockout (Atg7KO) HLE-B3 cells, treated with or without 200 μM H2O2 for 12 hours. The limma package in R was used to identify significantly differentially expressed genes (DEGs). Gene Ontology (GO) annotation, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis, and Reactome pathway analysis were conducted on the identified DEGs using Metascape. Additionally, the STRING online tool and Cytoscape software were employed to construct the protein-protein interaction (PPI) network.

Results: A total of 6,156 differentially expressed genes (DEGs) were identified, including 5,196 up-regulated and 960 down-regulated genes. Previous studies have highlighted 55 genes associated with pyroptosis. Gene Set Enrichment Analysis (GSEA) indicated that most up-regulated genes and pathways were related to IL18, IL2, IL4, Notch, MAPK signaling pathways, various cytokines, and the inflammatory response. In contrast, down-regulated genes and pathways were primarily linked to FOXM1 and PLK1. A further search in the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases identified DEGs related to pyroptosis. The PPI network analysis revealed that IL6, TNF, IL1A, IL1β, and NLRP3 had high connectivity, suggesting potential interactions and mutual influence among these proteins.

Conclusion: Pyroptosis significantly affects the expression of inflammatory cytokines in human lens epithelial cells, particularly interleukin 6 (IL-6), tumor necrosis factor (TNF), interleukin 1 alpha (IL-1A), interleukin 1 beta (IL-1β), and NLRP3. The regulation of these cytokines may be crucial in the pathogenesis of age-related cataracts, presenting potential therapeutic targets for intervention.

INTRODUCTION

Age-related cataract (ARC) is a major cause of global blindness, primarily linked to the aging process and the resulting lens opacity. In 2020, cataracts accounted for blindness in approximately 15.2 million individuals aged 50 years and older worldwide Pesudovs et al. (2021). A significant disparity exists in surgical expertise among practitioners across various geographical regions, particularly in economically disadvantaged areas where access to essential surgical equipment and structured training programs is severely limited. This situation highlights the urgent need for alternative therapeutic approaches. Recently, precision-targeted therapies have gained prominence in ophthalmology, demonstrating promising results. For example, anti-VEGF agents have been effective in managing retinal vascular disorders Razavi et al. (2024), while tocilizumab (an anti-IL-6 receptor monoclonal antibody) Perez-Moreiras et al. (2018) and rituximab (a CD20 monoclonal antibody) Wang et al. (2023) are used in treating active thyroid eye disease. There is growing interest in exploring non-surgical strategies to slow the progression of lens opacity.

This research area holds significant potential, as it could reduce the burden on healthcare systems and improve the quality of life for millions affected by this condition. Current studies focus on uncovering the underlying mechanisms of lens opacity and identifying potential therapeutic targets for non-surgical interventions. These efforts may lead to the development of new pharmacological agents or non-invasive therapies that could slow the progression of ARC, offering renewed hope to those suffering from this debilitating condition.

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In recent years, advancements in research have significantly deepened our molecular understanding of the various types of programmed cell death (PCD), encompassing several genetically defined endogenous pathways Fink et al. (2005). Among these, apoptosis is the most widely recognized form of programmed cell death, characterized by the activation of specific caspases (cysteine-dependent aspartate-specific proteases) that orchestrate the systematic disassembly of cells Zhang et al. (2018). It has been shown that the apoptosis of lens epithelial cells is a fundamental cellular mechanism underlying the onset and progression of non-congenital cataracts. Recent studies have highlighted the crucial role of autophagy in the pathogenesis of this condition. Evidence suggests Cui et al. (2024) that a reduction in the ubiquitin-mediated degradation of ATG16L1 enhances autophagy activity, which subsequently alleviates cataract symptoms in the cx50 zebrafish model. This finding highlights the important connection between autophagy and cataract development, offering valuable insights into potential therapeutic targets for cataract treatment.

Accumulating evidence has confirmed that pyroptosis is involved in the pathogenesis of both non-infectious and infectious diseases, such as brain injury, heart attack, and cancer, and plays a critical role in controlling microbial infections Jin et al. (2017).

Upon stimulation, cells assemble a multiprotein complex known as the inflammasome. This complex activates pro-caspase-1, converting it into the active form of caspase-1. The active enzyme then cleaves gasdermin D (GSDMD) at its central linker region, releasing the N-terminal domain of GSDMD Zhang et al. (2021). These fragments create pores in the plasma membrane, leading to cellular swelling and lytic cell death. Additionally, active caspase-1 processes inflammatory cytokines, including IL-1β and IL-18, converting them into their biologically active forms. These mature cytokines are released into the extracellular matrix through ruptured membranes, amplifying the proinflammatory response associated with pyroptosis Shi et al. (2017). Mature IL-1β acts as a significant proinflammatory mediator, recruiting innate immune cells to sites of infection and regulating the activity of adaptive immune cells. Concurrently, mature IL-18 stimulates the production of interferon (IFN-γ) and improves the cytolytic functions of natural killer cells and T cells, thereby improving the clearance of pathogenic microorganisms and abnormal cells within the organism Dinarello et al. (2009).

Pyroptosis has been identified as being associated with oxidative stress, a contributing factor in cataract development, and may present new therapeutic opportunities for cataract treatment Shi et al. (2015). Research suggests that the activation of reactive oxygen species (ROS) can trigger the NLR family pyrin domain containing 3 (NLRP3) and caspase-1, leading to the production of interleukin-1 beta (IL-1β) and interleukin-18 (IL-18). This process ultimately results in cell death through both pyroptosis and apoptosis in astroglial cells Alfonso-Loeches et al. (2014). In the genomic era, the use of gene chips has become common for investigating disease mechanisms, offering new insights into pathogenesis at the genetic level. Thus, the objective of this study is to explore the role of pyroptosis in age-related cataracts through bioinformatics analysis, providing a foundation for future research on this condition.

MATERIALS AND METHODS

Data Source

The gene expression dataset GSE161701 was acquired from the Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo). This dataset includes 12 chips profiling gene expression through high-throughput sequencing of human lens epithelial cell samples. The samples consist of wild-type (WT) HLE-B3 cells and Atg7 knockout (Atg7KO) HLE-B3 cells, both treated with or without 200 μM hydrogen peroxide (H2O2) for 12 hours, with three biological replicates for each condition. The Atg7 gene, known as a crucial protein in the autophagy process, when knocked out, can significantly impair autophagic activity. Previous studies have indicated Guo et al. (2021) that both autophagy and pyroptosis are vital mechanisms of programmed cell death. The interaction between these pathways in cellular physiology and pathology may play a significant role in the development and progression of cataracts. Moreover, a decline in autophagic function is commonly observed in age-related pathological conditions, including age-related cataracts. Therefore, using Atg7 knockout HLE-B3 cells offers a more accurate representation of the pathological state associated with cataracts Pu et al. (2017). The GSE161701 dataset was based on the GPL24676 platform.

Data Preprocessing

Differentially expressed genes (DEGs) were identified using the limma package within the R programming environment. The criteria for determining statistical significance included an adjusted p-value of less than 0.05 and an absolute log2 fold change (logFC) exceeding 1.5. Genes with a logFC greater than 1.5 were classified as up-regulated, while those with a logFC less than -1.5 were categorized as down-regulated. We subsequently identified 55 genes associated with pyroptosis based on findings from previous research Pu et al. (2017), Ye et al. (2021), Deng et al. (2022), Shao et al. (2021).

GSEA

To gain a comprehensive understanding of the biological mechanisms related to pyroptosis, we performed a Gene Set a Gene Set Enrichment Analysis (GSEA) using the online platform available at https://www.gsea-msigdb.org. This analysis focused on identifying potential molecular pathways associated with the set of 55 genes implicated in

pyroptosis. The gene sets corresponding to canonical pathways were obtained from the Molecular Signatures Database, accessible at http://www.gsea-msigdb.org/msigdb/index.jsp. We set a threshold for significance, considering a false discovery rate (FDR) of less than 0.25 and a p-value of less than 0.05 as criteria for determining statistical relevance.

GO and KEGG analysis

DAVID (https://david.ncifcrf.gov) is a comprehensive online tool suite used for batch annotation and Gene Ontology (GO) term enrichment analysis, highlighting the most relevant GO terms associated with specific genes. In the context of GO analysis, the seven pyroptosis-related genes linked to age-related cataracts were categorized into three distinct classes: Molecular Function (MF), Biological Process (BP), and Cellular Component (CC).

Subsequently, an enrichment analysis was performed using the Kyoto Encyclopedia of Genes and Genomes (KEGG) via Metascape (http://metascape.org) to predict the signaling pathways in which these genes may be involved. Only terms with p values less than 0.01 and comprising three or more enriched genes were considered statistically significant.

Protein-protein interaction Network Analysis (PPI)

To explore the functional interconnections among the seven pyroptosis-related genes associated with age-related cataracts, protein-protein interaction (PPI) networks were constructed using the STRING database (https://cn.string-db.org). This database covers nearly all functional interactions among expressed proteins, with interactions yielding a combined score exceeding 0.4 considered statistically significant. The results of this analysis were then visualized using Cytoscape software (version 3.8.0).

RESULTS

Preliminary analysis of GSE161701 dataset

An analysis of the GSE161701 dataset identified a total of 11,287 genes, with 6,156 classified as differentially expressed genes (DEGs). From previous research, 55 genes associated with pyroptosis were selected for further examination (Fig. 1).

The volcano plot for GSE161701 shows 5,196 upregulated genes and 960 downregulated genes (Fig. 2A). A Venn diagram reveals that 7 genes are common between the DEGs and the pyroptosis-related genes relevant to age-related cataracts (illustrated in Fig. 2B).

Additionally, a heatmap and boxplot depicting the 7 pyroptosis-related DEGs, including IL1β, IL1A, IL6, TNF, PSTPIP2, TNFAIP3, and NLRP3, are presented (Fig. 2C, D).

Figure 1: Flowchart of the study. DEGs: Differentially Expressed Genes; GSEA: Gene Set Enrichment Analysis; GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; PPI: Protein-Protein Interaction.

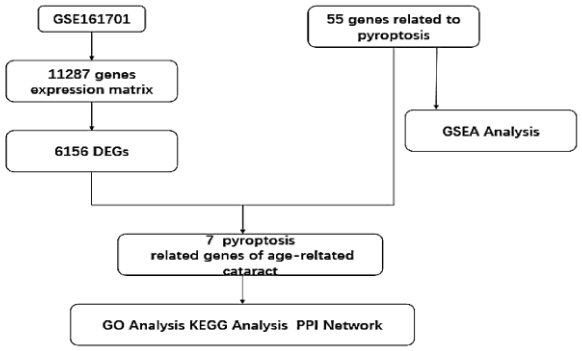
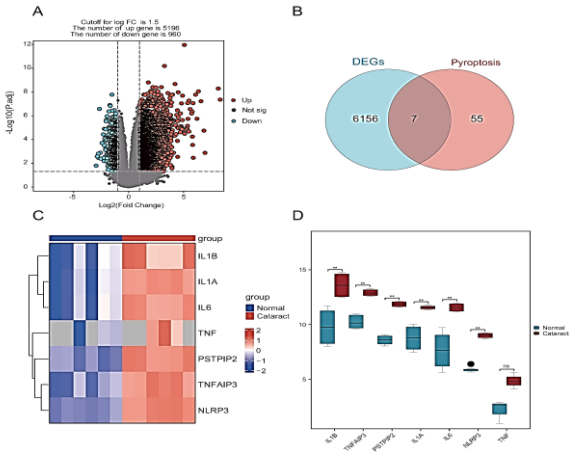


Figure 2: Preliminary analysis of the GSE161701 dataset.

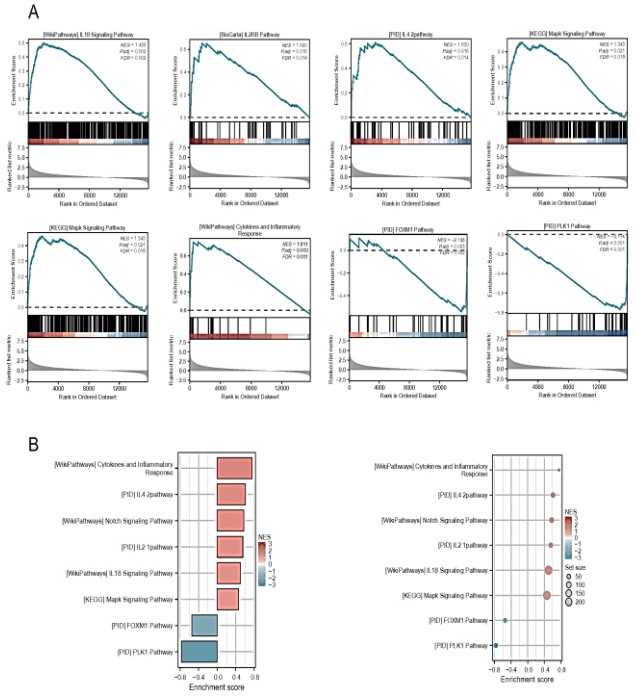


(A) Volcano plot of differentially expressed genes. Red nodes represent upregulated DEGs with $p < 0.05$ and logFC > 1.5; blue nodes represent downregulated DEGs with $p < 0.05$ and logFC < −1.5. (B) Venn diagram showing the overlap of DEGs screened from GSE161701. (C, D) Heatmap and boxplot of 7 pyroptosis-related genes in age-related cataracts.

GSEA

The expression data for 55 pyroptosis-related genes were input into the Gene Set Enrichment Analysis (GSEA) software, utilizing both the Hallmark and KEGG gene set databases to evaluate the overall expression profile of these pyroptosis genes. The analysis revealed that most upregulated genes and associated pathways were linked to the IL18 signaling pathway, IL2 signaling pathway, IL4 signaling pathway, Notch signaling pathway, MAPK signaling pathway, as well as cytokine activity and inflammatory responses. In contrast, the analysis showed that most downregulated genes and pathways were associated with the FOXM1 signaling pathway and the PLK1 signaling pathway (Fig. 3A, B).

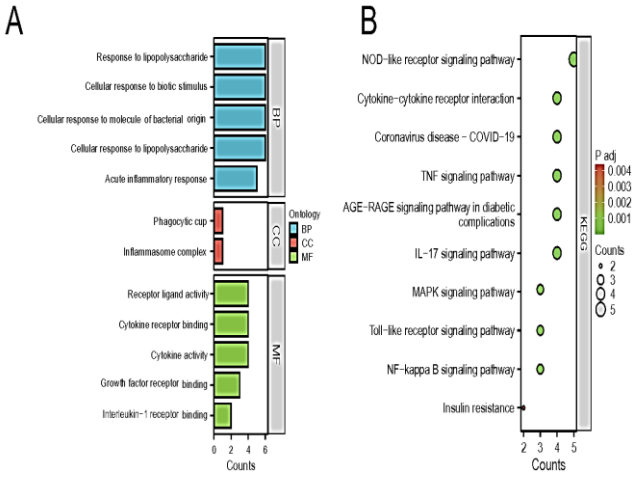
Figure 3: Gene Set Enrichment Analysis (GSEA) of 55 pyroptosis-related genes using the Hallmark gene set database. FDR < 0.25 and p < 0.05 were used as cutoff criteria. The results show that most of the upregulated genes and pathways are involved in the IL18, IL2, IL4, Notch, and MAPK signaling pathways, as well as cytokine activity and inflammatory responses. Conversely, most downregulated genes and pathways are involved in the FOXM1 and PLK1 signaling pathways.



GO and KEGG Analysis

To investigate the involvement of the seven pyroptosis-related genes in age-related cataracts, differential gene analysis was conducted using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) methodologies. The results from the GO Biological Process (BP) analysis indicated that these genes were predominantly enriched in processes such as the cellular response to lipopolysaccharide, responses to biotic stimuli, reactions to bacterial-derived molecules, and acute inflammatory responses, among others. The Cellular Component (CC) analysis of GO specifically highlighted enrichment in terms such as phagocytic cup and inflammasome complex. Furthermore, the Molecular Function (MF) terms identified in the GO analysis primarily encompassed receptor-ligand activity, cytokine receptor binding, cytokine activity, growth factor receptor binding, and interleukin-1 receptor binding, among others (Fig. 4A). The KEGG pathway annotation revealed that the genes of interest were significantly associated with various pathways, including the NOD-like receptor signaling pathway, cytokine-cytokine receptor interaction, Coronavirus disease (COVID-19), TNF signaling pathway, and the AGE-RAGE signaling pathway in diabetes, among others (Fig. 4B).

Figure 4: GO and KEGG enrichment maps.

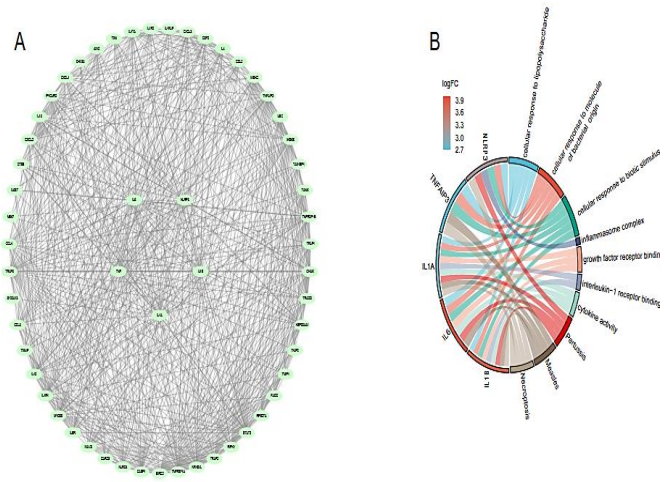


(A) GO enrichment map. (B) KEGG enrichment map. GO = Gene Ontology; BP = Biological Process; CC = Cellular Component; MF = Molecular Function; KEGG = Kyoto Encyclopedia of Genes and Genomes.

PPI Network Analysis

The pyroptosis-associated genes identified in the context of age-related cataracts were entered into the STRING database to construct a protein-protein interaction (PPI) network. Cytoscape was then used to visualize the PPI network diagram. Using the cytoHubba plug-in, key hub nodes within the network were identified, with the five most significant genes being IL6, TNF, IL1A, IL1β, and NLRP3 (Fig. 5A). Additionally, KEGG pathway analysis indicated that these top five genes were predominantly associated with pathways related to necroptosis, measles, pertussis, cytokine activity, interleukin-1 receptor binding, growth factor receptor binding, inflammasome complex formation, and cellular responses to biotic stimuli, bacterial-derived molecules, and lipopolysaccharide (Fig. 5B).

Figure 5: (A) PPI network diagram of pyroptosis-related genes in age-related cataracts, highlighting the top 5 genes: IL6, TNF, IL1A, IL1β, and NLRP3. (B) Chord diagram of KEGG analysis for these 5 genes.



DISCUSSION

As the population ages, the incidence of cataracts has been steadily rising. Despite significant advances in molecular biology and cytology, the exact mechanisms underlying cataract formation remain unclear Song et al. (2018). Recent research has increasingly focused on the mechanisms of pyroptosis in various diseases, with efforts to identify the genes and pathways involved in this process. Pyroptosis is a pro-inflammatory form of cell death mediated by gasdermins, a family of proteins capable of forming transmembrane pores, which can be activated through both inflammasome-dependent and inflammasome-independent mechanisms. When pyroptosis occurs uncontrollably, it triggers inflammatory responses in nearby cells and tissues, exacerbating inflammatory damage Chen et al. (2022). Research by Shi et al. Jin et al. (2018) suggests that pyroptosis may contribute to cataract development in a model involving H2O2-treated lens epithelial cells (LECs) through the CASP1/IL-1β signaling pathway. Further studies have shown that exposure to short-wavelength blue light can induce pyroptosis by activating either the canonical or noncanonical caspase-1/GSDMD signaling pathways in LECs. Notably, the expression levels of caspase-1 and GSDMD in LECs were found to vary depending on the duration of blue light exposure Wang et al. (2021).

The aim of this research was to identify genes associated with pyroptosis that play a role in age-related cataracts, thereby providing insights into the underlying mechanisms of this condition and identifying potential therapeutic targets for future clinical interventions. In this study, genes relevant to age-related cataracts were sourced from the Gene Expression Omnibus (GEO), while those linked to pyroptosis were obtained from previous studies Wu et al. (2021). The analysis identified 6,156 differentially expressed genes (DEGs) related to age-related cataracts, along with 55 genes associated with pyroptosis, including seven specifically related to pyroptosis in the context of age-related cataracts.

The results of the Gene Set Enrichment Analysis (GSEA) revealed that a significant portion of the upregulated genes and associated pathways were connected to the IL18, IL2, IL4, Notch, and MAPK signaling pathways, as well as cytokine activity and inflammatory responses. In contrast, the analysis showed that most of the downregulated genes and pathways were linked to the FOXM1 and PLK1 signaling pathways.

The Metascape online tool was employed for Gene Ontology (GO) annotation, as well as for the enrichment analysis of KEGG and Reactome pathways. The analysis indicated that the upregulated genes were significantly enriched in pathways related to the regulation of response to lipopolysaccharide (LPS), cellular responses to biotic stimuli, cellular responses to LPS, the NOD-like receptor signaling pathway, the TNF signaling pathway, and Coronavirus disease (COVID-19). It has been observed that LPS can activate p38, suggesting a potential mechanism by which the inhibition of aldose reductase (AR) reduces inflammation. Pandey et al. (2012) proposed that inhibiting AR contributes to a reduction in reactive oxygen species (ROS) production and the associated oxidative stress, both of which are key factors in promoting the pro-inflammatory response in cells exposed to LPS.

The PPI network was constructed using the STRING online tool and Cytoscape software. IL1β, IL1A, IL6, TNF, PSTPIP2, TNFAIP3, and NLRP3 were identified as the top seven genes in the PPI network, owing to their high connectivity.

The top five hub genes—IL6, TNF, IL1A, IL1β, and NLRP3—were all significantly upregulated. To verify the expression of these genes in age-related cataracts, relevant literature was reviewed and summarized in Table 1 Engelbrecht et al. (2020), Hamid et al. (2016), Dong et al. (2019), Lian et al. (2023). These genes require further experimental validation, particularly in the context of age-related cataracts.

The original IL6 family of cytokines consists of seven members: IL6, LIF, CNTF, CLCF1, OSM, CT-1, and IL11. Soluble IL6Ra (sIL-6Ra) interacts with IL-6 to form the IL-6/sIL-6Ra complex, which subsequently induces IL6 trans-signaling by binding to the cell membrane-expressed gp130 Skuratovskaia et al. (2021). The initiation of IL6 signaling through gp130 is primarily mediated by the phosphorylation of JAK family kinases, which are constitutively associated with the cytoplasmic region of gp130. JAK1 triggers the phosphorylation and homodimerization of STAT3, leading to its translocation into the nucleus and subsequent transcriptional activity Xu et al. (2023). IL6 trans-signaling is known to enhance IL-6 activity under inflammatory conditions and inhibit intraocular T-cell apoptosis, potentially exacerbating or prolonging the inflammatory and oxidative stress processes closely related to age-related cataracts Forcina et al. (2022).

TNF-α is a type of pyrogen that can increase the secretion of IL1β by stimulating macrophages, while IL1β can, in turn, stimulate other cells to release IL6 Charatcharoenwitthaya et al. (2007). IL1β also plays a role in inducing inflammation and inflammatory responses, promoting the expression of IL6 and TNF-α, and stimulating immune and stromal cells to produce more IL1β Cuesta et al. (2002). This creates a vicious cycle, exacerbating the inflammatory response. Additionally, the properties of IL6 are similar to those of IL1β, further accelerating the inflammatory process. Elevated levels of TNF-α in cataract lenses also activate the NF-kB signaling pathway, which is involved in cataractogenesis Takai et al. (2012). Both IL-1α and IL-1β are synthesized as precursor proteins that undergo proteolytic cleavage. They share IL-1R as their common receptor, a key event in triggering

Table 1: The expression of related genes level in age-related cataract by literature.

	Express	Type	Sample	Conclusion
IL6	Upregulation	Cytokines	Tear	Higher tear levels of IL-6 correlated with age of cataract patients Pandey et al. (2012)
TNF-α	Upregulation	Cytokines	Serum	TNF-α levels significantly increased in age-related cataract as compared to normal healthy Individuals Engelbrecht et al. (2020)
IL1A	Upregulation	Cytokines	Tear	IL1A levels increased in age-related cataract as compared to control, but $P > 0.05$ Pandey et al. (2012)
IL1β	Upregulation	Cytokines	Serum	The serum levels of IL6, IL1β, CRP and TNF-α in the observation group were higher than those in the control group Hamid et al. (2016)
NLRP3	Upregulation	mRNA	HLECs	The TXNIP/NLRP3 inflammasome pathway promotes HG-induced inflammation and HLEC pyroptosis, which is negatively regulated by SIRT1 Dong et al. (2019)
HLEC: Human lens epithelial cells				

inflammatory and pyroptosis responses Zeng et al. (2019). IL-1α is present in the cell in a fully bioactive form, so when necrotic cell death occurs, it results in the release of full-length IL-1α, which acts as an alarmin. Similar to S100A proteins or HMGB1, these preformed proteins are expelled from the cell after membrane disruption to induce inflammation Chen et al. (2007). In contrast, IL-1β cannot act as an alarmin until it is processed to its active form. Inflammasomes, which are cytosolic protein complexes responsible for activating inflammatory caspases, play a critical role here. Once activated, inflammasomes cleave IL-1β and IL-18 and release IL-1α, IL-1β, and IL-18 as pro-inflammatory mediators of pyroptosis. Caspase-1, along with pro-IL-1β and pro-IL-18, are substrates of caspase-1; once activated, caspase-1 cleaves these mediators into their biologically active forms, which are then secreted Kesavardhana et al. (2020).

Inflammasomes structurally consist of a NOD-like receptor (NLR) protein, such as NLRP1, NLRP3, or NLRC4, and the adaptor protein ASC, through which caspase-1 is recruited to the complex Platnich et al. (2019). NLRP3 plays a crucial role in regulating innate immune function. Activation of the NLRP3 inflammasome depends on ROS accumulation, which then mediates caspase-1 activation, leading to increased expression of proinflammatory IL-1β Im et al. (2014). Zou et al. (2020) proposed that NLRP3 may play a functional role in cataract progression due to the significant increase in NLRP3 mRNA and protein expressions in H2O2-induced HLEB3 cells compared to controls. Additionally, the protein levels of caspase-1 and IL-1 also increased. These phenotypic changes may be linked to pyroptosis. This investigation focused on analyzing differentially expressed genes (DEGs) to identify potential genes and pathways associated with pyroptosis in the context of cataracts. However, this approach has certain limitations, highlighting the need for validation through additional independent datasets. Firstly, the experimental conditions for wild-type and Atg7KO HLE-B3 cells in the GSE161701 dataset, which were subjected to H2O2 treatment, were not adequately specified. This raises concerns about their accuracy in representing the physiological and pathological conditions of age-related cataracts. Secondly, while existing literature highlights the significant roles of autophagy and pyroptosis in cataract development, the GSE161701 dataset used in this study does not provide direct evidence to support these claims. We acknowledge that some interpretations in the manuscript may be overly inferred from the available data. Lastly, due to time and resource constraints, further experimental validation is currently unfeasible. As a result, there is a lack of direct experimental evidence to confirm the specific contributions of autophagy and pyroptosis mechanisms in cataract pathogenesis. Moving forward, we plan to investigate the roles of autophagy and pyroptosis in cataract development through additional experimental validation and thorough data analysis, systematically addressing the existing limitations to improve the reliability and accuracy of our conclusions.

CONCLUSION

In conclusion, this investigation identifies several genes and pathways that may contribute to the molecular mechanisms underlying age-related cataracts. These findings improve our understanding of the role of pyroptosis in cataract development and suggest that targeting pyroptosis could be a viable strategy for preventing cataract formation. Specifically, key genes, including IL6, TNF, IL1A, IL1β, and NLRP3, were identified as potentially linked to the pathogenesis of pyroptosis-related genes in age-related cataracts.

It is important to note that these results were derived from bioinformatics analyses, and further research is needed to explore these connections in greater detail.

DECLARATIONS

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Authors' contributions

All the authors of this article have read and approved the manuscript. Mengtian Bai（first author）, Bo Long（co-first author）, and Yun Li (primary corresponding author) completed the first draft of the article and extensive revisions, playing an extremely important role in revising and embellishing the article.

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Competing interests

All the authors declare no competing interests

Data availability

The data sets during and/or analyzed during the current study are available from the first author and corresponding author upon reasonable request. The e-mail address is 308347673@qq.com.

REFERENCES

1. Pesudovs K, Lansingh VC, Kempen JH, et al. 2021. Cataract-related blindness and vision impairment in 2020 and trends over time in relation to VISION 2020: The Right to Sight: An analysis for the Global Burden of Disease Study. Investig Ophthalmol Vis Sci. 62:3523.

2. Razavi P, Baldwin G, Garg I, et al. 2024. Changes in wider field swept-source OCT angiography vascular metrics with anti-vascular endothelial growth factor therapy in central retinal vein occlusion. Graefes Arch Clin Exp Ophthalmol. 262(7):2111-20.

3. Perez-Moreiras JV, Gomez-Reino JJ, Maneiro JR, et al. 2018. Efficacy of Tocilizumab in Patients with Moderate-to-Severe Corticosteroid-Resistant Graves Orbitopathy: A Randomized Clinical Trial. Am J Ophthalmol. 195:181-90.

4. Wang Y, Hu H, Chen L, et al. 2023. Observation study of using a small dose of rituximab treatment for thyroid-associated ophthalmopathy in seven Chinese patients: One pilot study. Front Endocrinol (Lausanne). 13:1079852.

5. Fink SL, Cookson BT. 2005. Apoptosis, pyroptosis, and necrosis: mechanistic description of dead and dying eukaryotic cells. Infect Immun. 73(4):1907-16.

6. Zhang Y, Chen X, Gueydan C, et al. 2018. A Plasma membrane changes during programmed cell deaths. Cell Res. 28(1):9-21.

7. Cui Y, Yu X, Bao J, et al. 2024. Lens autophagy protein ATG16L1: a potential target for cataract treatment. Theranostics. 14(10):3984-96.

8. Jin X, Jin H, Shi Y, et al. 2017. Long Non-Coding RNA KCNQ1OT1 Promotes Cataractogenesis via miR-214 and Activation of the Caspase-1 Pathway. Cell Physiol Biochem. 42(1):295-05.

9. Zhang Y, Jiao Y, Li X, et al. 2021. Pyroptosis: A New Insight into Eye Disease Therapy. Front Pharmacol. 12:797110.

10. Shi J, Gao W, Shao F. 2017. Pyroptosis: Gasdermin-Mediated Programmed Necrotic Cell Death. Trends Biochem Sci42(4):245-54.

11. Dinarello CA. 2009. Immunological and inflammatory functions of the interleukin-1 family. Annu Rev Immunol. 27:519-50.

12. Shi J, Zhao Y, Wang K, et al. 2015. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. Nature. 526(7575):660-5.

13. Alfonso-Loeches S, Ureña-Peralta JR, Morillo-Bargues MJ, et al. 2014. Role of mitochondria ROS generation in ethanol-induced NLRP3 inflammasome activation and cell death in astroglial cells. Front Cell Neurosci. 8:216.

14. Guo R, Wang H, Cui N. 2021. Autophagy Regulation on Pyroptosis: Mechanism and Medical Implication in Sepsis. Mediators Inflamm. 9925059.

15. Pu Q, Gan C, Li R, et al. 2017. Atg7 Deficiency Intensifies Inflammasome Activation and Pyroptosis in Pseudomonas Sepsis. J Immunol. 198(8):3205-13.

16. Ye Y, Dai Q, Qi H. 2021. A novel defined pyroptosis-related gene signature for predicting the prognosis of ovarian cancer. Cell Death Discov. 7(1):71.

17. Deng M, Sun S, Zhao R, et al. 2022. The pyroptosis-related gene signature predicts prognosis and indicates immune activity in hepatocellular carcinoma. Mol Med. 28(1):16.

18. Shao W, Yang Z, Fu Y, et al. 2021. The Pyroptosis-Related Signature Predicts Prognosis and Indicates Immune

Microenvironment Infiltration in Gastric Cancer. Front Cell Dev Biol. 9:676485.

19. Song P, Wang H, Theodoratou E, et al. 2018. The national and subnational prevalence of cataract and cataract blindness in China: a systematic review and meta-analysis. J Glob Health. 8(1):010804.

20. Chen M, Rong R, Xia X. 2022. Spotlight on pyroptosis: role in pathogenesis and therapeutic potential of ocular diseases. J Neuroinflammation. 19(1):183.

21. Jin X, Jin H, Shi Y, et al. 2018. Pyroptosis, a novel mechanism implicated in cataracts. Mol Med Rep. 18(2):2277-85.

22. Wang X, Song Z, Li H, et al. 2021. Short-wavelength blue light contributes to the pyroptosis of human lens epithelial cells (hLECs). Exp Eye Res. 212:108786.

23. Wu J, Zhu Y, Luo M, et al. 2021. Comprehensive Analysis of Pyroptosis-Related Genes and Tumor Microenvironment Infiltration Characterization in Breast Cancer. Front Immunol. 12:748221.

24. Pandey S, Srivastava SK, Ramana KV. 2012. A potential therapeutic role for aldose reductase inhibitors in the treatment of endotoxin-related inflammatory diseases. Expert Opin Investig Drugs. 21(3):329-39.

25. Engelbrecht C, Sardinha LR, Rizzo LV. 2020. Cytokine and Chemokine Concentration in the Tear of Patients with Age-Related Cataract. Curr Eye Res. 45(9):1101-06.

26. Hamid S, Gul A, Hamid Q. 2016. Relationship of cytokines and AGE products in diabetic and non-diabetic patients with cataract. Int J Health Sci (Qassim). 10(4):507-15.

27. Dong Y, Mu GY, Chen F, et al. 2019. Correlation between MMP-2 gene polymorphism and cataract susceptibility. Eur Rev Med Pharmacol Sci. 23(8):3167-72.

28. Lian L, Le Z, Wang Z, et al. 2023. SIRT1 Inhibits High Glucose-Induced TXNIP/NLRP3 Inflammasome Activation and Cataract Formation. Invest Ophthalmol Vis Sci. 64(3):16.

29. Skuratovskaia D, Komar A, Vulf M, et al. 2021. IL-6 Reduces Mitochondrial Replication, and IL-6 Receptors Reduce Chronic Inflammation in NAFLD and Type 2 Diabetes. Int J Mol Sci. 22(4):1774.

30. Xu F, Wang S, Wang Y, et al. 2023. Inhibition of gp130 alleviates LPS-induced lung injury by attenuating apoptosis and inflammation through JAK1/STAT3 signaling pathway. Inflamm Res. 72(3):493-07.

31. Forcina L, Franceschi C, Musarò A. 2022. The hormetic and hermetic role of IL-6. Ageing Res Rev. 80:101697.

32. Charatcharoenwitthaya N, Khosla S, Atkinson EJ, et al. 2007. Effect of blockade of TNF-alpha and interleukin-1 action on bone resorption in early postmenopausal women. J Bone Miner Res. 22(5):724-29.

33. Cuesta MC, Quintero L, Pons H, et al. 2002. Substance P and calcitonin gene-related peptide increase IL-1 beta, IL-6 and TNF alpha secretion from human peripheral blood mononuclear cells. Neurochem Int. 40(4):301-06.

34. Takai Y, Tanito M, Ohira A. 2012. Multiplex cytokine analysis of aqueous humor in eyes with primary open-angle glaucoma, exfoliation glaucoma, and cataract. Invest Ophthalmol Vis Sci. 53(1):241-47.

35. Zeng C, Wang R, Tan H. 2019. Role of Pyroptosis in Cardiovascular Diseases and its Therapeutic Implications. Int J Biol Sci. 15(7):1345-57.

36. Chen CJ, Kono H, Golenbock D, et al. 2007. Identification of a key pathway required for the sterile inflammatory response triggered by dying cells. Nat Med. 13(7):851-56.

37. Kesavardhana S, Malireddi RKS, Kanneganti TD. 2020. Caspases in Cell Death, Inflammation, and Pyroptosis. Annu Rev Immunol. 38:567-95.

38. Platnich JM, Muruve DA. 2019. NOD-like receptors and inflammasomes: A review of their canonical and non-canonical signaling pathways. Arch Biochem Biophys. 670:4-14.

39. Im H, Ammit AJ. 2014. The NLRP3 inflammasome: role in airway inflammation. Clin Exp Allergy. 44(2):160-72.

40. Zou Y, Cui B, Liang P, et al. 2020. Inhibition of NLRP3 Protects Human Lens Epithelial Cells against Oxidative Stress-Induced Apoptosis by NF-ϰB Signaling. Ophthalmic Res. 63(2):174-81.

