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Epigenetic and Posttranscriptional Regulation in Retinoblastoma

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Abstract

The Retinoblastoma 1 (*RB1*) gene, located on chromosome 13q14 and encodes the tumor-suppressor retinoblastoma protein, is the cause of Retinoblastoma. The mutational inactivation of both gene alleles brings on this cancer. Retinoblastoma (RB) high-risk histopathological characteristics indicate metastasis or local recurrence with rapid progresses following *RB1* inactivation. There is growing interest in regulatory activities unconnected to the coding region of the genome, or exome, in addition to epigenetic control mechanisms. The altered epigenome is significant, though by no means the only, problem in the etiology of Retinoblastoma. After all, cancer development is a multistep process in which numerous dissimilar genetic, epigenetic, and posttranscriptional modifications result in a shared phenotype. This study emphasizes the most recent developments in posttranscriptional change and epigenetics related to retinoblastoma tumor biology. Here, we highlight the novel biomarkers the retinoblastoma tumor has expressed to improve patient survival.

Keywords

Retinoblastoma, Epigenetic, ncRNAs, miRNAs, lncRNAs, circRNAs, ceRNAs

1. Introduction

Retinoblastoma (RB), which accounts for 6% of pediatric cancer cases and occurs in one in every 15,000 - 20,000 live births, is the most prevalent primary intraocular malignant tumor in pediatric patients worldwide [1]. Pediatric cancer can be hereditary or spontaneous, and RB is known to be caused by the biallelic inactivation of the RB1 gene, which is situated at the 13q14 region of chromosome 13 [2]. Due to somatic and germline mutations in the tumor suppressor

RB1 gene, RB can be inherited or acquired. The functional retinoblastoma protein (*pRB*), which is necessary for chromosomal integrity, is evidenced by studying the process that grants RB an infinite capacity for proliferation [3].

Studies have demonstrated that *RB1* knockdown induced cone precursors' development, proliferation, and malignancy in dissociated retinal cultures [4]. These cone precursors formed tumors in orthotopic xenografts with histologic characteristics and protein expression profiles typical of differentiated human RB. Some other oncogenes and suppressors have been discovered. The genes that promote RB progression are the chromatin remodeling factors such as murine double minute 4 (*MDM*4), *kinesin family member* 14 (KIF14), *DNA factor remodeling* (*DFR*), transcription factor *E2F3*, and the tumor suppressor *cadherin 11* (*CDH11*) [5].

2. Epigenetic Biomarkers in Retinoblastoma

Epigenetic regulation's crucial significance in Retinoblastoma is a newly discovered field. Retinoblastoma could develop and spread due to separate or combined genetic and epigenetic processes. There has been remarkable progress in understanding the genetic changes that lead to retinoblastoma pathogenesis, but less in epigenetic modification. Site-specific DNA methylation, histone modifications, long non-coding RNA, modification of microRNA (miRNA) mediated gene silencing, and ATP-dependent chromatin remodeling are examples of epigenetic modifications that silence tumor suppressor genes and activate oncogenes. It has been shown that the inactivation of *RB1* can lead to dysregulation of the tumor suppressor and oncogenic pathways through epigenetic mechanisms. Future therapies and diagnoses will be possible with a better understanding of the epigenetic alterations in retinal fibroblastoma [1].

3. DNA Methylation Biomarkers of Retinoblastoma

Although the gene's promoter region remains unmethylated despite having a high density of CpG islands, it is well known that methylation occurs mainly in the gene's CpG-poor coding region in normal tissue. In an ideal situation, this methylation pattern persists, but when it becomes unbalanced across the genome, it turns healthy cells into malignant ones. DNA methyltransferase expression is elevated in cancerous cells, and the unmethylated CpG island in the promoter region of the gene is the site of localized hypermethylation. The gene's transcription is repressed as a result of this hypermethylation. Tumor suppressor genes are hypermethylated in malignant cells, while oncogenes are hypomethylated. Hypermethylation of the CpG island in the gene's promoter region is one of the primary mechanisms by which cancer-related genes like *RB1*, cyclin-dependent kinase inhibitor 2A (*CDKN2A*/p16), von Hippel-Lindau tumor suppressor (*VHL*), MutL homolog 1 (*MLH*), O6-methylguanine-DNA methyltransferase (*MGMT*), and ras-associated domain family 1A (*RASSF1A*) transformed the cells [6].

3.1. Histone Modification Biomarkers of Retinoblastoma

One of the most crucial processes for controlling the expression of genes in eukaryotes is the posttranslational modification of nucleosomal histones, which changes chromatin into active or inactive chromatin. Histone posttranslational modifications can take many forms, including methylation, acetylation, phosphorylation, and ubiquitination.

3.2. Biomarkers from Non-Coding RNA Regulation in Retinoblastoma

Many processes, including control by non-coding RNAs, are part of epigenetics and posttranscriptional processes, generally considered vital in ocular diseases (ncRNAs). Despite being unable to be translated into proteins, non-coding RNAs (ncRNAs) constitute the most significant portion of the human genome and have a greater impact on many biological functions than coding RNAs [7].

Long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs) are among the different classes of non-coding RNAs that have been discovered. These ncRNAs play a role in the onset, pathogenesis, and development of many eye diseases, including cataracts, premature retinopathy, age-related macular degeneration, eye tumors, etc. Recent studies examining ncRNAs' function in RB have seen an increase in recent years. In this context, ncRNAs are regarded as relevant and innovative biomarkers not only for the early diagnosis of this tumor but also for providing a therapeutic and prognostic approach to improving the survival and quality of life of RB patients [8].

4. microRNA Biogenesis

Small non-coding RNAs called microRNAs (miRNA) function as negative post-transcriptional regulators by degrading or suppressing the translation of messenger RNAs (mRNAs) [9]. MicroRNAs have between 18 and 24 nucleotides. Generating miRNAs begins with DNA sequences known as miRNA genes or gene clusters that are only transcripted as miRNA molecules or collectively as polycistronic transcripts, respectively. A protein-coding gene's intron or untranslated region (UTR) may also be where miRNAs are found. The primary miRNA-generating processes are canonical and non-canonical biogenesis pathways (**Figure 1**).

5. Canonical miRNA Biogenesis

RNA polymerase II and III can perform the conventional transcription of miRNA genes. Whereas RNA polymerase III transcribes miRNA genes in repetitive DNA sequences, RNA polymerase II transcribes miRNA genes in intergenic or intronic regions. Pre-miRNAs are released into the cytoplasm after being transcribed by the protein Exportin-5 (*EXP5*) [10].

The RNase III endonuclease *DROSHA* and its cofactor *DGCR8* convert the pre-miRNA into a shorter miRNA precursor in the cytoplasm (pre-miRNA).

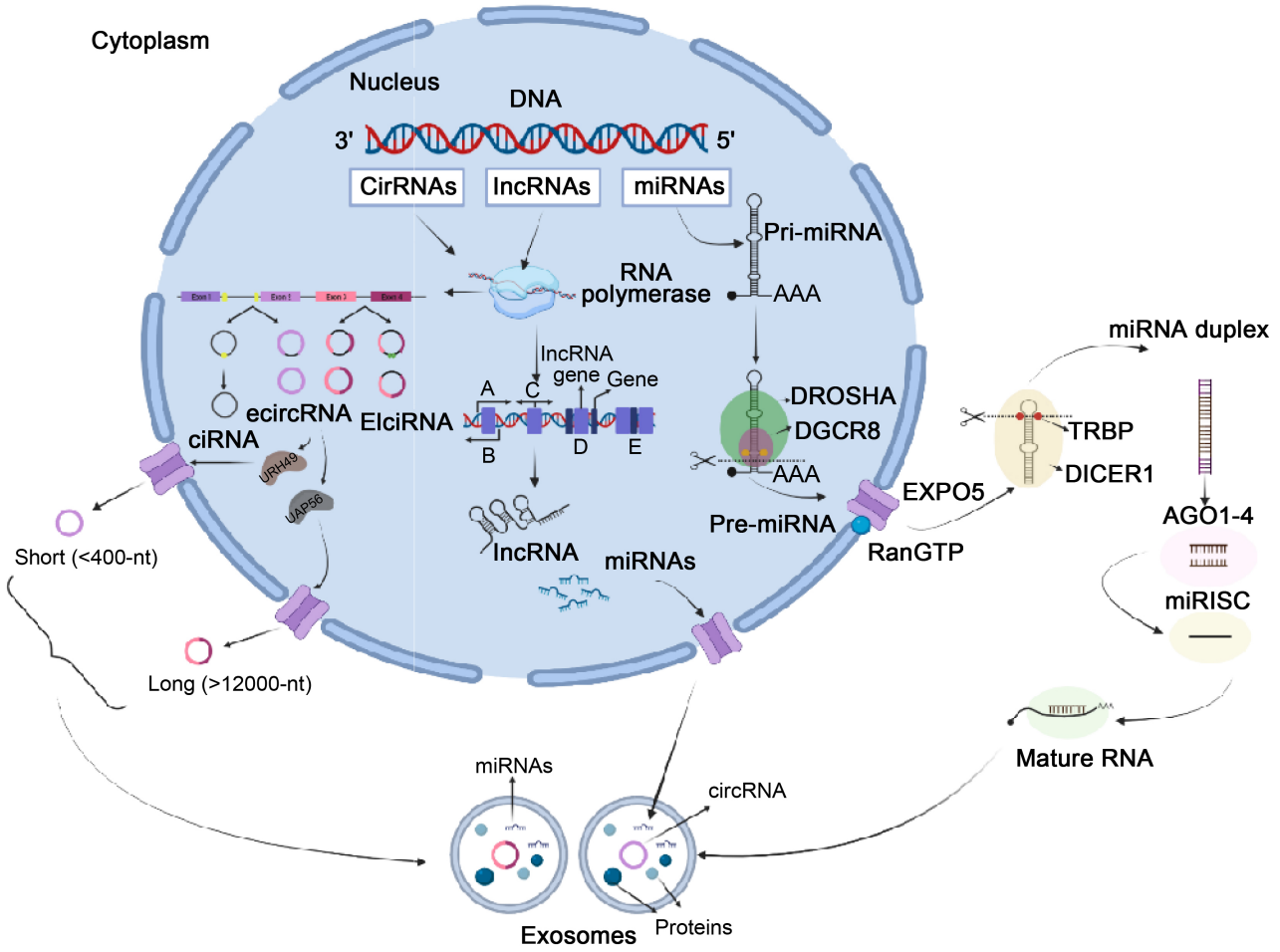

Figure 1. Biogenesys non-coding RNA. circRNAs can be classified into intronic circRNA (ciRNA), exonic-circRNA (ecircRNA), and exon-intron circRNA (ElciRNA). lncRNA can be generated in various types: (A) Sense; (B) Antisense; (C) Divergent; (D) Intergenic; (E) Intronic, and miRNAs, which are processed and secreted by exosomes. Created with BioRender.com.

Pre-miRNA is transformed into a mature and functional miRNA once it reaches the cytoplasm by the RNase III endonuclease Dicer and its cofactor TRBP [11]. The hairpin structure of pre-miRNA includes a stem and a loop. Pre-miRNA size and length can differ based on the species and cell type. The pre-miRNA is exported to the cytoplasm by Exportin-5 following processing by DROSHA.

In the RNA-induced silencing complex, the mature miRNA attaches to effector proteins that silence genes, such as the Argonaute protein (*AGO*) (*RISC*). The RISC complex binds to the 3'UTR region of target mRNAs to silence gene expression by mRNA degradation or translation repression [10].

In conclusion, the synthesis of miRNAs is a multistage, tightly controlled process involving several protein components. Creating miRNA-based therapeutics and discovering new therapeutic targets depend on our ability to comprehend miRNA production.

6. Non-Canonical miRNA Biogenesis

In addition to the canonical pathway, unexpected non-coding RNAs may be

converted into miRNAs through different mechanisms depending on the cell type and cellular state. The same proteins from the canonical pathway are combined differently to produce functionally equivalent miRNAs in the non-canonical pathway. *Drosha/DGCR8*-independent and Dicer-independent are the two main non-canonical miRNA biogenesis mechanisms that are distinguished [12].

MiRtrons biogenesis is an illustration of the first. By examining critical characteristics such as guanine concentration, hairpin length, free energy, and bulges in the stem region, miRtrons may be separated from conventional miRNAs [12]. The whole intronic sequence of the mRNA-expressing genes in which they are found is matched by miRtron-derived pri-miRNAs. Splicing is used to process them rather than the microprocessor complex. After splicing, pre-miRNAs produced by the miRtron are exported to the cytoplasm by XPO5, where Dicer completes the process to create a mature miRNA.

Pre-miR-451 is an illustration of a non-canonical Dicer-independent mechanism for miRNA production. Drosha first breaks it down to release the pre-miRNA, and then it is loaded into Ago2 in the cytoplasm to stimulate the maturation of this microRNA. Because Pre-stem-loop miR-451's structure is too short to detect and process effectively, Dicer does not digest it. As a result, it appears that Ago2 is essential in this pathway for efficient guide strand selection and RISC loading. This miRNA plays a role in the development and growth of tumors in several malignancies. It is downregulated in epithelial cancers that become invasive adenocarcinomas after losing their basolateral polarity, as shown in non-small cell lung carcinoma, colorectal cancer, and gastric cancer (NSCLC) [12].

7. microRNAs in RB

Using circulating miRNAs may have some benefits, such as being a non-invasive biomarker and being easily accessible and quick to detect, making them a novel platform for diagnostic and therapeutic use. Several lines of research suggested that miRNAs can alter the behavior of cells under different settings by selectively targeting a range of cellular and molecular targets. Several events may cause RB to initiate and develop when the expression of miRNAs is dysregulated. For instance, let-7b is among the let-7 family members whose deregulation is linked to the onset and development of RB. Many genes, including high-mobility group A1 (*HMGA1*) and high-mobility group A2 (*HMGA2*), play essential roles in RB development and may be upregulated due to let-7b's downregulation [9]. Others have shown that miR-34 functions as a tumor suppressor in RB cells and is a potential therapeutic target [11].

Zhao *et al*. evaluated the expression of several miRNAs in human RB tissues using the microarray approach. Specific miRNAs were validated using the in situ hybridization method and Northern blot analysis. According to their findings, patients with RB had higher levels of several tissue-specific miRNAs, including miR-129-1, miR-494, miR-198, miR-492, miR-513-2, let-7e, miR-513-1, miR-503,

miR-518c, miR-129-2, miR-498, miR-320, and miR-373, than healthy individuals. According to these results, multiple miRNAs might be used as novel diagnostic biomarkers for patients with different stages of RB [14].

It has been discovered that RB growth and progression may be influenced by a particular class of microRNA called miRNA-22. In 2012, researchers analyzed the expression and use of miRNA-22 in retinoblastoma cells. When retinoblastoma cells were compared to healthy retinal cells, they discovered that miRNA-22 was dramatically downregulated. Moreover, overexpressing miRNA-22 prevented retinoblastoma cells from proliferating and growing, indicating that this microRNA may have a tumor-suppressive function. In RB cells, the researchers also discovered two putative miRNA-22 targets, which may shed light on the molecular processes underlying the genesis of this disease [15].

The present work examined curcumin's impact on the expression of miRNAs in human Y79 retinoblastoma cells. In a functional search for miRNAs that support *in vitro* cell migration and have prometastatic potential, miR-373 was found. MiR-373 expression is higher in RB tumors than in normal retinas, indicating a potential function in the tumor pathway. The study discovered that curcumin treatment changed the expression of several miRNAs, including the overexpression of miR-22, which has previously been demonstrated to have tumor-suppressive effects in RB. Moreover, miR-21 expression was reduced by curcumin treatment, which has been linked to carcinogenic features in many malignancies [15].

Beta *et al*. looked at the expression of several serum miRNAs in RB patients. Pooled serums from 14 patients with advanced RB and 14 normal volunteers were used to provide miRNAs. According to their findings, children with RB had higher levels of 21 serum miRNAs and lower levels of 24 serum miRNAs than the healthy group. They demonstrated that deregulating different serum miRNAs, such as miR-17, miR-18a, and miR-20a, might stimulate cell proliferation and prevent apoptosis in RB cells by influencing many cellular and molecular targets. Hence, it appears that the discovery of novel circulating miRNAs and their cellular and molecular targets may offer a new diagnostic tool for the early identification of RB patients. Also, finding new biomarkers may help us understand the biological mechanisms involved in the pathogenesis of RB. Several studies evaluated circulating miRNAs in RB patients as diagnostic, prognostic, and therapeutic biomarkers. Hence, we proposed that these molecules may be employed as a new diagnostic and therapeutic platform in RB patients [16].

Liu and Col. evaluated circulating miRNAs as a diagnostic biomarker in RB patients. They demonstrated that the downregulation of several plasma miRNAs, such as miR-320, let-7e, and miR-21, is linked to the development of RB. The study used 65 plasma samples from patients with RB and 65 samples from healthy volunteers as controls. These results indicated that circulating miRNAs might be used as diagnostic biomarkers in RB patients [17].

Also linked to tumor suppressor properties is miR-34. Studies have shown

that the miR-34 family is transcriptionally activated by p53. Variable levels of miR-34a expression have been noted, and it has been proposed that miR-34a knockdown by anti-miR compounds may increase RB cell proliferation and chemotherapy resistance. Two RB cell lines are frequently employed (Y79 and Weri-Rb1). When topotecan and miR-34a were coupled, these scientists also noticed significant RB cell growth suppression. This finding is consistent with earlier research showing a comparable growth suppression with a combination of topotecan and the *p53* activator nutlin-3. Overall, the data are consistent with miR-34a acting as a tumor suppressor in the healthy retina [18].

Several malignancies have been investigated concerning the miR17-92 cluster (OncomiR-1). In RB, miR-17-92 promotes carcinogenesis through proliferation control, at least in part by directly suppressing important cell cycle regulators such as *p21CIP1* and *p57KIP2*. According to the references, miR-1792 cooperates with the death of RB's family members to support RB [18]. (**Table 1**)

8. Long Non-Coding RNA (lncRNA)

Non-coding RNAs greater than 200 nucleotides, known as long non-coding RNAs (lncRNAs), have a limited capacity to encode proteins. LncRNAs are essential biological molecules linked to cancer, according to growing evidence. They can modulate many biological processes, including cell division, death, migration, invasion, and differentiation [20]. (**Table 2**)

8.1. lncRNA Biogenesis

RNA polymerase II transcription, splicing, and posttranscriptional alterations, like 5' capping and polyadenylation, are all critical steps in the complicated process of lncRNA formation [24]. The Xist gene, which causes the inactivation of the X chromosome in female animals, is one well-studied example of lncRNA biogenesis. A persistent RNA molecule known as Xist wraps the whole X chromosome after being extensively spliced and polyadenylated [25]. *XIST* is translated from the X chromosome. The function of chromatin remodeling complexes, such as the Polycomb Repressive Complex 2 (*PRC2*), in controlling lncRNA expression is another crucial element of lncRNA biogenesis. LncRNAs serve as scaffolding for the *PRC2* recruitment to particular genomic loci and chromatin [26].

8.2. lncRNA in RB

Recent research has revealed that lncRNAs play a crucial part in the development of RB. In particular, RB patients had increased levels of the lncRNAs Hox transcript antisense intergenic RNA (*HOTAIR*), differentiation antagonizing non-protein coding RNA (*DANCR*), colon cancer-associated transcript 1 (*CCAT1*), and nuclear-enriched abundant transcript 1 (*NEAT1*), which exacerbated the onset and progression of RB. However, other lncRNAs, such as *MT1JP*, suppressed tumor growth in RB [5].

Table 1. Altered miRNAs in retinoblastoma.

miRNA	Expression	Target	Type of biomarker	Type of sample	References
let-7	Down	*HMGA1*; *HMGA2*; *Ras*; *Myc*	Proliferation	Y79	[9] [19]
let-7e	Down			Plasma	[17]
let-7g	Up	*NRAS*; *TGFBR1*; *IGF1R*; *MYCN*; *MAPK6*; *TP53*		Y79	[15]
miR-18a	Up		Proliferation; Apoptosis	Serum	[16]
miR-20a	Up		Proliferation; Apoptosis	Serum	[16]
miR-21	Up	*PTEN*/*Akt* pathway	Proliferation; Migration; Invasion	Plasma	[17]
miR-22	Up	*ESR1*; *BCL9L*; *ERBB3*; *SP1*; *SATB2*; *RAB5B*; *CAV3*		Y79	[15]
miR-31	Down	*STK40*, *PPP6C*; *DLL3*	Proliferation; apoptosis	Weri-Rb1, Y79	[20]
miR-34a	Up	*MDMX*; *Sirtl*; *HMGB1*; *p53*	Tumor suppressor; proliferation	Y79	[13]
miR-129-1; 2	Up	*EF2*; cell cycle	Tumorogenesis	Tissue human	[14]
miR-198	Up	*EF2*; cell cycle	Tumorogenesis	Tissue human	[14]
miR-25-3p	Up		Cell proliferation, migration; invasion	Weri-Rb1, Y79, SO-RB50; tumor tissues	[14]
miR-224-3p	Up	*LATS2/Hippo-YAP* axis	Proliferation; angiogenesis	RB cell lines (Y79) and tumor tissues	[21]
miR-320	Up/Down	*EF2*; cell cycle	Tumorogenesis	Tissue human; plasma	[14] [17]
miR-373	Up	*EF2*; cell cycle	Tumorogenesis	Tissue human	[15]
miR-492	Up	*EF2*; cell cycle	Tumorogenesis	Tissue human	[14]
miR-494	Up	*EF2*; cell cycle	Tumorogenesis	Tissue human	[14]
miR-498	Up	*EF2*; cell cycle	Tumorogenesis	Tissue human	[14]
miR-503	Up	*EF2*; cell cycle; *CBX4*; *IGF1*; *M CPEB2*; *PIK3R1*	Tumorogenesis	Tissue human	[14] [15]
miR-513-1; 2	Up	*EF2*; cell cycle	Tumorogenesis	Tissue human	[19]
miR-518c	Up	*EF2*; cell cycle	Tumorogenesis	Tissue human	[19]
miR17-92 (OncomiR-1)	Up	*p21CIP1*; *p57KIP2*; *EpCAM STAT3*	Proliferation; cell cycle; inhibit differentiation; angiogenesis	Y79; Tissue human	[18] [22]

The human genome contains the 2628-nucleotide lncRNA *CCAT1*, which is adjacent to the gene for the transcription factor *c-Myc*. In this study, RB tissues had considerably higher levels of lncRNA *CCAT1* expression than normal tissues. Moreover, Zhang *et al*. discovered that lncRNA *CCAT1* was markedly higher in RB SO-RB50, Y79, and WERI-RB1 cells than in the normal podiatric retina. Hence, lncRNA *CCAT1* requires further investigation to explore its regulatory role in RB [25].

Increased lncRNA HOX transcript antisense RNA (*HOTAIR*) expression in RB tissues has been identified by microarray analysis as a factor in accelerated RB development and metastasis. The potential therapeutic target of *HOTAIR* for RB and the ability of RB cells to proliferate and invade are suppressed when *HOTAIR* is knocked down [28].

According to Yang *et al*., *HOTAIR* influences the survival, apoptosis, and epithelial-mesenchymal transition of RB cells via sponging miR-613. It is significant to note that overexpression of miR-20b-5p has been shown to inhibit RB cell growth and promote apoptosis. However, it has not yet been determined if *HOTAIR* can act as the ceRNA of miR-20b-5p to control RB development. The authors examined the ceRNA mechanism of the lncRNA *HOTAIR* in RB development, looking for further RB diagnosis and treatment. There are numerous malignant tumors, including non-small-cell lung carcinoma (*NSCLC*), colorectal cancer, and colon cancer, where the well-known lncRNA KCNQ1OT1, which functions as an oncogene, was substantially expressed. KCNQ1OT1 served as a sponge for miR-217, miR-212-3, and miR-504 and was involved in developing tumors, their spread, and their resistance to treatment. miR-124 was found to be down-regulated in RB tissues and cell lines, according to a prior study. Moreover, the miR-124/*STAT3* axis partially inhibited the effects of the lncRNA*XIST* on cell proliferation, cell cycle arrest, and cell death in RB cells [30]. Nonetheless, further research needs to be done on KCNQ1OT1's expression and biological impact in RB [29].

The X-inactive specific transcript (*XIST*), a long non-coding RNA (lncRNA), plays a significant role in the inactivation of the X chromosome. In particular, *XIST* functions as a tumor suppressor or a tumor-promoting lncRNA in various human cancers. Moreover, *XIST* expression is increased in RB tissues and cell lines, and when *XIST* is knocked down, RB cell proliferation is inhibited, and apoptosis is induced. As a competing endogenous RNA (ceRNA) of miR-101, *XIST* raises the expression levels of *ZEB1* and ZEB2, promoting the progression of RB cells and their epithelial-to-mesenchymal transformation [31]. It was determined that *XIST* was an oncogenic lncRNA in RB in 2021. In cervical cancer, *XIST* enhanced cell proliferation and inhibited cell apoptosis via miR-140-5p, according to a prior study. Furthermore, miR-140-5p has been shown to induce cell death in RB while inhibiting cell proliferation, migration, and invasion [32].

Wang *et al*. demonstrated that differentiation-antagonizing non-protein-coding RNA (*DANCR*) was overexpressed in RB cell lines and tissues and that by stimulating proliferation, migration, invasion, and epithelial-mesenchymal transi-

tion (EMT) by acting as a competing endogenous RNA (ceRNA) of the miRNAs miR-34c and miR-613, *DANCR* worsened disease-free survival (DFS) ($p = 0.0084$) and OS ($p = 0.0056$). The lncRNA colon cancer-associated transcript 1 (*CCAT1*) induced similar changes in RB samples, in this case, through the miR-218-5p/*MTF2* axis [33].

Furthermore, increased levels of the promoter of *CDKN1A* antisense DNA damage-activated RNA (*PANDAR*), a newly identified lncRNA, were reported to be associated with unfavorable clinicopathological characteristics such as optic nerve invasion and advanced International Intraocular Retinoblastoma Classification (IIRC) stage; this was partly due to *PANDAR* inhibiting apoptosis when interacting with the Bcl-2/caspase-3 pathway [34]. Similarly, evidence has been reported for the clinical relevance of testis-associated highly conserved oncogenic long non-coding RNA (THOR), whose overexpression enhances the malignant phenotype of RB in association with the oncogene *c-Myc* and the gene encoding insulin-like growth factor 2 mRNA-binding protein 1 (*IGF2BP1*). Lastly, small nucleolar RNA host gene 14 (*SNHG14*) and plasmacytoma variant translocation 1 (*PVT1*), two other lncRNAs that promote tumor aggressiveness and lower OS ($p < 0.001$ and $p < 0.032$), respectively, were reported to act by sponging, respectively, the miRNAs miR-124 and miR-488-3p [35].

Taurine upregulated gene 1 (*TUG1*) is a 7.1-kb lncRNA encoded on chromosome 11A1 that was first identified as an essentialregulator of retinal and normal photoreceptor development that is expressed in retinal tissues. More recent work has highlighted roles for *TUG1* as a modulator of key oncogenic processes such as invasion, metastasis, cell cycle progression, proliferation, and apoptosis. *TUG1* has also been linked to radioresistance and angiogenesis in the context of hepatoblastoma [36].

TUG1 was upregulated in RB cells, and the absence of *TUG1* repressed cell proliferation, whereas accelerated cell apoptosis in RB. In brief, *TUG1* is an oncogenic gene in RB, and sponge of miR-516b-5p and upregulated *H6PD* to promote cell growth in RB, possibly inspiring future studies to find an effective target for RB treatment [37].

PROX1-antisense RNA1 *(PROX1-AS1*) has been reported to participate in the progression of various cancers, such as ovarian and prostate cancer. Moreover, *PROX1-AS1* can promote gastric cancer and thyroid proliferation and metastasis. In RB, reducing*PROX1-AS1* could upregulate miR-519d-3p to restrain the malignant behaviors and drug resistance of RB cells via silencing *SOX2* [38].

Metastasis associated with lung adenocarcinoma transcript 1 (*MALAT1*) is a highly conserved mRNA-like lncRNA and was first identified with high expression in metastatic non-small cell lung cancer. According to previous studies, *MALAT1* is overexpressed in many other human malignancies, including breast, pancreas, colon, prostate, and liver cancers. Functional studies of *MALAT1* demonstrated that its deregulation influences multiple cancer cells' proliferation, invasion, and/or metastasis. With these findings, it was concluded that *MALAT1* is critical for cancer development. However, the mechanism of *MALAT1* in tu-

mor cell growth regulation, especially in RB, is still unclear. Liu and Col. identified the role of lncRNA MALAT1 and miR-124 in RB. The study found that *MALAT1* silence upregulated miR-124 expression in RB cells, which reversed the inhibitory effect of miR-124 on tumor growth of RB cells. *MALAT1* expression could be regulated in RB cells treated with miR-124 overexpression. Also, miR-124 increases the expression of E-cadherin, considered a hallmark of epithelial cells and a repressor of cell invasion and metastasis. These findings suggest that miR-124 is essential in RB's invasive and/or metastatic potential [39].

Long non-coding RNA (lncRNA) *KCNQ1OT1* was reportedly tightly associated with tumorigenesis and the progression of multiple cancers. Emerging research suggested that *KCNQ1OT1* was involved in the occurrence, metastasis, and drug resistance of tumors acting as a sponge for miRNAs, such as miR-217, miR-212-3, and miR-504. The function and mechanism of *KCNQ1OT1* of RB are proliferation and migration [40]. (**Table 2**)

9. Circular RNAs (circRNAs)

Circular RNA (circRNA) is a novel class of non-coding RNA that predominantly controls gene activity to regulate biological processes. circRNA is a non-coding RNA, but in some situations, it can act as a translational template for the synthesis of proteins, leading to the production of functional proteins. As circRNAs have many miRNA binding sites, they act like sponges, soaking up miRNAs. By base pairing, circRNA may also engage in interactions with other RNAs. Additionally, circRNA may restrict the function of proteins by interacting with them CircRNAs have recently been shown to regulate and control alternative splicing and host gene expression, interact with RNA-binding proteins that control transcription, and affect cis-transcriptional regulation [47].

9.1. circRNAs Biogenesis

According to their parts, the circRNAs in eukaryotes can be divided into three subtypes: 1) exonic circRNAs (EcircRNAs), produced by the circularization of one or more exons; 2) exon-intron circRNAs (EIciRNAs), circularized from exons with introns reserved; and 3) intronic circRNAs [(ci)RNAs], made entirely of introns. The sequence of circRNAs is assembled head-to-tail by a 3', 5' phosphodiester covalent bond. In contrast to conventional splicing, "back-splicing", which is how circRNAs are often created, involves connecting an upstream 3' acceptor and a downstream 5' donor.

In addition, five groups of circRNAs can be classified according to where they are about nearby coding RNA: 1) and 2) "exonic" and "intronic" formed, respectively, by exons and introns; 3) "antisense": transcribed into the opposing strand from their gene locus being overlapped by linear isoforms; 4) "sense overlapping": produced by the same gene locus but does not belong to the "exonic" or "intronic" circRNA; 5) "intergenic": transcribed from the location that is outside the gene loci [42].

Table 2. Altered lncRNAs in retinoblastoma.

lncRNA	Expression	Target	miRNAs	Type of biomarker	Type of sample	References
RNA HCP5	Up	*HDAC9*	miR-3619-5p	Anti-tumoral	HXO-RB44, Y79, SO-RB50, Weri-Rb1;Tissue human	[41]
lncRNA CCAT1	Up	*c-Myc*	miR-218-5p;	Proliferation, migration, invasion; EMT; apoptosis	SO-RB50; Y79; WERI-RB1	[27]
lncRNA DANCR	Up	*MMP-9*	miR-34c; miR-613	Proliferation, migration, invasion; EMT	Weri-Rb1, Y79, SO-RB50, HXO-RB44) and tumor tissues	[42]
lncRNA NEAT1	Up	*CXCR4*	miR-204; miR-124	Proliferation; Migration;	Weri-Rb1, Y79, SO-RB50) and tumor tissues	[23]
lncRNA XIST	Up	*STAT3*; *SOX4*; *ZEB1*; *ZEB2*	miR-124; miR-140-p; miR-191-5p; miR-101	Proliferation; Migration; Invasion	Y79; Tissue human	[30] [31]
lncRNA HOXA11-AS	Up	*NEK3*	miR-506-3p	Metastasis; Development	HXO-RB44, Y79, SO-RB50, Weri-Rb1	[43]
lncRNA TUG1	Up	*H6PD*	miR-516b-5p	Progession; Epithelial-Mesenchymal Transition	HXO-RB44, Y79, SO-RB50, Weri-Rb1; Tissue human	[37] [44]
lncRNA PVT1	Up	*NOTCH*	miR-488-3p; miR-124	Progession	HXO-RB44, Y79, SO-RB50, Weri-Rb1;Tissue human	[35]
lncRNA PROX1-AS1	Up	*SOX2*	miRNA-519d-3p	Drug Resistence; Proliferation, Migration; Invasion	HXO-RB44, Y79, SO-RB50, Weri-Rb1;Tissue human	[38]
lncRNA MALAT1	Up		miR-124/STX17, miR-20b-5p/STAT3, miR-655-3p/ATAD2 and miR-124/Slug axis	Proliferation, Migration; Invasion; EMT	HXO-RB44, Y79, SO-RB50, Weri-Rb1;Tissue human	[39] [45]
lncRNA MKLN1	Down			Tumorogenesis	Y79; WERI-RB1	[46]
lncRNA HOTAIR	Up	*RRM2*; *PI3K*; *AKT*	miR-613; miR-20b-5p	Proliferation; Epithelial-Mesenchymal Transition	Y79	[28] [29]
lncRNA KCNQ1OT1	Up	*SIRT1*; *JUNK*	miR-217; miR-212-3; miR-504	Proliferation; Migration	HXO-RB44, Y79, SO-RB50, Weri-Rb1; Tissue human	[40]

9.2. circRNAs in RB

According to preliminary studies, dysregulated circRNAs may play tumor-suppressive and oncogenic roles in the origin and progression of cancer. By controlling the biologically malignant behaviors of cancer cells, such as proliferation, apoptosis, and metastasis, they may affect many cellular processes and aid in the growth of tumors. These genes can change in various ways, such as when new oncogenes appear or old proto-oncogenes become overexpressed. Tumor suppressor genes (*TSGs*) prevent cell proliferation by reversing the process [42].

By disrupting the *AKT*/*mTOR* signaling pathway, Circ 0001649 limits RB cell proliferation and death, and its low expression level predicts a poor prognosis for patients [48]. Circ ODC1 promotes RB cell proliferation and positively controls SKP2 [49]. Unexpectedly, circ 0000527's high expression was shown to be strongly correlated with the degree of differentiation and cTNM staging in another investigation, which found that RB tissues and cells had a drastically enhanced level of this gene's expression. According to these results, circ 0000527 was likely to suggest that RB patients will have a bad prognosis. Moreover, circ 0000527 overexpression markedly reduced cell apoptosis while increasing cell proliferation, motility, and invasion [50]. Circ 0000527, however, had the reverse result after being knocked down. At the same time, miR-646 expression in RB showed a significant decrease, and since miR-646 has several binding sites for circ_0000527, further studies confirmed that circ_0000527 negatively regulates miR-646 expression. In addition, acting as a sponge for miR-1236-3p, which targeted SMAD2 directly, and as a result, miR-1236-3p expression was reduced in RB tissues and cells [51].

According to reports, Circ 0099; 198 is highly expressed in RB and reduces the expression of miR-1287, which controls the expression of *LRP6* [52].

Circ 0000034 was the unique circRNA studied with a single target, miR-361-3p, whose targets could potentially affect the mechanisms underlying RB and are crucial elements in the initiation and development of this malignancy. MiR-361-3p controls the expression of STX17 by targeting. Because miR-361-binding 3p's sites are sponging *STX17*, there is a rise in the expression of circ 0000034. On the other hand, investigations in RB have shown a reduction in miR-361-3p expression [53]. Circ 0000034's inability to sponge miR-361-3p revealed that circ 0000034's silencing significantly reduced RB development. By controlling the expression of *ADAM19* in this situation, miR-361-3p prevents RB development [54].

The *E2F* family of transcription factors has been illustrated as a critical regulator related to various tissues' proliferation, differentiation, and apoptosis. *E2F* transcription factor 5 (*E2F5*), a member of the *E2F* family, has been characterized as a transcriptional repressor that can regulate cell proliferation through its interaction with the RB protein to inhibit target gene transcription. In addition, it has been documented to play critical roles in cancer development, including

RB. The circ_0084811 was discovered to be distinctly overexpressed in RB cells. Through mechanistic studies, it was established that the enrichment of H3K27ac in the circ_0084811 promoter caused the overexpression of circ_0084811 in RB cells. Functionally, inhibition of circ_0084811 diminished RB cell proliferation and stimulated cell apoptosis [55].

circ_0075804 regulated tumorigenesis in RB, performed an animal study using xenograft mice model. Similar to the former findings *in vitro*, circ_0075804 silencing notably suppressed xenograft tumor growth. The expression of circ_0075804 and PEG10 protein was reduced, whereas miR-138-5p expression was increased in tumor tissues with the silencing of circ_0075804. Circ_0075804 silencing increased Bax and E-cadherin expression and reduced the level of Bcl-2 in tumor tissues [56].

CircDHDDS, a miR-361-3p molecular sponge, similarly controlled the expression of WNT3A. The circDHDDS/miR-361-3p/WNT3A axis thus facilitated RB development by controlling RB cell proliferation, cell cycle regulation, migration, and invasion. Circ 0000034 is one of the primary circRNAs in RB, as evidenced by the fact that its expression rises in RB and that silencing it prevents the formation and progression of RB [57]. (**Table 3**)

Table 3. Altered circRNAs in retinoblastoma.

circRNA	Expression	Target	miRNAs	Type of biomarker	Type of sample	References
circ_0099; 198		*LRP6*	miR-1287			[52]
Circ_0001649	Down	*AKT*/*mTOR*	miR-331-3p; miR-338-5p	Proliferation	Y79; Human Tissue	[48] [58]
circ_0084811	Up	*E2F5*	miR-18a-5p; miR-18b-5p	Proliferation; Apoptosis	Y79, WERI-Rb-1; ARPE-19	[55]
circ-0075804	Up	*E2F3*; *HNRNPK*; *PEG10*; *LASP1*	miR-138-5p; miR-1287-5p	Tumorogenesis; Proliferation	Y79; Tissue human	[59] [56]
circ_0000527	Up	*XIAP*; *HDAC9*; *BCL-2*	miR-98-5p; miR-5p; miR-27a-3p; miR-646	Apoptosis; Proliferation	Tissue human	[60]
circ_0093996	Up	*TET1*; *PDCD4*	miR-183	Tumorogenesis	Tissue human	[61]
circ_0000034	Up	*DHDDS*; *ADAM19*; *STX17*	miR-361-3p; microRNA-361-3p	Tumorogenesis; Progression	Tissue human	[53] [54]
circ_ODC1	Up	*SKP2*	miR-422a	Proliferation		[49]
circDHDDS	Up	*WNT3A*	miR-361-3p	Proliferation, Cell Cycle, Migration; Invasion	Tissue human	[57]
CircMKLN1		*PDCD4*	miR-425-5p	Progression		[46]
CircCUL2		*E2F2*	miR-214-5p			[62]

Table 4. Altered ceRNAs in retinoblastoma.

ceRNA	Expression	Target	miRNAs	Type of biomarker	Type of sample	References
Circ-E2F3	Up	*ROCK1*	miR-204-5p	Proliferation; Metastasis; Apoptosis	HXO-RB44, Y79, SO-RB50, Weri-Rb1; Tissue human	[45]
TRPM2-A	Up	*WEE1*	miR-497	Proliferation; Metastasis;	Tissue human	[65]
DANCR	UP	*MMP-9*	miR-34c and miR-613 in RB	Proliferation Metastasis	Tissue human	[32]
hsa_circ_0015965	Up	*NOTCH1*	lncRNA MEG3-hsa-miR-378a-5p	Malignant progression	Tissue human	[65]

9.3. The ceRNAs Axes in RB

In recent years, increasing numbers of reports have found that circRNAs play a role in the biological functions of a competing endogenous RNAs (ceRNA) network. circRNAs act as ceRNAs to regulate several biological processes as cell proliferation, apoptosis, invasion, and migration. The term' ceRNA' was created in 2011 to characterize this additional layer of posttranscriptional control [63].

The fact that ceRNA interaction networks are multifactorial means that they may be valuable in investigating complicated diseases such as RB in terms of therapeutic targets since the levels of several disease-related RNAs change simultaneously by targeting just one of them.

Most circRNAs examined as ceRNA axes have higher expression levels, although lower levels of the desired ceRNA axis limit circTET1 in RB. In typical circumstances, the ceRNA axes within the cell are in equilibrium. The trend toward abnormal conditions can be accelerated by varying the expression of each axis component.

According to Huang *et al*. [45], Circ-E2F3 stimulates the miR-204-5p/*ROCK1* pathway, which advances RB. In a study by Li *et al*. [64], the miR-497/WEE1 axis allows *TRPM2-AS* to function as an oncogenic lncRNA in RB. *DANCR* serves as a ceRNA that targets miR-34c and miR-613 in the RB, as Wang *et al*. [32] demonstrated, to facilitate MMP-9-mediated progression and metastasis.

Recently, Jie Sun *et al*., 2023, demonstrated that the hsa_circ_0015965/lncRNA MEG3-has-miR-378a-5p-NOTCH1pathway promotes the malignant progression of RB [64]. (**Table 4**)

10. Conclusion

The most frequent intraocular tumor in children is Retinoblastoma (RB), and during the past 50 years, the prognosis has improved. Initially, non-coding RNAs (ncRNAs) were believed to be the byproducts of random transcription with no purpose. However, the functional significance of ncRNAs in cellular physiology and pathological processes has recently come to light thanks to new

research. Significant interest in and evidence of a close relationship between miRNA, lncRNA, and circRNA and tumor growth have been generated. The competitive endogenous RNA (ceRNA) theory states that mRNAs, lncRNAs, and circRNAs compete for the same miRNA, which affects target mRNAs. A growing body of research has shown that ceRNAs are crucial to the development of RB. In detail, this article examines the miRNAs, lncRNAs, circRNAs, and cecRNAs involved in RB. The results of the summary analysis of the ncRNAs and associated ceRNA networks in RB may offer fresh insights and approaches for creating customized RB therapeutics.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Sun, J. (2020) Biomarkers in Retinoblastoma. *International Journal of Ophthalmology*, **13**, 325-341. https://doi.org/10.18240/ijo.2020.02.18

[2] Knudsen, E., Sexton, C. and Mayhew, C. (2006) Role of the Retinoblastoma Tumor Suppressor in the Maintenance of Genome Integrity. *Current Molecular Medicine*, **6**, 749-757. https://doi.org/10.2174/1566524010606070749

[3] Sun, J., Xi, H.Y., Shao, Q. and Liu, Q.H. (2020) Biomarkers in Retinoblastoma. *International Journal of Ophthalmology*, **13**, 325-341. https://doi.org/10.18240/ijo.2020.02.18

[4] Bremner, R. and Sage, J. (2014) The Origin of Human Retinoblastoma. *Nature*, **514**, 313. https://doi.org/10.1038/nature13748

[5] Thériault, B.L., Dimaras, H., Gallie, B.L. and Corson, T.W. (2014) The Genomic Landscape of Retinoblastoma: A Review. *Clinical & Experimental Ophthalmology*, **42**, 33-52. https://doi.org/10.1111/ceo.12132

[6] Singh, U., Malik, M.A., Goswami, S., Shukla, S. and Kaur, J. (2016) Epigenetic Regulation of Human Retinoblastoma. *Tumor Biology*, **37**, 14427-14441. https://doi.org/10.1007/s13277-016-5308-3

[7] Guzel, E. (2019) Tumor Suppressor and Oncogenic Role of Long Non-Coding RNAs in Cancer. *Northern Clinics of Istanbul*, **7**, 81-86. https://doi.org/10.14744/nci.2019.46873

[8] Fernandez-Diaz, D., Rodriguez-Vidal, C., Silva-Rodríguez, P., Paniagua, L., Blanco-Teijeiro, M.J., Pardo, M., *et al.* (2022) Applications of Non-Coding RNAs in Patients with Retinoblastoma. *Frontiers in Genetics*, **13**, Article ID: 842509. https://doi.org/10.3389/fgene.2022.842509

[9] Delsin, L.E.A., Salomao, K.B., Pezuk, J.A. and Brassesco, M.S. (2019) Expression Profiles and Prognostic Value of miRNAs in Retinoblastoma. *Journal of Cancer Research and Clinical Oncology*, **145**, 1-10. https://doi.org/10.1007/s00432-018-2773-7

[10] Bartel, D.P. (2018) Metazoan MicroRNAs. *Cell*, **173**, 20-51. https://doi.org/10.1016/j.cell.2018.03.006

[11] Ha, M. and Kim, V.N. (2014) Regulation of microRNA Biogenesis. *Nature Reviews Molecular Cell Biology*, **15**, 509-524. https://doi.org/10.1038/nrm3838

[12] Annese, T., Tamma, R., de Giorgis, M. and Ribatti, D. (2020) microRNAs Biogene-

sis, Functions and Role in Tumor Angiogenesis. Frontiers in Oncology, **10**, Article ID: 581007. https://doi.org/10.3389/fonc.2020.581007

[13] Dalgard, C.L., Gonzalez, M., deNiro, J.E. and O'Brien, J.M. (2009) Differential MicroRNA-34a Expression and Tumor Suppressor Function in Retinoblastoma Cells. *Investigative Opthalmology & Visual Science*, **50**, 4542. https://doi.org/10.1167/iovs.09-3520

[14] Zhao, J.J., Yang, J., Lin, J., *et al*. (2009) Identification of miRNAs Associated with Tumorigenesis of Retinoblastoma by miRNA Microarray Analysis. *Child's Nervous System*, **25**, 13-20. https://doi.org/10.1007/s00381-008-0701-x

[15] Sreenivasan, S., Thirumalai, K., Danda, R. and Krishnakumar, S. (2012) Effect of Curcumin on miRNA Expression in Human Y79 Retinoblastoma Cells. *Current Eye Research*, **37**, 421-428. https://doi.org/10.3109/02713683.2011.647224

[16] Beta, M., Venkatesan, N., Vasudevan, M., *et al*. (2013) Identification and *in Silico* Analysis of Retinoblastoma Serum microRNA Profile and Gene Targets towards Prediction of Novel Serum Biomarkers. *Bioinformatics and Biology Insights*, **7**, 21-34. https://doi.org/10.4137/BBI.S10501

[17] Liu, S.S., Wang, Y.S., Sun, Y.F., *et al*. (2014) Plasma microRNA-320, microRNA-let-7e, and microRNA-21 as Novel Potential Biomarkers for the Detection of Retinoblastoma. *Biomedical Reports*, **2**, 424-428. https://doi.org/10.3892/br.2014.246

[18] Reis, A.H.O., Vargas, F.R. and Lemos, B. (2012) More Epigenetic Hits than Meets the Eye: microRNAs and Genes Associated with the Tumorigenesis of Retinoblastoma. *Frontiers in Genetics*, **3**, 284. https://doi.org/10.3389/fgene.2012.00284

[19] Mitra, M., Mohanty, C., Harilal, A., *et al*. (2012) A Novel *in Vitro* Three-Dimensional Retinoblastoma Model for Evaluating Chemotherapeutic Drugs. *Molecular Vision*, **18**, 1361-1378.

[20] Montoya, V., Fan, H., Bryar, P.J., *et al*. (2015) Novel miRNA-31 and miRNA-200a-Mediated Regulation of Retinoblastoma Proliferation. *PLOS ONE*, **10**, e0138366. https://doi.org/10.1371/journal.pone.0138366

[21] Song, L., Huang, Y., Zhang, X., *et al*. (2020) Downregulation of microRNA-224-3p Hampers Retinoblastoma Progression via Activation of the Hippo-YAP Signaling Pathway by Increasing LATS2. *Investigative Opthalmology & Visual Science*, **61**, 32. https://doi.org/10.1167/iovs.61.3.32

[22] Jo, D.H., Kim, J.H., Cho, C.S., *et al*. (2014) STAT3 Inhibition Suppresses the Proliferation of Retinoblastoma through Down-Regulation of the Positive Feedback Loop of STAT3/miR-17-92 Clusters. *Oncotarget*, **5**, 11513-11525. https://doi.org/10.18632/oncotarget.2546

[23] Zhang, T., Yang, J., Gong, F., *et al*. (2020) Long Non-Coding RNA CASC9 Promotes the Progression of Retinoblastoma via Interacting with miR-145-5p. *Cell Cycle*, **19**, 2270-2280. https://doi.org/10.1080/15384101.2020.1802813

[24] Mattick, J.S. and Rinn, J.L. (2015) Discovery and Annotation of Long Non-Coding RNAs. *Nature Structural & Molecular Biology*, **22**, 5-7. https://doi.org/10.1038/nsmb.2942

[25] Gendrel, A.V. and Heard, E. (2014) Non-Coding RNAs and Epigenetic Mechanisms during X-Chromosome Inactivation. *Annual Review of Cell and Developmental Biology*, **30**, 561-580. https://doi.org/10.1146/annurev-cellbio-101512-122415

[26] Rinn, J.L. and Chang, H.Y. (2012) Genome Regulation by Long Non-Coding RNAs. *Annual Review of Biochemistry*, **81**, 145-166. https://doi.org/10.1146/annurev-biochem-051410-092902

[27] Zhang, H., Zhong, J., Bian, Z., *et al*. (2017) Long Non-Coding RNA CCAT1 Promotes Human Retinoblastoma SO-RB50 and Y79 Cells through Negative Regulation of miR-218-5p. *Biomedicine & Pharmacotherapy*, **87**, 683-691. https://doi.org/10.1016/j.biopha.2017.01.004

[28] Fu, K., Zhang, K. and Zhang, X. (2022) LncRNA HOTAIR Facilitates Proliferation and Represses Apoptosis of Retinoblastoma Cells through the miR-20b-5p/RRM2/PI3K/AKT Axis. *Orphanet Journal of Rare Diseases*, **17**, 119. https://doi.org/10.1186/s13023-022-02206-y

[29] Yang, G., Fu, Y., Lu, X., *et al*. (2018) LncRNA HOTAIR/miR-613/c-met Axis Modulated Epithelial-Mesenchymal Transition of Retinoblastoma Cells. *Journal of Cellular and Molecular Medicine*, **22**, 5083-5096. https://doi.org/10.1111/jcmm.13796

[30] Hu, C., Liu, S., Han, M., Wang, Y. and Xu, C. (2018) RETRACTED: Knockdown of lncRNA XIST Inhibits Retinoblastoma Progression by Modulating the miR-124/STAT3 Axis. *Biomedicine & Pharmacotherapy*, **107**, 547-554. https://doi.org/10.1016/j.biopha.2018.08.020

[31] Xu, Y., Fu, Z., Gao, X., Wang, R. and Li, Q. (2021) Long Non-Coding RNA XIST Promotes Retinoblastoma Cell Proliferation, Migration, and Invasion by Modulating microRNA-191-5p/Brain-Derived Neurotrophic Factor. *Bioengineered*, **12**, 1587-1598. https://doi.org/10.1080/21655979.2021.1918991

[32] Wang, Y., Sun, D., Sheng, Y., Guo, H., Meng, F. and Song, T. (2020) XIST Promotes Cell Proliferation and Invasion by Regulating miR-140-5p and SOX4 in Retinoblastoma. *World Journal of Surgical Oncology*, **18**, 49. https://doi.org/10.1186/s12957-020-01825-8

[33] Wang, J., Yang, Y. and Li, K. (2018) Long Non-Coding RNA DANCR Aggravates Retinoblastoma through miR-34c and miR-613 by Targeting MMP-9. *Journal of Cellular Physiology*, **233**, 6986-6995. https://doi.org/10.1002/jcp.26621

[34] Sheng, L., Wu, J., Gong, X., Dong, D. and Sun, X. (2018) SP1-Induced Upregulation of lncRNA PANDAR Predicts Adverse Phenotypes in Retinoblastoma and Regulates Cell Growth and Apoptosis *in Vitro* and *in Vivo*. *Gene*, **668**, 140-145. https://doi.org/10.1016/j.gene.2018.05.065

[35] Wu, X.Z., Cui, H.P., Lv, H.J. and Feng, L. (2019) Knockdown of lncRNA PVT1 Inhibits Retinoblastoma Progression by Sponging miR-488-3p. *Biomedicine & Pharmacotherapy*, **112**, Article ID: 108627. https://doi.org/10.1016/j.biopha.2019.108627

[36] Wang, H., Zhang, Z., Zhang, Y. and Li, L. (2022) Knockdown of the Long Non-Coding RNA TUG1 Suppresses Retinoblastoma Progression by Disrupting the Epithelial-Mesenchymal Transition. *Cell Transplantation*, **31**, 1-10. https://doi.org/10.1177/09636897221078026

[37] Xiu, C., Song, R. and Jiang, J. (2021) TUG1 Promotes Retinoblastoma Progression by Sponging miR-516b-5p to Upregulate H6PD Expression. *Translational Cancer Research*, **10**, 738-747. https://doi.org/10.21037/tcr-19-1480

[38] Chen, Y., Lu, B., Liu, L., Pan, X., Jiang, C. and Xu, H. (2021) Long Non-Coding RNA PROX1-AS1 Knockdown Upregulates microRNA-519d-3p to Promote Chemosensitivity of Retinoblastoma Cells via Targeting SOX2. *Cell Cycle*, **20**, 2149-2159. https://doi.org/10.1080/15384101.2021.1971352

[39] Liu, S., Yan, G., Zhang, J. and Yu, L. (2018) Knockdown of Long Non-Coding RNA (lncRNA) Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1) Inhibits Proliferation, Migration, and Invasion and Promotes Apoptosis by Targeting miR-124 in Retinoblastoma. *Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics*, **26**, 581-591.

https://doi.org/10.3727/096504017X14953948675403

[40] Zhang, H., Yang, X., Xu, Y. and Li, H. (2021) KCNQ1OT1 Regulates the Retinoblastoma Cell Proliferation, Migration, and SIRT1/JNK Signaling Pathway by Targeting miR-124/SP1 Axis. *Bioscience Reports*, **41**, BSR20201626. https://doi.org/10.1042/BSR20201626

[41] Zhu, Y. and Hao, F. (2021) Knockdown of Long Non-Coding RNA HCP5 Suppresses the Malignant Behavior of Retinoblastoma by Sponging miR-3619-5p to Target HDAC9. *International Journal of Molecular Medicine*, **47**, Article No. 74. https://doi.org/10.3892/ijmm.2021.4907

[42] Zhang, C., Hu, J. and Yu, Y. (2020) circRNA Is a Rising Star in Researches of Ocular Diseases. *Frontiers in Cell and Developmental Biology*, **8**, 850. https://doi.org/10.3389/fcell.2020.00850

[43] Han, N., Zuo, L., Chen, H., Zhang, C., He, P. and Yan, H. (2019) Long Non-Coding RNA Homeobox A11 Antisense RNA (HOXA11-AS) Promotes Retinoblastoma Progression via Sponging miR-506-3p. *OncoTargets and Therapy*, **12**, 3509-3517. https://doi.org/10.2147/OTT.S195404

[44] Zhou, H., Sun, L. and Wan, F. (2019) Molecular Mechanisms of TUG1 in the Proliferation, Apoptosis, Migration, and Invasion of Cancer Cells (Review). *Oncology Letters*, **18**, 4393-4402. https://doi.org/10.3892/ol.2019.10848

[45] Huang, Y., Xue, B., Pan, J. and Shen, N. (2021) Circ-E2F3 Acts as a ceRNA for miR-204-5p to Promote Proliferation, Metastasis, and Apoptosis Inhibition in Retinoblastoma by Regulating ROCK1 Expression. *Experimental and Molecular Pathology*, **120**, Article ID: 104637. https://doi.org/10.1016/j.yexmp.2021.104637

[46] Xu, L., Long, H., Zhou, B., Jiang, H. and Cai, M. (2021) CircMKLN1 Suppresses the Progression of Human Retinoblastoma by Modulation of miR-425-5p/PDCD4 Axis. *Current Eye Research*, **46**, 1751-1761. https://doi.org/10.1080/02713683.2021.1927110

[47] Guo, N., Liu, X., Pant, O.P., *et al*. (2019) Circular RNAs: Novel Promising Biomarkers in Ocular Diseases. *International Journal of Medical Sciences*, **16**, 513-518. https://doi.org/10.7150/ijms.29750

[48] Xing, L., Zhang, L., Feng, Y., Cui, Z. and Ding, L. (2018) Downregulation of Circular RNA hsa_circ_0001649 Indicates Poor Prognosis for Retinoblastoma and Regulates Cell Proliferation and Apoptosis via AKT/mTOR Signaling Pathway. *Biomedicine and Pharmacotherapy*, **105**, 326-333. https://doi.org/10.1016/j.biopha.2018.05.141

[49] Du, S., Wang, S., Zhang, F. and Lv, Y. (2020) SKP2, Positively Regulated by circ_ODC1/miR-422a Axis, Promotes the Proliferation of Retinoblastoma. *Journal of Cellular Biochemistry*, **121**, 322-331. https://doi.org/10.1002/jcb.29177

[50] Zhang, L., Wu, J., Li, Y., Jiang, Y., Wang, L., Chen, Y., *et al*. (2020) Circ-0000527 Promotes the Progression of Retinoblastoma by Regulating miR-646/LRP6 Axis. *Cancer Cell International*, **20**, 301. https://doi.org/10.1186/s12935-020-01396-4

[51] Yu, B., Zhao, J. and Dong, Y. (2021) Circ_0000527 Promotes Retinoblastoma Progression through Modulating miR-98-5p/XIAP Pathway. *Current Eye Research*, **46**, 1414-1423. https://doi.org/10.1080/02713683.2021.1891255

[52] Jiang, Y., Xiao, F., Wang, L., Wang, T. and Chen, L. (2021) Hsa_circ_0099,198 Facilitates the Progression of Retinoblastoma by Regulating miR-1287/LRP6 Axis. *Experimental Eye Research*, **206**, Article ID: 108529. https://doi.org/10.1016/j.exer.2021.108529

[53] Liu, H., *et al*. (2020) Circular RNA circ_0000034 Upregulates STX17 Level to Pro-

mote Human Retinoblastoma Development via Inhibiting miR-361-3p. *European Review for Medical and Pharmacological Sciences*, **24**, 12080-12092.

[54] Jiang, Y., Xiao, F., Wang, L., Wang, T. and Chen, L. (2021) Circular RNA has_circ_0000034 Accelerates Retinoblastoma Advancement through the miR-361-3p/ADAM19 Axis. *Molecular and Cellular Biochemistry*, **476**, 69-80. https://doi.org/10.1007/s11010-020-03886-5

[55] Jiang, G., Qu, M., Kong, L., Song, X. and Jiang, S. (2022) hsa_circ_0084811 Regulates Cell Proliferation and Apoptosis in Retinoblastoma through miR-18a-5p/miR-18b-5p/E2F5 Axis. *BioMed Research International*, **2022**, Article ID: 6918396. https://doi.org/10.1155/2022/6918396

[56] Zhang, Y., Dou, X., Kong, Q., Li, Y. and Zhou, X. (2022) Circ_0075804 Promotes the Malignant Behaviors of Retinoblastoma Cells by Binding to miR-138-5p to Induce PEG10 Expression. *International Ophthalmology*, **42**, 509-523. https://doi.org/10.1007/s10792-021-02067-7

[57] Wang, H., Li, M., Cui, H., Song, X. and Sha, Q. (2020) CircDHDDS/miR-361-3p/WNT3A Axis Promotes the Development of Retinoblastoma by Regulating Proliferation, Cell Cycle, Migration, and Invasion of Retinoblastoma Cells. *Neurochemical Research*, **45**, 2691-2702. https://doi.org/10.1007/s11064-020-03112-0

[58] Liu, T., Song, Z. and Gai, Y. (2018) Circular RNA circ_0001649 Acts as a Prognostic Biomarker and Inhibits NSCLC Progression via Sponging miR-331-3p and miR-338-5p. *Biochemical and Biophysical Research Communications*, **503**, 1503-1509. https://doi.org/10.1016/j.bbrc.2018.07.070

[59] Zhao, W., Wang, S., Qin, T. and Wang, W. (2020) Circular RNA (circ-0075804) Promotes the Proliferation of Retinoblastoma via Combining Heterogeneous Nuclear Ribonucleoprotein K (HNRNPK) to Improve the Stability of E2F Transcription Factor 3 E2F3. *Journal of Cellular Biochemistry*, **121**, 3516-3525. https://doi.org/10.1002/jcb.29631

[60] Zuo, X., Fu, C., Xie, J., Wang, X. and Yan, Z. (2022) Hsa_circ_0000527 Downregulation Suppresses the Development of Retinoblastoma by Modulating the miR-27a-3p/HDAC9 Pathway. *Current Eye Research*, **47**, 115-126. https://doi.org/10.1080/02713683.2021.1925697

[61] Lyu, J., Wang, Y., Zheng, Q., Hua, P., Zhu, X., Li, J., *et al*. (2019) Reduction of Circular RNA Expression Associated with Human Retinoblastoma. *Experimental Eye Research*, **184**, 278-285. https://doi.org/10.1016/j.exer.2019.03.017

[62] Zhang, H., Qiu, X.W., Song, Z.J., *et al*. (2022) CircCUL2 Suppresses Retinoblastoma Cells by Regulating miR-214-5p/E2F2 Axis. *Anticancer Drugs*, **33**, e218-e227. https://doi.org/10.1097/CAD.0000000000001190

[63] Asadi, M.R., Moslehian, M.S., Sabaie, H., Sharifi-Bonab, M., Hakimi, P., Hussen, B.M., *et al*. (2022) circRNA-Associated CeRNAs Regulatory Axes in Retinoblastoma: A Systematic Scoping Review. *Frontiers in Oncology*, **12**, Article ID: 910470. https://doi.org/10.3389/fonc.2022.910470

[64] Sun, J., Gan, L., Ding, J., Ma, R., Qian, J. and Xue, K. (2023) Identification of Non-Coding RNAs and Their Functional Network Associated with Optic Nerve Invasion in Retinoblastoma. *Heliyon*, **9**, e13813. https://doi.org/10.1016/j.heliyon.2023.e13813

[65] Li, A., Yang, J., Zhang, T., Li, L. and Li, M. (2021) Long Non-Coding RNA TRPM2-AS Promotes the Growth, Migration, and Invasion of Retinoblastoma via miR-497/WEE1 Axis. *Frontiers in Pharmacology*, **12**, Article ID: 592822. https://doi.org/10.3389/fphar.2021.592822