Pathology - Research and Practice 238 (2022) 154094

Contents lists available at ScienceDirect

Pathology - Research and Practice

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

Review

Circular RNAs in neuroblastoma: Pathogenesis, potential biomarker, and therapeutic target

Mohsen Karami Fath [a], Sasan Pourbagher Benam [b], Kiana Salmani [c], Sina Naderi [d], Zahra Fahham [e], Shamim Ghiabi [f], Seyed Armin Houshmand Kia [g], Malihe Naderi [h,k], Maryam Darvish [i], Ghasem Barati [j,*]

[a] Department of Cellular and Molecular Biology, Faculty of Biological Sciences, Kharazmi University, Tehran, Iran
[b] Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran
[c] Department of Genetics, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran
[d] Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran
[e] Faculty of Biology, Technische Universitat Dresden, Dresden, Germany
[f] Department of Medical Chemistry, Faculty of Pharmacy, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran
[g] Faculty of Pharmacy, Final International University, Girne, Republic of Cyprus
[h] Department of Microbiology and Microbial Biotechnology, Faculty of Life Science and Biotechnology, Shahid Beheshti University, Tehran, Iran
[i] Department of Medical Biotechnology, Faculty of Medicine, Arak University of Medical Sciences, Arak, Iran
[j] Stem Cell Technology Research Center, Tehran, Iran
[k] Department of Microbiology, Faculty of Medicine, Golestan University of Medical Sciences, Gorgan, Iran

ARTICLE INFO

Keywords:
Circular RNA
Neuroblastoma
Cancer pathogenesis
Diagnostic biomarker
Tumor targeted therapy

ABSTRACT

Neuroblastoma (NB) is a common cancer in childhood responsible for 15 % of fatalities by pediatric cancers. Epigenetic factors play an important role in the pathogenesis of NB. Recently, it has been demonstrated that circular RNAs (circRNAs, ciRNAs), a newly identified class of non-coding RNAs, are also dysregulated in NB. CircRNAs mediate their functions by regulating gene expression mainly through microRNA (miRNA) sponging. The dysregulation (abnormal upregulation or downregulation) of circRNAs is involved in tumorigenesis of a variety of tumors including NB. It seems that the expression of some circRNAs is correlated with NB prognosis and clinical features. CircRNAs might be favorable as a diagnostic/prognostic biomarker and therapeutic target. However, due to the lack of studies, it is difficult to make a conclusion regarding the clinical benefits of circRNAs. In this review, we discussed the circRNAs that experimentally have been proved to be dysregulated in NB tissues and cancer cells.

Abbreviations: AGO2, Argonaute 2; ALDH3A1, Aldehyde dehydrogenase 3 family member A1; ALK, Anaplastic lymphoma kinase; AML, Acute myeloid leukemia; ATRX, α-thalassemia X-linked intellectual disability; BHB, Bulge-helix-bulge; BRD4, Bromodomain protein 4; ciRNAs, Intronic circRNAs; CRC, Colorectal cancer; DGCR8, DiGeorge Syndrome Critical Region 8; DMRT2, Doublesex and mab-3 related transcription factor 2; DNMT, DNA methyltransferases; EcRNAs, Exonic circRNAs; EIciRNAs, Exonic-intronic circRNAs; EIP-22, EWSR1 inhibitory peptide of 22 amino acids; GLI1, Glioma-associated oncogene 1; HAT, Histone acetyl-transferases; HDAC, Histone deacetylases; HDM, Histone demethylases; HMT, Histone methyltransferases; HuR, Human antigen R; LDH, Lactate dehydrogenase; lncRNAs, Long non-coding RNAs; MBL, Muscleblind; miRNAs, microRNAs; MYO10, Myosin X; NB, Neuroblastoma; NDUFA1, NADH:ubiquinone oxidoreductase subunit A1; NDUFAF5, NADH, ubiquinone oxidoreductase complex assembly factor 5; NOL4L, Nucleolar protein 4 like; NSCLC, Non-small-cell lung carcinoma; ORFs, Open reading frames; PAK2, P21-activated kinase 2; PLK4, Polo-like kinase 4; PTPN11, Protein tyrosine phosphatase nonreceptor type 11; PRPS1, Phosphoribosyl pyrophosphate synthetase 1; RBPs, RNA binding proteins; shRNA, Short hairpin RNA; TERT, Telomerase reverse transcriptase; Tiam1, T lymphoma invasion and metastasis protein 1; TricRNAs, CircRNAs are derived from pre-tRNA transcripts; TSEN, tRNA splicing endonuclease; UTR, Untranslated region; VAP, Valproic acid; ZRF1, Zuotin-related factor 1.

* Corresponding author.
E-mail address: m.gh.barati@gmail.com (G. Barati).

https://doi.org/10.1016/j.prp.2022.154094
Received 24 July 2022; Received in revised form 22 August 2022; Accepted 23 August 2022
Available online 28 August 2022

1. Introduction

Neuroblastoma (NB) is a tumor of the peripheral nervous system and considered as one of the most common solid tumors in childhood. The tumor is derived from primitive sympathetic neural crest cells. While in about 50 % of cases the tumors spontaneously regress, the clinical manifestations in half of the affected children vary from a benign tumor to deadly metastatic courses. NB has an aggressive nature with a high likelihood to develop metastatic disease accounting for about 15 % of fatalities by pediatric cancers [1,2]. The location of the tumor is an important factor in determining the disease manifestation. Adrenal glands are considered as the most common origin of the tumor accounting for 48 % of total tumor numbers. Other tumor locations include extra-adrenal abdomen, posterior mediastinum, thorax, neck, and pelvis [1]. Abdominal tumors manifest with painful constipation and distention that may compress renal vessels leading to hypertension. Thoracic neuroblastomas may compress the airways and manifest with scoliosis [1,3]. Paravertebral tumors lead to painful motor sensory deficits or Horner syndrome by compressing the spinal canal [4]. Furthermore, the tumor can metastasize into other organs (including lymph nodes, bone marrow, and liver) making the treatment difficult [5]. Besides the location of the tumor, the age of the diagnosis is also involved in the prognosis of cancer. Most of the affected cases are diagnosed during the first three months of their life. The 5-years survival rate is higher in children diagnosed before their first year of life [6]. In addition, the clinical manifestation may be dependent on race and ethnicity [7]. While surgical interventions may not improve the neurologic symptoms, early diagnosis and applying non-surgical treatment modalities could be helpful to improve treatment outcomes [8]. Some genetic aberrations in genes responsible for the regulation of cell cycle, proliferation, and programmed cell death are involved in the pathogenesis of the disease. Later studies have also shown that epigenetic factors including DNA methylation, histone modification, and non-coding RNAs could directly be associated with tumor initiation and progression [9]. Non-coding RNAs including long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) have been demonstrated to be dysregulated in cancers including NB [10–12]. Recently, it has been demonstrated that circular RNAs (circRNAs, ciRNAs), a newly identified class of non-coding RNAs, are also dysregulated in NB [13].

2. Circular RNAs

Non-coding RNAs are believed to regulate gene expression in eukaryotic cells. Among them, miRNAs and lncRNAs have been well characterized and elucidated. MiRNAs with 19–23 nucleotides in length regulate gene expression at both transcriptional and post-translational levels by binding to their complementary sequences on the untranslated region (UTR) of mRNA targets. The miRNA-mRNA complex inhibits mRNA translation and also induces mRNA degradation by recruiting RNA binding proteins including DiGeorge Syndrome Critical Region 8 (DGCR8) and a ribonuclease III enzyme, Drosha [14]. LncRNAs mediate their functions through altering chromatin configuration, mRNA expression, splicing, mRNA stability, and post-translational modifications [15]. CircRNAs, a newly identified class of non-coding RNAs, are also involved in the regulation of gene expression in eukaryotic cells. CircRNAs are single-stranded; however, their ends bind together and form a circular polynucleotide structure. Due to their circular nature, they are resistant to exonucleases and thus have higher stability than miRNAs and lncRNAs [16]. Most of the circRNAs are synthesized from exonic, intronic, or exonic/intronic pre-mRNA transcript sequences in a processed called “back splicing” generating exonic circRNAs (EcRNAs), intronic circRNAs (ciRNAs), or exonic-intronic circRNAs (EIciRNAs) [16]. Fig. 1 shows the biogenesis of circRNAs from pre-mRNA transcripts. Back splicing is considered as an alternative to canonical splicing that recruits the canonical spliceosome machinery to produce circRNAs [17]. In addition, some of the circRNAs are derived from pre-tRNA transcripts (TricRNAs). Cleaving bulge-helix-bulge (BHB) motifs on pre-tRNA transcripts by tRNA splicing endonuclease (TSEN) complex results in the formation of TricRNAs [18]. The biogenesis of circRNAs from pre-mRNA and pre-tRNA transcripts is regulated by several RNA binding proteins (RBPs) including Muscleblind (MBL) and adenosine deaminases which positively or negatively regulate the circularization process [19–21].

CircRNAs play an important role in regulating gene expression in eukaryotes. They implement different mechanisms to regulate gene expression from transcription to translation levels. In the nucleus, ciRNAs and EIciRNAs could regulate their parental gene expression positively or negatively. They enhance the polymerase II elongation and thus increase the expression level of their parental genes [22]. On contrary, they could recruit the spliceosome machinery to induce back splicing and thus suppressing parental gene expression [23]. The most important

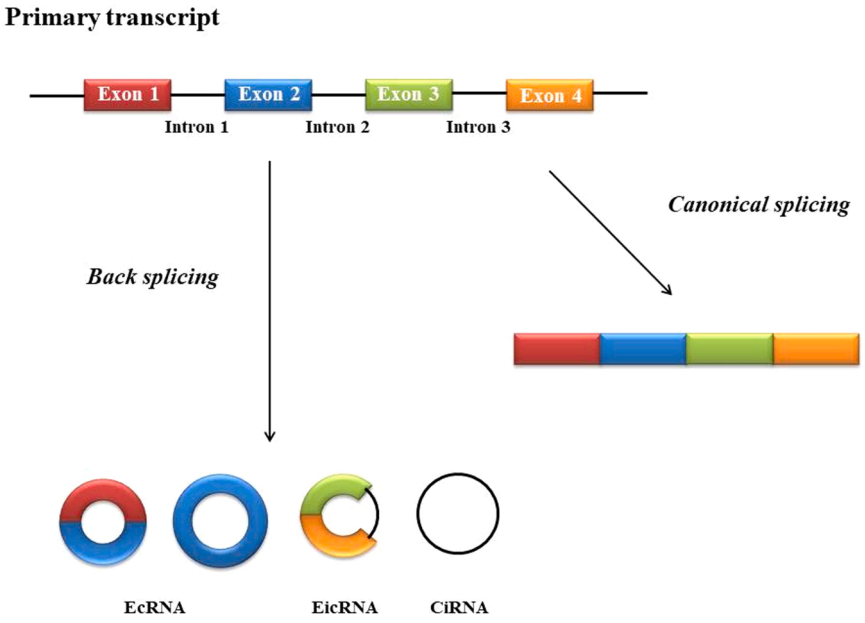

Fig. 1. The biogenesis of circRNAs from pre-mRNA transcripts. EcRNAs: Exonic circRNAs; EIciRNAs: Exonic-intronic circRNAs; ciRNAs: pre-mRNA intronic circRNA.

function of circRNAs is miRNA sponging in which circRNAs bind to the specific sequences on their miRNA targets and suppress their functions. As miRNAs are known as a master gene regulation element, circRNAs are expected to have a crucial role in the regulation of gene expression [24]. CircRNAs could also bind to their protein targets owing to their sequences as well as their secondary and tertiary structures, and thus regulate specific regulatory proteins in a process called "protein decoy" [25]. It has also been demonstrated that some circRNAs contain open reading frames (ORFs) and could translate to small regulatory peptides involved in the regulation of specific mRNA translation [26].

Due to their functions in regulating gene expression, circRNAs have direct impacts on many cellular behaviors such as growth, proliferation, and differentiation [27,28]. However, many studies have reported that the aberrant expression of circRNAs due to chromosomal abnormalities or aberrant biogenesis is correlated with many pathological disorders such as lung cancer, hepatocarcinoma, glioma, oral cancers, colorectal cancer (CRC), breast cancer, as well as NB [16,29]. Dysregulation of circRNAs has been shown to be involved in cancer initiation, promotion, and metastasis [16,30] suggesting their potential role as a diagnostic/prognostic biomarker and therapeutic target [31,32]. Several experimental studies have reported the aberrant expression of circRNAs in NB. In the following section, these circRNAs have been discussed.

3. Dysregulated circRNAs in NB

The dysregulation of circRNAs could be associated with human diseases such as cancers. Several studies have evaluated the circRNAs that are differentially expressed in NB tissues in comparison to normal tissues. Zhang et al. retrieved data on circRNA and mRNA expression of NB and normal cell lines from Sequence Read Archive (SRA). They evaluated 39022 circRNAs and found that 29 of them are differentially expressed. Using pathway analysis by molecular signatures database (MSigDB16), they found that circ_0005379 may be a key regulator in NB cell lines. They also found that circ_0002343 targets the PI3K/Akt/mTOR signaling components and may be involved in the regulation of the pathway. In addition, they suggest that circ_0001361 might be associated with epithelial-mesenchymal transition (EMT) in cancer cells [33]. Table 1 shows circRNAs that experimentally proved to have a role in the pathogenesis of NB. In this section, these circRNAs have been discussed.

3.1. Circ_0132813/7 (Circ-CUX1)

Circ-cut like homeobox 1 (circ-CUX1; hsa_circ_0132813) is derived from CUX gene which is located on chromosome 7 (chr7:101870650–101870949) [34]. The overexpression of circ-CUX1 in NB tissues and cell lines has been reported in several experimental studies [34–37]. A study by Zhang et al. reported that circ-CUX1 is upregulated in NB tissues. In vitro experiments proved that circ-CUX1 accelerates proliferation, invasion, and migration, and induces glycolysis of NB cancer cells. In vivo, the knockdown of circ-CUX1 has been shown to suppress tumor progression. They found that circ-CUX1 acts through miR-16–5p/DMRT2 axis [35]. The miR-16–5p is a tumor suppressor which is downregulated in various types of cancers [38–40]. In NB, it has been shown that miR-16–5p targets *MYCN* mRNA and subsequently suppresses the tumor progression [41]. Doublesex and mab-3 related transcription factor 2 (DMRT2) is a DNA binding protein with a zinc finger domain. It has an important role in development as its knockdown presented serious defects during embryogenesis [42,43]. However, the mechanism of DMRT2 in tumorigenesis remains unclear.

A study by Fang et al. showed that circ-CUX1 acts through miR-432–5p/NOL4L axis [36]. The miR-432–5p has been reported to act as a tumor suppressor in a variety of cancers including lung cancer [44], prostate cancer [45], breast cancer [46], and colon cancer [47]. Das and colleagues also have shown that miR-432–5p downregulation is associated with NB progression [48]. Nucleolar protein 4 like (NOL4L, also known as C20orf112) which is located on chromosome 20 is an oncogene and facilitates tumor progression in various types of cancers including ovarian cancer [49] and leukemia [50]. The upregulation of NOL4L also has been reported in NB [51]. Fig. 2 shows the mechanism of circ-CUX1 in NB cancer cell progression.

Yang and colleagues also showed the upregulation of circ-CUX1 in NB tissues. However, they found a different mechanism in which circ-CUX1 promotes tumor progression. Circ-CUX1 has been shown to encode a 113 amino acid protein isoform (p113). P113 isoform is located in the nucleus and interacted with bromodomain protein 4 (BRD4) and

Table 1
Dysregulated circRNAs in neuroblastoma.

CircRNA	Expression	Function in NB	Mechanism	Reference
Circ_0132813 (Circ-CUX1)	Upregulated	Promotion of proliferation and invasion and induction of glycolysis metabolism in cancer cells	Circ-CUX1acts through miR-16–5p/DMRT2 axis, miR-432–5p/NOL4L axis, and miR-338–3p/PHF20 axis.	[34–37]
Circ_0129276 (CircKIF2A)	Upregulated	Promotion of proliferation and invasion and induction of glycolysis metabolism in cancer cells	CircKIF2A acts through miR-129–5p/PLK4 and also miR-377–3p/PRPS1 axis.	[56,104]
Circ0125803	Upregulated	Facilitating tumor progression	Circ0125803 acts through miR-197–5p/E2F1 axis.	[105]
CircDLGAP4	Upregulated	Promotion of proliferation and invasion and induction of glycolysis metabolism in cancer cells	CircDLGAP4 acts through the miR-143/hexokinase 2 axis.	[70]
CircACAP2	Upregulated	Promotion of migration and invasion, and inhibition of apoptosis in cancer cells	CircACAP2 acts through the miR-143/hexokinase 2 axis.	[65]
Circ_0013401	Upregulated	Induction of tumor growth and metastasis and prevention of tumor apoptosis and autophagy	Circ_0013401 acts through the miR-195/PAK2 axis.	[71]
CircPDE5A (Circ_0002474)	Upregulated	Promotion of proliferation and invasion and induction of glycolysis metabolism in cancer cells	CircPDE5A acts through miR-362–5p/NOL4L axis	[101]
Circ_0133622 (CircDGKB)	Upregulated	Promotion of tumor cell proliferation, migration, and invasion; Inhibition of tumor cell apoptosis	CircDGKB mediates its function through miR-873 sponging and subsequently induces the expression of GLI1.	[13]
Circ_0135889 (CircAGO2)	Upregulated	Promotion of cancer cell growth and invasion	CircAGO2 interacts with HuR protein and thus regulates the function of AGO2/miRNA complex.	[94]
CircRNA-TBC1D4, circRNA-NAALAD2 and circRNA-TGFBR3	Downregulated	Inhibition of cancer cell proliferation and migration	CircRNA-TBC1D4, circRNA-NAALAD2 and circRNA-TGFBR3 are miR-21-related circRNAs and target oncogenic miR-21.	[100]

DMRT2: Doublesex and mab-3 related transcription factor 2; **NOL4L**: Nucleolar protein 4 like; **PHF20**: PHD Finger Protein 20; **PLK4**: Polo-like kinase 4; **PRPS1**: Phosphoribosyl pyrophosphate synthetase 1; **PAK2:** P21-activated kinase 2; **GLI1**: Glioma-associated oncogene 1; **AGO2**: Argonaute 2; **HuR**: Human antigen R;

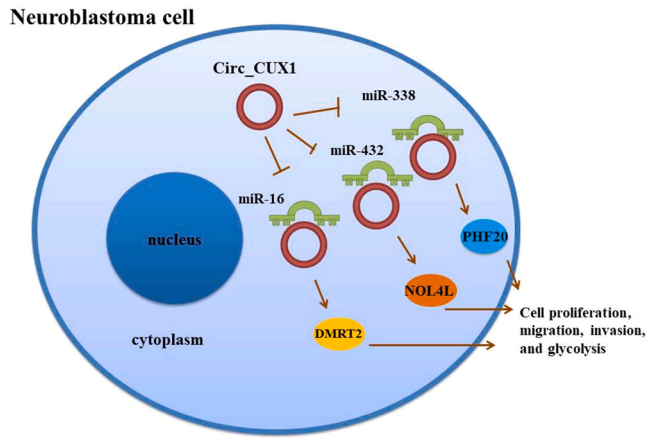

Fig. 2. Mechanism of circ-CUX1 in neuroblastoma cancer cell progression. Circ-CUX1 sponges several miRNA targets including miR-16, miR-432, and miR-338 which suppress the expression of tumor suppressor-like proteins including DMRT2, NOL4L, and PHF20, inducing cell proliferation, migration, invasion, and glycolysis. DMRT2: Doublesex and mab-3 related transcription factor 2; NOL4L: Nucleolar protein 4 like; PHF20: PHD Finger Protein 20.

Zuotin-related factor 1 (ZRF1) to form and transactivate a transcriptional complex, inducing the expression of aldehyde dehydrogenase 3 family member A1 (ALDH3A1), NADH:ubiquinone oxidoreductase subunit A1 (NDUFA1), and NADH: ubiquinone oxidoreductase complex assembly factor 5 (NDUFAF5). These genes are involved in enhancing lipid metabolism (fatty acid production and oxidation) and mitochondrial activity [52]. Spontaneous fatty acid production and oxidation have been shown to drive tumor cell progression [53]. In addition, it is well demonstrated that the upregulation of respiratory components of mitochondria is necessary for tumor growth [54].

3.2. Circ_0129276 (CircKIF2A)

Mahmoudi and colleagues have evaluated the expression level of circRNAs in NB. They demonstrated 107 upregulated and 47 downregulated circRNAs. Circ_0129276 (CircKIF2A) was one of the upregulated circRNAs [55]. In another study, Yang et al. evaluated the expression level and function of circKIF2A in NB tissues and cell lines. They showed that circKIF2A is involved in cancer cell proliferation and invasion. The results also indicated the role of circKIF2A in increasing the level of glycolysis in cancer cells to provide energy metabolism for cell growth and function. In vivo experiments showed that the knockdown of circKIF2A suppresses the tumorigenesis in the murine xenograft model of NB. Chromatin immunoprecipitation and dual luciferase assay indicated that circKIF2A acts through miR-129–5p/PLK4 axis [56]. The miR-129–5p is a tumor suppressor and its expression decreases in cancer cells. It has been reported that miR-129 inhibits the expression of myosin X (MYO10), a protein that contributes to cell invasion and migration in NB tissue [57]. Polo-like kinase 4 (PLK4) is an oncogene that drives tumorigenesis in a variety of cancers including colorectal cancer [58], glioblastoma [59], and breast cancer [60]. PLK4 also targets miR-338 to induce tumorigenesis in NB tissues [61].

Quan Jin and colleagues also showed that the level of circKIF2A increases in NB tissues. Their results indicated that circKIF2A mediates its functions through miR-377–3p/PRPS1 axis. The miR-377 is a tumor suppressor and suppresses the growth and migration of cancer cells [62]. The level of miR-377 expression has been shown to be decreased in NB tissues [63]. PRPS1 (Phosphoribosyl pyrophosphate synthetase 1) also induces the tumorigenicity of NB in children [64]. However, the exact mechanism remains unclear. Fig. 3 shows the mechanism of circKIF2A in NB cancer cell progression.

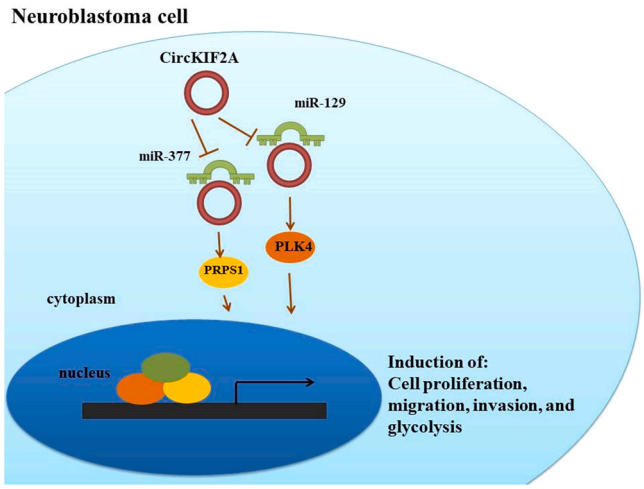

Fig. 3. Mechanism of circKIF2A in neuroblastoma cancer cell progression. CircKIF2A sponges several miRNA targets including miR-129 and miR-377 which suppress the expression of PLK4 and PRPS1, inducing cell proliferation, migration, invasion, and glycolysis. PLK4: Polo-like kinase 4; PRPS1: Phosphoribosyl pyrophosphate synthetase 1.

3.3. CircACAP2 and circDLGAP4

Zhu and colleagues showed the upregulation of circACAP2 in NB tissue and cell lines. CircACAP2 has been demonstrated to promote migration and invasion, inhibit apoptosis, and increase glycolysis in NB cancer cells. CircACAP2 sponged miR-143–3p which regulates the expression of hexokinase 2, an enzyme involved in the glycolysis pathway [65]. The interaction between miR-143 and hexokinase 2 has been reported in other cancers such as breast cancer [66] and bladder cancer [67]. Hexokinase 2 is a key enzyme in glucose metabolism. Therefore, miR-143 regulates the expression of hexokinase 2 and decreases energy metabolism. CircACAP2 also has been reported to be upregulated in other cancers including colon cancer and breast cancer. In colon cancer, circACAP2 acts through miR-21–5p/T lymphoma invasion and metastasis protein 1 (Tiam1) axis to promote cancer cell proliferation, migration, and invasion [68]. It has been demonstrated that circACAP2 targets the miR-29a/b-3p-COL5A1 axis to induce proliferation and metastasis of breast cancer cells [69]. Similar to circACAP2, a study by Wei-Qiang indicated that circDLGAP4 which is upregulated in NB, acts through the miR-143/hexokinase 2 axis to induce proliferation and metastasis of cancer cells [70].

3.4. Circ_0013401

A study by Zhu et al. indicated the role of circ_0013401 in NB. They reported a higher level of circ_0013401 in tumor tissue samples of patients with NB. The results indicated that circ_0013401 accelerates tumor growth and metastasis while preventing tumor apoptosis and autophagy in NB. Dual luciferase assay showed that circ_0013401 mediates its function by sponging miR-195. In vivo studies indicated the role of circ_0013401 in tumor formation in a mouse model of NB [71]. The miR-195 is considered as a tumor suppressor and its expression decreases in a variety of tumors including bladder cancer [72], glioma [73], breast cancer [74], and acute myeloid leukemia (AML)[75]. It has been also reported that the expression of miR-195 is correlated with prognosis of the disease in bladder cancer [72]. In addition, a diagnostic/prognostic value of miR-195 expression has been indicated in patients with AML [75]. miR-195 directly targets an anti-apoptotic molecule called Cytokine-induced apoptosis inhibitor 1 (CIAPIN1) and therefore induces tumor cell apoptosis [76]. PAK2 (P21-activated kinase 2) is a serine/threonine kinase that is a downstream enzyme in GTPase and Rho-induced pathways [77]. PAK2 expression has been reported to

be increased in tumors including lung, breast, pancreatic, and gastric cancers [78–81]. PAK2 is also activated by Rac and Cdc42 as well as Caspase-3 protease. Functional studies have reported that PAK2 overexpression contributes to promoting cell growth, proliferation, mobility, and invasion. In addition, PAK2 has a regulatory effects of apoptosis [82].

3.5. Circ_0133622 (CircDGKB)

Yang et al. have found that the expression level of circ_0133622 (circDGKB) increases in tumor tissue samples and cell lines of NB. The results also indicated that the expression level of circDGKB is positively correlated with poor prognosis and negatively correlated with survival rate. By luciferase reporter assay, they demonstrated that circDGKB mediates its function through miR-873/GLI1 axis [13]. The miR-873 functions as a tumor suppressor and previous studies have reported its tumor suppressive effects in some human tumors including gastric cancer [83], breast cancer [84], and non-small-cell lung carcinoma (NSCLC)[85]. Zhu and coworkers showed that miR-873 suppress colon cancer cell proliferation and progression by targeting AKT pathway [86]. Cao et al. also showed that miR-873 directly targets GLI1 in gastric cancer and induces apoptosis in tumor cells [83]. GLI1 (glioma-associated oncogene 1) is a terminal effector in Hedgehog (HH) signaling pathway. The pathway is involved in tumor progression of a variety of tumors including NB [87], breast cancer [88], glioma [89], prostate cancer [90], cervical cancer [91], colorectal cancer [92], and pancreatic cancer [93].

3.6. Circ_0135889 (CircAGO2)

A study by Chen and colleagues showed that circ_0135889 (circAGO2) is upregulated in some types of human tumor tissues and cell lines including gastric cancer, prostate cancer, colorectal cancer, as well as NB. They also showed that the expression level of circAGO2 is correlated with prognosis in patients with cancers. CircAGO2 is derived from Argonaute 2 (*AGO2*) encoding gene [94]. AGO2 is the main protein in the RNA-induced silencing complex (RISC) contributing to miRNA-mediated gene silencing [95]. Further in vitro and in vivo experiments showed that circAGO2 promotes cancer cell growth and invasion. However, it has been indicated that circAGO2 does not mediate its functions by affecting the AGO2 transcription or translation. CircAGO2 seems to interact with human antigen R (HuR) protein which in turn regulates the function of AGO2/miRNA complex [94]. HuR expression increases in many types of cancers and contributes to suppressing genes involved in tumor progression (such as *cyclin A*, *cyclin B1*, and *c-fos*)[96,97] and inducing genes involved in tumor suppression (such as *p16* and *c-Myc*)[98,99].

3.7. CircRNA-TBC1D4, circRNA-NAALAD2c, and circRNA-TGFBR3

Lin et al. have evaluated the expression level of circRNAs in NB tissue samples in comparison to normal adjacent tissues. Using RNA-seq technology, they found that 4704 circRNAs are differentially expressed (2462 upregulated and 2242 downregulated circRNAs). As miR-21 is an important oncogene and contributes to NB progression, they selected miR-21-related circRNAs for further experiments. CircRNA-TBC1D4, circRNA-NAALAD2, and circRNA-TGFBR3 were selected as they directly sponge miR-21. The results indicated that these circRNAs are downregulated in NB tissue samples. In addition, they reported that the expression of these circRNAs was correlated to each other. Moreover, their expression was correlated with poor prognosis in patients with NB [100].

3.8. Other circRNAs

Chen and coworkers have reported the upregulation of circRNA phosphodiesterase 5 A (circPDE5A, hsa_circ_0002474) in NB tissues and cell lines. They found that circPDE5A acts through miR-362–5p/NOL4L axis [101]. A previous study has shown that miR-362–5p has a tumor suppressor function by targeting phosphatidylinositol 3-kinase-C2β and its expression decreases in NB tissues [102]. Tang et al. have analyzed the expression of circRNAs in NB tissues using high-throughput microarray analysis. The results showed that circ0125803 is highly upregulated in NB tissues. The results also indicated that the knockdown of circ0125803 reduces cancer growth and invasion. Circ0125803 has shown to mediate its function through miR-197–5p/E2F1 axis [103].

4. CircRNA as a diagnostic or/and prognostic biomarker

The diagnosis of NB and evaluation of the disease progression in children require imaging techniques such as computed tomography (CT) that have a high cost to patients (and their parents) [1]. CircRNAs seem to have a critical role in the pathogenesis of NB. Therefore, they might be used as a diagnostic or/and prognostic biomarker. Several studies have indicated the correlation between circRNA expression and disease prognosis. The expression level of circDGKB has been reported to be positively correlated with poor prognosis and negatively correlated with survival rate [13]. Chen and colleagues also showed that the expression level of circAGO2 is correlated with prognosis in patients with cancers [94]. These results indicate that circRNAs might be used as a prognostic or/and diagnostic marker.

Lin et al. have evaluated the expression level of circRNA-TBC1D4, circRNA-NAALAD2, and circRNA-TGFBR3 in NB tissue samples and found that their expression is downregulated. They also showed that the expression of each of these circRNAs is correlated with specific clinical features of the disease. The expression of circRNA-TBC1D4 was correlated with *MYCN* number and lactate dehydrogenase (LDH) concentration. The expression of circRNA-NAALAD2 was also correlated with LDH concentration while the expression of circRNA-TGFBR3 was correlated with the histological classification of the disease [100]. These results indicated that the level of circRNA-TBC1D4, circRNA-NAALAD2, and circRNA-TGFBR3 may be favorable to serve as a prognostic biomarker in patients with NB. Yang et al. have indicated the potential role of circ_0133622 (circDGKB) as a diagnostic marker in patients with NB. They measured the level of circDGKB in blood samples of patients in comparison to healthy individuals. The results showed that circDGKB is upregulated in blood samples of patients with NB indicating the role of circDGKB expression level measurement as a diagnostic marker. In addition, the analysis showed that the level of circDGKB is correlated with the clinical features of the disease. The survival rate also has been indicated to be lower in patients with a higher level of circDGKB [13]. However, more evidence about the correlation between the level of circRNA and disease status in body fluids such as serum and saliva is required to prove the power of circRNAs as diagnostic and/or prognostic biomarkers.

5. CircRNA as a therapeutic target

NB is a cancer of children responsible for 15 % of childhood cancer-related mortality [1,2]. Several genetic alterations have been reported in NB cancer cells. However, epigenetic factors play a key role in the pathogenesis of cancer. CircRNAs are newly identified RNAs and their aberrant expression contributes to the pathogenesis of many diseases and cancers including NB. Several studies have reported that circRNA aberrant expression correlates with poor prognosis in patients with NB [13,100]. Moreover, due to their role in the pathogenesis of the disease, circRNAs may be favorable targets for targeted therapy of NB and other cancers. Li and colleagues have evaluated the potential of circCUX1 as a therapeutic target in NB. They targeted circ-CUX1/EWSR1/MAZ axis with a peptide that blocks circ-CUX1-EWSR1 interaction in NB cell lines. EWSR1 inhibitory peptide of 22 amino acids (EIP-22) as a cell-penetrating peptide was designed to block the interaction between

circCUX1 and EWSR1. The results indicated that the blockage of circCUX1/EWSR1 interaction in SH-SY5Y cells by EIP-22 results in a suppression of cell growth and migration. In a murine model of NB, the administration of EIP-22 via tail vein also reduced the lung metastatic of SH-SY5Y cancer cells and improved the survival rate in EIP-22-receiving mice. In addition, the knockdown of circCUX1 with a lentiviral vector blocked aerobic glycolysis in a murine model of NB [34]. In another study, Chen et al. showed an increased level of circAGO2 in multiple tumor tissues such as NB. They have used a lentiviral vector encoding short hairpin RNA (shRNA) to target circAGO2 in cancer cells. In a preclinical nude mice model of cancer, they demonstrated that shRNA results in a suppression of cancer progression [94]. These studies have shown the potential of circRNAs as a therapeutic target in NB. However, the studies are limited to conclude the potential of anti-circRNA therapy in cancers.

6. Concluding remarks

Epigenetic regulators have a critical role in the pathogenesis of NB. Among them, circRNAs are involved in the proliferation, invasion, and migration of NB cancer cells. The dysregulation of circRNAs has been reported in NB tissues and cell lines. In addition, knockdown studies have indicated their role in the pathogenesis of the disease. Increasing our knowledge about the function of circRNAs in NB might help the disease diagnosis and treatment.

CircRNA expression seems to be correlated with NB prognosis and clinical features [13,100]. However, the use of NB tissue limits circRNAs to be used as a prognostic as well as diagnostic biomarker in the clinical setting. Although a study by Yang et al. has indicated the potential role of circDGKB in blood samples as a diagnostic biomarker in patients with NB [13], due to the lack of studies, it is difficult to make a conclusion regarding the clinical benefits of circRNAs as a biomarker.

Studies that are discussed in Table 1 indicated that the knockdown of circRNAs (such as circ-CUX1, circKIF2A, circ_0013401, circDGKB, circAGO2, circPDE5A, circACAP2, and circDLGAP4) suppresses tumor progression in xenograft animal model of NB. It shows that these circRNAs could be used as a therapeutic target. On contrary, some circRNAs such as circRNA-TBC1D4, circRNA-NAALAD2c, and circRNA-TGFBR3 have been shown to have a protective role in NB and they might be favorable as a therapeutic agent for treating the disease.

Several factors may interfere with the interpretation of data from the circRNA expression level. The expression of circRNAs may be varied in different stages of NB. Moreover, different genomic and epigenomic backgrounds of patients in different studies may affect circRNA expression. The data from circRNA analysis in patients with NB is better to be interpreted along with the imaging techniques as well as histopathological characteristics of patients especially when circRNAs are going to be used as a biomarker.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics approval and consent to participate

There was no involvement of humans or animals in this study.

CRediT authorship contribution statement

M.KF., G.B., S.PB., K.S., and S.N. wrote Section 4 (Dysregulated circRNAs). Z.F., S.G., SA.HK., M.N., G.B., and M.D. wrote the rest of the manuscript. M.KF. and G.B. designed the manuscript and prepared the figures. All authors read and approved the final version of the manuscript.

Conflict of Interest

All authors declare no conflict of interest.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgments

None.

References

[1] C.C. Swift, M.J. Eklund, J.M. Kraveka, A.L. Alazraki, Updates in diagnosis, management, and treatment of neuroblastoma, RadioGraphics 38 (2018) 566–580.
[2] S. Mueller, K.K. Matthay, Neuroblastoma: biology and staging, Curr. Oncol. Rep. 11 (2009) 431.
[3] W.-G. He, Y. Yan, W. Tang, R. Cai, G. Ren, Clinical and biological features of neuroblastic tumors: a comparison of neuroblastoma and ganglioneuroblastoma, Oncotarget 8 (2017) 37730–37739.
[4] Z.F. Pollard, M.F. Greenberg, M. Bordenca, J. Lange, Atypical acquired pediatric horner syndrome, Arch. Ophthalmol. 128 (2010) 937–940.
[5] T. Hildebrandt, H. Traunecker, Neuroblastoma: a tumour with many faces, Curr. Paediatr. 15 (2005) 412–420.
[6] R. Rabinowicz, M. Barchana, I. Liphshiz, B. Futerman, S. Linn, M. Weyl-Ben-Arush, Cancer incidence and survival among children and adolescents in israel during the years 1998 to 2007, J. Pediatr. Hematol. /Oncol. (2012) 34.
[7] W.B. London, R.P. Castleberry, K.K. Matthay, A.T. Look, R.C. Seeger, H. Shimada, et al., Evidence for an age cut-off greater than 365 days for neuroblastoma risk group stratification in the Children's Oncology Group (COG), J. Clin. Oncol. 23 (2005), 8500-8500.
[8] P. Jabbari, S. Hanaei, N. Rezaei, State of the art in immunotherapy of neuroblastoma, Immunotherapy 11 (2019) 831–850.
[9] I.S. Fetahu, S. Taschner-Mandl, Neuroblastoma and the epigenome, Cancer Metastas-.-. Rev. 40 (2021) 173–189.
[10] C. Welch, Y. Chen, R.L. Stallings, MicroRNA-34a functions as a potential tumor suppressor by inducing apoptosis in neuroblastoma cells, Oncogene 26 (2007) 5017–5022.
[11] J.S. Wei, Y.K. Song, S. Durinck, Q.R. Chen, A.T.C. Cheuk, P. Tsang, et al., The MYCN oncogene is a direct target of miR-34a, Oncogene 27 (2008) 5204–5213.
[12] J. Chen, L. Hongting, L. Shaoping, C. Xin, D. Qian, MiR-34-a acts as a suppressor in neuroblastoma progression by targeting CD44, J. Pak. Med Assoc. 67 (2017) 1524–1531.
[13] J. Yang, L. Yu, J. Yan, Y. Xiao, W. Li, J. Xiao, et al., Circular RNA DGKB promotes the progression of neuroblastoma by targeting miR-873/GLI1 axis, Front. Oncol. (2020) 10.
[14] A.M. Denli, B.B. Tops, R.H. Plasterk, R.F. Ketting, Hannon GJJN processing of primary microRNAs by the microprocessor complex, Nature 432 (2004) 231–235.
[15] J.C.R. Fernandes, S.M. Acuña, J.I. Aoki, L.M. Floeter-Winter, S.M. Muxel, Long non-coding RNAs in the regulation of gene expression: physiology and disease, Non-Coding RNA 5 (2019) 17.
[16] J. Li, D. Sun, W. Pu, J. Wang, Y. Peng, Circular RNAs in cancer: biogenesis, function, and clinical significance, Trends Cancer 6 (2020) 319–336.
[17] L.S. Kristensen, M.S. Andersen, L.V.W. Stagsted, K.K. Ebbesen, T.B. Hansen, J. Kjems, The biogenesis, biology and characterization of circular RNAs, Nat. Rev. Genet. 20 (2019) 675–691.
[18] C.A. Schmidt, J.D. Giusto, A. Bao, A.K. Hopper, A.G. Matera, Molecular determinants of metazoan tricRNA biogenesis, Nucleic Acids Res. 47 (2019) 6452–6465.
[19] R. Ashwal-Fluss, M. Meyer, R. Pamudurti Nagarjuna, A. Ivanov, O. Bartok, M. Hanan, et al., circRNA biogenesis competes with Pre-mRNA splicing, Mol. Cell 56 (2014) 55–66.
[20] J. Conn Simon, A. Pillman Katherine, J. Toubia, M. Conn Vanessa, M. Salmanidis, A. Phillips Caroline, et al., The RNA binding protein quaking regulates formation of circRNAs, Cell 160 (2015) 1125–1134.
[21] A. Ivanov, S. Memczak, E. Wyler, F. Torti, T. Porath Hagit, Orejuela, R. Marta, et al., Analysis of intron sequences reveals hallmarks of circular RNA biogenesis in animals, Cell Rep. 10 (2015) 170–177.
[22] Z. Li, C. Huang, C. Bao, L. Chen, M. Lin, X. Wang, et al., Exon-intron circular RNAs regulate transcription in the nucleus, Nat. Struct. Mol. Biol. 22 (2015) 256–264.
[23] D. Liang, D.C. Tatomer, Z. Luo, H. Wu, L. Yang, L.-L. Chen, et al., The output of protein-coding genes shifts to circular RNAs when the Pre-mRNA processing machinery is limiting, Mol. Cell 68 (2017) 940–954, e943.
[24] Q. Lu, T. Liu, H. Feng, R. Yang, X. Zhao, W. Chen, et al., Circular RNA circSLC8A1 acts as a sponge of miR-130b/miR-494 in suppressing bladder cancer progression via regulating PTEN, Mol. Cancer 18 (2019) 111.
[25] K. Abdelmohsen, A.C. Panda, R. Munk, I. Grammatikakis, D.B. Dudekula, S. De, et al., Identification of HuR target circular RNAs uncovers suppression of PABPN1 translation by CircPABPN1, RNA Biol. 14 (2017) 361–369.

[26] M. Zhang, N. Huang, X. Yang, J. Luo, S. Yan, F. Xiao, et al., A novel protein encoded by the circular form of the SHPRH gene suppresses glioma tumorigenesis, Oncogene 37 (2018) 1805–1814.
[27] D. van Rossum, B.M. Verheijen, R.J. Pasterkamp, Circular RNAs: novel regulators of neuronal development, Front. Mol. Neurosci. (2016) 9.
[28] R. Chen, S. Lei, T. Jiang, J. Zeng, S. Zhou, Y. She, Roles of lncRNAs and circRNAs in regulating skeletal muscle development, Acta Physiol. 228 (2020), e13356.
[29] K.L. Harper, E. McDonnell, A. Whitehouse, CircRNAs: from anonymity to novel regulators of gene expression in cancer (Review), Int. J. Oncol. 55 (2019) 1183–1193.
[30] L.-P. Zhu, Y.-J. He, J.-C. Hou, X. Chen, S.-Y. Zhou, S.-J. Yang, et al., The role of circRNAs in cancers, Biosci. Rep. 37 (2017) 1–11.
[31] L. Verduci, E. Tarcitano, S. Strano, Y. Yarden, G. Blandino, CircRNAs: role in human diseases and potential use as biomarkers, Cell Death Dis. 12 (2021) 468.
[32] Q. Zhou, L.-L. Ju, X. Ji, Y.-L. Cao, J.-G. Shao, L. Chen, Plasma circRNAs as biomarkers in cancer, Cancer Manag Res 13 (2021) 7325–7337.
[33] L. Zhang, H. Zhou, J. Li, X. Wang, X. Zhang, T. Shi, et al., Comprehensive characterization of circular RNAs in neuroblastoma cell lines, Technol. Cancer Res. Treat. 19 (2020), 1533033820957622.
[34] H. Li, F. Yang, A. Hu, X. Wang, E. Fang, Y. Chen, et al., Therapeutic targeting of circ-CUX1/EWSR1/MAZ axis inhibits glycolysis and neuroblastoma progression, EMBO Mol. Med. 11 (2019), e10835.
[35] X. Zhang, J. Zhang, Q. Liu, Y. Zhao, W. Zhang, H. Yang, Circ-CUX1 accelerates the progression of neuroblastoma via miR-16-5p/DMRT2 axis, Neurochem. Res. 45 (2020) 2840–2855.
[36] Y. Fang, Y. Yao, K. Mao, Y. Zhong, Y. Xu, Circ_0132817 facilitates cell proliferation, migration, invasion and glycolysis by regulating the miR-432-5p/NOL4L axis in neuroblastoma, Exp. Brain Res. 239 (2021) 1841–1852.
[37] Y. Wang, Q. Niu, J. Dai, H. Shi, J. Zhang, circCUX1 promotes neuroblastoma progression and glycolysis by regulating the miR-338-3p/PHF20 axis, Gen. Physiol. Biophys. 40 (2021) 17–29.
[38] H. Liang, Z. Fu, X. Jiang, N. Wang, F. Wang, X. Wang, et al., miR-16 promotes the apoptosis of human cancer cells by targeting FEAT, BMC Cancer 15 (2015) 448.
[39] N. Bandi, S. Zbinden, M. Gugger, M. Arnold, V. Kocher, L. Hasan, et al., miR-15a and miR-16 are implicated in cell cycle regulation in a Rb-dependent manner and are frequently deleted or down-regulated in non–small cell lung cancer, Cancer Res. 69 (2009) 5553–5559.
[40] T. Wang, J. Hou, Z. Li, Z. Zheng, J. Wei, D. Song, et al., miR-15a-3p and miR-16-1-3p negatively regulate Twist1 to repress gastric cancer cell invasion and metastasis, Int J. Biol. Sci. 13 (2017) 122–134.
[41] S. Chava, C.P. Reynolds, A.S. Pathania, S. Gorantla, L.Y. Poluektova, D. W. Coulter, et al., miR-15a-5p, miR-15b-5p, and miR-16-5p inhibit tumor progression by directly targeting MYCN in neuroblastoma, Mol. Oncol. 14 (2020) 180–196.
[42] K.W. Seo, Dmrt2 and Pax3 double-knockout mice show severe defects in embryonic myogenesis, Comp. Med. 57 (2007) 460–468.
[43] A. Bouman, Q. Waisfisz, J. Admiraal, M. van de Loo, R.R. van Rijn, D. Micha, et al., Homozygous DMRT2 variant associates with severe rib malformations in a newborn, Am. J. Med. Genet. Part A 176 (2018) 1216–1221.
[44] C. Hu, R. Jiang, Z. Cheng, Y. Lu, L. Gu, H. Li, et al., Ophiopogonin-B suppresses epithelial-mesenchymal transition in human lung adenocarcinoma cells via the Linc00668/miR-432-5p/EMT axis, J. Cancer 10 (2019) 2849–2856.
[45] C. Dong, B. Fan, Z. Ren, B. Liu, Y. Wang, CircSMARCA5 facilitates the progression of prostate cancer through miR-432/PDCD10 axis, Cancer Biother. Radiopharm. 36 (2021) 70–83.
[46] S. Li, H. Jia, Z. Zhang, D. Wu, DRAIC promotes growth of breast cancer by sponging miR-432-5p to upregulate SLBP, Cancer Gene Ther. (2021).
[47] M. Luo, Z. Hu, Y. Kong, L. Li, MicroRNA-432–5p inhibits cell migration and invasion by targeting CXCL5 in colorectal cancer, Exp. Ther. Med 21 (2021) 301.
[48] E. Das, N.P. Bhattacharyya, MicroRNA-432 contributes to dopamine cocktail and retinoic acid induced differentiation of human neuroblastoma cells by targeting NESTIN and RCOR1 genes, FEBS Lett. 588 (2014) 1706–1714.
[49] S. Nagasawa, K. Ikeda, K. Horie-Inoue, S. Sato, A. Itakura, S. Takeda, et al., Systematic identification of characteristic genes of ovarian clear cell carcinoma compared with high-grade serous carcinoma based on RNA-sequencing, Int. J. Mol. Sci. 20 (2019) 4330.
[50] M.C. Guastadisegni, A. Lonoce, L. Impera, F. Di Terlizzi, G. Fugazza, S. Aliano, et al., CBFA2T2 and C20orf112: two novel fusion partners of RUNX1 in acute myeloid leukemia, Leukemia 24 (2010) 1516–1519.
[51] Z. Yu, J. Zhang, J. Han, Silencing CASC11 curbs neonatal neuroblastoma progression through modulating microRNA-676-3p/nucleolar protein 4 like (NOL4L) axis, Pediatr. Res. 87 (2020) 662–668.
[52] F. Yang, A. Hu, Y. Guo, J. Wang, D. Li, X. Wang, et al., p113 isoform encoded by CUX1 circular RNA drives tumor progression via facilitating ZRF1/BRD4 transactivation, Mol. Cancer 20 (2021) 123.
[53] J.-S. Lee, S.H. Kim, S. Lee, J.H. Kang, S.-H. Lee, J.-H. Cheong, et al., Gastric cancer depends on aldehyde dehydrogenase 3A1 for fatty acid oxidation, Sci. Rep. 9 (2019) 16313.
[54] A. Viale, P. Pettazzoni, C.A. Lyssiotis, H. Ying, N. Sánchez, M. Marchesini, et al., Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function, Nature 514 (2014) 628–632.
[55] E. Mahmoudi, D. Kiltschewskij, C. Fitzsimmons, M.J. Cairns, Depolarization-associated CircRNA regulate neural gene expression and in some cases may function as templates for translation, Cells 9 (2020) 25.
[56] Y. Yang, H. Pan, J. Chen, Z. Zhang, M. Liang, X. Feng, CircKIF2A contributes to cell proliferation, migration, invasion and glycolysis in human neuroblastoma by regulating miR-129-5p/PLK4 axis, Mol. Cell. Biochem. 476 (2021) 2513–2525.
[57] X. Wang, J. Li, X. Xu, J. Zheng, Q. Li, miR-129 inhibits tumor growth and potentiates chemosensitivity of neuroblastoma by targeting MYO10, Biomed. Pharmacother. 103 (2018) 1312–1318.
[58] Z. Liao, H. Zhang, P. Fan, Q. Huang, K. Dong, Y. Qi, High PLK4 expression promotes tumor progression and induces epithelial-mesenchymal transition by regulating the Wnt/β-catenin signaling pathway in colorectal cancer, Int. J. Oncol. (2019) 479–490. Corrigendum in /10.3892/ijo.2021.5213 Corrigendum in /10.3892/ijo.2021.5291.
[59] J. Wang, J. Zuo, M. Wang, X. Ma, K. Gao, X. Bai, et al., Polo-like kinase 4 promotes tumorigenesis and induces resistance to radiotherapy in glioblastoma, Oncol. Rep. 41 (2019) 2159–2167.
[60] M. Marina, H.I. Saavedra, Nek2 and Plk4: prognostic markers, drivers of breast tumorigenesis and drug resistance, Front Biosci. (Landmark Ed.) 19 (2014) 352–365.
[61] N. Zhang, F. Liu, T. Ma, Z. Zhang, LncRNA SNHG1 contributes to tumorigenesis and mechanism by targeting miR-338-3p to regulate PLK4 in human neuroblastoma, Eur. Rev. Med. Pharm. Sci. 23 (2019) 8971–8983.
[62] H. Wu, H.Y. Liu, W.J. Liu, Y.L. Shi, D. Bao, miR-377-5p inhibits lung cancer cell proliferation, invasion, and cell cycle progression by targeting AKT1 signaling, J. Cell. Biochem. 120 (2019) 8120–8128.
[63] H. Yang, J. Guo, M. Zhang, A. Li, LncRNA SNHG4 promotes neuroblastoma proliferation, migration, and invasion by sponging miR-377-3p, Neoplasma 67 (2020) 1054–1062.
[64] Y. Ge, S. Tan, J. Bi, M. Rao, Y. Yu, L. Tian, SNHG16 knockdown inhibits tumorigenicity of neuroblastoma in children via miR-15b-5p/PRPS1 axis, NeuroReport 31 (2020) 1225–1235.
[65] J. Zhu, X.-L. Xiang, P. Cai, Y.-L. Jiang, Z.-W. Zhu, F.-L. Hu, et al., CircRNA-ACAP2 contributes to the invasion, migration, and anti-apoptosis of neuroblastoma cells through targeting the miRNA-143-3p-hexokinase 2 axis, Transl. Pedia 10 (2021) 3237–3247.
[66] Y. Guo, F. Liang, F. Zhao, J. Zhao, Resibufogenin suppresses tumor growth and Warburg effect through regulating miR-143-3p/HK2 axis in breast cancer, Mol. Cell. Biochem. 466 (2020) 103–115.
[67] J. Chen, Y. Yu, H. Li, Q. Hu, X. Chen, Y. He, et al., Long non-coding RNA PVT1 promotes tumor progression by regulating the miR-143/HK2 axis in gallbladder cancer, Mol. Cancer 18 (2019) 33.
[68] J.H. He, Y.G. Li, Z.P. Han, J.B. Zhou, W.M. Chen, Y.B. Lv, et al., The CircRNA-ACAP2/Hsa-miR-21-5p/ Tiam1 regulatory feedback circuit affects the proliferation, migration, and invasion of colon cancer SW480 cells, Cell. Physiol. Biochem. 49 (2018) 1539–1550.
[69] B. Zhao, X. Song, H. Guan, CircACAP2 promotes breast cancer proliferation and metastasis by targeting miR-29a/b-3p-COL5A1 axis, Life Sci. 244 (2020), 117179.
[70] W.-Q. Tan, L. Yuan, X.-Y. Wu, C.-G. He, S.-C. Zhu, M. Ye, Exosome-delivered circular RNA DLGAP4 induces chemoresistance via miR-143-HK2 axis in neuroblastoma, Cancer Biomark. 34 (2022) 375–384.
[71] S. Zhu, X. Tang, X. Gao, J. Zhang, Y. Cui, D. Li, et al., hsa_circ_0013401 accelerates the growth and metastasis and prevents apoptosis and autophagy of neuroblastoma cells by sponging mir-195 to release PAK2, Oxid. Med. Cell. Longev. 2021 (2021), 9936154.
[72] K. Yang, H. Tang, M. Ding, Y. Guo, K. Kai, J. Xiao, et al., Expression of miR-195 and MEK1 in patients with bladder cancer and their relationship to prognosis, Int J. Clin. Exp. Pathol. 12 (2019) 843–850.
[73] L.-P. Chen, N.-N. Zhang, X.-Q. Ren, J. He, Y. Li, miR-103/miR-195/miR-15b Regulate SALL4 and inhibit proliferation and migration in glioma, Molecules 23 (2018) 2938.
[74] L. Yang, Y. Cai, D. Zhang, J. Sun, C. Xu, W. Zhao, et al., miR-195/miR-497 regulate CD274 expression of immune regulatory ligands in triple-negative breast cancer, JBC 21 (2018) 371–381.
[75] Z. Hong, R. Zhang, H. Qi, Diagnostic and prognostic relevance of serum miR-195 in pediatric acute myeloid leukemia, Cancer Biomark. 21 (2018) 269–275.
[76] Q. Xu, J.-L. Xu, W.-Q. Chen, W.-X. Xu, Y.-X. Song, W.-J. Tang, et al., Roles and mechanisms of miR-195–5p in human solid cancers, Biomed. Pharmacother. 150 (2022), 112885.
[77] P. Binder, S. Wang, M. Radu, M. Zin, L. Collins, S. Khan, et al., Pak2 as a novel therapeutic target for cardioprotective endoplasmic reticulum stress response, Circ. Res. 124 (2019) 696–711.
[78] Q. Li, X. Wu, L. Guo, J. Shi, J. Li, MicroRNA-7-5p induces cell growth inhibition, cell cycle arrest and apoptosis by targeting PAK2 in non-small cell lung cancer, FEBS Open Bio 9 (2019) 1983–1993.
[79] H. Liu, S.H. Shin, H. Chen, T. Liu, Z. Li, Y. Hu, et al., CDK12 and PAK2 as novel therapeutic targets for human gastric cancer, Theranostics 10 (2020) 6201–6215.
[80] G.W. Yao, J.R. Bai, D.P. Zhang, P21 activated kinase 2 promotes pancreatic cancer growth and metastasis, Oncol. Lett. 17 (2019) 3709–3718.
[81] Y. Zhang, L. Wester, J. He, T. Geiger, M. Moerkens, R. Siddappa, et al., IGF1R signaling drives antiestrogen resistance through PAK2/PIX activation in luminal breast cancer, Oncogene 37 (2018) 1869–1884.
[82] W.-W. Deng, L. Wu, L.-L. Bu, J.-F. Liu, Y.-C. Li, S.-R. Ma, et al., PAK2 promotes migration and proliferation of salivary gland adenoid cystic carcinoma, Am. J. Transl. Res 8 (2016) 3387–3397.
[83] D. Cao, T. Yu, X. Ou, MiR-873–5 P controls gastric cancer progression by targeting hedgehog-GLI signaling, Die Pharm. - Int. J. Pharm. Sci. 71 (2016) 603–606.

[84] J. Cui, Y. Yang, H. Li, Y. Leng, K. Qian, Q. Huang, et al., MiR-873 regulates ERα transcriptional activity and tamoxifen resistance via targeting CDK3 in breast cancer cells, Oncogene 34 (2015) 3895–3907.
[85] S. Jin, J. He, J. Li, R. Guo, Y. Shu, P. Liu, MiR-873 inhibition enhances gefitinib resistance in non-small cell lung cancer cells by targeting glioma-associated oncogene homolog 1, Thorac. Cancer 9 (2018) 1262–1270.
[86] Y. Zhu, X. Zhang, M. Qi, Y. Zhang, F. Ding, miR-873-5p inhibits the progression of colon cancer via repression of tumor suppressor candidate 3/AKT signaling, J. Gastroenterol. Hepatol. 34 (2019) 2126–2134.
[87] Y. Diao, M.F.-U. Rahman, Y. Vyatkin, A. Azatyan St., G. Laurent, P. Kapranov, et al., Identification of novel GLI1 target genes and regulatory circuits in human cancer cells, Mol. Oncol. 12 (2018) 1718–1734.
[88] L. Xu, Y.-J. Kwon, N. Frolova, A.D. Steg, K. Yuan, M.R. Johnson, et al., Gli1 promotes cell survival and is predictive of a poor outcome in ERα-negative breast cancer, Breast Cancer Res. Treat. 123 (2010) 59–71.
[89] V. Clement, P. Sanchez, N. de Tribolet, I. Radovanovic, Ruiz i Altaba A HEDGEHOG-GLI1 signaling regulates human glioma growth, cancer stem cell self-renewal, and tumorigenicity, Curr. Biol. 17 (2007) 165–172.
[90] G. Chen, Y. Goto, R. Sakamoto, K. Tanaka, E. Matsubara, M. Nakamura, et al., GLI1, a crucial mediator of sonic hedgehog signaling in prostate cancer, functions as a negative modulator for androgen receptor, Biochem. Biophys. Res. Commun. 404 (2011) 809–815.
[91] A. Nayak, S.R. Satapathy, D. Das, S. Siddharth, N. Tripathi, P.V. Bharatam, et al., Nanoquinacrine induced apoptosis in cervical cancer stem cells through the inhibition of hedgehog-GLI1 cascade: Role of GLI-1, Sci. Rep. 6 (2016) 20600.
[92] J. Cheng, R. Deng, C. Wu, P. Zhang, K. Wu, L. Shi, et al., Inhibition of SALL4 suppresses carcinogenesis of colorectal cancer via regulating Gli1 expression, Int J. Clin. Exp. Pathol. 8 (2015) 10092–10101.
[93] H. Gan, H. Liu, H. Zhang, Y. Li, X. Xu, X. Xu, et al., SHh-Gli1 signaling pathway promotes cell survival by mediating baculoviral IAP repeat-containing 3 (BIRC3) gene in pancreatic cancer cells, Tumor Biol. 37 (2016) 9943–9950.
[94] Y. Chen, F. Yang, E. Fang, W. Xiao, H. Mei, H. Li, et al., Circular RNA circAGO2 drives cancer progression through facilitating HuR-repressed functions of AGO2-miRNA complexes, Cell Death Differ. 26 (2019) 1346–1364.
[95] G. Meister, M. Landthaler, A. Patkaniowska, Y. Dorsett, G. Teng, T. Tuschl, Human Argonaute2 mediates RNA cleavage targeted by miRNAs and siRNAs, Mol. Cell 15 (2004) 185–197.
[96] W. Wang, M.C. Caldwell, S. Lin, H. Furneaux, M. Gorospe, HuR regulates cyclin A and cyclin B1 mRNA stability during cell proliferation, EMBO J. 19 (2000) 2340–2350.
[97] W. Wang, X. Yang, V.J. Cristofalo, N.J. Holbrook, M. Gorospe, Loss of HuR is linked to reduced expression of proliferative genes during replicative senescence, Mol. Cell. Biol. 21 (2001) 5889–5898.
[98] N. Chang, J. Yi, G. Guo, X. Liu, Y. Shang, T. Tong, et al., HuR uses AUF1 as a cofactor to promote p16INK4 mRNA decay, Mol. Cell. Biol. 30 (2010) 3875–3886.
[99] H.H. Kim, Y. Kuwano, S. Srikantan, E.K. Lee, J.L. Martindale, M. Gorospe, HuR recruits let-7/RISC to repress c-Myc expression, Genes Dev. 23 (2009) 1743–1748.
[100] W. Lin, Z. Wang, J. Wang, H. Yan, Q. Han, W. Yao, et al., circRNA-TBC1D4, circRNA-NAALAD2 and circRNA-TGFBR3: Selected Key circRNAs in neuroblastoma and their associations with clinical features, Cancer Manag Res 13 (2021) 4271–4281.
[101] Y. Chen, L. Lin, X. Hu, Q. Li, M. Wu, Silencing of circular RNA circPDE5A suppresses neuroblastoma progression by targeting the miR-362-5p/NOL4L axis, Int. J. Neurosci. (2021) 1–11.
[102] K. Wu, L. Yang, J. Chen, H. Zhao, J. Wang, S. Xu, et al., miR-362-5p inhibits proliferation and migration of neuroblastoma cells by targeting phosphatidylinositol 3-kinase-C2β, FEBS Lett. 589 (2015) 1911–1919.
[103] J. Tang, F. Liu, D. Huang, C. Zhao, J. Liang, F. Wang, et al., circ0125803 facilitates tumor progression by sponging miR-197-5p and upregulating E2F1 in neuroblastoma, Pathol., Res. Pract. 233 (2022), 153857.
[104] Q. Jin, J. Li, F. Yang, L. Feng, X. Du, Circular RNA circKIF2A contributes to the progression of neuroblastoma through regulating PRPS1 expression by sponging miR-377-3p, Biochem. Genet. (2022).
[105] J. Tang, F. Liu, D. Huang, C. Zhao, J. Liang, F. Wang, et al., circ0125803 facilitates tumor progression by sponging miR-197–5p and upregulating E2F1 in neuroblastoma, Pathol. Res. Pract. 233 (2022), 153857.