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Gene Section
Review

MIR200C (microRNA 200c)

Merve Mutlu, Özge Saatçi, Umar Raza, Erol Eyüpoglu, Emre Yurdusev, Özgür Sahin

Department of Molecular Biology and Genetics, Faculty of Science, Bilkent University, 06800, Ankara, Turkey (MM, ÖSaa, UR, EE, EY, ÖSah)

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Abstract

MicroRNAs (miRNAs) are 20-22 nucleotide long small non-coding RNAs and have a function of regulation of gene postranscriptionally via targeting mainly the 3'UTRs of the genes. miR-200c is a member of miR-200 family with 4 other family members (miR-200a, miR-200b, miR-429 and miR-141) located in chromosome 12 (12q13.31) together with miR-141. miRNAs can be classified as oncomiRs and tumor suppressors according to their target gene and which tissue they are expressed. miR-200c has been shown to be a tumor suppressor in various cancer types. miR-200c has been initially shown to regulate epithelial-mesenchymal transition (EMT) by downregulating ZEB1/2 and upregulating E-cadherin, known epithelial marker. Afterwards, it has been demonstrated that miR-200c also have other important functions in proliferation, cell cycle control, apoptosis, anoikis, invasion, and metastasis of cancer and also in other diseases. Furthermore, miR-200c is a well-established prognostic and diagnostic marker in different cancer types.

Keywords
miR-200c, tumor suppressor, epithelial-mesenchymal transition (EMT), ZEB1/2, TGF-β signaling pathway, cancer

Identity

Other names: hsa-mir-200c, MIRN200C, mir-200c

HGNC (Hugo): MIR200C

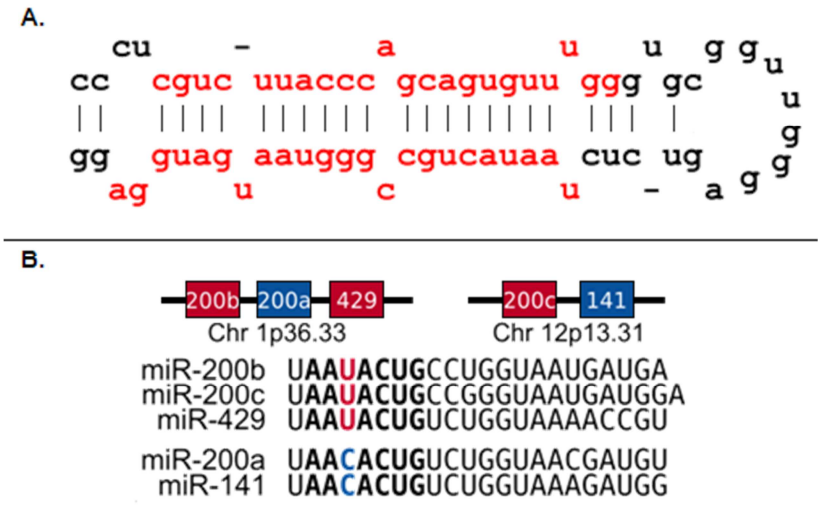
Location: 12p13.31

Local order
Based on MapViewer Genes on Sequence, genes flanking MIRN200C oriented from centromere to telomere on 12q13.31 are:
- ATN1; atrophin 1, 12q13.31
- U7; U7 small nuclear 1, 12q13.31
- C12orf57; chromosome 12 open reading frame 57, 12q13.31
- PTPN6; protein tyrosine phosphatase, non-receptor type 6, 12q13.31
- **MIRN200C**; microRNA 200c, 12q13.31
- MIRN141; microRNA 141, 12q13.31
- snoU89; small nucleolar RNA U89, 12q31.1
- PHB2; prohibitin 2, 12q31.1.

DNA/RNA

Description

miR-200c belongs to the miR-200 family, which consists of 5 members with two different chromosomal locations: miR-200c and miR-141 are located on chromosome 12p13 and miR-200a, miR-200b and miR-429 are located on 1p36.
This family is frequently downregulated upon the progression of tumors and maps to fragile chromosomal regions.
Members of this family are important regulators of epithelial-to-mesenchymal transition (EMT) and metastasis.



A. Stem-loop structure of hsa-mir-200c (precursor miRNA). **B.** The miR-200 family members. The human miR-200 family is located in two fragile chromosomal regions on 1p36.33 (200b, 200a and 429) and 12p13.31 (200c and 141), respectively. It consists of two clusters based on seed sequence similarity: miR-200bc/429 (red) and 200a/141 (blue), distinguished by a single nucleotide change (U to C) (source: Uhlmann et al., 2010, Oncogene).

Transcription

miRNAs are generally transcribed by RNA polymerase II.
hsa-mir-200c (precursor miRNA)
Accession: MI0000650
Length: 68 bp
Sequence: 5'-CCCUCGUCUUACCCAGCAGUGUUUGGGUGCGGUUGGGAGUCUCUAAUACUGCCGGGUAAUGAUGGAGG-3'
hsa-miR-200c* (-5p) (mature miRNA)
Accession: MIMAT0004657
Length: 23
Sequence: 5'-CGUCUUACCCAGCAGUGUUUGG-3'
hsa-miR-200c-3p (mature miRNA)
Accession: MIMAT0000617
Length: 23
Sequence: 5'-UAAUACUGCCGGGUAAUGAUGGA-3'

Pseudogene

No reported pseudogenes.

Protein

Note
microRNAs are not translated into proteins.

Mutations

Note
1) rs12904G>A single nucleotide polymorphism in the 3'UTR sequence of EFNA1, a target of miR-200c, results in susceptibility to gastric cancer (Li et al., 2014b).

2) rs1045385A>C SNP in the 3'UTR sequence of AP-2a mRNA increases AP-2a expression and results in cisplatin resistance in HEC-1A cell line of endometrial cancer (Wu et al., 2011).

Implicated in

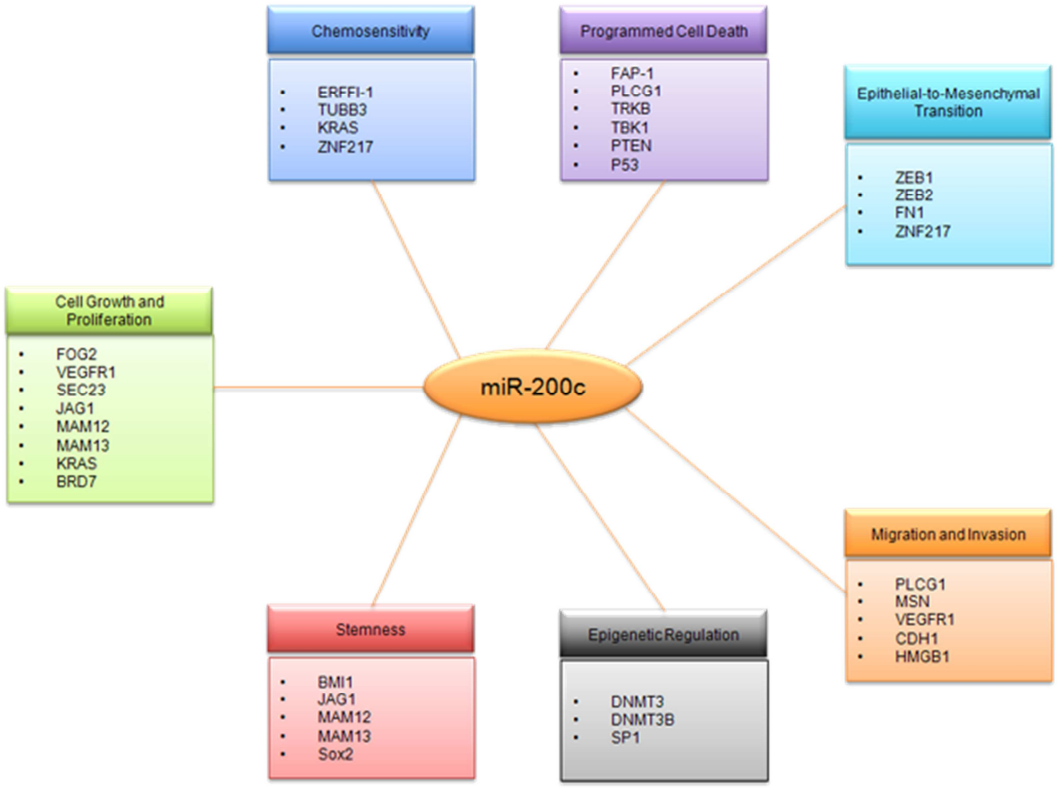
Cancer development

See figure below.

Bladder cancer

Prognosis
Loss of miR-200c expression was found to be associated with disease progression and poor outcome in 100 stage T1 bladder tumor patients (Wiklund et al., 2011a). Urinary miR-200 family levels are repressed in patients with bladder cancer (Wang et al., 2012).

Oncogenesis
Deep sequencing of nine bladder urothelial carcinomas (BUC) and matched normal urothelium revealed that the miR-200c/141 cluster is upregulated in bladder cancer (Han et al., 2011). Consistently, a study comparing miRNA expression patterns by microarray in 27 invasive and 30 superficial bladder tumors with 11 normal urothelia found that miR-200c was upregulated in bladder tumors compared to normal urothelium; however, expression of miR-200c was reduced in invasive compared to non-invasive tumors due to promoter hypermethylation (Wiklund et al., 2011a). Furthermore, microarray miRNA analysis of 43 primary tumors (10 colon, 10 bladder, 13 breast and 10 lung cancers) and matched lymph node metastases revealed that miR-200c and other miR-200 family members are downregulated in



miR-200c targets several genes regulating numerous processes involved in cancer development and progression.

metastases compared to primary tumors (Baffa et al., 2009).

Mechanistically, miR-200c has been implicated in the regulation of epithelial-to-mesenchymal transition (EMT) in bladder cancer cells. A comparison of nine bladder cancer cell lines revealed a correlation between high expression of miR-200c (and fellow miR-200 family member miR-200b) and epithelial phenotype (Adam et al., 2009). The same study also reported that miR-200c expression reverses resistance to anti-EGFR therapy in bladder cancer cell lines through targeting ERRFI-1.

However, contradictory to these results, in another study, it was found that the levels of miR-200c was upregulated in infiltrating BUC patients as compared with non-infiltrating BUC patients (Xie et al., 2012). These results were supported in a recent study, which again demonstrated that the levels of miR-200c were significantly higher in infiltrating carcinoma than in high grade bladder tumors (Lee et al., 2014).

Breast cancer

Prognosis

Diagnosis. Circulating tumor cell (CTC)-positive metastatic breast cancer patients had significantly higher levels of miR-200c than CTC-negative metastatic breast cancer patients and miR-200c along with some other miRNAs were suggested to be potential predictive markers for CTC status of metastatic breast cancer patients (Madhavan et al., 2012).

miR-200c was found to be downregulated in breast cancer patients that are irresponsive to neoadjuvant chemotherapy than patients who respond (Chen et al., 2013c).

Oncogenesis

A double-negative feedback loop between ZEB family transcription factors and the miR-200 family was shown to regulate EMT in different cell systems, including breast cancer cells (Burk et al., 2008). Moreover, expression of miR-200c was revealed to be activated by p53, resulting in induction of EMT in mammary epithelial cells upon loss of p53 (Chang et al., 2011). Loss of p53 was positively correlated with expression of ZEB1 and negatively correlated with expression of miR-200c and E-Cadherin in 106 breast tumor specimens.

miRNA microarray analysis of 43 primary tumors (10 colon, 10 bladder, 13 breast and 10 lung cancers) and matched lymph node metastases revealed that miR-200c and other miR-200 family members are downregulated in metastases compared to primary tumors (Baffa et al., 2009). Moreover, miR-200c and other miR-200 family members were shown to be underexpressed in the aggressive claudin-low subtype of breast cancer, which displays an EMT-like gene expression signature (Herschkowitz et al., 2011). In contrast, luminal breast cancers, which have a more

epithelial-like phenotype and a better clinical prognosis, express high levels of miR-200c (Bockmeyer et al., 2011). Besides ZEB family, miR-200c can modify metastasis by targeting HMGB1, ZNF217 and a truncated form of VEGFR-1 (Chang et al., 2014a; Bai et al., 2014b; Mezquita et al., 2014). miR-200c was also found to be an inhibitor of tumor progression and therapy resistance by targeting KRAS and ZNF217 (Bai et al., 2014b; Kopp et al., 2014).

Re-expression of the miR-200 family in aggressive breast cancer cells was shown to inhibit experimental lung metastasis (Ahmad et al., 2011) and decreased expression of it is associated with lymph node metastases in triple negative breast cancer (Berber et al., 2014). In contrast, another study reported that miR-200c is upregulated in breast cancer patients with lymph node metastasis (Wang et al., 2013). It was also shown to promote colonization of breast cancer cells (Dykxhoorn et al., 2009). The level of miR-200c was also found to be high in patients with various cancers including breast cancer that develop poly-metastases and it was reasoned that miR-200c is aiding colonization in the late stages of metastasis by reverting EMT (Lussier et al., 2011). In in vitro assays, miR-200c suppresses migration and invasion of breast cancer cells through various mechanisms, including targeting of ZEB1/ZEB2, PLCG1, moesin and fibronectin (Korpal et al., 2008; Uhlmann et al., 2010; Howe et al., 2011; Gerhauser, 2013).

miR-200c also targets stem cell factors such as BMI1, and downregulation of miR-200c was shown to be characteristic of breast cancer stem cells (Shimono et al., 2009) and DNA methylation was found to be the cause of the repression in breast cancer stem cell like populations (Lim et al., 2013). A natural compound, resveratrol, is increasing the activity of Ago2 and as a result inhibiting breast cancer stem cell-like characteristics by increasing the activity of tumor suppressor miRNAs including miR-200c (Hagiwara et al., 2012).

Furthermore, miRNA microarray analysis revealed that miR-200c is downregulated in breast cancer cells with acquired resistance to cisplatin (Pogribny et al., 2010). It was also found to be downregulated in doxorubicin resistant MCF-7 and BT474 breast cancer cells (Chen et al., 2013c; Kopp et al., 2012). It was also associated with trastuzumab resistance, which was found to be reverse by upregulation of miR-200c through the blockage of TGF-B signaling (Bai et al., 2014b).

miR-200c is also associated with increase in radiosensitivity in breast cancer cells by inhibiting cell proliferation, and by increasing apoptosis and DNA double-strand breaks. TBK1 was found to be a direct target of miR-200c and its downregulation by miR-200c is partially responsible for increased apoptosis (Lin et al., 2013).

CAFs and microenvironment

Oncogenesis

Eleven dysregulated miRNAs including miR-200c were identified in cancer-associated fibroblasts (CAFs) cultured from six resected breast tumor tissues that had not previously received radiotherapy or chemotherapy treatment. MiR-200c was found to be up-regulated in CAFs compared to normal fibroblasts (NFs) (Zhao et al., 2012). miR-200c targets Flt1/VEGFR1 gene which play an important role in enhancement of cell invasion in CAFs isolated from murine lung adenocarcinomas (Roybal et al., 2011).

Colorectal cancer

Prognosis

Kaplan-Meier survival analysis of 24 colorectal cancer patients suggested that high expression of miR-200c was associated with decreased overall survival (Xi et al., 2006). miR-200c levels in plasma and serum can serve as a potential noninvasive biomarker for CRC prognosis/screening and predicting metastasis (Zhang et al., 2013; Toiyama et al., 2014). Fluoropyrimidines treated two separate groups of individuals showed high levels of miR-200c, along with other members of miR-200 family, and found associated with longer overall and disease-free survival (Diaz et al., 2014).

Oncogenesis

Analysis of miR-200c expression in 24 colorectal cancer (CRC) biopsies and matched normal samples by qRT-PCR revealed that miR-200c is overexpressed in CRC tumors compared to normal tissue (Xi et al., 2006). Furthermore, microarray miRNA analysis of 43 primary tumors (10 colon, 10 bladder, 13 breast and 10 lung cancers) and matched lymph node metastases revealed that miR-200c and other miR-200 family members are downregulated in metastases compared to primary tumors (Baffa et al., 2009). miR-200c was also among miRNAs found upregulated in CRC tissue as compared to normal colonic mucosa shown in a microarray analysis followed by RT-PCR (Tsunoda et al., 2011). K-Ras driven expression of miR-200c and other miRNAs in a 3D culture specific manner suggested a role for miR-200c in regulating colorectal tumor development in vivo (Tsunoda et al., 2011; Ota et al., 2012). In an independent study, miR-200c was found to be associated with the development of CRC (Chen et al., 2012). By directly tageting ZEB1, miR-200c inhibited metastasis in CRC cells SW480/620 (Chen et al., 2012). Epigenetically regulated low expression of miR-200c contributes to EMT and metastatic potential of CRC, and transfecting CRC cells lines with miR-200c lead to increased proliferation but reduced invasion and migration (Hur et al., 2013).

miR-200c regulates Sox2 expression in a negative feedback loop in CRC and this regulation is associated with stemness, growth and metastatic potential of CRC (Lu et al., 2014). On the contrary, miR-200c has also been shown to work as oncogene in CRC where it takes part in inhibiting apoptosis and its silencing leads towards upregulation of Pten and p53 tumor suppressor genes (Chen et al., 2014b).

Endometrial cancer

Disease

Endometrial carcinoma; endometrial carcinosarcoma.

Prognosis

miR-200c was shown to be a prognostic marker of overall survival. High levels of miR-200c were associated with lower chance of survival in patients with endometrioid endometrial cancer (Torres et al., 2013).

Oncogenesis

miRNA microarray analysis of four endometrial endometrioid carcinomas and four normal endometrial tissue samples showed that miR-200c and other miR-200 family members were overexpressed in cancerous compared to normal tissue (Lee et al., 2011). These results were supported by other studies which showed that miR-200c expression is significantly upregulated in endometrial tumors compared to normal tissues (Karaayvaz et al., 2012) as well as to complex atypical hyperplasia (CAH) and simple hyperplasia (SH) cases (Lee et al., 2012). Inhibition of miR-200c decreased the growth of endometrial carcinoma cells (Lee et al., 2011). It was shown that it inhibits the expression of BRD7, which was reported as a potential tumor suppressor gene that prevents B-catenin from entering into nuclues. Inhibition of BRD7 by miR-200c results in increased expression of B-catenin transcriptional target genes, cyclin D1 and c-myc (Park et al., 2012). Inhibition of miR-200c decreased the growth of endometrial carcinoma cells (Lee et al., 2011). In contrast, an analysis of miR-200c expression levels in five endometrial cancer and normal endometrial cell lines suggested that miR-200c is lower in cell lines derived from aggressive cancer compared to those derived from less aggressive cancer or normal endometrial epithelium (Cochrane et al., 2009). Restoration of miR-200c expression in aggressive endometrial cancer cells reduced their migration and invasion and increased their sensitivity to microtubule-targeting chemotherapeutic agents, at least in part through targeting TUBB3 (Cochrane et al., 2009; Cochrane et al., 2010; Howe et al., 2011). In a panel of 23 endometrial carcinosarcomas, which are composed of mixed populations of epithelial-like and mesenchymal-like cells, miR-200c and other miR-200 family members were found to be downregulated in the mesenchymal components of the tumors compared to the epithelial components (Castilla et al., 2011) and it was found to be methylated during EMT in both in vitro and in vivo models (Díaz-Martín et al., 2014). These results are consistent with the established role of the miR-200 family in suppression of epithelial- mesenchymal transition.

Esophageal cancer

Prognosis

In a panel of 98 esophageal cancer patients treated with preoperative chemotherapy and surgery, expression of miR-200c was associated with shortened overall survival and poor response to chemotherapy, potentially through upregulation of the Akt signaling pathway (Hamano et al., 2011). In another study higher miR-200c expression in serum collected from 64 esophageal cancer patients who have received neoadjuvant chemotherapy has shown to be associated with poor response to chemotherapy and shortened progression free survival (Tanaka et al., 2013).

Oncogenesis

qRT-PCR analysis of miR-200 expression levels in 17 patients with Barrett's esophagus and 20 patients with esophageal adenocarcinoma indicated that miR-200c is downregulated during cancer progression from normal epithelium through Barrett's esophagus to esophageal adenocarcinoma (Smith et al., 2011). In contrast, another study on 98 esophageal cancer patients treated with preoperative chemotherapy and surgery found that miR-200c was expressed at higher levels in the tumor than in normal tissue (Hamano et al., 2011).

Gastric cancer

Prognosis

Significantly higher expression level of miR-200c in blood has been observed in gastric cancer patients as compared to controls and also found as good predictor of overall and progression free survival in gastric cancer patients (Valladares-Ayerbes et al., 2012). miR-200c, mir-200b and miR-125 were found to be targeting most of the genes driving mesenchymal subtype of gastric cancer; a subtype which is associated with poor overall survival in gastric cancer. Functional analysis showed that miR-200b suppresses ZEB1, augments E-cadherin and inhibit cell migration and tumor growth in a mouse model (Song et al., 2014).

Oncogenesis

Three miRNAs from miR-200 family (miR-200a, -200b, -200c) found downregulated in gastric adenocarcinoma and miR-200a, when upregulated, suppressed EMT and tumor growth by modulating Wnt/β-catenin signaling pathway through targeting

ZEB1 and ZEB2 (Cong et al., 2013). Co-delivering miR-200c with docetaxel by nanoparticles significantly enhanced cytotoxicity of docetaxel and suppressed tumor growth in vivo possibly by decreasing TUBB3 levels and by reversing EMT (Liu et al., 2013). miR-200b and miR-200c, when overexpressed in gastric cancer cells, reduced DNA methylation by targeting DNMT3A, DNMT3B and SP1, and also reduced tumor growth and migration capacity by re-expressing of p16, RASS1A1, and E-cadherin (Tang et al., 2013). Overexpressing miR-200c in gastric cancer tissues and cells (SGC7901 and SGC7901/DDP) led to enhancing cisplatin sensitivity in these cells possibly by targeting RhoE (Chang et al., 2014b). miR-141, another member of miR-200 family, also found suppressing proliferation, colony formation, migration and invasion capabilities of gastric cancer cells partially by targeting HDGF (Chen et al., 2014a). A study conducted on miRNA binding site SNPs located in the 3'UTRs of genes involved in gastric cancer susceptibility revealed that ephrin-A1 (EFNA1) gene is significantly associated with risk of gastric cancer as miR-200c binding site SNP (rs12904 G>A) in the 3'UTR of EFNA1 can significantly modulate EFNA1 expression (Li et al., 2014b).

Germ cell tumors

Disease

Germinoma; yolk sac tumors.

Prognosis

Diagnosis. Microarray analysis of 25 germ cell tumors and subsequent validation by qRT-PCR in 10 independent samples identified miR-200c overexpression in yolk sac tumors compared to germinoma (Murray et al., 2010).

Head and neck cancer

Disease

Squamous cell carcinoma; spindle cell carcinoma.

Oncogenesis

miR-200c was significantly downregulated in a panel of 30 spindle cell carcinomas (which display a mesenchymal-like phenotype) compared to normal mucosa as determined by qRT-PCR (Zidar et al., 2011). In contrast, expression levels of miR-200c in 30 squamous cell carcinomas were comparable to normal tissue. A xenotransplantation study has shown that miR-200c directly targets BMI1 and overexpression of miR-200c or BMI1 knockdown inhibited lung metastasis and prolonged the survival of mice suggesting therapeutic potential miR-200c in head and neck squamous cell carcinoma (Lo et al., 2011). HGF-driven downregulation of miR-200c leads to enhanced ZEB1/E-cadherin mediated epithelial to mesenchymal transition in head and neck squamous cell carcinoma (Susuki et al., 2011). miR-200c, along with other miRNAs, play important roles e.g., regulation of stemness and epithelial mesencymal transition in head and neck tumor cells (Tu et al., 2013). Targeting HPV 16 E6-p300 interaction with a CH1-domain inhibitor resulted in enhanced functional reactivation of p53 tumor suppressor as a result of upregulation of miR-200c and miR-34a expression levels (Xie et al., 2014). In head and neck squamous cell carcinoma, promoter hypermethylation of miR-200c targets (Zeb1/Zeb2) has been reported to somehow mask the effects associated with miR-200 family regulation of EMT and migration (Tamagawa et al., 2014).

Huntington' disease

Cytogenetics

A significant alteration of miR-200 family members, miR-200a, and miR-200c has been observed in the cerebral cortex and the striatum, at the early stage of disease progression in a mouse model of Huntington's disease. Elevated levels of miR-200c results in downregulation of some target genes, which have been suggested to play important roles in synaptic function, axonal trafficking, neurotransmitter release, neurogenesis, and neuronal survival (Jin et al., 2012).

Leiomyomas

Oncogenesis

It was found that TIMP2, FBLN5, and VEGFA as direct targets of miR-200c in leiomyomas and the expression of miR-200c was significantly lower in leiomymas compared to matched myometrium (Chuang et al., 2012).

Liver cancer

Prognosis

Diagnosis. miR-200c has been suggested as a biomarker to distinguish hepatocellular carcinoma from liver metastases (Barshack et al., 2010).

miR-429, a member of miR-200 family, was shown to be a prognostic marker in a hepatocellular carcinoma (HCC) tissue microarray study as it was upregulated and shown to promote liver tumor initiating cell properties by targeting Rb binding protein 4 (Li et al., 2014a).

Oncogenesis

miRNA microarray analysis of 92 primary hepatocellular carcinomas and 9 HCC cell lines identified miR-200c as a microRNA that is upregulated by p53 (Kim et al., 2011). Increased expression of miR-200c results in downregulation of transcriptional repressors ZEB1 and ZEB2, suggesting a role for p53-mediated regulation of miR-200c in suppression of EMT. miR-200c was reported to be underexpressed in benign liver tumors compared to HCC (Ladeiro et al., 2008); miR-200c levels were determined by qRT-PCR in

two sets of tumors (first set: 18 benign tumors, 28 hepatocellular carcinomas; second set: 12 benign tumors, 22 hepatocellular carcinomas). miR-200c, along with other miRNAs, was found to be downregulated in both HCC and intrahepatic cholangiocarcinoma (ICC) (Karakatsanis et al., 2013). Targeting liver cancer cells with miR-200b, member of miR-200 family, not alone but simultaneously with DNA methyl transferase inhibitor reduced the metastatic potential of these cells irrespective of E-cadherin levels (Ding et al., 2012). Transcriptome profiling of 23 ICC and combined HCC tumor specimens using microarrays have revealed miR-200c/EMT as common signaling pathway activated in ICC stem cells. Furthermore, NCAM1, known hepatic stem cell marker, was found to be a direct target of miR-200c (Oishi et al., 2012). While analyzing the expression of a member of miR-200 family, miR-429, in 138 pathology diagnosed HCC patients, this miRNA was found upregulated in tumor tissues and contributing to cell proliferation and inhibiting apoptosis (Huang et al., 2013). Simultaneous silencing of miR-141 and miR-200c has been reported to be responsible for developing HCC with bile duct tumor thrombosis by activation of ZEB-1 mediated EMT in a study conducted on patients having HCC with or without bile duct tumor thrombus (Yeh et al., 2014).

Lung cancer

Prognosis

qRT-PCR analysis of miR-200c expression levels in 70 non-small cell lung cancer (NSCLC) patients revealed that high expression of miR-200c was associated with reduced overall survival (Liu et al., 2011). Another study investigated serum microRNAs as cancer biomarkers showed that miR200c is associated with NSCLC, suggesting a potential usage for diagnosis (Liu et al., 2012b). Re-expression of miR-200 family miRNAs has been found to target and downregulate the previously identified prognostic biomarkers in metastatic NSCLC suggesting the importance of these miRNAs in regulating metastatic potential of lung cancer (Pacurari et al., 2013).

Oncogenesis

Treatment of immortalized human bronchial epithelial cells with tobacco carcinogens was shown to induce an EMT-like phenotype and stem-cell like properties (Tellez et al., 2011). Quantification of miRNA levels by qRT-PCR in combination with bisulfite sequencing and chromatin immunoprecipitation revealed that these changes are accompanied by epigenetic silencing of miR-200c and other EMT-regulating microRNAs, suggesting that loss of miR-200c contributes to transformation of lung epithelial cells. In contrast, miRNA microarray analysis of six NSCLCs and matched adjacent normal tissue revealed that miR-200c is upregulated in NSCLC compared to healthy tissue (Liu et al., 2011). This finding was further validated in 70 lung carcinomas and matched normal tissue by qRT-PCR.

Several studies have reported that miR-200c can repress invasion and metastasis of lung cancer cells. Firstly, low expression of miR-200c and other miR-200 family members was associated with increased metastatic potential in a syngeneic mouse model of lung adenocarcinoma, and re-expression of miR-200 family members in these cell lines prevented EMT and metastasis (Gibbons et al., 2009). Secondly, miR-200c was shown to be downregulated by promoter hypermethylation in invasive NSCLC cell lines, and re-expression of miR-200c reduced the invasive potential of these cell lines (Ceppi et al., 2010). Furthermore, microarray miRNA analysis of 43 primary tumors (10 colon, 10 bladder, 13 breast and 10 lung cancers) and matched lymph node metastases revealed that miR-200c and other miR-200 family members are downregulated in metastases compared to primary tumors (Baffa et al., 2009). Finally, low expression of miR-200c in 69 primary lung tumors was correlated with lymph node metastases (Ceppi et al., 2010).

Mechanistically, the Notch ligand Jagged2 was shown to suppress expression of miR-200 family members, resulting in induction of EMT and increased metastatic potential (Yang et al., 2011). Moreover, miR-200c and fellow miR-200 family member miR-200b target VEGFR, which also contributes to invasion and metastasis (Roybal et al., 2011).

It was demonstrated that miR-200c which is normally downregulated in lung cancer tissue, is upregulated by transfection in H460 cells resulted in higher levels of apoptotic cells in comparison with untransfected ones (Bai et al., 2014a). In addition, miR-200c enhanced the antitumor effect of reservatol (RESV).

Drug sensitivity can be restored in EMT driven erlotinib (EGFR inhibitor) resistant NSCLC by using a single agent, silibinin, which fully reverses the high miR-21/low miR-200c signature and represses mesenchymal markers SNAIL, ZEB and N-Cadherin (Cufí et al., 2013). Moreover, VEGF family is an important regulator of angiogenesis and VEGFR2 has been identified as direct target of miR-200c. Ectopic miR-200c expression radio-sensitized the A549 cells by VEGF-VEGFR2 pathway leading to inhibition of its downstream pro-survival signaling and angiogenesis (Shi et al., 2013). Finally, acquired resistance to EGFR inhibitors in lung cancer cells is found to be associated with EMT (characterized by downregulation of miR-200c) and/or stem like properties (increased ALDH1A1 levels, increase of

side population and self renewal capability) (Shien et al., 2013).

Lymphoma

Prognosis

High expression levels of miR-200c was found to be associated with decreased overall survival and time from initial diagnosis to the first relapse in diffuse large B-cell lymphoma (DLBCL) (Berglund et al., 2013).

Oncogenesis

miR-200c was found directly targeting polycomb protein BMI1 In radiation induced thymic lymphoma (RITL) model of BALB/c mice and adenovirus mediated overexpression of miR-200c reduced tumorigenesis in vivo suggesting it as a novel therapeutic method to treat RITL (Cui et al., 2014). Genome-wide expression profiling of nine H. pylori-positive and nine H. pylori-negative gastric diffuse large B-cell lymphomas and further confirmation in 30 samples for each has revealed that miR-200c inhibits ZEB1 in H. pylori-positive gastric diffuse large B-cell lymphoma which, in turn, upregulates BCL6 and results in less aggressive behavior of H. pylori-positive gastric diffuse large B-cell lymphomas (Huang et al., 2014).

Malignant pleural mesothelioma

Prognosis

Diagnosis. miR-200c has been proposed as a biomarker to distinguish malignant pleural mesothelioma from lung adenocarcinoma and lung metastases of other carcinomas. miRNA microarray expression profiling of 10 lung adenocarcinomas and 15 mesotheliomas revealed that miR-200c is reduced in mesothelioma (Gee et al., 2010). This result was further confirmed by qRT-PCR in a set of 100 mesotheliomas and 32 lung adenocarcinomas. Similarly, microRNA microarray analysis of 7 malignant pleural mesotheliomas and 97 carcinomas of various origins also identified miR-200c as underexpressed in mesotheliomas compared to the carcinoma samples, and differential expression levels of miR-200c and two other microRNAs could successfully be used to distinguish between malignant pleural mesothelioma and other types of cancer (Benjamin et al., 2010).

Melanoma

Oncogenesis

Analysis of miR-200c expression levels in a panel of 10 melanoma cell lines by qRT-PCR showed that miR-200c is overexpressed in many of these cell lines compared to normal melanocytes (Elson-Schwab et al., 2010). On the contrary, overexpression of miR-200c in melanoma cells significantly decreased proliferation, migratory capacity and drug resistance by targeting BMI-1, ABCG2, ABCG5, and MDR1 and enhancing E-cadherin levels. Overexpression of miR-200c also inhibited melanoma xenograft growth and metastasis in vivo (Liu et al., 2012a). Decreased levels of miR-200a, miR-200c, and miR-203 correlated with increasing tumor thickness in a series of 23 frozen primary melanomas. A functional validation study using an anti-miR200 strategy demonstrated that loss of miR-200 expression in melanoma cell lines reduced E-cadherin expression (van Kempen et al., 2012). Overexpressing miR-200c in mouse melanoma B16F10 CD44+CD133+ CSCs led to the reduced cell proliferation, colony formation, cell migration and invasion potential in vitro as well as tumorigenicity in vivo but not in B16F10 cells and B16F10 non-CD44+ CD133+ CSCs (Dou et al., 2013).

Oral squamous carcinoma

Prognosis

Significant expression alteration of miR-200 family including miR-200c was shown in oral squamous carcinoma patients compared to healthy controls tested from saliva. This demonstrates a potential biomarker property of miR-200c that can be used in clinical application with oral rinse (Wiklund et al., 2011b).

Ovarian cancer

Prognosis

High expression of miR-200c was found correlated with decreased progression-free and overall survival in a panel of 20 serous ovarian cancer patients (Nam et al., 2008). In contrast, a study investigating microRNA expression profiles in a total of 144 patients with epithelial ovarian cancer found that low expression of miR-200c was associated with increased progression-free and overall survival (Marchini et al., 2011).

Similarly, high expression of miR-200c was correlated with response to chemotherapy and decreased risk of disease recurrence in a panel of 57 patients with serous ovarian carcinoma (Leskela et al., 2010). In a study for identification of differentially expressed miRNAs in high-grade serous ovarian carcinoma (HGSC), clear cell ovarian carcinoma (CCC) and ovarian surface epithelium (OSE), high miR-200c-3p expression has been associated with poor progression-free ($p = 0.031$) and overall ($p = 0.026$) survival in HGSC patients (Kim et al., 2014).

Diagnosis. MiR-200c along with other miR-200 family miRNAs (miR-141, miR-200a, miR-200b) has been found preferentially upregulated in epithelial ovarian cancer suggesting its role as a potential biomarker for this cancer type (Chen et al., 2013d).

Oncogenesis

miR-200c was found to be overexpressed in a panel of 20 serous ovarian carcinomas compared to 8 normal ovarian tissues by miRNA microarray analysis (Nam et al., 2008). Similarly, increased expression of miR-200c compared to normal ovary (n=15) was reported for serous, endometrioid and clear cell ovarian carcinoma in a series of 69 cancer specimens.

Expression of miR-200c was correlated with E-Cadherin levels in 36 primary ovarian carcinomas (Park et al., 2008). The regulatory effect of miR-200c on EMT has been shown to be mediated through targeting of ZEB1 and ZEB2, which transcriptionally repress E-Cadherin (Gregory et al., 2008; Korpal et al., 2008; Park et al., 2008). In this same line of comparative study, miRNA microarray and qPCR analysis, it has been shown elevated expression level of miR-200c on ovarian carcinoma effusions (Vaksman et al., 2011).

Re-expression of miR-200c in aggressive ovarian cancer cell lines was shown to reduce their migratory capacity; however, this effect appears to be independent of E-Cadherin expression (Cochrane et al., 2010). Furthermore, forced expression of miR-200c has been reported to sensitize ovarian cancer cells to paclitaxel treatment due to downregulation of miR-200c target gene TUBB3 (Cochrane et al., 2009; Cochrane et al., 2010). Reduction in endogenous PTEN levels and upregulation of phopho-Akt levels were reported in miR-200c transfected ovarian cancer stem cells (OCSCs) (Luo et al., 2013). miR-200c was also shown to be downregulated in a subpopulation of the ovarian cancer cell line OVCAR3 expressing the cancer stem cell marker CD133 (Guo et al., 2011). In CD117+ CD44+ OCSCs, miR-200c expression has been reduced. Overexpression of miR-200c in these OCSCs upregulated E-cadherin expression, downregulated ZEB-1 and Vimentin expression in vitro. Also miR-200c upregulation showed inhibitory effect in CD117+ CD44+ OCSCs in xenograft growth and lung metastasis in nude mice (Chen et al., 2013b).

Pancreatic cancer

Prognosis

In a panel of 99 pancreatic cancer patients, high expression of miR-200c was associated with increased overall survival (Yu et al., 2010).

Oncogenesis

Downregulation of miR-200c and other miR-200 family members has been observed in gemcitabine-resistant pancreatic cancer cell lines (Li et al., 2009; Ali et al., 2010). miR-200c has also been suggested to have a stemness-inhibiting function in pancreatic cancer cells through targeting of stem cell factors such as Bmi1 (Wellner et al., 2009).

A double-negative feedback loop between ZEB family transcription factors and the miR-200 family was shown to regulate EMT in different cell systems, including pancreatic cancer cells (Burk et al., 2008). Consistently, high expression of miR-200c was shown to be associated with decreased invasive behavior in a panel of six pancreatic cancer cell lines, and miR-200c expression was correlated with E-Cadherin levels in pancreatic cancer specimens and cell lines (Yu et al., 2010). Overexpression of miR-200c in pancreatic cancer cell lines resulted in upregulation of E-Cadherin expression and reduced invasion but stimulated proliferation.

miRNA expression profiling of various stages in a mouse model of multistep tumorigenesis of the pancreas revealed that miR-200c is downregulated in metastases and metastasis-like tumors (Olson et al., 2009). Moreover, miR-200c also targets components of the Notch pathway, which is aberrantly activated in pancreatic cancer (Brabletz et al., 2011). Undifferentiated, aggressive pancreatic adenocarcinomas were shown to have higher expression of ZEB1 and Notch pathway components and lower expression of miR-200c compared to differentiated tumors.

In contrast to the studies described above, which suggest a metastasis-suppressing function for miR-200c in pancreatic cancer, a comparison of 16 pancreatic ductal adenocarcinoma cell lines found that miR-200c expression was upregulated in the highly metastatic cell lines (Mees et al., 2010). Interaction of MUC1 and ZEB1 at the promoter of miR-200c/141, results in transcriptional repression of these miRNAs leading to enhanced progression of pancreatic cancer (Mohr et al., 2013). In addition to regulation of proteins that modulate EMT in pancreatic adenocarcinoma, miR-200c has also been found to target cell surface mucins (MUC4 and MUC16), which play essential role in progression and metastasis in pancreatic adenocarcinoma (Radhakrishnan et al., 2013). In another study it was shown how metformin provokes the death of cancer stem cells in human pancreatic cancer cells (Bao et al., 2012). It was further demonstrated that metformin depleted a set of expression of cancer stem cell markers together with repression of miRNAS including miR-200c.

Prolactinoma cancer

Oncogenesis

miR-200c was shown to be upregulated in a rat prolactinoma cell line, MMQ. A marine drug SZ-685C induces apoptosis of these cells via downregulation of miR-200c. Moreover, overexpression of miR-200c was found to be attenuating the apoptotic effect of SZ-685C (Chen et al., 2013a).

Prostate cancer

Prognosis

Plasma levels of miR-200c has been identified as a potential biomarker to differentiate localized prostate cancer from metastatic castration resistant prostate cancer (Watahiki et al., 2013).

Oncogenesis

miRNA sequencing demostrated that miR-200c was upregulated in primary prostate carcinoma tissue (Szczyrba et al., 2011). In contrast, prostate cancer cells with EMT phenotype were found to have stem-cell like properties and express low levels of miR-200 family members (Kong et al., 2010). In approximately 50% of prostate cancer patients, chromosomal translocations that juxtapose the androgen-sensitive transmembrane protease, serine 2 (TMPRSS2) gene promoter to the oncogenic ETS-family transcription factor ERG result in excessive ERG overexpression which in turn directly represses miR-200c and promotes EMT by upregulating ZEB1 (Kim et al., 2013). Overexpression of miR-200c reversed EMT and stem-cell like properties, in part due to targeting of Notch-1. miR-200c was also shown to target the Notch ligand Jagged1, resulting in decreased proliferation of metastatic prostate cancer cells (Vallejo et al., 2011).

Renal cancer

Disease

Clear cell carcinoma (CCC); chromophobe renal cell carcinoma (ChCC).

Prognosis

Diagnosis. miR-200c has been found to be specifically expressed in ChCC and has been suggested as one of the microRNAs that can be used to distinguish between RCC subtypes (Fridman et al., 2010). In addition, miR-200c is one of the five miRNAs used as a biomarker subset allowing to characterize clear-cell renal cell carcinoma (ccRCC), papillary RCC (pRCC) types 1 and 2 and normal tissue with high accuracy (Wach et al., 2013).

Oncogenesis

miR-200c was found to be significantly downregulated in CCC compared to normal kidney in a panel of 16 CCCs, 4 ChCCs and 6 normal kidneys both by microarray analysis and by qRT-PCR (Nakada et al., 2008). Furthermore, miR-200c expression was inversely correlated with expression of its target gene ZEB1 in these specimens. The downregulation of miR-200c in CCC was also confirmed by a second study comparing a total of 25 CCC and matched adjacent normal tissue (Liu et al., 2010). miR-200c has also been shown to be one of the most downregulated miRNAs in a comparative study with 70 matched pairs of clear cell renal cell carcinoma and normal kidney tissues (White et al., 2011).

miR-200c negatively affects metastasis of RCC cells by upregulating E-cadherin upon ZEB1 in addition to its effective role on AKT protein. Hence, AKT-miR-200c-E-cadherin pathway may have importance in EMT within RCC. In a series of functional studies of mir-200c, it has been shown that induction of miR-200c expression by Ochratoxin A (OTA) in porcine renal proximal tubular cells attenuates Nrf2 and HO-1 expression and elevates ROS and profibrotic TGF-β expression (Stachurska et al., 2013). Furthermore, it has been demonstrated that the renal cortical content of miR-200c was increased with aging. Increased miR-200c contents were associated with reduced expression of its target, ZEB2 (Sataranatarajan et al., 2012). Finally, multidrug resistance linked proteins appears to be prominently influenced by a set of five miRNAs including mir-200c used to discriminate renal tumor from normal tissue (Wach et al., 2013).

Thyroid carcinoma

Prognosis

Diagnosis. Deregulated miR-200c, along with other miRNAs, has been reported as a marker for metastatic medullary thyroid carcinoma (Santarpia et al., 2013).

Oncogenesis

The expression of miR-200 family members, including miR-200c, was found to be downregulated in undifferentiated, aggressive anaplastic thyroid carcinoma compared to both normal tissue and well-differentiated papillary and follicular thyroid carcinomas (Braun et al., 2010). Overexpression of the miR-200 family induced mesenchymal-to-epithelial transition and reduced invasion of ATC cells. Overexpression of mir-200c in metastatic medullary thyroid carcinoma improves E-cadherin levels by directly targeting ZEB1 and ZEB2 or by enhanced expression of TGF-β (Santarpia et al., 2013).

Wilms tumor

Oncogenesis

miRNA expression was analyzed in tissue samples including alveolar rhabdomyosarcoma (RMA) and malignant rhabdoid tumor (MRT) as well as in the rhabdomyosarcoma (RMS) cell lines (Rh30 and RD). It has been shown that miR-200c expression inhibits migration, and miR-200c was shown be expressed at a lower level in RMA than in MRT (Armeanu-Ebinger et al., 2012).

Microbiota

Cytogenetics

The intestinal levels of miR-200c, together with 5 other miRNAs, varied upon Listeria infection and

for 5 of these miRNAs including miR-200c, this alteration was found to be dependent on the presence of intestinal microbiota of mice (Archambaud et al., 2013).

Obesity

Cytogenetics

microRNA expression analysis showed mouse miR-200c (mmu-miR-200c) downregulation in the presence of high fat diet in C57BLJ6 mice (Chartoumpekis et al., 2012). Leptin deficient ob/ob mice manifest up-regulated miR-200a, miR-200b and miR-429 levels and leptin treatment decreases the amount of these miRNAs. Besides, through overexpression and downregulation studies it was shown that miR-200a might be a target for obesity since its inverse expression relationship with leptin and insulin signaling (Crépin et al., 2014).

Stem cells, differentiation and reprogramming

Cytogenetics

Direct transfection of three mature miRNAs (mir-200c, -302s and -369s) with increased expression levels in embryonic stem cells and induced pluripotent stem cells can reprogram mouse and human cells to pluripotency. Transfection of miRNAs reduced the risk of mutations and tumorigenesis compared to induced pluripotent stem cells (IPSCs) by introduction of four transcription factors Oct3/4, Sox2, c-Myc and Klf4 (Miyoshi et al., 2011; Miyazaki et al., 2012). miR-200 family also regulates two of the Yamanaka factors Oct4/Sox2 in a specific manner and induces somatic cell reprogramming with the involvement of the miR-200/ZEB2 pathway (Wang et al., 2013). miR-200c, along with miR-150, has been reported to play an important role in human embryonic stem cell differentiation towards endothelial lineage and chick embryonic blood vessel formation by targeting ZEB1 (Luo et al., 2013).

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