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MetastamiRs in Renal Cell Carcinoma: An Overview of MicroRNA Implicated in Metastatic Kidney Cancer

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Abstract: MicroRNAs are short noncoding RNAs that regulate post-transcriptional protein expression. Aberrant microRNA expression has been widely implicated in cancer biology with various effects depending on the affected downstream target(s). In renal cell carcinoma, microRNAs have been shown to influence metastasis by targeting oncogenes or tumor suppressors in complex regulatory networks - leading them to be coined "metastamiRs." This chapter aims to identify the microRNAs responsible for metastasis in renal cell carcinoma, review their molecular function and oncologic outcome, and discuss their potential roles for diagnosis, prognosis, and therapy.

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INTRODUCTION

MicroRNAs (miRNA) belong to a class of short noncoding RNAs that regulate post-transcriptional gene expression. They preferentially bind to a complementary sequence typically on the 3' untranslated region (UTR) of their respective messenger RNA (mRNA) to directly repress translation and/or target the mRNA for degradation (1). A single miRNA can target several different mRNA; conversely, a mRNA transcript can be regulated by several different miRNAs in a complex network of interwoven biological processes (2). More recently, miRNA dysregulation with respect to cancer biogenesis and progression has become an increasing topic of interest. Numerous *in silico* and *in vitro* studies have elucidated the regulatory pro- and anti-cancer mechanisms by which these miRNAs act - termed "metastamiRs" (3, 4). MetastamiRs are ubiquitous in their involvement of metastasis, including cancer cell proliferation and colonization, angiogenesis, cell adhesion and migration, apoptosis, and the epithelial-to-mesenchymal transition (EMT). MetastamiRs can be categorized as metastasis-promoting or metastasis-suppressing miRNA. This chapter l focuses on metastamiRs in renal cell carcinoma (RCC) and their role in metastatic progression, diagnosis, and prognostication.

RCC, while not among the most common tumors, comprises 2.2% of all diagnosed malignancies, with a majority of cases (75%) being the clear cell subtype (5, 6). While the 5-year survival rate for localized RCC is greater than 93%, metastatic disease is not uncommon in patients diagnosed with RCC (7). An estimated 18% of patients with RCC are thought to have metastatic disease at the time of diagnosis (synchronous metastases), and 20–50% of patients with RCC are believed to develop subsequent metastatic disease during follow-up after surgical extirpation, such as partial or radical nephrectomy (8–10). The likelihood of developing metastatic RCC (mRCC) is correlated strongly with clinical staging (which in itself is based on tumor size and invasion) as well as tumor grade and histologic findings. Currently there does not exist a reliable method for predicting metastases of RCC. In light of this clinical need, there has been ongoing research into miRNAs as potential non-invasive diagnostic biomarkers, predictors of metastases, and likely therapeutic targets. This chapter aims to consolidate current perspectives on various miRNA implicated in mRCC, primarily focusing on clear cell RCC (ccRCC).

Early studies in the identification of metastamiRs implicated in RCC utilized microarrays and qPCRs to compare miRNA profiles between primary tumors that did and did not metastasize. Heinzelmann et al. were among the first to assert specific miRNA (miR-451, miR-221, miR-30a, miR-10b, and miR-29a) as signatures that would distinguish between metastatic and nonmetastatic ccRCC (11). Subsequent studies have identified more metastamiR candidates, with many studies focusing on elucidating the molecular mechanism behind

the tumor suppressive or oncogenic effects of these respective metastamiRs as well as their prognostic potential (5, 6, 12). While each new study continues to highlight the complex and variegated nature of miRNA regulation of ccRCC, we are slowly improving our understanding of the role of miRNAs in the metastatic process.

METASTASIS-PROMOTING MIRNAS IN CCRCC

MiRNA that support oncogenesis are nearly always upregulated in mRCC and promote cancer cell viability, proliferation, invasion, and migration. Some mechanisms by which these miRNAs contribute to metastasis involve downregulation of genes involved in cell adhesion (E-cadherin) to facilitate EMT and inhibition of apoptotic proteins. Targets of metastasis-promoting miRNAs include tumor suppressors such as PTEN and APC. In RCC, they have also been demonstrated to inhibit long non-coding RNA (lncRNA) with tumor suppressor activities, such as miR-7 (9). *In vitro* studies of metastasis-promoting miRNAs have shown that their overexpression can worsen chemoresistance, as is the case with miR-221 (13, 14). A list of metastasis-promoting miRNAs and their respective targets, functions, and associated references can be found in Table 1 (13–58).

TABLE 1 **Summary of metastasis-promoting miRNAs involved in ccRCC with impacted pathways, targets, and resulting oncologic outcome**

miRNA	Target/Regulator	Function	Reference
miR-7	MEG3	Inhibits lncRNA MEG3 to downregulate RASL11b, resulting in increased cell proliferation, migration, invasion.	13, 15
miR-21-5p	SOX5, TIMP3, PDCD4, CASC2, PTEN	Downregulates PDCD4/c-Jun pathway to promote cell transformation, proliferation, and metastasis. Reduces chemosensitivity to various drugs. Inhibits specific tumor-suppressive lncRNA. Mediates metformin growth inhibition via PTEN/Akt/mTOR pathway.	16–25
miR-92a-3p	FBXW7	Promotes RCC proliferation and cell colony formation.	26
miR-106b/-5p	LZTFL1, SERP1, DKK2, SETD2, Capicua	Facilitates cell aggressiveness and stem-cell like phenotype via Wnt/β-catenin signaling. Promotes cell proliferation and invasion via MAPK signaling. Inhibits apoptosis.	27–31

Table continued on following page

TABLE 1 Summary of metastasis-promoting miRNAs involved in ccRCC with impacted pathways, targets, and resulting oncologic outcome (Continued)

miRNA	Target/Regulator	Function	Reference
miR-122	Dicer, occludin, Sprouty2, FOXO3	Promotes cell proliferation, migration, invasion, EMT. Downregulates Dicer and its subsequent downstream miR-200 tumor suppressor families.	32–35
miR-125b	VDR	Promotes cell proliferation, migration, inhibits apoptosis.	36–38
miR-155-5p	FOXO3a, E2F2, PEG3, AIF	Promotes cell proliferation, migration, invasion, EMT, inhibits apoptosis. Associated with sunitinib chemoresistance and decreased time to cancer progression.	39–44
miR-193a-3p	ST3GalIV, PTEN	Promotes cell growth, migration via PI3k/Akt pathway.	45, 46
miR-221	VEGFR2, TIMP2	Promotes cell proliferation, migration, invasion. Increases sunitinib chemoresistance by downregulating VEGFR2.	14, 47, 48
miR-223-3p	FBXW7, SLC4A4, hZIP1	Promotes cell proliferation, metastasis.	49–51
miR-592	SPRY2	Promotes cell proliferation, migration, invasion.	52
miR-630	OCT2	Promotes cell proliferation, migration, invasion.	53–55
miR-671-5p	APC	Promotes cell migration and invasion via Wnt signaling.	56
miR-720	E-cadherin, beta-catenin	Promotes cell proliferation, migration, invasion.	57
miR-1293	HAO_2	Increases cell viability, promotes cell migration, invasion.	58

METASTASIS-SUPPRESSING MIRNA IN CCRCC

Conversely to metastasis-promoting miRNA, miRNAs that suppress metastasis in mRCC tend to be downregulated in tumor cells. They generally function to inhibit cell proliferation, migration, promote apoptosis, and are associated with increased overall survival. For example, metastasis-suppressing miRNAs target oncogenes including AKT, VEGFA, and mTOR to downregulate known cellular proliferative pathways. Some miRNA such as the miR-101, miR-126, and miR-200 families are associated with responses to specific chemotherapy regimens; in these cases, downregulation of these miRNAs has been shown to lead to increased resistance to chemotherapy (59–61). A list of tumor suppressor miRNA and their respective targets, functions, and associated references can be found in Table 2 (11, 59–183).

TABLE 2 Summary of metastasis-suppressing miRNAs involved in ccRCC with impacted pathways, targets, and resulting oncologic outcome

miRNA	Target/Regulator	Function	Reference
Let-7b-5p, 7c-5p	AKT2	Downregulates AKT2 and increases sensitivity of cancer cells to 5-fluorouracil.	11, 62, 63
miR-10a-5p	SKA1, BDNF	Downregulates BDNF to inhibit invasion and EMT of cancer cells; inhibition of SKA1 suppresses tumor invasion and migration and improves overall survival.	11, 16, 63–67
miR-10b-5p	HOXA3, CREB1	Suppresses HOXA3 to inhibit cell proliferation, migration, invasion (via the FAK/YAP pathway).	68–71
miR-26a-5p	OGT, LOXL2, PLOD2, PTEN, E2F7	Affects a variety of cell-signaling pathways via downregulation of the aforementioned genes to control cancer cell proliferation, migration, invasion.	63, 72–79
miR-29a	LOXL2	Downregulates LOXL2 to inhibit cancer cell migration and invasion.	11, 78
miR-29c-3p	DUXAP8, DUXAP9, COL1A1, COL1A2, LOXL2	Downregulates DUXAP8/P9, pseudogenes implicated in tumor growth and associated with poorer disease prognosis.	63, 78, 80
miR-30a/-5p/-3p	ZEB2, GALNT7, GRP78, ATG12, WNT2, RUNX2, IGF-1R, ADAM9, LRP6, DLL4	Targets a myriad of genes involved in cell proliferation, migration, known tumorigenesis pathways (i.e., HIF2a).	11, 81–90
miR-30c-5p	HSPA5, MTA1	Downregulates proteins involved in EMT, inhibits cell invasion, and enhances sensitivity of cells to anticancer drugs.	11, 91–93
miR-30e-3p	Snail1	Inhibits cell invasion and migration in ccRCC.	94
miR-99a/-3p	mTOR, RRM2	Induces G1 cell-cycle arrest via inhibition of mTOR; effects apoptosis via inhibition of RRM2 in sunitinib-resistant RCC.	95, 96
miR-101/-5p/-3p	DONSON, UHRF1, EZH2	Downregulates EZH2 (histone methyltransferase) and DONSON (overexpressed in sunitinib-resistance) to decrease cell proliferation and improve survival. Suppresses the UHRF1 pathway (nucleotide excision and base repair), which plays a role in sunitinib-resistant RCC.	59, 97–99

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TABLE 2 Summary of metastasis-suppressing miRNAs involved in ccRCC with impacted pathways, targets, and resulting oncologic outcome (Continued)

miRNA	Target/Regulator	Function	Reference
miR-106a-5p/-3p	IRS-2, VEGFA, PAK5	Downregulates VEGFA, inhibits cell proliferation (via cell cycle arrest at S-G2 phase) by silencing PAK5 (-5p). Inhibits RCC proliferation via downregulation of IRS-2 (-3p).	100–102
miR-126	ROCK1, EGFL7, SERPINE1, SLC7A5	Inhibits cell proliferation, migration, tumor angiogenesis (via EGFL7 and ROCK1). Deactivation leads to a pseudohypoxic state due to increased HIF1α, resulting in increased cell motility and drug resistance.	60, 103, 104
miR-129-3p	TRPM7, SOX4, FAK, MMP-2/9	Impairs cell migration and invasion via direct targeting of multiple oncogenes.	105, 106
miR-133b	MMP9	Inhibits cell proliferation, invasion, induces apoptosis, and improves chemosensitivity (via ERK pathway).	107, 108
miR-135a	c-myc	Inhibits cell proliferation, induces G0/G1 arrest.	109, 110
miR-138	SOX4/9, TMEM40, EZH2, vimentin, HIF1α	Attenuates EMT, induces senescence, suppresses cell migration, invasion, and pseudohypoxic state	111–116
miR-141-3p	EAPP, HS6ST2, LOX, TGFB2, EphA2, NEK6	Downregulates EMT, focal adhesion, ErbB signaling pathways.	117–120
miR-143	HK2, ABL2	Inhibits cell proliferation, adhesion, migration, EMT.	121, 122
miR-145-5p	HK2, ADAM17, HS6ST2, LOX	Synergistic tumor-suppressive effects with miR-141-3p, miR-143. Involved in VHL-independent downregulation of HIF2α.	119, 122–125
miR-149	FOXM1	Suppresses cell migration, invasion, promotes apoptosis.	126, 127
miR-182-5p	MALAT1, IGF1R, FLOT1	Impairs cell proliferation (via G1 and S phase cell cycle arrest), migration, and invasion.	128–130
miR-186	E-cadherin, CDK6, SSP1	Inhibits cell proliferation, migration, invasion.	131–133
mir-199a-5p/-3p	GSK-3β, ROCK1, TGFBR1, JunB	Inhibits cell proliferation, migration, invasion, promotes apoptosis.	134–137

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TABLE 2 Summary of metastasis-suppressing miRNAs involved in ccRCC with impacted pathways, targets, and resulting oncologic outcome (Continued)

miRNA	Target/Regulator	Function	Reference
mir-200a/b/c	CAV1, FLOT1, HO-1	All members of miR-200 family found to be downregulated in RCC. Inhibit cell proliferation and invasion, regulate EMT, ErbB pathway (200a), focal adhesion (200b/c). Sensitizes cancer cells to sorafenib and imatininb via targeting HO-1 (200c).	61, 138–140
miR-203	CAV1, HOTAIR, ZEB2, FGF2	Inhibits EMT, migration, invasion via inactivation of PI3K/AKT pathway.	141–145
miR-206	CDK4/6/9, CCND1, VEGFA, GAK	Regulates cell cycle, causes mitotic arrest at G0/G1, suppresses cell proliferation, invasion, migration.	146–150
miR-212-5p	TBX15, FOXA1, XIAP	Inhibits cell proliferation, invasion, migration, promotes apoptosis.	151–153
miR-214	LIVIN	Inhibits cell proliferation, promotes chemosensitivity of cells.	154, 155
miR-215	SIP1/ZEB2,	Decreases cell invasion and inhibits proliferation.	156
miR-218	CAV2, GAB2, BCL9, CIP2A	Inhibits cell invasion, proliferation, migration via focal adhesion, inhibits tumor angiogenesis.	157–160
miR-362-3p	NLK, SP1, G3BP1	Attenuates sunitinib resistance, suppresses cell proliferation, invasion via AKT/FOXO3 signaling.	109, 161, 162
miR-363	S1PR1, Twist1, CREB1, Snail1	Inhibits cell proliferation, migration, invasion, EMT, promotes apoptosis.	71, 163–165
miR-372	ATAD2, IGF2BP1	Inhibits cell invasion, migration, EMT.	166, 167
miR-375	YWHAZ, YAP1	Inhibits cell proliferation, migration, invasion.	168, 169
miR-429	CRKL, VEGF, AKT1, Sp1	Inhibits cell proliferation, migration, invasion, EMT (via SOS1/MEK/ERK/MMP pathway).	170–174
miR-451	PSMB8	Inhibits cell proliferation and invasion.	11, 175
miR-492	–	Decreases cell proliferation, suppresses EMT, promotes apoptosis.	176
miR-497	VEGFR2, PD-L1	Inhibits cell proliferation, migration, invasion, immunomodulation (downregulates PD-L1), improves chemosensitivity to sorafenib.	177–180

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TABLE 2 **Summary of metastasis-suppressing miRNAs involved in ccRCC with impacted pathways, targets, and resulting oncologic outcome (Continued)**

miRNA	Target/Regulator	Function	Reference
miR-532	AQP9	Attenuates cell proliferation, invasion, migration.	63, 181
miR-765	PLP2	Inhibits cell proliferation, invasion; eliminates accumulation of abnormal lipids involved in cancer cell metabolism.	182
miR-1285	TGM2	Inhibits cell proliferation, invasion, migration.	183

CONTRADICTORY METASTAMIRS

In light of the complexity behind miRNA regulation of ccRCC, it is not uncommon in the literature for there to be conflicting reports of a specified metastamiR. For example, in some studies, miR-15a was found to be downregulated in ccRCC tissues and found to inhibit cell proliferation and invasion (63, 74, 184). However, several other studies have reported miR-15a was overexpressed in ccRCC tissue samples and cell lines and that it enhanced cell proliferation, invasion, and was associated with a poorer prognosis (185–187). Interestingly enough, miR-15a was shown to inhibit both eIF4E, a downstream effector of mTOR, as well as BTG2, a known antiproliferative protein that affects the PI3K/Akt/mTOR pathway downstream (180, 183). In the case of miR-22, Gong et al. showed that miR-22 was overexpressed in RCC cell lines and tissues, demonstrated to enhance cell invasion *in vitro*, and was correlated with a worse overall prognosis and survival (188). However, two other studies had shown miR-22 to have tumor suppressive traits and demonstrated *in vitro* that miR-22 overexpression could inhibit cell migration, proliferation, invasion, and reverse oncogenic effects via direct targeting of Erb-B2 and PTEN (189, 190). A more detailed description of conflicting metastamiRs in RCC can be found in Table 3.

It is difficult to surmise how and why certain miRNA were found to have conflicting expression levels in RCC. While clearly further experiments are needed to elucidate these mechanisms, these findings also reflect how multifaceted and heterogeneous RCC can be. An interesting notion could be that some dysregulated miRNAs exhibit different expression levels with regards to metastatic and non-metastatic tumors. For example, while miR-146a-5p was demonstrated to be upregulated in primary renal cell tumors, it was shown to be downregulated in metastatic renal cell tumors, and perhaps could be implicated in the transition between primary tumor and metastasis (223). Examples such as miR-146a-5p exemplify the complexity of the network of miRNA regulation in carcinogenesis and highlights how miRNA regulatory function is oftentimes both cancer- and target-specific.

TABLE 3 MetastamiRs with conflicting data in ccRCC

miRNA	Conflicting Findings	References
miR-15a	Promotes cell migration, invasion, and proliferation via inhibition of BTG2; associated with worse survival.	185–187
	Underexpressed in small renal masses; suppresses cell proliferation and invasion via inhibition of eIF4E and OGT.	63, 74, 184
miR-22	Promotes cell invasion, predicts worse prognosis and overall survival.	188
	Suppresses cell proliferation, invasion, promotes apoptosis (via Erb-B2, PTEN).	189, 190
miR-23b/-3p	Has oncogenic properties via inhibition of PTEN; higher expression correlated with worse survival.	191
	Inhibits cell proliferation, migration, and invasion; increased expression correlates with improved survival.	63, 192–194
miR-28-5p	Promotes chromosomal instability via Mad2 inhibition in VHL-associated RCC.	195
	Suppresses cell migration and invasion via targeting RAP1B.	196
miR-29b	Promotes cell invasion and proliferation by targeting KIF1B.	197
	Inhibits tumor cell migration and invasion via LOXL2 expression.	78
miR-34a	Overexpressed in RCC; inhibition can rescue tumor suppressive functions (p53-DAPK).	198–201
	Downregulated in RCC in patient serum and tissue; inhibits cell proliferation by targeting Notch1.	202, 203
miR-139-5p	Upregulated in mRCC.	204
	Lower expressions correlated with worse survival, increased risk of RCC recurrence.	205–207
miR-144/-3p	Promotes cell migration, invasion, sunitinib resistance via downregulating ARID1A.	208
	Inhibits cell proliferation and invasion via targeting mTOR, MAP3K8.	209, 210
miR-204-5p	Upregulated in mRCC.	204
	Suppresses tumor growth via inhibition of autophagy; downregulation promotes tumorigenesis; inhibits proliferation and invasion via RAB22A inhibition.	211–213
miR-210-3p	Upregulated in all types of RCC, potential biomarker for mRCC.	214–216
	Suppression of tumorigenesis and EMT via inhibition of TWIST1; reduced expression leads to chemotherapy resistance via increased ABCC1, MDR-1 levels.	217, 218
miR-224	Upregulated in tissue and exosome samples; promotes invasion in ccRCC via OCLN; associated with upregulated PD-L1 on cancer cells.	46, 219–221
	Decreased expression (via ceRNA LINC01094) promotes ccRCC development.	222

NON-CCRCC METASTAMIRS

As ccRCC makes up an overwhelming majority of all cases of RCC (80–90%), it stands as no surprise that much of the research in metastamiRs is regarding ccRCC. Few studies of metastamiRs implicated in other RCC subtypes exist in literature currently. While papillary RCC (pRCC) is the second-most common subtype of RCC, it is still rare in comparison to ccRCC and its pathogenesis is not nearly as understood as its counterpart (224). Wala et al. utilized an integrated genomic analysis to identify miR-199a-3p as a likely tumor suppressor in pRCC by preventing dysregulation of genes in the focal adhesion pathway and maintaining integrity of the extracellular matrix (224). This finding is not unique to pRCC and it is consistent with other studies (Table 1) demonstrating miR-199a's role as a tumor suppressor in ccRCC. Likewise, Samaan et al. demonstrated miR-210 as a potential prognostic marker in ccRCC, but the expression levels were more attenuated in other subtypes of RCC including papillary, chromophobe, and benign oncocytoma (216). Several studies have also looked at differing miRNA signatures in being able to uniquely identify the subtypes of RCC (225, 226). Given the paucity of miRNA studies exclusive to pRCC or chromophobe RCC, it remains difficult at this time to draw conclusions of metastamiRs in non-ccRCC tumors.

ROLE OF LNCRNA IN METASTAMIR REGULATION IN RCC

Recently, emerging studies have shown lncRNA plays an important regulatory role alongside metastamiRs in RCC. Sun et al. showed how the lncRNA XIST directly interacts with oncomiR miR-106b-5p to silence its effects on downstream genes, resulting in tumor suppression activity (227). Other studies have demonstrated how certain lncRNA, such as MALAT1, act as a "sponge" that can silence tumor suppressor miRNA, resulting in increased cell proliferation and invasion; experiments have subsequently shown how knocking down these lncRNA can rescue tumor suppressive miRNAs and their respective functions (128, 145, 228). The relationship between lncRNA and metastamiRs presents a novel development that, with further studies, may also portend future directions in prognosis and treatment.

MIRNAS AS BIOMARKERS OR THERAPY IN RCC

As shown in the above tables, several metastamiRs have been postulated to be useful as potential biomarkers of prognosis, disease progression, or metastasis. Several metastamiRs could also serve as potential predictors for responsiveness to chemotherapeutic regimens (229). One of the more promising prognosticators for disease progression is the oncomiR miR-21, as several studies have commented on its potential utility as a ccRCC-specific miRNA signature of disease progression (24, 25, 135, 193). Similarly, miR-10b and the miR-200 family are tumor suppressors that have been demonstrated to be downregulated in mRCC and are

quantitatively associated with worse prognosis (68, 135, 138, 139). While several more metastamiRs have been proposed as predictors of disease progression, conflicting reports of their function in literature ultimately makes their utility inconclusive at this time (see Table 3). Thus, no metastamiR has currently supplanted existing calculators and nomograms for RCC prognosis, namely MSKCC, UCLA, and SSIGN (229). Furthermore, there are no clinical trials or practices to date of utilizing miRNA-targeted therapies for patients with mRCC. More research is needed to strengthen existing conclusions and clarify conflicting findings of metastamiRs in the treatment, diagnosis, and prognosis of RCC.

CONCLUSION

MiRNAs play a paramount role in cancer biogenesis, and in the case of RCC, miRNA expression can either promote or suppress the metastatic process by affecting cell proliferation, migration, invasion, and viability. Several miRNAs have also been associated with increased resistance to standard chemotherapeutic regimens (i.e., sunitinib) for RCC. While many of the metastamiRs discussed concerning RCC can be categorized broadly as metastasis-promoting or metastasis-suppressing miRNA, there remain a significant number of miRNA with seemingly contradicting properties - a testament to the complexity of miRNA regulation underpinning mRCC. In addition to directly inhibiting downstream mRNA, some metastamiRs have been postulated to interact with lncRNA and act as a "sponge" to prevent their oncogenic or tumor suppressive abilities. In terms of impending development, miRNAs have potential to function as prognostic indicators for predicting patient response to treatment or patient survival, though no current nomogram or prognostic calculator for RCC survival currently incorporates miRNA, and their role in targeted therapy and diagnosis remain to be seen. Future research of miRNA in RCC will likely see further investigation into elucidating the molecular underpinnings behind the contradictory metastamiRs as well as the possibility of their role in patient-centered targeted treatment and prediction of metastatic disease.

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