Pathology - Research and Practice 215 (2019) 152435

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Review

Long non-coding RNAs in retinoblastoma

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ARTICLE INFO

Keywords:
lncRNA
Retinoblastoma
Prognosis
Therapy

ABSTRACT

Retinoblastoma represents 3% of all childhood cancers and is the most common intraocular malignant tumor with a highly aggressive and metastatic phenotype. While recent genetic and epigenetic studies have reported new insights into the mechanism of retinoblastoma development, the involvement of regulatory non-coding RNAs remains unclear. Long non-coding RNAs (lncRNAs) are a group of endogenous non-protein-coding RNAs with the capacity to regulate gene expression at multiple levels. Recent evidence has shown that lncRNAs can regulate many cellular processes, such as cell proliferation, differentiation, migration, and invasion. Several lncRNAs, including BANCR, AFAP1-AS1, NEAT1, XIST, ANRIL, PlncRNA-1, HOTAIR, PANDAR, DANCR, and THOR, promote the progression and metastasis of retinoblastoma. However, some lncRNAs, such as MEG3, MT1JP, and H19, play a tumor suppressive role. Our review summarizes the functional role of lncRNAs in retinoblastoma and their potential clinical applications for diagnosis, prognosis, and treatment.

1. Introduction

Retinoblastoma represents 3% of all childhood cancers and is the most common intraocular malignant tumor [1,2]. The worldwide incidence rate of retinoblastoma is approximately 1/15000, with no racial, regional, or gender differences [3]. The average age of diagnosis is 12 months for bilateral retinoblastoma and 24 months for unilateral retinoblastoma. Approximately 30%–40% of retinoblastoma cases exhibit bilateral onset. Among newly diagnosed retinoblastoma cases, only 6% were found to be familial, while 94% were sporadic [3,4]. Retinoblastoma is highly malignant and likely causes death due to intracranial metastasis, accounting for 1% of all infant deaths [5]. Untreated retinoblastoma usually develops rapidly, destroying the eyeball structure and leading to blindness [6]. Furthermore, the tumor can directly infiltrate into the brain through the optic nerve or spread through the blood to the lung, bone, and other systemic organs [7]. It affects human health and quality of life, and also imparts tremendous emotional, medical, and economic burden on patients and society. Despite the rapid development of retinoblastoma therapeutic strategies in recent years, the survival rate of retinoblastoma patients is still very low, mainly due to the limitation of early diagnosis of the disease [8,9]. Therefore, early diagnosis and timely treatment are of great significance in preventing visual impairment and metastasis caused by retinoblastoma.

About 70%–90% of the genes in the human genome is transcribed into RNA. Only 2% of the total RNA is translated into protein [10]. The rest of the RNA that is not translated into protein is called non-coding RNA (ncRNA) [11]. ncRNA that is 200 nucleotides or shorter is categorized as short-chain ncRNA, while ncRNA longer than 200 nucleotides is considered long-chain ncRNA (lncRNA) [12,13]. The ncRNAs molecule, which is mainly transcribed by RNA polymerase II, lacks a clear open reading frame. Initially, it was considered to be transcriptional noise and drew little attention [14,15]. Thanks to recent advances in genome sequencing technology, both linear ncRNAs (e.g., miRNAs and lncRNAs) and circular ncRNAs (e.g., circRNAs) have been confirmed as crucial regulating molecules in various human diseases, especially in tumorigenesis and progression [14–16]. The function of lncRNA in various biological processes is conferred primarily by binding with miRNAs as sponges or interacting with proteins, including those active in cell proliferation, migration, invasion, and apoptosis [17]. Current studies have shown that lncRNAs can regulate gene expression at various levels, such as epigenetic, transcriptional, and post-transcriptional levels. It has been found that an increasing number of lncRNAs is involved in several biological processes, such as genomic imprinting, histone modification, chromatin remodeling, and cell cycle regulation [13,18,19]. lncRNAs elicit functional outcomes through interactions with DNA, chromatin, signaling and regulatory proteins, and a variety of cellular RNA species. lncRNA mechanisms rely on interactions with cellular macromolecules [20]. There are three main pathways: (a) chromatin-bound lncRNAs can regulate gene expression by controlling local chromatin architecture or directing the recruitment of regulatory molecules to specific loci. (b) lncRNA interactions with

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https://doi.org/10.1016/j.prp.2019.152435
Received 13 March 2019; Received in revised form 15 April 2019; Accepted 3 May 2019

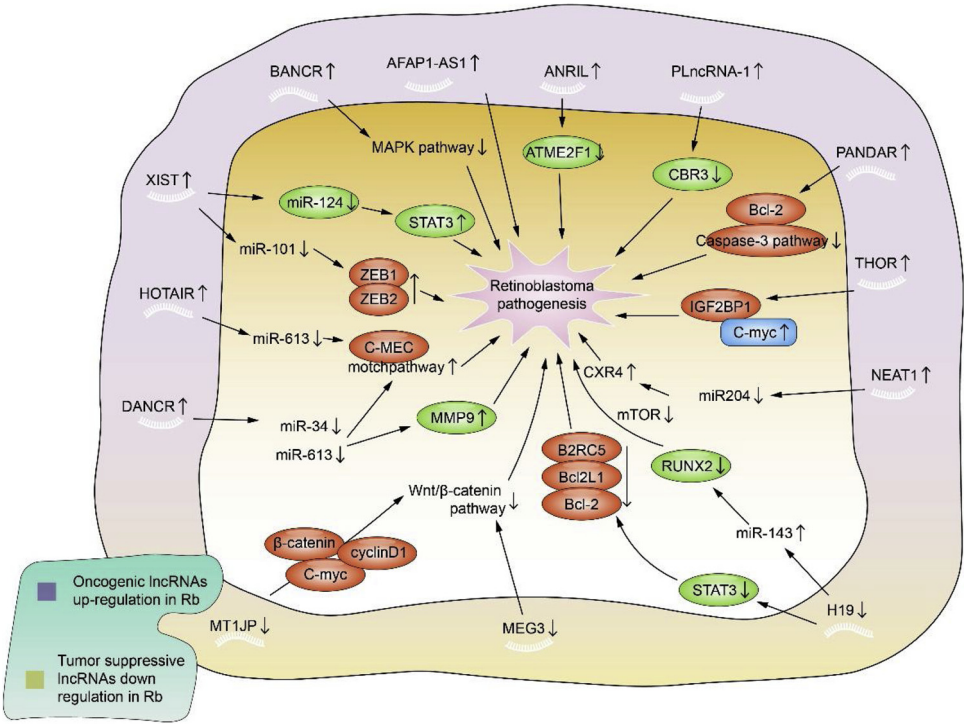

Fig. 1. Functional roles of lncRNAs in retinoblasnoma.

multiple proteins can promote the assembly of protein complexes or impair protein-protein interactions. (c) mRNA interactions with lncRNA can recruit protein machinery involved in multiple aspects of mRNA metabolism to affect splicing, mRNA stability, or translation; lncRNA can also sequester miRNA away from target mRNA [20]. Furthermore, cancer-specific lncRNA expression patterns appear more tissue- and stage-specific than those of protein-coding genes, thus making lncRNA a prime target for cancer therapy [21]. Until now, only a small number of lncRNAs have been well elucidated, but most of them are still largely unknown and need further study Fig. 1.

Recently, numerous studies indicated that aberrant expression of lncRNAs was involved in tumorigenesis and cancer progression of retinoblastoma [22]. Emerging evidence also demonstrated that some lncRNAs, such as MALAT1, H19, and BANCR, are associated with the diagnosis and prognosis of retinoblastoma [23–25]. The differential expression of lncRNA in retinoblastoma and normal tissues may make it a potential biomarker for retinoblastoma diagnosis. In addition, it may be a potential therapeutic target for retinoblastoma. This article reviews the research on the role of lncRNA in retinoblastoma and provides a new basis for the diagnosis and treatment of retinoblastoma.

2. Upregulated lncRNA in retinoblastoma

2.1. AFAP1-AS1

The actin filament-associated protein1-antisense RNA1(AFAP1-AS1) gene was first identified in esophageal adenocarcinoma and normal tissues. It is located on chromosome 4 and is a protein-coding gene [26]. Further experiments have demonstrated that AFAP1-AS1 was overexpressed in cancer tissues and cell lines, such as colon cancer [27], breast cancer [28], and non-small cell lung cancer [29]. In multiple types of cancers, including retinoblastoma, the expression of AFAP1-AS1 is upregulated. Overexpression of AFAP1-AS1 is closely associated with tumor size, lymphatic metastasis, distant metastasis, tumor node-metastasis (TNM) stage, and poor prognosis of cancer patients. Hao et al. studied the effects of AFAP1-AS1 on proliferation, cell cycle, migration, and invasion of retinoblastoma cells. The expression of AFAP1-AS1 was upregulated in retinoblastoma tissues and cell lines. Meanwhile, Hao et al. found that AFAP1-AS1 expression was closely associated with retinoblastoma clinicopathological features, such as tumor size, choroidal invasion, and optic nerve invasion. in vitro experiments showed that the downregulation of AFAP1-AS1 inhibited the proliferation, migration, and invasion of retinoblastoma cells, and suppressed the cell cycle. In conclusion, AFAP1-AS1 plays a carcinogenic role in retinoblastoma [30,31].

2.2. BANCR

BRAF-activated noncoding RNA (BANCR) is a 4-exon transcript, a 693-bp-long lncRNA encoded on chromosome 9, and is highly expressed in retinoblastoma tissues and cell lines [32]. BANCR is involved in a variety of human malignant tumors, including lung cancer, colorectal cancer, melanoma, and gastric cancer [32–35]. Su et al. first found that the expression of BANCR was significantly upregulated in retinoblastoma tissues and cell lines, and was positively associated with tumor size, choroidal invasion, and optic nerve invasion. Moreover, knock-down of BANCR significantly suppressed the retinoblastoma cell proliferation, migration, and invasion in vitro. Patients with high BANCR expression showed a poor prognosis and low survival rate. These data indicated that overexpression of BANCR contributes to the promotion and progression of retinoblastoma [36].

2.3. NEAT1

The human nuclear enriched abundant transcript 1 (NEAT1) gene encodes two lncRNA isoforms that play a key role in nuclear paraspeckles, which are involved in regulating RNA splicing and transcription [37–39]. NEAT1 functions as an oncogenic factor in multiple types of cancer, including retinoblastoma, and its expression is under the regulation of the miR-204/CXCR4 axis. The expression levels of NEAT1 and CXCR4 increased, and miR204 decreased in the xenograft mouse model. The downregulation of NEAT1 significantly reduced the proliferation and migration of retinoblastoma cells, but promoted the apoptosis of retinoblastoma cells. In addition, NEAT1 promoted

invasion through inducing epithelial–mesenchymal transition (EMT). NEAT1 could be a new diagnostic biomarker and therapy target for retinoblastoma [40].

2.4. XIST

It has previously been found that inactive specific transcript (XIST) functioned as an oncogene in osteosarcoma [41] and hepatocellular carcinoma [42], but as a tumor suppressor in breast cancer [43] and prostate cancer [44]. XIST mainly acts via miR-101/ZEB1 or ZEB2 signals. Chang et al. found that the expression of XIST, ZEB1, and ZEB2 increased, while that of miR-101 decreased in retinoblastoma tissues and cells. XIST knockout significantly inhibits cell proliferation, migration, invasion, and EMT, and promotes Weri-Rb cell apoptosis and caspase-3 activity. XIST may downregulate the expression of ZEB1 and ZEB2 via endogenous competitive microRNA targets, which may provide a novel therapeutic target for retinoblastoma [45]. In addition, Liu et al. found that the expression of XIST was negatively correlated with miR-124 in retinoblastoma tissues. Inhibition of miR-124 partially reversed XIST-mediated cell proliferation, cell cycle arrest, and apoptosis [46]. In addition, XIST regulated the expression of signal transducer and activator of transcription 3 (STAT3). XIST promotes retinoblastoma progression by regulating the miR-124/STAT3 axis [46].

2.5. ANRIL

Antisense non-coding RNA in the INK4 locus (ANRIL) is found in several types of human tumors, and is considered to be involved in cancer progression [47]. ANRIL was significantly upregulated in many cancers, including esophageal, cervical, and gastric cancer [48–50]. It has been shown to regulate the proliferation, apoptosis, and invasion of retinoblastoma HXO-RB44 cells via the ATM-E2F1 signaling pathway. Interestingly, silencing of ANRIL increased the expression of INK4b, INK4a, p53, and pRB in vivo. Yu et al. demonstrated that overexpression of ANRIL promoted viability, migration, and invasion of retinoblastoma cells by activating the MEK/ERK and Wnt/β-catenin pathways, as well as downregulating miR-24 and upregulating c-Myc [51]. These findings indicated that ANRIL exhibits oncogenic properties in human retinoblastoma and provides a potential therapeutic target for targeted interventional therapy of human retinoblastoma [52].

2.6. PlncRNA

Prostate cancer-upregulated long noncoding RNA 1 (PlncRNA-1, also known as CBR3-AS1) is a lcnRNA which was first found to be generally overexpressed in prostate cancer cell lines and tissues [53]. PlncRNA has been reported to promote cell proliferation and hepatic metastasis in colorectal cancer and prostate cancer progression [54,55]. Liu et al. also reported that the expression of PlncRNA-1 negatively regulated the expression of CBR3, which indicated its role in regulating the proliferation, migration, and invasion of retinoblastoma cells [56].

2.7. HOTAIR

The HOX antisense intergenic RNA (HOTAIR) gene located on chromosome 12 between HOXC11 and HOXC12, covers a length of 2.2 kb [57]. Numerous studies have shown that HOTAIR expression is upregulated in human cancers, including breast cancer, liver cancer, and colorectal cancer [58–60]. Previous studies have reported that HOTAIR acts as an oncogene for promoting retinoblastoma development. Fu et al. confirmed that HOTAIR directly targets miR-613. c-Met is the direct target gene of miR-613. This signaling axis plays an important role in regulating cell viability, apoptosis, and EMT-specific protein expression of retinoblastoma cells. Fu et al. also demonstrated that higher HOTAIR expression, lower miR-613 expression, larger tumor size, and grade T3 + T4 had significant statistical relevance to the undesirable overall survival (OS) rate [61]. Another study showed that knockdown of HOTAIR attenuated the endogenous Notch signaling pathway in vitro and in vivo. In addition, HOTAIR has been indicated as a potential therapeutic biomarker for retinoblastoma, and silencing of HOTAIR attenuated proliferation, migration, and invasion of retinoblastoma cells [62].

2.8. PANDAR

PANDAR, the Promoter of CDKN1A Antisense DNA damage Activated RNA, is a novel lncRNA consisting of 1506 nucleotides and located at chromosome 6p21.2. Accumulating evidence has demonstrated that PANDAR is upregulated in different human tumors, such as pancreatic ductal adenocarcinoma, hepatocellular carcinoma, and bladder cancer [63–65]. PANDAR has been found to play a carcinogenic role in RB. It documented that high PANDAR expression in RB tumors was correlated with advanced International Intraocular Retinoblastoma Classification (IIRC) staging, positive optic nerve invasion, and poor differentiation grade [66]. Sp1 can directly bind to the promoter region of PANDAR and induce its transcription. In addition, PANDAR silencing inhibits tumor growth in vitro and in vivo. PANDAR partially inhibits cell apoptosis by interfering with the Bcl-2/caspase-3 pathway, which may provide potential therapeutic targets for the treatment of RB [66].

2.9. DANCR

Differentiation antagonizing non-protein coding RNA (DANCR) was first identified in osteoclastogenesis [67]. In recent years, emerging studies have demonstrated the involvement of this oncogenic lncRNA in the tumorigenesis of many tumors, including cervical cancer, non-small cell lung cancer, and bladder cancer [68–70]. Wang et al. found that DANCR was upregulated in retinoblastoma tissues and cells. RB patients with high DANCR levels had poor OS and disease free survival (DFS) than those with low DANCR levels, as measured by Kaplan–Meier analysis. DANCR plays a role as an miRNA “sponge,” and competes with endogenous RNA (ceRNA) for miR-34c and miR-613 to regulate retinoblastoma progression by targeting MMP-9 [71]. DANCR knockout inhibited the proliferation, migration, invasion, and expression of epithelial mesenchymal transition (EMT)-related proteins (n-cadherin and vimentin) in RB cells. These results demonstrate the in-depth role of DANCR in retinoblastoma carcinogenesis, suggesting a detailed mechanism of cancer progression [71].

2.10. THOR

THOR (ENSG00000226856), which is expressed in the testis and a broad range of human cancers, has been shown to be related to insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1). It is involved in the expression of several oncogenic genes, including CD44, IGF2, and c-myc [72]. THOR is upregulated in retinoblastoma, enhancing its binding with the TGF-2bp1 protein. Upregulation of c-myc significantly promotes the malignant phenotypic transformation of retinoblastoma cells. The THOR cascade may be another potential target for the treatment of retinoblastoma [73] (Table1).

3. Downregulated lncRNAs in retinoblastoma

3.1. MEG3

Maternally expressed gene 3 (MEG3), which is located on chromosome 14q32 [74], represents an important tumor suppressor gene in human cancers, such as non-small cell lung cancer, cervical cancer, and bladder cancer [75–77]. Multivariate analysis confirmed that MEG3 methylation was considered as an independent prognostic indicator for patients with GC. in addition to the standard IIRC stages, nodal or distant metastasis, and optic nerve invasion [78]. MEG3 is also a tumor

Table 1
Characterization of up-regulated lncRNAs in retinoblastoma.

LncRNA Name	Expression	Cell lines	Number ofspecimens	Location	Function	related genes	role	refrence
AFAP1-AS1	up			Chr4	promote tumor size, choroidal infiltration, optic nerve infiltration, cell proliferation and migration		oncogenic	28, 29
BANCR	up	Weri-Rb1, Y79	60	Chr9,34,35	promote tumor size, choroidal infiltration, optic nerve infiltration, cell proliferation and migration		oncogenic	34
NEAT1	up	Y79, Weri-Rb1, and SO-RB50	29	Chr11p	promote cell proliferation and migration, inhibit apoptosis	miR-204,CXCR4	oncogenic	38
XIST	up	Weri-Rb1, Y79	35		promote cell proliferation, migration, invasion and EMT process, inhibit apoptosis and caspase3 activity	miR-101,ZEB1,ZEB2,miR-124,STAT3	oncogenic	43,44
ANRIL	up	HXO-RB44, Y79	27	Chr9p21	promote proliferation inhibit apoptosis	ATM,E2F1miR24	oncogenic	49,53
PlncRNA-1	up	Weri-Rb1, Y79	38	Chr21	promote proliferation, migration and invasion	CBR3	oncogenic	53
HOTAIR	up	HXO-RB44, Y79	350	Chr12	promote proliferation, migration and invasion	miR-613,c-met	oncogenic	58,59
PANDAR	up	Weri-Rb1, Y79	82	Chr6p21,2	advanced IIRC stage, promote optic nerve invasion and tumor growth, inhibit apoptosis		oncogenic	63
DANCR	up	Weri-Rb1, Y79, SO-RB50, and HXO-RB44	57	Chr4	promote cell proliferation, migration, invasion and EMT process,	miR-34c, miR-613, RB gene MM9-9	oncogenic	67
THOR	up	Weri-Rb1, Y79	15		promote tumorigenesiss cell growth, migration and inhibit cell apoptosi	c-myc, IGF2BP1	oncogenic	69

suppressor gene expressed in retinoblastoma. It inhibited the proliferation of retinoblastoma cells by regulating the Wnt/β-catenin pathway and promoted apoptosis of RB cells via the p53 pathway, and thus, serves as a prognostic biomarker and molecular therapeutic target [25,78].

3.2. MT1JP

Metallothionein 1 J, pseudogene (MT1JP) modulates a series of cancer hallmark traits associated with p53, such as cell cycle, apoptosis, proliferation, migration, and invasion modulation, by acting as a p53 regulator [79]. Several studies have reported that MT1JP acts as a tumor suppressor in a variety of cancers, including gastric cancer. This was also observed in retinoblastoma [80]. Han et al. reported that MT1JP can negatively regulate the Wnt/beta-catenin signaling pathway during the formation of retinoblastoma. In addition, low expression of MT1JP is related to poor prognosis, such as optic nerve invasion and nodal or distant metastasis in patients with RB [81]. Thus, MT1JP may act as a tumor suppressor that can predict the prognosis of retinoblastoma. MT1JP is a potential therapeutic target of retinoblastoma [81].

3.3. H19

H19 is one of the first lncRNAs identified. It is located downstream of the sense of IGF2. It plays an oncogenic role in some tumors and an anti-oncogenic role in other tumors. Li et al. found that compared with the control group, the level of H19 in RB cells and tissues was significantly increased. In addition, the expression of H19 is associated with many proteins, such as cyclin-dependent kinase 1, B-cell lymphoma-related X protein, apoptotic regulatory factor, tumor protein p53, vimentin, cadherin 13, and matrix metalloproteinase 9. H19 may play an important role in tumorigenesis and may be a potential target for the treatment and prognosis of retinoblastoma [82].

In retinoblastoma, H19 may inhibit the progression of retinoblastoma by binding to the miR-17-92 cluster, upregulating p21 expression, inhibiting STAT3 phosphorylation, and downregulating the expression of Bcl2, Bcl2l1, and Birc5; these functions suggest that upregulating H19 may be a promising therapeutic strategy for retinoblastoma [83]. Another study revealed that knocking down lncRNA-H19 in human RB Y79 cells repressed cell viability, migration, and invasion, while it promoted apoptosis in Y79 cells. Knockdown of lncRNA-H19 acted as a tumor suppressor in Y79 cells by upregulating miR-143. Moreover, miR-143 exerted tumor suppressive effects on Y79 cells by targeting RUNX2 and inhibiting the PI3K/AKT/mTOR pathway [84] (Table2).

4. Conclusions

Retinoblastoma is an aggressive form of intraocular cancer usually occurring during childhood with rapid metastatic progression. Early diagnosis is crucial for retinoblastoma management, as advanced stages of retinoblastoma are refractory to conventional treatment and are associated with poor survival outcomes. lncRNAs were initially considered to be genetic noise and were therefore termed as “genomic dark matter”. However, emerging studies have revealed their importance. Although thousands of lncRNAs have been identified, only a few have been functionally characterized. Current research has revealed the importance of lncRNA in tumorigenesis and tumor progression. In retinoblastoma, several lncRNAs have been demonstrated to be differentially expressed and potent regulators of retinoblastoma progression and metastasis. These lncRNAs include BANCR, AFAP1-AS1, NEAT1, XIST, ANRIL, PlncRNA-1, HOTAIR, PANDAR, DANCR, and THOR. However, some lncRNAs play a tumor suppressive role, such as MEG3, MT1JP, and H19. More studies are required to understand the regulation and mechanisms of lncRNAs in retinoblastoma. Moreover, the

Table 2
Characterization of down-regulated lncRNAs in retinoblastoma.

	expression	cell lines	Number ofspecimens	Location	Function	related genes	role	refrence
MEG3	down		63	Chr14q32	Inhibit proliferation and promote apoptosis		tumor suppressor	23, 74
MT1JP	down	Weri-Rb1, Y79	44		Represe cell migration and invasion via triggering EMT alteration	cyclin D, c-Myc	tumor suppressor	76, 77
H19	down	Y79		Chr11p15,5	promote apoptosis of Y79 cell	miR-143, RUNX2, miR-17-92	tumor suppressor	79, 80

clinical utilities of lncRNAs remain unclear. Thus, future investigations are needed to elucidate the upstream and downstream mechanisms, as well as clinical implications of lncRNAs in retinoblastoma.

Conflicts of interest

The authors declare no competing financial interests.

References

[1] Dimaras H, Corson TWJJoNR: Retinoblastoma, the visible CNS tumor: A review. 2018(7 Suppl.).
[2] Rao R, Honavar SGJIJoP: Retinoblastoma. 2017:1-8.
[3] reviews FPJCm: Cancers of the eye.%A Maheshwari A. 2018, undefined(undefined):undefined.
[4] Bishop JO, Madson ECJSoO: Retinoblastoma. Review of the current status. 1975, 19(6):342.
[5] He M, An Y, Gao Y, Qian X, Li G, Qian JJMV: Screening of RB1 gene mutations in Chinese patients with retinoblastoma and preliminary exploration of genotype—phenotype correlations. 2014, 20(2):545.
[6] Aerts I, Lumbrosole RL, Gauthiervillars M, Brisse H, Doz F: [Retinoblastoma update]. 2015.
[7] Correa-Acosta A, GonzÃ lez-Alviar ME, Gaviria-Bravo MLJASEO: Retinoblastoma and optic nerve enhancement in a brain magnetic resonance scan: is it always a metastasis? 2018.
[8] Liu WL, Zhong-Yao WU, Yang HSJCJoC: Survival rate and the prognostic factors of retinoblastoma. 2010.
[9] Sang JP, Woo SJ, Park KHJIOVS: Incidence of Retinoblastoma and Survival Rate of Retinoblastoma Patients in Korea Using the Korean National Cancer Registry Database (1993–2010)Incidence and Survival of Retinoblastoma in Korea. 2014, 55(5):2816-2821.
[10] Liu Y, Luo D, Zhao H, Zhu Z, Hu W, Cheng CHJPO: Inheritable and precise large genomic deletions of non-coding RNA genes in zebrafish using TALENs. 2013, 8(10):e76387.
[11] Wapinski O, Chang HYJTiCB: Long noncoding RNAs and human disease. 2011, 21(6):354-361.
[12] Herriges MJ, Swarr DT, Morley MP, Rathi KS, Peng T, Stewart KM, Morrisey EEJG, Development: Long noncoding RNAs are spatially correlated with transcription factors and regulate lung development. 2014, 28(12):1363.
[13] B. Ricciuti, C. Mencaroni, L. Paglialunga, F. Paciullo, L. Crino, R. Chiari, Metro G: long noncoding RNAs: new insights into non-small cell lung cancer biology, diagnosis and therapy, Med. Oncol. 33 (2) (2016) 18.
[14] J Li., L Huang, Z L, X Z, S T, X J, physiology CYJJoc: Functions and roles of long noncoding RNA in cholangiocarcinoma. 2019, undefined(undefined):undefined.
[15] Golabchi K, Soleimani-Jelodar R, Aghadoost N, Momeni F, Moridikia A, Nahand JS, Masoudifar A, Razmjoo H, Mirzaei HJJoCP: MicroRNAs in Retinoblastoma: Potential diagnostic and therapeutic biomarkers. 2017, 233(4).
[16] M.J. Saeedi Borujeni, E. Esfandiary, A. Baradaran, A. Valiani, M. Ghanadian, P. Codoner-Franch, R. Basirat, E. Alonso-Iglesias, H. Mirzaei, Yazdani A: molecular aspects of pancreatic beta-cell dysfunction: oxidative stress, microRNA, and long noncoding RNA, J. Cell. Physiol. 234 (6) (2019) 8411–8425.
[17] K D, J Q, F Y, X J, X P, X S, S Z, Q R, J L, OncoTargets LXJ et al. lncRNAs as potential molecular biomarkers in the clinicopathology and prognosis of cholangiocarcinoma: a systematic review and meta-analysis. 2019, 12(undefined):1905-1915.
[18] Marchese FP, Raimondi I, Huarte MJGB: The multidimensional mechanisms of long noncoding RNA function. 2017, 18(1):206.
[19] Ellatif SKA, Gutschner T, Diederichs S: Long Noncoding RNA Function and Expression in Cancer; 2012.
[20] AM S, cell CHJC: Long Noncoding RNAs in Cancer Pathways. 2016, 29(4):452-463.
[21] W S, Y Y, C X, Y X, research GJJJoc, oncology c: Roles of long noncoding RNAs in gastric cancer and their clinical applications. 2016, 142(11):2231-2237.
[22] Yang Q, Xu E, Dai J, Liu B, Han Z, Wu J, Zhang S, Peng B, Zhang Y, Jiang YJT et al. A novel long noncoding RNA AK001796 acts as an oncogene and is involved in cell growth inhibition by resveratrol in lung cancer. 2015, 285(2):79-88.
[23] Tian X, Xu GJBO: Clinical value of lncRNA MALAT1 as a prognostic marker in human cancer: systematic review and meta-analysis. 2015, 5(9):e008653.
[24] Zhang H, Zhong J, Bian Z, Fang X, Peng Y, Hu YJB, Pharmacotherapy: Long noncoding RNA CCAT1 promotes human retinoblastoma SO-RB50 and Y79 cells through negative regulation of miR-218-5p. 2017, 87:683-691.
[25] Gao YL, Xiao He LU, University JJRAiO: LncRNA-MEG3 mediated apoptosis of retinoblastoma by regulating P53 pathway. 2017.
[26] F X, L Y, H B, Z G, Y W, F W, Y T, X L, Q L, H W et al. Long noncoding RNA AFAP1-AS1 acts as a competing endogenous RNA of miR-423-5p to facilitate nasopharyngeal carcinoma metastasis through regulating the Rho/Rac pathway.%A Lian Y. 2018, 37(1):253.
[27] L F, J L, Z L, S Z, L S, C G, X L, Q L, W Z, M Z et al. High Expression of lncRNA AFAP1-AS1 Promotes the Progression of Colon Cancer and Predicts Poor Prognosis. %A Bo H. 2018, 9(24):4677-4683.
[28] X Q, pharmacology XXJFi: AFAP1-AS1 Promotes Epithelial-Mesenchymal Transition and Tumorigenesis Through Wnt/β-Catenin Signaling Pathway in Triple-Negative Breast Cancer.%A Zhang K. 2018, 9(undefined):1248.
[29] K W, C G, JK Z, W P, Y D, Y Z, Y Z, L L, YQ W, Cellular PYJ et al. Long non-coding RNA AFAP1-AS1 plays an oncogenic role in promoting cell migration in non-small

cell lung cancer.%A He J. 2018, 75(24):4667-4681.
[30] Hao F, Mou Y, Zhang L, Wang S, Yang YJBR: LncRNA AFAP1-AS1 is a prognostic biomarker and serves as oncogenic role in retinoblastoma. 2018, 38(3).
[31] X Z, X J, K L, Y X, Z L, L H, J L, Cui Y%J Pathology r, practice: The role of long non-coding RNA AFAP1-AS1 in human malignant tumors.%A Ji D. 2018, 214(10):1524-1531.
[32] X. Yu, H. Zheng, G. Tse, M.T. Chan, Wu WK: long non-coding RNAs in melanoma, Cell Prolif. 51 (4) (2018) e12457.
[33] A. He, Y. Liu, Z. Chen, J. Li, M. Chen, L. Liu, X. Liao, Z. Lv, Y. Zhan, C. Zhuang, et al., Over-expression of long noncoding RNA BANCR inhibits malignant phenotypes of human bladder cancer, J. exp. clinical cancer Res.: CR 35 (1) (2016) 125.
[34] Z. Liu, T. Yang, Z. Xu, Cao X: upregulation of the long non-coding RNA BANCR correlates with tumor progression and poor prognosis in esophageal squamous cell carcinoma, Biomed. Pharmacother. 82 (2016) 406–412.
[35] Y. Wang, X. Lin, X. Fu, W. Yan, F. Lin, P. Kuang, Y. Luo, E. Lin, X. Hong, Wu G: long non-coding RNA BANCR regulates cancer stem cell markers in papillary thyroid cancer via the RAF/MEK/ERK signaling pathway, Oncol. Rep. 40 (2) (2018) 859–866.
[36] S. Su, J. Gao, T. Wang, J. Wang, H. Li, Wang Z: long non-coding RNA BANCR regulates growth and metastasis and is associated with poor prognosis in retinoblastoma, Tumour biology: j. Int. Society Oncodev. Bio.Med. 36 (9) (2015) 7205–7211.
[37] Biomedicine TMJ, Biomedecine p, pharmacotherapie: Nuclear Enriched Abundant Transcript 1 (NEAT1): A long non-coding RNA with diverse functions in tumorigenesis.%A Ghaforui-Fard S. 2018, 111(undefined):51-59.
[38] F P, oncology PMJM: Involvement of the long noncoding RNA NEAT1 in carcinogenesis.%A Klec C. 2019, 13(1):46-60.
[39] NG W, research STJN-cR: NEAT1 and paraspeckles in neurodegenerative diseases: A missing lnc found?%A An H. 2018, 3(4):243-252.
[40] J Y, M L, L L, physiology LAJJoc: Long noncoding RNA NEAT1 promotes the growth of human retinoblastoma cells via regulation of miR-204/CXCR4 axis.%A Zhong W. 2018, undefined(undefined):undefined.
[41] Yang C, Wu K, Wang S, Wei GJJoCB: Long Non-Coding RNA XIST Promotes Osteosarcoma Progression by Targeting YAP via miR-195-5p. 2018.
[42] Chang S, Chen B, Wang X, Wu K, Sun YJBC: Long non-coding RNA XIST regulates PTEN expression by sponging miR-181a and promotes hepatocellular carcinoma progression. 2017, 17(1):248.
[43] Zheng R, Lin S, Guan L, Yuan H, Liu K, Liu C, Ye W, Liao Y, Jia J, Zhang RJB et al. Long non-coding RNA XIST inhibited breast cancer cell growth, migration, and invasion via miR-155/CDX1 axis. 2018, 498(4):1002.
[44] Du Y, Weng XD, Wang L, Liu XH, Zhu HC, Guo J, Ning JZ, Xiao CCJO: LncRNA XIST acts as a tumor suppressor in prostate cancer through sponging miR-23a to modulate RKIP expression. 2017, 8(55):94358-94370.
[45] H L, pharmacology WRJEjo: LncRNA XIST promotes the epithelial to mesenchymal transition of retinoblastoma via sponging miR-101.%A Cheng Y. 2019, 843(undefined):210-216.
[46] S L, M H, Y W, Biomedicine XCJ, Biomedecine p, pharmacotherapie: Knockdown of lncRNA XIST inhibits retinoblastoma progression by modulating the miR-124/STAT3 axis.%A Hu C. 2018, 107(undefined):547-554.
[47] Wan G, Mathur R, Hu X, Liu Y, Zhang X, Peng G, Lu XJCS: Long non-coding RNA ANRIL (CDKN2B-AS) is induced by the ATM-E2F1 signaling pathway. 2013, 25(5):1086-1095.
[48] J S, W P, C L, Oncology QZJJoBUOojotBUo: Upregulation of long noncoding RNA ANRIL correlates with tumor progression and poor prognosis in esophageal squamous cell carcinoma.%A Cao T. 2018, 23(6):1862-1866.
[49] Y J, P W, Y L, WJ Z, JF C, W D, reports YFJO: Tumor suppressor PLZF regulated by lncRNA ANRIL suppresses proliferation and epithelial mesenchymal transformation of gastric cancer cells.%A Wang JB. 2019, 41(2):1007-1018.
[50] YJ L, Y H, markers CPJCbsAoD: Down-regulation of long non-coding RNA ANRIL inhibits the proliferation, migration and invasion of cervical cancer cells.%A Zhang WY. 2018, 23(2):243-253.
[51] F Y, G P, macromolecules ZGJIjob: ANRIL acts as onco-lncRNA by regulation of microRNA-24/c-Myc, MEK/ERK and Wnt/β-catenin pathway in retinoblastoma. 2019, 128(undefined):583-592.
[52] reports PXJB: The silencing of long non-coding RNA ANRIL suppresses invasion, and promotes apoptosis of retinoblastoma cells through the ATM-E2F1 signaling pathway.%A Yang Y. 2018, 38(6):undefined.
[53] Cui Z, Ren S, Lu J, Wang F, Xu W, Sun Y, Wei M, Chen J, Gao X, Xu CJUO: The prostate cancer-up-regulated long noncoding RNA PlncRNA-1 modulates apoptosis and proliferation through reciprocal regulation of androgen receptor. 2013, 31(7):1117-1123.
[54] Fang Z, Xu C, Li Y, Cai X, Ren S, Liu H, Wang Y, Wang F, Chen R, Qu MJCL: A feedforward regulatory loop between androgen receptor and PlncRNA-1 promotes prostate cancer progression. 2016, 374(1):62-74.
[55] Jia GQ, Zhang MM, Wang K, Zhao GP, Pang MH, Chen ZYJJoCB: Long non-coding RNA PlncRNA-1 promotes cell proliferation and hepatic metastasis in colorectal cancer. 2018, 119(8):7091.
[56] F H, life ZLJI: PlncRNA-1 is overexpressed in retinoblastoma and regulates retinoblastoma cell proliferation and motility through modulating CBR3.%A Wang S. 2018, 70(10):969-975.
[57] Khalil AM, Mitchell G, Maite H, Manuel G, Arjun R, Dianali RM, Kelly T, Aviva P, Bernstein BE, Alexander VOJPotNAoSotUSoA: Many human large intergenic noncoding RNAs associate with chromatin-modifying complexes and affect gene expression. 2009.
[58] Gupta RA, Nilay S, Wang KC, Jeewon K, Horlings HM, Wong DJ, Miao-Chih T, Tiffany H, Pedram A, Rinn JL, %J Nature: Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. 2010, 464(7291):1071-1076.
[59] Masahisa I, Ryunosuke K, Kohei S, Genta S, Yusuke T, Junji K, Sayuri A, Shin S, Takeshi I, Tomoya SJOR: Clinical significance of the expression of long non-coding RNA HOTAIR in primary hepatocellular carcinoma. 2013, 29(3):946-950.
[60] Zhe Y, Lin Z, Li-Ming W, Ming-Chun L, Hai-Yang X, Feng Z, Shu-Sen ZJAoSO: Overexpression of long non-coding RNA HOTAIR predicts tumor recurrence in hepatocellular carcinoma patients following liver transplantation. 2011, 18(5):1243-1250.
[61] Y F, X L, M W, H D, cellular LQJJo, medicine m: LncRNA HOTAIR/miR-613/c-met axis modulated epithelial-mesenchymal transition of retinoblastoma cells.%A Yang G. 2018, 22(10):5083-5096.
[62] S L, Y L, C Z, H G, L T, biosciences WHJJo: Long non-coding RNA regulates proliferation and invasion via activating Notch signalling pathway in retinoblastoma. %A Dong C. 2016, 41(4):677-687.
[63] E F, L S, W J, Y Y, Y Y, Biomedicine XYJ, Biomedecine p, pharmacotherapie: An increased expression of long non-coding RNA PANDAR promotes cell proliferation and inhibits cell apoptosis in pancreatic ductal adenocarcinoma.%A Jiang Y. 2017, 95(undefined):685-691.
[64] Peng W, Fan HJB, Pharmacotherapy: Long non-coding RNA PANDAR correlates with poor prognosis and promotes tumorigenesis in hepatocellular carcinoma. 2015, 72:113-118.
[65] Zhan Y, Lin J, Liu Y, Chen M, Chen X, Zhuang C, Liu L, Xu W, Chen Z, He AJJoE et al. Up-regulation of long non-coding RNA PANDAR is associated with poor prognosis and promotes tumorigenesis in bladder cancer. 2016, 35(1):83.
[66] J W, X G, D D, Gene SXJ: SP1-induced upregulation of lncRNA PANDAR predicts adverse phenotypes in retinoblastoma and regulates cell growth and apoptosis in vitro and in vivo.%A Sheng L. 2018, 668(undefined):140-145.
[67] X T, PC G, SZ X, Lin XJ%J Bioscience b, biochemistry: Long non-coding RNA-DANCR in human circulating monocytes: a potential biomarker associated with postmenopausal osteoporosis. 2015, 79(5):732-737.
[68] H J, Y Z, Y M, Z F, X L, science DLJC: DANCR-mediated microRNA-665 regulates proliferation and metastasis of cervical cancer through the ERK/SMAD pathway.%A Cao L. 2018, undefined(undefined):undefined.
[69] J G, S H, D L, M Z, T H, J Z, Z G, OncoTargets XJJ, therapy: Long non-coding RNA DANCR promotes the progression of non-small-cell lung cancer by inhibiting p21 expression.%A Guo L. 2019, 12(undefined):135-146.
[70] X C, R X, M H, W D, J H, J Z, Q Z, H L, J H, Therapy LTJMttjotASoG: DANCR Promotes Metastasis and Proliferation in Bladder Cancer Cells by Enhancing IL-11-STAT3 Signaling and CCND1 Expression.%A Chen Z. 2019, undefined(undefined):undefined.
[71] Y Y, physiology LKJJoc: Long noncoding RNA DANCR aggravates retinoblastoma through miR-34c and miR-613 by targeting MMP-9.%A Wang JX. 2018, 233(10):6986-6995.
[72] Hosono Y, Niknafs YS, Prensner JR, Iyer MK, Dhanasekaran SM, Mehra R, Pitchiaya S, Tien J, Escara-Wilke J, Poliakov AJC: Oncogenic Role of THOR, a Conserved Cancer/Testis Long Non-coding RNA. 2017, 171(7):1559.
[73] LncRNA THOR acts as a retinoblastoma promoter through enhancing the combination of c-myc mRNA and IGF2BP1 protein.%A Shang Y%J Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2018, 106(undefined):1243-1249.
[74] Yunli Z, Xun Z, Anne KJJoME: MEG3 noncoding RNA: a tumor suppressor. 2012, 48(3):45-53.
[75] Lu KH, Wei L, Liu XH, Ming S, Zhang ML, Wu WQ, Xie WP, Hou YYJBC, 13,1: Long non-coding RNA MEG3 inhibits NSCLC cells proliferation and induces apoptosis by affecting p53 expression. 2013, 13(1):461-461.
[76] Ying L, Huang Y, Chen H, Wang Y, Xia L, Chen Y, Liu Y, Qiu FJMB: Downregulated MEG3 activates autophagy and increases cell proliferation in bladder cancer. 2013, 9(3):407-411.
[77] Zhang J, Yao T, Wang Y, Yu J, Liu Y, Lin ZJCB, Therapy: Long noncoding RNA MEG3 is downregulated in cervical cancer and affects cell proliferation and apoptosis by regulating miR-21. 2016, 17(1):104-113.
[78] Gao Y, Lu XJTB: Decreased expression of MEG3 contributes to retinoblastoma progression and affects retinoblastoma cell growth by regulating the activity of Wnt/β-catenin pathway. 2016.
[79] Liu L, Yue H, Liu Q, Yuan J, Li J, Wei G, Chen X, Lu Y, Guo M, Luo JJO: LncRNA MT1JP functions as a tumor suppressor by interacting with TIAR to modulate the p53 pathway. 2016, 7(13):15787-15800.
[80] Zhang G, Li S, Lu J, Ge Y, Wang Q, Ma G, Zhao Q, Wu D, Gong W, Du MJMC: LncRNA MT1JP functions as a ceRNA in regulating FBXW7 through competitively binding to miR-92a-3p in gastric cancer. 2018, 17(1):87.
[81] F H, XM Z, medical LYJErf, sciences p: LncRNA MT1JP acts as a tumor inhibitor via reciprocally regulating Wnt/β-Catenin pathway in retinoblastoma.%A Bi LL. 2018, 22(13):4204-4214.
[82] Li L, Chen W, Wang Y, Tang L, Han MJOL: Long non-coding RNA H19 regulates viability and metastasis, and is upregulated in retinoblastoma. 2018, 15(6):8424.
[83] Zhang A, Shang W, Nie Q, Li T, Li SJJoCB: Long non-coding RNA H19 suppresses retinoblastoma progression via counteracting miR-17-92 cluster. 2017, 119(4).
[84] M W, Biomedicine YFJ, Biomedecine p, pharmacotherapie: Knockdown of lncRNA-H19 inhibits cell viability, migration and invasion while promotes apoptosis via microRNA-143/RUNX2 axis in retinoblastoma.%A Qi D. 2019, 109(undefined):798-805.