NDUFA13 (NADH:ubiquinone oxidoreductase subunit A13)

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Abstract
Short communication on NDUFA13, with data on DNA/RNA, on the protein encoded and where this gene is implicated.

Keywords
NDUFA13; GRIM-19; mitochondria complex I; apoptosis.

Identity
Other names: B16.6, CDA016, CGI-39, GRIM-19, GRIM19, complex I B16.6 subunit
HGNC (Hugo): NDUFA13

Location (base pair): Starts at 19515989 and ends at 19528126 bp (according to COSMIC)
Local order: Orientation: Forward Strand. Between theGATAD2A and YJEFN3 genes.

DNA/RNA
Note
NDUFA13 is a protein-coding gene, which encodes a subunit of the mitochondrial respiratory chain NADH dehydrogenase (Complex I).

cDNA Nucleotide Sequence
ATGGGCCCCTAAAAGGCTGAAGAGACATCCTCCGCGGCGG6666CTATGG6C5CAATGACTACAACACG6A
ACTGGCCGGCGTCGAAGGACTGTG6G6GCTACAGATGCCCATAGGAAATGGAACTCGAATCAGCAGCAGCA
CAGAAGCTAATGGAAGTGG6AANCTGAGAGCCAGCAGCCCTAAAAGAAGGGACGAGGAGAGCTTGGAGAA
AGGAGCATTACATGAAAGGACG6G6CAGCTGGAGAAGCTTGGAGAAGCTTGGAGAAGCTTGGAGAAGCTTGGAGA
GGGCCCGCTTGTACGCGGGAGCTGCTGGCTGGCACAACAGAGGAAGGACTCTCTCTCCATGCGAGCCACGCGCTCT
ATGGTACAGTACGAG

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**Description**

The NDUFA13 gene, with 18995 bases in length (NG_013380), consists 5 exons and 4 introns. It was first identified and isolated by antisense knock-out techniques, in a study aiming the identification of gene products that participate in synergistic growth-suppressive actions (Angell et al., 2000). Expression of NDUFA13 is induced by IFNB1/IFN-beta combined with all-trans-retinoic acid.

**Transcription**

The NDUFA gene is characterized by 7 transcripts. Three are protein coding transcripts. The transcribed mRNA of NDUFA13 gene has 557 bp (NM_015965). RNA is expressed in all tissues. Two other transcripts are protein coding, one with 120 aa and another with 150 aa. Two transcripts are nonsense mediated decay and two other retain an intron, none of these 4 coding for proteins. Transcripts originating from an upstream promoter and capable of expressing a protein with a longer N-terminus have been found, but their biological validity has not been determined. (Provided by RefSeq, Oct 2009).

**Protein**

**Note**

Protein class: disease related genes, mitochondrial proteins, predicted membrane proteins.

**Description**

The human NDUFA13 gene encodes for a 16KDa protein and 144 amino acids, purified from mitochondria. It was first identified as a novel cell death-regulatory gene whose inactivation confers growth advantage to cells in the presence of IFN/RA (Angell et al., 2000). This protein has a modified residue at position 2, an alanine that can be acetylated. The transmembrane portion of NDUFA13 protein encompasses amino acids at positions 30 to 51, being 22 residues long, and has a helical shape. The 43 aa region consisting of residues 102 to 144, is important for inducing cell death. Translation (144 aa)
Amino acids: 144. Molecular weight: 16KD. The NDUFA13 gene encodes for a protein that belongs to the family of NADH dehydrogenase ubiquitone 1 alpha subcomplex 13.

**Expression**


**Localisation**

Mitochondria inner membrane, Single-pass membrane protein, Matrix side, Nucleus. (UniProt Q9P0J0).

Diagram of the NDUFA13 protein. Numbers indicate amino acids. The box inside represents the transmembrane domain (TM). The domains indicated by the blue key represent sequences for mitochondrial targeting, maintenance of Δψm, and enhancing assembly.
**Function**

Molecular function: catalytic - oxidoreductase activity - and it is involved in metabolic processes and biological regulation.

NDUFA13 was described in 2004 as a gene product with a specific role in IFN-RA-induced cell death, as a functional component of mitochondrial complex I and as being essential for early embryonic development (Huang et al., 2004).

Cell death regulatory protein that promotes apoptosis, is a negative regulator of cell growth, and it is involved in mitochondrial metabolism (Angell et al., 2000; Lufei et al., 2003).

Accessory subunit of the mitochondrial membrane respiratory chain NADH dehydrogenase (Complex I). Involved in the interferon/all-trans-retinoic acid (IFN/RA) induced cell death, which is inhibited by interaction with viral IRF1. Prevents the transactivation of STAT3 target genes (Lufei et al., 2003; Zhang et al., 2003).

Diseases associated with NDUFA13 include thyroid Hürthle cell carcinoma, and kidney cancer. GO annotations related to this gene include NADH dehydrogenase activity and NADH dehydrogenase (ubiquinone) activity.

**Homology**

NDUFA13 score.

There are still 120 uncharacterized proteins in different species including Homo sapiens, with homologies varying from 28% to 100% (Homo sapiens).

Nine predicted proteins with homologies between 40% and 52% have also been identified in different species (B2014110593WH1M8NCV).

**Mutations**

Loss of expression and occurrence of mutations in the NDUFA13 gene in a variety of primary human cancers-lung, kidney, prostate, thyroid, ovary, colon, esophagus and brain (Alchanati et al., 2006; Máximo et al., 2008; Zhou et al., 2009; Fan et al., 2012) - have been described, indicating its potential role as tumor suppressor.

Depletion or overexpression of NDUFA13 promotes and suppresses, respectively, tumor growth (Angell et al., 2000; Máximo et al., 2008; Huang et al., 2010).

Levels of expression of NDUFA13 are a good prognostic marker for colorectal cancer (Hao et al., 2015) and loss of expression correlate with malignancy in Hürthle cell tumours (Donatini et al., 2015).

**Germinal**

One germline missense mutation of NDUFA13 has been identified in one patient with apparently sporadic Hürthle cell carcinoma: G264C substitution in exon 1 (Máximo et al., 2005).

**Somatic**

Three missense mutations have been identified in three out of 20 cases of sporadic Hürthle cell carcinomas: a C77T and a A247G in exon 1, and a G593C in exon 5 (Máximo et al., 2005).

Three somatic mutations of NDUFA13 gene have been identified in a set of primary head and neck tumors (Nallar et al., 2013).
Wild-type NDUFA13 suppresses cellular transformation by a constitutively active form of STAT3, whereas tumor-derived mutants (L71P, L91P and A95T) significantly lost their ability to associate with STAT3, block gene expression and suppress cell transformation and tumor growth in vivo. These three mutants have also lost their capacity to prevent metastasis.

**Implicated in**

*Various cancers, arthritis and mouse embryo development and implantation.*

**Disease**
Renal Cell Carcinomas (RCC), inflammatory bowel diseases, Kaposi sarcoma, Hürthle cell carcinomas, lung cancer, hepatocellular carcinoma, colorectal cancer (CRC), prostate carcinoma, cervical carcinoma, breast carcinomas, head and neck squamous cell carcinoma.

**Prognosis**
NDUFA13 mRNA and protein expression are significantly lower in colorectal cancer than in normal tissues. It is suggested that low NDUFA13 expression is closely associated with colorectal cancer progression and might be a very promising prognostic biomarker for CRC patients (Hao et al., 2015). Moreover, in breast cancers, nonexpression of NDUFA13 is significantly associated with lymph node metastasis, advanced tumor-node-metastasis stage, triple-negative which is a mark of bad prognosis (Zhou et al., 2013).

**Embryo development and implantation**
The expression of NDUFA13 in mouse preimplantation embryos changes at different developmental phases suggesting an important role during embryonic development (Cui et al., 2012). Other authors have seen that downregulation of NDUFA13 affects mouse oocyte viability, maturation and embryo development and implantation (Chao et al., 2015).

**Thyroid cancer**
Somatic and germline mutations, 15% and 5%, respectively, in NDUFA13, were described in Hürthle cell tumors of the thyroid (Máximo et al., 2005). These mutations were described as the first nuclear gene mutations specific to Hürthle cell tumors and it was proposed that such mutations may be involved in the genesis of sporadic as well as familial Hürthle cell tumors through the dual function of NDUFA13 in mitochondria metabolism and cell death.
**Renal cell carcinoma**

NDUFA13 expression is lost or severely decreased in primary RCC (Alchanati et al., 2006). The presence of NDUFA13 protein was evaluated by Western blot in 11 cases of RCC and it was absent, weakly or moderately present in 4, 6 and 1 cases, respectively, compared with normal counterpart (Alchanati et al., 2006). The pattern of mRNA expression correlated with the level of protein expression by Western blot analysis. In the same study, an immunostaining evaluation showed intense nuclear membrane and cytoplasmic staining in proximal tubular epithelium in normal kidney, whereas NDUFA13 expression was absent in 93% of the cases. Downregulation of NDUFA13 is associated with enhanced cell proliferation which is proposed to act via uninhibited STAT3 regulatory pathway (Alchanati et al., 2006).

**Prostate cancer**

NDUFA13 protein expression is not significantly decreased in prostate cancer. Loss of NDUFA13 staining by immunohistochemistry was found in only 2 out of 17 prostate carcinomas (Alchanati et al., 2006).

**Kaposi’s sarcoma**

NDUFA13 inhibits INF/retinoic acid-induced cell death (Seo et al., 2002).

**Lung cancer**

There is a negative correlation between the expression level of NDUFA13 and the stage of the primary lesion of non-small cell lung carcinomas (NSCLC). Downregulation of NDUFA13 was described in NSCLC stages III-IV compared to stages I-II (Fan et al., 2012). GRIM-19 is mainly located in the cytoplasm in lung inflammation tissues, but located in the nucleus in lung cancer tissues (Fan et al., 2012).

**Hepatocellular carcinoma**

Expression levels of NDUFA13 are significantly lower in hepatocellular carcinoma patients with deteriorating differentiation states, hepatic capsule invasion and microvascular invasion (Hao et al., 2012).

**Gliomas**

Gliomas express NDUFA13 at low levels and this plays a major role in tumorigenesis of the brain. NDUFA13 mRNA and protein levels are significantly lower in gliomas than in control brain tissues. NDUFA13 expression levels negatively correlates with malignancy of the gliomas (Zhang et al., 2011).

**Cervical cancer**

Zhou et al. have shown that reduction of the levels of NDUFA13 protein occurs in primary cervical cancers, and is associated with hyperactivation of STAT3 (Zhou et al., 2009; Chen et al., 2015).

**Breast cancer**

Nonexpression of NDUFA13 is significantly associated with lymph node metastasis, advanced tumor-node-metastasis stage, triple-negative phenotype and low NDUFA13 expression is correlated with STAT3 overexpression (Zhou et al., 2013).

**Colorectal cancer**

NDUFA13 shows low or absent expression in colorectal carcinomas. mRNA and protein expression are lower in colorectal carcinoma than in normal tissues (Hao et al., 2015).

**Head and neck squamous cell carcinoma**

Decreased expression of NDUFA13 due to hypermethylation is correlated with cell proliferation in head and neck squamous cell carcinoma (Zhang et al., 2015).

**Inflammatory bowel disease**

NDUFA13 expression is decreased in inflamed mucosa of patients with inflammatory bowel disease (Barnich et al., 2005).

**Bladder urothelium**

NDUFA13 protein expression is not significantly decreased in bladder tumors. Loss of NDUFA13 staining by immunohistochemistry was found in only 1 of 6 transitional cell carcinomas of the renal pelvis (Alchanati et al., 2006).

**Arthritis**

NDUFA13 attenuates murine autoimmune arthritis (Moon et al., 2014).

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