



Sophisticated Gene Regulation for a Complex Physiological System: The Role of Non-coding RNAs in Photoreceptor Cells

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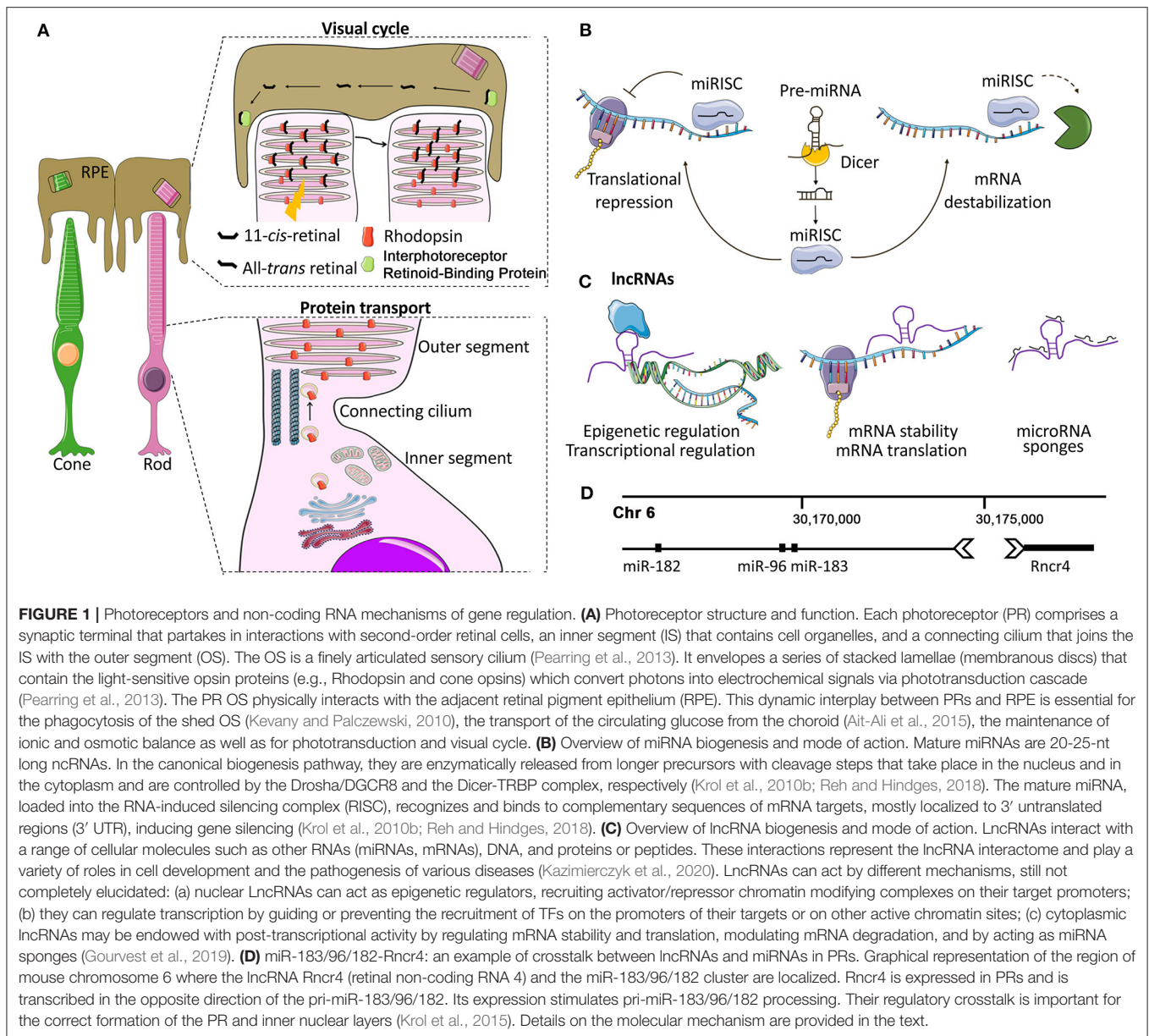
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Photoreceptors (PRs) are specialized neuroepithelial cells of the retina responsible for sensory transduction of light stimuli. In the highly structured vertebrate retina, PRs have a highly polarized modular structure to accommodate the demanding processes of phototransduction and the visual cycle. Because of their function, PRs are exposed to continuous cellular stress. PRs are therefore under pressure to maintain their function in defiance of constant environmental perturbation, besides being part of a highly sophisticated developmental process. All this translates into the need for tightly regulated and responsive molecular mechanisms that can reinforce transcriptional programs. It is commonly accepted that regulatory non-coding RNAs (ncRNAs), and in particular microRNAs (miRNAs), are not only involved but indeed central in conferring robustness and accuracy to developmental and physiological processes. Here we integrate recent findings on the role of regulatory ncRNAs (e.g., miRNAs, lncRNAs, circular RNAs, and antisense RNAs), and of their contribution to PR pathophysiology. We also outline the therapeutic implications of translational studies that harness ncRNAs to prevent PR degeneration and promote their survival and function.

Keywords: photoreceptors, cones, rods, retina, non-coding RNAs, microRNAs, lncRNAs, circRNAs

INTRODUCTION

Photoreceptors (PRs) are specialized neuronal cells adapted to the conversion of light stimuli into electrical signals. Rods are sensitive to dim light and essential for night vision, while cones enable high acuity daylight vision and color perception (**Figure 1A**). PRs are among the cell types of our organism that are exposed to high levels of cellular stressors (e.g., light exposure and sustained protein synthesis). First, PRs have an elevated metabolic demand due to the high rates of ion transport, opsin protein turnover, and trafficking from inner (IS) to outer segments (OS) (**Figure 1A**). This high energy requirement, which is almost double for a cone compared to a rod cell (Ingram et al., 2020), renders PRs vulnerable to fluctuations in energy flow. The high rate of protein synthesis poses a challenge to proteostasis (Athanasίου et al., 2013) and may expose PRs to endoplasmic reticulum stress. Second, the inevitable photo-oxidative stress requires continual clearance of Reactive Oxygen Species (Organisciak and Vaughan, 2010). In addition, PRs need to remove the toxic retinoid byproducts of the visual cycle (**Figure 1A**).



The structural and functional integrity of PRs is crucial for vision. Defects or mere fluctuations in any of the key molecular processes involved in PR homeostasis (e.g., energy

Abbreviations: AAV, adeno-associated viral vector; asRNA, antisense RNA; CC, connecting cilium; ceRNA, competitive endogenous RNA; circRNA, circular RNA; cKO, conditional knockout; CNV, choroidal neovascularization; Dgcr8, DiGeorge Critical Region 8; ERG, electroretinography; hPSCs, human pluripotent stem cells; IS, inner segment; KO, knockout; lincRNAs, large intergenic non-coding RNAs; lncRNA, long non-coding RNA; MALAT1, Metastasis Associated Lung Adenocarcinoma Transcript 1; MEG3, Maternally Expressed 3; miRNA, microRNA; ncRNA, non-coding RNA; ONL, outer nuclear layer; OS, outer segment; P, postnatal day; PRs, photoreceptors; RGC, retinal ganglion cells; RPC, retinal progenitor cells; RP, Retinitis Pigmentosa; RPE, Retinal Pigment Epithelium; TRPM1/3, transient receptor potential cation channel subfamily M member 1/3; TUG1, Taurine Upregulated Gene 1.

metabolism including retinal blood flow, lipofuscin clearance, protein sorting, vesicle, and intra-flagellar transport, etc.) due to genetic changes or environmental insults can lead to PR dysfunction, cell death, and ultimately to blindness (Pearring et al., 2013). Because of their high metabolic activity, PR dysfunction is often the only phenotypic read-out of mutations in genes with ubiquitous expression, such as in the case of key ciliary genes (e.g., *CEP290* and *RPGR*) or splicing factors (e.g., *PRPF31*).

Non-coding RNAs (ncRNAs) are established as key regulators of several developmental and physiological processes. Here we discuss the role of regulatory ncRNAs in conferring robustness to PR development and function. Because of space limitations, ncRNAs that impact PR homeostasis through

non-cell-autonomous processes (e.g., expression in other retinal cell-types or extracellular vesicles; Xu et al., 2019; Morris et al., 2020; Wooff et al., 2020) are not discussed in this mini-review.

miRNA-MEDIATED REGULATION IS ESSENTIAL FOR PHOTORECEPTOR MATURATION, FUNCTION, AND SURVIVAL

MiRNAs have emerged as an intriguing class of regulatory ncRNAs because of their powerful and well-conserved mechanism of sequence-specific post-transcriptional gene regulation (Bartel, 2018; **Figure 1B**). In particular, each miRNA is predicted to recognize on average 200 mRNA targets (Bartel, 2018), allowing for a pleiotropic fine-tuning of correlated pathways that confers robustness to biological processes (Ebert and Sharp, 2012). This multiple targeting, together with sequence similarities (i.e., miRNA families) and functional redundancy complicate the study of miRNA function.

An important piece of information to start deciphering miRNA function in the retina came from studies which defined miRNA expression in this tissue (Karali and Banfi, 2019). PR-expressed miRNAs were identified either by RNA *in situ* hybridization approaches (Kapsimali et al., 2007; Karali et al., 2007, 2010; Xu et al., 2007; Zhuang et al., 2020) or by small RNA-Seq analysis of sorted cone cells (Busskamp et al., 2014). More detailed information on the miRNA complement of PRs may derive from single-cell based sequencing approaches adapted to small RNA analysis, as already reported for mRNAs (Macosko et al., 2015; Lukowski et al., 2019; Peng et al., 2019). Besides their PR-specific expression, altered miRNA expression profiles in retinal degeneration models, even at early pre-symptomatic stages, underscored miRNA significance in PR pathophysiology (Loscher et al., 2007, 2008; Genini et al., 2014; Saxena et al., 2015; Palfi et al., 2016; Anasagasti et al., 2018).

Photoreceptor-Specific Depletion of miRNA Biogenesis Impacts Photoreceptor Morphogenesis and Function

Functional studies based on global disruption of miRNA processing in post-mitotic PR cells, mostly through generation of *Drosha/Dgcr8* or *Dicer1* conditional knockout (cKO) mouse models, demonstrated the importance of miRNAs for PR function and survival. In one example, miRNA depletion in mature rod PRs of *Dicer1* conditional-knockout (cKO) mice led to an early-onset severe retinal degeneration (Sundermeier et al., 2014). The initial disorganization of rod OS in cKO mice was followed by an almost complete loss of PR nuclei in the ONL, depletion of the visual chromophore and severely reduced rod-mediated scotopic electroretinography (ERG). However, the cKO retinas did not display primary defects in phototransduction or in the visual cycle, suggesting that observed degeneration could be due to defects in rod maturation or homeostasis.

MiRNA depletion in adult differentiated cones following conditional *Dgcr8* ablation, led to loss of cone OS and impaired cone-mediated responses both in ERG as well as in *ex vivo* whole-cell patch clamp tests (Busskamp et al., 2014). However,

cone numbers did not diminish significantly, suggesting there was no direct impact on cone cell death. Adeno-associated viral vector (AAV)-based reintroduction of the PR-enriched miRNAs miR-182 and miR-183 was sufficient to prevent cone OS loss *in vivo*, while expression of the miR-183/96/182 cluster in three-dimensional optic cup cultures from mouse embryonic stem cells induced the formation of additional PR structural components (i.e., IS, CC, and OS).

More recently, the conditional loss of *Dicer1* in developing cones was shown to cause early onset cone dystrophy (Aldunate et al., 2019). Already at 3 weeks of age, *Dicer1*-depleted cones had shortened and abnormal OS. This structural disorganization gradually led to loss of cone PRs and reduced photopic vision. Conversely, rod survival and function were not affected.

Considering the well-established mutual interdependence between the retina and the retinal pigment epithelium (RPE), it is indisputable that proper miRNA expression in the latter tissue is also essential for PR morphogenesis and function. This was demonstrated with the conditional deletion of *Dicer1* in the developing RPE which dramatically impacted on OS formation and PR survival in a non-cell-autonomous manner (Ohana et al., 2015).

Functional Significance of Specific miRNAs in PRs

Loss-of-function studies of specific miRNAs have provided further insights on miRNA function in PRs (**Table 1**). A well-studied example is the light-regulated polycistronic miRNA cluster composed of miR-183/96/182 (Krol et al., 2010a). Collectively, this miRNA cluster accounts for almost half of the total miRNA population in human retina samples. MiR-182 and miR-183 are the most highly expressed retinal miRNAs (Karali et al., 2016), and are highly enriched in PRs (Karali et al., 2007, 2010; Xu et al., 2007; Zhu et al., 2011; Lumayag et al., 2013; Busskamp et al., 2014; Sundermeier et al., 2014). Sponge-mediated inactivation of the miR-183/96/182 cluster in mouse mature rods did not induce apparent morphological or functional defects under normal light conditions. Instead, it sensitized retinas to bright light-induced retinal degeneration, suggesting this cluster has a protective role under stress conditions (Zhu et al., 2011). On the contrary, constitutive gene-trap-based inactivation of the miR-183/96/182 cluster in mice not only increased susceptibility to light damage but led to an early-onset progressive retinal degeneration associated with defects in the phototransduction cascade and the PRs' synaptic connectivity (Lumayag et al., 2013). In agreement, miR-183/96/182 *null* mice, obtained by targeted recombination, display profound defects in vision and other sensory functions, mainly due to impaired terminal differentiation of sensory neurons. PR ciliogenesis and OS formation was delayed leading to early-onset degeneration (Fan et al., 2017). Finally, the double miR-183 and miR-96 KO mouse had defects in cone polarization and OS morphogenesis that gradually led to PR degeneration, underscoring their importance for PR maturation and maintenance (Xiang et al., 2017). The authors proposed that the effect of miR-183 and miR-96 on PR development is mediated through the regulation

TABLE 1 | Summary of representative non-coding RNAs with a role in photoreceptor function and maintenance.

ncRNAs	Function and main features	Therapeutic perspectives	References
miRNAs			
miR-182, miR-183, miR-96	Their expression is light-regulated; inactivation is linked to PR and synaptic transmission dysfunction, impairment of cone maturation and maintenance, with progressive degeneration; increased expression preserves cone OS in <i>Dicer1</i> -ablated PRs		Krol et al., 2010a; Zhu et al., 2011; Lumayag et al., 2013; Busskamp et al., 2014; Fan et al., 2017; Xiang et al., 2017; Wu et al., 2019; Peskova et al., 2020; Zhang et al., 2020a
miR-124	Predominantly localized to PR IS; promotes maturation and survival of cone photoreceptors by targeting <i>Lhx2</i>	Intravitreal miR-124 administration decreases microglia infiltration and PR cell death in mice after light-induced damage	Karali et al., 2007; Sanuki et al., 2011; Chu-Tan et al., 2018
miR-204, miR-211	Silencing in medaka-fish has a negative impact on PR maintenance and function, leading to increased apoptosis Genetic inactivation of miR-211 in mice leads to progressive cone dystrophy, cone loss, and alterations in visual function. A point mutation in the miR-204 mature sequence associated with retinal dystrophy and coloboma in humans	AAV-mediated subretinal delivery in mouse models of RP promotes PR survival and preserves retinal function through a synergistic effect on innate immunity, inflammatory response and cell death	Conte et al., 2015; Barbato et al., 2017; Karali et al., 2020
miR-6937-5p	Upregulated at early stages of retinal degeneration in <i>rd10</i> mice	AAV-mediated inhibition in <i>rd10</i> mice delays PR demise and vision loss	Anasagasti et al., 2018, 2020
LncRNAs			
<i>TUG1</i>	Involved in PR development and survival; loss-of-function is associated with defects in PR differentiation, structural defects of the OS and increased apoptosis		Young et al., 2005
<i>Vax2os1</i>	Controls cell cycle progression and proliferation of PR progenitors; increased expression delays PR differentiation and enhances apoptosis		Alfano et al., 2005; Meola et al., 2012
<i>MEG3</i>	Significantly upregulated in light-induced retinal degeneration	<i>MEG3</i> silencing protects against light-induced retinal degeneration; regulates PR apoptosis by preventing p53 degradation	Wang et al., 2012; Zhou et al., 2012; Zhu et al., 2018
<i>MALAT1</i>	<i>MALAT1</i> expression is lost in rod PRs with putative degeneration, suggesting its involvement in rod PR survival and retinal preservation	Intravitreal injection of <i>MALAT1</i> -siRNA in mice with diabetes-induced and in oxygen-induced retinopathy reduced secondary PR loss	Lukowski et al., 2019; Wang et al., 2020; Zhang et al., 2020b
<i>RNCR4</i> (BB283400)	Regulates proper thickness of PR and inner nuclear layers by regulating pri-miR-183/96/182 processing		Krol et al., 2015
<i>circ-Tulp4</i>	Acts as a miR-26a/671/204 sponge; AAV-circ-Tulp4-shRNA-treated retinas show severe PR degeneration		Chen et al., 2020

PRs, Photoreceptors; OS, Outer Segment; IS, Inner Segment; AAV, adeno-associated viral vector; RP, Retinitis Pigmentosa.

of the taurine transporter *Slc6a6*. Recently, miR-183 KO mice presented mild yet progressive defects in ERG responses (Zhang et al., 2020a). Additionally, miR-182-depleted mice showed a thinner IS/OS layer, a progressive reduction of scotopic and photopic ERG responses and increased sensitivity to light-damage compared to control littermates (Wu et al., 2019). In contrast, a study assessing the potential redundancy of the cluster members reported the absence of retinal defects in single, double, and triple mir-183/96/182 mutant zebrafish (Fogerty et al., 2019).

Discrepancies in the phenotypic severity among the above-mentioned models may stem from differences in the

methodology, developmental timing, and cell-type specificity of the cluster ablation. Nevertheless, the phenotypes are consistent with the role of the miR-183/96/182 cluster in PR differentiation and synaptic connectivity, signal transduction, transmembrane transport, cell-adhesion, regulation of circadian rhythm and apoptosis (Xu et al., 2007; Dambal et al., 2015; Palfi et al., 2016). Moreover, several mRNA targets that partake in these processes were shown to be regulated by the 183/96/182 cluster members such as *Crb1* (Krol et al., 2015), *Mitf*, *Adcy6* (Xu et al., 2007), *Rnf217* (Xiang et al., 2017; Zhang et al., 2020a), *Rac1*, *Slc6a9* (Palfi et al., 2016), *Slc1a1*

(Krol et al., 2010a), *Slc6a6* (Xiang et al., 2017), and *Casp2* (Zhu et al., 2011).

Another miRNA that contributes to PR survival is miR-124, an abundant neuronal-specific miRNA expressed in all neural cells of the retina (Kapsimali et al., 2007; Karali et al., 2007, 2011, 2016; Liu et al., 2011; Sanuki et al., 2011). In adult PRs, miR-124 is predominantly localized in the IS (Karali et al., 2007; Sanuki et al., 2011). Upon degeneration induced by photo-oxidative damage, miR-124 aberrantly redistributed from PRs to the inner retina (Chu-Tan et al., 2018). This mislocalization of miR-124 was likely mediated by extracellular vesicles, as it was impaired following exosome-depletion (Wooff et al., 2020). MiR-124 depletion in a mouse KO for *Rncr3*, its main host gene, resulted in cone mislocalization and demise. Rod PRs were not significantly affected indicating that miR-124 is important primarily for cone survival by targeting *Lhx2* (Sanuki et al., 2011).

The miR-204/211 family is expressed in diverse ocular tissues consistent with its pleiotropic role in eye development (Shiels, 2020). MiR-204 and miR-211 are intragenic miRNAs transcribed from introns of the *Trpm3* and *Trpm1* genes, respectively (Barbato et al., 2017; Shiels, 2020). In the posterior eye, miR-204 is strongly expressed in the RPE and INL (Karali et al., 2007, 2011, 2016) but also detectable in PRs (Conte et al., 2015). Although PRs are not the primary site of miR-204 expression, morpholino-mediated knockdown of miR-204 adversely impacted PR maintenance and function in medaka-fish (Conte et al., 2015). Similarly, the targeted inactivation of miR-211 caused progressive cone dystrophy characterized by reduced cone-elicited ERG responses and cell density in mouse. Transcriptome analysis suggested that miR-211 can impact retinal metabolism by controlling genes involved in glucose and lipid metabolism (Barbato et al., 2017). The higher metabolic demand of cones (Cheng et al., 2020) that renders them susceptible to energy fluctuations, could explain why cones (rather than rods) were predominantly affected by miR-211 loss (Barbato et al., 2017). Likewise, the rapid light-regulated turnover of miR-204/211 in the murine retina, similar to that of the miR-183/96/182 cluster, has been postulated to facilitate activity-dependent expression changes in neuronal cells (Krol et al., 2010a). Remarkably, a heterozygous point mutation within the seed region of miR-204 segregated with a dominant retinal dystrophy characterized by severe PR loss and diminished ERG responses, presumably through a gain-of-function mechanism (Conte et al., 2015).

ROLE OF SPECIFIC lncRNAs IN PHOTORECEPTORS

Long non-coding RNAs (lncRNAs) are a class of transcripts longer than 200 nucleotides with limited protein-coding potential. They exceed mRNAs in quantity and participate in various biological processes and functions across different cell types (Blackshaw et al., 2004; Briggs et al., 2015; Quek et al., 2015; Clark and Blackshaw, 2017; Kopp and Mendell, 2018). lncRNAs can act as decoys of transcription factors (TF) and miRNAs (Hansen et al., 2013), interact with chromatin modifiers to

regulate epigenetic states (Rinn and Chang, 2012), or participate in nuclear topological organization (Ip and Nakagawa, 2012) and in protein-complex scaffolding (Ribeiro et al., 2018; **Figure 1C**). lncRNAs have recently been found to contribute to PR function (**Table 1**).

The availability of high-throughput sequencing approaches has facilitated the comprehensive and unbiased identification of lncRNAs in the retina. Palczewski and colleagues identified a group of 18 highly conserved large intergenic non-coding RNAs (lincRNAs) in the retina, some of which localized to specific retinal layers, especially to the PR layer (Mustafi et al., 2013).

One of the first lncRNAs studied in the retina was the *Taurine Upregulated Gene 1 (TUG1)*. Loss-of-function of *TUG1* in the developing retina showed its implication in normal PR development, by acting on transcriptional regulation of PR-specific genes through a yet unknown mechanism. *TUG1* absence in the newborn retina led to structural defects in PR OS accompanied by increased apoptosis and expression changes of key TFs and marker genes of differentiated PRs (Young et al., 2005). A recent study reported the dynamics of the non-coding transcriptome in developing and mature PRs, focusing on rod-enriched lncRNAs controlled by the rod differentiation factor *Nrl*. The dynamic expression of the non-coding transcriptome during rod maturation is consistent with its functional relevance in the morphogenesis of OS membrane discs and synapse formation (Zelinger et al., 2017). The authors also identified a functional role of antisense RNAs (asRNAs), a subclass of lncRNAs that originate from the opposite strand of 20–40% of protein-coding genes, in PR formation. AsRNAs were identified as putative regulators of eye development because of their overlap with the mRNAs of TFs known to play key roles in vertebrate eye development (Alfano et al., 2005). Among them *Vax2os1*, where “os” stands for “opposite strand,” shows an expression confined to the ventral portion of the eye and is predominantly detected in the layers where PR progenitors and differentiated cells reside. Consistent with this expression pattern, *Vax2os1* overexpression in the retina impaired cell cycle progression of PR progenitors and delayed PR differentiation. At later developmental stages, this perturbation led to increased apoptosis in the PR layer (Meola et al., 2012).

Recently, the *Maternally Expressed 3 (MEG3)* was shown to be involved in the pathogenesis of light-induced retinal degeneration. *MEG3* expression is significantly upregulated upon light insult whereas its silencing protects against light-induced retinal degeneration *in vivo* and *in vitro* by decreasing caspase 3/7 activity and proapoptotic protein (Bax) levels while upregulating antiapoptotic protein (Bcl-2) expression. Mechanistically, *MEG3* regulates PR apoptosis by acting as a p53 decoy, preventing MDM2-mediated p53 degradation (Wang et al., 2012; Zhou et al., 2012; Zhu et al., 2018).

Another lncRNA strongly upregulated in stress conditions is *MALAT1*, expressed in all retinal layers (Yao et al., 2016). *MALAT1* expression in rod PRs was reduced upon longer post-mortem times, prompting the authors to suggest that such downregulation may be linked to an early stage of rod PR degeneration (Lukowski et al., 2019).

An interesting example of crosstalk between lncRNAs and miRNAs in PR cells is represented by the lncRNA *Rncr4* (retinal non-coding RNA 4) and the miR-183/96/182 cluster (Krol et al., 2015; **Figure 1D**). *Rncr4* is expressed in maturing PRs in the opposite direction to the pri-miR-183/96/182. Its expression stimulates pri-miR-183/96/182 processing by acting on the activity of the DEAD-box RNA helicase/ATPase Ddx3x, an inhibitor of pri-miR-183/96/182 maturation in early postnatal PRs. Alteration of the timing of miR-183/96/182 formation led to early accumulation of mature miR-183/96/182 and caused profound irregularities in the thickness of the PR and inner nuclear layers (Krol et al., 2015).

A novel class of ncRNAs with tissue- and stage-specific expression patterns are the circular RNAs (circRNAs) whose circular characteristic confers increased stability compared to linear transcripts (Rybak-Wolf et al., 2015; Han et al., 2017). CircRNAs display high expression, evolutionary conservation, specificity of action and stability. They are involved in numerous biological processes and are differentially expressed in various diseases (Ghosal et al., 2013; Lukiw, 2013; Li et al., 2015; Peng et al., 2015; Zhao and Shen, 2017), including diabetic retinopathy, highlighting their potential as biomarkers and as predictors of response to treatments (Li et al., 2015; Chen et al., 2016; Shan et al., 2017; Zhang et al., 2017, 2018). Transcriptome profiling of circRNAs at five different developmental stages in wild-type and degenerating retinas (*rd8* mouse model; Mehalow et al., 2003) identified circRNAs with a dynamic and strong expression pattern. These circRNAs were found to target miRNAs in the retina, acting as competitive endogenous RNAs (ceRNAs). Specifically, *Cdr1as* acted as miR-204/677/378 sponge, *circHpk2* as a miR-124 sponge, *circTulp4* as a miR-26a/671/204 sponge, and *circAnkib1* as a miR-195a sponge. Functional analysis of *circ-Tulp4* revealed that its reduction leads to downregulation of miR-204-5p and miR-26a-5p targets (i.e., *Meis2*, *Cdh2*, *Mitf*, and *Pde4b*) which are major players in retinal development and function. Accordingly, AAV-*circTulp4*-shRNA-treated retinas showed severe PR degeneration with attenuated scotopic and photopic ERG responses confirming that *circTulp4* is indispensable for proper retinal function. The authors observed that the levels of some circRNAs, but not those of their corresponding linear transcripts, increased before disease onset in the retina of *rd8* mice (Chen et al., 2020). More comprehensive transcriptome studies extended to additional models are needed to support the hypothesis that circRNA expression alterations may be early markers of PR degeneration.

PERSPECTIVES

Advancements in understanding the role of ncRNAs in PR development and function prompted the design of new strategies to promote PR survival (**Table 1**). Specifically, miRNA modulation can impact simultaneously on several biological

processes that exacerbate PR degeneration as shown in the following examples of miRNA-based therapeutics. First, intravitreal delivery of miR-124 mimics reduced microglia infiltration and PR cell death following light-induced damage in mice, possibly by modulating *ccl2* levels (Chu-Tan et al., 2018). In a similar approach, the subretinal delivery of AAV-miR-204 in a mouse model of dominant RP (i.e., the transgenic *RHO-P347S*) promoted PR survival and preserved retinal function through synergistic effects on innate immunity, inflammatory responses, and cell death (Karali et al., 2020). miR-204 exerted this protective effect, at least partially, by downregulating the expression of *Siglec1* and *Xaf1* (Karali et al., 2020). Finally, AAV-mediated inhibition of miR-6937-5p in *rd10* mice delayed PR and vision loss (Anasagasti et al., 2020). This miRNA was upregulated at early stages of retinal degeneration in *rd10* mice (Anasagasti et al., 2018). Recently, intravitreal injection of *MALAT1*-siRNA in diabetes-induced mice reduced the functional and morphological damage of rods and cones, indicating its protective, likely indirect, effect against secondary PR loss (Zhang et al., 2020b). Similarly, *MALAT1* increase in oxygen-induced retinopathy was counteracted by intravitreal injection of *MALAT1*-siRNA, which significantly improved the retinal phenotype (Wang et al., 2020). Although these results highlight *MALAT1* silencing as a possible therapeutic strategy for different forms of retinopathy, the direct functional role of *MALAT1* in PRs remains unclear, especially in light of the results linking its reduction to PR degeneration (Lukowski et al., 2019). The discrepancy between the above observations warrant further investigation aimed at a better clarification of the role of *MALAT1* in the different retinal cell types.

These studies underscore the therapeutic potential of ncRNA-based approaches in mutation- and gene-independent approaches. Such strategies are particularly relevant for inherited retinal diseases due to their high genetic heterogeneity (Carrella et al., 2020). Moreover, they are appealing for gain-of-function and dominant negative mutations where gene supplementation is not appropriate to overturn the consequences of the genetic lesion. Similar attempts applied to non-retinal conditions yielded encouraging outcomes confirming the translational potential of ncRNA-based therapies in human disease (Hanna et al., 2019; Dammes and Peer, 2020).

AUTHOR CONTRIBUTIONS

SC and SB conceived the manuscript. SC and MK wrote the first draft of the manuscript. SB edited the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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