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Gene Section
Mini Review

MIR222 (microRNA 222)

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Identity

Other names: MIRN222 (microRNA 222); hsa-mir-222; miR-222

HGNC (Hugo): MIR222

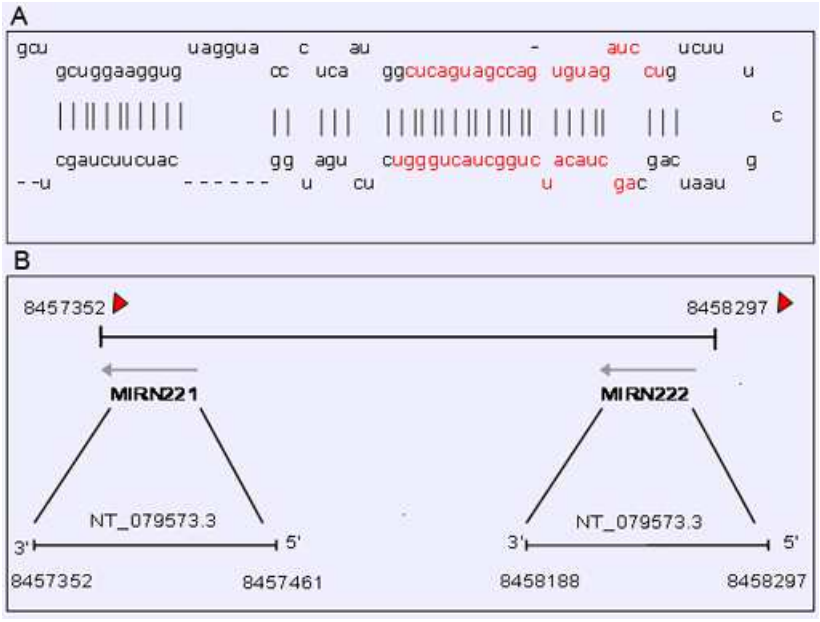
Location: Xp11.3

Local order: Based on Mapviewer (Master Map: Genes on sequence), genes flanking miR-221 and miR-222 oriented from centromere to telomere on Xp11.3 are:
KRT8P14 (Xp11.3): keratin 8 pseudogene 14,
LOC392452 (Xp11.3): hypothetical LOC392452,
MIRN221 (Xp11.3) : microRNA 221,
MIRN222 (Xp11.3) : microRNA 222,
LOC100128442 (Xp11.3): hypothetical LOC100128442,
LOC100130359 (Xp11.3): hypothetical LOC100130359.

DNA/RNA

Description

miR-221 and 222 are located in an intergenic region. miR-221 and miR-222 are clustered genes, containing identical seed sequences and both map to the X chromosome separated by 727 bases. The positions of these cluster microRNAs are:
hsa-mir-222 X: 45491365-45491474
has-mir-221 X: 45490529-45490638.



A: Stem-loop structure of miR-222. B: Genomic localization of miR-221 (MIRN221) and miR-221(MIRN222) on chromosomal band Xp11.3.

Transcription

In general, the microRNA genes are transcribed by RNA polymerase II, whereas RNA polymerase III is also responsible for transcription of some other microRNAs. It is not known which RNA polymerase transcribes miR-221/miR-222. miR-221 and miR-222 were shown to be expressed as a single pri-microRNA transcript in c-kit positive HUVEC cells.
Pre-microRNA 222 (precursor microRNA)
Accession: MI0000299.
Length:110 bp.
Sequence:
5'-GCUGCUGGAAGGUGUAGGUACCCUCAAU GGCUCAGUAGCCAGUGUAGAUCCUGUCUUUC GUAAUCAGCAGCUACAUCUGGCUACUGGGUC UCUGAUGGCAUCUUCUA GCU-3'.
Mature miR-222
Accession: MIMAT0000279.
Length: 21 nucleotides.
Sequence: 69 - agcuacaucuggcuacugggu – 89.

Pseudogene

No pseudogenes were reported for mir-221 and 222.

Protein

Note
MicroRNAs are not translated into amino acids.

Implicated in

Differentiation and erythropoiesis

Note
Induction of 12-O-tetradecanoylphorbol-13-acetate (TPA), a differentiation stimulator of HL-60 cells, caused growth arrest and the adherent phenotype in 60% of HL-60 cells. MicroRNA expression was analyzed in these TPA treated differentiating HL-60 cells. According to the results of microarray analysis, miR-221 and miR-222 were up-regulated about 3-folds in TPA induced HL-60 cells. On the other hand, the expression of c-kit receptor was down- regulated in these cells, which suggested that c-kit, as was previously reported, the target of miR-221/222. miR-221 and miR-222 were shown to be down-regulated in erythropoietic culture of cord blood CD34-positive progenitor cells and it was suggested that this reduction could cause erythropoiesis, as the expression of targeted key mRNAs were not blocked. However, in another study, the expression of miR-221 (but not miR-222) was shown to be increased during erythropoietic cultures of human CD34 cord blood cells. Further studies also indicated up-regulation of miR-221. Differentially expressed miRNAs during erythropoiesis were detected in cord blood-derived CD34 cells and expression of miR-221 temporarily increased from day 0 to day 2, while its expression returned to the basal level (same as day 0) from day 2 to day 12 of erythropoiesis. Such a fluctuation in the miRNA expression, however, was not found for miR-222 in these cells. Together, these results suggest a need for further investigation to clarify this difference. Also in kit positive TF-1 erythroleukemic cell line which expresses high amounts of kit protein and low levels of miR-221/miR-222, transfection of these microRNAs blocked proliferation of these cells.

Angiogenesis, proliferation and cell migration

Note
miR-222 and miR-221 were found to be highly expressed in human cord blood derived CD34 - Hematopoietic Progenitor Cells (HPCs) and Human Umbilical Vein Endothelial cells (HUVECs). HUVECs were used as an in vitro model for angiogenesis as they can form capillary like tubes when exposed to appropriate stimulation. miR-221/miR-222 were shown to be transcribed in a common pri-microRNA in c-kit-positive HUVECs, suggesting a coordinated transcriptional regulation. Another group examined the effect of miR-221/miR-222 expression on the c-kit transcript and protein and they found that the level of c-kit protein was reduced in HUVECs transfected with miR-221/ miR-222, without a change of mRNA levels, which indicated the posttranslational down-regulation effect of these microRNAs on c-kit protein. In addition miR-221/miR-222 transfected cells were not able to do wound healing and tube formation. In another study, down-regulation of eNOS (an angiogenesis regulator) protein by miR-221/miR-222 was claimed and because no target sites for these microRNAs in 3'-UTR of eNOS were present, it was suggested that the regulation could be indirect via gene expression, translational efficiency or post-translational pathways. Interestingly, over-expression of miR-221/miR-222 in endothelial cells reduced angiogenesis and cell proliferation whereas conversely in cancer cells, up-regulation of miR-221/miR-222 increased cell proliferation by targeting cell cycle inhibitor p27, possibly indicating that the modulation of proliferation depends on the cell type.

Prostate cancer

Note
In a study, PC3 cells (aggressive prostate carcinoma) and LNCaP and 22Rv1 cell line (slowly growing carcinomas) were tested and a reverse correlation between the expression of miR-221/miR-222 and p27 tumor suppressor was observed. In addition, over-expression of miR-221/miR-222 altered the growth rate of these cells, by triggering a shift from G1 to S phase of the cell cycle.

Papillary thyroid carcinoma

Note
When comparing the expression level of 23 microRNAs in 15 Papillary Thyroid Cancer (PTC) tumors with normal thyroid tissue, a group of

researchers found that miR-221/ miR-222 were among the five over-expressed microRNAs in PTC tumors by performing microarray analysis (the results were also confirmed with RT-PCR and Northern blot). Interestingly, quantitative real-time PCR results revealed that miR-221 was over-expressed in normal thyroid tissues of PTC patients when compared to normal thyroid tissues of individuals without clinical thyroid disease, indicating the possible importance of this microRNA in early stages of PTC carcinogenesis.

Lung cancer

Note

A microRNA expression investigation was performed in NSCLC (non-small cell lung cancer) cells either resistant or sensitive to TRAIL (TNF-related apoptosis-inducing ligand) to reveal roles of microRNAs in TRAIL resistance. The microarray and real-time PCR analysis showed that miR-221 and miR-222 were remarkably up-regulated in TRAIL-resistant and down-regulated in TRAIL-sensitive NSCLC cells. Also miR-222 over-expression in CALU-1 cells (TRAIL-resistant) was confirmed by Northern blotting. In addition, transfecting CALU-1 cells (TRAIL-resistant lung cells) with anti- miR-221/miR-222, caused TRAIL sensitivity. Consistently over-expression of these microRNAs produced TRAIL-resistant NSCLC cells. Moreover, p27 tumor suppressor and proto-oncogene kit receptor, which are the known targets of miR-221/miR-222, were shown to be up-regulated in TRAIL-sensitive and down-regulated in TRAIL-resistant NSCLC. These microRNAs were also suggested to modulate the expression of Mcl-1 (myeloid cell leukemia sequence 1) and FADD (Fas-associated protein with death domain) indirectly. Giving these, miR-221 and miR-222 were shown to be responsible for sensitivity to TRAIL in NSCLC cells and could be considered as important targets for diagnostic and therapeutic purposes in NSCLC.

Pancreatic cancer

Note

For the purpose of finding a microRNA signature in pancreatic cancers, the expression of over 200 microRNA precursors was investigated by real-time PCR in benign tissue, normal pancreas, chronic pancreatitis and pancreatic cancer cell lines. The results showed that a number of microRNAs were over-expressed in the tumors, when compared to normal pancreas. miR-221 was among the microRNAs that were over-expressed in adenocarcinomas and endocrine pancreas cancers. Based on PCR results, over-expression of mature miR-222 was also suggested (similar to miR-221) in pancreas cancer.

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