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Lysosomal-associated protein transmembrane-4 beta: a novel potential biomarker for cancer therapy with multiple functions

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LAPTM4B, which is a proto-oncogene, plays important roles in cancer progression, including clinical stages and pathologic grades.[1] The *LAPTM4B* gene encodes the lysosomal-associated protein transmembrane-4 beta (LAPTM4B) protein and *LAPTM4B* is cloned from hepatocellular carcinoma (HCC).[2] There is increasing evidence that *LAPTM4B* is a novel oncogene, which is over-expressed in many human solid tumors.[3] Furthermore, the up-regulation of LAPTM4B is associated with chemotherapy resistance, as well as poor clinical outcomes and prognoses.[4,5] LAPTM4B also promotes cell survival, growth, proliferation, metastasis, tolerance to metabolic stress, and autophagy.[6] Thus, the LAPTM4B protein may represent an excellent candidate for individualized treatment and tumor monitoring.

A previous study showed that LAPTM4B expression was associated with negative clinical outcomes, significantly decreased OS, and poor prognoses in non-small cell lung cancer (NSCLC) patients.[7] Conversely, the down-regulation of LAPTM4B inhibited tumor progression, cell survival, cell proliferation, tumorigenesis, invasion, and metastasis in ovarian cancer cells.[8] In addition, microRNA (miR)-188-5p down-regulated LAPTM4B, and distinctly reduced metastasis and tumor growth in prostate cancer cells.[9] Mechanistic evidence suggests that long non-coding RNAs (lncRNAs) are crucial contributors to LAPTM4B expression in tumors: the HCC-associated lncRNA modulated LAPTM4B expression by binding to miR-196b, miR-15a, and miR-196a in HCC.[10] Interestingly, the transcription factors activator protein 4 and cyclic adenosine monophosphate responsive element binding protein-1 regulate LAPTM4B expression by binding to the *LAPTM4B* promoter region in breast cancer and HCC [Figure 1].[11-13] Thus, targeting LAPTM4B might be a potential therapeutic option for several solid carcinomas. These results suggest that LAPTM4B is instrumental in the survival, growth, invasion, and migration of several types of cancer cells.

Multidrug resistance plays a pivotal role in cancer chemotherapy. LAPTM4B over-expression was significantly associated with chemotherapy resistance in ovarian cancers.[14] In addition, matrix metalloproteinases (MMP) over-expression was also associated with drug resistance, and LAPTM4B over-expression facilitated MMP2 and MMP9 expression.[8] Furthermore, LAPTM4B-35 up-regulation increased the resistance of cancer cells to adriamycin-induced apoptosis in HCC.[15] And LAPTM4B-35 over-expression protected cells from epirubicin damage by subverting the caspase cascade as well as the activation of caspase-3 and caspase-9 [Figure 1].[16]

Angiogenesis plays an active role in tumor development and growth. A growing body of evidence suggests that LAPTM4B over-expression might increase the expression of vascular endothelial growth factor (VEGF). Clinicopathologic studies have shown that LAPTM4B over-expression promotes tumor angiogenesis in NSCLC tissues.[17] LAPTM4B-35 and VEGF were significantly up-regulated and VEGF expression was positively associated with LAPTM4B-35 expression in cervical intra-epithelial neoplasia and cervical cancer compared with the controls.[18] LAPTM4B down-regulation also down-regulated several cancer-related proteins in cervical cancer cells, including VEGF, cyclin-dependent kinase 12, hypoxia inducible factor 1 subunit alpha, MMP-2, and MMP-9 and dramatically blocked VEGF expression.[19]

Autophagy is a conserved metabolic process. Functional and mechanistic studies have demonstrated that LAPTM4B promotes autophagy when cells are subjected to stress (such as nutrient deprivation) and gene toxicity [Figure 1].[20] And LAPTM4B is localized to lysosomes.[21] Autolysosomes are fused with the lysosomes to form the autophagolysosome, which is a critical step for the autophagy. Interestingly, autophagy induced by serum starvation was blocked by

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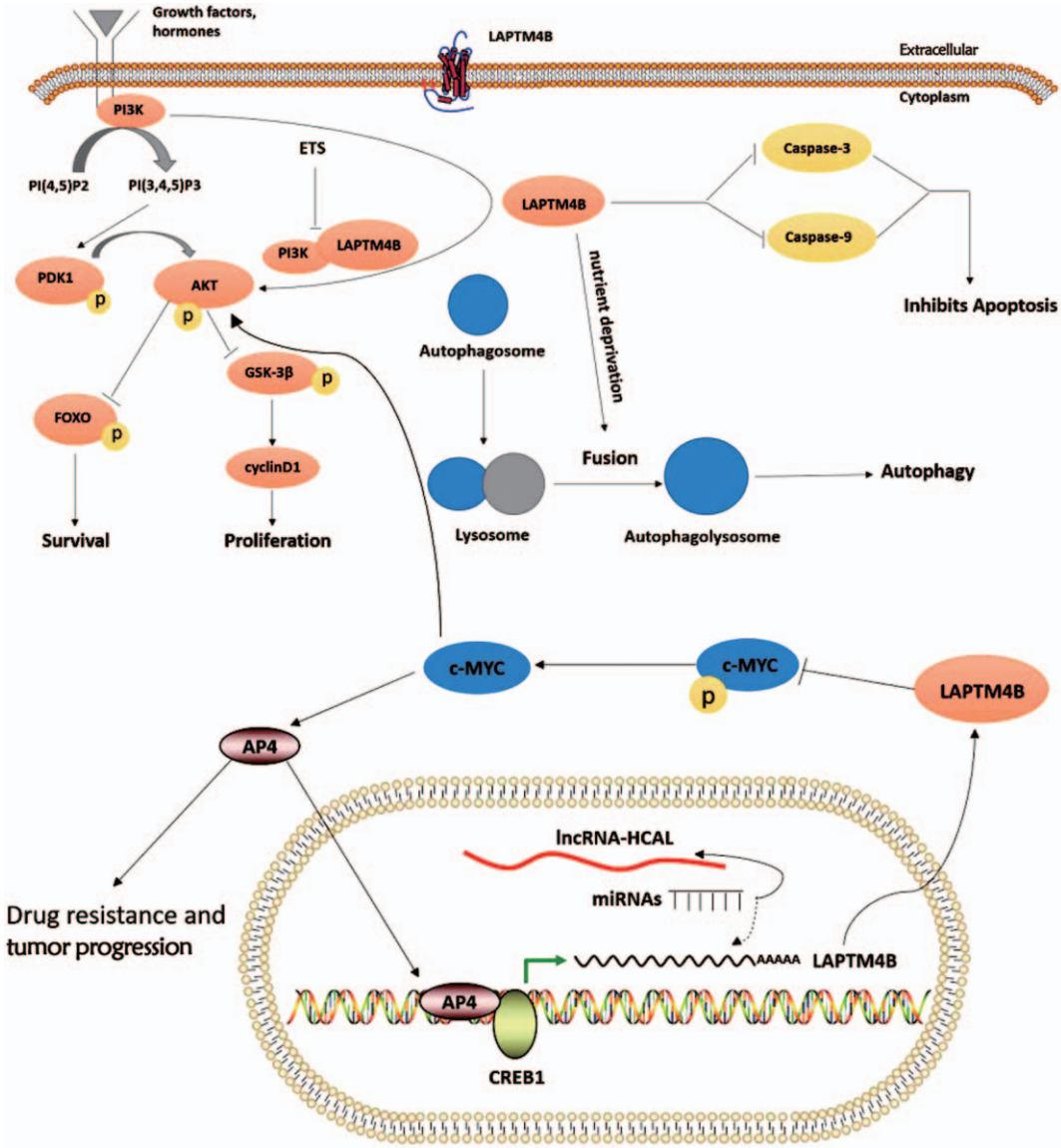

Figure 1: PI3K/AKT signaling pathway activation and potential functions of *LAPTM4B* in cancers. The transcription factors AP4 and CREB1 promote *LAPTM4B* gene transcription and lncRNA-HCAL increases *LAPTM4B* mRNA abundance by serving as a ceRNA by binding to miRNAs. The aberrant expression of LAPTM4B contributes to autophagy under various stress. LAPTM4B represses MYC phosphorylation. Then, MYC activates PI3K/AKT signaling pathway and promotes AP4 expression. PI3K: Phosphoinositide 3 kinase; AKT: Protein kinase B; LAPTM4B: Lysosomal-associated protein transmembrane-4 beta; AP4: Activator protein 4; CREB1: Cyclic adenosine monophosphate responsive element binding protein-1; lncRNA: Long non-coding RNA; HCAL: Hepatocellular carcinoma-associated lncRNA; ceRNA: Competing endogenous RNA; miRNA: MicroRNA; c-Myc: MYC proto-oncogene; PI(4,5)P2: Phosphatidylinositol 4,5-bisphosphate; PI(3,4,5)P3: Phosphatidylinositol 3,4,5-trisphosphate; PDK1: Pyruvate dehydrogenase kinase 1; p: Phosphorylation; FOXO: Forkhead box, sub-group O; GSK-3β: Glycogen synthase kinase 3 beta; ETS: Ethylglyoxal bisthiosemicarbazon.

epidermal growth factor receptor (EGFR) knockdown in MDA-MB-231 cells, indicating the fundamental role played by EGFR in autophagy.[22] Moreover, LAPTM4B and EGFR were co-localized in the endosomes.[23] LAPTM4B also interacts with Beclin1 and EGFR to promote autophagy in nasopharyngeal carcinoma radioresistance.[24]

Signaling pathways are essential for tumor occurrence and formation. LAPTM4B is involved in the phosphoinositide 3 kinase/protein kinase B (PI3K/AKT) signaling pathways of many cancers. The PI3K/AKT signaling pathway is involved in the cell survival process. LAPTM4B markedly improves the survival and proliferation of cancer cells, while inhibiting apoptosis and facilitating multidrug resistance through drug efflux by activating the PI3K/AKT signaling pathway [Figure 1].

The LAPTM4B over-expression increased the phosphorylation of Bad and AKT, and regulated cancer cell survival and anti-apoptosis by PI3K/AKT.[25] Moreover, in cells over-expressing LAPTM4B-35, PI3K interacts with LAPTM4B and then increases the phosphorylation of AKT (p-AKT) S473 [Figure 1].[15] In contrast, down-regulation of LAPTM4B-35 reverses p-AKT S473 expression.[26] Co-immunoprecipitation and western blotting studies indicated that ethylglyoxal bisthiosemicarbazon, which is lethal to cancer cells by disrupting LAPTM4B expression, significantly reduces the p-AKT by decreasing LAPTM4B expression in LAPTM4B-over-expressing cell lines.[27] Thus, LAPTM4B is involved in the PI3K/AKT signaling pathway, and plays a fundamental role in the activation of PI3K/AKT signaling. Therefore, the PI3K/AKT signaling pathway, in combination with LAPTM4B,

may represent a target for the amelioration of multidrug resistance in cancer therapy.

The LAPTM4B is over-expressed in several human cancers, suggesting that LAPTM4B might be a useful independent biomarker for the prognosis of some malignant tumors. LAPTM4B facilitates multidrug resistance, malignant transformation, proliferation, autophagy, and drug efflux by activating the PI3K/AKT signaling pathway. Furthermore, LAPTM4B over-expression markedly increases angiogenesis by regulating VEGF expression. Promisingly, LAPTM4B may facilitate angiogenesis by boosting a crucial growth factor involved in cancer. Thus, the LAPTM4B-VEGF axis may be a potential candidate target for cancer therapy. Furthermore, LAPTM4B is indispensable for the autophagy process. Due to the multiple roles of LAPTM4B in cancers, it may represent a potential therapeutic target in the future.

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Conflicts of interest

None.

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