Journal of Human Genetics (2017) 62, 49–56

www.nature.com/jhg

REVIEW

Aberrantly expressed microRNAs in bladder cancer and renal cell carcinoma

Akira Kurozumi[1,2], Yusuke Goto[1,2], Atsushi Okato[1,2], Tomohiko Ichikawa[2] and Naohiko Seki[1]

Bladder cancer (BC) and renal cell carcinoma (RCC) are frequently diagnosed urinary tract cancers. Recently developed molecular-targeted therapies for RCC have shown remarkable therapeutic efficacy; however, no targeted therapeutics are currently approved for the treatment of BC, and few effective treatment options exist. Current studies have shown that small noncoding RNA molecules have major roles in cancer cells. MicroRNAs (miRNAs) are endogenous small noncoding RNA molecules that regulate protein-/nonprotein-coding RNAs in human cells. A large body of evidence suggests that aberrantly expressed miRNAs are deeply involved in the pathogenesis of human cancers. In this paper, we review recently published miRNA expression signatures of BC and RCC. We focus on downregulated or upregulated miRNAs in multiple signatures and discuss putative target genes of miRNAs. Comparisons of RCC and BC expression signatures revealed that the two types of cancer showed opposite expression patterns for *miR-200* family miRNAs (i.e., *miR-141/200c* and *miR-200a/200b/429*). We discuss *in silico* analysis of genes targeted by *miR-200* family miRNAs and the molecular mechanisms underlying BC and RCC.
Journal of Human Genetics (2017) **62,** 49–56; doi:10.1038/jhg.2016.84; published online 30 June 2016

INTRODUCTION

Bladder cancer (BC) and renal cell carcinoma (RCC) are frequently diagnosed urinary tract cancers, and ~429 000 and 338 000 new cases, respectively, were diagnosed worldwide in 2012.[1] Recently developed molecular-targeted therapies for RCC have shown remarkable therapeutic efficacy; however, no targeted therapeutics are currently approved for the treatment of BC. Consequently, the survival rate for invasive BC has not improved in the past decade.

BC is the eighth leading cause of death in men in the United States of America, accounting for an estimated 4% of deaths in men in 2016.[2] For non-muscle-invasive BC, transurethral surgical resection and intravesical installation of immunotherapeutic agents such as bacillus Calmette-Guerin or chemotherapeutic agents such as mitomycin C are the primary suggested treatments; however, the recurrence rate is high for this type of BC. Moreover, the prognosis of patients with muscle-invasive BC is poor, with a 5-year survival rate of <50%. Specifically, metastatic BC is difficult to treat, with a median survival of ~8 months without treatment and 14 months with treatment.[3] Despite the high prevalence and mortality rates of BC, its molecular mechanisms are poorly understood and the primary approach to treat metastatic BC remains cisplatin-based conventional chemotherapy.

RCC accounts for over 80% of kidney cancers. Kidney cancer is the seventh leading cause of newly diagnosed cancer in the United States of America. The incidence of RCC is increasing because of recent improvements in screening methods; that is, ultrasound and computed tomography. In localized RCC, surgery is the standard curative treatment. Although recent molecular-targeted agents have improved prognoses in patients with advanced RCC, the 5-year survival rate is still low (12.3%) because of recurrence or distant metastasis.[4] Therefore, understanding the molecular mechanisms underlying BC and RCC using current genomic technologies is urgently needed.

MicroRNAs (miRNAs) are a class of small (19–22 nucleotides) noncoding RNA molecules that regulate protein-coding/noncoding RNA expression in a sequence-dependent manner.[5,6] A large body of evidence has suggested that miRNAs are aberrantly expressed in many human cancers and are deeply involved in cancer pathogenesis.[7–9] Some highly expressed miRNAs in cancer tissues may function as oncogenes by repressing tumor suppressors; conversely, miRNAs expressed at low levels in cancer tissues may function as tumor suppressors by negatively regulating oncogenes.[7,10] Aberrant expression of miRNAs may be caused by disruption of the RNA network in cancer cells.[7,9,10] Therefore, identification of aberrantly expressed miRNAs in cancer cells may provide important insights into novel RNA networks in cancer cells. In this review, we summarize aberrantly expressed miRNAs based on current BC and RCC miRNA signatures.[11–23] We discuss the dysregulated expression of the *miR-200* family and *miR-200* family target genes in BC and RCC.

miRNA expression signatures in BC

We reviewed seven recently published miRNA expression signatures comparing BC and normal bladder epithelium (Table 1).[11–17] The analysis platforms varied between studies. Two recent signatures were constructed from deep sequencing, and the other five signatures were

[1]Department of Functional Genomics, Graduate School of Medicine, Chiba University, Chiba, Japan and [2]Department of Urology, Graduate School of Medicine, Chiba University, Chiba, Japan
Correspondence: Dr N Seki, Department of Functional Genomics, Graduate School of Medicine, Chiba University, 1-8-1 Inohana Chuo-ku, Chiba 260-8670, Japan.
E-mail: naoseki@faculty.chiba-u.jp
Received 2 April 2016; revised 25 May 2016; accepted 26 May 2016; published online 30 June 2016

Table 1 Differentially expressed miRNAs in BC

Author	Year	Sample	Number of tissues (normal/cancer)	Downregulated miRNAs	Upregulated miRNAs	Analysis platform
Itesako *et al.*[11]	2014	Clinical tissue	10 (5/5)	*miR-1, miR-133a, miR-145, let-7c, miR-133b, miR-143, miR-139-5p, miR--145*, miR-490-3p, miR-3914, miR-204, miR-99a*, miR-206, miR-383, miR--125b, miR-99a, miR-451, miR-144*, miR-3656, miR-486-5p, miR-218-1*, miR-195, miR-139-3p, miR-100, miR-1265, miR-30a*, miR-23b, miR-3622a-5p, miR-143*, miR-144, miR-125b-2*, miR-887, miR-1258, miR-490-5p, miR-30c-2*, miR-129*, miR-199b-5p, miR-1247, miR-873, miR-497, miR--338-5p, miR-223, miR-202, miR-30a, miR-199a-3p, miR-1298, miR-202*, miR-199b-3p, miR-100*, miR-130a, miR-3154, miR-125b-1*, miR-137, miR--337-3p, miR-299-5p, miR-152, miR-199a-5p, miR-23b*, miR-338-3p, miR-127-3p*	Data not shown	Deep sequencing (Illumina Genome Analyzer IIx, Illumina Inc, San Diego, CA, USA)
Han *et al.*[12]	2011	Clinical tissue (FFPE)	18 (9/9 (adjacent))	*miR-490-5p, miR-99a*, miR-490-3p, miR-125b-2*, miR-99a, miR-133a, miR--1, miR-125b, miR-145, miR-195, miR-143*, miR-145*, let-7c, miR-100, miR-143*	*miR-96, miR-182, miR-183, miR-429, miR-141, miR-200c, miR-200a, miR-200b, miR-18a, miR-7, miR-25*, miR-19b, miR-19a, miR-17, miR-20a*	Deep sequencing (Illumina Genome Analyzer IIx, Illumina Inc.)
Canturk *et al.*[13]	2014	Clinical tissue	35 (8/27)	*let-7c, miR-125b-5p, miR-143-3p, miR-145-5p, miR-193a-3p, miR-195-3p, miR-23b-3p, miR-23b-5p, miR-27b-3p, miR-30a-5p, miR-572, miR-57-3p, miR-638*	*miR-141-3p, miR-193b-5p, miR-370, miR-200b-3p, miR-210*	Microarray (Agilent for 723 human and 76 viral miRNAs)
Ratert *et al.*[14]	2013	Clinical tissue	24 (8/16)	*miR-100, miR-125b, miR-130a, miR-139-5p, miR-143, miR-145, miR-145*, miR-148a, miR-195, miR-199a-3p, miR-214, miR-222, miR-490-5p, miR-564*	*miR-7, miR-19a, miR-19b, miR-20a, miR-106b, miR-130b, miR-141, miR-200a, miR-200a*, miR--205, miR-210*	Microarray (Agilent 8-plex 15K miRNA microarrays (Agilent Technologies Inc, Santa Clara, CA, USA) for 799 miRNAs)
Dyrskjot *et al.*[15]	2009	Clinical tissue	117 (11/106)	*miR-455-5p, miR-143, miR-145, miR-126*, miR-26a, miR-125b, miR-498, miR-489, miR-503, miR-29a, miR-302b, miR-29c*	*miR-519e*, miR-193a-3p, miR-21, miR-20a, miR--198, miR-510, miR-184, miR-492*	Microarray ((miRCURY LNA, Exiqon) ready to spot v.7.1)
Friedman *et al.*[16]	2009	Clinical tissue	18 (9/9 (adjacent))	*miR-1, miR-101, miR-143, miR-145, miR-29c, miR-127*	*miR-183, miR-182, miR-203, miR-224, miR-196a, miR-10a*	Microarray (LC Sciences, Houston, TX, USA)
Lin *et al.*[17]	2009	Clinical tissue	12 (6/6 (adjacent))	*let-7, miR-23b, miR-29a, miR-30-5p, miR-125a, miR-125b, miR-126, miR-143, miR-145, miR-150, miR-193a, miR-195, miR-199b, miR-221*	*miR-17-5p, miR-18a, miR-19, miR-20a, miR-25, miR-31, miR-93, miR-106a, miR-200a, miR-200c, miR-210, miR-324-5p*	Microarray (CapitalBio, Beijing, China)

Abbreviations: BC, bladder cancer; FFPE, formalin-fixed, paraffin-embedded; miRNA, microRNA.

Table 2 Frequently down-or upregulated miRNAs in BC

No. of studies	*Hsa-mature sequence*	*Stem-loop sequence*	*Locus*	*Clustered miRNAs (within 10 kbp)*
Downregulated miRNAs				
6	*Hsa-miR-125b*	*Hsa-miR-125b-1*	11q24.1	—
		Hsa-miR-125b-2	21q21.1	—
6	*Hsa-miR-143-3p*	*Hsa-miR-143*	5q32	*Hsa-miR-145*
5	*Hsa-miR-145-5p*	*Hsa-miR-145*	5q32	*Hsa-miR-143*
4	*Hsa-miR-145-3p*	*Hsa-miR-145*	5q32	*Hsa-miR-143*
4	*Hsa-miR-195-5p*	*Hsa-miR-195*	17p13.1	*Hsa-miR-497*
4	*Hsa-let-7c-5p*	*Hsa-let-7c*	21q21.1	*Hsa-miR-99a*
3	*Hsa-miR-23b-3p*	*Hsa-miR-23b*	9q22.32	*Hsa-miR-27b/hsa-miR-3074/hsa-miR-24-1*
3	*Hsa-miR-100-5p*	*Hsa-miR-100*	11q24.1	*Hsa-let-7a-2*
3	*Hsa-miR-490-5p*	*Hsa-miR-490*	7q33	—
Upregulated miRNAs				
4	*Hsa-miR-20a-5p*	*Hsa-miR-20a*	13q31.3	*Hsa-miR-17/hsa-miR-18a/hsa-miR-19a/hsa-miR-19b-1/hsa-miR-92a-1*
3	*Hsa-miR-141-3p*	*Hsa-miR-141*	12p13.31	*Hsa-miR-200c*
3	*Hsa-miR-200a-3p*	*Hsa-miR-200a*	1p36.33	*Hsa-miR-200b/hsa-miR-429*
3	*Hsa-miR-210-3p*	*Hsa-miR-210*	11p15.5	—

Abbreviations: BC, bladder cancer; miRNA, microRNA.

constructed from microarray-based analyses. Array-based technologies rapidly identify differentially expressed miRNAs. However, detected miRNAs depend on the number of the probes mounted on the array. Recent development of deep-sequencing technologies proved the novel miRNAs and minor miRNAs such as passenger strands. Several studies demonstrated that passenger strands of miRNAs acted as tumor-suppressive miRNAs in several cancers.[24,25] In this review, to clearly summarize these miRNA signatures, we focused on commonly downregulated miRNAs or upregulated miRNAs regardless of the platforms and backgrounds of clinical tissues. We sorted these miRNAs by the number of studies because we assumed that miRNAs found in more signatures may have important roles in BC (Table 2).

Downregulated miRNAs in multiple BC signatures

Six of seven signatures showed downregulation of *miR-125b* and *miR-143-3p* in BC clinical tissues. Multiple articles described the tumor-suppressive role of *miR-125b* in BC, showing that this miRNA targeted oncogenes such as *E2F3*, *SphK1*, *SIRT7*, *MALAT1* and *MMP13*.[26–29] *miR-125b* functions as a tumor suppressor in ovarian cancer, breast cancer, osteosarcoma and bladder cancer.[26–32] However, in prostate cancer, glioma and leukemia, *miR-125b* functions as an oncogene by targeting tumor suppressors.[33–35]

miR-143-3p, *miR-145-5p* and *miR-145-3p* are clustered on chromosome 5q32, and multiple signatures have shown that these miRNAs are downregulated in BC. Putative oncogenes regulated by *miR-143* or *miR-145* in BC include *ERK5*, *Akt*, *FSCN1*, *IGF1R*, *PAK1* and *PAI-1*.[36–40] Interestingly, miRNAs in this cluster function as tumor suppressors in a variety of cancers, including BC, and few reports have described oncogenic roles of *miR-143* or *miR-145*.[40–43] Thus, members of the *miR-143/145* cluster commonly function as tumor suppressors, independent of the cancer type.

Upregulated miRNAs in multiple BC signatures

miR-20a-5p was the most frequently upregulated miRNA in BC (Table 2). *miR-20a* has an oncogenic function in colorectal cancer and gallbladder carcinoma,[44,45] but a tumor-suppressive function in hepatocellular carcinoma, oral squamous cell carcinoma and pancreatic carcinoma.[46–48] *miR-20a* is clustered with *miR-17/18a/19a/19b-1/92a-1* on chromosome 13q31.3; this cluster is known as the *miR-17-92* cluster. Several reports have demonstrated the oncogenic function of this cluster in various types of cancers.[49–51] Furthermore, *miR-18a*, *miR-19a* and *miR-19b* have also been shown to be upregulated in multiple BC profiles (Table 1). Additionally, upregulation of *miR-19a* in tissues and plasma samples from patients with BC has been reported, and this miRNA has been shown to act as an oncogene by targeting *PTEN*, which may have a significant role in human BC.[52,53]

miRNA expression signatures of RCC

We also reviewed six recently published miRNA expression signatures comparing RCC and normal kidney tissue using clinical specimens (Table 3).[18–23] Two signatures were constructed from deep sequencing and the other four signatures were constructed from microarrays. Commonly downregulated miRNAs or upregulated miRNAs in multiple signatures are listed in Table 4, sorted according to the number of signatures.

Downregulated miRNAs in multiple RCC signatures

According to miRNA expression signatures in RCC, five of six signatures showed downregulation of *miR-141* and *miR-200c* in RCC tissues compared with normal tissues (Table 4). *miR-141* and *miR-200c* are clustered within 10 kbp. Recent studies have shown that these miRNAs are downregulated in several cancers, including RCC, and regulate the epithelial-to-mesenchymal transition (EMT) by targeting E-cadherin transcriptional repressors, such as zinc-finger E-box-binding homeobox 1 and 2 (*ZEB1* and *ZEB2*).[54–58] Furthermore, *miR-429*, the third most frequently downregulated miRNA in RCC, forms a cluster with *miR-200a/200b*, and *miR-141/200c* and *miR-200a/200b/429* are members of the *miR-200* family.[55] The *miR-200* family has been reported to be associated with the EMT, either inhibiting or inducing the EMT depending on the cancer type.[55,59] In RCC, many reports have indicated that miRNAs in this family have tumor-suppressive roles and inhibit the EMT.[55,60] Nakada *et al.*[60] reported that *miR-141* and *miR-200c* are downregulated in clear-cell RCC and that these miRNAs may be involved in suppression of *CDH1*/E-cadherin transcription by upregulation of *ZFHX1B*. These

Table 3 Differentially expressed miRNAs in RCC

Author	*Year*	*Sample*	*Number of tissues (normal/cancer)*	*Downregulated miRNAs*	*Upregulated miRNAs*	*Analysis platform*
Ge *et al.*[18]	2015	Clinical tissue	116 (58/58 (adjacent))	*miR-660, miR-30b, miR-204, miR-874, miR-127, miR--199a-2, miR-199b, miR-335, miR-3065, miR-10a, miR--500a, miR-199a-1, miR-675, miR-200b, miR-187, miR-217, miR-363, miR-429, miR-203, miR-362, miR-9-1, miR-9-2, miR-508, miR-200c, miR-141*	*miR-210, miR-155, miR-592, miR-224, miR-142, miR--1270-1, miR-21, miR-452, miR-584, miR-215, miR-629*	Deep sequencing (Illumina Genome Analyzer (Illumina Inc) and HiSeq platforms (Illumina Inc))
Osant *et al.*[19]	2012	Clinical tissue	33 (11/22)	*miR-129b-2-3p, miR-200c-3p, miR-138-1-5p, miR-141-3p, miR-138-2-5p, miR-577-5p, miR-187-3p, miR-199b-5p, miR-874-3p, miR-501-3p, miR-766-3p, miR-203-3p, miR--106a-5p, miR-149-5p, miR-363-3p, miR-20b-5p, miR--891a-5p, miR-532-3p, miR-200b-5p, miR-429-3p, miR-107-3p, miR-200b-3p, miR-532-5p, miR-10a-5p, miR--494-3p, miR-125b-2-5p, miR-214-3p, miR-409-3p*	*miR-122-5p, miR-224-5p, miR-210-3p, miR-210-5p, miR-155-5p, miR-503-5p, miR-497-3p, miR-21-3p, miR-34a-5p, miR-193a-3p, miR-1271-5p, miR-181c-5p, miR-455-5p, miR-34a-3p, miR-21-5p, miR-15a-5p, miR-148a-3p, miR-27a-3p*	Deep sequencing (Illumina Genome Analyzer II (Illumina Inc))
He *et al.*[20]	2015	Clinical tissue	18 (9/9 (adjacent))	*miR-125b, miR-142-3p, miR-199a-5p, miR-22, miR-299-3p, miR-29a, miR-429, miR-532-5p*	*miR-452, miR-487a, miR-491-3p, miR-200c*	Microarray (miRCURY LNA, Exiqon)
Hidaka *et al.*[21]	2012	Clinical tissue	15 (5/10)	*miR-141, miR-200c, miR-187, miR-509-5p, miR-135a, miR-508-3p, miR-1285, miR-206, miR-218, miR-133b, miR-1291, let-7g*, miR-204, miR-429, miR-370, miR-363, miR-335, miR-1, miR-1255B, miR-362-3p*	Data not shown	Microarray (The TaqMan MicroRNA Array Set v.2.0 (Applied Biosystems, Foster City, CA, USA) for 778 miRNAs)
Weng *et al.*[22]	2010	Frozen and FFPE tissues	Frozen 6 (3/3 (adjacent)) FFPE 6 (3/3 [adjacent])	*miR-184, miR-200c, miR-141, miR-9, miR-934, miR-138, miR-135b, miR-335, miR-199b-5p, miR-375, miR-129-5p, miR-483-3p, miR-509-3p, miR-508-3p, miR-514, miR-891a, miR-509-5p, miR-506, miR-206*	*miR-122, miR-875-5p, miR-599, miR-210, miR-885-5p, miR-1270, miR-592, miR-155, miR-224, miR–599, miR-486-3p*	Microarray (MicroRNA Human Version 2 Microarray (Agilent Technologies Inc); probes for 723 human, Sanger miRBase 10.1)
Jung *et al.*[23]	2009	Clinical tissue	168 (84/84 (adjacent))	*miR-184, miR-514, miR-200c, miR-510, miR-141, miR-138, miR-429, miR-200b, miR-363, miR-532, miR-660, miR-362, miR-200a, miR-10a, miR-502, miR-204, miR-30a-3p, miR-500, miR-30c, miR-30a-5p*	*miR-122a, miR-18a*, miR-452*, miR-224, miR-210, miR-34b, miR-155, miR-34a, miR-130b, miR-21, miR--142-5p, miR-193a, miR-18a*	Microarray (Agilent 8-plex 15K (Agilent Technologies Inc) for 534 miRNAs)

Abbreviations: FFPE, formalin-fixed, paraffin-embedded; miRNA, microRNA; RCC, renal cell carcinoma.

Table 4 Frequently down-or upregulated miRNAs in RCC

No. of studies	*Hsa-mature sequence*	*Stem-loop sequence*	*Locus*	*Clustered miRNAs (within 10 kbp)*
Downregulated miRNAs				
5	*Hsa-miR-141-3p*	*Hsa-miR-141*	12p13.31	*Hsa-miR-200c*
5	*Hsa-miR-200c-3p*	*Hsa-miR-200c*	12p13.31	*Hsa-miR-141*
4	*Hsa-miR-429*	*Hsa-miR-429*	1p36.33	*Hsa-miR-200b/hsa-miR-200a*
4	*Hsa-miR-363-3p*	*Hsa-miR-363*	Xq26.2	*Hsa-miR-106a/hsa-miR-18b/hsa-miR-20b/hsa-miR-19b-2/hsa-miR-92a-2*
3	*Hsa-miR-200b-3p*	*Hsa-miR-200b*	1p36.33	*Hsa-miR-200a/hsa-miR-429*
3	*Hsa-miR-362-3p*	*Hsa-miR-362*	Xp11.23	*Hsa-miR-532/hsa-miR-188/hsa-miR-500a/hsa-miR-501/hsa-miR-500b/hsa-miR-660/hsa-miR-502*
3	*Hsa-miR-532-5p*	*Hsa-miR-532*	Xp11.23	*Hsa-miR-188/hsa-miR-500a/has-miR-362/hsa-miR-501/hsa-miR-500b*
3	*Hsa-miR-508-3p*	*Hsa-miR-508*	Xq27.3	*Hsa-miR-507/hsa-miR-506*
3	*Hsa-miR-10a-5p*	*Hsa-miR-10a*	17q21.32	—
3	*Hsa-miR-187-3p*	*Hsa-miR-187*	18q12.2	—
3	*Hsa-miR-204-5p*	*Hsa-miR-204*	9q21.12	—
3	*Hsa-miR-335-5p*	*Hsa-miR-335*	7q32.2	—
Upregulated miRNAs				
4	*Hsa-miR-155-5p*	*Hsa-miR-155*	21q21.3	—
4	*Hsa-miR-210-3p*	*Hsa-miR-210*	11p15.5	—
4	*Hsa-miR-224-5p*	*Hsa-miR-224*	Xq28	*Hsa-miR-452*
3	*Hsa-miR-21-5p*	*Hsa-miR-21*	17q23.1	—

Abbreviations: miRNA, microRNA; RCC, renal cell carcinoma.

findings suggest the importance of the EMT-related *miR-200* family in RCC oncogenesis and metastasis.

Upregulated miRNAs in multiple RCC signatures

Four of six signatures have shown upregulation of *miR-155*, *miR-210* and *miR-224* in RCC (Table 4).

Gao *et al.*[61] reported that *miR-155* contributes to the proliferation and invasion of clear-cell RCC by directly targeting *E2F2*, which has crucial roles in the regulation of cell proliferation. Upregulation of *miR-155* has also been found in several other types of cancer, such as colorectal cancer, breast cancer and lymphoma.[62–64]

miR-210 has been reported to function as an oncogene and have applications as a potential serum biomarker in RCC. Interestingly, *miR-210* has been reported to be a hypoxia-inducible miRNA. Given the key roles of the VHL-HIF pathway in RCC, the upregulation of *miR-210* may be one of the central mechanisms of RCC oncogenesis. *miR-210* is also frequently upregulated in other cancer tissues and has been shown to have an oncogenic function in other human cancers, including BC (Table 2).[65–71]

miR-224 has an oncogenic function in colorectal cancer, lung cancer, esophageal squamous cell carcinoma and RCC,[72–76] but a tumor-suppressive function in prostate cancer.[77] Cheng *et al.*[76] reported that *miR-224* was upregulated in clear-cell RCC and directly targeted type 1 iodothyronine deiodinase.[75]

COMPARISON OF MIRNA EXPRESSION SIGNATURES IN BC AND RCC

Careful analysis of Tables 2 and 4 showed that some members of the *miR-200* family (*miR-141/200c* and *miR-200a/200b/429*) are frequently upregulated in BC, but are frequently downregulated in RCC. This phenomenon indicates that these miRNAs have opposing roles in RCC and BC. Furthermore, these miRNAs may target tumor suppressors in BC and oncogenes in RCC.

The members of the *miR-200* family are clustered on two different chromosomal regions: *miR-141* and *miR-200c* are on chromosome 12p13.31, whereas *miR-200a*, *miR-200b* and *miR-429* are on chromosome 1p36.33. Additionally, members of the *miR-200* family are classified into two groups (*miR-141/200a* and *miR-200b/c/429*) according to their seed sequence.

In cancer, the promoter region of the *miR-141/200c* cluster is hypermethylated, and the *miR-200a/200b/429* cluster is silenced through polycomb group-mediated histone modifications.[78–80] Recent studies indicated that several types of transcription factors bound to the promoter region of *miR-200* family and these transcription factors regulated the transcription of the *miR-200* family positively or negatively. Among them, Krüppel-like factor 5 positively regulates the transcription of the *miR-200* family.[81] In contrast, *ZEB1*, *ZEB2* and B lymphoma Mo-MLV insertion region 1 homolog negatively regulate the transcription of *miR-200* family.[82,83] To investigate the expression levels of these transcriptional factors, we used gene expression omnibus (GEO) database. According to these database, Krüppel-like factor 5 was downregulated in RCC compared with normal kidney tissue (GEO accession nos. GSE22541 and GSE36895). Furthermore, *ZEB1*, *ZEB2* and B lymphoma Mo-MLV insertion region 1 homolog were downregulated in BC tissue compared with normal bladder epithelium (GEO accession nos. GSE11783 and GSE31684). Aberrant expression of transcription factors may have an influence on the expression status of the *miR-200* family in BC and RCC.

Next, we analyzed putative target genes for *miR-200* family in these two cancers. We performed genome-wide gene expression analysis and *in silico* analysis. First, we screened putative target genes of the *miR-200* family using TargetScan Release 7.0 (Whitehead Institute for Biomedical Research, Cambridge, MA, USA). Next, we analyzed a publicly available gene expression data set in the GEO database of BC and RCC (accession number: GSE36895, GSE22541, GSE11783 and GSE31684). To select putative genes that function as tumor suppressors in BC and oncogenes

Table 5 Putative target genes of the miR-200 family in RCC and BC

Target gene	Gene name	No. of conserved target sites of miR--200bc/429	No. of poorly conserved target sites of miR-200bc/429	No. of conserved target sites of miR--200a/141	No. of poorly conserved target sites of miR-200a/141	RCC GEO (GSE36895, GSE22541) average fold-change > 1 (a)	BC GEO (GSE11783, GSE31684) average fold-change < −1 (b)	(a)–(b)
TRPA1	*Transient receptor potential cation channel, subfamily A, member 1*	0	1	0	1	2.078	−3.402	5.480
RGS5	*Regulator of G-protein signaling 5*	0	2	0	1	2.239	−2.400	4.639
BHLHE41	*Basic helix–loop–helix family, member e41*	1	0	0	1	3.242	−1.105	4.347
TLR3	*Toll-like receptor 3*	0	2	0	1	2.049	−2.097	4.146
GPR20	*G-protein-coupled receptor 20*	0	1	0	1	1.676	−1.935	3.612
MEF2C	*Myocyte enhancer factor 2C*	0	1	0	1	1.429	−2.071	3.500
MAP1B	*Microtubule-associated protein 1B*	2	0	0	1	1.483	−1.707	3.190
CCDC85A	*Coiled-coil domain containing 85A*	0	1	0	2	1.223	−1.683	2.905
RGS18	*Regulator of G-protein signaling 18*	0	2	0	3	1.553	−1.349	2.901
HLA-DPA1	*Major histocompatibility complex, class II, DP α1*	0	1	0	1	1.294	−1.538	2.831
TCF4	*Transcription factor 4*	2	0	2	1	1.474	−1.323	2.797
CELF2	*CUGBP, Elav-like family member 2*	1	1	0	1	1.002	−1.791	2.794
NR3C1	*Nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)*	1	1	1	0	1.078	−1.660	2.738
PREX2	*Phosphatidylinositol-3,4,5-trisphosphate-dependent Rac exchange factor 2*	0	1	0	1	1.146	−1.586	2.732
SLFN5	*Schlafen family member 5*	0	1	0	1	1.379	−1.112	2.491
ITGA4	*Integrin, α4 (antigen CD49D, α4 subunit of VLA-4 receptor)*	0	1	0	1	1.224	−1.048	2.272
GNG2	*Guanine nucleotide-binding protein (G protein), γ2*	0	1	0	1	1.019	−1.029	2.048

Abbreviations: BC, bladder cancer; GEO, gene expression omnibus; GSE, GEO data series; miR, miRNA; RCC, renal cell carcinoma.

in RCC, we screened downregulated genes in BC compared with normal bladder epithelium (average log FC < -1) and upregulated genes in RCC compared with normal kidney tissue (average log FC >1). We merged these data sets, and 17 putative genes were identified (Table 5). These genes were sorted by the difference between expression in RCC and BC. *TRPA1* was upregulated in RCC and downregulated in BC and has putative target sites for members of the *miR-200* family. Therefore, we speculated that *TRPA1* may be critical in RCC and BC oncogenesis based on this search of *miR-200* family-regulated genes.

TRPA1 is a member of the transient receptor potential (TRP) cation channel subfamily. Although transient receptor potential channels function as key regulators of oncogenesis and metastasis, their oncogenic and tumor-suppressive roles are not consistent among different types of cancers.[84] As shown in Table 5, *TRPA1* may function as an oncogene in RCC but a tumor suppressor in BC. Furthermore, Veldhuis *et al.* reported that transient receptor potential and G-protein-coupled receptors function independently and synergistically to excite sensory nerves.[85] G-protein-coupled receptors are seven-transmembrane-spanning receptors that modulate several biological functions, including cancer progression.[86,87] Several G-protein-related genes (*RGS5*, *GPR*, *RGS18* and *GNG2*) have been shown to be upregulated in RCC and downregulated in BC (Table 5). Therefore, we hypothesize that G-protein-coupled receptor-transient receptor potential channel interactions may be key regulators of downstream signaling (oncogenic or tumor-suppressive pathways) in these two types of urinary tract cancers.

CONCLUSIONS

A growing body of evidence has shown that various aberrantly expressed miRNAs contribute to BC and RCC pathogenesis. The

discovery of noncoding RNA in the human genome has provided evidence of the complexity of the RNA network in normal and cancer cells. For further elucidation of novel RNA networks in cancer cells, miRNA information will need to be organized based on expression signatures. The present review highlighted recent findings of the aberrant expression of miRNAs in BC and RCC cells. The discovery of miRNA-regulated RNA networks in cancer cells has provided new opportunities for strategies in cancer diagnosis and treatment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This study was supported by the KAKENHI, grant numbers (B) 15K20071, (C) 15K10801 and (B) 25293333.

1 Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M. *et al.* Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int. J. Cancer* **136**, E359–E386 (2015).
2 Siegel, R. L., Miller, K. D. & Jemal, A. Cancer statistics, 2016. *Cancer J. Clin.* **66**, 7–30 (2016).
3 Bellmunt, J., Teh, B. T., Tortora, G. & Rosenberg, J. E. Molecular targets on the horizon for kidney and urothelial cancer. *Nat. Rev. Clin. Oncol.* **10**, 557–570 (2013).
4 Motzer, R. J., Jonasch, E., Agarwal, N., Beard, C., Bhayani, S., Bolger, G. B. *et al.* Kidney cancer, version 3.2015. *J. Natl. Compr. Cancer Netw.* **13**, 151–159 (2015).
5 Filipowicz, W., Bhattacharyya, S. N. & Sonenberg, N. Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight? *Nat. Rev. Genet.* **9**, 102–114 (2008).
6 Bartel, D. P. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* **116**, 281–297 (2004).
7 Nelson, K. M. & Weiss, G. J. MicroRNAs and cancer: past, present, and potential future. *Mol. Cancer Ther.* **7**, 3655–3660 (2008).
8 Goto, Y., Kurozumi, A., Enokida, H., Ichikawa, T. & Seki, N. Functional significance of aberrantly expressed microRNAs in prostate cancer. *Int. J. Urol.* **22**, 242–252 (2015).
9 Esquela-Kerscher, A. & Slack, F. J. Oncomirs—microRNAs with a role in cancer. *Nat. Rev. Cancer* **6**, 259–269 (2006).
10 Calin, G. A. & Croce, C. M. MicroRNA signatures in human cancers. *Nat. Rev. Cancer* **6**, 857–866 (2006).
11 Itesako, T., Seki, N., Yoshino, H., Chiyomaru, T., Yamasaki, T., Hidaka, H. *et al.* The microRNA expression signature of bladder cancer by deep sequencing: the functional significance of the miR-195/497 cluster. *PLoS ONE* **9**, e84311 (2014).
12 Han, Y., Chen, J., Zhao, X., Liang, C., Wang, Y., Sun, L. *et al.* MicroRNA expression signatures of bladder cancer revealed by deep sequencing. *PLoS ONE* **6**, e18286 (2011).
13 Canturk, K. M., Ozdemir, M., Can, C., Oner, S., Emre, R., Aslan, H. *et al.* Investigation of key miRNAs and target genes in bladder cancer using miRNA profiling and bioinformatic tools. *Mol. Biol. Rep.* **41**, 8127–8135 (2014).
14 Ratert, N., Meyer, H. A., Jung, M., Lioudmer, P., Mollenkopf, H. J., Wagner, I. *et al.* miRNA profiling identifies candidate mirnas for bladder cancer diagnosis and clinical outcome. *J. Mol. Diagn.* **15**, 695–705 (2013).
15 Dyrskjot, L., Ostenfeld, M. S., Bramsen, J. B., Silahtaroglu, A. N., Lamy, P., Ramanathan, R. *et al.* Genomic profiling of microRNAs in bladder cancer: miR-129 is associated with poor outcome and promotes cell death *in vitro*. *Cancer Res.* **69**, 4851–4860 (2009).
16 Friedman, J. M., Liang, G., Liu, C. C., Wolff, E. M., Tsai, Y. C., Ye, W. *et al.* The putative tumor suppressor microRNA-101 modulates the cancer epigenome by repressing the polycomb group protein EZH2. *Cancer Res.* **69**, 2623–2629 (2009).
17 Lin, T., Dong, W., Huang, J., Pan, Q., Fan, X., Zhang, C. *et al.* MicroRNA-143 as a tumor suppressor for bladder cancer. *J. Urol.* **181**, 1372–1380 (2009).
18 Ge, Y. Z., Wu, R., Xin, H., Zhu, M., Lu, T. Z., Liu, H. *et al.* A tumor-specific microRNA signature predicts survival in clear cell renal cell carcinoma. *J. Cancer Res. Clin. Oncol.* **141**, 1291–1299 (2015).
19 Osanto, S., Qin, Y., Buermans, H. P., Berkers, J., Lerut, E., Goeman, J. J. *et al.* Genome-wide microRNA expression analysis of clear cell renal cell carcinoma by next generation deep sequencing. *PLoS ONE* **7**, e38298 (2012).
20 He, H., Wang, L., Zhou, W., Zhang, Z., Wang, L., Xu, S. *et al.* MicroRNA expression profiling in clear cell renal cell carcinoma: identification and functional validation of key miRNAs. *PLoS ONE* **10**, e0125672 (2015).
21 Hidaka, H., Seki, N., Yoshino, H., Yamasaki, T., Yamada, Y., Nohata, N. *et al.* Tumor suppressive microRNA-1285 regulates novel molecular targets: aberrant expression and functional significance in renal cell carcinoma. *Oncotarget* **3**, 44–57 (2012).
22 Weng, L., Wu, X., Gao, H., Mu, B., Li, X., Wang, J. H. *et al.* MicroRNA profiling of clear cell renal cell carcinoma by whole-genome small RNA deep sequencing of paired frozen and formalin-fixed, paraffin-embedded tissue specimens. *J. Pathol.* **222**, 41–51 (2010).
23 Jung, M., Mollenkopf, H. J., Grimm, C., Wagner, I., Albrecht, M., Waller, T. *et al.* MicroRNA profiling of clear cell renal cell cancer identifies a robust signature to define renal malignancy. *J. Cell. Mol. Med.* **13**, 3918–3928 (2009).
24 Matsushita, R., Seki, N., Chiyomaru, T., Inoguchi, S., Ishihara, T., Goto, Y. *et al.* Tumour-suppressive microRNA-144-5p directly targets CCNE1/2 as potential prognostic markers in bladder cancer. *Br. J. Cancer* **113**, 282–289 (2015).
25 Matsushita, R., Yoshino, H., Enokida, H., Goto, Y., Miyamoto, K., Yonemori, M. *et al.* Regulation of UHRF1 by dual-strand tumor-suppressor microRNA-145 (miR-145-5p and miR-145-3p): Inhibition of bladder cancer cell aggressiveness. *Oncotarget* **7**, 28460–28487 (2016).
26 Huang, L., Luo, J., Cai, Q., Pan, Q., Zeng, H., Guo, Z. *et al.* MicroRNA-125b suppresses the development of bladder cancer by targeting E2F3. *Int. J. Cancer* **128**, 1758–1769 (2011).
27 Zhao, X., He, W., Li, J., Huang, S., Wan, X., Luo, H. *et al.* MiRNA-125b inhibits proliferation and migration by targeting SphK1 in bladder cancer. *Am. J. Transl. Res.* **7**, 2346–2354 (2015).
28 Han, Y., Liu, Y., Zhang, H., Wang, T., Diao, R., Jiang, Z. *et al.* Hsa-miR-125b suppresses bladder cancer development by down-regulating oncogene SIRT7 and oncogenic long noncoding RNA MALAT1. *FEBS Lett.* **587**, 3875–3882 (2013).
29 Wu, D., Ding, J., Wang, L., Pan, H., Zhou, Z., Zhou, J. *et al.* microRNA-125b inhibits cell migration and invasion by targeting matrix metallopeptidase 13 in bladder cancer. *Oncol. Lett.* **5**, 829–834 (2013).
30 Guan, Y., Yao, H., Zheng, Z., Qiu, G. & Sun, K. MiR-125b targets BCL3 and suppresses ovarian cancer proliferation. *Int. J. Cancer* **128**, 2274–2283 (2011).
31 Zhang, Y., Yan, L. X., Wu, Q. N., Du, Z. M., Chen, J., Liao, D. Z. *et al.* miR-125b is methylated and functions as a tumor suppressor by regulating the ETS1 proto-oncogene in human invasive breast cancer. *Cancer Res.* **71**, 3552–3562 (2011).
32 Wang, F., Yu, D., Liu, Z., Wang, R., Xu, Y., Cui, H. *et al.* MiR-125b functions as a tumor suppressor and enhances chemosensitivity to cisplatin in osteosarcoma. *Technol. Cancer Res. Treat.* (e-pub ahead of print 6 January 2016).
33 Shi, X. B., Xue, L., Yang, J., Ma, A. H., Zhao, J., Xu, M. *et al.* An androgen-regulated miRNA suppresses Bak1 expression and induces androgen-independent growth of prostate cancer cells. *Proc. Natl Acad. Sci. USA* **104**, 19983–19988 (2007).
34 Xia, H. F., He, T. Z., Liu, C. M., Cui, Y., Song, P. P., Jin, X. H. *et al.* MiR-125b expression affects the proliferation and apoptosis of human glioma cells by targeting Bmf. *Cell Physiol Biochem.* **23**, 347–358 (2009).
35 Bousquet, M., Quelen, C., Rosati, R., Mansat-De Mas, V., La Starza, R., Bastard, C *et al.* Myeloid cell differentiation arrest by miR-125b-1 in myelodysplastic syndrome and acute myeloid leukemia with the t(2;11)(p21;q23) translocation. *J. Exp. Med.* **205**, 2499–2506 (2008).
36 Noguchi, S., Mori, T., Hoshino, Y., Maruo, K., Yamada, N., Kitade, Y. *et al.* MicroRNA-143 functions as a tumor suppressor in human bladder cancer T24 cells. *Cancer Lett.* **307**, 211–220 (2011).
37 Chiyomaru, T., Enokida, H., Tatarano, S., Kawahara, K., Uchida, Y., Nishiyama, K. *et al.* miR-145 and miR-133a function as tumour suppressors and directly regulate FSCN1 expression in bladder cancer. *Br. J. Cancer* **102**, 883–891 (2010).
38 Zhu, Z., Xu, T., Wang, L., Wang, X., Zhong, S., Xu, C. *et al.* MicroRNA-145 directly targets the insulin-like growth factor receptor I in human bladder cancer cells. *FEBS Lett.* **588**, 3180–3185 (2014).
39 Kou, B., Gao, Y., Du, C., Shi, Q., Xu, S., Wang, C.Q. *et al.* miR-145 inhibits invasion of bladder cancer cells by targeting PAK1. *Urol. Oncol.* **32**, 846–854 (2014).
40 Villadsen, S. B., Bramsen, J. B., Ostenfeld, M. S., Wiklund, E. D., Fristrup, N., Gao, S. *et al.* The miR-143/-145 cluster regulates plasminogen activator inhibitor-1 in bladder cancer. *Br. J. Cancer* **106**, 366–374 (2012).
41 Kent, O. A., Chivukula, R. R., Mullendore, M., Wentzel, E. A., Feldmann, G., Lee, K. H. *et al.* Repression of the miR-143/145 cluster by oncogenic Ras initiates a tumor-promoting feed-forward pathway. *Genes Dev.* **24**, 2754–2759 (2010).
42 Kojima, S., Enokida, H., Yoshino, H., Itesako, T., Chiyomaru, T., Kinoshita, T. *et al.* The tumor-suppressive microRNA-143/145 cluster inhibits cell migration and invasion by targeting GOLM1 in prostate cancer. *J. Hum. Genet.* **59**, 78–87 (2014).
43 Yoshino, H., Enokida, H., Itesako, T., Kojima, S., Kinoshita, T., Tatarano, S. *et al.* Tumor-suppressive microRNA-143/145 cluster targets hexokinase-2 in renal cell carcinoma. *Cancer Sci.* **104**, 1567–1574 (2013).
44 Xu, T., Jing, C., Shi, Y., Miao, R., Peng, L., Kong, S. *et al.* MicroRNA-20a enhances the epithelial-to-mesenchymal transition of colorectal cancer cells by modulating matrix metalloproteinases. *Exp. Ther. Med.* **10**, 683–688 (2015).
45 Chang, Y., Liu, C., Yang, J., Liu, G., Feng, F., Tang, J. *et al.* MiR-20a triggers metastasis of gallbladder carcinoma. *J. Hepatol.* **59**, 518–527 (2013).
46 Fan, M. Q., Huang, C. B., Gu, Y., Xiao, Y., Sheng, J. X. & Zhong, L. Decrease expression of microRNA-20a promotes cancer cell proliferation and predicts poor survival of hepatocellular carcinoma. *J. Exp. Clin. Cancer Res.* **32**, 21 (2013).
47 Chang, C. C., Yang, Y. J., Li, Y. J., Chen, S. T., Lin, B. R., Wu, T. S. *et al.* MicroRNA-17/20a functions to inhibit cell migration and can be used a prognostic marker in oral squamous cell carcinoma. *Oral Oncol.* **49**, 923–931 (2013).
48 Yan, H., Wu, J., Liu, W., Zuo, Y., Chen, S., Zhang, S. *et al.* MicroRNA-20a overexpression inhibited proliferation and metastasis of pancreatic carcinoma cells. *Hum. Gene Ther.* **21**, 1723–1734 (2010).
49 Chow, T. F., Mankaruos, M., Scorilas, A., Youssef, Y., Girgis, A., Mossad, S *et al.* The miR-17-92 cluster is over expressed in and has an oncogenic effect on renal cell carcinoma. *J. Urol.* **183**, 743–751 (2010).

50 Takakura, S., Mitsutake, N., Nakashima, M., Namba, H., Saenko, V. A., Rogounovitch, T. I. *et al.* Oncogenic role of miR-17-92 cluster in anaplastic thyroid cancer cells. *Cancer Sci.* **99**, 1147–1154 (2008).
51 Hayashita, Y., Osada, H., Tatematsu, Y., Yamada, H., Yanagisawa, K., Tomida, S. *et al.* A polycistronic microRNA cluster, miR-17-92, is overexpressed in human lung cancers and enhances cell proliferation. *Cancer Res.* **65**, 9628–9632 (2005).
52 Feng, Y., Liu, J., Kang, Y., He, Y., Liang, B., Yang, P. *et al.* miR-19a acts as an oncogenic microRNA and is up-regulated in bladder cancer. *J. Exp. Clin. Cancer Res.* **33**, 67 (2014).
53 Calderaro, J., Rebouissou, S., de Koning, L., Masmoudi, A., Herault, A., Dubois, T *et al.* PI3K/AKT pathway activation in bladder carcinogenesis. *Int. J. Cancer* **134**, 1776–1784 (2014).
54 Gregory, P. A., Bert, A. G., Paterson, E. L., Barry, S. C., Tsykin, A., Farshid, G. *et al.* The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1. *Nat. Cell Biol.* **10**, 593–601 (2008).
55 Yoshino, H., Enokida, H., Itesako, T., Tatarano, S., Kinoshita, T., Fuse, M. *et al.* Epithelial–mesenchymal transition-related microRNA-200 s regulate molecular targets and pathways in renal cell carcinoma. *J. Hum. Genet.* **58**, 508–516 (2013).
56 Xu, F., He, H., Huang, W., Lin, Y., Luo, S., Du, Q. *et al.* Decreased expression of MicroRNA-200 family in human breast cancer is associated with lymph node metastasis. *Clin. Transl. Oncol.* **18**, 283–288 (2016).
57 Kim, T., Veronese, A., Pichiorri, F., Lee, T. J., Jeon, Y. J., Volinia, S. *et al.* P53 regulates epithelial–mesenchymal transition through microRNAs targeting ZEB1 and ZEB2. *J. Exp. Med.* **208**, 875–883 (2011).
58 Park, S. M., Gaur, A. B., Lengyel, E. & Peter, M. E. The miR-200 family determines the epithelial phenotype of cancer cells by targeting the E-cadherin repressors ZEB1 and ZEB2. *Genes Dev.* **22**, 894–907 (2008).
59 Massoner, P., Thomm, T., Mack, B., Untergasser, G., Martowicz, A., Bobowski, K. *et al.* EpCAM is overexpressed in local and metastatic prostate cancer, suppressed by chemotherapy and modulated by MET-associated miRNA-200c/205. *Br. J. Cancer* **111**, 955–964 (2014).
60 Nakada, C., Matsuura, K., Tsukamoto, Y., Tanigawa, M., Yoshimoto, T., Narimatsu, T. *et al.* Genome-wide microRNA expression profiling in renal cell carcinoma: significant down-regulation of miR-141 and miR-200c. *J. Pathol.* **216**, 418–427 (2008).
61 Gao, Y., Ma, X., Yao, Y., Li, H., Fan, Y., Zhang, Y. *et al.* miR-155 regulates the proliferation and invasion of clear cell renal cell carcinoma cells by targeting E2F2. *Oncotarget* **7**, 20324–20337 (2016).
62 Li, T., Yang, J., Lv, X., Liu, K., Gao, C., Xing, Y. *et al.* miR-155 regulates the proliferation and cell cycle of colorectal carcinoma cells by targeting E2F2. *Biotechnol. Lett.* **36**, 1743–1752 (2014).
63 Jiang, S., Zhang, H. W., Lu, M. H., He, X. H., Li, Y., Gu, H. *et al.* MicroRNA-155 functions as an OncomiR in breast cancer by targeting the suppressor of cytokine signaling 1 gene. *Cancer Res.* **70**, 3119–3127 (2010).
64 Merkel, O., Hamacher, F., Griessl, R., Grabner, L., Schiefer, A. I., Prutsch, N. *et al.* Oncogenic role of miR-155 in anaplastic large cell lymphoma lacking the t(2;5) translocation. *J. Pathol.* **236**, 445–456 (2015).
65 Camps, C., Buffa, F. M., Colella, S., Moore, J., Sotiriou, C., Sheldon, H. *et al.* hsa-miR-210 is induced by hypoxia and is an independent prognostic factor in breast cancer. *Clin. Cancer Res.* **14**, 1340–1348 (2008).
66 Liu, T. Y., Zhang, H., Du, S. M., Li, J. & Wen, X. H. Expression of microRNA-210 in tissue and serum of renal carcinoma patients and its effect on renal carcinoma cell proliferation, apoptosis, and invasion. *Genet. Mol. Res.* **15**, 1–9 (2016).
67 Petrozza, V., Carbone, A., Bellissimo, T., Porta, N., Palleschi, G., Pastore, A. L. *et al.* Oncogenic microRNAs characterization in clear cell renal cell carcinoma. *Int. J. Mol. Sci.* **16**, 29219–29225 (2015).
68 Iwamoto, H., Kanda, Y., Sejima, T., Osaki, M., Okada, F. & Takenaka, A. Serum miR-210 as a potential biomarker of early clear cell renal cell carcinoma. *Int. J. Oncol.* **44**, 53–58 (2014).
69 Nakada, C., Tsukamoto, Y., Matsuura, K., Nguyen, T. L., Hijiya, N., Uchida, T. *et al.* Overexpression of miR-210, a downstream target of HIF1alpha, causes centrosome amplification in renal carcinoma cells. *J. Pathol.* **224**, 280–288 (2011).
70 Zhao, A., Li, G., Peoc'h, M., Genin, C. & Gigante, M. Serum miR-210 as a novel biomarker for molecular diagnosis of clear cell renal cell carcinoma. *Exp. Mol. Pathol.* **94**, 115–120 (2013).
71 Yang, Y., Qu, A., Liu, J., Wang, R., Liu, Y., Li, G. *et al.* Serum miR-210 contributes to tumor detection, stage prediction and dynamic surveillance in patients with bladder cancer. *PLoS ONE* **10**, e0135168 (2015).
72 Li, T., Lai, Q., Wang, S., Cai, J., Xiao, Z., Deng, D. *et al.* MicroRNA-224 sustains Wnt/beta-catenin signaling and promotes aggressive phenotype of colorectal cancer. *J. Exp. Clin. Cancer Res.* **35**, 21 (2016).
73 Cui, R., Kim, T., Fassan, M., Meng, W., Sun, H. L., Jeon, Y. J. *et al.* MicroRNA-224 is implicated in lung cancer pathogenesis through targeting caspase-3 and caspase-7. *Oncotarget* **6**, 21802–21815 (2015).
74 He, X., Zhang, Z., Li, M., Li, S., Ren, L., Zhu, H. *et al.* Expression and role of oncogenic miRNA-224 in esophageal squamous cell carcinoma. *BMC Cancer* **15**, 575 (2015).
75 Boguslawska, J., Wojcicka, A., Piekielko-Witkowska, A., Master, A. & Nauman, A. MiR-224 targets the 3'UTR of type 1 5'-iodothyronine deiodinase possibly contributing to tissue hypothyroidism in renal cancer. *PLoS ONE* **6**, e24541 (2011).
76 Cheng, T., Wang, L., Li, Y., Huang, C., Zeng, L. & Yang, J. Differential microRNA expression in renal cell carcinoma. *Oncol. Lett.* **6**, 769–776 (2013).
77 Goto, Y., Nishikawa, R., Kojima, S., Chiyomaru, T., Enokida, H., Inoguchi, S. *et al.* Tumour-suppressive microRNA-224 inhibits cancer cell migration and invasion via targeting oncogenic TPD52 in prostate cancer. *FEBS Lett.* **588**, 1973–1982 (2014).
78 Neves, R., Scheel, C., Weinhold, S., Honisch, E., Iwaniuk, K. M., Trompeter, H. I. *et al.* Role of DNA methylation in miR-200c/141 cluster silencing in invasive breast cancer cells. *BMC Res. Notes* **3**, 219 (2010).
79 Castilla, M. A., Diaz-Martin, J., Sarrio, D., Romero-Perez, L., Lopez-Garcia, M. A., Vieites, B. *et al.* MicroRNA-200 family modulation in distinct breast cancer phenotypes. *PLoS ONE* **7**, e47709 (2012).
80 Lim, Y. Y., Wright, J. A., Attema, J. L., Gregory, P. A., Bert, A. G., Smith, E. *et al.* Epigenetic modulation of the miR-200 family is associated with transition to a breast cancer stem-cell-like state. *J. Cell Sci.* **126**, 2256–2266 (2013).
81 Zhang, B., Zhang, Z., Xia, S., Xing, C., Ci, X., Li, X. *et al.* KLF5 activates microRNA 200 transcription to maintain epithelial characteristics and prevent induced epithelial-mesenchymal transition in epithelial cells. *Mol. Cell. Biol.* **33**, 4919–4935 (2013).
82 Burk, U., Schubert, J., Wellner, U., Schmalhofer, O., Vincan, E., Spaderna, S. *et al.* A reciprocal repression between ZEB1 and members of the miR-200 family promotes EMT and invasion in cancer cells. *EMBO Rep.* **9**, 582–589 (2008).
83 Dimri, M., Kang, M. & Dimri, G. P. A miR-200c/141-BMI1 autoregulatory loop regulates oncogenic activity of BMI1 in cancer cells. *Oncotarget* **7**, 36220–36234 (2016).
84 Rodrigues, T., Sieglitz, F. & Bernardes, G. J. Natural product modulators of transient receptor potential (TRP) channels as potential anti-cancer agents. *Chem. Soc. Rev.* (e-pub ahead of print 18 February 2016).
85 Veldhuis, N. A., Poole, D. P., Grace, M., McIntyre, P. & Bunnett, N. W. The G protein-coupled receptor-transient receptor potential channel axis: molecular insights for targeting disorders of sensation and inflammation. *Pharmacol. Rev.* **67**, 36–73 (2015).
86 Yekkirala, A. S. Two to tango: GPCR oligomers and GPCR-TRP channel interactions in nociception. *Life Sci.* **92**, 438–445 (2013).
87 O'Hayre, M., Vazquez-Prado, J., Kufareva, I., Stawiski, E. W., Handel, T. M., Seshagiri, S. *et al.* The emerging mutational landscape of G proteins and G-protein-coupled receptors in cancer. *Nat. Rev. Cancer* **13**, 412–424 (2013).