Table SI. miRNAs in age-related cataracts.

First author/s, year	Name	Dysregulation	Functions	Associated network	(Refs.)
Li *et al*, 2020	miR-182-5p	Downregulated	Promotes proliferation, and inhibits ROS production and apoptosis in H_2O_2-exposed LECs *in vitro*.	miR-182-5p/NOX4, ROS, p38 MAPK	(1)
Fan *et al*, 2017; Wang *et al*, 2022; Xiang *et al*, 2016; Feng *et al*, 2023	miR-34a	Upregulated	Inhibits proliferation, induces apoptosis and facilitates oxidative stress of LECs, and accelerates opacification of mouse lenses *in vitro*.	miR-34a/Notch2; miR-34a/E2F3; miR-34a/HK1/caspase3; miR-34a-5p/GPX3	(2-5)
Kang *et al*, 2023	miR-125a-3p	Upregulated	Promotes apoptosis and decreases viability of UV-irradiation-treated LECs *in vitro*.	miR-125a-3p/TMBIM4	(6)
Li *et al*, 2015; Li *et al*, 2019; Abdullah *et al*, 2019; Liu *et al*, 2019	miR-15a	Upregulated	Inhibits proliferation and promotes apoptosis of H_2O_2-treated LECs *in vitro*.	miR-15a/BCL2, E2F3; miR-15a/BCL2, MCL1	(7-10)
Lu *et al*, 2018	miR-24	Upregulated	Increases cell death and apoptosis of H_2O_2-treated LECs *in vitro*.	miR-24/p53	(11)
Gong *et al*, 2019	miR-221	Upregulated	Decreases the viability and promotes apoptosis of LECs *in vitro*.	miR-221/SIRT1, E2F3	(12)
Liu *et al*, 2021; Zhang *et al*, 2021	miR-124	Upregulated	Promotes apoptosis of H_2O_2-exposed LECs *in vitro*.	miR-124/SPRY2, MMP-2; miR-124/PTB/Fas	(13,14)
Ren *et al*, 2018	miR-326	Unknown	Promotes apoptosis of H_2O_2-exposed LECs *in vitro*. Furthermore, administration of its antagomir delays cataract development in rats with selenite-induced cataracts.	miR-326/FGF1/βB2	(15)
Fang *et al*, 2024	miR-29a-3p	Unknown	Promotes apoptosis of H_2O_2-treated LECs *in vitro*. Furthermore, administration of its antagomir delays cataract development in rats with selenite-induced cataracts.	miR-29a-3p/CAND1	(16)
Zhang *et al*, 2016	miR-133b	Downregulated	Inhibits apoptosis and increases the viability of LECs *in vitro*.	miR-133b/BCL2L2	(17)
Zhou *et al*, 2019	miR‐23b‐3p	Upregulated	Induces apoptosis and inhibits autophagy in H_2O_2-exposed LECs *in vitro*.	miR-23b-3p/SIRT1	(18)
Yao *et al*, 2021	miR-23a-3p	Unknown	Inhibits proliferation and promotes apoptosis of H_2O_2-exposed LECs *in vitro*.	miR-23a-3p/BCL2	(19)
Xu *et al*, 2023	miR-210-3p	Upregulated	Inhibits viability and migration, promotes apoptosis, and facilitates oxidative damage in H_2O_2-exposed LECs *in vitro*.	miR-210-3p/ATG7	(20)
Luo *et al*, 2023	miR-222-3p	Upregulated	Inhibits proliferation and promotes apoptosis of UV irradiation-exposed LECs *in vitro*.	miR-222-3p/MGMT	(21)
Shi *et al*, 2018	miR-181a	Unknown	Promotes apoptosis and aggravates oxidative damage in H_2O_2-exposed LECs *in vitro*.	miR-181a/CASP3, BAX, COX-2	(22)
Gao *et al*, 2020; Liu *et al*, 2019	miR-378a	Upregulated	Inhibits proliferation and promotes apoptosis of LECs *in vitro*.	miR-378a/ROS, PI3K/AKT; miR-378a-5p/E2F3	(23,24)

Qin *et al*, 2014; Zhao *et al*, 2016	miR-125b	Downregulated	Inhibits apoptosis of UV-irradiation-exposed LECs *in vitro*.	miR-125b/p53	(25,26)
Yao and Yan, 2020	miR-182	Unknown	Inhibits oxidative stress and epithelial cell apoptosis in the lens of cataract rats.	miR-182/PI3K/Akt	(27)
Kang *et al*, 2019	miR-3912-5p	Unknown	Binds to the 3' UTR of BER pathway genes and affects disease susceptibility.	miR-3912-5p/NEIL2	(28)
Zou *et al*, 2018	miR-589-5p	Unknown	Bind to the 3' UTR of NER pathway genes and affects disease susceptibility.	miR-589-5p/XPC	(29)
Lu *et al*, 2018	miR-211	Upregulated	Inhibits proliferation and promotes apoptosis of LECs *in vitro*.	miR-211/SIRT1	(30)
Cao *et al*, 2021	let-7c-5p	Upregulated	Inhibits autophagic degradation in UV irradiation-exposed LECs *in vitro*.	let-7c-5p/ERCC6	(31)
Dong *et al*, 2016	let-7b	Upregulated	Induces apoptosis of UV irradiation-exposed LECs *in vitro*.	let-7b/Lgr4	(32)
Li *et al*, 2020	let-7c-3p	Downregulated	Attenuates apoptosis and autophagy of H_2O_2-treated LECs *in vitro*.	let-7c-3p/ATG3	(33)
Gao *et al*, 2020; Mei *et al*, 2020	miR-630	Upregulated	Promotes apoptosis, and inhibits proliferation and migration of LECs *in vitro*.	miR-630/ALCAM; miR-630/E2F3	(23,34)
Wang and Ren, 2023	miR-187	Upregulated	Induces apoptosis and aggravates oxidative damage in H_2O_2-exposed LECs *in vitro*. Furthermore, administration of its antagomir delays cataract development in the Emory mouse model of senile cataracts.	Unknown	(35)

NOX4, nicotinamide adenine dinucleotide phosphate oxidase subunit 4; ROS, reactive oxygen species; E2F3, E2F transcription factor 3; HK1, hexokinase 1; GPX3, glutathione peroxidase 3; TMBIM4, transmembrane Bax inhibitor motif containing 4; MCL1, myeloid cell leukemia sequence 1; SIRT1, silent information regulator 1; SPRY2, protein sprouty homolog 2; PTB, polypyrimidine tract-binding protein; FGF1, fibroblast growth factor 1; βB2, β-crystallin B2; BCL2L2, B-cell lymphoma-2-like-2; ATG7, autophagy-related gene; CASP3, apoptosis-related gene caspase-3; COX-2, cyclooxygenase 2; NEIL2, Nei-like DNA glycosylase 2; Lgr4, leucine-rich repeat containing G protein-coupled receptor 4; ALCAM, activated leukocyte cell adhesion molecule; 3' UTR, 3' untranslated region; BER, base excision repair; NER, neucleotide excision repair; CAND1, cullin-associated NEDD8-dissociated protein 1; ERCC6, excision repair cross-complementing rodent repair deficiency, complementation group 6; H_2O_2, hydrogen peroxide; HK1, hexokinase 1; LEC, lens epithelial cell; MGMT, O6-methylguanine-DNA methyltransferase; miRNA/miR, microRNA; UV, ultraviolet; XPC, xeroderma pigmentosum complementation group C.

Table SII. Long non-coding RNAs in age-related cataracts.

First author/s, year	Name	Dysregulation	Functions	Associated network	(Refs.)
Li *et al*, 2017; Shen and Zhou, 2021; Sun *et al*, 2023	TUG1	Upregulated	Inhibits the viability and promotes apoptosis of H_2O_2-exposed or UV irradiation-exposed LECs *in vitro*.	TUG1/miR-196a-5p; TUG1/miR-421/caspase-3; TUG1/miR-29b/Smac	(36-38)
Jin *et al*, 2017; Xu *et al*, 2022; Zhang and Cheng, 2021	KCNQ1OT1	Upregulated	Promotes apoptosis and pyroptosis, and aggravates oxidative stress in H_2O_2-exposed LECs *in vitro*.	KCNQ1OT1/miR-223-3p/BCL2L2; KCNQ1OT1/miR-214/caspase-1; KCNQ1OT1/miR-124-3p/BCL2L11	(39-41)
Guo *et al*, 2023; Zhou *et al*, 2020	NEAT1	Upregulated	Promotes apoptosis, aggravates oxidative damage and inhibits proliferation of H_2O_2-exposed LECs *in vitro*.	NEAT1/NF-κB p65, p38 MAPK; NEAT1/miR-124-3p/DAPK1	(42,43)
Li *et al*, 2023	DCLRE1A	Upregulated	Promotes repair of oxidative DNA damage, enhances cell viability and inhibits apoptosis of H_2O_2-exposed LECs *in vitro*.	Unknown	(44)
Cheng *et al*, 2019; Liu *et al*, 2018	H19	Upregulated	Inhibits apoptosis, alleviates oxidative damage, and enhances the proliferation and migration of H_2O_2-exposed or UV irradiation-exposed LECs *in vitro*.	H19/miR-675/CRYAA; H19/miR-29a/TDG	(45,46)
Tu *et al*, 2020; Zhang *et al*, 2024	MEG3	Upregulated	Promotes apoptosis and ferroptosis in H_2O_2-exposed LECs *in vitro*, and exacerbates oxidative stress-induced lens opacity.	MEG3/PTBP1/GPX4; MEG3/miR-223, p53/TP53INP1	(47,48)
Xiang *et al*, 2019	PLCD3-OT1	Downregulated	Increases viability and inhibits apoptosis in UV irradiation-exposed LECs *in vitro*.	PLCD3-OT1/miR-224-5p/PLCD3	(49)
Zhou *et al*, 2020	NONHSAT143692.2	Downregulated	Inhibits apoptosis, alleviates oxidative damage and promotes the proliferation of UV irradiation-exposed LECs *in vitro*.	NONHSAT143692.2/miR-4728-5p/OGG1	(50)
Jing *et al*, 2020	OIP5-AS1	Upregulated	Promotes apoptosis of H_2O_2-exposed LECs *in vitro* and exacerbates lens opacity.	TFAP2A/OIP5-AS1/POLG	(51)
Tu *et al*, 2019	GPX3-AS	Downregulated	Inhibits apoptosis of H_2O_2-exposed LECs *in vitro*.	GPX3-AS/GPX3	(52)

Smac, second mitochondria-derived activator of caspases; BCL2L2, B-cell lymphoma-2-like-2; BCL2L11, BCL-2-like 11; DAPK1, death-associated protein kinase 1; CRYAA, crystallin αA; TDG, thymine DNA glycosylase; GPX4, glutathione peroxidase 4; PLCD3, 1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase δ3; OGG1, 8-oxoguanine DNA glycosylase; POLG, polymerase γ; TFAP2A, transcription factor AP-2 (activating enhancer binding protein 2α); GPX3, glutathione peroxidase 3; H_2O_2, hydrogen peroxide; LEC, lens epithelial cell; miR, microRNA; PTBP1, polypyrimidine tract binding protein 1; UV, ultraviolet.

Table SIII. Circular RNAs in age-related cataracts.

First author/s, year	Name	Dysregulation	Functions	Associated network	(Refs.)
Chen *et al*, 2023; Cui *et al*, 2020; Liu *et al*, 2018	circHIPK3	Downregulated	Enhances viability and proliferation, inhibits apoptosis, and mitigates oxidative damage in H_2O_2-exposed LECs *in vitro*.	circHIPK3/miR-221-3p/PI3K/AKT; circHIPK3/miR-193a/CRYAA; circHIPK3/miR-495-3p/HDAC4	(53-55)
Liang *et al*, 2020; Xu *et al*, 2021	circZNF292	Downregulated	Inhibits apoptosis, alleviates oxidative damage, and enhances viability of H_2O_2-exposed LECs *in vitro*.	circZNF292/miR-222-3p/E2F3; circZNF292/miR-23b-3p	(56,57)
Zhou *et al*, 2021	circ_EPB41	Downregulated	Ameliorates apoptosis in UV irradiation-exposed LECs *in vitro*.	circ_EPB41/miR-24-3p/BPNT1	(58)
Liu *et al*, 2022	circ_0060,144	Downregulated	Promotes proliferation, inhibits apoptosis and alleviates oxidative damage of LECs *in vitro*.	circ_0060,144/miR-23b-3p/HIPK3	(59)
He *et al*, 2022; Wu *et al*, 2024	circ_0122396	Downregulated	Promotes proliferation, and attenuates apoptosis and oxidative stress of H_2O_2-exposed LECs *in vitro*.	circ_0122396/miR-15a-5p/FGF1; circ_0122396/miR-23a-3p/MMP16	(60,61)
Cui *et al*, 2024; Ma *et al*, 2023	circMAP3K4	Downregulated	Enhances proliferation, inhibits apoptosis and senescence, alleviates cell cycle arrest and decreases oxidative stress in H_2O_2-exposed LECs *in vitro*.	circMAP3K4/miR-630/ERCC6; circMAP3K4/miR-193a-3p/PLCD3	(62,63)
Wang *et al*, 2021	circ_0004058	Downregulated	Inhibits apoptosis and promotes autophagy of H_2O_2-exposed LECs *in vitro*.	circ_0004058/miR-186/ATG7	(64)
Mao and Zhang, 2025	hsa_circ_0105558	Upregulated	Promotes apoptosis and aggravates the oxidative damage of H_2O_2-treated LECs *in vitro*.	hsa_circ_0105558/miR-182-5p/ATF6	(65)
Liu *et al*, 2021	circMRE11A	Upregulated	Inhibits viability and induces cell cycle arrest of UV irradiation-exposed LECs *in vitro*. Accelerates lens aging and opacification in mice.	circMRE11A/UBXN1/ATM	(66)
Wu *et al*, 2022	circMED12L	Downregulated	Alleviates viability inhibition and apoptotic and oxidative damage of H_2O_2-exposed LECs *in vitro*.	circMED12L/miR-34a-5p/ALCAM	(67)

Fang *et al*, 2023	circRNA 06209	Unknown	Enhances proliferation and inhibits apoptosis of H_2O_2-exposed LECs *in vitro*, and inhibits selenite-induced cataract formation in a rat model.	circRNA 06209/miR-6848-5p/ALOX15	(68)
Sun *et al*, 2024	circ_HLCS	Downregulated	Attenuates proliferation inhibition and apoptosis of UV irradiation-exposed LECs *in vitro*.	circ_HLCS/miR-338-3p/BPNT1	(69)
Li *et al*, 2023	has_circ_0007905	Upregulated	Inhibits proliferation and causes apoptosis in LECs *in vitro*.	METTL3/has_circ_0007905/miR-6749-3p/EIF4EBP1	(70)
Li *et al*, 2024	circSTRBP	Upregulated	Inhibits proliferation, promotes apoptosis and facilitates oxidative stress in H_2O_2-exposed LECs *in vitro*.	circSTRBP/IGF2BP1/NOX4	(71)
Guo *et al*, 2023	circSTK39	Downregulated	Alleviates proliferation inhibition and apoptotic and oxidative damage in H_2O_2-exposed LECs *in vitro*.	circSTK39/miR-125a-5p/ERCC6	(72)

HIPK3, homeodomain interacting protein kinase 3; CRYAA, crystallin αA; HDAC4, histone deacetylase 4; E2F3, E2F transcription factor 3; BPNT1, 3'(2'), 5'-bisphosphate nucleotidase 1; FGF1, fibroblast growth factor 1; PLCD3, phospholipase C δ3; ATG7, autophagy-related gene 7; ATF6, activating transcription factor 6; UBXN1, UBX domain-containing protein 1; ATM, ataxia-telangiectasia mutated kinase; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; NOX4, nicotinamide adenine dinucleotide phosphate oxidase subunit 4; ERCC6, excision repair cross-complementing rodent repair deficiency, complementation group 6; ALCAM, activated leukocyte cell adhesion molecule; ALOX15, recombinant arachidonate-15-lipoxygenase; circ, circular RNA; EIF4EBP1, eukaryotic translation initiation factor 4E binding protein 1; H_2O_2, hydrogen peroxide; LEC, lens epithelial cell; METTL3, methyltransferase-like 3; miR, microRNA; UV, ultraviolet.

Table SIV. DNA methylation in age-related cataracts.

First author/s, year	Gene	Cell/tissue type	Methylation measures	Main findings	(Refs.)
Wang *et al*, 2016	*ERCC6*	LECs of patients with ARNCs and age-matched controls who had their transparent lens extracted because of vitreoretinal diseases; HLE-B3 cells; 239T cell lines	Levels of cytosine hypermethylation in a special CpG site that controls ERCC6 transcription using pyrosequencing	mRNA and protein expression levels of ERCC6 in LECs were lower in ARNCs than in the controls; UVB radiation triggered hypermethylation of the CpG site in the ERCC6 promoter, histone H3K9 deacetylation of ERCC6 and repression of ERCC6 gene expression.	(73)
Zhou *et al*, 2012	*CRYAA*	Human lens epithelium samples of patients with ARNCs and non-ARC patients	Methylation status of the CpG islands of CRYAA promoter using BSP	mRNA and protein levels of CRYAA were reduced in the lens epithelia of ARNC cases, which corresponded to hypermethylation of the CpG island of the CRYAA promoter.	(74)
Wang *et al*, 2015	*OGG1*	Lens cortex of patients with ARCs and age-matched individuals who had their transparent lens extracted because of vitreoretinal diseases	Methylation status of CpG islands near OGG1 in DNA extracted from lens cortex using BSP	mRNA and protein levels of OGG1 were reduced in the lens cortex of ARC; the CpG island in the first exon of OGG1 displayed hypermethylation in the DNA extracted from the lens cortex of ARC.	(75)
Gao *et al*, 2015	*Keap1*	Healthy clear lenses from donors aged between 15 and 80 years and cataract lenses from patients aged between 45 and 90 years	Age-dependent DNA methylation status in the promoter region of the Keap1 gene using BSP	DNA demethylation in the Keap1 promoter increased with age; demethylation of the Keap1 promoter was found in cataract lenses and clear lenses of patients aged between 66 and 80 years.	(76)
Wang *et al*, 2024	*COL4A1*	HLE-B3 cells; anterior lens capsules of Sprague Dawley rats	Methylation status of CpG islands located in the COL4A1 promoter using BSP	DNA hypermethylation of COL4A1 promoter CpG islands was associated with decreased COL4A1 expression in UVB-induced HLE-B3 cells and anterior lens capsules of rats.	(77)
Zhu *et al*, 2015	*WRN*	Anterior lens capsules from patients with ARCs and age-matched non-ARC patients	Methylation status of the CpG islands of the WRN promoter in the DNA extracted from the anterior lens capsules and cortex using BSP	WRN expression was decreased in the ARC anterior lens capsules; the CpG island of the WRN promoter in the ARC anterior lens capsules displayed hypermethylation compared with the samples from non-ARC patients.	(78)

Li *et al*, 2014	*MGMT*	Centred anterior capsules of the lens from eyes with ARCs and rhegmatogenous retinal detachment eyes undergoing vitrectomy combined with extracapsular cataract extraction	Methylation status of the CpG islands of DNA repair genes using BSP	mRNA levels of 10 DNA repair genes were decreased, and the levels of one DNA repair gene were increased in LECs of patients with ARC. The promoter region of the MGMT gene was hypermethylated in ARC tissue compared with tissue without ARC.	(79)
Chen *et al*, 2017	*GSTP1*	Anterior LE, LC and LN of patients with ARNCs and age-matched controls with normal or mild ARNC severity	Methylation status of two CpG islands near the GSTP1 promoter (the regions from -819 to -533 bp and from -201 to +86 bp, respectively) using BSP	GSTP1 mRNA and protein levels were reduced in the lens epithelium and cortex of ARNC cases compared with controls. The changes corresponded to hypermethylation of the GSTP1 promoter CpG islands.	(80)
Li *et al*, 2016	*GSTM3*	The LECs and lens cortex of patients with ARCs and patients with vitreoretinal diseases who received transparent lens extraction; HLE cell lines, SRA01/04 and HLE-B3	Methylation status of the GSTM3 promoter in the DNA extracted from the LECs and lens cortex, and in HLE cell lines, using BSP and pyrosequencing	Expression levels of GSTM3 were decreased in ARC lens tissues, which was associated with hypermethylation of the GSTM3 promoter. Lower levels of GSTM3 were detected in HLEB3 cells than in SRA01/04 cells, while HLEB3 cells displayed hypermethylation of GSTM3 and SRA01/04 cells did not.	(81)
Jin *et al*, 2015	*Klotho*	LECs of normal transparent lenses and ARCs	Methylation level of the Klotho gene using MSP	Klotho was positively expressed in the LECs of healthy individuals at the mRNA and protein level. Its promoter showed increased methylation as age increased, resulting in Klotho gene silencing and downregulated expression or no expression of the Klotho protein.	(82)

ARNCs, age-related nuclear cataracts; UVB, ultraviolet-B; ERCC6, excision repair cross-complementing rodent repair deficiency, complementation group 6; CRYAA, crystallin αA; BSP, bisulfite-sequencing PCR; OGG1, 8-oxoguanine DNA glycosylase 1; Keap1, kelch-like ECH-associated protein 1; WRN, Werner syndrome gene; MGMT, O6-methylguanine-DNA methyl-transferase; GSTP1, glutathione S-transferase P1; LE, lens epithelium; LC, lens peripheral cortex; LN, lens nucleus; GSTM3, glutathione S-transferase Mu 3; MSP, methylation specific polymerase chain reaction; ARC, age-related cataract; COL4A1, collagen type IV α1 chain; LEC, lens epithelial cell.

Table SV. Histone modifications in age-related cataracts.

A, Acetylation

First author/s, year	Modification sites	Gene	Effects/main findings	(Refs.)
Wang *et al*, 2016	H3K9	ERCC6	In HLE-B3 cells, HDAC1 recruitment at the ERCC6 promoter was induced after exposure to UVB and deacetylation of H3K9 increased in this region; inhibition of HDAC1 activated the ERCC6 promoter and restored gene expression.	(73)
Zhu *et al*, 2015	H3	WRN	Acetylated H3 levels were lower in all three subtypes of ARCs than in the non-ARCs in anterior lens capsules.	(78)
Li *et al*, 2016	H3	GSTM3	Acetylated H3 levels were lower in HLE-B3 cells than in SRA01/04 cells; after treatment with histone deacetylase inhibitor, HLE-B3 cells exhibited increased GSTM3 expression.	(81)
Chen *et al*, 2017	H3 and H4	GSTP1	Acetylated H3 and H4 levels were lower in the lens epithelium of patients with ARNC compared with non-ARNC controls.	(80)
Rong *et al*, 2016	H3 and H4	SOD1	Both H3 and H4 were deacetylated at -600 bp of the SOD1 promoter in the lens epithelium of ARC; reducing histone acetylation with a HAT inhibitor could decrease SOD1 expression and induce cataract formation *in vitro*; the HDAC inhibitor effectively prevented the cataract formation effect of the HAT inhibitor.	(83)

B, Methylation

First author/s, year	Modification sites	Gene	Effects/main findings	(Refs.)
Zhu *et al*, 2015	H3K9	WRN	Methylated H3K9 was increased in all three subtypes of ARCs compared with in the non-ARCs in anterior lens capsules.	(78)
Li *et al*, 2016	H3K9	GSTM3	Trimethylated H3K9 levels were higher in HLE-B3 cells than in SRA01/04 cells.	(81)
Chen *et al*, 2017	H3K4 and H3K9	GSTP1	Methylated H3K4 was reduced while methylated H3K9 was increased in lens epithelium of ARNC cases.	(80)

UVB, ultraviolet-B; WRN, Werner syndrome gene; GSTM3, glutathione S-transferase Mu 3; GSTP1, glutathione S-transferase P1; ARNC, age-related nuclear cataract; SOD1, superoxide dismutase 1; ARC, age-related cataract; ERCC6, excision repair cross-complementing rodent repair deficiency, complementation group 6; HAT, histone acetyltransferase; HDAC1, histone deacetylase 1.

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