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Review

Circular and long non-coding RNAs and their role in ophthalmologic diseases

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Long non-coding RNAs are >200-nucleotide-long RNA molecules which lack or have limited protein-coding potential. They can regulate protein formation through several different mechanisms. Similarly, circular RNAs are reported to play a critical role in post-transcriptional gene regulation. Changes in the expression pattern of these molecules are known to underlie various diseases, including cancer, cardiovascular, neurological and immunological disorders (Rinn & Chang, 2012; Sun & Kraus, 2015). Recent studies suggest that they are differentially expressed both in healthy ocular tissues as well as in eye pathologies, such as neovascularization, proliferative vitreoretinopathy, glaucoma, cataract, ocular malignancy or even strabismus (Li *et al.*, 2016). Aetiology of ocular diseases is multifactorial and combines genetic and environmental factors, including epigenetic and non-coding RNAs. In addition, disorders like diabetic retinopathy or age-related macular degeneration lack biomarkers for early detection as well as effective treatment methods that would allow controlling the disease progression at its early stages. The newly discovered non-coding RNAs seem to be the ideal candidates for novel molecular markers and therapeutic strategies. In this review, we summarized the current knowledge about gene expression regulators – long non-coding and circular RNA molecules in eye diseases.

Key words: ophthalmologic diseases, neovascularization, retinopathy, AMD, ocular malignancy, long non-coding RNAs, circRNAs

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Abbreviations: ADARs, adenosine deaminases acting on RNA; AGA, Amadori-glycated albumin; AMD, age-related macular degeneration; A-to-I, adenosine to inosine; CDKN2B-AS1, cyclin-dependent kinase inhibitor 2B antisense non-coding RNA; circRNA, circular RNA; CN, corneal neovascularization; CNV, choroidal neovascularization; CRYBB2, Crystallin Beta B2; DR, Diabetic retinopathy; ecircRNA, exonic circRNA; ElciRNAs, exonic, exon-intron; EMT, endothelial-mesenchymal transition; EMT, epithelial-mesenchymal transition; EOMs, extraocular muscles; ERM, epiretinal membrane; FXS, Fragile X syndrome; GAS5, Growth Arrest Specific 5; GFS, glaucoma filtration surgery; GTF; glaucoma Tenon's capsule fibroblasts; HRECs, human retinal endothelial cells; IL-1β, interleukin-1β; IL-6, interleukin-6; iNOS, Nitric Oxide Synthases isoform; IOP, increased intraocular pressure; IRESs, internal ribosome entry sites; LECs, lens epithelial cells; lincRNAs, long intergenic RNAs; lncRNA, long non-coding RNA; m6A, N6- methyladenosine; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemotactic protein-1; MIAT, Myocardial infarction associated transcript; miRNA, microRNAs; MBL/MBNL1, Muscleblind-Like/Muscleblind Like Splicing Regulator 1; NF-κB, nuclear factor κB; Nrf2, nuclear factor 2; NTG, normal tension glaucoma; PANDAR, promoter of CDKN1A antisense DNA damage-activated RNA, PCO, Posterior capsule opacification; PDGF, Platelet-Derived Growth Factor; PDR, proliferative diabetic retinopathy; PlncRNA-1, prostate cancer-up-regulated long noncoding RNA 1; POAG, primary open angle glaucoma; PRC2; polycomb repressive complex 2; pre-mRNA, pre-messenger RNA; PVR, Proliferative vitreoretinopathy; QKI protein, Quaking protein; RBPs, RNA binding proteins; RCA, rolling circle amplification; RNCR2, retinal ncRNA 2; RNCR3, retinal ncRNA3; ROP, retinopathy of prematurity; RPE, retinal pigment epithelial; sORF, small open reading frame; SOX2OT, SOX2 overlapping transcript; STAT3, signal transducer and activator of transcription 3; TGFβ1, transforming growth factor β1; TGFβ2, transforming growth factor β2; THOR, testis-associated highly conserved oncogenic lncRNA; TNFα, tumour necrosis factor-alpha; VEGF, Vascular Endothelial Growth Factor; VKH, Vogt-Koyanagi-Harada; XIST, X-inactive specific transcript

INTRODUCTION

Functional regulation of gene expression at the epigenetic, transcriptional and post-transcriptional stage has recently been thoroughly analyzed. It is well established that changes in the long non-coding RNA (lncRNA) and circular RNA (circRNA) levels are associated with the occurrence of multiple disorders, including ocular diseases. Both lncRNAs and circRNAs are relatively newly discovered molecules, but with other non-coding RNA molecules and proteins, they form a network of interactions regulating all cellular processes (Sun & Kraus, 2015; Tan, 2014; Zhong *et al.*, 2018). Ophthalmological diseases constitute a huge group of various multifactorial disorders, often associated with other systemic diseases. Recently, it was proven that epigenetics and non-coding RNAs must also be taken into account as key players in their development. Here we recapitulate the current data about lncRNAs and circRNAs in ophthalmology and exhibit their potential as molecular markers and therapeutic targets.

CIRCULAR AND LONG NON-CODING RNAS

lncRNAs are defined as RNA transcripts with little or no coding potential (Sun & Kraus, 2015). They are longer than 200 nucleotides (nt) and were recently shown to be involved in numerous cellular processes ranging from pluripotency of embryonic stem cells, cell-cycle regulation, to the development of cancer, and other diseases. lncRNAs force the formation of ribonucleic-protein complexes, which in turn impact the regulation of gene expression (Rinn & Chang, 2012). According to the genome location, morphology, sequence, structure, and function features, lncRNAs can be categorized into different groups (Wang *et al.*, 2017a). They can be detected in areas separated from genes encoding known protein-coding transcripts (lincRNAs – long intergenic RNAs) as well as inside protein-coding genes. Genic lncRNAs are situated in exonic or intronic regions and

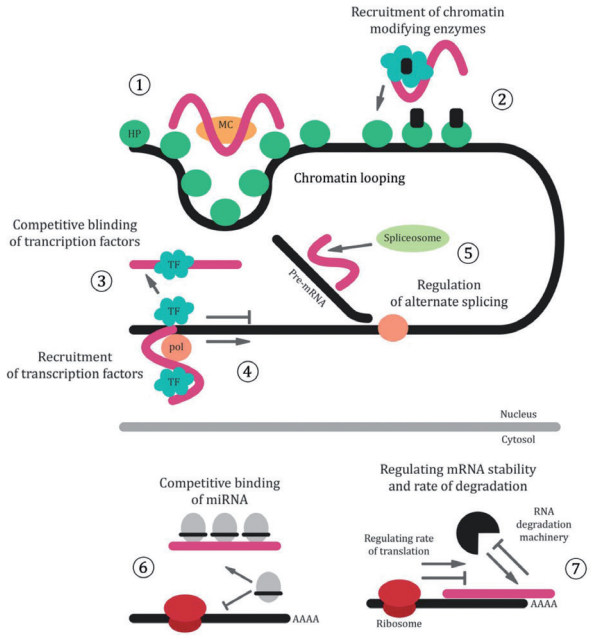

Figure 1. Summary of the lncRNA mechanisms of action.
lncRNAs (fuchsia line) affect gene expression in the nucleus by controlling chromatin looping ①, recruiting chromatin-modifying enzymes to the DNA ②, acting as a decoy to decrease transcription factor availability ③, recruiting transcription factors to the promoter site ④, regulating alternative splicing of the transcript ⑤. In the cytoplasm, they control miRNA availability by competing with miRNA target sites on the mRNA ⑥ or by binding to the mRNA to control the rate of translation or RNA degradation ⑦. Abbreviations: HP – histone proteins; MC – mediator complex; pol – RNA polymerase; TF – transcription factor.

can also be divided into those that overlap protein-coding loci in the sense or antisense direction (Sun & Kraus, 2015). The biogenesis of lncRNAs, like mRNAs, occurs in the nucleus and depends on RNA Polymerase II and III. lncRNA promotors coincide with epigenetic modifications that regulate transcription factor binding in order to favour or diminish gene expression (Beermann *et al.*, 2016). Post-transcriptional processing of lncRNAs also shares similar modifications with mRNAs including 5'-capping (Ayupe *et al.*, 2015), 3'-polyadenylation, canonical and alternative splicing events and RNA editing processes (Bond & Fox, 2009; Khandelwal *et al.*, 2015). Interestingly, it was observed that lncRNAs are capable of forming secondary structures based on base-pairing or ribose backbone interactions that determine the final function of the molecule (Beermann *et al.*, 2016; Mercer *et al.*, 2009). High-throughput sequencing of lncRNAs showed that they contain modified bases that also impact their structure and function (Kellner *et al.*, 2010). In addition, post-transcriptional lncRNA modifications are often reversible which confirms that the functional regulation of these molecules is highly complex (Mercer & Mattick, 2013).

Gene regulation by lncRNAs occurs at many different levels, through nuclear and cytoplasmic mechanisms. The cellular localization of a lncRNA can indicate its mode of action. Nuclear lncRNAs can be involved in histone modification or direct transcriptional regulation. Cytoplasmic lncRNAs regulate expression at the post-transcriptional level by "sponging" miRNA or interacting with RNA-binding proteins (Long *et al.*, 2017). Figure 1 presents the mechanisms of action of long non-coding RNAs.

lncRNAs were shown to regulate gene expression by their ability to interact with DNA, RNA, and proteins (Tang *et al.*, 2017). Hence, the dysregulation of lncRNA expression patterns can impact cell functions which manifests as a pathological process in disease. Profiling of lncRNAs revealed a difference in their expression between normal and carcinogenic cells (Rasool *et al.*, 2016) and they were recognized as having oncogenic and suppressive roles in neoplasia (Yan & Wang, 2012). For example, down-regulation of *H19*, a widely known lncRNA having a role in cancerogenesis, reduces the growth of breast and lung cancers (Chen *et al.*, 2017b; Tessier *et al.*, 2004). In bladder cancer, the up-regulation of metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) is associated with the blocking of apoptosis and enhancing cancer cell proliferation and migration (Taheri *et al.*, 2018). lncRNAs are involved in regulating the ageing process, thereby contributing to the development of age-related diseases such as obesity, diabetes, and neurodegeneration. One of the previously mentioned lncRNAs, *H19*, was reported to control imprinting of various genes, including insulin-like growth factor 2, and to be involved in fat metabolism and deposition (Kim *et al.*, 2016). Many lncRNAs play a role in the regulation of gene expression in the central nervous system. They were described to contribute to synapse formation, maturation of neurons, oligodendrocytes and neuronal-glial fate transition as well as to the regulation of hippocampal development (Mercer *et al.*, 2010). An interesting example of disorders involving lncRNAs is Fragile X syndrome (FXS), a heritable mental disorder caused by expansion of triplet nucleotide repeats in *FMR1* gene encoding FMRP – neuronal development protein. It was reported that a vast majority of lncRNAs, which may play a role in FXS, originate from *FMR1* gene (Pastori & Wahlestedt, 2012). There are many other disorders triggered by lncRNA dysregulation, such as rheumatic diseases (Tang *et al.*, 2017), cardiovascular diseases (Sallam *et al.*, 2018) and autoimmune diseases. The regulatory networks in various disorders where gene expression patterns are disturbed often involve lncRNA-miRNA-mRNA interactions and still remain to be precisely characterized in order to better understand the pathomechanisms (Zhang *et al.*, 2017d).

Circular RNAs (circRNA) – the newly described class of single-stranded, non-coding and ubiquitously expressed RNAs, which has been broadly studied in recent years also can serve as useful markers in ocular diseases. circRNAs are commonly classified into three types: exonic circRNAs, exonic-intronic circRNAs, and intronic circRNAs. Most exonic circRNAs occur in the cytoplasm, whereas the other two are mainly found in the nucleus (Memczak *et al.*, 2013). The first circRNA transcripts were identified in the early 1990s, but a breakthrough in circRNA research occurred in 2013 after the Salzman's group provided evidence that certain human transcripts prefer a circular form rather than linear (Salzman *et al.*, 2012). circRNAs can arise from virtually any part of the genome (exonic and non-coding, transcripts antisense to 5' and 3' UTRs or intergenic regions) which causes significant differences in the length of molecules (Rong *et al.*, 2017). Circular transcripts are considered to be ubiquitous and evolutionary conserved among species, suggesting a significant regulatory role.

Biogenesis of circular transcripts is a highly regulated process. Covalently closed RNA molecules might appear as the result of direct RNA ligation, circularization of introns which escaped from debranching or may derive from the intermediates of processed RNAs. Howev-

er, the large majority are generated from pre-messenger RNA (pre-mRNA) in the back-splicing process (Wang & Wang, 2015). Back-splicing is the more advanced type of splicing, however, circRNA that cannot be formed in the canonical manner still requires the presence of canonical spliceosomal machinery and signals (Chen & Yang, 2015). In contrast to canonical splicing, where an upstream 5' splice donor site binds to the downstream 3' splice acceptor site in a sequential order to generate the linear transcripts, back-splicing involves reverse orientation that links a downstream 5' splice donor site to an upstream 3' splice acceptor resulting in exons in a reversed order (Zhang *et al.*, 2014).

The biogenesis of circRNA also depends on the location of the sequence within the genome. Hence, two general factors promoting the circularization are known – *cis*-elements and *trans*-factors-dependent. Circular RNAs classification is based on their origin, taking into account the contribution of *cis*-elements: exonic, exon-intron (EIciRNAs) and intronic molecules (Jeck *et al.*, 2013). However, Jeck *et al.* provided evidence (2013) that nearly all circRNAs comprise of exonic sequences of protein-coding genes, formed from one or multiple exons, most frequently 1-5 (Memczak *et al.*, 2013). A variety of RNA-binding proteins – *trans*-factors also has a significant role in the production of circRNA. Muscleblind (MBL/MBNL1) splicing factor promotes the circularization of certain transcripts. Moreover, Ashwal-Fluss and coworkers in 2014 (Ashwal-Fluss *et al.,* 2014) described the circular form of Muscleblind (*circMbl*) in flies and humans, resulting from the circularization of the second exon. They discovered putative MBL binding sites present within the intronic regions flanking the second exon. This led to the conclusion that certain MBL isoforms might promote their own exon circularization. Indeed, the level of *circMbl* was decreased after knockdown of endogenous *MBL*, demonstrating its function as a *circMbl* promoting factor (Ashwal-Fluss *et al.*, 2014). The following example of binding elements, adenosine deaminases acting on RNA – ADARs, which are known to convert adenosine to inosine in double-stranded RNA, were reported to affect the circRNAs biogenesis in a negative manner. It is suggested that negative regulation is associated with their function – adenosine to inosine (A-to-I) RNA editing. High level of A-to-I editing in double-stranded RNA is known to deplete RNA pairing, which results in diminished pairing and closing of the ends, while lower levels of ADAR promote more stable pairing across the introns and back-splicing for circular RNA production (Chen & Yang, 2015). The abundance of circRNAs in humans is also regulated by Quaking (QKI) – RNA binding protein, which mediates exon circularization by binding at up- and downstream position of circRNA-forming exons and dimerization coupled with bringing 3' and 5' ends of the exon in close proximity which results in joining (Salzman, 2016). Intriguingly, the circularization of linear transcripts is possible after the insertion of Quaking binding sites into the flanking region of linear RNAs (Conn *et al.*, 2015). Even though circular RNA molecules are a relatively new class of long, non-coding RNAs, extensive research has been carried out to determine the function they perform. Many circRNAs are currently considered as regulatory molecules, particularly affecting the function of microRNAs (miRNA), due to the presence of a number of binding sites allowing the interaction to occur. This type of relationship results in circRNA-mediated repression of miRNA function, where endogenous circular transcripts work as miRNA sponges. It was shown that conserved

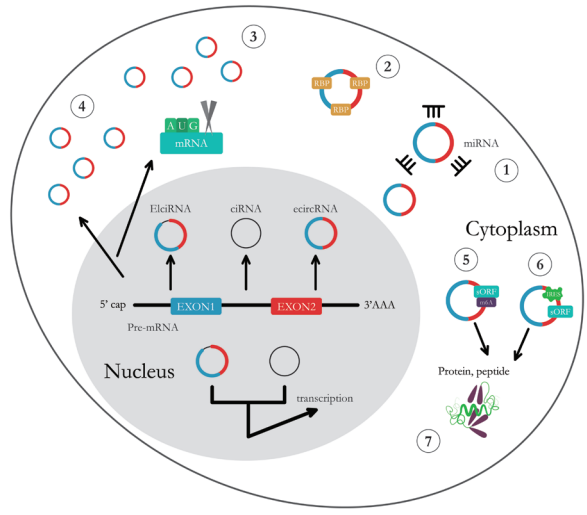

Figure 2. The function of circRNAs in eukaryotic cells.
circRNAs function as microRNA (miRNA) sponges ①. circRNAs bind RNA binding proteins (RBPs) as transcription regulators ②. circRNAs remove start codons from mature mRNAs to reduce protein translation ③. circRNA production competes with canonical pre-mRNA splicing in gene regulation ④. The translation of circRNAs is driven by m6A ⑤. circRNAs with internal ribosome entry sites (IRESs) can be translated ⑥. ElciRNAs and ciRNAs promote transcription ⑦. Abbreviations: ecircRNA – exonic circRNA; ElciRNA – exonic-intronic circRNA; IRES – internal ribosome entry site; m6A – N^6-methyladenosine; RBP – RNA binding protein; sORF – small open reading frame.

miRNA and AGO protein binding sites are enriched in circRNAs. For at least one specific circRNA, *ciRS-75* (also called *CDR1as*), has more than 70 binding sites for *miR-7*. It was shown *in vivo* that this circRNA impairs the regulatory role of *miR-7*. However, whether or not all circRNAs function as miRNA sponges is still not clear. An additional function of circRNAs is the transport of miRNAs. However, available experimental data are not very comprehensive, especially for their global regulation and function (Memczak *et al.*, 2013). Apart from the function as miRNA sponges, circRNAs were shown to regulate alternative splicing and to modulate the expression of parental genes (Guo *et al.*, 2014; Salzman *et al.*, 2013; Salzman *et al.*, 2012; Zhang *et al.*, 2013). Recently, circRNAs were studied in relation to their role in the translation of proteins or peptides (Pamudurti *et al.*, 2017). Four mechanisms of circRNA protein or peptide translation have been identified up to now: (1) involving internal ribosome entry sites (IRESs) within synthetic circRNA; (2) effective circRNAs translation via rolling circle amplification (RCA); (3) translation driven by N^6-methyladenosine (m6A) and (4) a novel cap-independent translation mechanism (Li *et al.*, 2017c; Wang & Wang, 2015; Yang *et al.*, 2017). More importantly, it is becoming evident that circRNAs may be involved in many types of non-neoplastic diseases, such as e.g. atherosclerotic vascular disease risk, neurological disorders, prion and Alzheimer diseases, rheumatoid arthritis or kidney injury. circRNAs can play a crucial role in tumorigenic processes in different types of cancers, such as: ovarian carcinoma, bladder, papillary thyroid, colorectal, lung or breast cancers (Hu *et al.*, 2018b; Ren *et al.*, 2018; Wang *et al.*, 2018b; Yang *et al.*, 2018a; Zhang *et al.*, 2018). circRNAs were described also as potential disease biomarkers in human saliva and blood and as biomarkers for ageing and gastric cancer (Bachmayr-Heyda *et al.*,

2015; Guo *et al.*, 2014; Memczak *et al.*, 2015; Zhang *et al.*, 2013). Taken together, these findings indicate that circRNAs have regulating roles in biological development and disease initiation and progression. These properties of circRNA give them the potential to become new clinical diagnostic and prognostic markers and to provide new insight into the treatment of disease. The function of circRNAs in cells is shown in Fig. 2.

CIRCRNAS AND LNCRNAS IN OCULAR DISEASES

Neovascularization

Formation of new blood vessels is a process necessary for proper development, but under pathological conditions such as tissue damage or hypoxia abnormal vascular growth occurs. Neovascularization is associated with a number of ocular disorders including corneal injury or infection, retinopathy of prematurity (ROP), age-related macular degeneration (AMD) and proliferative diabetic retinopathy (PDR) (Xu *et al.*, 2014; Zhang *et al.*, 2017c). In all of these conditions the genetic background plays a significant role, however, it does not fully explain the diversity of the clinical picture. Participation of lncRNAs and circRNAs in most biological processes, including cell differentiation, proliferation, and apoptosis, can describe the relationship between gene expression and environmental factors affecting the progress of these diseases (Yan *et al.*, 2014).

Corneal neovascularization

The causes of corneal neovascularization (CN) include infections, injuries, and graft rejections. The process is strictly controlled by two counterbalancing systems: stimulators and inhibitors of angiogenesis, and can lead to severe vision loss or even blindness (Huang *et al.*, 2015). Huang *et al.* provided evidence that lncRNAs are potential regulators of CN pathogenesis. They identified 154 lncRNAs differentially expressed between normal and vascularized corneas of which 60 were down-regulated, and 94 were up-regulated. Expression patterns of randomly selected lncRNAs were also compared to the patterns of antiangiogenic factors – Platelet-Derived Growth Factor (PDGF) and endostatin, and proangiogenic factors – Vascular Endothelial Growth Factor (VEGF) and Nitric Oxide Synthases isoform (iNOS). For example, the human ortholog of *NR_033585* was significantly up-regulated in the vascularized corneas and demonstrated similar expression profile as VEGF. By contrast, the human ortholog of lincRNA: chr8:129102060–129109035 reverse strand, was markedly down-regulated and resembled PDGF and endostatin in action (Huang *et al.*, 2015). This study provided a novel insight into CN pathogenesis and showed that lncRNAs can become potential targets for its prevention or treatment (Li *et al.*, 2016).

Retinopathy of Prematurity

Retinopathy of prematurity (ROP) occurs in premature neonates, in whom at the time of birth the retina remains incompletely vascularized. Instead of proper vascular development, vasculogenesis in the premature neonatal retina is disrupted. At the border of the avascular retina, abnormal vessels grow into the vitreous resulting in haemorrhage and tractional detachment of the retina (Neely & Gardner, 1998). Development of the retina and its vascularization is a complicated process, and it depends on many factors, which include long non-coding RNAs. *Vax2os I* is a retina-specific lncRNA that regulates the cell cycle in photoreceptor progenitor cells. Disturbances in its expression pattern result in the delay of the differentiation process (Meola *et al.*, 2012). *TUG 1* is another lncRNA found in developing retina. It is responsible for the formation of photoreceptors by activation of specific genes and is also expressed in endothelial cells during ROP (Michalik *et al.*, 2014; Young *et al.*, 2005). Bioinformatics analysis performed by Yang *et al.* showed several circular and long non-coding RNAs involved in ROP development and progression. They correlated the expression of lncRNAs *POLDIP2, GAS5, NEFL* and *UHRF1* with *miRNA-128-3p* and *miRNA-9-5p* levels which significantly differ between retinas of neonatal mice and rats with and without ROP. Similarly, circRNA *ZNF280C_hsa_circ_001211* and *SIAE_hsa_circ_002083* are also differentially expressed in ROP. Their exact function is still unclear, but the authors implied an association with TGFβ and PI3K-Akt signalling pathways responsible for cell migration and angiogenesis (Yang *et al.*, 2018c). *In vitro* and *in vivo* studies of lncRNA metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) revealed that it regulates angiogenesis in developing retina as well as in disorders related to hypoxia. Silencing *MALAT 1* expression by siRNA resulted in a reduction of total MALAT 1 levels, both cytoplasmic and nuclear and increased basal endothelial cell migration, whereas cell proliferation was down-regulated. Therefore, inhibition of this lncRNA may become a potential therapeutic strategy for pathological retinal neovascularization (Michalik *et al.*, 2014).

Age-related Macular Degeneration

Age-related macular degeneration (AMD) is one of the most common causes of adult blindness in developed countries. Clinically, it can be classified into two categories: non-neovascular (also known as "dry" or "nonexudative") or neovascular (also known as "wet" or "exudative") (Yonekawa *et al.*, 2015). Wet AMD is associated with neovascularization originating from the choroidal vasculature and extending into subretinal space (Neely & Gardner, 1998). The probability of occurrence of AMD is associated with both environmental factors and genetic background.

Caucasian race, female gender, age over 50, Caucasian race, female gender, age over 50, polymorphism in complement factor H in the 1q32 region and variation in the *ARMS2* gene on chromosome 10 are well established unmodifiable risk factors. Cigarette smoking is the only proven modifiable factor. However, the influence of other environmental factors such as diet is not excluded (Yonekawa *et al.*, 2015).

AMD is a multifactorial disease that can also be associated with the dysregulation of non-coding RNAs. *Vax2os1* and *Vax2os2* are lncRNAs that can interact with nuclear factor κB (NF-κB). NF-κB is a transcription factor involved in the regulation of the expression of more than 100 genes. It plays an essential role in cell migration, invasion and inflammation reaction during angiogenesis (Kaarniranta & Salminen, 2009). In the murine model of choroidal neovascularization (CNV) as well as in aqueous humour of CNV patients *Vax2os1* and *Vax2os2* are significantly down-regulated. They are antisense transcripts of *Vax2* gene, a critical regulator of eye development, and are highly expressed in the choroid and retinal vasculature. They can be potentially used as biomarkers of early CNV (Li *et al.*, 2016; Xu *et al.*, 2014).

Dry AMD progression is slower than wet AMD and less likely leads to loss of the central visual field. It also causes severe visual impairment, especially in the advanced form of the disease called geographic atrophy which can develop in areas of regressed large drusen but also independently, in areas of prior pigmentary changes suggesting RPE dysfunction (Yonekawa *et al.*, 2015). Early AMD was reported to be influenced by oxidative stress, abnormal lipid metabolism, cell apoptosis and dysfunction of the immune system, whereas lncRNAs are also associated with these processes (Sun & Kraus, 2015). Zhu *et al.* found 64 lncRNAs dysregulated in early AMD and established that they could play an important role in AMD development. Mapping of lncRNA-related dysregulated mRNAs showed that most of them locate in phototransduction and purine metabolism pathways. They evaluated the expression level of one lncRNA – *RP11-23406.2 in vitro* and studied its activity in the ageing model of cultured retinal pigmented epithelium (ARPE-19) cells. *RP-1123406.2* was downregulated in early AMD, and its exogenous application improved cell viability and reduced the rate of early apoptosis (Zhu *et al.*, 2017). *ZNF503-AS1* is an intergenic lncRNA up-regulated during RPE differentiation and down-regulated in RPE-choroid of atrophic AMD. It can potentially promote RPE differentiation through inhibiting its target – *ZNF503*. *ZNF503-AS1* is regulated by NF-κB which is involved in cellular processes such as inflammation and differentiation of RPE. Targeting both *RP-1123406.2* and *ZNF503-AS1* is a potential therapeutic strategy for atrophic AMD (Chen *et al.*, 2017a).

Diabetic retinopathy

Diabetic retinopathy (DR) is one of the most common vascular complications in patients with long-term diabetes. Changes in microvascular circulation in the retina under hyperglycemia conditions include increased proliferation and permeability of endothelial cells, abnormal neovascularization, and edema. Elevated blood glucose level results in oxidative stress, inflammation, neuronal dysfunction, apoptosis of the retinal ganglion cells and activation of glial cells. In all of these processes, lncRNAs play a significant role by interacting with chemokine and mitogen-activated protein kinase (MAPK) signalling pathways (Gong & Su, 2017; Pradhan *et al.*, 2016).

Myocardial infarction associated transcript (*MIAT*) is a retinal ncRNA 2 (*RNCR2*) that is highly expressed in retinal precursor cells and the retinas of diabetic rats. Its expression is also observed in Müller cells isolated from diabetic mice. Apoptotic activity is associated with the interaction with NF-κB (heterodimer that comprises p65 and p50) which selectively binds to the *MIAT* promoter. *MIAT* silencing under diabetic conditions inhibits apoptosis and improves visual functions (Gong & Su, 2017; Zhang *et al.*, 2017a).

Another lncRNA involved in the regulation of epithelial cell function is *MALAT1*. Its cooperation with p38 MAPK signalling pathway affects cell proliferation, migration, and tube formation. Knockdown of *MALAT1* in cell lines induces a change of phenotype from proliferative to migratory, and *in vivo* silencing reduces vascular growth (Michalik *et al.*, 2014). Diabetic retinopathy progression is influenced by a complex crosstalk between angiogenesis and inflammation. *MALAT1* also participates in inflammatory activation. Under hyperglycemic conditions, it is upregulated in human retinal endothelial cells (HRECs). Its siRNA silencing reduces the expression of several inflammatory cytokines, including tumour necrosis factor-alpha (TNFα), interleukin-6 (IL-6), interleukin-1β (IL-1β) and monocyte chemotactic protein-1 (MCP-1). Also, the histone methyltransferase component of polycomb repressive complex 2 (PRC2) was downregulated in HERCs treated with *siMALAT1*, demonstrating its ability to influence the expression on the protein level. Reduction of TNFα, IL-6, IL-1β and MCP1 levels in *MALAT1* knockdown mice with induced diabetes confirmed the importance of *MALAT1* genes in the regulation of inflammation (Biswas *et al.*, 2018). *MALAT1* also promotes the inflammatory reaction in microglial cells by 'sponging' *miR-124*. Overexpression of *MALAT1* in Amadori-glycated albumin (AGA) treated microglial cells results in downregulation of *miR-124* which in turn leads to MCP-1 upregulation (Dong *et al.*, 2018).

MEG3 can be responsible for enhanced retinal vessel dysfunction, capillary degeneration, increased epithelial permeability, and inflammation. It is significantly downregulated in diabetic mice retinas and re-establishing its expression may serve as a therapeutic strategy in diabetes-related vascular complications (Qiu *et al.*, 2016).

SOX2 overlapping transcript (*SOX2OT*) and retinal ncRNA3 (*RNCR3*) are lncRNAs also dysregulated under hyperglycemic conditions. *SOX2OT* is involved in pathways of apoptosis and cell viability connected with transcription factor NRF2 and its target – *HO-1* gene. It is downregulated in retinal ganglion cell lines exposed to high glucose levels and oxidative stress and in the retina of diabetic mice (Li *et al.*, 2017a). *RNCR3* participates in the retinal development and neuronal and oligodendrocyte differentiation. It is also up-regulated in RF/6A cell line and the retina of diabetic mice, similarly to some interleukins and inflammatory factors like VEGF and TNFα (Liu *et al.*, 2016; Rapicavoli *et al.*, 2010).

Interaction of circular RNAs with miRNAs involved in proliferative and apoptotic pathways may also affect the retinal vascular dysfunction. Zhang *et al.* identified 529 circRNAs differentially expressed between diabetic and non-diabetic retinas. They thoroughly analyzed *circ_0005015* expression profile and confirmed it is up-regulated in the plasma, vitreous samples and fibrovascular membranes of diabetic patients. *circ_0005015* regulates retinal endothelial cell proliferation, migration, and tube formation. MMP-2, XIAP, and STAT3 are proteins involved in regulation of cell cycle, proliferation, and apoptosis. *circ_0005015* acts as a sponge for *miR-519d-3p* inhibiting its activity and interfering with MMP-2, XIAP, and STAT3 expression (Zhang *et al.*, 2017b).

The *circHIPK3* expression is also up-regulated in retinal endothelial cells exposed to high glucose concentration. It acts as an endogenous *miR-30a-3p* sponge. Similarly to *circ_0005015*/*miR-519d-3p*, it effectively up-regulates vascular endothelial growth factors expression and intensifies endothelial proliferation, vascular leakage, and inflammation (Shan *et al.*, 2017).

Proliferative vitreoretinopathy

Proliferative vitreoretinopathy (PVR) is a serious complication of retinal detachment and vitreoretinal surgery. It can lead to severe vision reduction due to retinal redetachment caused by the formation of preretinal and epiretinal membrane (ERM) tractions. Several cell types are associated with the PVR pathogenesis, including retinal pigment epithelial (RPE) cells, fibroblasts, glial cells, and inflammatory cells. RPE cells are the largest cellular component in epiretinal membranes, and, importantly, they undergo dedifferentiation process – epithelial-mesenchymal transition (EMT) – in which they acquire

a mesenchymal phenotype (Kaneko & Terasaki, 2017; Yang *et al.*, 2016). This process is the main contributor to PVR progression and involves a number of molecular pathways affecting cell proliferation and migration. Zhou *et al.* established that 78 lncRNAs were abnormally expressed in ERMs of PVR patients. They focused on *MALAT1* whose up-regulation contributed to RPE cell proliferation, migration, and epithelial-mesenchymal transition. It was also found that its level in peripheral blood samples of the patients differs before and after PVR surgical treatment. This evidence suggests *MALAT1* could be used for the diagnosis and monitoring of PVR progression (Wan *et al.*, 2017; Zhou *et al.*, 2015).

Yang and coworkers (Yang *et al.*, 2016) confirmed the role of *MALAT1* in PVR pathogenesis. They reported it is involved in EMT upon transforming growth factor β1 (TGFβ1) induction. Knock-down of *MALAT1* by specific siRNA resulted in TGFβ1-induced morphological change inversion, suppression of migration and proliferation of RPE cells.

Glaucoma

Glaucoma is the leading cause of irreversible vision loss. It is a group of eye diseases characterized by retinal neurodegeneration comprising retinal ganglion cell loss, optic disc excavation that results in progressive loss of visual field (Abu-Amero *et al.*, 2015). The most common type of glaucoma is primary open angle glaucoma (POAG) in which the anterior iridocorneal chamber angle is opened. The condition is often associated with increased intraocular pressure (IOP), but can also occur with normal IOP – normal tension glaucoma (NTG). Glaucoma is a multifactorial disorder with genetic and epigenetic components (Abu-Amero *et al.*, 2015; Gauthier & Liu, 2017).

The cyclin-dependent kinase inhibitor 2B antisense non-coding RNA (*CDKN2B-AS1*) also known as *ANRIL* is a lncRNA transcribed in an antisense direction, located on chromosome 9p21. Several studies showed that *ANRIL* is associated with POAG, but its effects are not thoroughly understood. The genotype/phenotype analysis revealed a significant correlation between *CDKN2B-AS1* and decreased intraocular pressure in POAG patients. It suggests that *ANRIL* modifies the vulnerability of the optic nerve and modulates neurodegeneration. Patients carrying the risk alleles in *ANRIL* region are predisposed to develop POAG at lower IOP levels and to exhibit normal tension glaucoma (Nakano *et al.*, 2012; Shiga *et al.*, 2017).

Wang *et al.* investigated *cZRANB1* – a circRNA significantly upregulated in glaucoma-induced retinal neurodegeneration. It is mainly expressed in the cytoplasm of glial cells, implying a regulatory activity at the post-transcriptional level. It also may suppress the expression of *miR-217* resulting in increased Müller cells proliferation. *cZRANB1* knock-down decreases retinal reactive gliosis and reduces glaucoma-induced retinal ganglion cell apoptosis. Additionally, they established that overexpression of transcription factor RUNX2 reverses *cZRANB1* knockdown effects. The *cZRANB1*/*miR-217*/RUNX2 signalling network is a potential therapeutic target for treating retinal neurodegeneration (Wang *et al.*, 2018a).

Extensive proliferation of glaucoma Tenon's capsule fibroblasts (GTF) and subsequent scaring is the main cause of glaucoma filtration surgery (GFS) failure. Transforming growth factor β2 (TGFβ2) is upregulated after GFS surgery. It regulates proliferative ability, apoptosis, and differentiation of fibroblasts. TGFβ2 acts via different molecular pathways, including interacting with nuclear factor 2 (Nrf2), which is involved in retinal ganglion cells apoptosis and fibroblasts proliferation. Wang *et al.* investigated the role of *MEG3* lncRNA in the TGFβ2-stimulated proliferation of fibroblasts. The overexpression of *MEG3* was correlated with Nrf2 up-regulation. Their possible direct interaction causes a synergistic effect of reduced GTF proliferation, suggesting that *MEG3* may act as a therapeutic tool for improving glaucoma filtration surgeries (Wang *et al.*, 2017b).

TGFβ is also involved in lncRNA Growth Arrest Specific 5 (*GAS5*) pathway. Retinal ganglion cells (RGC) transfected with siRNA targeting *GAS5* showed increased proliferation and differentiation. The axon length was significantly improved in *GAS5*-low-expression group compared to the control group. These results revealed that high expression of lncRNA *GAS5* may promote glaucoma progression and ganglion cell degeneration. RGCs treated with exogenously administrated TGFβ demonstrated decreased *GAS5* levels in a time- and dose-dependent manner, indicating its protective potential in glaucoma neurodegeneration (Xu & Xing, 2018).

OTHER OPHTHALMOLOGIC DISORDERS

Ocular malignancy

The expression of lncRNAs in cancerogenesis is well established. Du and coworkers (Du *et al.*, 2013) performed a global analysis of more than 10 000 lncRNA genes in 1 300 tumour samples of different cancer types. They determined lncRNAs are associated with cellular oncogenic potential and promote metastasis but may also act as tumour suppressors (Du *et al.*, 2013; Sun & Kraus, 2015).

There are several lncRNAs related to uveal melanoma. *CRNDE* is a lncRNA that promotes cell proliferation and invasion through the mTOR signalling pathway and modulates the methylation status of histones. Mutation SF3B1 related to the alternative splicing of *CRNDE* genes is associated with good prognosis in patients with uveal melanoma (Furney *et al.*, 2013). Another lncRNA – *LINC-ROR* is up-regulated in ocular melanoma cell lines and tumour specimens. By repelling the histone methyltransferase EHMT2 (also known as G9a), it activates the *TESC* promoter and causes an oncogenic effect (Fan *et al.*, 2015; Wan *et al.*, 2017).

Robertson and coworkers (Robertson *et al.*, 2017) provided a comprehensive multiplatform analysis of 80 uveal melanomas. They identified four molecularly distinct tumour subtypes, two associated with poor prognosis (monosomy of chromosome 3 – M3) and two with better prognosis (disomy of chromosome 3 – D3). Investigating the expression profile of 8,167 lncRNAs, they noted that well-established cancer-associated *LINC00152* (*CYTOR*) and *BANCR* are overexpressed in poor-prognosis subgroups. The upregulation of *LINC00152* and *BANCR* correlates with invasion, cell migration and proliferation (Robertson *et al.*, 2017). Also, lncRNA *PVT1*, localized in well-known cancer risk region 8q24, was among the most differentially expressed transcripts in poor-prognosis groups. Its oncogenic potential is associated with MYC transcription factors. *PVT1* controls MYC expression at the post-transcriptional level by increasing the protein's stability and promotes cell proliferation (Colombo *et al.*, 2015). The quantity of *PVT1*,

Table 1. Long non-coding RNAs and circular RNAs in ophthalmologic disorders.

Ocular disease	lncRNA	Dysregulation	Function	References
Corneal Neovascularisation	NR_033585	Up-regulated	Stimulates angiogenesis	Huang *et al.*, 2015
	chr8:129102060–129109035	Down-regulated	Stimulates angiogenesis	Huang *et al.*, 2015
Retinopathy of Prematurity	Vax2os1		Regulates cell cycle in photoreceptor progenitor cells	Meola *et al.*, 2012
	TUG1		Formation of photoreceptors	Young *et al.*, 2005
	RNCR2/MIAT		Retinal cell fate specification	Rapicavoli *et al.*, 2010
	MALAT1		Regulates angiogenesis in developing retina	Michalik *et al.*, 2014
Wet Age-related Macular Degeneration	Vax2os1 Vax2os2	Down-regulated	Regulate eye development by interacting with NF- κB	Kaarniranta & Salminen, 2009
Dry Age-related Macular Degeneration	RP11-23406.2	Down-regulated	Associated with apoptosis and cell viability pathways	Zhu *et al.*, 2017
Diabetic Retinopathy	RNCR2/MIAT	Up-regulated	Promotes epithelial cell proliferation, migration, and tube formation, interacts with NF- κB	Rapicavoli *et al.*, 2010
	MALAT1		Affects cell proliferation, migration, and tube formation, interacts with p38 MAPK	Michalik *et al.*, 2014
	MEG3	Down-regulated	Enhances retinal vessel dysfunction	Qiu *et al.*, 2016
	SOX2OT	Down-regulated	Promotes neurodegeneration, apoptosis, affects cell viability	Li *et al.*, 2017a
	RNCR3	Up-regulated	Increases cell viability, proliferation, and migration	Liu *et al.*, 2016
	circ_0005015	Up-regulated	Acts as a *miR-519d-3p* sponge, regulates endothelial cell proliferation, migration and tube formation	Zhang *et al.*, 2017b
	circHIPK3	Up-regulated	Acts as *miR-30a-3p* sponge, intensifies endothelial proliferation, vascular leakage, and inflammation	Shan *et al.*, 2017
Proliferative Vitreoretinopathy	MALAT1	Up-regulated	Promotes epithelial-mesenchymal transition	Yang *et al.*, 2016
Primary Open Angle Glaucoma	CDKN2B-AS1/ANRIL		Modifies the vulnerability of the optic nerve and modulates neurodegeneration	Nakano *et al.*, 2012; Shiga *et al.*, 2017
	cZRANB1	Up-regulated	Suppresses the expression of *miR-217,* increases Müller cell proliferation	Wang *et al.*, 2018a
Uveal melanoma	CRNDE	Up-regulated	Promotes cell proliferation and invasion	Furney *et al.*, 2013
	LINC-ROR	Up-regulated	Induces pro-oncogenic effect	Fan *et al.*, 2015
	LINC00152	Up-regulated	Induces proliferation, cell invasion, and migration	Robertson *et al.*, 2017

	BANCR	Up-regulated	Induces proliferation, cell invasion and migration	Robertson *et al.*, 2017
	PVT1	Up-regulated	Stabilization of MYC protein, cooperation with MYC protein	Colombo *et al.*, 2015
Retinoblastoma	MEG3	Down-regulated	Early stages marker	Gao & Lu, 2016
	BANCR	Up-regulated	Promotes choroidal invasion and optic nerve invasion	Su *et al.*, 2015
	AFAP1-AS1	Up-regulated	Induces proliferation, cell migration and invasion	Hao *et al.*, 2018
	HOTAIR	Up-regulated	Induces proliferation, cell migration and invasion Targets *miR-613*	Yang *et al.*, 2018b
	H19	Up-regulated	Promotes proliferation, cell migration and invasion	Li *et al.*, 2018a
	PANDAR	Up-regulated	Induces proliferation, cell migration and invasion	Sheng *et al.*, 2018
	PlncRNA1	Up-regulated	Promotes proliferation, cell migration and invasion	Wang *et al.*, 2018c
	LINC00152	Up-regulated	Promotes proliferation, cell migration and invasion	Li *et al.*, 2018b
	THOR	Up-regulated	Induces proliferation, cell migration and invasion	Shang, 2018
	XIST	Up-regulated	Induces proliferation, cell migration and invasion Targets *miR-124*	Hu *et al.*, 2018a
Uveitis	Rs6871626		Up-regulating IL10 expression	Yue *et al.*, 2018
Strabismus	lncMyoD		Regulation of muscles differentiation	Ma *et al.*, 2018
	lnc133b		Regulation of muscles differentiation	Ma *et al.*, 2018
Cataract	MIAT	Up-regulated	Stimulates proliferation and migration of lens epithelial cells	Shen *et al.*, 2016
	TUG1	Up-regulated	Suppresses *miR-421*, induction of apoptosis	Li *et al.*, 2017b
	KCNQ1OT1	Up-regulated	Stimulates proliferation and epithelial-mesenchymal-transition	Chen *et al.*, 2018

as well as *LINC00152*, was significantly dependent on DNA methylation.

CYSLTR2 may act as a better prognostic marker of uveal melanoma as its expression was markedly lower in the D3 molecular subtype of the tumour (Robertson *et al.*, 2017).

Retinoblastoma is an embryonic malignant tumour that arises from foetal stem cells in the nuclear layer of the retina. It is the most frequent primary intraocular malignancy in children. *MEG3* is a potential therapeutic target and disease-specific marker for early diagnosis of this tumour. It is down-regulated in retinoblastoma samples, and its levels are associated with the stages of cancer. The *MEG3* level in early-stage patients was significantly higher than in advanced-stage patients and correlated with nodal or distant metastasis. Its down-regulation correlates with progression and poor prognosis in retinoblastoma and is an independent marker for predicting the clinical outcome of retinoblastoma patients (Gao & Lu, 2016).

AFAP1-AS1 (actin filament-associated protein 1 antisense RNA 1) overexpression is strongly correlated with tumour size, optic nerve invasion, and choroidal invasion. Knockdown of *AFAP1-AS1* decreased cell proliferation, migration, and invasion and blocked cell cycle progression (Hao *et al.*, 2018). Similarly, *HOTAIR* (HOX antisense intergenic RNA) high expression was noticed in retinoblastoma tumours bigger than 10 mm, bilateral and with lymph nodal metastasis. Contrarily, *miR-613* was significantly down-regulated in the same samples.

HOTAIR targets *miR-613* and promotes endothelial-mesenchymal transition (EMT) in retinoblastoma cells and its silencing with siRNA resulted in *miR-613* upregulation and induced apoptosis (Yang *et al.*, 2018b).

H19 and *PANDAR* (promoter of CDKN1A antisense DNA damage-activated RNA) are also overexpressed in RB cells. They affect cell proliferation, invasion, and migration through vimentin, CDK1, p53 and E-cadherin regulation (Li *et al.*, 2018a; Sheng *et al.*, 2018).

PlncRNA-1 (prostate cancer-up-regulated long noncoding RNA 1) modulates carbonyl reductase 3 (CBR3) activity, and *LINC00152* (long noncoding RNA00152) inactivates Ki-67, Bcl-2, and MMP-9 at the post-transcriptional level. In both cases increased proliferation, invasion and migration were observed (Li *et al.*, 2018b; Wang *et al.*, 2018c).

XIST (X-inactive specific transcript) oncogenic activity is associated with its ability to 'sponge' *miR-124* and thereby to up-regulate the signal transducer and activator of transcription 3 (STAT3). Its knock-down resulted in significant inhibition of cell proliferation, cell cycle arrest at the G1/G0 phase and the promotion of apoptosis, probably through negative regulation of *miR-124*/STAT3 axis (Hu *et al.*, 2018a).

Overexpression of *THOR* (testis-associated highly conserved oncogenic lncRNA) significantly enhances the malignant phenotype transformation of retinoblastoma cells. The process is mediated through up-regulation of c-Myc expression *via* enhancing its interaction with TGF2BP1 protein (Shang, 2018).

BANCR is also an oncogenic lncRNA, and its overexpression in both retinoblastoma tissues and cell lines is associated with tumour size, choroidal invasion, and optic nerve invasion. Silencing *BANCR* results in suppression of proliferation, migration, and cell invasion. Its overexpression is correlated with an unfavourable prognosis and, similarly to lncRNAs mentioned above, it can be used as an independent prognostic biomarker for retinoblastoma patients. It is also a promising therapeutic target (Su *et al.*, 2015).

Uveitis

The genetic background of autoimmune diseases is established. Almost 50% of anterior uveitis patients carry the human leucocyte antigen B27 (HLA-B27). Vogt-Koyanagi-Harada (VKH) disease and Behcet's disease (BD) are both autoimmune syndromes that include uveitis. They are also both associated with several genes, for example, *IL17F, IL23A, TNFAIP3*, and *HLA-DR4, HLA-DRw53* (VKH) and *HLA-B51* (BD). Although many genes are connected with autoimmune uveitis, its exact aetiology is still unclear. Yue *et al.* revealed that some lncRNAs also are involved in the inflammatory response in VKH and BD patients. *Rs6871626* was shown to increase anti-inflammatory cytokine IL-10 production by regulating the *LOC285627* gene expression (Yue *et al.*, 2018). Because lncRNAs are relatively recently discovered molecules, their exact role in autoimmune uveitis is yet to be determined.

Strabismus

Strabismus is a common ocular disorder that is caused by the impairment of central neural pathways and maladjusted extraocular muscles (EOMs). EOMs control eye position and play a crucial role in the development of this ailment. Ultrastructural examination of EOMs samples revealed myofilament disintegration, sarcomere destruction, collagen biosynthesis and fibrosis. There are also few lncRNAs regulating muscles differentiation, for example – *lncMyoD* or *lnc133b*. Ma *et al.* detected a set of coding and lncRNAs dysregulated in EMOs indicating that they are also involved in the pathogenesis of strabismus, but their participation is not yet fully defined (Ma *et al.*, 2018).

Cataract

Age-related cataract is one of the most common chronic disorders of ageing. Posterior capsule opacification (PCO) is a frequent complication of the cataract surgery. Many morphological and functional changes take place during cataract pathogenesis, including increased proteolysis, altered cell cycle, DNA damage and the change in growth and differentiation of lens epithelial cells (LECs). Shen *et al.* examined the role of lncRNAs in cataract development. They identified 38 differentially expressed lncRNAs in cataractous lenses, among which *MIAT* was the most abundant. It was overexpressed in pathological tissue, plasma fraction of the whole blood and aqueous humour of the cataract patients. *MIAT* was also involved in posterior capsule opacification process, and its knock-down inhibited TNF-α-induced proliferation and migration of LECs. This study provided a novel insight into the pathogenesis of age-related cataract and suggests that *MIAT* can act as a cataract-specific biomarker and that its silencing can affect PCO formation (Shen *et al.*, 2016; Wan *et al.*, 2017).

Recently a few more lncRNAs were identified to be associated with cataract occurrence. Li *et al.* observed that *TUG1* and caspase-3 were overexpressed and the *miR-421* expression was reduced in cataract lenses compared to healthy tissue. *TUG1* negatively regulated *miR-421* expression and promoted UV irradiation-induced SAR01/04 cells apoptosis (Li *et al.*, 2017b).

Similarly to *TUG1*, *KCNQ1OT1* is also overexpressed in human cataract lens anterior capsular samples and SRA01/04 cell line treated with H_2O_2. Down-regulation of *KCNQ1OT1* inhibited SRA01/04 cell proliferation and epithelial-mesenchymal-transition (EMT), which are the key phases in cataract formation. This effect was related to the impact of *KCNQ1OT1* on SMAD4, a critical intracellular mediator of proliferation and EMT.

Crystallin gene mutations, especially βB2 crystallin (CRYBB2), are associated with cataract formation. Jia *et al.* identified 149 up-regulated, and 180 down-regulated lncRNAs in CRYBB2 knock-out induced cataract mice model *versus* healthy mice. The paper highlighted the need for further research on dysregulated lncRNAs (Jia *et al.*, 2018).

In conclusion, the formation of the cataract is an extremely complex issue associated with several mechanisms and complex networks in which lncRNAs play an important role (Chen *et al.*, 2018).

CONCLUSIONS

The complexity of cellular processes still leaves much to be discovered. However, a better understanding of epigenetic relationships in cellular pathways gives us the possibility to develop effective and specific biomarkers and novel therapeutic strategies in various ophthalmologic diseases. As summarized in Table 1, there are several dysregulated lncRNAs and circRNAs in ophthalmologic disorders, but their exact participation in the development of these types of diseases is still poorly understood, and more research is required.

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