Aging of the human eye lens: Epigenetic landscape and therapeutic targets in age-related cataracts (Review)

WENXIN YANG*, YINGYING ZHENG*, SILONG CHEN, JIARUI GUO, ZICAI PAN and YIBO YU

Eye Center, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310009, P.R. China

Received June 5, 2025; Accepted September 15, 2025

DOI: 10.3892/ijmm.2025.5657

Abstract. Age-related cataracts (ARCs) are the predominant cause of blindness globally and are characterized by progressive opacification of the ocular lens. Although oxidative stress, ultraviolet radiation and metabolic dysfunction are well-documented etiological factors, growing evidence implicates epigenetic dysregulation as a critical pathogenic mechanism in ARCs. Epigenetics refers to heritable changes in gene expression that occur without alterations to the underlying DNA sequence. The primary epigenetic alterations include non-coding RNAs, DNA methylation, histone modifications, RNA modifications and chromatin remodelling. Epigenetic modifications dynamically regulate gene expression profiles in lens epithelial cells, modulating critical cellular processes such as proliferation, the oxidative stress response and DNA repair, all of which are essential for maintaining lens transparency. Epigenetic research offers novel insights into the molecular mechanisms underlying ARCs and may yield therapeutic strategies targeting dysregulated epigenetic pathways. The present review discusses current evidence on epigenetic mechanisms in ARC pathogenesis, delineating their roles in lens opacity development and highlighting potential targets for clinical intervention.

Contents

Correspondence to: Professor Yibo Yu, Eye Center, The Second Affiliated Hospital, Zhejiang University School of Medicine, 1 Xihu Road, Hangzhou, Zhejiang 310009, P.R. China
E-mail: yuyibo@zju.edu.cn

*Contributed equally

Key words: age-related cataract, epigenetics, non-coding RNA, DNA methylation, histone modification, N^6-methyladenosine modification

1. Introduction

Cataracts. Cataracts, characterized by progressive opacification of the ocular lens, are the leading cause of visual impairment and blindness worldwide (1). Cataracts can be classified into age-related cataracts (ARCs), congenital cataracts and secondary cataracts caused by other reasons (2). ARCs, also known as senile cataracts, constitute the most prevalent cataract subtype, with typical onset after 50-60 years of age (3). Currently, no clinically proven interventions exist to prevent ARC progression. Surgery remains the gold-standard therapeutic approach, achieving rapid visual rehabilitation in most cases (4). Despite surgical efficacy, ARCs persist as a critical global health challenge due to high patient volume, substantial surgical costs and potential postoperative complications (5,6). Therefore, continuous and dedicated efforts are required to develop improved therapeutic strategies for ARC prevention and treatment.

Oxidative stress. ARCs develop through the long-term interplay of multiple pathogenic factors, with complex and heterogeneous underlying mechanisms. To date, multiple risk factors, including aging, diabetes, genetic predisposition, oxidative stress and ultraviolet (UV) radiation exposure, have been implicated in ARC pathogenesis (3). The current understanding of ARC pathogenesis strongly implicates reactive oxygen species (ROS) accumulation as a key driver, with numerous studies demonstrating the pathogenic roles of superoxide anion (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radicals (·OH) generated during aerobic metabolism (7-9). Excessive ROS induce oxidative stress by chemically modifying and damaging critical cellular components (10). Oxidative stress, in turn, causes modifications in lens proteins (including enzymes, crystallins and other chaperones), thereby reducing their solubility and stability, and ultimately promoting crystallin aggregation (11). These alterations induce light scattering within the lens, progressively leading to lens opacity and subsequent visual acuity impairment (12). Oxidative stress also directly damages lens epithelial cells (LECs), which are critical for maintaining lens transparency and metabolic homeostasis, through the peroxidation of proteins, lipids and DNA, while concurrently activating signalling pathways and transcription factors (11,13-17). As the most metabolically active components of the lens, LECs possess a sophisticated antioxidant defence system to mitigate oxidative stress (18,19).

However, when ROS levels exceed the antioxidant capacity of LECs, oxidative damage to the LECs triggers apoptosis, an early event in ARC pathogenesis (20,21).

Epigenetic modifications. Epigenetics refers to alterations in gene expression without changes to the DNA sequence in response to environmental, developmental and nutritional factors (22,23). These alterations are reversible and subject to dynamic regulation, leading to heritable changes in gene expression and cellular phenotypes (24). Extensive research has demonstrated that epigenetic mechanisms function as pivotal regulators of disease pathogenesis, influencing initiation, progression, prevention and treatment (25,26). The emergence of aberrant epigenetic changes is associated with the pathogenesis of various diseases, including cancer, diabetes, Alzheimer's disease and other age-related disorders (27-30). Epigenetic modifications not only underlie the molecular mechanisms driving disease development but also serve as promising biomarkers for clinical diagnosis and enable precision-targeted therapeutic interventions (31,32). Epigenetic modifications primarily encompass DNA methylation, histone modifications, RNA modifications, non-coding RNAs (ncRNAs) and chromatin remodelling. A substantial body of research has established the critical involvement of epigenetic processes in gene expression regulation, DNA damage repair, and cell cycle control and aging, highlighting their fundamental importance in molecular biology and genetics (33-35).

Breakthroughs in epigenetic research related to ocular diseases have only emerged within the past decade. Epigenetic modifications have grown into a leading frontier in biomedical research, with accumulating studies revealing their regulatory impact on several ocular diseases such as cataracts, glaucoma, diabetic retinopathy and age-related macular degeneration (36-39). Epigenetic research can deepen the understanding of the molecular mechanisms of ocular diseases and open novel avenues for the development of epigenome-targeted treatments. The present review summarizes current advances in epigenetic research on ARCs, discussing the implications of these research advances for future investigations and the therapeutic potential of epigenetic interventions in ARCs.

2. Epigenetic modifications in ARCs

Epigenetic modifications represent heritable changes in gene expression that occur independently of alterations in the underlying DNA sequence (40). Epigenetic modifications, including ncRNAs, DNA methylation, histone modifications and N^6-methyladenosine (m^6A) modification, are now widely acknowledged as key molecular drivers in the development of ARCs (41-43). A deeper understanding of these epigenetic mechanisms will elucidate disease pathogenesis and enable targeted epigenetic therapies for ARCs. The subsequent sections will first introduce key epigenetic alterations, including ncRNAs, DNA methylation, histone modifications and m^6A modification, and then systematically examine their roles in ARC pathogenesis.

ncRNAs. The central dogma of molecular biology describes the flow of genetic information from DNA to RNA to protein (44,45). For decades, research on cataract pathogenesis has predominantly focused on protein-coding genes. However, advances in sequencing technologies have enabled the identification of numerous unique ncRNAs and confirmed their cellular presence. ncRNAs represent a class of RNA molecules that lack protein-coding sequences and are consequently not translated into polypeptides or proteins. This category includes microRNAs (miRNAs/miRs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), transfer RNA-derived small RNAs (tsRNAs) and small nuclear RNAs (46). Through specific interactions with DNA, RNA and proteins, ncRNAs precisely regulate nearly all biological pathways, including signal transduction (47), transcriptional and post-transcriptional regulation (48,49), translational repression (50), and translation initiation regulation (51) (Fig. 1). ncRNAs operate in both physiological and pathological contexts, exhibiting strong potential as novel molecular biomarkers and therapeutic targets (52-54). Consequently, ncRNAs serve a pivotal role in the pathogenesis and progression of ARCs, as extensively documented in several studies (55-57). The present review primarily focuses on reviewing advances in research on the four major ncRNAs (miRNAs, lncRNAs, circRNAs and tsRNAs) and their regulatory networks in ARCs.

miRNAs. miRNAs are the most extensively studied and best characterized small ncRNAs to date. miRNAs are small ncRNA molecules, typically 20-30 nucleotides in length, that serve critical roles in structural, enzymatic and regulatory processes across biological systems (58). Precursor miRNAs undergo a tightly regulated series of nuclear and cytoplasmic processing steps mediated by the endoribonucleases DROSHA and DICER, respectively, ultimately yielding mature miRNAs. The mature miRNAs are then incorporated into the RNA-induced silencing complex and regulate gene expression by binding to the 3' untranslated region (UTR) of target mRNAs, leading to either mRNA degradation or translational repression (58,59). miRNAs have also been reported to interact with other regions, such as the 5' UTR, coding sequence and gene promoters (60,61). Furthermore, accumulating evidence has demonstrated that miRNAs can post-transcriptionally activate gene expression in specific contexts, challenging the conventional paradigm of miRNA-mediated silencing and highlighting their functional versatility (62-64). Notably, miRNAs form intricate, highly interconnected regulatory networks, wherein individual miRNAs typically regulate multiple mRNA targets, and conversely, most mRNAs are subject to combinatorial regulation by multiple miRNAs (65). Diverse physiological and pathological processes, including apoptosis (66), autophagy (67), oxidative stress (68), senescence (69) and DNA repair (70), have been shown to influence the biological characteristics of LECs in ARC, as evidenced by both *in vitro* experiments and animal studies. miRNAs have been demonstrated to serve important roles in these processes, making it plausible that miRNAs are closely associated with cataract formation (Table SI).

Studies have revealed alterations in miRNA expression profiles between transparent and cataractous lenses (71-73). For example, miRNA let-7b expression exhibits a positive association with patient age, and elevated miRNA let-7b expression is associated with higher nuclear (N), cortical (C) and posterior subcapsular (P) cataract scores according to the Lens Opacities Classification System III (74) in patients with

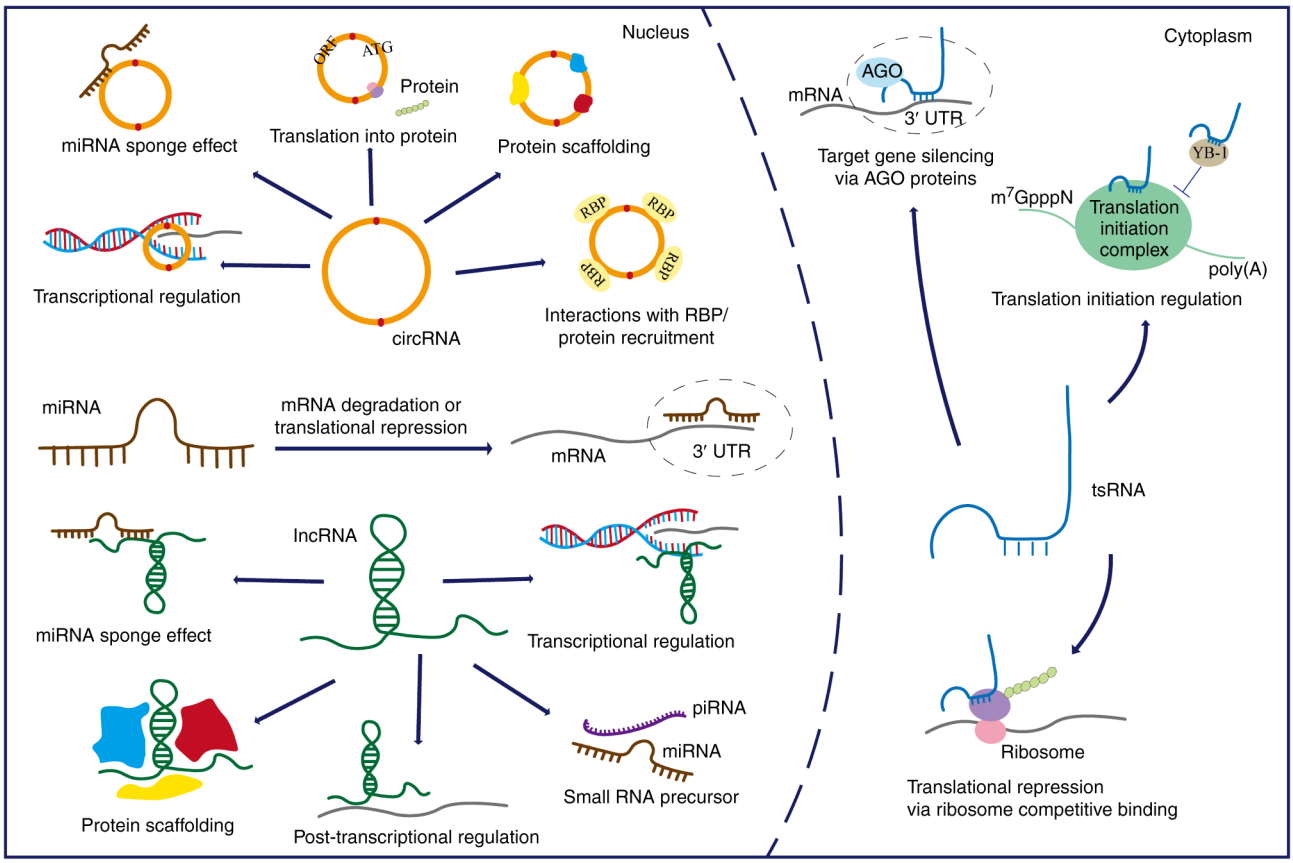

Figure 1. Functional landscape of non-coding RNAs. miRNA, microRNA; lncRNA, long non-coding RNA; circRNA, circular RNA; tsRNA, transfer RNA-derived small RNA; piRNA, PIWI interacting RNA; ORF, open reading frame; RBP, RNA-binding protein; 3' UTR, 3' untranslated region; AGO, Argonaute; YB-1, Y-box binding protein 1.

ARCs (73). Similarly, miR-34a expression levels vary among patients of different ages, with moderate associations observed between high N, C and P cataract scores and high miR-34a levels (75). Elevated levels of miR-210-3p have been identified in the aqueous humour of patients with ARCs, and the elevation demonstrated strong diagnostic potential for ARCs while being associated with oxidative stress marker levels (76). miR-15a and miR16-1 are expressed at a higher level in the LECs of patients with cataracts compared with normal controls (77). Notably, ARCs can be classified into distinct subtypes based on the location of opacification, including cortical cataracts, nuclear cataracts (NCs), and posterior and anterior subcapsular cataracts (ASCs), while the remainder is classified as mixed cataracts, and differential expression of miRNAs has been observed among these subtypes (72). The expression levels of let-7a-5p, let-7d-5p, let-7g-5p and miR-23b-3p differ between patients with NC and ASC, as measured in lens epithelium samples (72). Thus, aberrant miRNA expression levels may not only act as risk factors in the formation and progression of ARC, but also serve as potential biomarkers for ARCs based on their differential expression patterns in different severity stages and subtypes of ARCs. However, no miRNAs are used for clinical diagnosis currently, requiring further validation in clinical practice.

miRNAs typically function by binding to target mRNAs and inhibiting translation (58,59). Thus, specific miRNAs indirectly contribute to cataract formation by regulating key factors involved in cellular processes such as apoptosis, proliferation and oxidative stress. For instance, miR-23b-3p promotes apoptosis and inhibits autophagy in LECs under oxidative stress by directly targeting and downregulating silent information regulator 1 (SIRT1), a critical mediator of oxidative stress resistance, thereby contributing to ARC pathogenesis (78). Similarly, miR-211 induces apoptosis and decreases cell viability by suppressing SIRT1 expression (79). E2F transcription factor 3 (E2F3), a member of the E2F transcription factor family, serves essential roles in regulating cell proliferation, apoptosis and differentiation (80,81). As a key cell cycle regulator, E2F3 promotes cell cycle re-entry in quiescent lens cells. However, aberrant cell cycle re-entry may trigger programmed cell death (82-84), and has been observed in LECs, which is closely linked to ARC pathogenesis (85). Experimental evidence has identified miR-34a (86), miR-15a (87), miR-221 (88), miR-630 and miR-378a-5p (89), as direct post-transcriptional suppressors of E2F3, collectively contributing to lens opacity progression. miR-34a, the expression of which is increased in the cataractous lens, triggers mitochondria-mediated apoptosis and oxidative stress by suppressing Notch2 (90). In addition, the upregulation of miR-34a together with the downregulation of hexokinase 1 (HK1) inhibits the proliferation and induces the apoptosis of LECs, thus accelerating the opacification of mouse lenses via the HK1/caspase 3 signalling pathway (91). Furthermore, Cao *et al* (67) demonstrated that miRNA let-7c-5p directly

targeted excision repair cross-complementing rodent repair deficiency, complementation group 6 (ERCC6), and thus, inhibited its role in autophagy, a process necessary for maintaining lens transparency through degradation of misfolded proteins and damaged organelles. miR-378a is upregulated in human cataract tissues and inhibits LEC proliferation while promoting apoptosis by modulating the ROS/PI3K/AKT signalling pathway (92).

Emerging evidence has indicated that certain miRNAs function as cataract suppressors by preventing lens opacification (68,93,94). Given that ARC pathogenesis is associated with apoptotic cell death in the lens, extensive research has highlighted dysregulated apoptosis of LECs as a key pathogenic mechanism in cataract development (95-97). Bcl-2 family proteins are essential for the intrinsic apoptotic pathway (98). B-cell lymphoma-2-like-2 (BCL2L2), a Bcl-2 family member, is an important regulator of apoptosis (99). Zhang *et al* (93) identified BCL2L2 as a direct target of miR-133b, demonstrating that miR-133b-mediated downregulation of BCL2L2 expression led to apoptosis inhibition. While BCL2L2 promoted apoptosis, miR-133b functioned as an anti-apoptotic regulator by suppressing BCL2L2 expression (93). Likewise, miR-182, which is implicated in various ophthalmic disorders, including pterygium (100), glaucoma (101) and age-related macular degeneration (102), protects LECs against oxidative stress-induced apoptosis by regulating the nicotinamide adenine dinucleotide phosphate oxidase subunit 4 (NOX4) and p38 MAPK signalling pathway (68). Furthermore, miR-125b is downregulated in ARC lens tissue, where it suppresses p53 mRNA expression and exerts anti-apoptotic effects on LECs (94). Although numerous miRNAs have been demonstrated to attenuate lens opacity progression, experimental validation by *in vivo* studies conducted in animals, such as rats or rabbits, remains limited. To the best of our knowledge, only three *in vivo* studies have been reported at present. Administration of antagomirs targeting miR-326 (103), miR-29a-3p (104) and miR-187 (105) independently inhibited cataract formation in animal models of ARC, suggesting their potential as non-surgical therapeutic candidates.

Single nucleotide polymorphisms (SNPs) within miRNA binding sites can affect the base pairing between miRNAs and their target mRNAs, thereby altering miRNA-mediated gene regulation (106). Oxidative DNA damage and impaired DNA repair capacity in LECs are strongly involved in ARC pathogenesis (107,108). Accumulating data have demonstrated that SNPs within miRNA binding sites of oxidative DNA damage repair genes may modulate ARC susceptibility (70,109,110). Zou *et al* (70) systematically analysed 10 miRNA-binding SNPs located in the 3' UTRs of seven oxidative damage-related genes. Their findings demonstrated that the C allele of XPC-rs2229090 increased susceptibility to the nuclear type of ARC (ARNC). Mechanistically, the C allele exhibited stronger binding affinity for hsa-miR-589-5p compared with the G allele, resulting in reduced XPC expression and impaired DNA repair capacity in LECs (70). Furthermore, Kang *et al* (109) demonstrated that the protective effect of Nei-like DNA glycosylase 2 (NEIL2)-rs4639T in ARCs may be mediated through maintenance of normal NEIL2 expression levels, potentially via disruption of the binding of rs4639T with hsa-miR-3912-5p. Additionally, the rs78378222 polymorphism in the p53 3' UTR contributes to ARC pathogenesis by regulating miR-125b-mediated apoptosis in LECs (110). Taken together, these findings suggest that SNP-mediated alterations in miRNA-dependent post-transcriptional regulation constitute a novel pathogenic mechanism in ARCs and reveal novel therapeutic targets.

In general, research on miRNA alterations in ARCs has reached a relatively mature stage, with comprehensive studies demonstrating the crucial roles of miRNAs in mediating LEC lesions *in vitro* and cataract progression *in vivo* (103-105). Exosomal miRNAs have become a research focus; however, their relationship with ARCs remains poorly understood. At present, only two studies have demonstrated the roles of exosomal miR-222-3p in ARC formation and miR-125a-3p in disease progression (66,111). Exosomes are 50-200-nm extracellular nanovesicles derived from multivesicular bodies in the cytoplasm and serve as an important medium of intercellular communication (112,113). Exosomes regulate receptor cells and tissues by transmitting effectors, including proteins, mRNAs or miRNAs (114). Various types of cells can secret miRNAs via exosomes, a process that protects miRNAs from degradation and ensures their function in target cells (115). Exosomes transport miRNAs to target cells without being degraded by RNAses, making exosomal miRNAs more stable and reliable biomarkers than their non-exosomal counterparts (116). Exosomal miRNAs are emerging as promising biomarkers for aging and age-related diseases (117-119). Furthermore, exosomes represent promising drug delivery vehicles due to their inherent advantages, including high biocompatibility, high biological barrier penetration and high circulatory stability (120). Therefore, investigating exosomal miRNAs could help to elucidate the pathogenesis of ARCs, facilitate biomarker identification and enable the development of innovative intervention strategies.

lncRNAs. Alongside short miRNAs, a wide array of longer transcripts, referred to as lncRNAs, has been increasingly characterized. lncRNAs are >200 bp long, and exhibit relatively low expression levels, poor stability and limited evolutionary conservation (121). Therefore, lncRNA research presents considerable challenges due to these inherent molecular characteristics, and is only recently undergoing a surge. Notably, similar to miRNAs, most lncRNAs are associated with human diseases; however, in contrast to their smaller counterparts, lncRNAs exhibit cell type-specific expression patterns and distinct subcellular localization (122). lncRNAs perform diverse regulatory functions, including acting as miRNA sponges, signal mediators, molecular decoys, chromatin modifiers, and regulators of gene expression and pre-mRNA splicing (123,124). Among these functions, their role as competing endogenous RNAs (ceRNAs) or miRNA sponges is particularly significant. The ceRNA hypothesis, first proposed by Salmena *et al* (125) in 2011, suggests that lncRNAs regulate gene expression post-transcriptionally by competitively binding to miRNAs via shared miRNA response elements, thereby preventing miRNA-mRNA interactions. Through diverse molecular mechanisms, lncRNAs regulate critical biological processes such as stem cell maintenance, cellular differentiation and chromatin remodelling, as well as transcription, splicing, translation, degradation and transport of mRNA (126,127). Previous studies have indicated that lncRNAs are highly active in ARCs, where they may

either promote or suppress disease initiation and progression (Table SII) (128-130).

In 2017, Zhang *et al* (131) collected anterior capsular samples from both healthy controls and patients with ARCs and conducted high-throughput sequencing to detect differentially expressed lncRNAs, identifying 7,041 candidate lncRNAs with differential expression. To investigate the comprehensive profile of ncRNAs and their interaction network in cataractogenesis, a study conducted in 2022 employed autophagy-related gene 7 (ATG7)-knockout LECs to inhibit autophagy under oxidative stress conditions, and performed detailed analyses of RNA sequencing data to characterize mRNA and lncRNA expression profiles in LECs exposed to oxidative stress. The authors identified 263 upregulated and 336 downregulated differential lncRNAs between wild-type and ATG7-deficient LECs treated with H_2O_2, among which 24 lncRNAs showed potential interactions with 10 cataract-related miRNAs (132). Collectively, these studies establish that lncRNAs and their associated ceRNA networks (lncRNA-miRNA-mRNA axis) are heavily involved in ARC pathogenesis (131,132).

Emerging evidence has established the pivotal role of numerous lncRNAs as pathogenic drivers in ARC pathogenesis. As aforementioned, lncRNAs can act as ceRNAs or endogenous miRNA sponges, effectively sequestering miRNAs and attenuating their post-transcriptional repression of target mRNAs (125). Building upon this theoretical framework, Jin *et al* (133) experimentally validated miR-214 as a direct target of lncKCNQ1OT1. Their findings demonstrated that lncKCNQ1OT1 knockdown upregulated miR-214 expression and subsequently downregulated the expression of its downstream effector caspase-1, indicating the pathogenic role of the lncKCNQ1OT1/miR-214/caspase-1 axis in cataract formation (133). Furthermore, lncKCNQ1OT1 functions as a molecular sponge for miR-223-3p, which directly targets BCL2L2. Through the lncKCNQ1OT1/miR-223-3p/BCL2L2 axis, lncKCNQ1OT1 promotes apoptosis and pyroptosis, while exacerbating oxidative damage in H_2O_2-treated LECs (134). Another study demonstrated that lncKCNQ1OT1 downregulation protected LECs from oxidative stress-induced damage via the miR-124-3p/BCL-2-like 11 pathway (135). In addition to lncKCNQ1OT1, TUG1 is another well-characterized lncRNA that exacerbates the pathogenesis of ARC, and has been shown to promote apoptosis in H_2O_2 or UV irradiation-treated LECs through three distinct molecular pathways: TUG1/miR-196a-5p (136), TUG1/miR-421/caspase-3 (20) and TUG1/miR-29b/second mitochondria-derived activator of caspases (137). Furthermore, research has identified multiple novel pathogenic lncRNAs, including NEAT1 (129,138), MEG3 (139,140) and OIP5-AS1 (141), with additional candidates expected to emerge as research progresses.

By contrast, other studies have indicated that certain lncRNAs exert protective effects to prevent ARC progression. For example, lncRNA phospholipase C δ3 (PLCD3)-OT1 may act as a ceRNA to promote PLCD3 expression by sponging miR-224-5p, thus promoting cell proliferation and viability, and inhibiting apoptosis, under oxidative stress conditions (142). Similarly, lncRNA NONHSAT143692.2 modulates 8-oxoguanine DNA glycosylase (OGG1) expression in LECs by competitively binding to miR-4728-5p, thereby protecting LECs from cell apoptosis and oxidative damage (130). Furthermore, Cheng *et al* (143) revealed that lncRNA H19 suppressed apoptosis, mitigated oxidative damage, and promoted proliferation and viability in UV irradiation-treated LECs through the functional interplay of lncRNA H19, miR-29a and thymine DNA glycosylase.

Although acting as miRNA sponges represents a well-established function of lncRNAs (144-146), their other regulatory functions are also implicated in cataract pathogenesis. lncRNAs are typically classified into five major classes according to their relative genomic locations: Antisense (AS), intergenic, overlapping, intronic and full lapping (147). Within these lncRNA classes, AS lncRNAs, which are reverse-strand complements of their endogenous protein-coding counterparts, are generally non-protein-coding and account for a substantial proportion of the entire long non-coding transcriptome (148-150). Previous studies have demonstrated that natural AS transcripts participate in diverse biological processes by regulating sense gene expression at multiple levels, including transcriptional regulation via gene promoter activation, and post-transcriptional regulation through mRNA stabilization and translational modulation (151,152). Glutathione peroxidase 3 (GPX3)-AS has been found to upregulate GPX3 expression at both the mRNA and protein levels, enhancing the activity of this ROS scavenger to inhibit LEC apoptosis, thereby revealing a potential therapeutic target for ARCs (153). Furthermore, lncRNAs can also serve as direct precursors for miRNA biogenesis (154). A representative example is lncRNA H19, which serves as the precursor for miR-675, where H19 downregulation leads to reduced miR-675 expression. lncRNA H19 modulates LEC function via miR-675-mediated regulation of crystallin αA (CRYAA) expression, offering novel insights into ARNC pathogenesis (155).

Overall, lncRNAs participate in ARC pathogenesis through multifaceted regulation of LEC biology, including oxidative stress responses and apoptotic pathways. Given their functional versatility and multi-target nature, the precise roles and regulatory networks of several lncRNAs in ARC pathogenesis have yet to be comprehensively characterized. Furthermore, although *in vitro* experiments offer valuable mechanistic insights, their translational relevance to whole organisms remains limited. To the best of our knowledge, no *in vivo* models investigating lncRNAs in ARCs have been reported at present. Animal models, which better recapitulate the complexity of physiological systems, are crucial for validating the observed *in vitro* effects.

circRNAs. circRNAs are single-stranded, covalently closed RNA molecules without 5' caps and 3' poly-A tails, and are usually produced through a back-splicing process (156,157). The absence of both 5' caps and 3' polyadenylated tails renders circRNAs resistant to exonuclease-mediated degradation, thus ensuring their stability and longevity in cellular processes (158). circRNAs possess distinctive properties and diverse functions that continue to be elucidated. Similar to lncRNAs, circRNAs can function as efficient miRNA sponges, representing one of their most well-characterized regulatory modes (159-161). Beyond their well-known role as miRNA sponges, studies have revealed that circRNAs can also interact with RNA-binding proteins (162), regulate RNA splicing and transcription (163,164), and undergo translation into functional peptides or proteins (165,166). circRNAs also participate in

a wide range of biological processes, including fibrosis, cell apoptosis, proliferation, differentiation and angiogenesis (167). In recent years, their roles as vital regulators in multiple ocular diseases have attracted increasing attention (168-170). Similar to linear ncRNAs, circRNAs are implicated in cataract formation (Table SIII) (171-173). The circRNA/miRNA/mRNA regulatory network has advanced the understanding of the molecular basis of cataractogenesis.

Studies have characterized specific circRNAs that contribute to ARC pathogenesis. For example, hsa_circ_0105558 promotes apoptosis and aggravates the oxidative damage of LECs under H_2O_2 exposure through the miR-182-5p/activating transcription factor 6 axis (174). hsa_circ_0007905 upregulates eukaryotic translation initiation factor 4E binding protein 1 (EIF4EBP1) expression by competitively binding to miR-6749-3p, consequently enhancing LEC apoptosis while inhibiting LEC proliferation, resulting in ARC progression (175). Notably, hsa_circ_0007905 expression in LECs is upregulated through methyltransferase like 3 (METTL3)-mediated m^6A modification (175). A comprehensive discussion of m^6A modifications of circRNAs is presented in the m^6A modification section. Notably, circMRE11A_013 (circMRE11A) acts primarily as a molecular scaffold that interacts with UBX domain-containing protein 1 rather than functioning as a miRNA sponge, and promotes excessive activation of ataxia-telangiectasia mutated kinase (ATM), ultimately inducing LEC cell cycle arrest and senescence through the ATM/p53/p21 signalling pathway (176). Furthermore, recombinant adeno-associated virus vector virions of circMRE11A have been injected into the mouse vitreous cavity, providing *in vivo* evidence that circMRE11A drives lens aging and opacification in mice (176). In addition to circMRE11A, circSTRBP (hsa_circ_0088,427) exerts its biological effects independently of miRNA sponging activity by interacting with insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1), and enhances the stability and expression of NOX4 mRNA in LECs (171). circSTRBP exacerbates H_2O_2-induced oxidative stress and apoptosis in LECs by enhancing NOX4 mRNA stability through IGF2BP1 recruitment, providing novel perspectives for ARC intervention (171).

Emerging evidence has identified multiple protective circRNAs in ARC pathogenesis, with several candidates exhibiting potent antioxidant and anti-apoptotic effects in LECs. circRNA homeodomain interacting protein kinase 3 (circHIPK3) promotes viability and proliferation, inhibits apoptosis, and alleviates oxidative damage in H_2O_2-treated LECs via three distinct molecular pathways: circHIPK3/miR-221-3p/PI3K/AKT (177), circHIPK3/miR-193a/CRYAA (178) and circHIPK3/miR-495-3p/histone deacetylase 4 (HDAC4) (179). circ_0060,144 regulates HIPK3 expression by sponging miR-23b-3p, thereby influencing LEC homeostasis through regulation of proliferation, apoptosis and the oxidative stress response (180). UV radiation downregulates circRNA erythrocyte membrane protein band 4.1 expression, which subsequently reduces 3'(2'), 5'-bisphosphate nucleotidase 1 levels via miR-24-3p binding, thus inhibiting proliferation and promoting apoptosis in LECs (181). Furthermore, circRNA 06209 acts as a ceRNA by sequestering miR-6848-5p to neutralize its suppressive effect on arachidonate 15-lipoxygenase, ultimately promoting proliferation and inhibiting apoptosis in H_2O_2-treated LECs (182). Notably, injection of a circRNA_06209-overexpressing plasmid into a Na_2SeO_3-induced cataract model attenuated lens opacity while reducing insoluble protein aggregation and increasing soluble protein levels in the lens, demonstrating the anti-cataract efficacy of circRNA_06209 in both *in vitro* and *in vivo* settings (182).

Given that circRNAs exhibit high stability, evolutionary conservation across species and tissue specificity (183), investigating ARC-related circRNAs as potential biomarkers or therapeutic targets could open novel avenues for the diagnosis, prevention and treatment of ARCs. However, only a limited number of circRNAs in ARCs have well-characterized biological functions and mechanistic pathways. While circRNAs employ diverse molecular mechanisms and functions, current research on their roles in ARCs has largely focused on their function as miRNA sponges and their interactions with proteins (171,174,184-186), suggesting that novel functions or mechanisms remain to be identified.

tsRNAs. tsRNAs constitute a family of small ncRNAs produced by the cleavage of precursor or mature transfer RNAs (tRNAs) via specific endonucleases (187). tsRNAs are mainly classified into two types: tRNA halves and tRNA-derived fragments, based on the cleavage position of the precursor or mature tRNAs (188). Advances in high-throughput sequencing technologies have revealed that tsRNAs serve crucial roles in the regulation of gene expression, post-transcriptional modifications, apoptotic inhibition and protein translation (189-191), while their dysregulation contributes to various pathological processes in diseases such as cancer, cardiovascular diseases and Alzheimer's disease (192-194). Investigations have begun to reveal the crucial involvement of tsRNAs in ophthalmic diseases (195-197). Through integrated next-generation sequencing analysis, a study conducted in 2022 systematically established the first evidence of the changes in tsRNA profiles in Emory mice, a well-characterized model for human ARCs (198). A total of 422 differentially expressed tsRNAs were identified in 8-month-old mice (156 upregulated and 266 downregulated), with Gene Ontology (GO) analysis revealing that these target genes were predominantly enriched in processes including but not limited to camera-type eye development and sensory organ development (198). As tsRNA research remains in its infancy, further investigations focusing on the association between tsRNAs and ARCs, as well as their underlying molecular mechanisms, are needed to provide novel insights into cataractogenic processes and ARC disease management.

ncRNA regulatory networks. Understanding ncRNA functions in isolation becomes increasingly difficult due to intricate regulatory networks among ncRNAs. These networks involve multiple layers of interaction: ncRNAs frequently share common protein-coding mRNA targets; miRNAs functionally interact with other ncRNA species rather than operating in isolation; and lncRNAs and circRNAs, in turn, regulate the abundance of available miRNAs (199). ncRNA networks serve a pivotal role in ARC pathogenesis by modulating gene expression, oxidative stress responses and pathological processes in LECs, indicating potential targets for early diagnosis and therapeutic intervention (134,200).

In addition to the networks among different types of ncRNAs, such as the aforementioned ceRNAs, interactions also exist between the same type of ncRNAs. Emerging research across various diseases, including cancers and cardiovascular diseases, has revealed that certain miRNAs can be involved in the same biological pathways either as effectors or regulators (201). Krek *et al* (202) demonstrated that myotrophin (*Mtpn*) was a direct target of miR-124, let-7b and miR-375, as evidenced by small interfering RNA (siRNA)-mediated downregulation of *Mtpn* protein levels and suppression of luciferase activity in dual-luciferase reporter assay. Cotransfection of the luciferase reporter and a pool of siRNA duplexes designed to mimic the function of miR-124, let-7b and miR-375, resulted in normalized luciferase activity that was substantially less than the activity in any of the groups transfected with a single siRNA, revealing cooperative regulation of *Mtpn* by these miRNAs (202). Similarly, lncRNAs could interact with each other by co-regulating genes participating in the same or similar biological functions (203). Multiple lncRNAs, such as OIP5-AS1, TUG1 and NEAT1, have been implicated in the synergistic regulation of genes and pathways in cancer (204). Current research on ncRNAs in ARCs primarily focuses on their dysregulation in ARCs and the ceRNA mechanism (104,140,174,205). The cooperative interactions among ncRNAs remain poorly characterized and require further analyses and validation to achieve a comprehensive understanding of the cooperative behaviours of ncRNAs in ARC pathogenesis.

DNA methylation. DNA methylation, a fundamental epigenetic modification, stably modulates gene expression through heritable regulatory mechanisms, influencing diverse physiological processes and disease pathogenesis (206). In mammals and humans, DNA methylation critically participates in numerous biological processes, including genomic imprinting (207), X-chromosome inactivation (208), transcriptional regulation (209) and tumorigenesis (210). DNA methylation is a covalent chemical modification involving the selective addition of methyl groups to DNA molecules, catalysed by DNA methyltransferases (211). Although DNA methylation occurs at various sites, including the C5 position of cytosine (212), N6 position of adenine (213) and N7 position of guanine (214), 5-methylcytosine (m^5C) remains the most prevalent and extensively studied modification in humans, representing the principal focus of DNA methylation research (215-217). The term 'DNA methylation' in general primarily refers to the methylation of the 5th carbon atom of cytosine within cytosine-phosphate-guanine (CpG) sites, yielding m^5C (215,218).

CpG sites, consisting of cytosine-guanine dinucleotides, are distributed throughout the genome (219). These sites frequently cluster in CpG islands, genomic regions with a high density of CpG dinucleotides, which are predominantly located near gene promoters (220). CpG islands are critical regulatory elements for gene expression, as promoter DNA methylation can inhibit transcription factor binding or recruit methyl-CpG binding domain (MBD) proteins and HDACs, ultimately inducing gene silencing (221,222). Hypermethylation of CpG islands in promoter regions is strongly associated with transcriptional silencing, whereas unmethylated states are typically associated with active gene expression (108,223).

DNA methylation is catalysed and maintained by DNA methyltransferases (DNMTs) (224). DNMTs can be classified into two functional types: Maintenance DNA methyltransferase (DNMT1), which preserves the epigenetic inheritance of DNA methylation patterns during DNA replication, and *de novo* methyltransferases (including DNMT3A and DNMT3B), which establish new methylation patterns during development (225). During DNA methylation, cytosine protrudes from the DNA double helix into a cleft that can bind to the enzyme. Cytosine methyltransferase catalyses the transfer of an active methyl group from S-adenosylmethionine (SAM) to the C5 position of cytosine, forming m^5C (218). This modification alters gene expression without changing the DNA sequence and is one of the most important epigenetic regulatory mechanisms (226).

Previous studies in ophthalmology have indicated that aberrant DNA methylation disrupts the expression of key genes, such as *RHO*, *OPN1LW* and *TUBA1A* (227,228), contributing to the pathogenesis of various ocular diseases, such as corneal and conjunctival disorders, glaucoma (229), cataracts (230), retinal diseases (231), and ocular tumours (232). As the leading global cause of blindness, cataracts, particularly ARCs, serve as a paradigm of ocular aging, wherein epigenetic dysregulation synergizes with cumulative environmental stressors, including UV radiation and chemical exposures (233,234). While congenital and traumatic cataracts result from genetic mutations or physical injury, ARCs stem from progressive lens opacification associated with multiple factors, including oxidative stress, protein aggregation, and critically, DNA methylation-mediated silencing of protective genes in LECs (Table SIV) (108,235,236). For example, age-dependent hypermethylation of the Klotho gene, a key anti-aging factor, progressively silences its expression, leading to marked reduction or even complete loss of Klotho expression at both mRNA and protein levels, ultimately participating in ARC pathogenesis (237). Furthermore, both mRNA and protein expression of DNA methylation-related genes (DNMT3B and MBD3) are elevated in LECs of ARCs, further substantiating the involvement of DNA methylation in ARC development (238).

To characterize the epigenetic landscape of ARCs, several studies have examined genome-wide methylation patterns in ARC samples. Chen *et al* (239) employed the MethylationEPIC BeadChip (850K) to profile DNA methylation in anterior lens capsule membranes from patients with ARCs and control subjects. By integrating GO and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses with their previously published transcriptome sequencing data, the authors identified differentially methylated genes. Their analysis revealed 52,705 differentially methylated sites in the ARC group (13,858 hypermethylated and 38,847 hypomethylated) compared with the control group, which consisted of non-ARC patients, with GO and KEGG analyses highlighting functional associations with cell membrane components, calcium signalling pathways and their potential molecular mechanisms (239). Similarly, a study conducted in 2018 used DNA methylation microarrays, a high-throughput sequencing approach, to identify methylated genes, and revealed that aberrant methylation of collagen type IV α1 chain (COL4A1),

gap junction protein α3 and signal induced proliferation associated 1 like 3 was associated with ARCs (240). Further investigation is warranted to elucidate the role of these DNA methylation changes in ARC pathogenesis.

Oxidative stress is a well-established driver of LEC pathophysiology and a key contributor to ARC pathogenesis (7-9). Emerging evidence has further linked oxidative stress-induced DNA damage in LECs to cataract formation (241,242). Therefore, DNA methylation-mediated dysregulation of oxidative stress-related genes and DNA damage repair genes has emerged as a primary research focus, given its pivotal role in ARC development.

Oxidative stress-related genes. Methylation changes in oxidative stress-related genes, as epigenetic modifications of the antioxidant defence system, likely contribute to oxidative stress-induced lens damage in ARC (223,235,243).

One of the main antioxidant defence mechanisms is nuclear factor erythroid 2-related factor 2 (Nrf2) activation. Nrf2 is a central nuclear transcriptional factor, which controls the transcription of >200 protective genes, including 20 genes encoding antioxidant enzymes (244). The activity of the Nrf2 pathway is regulated through multiple mechanisms, both upstream and downstream, as well as by other signalling pathways (245). Kelch-like ECH-associated protein 1 (Keap1) is an oxidative stress sensor and a negative regulator of Nrf2 (246). Under basal conditions, Keap1 binds to Nrf2 in the cytoplasm, promoting its ubiquitin-mediated proteasomal degradation, and thus, maintaining Nrf2 at basal levels (247). During oxidative stress, elevated ROS disrupt the Keap1-Nrf2 interaction, enabling Nrf2 nuclear translocation. Within the nucleus, Nrf2 binds to antioxidant response elements in target gene promoters, inducing the expression of antioxidant enzymes that mediate ROS clearance (248). The Nrf2/Keap1 pathway serves as a master regulator of redox homeostasis, orchestrating the expression of key antioxidant enzymes, including heme oxygenase-1, GPX and superoxide dismutase (SOD), to mitigate oxidative damage (249,250).

The Nrf2/Keap1 pathway is a critical regulator of antioxidant defence in the lens, and its dysregulation may contribute to ARC pathogenesis (246). Age-dependent demethylation of the Keap1 promoter (223) upregulates Keap1 expression, enhancing Nrf2 proteasomal degradation and impairing Nrf2-mediated antioxidant defences. This redox imbalance, driven by Keap1 promoter demethylation, gives rise to ROS accumulation in LECs, ultimately promoting ARC development (223). The methylation status of the Keap1 promoter can be influenced by multiple exogenous and endogenous compounds. Valproic acid (VPA), an antiepileptic drug, alters the expression profiles of passive DNA demethylation pathway enzymes such as Dnmt1, Dnmt3a and Dnmt3b, and the active DNA demethylation pathway enzyme ten-eleven translocation 1 (TET1), leading to DNA demethylation in the Keap1 promoter of LECs (251). Similarly, sodium selenite, a widely used experimental cataract-inducing agent, suppresses Nrf2-dependent antioxidant protection while facilitating lenticular protein oxidation and cataract formation (246). Furthermore, methylglyoxal treatment in LECs results in loss of Keap1 promoter methylation and impairment of the Nrf2-dependent antioxidant system (252). By contrast, ferulic acid, a compound with well-documented antioxidant activity (253-255), protects LECs against ultraviolet A-triggered oxidative stress via inhibition of Keap1 promoter demethylation (245). Furthermore, co-treatment with exogenous acetyl-L-carnitine effectively counteracts homocysteine (Hcy)-induced Keap1 gene demethylation in LECs, while regulating Nrf2/Keap1 mRNA expression, restoring antioxidant protein levels and mitigating Hcy-driven ROS overproduction (256).

Under physiological conditions, the lens maintains high endogenous glutathione (GSH) levels, which serve an essential role in antioxidant defence by scavenging ROS and preserving proteins in their reduced state (257). GSH-S-transferases (GSTs) are a diverse group of phase II detoxification enzymes that catalyse the conjugation of GSH to both endogenous oxidative stress products and exogenous electrophilic compounds (258,259). All eukaryotic species possess multiple cytosolic and membrane-bound GST isoenzymes, and the cytosolic enzymes are encoded by at least five distantly related gene families (α, μ, π, σ and θ classes) (260). Furthermore, several GST isozymes modulate the MAPK signalling cascade, which mediates cellular responses to oxidative stress (261,262).

GSH S-transferase Mu 3 (GSTM3), a member of the μ-class subfamily, exhibits potent antioxidant activity (263). Li *et al* (243) investigated GSTM3 expression and epigenetic regulation in LECs and lens cortex tissues from patients with ARCs. Their findings revealed GSTM3 downregulation in ARC lenses compared with transparent lenses extracted from patients with vitreoretinal diseases, concomitant with hypermethylation of its promoter region (243). Given the critical role of GSTM3 in antioxidant defence, GSTM3 dysfunction induced by promoter methylation may impair cellular redox homeostasis, thereby exacerbating oxidative stress-mediated lens damage (243). In addition to GSTM3, π-class GSH S-transferase pi-1 (GSTP1) participates in the removal of oxidative adducts by transferring them to GSH (235). GSTP1 mRNA and protein levels are decreased in the lens epithelium and cortex of patients with ARNC compared with age-matched controls, consistent with hypermethylation of GSTP1 promoter CpG islands, suggesting a potential role for GSTP1 epigenetic alterations in ARC lenses (235).

DNA repair genes. Excessive ROS induce extensive oxidative DNA lesions in LECs (264), and oxidative stress-induced DNA damage is recognized as a pivotal factor in ARC pathogenesis (265). Higher levels of 8-hydroxy-2-deoxyguanosine, an established biomarker of oxidative DNA damage, have been observed in ARC lenses compared with normal controls (266). DNA repair pathways are essential for repairing DNA damage, which includes nucleotide excision repair (NER), base excision repair (BER), double-strand break (DSB) repair and direct repair, and their normal functions mainly depend on the expression and function of DNA repair genes (267,268).

NER is a highly conserved DNA repair pathway responsible for processing helix-destabilizing and/or -distorting DNA lesions, such as UV-induced photoproducts (269). During NER, Cockayne syndrome complementation group B (CSB), encoded by the ERCC6 gene, recruits NER repair factors to DNA damage sites and facilitates subsequent repair (67). CSB protein deficiency has been implicated in Cockayne syndrome (270). The expression of ERCC6 at both mRNA and protein levels is reduced in LECs of ARNCs, and

is associated with methylation of a CpG site in the ERCC6 promoter, suggesting epigenetic regulation of ERCC6 in LECs of ARNCs (108). Furthermore, ultraviolet-B (UVB) exposure contributes to ARNC development by inducing DNA damage, which is typically repaired via the NER mechanism (108). UVB-treated human lens epithelium B3 (HLE-B3) and 239T cells exhibit hypermethylation at the-441 CpG site (relative to the transcription start site) within the Sp1 transcription factor binding region of the ERCC6 promoter, along with increased recruitment of DNMT3B to this site (108).

OGG1 is a key enzyme in the BER pathway that specifically recognizes and excises the oxidatively damaged base 8-oxo-7,8-dihydroguanine, a mutagenic lesion that induces G:C→T:A transversions (271). Loss of functional OGG1 is associated with the pathogenesis of multiple age-related diseases, including Alzheimer's disease, age-related macular degeneration and ARCs (272-274). Hypermethylation of the first-exon CpG island of the OGG1 gene has been observed in the lens cortex of ARCs, and was associated with low OGG1 expression and impaired DNA repair function, and eventually contributed to lens opacity (275).

In addition, two other DNA repair genes exhibit epigenetic silencing in ARC: The Werner syndrome gene (WRN) and O6-methylguanine-methyltransferase (MGMT). WRN, which maintains genomic stability by repairing DNA DSBs (276), is hypermethylated in the promoter CpG island of ARC anterior lens capsules and its expression is decreased compared with those in normal controls (43). Similarly, MGMT, an enzyme that removes mutagenic adducts from the O-6 position of guanine, thereby protecting the genome against guanine-to-adenine transitions (277), has been observed to be hypermethylated and downregulated in ARCs (278). These deficiencies lead to the accumulation of unrepaired DNA lesions, driving cell dysfunction and genomic instability, which further promotes ARC progression (108).

Other genes. Numerous studies have established the indispensable role of lens crystallins in maintaining lens clarity, optical transparency and refractive function (279,280). CRYAA and αB-crystallin, the subunits of oligomeric α-crystallin, constitute ~35% of total lens proteins (281). In addition to serving as a major structural protein component of the lens, CRYAA exhibits molecular chaperone-like activity that protects other crystallins from thermally induced inactivation or aggregation, thereby being essential for maintaining lens transparency (280-282). Furthermore, CRYAA mediates cytoprotective effects against both thermal and oxidative stress in LECs (283), and a study has demonstrated that CRYAA can delay cataract formation by trapping denatured proteins prone to aggregation (279). CRYAA expression levels have been reported to be reduced in ARC lenses, with hypermethylation of the CRYAA gene promoter CpG islands representing a key mechanism for CRYAA downregulation (230). Evidence indicates that methylation of CpG sites in the CRYAA promoter directly reduces the DNA-binding capacity of the transcription factor Sp1 (236). Treatment with the DNA demethylating agent zebularine increases CRYAA expression in LECs, suggesting a potential novel therapeutic strategy for ARCs (230,236).

COL4A1 encodes the α1 chain of type IV collagen, the major collagen component of basement membranes (284). Genome-wide methylation analysis has revealed hypermethylation of the COL4A1 promoter region in anterior lens capsule samples from patients with ARCs (240). In both HLE-B3 cells and anterior lens capsules of rats, UVB irradiation induces DNA hypermethylation of COL4A1 promoter CpG islands, and thus, suppresses COL4A1 expression, indicating that epigenetic alterations of the COL4A1 promoter might be involved in UVB-induced lens damage in ARCs (285).

In summary, emerging evidence has highlighted the role of DNA methylation in the pathogenesis of ARCs, linking epigenetic dysregulation to oxidative stress, DNA damage and cellular dysfunction of LECs. Aberrant DNA methylation patterns in key genes may serve as potential biomarkers or therapeutic targets. Further studies based on large-scale clinical research and model systems are needed to identify and validate additional methylation signatures, elucidate underlying mechanisms and explore targeted epigenetic interventions.

Histone modification. As essential structural components, histone proteins form the fundamental building blocks of chromatin. Histones undergo posttranslational modifications (PTMs), which modulate their affinity for DNA, and thus, influence chromatin compaction states (286). These modifications are highly dynamic and continuously changing in response to histone-modifying enzyme activity, ultimately generating specific PTM patterns linked to epigenetic diseases (287). Posttranslational histone modifications include acetylation, methylation, phosphorylation, citrullination, ubiquitination and adenosine diphosphate ribosylation (288,289). Of these, histone acetylation and methylation have been most extensively studied, with substantial evidence supporting their associations with ARCs (Table SV) (43,108,235,243,290).

Histone acetylation is a reversible modification of multiple lysine residues on histone tails, and dynamically regulated by histone acetyltransferases (HATs) and HDACs (291). HATs are a class of enzymes that catalyse the transfer of acetyl groups to lysine residues on histone tails, promoting transcriptional activation by disrupting the interaction between histone tails and nucleosomal DNA, thus facilitating chromatin opening (292). By contrast, HDACs catalyse the removal of acetyl groups from histone tails and suppress transcriptional activity by producing a more condensed chromatin state (293). To date, HDACs have been classified into four major groups (classes I-IV) (294). Among these, SIRT1, a class III NAD^+-dependent deacetylase and a member of the sirtuin family, may be critical in protecting against oxidative stress-induced ocular damage, including ARCs (295). Notably, SIRT1 expression is upregulated in human ARCs, suggesting a compensatory mechanism in response to stressors such as UV radiation and oxidative damage. This upregulation may confer protection by modulating oxidative stress responses and inhibiting apoptosis of LECs (296,297).

Histone methylation refers to the transfer of methyl groups from SAM to specific lysine or arginine residues on histone proteins (298). This epigenetic modification is catalysed by histone methyltransferases, while its removal is mediated by histone demethylases (299). Lysine residues can undergo mono-, di- or tri-methylation, whereas arginine methylation is limited to mono- or di-methylated states (299).

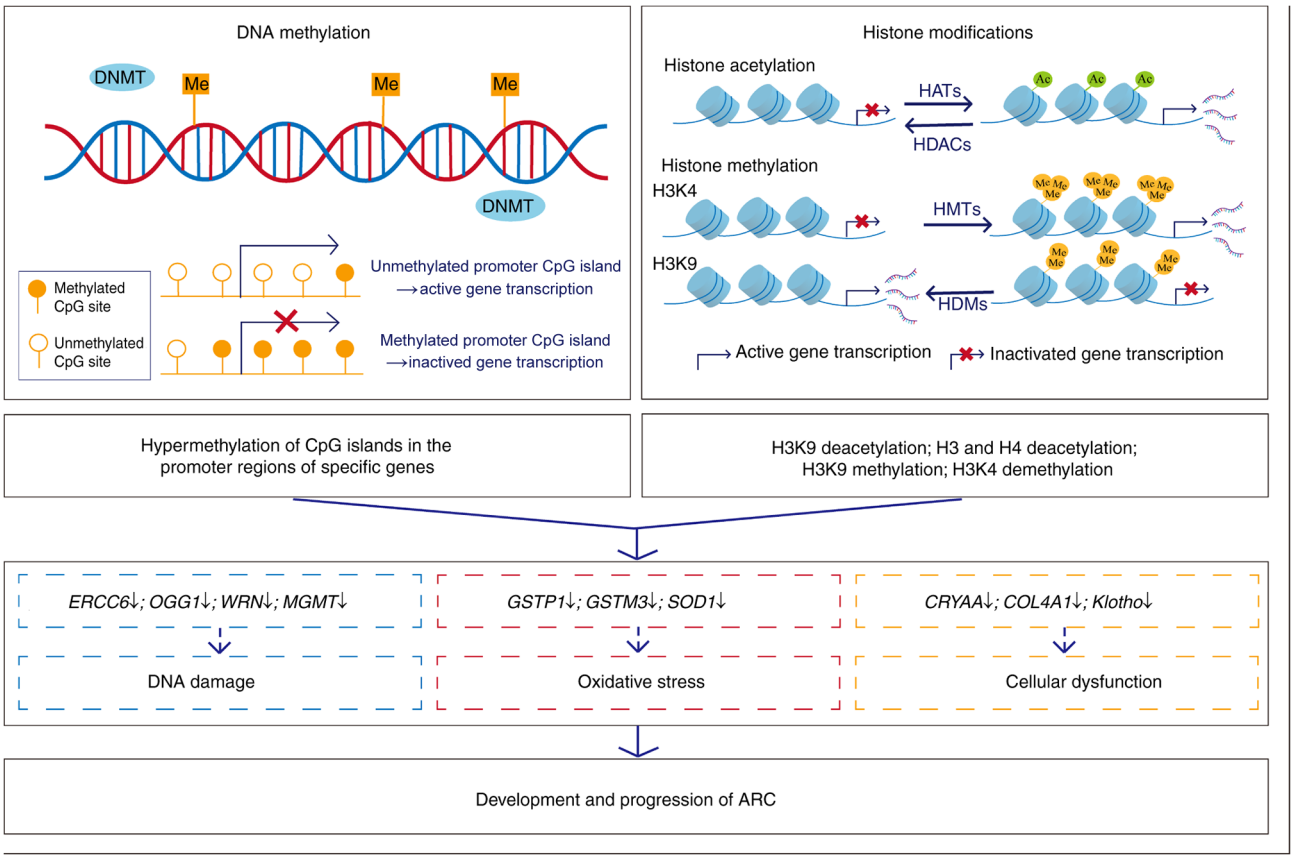

Figure 2. DNA methylation and histone modifications in ARC pathogenesis. ARC, age-related cataract; DNMT, DNA methyltransferase; Me, methyl group; HAT, histone acetyltransferase; Ac, acetyl group; HMT, histone methyltransferase; HDAC, histone deacetylase; HDM, histone demethylase; ERCC6, excision repair cross-complementing rodent repair deficiency, complementation group 6; OGG1, 8-oxoguanine DNA glycosylase 1; WRN, Werner syndrome gene; MGMT, O6-methylguanine-DNA methyl-transferase; GSTP1, glutathione S-transferase P1; GSTM3, glutathione S-transferase Mu 3; SOD1, superoxide dismutase 1; CRYAA, crystallin αA; COL4A1, collagen type IV α1 chain.

The functional impact of histone methylation on transcriptional regulation depends on both the modified residue and the degree of methylation (298). For instance, methylation at H3K4, H3K36 and H3K79 is associated with transcriptional activation, whereas methylation at H3K9, H3K27 and H4K20 promotes transcriptional repression (300). As histone methylation can either activate or repress gene expression, it serves as a critical regulator of transcriptional activity in LECs (235).

Histone modifications, along with DNA methylation, influence the expression of certain genes in LECs. Dysregulation of these genes exacerbates oxidative stress damage and DNA damage while impairing normal cellular functions, thereby promoting the development and progression of ARC (43,108,235-237,243,275,278,285,290) (Fig. 2). Notably, numerous genes implicated in ARCs are dually regulated by both DNA methylation and histone modifications (43,108,235,243). These epigenetic mechanisms do not operate in isolation but instead engage in dynamic crosstalk, wherein each modification reciprocally enhances or inhibits the other to modulate gene expression (301). For instance, one study has demonstrated that endogenous DNMT3A and DNMT3B are associated with HDAC activity, where DNMT3A facilitates transcriptional repression via specific molecular interactions between its ATRX-like PHD domain and both HDAC1 and the co-repressor RP58 (302). Consequently, future research examining the effects of DNA methylation and histone modifications on target genes should systematically consider the crosstalk between these two epigenetic mechanisms.

m^6A modification. Similar to DNA modifications, RNA modifications are dynamically regulated by specific enzymes that catalyse the addition or removal of chemical groups on RNA nucleotides. These modifications serve critical roles in molecular processes, including pre-mRNA splicing, nuclear export, transcript stability maintenance and translation initiation (303). Prevalent RNA modifications include m^6A, N1-methyladenosine, m^5C and 7-methylguanosine (m^7G) (304). Among these modifications, m^6A is the best-characterized modification, and is the primary focus in this section.

m^6A modification refers to the addition of a methyl group to the sixth nitrogen atom of adenosine (305), which regulates diverse cellular processes during development, differentiation and disease (306). m^6A modification is predominantly found in RRACH motifs (R=A/G; H=A/C/U) within the transcriptome, and shows enrichment in coding sequences, 3' UTRs and particularly the region around the stop codon (307,308). m^6A modification is a reversible and dynamic RNA modification added by 'writers', such as METTL3, METTL14 and Wilms tumor associated protein, and removed by 'erasers', including fat-mass and

obesity-associated protein and α-ketoglutarate-dependent dioxygenase alkB homologue 5 (ALKBH5) (303). The 'readers', which recognize m^6A methylation, mainly consist of IGF2 mRNA binding proteins (IGF2BP1/2/3), the YTH domain protein family (YTHDC1/2 and YTHDF1/2/3) and the heterogeneous nuclear ribonucleoprotein family (HNRNPC and HNRNPG) (309). m^6A modification is involved in cell proliferation, apoptosis and oxidative stress, which leads to the development of various ocular diseases, including ARCs (310,311). Research has revealed the role of m^6A modification dysregulation in ARC pathogenesis, where it modifies the epigenetic profile of the lens genome, thus increasing the susceptibility to ARCs (41).

In eukaryotic mRNA, m^6A is the most abundant post-transcriptional RNA modification, regulating RNA translation, splicing, stability and translocation through interactions with its methyltransferase, demethylase and methyl-binding protein (312). For example, METTL14 has been identified as a factor promoting m^6A modification of NEIL1, which leads to YTHDF2 recruitment, facilitating NEIL1 mRNA degradation, and ultimately compromising the protective functions of NEIL1 against oxidative damage, apoptosis and mitochondrial dysfunction (313). Furthermore, METTL3 elevates CPB1 expression by regulating the methylation levels of BACH transcriptional regulator 2, thereby accelerating apoptosis and oxidative stress in H_2O_2-treated LECs (311).

Emerging studies have demonstrated that m^6A modifications are widely present in circRNAs and lncRNAs (41,175,314,315). A study conducted in 2020 reported decreased m^6A abundance in total circRNAs from LECs of patients with ARCs, while m^6A regulators, including ALKBH5 and METTL14, were upregulated in ARC samples compared with normal controls (41). In 2023, Li *et al* (175) investigated the function and mechanism of m^6A modification of circRNAs in ARCs for the first time, and found that METTL3-mediated m^6A modification of hsa_circ_0007905 promoted apoptosis and inhibited the proliferation of LECs through the miR-6749-3p/EIF4EBP1 axis, contributing to ARC progression. Similar to circRNAs, m^6A methylation levels of lncRNAs could serve important roles in ARC pathogenesis, as confirmed by methylated RNA immunoprecipitation sequencing and RNA sequencing performed on ARC tissues (314). Furthermore, m^6A-modified lncRNA ENST00000586817 might regulate the expression of GPX4 through a cis mechanism and could thus be involved in ferroptosis in ARCs (315).

Research on the role and molecular mechanisms of m^6A modification in ARC progression remains in its early stages, and further investigation is required to identify more potential molecular targets to develop intervention strategies against ARCs. m^6A modification is regulated by methyltransferases, demethylases and m^6A recognition proteins, and consequently, the phenotypic changes of LECs in ARC pathogenesis may result from the combined effects of various m^6A modifications, necessitating further studies to elucidate the underlying regulatory networks. In addition, other types of RNA modifications, including m^5C and m^7G, may be implicated in certain ocular disorders such as uveal melanoma and ocular angiogenesis (304,316,317), and their potential connections with ARCs remain to be explored.

Epigenetic modifications and oxidative stress in ARCs. Oxidative stress is a well-documented etiological factor in ARCs (7-9), and thus, it is critical to further investigate the interplay between oxidative stress and epigenetic modifications in ARC pathogenesis.

Epigenetic regulation is implicated in oxidative stress-related processes crucial in the initiation and development of ARCs (223). ncRNA networks regulate the expression of oxidative stress-related genes such as NOX4, SIRT1 and GPX4, and aberrant levels of ncRNAs alter the levels of pro-oxidant markers and antioxidant enzymes in LECs (68,79,140). Clinically, associations have been observed between abnormal ncRNA expression and changes in oxidative stress markers in patients with ARCs (76). Wu *et al* (318) explored the relationship between miRNAs and oxidative stress-related genes, and found that cataract-regulated miRNAs could promote cataract formation not only by targeting the 3' UTR, which is a classic regulatory pathway, but also by binding to the TATA-box region of oxidative stress-related genes, leading to the subsequent elevation of pro-oxidative genes and inhibition of anti-oxidative genes. Furthermore, numerous critical genes that serve protective roles in oxidative stress processes, such as GSTP1, GSTM3 and SOD1, are regulated by DNA methylation and histone modifications (235,243,290). Additional oxidative stress-related genes implicated in ARC pathogenesis remain to be fully characterized, particularly regarding their functional contributions to disease progression and regulation through epigenetic mechanisms.

Oxidative stress induced by exogenous stimuli can also induce epigenetic alterations, since ROS can regulate the activity of epigenetic enzymes involved in DNA, RNA and histone modifications (319-321). For example, UVB exposure induces the recruitment of DNMT3b and HDAC1 at the ERCC6 promoter, thereby resulting in epigenetic alterations, including specific hypermethylation of the CpG site and H3K9 deacetylation of ERCC6 in LECs (108). At both cellular and organismal levels, UVB exposure enhances the expression of DNMTs, including DNMT1/2/3, and reduces the expression of TETs, including TET1/2/3, leading to hypermethylation of COL4A1 promoter CpG islands and subsequent inhibition of COL4A1 expression (285). Furthermore, ROS can directly induce the oxidation of m^5C to 5-hydroxymethylcytosine (5hmC) (322). 5hmC may activate DNA demethylation processes and serve as an intermediate of DNA demethylation, thus causing DNA hypomethylation (322). Numerous studies have indicated that dysregulation of 5hmC could be involved in multiple diseases, including cancer and neurodegenerative diseases (323,324). However, the association between 5hmC and ARCs remains to be fully elucidated.

3. Epigenetic regulation for the treatment of ARCs

Epigenetic modulators, including DNA methyltransferase inhibitors (DNMTis) and histone deacetylase inhibitors (HDACis), represent a novel class of therapeutic agents capable of correcting aberrant epigenetic modifications, providing innovative intervention strategies against molecular defects underlying cancer and other diseases. These compounds offer unique therapeutic advantages due to their reversible and targetable nature, enabling precise gene regulation without

modifying DNA sequences (325-327). The DNMTis azacitidine and decitabine are approved by the US Food and Drug Administration (FDA) for the treatment of myelodysplastic syndromes and acute myeloid leukaemia, and exert their effects by inhibiting DNMTs and reversing tumour-suppressor gene silencing through DNA demethylation (328,329). Several other epigenetic drugs, such as vorinostat, belinostat and romidepsin, are FDA-approved for the treatment of cutaneous T-cell lymphoma and peripheral T-cell lymphomas (330-332). Although DNMTis and HDACis have been extensively tested in clinical and preclinical trials for human diseases (333-335), their effects in ARCs remain poorly understood. The DNMTi 5-aza-2'-deoxycytidine (decitabine) restores the transcriptional activities of GSTP1 in LECs (235), and trichostatin A (TSA; HDACi) corrects the anacardic acid (HAT inhibitor)-induced imbalance between HATs and HDACs, causing increased SOD1 expression by reversing histone acetylation (290). These findings provide evidence that DNMTis and HDACis could rescue LECs from dysregulated expression of key genes induced by aberrant epigenetic alterations during ARC development. Notably, HDACis also exhibit antioxidant properties, as evidenced by multiple studies (336,337). Qiu *et al* (338) compared the protective effects of four HDACis, β-hydroxybutyrate, TSA, suberoylanilide hydroxamic acid (SAHA) and VPA, on HLECs following UVB exposure, and found that low concentrations of HDACis (1 μmol/l SAHA) mildly attenuated oxidative stress. Although these promising *in vitro* findings support these drugs as possible candidates for ARC intervention, further validation through well-controlled *in vivo* studies is required for their clinical application.

Alterations in the expression patterns of various ncRNAs have been reported in ARCs (41,72,131,198), suggesting that targeted modulation of aberrant ncRNA activity may hold therapeutic potential. Over the past decade, miRNA mimics and anti-miRNAs have demonstrated therapeutic promise in clinical trials for various diseases, such as advanced solid tumours, ulcerative colitis and hepatitis C virus infection (339-341), whereas no lncRNA drug has reached the clinical development stage (342). miRNA mimics replicate endogenous miRNA functions to compensate for miRNA deficiency in pathological conditions, while anti-miRNAs (antagomirs) are engineered to suppress endogenous miRNAs that contribute to disease progression (342). As aforementioned, administration of anti-miRNAs targeting miR-326, miR-29a-3p and miR-187 independently enhanced lens transparency and ameliorated lens damage in ARC animal models, indicating their potential as viable non-surgical alternatives for ARC intervention (103-105). Furthermore, with increasing recognition of the regulatory functions of circRNAs in disease pathogenesis, circRNAs are increasingly being considered as targets for therapeutic intervention (56,176,182). For instance, circRNA 06209 overexpression through plasmid injection in a rat model of ARCs reduced lens opacity (182). However, before ncRNA-based therapies advance to the preclinical stage, several challenges must be addressed, including RNA instability, immune activation and off-target effects (342).

Epigenetic modifiers hold potential for the prevention and treatment of ARCs, but there is still a long way ahead before these agents can be routinely implemented in clinical practice. Future studies should focus on: i) Identifying novel therapeutic targets and developing corresponding treatments; ii) investigating and optimizing intraocular drug delivery systems with high efficiency and biocompatibility; and iii) evaluating long-term safety and efficacy in both animal models and clinical trials.

4. Future directions and perspectives

Emerging technologies in epigenetic studies of ARCs. Technological breakthroughs and cutting-edge research have sparked growing interest in the pivotal role of epigenetics in ocular disease. Advances in omics and high-throughput sequencing technologies have facilitated the elucidation of the role of epigenetics in disease pathogenesis and the identification of potential targets. This section highlights two emerging technologies, single-cell multi-omics and spatial transcriptomics, and discusses their transformative potential in deciphering the epigenetic landscape of ARCs.

Single-cell multi-omics sequencing enables simultaneous single-cell profiling of chromatin accessibility, histone modifications, transcription factor binding, DNA methylation and transcriptome analysis (343). This approach has revealed cell type-specific epigenetic regulatory mechanisms in brain development (344), cancer evolution (345) and HIV-associated immune exhaustion (346). Tangeman *et al* (347) described the first single-cell multiomic atlas of lens development, depicting a comprehensive portrait of lens fibre cell differentiation and exploring congenital cataract-linked regulatory networks. However, to the best of our knowledge, single-cell multi-omics has not yet been applied in research on ARCs. Current research considers different omics levels individually, drawing conclusions from each level separately, without data integration for a cohesive understanding of the overall mechanisms. Single-cell multi-omics could revolutionize ARC research by offering a comprehensive understanding of the complex biological processes involved in ARC pathogenesis.

Spatial transcriptomics allows high-resolution profiling of gene expression in intact cell and tissue samples (348), and has made significant advances in recent years, exerting notable influence on diverse fields, such as tissue architecture, developmental biology and disease research, particularly in cancer and neurodegenerative diseases (349). Given the differential miRNA expression profiles among ARC subtypes defined by the location of lens opacity (72), there may be differences in gene expression profiles across different regions of the lens. To the best of our knowledge, spatial transcriptomics remains unexplored in epigenetic studies of ARCs. Spatial transcriptomics allows the quantification and illustration of gene expression profiles within the native spatial context (350), which could facilitate the identification of epigenetic biomarkers and microenvironmental interactions critical for understanding cataract pathogenesis.

Epigenetic clocks and ARCs. The epigenetic clock, also known as DNA methylation age (DNAmAge), is a biomarker for biological age prediction based on DNA methylation patterns at specific CpG sites (351). By modelling linear correlations between methylation levels and chronological aging, it serves as a molecular 'timer' that can estimate cellular aging rates more accurately than chronological age, with implications for

disease risk and lifespan prediction (352). Epigenetic age acceleration (EAA) exhibits strong associations with age-related diseases by reflecting discrepancies between DNAmAge and chronological age, acting as a predictive biomarker for conditions such as cardiovascular disorders, neurodegenerative diseases and type 2 diabetes (353).

To investigate the causal relationship between epigenetic clocks and common age-related eye diseases or glaucoma endophenotypes, Chen *et al* (354) conducted bidirectional two-sample Mendelian randomization and found that ARCs were linked to decreased HannumAge, a measure of extrinsic aging based on 71 age-related CpGs from whole blood samples of adults. Further research is warranted to determine whether quantifying EAA can effectively identify ARC susceptibility at early stages and whether it may serve as a basis for developing targeted interventions to delay lens opacification.

Conclusion. Breakthroughs in omics, bioinformatics and high-throughput sequencing technologies have accelerated discoveries regarding the role of epigenetics in ARCs, enabling a deeper understanding of the initiation and progression mechanisms of ARCs while potentially revolutionizing disease management approaches. The present review comprehensively summarizes advances in epigenetic research on ARCs, examining how ncRNAs, DNA methylation, histone modifications and m^6A modification contribute to ARC pathogenesis, and exploring their clinical potential for innovative therapeutic strategies. Epigenetics in ARCs is an emerging field with immense potential for diagnosis, treatment and prevention of lens opacities, as innovations over the past decade have identified numerous epigenetic alterations as potential biomarkers and intervention targets. Further studies are required to identify therapeutic targets and biomarkers, elucidate the precise mechanisms through which epigenetics influences disease pathogenesis, evaluate the efficacy and safety of novel epigenetic therapies, and translate these therapies into clinical practice.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Natural Science Foundation of China (grant no. 82371036), and the Key Research and Development Program of Zhejiang Province (grant no. 2025C02156).

Availability of data and materials

Not applicable.

Authors' contributions

WY collected the literature and drafted the manuscript. YZ, SC, JG and ZP reviewed the manuscript and made revisions to the manuscript. YY directed the work and revised the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Cicinelli MV, Buchan JC, Nicholson M, Varadaraj V and Khanna RC: Cataracts. Lancet 401: 377-389, 2023.
2. Shiels A and Hejtmancik JF: Mutations and mechanisms in congenital and age-related cataracts. Exp Eye Res 156: 95-102, 2017.
3. Asbell PA, Dualan I, Mindel J, Brocks D, Ahmad M and Epstein S: Age-related cataract. Lancet 365: 599-609, 2005.
4. Abdelkader H, Alany RG and Pierscionek B: Age-related cataract and drug therapy: Opportunities and challenges for topical antioxidant delivery to the lens. J Pharm Pharmacol 67: 537-550, 2015.
5. Meacock WR, Spalton DJ, Boyce J and Marshall J: The effect of posterior capsule opacification on visual function. Invest Ophthalmol Vis Sci 44: 4665-4669, 2003.
6. Yang C, An Q, Zhou H and Ge H: Research progress on the impact of cataract surgery on corneal endothelial cells. Adv Ophthalmol Pract Res 4: 194-201, 2024.
7. Beebe DC, Holekamp NM and Shui YB: Oxidative damage and the prevention of age-related cataracts. Ophthalmic Res 44: 155-165, 2010.
8. Kulbay M, Wu KY, Nirwal GK, Bélanger P and Tran SD: Oxidative stress and cataract formation: Evaluating the efficacy of antioxidant therapies. Biomolecules 14: 1055, 2024.
9. Lou MF: Redox regulation in the lens. Prog Retin Eye Res 22: 657-682, 2003.
10. Rahman K: Studies on free radicals, antioxidants, and co-factors. Clin Interv Aging 2: 219-236, 2007.
11. Berthoud VM and Beyer EC: Oxidative stress, lens gap junctions, and cataracts. Antioxid Redox Signal 11: 339-353, 2009.
12. Petrash JM: Aging and age-related diseases of the ocular lens and vitreous body. Invest Ophthalmol Vis Sci 54: ORSF54-ORSF59, 2013.
13. Babizhayev MA and Costa EB: Lipid peroxide and reactive oxygen species generating systems of the crystalline lens. Biochim Biophys Acta 1225: 326-337, 1994.
14. Dische Z and Zil H: Studies on the oxidation of cysteine to cystine in lens proteins during cataract formation. Am J Ophthalmol 34: 104-113, 1951.
15. Kleiman NJ and Spector A: DNA single strand breaks in human lens epithelial cells from patients with cataract. Curr Eye Res 12: 423-431, 1993.
16. Kruk J, Kubasik-Kladna K and Aboul-Enein HY: The role oxidative stress in the pathogenesis of eye diseases: Current status and a dual role of physical activity. Mini Rev Med Chem 16: 241-257, 2015.
17. Kubota M, Shui YB, Liu M, Bai F, Huang AJ, Ma N, Beebe DC and Siegfried CJ: Mitochondrial oxygen metabolism in primary human lens epithelial cells: Association with age, diabetes and glaucoma. Free Radic Biol Med 97: 513-519, 2016.
18. Brennan LA, McGreal RS and Kantorow M: Oxidative stress defense and repair systems of the ocular lens. Front Biosci (Elite Ed) 4: 141-155, 2012.
19. Cekić S, Zlatanović G, Cvetković T and Petrović B: Oxidative stress in cataractogenesis. Bosn J Basic Med Sci 10: 265-269, 2010.
20. Li G, Song H, Chen L, Yang W, Nan K and Lu P: TUG1 promotes lens epithelial cell apoptosis by regulating miR-421/caspase-3 axis in age-related cataract. Exp Cell Res 356: 20-27, 2017.
21. Li WC, Kuszak JR, Dunn K, Wang RR, Ma W, Wang GM, Spector A, Leib M, Cotliar AM, Weiss M, *et al*: Lens epithelial cell apoptosis appears to be a common cellular basis for non-congenital cataract development in humans and animals. J Cell Biol 130: 169-181, 1995.

22. Chen X, Xu H, Shu X and Song CX: Mapping epigenetic modifications by sequencing technologies. Cell Death Differ 32: 56-65, 2025.
23. Chen Y, Hong T, Wang S, Mo J, Tian T and Zhou X: Epigenetic modification of nucleic acids: From basic studies to medical applications. Chem Soc Rev 46: 2844-2872, 2017.
24. Mazzio EA and Soliman KF: Basic concepts of epigenetics: Impact of environmental signals on gene expression. Epigenetics 7: 119-130, 2012.
25. Dawson MA and Kouzarides T: Cancer epigenetics: From mechanism to therapy. Cell 150: 12-27, 2012.
26. Peixoto P, Cartron PF, Serandour AA and Hervouet E: From 1957 to nowadays: A brief history of epigenetics. Int J Mol Sci 21: 7571, 2020.
27. Gangisetty O, Cabrera MA and Murugan S: Impact of epigenetics in aging and age related neurodegenerative diseases. Front Biosci (Landmark Ed) 23: 1445-1464, 2018.
28. Nikolac Perkovic M, Videtic Paska A, Konjevod M, Kouter K, Svob Strac D, Nedic Erjavec G and Pivac N: Epigenetics of Alzheimer's disease. Biomolecules 11: 195, 2021.
29. Suárez R, Chapela SP, Álvarez-Córdova L, Bautista-Valarezo E, Sarmiento-Andrade Y, Verde L, Frias-Toral E and Sarno G: Epigenetics in obesity and diabetes mellitus: New insights. Nutrients 15: 811, 2023.
30. Sun L, Zhang H and Gao P: Metabolic reprogramming and epigenetic modifications on the path to cancer. Protein Cell 13: 877-919, 2022.
31. Okugawa Y, Grady WM and Goel A: Epigenetic alterations in colorectal cancer: Emerging biomarkers. Gastroenterology 149: 1204-1225.e12, 2015.
32. Trnkova L, Buocikova V, Mego M, Cumova A, Burikova M, Bohac M, Miklikova S, Cihova M and Smolkova B: Epigenetic deregulation in breast cancer microenvironment: Implications for tumor progression and therapeutic strategies. Biomed Pharmacother 174: 116559, 2024.
33. Henikoff S and Greally JM: Epigenetics, cellular memory and gene regulation. Curr Biol 26: R644-R648, 2016.
34. Meng H, Cao Y, Qin J, Song X, Zhang Q, Shi Y and Cao L: DNA methylation, its mediators and genome integrity. Int J Biol Sci 11: 604-617, 2015.
35. Wu Z, Zhang W, Qu J and Liu GH: Emerging epigenetic insights into aging mechanisms and interventions. Trends Pharmacol Sci 45: 157-172, 2024.
36. Desmettre TJ: Epigenetics in age-related macular degeneration (AMD). J Fr Ophtalmol 41: e407-e415, 2018.
37. Kapuganti RS and Alone DP: Current understanding of genetics and epigenetics in pseudoexfoliation syndrome and glaucoma. Mol Aspects Med 94: 101214, 2023.
38. Kowluru RA, Kowluru A, Mishra M and Kumar B: Oxidative stress and epigenetic modifications in the pathogenesis of diabetic retinopathy. Prog Retin Eye Res 48: 40-61, 2015.
39. Wang Y and Guan H: The role of DNA methylation in lens development and cataract formation. Cell Mol Neurobiol 37: 979-984, 2017.
40. Ling C and Rönn T: Epigenetics in human obesity and type 2 diabetes. Cell Metab 29: 1028-1044, 2019.
41. Li P, Yu H, Zhang G, Kang L, Qin B, Cao Y, Luo J, Chen X, Wang Y, Qin M, *et al*: Identification and characterization of N6-methyladenosine CircRNAs and methyltransferases in the lens epithelium cells from age-related cataract. Invest Ophthalmol Vis Sci 61: 13, 2020.
42. Wei YL and Sun H: Identification of hsa-mir-34a, hsa-mir-124, and hsa-mir-204 as signatures for cataract. J Cell Physiol 234: 10709-10717, 2019.
43. Zhu X, Zhang G, Kang L and Guan H: Epigenetic regulation of Werner syndrome gene in age-related cataract. J Ophthalmol 2015: 579695, 2015.
44. Crick F: Central dogma of molecular biology. Nature 227: 561-563, 1970.
45. Crick FH: On protein synthesis. Symp Soc Exp Biol 12: 138-163, 1958.
46. Kim SS and Lee SJV: Non-coding RNAs in caenorhabditis elegans aging. Mol Cells 42: 379-385, 2019.
47. Yao ZT, Yang YM, Sun MM, He Y, Liao L, Chen KS and Li B: New insights into the interplay between long non-coding RNAs and RNA-binding proteins in cancer. Cancer Commun (Lond) 42: 117-140, 2022.
48. Dykes IM and Emanueli C: Transcriptional and post-transcriptional gene regulation by long non-coding RNA. Genomics Proteomics Bioinformatics 15: 177-186, 2017.
49. Smillie CL, Sirey T and Ponting CP: Complexities of post-transcriptional regulation and the modeling of ceRNA crosstalk. Crit Rev Biochem Mol Biol 53: 231-245, 2018.
50. Luo S, He F, Luo J, Dou S, Wang Y, Guo A and Lu J: Drosophila tsRNAs preferentially suppress general translation machinery via antisense pairing and participate in cellular starvation response. Nucleic Acids Res 46: 5250-5268, 2018.
51. Kim HK, Xu J, Chu K, Park H, Jang H, Li P, Valdmanis PN, Zhang QC and Kay MA: A tRNA-derived small RNA regulates ribosomal protein S28 protein levels after translation initiation in humans and mice. Cell Rep 29: 3816-3824.e4, 2019.
52. Ardekani AM and Naeini MM: The role of MicroRNAs in human diseases. Avicenna J Med Biotechnol 2: 161-179, 2010.
53. Condrat CE, Thompson DC, Barbu MG, Bugnar OL, Boboc A, Cretoiu D, Suciu N, Cretoiu SM and Voinea SC: miRNAs as biomarkers in disease: Latest findings regarding their role in diagnosis and prognosis. Cells 9: 276, 2020.
54. Wawrzyniak O, Zarębska Ż, Rolle K and Gotz-Więckowska A: Circular and long non-coding RNAs and their role in ophthalmologic diseases. Acta Biochim Pol 65: 497-508, 2018.
55. Chen S, Zhang C, Shen L, Hu J, Chen X and Yu Y: Noncoding RNAs in cataract formation: Star molecules emerge in an endless stream. Pharmacol Res 184: 106417, 2022.
56. Zhang C, Hu J and Yu Y: CircRNA is a rising star in researches of ocular diseases. Front Cell Dev Biol 8: 850, 2020.
57. Zheng JL, Sun J, Zhang H and Zhang Y: Role of microRNA and lncRNA in lens development and cataract formation. Zhonghua Yan Ke Za Zhi 54: 390-395, 2018 (In Chinese).
58. Michlewski G and Cáceres JF: Post-transcriptional control of miRNA biogenesis. RNA 25: 1-16, 2019.
59. Bartel DP: MicroRNAs: Target recognition and regulatory functions. Cell 136: 215-233, 2009.
60. Broughton JP, Lovci MT, Huang JL, Yeo GW and Pasquinelli AE: Pairing beyond the seed supports MicroRNA targeting specificity. Mol Cell 64: 320-333, 2016.
61. O'Brien J, Hayder H, Zayed Y and Peng C: Overview of MicroRNA biogenesis, mechanisms of actions, and circulation. Front Endocrinol (Lausanne) 9: 402, 2018.
62. Majid S, Dar AA, Saini S, Yamamura S, Hirata H, Tanaka Y, Deng G and Dahiya R: MicroRNA-205-directed transcriptional activation of tumor suppressor genes in prostate cancer. Cancer 116: 5637-5649, 2010.
63. Place RF, Li LC, Pookot D, Noonan EJ and Dahiya R: MicroRNA-373 induces expression of genes with complementary promoter sequences. Proc Natl Acad Sci USA 105: 1608-1613, 2008.
64. Vasudevan S: Posttranscriptional upregulation by microRNAs. Wiley Interdiscip Rev RNA 3: 311-330, 2012.
65. Selbach M, Schwanhäusser B, Thierfelder N, Fang Z, Khanin R and Rajewsky N: Widespread changes in protein synthesis induced by microRNAs. Nature 455: 58-63, 2008.
66. Kang L, Luo J, Li P, Zhang G, Wei M, Ji M and Guan H: miR-125a-3p regulates apoptosis by suppressing TMBIM4 in lens epithelial cells. Int Ophthalmol 43: 1261-1274, 2023.
67. Cao Y, Li P, Zhang G, Kang L, Zhou T, Wu J, Wang Y, Wang Y, Chen X and Guan H: MicroRNA Let-7c-5p-mediated regulation of ERCC6 disrupts autophagic flux in age-related cataract via the binding to VCP. Curr Eye Res 46: 1353-1362, 2021.
68. Li ZN, Ge MX and Yuan ZF: MicroRNA-182-5p protects human lens epithelial cells against oxidative stress-induced apoptosis by inhibiting NOX4 and p38 MAPK signalling. BMC Ophthalmol 20: 233, 2020.
69. Zhang C, Chen M, Zhou N and Qi Y: Metformin prevents H_2O_2-induced senescence in human lens epithelial B3 cells. Med Sci Monit Basic Res 26: e923391, 2020.
70. Zou X, Kang L, Yang M, Wu J and Guan H: MicroRNA binding mediated Functional sequence variant in 3'-UTR of DNA repair gene XPC in age-related cataract. Sci Rep 8: 15198, 2018.
71. Wu C, Lin H, Wang Q, Chen W, Luo H, Chen W and Zhang H: Discrepant expression of microRNAs in transparent and cataractous human lenses. Invest Ophthalmol Vis Sci 53: 3906-3912, 2012.
72. Kim YJ, Lee WJ, Ko BW, Lim HW, Yeon Y, Ahn SJ and Lee BR: Investigation of MicroRNA expression in anterior lens capsules of senile cataract patients and MicroRNA differences according to the cataract type. Transl Vis Sci Technol 10: 14, 2021.
73. Peng CH, Liu JH, Woung LC, Lin TJ, Chiou SH, Tseng PC, Du WY, Cheng CK, Hu CC, Chien KH and Chen SJ: MicroRNAs and cataracts: Correlation among let-7 expression, age and the severity of lens opacity. Br J Ophthalmol 96: 747-751, 2012.

74. Chylack LT Jr, Wolfe JK, Singer DM, Leske MC, Bullimore MA, Bailey IL, Friend J, McCarthy D and Wu SY: The lens opacities classification system III. The longitudinal study of cataract study group. Arch Ophthalmol 111: 831-836, 1993.
75. Chien KH, Chen SJ, Liu JH, Chang HM, Woung LC, Liang CM, Chen JT, Lin TJ, Chiou SH and Peng CH: Correlation between microRNA-34a levels and lens opacity severity in age-related cataracts. Eye (Lond) 27: 883-888, 2013.
76. Xu C, Xu J, Zhang W, Zheng F and Lou X: Expression of miR-210-3p in the aqueous humor of patients with age-related cataracts and its effect on human lens epithelial cell injury induced by hydrogen peroxide. Arq Bras Oftalmol 87: e20220274, 2023.
77. Li Y, Liu S, Zhang F, Jiang P, Wu X and Liang Y: Expression of the microRNAs hsa-miR-15a and hsa-miR-16-1 in lens epithelial cells of patients with age-related cataract. Int J Clin Exp Med 8: 2405-2410, 2015.
78. Zhou W, Xu J, Wang C, Shi D and Yan Q: miR-23b-3p regulates apoptosis and autophagy via suppressing SIRT1 in lens epithelial cells. J Cell Biochem 120: 19635-19646, 2019.
79. Lu B, Christensen IT, Ma LW, Wang XL, Jiang LF, Wang CX, Feng L, Zhang JS and Yan QC: miR-211 promotes lens epithelial cells apoptosis by targeting silent mating-type information regulation 2 homolog 1 in age-related cataracts. Int J Ophthalmol 11: 201-207, 2018.
80. Maiti B, Li J, de Bruin A, Gordon F, Timmers C, Opavsky R, Patil K, Tuttle J, Cleghorn W and Leone G: Cloning and characterization of mouse E2F8, a novel mammalian E2F family member capable of blocking cellular proliferation. J Biol Chem 280: 18211-18220, 2005.
81. Shen ZG, Liu XZ, Chen CX and Lu JM: Knockdown of E2F3 inhibits proliferation, migration, and invasion and increases apoptosis in glioma cells. Oncol Res 25: 1555-1566, 2017.
82. Chen Q, Liang D, Yang T, Leone G and Overbeek PA: Distinct capacities of individual E2Fs to induce cell cycle re-entry in postmitotic lens fiber cells of transgenic mice. Dev Neurosci 26: 435-445, 2004.
83. Chong JL, Tsai SY, Sharma N, Opavsky R, Price R, Wu L, Fernandez SA and Leone G: E2f3a and E2f3b contribute to the control of cell proliferation and mouse development. Mol Cell Biol 29: 414-424, 2009.
84. Wenzel PL, Chong JL, Sáenz-Robles MT, Ferrey A, Hagan JP, Gomez YM, Rajmohan R, Sharma N, Chen HZ, Pipas JM, *et al*: Cell proliferation in the absence of E2F1-3. Dev Biol 351: 35-45, 2011.
85. Yan Q, Liu JP and Li DWC: Apoptosis in lens development and pathology. Differentiation 74: 195-211, 2006.
86. Xiang W, Lin H, Wang Q, Chen W, Liu Z, Chen H, Zhang H and Chen W: miR-34a suppresses proliferation and induces apoptosis of human lens epithelial cells by targeting E2F3. Mol Med Rep 14: 5049-5056, 2016.
87. Li Q, Pan H and Liu Q: MicroRNA-15a modulates lens epithelial cells apoptosis and proliferation through targeting B-cell lymphoma-2 and E2F transcription factor 3 in age-related cataracts. Biosci Rep 39: BSR20191773, 2019.
88. Gong W, Li J, Wang Y, Meng J and Zheng G: miR-221 promotes lens epithelial cells apoptosis through interacting with SIRT1 and E2F3. Chem Biol Interact 306: 39-46, 2019.
89. Gao W, Zhou X and Lin R: miR-378a-5p and miR-630 induce lens epithelial cell apoptosis in cataract via suppression of E2F3. Braz J Med Biol Res 53: e9608, 2020.
90. Fan F, Zhuang J, Zhou P, Liu X and Luo Y: MicroRNA-34a promotes mitochondrial dysfunction-induced apoptosis in human lens epithelial cells by targeting Notch2. Oncotarget 8: 110209-110220, 2017.
91. Feng L, Wei Y, Sun Y, Zhou L, Bi S, Chen W and Xiang W: MIR34A modulates lens epithelial cell apoptosis and cataract development via the HK1/caspase 3 signaling pathway. Aging (Albany NY) 15: 6331-6345, 2023.
92. Liu Y, Li H and Liu Y: microRNA-378a regulates the reactive oxygen species (ROS)/phosphatidylinositol 3-kinases (PI3K)/AKT signaling pathway in human lens epithelial cells and cataract. Med Sci Monit 25: 4314-4321, 2019.
93. Zhang F, Meng W and Tong B: Down-regulation of MicroRNA-133b suppresses apoptosis of lens epithelial cell by up-regulating BCL2L2 in age-related cataracts. Med Sci Monit 22: 4139-4145, 2016.
94. Qin Y, Zhao J, Min X, Wang M, Luo W, Wu D, Yan Q, Li J, Wu X and Zhang J: MicroRNA-125b inhibits lens epithelial cell apoptosis by targeting p53 in age-related cataract. Biochim Biophys Acta 1842: 2439-2447, 2014.
95. Gao M, Huang Y, Wang L, Huang M, Liu F, Liao S, Yu S, Lu Z, Han S, Hu X, *et al*: HSF4 regulates lens fiber cell differentiation by activating p53 and its downstream regulators. Cell Death Dis 8: e3082, 2017.
96. Li L, Fan DB, Zhao YT, Li Y, Kong DQ, Cai FF and Zheng GY: Two novel mutations identified in ADCC families impair crystallin protein distribution and induce apoptosis in human lens epithelial cells. Sci Rep 7: 17848, 2017.
97. Peng J, Zheng TT, Liang Y, Duan LF, Zhang YD, Wang LJ, He GM and Xiao HT: p-Coumaric acid protects human lens epithelial cells against oxidative stress-induced apoptosis by MAPK signaling. Oxid Med Cell Longev 2018: 8549052, 2018.
98. Youle RJ and Strasser A: The BCL-2 protein family: Opposing activities that mediate cell death. Nat Rev Mol Cell Biol 9: 47-59, 2008.
99. Zhang DJ, Du FF, Jing XY, Wang L, Liu D and Yang XQ: Sequence and expression regulation of the BCL2L2 gene in pigs. Gene 851: 146992, 2023.
100. İçme G, Yilmaz A, Dinç E, Görür A, Fidanci ŞB and Tamer L: Assessment of miR-182, miR-183, miR-184, and miR-221 expressions in primary pterygium and comparison with the normal conjunctiva. Eye Contact Lens 45: 208-211, 2019.
101. Liu Y, Bailey JC, Helwa I, Dismuke WM, Cai J, Drewry M, Brilliant MH, Budenz DL, Christen WG, Chasman DI, *et al*: A common variant in MIR182 is associated with primary open-angle glaucoma in the NEIGHBORHOOD consortium. Invest Ophthalmol Vis Sci 57: 4528-4535, 2016.
102. Szemraj M, Oszajca K, Szemraj J and Jurowski P: MicroRNA expression analysis in serum of patients with congenital hemochromatosis and age-related macular degeneration (AMD). Med Sci Monit 23: 4050-4060, 2017.
103. Ren H, Tao H, Gao Q, Shen W, Niu Z, Zhang J, Mao H, Du A and Li W: MiR-326 antagomir delays the progression of age-related cataract by upregulating FGF1-mediated expression of betaB2-crystallin. Biochem Biophys Res Commun 505: 505-510, 2018.
104. Fang R, Li HL, Lv NX, Yue PL, Jia YX, Liu ZC, Zhou HG and Song XD: Inhibition of miR-29a-3p alleviates apoptosis of lens epithelial cells via upregulation of CAND1. Curr Eye Res 49: 391-400, 2024.
105. Wang F and Ren Y: Nanofluorescence probe in detection of miR-187 and its correlation with oxidative stress response in cataracts. Altern Ther Health Med 29: 73-79, 2023.
106. Vymetalkova V, Pardini B, Rosa F, Jiraskova K, Di Gaetano C, Bendova P, Levy M, Veskrnova V, Buchler T, Vodickova L, *et al*: Polymorphisms in microRNA binding sites of mucin genes as predictors of clinical outcome in colorectal cancer patients. Carcinogenesis 38: 28-39, 2017.
107. Liu XC, Liu XF, Hu ZD and Li ZH: Polymorphisms of DNA repair genes XPD (Lys751Gln) and XRCC1 (Arg399Gln), and the risk of age-related cataract: A meta-analysis. Curr Eye Res 40: 676-682, 2015.
108. Wang Y, Li F, Zhang G, Kang L and Guan H: Ultraviolet-B induces ERCC6 repression in lens epithelium cells of age-related nuclear cataract through coordinated DNA hypermethylation and histone deacetylation. Clin Epigenetics 8: 62, 2016.
109. Kang L, Zou X, Zhang G, Xiang J, Wang Y, Yang M, Chen X, Wu J and Guan H: A variant in a microRNA binding site in NEIL2 3'UTR confers susceptibility to age-related cataracts. FASEB J 33: 10469-10476, 2019.
110. Zhao Y, Li X and Zhu S: rs78378222 polymorphism in the 3'-untranslated region of TP53 contributes to development of age-associated cataracts by modifying microRNA-125b-induced apoptosis of lens epithelial cells. Mol Med Rep 14: 2305-2310, 2016.
111. Luo J, Li P, Kang L, Ji M, Zhou T, Qin B, Zhang J and Guan H: Exosomal microRNA-222-3p increases UVB sensitivity of lens epithelium cells by suppressing MGMT. Int Ophthalmol 43: 1611-1628, 2023.
112. Denzer K, Kleijmeer MJ, Heijnen HF, Stoorvogel W and Geuze HJ: Exosome: From internal vesicle of the multivesicular body to intercellular signaling device. J Cell Sci 113: 3365-3374, 2000.
113. Meldolesi J: Exosomes and ectosomes in intercellular communication. Curr Biol 28: R435-R444, 2018.
114. Perez-Hernandez J, Olivares D, Forner MJ, Ortega A, Solaz E, Martinez F, Chaves FJ, Redon J and Cortes R: Urinary exosome miR-146a is a potential marker of albuminuria in essential hypertension. J Transl Med 16: 228, 2018.

115. Creemers EE, Tijsen AJ and Pinto YM: Circulating microRNAs: Novel biomarkers and extracellular communicators in cardiovascular disease? Circ Res 110: 483-495, 2012.
116. Turchinovich A, Samatov TR, Tonevitsky AG and Burwinkel B: Circulating miRNAs: Cell-cell communication function? Front Genet 4: 119, 2013.
117. Fan Q, Yang L, Zhang X, Peng X, Wei S, Su D, Zhai Z, Hua X and Li H: The emerging role of exosome-derived non-coding RNAs in cancer biology. Cancer Lett 414: 107-115, 2018.
118. Machida T, Tomofuji T, Ekuni D, Maruyama T, Yoneda T, Kawabata Y, Mizuno H, Miyai H, Kunitomo M and Morita M: MicroRNAs in salivary exosome as potential biomarkers of aging. Int J Mol Sci 16: 21294-21309, 2015.
119. Zamani P, Fereydouni N, Butler AE, Navashenaq JG and Sahebkar A: The therapeutic and diagnostic role of exosomes in cardiovascular diseases. Trends Cardiovasc Med 29: 313-323, 2019.
120. Li J, Wang J and Chen Z: Emerging role of exosomes in cancer therapy: Progress and challenges. Mol Cancer 24: 13, 2025.
121. Ponting CP, Oliver PL and Reik W: Evolution and functions of long noncoding RNAs. Cell 136: 629-641, 2009.
122. Moreno JA, Hamza E, Guerrero-Hue M, Rayego-Mateos S, García-Caballero C, Vallejo-Mudarra M, Metzinger L and Metzinger-Le Meuth V: Non-coding RNAs in kidney diseases: The long and short of them. Int J Mol Sci 22: 6077, 2021.
123. Goodall GJ and Wickramasinghe VO: RNA in cancer. Nat Rev Cancer 21: 22-36, 2021.
124. Javed Z, Khan K, Sadia H, Raza S, Salehi B, Sharifi-Rad J and Cho WC: LncRNA & Wnt signaling in colorectal cancer. Cancer Cell Int 20: 326, 2020.
125. Salmena L, Poliseno L, Tay Y, Kats L and Pandolfi PP: A ceRNA hypothesis: The Rosetta Stone of a hidden RNA language? Cell 146: 353-358, 2011.
126. Cesana M, Cacchiarelli D, Legnini I, Santini T, Sthandier O, Chinappi M, Tramontano A and Bozzoni I: A long noncoding RNA controls muscle differentiation by functioning as a competing endogenous RNA. Cell 147: 358-369, 2011.
127. Gong C and Maquat LE: lncRNAs transactivate STAU1-mediated mRNA decay by duplexing with 3' UTRs via Alu elements. Nature 470: 284-288, 2011.
128. Hong Y, Wu J, Sun Y, Zhang S, Lu Y and Ji Y: ceRNA network construction and identification of hub genes as novel therapeutic targets for age-related cataracts using bioinformatics. PeerJ 11: e15054, 2023.
129. Zhou T, Yang M, Zhang G, Kang L, Yang L and Guan H: Long non-coding RNA nuclear paraspeckle assembly transcript 1 protects human lens epithelial cells against H_2O_2 stimuli through the nuclear factor kappa b/p65 and p38/mitogen-activated protein kinase axis. Ann Transl Med 8: 1653, 2020.
130. Zhou T, Zhang J, Qin B, Xu H, Zhang S and Guan H: Long non-coding RNA NONHSAT143692.2 is involved in oxidative DNA damage repair in the lens by regulating the miR-4728-5p/OGG1 axis. Int J Mol Med 46: 1838-1848, 2020.
131. Zhang N, Zhang C, Wang X and Qi Y: High-throughput sequencing reveals novel lincRNA in age-related cataract. Int J Mol Med 40: 1829-1839, 2017.
132. Li H, Gao L, Du J, Ma T, Ye Z and Li Z: Differentially expressed gene profiles and associated ceRNA network in ATG7-deficient lens epithelial cells under oxidative stress. Front Genet 13: 1088943, 2022.
133. Jin X, Jin H, Shi Y, Guo Y and Zhang H: Long non-coding RNA KCNQ1OT1 promotes cataractogenesis via miR-214 and activation of the caspase-1 pathway. Cell Physiol Biochem 42: 295-305, 2017.
134. Zhang M and Cheng K: Long non-coding RNA KCNQ1OT1 promotes hydrogen peroxide-induced lens epithelial cell apoptosis and oxidative stress by regulating miR-223-3p/BCL2L2 axis. Exp Eye Res 206: 108543, 2021.
135. Xu Y, Zheng Y, Shen P and Zhou L: Role of long noncoding RNA KCNQ1 overlapping transcript 1/microRNA-124-3p/BCL-2-like 11 axis in hydrogen peroxide (H_2O_2)-stimulated human lens epithelial cells. Bioengineered 13: 5035-5045, 2022.
136. Shen Q and Zhou T: Knockdown of lncRNA TUG1 protects lens epithelial cells from oxidative stress-induced injury by regulating miR-196a-5p expression in age-related cataracts. Exp Ther Med 22: 1286, 2021.
137. Sun M, Li K, Li X, Wang H, Li L and Zheng G: lncRNA TUG1 regulates Smac/DIABLO expression by competitively inhibiting miR-29b and modulates the apoptosis of lens epithelial cells in age-related cataracts. Chin Med J (Engl) 136: 2340-2350, 2023.
138. Guo X, Li C, Wang Y, Jiang C and Yang L: Long non-coding RNA nuclear paraspeckle assembly transcript 1 downregulation protects lens epithelial cells from oxidative stress-induced apoptosis by regulating the microRNA-124-3p/death-associated protein kinase 1 axis in age-related cataract. Int Ophthalmol 43: 3413-3424, 2023.
139. Tu Y, Xie L, Chen L, Yuan Y, Qin B, Wang K, Zhu Q, Ji N, Zhu M and Guan H: Long non-coding RNA MEG3 promotes cataractogenesis by upregulating TP53INP1 expression in age-related cataract. Exp Eye Res 199: 108185, 2020.
140. Zhang X, Zheng C, Zhao J, Xu X and Yao J: LncRNA MEG3 regulates ferroptosis of lens epithelial cells via PTBP1/GPX4 axis to participate in age-related cataract. J Cell Physiol 239: e31330, 2024.
141. Jing R, Ma B, Qi T, Hu C, Liao C, Wen C, Shao Y and Pei C: Long noncoding RNA OIP5-AS1 promotes cell apoptosis and cataract formation by blocking POLG expression under oxidative stress. Invest Ophthalmol Vis Sci 61: 3, 2020.
142. Xiang J, Chen Q, Kang L, Zhang G, Wang Y, Qin B, Wu J, Zhou T, Han Y and Guan H: LncRNA PLCD3-OT1 functions as a CeRNA to prevent age-related cataract by sponging miR-224-5p and regulating PLCD3 expression. Invest Ophthalmol Vis Sci 60: 4670-4680, 2019.
143. Cheng T, Xu M, Qin B, Wu J, Tu Y, Kang L, Wang Y and Guan H: lncRNA H19 contributes to oxidative damage repair in the early age-related cataract by regulating miR-29a/TDG axis. J Cell Mol Med 23: 6131-6139, 2019.
144. Alkan AH and Akgül B: Endogenous miRNA sponges. Methods Mol Biol 2257: 91-104, 2022.
145. Alshahrani SH, Al-Hadeithi ZSM, Almalki SG, Malviya J, Hjazi A, Mustafa YF, Alawady AHR, Alsaalamy AH, Joshi SK and Alkhafaji AT: LncRNA-miRNA interaction is involved in colorectal cancer pathogenesis by modulating diverse signaling pathways. Pathol Res Pract 251: 154898, 2023.
146. Karagkouni D, Karavangeli A, Paraskevopoulou MD and Hatzigeorgiou AG: Characterizing miRNA-lncRNA Interplay. Methods Mol Biol 2372: 243-262, 2021.
147. Zhang Y, Cai S, Jia Y, Qi C, Sun J, Zhang H, Wang F, Cao Y and Li X: Decoding noncoding RNAs: Role of MicroRNAs and long noncoding RNAs in ocular neovascularization. Theranostics 7: 3155-3167, 2017.
148. Magistri M, Faghihi MA, St Laurent G III and Wahlestedt C: Regulation of chromatin structure by long noncoding RNAs: Focus on natural antisense transcripts. Trends Genet 28: 389-396, 2012.
149. Xue Y, Ma G, Zhang Z, Hua Q, Chu H, Tong N, Yuan L, Qin C, Yin C, Zhang Z and Wang M: A novel antisense long noncoding RNA regulates the expression of MDC1 in bladder cancer. Oncotarget 6: 484-493, 2015.
150. Zhang CL, Zhu KP and Ma XL: Antisense lncRNA FOXC2-AS1 promotes doxorubicin resistance in osteosarcoma by increasing the expression of FOXC2. Cancer Lett 396: 66-75, 2017.
151. He A, He S, Li X and Zhou L: ZFAS1: A novel vital oncogenic lncRNA in multiple human cancers. Cell Prolif 52: e12513, 2019.
152. Zong X, Nakagawa S, Freier SM, Fei J, Ha T, Prasanth SG and Prasanth KV: Natural antisense RNA promotes 3' end processing and maturation of MALAT1 lncRNA. Nucleic Acids Res 44: 2898-2908, 2016.
153. Tu Y, Li L, Qin B, Wu J, Cheng T, Kang L and Guan H: Long noncoding RNA glutathione peroxidase 3-antisense inhibits lens epithelial cell apoptosis by upregulating glutathione peroxidase 3 expression in age-related cataract. Mol Vis 25: 734-744, 2019.
154. Zhu M, Dong Q, Bing J, Songbuerbatu, Zheng L, Dorjee T, Liu Q, Zhou Y and Gao F: Combined lncRNA and mRNA expression profiles identified the lncRNA-miRNA-mRNA modules regulating the cold stress response in Ammopiptanthus nanus. Int J Mol Sci 24: 6502, 2023.
155. Liu X, Liu C, Shan K, Zhang S, Lu Y, Yan B and Luo Y: Long non-coding RNA H19 regulates human lens epithelial cells function. Cell Physiol Biochem 50: 246-260, 2018.
156. Harland R and Misher L: Stability of RNA in developing Xenopus embryos and identification of a destabilizing sequence in TFIIIA messenger RNA. Development 102: 837-852, 1988.
157. Zhang XO, Dong R, Zhang Y, Zhang JL, Luo Z, Zhang J, Chen LL and Yang L: Diverse alternative back-splicing and alternative splicing landscape of circular RNAs. Genome Res 26: 1277-1287, 2016.
158. Jeck WR, Sorrentino JA, Wang K, Slevin MK, Burd CE, Liu J, Marzluff WF and Sharpless NE: Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA 19: 141-157, 2013.

159. Kristensen LS, Andersen MS, Stagsted LVW, Ebbesen KK, Hansen TB and Kjems J: The biogenesis, biology and characterization of circular RNAs. Nat Rev Genet 20: 675-691, 2019.
160. Panda AC: Circular RNAs Act as miRNA sponges. Adv Exp Med Biol 1087: 67-79, 2018.
161. Tong KL, Tan KE, Lim YY, Tien XY and Wong PF: CircRNA-miRNA interactions in atherogenesis. Mol Cell Biochem 477: 2703-2733, 2022.
162. Conn SJ, Pillman KA, Toubia J, Conn VM, Salmanidis M, Phillips CA, Roslan S, Schreiber AW, Gregory PA and Goodall GJ: The RNA binding protein quaking regulates formation of circRNAs. Cell 160: 1125-1134, 2015.
163. Ashwal-Fluss R, Meyer M, Pamudurti NR, Ivanov A, Bartok O, Hanan M, Evantal N, Memczak S, Rajewsky N and Kadener S: circRNA biogenesis competes with pre-mRNA splicing. Mol Cell 56: 55-66, 2014.
164. Li Z, Huang C, Bao C, Chen L, Lin M, Wang X, Zhong G, Yu B, Hu W, Dai L, *et al*: Exon-intron circular RNAs regulate transcription in the nucleus. Nat Struct Mol Biol 22: 256-264, 2015.
165. Pamudurti NR, Bartok O, Jens M, Ashwal-Fluss R, Stottmeister C, Ruhe L, Hanan M, Wyler E, Perez-Hernandez D, Ramberger E, *et al*: Translation of CircRNAs. Mol Cell 66: 9-21.e7, 2017.
166. Yang Y, Fan X, Mao M, Song X, Wu P, Zhang Y, Jin Y, Yang Y, Chen LL, Wang Y, *et al*: Extensive translation of circular RNAs driven by N^6-methyladenosine. Cell Res 27: 626-641, 2017.
167. Liu J, Liu T, Wang X and He A: Circles reshaping the RNA world: From waste to treasure. Mol Cancer 16: 58, 2017.
168. Qiu JN, Shan K, Xiang J, Gu JY, Zhou RM, Zhang XL, Zhang CR and Xu JJ: Comprehensive analysis of circRNA-associated-ceRNA networks in human corneal endothelial dysfunction. Cornea 41: 1545-1552, 2022.
169. Qu B, Wang J, Li Y, Wu X and Zhang M: Hsa_circ_0023826 protects against glaucoma by regulating miR-188-3p/MDM4 axis. Acta Biochim Pol 70: 253-260, 2023.
170. Tian H, Zhao L, Li H, Huang Y and Wang Y: Circular RNA in retina: A potential biomarker and therapeutic target. Ophthalmic Res 66: 516-528, 2023.
171. Li D, Che X, Gao N and Li J: CircSTRBP contributes to H_2O_2-induced lens epithelium cell dysfunction through increasing NOX4 mRNA stability by recruiting IGF2BP1. Exp Eye Res 241: 109817, 2024.
172. Wang Y, Zhang G, Li P, Kang L, Qin B, Cao Y, Luo J, Chen X, Qin M and Guan H: Profiling and integrated analysis of the ERCC6-regulated circRNA-miRNA-mRNA network in lens epithelial cells. Curr Eye Res 46: 1341-1352, 2021.
173. Xu X, Gao R, Li S, Jiang K, Sun X and Zhang J: Circular RNA circZNF292 regulates H_2O_2-induced injury in human lens epithelial HLE-B3 cells depending on the regulation of the miR-222-3p/E2F3 axis. Cell Biol Int 45: 1757-1767, 2021.
174. Mao W and Zhang Z: The Hsa_circ_0105558/miR-182-5p/ATF6 cascade affects H_2O_2-triggered oxidative damage and apoptosis of human lens epithelial cells. Biochem Genet 63: 1241-1257, 2025.
175. Li R, Zhu H, Li Q, Tang J, Jin Y and Cui H: METTL3-mediated m6A modification of has_circ_0007905 promotes age-related cataract progression through miR-6749-3p/EIF4EBP1. PeerJ 11: e14863, 2023.
176. Liu J, Zhang J, Zhang G, Zhou T, Zou X, Guan H and Wang Y: CircMRE11A_013 binds to UBXN1 and integrates ATM activation enhancing lens epithelial cells senescence in age-related cataract. Aging (Albany NY) 13: 5383-5402, 2021.
177. Cui G, Wang L and Huang W: Circular RNA HIPK3 regulates human lens epithelial cell dysfunction by targeting the miR-221-3p/PI3K/AKT pathway in age-related cataract. Exp Eye Res 198: 108128, 2020.
178. Liu X, Liu B, Zhou M, Fan F, Yu M, Gao C, Lu Y and Luo Y: Circular RNA HIPK3 regulates human lens epithelial cells proliferation and apoptosis by targeting the miR-193a/CRYAA axis. Biochem Biophys Res Commun 503: 2277-2285, 2018.
179. Chen S, Wang M, Jian R, Li H, Liu G, Zhou C, Xiong Y and Wang W: Circ_HIPK3 Inhibits H_2O_2-induced lens epithelial cell injury in age-related cataract depending on the regulation of miR-495-3p/HDAC4 pathway. Biochem Genet 61: 565-577, 2023.
180. Liu T, Zhao L, Yan D and Wang N: Circ_0060,144 inhibits the occurrence and development of age-related cataract via the miR-23b-3p/HIPK3 axis. Exp Eye Res 222: 109179, 2022.
181. Zhou C, Huang X, Li X and Xiong Y: Circular RNA erythrocyte membrane protein band 4.1 assuages ultraviolet irradiation-induced apoptosis of lens epithelial cells by stimulating 5'-bisphosphate nucleotidase 1 in a miR-24-3p-dependent manner. Bioengineered 12: 8953-8964, 2021.
182. Fang R, Li JH, Li HL, Yue PL, Ding XF, Jia YX, Liu ZC, Zhou HG, Yang C and Song XD: CircRNA 06209 inhibits cataract development by sponging miR-6848-5p and regulating ALOX15 expression. Exp Eye Res 235: 109640, 2023.
183. Li R, Jiang J, Shi H, Qian H, Zhang X and Xu W: CircRNA: A rising star in gastric cancer. Cell Mol Life Sci 77: 1661-1680, 2020.
184. Cui F, Sun Z, Zhang X and Liu C: CircMAP3K4 suppresses H_2O_2-induced human lens epithelial cell injury by miR-630/ERCC6 axis in age-related cataract. Curr Eye Res 49: 487-495, 2024.
185. Sun L, Li F, Bai S and Bi C: CircRNA HLCS regulates lens epithelial cell apoptosis via miR-338-3p/BPNT1 axis. Int Ophthalmol 44: 142, 2024.
186. Wu Q, Liu H, Ma B and Wang C: Circular RNA Circ_0122396 regulates human lens epithelial cell progression by regulating miR-23a-3p and MMP16 in age-related cataract. Curr Eye Res 49: 1161-1170, 2024.
187. Liu B, Cao J, Wang X, Guo C, Liu Y and Wang T: Deciphering the tRNA-derived small RNAs: Origin, development, and future. Cell Death Dis 13: 24, 2021.
188. Xie Y, Yao L, Yu X, Ruan Y, Li Z and Guo J: Action mechanisms and research methods of tRNA-derived small RNAs. Signal Transduct Target Ther 5: 109, 2020.
189. Pan J, Liu Z, Shen B, Xu J, Dai G, Xu W, Wang J, Li L and Cheng L: tsRNA-04002 alleviates intervertebral disk degeneration by targeting PRKCA to inhibit apoptosis of nucleus pulposus cells. J Orthop Surg Res 18: 413, 2023.
190. Zeng T, Hua Y, Sun C, Zhang Y, Yang F, Yang M, Yang Y, Li J, Huang X, Wu H, *et al*: Relationship between tRNA-derived fragments and human cancers. Int J Cancer 147: 3007-3018, 2020.
191. Zhang L, Liu J and Hou Y: Classification, function, and advances in tsRNA in non-neoplastic diseases. Cell Death Dis 14: 748, 2023.
192. Wang S, Luo Z, Yuan L, Lin X, Tang Y, Yin L, Liang P and Jiang B: tRNA-derived small RNAs: Novel insights into the pathogenesis and treatment of cardiovascular diseases. J Cardiovasc Transl Res 16: 300-309, 2023.
193. Zhang X, Trebak F, Souza LAC, Shi J, Zhou T, Kehoe PG, Chen Q and Feng Earley Y: Small RNA modifications in Alzheimer's disease. Neurobiol Dis 145: 105058, 2020.
194. Zhou M, He X, Zhang J, Mei C, Zhong B and Ou C: tRNA-derived small RNAs in human cancers: Roles, mechanisms, and clinical application. Mol Cancer 23: 76, 2024.
195. Han X, Cai L, Lu Y, Li D and Yang J: Identification of tRNA-derived fragments and their potential roles in diabetic cataract rats. Epigenomics 12: 1405-1418, 2020.
196. Ma Y, Zhang Y, Zhang HY, Zhao Y, Li XM, Jiang YF, Yao MD, Jiang Q and Yan B: Dual anti-angiogenic and anti-inflammatory action of tRNA-Cys-5-0007 in ocular vascular disease. J Transl Med 22: 562, 2024.
197. Peng Y, Zou J, Wang JH, Zeng H, Tan W, Yoshida S, Zhang L, Li Y and Zhou Y: Small RNA sequencing reveals transfer RNA-derived small RNA expression profiles in retinal neovascularization. Int J Med Sci 17: 1713-1722, 2020.
198. Zhang G, Kang L, Li P, Ran Q, Chen X, Ji M and Guan H: Genome-wide repertoire of transfer RNA-derived fragments in a mouse model of age-related cataract. Curr Eye Res 47: 1397-1404, 2022.
199. Anastasiadou E, Jacob LS and Slack FJ: Non-coding RNA networks in cancer. Nat Rev Cancer 18: 5-18, 2018.
200. Ma Y, Liu Y, Shu B, Yang J, Lv L, Zhou L, Wang L and Shi Z: CircMAP3K4 protects human lens epithelial cells from H_2O_2-induced dysfunction by targeting miR-193a-3p/PLCD3 axis in age-related cataract. Cell Cycle 22: 303-315, 2023.
201. Xu J, Shao T, Ding N, Li Y and Li X: miRNA-miRNA crosstalk: From genomics to phenomics. Brief Bioinform 18: 1002-1011, 2017.
202. Krek A, Grün D, Poy MN, Wolf R, Rosenberg L, Epstein EJ, MacMenamin P, da Piedade I, Gunsalus KC, Stoffel M and Rajewsky N: Combinatorial microRNA target predictions. Nat Genet 37: 495-500, 2005.
203. Shao T, Wang G, Chen H, Xie Y, Jin X, Bai J, Xu J, Li X, Huang J, Jin Y and Li Y: Survey of miRNA-miRNA cooperative regulation principles across cancer types. Brief Bioinform 20: 1621-1638, 2019.
204. Chiu HS, Somvanshi S, Patel E, Chen TW, Singh VP, Zorman B, Patil SL, Pan Y, Chatterjee SS; Cancer Genome Atlas Research Network, *et al*: Pan-cancer analysis of lncRNA regulation supports their targeting of cancer genes in each tumor context. Cell Rep 23: 297-312.e12, 2018.

205. Zhang K, Chen L, Qu L and Yan H: A comprehensive investigation of identifying miRNA biomarkers and their potential role in age-related cataract by meta-analysis and bioinformatics analysis. Graefes Arch Clin Exp Ophthalmol 263: 1307-1325, 2025.
206. Michalak EM, Burr ML, Bannister AJ and Dawson MA: The roles of DNA, RNA and histone methylation in ageing and cancer. Nat Rev Mol Cell Biol 20: 573-589, 2019.
207. Dossin F, Pinheiro I, Żylicz JJ, Roensch J, Collombet S, Le Saux A, Chelmicki T, Attia M, Kapoor V, Zhan Y, *et al*: SPEN integrates transcriptional and epigenetic control of X-inactivation. Nature 578: 455-460, 2020.
208. Grigoryan A, Pospiech J, Krämer S, Lipka D, Liehr T, Geiger H, Kimura H, Mulaw MA and Florian MC: Attrition of X chromosome inactivation in aged hematopoietic stem cells. Stem Cell Reports 16: 708-716, 2021.
209. Kulis M, Queirós AC, Beekman R and Martín-Subero JI: Intragenic DNA methylation in transcriptional regulation, normal differentiation and cancer. Biochim Biophys Acta 1829: 1161-1174, 2013.
210. Nishiyama A and Nakanishi M: Navigating the DNA methylation landscape of cancer. Trends Genet 37: 1012-1027, 2021.
211. May MS and Hattaman S: Deoxyribonucleic acid-cytosine methylation by host- and plasmid-controlled enzymes. J Bacteriol 122: 129-138, 1975.
212. Kohli RM and Zhang Y: TET enzymes, TDG and the dynamics of DNA demethylation. Nature 502: 472-479, 2013.
213. Harris AJ and Goldman AD: The complex phylogenetic relationships of a 4mC/6mA DNA methyltransferase in prokaryotes. Mol Phylogenet Evol 149: 106837, 2020.
214. Thomas B, Matson S, Chopra V, Sun L, Sharma S, Hersch S, Rosas HD, Scherzer C, Ferrante R and Matson W: A novel method for detecting 7-methyl guanine reveals aberrant methylation levels in Huntington disease. Anal Biochem 436: 112-120, 2013.
215. Hashimoto H, Pais JE, Zhang X, Saleh L, Fu ZQ, Dai N, Corrêa IR Jr, Zheng Y and Cheng X: Structure of a Naegleria Tet-like dioxygenase in complex with 5-methylcytosine DNA. Nature 506: 391-395, 2014.
216. Angeloni A and Bogdanovic O: Enhancer DNA methylation: Implications for gene regulation. Essays Biochem 63: 707-715, 2019.
217. Zeng Y and Chen T: DNA methylation reprogramming during mammalian development. Genes (Basel) 10: 257, 2019.
218. Zong FF, Jia DD, Huang GK, Pan M, Hu H, Song SY, Xiao L, Wang RW and Liang L: New perspectives on DNA methylation modifications in ocular diseases. Int J Ophthalmol 18: 340-350, 2025.
219. Li Y, Chen X and Lu C: The interplay between DNA and histone methylation: Molecular mechanisms and disease implications. EMBO Rep 22: e51803, 2021.
220. Bird A: DNA methylation patterns and epigenetic memory. Genes Dev 16: 6-21, 2002.
221. Boyes J and Bird A: DNA methylation inhibits transcription indirectly via a methyl-CpG binding protein. Cell 64: 1123-1134, 1991.
222. Cvekl A and Mitton KP: Epigenetic regulatory mechanisms in vertebrate eye development and disease. Heredity (Edinb) 105: 135-151, 2010.
223. Gao Y, Yan Y and Huang T: Human age-related cataracts: epigenetic suppression of the nuclear factor erythroid 2-related factor 2-mediated antioxidant system. Mol Med Rep 11: 1442-1447, 2015.
224. Jin B and Robertson KD: DNA methyltransferases, DNA damage repair, and cancer. Adv Exp Med Biol 754: 3-29, 2013.
225. Kim DJ: The role of the DNA methyltransferase family and the therapeutic potential of DNMT inhibitors in tumor treatment. Curr Oncol 32: 88, 2025.
226. Asada M, Hayashi H and Takagi N: Possible involvement of DNA methylation and protective effect of zebularine on neuronal cell death after glutamate excitotoxity. Biol Pharm Bull 45: 770-779, 2022.
227. Liu S, Hu C, Luo Y and Yao K: Genome-wide DNA methylation profiles may reveal new possible epigenetic pathogenesis of sporadic congenital cataract. Epigenomics 12: 771-788, 2020.
228. Song J, VanBuskirk JA and Merbs SL: Regulation of opsin gene expression by DNA methylation and histone acetylation. Int J Mol Sci 23: 1408, 2022.
229. Johnson WM, Finnegan LK, Hauser MA and Stamer WD: lncRNAs, DNA methylation, and the pathobiology of exfoliation glaucoma. J Glaucoma 27: 202-209, 2018.
230. Zhou P, Luo Y, Liu X, Fan L and Lu Y: Down-regulation and CpG island hypermethylation of CRYAA in age-related nuclear cataract. FASEB J 26: 4897-4902, 2012.
231. Baird PN and Wei L: Age-related macular degeneration and DNA methylation. Epigenomics 5: 239-241, 2013.
232. Chai P, Jia R, Li Y, Zhou C, Gu X, Yang L, Shi H, Tian H, Lin H, Yu J, *et al*: Regulation of epigenetic homeostasis in uveal melanoma and retinoblastoma. Prog Retin Eye Res 89: 101030, 2022.
233. Wolff SP: Cataract and UV radiation. Doc Ophthalmol 88: 201-204, 1994.
234. Li X, Xie J, Xu J, Deng L, Cao G, Huang S, Zeng C, Liu C, Zhu S, He G, *et al*: Long-term exposure to ambient $PM_{2.5}$ and age-related cataracts among chinese middle-aged and older adults: Evidence from two national cohort studies. Environ Sci Technol 57: 11792-11802, 2023.
235. Chen J, Zhou J, Wu J, Zhang G, Kang L, Ben J, Wang Y, Qin B and Guan H: Aberrant epigenetic alterations of glutathione-S-transferase P1 in age-related nuclear cataract. Curr Eye Res 42: 402-410, 2017.
236. Liu X, Zhou P, Fan F, Li D, Wu J, Lu Y and Luo Y: CpG site methylation in CRYAA promoter affect transcription factor Sp1 binding in human lens epithelial cells. BMC Ophthalmol 16: 141, 2016.
237. Jin SL, Zhang Y, Chen ZH, Qian DW, Qine YJ, Yongjie Q, He SK and Guo HK: Epigenetic changes of the Klotho gene in age-related cataracts. Eur Rev Med Pharmacol Sci 19: 2544-2553, 2015.
238. Wang Y, Zhang G, Kang L and Guan H: Expression profiling of DNA methylation and transcriptional repression associated genes in lens epithelium cells of age-related cataract. Cell Mol Neurobiol 37: 537-543, 2017.
239. Chen X, Su D, Sun Z, Fu Y, Hu Y, Zhang Y, Zhang X, Wei Q, Zhu W, Ma X and Hu S: Preliminary study on whole genome methylation and transcriptomics in age-related cataracts. Gene 898: 148096, 2024.
240. Wang L, Li P and Guo X: Screening of methylation genes in age-related cataract. Int J Ophthalmol 11: 1102-1107, 2018.
241. Pendergrass W, Penn P, Possin D and Wolf N: Accumulation of DNA, nuclear and mitochondrial debris, and ROS at sites of age-related cortical cataract in mice. Invest Ophthalmol Vis Sci 46: 4661-4670, 2005.
242. Zhang Y, Zhang L, Zhang L, Bai J, Ge H and Liu P: Expression changes in DNA repair enzymes and mitochondrial DNA damage in aging rat lens. Mol Vis 16: 1754-1763, 2010.
243. Li B, Zhou J, Zhang G, Wang Y, Kang L, Wu J, Chen J and Guan H: Relationship between the altered expression and epigenetics of GSTM3 and age-related cataract. Invest Ophthalmol Vis Sci 57: 4721-4732, 2016.
244. Rushmore TH, Morton MR and Pickett CB: The antioxidant responsive element. Activation by oxidative stress and identification of the DNA consensus sequence required for functional activity. J Biol Chem 266: 11632-11639, 1991.
245. Ling X, Zhu L, Yan Y, Qian H, Kang Z, Ye W, Xie Z and Xue C: Ferulic acid protects human lens epithelial cells against UVA-induced oxidative damage by downregulating the DNA demethylation of the keap1 promoter. J Biochem Mol Toxicol 38: e70031, 2024.
246. Palsamy P, Bidasee KR and Shinohara T: Selenite cataracts: Activation of endoplasmic reticulum stress and loss of Nrf2/Keap1-dependent stress protection. Biochim Biophys Acta 1842: 1794-1805, 2014.
247. Rabbani PS, Soares MA, Hameedi SG, Qian H, Kang Z, Ye W, Xie Z and Xue C: Dysregulation of Nrf2/Keap1 redox pathway in diabetes affects multipotency of stromal cells. Diabetes 68: 141-155, 2019.
248. Raghunath A, Sundarraj K, Nagarajan R, Arfuso F, Bian J, Kumar AP, Sethi G and Perumal E: Antioxidant response elements: Discovery, classes, regulation and potential applications. Redox Biol 17: 297-314, 2018.
249. Li J, Wang T, Liu P, Yang F, Wang X, Zheng W and Sun W: Hesperetin ameliorates hepatic oxidative stress and inflammation via the PI3K/AKT-Nrf2-ARE pathway in oleic acid-induced HepG2 cells and a rat model of high-fat diet-induced NAFLD. Food Funct 12: 3898-3918, 2021.
250. Osama A, Zhang J, Yao J, Yao X and Fang J: Nrf2: A dark horse in Alzheimer's disease treatment. Ageing Res Rev 64: 101206, 2020.
251. Palsamy P, Bidasee KR and Shinohara T: Valproic acid suppresses Nrf2/Keap1 dependent antioxidant protection through induction of endoplasmic reticulum stress and Keap1 promoter DNA demethylation in human lens epithelial cells. Exp Eye Res 121: 26-34, 2014.

252. Palsamy P, Bidasee KR, Ayaki M, Augusteyn RC, Chan JY and Shinohara T: Methylglyoxal induces endoplasmic reticulum stress and DNA demethylation in the Keap1 promoter of human lens epithelial cells and age-related cataracts. Free Radic Biol Med 72: 134-148, 2014.
253. Zduńska K, Dana A, Kolodziejczak A and Rotsztejn H: Antioxidant properties of ferulic acid and its possible application. Skin Pharmacol Physiol 31: 332-336, 2018.
254. Rampelotto CR, Pereira VG, da Silva Silveira L, Rossato A, Machado AK, Sagrillo MR, Gündel A, Burger ME, Schaffazick SR and de Bona da Silva C: Ferulic acid-loaded nanocapsules: Evaluation of mucosal interaction, safety and antioxidant activity in human mononucleated cells. Toxicol In Vitro 78: 105259, 2022.
255. Mathew S and Abraham TE: Ferulic acid: an antioxidant found naturally in plant cell walls and feruloyl esterases involved in its release and their applications. Crit Rev Biotechnol 24: 59-83, 2004.
256. Yang SP, Yang XZ and Cao GP: Acetyl-l-carnitine prevents homocysteine-induced suppression of Nrf2/Keap1 mediated antioxidation in human lens epithelial cells. Mol Med Rep 12: 1145-1150, 2015.
257. Giblin FJ: Glutathione: A vital lens antioxidant. J Ocul Pharmacol Ther 16: 121-135, 2000.
258. Sheehan D, Meade G, Foley VM and Dowd CA: Structure, function and evolution of glutathione transferases: Implications for classification of non-mammalian members of an ancient enzyme superfamily. Biochem J 360: 1-16, 2001.
259. Whalen R and Boyer TD: Human glutathione S-transferases. Semin Liver Dis 18: 345-358, 1998.
260. Hayes JD and Pulford DJ: The glutathione S-transferase supergene family: Regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. Crit Rev Biochem Mol Biol 30: 445-600, 1995.
261. Choi YJ, Yeo HJ, Shin MJ, Youn GS, Park JH, Yeo EJ, Kwon HJ, Lee LR, Kim NY, Kwon SY, *et al*: Tat-GSTpi inhibits dopaminergic cells against MPP^+-induced cellular damage via the reduction of oxidative stress and MAPK activation. Biomedicines 11: 836, 2023.
262. Laborde E: Glutathione transferases as mediators of signaling pathways involved in cell proliferation and cell death. Cell Death Differ 17: 1373-1380, 2010.
263. Hayes JD and McLellan LI: Glutathione and glutathione-dependent enzymes represent a co-ordinately regulated defence against oxidative stress. Free Radic Res 31: 273-300, 1999.
264. Babizhayev MA: Generation of reactive oxygen species in the anterior eye segment. Synergistic codrugs of N-acetylcarnosine lubricant eye drops and mitochondria-targeted antioxidant act as a powerful therapeutic platform for the treatment of cataracts and primary open-angle glaucoma. BBA Clin 6: 49-68, 2016.
265. Sorte K, Sune P, Bhake A, Shivkumar VB, Gangane N and Basak A: Quantitative assessment of DNA damage directly in lens epithelial cells from senile cataract patients. Mol Vis 17: 1-6, 2011.
266. Xu B, Kang L, Zhang G, Wu J, Zhu R, Yang M and Guan H: The changes of 8-OHdG, hOGG1, APE1 and Pol β in lenses of patients with age-related cataract. Curr Eye Res 40: 378-385, 2015.
267. Chatterjee N and Walker GC: Mechanisms of DNA damage, repair, and mutagenesis. Environ Mol Mutagen 58: 235-263, 2017.
268. Maugeri-Saccà M, Bartucci M and De Maria R: DNA damage repair pathways in cancer stem cells. Mol Cancer Ther 11: 1627-1636, 2012.
269. Kong M, Liu L, Chen X, Driscoll KI, Mao P, Böhm S, Kad NM, Watkins SC, Bernstein KA, Wyrick JJ, *et al*: Single-molecule imaging reveals that Rad4 employs a dynamic DNA damage recognition process. Mol Cell 64: 376-387, 2016.
270. Licht CL, Stevnsner T and Bohr VA: Cockayne syndrome group B cellular and biochemical functions. Am J Hum Genet 73: 1217-1239, 2003.
271. Fleming AM and Burrows CJ: 8-Oxo-7,8-dihydroguanine, friend and foe: Epigenetic-like regulator versus initiator of mutagenesis. DNA Repair (Amst) 56: 75-83, 2017.
272. Dinçer Y, Akkaya Ç, Mutlu T, Yavuzer S, Erkol G, Bozluolcay M and Guven M: DNA repair gene OGG1 polymorphism and its relation with oxidative DNA damage in patients with Alzheimer's disease. Neurosci Lett 709: 134362, 2019.
273. Synowiec E, Blasiak J, Zaras M, Szaflik J and Szaflik JP: Association between polymorphisms of the DNA base excision repair genes MUTYH and hOGG1 and age-related macular degeneration. Exp Eye Res 98: 58-66, 2012.
274. Wu X, Lai W, Lin H and Liu Y: Association of OGG1 and MTHFR polymorphisms with age-related cataract: A systematic review and meta-analysis. PLoS One 12: e0172092, 2017.
275. Wang Y, Li F, Zhang G, Kang L, Qin B and Guan H: Altered DNA methylation and expression profiles of 8-oxoguanine DNA glycosylase 1 in lens tissue from age-related cataract patients. Curr Eye Res 40: 815-821, 2015.
276. Yan H, McCane J, Toczylowski T and Chen C: Analysis of the Xenopus Werner syndrome protein in DNA double-strand break repair. J Cell Biol 171: 217-227, 2005.
277. Tranah GJ, Bugni J, Giovannucci E, Ma J, Fuchs C, Hines L, Samson L and Hunter DJ: O6-methylguanine-DNA methyltransferase Leu84Phe and Ile143Val polymorphisms and risk of colorectal cancer in the nurses' health study and physicians' health study (United States). Cancer Causes Control 17: 721-731, 2006.
278. Li F, Wang Y, Zhang G, Zhou J, Yang L and Guan H: Expression and methylation of DNA repair genes in lens epithelium cells of age-related cataract. Mutat Res 766-767: 31-36, 2014.
279. Andley UP: Effects of alpha-crystallin on lens cell function and cataract pathology. Curr Mol Med 9: 887-892, 2009.
280. Horwitz J: Alpha-crystallin can function as a molecular chaperone. Proc Natl Acad Sci USA 89: 10449-10453, 1992.
281. Thampi P, Hassan A, Smith JB and Abraham EC: Enhanced C-terminal truncation of alphaA- and alphaB-crystallins in diabetic lenses. Invest Ophthalmol Vis Sci 43: 3265-3272, 2002.
282. Horwitz J: Alpha-crystallin. Exp Eye Res 76: 145-153, 2003.
283. Christopher KL, Pedler MG, Shieh B, Ammar DA, Petrash JM and Mueller NH: Alpha-crystallin-mediated protection of lens cells against heat and oxidative stress-induced cell death. Biochim Biophys Acta 1843: 309-315, 2014.
284. Wang Z, Sun Y, Zhang Y, Zhang Y, Zhang R, Li C, Liu X, Pan F, Qiao D, Shi X, *et al*: Identification of seven variants in the col4a1 gene that alter RNA splicing by minigene assay. Clin Genet 106: 336-341, 2024.
285. Wang L, Zhu D, Yang Y, He Y, Sun J, Li YM, Wang ZJ and Li P: DNA hypermethylation of COL4A1 in ultraviolet-B-induced age-related cataract models in vitro and in vivo. Int J Ophthalmol 17: 1791-1799, 2024.
286. Fujisawa T and Filippakopoulos P: Functions of bromodomain-containing proteins and their roles in homeostasis and cancer. Nat Rev Mol Cell Biol 18: 246-262, 2017.
287. Bhaumik SR, Smith E and Shilatifard A: Covalent modifications of histones during development and disease pathogenesis. Nat Struct Mol Biol 14: 1008-1016, 2007.
288. Zhang Z, Fu J, Rack JGM, Li C, Voorneveld J, Filippov DV, Ahel I, Luo ZQ and Das C: Legionella metaeffector MavL reverses ubiquitin ADP-ribosylation via a conserved arginine-specific macrodomain. Nat Commun 15: 2452, 2024.
289. Zhu D, Zhang Y and Wang S: Histone citrullination: A new target for tumors. Mol Cancer 20: 90, 2021.
290. Rong X, Qiu X, Jiang Y, Li D, Xu J, Zhang Y and Lu Y: Effects of histone acetylation on superoxide dismutase 1 gene expression in the pathogenesis of senile cataract. Sci Rep 6: 34704, 2016.
291. Kouzarides T: Chromatin modifications and their function. Cell 128: 693-705, 2007.
292. de Lera AR and Ganesan A: Epigenetic polypharmacology: From combination therapy to multitargeted drugs. Clin Epigenetics 8: 105, 2016.
293. Scarano N, Brullo C, Musumeci F, Millo E, Bruzzone S, Schenone S and Cichero E: Recent advances in the discovery of SIRT1/2 inhibitors via computational methods: A perspective. Pharmaceuticals (Basel) 17: 601, 2024.
294. Li G, Jiang H, Chang M, Xie H and Hu L: HDAC6 α-tubulin deacetylase: A potential therapeutic target in neurodegenerative diseases. J Neurol Sci 304: 1-8, 2011.
295. Mimura T, Kaji Y, Noma H, Funatsu H and Okamoto S: The role of SIRT1 in ocular aging. Exp Eye Res 116: 17-26, 2013.
296. Ağaoğlu NB, Varol N, Yıldız SH, Karaosmanoğlu C, Duman R, Özdemir Erdoğan M and Solak M: Relationship between SIRT1 gene expression level and disease in age-related cataract cases. Turk J Med Sci 49: 1068-1072, 2019.
297. Zheng T and Lu Y: Changes in SIRT1 expression and its downstream pathways in age-related cataract in humans. Curr Eye Res 36: 449-455, 2011.

298. Zentner GE and Henikoff S: Regulation of nucleosome dynamics by histone modifications. Nat Struct Mol Biol 20: 259-266, 2013.
299. Bannister AJ and Kouzarides T: Regulation of chromatin by histone modifications. Cell Res 21: 381-395, 2011.
300. Black JC, Van Rechem C and Whetstine JR: Histone lysine methylation dynamics: Establishment, regulation, and biological impact. Mol Cell 48: 491-507, 2012.
301. Cheng X: Structural and functional coordination of DNA and histone methylation. Cold Spring Harb Perspect Biol 6: a018747, 2014.
302. Bachman KE, Rountree MR and Baylin SB: Dnmt3a and Dnmt3b are transcriptional repressors that exhibit unique localization properties to heterochromatin. J Biol Chem 276: 32282-32287, 2001.
303. Shi H, Chai P, Jia R and Fan X: Novel insight into the regulatory roles of diverse RNA modifications: Re-defining the bridge between transcription and translation. Mol Cancer 19: 78, 2020.
304. Tang J, Zhou C, Ye F, Zuo S, Zhou M, Lu L, Chai P and Fan X: RNA methylation homeostasis in ocular diseases: All eyes on Me. Prog Retin Eye Res 105: 101335, 2025.
305. Jia G, Fu Y and He C: Reversible RNA adenosine methylation in biological regulation. Trends Genet 29: 108-115, 2013.
306. Kumari R, Ranjan P, Suleiman ZG, Goswami SK, Li J, Prasad R and Verma SK: mRNA modifications in cardiovascular biology and disease: With a focus on m6A modification. Cardiovasc Res 118: 1680-1692, 2022.
307. Dominissini D, Moshitch-Moshkovitz S, Schwartz S, Salmon-Divon M, Ungar L, Osenberg S, Cesarkas K, Jacob-Hirsch J, Amariglio N, Kupiec M, *et al*: Topology of the human and mouse m6A RNA methylomes revealed by m6A-seq. Nature 485: 201-206, 2012.
308. Meyer KD, Saletore Y, Zumbo P, Elemento O, Mason CE and Jaffrey SR: Comprehensive analysis of mRNA methylation reveals enrichment in 3' UTRs and near stop codons. Cell 149: 1635-1646, 2012.
309. Zaccara S, Ries RJ and Jaffrey SR: Reading, writing and erasing mRNA methylation. Nat Rev Mol Cell Biol 20: 608-624, 2019.
310. Chen X, Wang Y, Wang JN, Cao QC, Sun RX, Zhu HJ, Zhang YR, Ji JD and Liu QH: m^6A modification of circSPECC1 suppresses RPE oxidative damage and maintains retinal homeostasis. Cell Rep 41: 111671, 2022.
311. Sheng Z, Pan Y, Shao L and Bao Y: METTL3 mediates CPB1 expression by regulating transcription factor BACH2 to promote apoptosis and oxidative stress of lens epithelial cells. J Bioenerg Biomembr 57: 161-171, 2025.
312. Wang T, Kong S, Tao M and Ju S: The potential role of RNA N6-methyladenosine in cancer progression. Mol Cancer 19: 88, 2020.
313. Kang L, Bao S, Li P, Zhang G, Zhu X, Ji M and Guan H: METTL14-mediated depression of NEIL1 aggravates oxidative damage and mitochondrial dysfunction of lens epithelial cells through regulating KEAP1/NRF2 pathways. Cell Signal 127: 111623, 2025.
314. Ye HF, Zhang X, Zhao ZN, Zheng C, Fei P, Xu Y, Lyu J, Chen JL, Guo XX, Zhu H and Zhao PQ: Characterization of N^6-methyladenosine long non-coding RNAs in sporadic congenital cataract and age-related cataract. Int J Ophthalmol 17: 1973-1986, 2024.
315. Wang Y, Li P, Wang C, Bao S, Wang S, Zhang G, Zou X, Wu J, Guan Y, Ji M and Guan H: Lens epithelium cell ferroptosis mediated by m^6A-lncRNA and GPX4 expression in lens tissue of age-related cataract. BMC Ophthalmol 23: 514, 2023.
316. Luo G, Xu W, Chen X, Wang S, Wang J, Dong F, Hu DN, Reinach PS and Yan D: NSUN2-mediated RNA m^5C modification modulates uveal melanoma cell proliferation and migration. Epigenetics 17: 922-933, 2022.
317. Zhao Y, Kong L, Pei Z, Li F, Li C, Sun X, Shi B and Ge J: m^7G methyltransferase METTL1 promotes post-ischemic angiogenesis via promoting VEGFA mRNA translation. Front Cell Dev Biol 9: 642080, 2021.
318. Wu C, Liu Z, Ma L, Pei C, Qin L, Gao N, Li J and Yin Y: MiRNAs regulate oxidative stress related genes via binding to the 3' UTR and TATA-box regions: A new hypothesis for cataract pathogenesis. BMC Ophthalmol 17: 142, 2017.
319. Gu X, Sun J, Li S, Wu X and Li L: Oxidative stress induces DNA demethylation and histone acetylation in SH-SY5Y cells: Potential epigenetic mechanisms in gene transcription in Aβ production. Neurobiol Aging 34: 1069-1079, 2013.
320. Niu Y, DesMarais TL, Tong Z, Yao Y and Costa M: Oxidative stress alters global histone modification and DNA methylation. Free Radic Biol Med 82: 22-28, 2015.
321. Li Q, Li X, Tang H, Jiang B, Dou Y, Gorospe M and Wang W: NSUN2-mediated m5C methylation and METTL3/METTL14-mediated m6A methylation cooperatively enhance p21 translation. J Cell Biochem 118: 2587-2598, 2017.
322. Wu Q and Ni X: ROS-mediated DNA methylation pattern alterations in carcinogenesis. Curr Drug Targets 16: 13-19, 2015.
323. Chouliaras L, Mastroeni D, Delvaux E, Grover A, Kenis G, Hof PR, Steinbusch HW, Coleman PD, Rutten BP and van den Hove DL: Consistent decrease in global DNA methylation and hydroxymethylation in the hippocampus of Alzheimer's disease patients. Neurobiol Aging 34: 2091-2099, 2013.
324. Sjöström M, Zhao SG, Levy S, Zhang M, Ning Y, Shrestha R, Lundberg A, Herberts C, Foye A, Aggarwal R, *et al*: The 5-hydroxymethylcytosine landscape of prostate cancer. Cancer Res 82: 3888-3902, 2022.
325. Vatapalli R, Rossi AP, Chan HM and Zhang J: Cancer epigenetic therapy: Recent advances, challenges, and emerging opportunities. Epigenomics 17: 59-74, 2025.
326. Gomez S, Tabernacki T, Kobyra J, Roberts P and Chiappinelli KB: Combining epigenetic and immune therapy to overcome cancer resistance. Semin Cancer Biol 65: 99-113, 2020.
327. Zhang P and Zhang M: Epigenetic alterations and advancement of treatment in peripheral T-cell lymphoma. Clin Epigenetics 12: 169, 2020.
328. Raj K and Mufti GJ: Azacytidine (Vidaza(R)) in the treatment of myelodysplastic syndromes. Ther Clin Risk Manag 2: 377-388, 2006.
329. Welch JS, Petti AA, Miller CA, Fronick CC, O'Laughlin M, Fulton RS, Wilson RK, Baty JD, Duncavage EJ, Tandon B, *et al*: TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. N Engl J Med 375: 2023-2036, 2016.
330. Duvic M and Vu J: Vorinostat in cutaneous T-cell lymphoma. Drugs Today (Barc) 43: 585-599, 2007.
331. McDermott J and Jimeno A: Belinostat for the treatment of peripheral T-cell lymphomas. Drugs Today (Barc) 50: 337-345, 2014.
332. Smolewski P and Robak T: The discovery and development of romidepsin for the treatment of T-cell lymphoma. Expert Opin Drug Discov 12: 859-873, 2017.
333. Kim YH, Bagot M, Pinter-Brown L, Rook AH, Porcu P, Horwitz SM, Whittaker S, Tokura Y, Vermeer M, Zinzani PL, *et al*: Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): An international, open-label, randomised, controlled phase 3 trial. Lancet Oncol 19: 1192-1204, 2018.
334. Geissler K, Koristek Z, Del Castillo TB, Novák J, Rodríguez-Macías G, Metzelder SK, Illes A, Mayer J, Arnan M, Keating MM, *et al*: Oral decitabine/cedazuridine versus intravenous decitabine for acute myeloid leukaemia: A randomised, crossover, registration, pharmacokinetics study. Br J Haematol 205: 1734-1745, 2024.
335. Fu S, Hu W, Iyer R, Kavanagh JJ, Coleman RL, Levenback CF, Sood AK, Wolf JK, Gershenson DM, Markman M, *et al*: Phase 1b-2a study to reverse platinum resistance through use of a hypomethylating agent, azacitidine, in patients with platinum-resistant or platinum-refractory epithelial ovarian cancer. Cancer 117: 1661-1669, 2011.
336. Mathew OP, Ranganna K and Milton SG: Involvement of the antioxidant effect and anti-inflammatory response in butyrate-inhibited vascular smooth muscle cell proliferation. Pharmaceuticals (Basel) 7: 1008-1027, 2014.
337. Ziemka-Nalecz M and Zalewska T: Neuroprotective effects of histone deacetylase inhibitors in brain ischemia. Acta Neurobiol Exp (Wars) 74: 383-395, 2014.
338. Qiu X, Rong X, Yang J and Lu Y: Evaluation of the antioxidant effects of different histone deacetylase inhibitors (HDACis) on human lens epithelial cells (HLECs) after UVB exposure. BMC Ophthalmol 19: 42, 2019.
339. Hong DS, Kang YK, Borad M, Sachdev J, Ejadi S, Lim HY, Brenner AJ, Park K, Lee JL, Kim TY, *et al*: Phase 1 study of MRX34, a liposomal miR-34a mimic, in patients with advanced solid tumours. Br J Cancer 122: 1630-1637, 2020.
340. Ottosen S, Parsley TB, Yang L, Zeh K, van Doorn LJ, van der Veer E, Raney AK, Hodges MR and Patick AK: In vitro antiviral activity and preclinical and clinical resistance profile of miravirsen, a novel anti-hepatitis C virus therapeutic targeting the human factor miR-122. Antimicrob Agents Chemother 59: 599-608, 2015.

341. Vermeire S, Sands BE, Tilg H, Tulassay Z, Kempinski R, Danese S, Bunganič I, Nitcheu J, Santo J, Scherrer D, *et al*: ABX464 (obefazimod) for moderate-to-severe, active ulcerative colitis: a phase 2b, double-blind, randomised, placebo-controlled induction trial and 48 week, open-label extension. Lancet Gastroenterol Hepatol 7: 1024-1035, 2022.
342. Winkle M, El-Daly SM, Fabbri M and Calin GA: Noncoding RNA therapeutics-challenges and potential solutions. Nat Rev Drug Discov 20: 629-651, 2021.
343. Zhang X, Qiu H, Zhang F and Ding S: Advances in single-cell multi-omics and application in cardiovascular research. Front Cell Dev Biol 10: 883861, 2022.
344. Armand EJ, Li J, Xie F, Luo C and Mukamel EA: Single-cell sequencing of brain cell transcriptomes and epigenomes. Neuron 109: 11-26, 2021.
345. Nam AS, Chaligne R and Landau DA: Integrating genetic and non-genetic determinants of cancer evolution by single-cell multi-omics. Nat Rev Genet 22: 3-18, 2021.
346. Liu X, Zhang L, Li X, Chen L, Lu L, Yang Y, Wu Y, Zheng L, Tang J, Wang F, *et al*: Single-cell multi-omics profiling uncovers the immune heterogeneity in HIV-infected immunological non-responders. EBioMedicine 115: 105667, 2025.
347. Tangeman JA, Rebull SM, Grajales-Esquivel E, Bendezu-Sayas S, Robinson ML, Lachke SA and Del Rio-Tsonis K: Integrated single-cell multiomics uncovers foundational regulatory mechanisms of lens development and pathology. Development 151: dev202249, 2024.
348. Vickovic S, Eraslan G, Salmén F, Klughammer J, Stenbeck L, Schapiro D, Äijö T, Bonneau R, Bergenstråhle L, Navarro JF, *et al*: High-definition spatial transcriptomics for in situ tissue profiling. Nat Methods 16: 987-990, 2019.
349. Robles-Remacho A, Sanchez-Martin RM and Diaz-Mochon JJ: Spatial transcriptomics: emerging technologies in tissue gene expression profiling. Anal Chem 95: 15450-15460, 2023.
350. Cilento MA, Sweeney CJ and Butler LM: Spatial transcriptomics in cancer research and potential clinical impact: A narrative review. J Cancer Res Clin Oncol 150: 296, 2024.
351. Duan R, Fu Q, Sun Y and Li Q: Epigenetic clock: A promising biomarker and practical tool in aging. Ageing Res Rev 81: 101743, 2022.
352. Horvath S, Lu AT, Haghani A, Zoller JA, Li CZ, Lim AR, Brooke RT, Raj K, Serres-Armero A, Dreger DL, *et al*: DNA methylation clocks for dogs and humans. Proc Natl Acad Sci USA 119: e2120887119, 2022.
353. Margiotti K, Monaco F, Fabiani M, Mesoraca A and Giorlandino C: Epigenetic clocks: In aging-related and complex diseases. Cytogenet Genome Res 163: 247-256, 2023.
354. Chen J, Yuan XL, Zhou X, Xu J, Zhang X and Duan X: Mendelian randomization implicates causal association between epigenetic age acceleration and age-related eye diseases or glaucoma endophenotypes. Clin Epigenetics 16: 106, 2024.