FXYD3 (FXYD domain containing ion transport regulator 3)

Hiroto Yamamoto, Shinji Asano

Department of Molecular Physiology, College of Pharmaceutical Sciences, Ritsumeikan University, Kusatsu, Shiga 525-8577, Japan (HY, SA)

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Identity

Other names: MAT8, PLML
HGNC (Hugo): FXYD3

Location: 19q13.12
Local order: Centromere, SCN1B, HPN, FXYD3, LG14, FXYD1, FXYD7, FXYD5, Telomere.

Note
FXYD3 is a member of the FXYD family proteins, which regulate Na+,K+-ATPase activity to precisely adjust the physiological ion balance of the tissue.

DNA/RNA

Note
Morrison and Leder (1994) originally found that FXYD3 mRNA was overexpressed in murine breast cancer induced by neu or ras oncogenes, but not by c-myc or int-2.

FXYD3 has two splicing variants (FXYD3a and FXYD3b). FXYD3a and 3b are short and long isoforms of FXYD3, respectively.

Description
DNA contains 8494 bp composed of 9 (FXYD3a) or 8 (FXYD3b) exons.

Transcription
The FXYD3a mRNA has an in-frame deletion of 78 nucleotides in the coding sequence compared to the FXYD3b mRNA. FXYD3a mRNA is a major transcript product expressed in normal tissues as well as in breast, colon, stomach and pancreas cancer cells. Transcription of FXYD3 mRNA was down-regulated by TGF-b signaling in human mammary epithelial cells (Yamamoto et al., 2011).

Pseudogene
No pseudogenes reported.
Amino acid alignments of human FXYD3a and 3b proteins. An underline represents the FXYD (Phe-Xaa-Tyr-Asp) motif. A box represents the transmembrane segment. FXYD3b protein has 26 more amino acids in the cytoplasmic domain compared to FXYD3a protein.

**Protein**

**Description**
FXYD3 is a member of the "FXYD" family proteins, which consist of seven members of small proteins and share a signature sequence of four amino acids "FXYD" located in the ectodomain close to the transmembrane segment. Human FXYD3 protein contains a hydrophobic domain at the N terminus encoding a cleavable signal peptide, and adopts a type I topology. On the other hand, mouse FXYD3 may have two transmembrane domains because of the lack of cleavable signal peptide.

**Expression**
Mammary gland, lung, stomach, pancreas and intestine.

**Localisation**
Plasma membrane and intracellular membrane compartment.

**Function**
FXYD family proteins perform fine tuning of ion transport by associating with and modulating the pump activity of Na+,K+-ATPase molecules and modifying the activity of ion channels (Geering, 2006). FXYD3a slightly decreased the apparent affinity both for intracellular Na+ (up to 40%) and extracellular K+ (15 to 40%) of Na+,K+-ATPase whereas FXYD3b slightly increased the apparent affinity for intracellular Na+ (about 15%) and decreased the apparent affinity for extracellular K+ (up to 50%). Both FXYD3 isoforms induced a hyperpolarization-activated chloride current in Xenopus oocytes (Bibert et al., 2006). Two cysteine residues at cytoplasmic domain of FXYD3 were glutathionylated by oxidative stress. As a result, glutathionylation of Na+,K+-ATPase beta1 subunit by oxidative stress was prevented and the pump activity of Na+,K+-ATPase was maintained (Bibert et al., 2011). FXYD3 is responsible for cancer cell proliferation. Suppression of FXYD3 expression caused a significant decrease in cellular proliferation of breast, prostate and pancreatic cancer cell lines. In colon cancer cell line Caco-2, silencing of FXYD3 mRNA with shRNA specific for FXYD3 increased the apoptosis rate and inhibited the differentiation to enterocyte-like phenotype (Bibert et al., 2009).

**Homology**
FXYD family proteins have invariant amino acids in a signature sequence of FXYD motif and two conserved glycines and a serine residue (Sweadner and Rael, 2000). In mammals, this family contains seven members including FXYD1 (phospholemman), FXYD2 (the gamma-subunit of Na+,K+-ATPase), FXYD3 (Mat-8), FXYD4 (corticosteroid hormone-induced factor), FXYD5 (dysadherin), FXYD6 (phosphohippolin) and FXYD7. FXYD family proteins are expressed in specific tissues to regulate Na+,K+-ATPase activity, and precisely adjust the physiological ion balance of the tissues.

**Mutations**

**Somatic**
Okudela et al. (2009) showed that somatic mutation (D19H) occurred only in a lung cancer cell line, H2087.
This mutation is very rare in lung cancer cell lines and primary lung cancers. Exogenous expression of wild-type FXYD3, but not the mutant (FXYD3/D19H), enhanced the cortical actin density in a lung cancer cell line, H1299. FXYD3/D19H distorted the outline of nuclear envelope in H1299 cells, suggesting that loss of FXYD3 function attenuates the integrity of the nuclear envelope and the cytoskeleton.

**Implicated in**

**Breast cancer**

**Note**
Down-regulation of FXYD3 mRNA via siRNA for FXYD3 decreased the proliferation of MCF-7 breast cancer cells.

**Disease**
Yamamoto et al. (2009) reported that FXYD3 protein was overexpressed in human breast cancer specimens; invasive ductal carcinomas and intra-ductal carcinomas compared with surrounding normal mammary glands. On the other hand, FXYD3 expression was low in benign lesion specimens; mastopathy, fibroadenoma and phyllodes tumors. Distribution pattern of FXYD3 expression was divided into two groups. In one group, expression was observed mainly in the cytoplasm. In the other group, expression was observed both in the cytoplasm and at the cell surface.

**Pancreas cancer**

**Note**
Down-regulation of FXYD3 mRNA by stable antisense transfection decreased the proliferation of T3M4 pancreatic cancer cells.

**Disease**
Kayed et al. (2006) reported that FXYD3 was overexpressed in pancreatic cancer, and contributed to its proliferative activity and malignancy. There was no significant difference in FXYD3 mRNA expression levels between chronic pancreatitis and normal pancreatic tissues whereas FXYD3 mRNA levels were 3.9-fold increased in pancreatic ductal adenocarcinoma cells compared to normal ductal cells. FXYD3 protein expression was almost absent in normal pancreatic tissues. In contrast, chronic pancreatitis and pancreatic ductal adenocarcinoma tissues showed up-regulation of FXYD3 protein which was expressed in cytoplasm and plasma membrane. Pancreas cancer cells that had metastasized to the liver and regional lymph nodes also exhibited strong expression of FXYD3 protein.

**Urothelial carcinoma**

**Disease**
Zhang et al. (2011) reported FXYD3 mRNA as a promising prognosis marker of renal and bladder urothelial carcinoma (UC). Microarray gene expression data showed that FXYD3 mRNA was increased in UC whereas it was not observed in normal kidney tissues and other type of tumors including papillary, oncocytoma, chromophobe, and clear cell renal carcinoma. FXYD3 protein was expressed in about 90% of UC from renal pelvis, and 63% of UC from bladder, however, it was not expressed in normal kidney and bladder stromal tissues.

**Prognosis**
Martin-Aguilera et al. (2008) reported that a combination of FXYD3 and KRT20 (a member of the keratin family) genes yielded a 100% sensitivity and specificity differentiating lymph nodes with bladder UC dissemination from controls. However, there was no significantly worse survival of patients presenting qRT-PCR positive compared to negative lymph nodes after a median follow-up of 35 months.

**Lung cancer**

**Disease**
Okudela et al. (2009) reported that FXYD3 mRNA and protein levels were down-regulated in some lung cancer cell lines. Epigenetic modifications such as DNA methylation and histone acetylation seem to affect FXYD3 expression. In normal lung epithelial cells, FXYD3 protein was extensively expressed on the basolateral membrane of bronchial epithelial cells, and in cytoplasm where it was concentrated at the perinuclear site of alveolar epithelial cells. In lung cancer, particularly in poorly differentiated cancers, FXYD3 expression was low or faint. Down-regulation of FXYD3 was more prominent in large cell carcinomas and small cell carcinomas than in adenocarcinomas. FXYD3 expression was decreased significantly as the histological grade of squamous cell carcinoma progressed from well to poorly differentiated.

**Prostate cancer**

**Note**
Grzmil et al. (2004) reported that FXYD3 (MAT-8) plays an important role in cellular growth of prostate carcinomas. In prostate tumors (6 out of 11), FXYD3 mRNA expression was increased (> 2 times) up to 35-fold compared to normal tissues. FXYD3 mRNA was also expressed in prostate cancer cell lines, PC3, DU-145 and LNCaP. Silencing of FXYD3 mRNA via siRNA specific for FXYD3 led to significant decrease in proliferation of PC3 and LNCaP.

**Colon cancer**

**Disease**
Kayed et al. (2006) showed that FXYD3 mRNA expression was decreased in colon cancers (n=40) compared to normal colon tissues (n=27). Widegren et al. (2009) reported that FXYD3 seems to be involved in the development of the relatively earlier stages of colorectal cancers. FXYD3 protein expression was significantly higher in primary tumor compared to adjacent normal mucosa in the matched cases, while
there was no significant difference in the expression between primary tumor and metastasis in the lymph nodes. FXYD3 protein expression was positively related to the expression of Ras, P53, Legumain and proliferative cell nuclear antigen. Although FXYD3 expression in Dukes stage A-C tumors was higher than that in stage D tumors, there was no relationship between FXYD3 expression and survival in the whole group of the patients.

**Prognosis**
Loftas et al. (2009) reported that in rectal cancers, FXYD3 expression was a prognosis factor independent of tumor stage and differentiation in patients receiving preoperative radiotherapy: strong expression was associated with an unfavorable prognosis. In the primary tumors, FXYD3 expression was increased compared with normal mucosa. There were less tumor necrosis and a higher rate of developing distant metastasis after radiotherapy in tumors with high FXYD3 expression.

**Gastric cancer**
Zhu et al. (2010) reported that up-regulation of FXYD3 protein expression seems to be involved in tumorigenesis and invasion of gastric adenocarcinoma. FXYD3 protein was present in the cytoplasm of normal gastric epithelial cells as well as gastric cancer cells. The rate of FXYD3 strong expression was significantly higher in cancer (51% of 51) than in normal mucosa (10% of 29). FXYD3 was expressed strongly in ulcerative/infiltrating types of cancers compared to polypoid/fungating ones. However, FXYD3 expression was not correlated with patient's gender, age, tumor size, lymph node status and histological grade.

**Glioma**
Wang et al. (2009) reported that FXYD3 expression seems to be involved in glioma development. The frequency of strong FXYD3 expression was higher in the primary tumors compared to normal brain tissues. FXYD3 expression was significantly more increased in females than males, and in multiple site gliomas than single sites. There was no difference of FXYD3 expression regarding age, tumor location, size, histological type, and tumor grade.

**References**


This article should be referenced as such: