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Review

Dysregulation of non-coding RNAs in Wilms tumor

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ABSTRACT

Wilms tumor (WT) as the most frequent pediatric tumor of kidney has been shown to be associated with dysregulation of non-coding RNAs. miR-200c, miR-155–5p, miR-1180, miR-22–3p, miR-483–5p, miR-140–5p, miR-92a-3p, miR-483–3p, miR-572, miR-539 and miR-613 are among dysregulated miRNAs in this tumor. Moreover, a number of long non-coding RNAs such as CRNDE, XIST, SNHG6, MEG3, LINC00667, MEG8, DLGAP1-AS2 and SOX21-AS1 have been shown to be dysregulated in WT. Finally, distinct studies have reported down-regulation of circCDYL and up-regulation of circ0093740 and circSLC7A6 in this tumor. Dysregulation of these transcripts represents a new avenue for identification of the pathetiology of this pediatric tumor as well as design of targeted therapies.

1. Introduction

Wilms tumor (WT) is the most frequent pediatric tumor of kidney. This tumor can be manifested as a single nodule, multifocal unilateral tumors or bilateral lesions [28]. This type of tumor has three histological constituents, i.e. blastemal, epithelial and stromal components. There are extensive differences in the fraction and degree of maturation of blastemal, epithelial and stromal components among different tumors which make the histological manifestation of each tumor distinctive [28]. Anaplastic changes can occur in these components, particularly blastema, resulting in focal or diffuse anaplasia. Tumors with diffuse anaplasia as well as those with blastemal predominance (after preoperative chemotherapy) are considered as high-risk tumors needing more aggressive therapies [28]. Since WT is a rare tumor, its diagnosis is a challenging issue. Identification of the complex pathological manifestations of WT is necessary for precise diagnosis, subtyping and staging. These steps are prerequisite of establishment of appropriate treatments. While pathological examination is currently the gold standard method of diagnosis and prognosis evaluation, molecular biomarkers have been suggested to facilitate diagnostic and prognostic approaches in future [28]. Notably, non-coding RNAs have been shown to be dysregulated in this type of tumor. Dysregulation of these transcripts represents a new avenue for identification of the pathetiology of this pediatric tumor as well as design of targeted therapies[1,11,12,31]. In the current review, we summarize the impact of microRNAs (miRNAs), long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) in the pathogenesis of WT.

2. Dysregulation of miRNAs

miRNAs are a group of non-coding RNAs with sizes about 22 nucleotides that regulate expression of genes through base-pairing mechanisms. They can either suppress mRNA translation or degrade mRNA [4]. Expression of several miRNAs has been examined in WT samples compared with normal kidney samples or adjacent non-cancerous tissue (ANCT) samples. For instance, Bazzaz et al. have assessed expression of the important oncomiR miR-21 in WT tissues using chromogenic in situ hybridization (CISH) as well as quantitative real-time PCR technique. Although real-time PCR analyses have demonstrated up-regulation of miR-21 in 4 tumor samples compared to normal kidney specimens,

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significant ISH signal has not been detected in any of these samples. Based on these observations, authors have concluded that insignificant participation of miR-21 in the pathogenesis of WT [3].

Another study has demonstrated down-regulation of miR-200c in WT samples compared with adjacent non-cancerous tissues. Transfection of WT cells with miR-200c mimic has resulted in attenuation of proliferation ability of cells as well as their colony forming capacity. Up-regulation of miR-200c has also enhanced Bcl-2/Bax ratio and increased the apoptosis rate of WT cells. Moreover, up-regulation of miR-200c has reduced intracellular levels of phosphorylated Akt and expression of its downstream protein GLUT1. Taken together, up-regulation of miR-200c could inhibit cell proliferation and promote cell apoptosis via suppression of the Akt/GLUT1 signaling [46].

Luo et al. have demonstrated down-regulation of miR-155–5p in blood and tissue samples of WT patients who did not get chemotherapy prior to surgery. However, this miRNA has been found to be up-regulated in WT tissues of patients who had taken chemotherapy prior to surgery. Authors have also detected up-regulation of IGF2, PI3K, AKT and mTOR in WT samples. Moreover, expression levels of miR-155–5p and IGF2 have been correlated with TNM stage and lymphatic metastasis. Mechanistically, miR-155–5p could down-regulate IGF2 through binding to its 3′ UTR. Functional assays have shown that up-regulation of miR-155–5p and IGF2 silencing can suppress proliferation, migration and invasion of WT cells and induce their apoptosis. Thus, miR-155–5p acts as a tumor suppressor via decreasing activity of the PI3K/AKT/mTOR axis through targeting IGF2 [27]. Fig. 1 demonstrates the impact of miRNAs on cancer0related signaling pathways in WT.

miR-1180 is another oncogenic miRNA whose expression has been found to be up-regulated in WT samples compared with adjacent tissues. miR-1180 silencing has increased apoptosis of SK-NEP-1 cells in vitro. Besides, miR-1180 has been shown to target p73. In vivo studies have confirmed inhibition of tumor growth by miR-1180 inhibitor. Taken together, miR-1180 has been suggested as a therapeutic target for treatment of WT [14]. Another study has demonstrated down-regulation of miR-22–3p in WT parallel with up-regulation of AKT3. Up-regulation of miR-22–3p could inhibit proliferation and invasiveness of these cells through binding with AKT3. Taken together, miR-22–3p could inhibit proliferation and invasiveness of WT cells through decreasing expression of AKT3 [25]. Table 1 summarizes dysregulated miRNAs in WT and the impact of their dysregulation on clinical outcomes.

3. Dysregulation of lncRNAs

LncRNAs have several similarities with mRNAs, but lacking open reading frames. They regulate expression of genes at several levels through modulating chromatin configuration, sponging miRNAs and interacting with proteins and RNAs. LncRNAs have also been shown to be dysregulated in WT. For instance, the oncogenic lncRNA CRNDE has been shown to be up-regulated in WT tissues compared with adjacent normal samples. Up-regulation of this lncRNA has been associated with

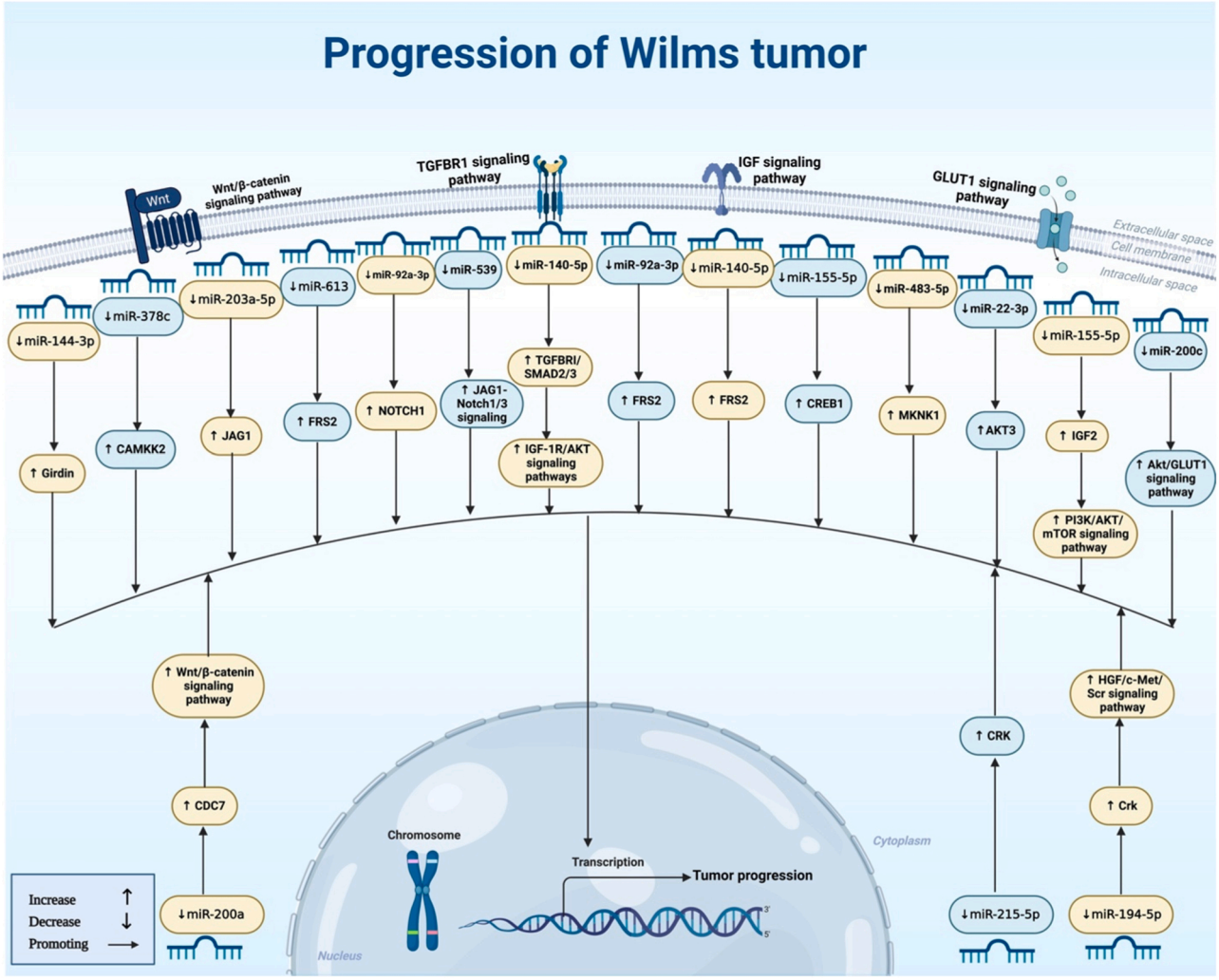

Fig. 1. An overview of dysregulated miRNAs in Wilms tumor and their impact on cancer-related signaling pathways. Detailed information about these miRNAs can be found in Table 1.

Table 1
miRNAs and Wilms tumor (Δ: knock-down or deletion, WT: Wilms tumor, ANCTs: adjacent non-cancerous tissues, OS: overall survival).

miRNA	Pattern of Expression	Clinical Samples/Animal Model	Assessed Cell Lines	Targets / Regulators	Signaling Pathways	Description	Reference
miR-21	no difference	24 samples of WT and 6 normal kidneys as controls	_	_	_	_	[3]
miR-200c	Downregulated	20 pairs of tumor tissues and ANCTs	Wilms tumor cells	_	↑ Akt/GLUT1 signaling pathway	↑ miR-200c: ↓ proliferation, colony formation, and ↑ apoptosis	[46]
miR-155–5p	Downregulated in tissues which never received antitumor treatment but upregulated in tissues which received chemotherapy	87 samples of WT (27 patients received chemotherapy or radiotherapy and 60 did not receive any preoperative adjuvant therapies).	G401, SK-NEP-1, HK-2	↑ IGF2	↑ PI3K/AKT/mTOR signaling pathway	↑ miR-155–5p: ↓ proliferation, migration, invasion and ↑ apoptosis Downregulation of miR-200 was correlated with TNM stage and lymphatic metastasis.	[27]
miR-1180	Upregulated	30 pairs of tumor tissues and ANCTs, BALB/c-nu mice	SK-NEP-1	↓ p73	_	Δ miR-1180: ↓ proliferation and ↑ apoptosis Downregulation of miR-1180 was correlated with histopathological type, NWTS stage, and lymphatic metastasis. Δ miR-1180: ↓ tumor volume and tumor weight in vivo	[14]
miR-22–3p	Downregulated	27 pairs of tumor tissues and ANCTs	17–94 and WIT49	↑ AKT3	_	↑ miR-22–3p: ↓ proliferation and invasion	[25]
miR-483–5p	Downregulated	28 pairs of tumor tissues and ANCTs female BALB/c nu/nu mice	GHINK-1	↑ MKNK1	_	↑ miR-483–5p: ↓ proliferation and colony formation, ↑ apoptosis Low expression levels of miR-483–5p were correlated with unfavorable histology subtypes, lymphatic metastasis, and late clinical stage. ↑ miR-483–5p: ↓ tumor volume and tumor weight, ↑ apoptosis in vivo	[23]
miR-155–5p	Downregulated	40 pairs of tumor tissues and ANCTs	G401	_	_	↑ miR-155–5p: ↓ proliferation and migration, ↑ apoptosis Low expression levels of miR-155–5p were correlated with TNM stage.	[26]
miR-155–5p	Downregulated	37 pairs of tumor tissues and ANCTs	G401	↑ CREB1	_	↑ miR-155–5p: ↓ proliferation, ↑ apoptosis and cell cycle arrest	[48]
miR-140–5p	Downregulated	Tumor tissues, BALB/c nude mice	HK-2, WiT49 and 17–94	↑ FRS2	_	↑ miR-140–5p: ↓ proliferation, migration, and invasion, ↑ apoptosis ↑ miR-140–5p: ↓ tumor volume and tumor weight in vivo	[17]
miR-92a-3p	Downregulated	Tumor tissues, BALB/c nude mice	HK-2, WiT49 and 17–94	↑ FRS2	_	↑ miR-92a-3p: ↓ proliferation, migration, and invasion, ↑ apoptosis ↑ miR-92a-3p: ↓ tumor volume and tumor weight in vivo	
miR-140–5p	Downregulated	23 pairs of tumor tissues and ANCTs	G401 and WT-CLS1, HEK-293 T	↑ TGFBRI/ SMAD2/3	↑ IGF-1R/AKT signaling pathways	↑ miR-140–5p: ↓ proliferation and metastasis Low expression levels of miR-140–5p were correlated with higher tumor stage and unfavorable histology.	[24]
miR-483–3p	Upregulated	_	Wit49, 17.94	↓ PTEN	↓ AKT Pathway	↑ miR-483–3p: ↑ proliferation, migration, invasion, EMT process, and ↓ sensitivity of cells after doxorubicin treatment, and doxorubicin-induced apoptosis	[6]
miR-572	Upregulated	61 pairs of tumor tissues and ANCTs	HFWT and 17–94	↓ CDH1	_	↑ miR-572: ↑ metastasis and EMT process High expression levels of miR-572 were correlated with the histological type, the lymphatic metastasis and the NWTS-5 stage and shorter OS.	[43]
miR-539	Downregulated	42 pairs of tumor tissues and ANCTs	SK-NEP-1	_	↑ JAG1-Notch1/3 signaling	↑ miR-539: ↓ proliferation, migration, invasion, and EMT process Low expression levels of miR-539 were correlated with NWTS-5 stage, lymph node metastasis and histological type and shorter OS.	[34]
miR-92a-3p	Downregulated	GEO database: GSE50505, GSE57370, GSE17342 68 pairs of tumor tissues and ANCTs	primary cells from a Wilms tumor	↑ NOTCH1	_	↑ miR-92a-3p: ↓ proliferation, migration, invasion Patients with low levels of miR-92a-3p showed poorer OS.	[52]

(*continued on next page*)

Table 1 (*continued*)

miRNA	Pattern of Expression	Clinical Samples/Animal Model	Assessed Cell Lines	Targets / Regulators	Signaling Pathways	Description	Reference
miR-613	Downregulated	32 pairs of tumor tissues and ANCTs	SK-NEP-1 and G401	↑ FRS2	_	↑ miR-613: ↓ proliferation, migration, invasion, viability, and ↑ G0/G1 phase arrest	[38]
miR-203a-5p	Downregulated	49 pairs of tumor tissues and ANCTs	G401 and SK-NEP-1	↑ JAG1	_	↑ miR-203a-5p: ↓ migration, invasion Low expression levels of miR-203a-5p were correlated with lymphatic metastasis and worse prognosis.	[2]
miR-378c	Downregulated	20 pairs of tumor tissues and ANCTs nude mice	Sk-Nep1, G-401, WT-CLS1, HS27 and control BJ fibroblasts	↑ CAMKK2	_	↑ miR-378c: ↓ migration and invasion ↑ miR-378c: ↓ tumor development in vivo	[42]
miR-891b	Upregulated	_	WIT49 and RM1	_	↑ PI3K/AKT/mTOR and NF-κB pathways	Salidroside treatment: ↓ miR-891b levels SO ↓ viability, migration, invasion, ↑ apoptosis	[15]
miR-21	Upregulated	89 pairs of tumor tissues and ANCTs	_	↓ PTEN	_	High expression levels of miR-21 were correlated with age, late clinical stage, histopathological tumor type, lymphatic metastasis and shorter OS.	[7]
miR-590	Upregulated	65 pairs of tumor tissues and ANCTs	G401	↓ WT1	_	↑ miR-590: ↑ proliferation High expression levels of miR-590 were correlated with with with stage III or IV.	[13]
miR-21	Upregulated	41 pairs of tumor tissues and ANCTs	SK-NEP-1	↓ PTEN	↑ PI3K/AKT signaling pathway	Δ miR-21: ↓ proliferation and invasion, ↑ apoptosis High expression levels of miR-21 were correlated with age, late clinical stage, unfavorable histopathological type and lymphatic metastasis.	[8]
miR-199b	Upregulated	24 pairs of tumor tissues and ANCTs	17.94 and WiT49	↓ RUNX3	_	Δ miR-199b: ↓ proliferation and invasion	[47]
miR-194–5p	Downregulated	60 pairs of tumor tissues and ANCTs	nephroblastoma cells	↑ Crk	↑ HGF/c-Met/Scr signaling pathway	↑ miR-194–5p: ↓ migration, invasion, and EMT process Low expression levels of miR-194–5p were correlated with the age, TMN stage, histopathological type, and lymphatic metastasis.	[22]
miR-144–3p	Downregulated	40 pairs of tumor tissues and ANCTs	G401, HEK-293 T	↑ Girdin	_	↑ miR-144–3p: ↓ proliferation, migration, invasion	[21]
miR-215–5p	Downregulated	13 pairs of tumor tissues and ANCTs	CC-HEK-1, G401 and WT-CLS1	↑ CRK	_	↑ miR-215–5p: ↓ proliferation, migration, and colony formation	[19]
miR-190b	Upregulated	44 pairs of tumor tissues and ANCTs	SK-NEP-1	↓ PTEN	_	↑ miR-190b: ↑ proliferation, migration, invasion, and ↓ apoptosis High expression levels of miR-190b were correlated with unfavorable histology, more lymph node metastasis and advanced NWTS-5 stage.	[33]
miR-140–5p	Downregulated	60 pairs of tumor tissues and ANCTs	WT_CLS1 and SK-NEP-1	_	_	↑ miR-140–5p: ↓ proliferation	[16]
miR-370	Upregulated	60 pairs of tumor tissues and ANCTs	WT_CLS1 and SK-NEP-1	_	_	↑ miR-370: ↑ proliferation	
miR-200a	Downregulated	TARGET database (132 Wilm's tumor tissues and 6 healthy control tissues) GEO database (GSE57370: 62 Wilm's tumor tissues and 4 healthy control tissues)	SK-NEP-1 and HK-2	↑ CDC7	↑ Wnt/β-catenin signaling pathway	↑ miR-200a: ↓ viability, ↑ apoptosis Low expression level of miR-200a was correlated with death and shorter OS.	[20]
miR-200c-3p	Downregulated	32 pairs of tumor tissues and ANCTs	SK-NEP-1	↑ FRS2	_	↑ miR-200c-3p: ↓ proliferation, migration, and invasion Low expression levels of miR-200c-3p were correlated with advanced stages and lymph node metastasis.	[18]
miR-193b-3p	Downregulated	_	G-401 and WiT49	↑ KLF4	_	Triptolide treatment: ↑ miR-193b-3p levels SO ↓ viability, migration, and ↑ apoptosis	[45]
miR-429	Downregulated	_	G401	↑ c-myc	_	↑ miR-429: ↓ proliferation and ↑ G0/G1 phase arrest	[37]

higher risk of lymph node metastasis. CRNDE silencing has reduced proliferation and metastatic capacities of cells. Notably, expression of miR-424 has been negatively correlated with levels of CRNDE in WT tissues. Mechanistically, CRNDE can promote progression of WT through influencing expression of miR-424 [9]. XIST oncogenic lncRNA is another up-regulated lncRNA in tumor tissues of patients with renal cell carcinoma compared with adjacent tissues. Patients having up-regulation of XIST have been shown to harbor higher risk of distant metastasis and have poorer overall survival rate. Functional studies have shown attenuation of metastatic capacity of WT cells following XIST silencing. Expression levels of XIST and miR-193a-5p have been negatively correlated in cancer samples [41]. In addition, SNHG6 has been shown to be elevated in WT tissues and cells. SNHG6 is an oncogenic lncRNA that promotes proliferation and glycolysis and decreases apoptosis of WT cells. SNHG6 has been shown to target miR-429 to release FRS2 from its inhibitory effects. In vivo studies have confirmed that SNHG6 knock down has inhibited growth of WT via modulating miR-429/FRS2 axis [39]. Fig. 2 shows an overview of dysregulated lncRNAs in Wilms tumor and their effects on expression of miRNAs.

MEG3 has been shown to be down-regulated in WT tissues and blood specimens. Up-regulation of MEG3 could reduce proliferation, invasiveness and migration of CLS1 cells. Suppression of MEG3 in WiT49 cells could promote growth and metastatic ability of cancer cells. Mechanistically, MEG3 regulates expression levels of β-catenin through modulation of the Wnt/β-catenin pathway [36].

Another study has demonstrated dysregulation of DLGAP1-AS2, RP11–93B14.6 and RP11554F20.1 in WT patients. Notably, these lncRNAs have prognostic value in this type of cancer. The three-lncRNA signature has been associated with survival of these patients. Based on the results of functional enrichment assessments target genes of these lncRNAs might participate in important cancer-related pathways [29].

SOX21-AS1 has also been shown to be up-regulated in WT samples and cells compared with adjacent non-cancerous tissues and normal embryonic renal cells, respectively. Over-expression of this lncRNA has been associated with larger tumor dimensions, advanced stage or unfavorable histopathological type. SOX21-AS1 silencing has inhibited proliferation and colony forming capacity of WT cells, and prompted cell-cycle arrest via increasing expression of p57 [44].

MYLK-AS1 is another up-regulated lncRNA in WT samples whose expression is associated with expression of CCNE1 in these samples. Based on the results of Kaplan-Meier analyses, CCNE1 up-regulation is associated with lower overall survival of patients. Functional studies have shown that TCF7L2 can specifically bind to MYLK-AS1 and enhance expression of CCNE1. MYLK-AS1 silencing could suppress expression of CCNE1 and affect proliferation and cell cycle distribution of WT cells. In vivo studies have also validated the effect of MYLK-AS1 silencing in reduction of tumorigenic capacity of WT [51]. Table 2 shows dysregulated lncRNAs in WT and their function in tumorigenesis.

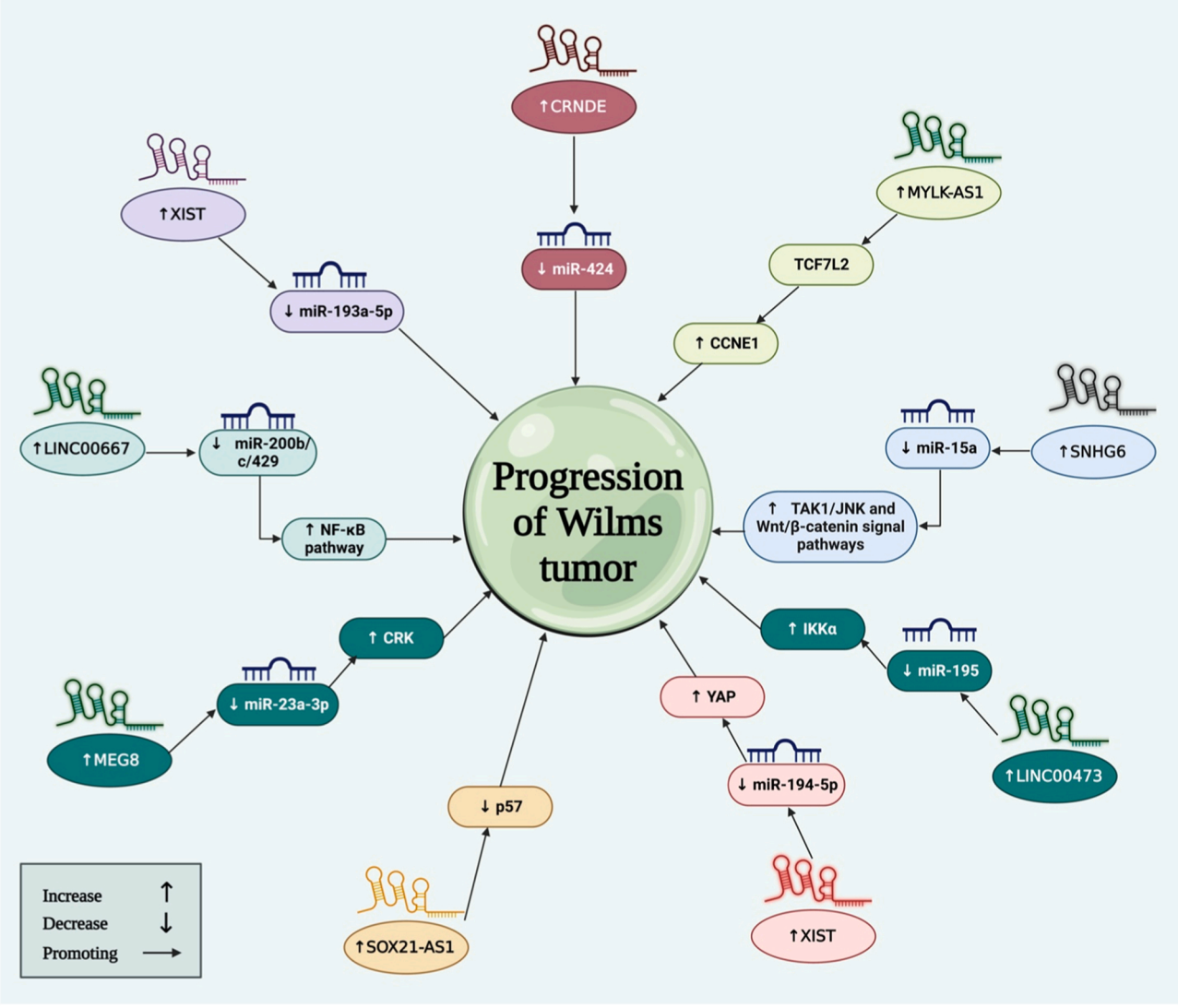

Fig. 2. An overview of dysregulated lncRNAs in Wilms tumor.

4. Dysregulation of circRNAs

Distinct studies have shown dysregulation of certain circRNAs in WT. Zhou et al. have shown down-regulation of circCDYL in WT tissues compared with adjacent non-malignant tissues. Forced over-expression of circCDYL has reduced proliferation, migratory potential, and invasiveness of WT cells. Functional studies have shown that circCDYL functions as a miRNA sponge to decrease miR-145–5p levels and subsequently increase expression of TJP1. Taken together, circCDYL/miR-145–5p/TJP1 axis has been identified as a functional axis in the pathogenesis of WT [49].

Cao et al. have used a high-throughput microarray sequencing method for identification of dysregulated circRNAs in WT. This strategy has led to identification of circ0093740 as a commonly up-regulated circRNA in WT cells and clinical samples. Circ0093740 silencing has suppressed proliferation and migration of WT. This circRNA increases

Table 2
lncRNAs and Wilms tumor (Δ: knock-down or deletion, ANCTs: adjacent non-cancerous tissues, OS: overall survival, TNM: tumor-node-metastasis).

lncRNA	Pattern of Expression	Clinical Samples/ Animal Model	Assessed Cell Lines	Targets / Regulators	Signaling Pathways	Description	Reference
CRNDE	Upregulated	89 pairs of tumor tissues and ANCTs	HFWT, WTCLS1, 17–94, HK-2	↓ miR-424	_	Δ CRNDE: ↓ proliferation and metastasis High expression levels of CRNDE were correlated with hlymph node metastasis.	[9]
XIST	Upregulated	43 pairs of tumor tissues and ANCTs	HFWT and 17–94	↓ miR-193a-5p	_	Δ XIST: ↓ metastasis High expression levels of XIST were correlated with distant metastasis and shorter OS.	[41]
XIST	Upregulated	49 pairs of tumor tissues and ANCTs	WT G401 and HK-2 cell	↓ miR-194–5p, ↑ YAP	_	Δ XIST: ↓ proliferation, migration, and invasion and ↑ apoptosis High expression levels of XIST were correlated with TNM staging and shorter OS.	[30]
SNHG6	Upregulated	_	_	↓ miR-429, ↑ FRS2	_	↑ SNHG6: ↑ proliferation, glycolysis and ↓ apoptosis	[39]
SNHG6	Upregulated	20 pairs of tumor tissues and ANCTs	G401 and SK-NEP-1	↓ miR-15a	↑ TAK1/JNK and Wnt/β-catenin signal pathways	Δ SNHG6: ↓ proliferation, migration and incursion, ↑ apoptosis	[35]
MEG3	Downregulated	54 pairs of tumor tissues and ANCTs	WT-CLS1 and WiT49	_	↑ Wnt/β-catenin pathway	↑ MEG3: ↓ proliferation, migration and invasion Low expression levels of MEG3 were correlated with histological type, lymph node metastasis and NWTS-5 stage.	[36]
LINC00667	Upregulated	25 pairs of tumor tissues and ANCTs male BALB/C nude mice	CC-HEK-1, WT-1 and WT-2	↓ miR-200b/c/429	↑ NF-κB pathway	Δ LINC00667: ↓ proliferation, migration and invasion ↓ miR-200b/c/429: ↓ influence of LINC00667 depletion on tumor growth in vivo	[10]
MEG8	Upregulated	_	WT cells	↓ miR-23a-3p, ↑ CRK	_	Δ MEG8: ↓ viability, migration and invasion High expression levels of MEG8 were correlated with histologic type, lymphatic metastasis, and National Wilms Tumor Study (NWTS) stage	[32]
DLGAP1-AS2	Downregulated	TARGET database Plus 130 WT tissues and six normal tissues	_	_	_	Low expression levels of DLGAP1-AS2 were correlated with shorter OS.	[29]
RP11–93B14.6	Upregulated	TARGET database Plus 130 WT tissues and six normal tissues	_	_	_	High expression levels of RP11–93B14.6 were correlated with shorter OS.	
RP11–554F20.1	Upregulated	TARGET database Plus 130 WT tissues and six normal tissues	_	_	_	High expression levels of RP11–554F20.1 were correlated with shorter OS.	
SOX21-AS1	Upregulated	40 pairs of tumor tissues and ANCTs	WiT49, WT-CLS1, HEK293	↓ p57	_	Δ SOX21-AS1: ↓ proliferation and colony formation, and ↑ cell-cycle arrest High expression levels of SOX21-AS1 were correlated with large tumor size, advanced National Wilms Tumor Study (NWTS) stage or unfavorable histopathological type.	[44]
LINC00473	Upregulated	15 pairs of tumor tissues and ANCTs nude mice	SK-NEP-1	↓ miR-195, ↑ IKKα	_	Δ LINC00473: ↓ viability, and ↑ apoptosis, G1/S phase arrest High expression levels of LINC00473 were correlated with higher stage and unfavorable histology Wilms tumor. Δ LINC00473: ↓ tumor growth and tumor volume in vivo	[50]
MYLK-AS1	Upregulated	38 pairs of tumor tissues and ANCTs female BALB/c nude mice	HEK-293 T	TCF7L2, and ↑ CCNE1	_	Δ MYLK-AS1: ↓ proliferation, and colony formation High expression levels of MYLK-AS1 were correlated with shorter OS.	[51]

Table 3
circRNAs and Wilms tumor (Δ: knock-down or deletion, ANCTs: adjacent non-cancerous tissues).

circRNA	Pattern of Expression	Clinical Samples/Animal Model	Assessed Cell Lines	Targets / Regulators	Description	Reference
circCDYL	Downregulated	25 pairs of tumor tissues and ANCTs athymic BALB/c nude mice	SK-NEP-1 and G401	↑ miR-145–5p, ↓ TJP1	↑ circCDYL: ↓ proliferation, migration, and invasion ↑ circCDYL: ↓ metastasis in vivo	[49]
circ0093740	Upregulated	3 pairs of tumor tissues and ANCTs nude mice	SKNEP1, G401, HANB, and HEK293T	↓ miR-136/145, ↑ DNMT3A	Δ circ0093740: ↓ proliferation, and migration Δ circ0093740: ↓ metastasis in vivo	[5]
circSLC7A6	Upregulated	32 pairs of tumor tissues and ANCTs BALB/c nude mice	HFWT, WiT49, 17–94, HK-2	miR-107/ ABL	Δ circSLC7A6: ↓ WT progression	[40]

growth and migration potential of WT cells through sponging miR-136/145 and increasing expression of DNMT3A. Thus, circ0093740/miR-136/145/DNMT3A axis has been identified as an important molecular axis in pathoetiology of WT [5]. Table 3 summarizes the outlines of studies that reported dysregulation of circRNAs in WT.

5. Discussion

WT is a pediatric tumor with diverse subtypes and clinical outcome. Identification of underlying cause and the mechanisms of disease heterogeneity have importance in the design of targeted therapies for this kind of cancer. Three types of non-coding RNAs i.e. miRNAs, lncRNAs and circRNAs have been reported to be dysregulated in this type of tumor. They can be classified to tumor suppressors and oncogenes according to their function in WT. miRNAs are not only the mostly assessed type of non-coding RNAs in WT, but also the main route of participation of the other classes of non-coding RNAs in the pathoetiology of this type of cancer. In fact, lncRNAs and circRNAs exert their roles in the pathogenesis of WT mainly through acting as miRNA sponges. XIST acts as a molecular sponge for miR-193a-5p and miR-194–5p. Moreover, SNHG6 has been shown to sponge miR-429 and miR-15a. In addition to these two up-regulated lncRNAs in WT, four others oncogenic lncRNAs, namely CRNDE, LINC00667, MEG8 and LINC00473 have been shown to function as sponges for miR-424, miR-200b/c/429, miR-23a-3p and miR-195, respectively. Moreover, circCDYL and circ0093740 have been reported to act as sponges for miR-145–5p and miR-136/145, respectively. Taken together, the functional network between lncRNAs, circRNAs and miRNAs has importance in the pathogenesis of WT. Thus, identification of this type of interaction between these classes of non-coding RNAs can lead to design of multi-gene diagnostic and prognostic panels as well as establishment of novel therapeutic modalities.

Although several studies have demonstrated dysregulation of non-coding RNAs in WT samples, the impact of these transcripts in early and non-invasive diagnosis of WT has not been evaluated completely. miR-155–5p and MEG3 are two non-coding RNAs reported to be dysregulated in the peripheral blood of patients with WT. Other non-coding RNAs might also been dysregulated in the circulation of these patients. Future studies are needed to assess their dysregulation of these transcripts in the course of WT and their relevance with the clinical outcomes. Since non-coding RNAs, particularly miRNAs and circRNAs have stable expression in biofluids, these transcripts are potential biomarkers for non-invasive diagnostic purposes and patients' follow-up after surgical removal of tumors. Moreover, they can predict response of patients to therapeutic agents, thus they can be used for design of personalized chemotherapeutic regimens. To achieve this goal, it is necessary to conduct high throughput sequencing methods to evaluate expression of non-coding RNAs in different samples from diverse ethnicities. Identification of the relationship between expression levels of different classes of non-coding RNAs facilitates recognition of involved cellular pathways in the pathogenesis of WT.

Expression of non-coding RNAs might also been affected by chemotherapy. For instance, miR-155–5p has been shown to be down-regulated in tumor tissues of patients who never received antitumor treatment but up-regulated in tissues of patients who received chemotherapy. The impact of chemotherapy on expression of other non-coding RNAs or the role of these transcripts in determination of response to these agents should be assessed in future studies.

In brief, several oncogenic and tumor suppressor non-coding RNAs have been shown to be dysregulated in WT. Although changes in methylation patterns, somatic mutations, and loss of heterozygosity might be involved in this process, the available literature has only focused on the impact of their dysregulation in the progression of WT. There is not explicit data on the mechanism of dysregulation of non-coding RNAs n this tumor. Akt/GLUT1, PI3K/AKT/mTOR, IGF-1R/AKT, JAG1/Notch1/3, Wnt/β-catenin and NF-κB are the main signaling pathways mediating the effects of non-coding RNAs in WT.

Although directed therapies against non-coding RNAs have been tested in animal models and cell line studies, the efficacy and safety of these therapies have not been examined in clinical settings. Identification of appropriate methods for directing these therapeutic agents to specific sites in the body is another important issue. This aim can be achieved through using tissue-specific surface antigens in the delivery systems.

Future high throughput studies should assess expression of lncRNAs, miRNAs and circRNAs in clinical samples and animal models of WT and find the correlations between expressions of these transcripts and clinical outcome of patients in prospective and follow-up studies. Moreover, multiomic analyses can facilitate identification of relevant signaling pathways and molecules in this regard and pave the way for design of targeted therapies.

Ethics approval and consent to participant

Not applicable.

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CRediT authorship contribution statement

SGF wrote the manuscript and revised it. MT supervised and designed the study. EJ, SS, SRA and BMH collected the data and designed the figures and tables. All authors read and approved the submitted version.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

Data Availability

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

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Consent of publication

Not applicable.

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