Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section
Review

MIR141 (microRNA 141)

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Identity

Other names: MIRN141
HGNC (Hugo): MIR141
Location: 12p13.31
Local order: From telomere to centromere (from USCS RefSeq genes): C12orf57 (chromosome 12 open reading frame 57), PTPN6 (protein tyrosine phosphatase non-receptor type 6), MIR200C (miRNA-200c), MIR141 (miRNA-141), PHB2 (prohibitin 2), SCARNA12 (small cajal body specific RNA 12), EMG1 (essential for mitotic growth nucleolar protein homolog (S. cerevisiae)).

DNA/RNA

Note
miR-141 belongs to the miR-200 family of microRNAs (also referred to as miRNAs or miRs). This family is composed by five distinct miRNAs, classified into two subfamilies according to the sequence homology in their seed region (sequence of the miRNA defining its target specificity corresponding to nucleotides 2-7). The first subfamily includes the miR-141 and miR-200a and the second one is composed by the miR-200b, miR-200c and miR-429. These miRNAs are located within two clusters on different genomic loci: miR-200b, miR-200a and miR-429 are located on chromosome 1 in the human genome (chromosome 4 in mouse) and miR-141 and miR-200c on human chromosome 12 (chromosome 6 in mouse).

Description
Genomic location in human genome: chr 12: 7073260-7073354 (GRCh37/hg19 Assembly).

Orientation: + strand.
The mature sequence of MIR-141-3P (most abundant) is uaacacugucugguaaagaugg (accession MIMAT0000432).
The sequence of MIR-141-5P (previously called miR-141*) is caucuuccaguacaguguugga (accession MIMAT0004598).

Transcription

miRNA genes are generally transcribed by RNA polymerase II to generate capped and poly-adenylated primary transcripts, called pri-miRNAs. Pri-miRNAs are processed in the nucleus by the RNase III enzyme, Drosha, generating stem-loop structured RNAs called precursor miRNAs, or pre-miRNAs.
The pre-miR-141 sequence is CGGCCGGCCCUGGGUCCAUCUUCCAGUACAG UGUUGGAUGGUCUAAUUGUGAAGCUCCUAAC ACUGUCUGGUAAAGAUGGCUCCCGGGUGGGU UC (accession MI0000457) and a schematic representation of the secondary structure of the stem-loop is shown above.
Pre-miRNAs are then exported to the cytoplasm. In the cytoplasm, another RNase III enzyme, Dicer, cleaves the pre-miRNAs, producing miRNAs duplexes of the mature miRNAs (5P and 3P) and then one of the strands is loaded into the miRNA-associated RNA-Induced Silencing Complex, RISC.
The mature miRNAs are very stable RNA molecules.

Pseudogene

Not found (Pseudogene.org Build 68 via GeneCards).
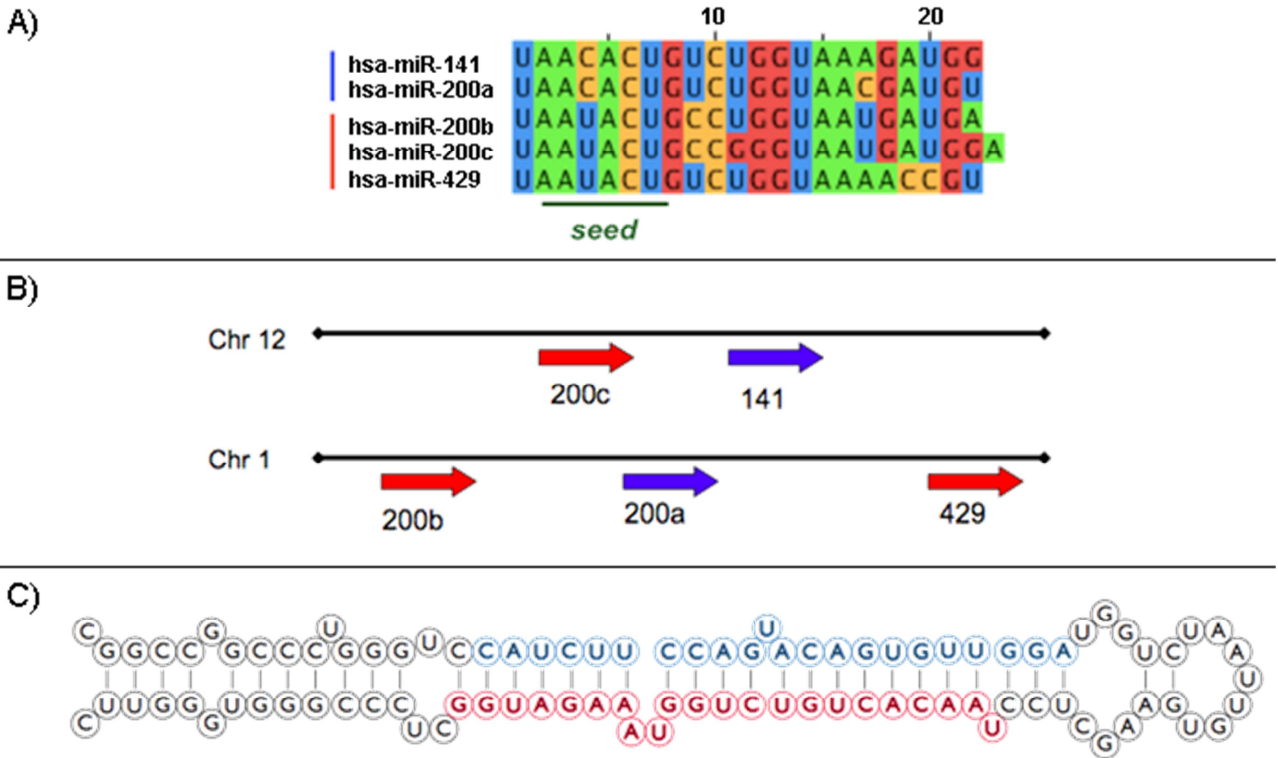
A) Sequence of the five members of miR-200 family. The seed sequence is underlined and the two subfamilies are indicated by the blue/red bars. **B)** Schematic representation of the genomic localization of the two clusters containing the miR-200 family members. **C)** Schematic representation of the secondary structure of the pre-miR-141 hairpin. The sequence of the mature miR-141-3P is indicated in red and the miR-141-5P (previously called miR-141*) is in blue.

Protein

Note

Not applicable, miRNAs are not translated into proteins.

Mutations

Note

SNP IDs rs34385807, rs111718468 (both located in precursor miRNA but not in mature miRNA). No involvement in pathogenesis described.

Implicated in

Ovarian cancer

Note

The miR-200 family members are reproducibly found up-regulated in ovarian tumors compared to normal cells and tissues, in several independent studies (Bendoraite et al., 2010; Iorio et al., 2007; Nam et al., 2008; Wyman et al., 2009; Yang et al., 2008). The identification of differentially expressed miRNAs relies in part on the choice of normal cells used to compare with the tumors. This is an important aspect since which cells are at the origin of Epithelial Ovarian Cancers (EOC) is still under debate. It has been postulated that EOC arise from ovarian surface epithelium (OSE) cells. Other theories suggest that they

originate from the fallopian tube or the Mullerian ducts (for review, Kurman and Shih, 2010). Among the previously cited studies, Iorio et al., 2007 and Nam et al., 2008

used normal ovary as control. The mesenchymal cell content in ovarian tissue compared to epithelial cancer cells could explain the observed enrichment of miR-200 members, which are highly expressed in epithelial cells. On the contrary, other studies compared ovarian tumors to normal human Ovarian Surface Epithelial (OSE) cells (Bendoraite et al., 2010; Wyman et al., 2009; Yang et al., 2008). All these five studies showed that miR-200 family miRNAs are highly expressed in EOC, suggesting that miR-200 over-expression is not only related to the epithelial versus mesenchymal content. Taken together, these data strongly suggest these miRNA could play a key role in ovarian tumorigenesis.

The prognostic value of miRNAs from the miR-200 family has been studied by several groups but the results are controversial. Two studies suggest that they can be associated with poor prognosis (Nam et al., 2008; Yang et al., 2008), while others indicate the opposite (Eitan et al., 2009; Hu et al., 2009; Leskelä et al., 2011; Marchini et al., 2011; Mateescu et al., 2011). Our unpublished analysis, based on a cohort of patients treated at the Institut Curie (Mateescu et al., 2011) and confirmed in other public available data (Cancer Genome Atlas Research Network, 2011) indicate that

individual miRNA from the miR-200 family cannot robustly predict prognosis.

Nevertheless, these miRNAs could have an important role on clinics as a diagnostic tool. As discussed above, miR-200 family members accumulate significantly at early phases of ovarian tumorigenesis. Moreover, these miRNAs are detected in the blood of ovarian cancer patients, indicating they could be interesting early detection biomarkers of EOC (Kan et al., 2012; Taylor and Gercel-Taylor, 2008).

Besides its potential application in diagnostics, the level of miR-141 and other miR-200s could also be useful for improvement in ovarian cancer patient care.

The levels of these miRNAs in association with other genes could be used for patient stratification and therapy choices (for review, Batista et al., 2013).

Prostate cancer

Note

In 2008, the proof of concept for the use of miRNAs in blood samples (serum/plasma), as biomarkers of human prostate cancers at early stages, has been established (Mitchell et al., 2008). Metastatic prostate patients were compared to healthy controls and miR-141 can distinguish with 100% specificity and 60% sensitivity patients with advanced prostate cancers from controls. In agreement with these results, another study showed that circulating miR-141 is a marker of high-risk prostate cancer (as well as miR-375) (Brase et al., 2011). These miRNAs are also up-regulated in tumor specimens and not only detected as circulating miRNAs. In another cohort of 21 prostate cancer patients, changes in miR-141 levels are correlated with variations of other biomarkers of prostate cancer disease, such as prostate specific antigen (PSA), circulating tumor cells (CTC) and lactate dehydrogenase (LDH) (Gonzales et al., 2011).

Accordingly, in this study, miR-141 can predict tumor progression, similarly as previously validated clinical biomarkers.

Colorectal cancer

Note

High miR-141 plasma level is associated with poor prognosis in colorectal cancer (CRC) and was proposed as a novel biomarker to find distant metastases, to be used together with the CEA (Carcinoembryonic Antigen) (Cheng et al., 2011). This was validated in two independent cohorts from different ethnic populations (US and China). Surprisingly, the elevated levels of miR-141 in plasma of stage IV CRC patients are not linked to elevated levels of miR-141 in tumor tissues at the primary sites. Some hypotheses to explain this result are that miR-141 could be elevated only in metastases and not in the primary tumor and that the circulating miR-141 could be a reflect of differential inflammatory response (Cheng et al., 2011).

In another screening for new miRNAs that could be used as biomarkers for the detection of colorectal

cancer, miR-141 was also detected up-regulated in the plasma of CRC patients (Wang et al., 2012b).

Lung cancer

Note

In human lung cancer cell lines, miR-141 levels distinguished the cell lines on the basis of their site of origin, with higher miR-141 levels in cells from a primary lung tumor than in cell lines derived from metastatic sites (Gibbons et al., 2009). It has been suggested that the metastatic process relies on the down-regulation of miR-200s. This hypothesis is supported by in vivo data in lung cancer mouse models showing that over-expression of miR-200b inhibited metastases formation (Gibbons et al., 2009).

Bladder cancer

Note

All members of miR-200 family, including miR-141, were up-regulated in a series of nine pairs of bladder urothelium carcinoma and matched normal urothelium analyzed by deep sequencing (Han et al., 2011). Another study revealed that miR-141 is up-regulated in bladder tumors compared to normal urothelium, but down-regulated in invasive compared to superficial tumors (Wiklund et al., 2011). Lower level of miR-141 was associated with increased DNA methylation and histone marks. In this cohort, loss of miR-200c (which is transcribed from the same genomic locus) was associated with poor outcome.

It has been described that miR-141 (among others) exhibit a lower expression in the urine of patients with bladder cancer compared to the control group (Wang et al., 2012a). Seventy-five samples were analyzed (24 controls) as well as nine patients before and after surgery. Interestingly, levels of miR-141, after surgery, increases back, up to the level of the control group. The confirmation of these results in larger cohorts using matched age and sex groups is needed. If confirmed, these results could indicate the potential role of miR-141 as a non-invasive biomarker for diagnostics and monitoring of bladder cancer.

Kidney cancer

Note

Investigation of expression profiles of miRNAs in renal cell carcinoma indicated that miR-141 levels are down-regulated in the clear cell carcinoma (CCC) subtype (the most common subtype of renal cell carcinoma) compared to normal kidneys (Nakada et al., 2008). Although the number of samples analyzed was limited (16 CCC samples and 6 controls) the down-regulation of miR-141 was observed in all 16 cases of CCC and of high amplitude (100-fold in average). miR-141 levels were not systematically down-regulated in chromophobe subtype, another subtype of renal cell carcinoma (Nakada et al., 2008). The exact mechanism that explain this down-regulation was not investigated but could be explained by copy number alterations

(losses) or the content of mesenchymal cells in the tumor samples compared to the normal kidneys.

Gastric cancer

Note

Another cancer type where miR-141 was down-regulated is gastric cancer. Thirty-five primary gastric cancer tissues were compared with pair-matched adjacent non-tumor tissues and the miR-141 was found significant lower in 80% of them (Du et al., 2009).

Thyroid cancer

Note

Anaplastic thyroid carcinoma (ATC) is a highly aggressive type of thyroid carcinoma. In contrast to well-differentiated thyroid carcinomas, such as papillary (PTC) and follicular (FTC), the prognosis for ATC is very poor. Microarray analyses of miRNA abundance in three primary ATCs versus three normal thyroid samples identified miR-141, as well as other miR-200s, as down-regulated in ATCs (Braun et al., 2010). Data in ATC cells indicate that miR-141 target TGFBR1 and SMAD2. Moreover, down-regulation of miR-141 distinguishes ATCs from other thyroid carcinomas, namely PTCs and FTCs.

Esophageal cancer

Note

In order to explore the role of miRNAs on chemotherapy resistance, a study using nine human esophageal squamous cell carcinoma cell lines compared the miRNA profiles of cisplatin-resistant versus sensitive cell lines (Imanaka et al., 2011). miR-141 was the most up-regulated miRNA in the resistant cell lines. It has been suggested that miR-141 confers resistance to cisplatin-induced apoptosis by targeting YAP1 (yes-associated protein), which induces apoptosis upon treatment with DNA-damage agents.

Cancers

Note

In summary, levels of miR-200 family members, including miR-141 were found misregulated in several different types of cancer. These miRNAs are potential biomarkers of various cancers and could be used in non-invasive diagnosis and monitoring of the disease. Accordingly, there are several patents published in the field.

Interestingly, miR-200 miRNAs were found up-regulated in ovarian cancer, superficial bladder tumors and in the blood of ovarian, colorectal and prostate patients, but down-regulated in kidney (CCC) and invasive gastric cancer as well as in the urine of bladder cancer patients.

The role of miR-200s in regulation of EMT process has been demonstrated, but some questions about its role in metastasis and tumor progression still need to be elucidated. Since high expression of miR-200s is associated with an epithelial phenotype, one can

hypothesize that miR-200 expression varies in the different steps of tumorigenesis. One can speculate that miR-200 levels are high in primary tumors, become low during metastatic processes, when cells acquire mesenchymal characteristics, and could again be up-regulated in the metastases, if they exhibit a more epithelial phenotype. In agreement with this theory, in a study that compared 43 primary tumors (colon, bladder, breast and lung) to their matched lymph node metastases, miR-141, as well as other miR-200s, was found down-regulated in metastatic cancers (Baffa et al., 2009).

Besides their potential as diagnostic markers, miR-141 and other miR-200s levels could also be indicative of response to chemotherapy, at least in ovarian and oesophageal cancers, as discussed before.

Much remains to be done in the field to prove the role of miR-141 in human cancers and its interest in clinics. Nevertheless, given the several studies already published, the miR-200 family will inevitably be considered in future developments of medical tools based on miRNAs in the field of cancer diagnosis and/or therapy.

Epithelial-mesenchymal transition (EMT)

Note

miR-200 family members, including miR-141 can regulate EMT by directly targeting ZEB1 and ZEB2 factors, which are repressors of E-cadherin (CDH1). Conversely, ZEB1/2 factors can negatively regulate the transcription of these miRNAs, establishing a negative feedback loop (Bendoraite et al., 2010; Bracken et al., 2008; Burk et al., 2008; Gregory et al., 2008; Korpal et al., 2008; Park et al., 2008).

Stemness

Note

EMT being associated with stemness properties (Mani et al., 2008), miR-200 family has been involved in stemness by targeting ZEB1 (Wellner et al., 2009). Moreover, in both normal mammary stem cells and breast cancer stem cells, levels of miR-200 family miRNAs are reduced compared to non-tumorigenic cancer cells (Shimono et al., 2009). In addition to ZEB1 and ZEB2, miR-200 family members also target BMI1 and SUZ12, components of the PRC1 and PRC2 Polycomb complexes, respectively (Iliopoulos et al., 2010; Shimono et al., 2009), which are important for growth and function of cancer stem cells.

Oxidative stress response

Note

miR-141 and other members of the miR-200 family are up-regulated following oxidative stress in different human and mouse cell lines (Magenta et al., 2011; Mateescu et al., 2011). Moreover, miR-141 and miR-200a directly target the p38 (MAPK14) transcript, which is an important redox sensor (Mateescu et al.,

2011). NRF2 pathway is a key cellular defense pathway against oxidative stress. These miRNAs, miR-141/200a, also affect directly this pathway by targeting one of its key regulators, the NRF2 repressor, KEAP1 (Eades et al., 2011; van Jaarsveld et al., 2012).

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