REVIEW

LAPTM4B: an oncogene in various solid tumors and its functions

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The oncogene Lysosome-associated protein transmembrane-4B (LAPTM4B) gene was identified, and the polymorphism region in the 5′-UTR of this gene was certified to be associated with tumor susceptibility. LAPTM4B-35 protein was found to be highly expressed in various solid tumors and could be a poor prognosis marker. The functions of LAPTM4B in solid tumors were also explored. It is suggested that LAPTM4B could promote the proliferation of tumor cells, boost invasion and metastasis, resist apoptosis, initiate autophagy and assist drug resistance.

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INTRODUCTION

Carcinogenesis is a complicated process that involves multiple stages with gene mutations accumulated, which results in deregulation of proliferation, invasion and metastasis, recurrence and drug resistance, leading to a poor prognosis. Despite the fact that more and more oncogenes have been found and various therapies targeting these oncogenes also have been developed in recent years, the cure rate of cancers is not satisfactory. Therefore, a lot of work about oncogenes and their relationship with carcinogenesis still needs to be done and is challenging.

In this review, we introduced the oncogene Lysosome-associated protein transmembrane-4B (LAPTM4B) gene, which was first cloned in hepatocellular carcinoma (HCC) cells. A series of research findings, such as structures of LAPTM4B gene and protein, transcription regulations of LAPTM4B gene, relationships between polymorphisms of LAPTM4B and tumor susceptibility and the functions of LAPTM4B in solid tumors, were summarized, and they are shown in this article.

CLONING AND IDENTIFICATION OF THE LAPTM4B GENE

A gene involved in the proliferation and/or differentiation of hepatocytes was originally cloned using rapid amplification of complementary DNA ends and reverse transcription–PCR in HCC tissues by Zhou Rouli in 2000.1 It was highly expressed in HCC, as well as in paired noncancerous liver and fetal liver cells, but showed very low expression in normal adult liver cells.1 The gene was designed by HUGO Gene Nomenclature Committee, and it was named as LAPTM4B (GenBank ACCESSION NM: AY057051, NM_018407, Gene ID 55353).

BLAST program analysis shows that the LAPTM4B gene is mapped to chromosome 8q22.1, spanning at least 50 kb. It is composed of seven exons separated by six introns and contains an open reading frame including 951 nucleotides. Extron 1 contains the 5′ untranslated sequence (5′-UTR) and the initiating methionine (Met). The mRNA of LAPTM4B is ~2.2 kb in length and is in agreement with the size of the mRNA observed in Northern blots. There are two polyadenylation signal sites in the 3′-UTR, AATAAA and AATTAAA. The alternative polyadenylation (AATAAA) may result in another 1.42-kb mRNA variant.2

STRUCTURE OF THE LAPTM4B PROTEIN

The full-length complementary DNA of LAPTM4B contains two translational initiation codons (ATG) with an interval of 273 bp, and encode two protein isoforms, LAPTM4B-35 and LAPTM4B-24, with molecular weights of 35 kDa and 24 kDa, respectively. LAPTM4B-35 contains 317 amino acid residues and has a pI at 9.07 because of its high content of arginine residues. LAPTM4B-24 comprised 226 amino acid residues and has a pI at 4.65 because of its high content of acidic amino acid residues.

Computer analysis shows that LAPTM4B is an integral membrane protein, with four transmembrane regions at 117–133, 163–179, 200–216 and 243–259 amino acids, respectively (Figure 1). It also has two extracellular domains (EC1 and EC2): one N-terminal and one C-terminal tail in the cytoplasm. The full amino acid sequence contains one N-glycosylation site, eight phosphorylation sites, six putative sites in the cytoplasm and four N-myristoylation sites. Structurally, LAPTM4B-35 differs from LAPTM4B-24 in that it contains extra 91 amino acid residues at the N terminus that harbors a proline-rich domain, PPRP. It serves as the binding site of the SH3 domain of some signaling molecules and has critical roles in the proliferation and metastatic potentials of tumor cells.3 Moreover, LAPTM4B contains several putative lysosomal targeting motifs in the C termini, including tyrosine-based (YXXΦ), PY (L/PPXY) and dileucine ([DE]XX[IL]I) motifs. Except for PY motifs, these motifs are recognized by major adapter proteins, which are involved in transporting from the Golgi to lysosomes.4 Its C-terminal PY motifs can interact with the E3 ubiquitin ligase neuronal precursor-cell expressed developmentally down-regulated 4(Nedd4), participating in the lysosomal and plasma membrane sorting.5

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Figure 1. Topology of LAPTM4B-24 (left) and LAPTM4B-35 (right) proteins. N encircled by a hexagon represents N-glycosylation site; P encircled by a circle represents phosphorylation site.

EXPRESSSONALYSIS OF LAPTM4B
Expression of LAPTM4B mRNA has been evaluated via Northern blotting, reverse transcription–PCR and hybridization in situ. LAPTM4B mRNA is expressed in a variety of human normal tissues: its expression is high in the testis, heart, skeletal muscle and uterus; moderate in ovary, kidney and pancreas; low in liver, spleen and thymus; and lowest in lung and peripheral leukocytes. It is also expressed highly in fetal kidney, heart and spleen (Figure 2).

Immunohistochemistry with an antibody specifically proved that LAPTM4B is highly expressed in fetal tissues. The asterisk represents the organ in which LAPTM4B is highly expressed in fetal tissues.

TRANSCRIPTIONAL REGULATION OF LAPTM4B
Moreover, overexpression of LAPTM4B in solid cancers may result from transcriptional regulation by transcription factors or micro-RNAs. In recent years, an increasing number of researches have focused on the upstream regulation of LAPTM4B. SP1 binds 558 bp upstream of LAPTM4B transcription initiation site, and it is correlated with high expression of LAPTM4B in hepatocellular carcinoma. In addition, cyclic AMP responsive element-binding protein-1 (CREB1) is a transcription factor that has a vital role in cell proliferation, differentiation and survival. It was also regarded as an oncogene that promotes tumor cell growth and proliferation. A previous study showed that CREB1 binds to the +157–165 fragment of LAPTM4B promoter region and then upregulates the transcription of LAPTM4B in breast cancer. MIr-188-5p also suppresses the expression of LAPTM4B through binding to its 3′-UTR area, which results in the inhibition of cell proliferation, invasion and migration in prostate cancer. Moreover, a study revealed that enforced expression of the homeobox transcription factor, which has an important role in hematopoietic stem cell self-renewal and expansion, could upregulate LAPTM4B expression in hematopoietic stem cells rather than in mature hematopoietic cells.

LAPTM4B POLYMORPHISM AND ITS IMPORTANCE IN SUSCEPTIBILITY TO CARCINOMAS
There are two alleles of LAPTM4B named LAPTM4B*1 and LAPTM4B*2 (GenBank numbers AY219176 and AY219177, respectively), encoding 35- and 40-kDa proteins, respectively. Allele *1 contains only one copy of a 19-bp sequence at the 5′-UTR of the first exon, whereas this segment of allele *2 is duplicated and tandemly repeated (Figure 3). Compared with allele*1, the extra 19-bp sequence changes the open reading frame of LAPTM4B gene and makes allele *2 encode one more protein isoform, a 40-kD protein. The mRNA of allele *1 starts translation only at nucleotide 157, because there are in-frame termination codons at nucleotides 40 and 103. However, the mRNA of allele *2 starts translation at nucleotide 17, which produces a protein with an extra 53 amino acids at its N terminus than allele*1 (Figure 4). The function of the 40-kDa protein encoded by allele*2 and its correlation with disease has not been elaborated so far. A more in-depth research will be required to clarify these points.

Previous studies have shown that LAPTM4B polymorphisms were related to susceptibility to HCC, breast cancer, non-small lung cancer, gastric cancer, cervical cancer, endometrial carcinoma, colorectal cancer, lymphoma, gallbladder carcinoma, ovarian carcinoma and malignant melanoma, but not to squamous cell carcinomas such as esophageal carcinoma, rectum carcinoma and nasopharyngeal carcinoma. Lately, a meta-analysis in Chinese Han population revealed that LAPTM4B allele *2 carriers exhibited a higher cancer risk compared with allele*1 homozygotes (for *1/2, odds ratio = 1.55, 95% confidence interval 1.367–1.758; for *2/2, odds ratio = 2.093, 95% confidence interval 1.651–2.629; for *1/2 + *2/2, odds ratio = 1.806, 95% confidence interval 1.527–2.137). Moreover, LAPTM4B allele *2 has been proven to be a risk factor for cancer (odds ratio = 1.487, 95% confidence interval 1.339–1.651).

FUNCTIONS OF LAPTM4B AND THE MECHANISMS THEREOF
LAPTM4B gene promotes the growth and proliferation of cells in various kinds of tumors. The proteins of LAPTM4B gene, LAPTM4B-35 and LAPTM4B-24, have an important role in promoting growth and proliferation of cells in many kinds of tumors. In HCC, the effect of LAPTM4B-35 on xenograft tumor growth of HepG2 cells was examined in BALB/c nude mice. The tumor growth of mice with stable overexpression of LAPTM4B-35 HepG2 cells was significantly more rapid than that in the Mock group, whereas the tumor...
growth of mice with stable knockdown of LAPT4B-35 HepG2 cells was slower than that in the Mock group. In addition, the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay also showed that the growth rate of stable knockdown LAPT4B-35 HepG2 cells was reversed after transfecting the LAPT4B-35 protein expression plasmid. In gallbladder carcinoma, MTT assay and anchorage-independent colony formation showed that HepG2 cells with depletion of LAPT4B-35 had a low growth rate in the CCK8 assay. The function of LAPT4B-35 was also confirmed in non-small cell lung cancer, where stable knockdown of LAPT4B-35 in Calu-6 lung cancer cells statistically reduced anchorage-dependent and anchorage-independent colonies. The mechanisms of LAPT4B-35 involved in promoting the growth and proliferation of carcinoma cells may attribute to affect proliferation-regulating proteins and activate the AKT signaling pathway. By activating AKT, glycogen synthase kinase 3β can be phosphorylated, and it results in the attenuation of phosphorylation and degradation of c-Myc. Besides, another downstream target of activated AKT, forkhead box O4, the transcription factor of p27, can also be phosphorylated, and it results in the inactivation of forkhead box O4. Recently, researchers found that LAPT4B-24 may also have a relationship with tumor growth. In Hela cells, LAPT4B-24 knockdown attenuated cell proliferation and reduced the cell size, which were restored by re-expression of LAPT4B-24.

LAPT4B gene promotes metastasis and invasion of tumor cells

LAPT4B gene can promote metastasis and invasion of tumor cells, which is line with a series of results. In HepG2 cells that overexpress LAPT4B-35, the Boyden chamber assay demonstrated that cell migration and invasion were promoted compared with mock cells. In addition, LAPT4B knockdown may also suppress HeLa cell migration in vitro. The ability to invade Matrigel was assessed using a Transwell assay. In parallel, knockdown of LAPT4B decreased invasion and migration of related proteins, such as matrix metalloprotein 2 (MMP-2), matrix metalloprotein 9 (MMP-9), CDK12 and HIF-1α. The promotion of metastasis and invasion by LAPT4B-35 may be contributed by the PPRP motif of LAPT4B-35, which can interact with SH3 domain-containing proteins that are involved in many signaling pathways. Besides, a series of clinical experiments showed that carcinomas derived from stomach, breast, colon, ovary, liver, pancreas, cervix, prostate, lung, endometrium and gallbladder with LAPT4B-35 overexpression may present more invasive characteristics.

LAPT4B gene inhibits apoptosis

Resistance to apoptosis is one of the classical characteristics of cancer cells. As it is an oncogene, overexpression of the LAPT4B gene has been shown to inhibit apoptosis function. After treating HCC cells with Adriamycin to induce apoptosis, the apoptosis rate was reduced in stable LAPT4B-35 overexpression HepG2 cells but it was increased in stable LAPT4B knockdown HepG2 cells as compared with the mock group. In addition, restoration of LAPT4B-35 by transfection of LAPT4B-35 expression plasmid into stable LAPT4B knockdown HepG2 cells reversed the apoptosis rate. Besides, a series of apoptosis-related proteins such as cleaved caspase-3 and PARP were decreased in stable LAPT4B overexpression HepG2 cells but increased in stable LAPT4B knockdown HepG2 cells. In gallbladder carcinoma cells, overexpression of LAPT4B can also attenuate epirubicin-induced apoptosis, which was confirmed by flow cytometry experiment and apoptosis-related protein analysis. In breast cancer, the doxorubicin-induced apoptosis rate of MDA-MB-231 and BT549 breast tumor cells increased after small interfering RNA targeting LAPT4B was transfected into them. On the other hand, some researchers thought that low LAPT4B expression could also inhibit the classical apoptosis pathway. A431 cells stably

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LAPTM4B gene and autophagy initiation

Autophagy is a salvage pathway that damages organelles to lysosomes for recycling energy and nutrients. A series of studies have demonstrated that autophagy has a dual function in tumorigenesis.\(^\text{53}\) On one hand, increased autophagy in normal cancer cells contributes to metabolic stress to promote tumorigenesis,\(^\text{54}\) and on the other hand, defective autophagy can also drive tumorigenesis by the accumulation of genotoxic cellular waste, which boosts the acquisition of gene mutations resulting in the transformation of precancerous cells.\(^\text{55}\) Owing to the functions of lysosomes in the completion of autophagy, the effect of LAPTM4B was also examined on the process of autophagy. Under the condition of starvation stress, breast cancer cells with LAPTM4B knockdown fail to undergo autophagosome–lysosome fusion and autolysosome formation. In addition, depletion of LAPTM4B in breast cancer cells leads to increased autophagosome but decreased autophagy flux, which suggests that LAPTM4B has a key role in later stages of autophagy maturation.\(^\text{56}\) For a further step, these findings were also explored in multiple kinds of cancer patients. A survey including 211 human autophagy-associated genes was conducted for tumor-related alterations to DNA sequence and RNA expression levels and their association with patient survival outcomes in multiple cancer types. In the survey, researchers found that the LAPTM4B gene was a positive modulator in autophagy progress but was differentially expressed in various kinds of cancer. Compared with normal tissue, LAPTM4B was highly expressed in lung adenocarcinoma and lung squamous cell carcinoma, but the expression was low in kidney renal clear cell carcinoma. Besides, mRNA of LAPTM4B was found to be increased or decreased in patients with disease-specific molecular alterations or clinical phenotypes, compared with patients not harboring those alterations or phenotypes in three cancers (Table 1).\(^\text{57}\) Recently, researchers found that LAPTM4B had functions in autophagy progress related with inactive epidermal growth factor receptor (EGFR) or active EGFR. The inactive EGFR was shown to initiate autophagy independent of its kinase activity, and serum starvation led to the accumulation of unphosphorylated EGFR at LAPTM4B-positive endosomes. Further, a series of assays showed that inactive EGFR that localized at endosomes interacted with LAPTM4B and stabilized each other. Regardless of whether EGFR or LAPTM4B was knocked down, the other one would be decreased accordingly, which finally led to the inhibition of autophagy. Investigating the mechanism of this, researchers suggested that inactive EGFR and LAPTM4B recruited exocyst subcomplex containing Sec5 to promote EGFR association with autophagy inhibitor Rubicon, which in turn dissociated Beclin1 to start autophagy.\(^\text{58}\) On the other side, LAPTM4B could promote active EGFR signaling by blocking EGF-stimulated EGFR intraluminal sorting and lysosomal degradation to inhibit autophagy. By enhancing the ubiquitination of Hrs by the E3 ubiquitin ligase Nedd4, LAPTM4B could inhibit the function of Hrs so that EGF-stimulated EGFR signaling could be prolonged.\(^\text{59}\)

Although LAPTM4B may have different roles in the EGFR-related autophagy progression, LAPTM4B facilitates the prosurvival functions of EGFR in cancer cells in both conditions.

**LAPTM4B motivates multidrug resistance**

Chemotherapy resistance is always a main obstacle in the progression of treatment. Some genes located at the 8q22 chromosome have been shown to be associated with chemotherapy resistance in breast cancer cells.\(^\text{60}\) The chemotherapy-resistant function of LAPTM4B has attracted the attention of researchers, as this gene is located in the same region. By using small interfering RNAs against LAPTM4B in BT549 cells, researchers found that cell lines without LAPTM4B increased the sensitivity to anthracyclines, doxorubicin and daunorubicin. Following the autofluorescence of doxorubicin, researchers showed that breast cancer cell lines with LAPTM4B gene knockdown resulted in a significant increase in nuclear localization of doxorubicin.\(^\text{56}\) Besides, LAPTM4B overexpression can also increase the efflux of chemodrugs such as paclitaxel and cisplatin, and LAPTM4B knockdown increases the intention of these drugs in HeLa cells. However, the LAPTM4B protein does not contain ATP-binding cassette, which means that the LAPTM4B protein cannot function as an efflux pump itself to be responsible for multidrug resistance. The other ATP-dependent membrane efflux transporter, P-glycoprotein, was demonstrated to be the assistant of LAPTM4B-35 protein in the progression of chemotherapy resistance. Besides drug efflux, other molecular mechanisms of LAPTM4B for multidrug resistance were explored. It is suggested that overexpression of LAPTM4B-35 also motivates chemotherapy resistance by the activation of the PI3K/AKT signaling pathway through interaction of PPRP motif contained in the N terminus of LAPTM4B-35 with the p85α regulatory subunit of PI3K.\(^\text{51}\) Recently, a study showed that LAPTM4B can promote AKT signaling by blocking EGFR degradation specifically, and this would be one mechanism for the role of LAPTM4B in chemotherapy resistance. LAPTM4B interacts with E3 ubiquitin ligase Nedd4 to promote ubiquitination of Hrs (an ESCRT-0 subunit), which inhibits the Hrs association with ubiquitinated EGFR and therefore inhibits EGFR intraluminal sorting and lysosomal degradation. At the same time, a PI3 kinase, PIPKιβ5, directly binds to LAPTM4B and antagonizes the function of LAPTM4B in EGFR sorting by generating PtdIns(4,5)P2 signals and recruiting SNX5 (Figure 5).\(^\text{59}\)

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**Table 1.** Autophagy-associated genes found to have significantly increased or decreased mRNA in patients with disease-specific molecular alterations or clinical phenotypes compared with patients not harboring those alterations or phenotypes in three cancer types

| Gene | BRCA | HNSC | LUAD |
|------|------|------|------|
| AKT1 mut↑ Basal-like↑ | | | |
| BRCA1 mut↑ BRCA2 mut↑ | | | |
| CDH1 mut↑ | GFR1 amp↑ | | |
| KMT2C mut↑ Luminal A↓ | HRAS mut↓ | | |
| MAP2K4 mut↑ MAP3K1 mut↑ | | | |
| MYC amp↑ NBN amp↑ | | | |
| TP53 mut↓ | | | |

Abbreviations: Amp, amplification; BRCA, invasive breast carcinoma; HNSC, head and neck squamous cell carcinoma; homdel, homozygous deletion; LUAD, lung adenocarcinoma; mut, mutant; spread N0↑.

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LAPTM4B may be a novel therapeutic target for cancer treatment. Although many kinds of molecular targeting drugs have been developed, some targeting therapies may be ineffective and require additional targets such as LAPTM4B for cancer treatment. Although EGFR TKIs block the cellular functions mediated by EGFR kinase signaling in non-small-cell lung cancers, they also activate a role for inactive EGFR in autophagy at the mean while, which could potentially provide a survival advantage and TKI resistance in cancers. Thus, cotargeting EGFR and other molecular may be a promising strategy to overcome TKI resistance in cancers. LAPTM4B as an oncogene, which promotes active EGFR signaling in cancer cells and be necessary in the progression of autophagy initiated by inactive EGFR, could be a cotargeting molecular in cancer treatment.62 In addition, restraining LAPTM4B from activating AKT signaling to suppress cell proliferation, breaking the interaction between LAPTM4B and SH3 domain-containing proteins to control cancer invasion and metastasis, inhibiting LAPTM4B to decrease late endosome ceramide export to ameliorate antiapoptosis condition and dissociating the LAPTM4B from the efflux pump P-glycoprotein to attenuate chemotherapy resistance can be potential cancer treatments.

Outstanding questions about LAPTM4B in cancer research
As we all know, LAPTM4B allele *2 contains an extra tandemly arranged 19-bp sequence at the 5′-UTR, which results in a 40-kDa protein. However, the function of the 40-kDa protein in cancer cells and the relation of the 40-kDa protein with the disease risk are not clear now. In addition, whether there are some different translocation modifications between two alleles affecting their function in tumor susceptibility is also unknown.

CONCLUSION AND PROSPECTIVE
LAPTM4B as a gene has been demonstrated to be a positive modulator in the progression of carcinogenesis. It is suggested that LAPTM4B has a key role in tumor proliferation, invasion and metastasis, anti-apoptosis, autophagy promotion and multidrug resistance. The protein of LAPTM4B gene, LAPTM4B-35, has been certified to be a poor prognostic factor in many kinds of solid tumors. LAPTM4B may become the new target of cancer therapy. In particular, in recent researches, the relationship between EGFR signaling and LAPTM4B indicated that LAPTM4B can facilitate prosurvival functions of EGFR in cancer cells and be regarded as a therapeutic target for EGFR-positive cancers or a combined target for anti-EGFR therapies.

ABBREVIATIONS
MMP-2, matrix metalloprotein 2; MMP-9, matrix metalloprotein 9.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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SEARCH STRATEGY AND SELECTION CRITERIA
References for this Review were identified through searches of PubMed with the search terms ‘LAPTM4B’ and ‘Neoplasms’. Articles were also identified through searches of the authors’ own files. Papers published in English or Chinese were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

AUTHOR CONTRIBUTIONS
YM acquired, analyzed and interpreted the data and drafted the manuscript. LW acquired, analyzed and interpreted the data and drafted the manuscript. DC acquired, analyzed and interpreted the data and drafted part of the manuscript. YC acquired, analyzed and interpreted the data. MZ acquired, analyzed and interpreted the data. J-JX acquired, analyzed and interpreted the data.
the data. RZ contributed to data interpretation, and revised the manuscript for important intellectual content. Q-YZ performed the study design, interpreted the data and revised the manuscript for important intellectual content.

REFERENCES

1 Liu JJ, Zhang J, Zhang N, Rui JA, Jin C, Zhou RL. Identification of new hepatocellular carcinoma related genes by fluorescent differential display. J Beijing Med Univ 2000; 05: 411–414.

2 Shao GZ, Zhou RL, Zhang QY, Zhang Y, Liu JJ, Rui JA et al. Molecular cloning and characterization of LAPTM44, a novel gene upregulated in hepatocellular carcinoma. Oncogene 2003; 22: 5060–5069.

3 Liu X, Xiong F, Wei X, Yang H, Zhou R. LAPTM4B-35, a novel tetratransmembrane protein and its PPRP motif play critical roles in proliferation and metastatic potential of hepatocellular carcinoma cells. Cancer Sci 2009; 100: 2335–2340.

4 Bonifacio JS, Traub LM. Signals for sorting of transmembrane proteins to endosomes and lysosomes. Annu Rev Biochem 2003; 72: 395–447.

5 Milkerit R, Rotin D. A role for the ubiquitin ligase Nedd4 in membrane sorting of LAPTM4 proteins. PLoS One 2011; 6: e27497.

6 Kasper G, Vogel A, Klamann I, Grone J, Petersen I, Weber B et al. LAPTM4A expression and polymorphism and susceptibility of gastric cancer. Ann Oncol Rep 2012: 39: 107–108.

7 Zhang H, Tian B Fau - Yu H, Yu H Fau - Yao H, Yao H Fau - Gao Z, Gao Z. LAPTM4B-35 protein as a potential therapeutic target in gastric cancer. Oncol Rep 2015; 34: 1023–1030 (Electronic).

8 Meng F, Tan S, Liu T, Song H, Lou G et al. Overexpression of LAPTM4B promotes growth of gallbladder carcinoma cells in vitro. Am J Surg Pathol 2019; 43: 4551–52.

9 Yang Y, Yang H, McNutt MA, Xiong F, Nie X, Li L et al. LAPTM4B overexpression is an independent prognostic marker in ovarian carcinoma. Oncol Rep 2008; 20: 1077–1083.

10 Yang H, Xiong F, Lin M, Yang Y, Nie X, Zhou RL. LAPTM4B-35 overexpression is a risk factor for tumor recurrence and poor prognosis in hepatocellular carcinoma. J Cancer Res Clin Oncol 2010; 136: 275–281.

11 Zhang H, Tian B Fau - Yu H, Yu H Fau - Yao H, Yao H Fau - Gao Z, Gao Z. LAPTM4B-35 protein as a potential therapeutic target in gastric cancer. Oncol Rep 2015; 34: 1023–1030 (Electronic).

12 Meng F, Tan S, Liu T, Song H, Lou G. Predictive significance of combined LAPTM4B and VEGF expression in patients with cervical cancer. Tumour Biol 2015; 37: 4894–4895.

13 Xue SL, Zhang QY, Zhou RL. Structural and SP1-binding Analysis of Promoter of Lysosome-associated protein transmembrane-4 Beta-35 overexpression is a novel independent prognostic marker in ovarian carcinoma. Oncol Rep 2010; 24: 93–103.

14 Yang Y, Yang H, McNutt MA, Xiong F, Nie X, Li L et al. LAPTM4B overexpression is an independent prognostic marker in ovarian carcinoma. Oncol Rep 2008; 20: 1077–1083.

15 Yang H, Xiong F, Lin M, Yang Y, Nie X, Zhou RL. LAPTM4B-35 overexpression is a risk factor for tumor recurrence and poor prognosis in hepatocellular carcinoma. J Cancer Res Clin Oncol 2010; 136: 275–281.

16 Zhang H, Tian B - Yu H, Yu H - Yao H, Yao H - Gao Z, Gao Z. LAPTM4B-35 protein as a potential therapeutic target in gastric cancer. Oncol Rep 2015; 34: 1023–1030 (Electronic).

17 Meng F, Tan S, Liu T, Song H, Lou G. Predictive significance of combined LAPTM4B and VEGF expression in patients with cervical cancer. Tumour Biol 2015; 37: 4894–4895.

18 Xue SL, Zhang QY, Zhou RL. Structural and SP1-binding Analysis of Promoter of Lysosome-associated protein transmembrane-4 Beta-35 overexpression is a novel independent prognostic marker in ovarian carcinoma. Oncol Rep 2010; 24: 93–103.

19 Meng F, Tan S, Liu T, Song H, Lou G. Predictive significance of combined LAPTM4B and VEGF expression in patients with cervical cancer. Tumour Biol 2015; 37: 4894–4895.

20 Yu X, Zhou R, Zhang Q, Yang Y, Shao G, Jin Y et al. Identification and characterization of LAPTM4B encoded by a human hepatocellular carcinoma-associated novel gene. Beijing Da Xue Xue Bao 2003; 35: 340–347.

21 Zhang G, Yang H, Ji X, Xiong F, Su J, McNutt MA et al. Correlation of LAPTM4B polymorphisms with hepaticcellular carcinoma in Chinese patients. Med Oncol 2012; 29: 2744–2749.

22 Wang S, Zhang QY, Zhou RL. Relationship between LAPTM4B gene polymorphism and susceptibility of primary liver cancer. Ann Oncol 2012; 23: 1864–1869.

23 Fan M, Liu Y, Zhou R, Zhang Q. Association of LAPTM4B gene polymorphism with breast cancer susceptibility. Cancer Epidemiol 2012; 36: 364–368.

24 Li X, Kong X, Chen X, Zhang N, Jiang L, Ma T et al. LAPTM4B allele *2 is associated with breast cancer susceptibility and prognosis. PLoS One 2012; 7: e44916.

25 Shaker O, Taha F, Salah M, El-Marzouky M. LAPTM4B gene expression and polymorphism as diagnostic markers of breast cancer in Egyptian patients. J Med Biochem 2015; 34: 393.

26 Tang H, Tian H, Yue W, Li L, Li S, Gao C et al. LAPTM4B polymorphism is associated with nonsmall cell lung cancer susceptibility and prognosis. Oncol Rep 2014; 31: 2454–2460.

27 Liu Y, Zhang QY, Qian N, Zhou RL. Relationship between LAPTM4B gene polymorphism and susceptibility of gastric cancer. Ann Oncol 2007; 18: 311–316.

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51 Li Y, Zou L, Li Q, Haibe-Kains B, Tian R, Li Y et al. Amplification of LAPTM4B and YWHAZ contributes to chemotherapy resistance and recurrence of breast cancer. Nat Med 2010; 16: 214–218.

52 Blom T, Li S, Dichilberger A, Back N, Kim YA, Loizides-Mangold U et al. LAPTM4B facilitates late endosomal ceramide export to control cell death pathways. Nat Chem Biol 2015; 11: 799–806.

53 Goldsmith J, Levine B, Debnath J. Autophagy and cancer metabolism. Methods Enzymol 2014; 542: 25–57.

54 Leone RD, Amaravadi RK. Autophagy: a targetable linchpin of cancer cell metabolism. Trends Endocrinol Metab 2013; 24: 209–217.

55 Yang ZJ, Chee CE, Huang S, Sinicrope FA. The role of autophagy in cancer: therapeutic implications. Mol Cancer Ther 2011; 10: 1533–1541.

56 Li Y, Zhang Q, Tian R, Wang Q, Zhao JJ, Iglehart JD et al. Lysosomal transmembrane protein LAPTM4B promotes autophagy and tolerance to metabolic stress in cancer cells. Cancer Res 2011; 71: 7481–7489.

57 Lebovitz CB, Robertson AG, Goya R, Jones SJ, Morin RD, Marra MA et al. Cross-cancer profiling of molecular alterations within the human autophagy interaction network. Autophagy 2015; 11: 1668–1687.

58 Tan X, Thapa N, Sun Y, Anderson RA. A kinase-independent role for EGF receptor in autophagy initiation. Cell 2015; 160: 145–160.

59 Tan X, Sun Y, Thapa N, Liao Y, Hedman AC, Anderson RA. LAPTM4B is a PtdIns(4,5) P2 effector that regulates EGFR signaling, lysosomal sorting, and degradation. EMBO J 2015; 34: 475–490.

60 Hu G, Chong RA, Yang Q, Wei Y, Blanco MA, Li F et al. MTDH activation by 8q22 genomic gain promotes chemoresistance and metastasis of poor-prognosis breast cancer. Cancer Cell 2009; 15: 9–20.

61 Li L, Wei XH, Pan YP, Li HC, Yang H, He QH et al. LAPTM4B: a novel cancer-associated gene motivates multidrug resistance through efflux and activating PI3K/AKT signaling. Oncogene 2010; 29: 5785–5795.

62 Tan X, Lambert PF, Rapraeger AC, Anderson RA. Stress-Induced EGFR Trafficking: mechanisms, functions, and therapeutic implications. Trends Cell Biol 2016; 26: 352–366.