AMFR (autocrine motility factor receptor)

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Identity

Other names: GP78, RNF45
HGNC (Hugo): AMFR
Location: 16q12.2

DNA/RNA

Description

The AMFR gene spans 64081 bases on minus

strand. The DNA of AMFR consists of 14 exons and the coding sequence starts in the first exon.

Transcription

The AMFR gene has two transcripts. One of these transcripts is 2249 bp long and is a processed transcript with no protein product. 3598 bp long second AMFR transcript is a protein coding transcript (accession number: NM_001144). The DNA has been cloned in 1999 (Shimizu et al., 1999).
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A schematic representation of the domain structure.

**Protein**

**Description**

AMFR belongs to the family of RING-Finger ubiquitin ligases. The complete protein contains 643 amino acids. The calculated molecular weight of AMFR is 73.0 kDa.

AMFR was originally isolated as a membrane glycoprotein from murine melanoma cells and was implicated in cell migration (Nabi and Raz, 1987). Subsequently, gp78/AMFR was identified as the tumor autocrine motility factor receptor mediating tumor invasion and metastasis (Nabi et al., 1990). A monoclonal antibody named 3F3A was generated against this protein and first sequence reported for human gp78/AMFR was in 1991 using this antibody (Watanabe et al., 1991). However, the protein product was only 321 amino acids (Watanabe et al., 1991). A sequence giving 643 amino acids protein product was cloned in 1999 (Shimizu et al., 1999).

gp78/AMFR has five to seven transmembrane domains according to different softwares like SACS MEMSAT and SOSUI. The protein has a long cytoplasmic tail composed of around 350 amino acids (Shimizu et al., 1999). Besides conveying E3 activity the multifunctional cytoplasmic tail is responsible for interaction with polyubiquitin, ubiquitin conjugating enzyme, p97/VCP and Ufd1. The RING finger domain of gp78/AMFR residing between amino acids 341 and 383 is a RING-H2 type domain containing two His residues in positions 4 and 5 (Fang et al., 2001). The Cue domain of gp78/AMFR residing between amino acids 456 and 497 is responsible for polyubiquitin binding and has been identified by having homologous sequences of yeast protein Cue1p (Ponting, 2000). The p97/VCP-interacting motif of gp78/AMFR consists of C-terminal amino acid residues between 614-643 and it is sufficient to bind to p97/VCP protein (Ballar et al., 2006). gp78/AMFR binds to its ubiquitin conjugating enzyme via a region called UBE2G2 binding region (G2BR) and this region is resides between amino acids 579 and 600 (Chen et al., 2006). Additionally, gp78/AMFR interacts directly with Ufd1 through residues 383-497 (Cao et al., 2007) and with INSIGs through its transmembrane domains (Song et al., 2005).

**Expression**

gp78/AMFR is relatively ubiquitously expressed in normal human cells, especially highly in liver, heart and lung. Northern blot analysis detected a 3.5-kb AMFR transcript in mouse heart, brain, liver, skeletal muscle, kidney, and testis, but not in spleen (Shimizu et al., 1999). gp78/AMFR is overexpressed in certain malignant tumors and human cancers of the lung, gastrointestinal tract, breast, liver, thymus, and skin (Chiu et al., 2008; Sjöblom et al., 2006; Tsai et al., 2007; Joshi et al., 2010).

**Localisation**

Endoplasmic reticulum membrane, multi-pass transmembrane protein (Fang et al., 2001).

**Function**

In 2001, it has been reported that gp78/AMFR possesses ubiquitin ligase (E3) activity (Fang et al., 2001) and can ubiquitinate both itself and other proteins for proteosomal degradation. gp78/AMFR is a member of multiprotein complex functioning in endoplasmic reticulum associated degradation (ERAD). gp78/AMFR not only functions as an E3 during ERAD but also couples retrotranslocation and deglycosylation to ubiquitination (Ballar et al., 2006; Li et al., 2005).

**Homology**

Homologues have been found in various species like bovine, chimpanzee (99.8 % homology), chicken, zebra fish, rat, C. elegans and mouse. gp78/AMFR shares 94.7 % of homology with murine gp78/AMFR.

**Mutations**

**Somatic**

D605V mutation has been reported in breast cancer (Sjöblom et al., 2006). Several SNPs have been found in gp78/AMFR gene both at coding regions and at UTRs and introns. See SNP database at NCBI.

**Implicated in**

**Sarcoma metastasis**

Note

gp78/AMFR targets KAI1, a known metastasis
suppressor protein for ubiquitin mediated proteasomal degradation (Tsai et al., 2007). Thus gp78/AMFR has role in metastasis of human sarcoma. Furthermore, a human sarcoma tissue microarray study documents that tumors with low gp78 expression has higher levels of KAI1 and high gp78 level lower KAI1 expression in tumors (Tsai et al., 2007).

**Breast cancer**

*Note*

gp78/AMFR expression in gp78 transgenic mammary glands induces mammary gland hyperplasia, increases duct number and network density and shows down-regulation of KAI1 metastasis suppressor (Joshi et al., 2010). Additionally, gp78/AMFR has been identified as one of the most mutated genes in breast cancer (Sjöblom et al., 2006). Consistently, gp78/AMFR is overexpressed in human breast cancer and is negatively associated with patients’ clinical outcome (Jiang et al., 2006).

**Gastric carcinoma**

*Note*

gp78/AMFR expression may be associated with the progression and invasion of gastric carcinoma as well as the prognoses of the patients (Hirono et al., 1996). Furthermore, by using same 3F3A antibody it was reported that gp78/AMFR expression is associated with lymph node metastasis and peritoneal dissemination in gastric carcinoma (Taniguchi et al., 1998).

**Colorectal cancer**

*Note*

gp78/AMFR expression is correlated high incidence of recurrence of the patients with colorectal cancer (Nakamori et al., 1994).

**Melanoma**

*Note*

It was showed by using 3F3A antibody that gp78/AMFR protein expression in human melanoma cell lines correlates to their metastatic potential. While in thin tumors weak/heterogenous gp78/AMFR expression predominated, in thick tumors the strong gp78/AMFR expression profile was predominant (Timár et al., 2002).

**Lung cancer**

*Note*

Using immunohistochemical staining the gp78/AMFR expression was showed to be associated with histologic type of tumor, mainly in adenocarcinoma (Kara et al., 2001).

**Hepatocellular carcinoma**

*Note*

The expression of gp78/AMFR significantly increased in hepatocellular carcinoma compared with pericarcinomatous liver tissues. Furthermore, there is a strong correlation between AMFR expression and invasion and metastasis of HCC (Wang et al., 2007).

**Bladder carcinoma**

*Note*

While in normal urothelium gp78/AMFR is not expressed, its expression is increased in bladder carcinoma specimens (Otto et al., 1994).

**Cardiovascular diseases and hypercholesterolemia**

*Note*

Accumulation of sterols in ER membranes triggers the binding of HMG CoA reductase, the rate limiting enzyme of cholesterol biosynthesis, to the Insig1-gp78/AMFR complex which is essential for the ubiquitination and proteasomal degradation of HMGCoA-reductase (Goldstein et al., 2006; Jo and DeBose-Boyd, 2010). gp78/AMFR is also the E3 ligase of apolipoprotein B100, the protein component of atherogenic lipoproteins, overproduction of which is a common feature of human dyslipidemia (Liang et al., 2003).

**Cystic fibrosis**

*Note*

gp78/AMFR degrades mutant cystic fibrosis transmembrane conductance regulator (CFTR∆F508) associated with cystic fibrosis (Ballar et al., 2010; Morito et al., 2008).

**Metabolism and disposition of drugs**

*Note*

gp78/AMFR participates in proteasomal degradation of CYP3A4, a dominant human liver cytochrome P450 enzyme functioning in the metabolism and disposition of drugs and responsible for many adverse drug-drug interactions (Kim et al., 2010; Pabarcus et al., 2009).

**Chronic obstructive pulmonary disease**

*Note*

gp78/AMFR expression is increased with the severity of emphysema (Min et al., 2011).

**Neurodegenerative diseases**

*Note*

gp78/AMFR may play a protective role against mutant huntingtin toxicity. Mutant huntingtin hinders polyubiquitin binding to the cue domain of gp78/AMFR and causes aggregation of ligase (Yang et al., 2010). gp78/AMFR also enhances ubiquitination, degradation, suppression of aggregation of mutant SOD1 associated with amyotrophic lateral sclerosis (ALS), and mutant ataxin-3 associated with Machado-Joseph disease. Furthermore, in spinal cords of ALS mice, gp78/AMFR expression is significantly up-regulated (Ying et al., 2009).
Alpha-1-antitrypsin deficiency

Note

gp78/AMFR targets mutant ATZ (Z-variant alpha-1-antitrypsin) associated with alpha-1-antitrypsin deficiency for the proteosomal degradation and increases its solubility (Shen et al., 2006).

References


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