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REVIEW

Potential roles of lncRNA MALAT1-miRNA interactions in ocular diseases

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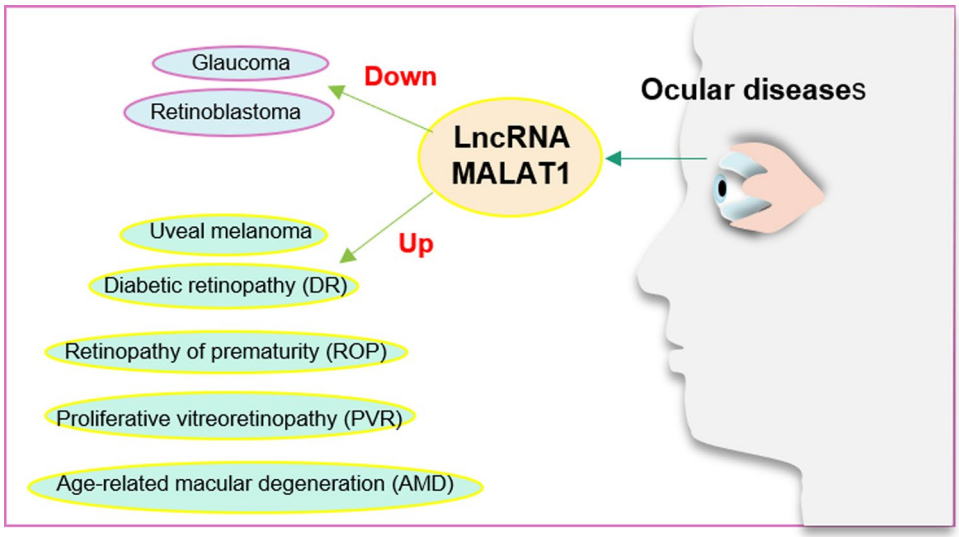
Abstract

Long non-coding RNAs (lncRNAs) are non-protein coding transcripts that are longer than 200 nucleotides in length. LncRNAs are implicated in gene expression at the transcriptional, translational, and epigenetic levels, and thereby impact different cellular processes including cell proliferation, migration, apoptosis, angiogenesis, and immune response. In recent years, numerous studies have demonstrated the significant contribution of lncRNAs to the pathogenesis and progression of various diseases, such as stroke, heart disease, and cancer. Further investigations have shown that lncRNAs have altered expression patterns in ocular tissues and cell lines during pathological conditions. The pathogenesis of various ocular diseases, including glaucoma, cataract, corneal diseases, proliferative vitreoretinopathy, diabetic retinopathy, and retinoblastoma, is influenced by the involvement of specific lncRNAs which play a critical role in the development and progression of these diseases. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is a well-researched lncRNA in the context of ocular diseases, which has been shown to exert its biological effects through several signaling pathways and downstream targets. The present review provides a comprehensive summary of the molecular mechanisms underlying the biological functions and roles of MALAT1 in ocular diseases.

Graphical abstract



Keywords Long non-coding RNAs · MALAT1 · Ocular diseases · miRNAs

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Introduction

Ophthalmic conditions, including glaucoma, cataract, diabetic retinopathy, and ocular neoplasms, are widely spread across the globe and have the potential to cause impaired vision and complete blindness, significantly compromising an individual's quality of life (Burton et al. 2021). Timely identification and prompt intervention play a pivotal role in mitigating the consequences of ocular disorders, as early detection and treatment are imperative in averting adverse outcomes associated with these conditions (Chen et al. 2023). While mutations in specific genes, such as RB1, ABCA4 (D'angelo et al. 2017; Khan et al. 2018), myocilin, and CYP1B1 (Rezaei Kanavi et al. 2022) have been linked to the development and progression of some ocular diseases, recent studies have highlighted the potential role of epigenetics, including non-coding RNAs (ncRNAs), in these conditions (Wang 2023). The exploration of ncRNAs, a diverse group of RNA molecules devoid of protein-coding capacity, has uncovered their pivotal regulatory roles within cellular processes (Olufunmilayo and Holsinger 2023). Extensive investigations into ncRNAs have unveiled their profound implications in crucial aspects such as developmental processes, disease advancement, and promising avenues for therapeutic interventions (Loganathan and Doss 2023).

Extensive research has revealed the dysregulation of various ncRNAs, including microRNAs (miRNAs), circular RNAs (circRNAs), and long non-coding RNAs (lncRNAs), in conditions such as glaucoma, cataract, diabetic retinopathy, and ocular tumors (Rong et al. 2021; Zhang et al. 2020a). These ncRNAs have been shown to impact important cellular processes, including angiogenesis, inflammation, cell proliferation, and apoptosis, which are critical in the development and progression of ocular diseases (Cataldi et al. 2021). Understanding the involvement of ncRNAs in ocular diseases holds promise for the development of novel diagnostic tools and therapeutic strategies targeting these ncRNA molecules (Shi et al. 2023).

LncRNAs, which are longer than 200 nucleotides, have been shown to play a role in ocular disorders, including cataracts, glaucoma, corneal neovascularization (CN), pterygium, diabetic retinopathy, proliferative vitreoretinopathy, retinal degeneration, and ocular tumors (Sharma and Singh 2023; Cao et al. 2023). Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), was first identified in non-small cell lung cancer (He et al. 2018). MALAT1, a type of lncRNA, has been extensively studied in the context of eye diseases, and accumulating evidence supports its involvement in several signaling pathways implicated in the pathogenesis of these diseases (Liu and Qu 2021; Zhang et al. 2019). The present review will center on the examination of the role of MALAT1 in various ocular disorders, with a particular emphasis on the potential of this lncRNA as a diagnostic and therapeutic target.

MALAT1 structure and function

MALAT1 is known as one of the most comprehensively discussed lncRNAs (Zhao et al. 2018). It is also identified as nuclear-enriched abundant transcript 2 (NEAT2) (Zhang et al. 2017). In humans, the genomic location of the MALAT1 gene has been identified as 11q13, while in mice, it is located on chromosome 19qA (Wilusz 2016). Following its initial identification in a screen for transcripts associated with the metastasis and survival of non-small cell lung cancer, subsequent investigations have demonstrated that the primary gene sequence of MALAT1 spans over 8 Kb and exhibits a high degree of conservation across 33 different mammalian species (Zhang et al. 2017). The transcript length of this gene is estimated to be around 7000 base pairs in humans and approximately 6700 base pairs in mice (Qiao et al. 2021). The transcription of MALAT1 is mediated by RNA polymerase II, and the promoter region of this gene is characterized by an open chromatin architecture, which has been demonstrated in various high-throughput studies and DNAase sensitivity assays (Arratia et al. 2023). The expression level of MALAT1 is notably high and comparable to that of highly transcribed housekeeping genes, such as β-actin (Arun et al. 2020). MALAT1 exhibits a widespread expression pattern across almost all human tissues, with the highest expression levels observed in the lung and pancreas (Pejman et al. 2017). The upregulation or deletion of MALAT1 in mammals has been shown to impact transcriptional changes in a context-dependent manner (Li et al. 2019; Kim et al. 2018). Based on accumulating evidence, it is likely that MALAT1 may exert its biological effects by modulating not only transcriptional levels but also pre-mRNA splicing (Nojima et al. 2018; Herzel et al. 2017). MALAT1 has been shown to function as a competing endogenous RNA (ceRNA) or miRNA sponge in various contexts, where it can effectively sequester miRNAs and prevent their interaction with downstream targets, thus modulating diverse cellular processes (Du et al. 2019). Although MALAT1 is believed to play a critical role in various cellular processes, studies using independent knockout animal models have shown that its deletion does not significantly impact normal animal physiology or development (Arun et al. 2020). In multiple animal knockout models, the absence of MALAT1 was observed to have no discernible influence on regular developmental processes, as mature organisms lacking MALAT1 did not exhibit any

identifiable abnormal phenotypes. Moreover, investigations focusing on the functional loss of MALAT1 in malignant lung or liver cells of human origin reported no significant alterations in cell cycle progression or proliferative capabilities (Eißmann et al. 2012). Additionally, a knockdown animal model targeting MALAT1 demonstrated an absence of discernible phenotypic or histological abnormalities, reinforcing the notion that MALAT1 may not be critically essential for the normal development or maintenance of the studied biological system (El-Brolosy and Stainier 2017).

Since its original identification, extensive clinical and fundamental investigations have contributed to our understanding of the diverse molecular and cellular roles of MALAT1. Notably, research has elucidated that the elimination of MALAT1 can mitigate retinal inflammation in animal models of diabetes and enhance the viability of retinal endothelial cells, thus resulting in the mitigation of retinal blood vessel damage and overall enhancement of retinal function (Liu et al. 2014). MALAT1 has been implicated in the etiology and advancement of retinal neurodegenerative disorders, as demonstrated in previous studies. Notably, in a glaucoma model, upregulation of MALAT1 has been shown to effectively inhibit the apoptosis of retinal ganglion cells. In this context, we present a comprehensive overview of the potential functions of MALAT1 in various ocular diseases (Yao et al. 2022).

Exploring the functional roles of lncRNA MALAT1 in ocular diseases

A comprehensive summary has been provided delineating the multifaceted functional contributions of MALAT1 in ocular diseases, encompassing glaucoma, proliferative vitreoretinopathy (PVR), retinoblastoma, uveal melanoma, diabetic retinopathy, age-related macular degeneration (AMD), and retinopathy of prematurity (ROP) (Table 1).

Glaucoma

Glaucoma is a group of optic neuropathic disorders classified in the neurodegenerative disorder category. The slow degeneration of retinal ganglion cells (RGCs) and their axons is its characteristic (Fernández-Albarral et al. 2021). Elevated intraocular pressure (IOP) is a persistent trait caused by a complex, largely unidentified set of genetic and environmental causes, and it is a major risk factor for glaucoma (Lee and Mackey 2022). RGC apoptosis in a rat model of glaucoma can be seen for the first time after two weeks, and it is consistent with decreased RGC numbers, indicating that apoptosis may be the main factor in decreased RGC numbers (Chen et al. 2011). MALAT1 expression affects RGC functions, such as RGC viability, proliferation, and apoptosis, revealing that MALAT1 plays an important role in RGC survival and morphology (Yao et al. 2022). Additionally, MALAT1 knockdown with knockout vector MALAT1-RNA interference (RNAi), significantly affects the survival of RGCs (Yang et al. 2016). The P13K/Akt signaling pathway can facilitate differentiated RGC neurite outgrowth (Zheng et al. 2011). Therefore, in both glaucoma and optic neuropathy, this pathway is required to prevent the occurrence of apoptosis and induce axonal regeneration (Li et al. 2008; Luo et al. 2007). MALAT1 can promote cell proliferation and inhibit cell apoptosis of RGCs via targeting miR-149-5p in glaucoma (Wang et al. 2021). Wang et al. showed that MALAT1 significantly reduced and miR-149-5p expression elevated in AH samples of glaucoma patients. In the mouse-derived RGC under pressurization culture, they indicated that the MALAT1 level was gradually decreased, and the miR-149-5p level was enhanced in RGCs with increasing pressure.

In high pressure-induced RGCs transfected with MALAT1, the protein level of Bcl-2 was elevated, and the protein levels of Bax, as well as cleaved caspase 3, were reduced. Inversely, MALAT1 knockdown repressed Bcl-2 expression and enhanced the expression of Bax and cleaved caspase 3. These data implicated that MALAT1 enhanced cell proliferation and partially inhibited cell death of glaucoma-like damaged RGCs via sponging miR-149-5p (Wang et al. 2021). Previous studies have proved that MALAT1 overexpression or miR-149 knockdown prevented apoptosis of RGCs via activating the PI3K/Akt pathway (Nie et al. 2018). MALAT1 expression could be a benefit for glaucoma treatment by miR-149 downregulation. In another study, the authors indicated that MALAT1 is poorly expressed in the serum of glaucoma patients (Zheng et al. 2020). Correlation between the pathological staging of glaucoma and the expression of MALAT1 suggests that severe glaucoma is reflected by low levels of MALAT1 expression. Furthermore, MALAT1 may be a critical marker for assessing the disease's severity (Zheng et al. 2020). The haplotype in MALAT1 affects its expression in human diseases like normal-tension glaucoma (NTG) (Jl and Sf 2021). Yue et al. reported that compared to NTG patients who carried other haplotypes, the MALAT1 level in the serum of GGGT patients was considerably lower, while miR-1 expression was higher. Sequence analysis identified potential miR-1 target sites on MALAT1 and IL-6, and luciferase assay demonstrated that miR-1 inhibits the expression of MALAT1 and IL-6. Meanwhile, MALAT1 also downregulates miR-1 expression, leading to an upregulation of IL-6 expression. The GGGT haplotype has been associated with a decreased risk of NTG (Jl and Sf 2021). IL-6 is a soluble protein that mediates inflammation, immune reactions, and hematopoiesis (Narazaki and

Table 1 Functional roles of lncRNA MALAT1 in ocular diseases

Ocular disorder	MALAT1 expression (up/down)	Interactions		Cell proliferation and progression (migration and invasion)	Cell line	Animal model	Patient-derived tissue	Gene targeting (shRNA, siRNA, RNAi, …)	Refs.
		Stimulation	Suppression						
Glaucoma	Down	Bax	miR-149-5p, Bcl-2	Cell proliferation/ progression		Mouse RGC cells	Human aqueous humor (AH) samples	siRNA	Wang et al. (2021)
	Up	IL-6	miR-1	progression	HUVEC and HTMC cells	–	peripheral blood	pcDNA vectors	Jl and Sf (2021)
	Down	…	miR-200a-3p, Bcl-2	Cell proliferation/ progression	661W cells	–		Si-RNA	Wu et al. (2021)
PVR	Up	TGF-β1	…	Cell proliferation/ progression	ARPE-19	–	Human primary RPE cells	siRNA	Yang et al. (2016)
RB	Up	STAT3	miR-20b-5p	Cell proliferation	ARPE-19, HXO-RB44, WERI-RB-1, SO-RB50, Y79	Male BALB/c nude mice	Human RB tissue samples	siRNA	Wang et al. (2020)
	Up	PI3K/AKT pathway, Bcl-2	miR-598-3p, Bax	Cell proliferation	Y79, SO-RB50, SO-RB70, HXO-RB44, WERI-RB-1	–	–	shRNA	Lin et al. (2022)
	Up	Bcl-2	Bax, miR-124	Cell progression	Y79	–	–	shRNA	Liu et al. (2018)
	Up	ATAD2	miR-655-3p	Cell proliferation/ progression	Y79, WERI-Rb-1	RB tumor xenograft mouse model	RB tissue samples	siRNA	Zhao et al. (2021)
	Up	STX17, LC3-II, Beclin1	miR-124, p62 protein	Cell proliferation	Y79, Weri-Rb1, SO-Rb50, HXO-RB44	–	–	siRNA	Huang et al. 2018)
	Down	Clecaspase-3, clecaspase-9, Bax	Bcl-2	Cell proliferation/ progression	Y79, Weri-Rb1	–	RB children's tissues	siRNA	Gao et al. (2020)
UM	Up	Slug, ADAM10	miR-140	Cell proliferation/ progression	MUM2C, OCM-1A, MUM-2B, C918	–	Uveal melanoma tissues	siRNA	Sun and Sun (2016)
	Up	HOXC4	miR-608	Cell proliferation/ progression	MUM-2B, C918, and M619	NOD/SCID male mice	–	siRNA	Wu et al. (2020)

Table 1 (continued)

Ocular disorder	MALAT1 expression (up/down)	Interactions		Cell proliferation and progression (migration and invasion)	Cell line	Animal model	Patient-derived tissue	Gene targeting (shRNA, siRNA, RNAi, …)	Refs.
		Stimulation	Suppression						
DR	Up	TNF-α, IL-6	–-	Cell proliferation/ progression	HRECs	Malat1 knockout (KO) mice (C57/BL6)	Vitreous humor from diabetic patients	siRNA	Biswas et al. (2018)
	Up	Keap1	Nrf2	–	Human retinal endothelial cells exposed to high glucose	Streptozotocin-induced diabetic mice (C57BL/6J mice)	Eye globes from human donors with DR	siRNA	Radhakrishnan and Kowluru (2021)
	Up	VEGFA	miR-200b-3p	Cell proliferation/ progression	RMECs	Streptozotocin-induced DR mouse model and a high-glucose/high-fat diet	–	–	Han et al. (2020a)
	Up	HIF-1α	miR-320a	Cell progression	mouse retinal microvascular endothelial cells (MRMECs) co-cultured with mouse retinal muller cells	–	–	–	Chen et al. (2022)
	Up	HIF-1α, VEGFA	miR-203a-3p	Cell proliferation/ progression	high glucose (HG) stimulated human retinal microvascular endothelial cells (HRMECs)	Oxygen-induced retinopathy (OIR) mouse model	–	–	Yu et al. (2020), Han et al. (2020b)
	Up	PDE6G	miR-378a-3p	Cell proliferation	retinal microvascular endothelial cells (RMECs) under high glucose	–	–	–	Li (2021)
	Up	–-	miR-125b / VE-cadherin/β-catenin	Cell proliferation/ progression	hRMECs	–	–	–	Liu et al. (2019)

Table 1 (continued)

Ocular disorder	MALAT1 expression (up/down)	Interactions		Cell proliferation and progression (migration and invasion)	Cell line	Animal model	Patient-derived tissue	Gene targeting (shRNA, siRNA, RNAi, …)	Refs.
		Stimulation	Suppression						
ROP	Up	CCN1, VEGF, AKT, IL-1β, TNF-α, IL-6	–	–	–	mice with oxygen-induced retinopathy (OIR)	–	siRNA	Wang and Wang (2020)
	–-	Early growth response protein 1 (EGR1)	miR-124–3p	Cell proliferation/progression	primary human umbilical vein endothelial cells (HUVECs) exposed to hypoxia	ROP mouse model	–	ceRNA	Xia et al. (2021)

Kishimoto 2022). Patients with NT have been found to have higher levels of serum IL-6 (Lin et al. 2014). Dysregulation of immune reactions may trigger glaucomatous neuropathy in patients with NTG (Jl and Sf 2021), indicating that IL-6 is involved in the progression of glaucoma. It is possible that MALAT1 can influence IL-6 expression and reduce miR-1 expression, causing the progression of NTG disease. In a study of 346 glaucoma patients (diagnosed based on structural and functional changes in the optic disc and visual field measurements or an open angle by gonioscopy) and 263 healthy controls, MALAT1 SNPs rs619586 (A > G), rs3200401 (C > T), and rs664589 (C > G) were associated with primary open-angle glaucoma (POAG) risk. The MALAT1 haplotypes ACG and ATC, comprised of rs619586, rs3200401, and rs664589, increased POAG risk (Huang et al. 2022). It is also hypothesized that protein-coding genes containing significant SNPs may possess response elements that affect the expression of MALAT1 (Yang et al. 2014)], which has been implicated in many diseases, including glaucoma (Lv et al. 2019; Chen et al. 2017). In another study, the effects of MALAT1 on apoptosis and proliferation rate of 661w cells were investigated by targeting MicroRNA-200a-3p (Wu et al. 2021). P661W is an RGC precursor-like cell line with the characteristics of retinal ganglia and photoreceptor cells (Sayyad et al. 2017). They revealed that MALAT1 inhibits the apoptosis of 661W cells by targeting microRNA-200a-3p, thereby preventing the progression of glaucoma (Wu et al. 2021). After downregulation of MALAT1 by si-MALAT1, the apoptosis rate increased. WB detection of apoptotic markers revealed that Bax and caspase3 protein increased and Bcl-2 protein decreased in 661W cells after transfection with si-MALAT1. After miR-200a-3p overexpression treatment, miR-200a-3p expression increased in 661W cells, inhibiting proliferation and promoting apoptosis. According to WB analysis of apoptotic markers, Bax and caspase3 proteins increased in 661W cells following miR-200a-3p mimics transfection (Wu et al. 2021). MALAT1 binds to miR-200a-3p in a targeted manner, increasing proliferation and decreasing apoptosis in RGC cells. Overall, MALAT1 seems to play a variable role in controlling and treating glaucoma according to the results of various studies. Further studies are needed to fully understand the role of MALAT1 in glaucoma and its potential as a therapeutic target.

Proliferative vitreoretinopathy (PVR)

Proliferative vitreoretinopathy (PVR) is a serious blinding complication that can occur before or after surgery in rhegmatogenous retinal detachment (RRD) patients (Wu and Eliott 2021). The development of a fibrous membrane at the neural retinal surface or inside the retina is caused by the proliferation of glial cells or retinal pigment epithelial (RPE)

cells (Pennock et al. 2014). Various cell types, including RPE cells, fibroblasts, glial cells, and inflammatory cells, are involved in PVR pathogenesis, with RPE cells playing a pivotal role (Pennock et al. 2014). RPE cells undergo epithelial-mesenchymal transition (EMT), leading to traction retinal detachment (Yang et al. 2015). MALAT1 is involved in TGF-β1-induced EMT of human RPE cells, shedding light on PVR pathogenesis (Yang et al. 2016). Yang et al. reported that MALAT1 expression was significantly elevated in RPE cells exposed to TGF-β1, and silencing MALAT1 with siRNA reduced TGF-β1-induced EMT, migration, and RPE cell proliferation via Smad2/3 signaling. Primary RPE cells incubated with PVR vitreous samples also showed significantly elevated MALAT1 (Yang et al. 2016). Knockdown of MALAT1 with siRNA significantly attenuated TGF-β1-induced EMT of RPE cells (Yang et al. 2016). These findings suggest that MALAT1 overexpression may play a pivotal role in the progression of TGF-β1 induced PVR disease. Zhou et al. revealed that MALAT1 levels were considerably up-regulated in the cellular and plasma fraction of peripheral blood of patients with PVR diagnosed as primary RRD with serious PVR (≥ Grade C) compared to healthy controls. Increased MALAT1 was positively associated with the severity of PVR pathology (Zhou et al. 2015). They also reported that MALAT1 expression was significantly reduced in PVR patients' cellular and plasma fraction of peripheral blood after operation treatment (Zhou et al. 2015). Ni et al. reported that there was no increase in the expression of MALAT1 in the PBMC of patients with PVR compared to the control group (Ni et al. 2020). Therefore, MALAT1 expression seems to be associated with the progression of PVR disease. However, more in-depth studies are needed to uncover the exact mechanism of this function. In the future, gene therapy using intravenous injection of siMALAT1 (MALAT1 siRNA) may be a potential treatment option to lower MALAT1 expression (Zhou et al. 2015).

Retinoblastoma

Retinoblastoma (RB) is a rare childhood eye malignancy that often affects both eyes (Kleinerman et al. 2053). RB is usually diagnosed at birth or in infancy and begins during fetal development (Dyer 2016). Currently, less than half of metastatic RB cases are untreatable with available curative approaches (Schwermer et al. 2017). Despite extensive knowledge of RB genetics, there has been limited progress in developing RB-targeted treatments (Nie et al. 2021). Given the potentially devastating consequences of RB, it is critical to gain a deeper understanding of its underlying molecular mechanisms and identify specific biomarkers that can facilitate early detection and targeted therapies, thereby improving outcomes and preserving vision in affected children (Zhang et al. 2019). To date, MALAT1 has been shown to be positively associated with RB pathogenesis. Elevated MALAT1 expression has been observed in human RB cells and tissues, and its deletion has been associated with decreased RB cell proliferation, inhibited in vivo tumor formation, and increased apoptotic capacity of human RB cells. MALAT1 functions as a ceRNA by negatively sponging miR-20b-5p to increase signal transducer and activator of transcription 3 (STAT3) expression (Wang et al. 2020), which is a regulator of cancer progression implicated in RB growth (Hu et al. 2018; Wang et al. 2022). MALAT1 silencing or miR-20b-5p overexpression resulted in inhibition of proliferation and induction of apoptosis in RB cells. Therefore, MALAT1 loss of function and miR-20b-5p mimic may be promising targets in RB therapy (Wang et al. 2020). Additionally, MALAT1 has also been found to promote RB cell viability and repress apoptosis by modulating the PI3K/Akt pathway (Liu et al. 2018). Furthermore, the MALAT1/miR-598-3p/PI3K/Akt network may serve as a diagnostic marker and curative molecule for RB (Lin et al. 2022). MiR-598-3p is a tumor suppressor that influenced cancer pathogenesis (Liu et al. 2017). MALAT1 overexpression or repressed miR-598-3p expression induced RB cell proliferation and suppressed apoptosis via activating the PI3K/Akt pathway (Li et al. 2018). Moreover, MALAT1 targeting miR-124 and their downstream targets (such as Slug) participate in RB progression by regulating the ERK/MAPK and Wnt/β-catenin signaling pathways (Liu et al. 2018). miR-124 downregulation leads to overexpression of Slug (a labile protein) and subsequently retinal carcinogenesis (Liu et al. 2018; Hirasawa et al. 2010). Furthermore, highly-expressed MALAT1 in RB tissues negatively regulates miR-655-3p expression, leading to increased proliferation, metastasis, EMT, and in vivo tumor growth. However, MALAT1 loss of function can repress these malignant features and induce RB cell apoptosis through sponging miR-655-3p (Zhao et al. 2021). ATPase family AAA domain containing 2 (ATAD2) is a novel oncoprotein that induces tumors in various advanced human malignancies. It has been identified as a candidate target of miR-655-3p, which negatively modulates ATAD2 to inhibit RB cell proliferation and induce apoptosis (Zhao et al. 2021; Hussain et al. 2018). This modulatory network highlights the role of MALAT1 as a potential diagnostic marker or therapeutic target for RB (Zhao et al. 2021). Current investigations revealed that combining lncRNAs with traditional cytotoxic chemotherapies may be a promising curative strategy for RB (Uppal et al. 2015; Esteller 2011). Understanding regulatory networks such as MALAT1/miR-655-3p/ATAD2 can improve the efficacy of chemotherapy for RB. In addition, an inverse correlation between MALAT1 and miR-124 has been reported in RB, suggesting that MALAT1 may aggravate RB cell autophagy

via miR-124-regulated STX17 modulation and contribute to chemoresistance-correlated autophagy (Huang et al. 2018). On the other hand, downregulation of MALAT1 has been detected in RB that was correlated with tumor size along with the classification and clinical grading of RB patients, and its upregulation induces RB cell apoptosis and suppresses cell growth, indicating that MALAT1 could be a potential clinical therapeutic target for RB (Gao et al. 2020).

Taken together, the accumulating evidence suggests that MALAT1 plays a crucial role in the pathogenesis of RB and holds promise as a potential diagnostic marker or therapeutic target for this disease. However, further investigations are needed to fully elucidate the underlying mechanisms of its action and explore its potential clinical applications.

Uveal melanoma

Uveal melanoma (UM) is a common ocular malignancy in adults, with a high mortality rate of 50% in UM patients originating in the choroid (80%), ciliary body (12%), and iris (8%). Recent studies have shown that abnormal expression of lncRNAs is involved in the pathological progression of UM (Zhang et al. 2019). Specifically, MALAT1 is highly expressed in UM tissues and cells, and its silencing has been found to inhibit migration, proliferation, invasion, and colony formation of uveal melanoma cells. Moreover, MALAT1 deletion induces miR-140 expression and represses slug and a disintegrin and metalloproteinase 10 (ADAM10) expression in UM cells (Sun and Sun 2016). ADAM10, a member of the ADAM sheddases family, has been implicated in the pathogenesis of numerous human cancers (Cheng et al. 2021), suggesting that MALAT1 may act as an oncogenic lncRNA in UM progression by targeting the Slug/ADAM10/miR-140 axis (Sun and Sun 2016). In addition, homeobox C4 (HOXC4) has been found to play a role in UM progression, with silenced HOXC4 suppressing proliferation, invasion, migratory abilities, and cell cycle progression in UM cells (Wu et al. 2020). Homeobox C4 (HOXC4), a regulatory gene in animal and plant development, participated in different human malignancies (Holland 2013; Liu et al. 2021; Luo and Farnham 2020). A recent study showed that miR-608 overexpression downregulated HOXC4 as its target gene in UM cells, which was rescued by high expression of MALAT1. MALAT1 sponged miR-608 to elevate HOXC4 expression, and silenced MALAT1 decreased HOXC4 expression to suppress in vivo tumor growth through sponging miR-608. Overall, inhibition of MALAT1 blocked UM progression through miR-608-regulated suppression of HOXC4 (Maeda et al. 2005).

Nowadays, combination treatments have shown higher efficacy than single-curative insights (Wilding 2017; Matsunaga et al. 2015). Artesunate, a potent derivative of Artemisinin, has been shown to exert anticancer effects in uveal melanoma cells by inducing apoptosis, and recent studies have suggested that the MALAT1/yes-associated protein (YAP) axis may play a crucial role in regulating the therapeutic effects of artesunate in these cells. Additionally, verteporfin enhances the artesunate-induced promotion of apoptosis in UM cells, suggesting its potential for use in managing UM (Jiu et al. 2021). Systematic investigations into the regulatory networks and functional roles of MALAT1 in UM tissues and cells can offer valuable insights into the underlying molecular mechanisms of this disease and potentially reveal novel therapeutic targets for the effective treatment of UM in the future.

Diabetic retinopathy

Diabetic retinopathy (DR) is a devastating ocular disorder causing vision impairment that imposes social and economic burdens on societies. Predictions reported that the prevalence of DR is about 35% worldwide and the prevalence of its leading vision deficits is around 10%. Various risk factors such as poor glycaemic control, hyperlipidemia, hypertension, albuminuria, and longer diabetes duration have a role in the appearance and development of DR (Abdulle et al. 2019). Biswas et al. demonstrated that MALAT1 plays a crucial role in regulating inflammation and epigenetic processes in DR, where it is known to associate with epigenetic mediators such as histones and methyltransferase (DNMTs), thereby modulating the expression of inflammatory genes. Additionally, elevated levels of MALAT1, tumor necrosis factor-alpha (TNF-α), and IL-6 were detected in the vitreous humor of diabetic patients (Biswas et al. 2018). It has been observed that diabetic patients experience increased oxidative stress, which can have deleterious effects on the retina. Specifically, the transcriptional activity of nuclear factor E2-related factor 2 (Nrf2), a key regulator of antioxidant genes, is known to be diminished in diabetic retinopathy, while the expression of retinal Keap1, a negative regulator of Nrf2, is upregulated, suggesting that dysregulation of the Nrf2 pathway may play a critical role in the development and progression of DR. Radhakrishnan et al. by exposing the retinal endothelial cells to high glucose regimes investigate the role of MALAT1 in the regulation of Keap1-Nrf2-antioxidant defense in DR. Glucose increased the levels of MALAT1 levels, while MALAT1 downregulation prohibited glucose-induced enhance of Keap1 and facilitated Nrf2-mediated antioxidant gene transcription. Thus, targeting MALAT1 may represent a promising approach to prevent oxidative stress-induced retinal damage in DR (Radhakrishnan and Kowluru 2021). A recent study has demonstrated that MALAT1 plays a

critical role in the neovascularization process in DR by modulating the miR-125b/vascular endothelial-cadherin (VE-cadherin) axis. It competitively binds to miR-125b and prevents its binding to VE-cadherin and by which causes the VE-cadherin upregulation. Moreover, MALAT1 knockdown leads to inhibition of cell proliferation, migration, and angiogenesis in human retinal microvascular endothelial cells (hRMECs) so provides a promising target for the anti-angiogenic treatment of DR (Liu et al. 2019). Another research group found that Yes-associated protein 1 (YAP1) promotes the angiogenesis of hRMECs via the MALAT1-mediated inhibition of miR-200b-3p that directly targeted vascular endothelial growth factor A (VEGF-A) (Han et al. 2020a). Also, it has been disclosed that MALAT1 can aggravate retinal angiogenesis by targeting the miR-320a/HIF-1α axis in DR (Chen et al. 2022). In addition, MALAT1 may affect angiogenesis in oxygen-induced retinopathy mouse models by sponging miR-203a-3p (Yu et al. 2020). miR-203a-3p via targeting hypoxia-inducible factor 1-alpha (HIF1-α) and VEGFA inhibits retinal angiogenesis and improves proliferative DR (PDR) (Han et al. 2020b).

Another study measuring the expression levels of several ncRNAs including MALAT1, miR-17-3p, miR-20b, and HOTAIR in the serum of DR patients suggested that these ncRNAs may provide promising noninvasive biomarkers for discriminating of PDR and non-proliferative DR (NPDR) from non-DR (NDR) patients. Regarding MALAT1, its expression levels significantly increase in the serum of DR, NPDR, and PDR patients compared to healthy subjects. Moreover, a significant increase of MALAT1 was also detected in the serum of DR and PDR patients when compared with NDR patients. Notably, when comparing patients with NPDR and proliferative PDR, a significant increase in the levels of MALAT1 was observed in the serum of PDR patients (Shaker et al. 2019). Emerging evidence suggests that the MALAT1/miR-378a-3p/PDE6G axis plays a key role in the pathogenesis of DR in RMECs, particularly under conditions of high glucose, indicating its potential as a therapeutic target for this condition (Li 2021).

Studies using animal models have demonstrated that MALAT1 levels are significantly increased in DR. Knocking down MALAT1 has been shown to improve DR in rats that were induced with streptozotocin, a chemical that causes diabetes-like symptoms. Additionally, MALAT1 knockdown reduces the proliferation, migration, and formation of new blood vessels in retinal endothelial cells, which are regulated by VEGF (Liu et al. 2014). Further research has revealed that MALAT1 regulates the function of endothelial cells by controlling the expression of genes involved in the cell cycle, such as cyclins (cyclinA2, cyclin B1, and cyclin B2), as well as genes that inhibit cell cycle progression (p21 and p27Kip1) (Jaé et al. 2019). In conditions of high glucose levels, MALAT1 upregulates the expression of PDE6G through miR-378a-3p. This leads to increased proliferation of retinal vascular endothelial cells and inhibition of apoptosis, or programmed cell death (Li 2021).

Another study investigated the impact of inhibiting MALAT1 on diabetic neurodegeneration induced by streptozocin in mice. The results showed that the MALAT1 up expressed in the retinas of diabetic control mice. However, its expression significantly decreased in the diabetic MALAT1-siRNA group compared to the diabetic control group. Both diabetic control and diabetic MALAT1-siRNA mice showed lower amplitudes in scotopic and photopic electroretinograms compared to the normal control mice. However, the diabetic MALAT1-siRNA mice showed higher amplitudes compared to the diabetic control mice. Totally, inhibiting the expression of MALAT1 by siRNA in the retina had a mitigating effect on retinal photoreceptors, thereby alleviating diabetic neurodegeneration. This study highlighted the role of MALAT1 in the development of diabetic neurodegeneration and suggested its potential as a therapeutic target to protect and preserve retinal function in diabetic patients (Zhang et al. 2020b). In a recent study, the expression of MALAT1 was found to be increased in retinal endothelial cells exposed to high glucose levels, leading to the production of inflammatory cytokines and angiogenesis. Additionally, MALAT1 expression is upregulated in the RPE of patients with geographic atrophy, a severe form of DR. This upregulation is associated with the downregulation of genes involved in RPE cell function and the promotion of RPE cell senescence. Inhibition of MALAT1 has been shown to reduce angiogenesis, proliferation, and migration of hRMECs. This is achieved through its targeting miR-125b and subsequent inhibition of VE-cadherin/-catenin complex. These findings suggest that MALAT1 could be a potential therapeutic target for disorders involving retinal neoangiogenesis, such as DR (Liu et al. 2019).

AMD

In addition to the role of MALAT1 in PVR, DR and RB, it has also been implicated in other ocular diseases such as age-related macular degeneration (AMD). AMD is a neurodegenerative eye disease that is the most common leading cause of visual loss and legal blindness in older population. The macula is a small central region of the retina which is responsible for fine and color vision, but its function affected by AMD. This disease involves the progressive destruction of photoreceptors and the underlying retinal pigment epithelium (RPE), resulting in vision loss (Sharma and Singh 2023).

Neovascularization

Retinal neovascularization, which defined as the abnormal growth of blood vessels in the retina, is a common manifestation of retinopathy of prematurity (ROP). A study conducted on animals found that MALAT1 mRNA was highly expressed in the retinas of mice with oxygen-induced retinopathy (OIR). Intravitreal injection of MALAT1 siRNA significantly decreased the severity of retinopathy. Also, the protein and mRNA expression levels of CCN1, VEGF and AKT and genes associated with inflammation including IL-1β, TNF-α, and IL-6 were significantly decreased compared to control groups. Therefore, MALAT1 may play a role in the process of retinal neovascularization in ROP, and using MALAT1 siRNA as a treatment could be a promising option to inhibition of this abnormal process (Wang and Wang 2020). Knockdown of MALAT1 can significantly impair the expression of various cell cycle regulators, leading to a marked inhibition of endothelial cell proliferation and neonatal retinal vascularization (Michalik et al. 2014).

Another study used microarray analysis to examine the expression of lncRNAs, miRNAs, and mRNAs in a mouse model of ROP and constructed ceRNA to understand the relationships between these molecules. Specifically, they focused on the interaction between MALAT1, miR-124–3p, and early growth response protein 1 (EGR1) in primary human umbilical vein endothelial cells (HUVECs) exposed to hypoxia and the ROP mouse model. Results revealed that MALAT1 by sponge miR-124–3p reduces its availability. Knocking down MALAT1 decreased the expression of EGR1 and inhibited the migration and proliferation of HUVECs in hypoxic conditions. In vivo study using OIR models revealed that intravitreal injection of miR-124–3p and shMALAT1 decreased EGR1 expression and significantly suppressed the neovascularization in the retina. Interestingly, when shMALAT1 and miR-124–3p antagomir were injected together, they promoted retinal neovascularization, counteracting the suppression caused by shMALAT1 alone. This finding disclosed the regulatory role of MALAT1/miR-124–3p/EGR1 axis in retinal neovascularization, which could help to a better understanding of the pathogenesis of ROP (Xia et al. 2021).

A recent study investigated the role of MALAT1 in the remodeling of retinal blood vessels and demonstrated that MALAT1 expression is significantly increased in the retinas of STZ-induced diabetic rats and mice. However, it's knocking down noticeably improved DR-related symptoms in vivo, such as the loss of pericytes, leakage from microvessels, degeneration of capillaries, and inflammation in the retina. Furthermore, in vitro experiment was found that MALAT1 knockdown regulates the proliferation, migration, and tube formation of retinal endothelial cells. This regulation of endothelial cell function is mediated by the interaction between MALAT1 and the p38/MAPK signaling pathway. The MALAT1 upregulation is a critical mechanism contributing microvascular dysfunction caused by diabetes. Therefore, inhibition of MALAT1 can be consider as a promising therapeutic approach for microvascular complications of diabetes by preventing angiogenesis (Liu et al. 2014).

Potential roles of MALAT1-miRNA interactions in ocular diseases are shown in Fig. 1. These effects can occur in the form of increased expression or decreased expression of MALAT1. Overall, these findings suggest that targeting MALAT1 could be a potential therapeutic approach for treating diabetic retinopathy and other ocular diseases involving abnormal blood vessel growth in the retina.

Perspectives

To date, several lncRNAs have been reported to be involved in eye development, such as MALAT1. LncRNAs play critical roles in regulating various processes involved in photoreceptor progenitor development and retinal cell fate specification. Microarray analysis and RNA sequencing have emerged as powerful and comprehensive tools for identifying dysregulated lncRNAs in ocular disorders. The utilization of high-throughput RNA sequencing technologies has significantly expanded our ability to identify and characterize lncRNAs on a much broader scale than previous studies. Several lncRNAs modulate special facets of protein activity. By providing novel insights into the molecular mechanisms underlying ocular disorders, lncRNAs have the potential to serve as promising targets for developing highly specific and less toxic drug therapies that are more effective than traditional protein-targeting drugs. Oligonucleotide analogs represent a promising approach for the sequestration of oncogenic gene binding to lncRNAs, enabling the suppression of tumor suppressor genes and providing a potentially effective therapeutic strategy for various ocular and other types of cancers. Comprehensive understanding of lncRNA functions and mechanisms of action is crucial for the development of more effective diagnostic and therapeutic approaches for ocular disorders and other diseases. In recent years, gene therapy has emerged as a promising approach for the treatment of various ocular disorders, particularly hereditary conditions such as retinitis pigmentosa and glaucoma, where it has shown significant potential for restoring visual function and preventing disease progression. Unlike conventional drugs or antibody-based therapies that typically offer only short-term benefits and require repeated applications, gene-based procedures provide targeted treatments that offer the potential for long-term therapeutic effects, making them an attractive option for the treatment

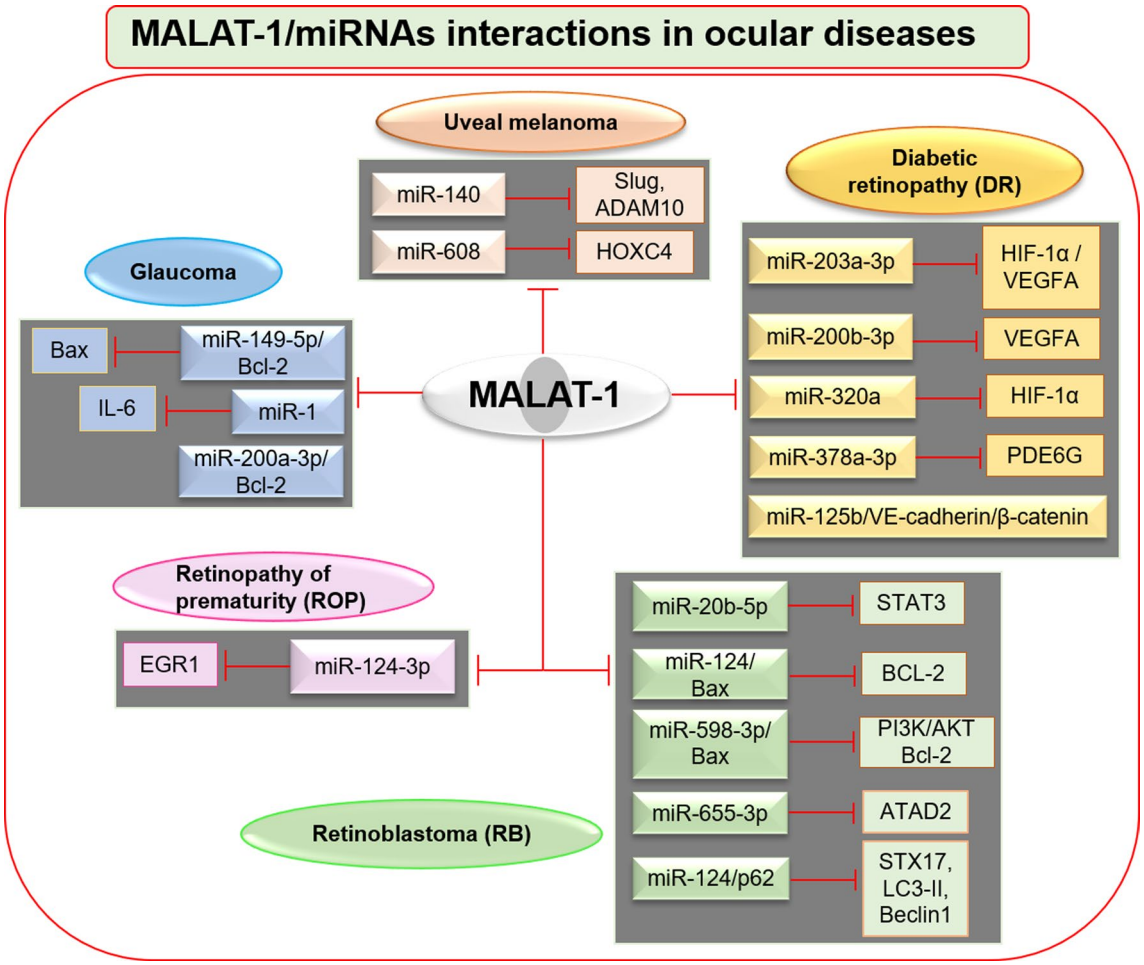

Fig. 1 The Functional Implications of lncRNA MALAT1-miRNA Interactions in Ocular Pathologies. MALAT1, a long non-coding RNA, has been implicated in the pathogenesis of various ocular diseases through its interactions with multiple miRNAs. Understanding the intricate interplay between MALAT1 and miRNAs may provide valuable insights into the underlying mechanisms of ocular diseases and potential therapeutic targets

of hereditary ocular disorders and other chronic diseases. Currently, siRNA-based drugs have emerged as a promising therapeutic strategy for ocular disorders, and emerging evidence suggests that lncRNAs may also play a crucial role in the diagnosis and prediction of these conditions, with their predictive value surpassing that of conventional markers. While research on the involvement of lncRNAs in ocular disorders has been relatively limited compared to other fields, the growing body of evidence has consistently highlighted their critical roles in various ocular diseases and the potential for lncRNA-based gene therapy as a promising approach for the treatment of these conditions. The current review provides a comprehensive summary of the functions of lncRNAs in ocular disorders, shedding light on their potential as therapeutic targets for the development of more effective treatments in the clinic. Despite the increasing interest in lncRNA research, many of their functions and mechanisms of action remain poorly understood, presenting significant challenges for their clinical implementation and underscoring the need for further investigation in this field.

Conclusion

The functional roles of MALAT1 in ocular diseases are diverse and encompass the regulation of angiogenesis, inflammation, apoptosis, extracellular matrix homeostasis, and epithelial cell behavior. Understanding the involvement of MALAT1 in these processes may provide valuable insights into the underlying mechanisms of ocular diseases and potentially open up avenues for the development of novel therapeutic strategies. Emerging evidence suggests that MALAT1 exerts its influence on ocular diseases through the intricate modulation of multiple miRNAs, including miR-149-5p, miR-1, miR-200a-3p, miR-20b-5p, miR-598-3p, miR-124, miR-655-3p, miR-140, miR-608,

miR-200b-3p, miR-320a, miR-203a-3p, miR-378a-3p, miR-125b, and miR-124–3p, thereby suggesting their potential involvement in the intricate pathogenesis of ocular diseases at a molecular level. However, further research is still needed to fully elucidate the precise mechanisms by which MALAT1 contributes to ocular diseases and to explore its potential as a therapeutic target.

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Declarations

Competing interests The authors declare that there is no competing interests.

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