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MicroRNA dysregulation interplay with childhood abdominal tumors

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Abstract
Abdominal tumors (AT) in children account for approximately 17% of all pediatric solid tumor cases, and frequently exhibit embryonal histological features that differentiate them from adult cancers. Current molecular approaches have greatly improved the understanding of the distinctive pathology of each tumor type and enabled the characterization of novel tumor biomarkers. As seen in abdominal adult tumors, microRNAs (miRNAs) have been increasingly implicated in either the initiation or progression of childhood cancer. Moreover, besides predicting patient prognosis, they represent valuable diagnostic tools that may also assist the surveillance of tumor behavior and treatment response, as well as the identification of the primary metastatic sites. Thus, the present study was undertaken to compile up-to-date information regarding the role of dysregulated miRNAs in the most common histological variants of AT, including neuroblastoma, nephroblastoma, hepatoblastoma, hepatocarcinoma, and adrenal tumors. Additionally, the clinical implications of dysregulated miRNAs as potential diagnostic tools or indicators of prognosis were evaluated.

Keywords miRNA · Neuroblastoma · Nephroblastoma · Hepatoblastoma · Hepatocarcinoma · Adrenal tumors

1 MicroRNA biogenesis and function

Fundamentally, all cellular programs are controlled by genes: growth, senescence, division, metabolism, stemness, mobility, apoptosis, and more. In turn, gene expression is also tightly regulated by different mechanisms, such as microRNAs (miRNAs). miRNAs are a class of small, non-protein coding RNA molecules (approximately 22 nucleotides long) that mediate post-transcriptional gene silencing [1]. These short RNA regulators are encoded by "miRNA genes," which are transcribed by RNA polymerase II as a primary miRNA (pri-miRNA) containing a 5′ CAP, a 3′ poly-A tail, and an internal hairpin-structured region. Pri-miRNA is then cleaved by the nuclear endoribonuclease Drosha into the precursor miRNA retaining the hairpin (pre-miRNA, ~ 70 nucleotides long), which is translocated by Exportin-5 to the cytoplasm, and then processed by another endoribonuclease (Dicer) into the miRNA duplex. Once loaded into the RNA-induced silencing complex (RISC), one strand of the duplex is destroyed while the other directs RISC to messenger RNAs (mRNAs) with partial (or total) complementary sequences [2]. RISC then interrupts the production of the protein by one of the different ways: inhibition of translation (which is reversible), decapping, deadenylation, or cleavage [3]. MiRNAs often, but not exclusively, hybridize with complementary sites within the 3′ untranslated region (UTR) of targeted mRNAs. One specific miRNA may target many different mRNAs, and thereby, one mRNA may also be controlled by many distinct miRNAs. The region comprising nucleotides 2 to 8 of the 5′ terminus of miRNAs is known as the "seed" sequence: a region of total complementarity to the targeted mRNA that is critical for miRNA pairing and function [3].

Sixty percent of all genes in the human genome display at least one conserved site for miRNA binding [4]. Consequently, all biological processes are regulated by this class of molecules [5–9]. Due to their roles in several key events, dysregulation of miRNAs has also been associated with diverse aspects of cancer biology [10]. Thus, in this review, we compile growing information on miRNAs' dysregulation along with a summary of opportunities for their use as specific biomarkers in most prominent pediatric abdominal tumors.

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2 Abdominal tumors in children

Abdominal tumors (AT) in the pediatric population, including renal tumors, sympathetic nervous system tumors, malignant liver tumors, and gonadal tumors, correspond to ~ 17% of all pediatric solid tumor cases [11]. Clinically, these masses vary in their clinical signs and symptoms, depending on the causative physiopathology: they can be largely asymptomatic and uncovered during routine clinical exam (as for nephroblastomas) or be observed in the context of a systemic disease in a severely ill patient. Many abdominal masses in children can develop *in utero* (i.e., congenital mesoblastic nephroma, teratomas, neuroblastoma, and mesenchymal hamartoma of the liver, among others). In this life period, other non-neoplastic or benign conditions need to be ruled out with differential diagnosis. These conditions encompass abdominal cystic lymphangiomas [12], benign liver lesions (infantile hepatic hemangioendothelioma, mesenchymal hamartoma of the liver, nodular regenerative hyperplasia, and focal nodular hyperplasia [13]), and congenital hydronephrosis [14]. Among the most common ATs in children are nephroblastoma (Wilms tumor), neuroblastoma, hepatoblastoma, germ-cell tumors, and rhabdomyosarcoma [11]. Contrary to what is observed for the adult population, ATs in children exhibit embryonal histologies, with direct implications on the neoplastic cell-of-origin, mechanisms related to tumorigenesis, and the therapeutic response of these lesions.

The evaluation of a child with an abdominal mass involves a number of diagnostic considerations on physical examination, including age and sex of the patient, the location of the mass, and the presence/absence of other related signs and symptoms [15]. Diagnostic imaging (through magnetic resonance imaging, computed tomography, and/or ultrasound techniques) and the determination of the organ or tissue of origin can provide sufficient information for a diagnosis. Most importantly, molecular approaches have greatly improved the understanding of the distinctive pathology of each tumor type and the characterization of novel biomarkers, thereby creating new opportunities for therapy refinement to maximize cure and reduce therapy-associated toxicities.

In this regard, miRNAs have emerged as valuable tools for early cancer detection and follow-up. These short non-coding RNAs have many clinical and therapeutic implications, mainly due to their stability and specificity which enables their use as diagnostic markers, for surveillance of tumor progression and for identification of the primary metastatic site. Differential expression of miRNAs can also be related to chemoresistance and control of therapeutic targets [16]. Of note, their evaluation can be performed through non-invasive methods, because miRNAs are detectable in biologic fluids such as saliva and plasma [17, 18].

Moreover, due to their multi-target nature, miRNAs act simultaneously on several signaling pathways, affecting processes such as metabolism control, cell differentiation, and apoptosis [19]. miRNAs that repress tumor suppressor genes and thereby favor tumor growth are called oncogenes or oncomiRs and are generally upregulated in tumors. Conversely, miRNAs that negatively regulate the expression of genes related to tumor growth are considered tumor suppressors and are downregulated in tumors. Their downregulation may result in mutations in genomic regions associated with cancer or in fragile sites of the genome [20], as a result of epigenetic modifications [21, 22], or through altered functioning of elements from their biogenesis machinery such as Dicer, Drosha, DGCR8, Argonaut, and Exportin-5 [23]. In this respect, the most striking evidence that malfunction of a pivotal enzyme involved in miRNA processing has direct implications in tumor development in children is portrayed by the DICER1 genetic syndrome, an autosomal dominant inherited condition that leads to abnormal endonuclease activity [24–26]. Described abdominal masses on DICER1-mutated children include cystic nephroma, Wilms tumor, and ovary cancer (particularly Sertoli-Leydig cell tumors) [26].

In the following sections, we present up-to-date information about the altered miRNAs and their interplay with most common abdominal cancers in children: neuroblastoma, nephroblastoma, hepatoblastoma, hepatocarcinoma, and adrenal tumors.

2.1 Neuroblastoma

Neuroblastoma (NB) is one of the most common solid tumors in children. It originates from precursor cells of the parasympathetic nervous system and accounts for 15% of cancer-related deaths during childhood. NBs have a heterogeneous clinical presentation and course, ranging from spontaneous regression to evolution into aggressive phenotypes and subsequent death. Chromosomal alterations are common in this pathology, including loss of 3p, 11q, and 14q and gain of 17q. Non-favorable forms of NB characteristically exhibit amplification of *MYCN* (MNA) and are associated with the loss of 1p and gain of 17p [27, 28].

MiRNA dysregulation plays an important role in the etiology of NB (Table 1). The first miRNA described as dysregulated in this tumor was miR-34a located at 1p36.23 [29–31]. *In vitro* reintroduction of miR-34a reduced cell proliferation and induced apoptosis with cell cycle arrest in cell lines carrying a 1p36 deletion [30, 31]. Target sequences for miR-34a at the 3′UTR of *MYCN* have since been repeatedly described [29, 31, 32]. *MYCN* in turn regulates miR-34a [33]. MiR-34a insertion in xenograft NB models reduced tumor growth and enhanced the survival of animals independently of *MYCN* amplification [34]. Other targets of miR-34a are often related to neuronal differentiation, cell signaling, molecular transport,

Table 1 Dysregulated miRNAs involved in NB

miRNA	Expression in tumor	Function	References
let-7; miR-19a/b, miR-101, miR-202, miR-449	Down	Regulation of MYCN	[32, 37]
miR-7a	Down	Targets TGF-β	[38]
miR-15a	Up	Targets RECK	[39]
miR-9 and miR-584-5p	Down	Targets MMP-14	[40, 41]
miR-17~92	Up	Regulated by MYCN/targets p21, BIM, RAS, TGF-β, DKK3, and ESR1/associated to poor prognosis	[42–50]
miR-17, miR-20b, miR-93, miR-106b	Up	Regulated by MYCN/targets CHD5	[51]
miR-21	Up	Correlated with lower rates of overall survival/chemoresistance	[52, 53]
miR-23a	Up	Targets CHD1 and E-cadherin	[54, 55]
miR-27b	Down	Targets EGFR; CREB; KRAS and GSK3β	[56]
miR-29a/b/c	Down	Regulation of MYCN/targets CDK6, DNMT3A, DNMT3B, and TGF-β	[32, 33, 57, 58]
miR-34a	Down	Regulation of MYCN and regulated by MYCN/targets BCL-2 and E2F3	[29–32]
miR-34b-3p	Down	Hypermethylated/regulation of MYCN/targets CCNE2 and E2F3	[57, 59]
miR-34b-5p and miR-34c-5p	Down	Hypermethylated/regulation of MYCN	[59
miR-124	Up	Targets AHR	[60]
miR-124-2-3p	Down	Hypermethylated/regulation of MYCN/RA-induced differentiation	[59, 61]
miR-125b	Down	Targets ADAMTS-1, CREB, ELK1, MMP2, p38 and STAT3/chemoresistance	[56, 62]
miR-137	Down	Chemoresistance	[63, 64]
miR-138	Down	Correlated with increase of telomerase activity	[65]
miR-145	Down	Associated with MYCN amplification in cell under hypoxia/targets HIF-2α	[66, 67]
miR-149	Down	Targets RAP1, AKT1, and E2F1	[68, 69]
miR-152	Up	Targets DNMT1	[70]
miR-181	Up	Targets CDON	[44, 71]
miR-181c	Down	Associated to poor prognosis/targets Smad7	[57, 72]
miR-183	Down	Regulated by MYCN and HDAC2/targets MCM	[730, 74]
miR-184	Down	Regulated by MYCN/targets AKT2	[75]
miR-187, miR-210	Up	Associated with MYCN amplification in cell under hypoxia	[66]
miR-190	Down	Indirectly regulates TrkB pathway	[76]
miR-192	Up	Associated with relapse/targets Dicer	[77]
miR-193b-3p	Down	Regulated of MYCN/targets Cyclin D1 and MCL-1	[78]
miR-195 and miR-196a	Down	Hypermethylated	[79]
miR-200a	Down	Targets AP-2γ	[80]
miR-204	Down	Regulated by MYCN/targets BCL-2 and NTRK2	[81, 82]
miR-221	Up	Indirectly regulates MYCN by targeting the NLK pathway	[37]
miR-329	Down	Targets KDM1A	[83]
miR-335	Down	Targets MNL3, FMN2 and DAAM2	[84]
miR-338-3p	Down	Targets PREX2a	[85]
miR-340	Down	Hypermethylated/targets SOX2	[79]
miR-362-5p	Down	Targets P13k-C2β	[866]
miR-375	Down	Regulation of MYCN/radioresistance	[32, 33, 87]
miR-376a	Down	Targets NFAT	[88]
miR-380	Up	Targets TP53 and HRAS	[89]
miR-421	Up	Regulated by MYNC/targets menin and ATM	[90, 91]
miR-449a	Down	Targets MFAP4, PKP4, TSEN15, CDK6, and LEF1	[92]
miR-451	Down	Targets MIF	[93]
miR-487b and miR-516a-5p	Down/up	Used for the risk stratification	[94]
miR-497	Down	Hypermethylated/targets WEE1/associated to poor prognosis	[79, 95, 96]
miR-506	Down	Targets ROCK1 and TGF-β	[97]

Table 1 (continued)

miRNA	Expression in tumor	Function	References
miR-520f	Down	Chemoresistance/targets NAIP	[98]
miR-542	Down	Associated with favorable prognosis /targets survivin	[44, 50, 57, 99, 100]
miR-558	Up	Regulated by MYCN/targets HPSE	[89, 101]
miR-572	Up	Associated to poor prognosis	[102]
miR-591	Down	Regulated by MYCN	[101]
miR-628	Down	Regulation of MYCN and associated with favorable prognosis /targets survivin	[44, 50, 103]
miR-659-3p	Down	Targets CNOT1	[104]
miR-885-5p	Down	Targets CDK2 and MCM5	[105]
miR-939	Down	Targets NF-KB	[88]
miR-1224-3p and miR-1260	Up	Induced metastasis	[56]
miR-1247	Down	Targets ZNF346	[106]
miR-1303	Up	Targets GSK3β and SFRP1	[67]
miR-34a, miR-9, miR-125a, miR-125b, miR-128, miR-124, miR-1, miR-10a, miR-10b, miR-103, miR-152, miR-340, miR-432, miR-338, miR-200b, miR-506-3p, miR-124-3p, and miR-664a-5p	Up	RA-induced differentiation	[30, 79, 107–110]
miRNAs miR-7, miR-20a, miR-301, miR-106a, miR-19a, miR-29b, miR-134, and miR-15b	Down	RA-mediated differentiation	[61, 107–109, 111, 112]

proliferation, cell cycle, apoptosis, and autophagy, such as YY1, the anti-apoptotic gene *BCL2*, and ribosomal proteins [32, 33, 35, 36].

Upregulation of miR-221 has also been described in several NB cell lines and NB tissues that overexpress MYCN. High expression of miR-221 indirectly increases *MYCN* levels by reducing lymphoid enhancer-binding factor 1 (LEF1) phosphorylation *via* targeting of Nemo-like kinase (NLK) contributing thereby to cell proliferation and cell cycle progression [37]. Conversely, *MYCN* expression can be repressed by other *MYCN*-3′UTR miRNAs such as miR-34c, miR-449, miR-19a/b, miR-29a/b/c, miR-101, let-7, miR-202, and miR-375 [32].

On the other hand, MYCN controls the expression of various miRNAs by binding to E-box sequences in the promoter region of their host genes [113], and therefore modulates signaling pathways involved in tumorigenesis [114]. Hence, MYCN regulates tumor suppressors such as miR-204 and miR-591, and oncogenic such as miR-558 [82, 101].

Similarly, MYCN regulates the miR-17~92 cluster activity, found to be highly expressed in MNA cell lines and responsible for the modulation of cellular proliferation, adhesion, and estrogen response through the regulation of RAS and TGF-β signaling pathways [42, 43]. The expression of this cluster comprising miR-17, miR-18, miR-19a, miR-20a, miR-19b, and miR-92-1 is associated with poor prognosis in NB [44, 45, 115]. High MYCN levels may contribute through miR-17~92 to make cells unresponsive to hormones and other ligands by repressing several nuclear hormone receptors (NHRs) essential for final neuronal differentiation [46]. Moreover, MYCN by the upregulation of miR-18a and miR-19a represses the expression of the estrogen receptor alpha (ERS1), a ligand-inducible transcription factor involved in neuronal differentiation [49].

Furthermore, MYCN indirectly controls the phosphatidylinositol 3-kinase (Pl3K) pathway, one of the most potent pro-survival pathways in cancer, by upregulating miR-184. This miRNA, in turn, regulates the expression of AKT2 (serine/threonine kinase), a major downstream effector of PI3K [75]. Moreover, MYCN cooperates with histone deacetylases (HDACs), to repress the expression of the tumor suppressor miR-183 [74].

Among tumor suppressor miRNAs that are underexpressed or absent in MNA tumors is miR-497. *In silico* analysis suggested the cell cycle regulator tyrosine kinase WEE1 as a possible target of miR-497, which is capable of reducing NB viability and increasing apoptosis *in vitro* [79, 95]. Its restoration promotes downregulation of genes related to the DNA damage response, cell cycle, cell growth, survival, and angiogenesis [96]. The same effect was observed in NB xenografts treated with miR-542-3p-loaded nanoparticles that resulted in repressed survivin expression, decreased proliferation, and high apoptosis [99].

2.1.1 Dysregulated miRNAs irrespective of MYCN status

Besides altered expression of miRNA in MNA, other profiles have been described regardless of *MYCN* copies. For instance, negative *MYCN* cells overexpress miR-210 and miR-145 under hypoxia [66]. Additionally, miR-1303 has been found to be upregulated in NB and described as driver of tumorigenesis through the inhibition of GSK3β and SFRP1 [116]. MiR-380 also acts as an oncogene by repressing *TP53* [89], while miR-558 can promote tumorigenesis and aggressiveness through the transcriptional activation of heparanase (HPSE), an endogenous endoglycosidase [117].

Conversely, other miRNAs have been described as tumor suppressors. MiR-323a-5p and miR-342-5p [118], miR-200a, which directly inhibits the expression of AP-2γ [80], and miR-362-5p which targets P13K-C2β [86] have all been identified. MiR-193b is also expressed at low levels in NB and its forced expression induces a cell cycle arrest and apoptosis by reducing the expression of MYCN, Cyclin D1, and MCL-1 [78]. Likewise, re-introduction of miR-885-5p inhibits cell proliferation, triggers cell cycle arrest, and promotes senescence and/or apoptosis through the downregulation multiple p53 targets and a number of factors involved in p53 pathway activity including cyclin-dependent kinase (CDK2) and the MCM-5 [105]. In addition, direct transfection with miR-138 mimics decreases viability and colony formation [65] while expression of miR-939 and miR-376a induces NB cell death [88]. More recently, the expression levels of miRNA-186-5p in tumor tissues were described as lower than those in adjacent tissues, and inversely associated with Eg5 (Kinesin-5), a molecular motor protein that is essential in mitosis [119]. Similar results were obtained for miR-2110, which regulates Tsukushi (TSK), a Wnt signaling inhibitor [120], and miR-144-3p whose loss stimulates cell proliferation, cell cycle progression, and cell migration through the homeobox protein A7 (HOXA7) [121]. Das et al. recently identified 67 epigenetically regulated miRNAs in tumor samples that also exhibit tumor suppressor functions [79]. Among those, the ectopic overexpression of miR-195, miR-196a, and miR-497 had a negative impact on the viability of several cell lines, providing further support to the concept that inactivation of these miRNAs is important for NB pathogenesis.

2.1.2 MiRNAs and NB prognosis

The differential expression of miRNAs in NB is also related to patient prognosis, complementing other predicting characteristics, such as *MYCN* amplification, low TRKA expression, and chromosomal aberrations [44, 122, 123]. While NBs associated with favorable prognoses mainly express miR-542-5p and miR-628 [50], tumors with poor prognosis express the mir-17~92 cluster, the miR-181 family, and miR-572 [44, 102]. Imprinting-controlled miRNAs such as miR-487b and miR-561-5p were also important for risk stratification [94]. Furthermore, higher miR-21 expression is correlated with lower rates of overall survival [52].

Moreover, mir-380-5p is highly expressed in MNA and has been associated with poor outcome. Its inhibition results in the induction of p53 expression and extensive apoptosis [89]. Similarly, miR-542-5p and miR-628 are absent in MNA cells and are associated with a favorable prognosis, since they were demonstrated to reduce tumor growth and induce apoptosis, downregulating survivin expression [44, 99, 100].

Alternatively, miR-335, miR-128, miR-542-5p, miR-338-3p, and miR-145, for instance, can suppress metastasis [67, 84, 85, 100], while miR-337-3p, miR-584-5p, and miR-9 inhibit this process by the direct repression of matrix metalloproteinase 14 (MMP14) [40, 41, 124]. Metastatic tumors also show downregulation of miR-7a, miR-29b, miR181c, miR-329, miR-516a-3p, miR-324-3p, miR-20a, miR-27b, miR-125b, and miR-93 [38, 56, 72, 83, 125]. Recently, it was demonstrated that miR-506 functions as a tumor suppressor in NB and acts directly downregulating Rho-associated coiled-coil containing protein kinase 1 (ROCK1) and the transforming growth factor (TGF)–β non-canonical pathways. Therefore, the lower expression of this miRNA contributes to invasion and migration of NB [97]. Furthermore, lower levels of miR-451 are linked to lymph node metastasis, tumor-node-metastasis stage, and distant metastases. This data was confirmed *in vitro*, where miR-451 overexpression resulted in diminished cell growth, invasion, and migration by directly targeting the 3′UTR of the macrophage migration inhibitory factor (MIF), a multifunctional cytokine with pro-tumorigenic effects [93].

Conversely, miR-380-5p, miR-23a, miR-558, miR-15a, miR-421, miR-1260, and miR-1224-3p are considered metastasis-inducing miRNAs [39, 56, 58, 89, 117]. The last one promotes proliferation and migration by inhibiting the tumor suppressor menin [90] and repressing ATM (ataxia-telangiectasia mutated), both targets related to cell cycle control [91]. Moreover, Fabri and colleagues demonstrated that the transfection with pre-miR-93-5p is able to reduce and upregulate both VEGF and IL-8 gene expression, leading to an increased angiogenesis and invasiveness in NB cells [126].

2.1.3 miRNAs involved in NB drug response

Chemoresistant NB cells present dysregulation of miR-125b, miR-501-5p, miR-204, miR-520b, miR-188-5p [62, 98], miR-21, and miR-143 [53]. Conversely, miR-204 enhances cisplatin and etoposide sensibility by directly targeting BCL2 [81]. Likewise, miR-125b dysregulation is associated to doxorubicin and etoposide resistance in NB through the inhibition of the truncated form of the surface tyrosine kinase receptor fl-trk-C, thereby controlling proliferation, survival, and differentiation [62]. MiR-137 also modulates the sensibility to

doxorubicin by regulating the activity of constitutive androstane receptor (CAR) [63] and through the inhibition of multidrug-resistant 1 (MDR1) gene [64]. MiR-93 and miR-7-1 overexpression is also associated with the treatment efficacy of green tea–derived polyphenols [127, 128].

MYCN amplification also alters how NB cells respond to retinoic acid (RA), suggesting that MYCN directly or indirectly regulates miRNAs involved in cell differentiation in NB. Two of the miRNAs downregulated during RA-induced differentiation, miR-181b and miR-92, were downregulated in MNA tumors. MiR-184 is also overexpressed when cells are exposed to RA, and it reduces cell viability and induces apoptosis in NB cell lines [123].

Likewise, miR-34a, miR-9, miR-125a, miR-125b, miR-128, miR-124, miR-1, miR-10a, miR-10b, miR-103, miR-152, miR-340, miR-432, miR-338, and miR-200b are described as upregulated during RA-induced differentiation. These miRNAs were validated as tumor suppressors, having as target genes related to proliferation, tumor survival, migration, and differentiation [30, 79, 107, 108]. Overexpression of miR-124 increased the expression levels of β-Tubulin III, MAP2, SYN, NF-M, and Nestin. Also, Foley et al. experimentally validated that the nuclear receptor corepressor 2 (NCOR2), which suppresses neurite outgrowth, is a target of miR-10a and miR-10b, which are highly overexpressed in NB cell lines. Inhibition of these mRNAs alone resulted in neural cell differentiation [111].

Similarly, Zhao et al. identified 14 differentiation-inducing miRNAs; among which, miR-506-3p and miR-124-3p had the most potent effect in BE(2)-C cells by downregulating expression of their targets CDK4 and STAT3 [110]. Conversely, miRNAs miR-7, miR-20a, miR-301, miR-106a, miR-19a, miR-29b, miR-134, and miR-15b were described as downregulated during RA-mediated differentiation [107, 112].

2.2 Nephroblastoma (Wilms tumor)

Wilms tumor (WT) is a renal embryonic tumor, representing the most common kidney tumor and the second most common abdominal solid tumor in children [129]. Patient prognosis can be defined based on WT histological classification. Tumors with favorable histology present blastemal, stromal, and epithelial cells. Monophasic blastemal tumors are highly invasive. Tumors with anaplasia comprise the unfavorable group [130]. Nephrogenic rests (NRs) are precursor lesions for WT and consist of nephroblastic tissue with small aggregates of blastemal, tubular, or stromal cells. Nephroblastomatosis is defined as the presence of multiple NRs [131].

Gene expression analysis has allowed WT classification into two molecular types. WT type I presents *WT1* mutations, associated with *CTNNB1* mutations. *WT1* encodes a zinc-finger (ZF) transcription factor that regulates the mesenchymal-epithelial transition during kidney development. Other alterations associated with this molecular type are the loss of heterozygosity in 11p13 to 11pter [132].

WT belonging to type II presents 11p15 alterations related to loss of imprinting or uniparental disomy of chromosome 11, leading to dysregulated *IGF2* expression [132]. Mutations in *WTX*, a gene located on the X chromosome, can occur in both, type I and II. Its protein is required for the assemblage of the β-catenin destruction complex, and modifications in this protein lead to altered activation of the Wnt pathway [133].

2.2.1 OncomiRs involved in WT

Kort and colleagues [134] were the first to describe the activation of oncomiR-1 in WT. This cluster (also known as miR-17~92 cluster) is overexpressed in this tumor [135] and is highly expressed in metastatic tumors in comparison to early tumor stages [134]. Members of the oncomir-1 family (miR-92, miR-17-5-p, and miR-20a) are also upregulated in WT compared with other renal cancer types and normal kidney tissue [134].

Likewise, miR-370 acts as an oncogene through the inhibition of the *WTX* gene, thus, stimulating proliferation and tumorigenicity. Activation of this miRNA is achieved by STAT3, an oncogenic transcription factor [136]. Another miRNA that acts by promoting proliferation and inhibition of apoptosis is miR-483-3p/5p, which is overexpressed in 100% of WT, and its location within intron 2 of the *IGF2* locus suggests that they might cooperate for tumor promotion [137].

Another miRNA associated with WT is miR-590 which is often upregulated and negatively modulates *WT1* by binding to its 3′UTR [138]. Also, independent groups have shown the upregulation of miR-19 and miR-21, both affecting WT proliferation and invasion through the inactivation of the PTEN/PI3k/Akt signaling pathway, and associated with the aggressive progression and poor prognosis in this tumor [139–141]. More recently, the upregulation of miR-572 was described in WT tissues and identified as a negative regulator of CDH1 expression, hence promoting metastasis and EMT [142]. Also, Gong et al. [143] found 154 differentially expressed miRNAs in WT samples. From those, 18 (mir-29b-2, mir-99a, mir-135a-1, mir-135a-2, mir-149, mir-181b-2, mir-200a, mir-483, mir-490, mir-509-2, mir-636, mir-660, mir-934, mir-940, mir-1248, mir-1269a, mir-3651, and mir-5002) were associated with overall survival and 5 of them were able to classify samples into high- and low-risk subgroups (mir-149, mir-7112, mir-940, mir-1248, and mir-490). Even so, the top 10 upregulated miRNAs were mir-383, mir-1269a, mir-1269b, mir-767, mir-548f-1, mir-2115, mir-301b, mir-105-1, mir-483, and mir-105-2. Alternatively, mir-934, mir-203a, mir-29c, mir-506, mir-29a, mir-30a, mir-514a-1, mir-514a-2, mir-514a-3, and mir-203b were the most underrepresented miRNAs.

2.2.2 Suppressor miRNAs in WT

Reduced expression of numerous suppressor miRNAs has also been described in WT. MiR-613 and miR-140-5p, for instance, are downregulated; while the first exerts a suppressive effect *via* targeting *FRS2* (fibroblast growth factor 2) [144], the second targets TGFBRI and IGF1R [145]. WT samples also show decreased miR-185 levels, a miRNA responsible to inhibit proliferation, anchorage-dependent growth, cell invasion, and tumor growth, through the suppression of *MYC* and *cyclin A1* [146]. Let-7 downregulation is also common and associated with the inhibition of the RNA binding protein, LIN28 (which consists of LIN28A and LIN28B) [147, 148]. These proteins are regularly elevated and associated with WT pathogenesis [148–150].

Other miRNAs that have been found downregulated in WT, such as miR-204 and miR-23a, correlate with the overexpression of target genes involved in kidney development [151, 152], while others associated with apoptosis avoidance, i.e., miR-1180, that regulates p73 [153]. In addition, differential miRNA expression can be observed in WT with distinct histology. Blastemal and mixed histological types show low expression of miR-141 and miR-200c. Moreover, NF shows reduced expression of miR-192, miR-194, miR-215, and miR-200c when compared with renal parenchyma. MiR-192, miR-215, miR-194, miR-141, and miR-200c target activating receptor type 2B (ACVR2B), a member of the TGF-β pathway that is differentially expressed in all types of nephroblastoma [154]. Low expression of mir-483-5p was also significantly correlated with unfavorable histology subtypes, lymphatic metastasis, and late clinical stage [155].

2.2.3 MiRNAs and WT therapeutic response

MiRNAs also participate in the molecular response of WT to chemotherapy [156]. The first study relating chemoresistance and blood miRNA expression profiles did not find differences between treated and untreated patients, although miR-766, miR-1246, miR-197, and miR-224 were upregulated while miR-20a, miR-20b, and miR-144* were found downregulated in WT samples in comparison with controls. However, this expression profile constitutes a miRNA signature independent of chemotherapeutic treatment [157].

Alternatively, Watson and colleagues [158] proposed a miRNA expression profile of resistant blastemal cells in high-risk WT that could be a predictor for therapeutic response in pre-treatment stages. In this model, miR-551b, miR-106b, miR-24, miR-542-3p, miR-331-3p, miR-223, miR-518b, miR-25, miR-30b, and miR-523 were found expressed in high-risk WT, conferring proliferative advantage and survival.

Furthermore, alterations in miRNA expression patterns could be due to dysregulation of genes involved in their biogenesis, such as *DROSHA* and *DGCR8* and in a minor frequency *DICER1*, *XPO5*, and *TARBP5* [154, 159, 160], whose mutations, despite rare, are correlated with a worse outcome [160] and drive chemotherapy resistance and recurrence [161].

2.3 Adrenal tumors

Adrenal tumors (AdT) can be classified according to their location into two groups: tumors of the adrenal cortex (TCA) and tumors of the adrenal medulla and extra-adrenal paraganglia (TAMP). TCAs comprise cortical carcinoma, cortical adenoma, sex cord-stromal tumors, adenomatoid tumor, mesenchymal and stromal tumors, hematological tumors, and secondary tumors. TAMPs include paraganglioma (head and neck paraganglioma and sympathetic paraganglioma), neuroblastic tumors (neuroblastoma, nodular ganglioneuroblastoma, intermixed ganglioneuroblastoma, and ganglioneuroma), composite pheochromocytoma, and composite paraganglioma [162]. AdT treatment is based on various factors such as the nature of adrenal mass, age at presentation, tumor size, and the functional status of the tumor [163].

MiRNA profiles have been proposed to differentiate benign from malignant ATs and even to distinguish subtypes [164]. Although the pathogenesis of sporadic ATs is poorly elucidated, it has been shown that miRNA expression can be used to improve the identification of malignant AdT with equal efficiency to the Weiss system. Indeed, miR-34a and miR-497 downregulation can distinguish between carcinomas and adenomas [165]. Moreover, specific microRNAs can be important disease formation and/or progression as is the case of miR-200b in massive macronodular adrenocortical tumor [166].

A recent work revealed 147 differentially expressed miRNAs when comparing adrenocortical carcinoma with adrenocortical adenomas. Specifically, miR-483, miR-153, miR-135, and miR-514 showed greater than tenfold expression in carcinoma samples [167]. Moreover, pathway analysis showed that p53 signaling is profoundly affected in adrenocortical carcinoma [167]. MiR-483-5p and miR-139-5p upregulation was also associated with in adrenocortical carcinoma aggressiveness, mainly through the modulation of MYCN-downstream-regulated gene family members 2 and 4 (NDRG2 and NDRG4) [168].

Other miRNAs like miR-24, miR-10b, miR-320a-3p, and miR-193a-3p have shown to regulate genes involved in cortisol biosynthesis or the interconversion between aldosterone and cortisol biosynthetic pathways [142, 169–171]. Moreover, miR-431 showed to increase the effects of doxorubicin and mitotane *in vitro* [172]. Nevertheless, none of those miRNAs has been analyzed in pediatric AdT.

In Brazil, the incidence of ACT in children is remarkably high (15 times greater than the world occurrence), due to a high frequency of a germline mutation in *TP53*. However, in children, the presence of the p.R337H germline mutation is

not a predictor of poor outcome [173]. Nonetheless, discriminating benign and malignant behavior is more challenging in the pediatric setting due to other clinical, pathological, and molecular features [174].

A pioneering study of miRNA profiling in childhood ACT performed by Doghman et al. revealed 26 mostly downregulated miRNAs when compared with normal counterparts [175]. A relation of miR-99a and miR-100 with IGF-1R, mTOR, and raptor expression was also observed pointing to the importance of those miRNAs in the regulation of these growth-associated pathways [175]. Nevertheless, despite IGF1R overexpression being common in pediatric ACT [176], the study of miR-100, miR-145, miR-375, and miR-126 and their correlation with *IGF1R* expression was not corroborated [177].

2.4 Hepatoblastoma

Hepatoblastoma (HB) is a rare malignant liver tumor of embryonic origin that affects the precursor cells of hepatocytes and often recapitulates the stages of liver development, displaying a combination of histological patterns [178]. HB presents a peak of incidence in the first 2 years of age and occurs more frequently in males with a frequency of 150 cases/year in the USA [179, 180]. The rates of diagnosis of this neoplasia have increased, calling the attention of oncologists for a better understanding of the biogenesis of the tumor [181, 182]. HB development is tightly linked to abnormal Wnt/β-catenin signaling, and among other embryonal tumors, presents with the highest rate (50–90%) of β-catenin mutations [183]. Amplification of the *MYC* oncogene also plays a role in the more aggressive phenotypes of HB [184, 185].

The international consensus classification of the histologic subtypes of hepatoblastoma includes five subtypes: fetal, embryonal, macrotrabecular, small cell undifferentiated, and cholangioblastic [186]. Besides histology, other criteria for stratification include age, tumor size, presence of metastasis at diagnosis, and level of expression of alpha-fetoprotein (AFP), considered a prognostic biomarker, and microvascular invasion of the tumor [187]. Most cases of HB are sporadic; however, one of the main high-risk factors associated with the presence of this tumor is the child's birth weight, with weight < 1.5 kg being more consistent with the worse prognosis [188–190]. Other risk factors are also correlated to HB including smoking and alcoholism during pregnancy, pre-eclampsia, infertility treatments, and some predisposing syndromes [191–195].

Even though the direction of multimodal treatment for HB depends on each presented clinical case, it generally consists of neoadjuvant chemotherapy, total or partial surgical resection of the liver, with or without adjuvant chemotherapy, with cisplatin and vincristine being the most commonly used chemotherapeutic drugs. In some cases, transplantation of the affected organ may be indicated. Hence, over the last 30 years, even though patients with non-resectable tumors or metastases still have a bad prognosis, better histopathologic classification, refinements in risk stratification, advances in chemotherapy, and a superior surgical resection have increased 5-year overall survival rates up to 80% [185, 196–199]. Nonetheless, further understanding of the histopathologic subtypes and molecular mechanisms responsible for the development and progression of HB are still necessary.

Magrelli et al. [200] were the first to point out that microRNA profiles could distinguish HB from non-tumor tissues and could characterize usable markers for the classification of pediatric liver tumors. These authors analyzed the expression pattern of 55 miRNAs in a small number of samples (n = 9; collected at the time of surgery or biopsy of primary-treated tumors after chemotherapy) through microarrays and qRT-PCR. From those, miR-125a-5p, miR-145, miR-150, miR-195, miR-199a-3p, miR-199a-5p, and miR-214 were upregulated. In addition, miR-106 and miR-148 were found to be downregulated in tumor samples. Moreover, when these microRNA contents were compared with hepatocellular carcinoma, upregulated miR-214, miR-199a-3p, miR-150, and miR-125a were able to distinguish both entities, suggesting them as strong biomarkers.

Another pioneer study performed in a cohort of 65 patients identified the overexpression of miR-371-3 with concomitant downregulation of miR-100, miR-125b-1, and let-7a-2; all of which were correlated with MYC amplification and hence contributing to more aggressive tumor phenotypes [201]. Other miRNAs such as miR-17-5p, miR-18a, and miR-221 are also influenced by MYC during the biogenesis of HB [202]. Comparatively, miR-492, which is transcribed from the coding sequence of the keratin 19 (KRT19) gene (another HB poor prognosis biomarker), was also characterized as a strong biomarker of worse prognosis during tumor progression of HB [203]. Of note, these co-expressed genes were particularly found in metastatic HB tumor samples.

Also, *in vitro* overexpression of miR-492 identified a broad range of differentially expressed transcripts, including several predicted targets such as TCF21 (transcription factor 21), CDKN2A (cyclin-dependent kinase inhibitor 2A), BID (BH3 interacting domain death agonist), and some liver-related enzymes such as ST6GAL1 (ST6 beta-galactoside alpha-2,6-sialyltransferase 1), BAAT (bile acid coenzyme A: amino acid *N*-acyltransferase), and GDA (guanine deaminase) [203]. More recently, CD44 was experimentally validated as direct and functional target of this miRNA and showed that miR-492 overexpression *in vitro* significantly enhances cell proliferation, anchorage-independent growth, migration, and invasion [204].

Moreover, a functional screening using 1712 miRNA mimics to identify possible miRNAs that could modulate

CTNNB1 expression post-transcriptionally showed that let-7i-3p, miR-449b-3p, miR-624-5p, and miR-885-5p were able to inhibit Wnt signaling activity attenuating cell proliferation and tumor growth *in vivo*. In parallel, miR-624-5p induced cell senescence and directly targeted the beta-catenin 3′ untranslated region [205].

When considering miRNA profiles among the different HB histological subtypes, overexpression of miR-18a and miR-19b [206] and downregulation of miR-122 were described in embryonal HB samples [207]. Fetal HB samples, in contrast, showed downregulation of miR-17-5-p, miR-195, miR-210, and miR-214 and upregulation of miR-221 when compared with non-tumor tissue. However, regardless of the histological subtype, miR-21, miR-222, and miR-224 levels were found useful to predict overall survival of HB patients [207].

Low expression of the members of the miR-34 family—miR-34a, miR-34b, and miR-34c—was described in HB and associated with unfavorable prognosis [208]. Six other miRNAs (miR-106b, miR-130b, miR-19a, miR-19b, miR-20a, and miR-301a) were strongly associated through bioinformatic tools with networks of interactions with lncRNAs and mRNAs; all of which may contribute to the malignant phenotype of HB [209], though this data still needs to be validated.

2.5 Hepatocarcinoma

Liver tumors are relatively rare in children and comprise 1–2% of all pediatric tumors. In this context, hepatocarcinoma (HCC) represents the second liver tumor in childhood, with an annual incidence of 0.3 to 0.45 cases per million, being more common in teenagers and more prevalent in males (3:1). The etiology of pediatric HCC has not been clarified yet; however, it is related to hepatitis B virus in areas with high incidence of infection. Nearly 30% of the pediatric cases are associated with cirrhosis and preexisting liver abnormalities [210]. The treatment of pediatric patients follows the same protocols as HB and includes cisplatin, doxorubicin, carboplatin, 5-fluorouracil, and vincristine. The 3-year event-free and overall survival for children, that presents complete resection of tumor following the standard treatment, is 72–82%. However, in patients with inoperable tumors or metastatic disease, survival decreases to 12–20% [211].

The constant search for new biomarkers and target therapies in HCC has culminated in the description of miRNA profiles associated with several cellular processes such as cell cycle, apoptosis, angiogenesis, invasion, and metastasis [212]; however, the literature is not attentive on pediatric tumors. Nonetheless, many functional validation assays have been performed in HepG2 and Hep3B cell lines which are derived from 15- and 8-year-old patients, respectively [213]. These cell lines will be the focus of this topic.

MiR-122 was one of the first miRNAs to be reported as downregulated in HCC. Its transfection in Hep3B cells caused a decrease in CCNG1 levels (cyclin G1 gene) [214]. Likewise, its modulation reduced cell viability and activated apoptosis in HepG2 and Hep2B cell lines through the regulation of *BCL-W*, *PKM2*, the *FOX* gene family, and members of Wnt/β-catenin signaling pathway [215–219].

More importantly, expression of miR-122 was related to the treatment response. Cisplatin exposure, for instance, enhances miR-122 expression in HepG2 cells [220], which in turn regulates the expression of multidrug resistance–related genes: *ABCB1*, *ABCC1*, *ABCG2*, and *ABCF2* [221, 222]. Moreover, miR-122 expression increases the levels of type I interferon (IFN), which acts as a tumor suppressor and could be important for HCC therapy [223].

On the other hand, miR-21 promotes proliferation and metastatic phenotype *in vitro* [224, 225] through the regulation of several targets including *HEPN1*, interleukin-12, *SOCS6*, and mitogen-activated protein kinase 3 [226–228]. MiR-21 also promotes migration and invasion by the miR-21-PDCD4-AP-1 feedback loop, downregulating key molecules as phosphor-c-jun and matrix metalloproteinases [229]. Furthermore, its expression is associated with IFN-α/5-FU treatment resistance [220, 230]. Besides these, a vast number of other miRNAs also act as tumor suppressors or stimulate growth and more aggressive tumor characteristics in HCC cell lines (Table 2).

3 Circulating miRNAs as biomarkers for pediatric abdominal tumors

As stated above, current challenges in the clinical management of tumors include the identification of easily detectable biomarkers with non-invasive techniques. In this scenario, the so-called liquid biopsies ultimately allow earlier cancer detection and the monitoring of tumor progression and/or treatment [352–354]. Recently, several studies have shown that despite their intracellular function, miRNAs are usually released outside the cells and get into circulation [355]. Valadi and coworkers were the first to highlight the presence of miRNAs in biological fluids in 2007 showing that exosomes of mouse and human mast cells carried both mRNAs and microRNAs [356]. Since then, a constant increasing number of research groups have reported on the use of circulating miRNAs as biomarkers for diagnosis/prognosis of different pathologies, including cancer [17, 357]. Of note, the different circulating miRNAs (c-miRNAs) involved in tumorigenesis can be detected in diverse sources, including blood, urine, serum, plasma, cerebrospinal fluid, or saliva [17, 354, 358–360]. Currently, there are different hypotheses that have been proposed to explain the presence of these c-miRNAs in biological fluids [361, 362] (Figure 1).

C-miRNAs have many qualities that render them suitable tumor biomarkers for translation into clinical practice,

Table 2 Many functional validation assays have been performed in hepatocarcinoma-derived cell lines (HepG2 and Hep3B) to characterize the role of miRNAs that act as tumor suppressors or stimulate growth and more aggressive tumors

MiRNA	Cell line	Manipulation	Action on phenotype	Reference
Let-7c; miR-15a-5p; miR-20a; miR-27a; miR-29c; miR-30a-5p; miR-98-5p; miR-122; miR-126; miR-141; miR-142-5p; miR-148b; miR-194; miR-195; miR-196b; miR-199a-5p; miR-212; miR-216b; miR-223; miR-548c-5p; miR-570; miR-590-5p; miR-608; miR-663; miR-1247; miR-1297	HepG2	Induced	Inhibited cell growth, induced apoptosis and cell cycle arrest	[231–243] [215–219] [244–264]
miR-1	HepG2 and Hep3B	Induced	Attenuated the proliferation	[265, 266]
miR-10; miR-135a; miR-155	HepG2	Induced	Increased cell migration and invasion	[267–270]
miR-17	HepG2	Induced	Modulated proliferation, migration, survival, morphogenesis, and colony formation and inhibited endothelial tube formation	[271]
miR-18a; miR-130b; miR-221; miR-494	HepG2	Inhibition	Suppressed the migration and invasion	[272–274]
miR-21	HepG2	Degradation	Decreased the viability of cells, induction of apoptosis and necrosis	[224–226, 228–230, 275, 276]
miR-26a; miR-506	HepG2	Induced	Inhibited angiogenesis	[277–279] [280, 281]
miR-26b; miR-214; miR-361-5p; miR-429; miR-433	HepG2 and Hep3B	Induced	Inhibited migration and invasion	[282–289]
miR-30e; miR-31-5p; miR-33a-3p; miR-33b; miR-34c-3p; miR-92a; miR-101; miR-136; miR-145; miR-146a; miR-206; miR-211; miR-320a; miR-335; miR-365; miR-486-5p; miR-876-5p; miR-1301	HepG2	Induced	Inhibited proliferation, migration, and invasion	[290–309]
miR-33a	HepG2	Inhibition	Decreased proliferation and induced apoptosis	[310]
miR-34a	HepG2	Induced	Inhibited migration and invasion; diminished ATP levels	[311, [312]
	HepG2	Induced		[313] [273] [314] [315]

Table 2 (continued)

MiRNA	Cell line	Manipulation	Action on phenotype	Reference
miR-95; miR-222; miR-543; miR-709			Promoted cell proliferation, cell cycle progression and cell migration	
miR-96; miR-184	HepG2	Inhibition	Reduced proliferations and clonogenicity	[316]. [317]
miR-107; miR-373; miR-511	HepG2	Induced	Promotes cell proliferation	[318–320
miR-124; miR-125b; miR-152; miR-200b; miR-203	HepG2 and Hep3b	Induced	Inhibited proliferation	[321–326; 324–326
miR-132	HepG2	Induced	Inhibited cell proliferation, colony formation, migration and invasion, and induced apoptosis	[327]
miR-133a; miR-154	HepG2	Induced	Suppressed proliferation, colony formation, migration, and invasion, induced cell cycle arrest at G0/G1 stage and cell apoptosis *in vitro*, and decreased tumor size and weight in xenograft model	[328–330]
miR-133b	HepG2; HepG2 and Hep3B	Induced	Attenuated proliferation and invasion and increased apoptosis	[331, 332]
miR-137	HepG2	Induced	Inhibited the proliferation, anchorage-independent growth, invasion, and migration, enhanced the sensitivity of HepG2 cells to antitumor drugs, effects *in vivo*	[333, 334]
miR-143	HepG2	Inhibited	Decreased cell growth, induced apoptosis and cell cycle arrest	[335, 336
miR-215	HepG2 and Hep3B	Induced	Chemoresistance	[337]
miR-224	HepG2	Induced	Malignant	[338, 339]
miR-338-3p; miR-503	HepG2	Induced	Inhibited cell growth and sensitizes HCC cells to therapies	[340–342]
miR-345	HepG2	Induced	Loss facilitated the cell mobility	[343]
miR-452	HepG2	Overexpression	Accelerated proliferation, induced cell cycle from G1 to S transition, and blocked apoptosis	[344, 345]
miR-454	HepG2	Inhibition		[346]

Table 2 (continued)

MiRNA	Cell line	Manipulation	Action on phenotype	Reference
			Reduced proliferation and invasion and epithelial mesenchymal transition	
miR-491	HepG2	Inhibition	Increase migration	[347]
miR-548a	HepG2	Induced	Increased growth	[348]
miR-584a-5p	HepG2	Induced	Promoted cell proliferation, colony forming ability and hampered cell apoptosis.	[348]
miR-592	HepG2	Induced	Suppressed long-term proliferation	[349]
miR-873	HepG2	Inhibition	Inhibited growth and metastasis and accelerated G1 phase arrest	[350]
miR-4262	HepG2	Induced	Inhibited apoptosis	[351]

including resistance to degradation (even at room temperature), or when subjected to multiple freeze-thaw cycles. Moreover, they are resistant to pH changes and fragmentation by chemicals or enzymes [357]. Consequently, a growing number of c-miRNAs have been reported to be dysregulated in the early stages of cancer, before the obvious clinical symptoms, clear biopsy, or image examination evidence [363–367]. Additionally, abnormal levels of distinct miRNAs can be surveyed during tumor progression or after metastasis, contribute for the distinction of tumors, assist treatment strategy assortment, monitor chemo- or radiotherapy response, and predict outcomes [368–370]. Thus, with these applications, it is possible to take serial samples in order to monitor tumor response to treatment or tumor progression in "real time" and to modify the therapy on the basis of disease evolution and patient responses [371–373].

Nevertheless, considering childhood abdominal tumors, the information about c-miRNAs is still scarce. For NB, only a few studies have portrayed differential expression of c-miRNAs. Haug et al. [374] were the first to profile populations of miRNAs inside small exosome-like vesicular particles secreted by MYCN-amplified NB cell lines (Kelly and SK-N-BE(2)-C). Eleven of the most abundantly expressed exosomal miRNAs were common to both cell lines (mir-16, mir-125b, mir-21, mir-23a, mir-24, mir-25, mir-27b, mir-218, mir-320a, mir-320b, and mir-92a). Mir-92a was the most highly expressed miRNA, though its role as an oncogene was uncertain [374]. Other miRNAs in serum from mouse models were described as downregulated (miR-1206, miR-548-5p, miR-548f, miR-639, miR-640, miR-641, miR-647, miR-662, miR-886-3p, miR-887, miR-888, miR-576-5p, and miR-600) or upregulated (miR-513a-5p, miR-198, miR-1280, miR-1304, miR-1308, miR-1908, miR-513b, miR-580, miR-1261, and miR-1268); all of which predicted the switch from favorable to HR-NB [375].

More recently, Zeka et al. [376] identified 9 c-miRNAs strongly associated with metastatic stage 4 disease and treatment response: miR-873-3p, miR-149-5p, miR-124-3p, miR-218-5p, miR-490-5p, miR-323a-3p, miR-10b-3p, miR-375, and miR-129-5p. Of note, exosomal miR199a-3p was also found upregulated and correlated with the severity of the disease. Also, when its mimics were transfected into SK-N-SH cells, the exosomes obtained from the culture supernatant increased proliferation and migration of SH-SY5Y cells *via* inhibiting the expression of the ubiquitin ligase NEDD4 (neural precursor cell expressed developmentally downregulated 4) [377].

A similar situation is observed for WT where some c-miRNAs have the diagnostic potential to differentiate patients with tumors from healthy controls with accuracy, sensitivity, and specificity. However, in 14 miRNAs that showed significantly higher abundance in the serum of patients, only higher expression of miR-100-5p, miR-130b-3p, and miR-143-3p was confirmed in an independent validation set [378].

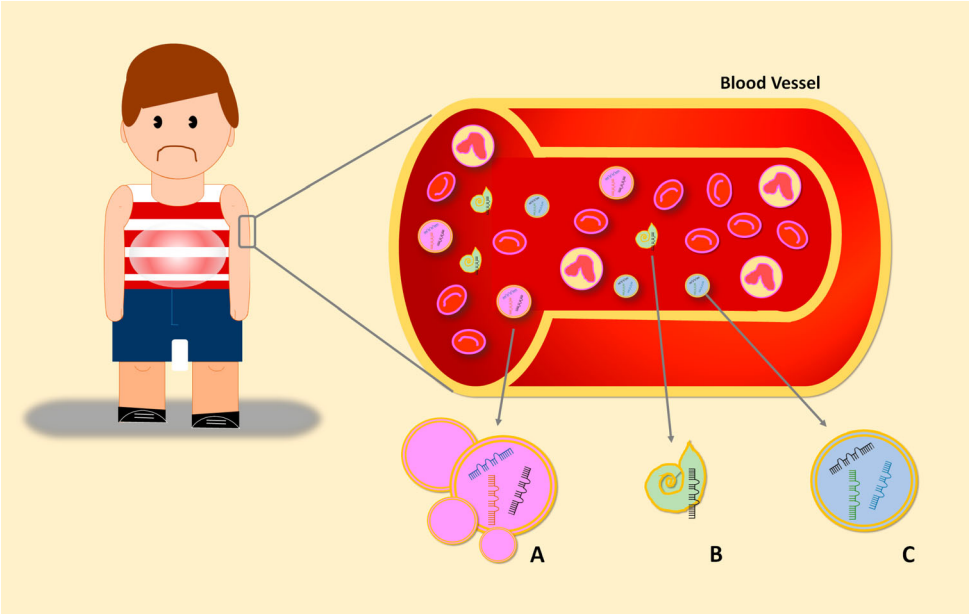

Fig. 1 Currently, liquid biopsies allow earlier cancer detection and the monitoring of tumor progression and/or treatment. Three different mechanisms have been proposed to explain the presence of these circulating miRNAs in biological fluids: A) passive release of miRNAs from broken cells due to injury, chronic inflammation, apoptosis or necrosis, B) release by active secretion by a protein-miRNA complex (e.g. high-density lipoprotein-HDL or Ago2 protein) and C) active secretion via exosomes

Likewise, serum levels of miR-34a, miR-34b, and miR-34-c are significantly lower when samples from patients diagnosed with HB are compared with healthy controls [208]. Also, exosomal miR-21 serum levels were found aberrantly higher when compared with serum samples from controls and considered an independent predictor of event-free survival [379], suggesting its use as a diagnostic and prognostic marker for the clinical targeting of HB [208, 379].

Comparatively, c-miRNAs have also been explored as biomarkers for ACT. Indeed, miR-34a and miR-483-5p have shown to be reliable serum biomarkers to distinguish benign from malignant tumors [380]. Increased expression of miR-483-5p in plasma was also described as a preoperative marker of malignancy by Decmann et al. [381]; however, the study of this miRNA in urine failed to show any applicability.

For HCC, the literature shows plenty of data on c-miRNA; even so, information is restricted to adult tumors. Therefore, liquid biopsy has been extensively used to monitor liver disease progression in subjects chronically infected with hepatitis viruses [382–384], to assess the risk of HCC in cirrhotic patients [385], or for the prediction of early response to sorafenib [386]. Exosomal miR-665 levels, for instance, were significantly higher in HCC than those in healthy subjects and associated with larger tumor size, local invasion, and advanced clinical stage. Moreover, the survival time of patients with the higher exosomal expression of miR-665 was significantly shorter [209]. Conversely, an inverse association of serum exosomal miR-638 with tumor size, vascular infiltration, and TNM stage was observed in HCC patients [387].

A recent meta-analysis based on 24 articles performed by Ding et al. [388] concluded that the increased levels of miR-21, miR-199, and miR-122 might be more specific for the diagnosis of HCC. However, the specificity of the detection method for a single or several individual HCC-related circulating miRNAs is quite poor. For example, increased serum levels of miR-122 are commonly found in HCC, but are also present in HBV/HCV infection, non-alcoholic fatty liver disease, cirrhosis, and alcohol-related liver disease; thus, it is useful for discriminating HCC patients from healthy controls, but not HCC patients from patients with other liver injuries. Based on this, it has been suggested that a panel c-miRNAs may offer more specificity and sensitivity as biomarkers for HCC diagnosis and prognosis prediction [389]. Following this line, Moshiri et al. [390] through droplet digital PCR confirmed a classifier consisting of miR-101-3p, miR-1246, and miR-106b-3p as the best diagnostic precision in plasma to differentiate HCC from cirrhotic patients or controls. Others identified a 3-miRNA panel (miR-92-3p, miR-107, and miR-3126-5p) as a valuable diagnostic marker for HCC, especially for early-stage patients [391].

4 Current clinical applications of miRNAs and future directions

Identifying the molecular signatures in distinct disease states will greatly improve diagnosis and optimize treatment. As seen in previous sections, miRNAs can be measured accurately and reproducibly and, over the last decade, their use as biomarkers in basic and clinical research has become a routine. Nonetheless, despite advances in diagnostic techniques, there is still a need for better characterization across a variety of neoplasia (mainly childhood tumors) and populations in order to transpose into clinical practice.

Unfortunately, there are still no miRNA-specific drugs, and the use of mimics or inhibitors *in vivo* is constrained because when injected intravascularly or subcutaneously, they are very quickly degraded and excreted [392], or show inefficient distribution or instability in the cell environment [393, 394]. Consequently, therapeutic miRNAs need carrier vectors. Diverse pre-clinical nanotechnology-based delivery systems are being explored for local or systemic distribution *in vitro* and in animal models [395].

In this regard, some examples can be cited. The systemic administration of nanoparticles encapsulating miR-34a into NB bearing mice, for instance, resulted in significantly decreased tumor growth, increased apoptosis, and a reduction in vascularization [396]. Likewise, transfection of a miR-122 mimic in a cationic lipid nanoparticle formulation showed to be preferentially taken up by hepatocytes and tumor cells in a mouse HCC model without causing systemic toxicity [397]. The growth of the xenographic HCC tumors treated by the nanoparticle/miR-221 inhibitor complexes was also significantly diminished [398].

Nevertheless, despite a plethora of potential delivery strategies, many drawbacks have been described, including lack of safety of viral vectors, accumulation of nanoparticles in certain organs with non-specific uptake and excretion, and limited loading capacity, among others (reviewed in [392]). Some studies have utilized alternative strategies to overcome these limitations, for example, the use of liposomes that accumulate more readily in the lung for treatment of injuries affecting that organ, modification of vectors with antibodies [399] or the viral capsids to target miRNA to specific organs/tissues, and use of metallic nanoparticles [400]. More recently, peptide nucleic acid analogs of miR-34a to target 3′UTR on MYCN mRNA showed promising results in NB Kelly with satisfactory uptake and stability [401].

The first antimiR-122 drug candidate Miravirsen (Santaris Pharma®) is currently in clinical phase II testing for the treatment of hepatitis C, with no dose-limiting adverse events [395, 402–405]. RG-101 (Regulus Therapeutics®), a hepatocyte targeted *N*-acetylgalactosamine conjugated oligonucleotide that also antagonizes miR-122, was well tolerated and resulted in substantial viral load reduction in patients with chronic HCV infection [406].

Currently, a liposomal injection carrying encapsulated miR-34 (MRX34; Mirna Therapeutics Inc.) began to be used for the treatment of patients with advanced solid tumors, showing acceptable safety and evidence of antitumor activity in a subset of patients despite some liposome-related toxicities [407]. This company also holds patents of other encapsulated liposomal nanoparticle formulations covering miR-101 and miR-215 (under phase I trials) (reviewed in [408]).

While the amount of evidence about miRNA dysregulation is scarce for some childhood abdominal tumors, the data compiled herein portrays the usefulness of miRNAs as biomarkers for diagnosis and patient outcome. The challenges to develop safe and effective alternatives for miRNA therapeutics are still considerable but the large volume of research occurring in this field will continue to improve and allow the rapid translation from bench to bedside trials.

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