ZMYND10 (zinc finger, MYND-type containing 10)

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Abstract

The candidate tumor suppressor gene ZMYND10/BLU, is located on the minimal deleted fragment of 110 kb in chromosomal region 3p21.3. It was initially identified by PCR in search of the b-catenin homolog in lung cancer. BLU codes for a protein with 440 amino acid residues, which contains a zinc finger myelogenous nervy domain (zMYND) motif on its carboxyl terminus. The characteristic domain defines a ZMYNND protein family, some of its member have been found in the frequently affected region translocated during acute leukemias, and were described to be transcriptional repressors. BLU/ZMYND10 is inactivated in a variety of human tumors due to genetic or epigenetic mechanisms, but the function is largely unknown. It has been reported that similar with certain tumor suppressors, it downregulates JNK/MAPK signaling to exert inhibition on growth and proliferation. ZMYND10 is implicated in the respiratory ciliary dyskinesia.

Identity

Other names: BLU, CILD22, FLU
HGNC (Hugo): ZMYND10
Location: 3p21.31
Local order
Telomeric to NPRL2/G21, and centromeric to RASSF1.

DNA/RNA

Note
NM_015896, 4.7 kb.

Description

The genomic size of the gene is about 4.5 kb.

The gene of 4.5-4.7 kb contains 12 (lung version, termed as canonic) or 11 (testis version) exons coding for a 2-kb, alternatively spliced mRNA, well expressed in lung and testis but not expressed in all other tested human tissues.
**Transcription**
The testis isoform contains 11 exons because of a complex selection of an alternative acceptor site.

**Pseudogene**
No known pseudogenes.

**Protein**

**Note**
NP_056980; ZMYND10 (zinc finger, myeloid, nervy and DEAF-1 (MYND)-type containing 10).

**Description**
The BLU protein is likely a soluble cytoplasmic protein and shares 30-32% identity over a stretch of 100-112 amino acids (residues 334-437 or 318-430) with proteins of the MTG/ETO family of transcription factors and the suppressins.
The most notable feature of the protein is a C-terminal MYND domain, spanning residues 394-430.
The MYND domain constitutes a protein-protein interaction surface that appears to allow these proteins to act as transcriptional co-repressors by association with a variety of chromatin remodelling and transcription.

**Expression**
Low level expression in most human tissues.

**Localisation**
A majority of its coding product is located in cytoplasm.

**Function**
The function of BLU/ZMYND10 is unknown. As a MYND-containing protein BLU/ZMYND10 is most likely to be involved in important transcriptional regulation pathways.
It has been reported that BLU regulate cell cycle progression through inhibition JNK signaling.

**Homology**
Shares 30-32% identity over a stretch of 100-112 amino acids (residues 334-437 or 318-430) with proteins of the MTG/ETO family of transcription factors and the suppressins.

**Mutations**

**Note**
The lung isoform is regarded as canonic isoform. The testis-specific protein isoform contains a different amino acid sequence between residues 199 and 234 as compared with the canonic lung-specific isoform.
Mutation of BLU/ZMYND10 within a given isoform is a rare event in lung cancer and other cancers since missense changes were detected in only 3/61 lung tumour-cell lines. The eight-gene set in the 120-kb region show that the mutation rate was in the range of 5%. Missense mutations were discovered in a sample of 61 lung cancer cell lines. It has been shown that, however, mutated ZMYND10 protein carrying substitution of some amino acid residues binds LRRC6 and contributes to pathogenesis of primary ciliary dyskinesia (PCD, or CILD22).

**Somatic**
Mutation carried by testis isoform 200-234: SLSLSTLSRMSTHNLPCILLVELLEHSPWSRREGG→RQWSVSQPPPQLAHLKRQRLHPVCFWSLSGP; results in the loss of one of three PKC phosphorylation sites (residues 229-231). The substitutions documented in PCD include: ZMYND10, VAL16GLY, SER29PRO, LEU39PRO, LEU266PRO, ARG369TRP, Tyr379CYS, and ASP198GLN, ARG407GLU in non-small cell lung cancer cells.

**Implicated in**

**Various cancers**

**Note**
The gene codes for the putative tumor suppressor BLU is primarily expressed in the lung and testis, as tissue-specific isoforms, but the level is low in other tissues. The expression is varied in lung cancer cells, but a non-small lung cancer line, A549 has high level of BLU. A majority of nasopharyngeal carcinoma-derived cell lines, however, has downregulated expression of BLU. Mutation of the gene is relatively rare.
Hypermethylation on BLU promoter has been detected ranging from 19% of primary non-small cell lung cancer to 66-74% of nasopharyngeal carcinoma (NPC).

**Disease**
Mutated BLU/ZMYND10 protein with several amino acid residues substitution has been shown to associate with LRRC6, and plays a role in the pathogenesis of primary ciliary dyskinesia. Hypermethylation and downregulation has been described as a frequent event in primary tumours such as glioma (80%), cervical squamous cell carcinomas (77%), NPC (66%), neuroblastoma (41-70%) and NSCLC (19-43%) with lower frequencies observed in gallbladder carcinomas (26%), ependymomas (13.6%) and SCLC (14%). It has been noted that in some tumors like glioma, methylation of BLU is an early detectable event; it was identified in stage II glioma and stage I/H cervical squamous cell carcinomas.

**Cytogenetics**
Unlike t(8;21) translocation frequently seen in acute myelogenous leukemia, involving ZMYND motif containing MTG8, no cytogenetic anomaly affecting BLU has been observed in malignancies.

**Hybrid/Mutated gene**
No fusion gene(s) involving BLU has been reported.

**Lung cancer**
Note
BLU is primarily expressed in lung and testis, with different isoforms. The mutation is rare. The expression is absent in a number of lung cancer cell lines, and in 19-43% of non-small lung cancer (NSLC) cases, BLU is silenced due to promoter hypermethylation (Agathangelou et al., 2003; Marsit et al., 2005). The incidence is higher in adenocarcinoma (AC) than in squamous cell carcinoma (SCC). Frequent methylation for BLU and RASSF1 has been observed but there is no significant association. In lung cancer patients, homozygous deletion of 3p21 region has been association with early age of cigarette smoking initiation.

**Nasopharyngeal carcinoma (NPC)**
Note
Downregulation of BLU expression was well correlated with the promoter hypermethylation in tumor specimens and cultured cell lines. Methylation on BLU promoter was identified in up to 66% of the tumors, and 6 out 7 passaged cell lines. BLU was observed to inhibit JNK signaling pathway, and cyclin D1 (CCND1) gene promoter activity, arrest cell cycle at G1 phase, and block in vitro and in vivo NPC cell growth.

**Glioma**
Note
BLU/ZMYND10 hypermethylation and downregulation has been described as a frequent event in up to 80% primary tumours of glioma. BLU/ZMYND10 methylation is an early event detectable in stage II glioma (Hesson et al., 2004). In glioma tumours methylation of BLU/ZMYND10 and/or RASSF1A, located adjacent to BLU/ZMYND10, was detected in more than 95% (52/54) primary tumours.

**Neuroblastoma**
Note
Methylation leading to downregulation of BLU has been described in up to 70% neuroblastoma (41-70%) (Abe et al., 2005). It was shown that methylation of promoter CGI's of RASSF1A (3p21) and BLU (3p21) was far more frequently observed in neuroblastomas with CpG island methylator phenotype (CIMP).

**Esophageal cancer**
Note
In esophageal squamous cell carcinoma (ESCC), BLU expression was downregulated in three out of four Asian esophageal carcinoma cell lines, and 4 out of 8 pairs of tumor and normal tissues. Methylation specific-PCR revealed the downregulation of BLU by epigenetic inactivation. However, exogenous expression of BLU did not functionally suppress tumorigenicity in nude mice. These results suggest that over-expression of BLU alone is not sufficient to inhibit tumorigenicity. (Yi Lo et al., 2006).

**Ovarian carcinoma**
Note
Epithelial ovarian carcinoma is usually present at the advanced stage, during which the patients generally have poor prognosis. Our study aimed to evaluate the correlation of gene methylation and the clinical outcome of patients with advanced-stage, high-grade ovarian serous carcinoma. The methylation status of eight candidate genes was first evaluated by methylation-specific PCR and capillary electrophoresis to select three potential genes including DAPK, CDH1, and BLU (ZMYND10) from the exercise group of 40 patients. The methylation status of these three genes was further investigated in the validation group consisting of 136 patients. Patients with methylated BLU had significantly shorter progression-free survival (PFS; hazard ratio (HR) 1.48, 95% CI 1.01-2.56, P=0.013) and overall survival (OS; HR 1.83, 95% CI 1.07-3.11, P=0.027) in the multivariate analysis. Methylation of BLU was also an independent risk factor for 58 patients.
undergoing optimal debulking surgery for PFS (HR 2.37, 95% CI 1.03-5.42, P=0.043) and OS (HR 3.96, 95% CI 1.45-10.81, P=0.007) in the multivariate analysis. A possible mechanism of BLU in chemoresistance was investigated in ovarian cancer cell lines by in vitro apoptotic assays. In vitro studies have shown that BLU could upregulate the expression of BAX and enhance the effect of paclitaxel-induced apoptosis in ovarian cancer cells. Our study suggested that methylation of BLU could be a potential prognostic biomarker for advanced ovarian serous carcinoma.

**Prognosis**

Its correlation with prognosis of serous ovarian carcinoma has been documented. The methylation status of eight candidate genes, including BLU was first evaluated by methylation-specific PCR and capillary electrophoresis from tumor tissues of ovarian carcinoma in a group of patients. Patients with methylated BLU had significantly shorter progression-free survival and overall survival in the multivariate analysis (Chiang et al., 2013).

**Myelodysplastic syndrome (MDS)**

**Note**

Hypermethylation in the promoter region and downregulation at mRNA and protein levels of BLU was detected in 34 of 79 (43%) MDS patient samples. There was a statistically significant difference in methylation frequency between different refractory anemia groups. The demethylating agent decitabine could partly reverse hypermethylation and restore the expression of the BLU gene. BLU promoter hypermethylation frequently occurs in higher risk MDS cases. BLU may play a role in the development and etiology of MDS.

**Primary ciliary dyskinesia (PCD)**

**Note**

ZMYND10 bound to LRRC6 in HEK293T and in human tracheal epithelial cells. These two proteins localized to both the basal body and the striated rootlet in Xenopus ciliated epithelial cells. The C-terminal MYND domain of ZMYND10 was insufficient for interaction with the CS domain of LRRC6; but a C-terminal fragment expanding 366-440 amino acids extending beyond the MYND domain was necessary for interaction (see the scheme of protein diagram). Similar studies using progressive truncating constructs of LRRC6 confirmed that the C-terminal CS domain of LRRC6 is sufficient for the binding with ZMYND10. The protein-protein interaction is abrogated by truncating mutations in either gene in patients with CILD.

References


This article should be referenced as such: