Role and mechanism of action of LAPTM4B in EGFR-mediated autophagy (Review)

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Abstract. LAPTM4B is upregulated in the majority of types of cancer and associated with cancer cell proliferation, survival and drug resistance, as well as poor patient prognosis. LAPTM4B knockdown inhibits autophagosome maturation in the context of metabolic stress. Autophagy is a homeostatic process that degrades and recycles intracellular components in response to metabolic stress. The function of autophagy is dual, as this process can either have a tumor suppressor or an oncogenic role. EGFR serves an important role in determining the tumor-suppressive or oncogenic roles of autophagy. EGFR family members regulate autophagy through various signaling pathways, including PI3K/AKT signaling. Notably, LAPTM4B also promotes cancer cell proliferation via the PI3K/AKT signaling pathway. In addition, LAPTM4B can enhance and prolong EGFR signal transduction by blocking active EGFR intraluminal sorting and lysosomal degradation. Thus, LAPTM4B may be associated with autophagy through EGFR signaling. The present review proposed that LAPTM4B participates in regulating autophagy through the EGFR pathway.

Contents

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1. Introduction

Autophagy is an evolutionarily conserved lysosome-mediated recycling process that is essential for the maintenance of cellular homeostasis and nutrient recycling (1,2). Autophagy is characterized by the formation of autophagosomes, which are vesicles with a lipid bilayer (1-3). Cytoplasmic constituents are engulfed into the autophagosome, which is delivered to the lysosome for degradation or nutrient recycling (1,2). Autophagosome formation, elongation, maturation and degradation are regulated in a time-dependent manner by autophagy-related genes (ATGs), such as Beclin 1, VPS34, ATG14, VPS15 and LC3 (1,3).

EGFR is a member of the ErbB tyrosine kinase transmembrane receptor family that is activated following binding to its ligand, EGF (4). EGFR signaling pathways serve important roles in cell survival, growth, proliferation and differentiation (5,6). EGFR can regulate epithelial tissue development and homeostasis under physiological conditions; however, it can also become a driver of tumorigenesis (7). In addition, EGFR also regulates the response of cancer cells to metabolic stress (6). Various types of cancer, such as non-small cell lung cancer, and head and neck carcinomas, are associated with EGFR mutations or upregulation (8). Targeted therapy for EGFR sensitive mutations such as 19 deletion, L858R and G719X with EGFR-tyrosine kinase inhibitors (TKIs) has become an important therapeutic method (8,9). However, drug resistance often develops following EGFR-TKI therapy (10). It has been demonstrated that autophagy serves an important role in drug resistance of EGFR-TKIs (11,12). A recent study has shown that EGFR signaling suppresses autophagy (13).

The LAPTM4B gene is located on chromosome 8q22.1 and was first identified in human hepatocellular carcinoma (HCC). LAPTM4B is a novel tetratransmembrane protein primarily localized in the late endosomes and lysosomes (14). Notably, endosomes may provide a membrane source for autophagosome (15). Lysosomes are essential for autophagosome maturation and degradation (3). It is also reported that LAPTM4B is required for autophagy initiation (16). Furthermore, LAPTM4B knockdown inhibits autophagosome maturation and autophagic flux in the context of a metabolic stress microenvironment (16-18). However, the role and mechanism of action of LAPTM4B in autophagy remains unclear. The present review proposes that LAPTM4B participates in regulating autophagy through the EGFR pathway.

2. LAPTM4B

The LAPTM4B gene is mapped to chromosome 8q22.1 (19). The two alleles of LAPTM4B gene, AY219176 and AY219177, encode 35- and 40-kDa proteins, respectively (19). Previous studies have demonstrated that polymorphisms in the LAPTM4B gene were associated with tumorigenesis, tumor proliferation and metastasis (20-24).

LAPTM4B is upregulated in several types of cancer and associated with cancer cell proliferation, survival, drug resistance and poor prognosis (19). For instance, the LAPTM4B-35 protein encoded by the AY219176 allele of LAPTM4B is upregulated in HCC, lung cancer, extrahepatic cholangiocarcinoma, gallbladder cancer and breast cancer (22-25). The LAPTM4B-35 protein promotes proliferation and chemotherapy resistance of carcinoma cells through the AKT signaling pathway and contributes to cell migration, invasion and metastasis via its proline-rich domain (PPRP motif), which can interact with SH3 domain-containing signaling molecules that are involved in several signaling pathways (25-27). A previous meta-analysis demonstrated that the AY219177 allele of LAPTM4B, encoding the 40-kDa protein, is a high-risk factor for cancer (24). LAPTM4B promotes chemotherapy resistance by increasing drug efflux and decreasing drug nuclear localization and drug-induced DNA damage *in vitro* and *in vivo* (18,27,28). LAPTM4B upregulation is associated with tumorigenesis, drug resistance and poor prognosis in hepatocellular, gallbladder, extrahepatic cholangiocarcinoma, ovarian, gastric and colon carcinoma (26,29-34) through autophagy (35). LAPTM4B silencing using short interfering (si)RNA inhibits autophagic flux, whereas its overexpression rescues cell autophagy flux in the context of metabolic stress (16,18). LAPTM4B can regulate autophagy by activating ATG3 transcription, which has been predicted using Gene Ontology analysis and animal experiments (17). However, the role of LAPTM4B in autophagy and the underlying mechanism remains to be elucidated.

3. The dual role of autophagy in human malignancies

Autophagy is a conserved lysosome-mediated type-II programmed cell death, which is specifically regulated by ATGs. Basal autophagy is essential for homeostasis and can be upregulated in response to metabolic stresses as a cell survival mechanism. Excess autophagy results in cell death by catabolizing essential cellular components (36,37).

Autophagy has a dual function, as it can act both as a tumor suppressor and promoter. In normal cells, homeostatic autophagy can keep cells from malignant transformation by degrading intracellular toxic components. Nevertheless, autophagy can counteract hypoxia, nutrient starvation and exposure to chemotherapy, allowing cancer cells to adapt to these stress conditions and promoting their survival. Autophagy also serves an important role in chemoresistance in osteosarcoma, as well as ovarian and lung carcinoma (38-44). A series of clinical trials have investigated the role of autophagy inhibitors, such as hydroxychloroquine (HCQ) or chloroquine (CQ), and autophagy inducers, including rapamycin, in tumor therapy (45-49). These results showed that HCQ or CQ inhibits autophagy, resulting in increased tumor shrinkage. HCQ (the only clinically-approved autophagy inhibitor) with an improved toxicity profile compared with CQ has been studied in several phase I/II clinical trials alone or in combination with other chemotherapeutic regimens such as cisplatin (35). However, rapamycin as an autophagy inducer also shows cytotoxic effects in tumor targeted therapy (35). Recent studies show that ATGs are involved in mediating resistance to chemotherapy and may represent potential therapeutic targets (50-54). EGFR serves an important role in determining whether autophagy will serve a tumor-suppressive or an oncogenic role (6).

4. EGFR-mediated autophagy pathways

EGFR is a transmembrane tyrosine kinase receptor that can regulate DNA synthesis and cell proliferation and serves critical roles both in physiological conditions and in cancer (8,55). Various types of cancer, such as non-small cell lung cancer, and head and neck carcinomas, are associated with EGFR mutations or upregulation (8). Notably, it has been reported that the activation of EGFR by its ligand, EGF, inhibits autophagy (13,16).

EGFR regulates autophagy through the activation of the PI3K/AKT/mTOR (56), EGFR-RAS (57-59), EGFR-Beclin 1 (13) and EGFR-STAT3 signaling pathways (Fig. 1). PI3K, AKT and mTOR, which are downstream molecules of the EGFR signaling pathway, negatively regulate autophagy through inhibition of the ULK1 complex (6). Activated EGFR phosphorylates PI3K, AKT and TSC1, which activates mTOR and leads to the formation of the mTOR complex (mTORC1 or mTORC2). The multiprotein complex mTORC1 negatively regulates autophagy through the phosphorylation of ULK1, which interferes with the interaction between ULK1 and AMPK thereby preventing the formation of ULK1, FIP200 and ATG13 complexes (5,60-62). UVRAG, which regulates autophagosome maturation by binding to HOPS (homotypic fusion and vacuole protein sorting) complex, can be phosphorylated by mTORC1. RUBICON antagonizes the HOPS complex and interacts with UVRAG to inhibit UVRAG-mediated autophagosome maturation (63). EGFR family members activate the RAS/MAPK pathway, which activates RAF. Activated RAF activates MEK1/2 and ERK1/2 through the phosphorylation of their kinase domains. The RAS/RAF-1/MEK1/2/ERK pathway promotes autophagy by blocking the interaction between Bcl-2/Mcl1 and Beclin 1 (58,62,64). In addition, it has been reported that the RAS signaling pathway may promote autophagy by upregulating ATG5 and ATG7 expression (57,65). EGFR suppresses autophagy by interacting with the Bcl-2-homology-3 and evolutionarily conserved domain of Beclin 1, which results in multisite tyrosine phosphorylation of Beclin 1 on residues Y229, Y233, and Y352 and increases binding to the negative regulators, Bcl-2 and RUBICON, but decreases binding to the VPS34 lipid kinase. In addition, EGFR signaling upregulates the expression of the anti-autophagic protein Bcl-2 through the STAT3 pathway. Activated STAT3 then translocates to the nucleus to upregulate of Bcl-2 expression (66,67). Bcl-2 inhibits autophagy by binding to Beclin 1 through its BH3 domain (68). Cytoplasmic STAT3 interacts with PKR through its SH2 domain, thereby preventing eIF2α hyperphosphorylation. Consequently, autophagy is inhibited by preventing LC3b and ATG5 cascading initiation (69,70).

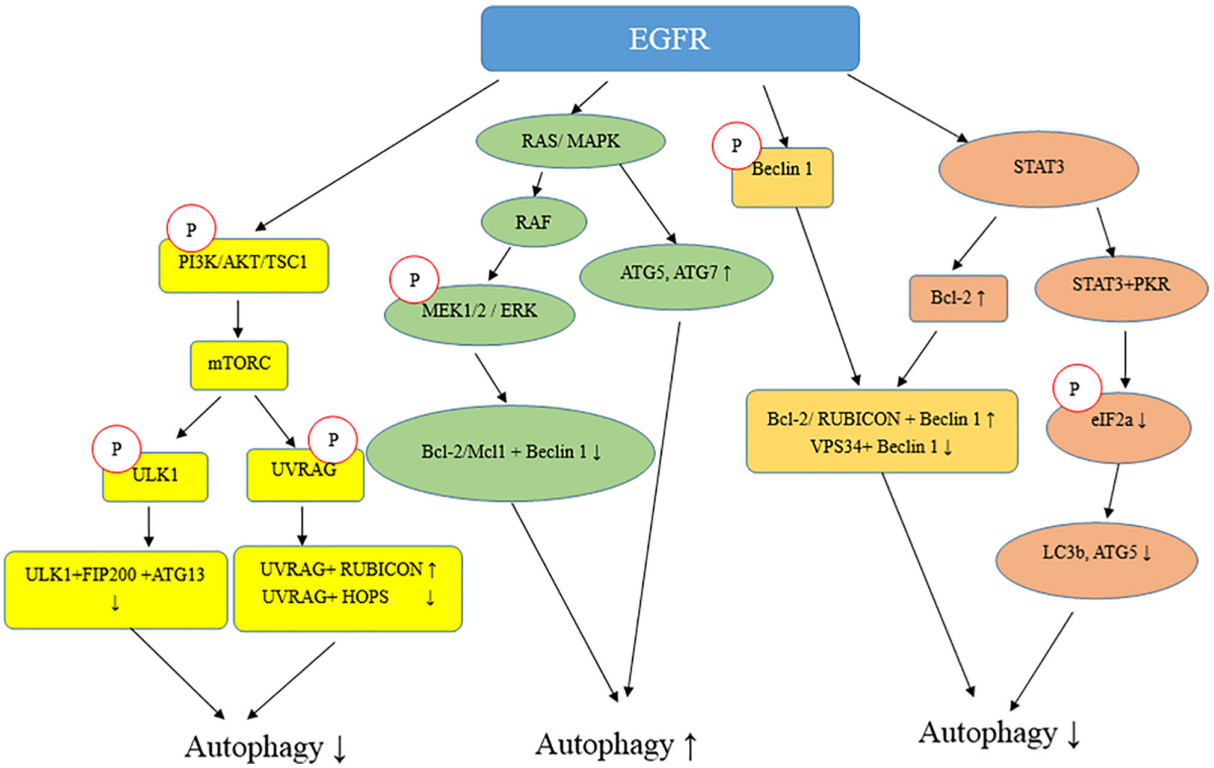

Figure 1. The EGFR signaling pathway is involved in autophagy. P, phosphorylation; ↑, increase; ↓, decrease.

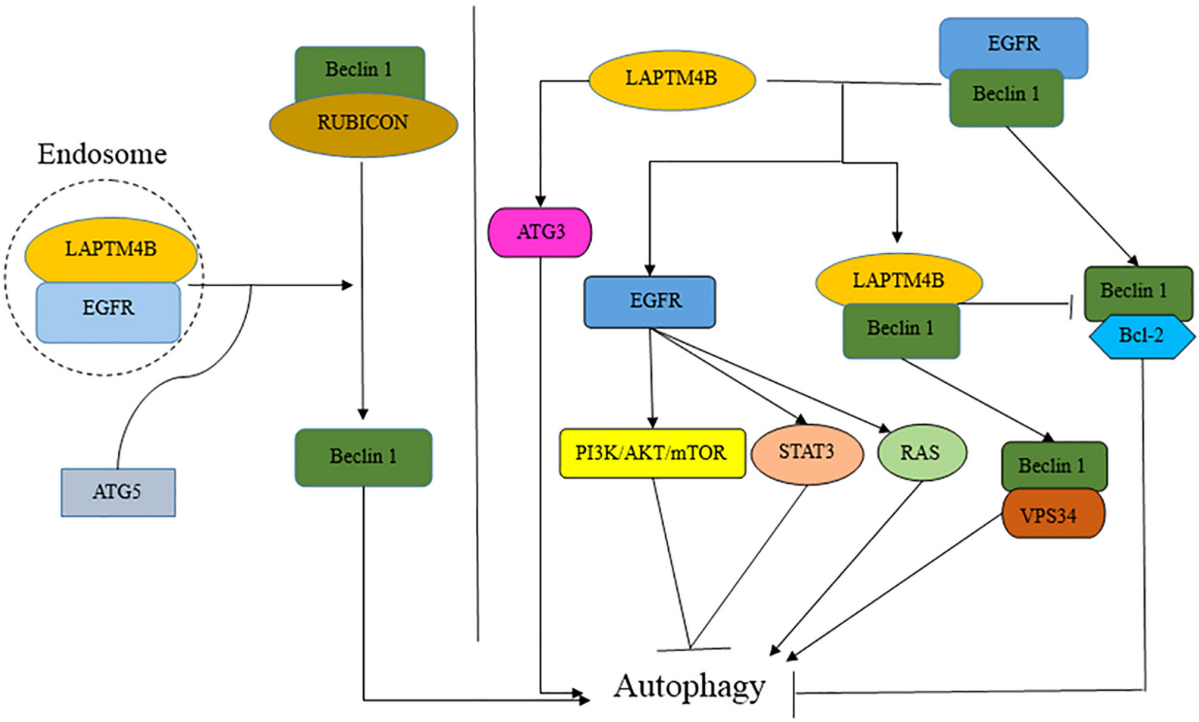

Figure 2. LAPTM4B regulates autophagy through the EGFR signaling pathway.

5. LAPTM4B and EGFR

The aforementioned role of EGFR in autophagy is kinase-dependent. It has been reported that inactive EGFR colocalized with LAPTM4B in both late and early endosomes and that these two molecules could interact and stabilize each other in cells grown in the absence of serum (16). As aforementioned, LAPTM4B is required for autophagy initiation. LAPTM4B silencing using siRNA inhibits autophagosome maturation and autophagic flux in the context of metabolic

stress (16,18). It may be hypothesized that LAPTM4B is involved in autophagy through the EGFR pathway.

LAPTM4B and EGFR are upregulated or mutated in the majority of types of cancer, including lung cancer and breast cancer, and associated with cancer cell proliferation and survival, drug resistance and poor prognosis (8,19). Tan *et al* (16) reported that inactive EGFR and LAPTM4B interact and stabilize each other at endosomes. However, as an endosomal protein, LAPTM4B could modulate inactive EGFR endosomal accumulation and inhibit EGF-stimulated EGFR lysosomal sorting (16). As aforementioned, EGFR phosphorylation is required for autophagy. A previous study has demonstrated that EGFR-TKIs or neutralizing antibody such as cetuximab induce autophagy and exert cytoprotective roles on cancer cells (71). In addition, EGFR silencing using siRNA strongly inhibits autophagosome formation (16). Notably, it has been demonstrated that LAPTM4B serves a key role in autophagy and EGFR gene mutations in clinical tumor samples (16,18,72). LAPTM4B is required for the endosomal accumulation of inactive EGFR and autophagy, and LAPTM4B is a cofactor for inactive EGFR-driven autophagy (16).

The mechanism of LAPTM4B in EGFR-mediated autophagy is as follows (Fig. 2). Beclin 1, as well as ATG3, -5, -6, -7, -8, -10 and -12 are important mediators of autophagy (2,3). On one hand, LAPTM4B interacts and stabilizes with inactive EGFR at endosomes, thus recruiting ATG5 to disassociate Beclin 1 from the RUBICON-Beclin 1 complex to trigger autophagy (16). On the other hand, the expression levels of LAPTM4B positively correlate with EGFR (16). In addition, Tian *et al* (73) demonstrate that Beclin1 interacted with the N- and C-terminal domains of LAPTM4B and compete with EGFR for LAPTM4B binding. Nevertheless, this study did not clarify the exact mechanism of the relationship between LAPTM4B and EGFR. Notably, the Beclin 1/EGFR complex can also inhibit autophagy (13). Thus, it may be hypothesized that LAPTM4B competes with EGFR to interact with Beclin1 to antagonize autophagy inhibition (Fig. 2). LAPTM4B may also regulate autophagy through EGFR signaling pathways, including PI3K/AKT/mTOR, EGFR-RAS, EGFR-STAT3.

6. Conclusions and future perspectives

LAPTM4B regulates autophagy either by directly activating ATG3 transcription, or through the EGFR pathway (whether active or inactive). The present review aimed to describe the role and mechanism of action of LAPTM4B in EGFR-mediated autophagy. EGFR-TKI therapy for EGFR sensitive mutations induces autophagy contributing to cancer cell survival. Considering the role of LAPTM4B in autophagy and chemotherapy resistance, full understanding of the association between LAPTM4B, EGFR and autophagy may provide insight into more effective therapeutic strategies for tumors such as non-small-cell lung carcinoma. LAPTM4B may be a potential candidate for future tumor treatment options, particularly in combination with other cancer driver gene targeted therapy such as EGFR-TKIs. The present review may provide useful information for future studies on the development of more effective targeted therapies compared with broad spectrum chemotherapy.

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Authors' contributions

XJ and HM drafted the manuscript. XJ and YD designed the study, supervised preparation of the manuscript and gave final approval of the version to be published. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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