MIR200C (microRNA 200c)

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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 nuclear 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.

Transcription

miRNAs are generally transcribed by RNA polymerase II.

hsa-mir-200c (precursor miRNA)
Accession: MI0000650
Length: 68 bp
Sequence: 5'-CCCUCGUCUUAACCGAGCUG UUUGGGUGCGUUGGAGUUGUCUCUAAACUGCG GGGUAAUGAUGGAGG-3'

hsa-miR-200c (mature miRNA)
Accession: MIMAT0000617
Length: 23
Sequence: 5'-UAAUACUGCCGGGUAAUGUGAUGG-3'

Pseudogene

No reported pseudogenes.

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).

**Protein**

Note
microRNAs are not translated into amino acids.

**Mutations**

Note
Gene mutations have not been described.

**Implicated in**

**Bladder cancer**

**Oncogenesis**
Deep sequencing of nine bladder urothelial carcinomas 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., 2011). 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). 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).

Re-expression of the miR-200 family in aggressive breast cancer cells was shown to inhibit experimental lung metastasis (Ahmad et al., 2011). In contrast, another study reported that miR-200c promotes colonization of breast cancer cells (Dykxhoorn et al., 2009). In in vitro assays, miR-200c suppresses migration and invasion of breast cancer cells through various mechanisms, including targeting of 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.

**Breast cancer**

**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).

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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). Furthermore, miRNA microarray analysis revealed that miR-200c is downregulated in breast cancer cells with acquired resistance to cisplatin (Pogribny et al., 2010).

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).

Oncogenesis
Analysis of miR-200c expression in 24 colorectal cancer biopsies and matched normal samples by qRT-PCR revealed that miR-200c is overexpressed in colorectal 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).

Endometrial cancer

Disease
Endometrial carcinoma; endometrial carcinosarcoma.

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). 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); this is consistent with the established role of the miR-200 family in suppression of epithelial-to-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).

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).

Germ cell tumors

Disease
Germinoma; yolk sac tumors.

Oncogenesis
Diagnosis. Microarray analysis of 25 germ cell tumors and subsequent validation by qRT-PCR in 10 independent samples identified miR-200c as overexpressed 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-PC (Zidar et al., 2011). In contrast, expression levels of miR-200c in 30 squamous cell carcinomas were comparable to normal tissue.

Liver cancer

Oncogenesis
Diagnosis. Due to its low expression in liver compared to other tissues, miR-200c has been suggested as a biomarker to distinguish hepatocellular carcinoma from liver metastases (Barshack et al., 2010). miRNA microarray analysis of 92 primary hepatocellular carcinomas and 9 hepatocellular carcinoma 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.
Mechanistically, the Notch ligand Jagged2 was shown with lymph node metastases (Ceppi et al., 2010). miR-200c in 69 primary lung tumors was correlated with metastasis (Gibbons et al., 2009). Secondly, miR-200c in lung adenocarcinoma, and re-expression of miR-200 resulted in induction of EMT and increased metastatic potential in a syngeneic mouse model of family members was associated with increased (Tellez et al., 2011). Quantification of miRNA levels was 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).

**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).

**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.

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**Malignant pleural mesothelioma**

**Oncogenesis**

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). Overexpression of miR-200c in melanoma cell lines resulted in a shift towards amoeboid type of migration, possibly through targeting of MARCKS.

**Ovarian cancer**

**Prognosis**

High expression of miR-200c was found to be 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 (Leskelä et al., 2010).

**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, endometroid 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). 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). 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).

**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).

**Prostate cancer**

**Oncogenesis**
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). 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).

**Oncogenesis**
Diagnosis. miR-200c has been found to be specifically expressed in chromophobe renal cell carcinoma and has been suggested as one of a set of microRNAs that can be used to distinguish between renal cell carcinoma subtypes (Fridman et al., 2010). miR-200c was found to be significantly downregulated in clear cell carcinoma 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 clear cell carcinomas and matched adjacent normal tissue (Liu et al., 2010).

**Thyroid carcinoma**

**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.
Various cancers

miR-200c target genes regulate numerous processes involved in cancer development and progression.

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