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Gene Section
Review

MINA (MYC induced nuclear antigen)

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Identity

Other names: DKFZp762O1912, FLJ14393, MDIG, MINA53, NO52
HGNC (Hugo): MINA
Location: 3q11.2
Note: MINA (myc induced nuclear antigen) is a gene whose expression is directly induced by c-MYC protein. The MINA gene encodes a protein with a molecular weight of 53 kDa that is localized in the nucleoplasm and nucleolus.

DNA/RNA

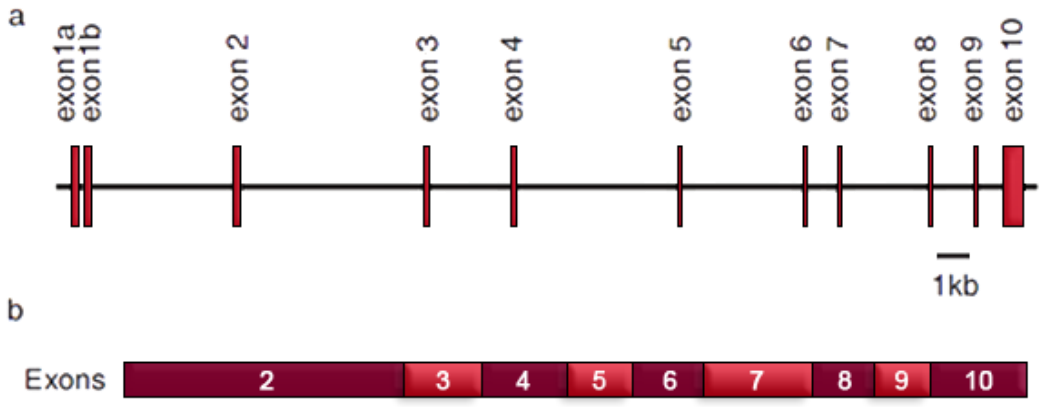
Description

The human MINA gene consists of twelve exons spanning a 30 kb. The translation start site locates in exon 2, which follows two distinct exons, exon 1a and exon 1b.

Thus, there are two transcription initiation sites in the human MINA gene. The exon 1b exists 0.25 kb downstream of the exon 1a. The stop codon (TAG) exists in the last exon, exon 10. The open reading frame of the coding region is 1398 bp, encoding 465 amino acids. mRNA encoding 464 amino acids (lacking 297Q) is also generated by alternative splicing due to the lack of the first three bp of exon 7.

Transcription

The human MINA coding sequence consists of 1398 bp from the start codon to the stop codon. In addition to the 1395 bp-coding sequence, multiple alternative spliced transcript variants have been found for this gene. c-MYC protein stimulates the transcription of MINA through the E-box near the transcription start sites (Tsuneoka et al., 2002). The expression of MINA is also induced by serum (Tsuneoka et al., 2002).



a. Exon-intron structure of the MINA gene. There are two transcription initiation sites at exon 1a and exon 1b.
b. mRNA for human MINA that encodes MINA protein. The protein is coded from exon 2 to exon 10.

Protein

Structural features of MINA protein. The positions of the JmjC domain is shown (green).

Description

Structure: MINA is a member of the jumonji C (JmjC) protein family, and suspected to hydroxylate some proteins to control gene expression.
Activation: The expression of mRNA is elevated by c-MYC protein, and frequently increased in various types of cancers, including human colon cancer, esophageal squamous cell carcinoma (ESCC). In some types of cancers such as ESCC, patients with high expression of MINA53 had shorter survival periods. MINA expression is also activated not only MYC but also by other factors, because there are lymphoma and lung cancer tissues where the expression of MYC is downregulated but the expression of MINA is elevated (Teye et al., 2007; Komiya et al., 2010). The expression of MINA is also activated and mineral dust in human alveolar macrophage and human lung cancer cell line, A549 (Zhange et al., 2005).

Expression

MINA is ubiquitously expressed. The expression of MINA is frequently increased in various types of human cancers. In mice, MINA expression is high in some non-neoplastic tissues, including spleen, thymus, colon and testis, but low in skeletal muscle, cerebellum, and seminal vesicle. In testis the expression of MINA is high in spermatogonia and mitotic prophase cells and weakly in early pachytene spermatocyte but absent in late pachytene spermatocytes (Tsuneoka et al., 2006).

Localisation

MINA is diffusely nucleoplasmic and some portion is accumulated in nucleolus (Tsuneoka et al., 2002).

Function

Specific inhibition of MINA expression suppressed cell proliferation in some cultured cell lines (Tsuneoka et al., 2002). Forced expression of MINA in NIH/3T3 cells induces cell transformation, and MINA-transfected NIH/3T3 clones produce tumor in nude mice (Komiya et al., 2010). Therefore, MINA has oncogenic potential. MINA is a nuclear protein and a member of the jumonji C (JmjC) protein family. Thus, MINA is suspected to hydroxylate some proteins to control gene expression, but its substrate is not clear.
Gene activation: MINA regulates several genes which are also regulated by MYC. Genes regulated by MINA but not by MYC include HGF, EGFR, and IL6 (Komiya et al., 2010).
Gene suppression: Recently, MINA was identified as a genetic determinant of T(H)2 bias. MINA specifically binds to and represses the IL4 promoter. MINA overexpression in transgenic mice impaired IL4 expression, whereas its knockdown in primary CD4(+) T cells led to IL4 de-repression. Therefore MINA controls helper T cell differentiation through an IL4-regulatory pathway (Okamoto et al,. 2009). These findings suggest that MINA may play a role on carcinogenesis also in the field of cancer immunology.
Ribosome biogenesis: MINA is accumulated in nucleolus (Tsuneoka et al., 2002). Immunolocalization studies revealed that MINA is highly concentrated in the granular component of nucleoli (Eilbracht et al., 2005). MINA is a constituent of free preribosomal particles but is absent from cytoplasmic ribosomes. MINA interacts with various ribosomal proteins as well as with a distinct set of non-ribosomal nucleolar proteins. These results suggest that MINA is directly involved in ribosome biogenesis, most likely during the assembly process of preribosomal particles (Eilbracht et al., 2005). MINA was also suggested to be involved in ribosomal RNA transcription (Lu et al., 2009).

Homology

The primary sequence of MINA has similarity to nucleolar protein NO66, which also has a JmjC domain. The JmjC domain of MINA has 50% identity to that of NO66. In 2010, it was report that NO66 directly interacts with Osterix (Osx), which is an osteoblast-specific transcription factor required for osteoblast differentiation and bone formation. NO66 exhibits a JmjC-dependent histone demethylase activity, which is specific for both H3K4me and H3K36me in vitro and in vivo. It was suggested that interactions between NO66 and Osx regulate Osx-target genes in osteoblasts by modulating histone methylation states (Sinha et al., 2010).

Implicated in

Neoplasm diseases

Note
Colon cancer, esophageal squamous cell carcinoma, gingival squamous cell carcinoma, subtypes of human lymphoma, renal cell carcinoma, neuroblastoma, gastric carcinoma, lung cancer and hepatoma.
Disease
MINA expression is elevated in several types of carcinomas.
Prognosis
MINA is preferentially expressed in some types of cancers with a poor prognosis, including esophageal squamous cell carcinoma, advanced
renal cell carcinoma, neuroblastoma. The expression levels of MINA may be used as a prognositic marker in these cancers. On the other hand, elevated expression of MINA in lung cancer patients is associated with favorable prognosis.

Colon cancer

Note

The expression of MINA is elevated in all the adenocarcinomas compared to adjacent non-neoplastic tissues, which shows little staining. MINA is expressed in all pathological grades of cancer as well as in the adenoma. Staining patterns of Ki-67, a biomarker for cell proliferation, are similar to those of MINA in most cases. While anti-Ki-67 antibody strongly stains some well-proliferating non-neoplastic cells including cells in the deeper part of the crypts and in lymphoid germinal centers, antibody to MINA rarely stained those cells. These results indicate that the elevated expression of MINA is a characteristic feature in colon cancer (Teye et al., 2004).

Esophageal cancer

Note

The expression of MINA in tumors is increased compared with that in adjacent non-neoplastic tissues. MINA was highly expressed in more than 80% of specimens. Anti-MINA antibody stained tumors more efficiently than antibody against Ki-67, a cell proliferation biomarker, in some cancer specimens. Patients with high expression of MINA has shorter survival periods, whereas the expression level of Ki-67 in ESCC shows no relationship to patient outcome (Tsuneoka et al., 2004).

Primary gingival squamous cell carcinoma

Note

A significant correlation was found between the expression of MINA and that of Ki-67 in patients with gingival squamous cell carcinoma or dysplastic gingiva. No significant correlation was noted between the expression of MINA or Ki-67 and prognostic factors such as the degree of differentiation, lymph node metastasis, stage, and tumor diameter (Kuratomi et al., 2006).

Lymphoma

Note

Although MINA expression is not prominent in lymphoma in general, it is related to tumor progression of B cell lymphoma (Teye et al., 2007).

Renal cell carcinoma (RCC)

Note

MINA is expressed in the nuclei of tumor cells and tubular nuclei of normal renal tissue.

The expression level of MINA is significantly higher in patients with poor prognostic factors

(stage IV, MVI-positive, and sarcomatoid RCC, and high Ki-67 LI). The prognosis of high MINA-expressing tumors was significantly poorer than that of non-MINA-high tumors (Ishizaki et al., 2007).

Neuroblastoma

Note

Surgically obtained neuroblastoma specimens were immunohistochemically stained to determine the MINA and Cap43 expression levels. A significant relationship was found between MINA and Ki-67, between MINA and neurotrophic tyrosine kinase, receptor, type 1 (TrkA), and between Cap43 and TrkA. The prognosis is significantly favorable in the Cap43 high-expression cases, whereas it is significantly poor in the MINA high-expression cases (Fukahori et al., 2007).

Gastric carcinomas

Note

Elevated expression of MINA was observed in 91.1% of the gastric carcinomas. No significant associations were found between MINA and clinicopathological characteristics such as sex, age, histological differentiation, distant metastasis and lymph node metastasis. However, there was a significant association with depth of invasion and TMN stage. MINA expression was positively associated with a proliferation marker, PCNA, level (Zhang et al., 2008).

Lung cancers

Note

The expression of MINA is elevated in lung cancer tissues (Lu et al., 2009; Komiya et al., 2010). The overexpression of MINA is an early event in lung cancer occurence (Lu et al., 2009; Komiya et al., 2010). Further, patients with negative staining for MINA has shorter survival than patients with positive staining for MINA, especially in stage I or with squamous cell carcinoma. These results suggest that overexpression of MINA in lung cancer patients is associated with favorable prognosis (Komiya et al., 2009). MINA may inhibit lung cancer cell invasion (Komiya et al., 2009).

Hepatoma

Note

MINA is diffusely expressed in the nuclei of cancer cells in the tumor nodule, and is often strong at the periphery of tumor nodules. MINA expression is higher in poorly differentiated hepatocellular carcinoma (HCC) than in well-differentiated HCC, and there is significant relationship between MINA expression and histological grade. The high MINA expression is associated with high expression of a proliferation marker, antibody to Ki-67. MINA expression is high in the tumors of > 2 cm of diameter than in ≤ 2 cm (Ogasawara et al., 2010 in press).

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