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REVIEW – OPEN ACCESS

LC3 and Beclin-1 as Markers of Autophagic Activity in Breast Cancer

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ABSTRACT

Autophagy is a catabolic pathway meaning "self-eating" that facilitates nutrient recycling from damaged and aged organelles and other impaired cellular components through lysosomal degradation. Regulation of this process has been associated with the development of cancer. It can play different roles at different tumors and developmental stages of tumors. In breast cancer, similarly, autophagy functions as a mechanism promoting survival or leading to death. Whereas, it is very important to define the role of autophagy as an effective treatment strategy in breast cancer cells. Therefore, in this review, the role of inhibited autophagy is discussed with specific RNAs targeting Beclin-1 and LC3 genes in breast cancer.

Keywords: Autophagy, beclin-1, breast cancer, LC3, siRNA

INTRODUCTION

Autophagy is a catabolic process that targets damaged and aged cellular organelles to lysosomes to break down damaged and defective cytoplasmic components. Autophagy can be studied in three main types: Macroautophagy, microautophagy, and chaperone-mediated autophagy. These types are characterized by different mechanisms of delivering cargo to the lysosome (1). The best characterized autophagic process is macroautophagy (1, 2) and is the focus of this review.

Autophagy is a housekeeping process. In normal cells, autophagy acts as an intracellular quality control mechanism. It does this by eliminating toxic substances, damaged organelles, misfolded proteins, and reducing oxidative stress, protecting them from damage for homeostasis and cell survival (2, 3). Furthermore, autophagy is strongly induced under metabolic stress such as nutrient starvation or hypoxic environment, and promotes metabolic adaptation for survival of cell. Therefore, the pro-survival and homeostatic functions of autophagy from yeast to mammals are evolutionarily preserved (1). In contrast, it also plays the role of a mechanism mediating cell death. It is not yet clear autophagy-dependent cell death mechanism, but under conditions of severe metabolic stress, excessive induced autophagy may lead to cell death, known as autophagic cell death (type II programmed cell death) (4–7). Recent research on autophagy and cancer suggests that autophagy may be important in regulating cancer development and in the tumor cells in anticancer treatment. It is reported that autophagy may be deregulated, suppressed, or over-activated in cancer cells (2). However, the role of autophagy in these processes is still not clear in terms of pro-survival (oncogenic) and pro-death (tumor suppressor function) in various cancer types (1, 2, 5). Similarly, autophagy is involved both suppression and progression of tumor in breast cancer (6). Some studies reported that decreased autophagy contributed to progression of breast cancer (7–11). For example, Bcl-2 binds to Beclin-1 and, is negatively regulated the autophagy. Beclin-1 is released from Bcl-2 in starvation conditions and thus autophagy is activated. Akar et al. (11) demonstrated that silencing of Bcl-2 by siRNA induces autophagic cell death and inhibits of proliferation in breast cancer cells and growth breast tumors in orthotopicxenograft models. Conversely, some studies have shown that there is increased autophagy associated with breast cancer poor prognosis (12–16). These researchers demonstrated that autophagy reduces tumor growth, invasion, and proliferation in breast cancer cells through inhibition by genetic and pharmacological inhibitors of autophagy inhibitors (15–18).

Consequently, the role of autophagy is still not understood in breast cells such as in other cancers. Therefore, in this review, we discussed some recent discoveries and ideas about effects of targeting autophagy in cancer. In the presented review, articles were selected by using keywords such as autophagy, cancer, LC3, Beclin-1, RNA interference (RNAi), siRNA, LC3-siRNA, Beclin-1 siRNA, breast cancer, autophagy inhibitors, phase study, in vivo, in vitro, and the articles published between 2005 and 2020 years were used.

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EXPRESSION of the AUTOPHAGY-RELATED PROTEINS, BECLIN-1, and LC3 in BREAST CANCER

Autophagy is often induced in cancer cells as a survival mechanism at various metabolic stresses. Thus, autophagy improves the survival of fast-growing cancer cells, particularly in the inner region of the inadequately vascularized tumor, by protecting them from nutrient-deprived conditions and low oxygen conditions. Furthermore, autophagy is used to maintain cellular adenosine triphosphate (ATP) production and the level of ATP in pre-cancer cells or cancer cells. In addition, it is reported that autophagy supports the tricarboxylic acid cycle in cancer cells to AT (2). Therefore, autophagy may act as a survival pathway for the cells in cancer development (19). Besides, autophagy also functions as mechanisms for cell death, which can explain its tumor suppressor effects (2, 19). It is reported that excessive activation of autophagy under stress conditions scan lead to autophagic cell death with degradation of critical cellular components (5). In addition, the required ATP for apoptosis and caspase activation is provided by autophagy, and also it supports to apoptotic cell death (20). Furthermore, role of autophagy is controversial in the tumor microenvironment. It has a function that can help trigger tumorigenesis or help to generate anticancer immune responses in the tumor microenvironment (2, 21). Consequently, autophagy is mediated a number of diverse biological mechanism such as cell survival and cell death in cancer cells. For this reason, autophagy has become a substantial issue for cancer research.

The process of autophagy involves the formation of double-membrane vacuoles, a condition called autophagosomes.

Autophagosome formation is a very complex process consisting of several stages including initiation, nucleation, elongation, and fusion with the lysosome. Various autophagy-linked (Atg) proteins, as Beclin-1 and the microtubule-related light chain-3 (LC3) protein, play a key role in this process (5) (Fig. 1). As shown in Figure 1, Beclin-1 and LC3 proteins, which function in different process of autophagy, are essential for autophagosome formation. Beclin-1, considered as a necessary component for the initiation of autophagy, takes part in the very early stage of autophagosome formation (nucleation phase). LC3 protein exists in two forms, LC3-I and LC3-II, of which LC3-I protein is also localized in the cytoplasm. When autophagy is induced by various stresses, the cytosolic form of LC3-I transforms into LC3-II, and then LC3-II binds to the autophagosome membrane (1–4). For this reason, LC3 and Beclin-1 are accepted as major markers of autophagic activity (1, 5, 15, 16), and autophagy is often evaluated by examining expression of LC3 and Beclin-1 by western blot and by quantitative reverse-transcription polymerase chain reaction in vitro or in vivo studies and clinical samples (2).

The direct link between autophagy and cancer was first demonstrated in studies conducted in the 1900s (22). Accordingly, it has been reported that Beclin-1 is deleted as a monoalel in approximately 40–75% of ovarian, brain, and prostate cancers (8, 23). Similarly, Beclin-1 is mono-allelically deleted in 40–50% of sporadic human breast cancers (22, 23). Therefore, it is suggested that Beclin-1 may be a tumor suppressor for sporadic breast cancer and autophagy may play a role in preventing development of these tumors (23). Beclin-1 protein level, which

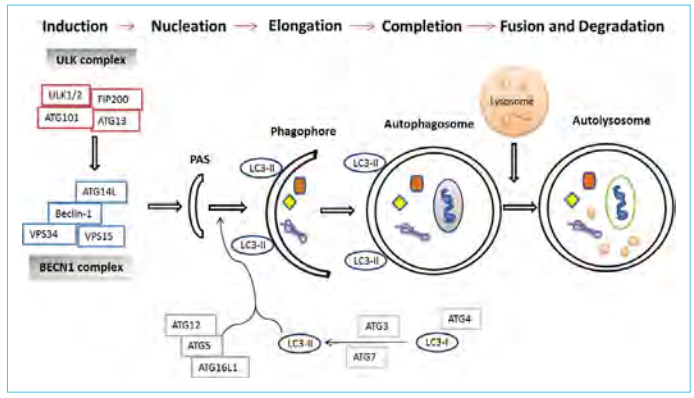

Figure 1. Phases of autophagy. Autophagy consists of several steps involving nucleation, elongation, maturation, finally fusion and degradation. The process starts by the association of the ULK1 and BECN1 complexes that form the basis for recruiting other autophagy-related (ATG) proteins as well as the lipidated form of LC3-II. LC3-I protein is formed from pro-LC3 with the contribution of ATG4. After, phosphatidyl-ethanolamine (PE) to LC3-I by ATG7 and ATG3 attached, and LC3-II is created. Then, the completed autophagosome fuses with a lysosome to form the autolysosome, where the proteins or organelles (e.i. mitochondria) undergo degradation by lysosomal enzymes

decreases due to haplo-deficiency of the Beclin-1 gene, causes poor prognosis and decrease in overall survival in breast cancer cases, in which case Beclin-1 protein plays the role of tumor suppressor (24–27). In particular, allelic deletion of Beclin-1 is observed in triple-negative breast cancer (TNBC) cell and low level of Beclin-1 expression correlates with triple-negative subtype of human breast cancers (7, 9). On the other hand, Beclin-1 is highly expressed in breast cancer cells compared to normal samples, indicating the upregulation of autophagy in breast cancer (27). In particular, Beclin-1 expression was highest in TNBC patients (28). However, Zhou et al. (27) were reported that high Beclin-1 expression was not significantly associated with any clinic-pathological parameter such as lymph node metastasis in patients with breast cancer. Conversely, Wang et al. (28) demonstrated that higher levels of Beclin-1 were associated with more lymph node metastasis and distant metastasis in TNBC patients. In addition, they indicated that Beclin-1 had a double effect of on TNBC cell growth and survival both in normal condition and in stress (28). Previously, we demonstrated that Beclin-1 expression was highest in TNBC cells (15), and Beclin-1 promoted cell proliferation, survival, migration, invasion, and contributes to tumor progression. Consequently, due to haplo insufficiency of the tumor suppressor Beclin-1 gene, the Beclin-1 level is reduced which consequently suppresses autophagy and causes breast cancer progression. However, interestingly, Beclin-1 level is increased, and high Beclin-1 level induces autophagic activity. Hence, proto-oncogenic role of Beclin-1 leads to breast cancer progression.

LC3 is the first mammalian protein that is recruited to the autophagosome membranes and involved in the formation of autophagosome. Therefore, LC3 is the most widely used marker to autophagy. On autophagy induction, cytosolic LC3-I converts

from the LC3-I to the LC3-II form, and LC3-II is localized in autophagosomes membranes. In this way, LC3-II form is highly regarded as a marker of autophagy (1, 2). Some studies demonstrated that LC3 expression level is reduced in cancer cells. Studies also demonstrated that reduced LC3 level was related to worse outcome in breast cancer cells (10). Especially, LC3 expression is low in TNBC and this is significantly correlated with advanced nodal invasion and a higher risk of distant metastasis and high mortality in TNBC patients (10). Besides, it has been shown that LC3 protein is highly expressed in breast cancer tissues and cell lines compared to normal breast tissues. Interestingly, while an increase in LC3 expression inhibited TNBC cells proliferation and suppressed growth of TNBC cells (29), Zhao et al. (13) and Lefort et al. (14) reported that high expression of LC3 was associated with progression and shorter survival in TNBC. Similarly, previously, we demonstrated that LC3 is highly expressed in MDA-MB-231 cells, and plays an important role in clonogenicity, survival, migration, and invasion TNBC. Furthermore, our previous data revealed that both LC3 and Beclin-1 lend to the regulation of expression of cylin-D1, integrin-β1, uPAR, PARP1, as well as the activity of Srcwhich are well known as mediators of the cell cycle, cell survival, and cell migration and invasion (15). The autophagosome formation and LC3 and Beclin-1 expressions are suppressed when the downregulation of FOXM1 gene using specific small interference RNAs (siRNAs) (30). Therefore, although all of these controversial findings, we think that autophagic activity increase in tumor cells, which may increase the oncogenic activity rather than tumor suppressor activity and a target for treatment especially in TNBCs.

TARGETING BECLIN-1 and LC3 GENES in BREAST CANCER

For more than 40 years, studies of hundreds have been made to understand the molecular basis and genetics of cancer. Discovery of RNAi has opened a new door to understanding the cancer genetic basis. Although RNAi is a natural phenomenon, siRNAs are synthesized as in vitro and used to silence expression of genes by targeting the mRNA expression in human cells. Thus, siRNAs to understand molecular mechanism and treat cancer has actively used by researchers (31).

The role of autophagy is still not understood in breast cancer cells. Whereas, for treatment, it is pivotal to determine how autophagy is involved in breast cancer tumorogenesis. Chemicals such as 3-methyladenine and bafilomycin-A1, which are pharmacological inhibitors of autophagy, are not particular to the autophagic process and thus cause secondary or off-target effects in cells (32). Therefore, role of autophagy in breast cancer cells has been investigated using specific siRNAs that target autophagy-related Beclin-1 and LC3 genes for autophagy inhibition. It has been reported that using siRNA targeting against Beclin-1 to inhibit autophagy promote cell deaths of breast cancer cells (33). Furthermore, high autophagic activity plays a role in the development of resistance of breast cancer cells to tumor necrosis factor relate apoptosis inducing ligand (TRAIL), thus cells achieved resistance to TRAIL. Suppressing autophagy by LC3-siRNA enhance TRAIL efficacy in TRAIL-resistant breast cancer cells and resulted in reduced the cell proliferation (34). Furthermore, autophagy inhibition with Beclin-1 siRNA decreases cell viability and autophagy inhibition can sensitize anti-estrogen-tamoxifen-resistant breast cancer cells (35). Similarly, it was demonstrated that Beclin-1-siRNA increased sensitivity to radiation in breast cancer cells (36). Accordingly, studies show that genetic inhibition of autophagy enhances the effects of chemotherapeutic agents or radiotherapy. Previously, we demonstrated that autophagy promotes important biological processes, as cell survival, proliferation, invasion, migration, and resistance to apoptosis and its inhibition mediated-Beclin-1-siRNA or -LC3-siRNA significantly suppresses these mechanism in TNBCs (15).

As a result, autophagy modulation as therapeutic target can be used to inhibit tumor growth and to enhance the efficacy of conventional therapies. Some pharmacological agents, which autophagy modulators such as temsirolimus and everolimus with FDA approval, are used in cancer therapies (19). At present, a number of small molecules to inhibition of autophagy such as ULK kinase inhibitors, Vps34 inhibitors, ATG4 inhibitors, chloroquine, hydroxyl, and chloroquine or as autophagy inducer as Temozolomide, Rapamycin, and Metformin are used in pre-clinical and clinical studies (19, 37). siRNA-based treatments are also used to inhibit or inducer autophagic activity in in vivo and in vitro for various cancer types (12, 15, 38). All these study results demonstrated that decreased autophagy can contribute to tumor progression, whereas increased autophagy may be a mechanism for tumor survival, and its role is still unclear in cancer cells.

CONCLUSION

Autophagy may be important in regulating cancer development and progression in tumor cells, under stress conditions such as hypoxia, nutrient deficiency, and even in determining the response of tumor cells to anticancer therapy. However, the role of autophagy in cancer and treatment responsiveness is undoubtedly controversial. This may be explained by dual effect of autophagy, as both a tumor suppressor and a protector of cancer cell survival, during carcinogenesis. However, both in vitro and in vivo or preclinical studies supporting autophagy inhibition as an anticancer strategy exist to treatment of breast cancer patients (39). Moreover, the role of pro-survival autophagy is shown as a from hallmarks of cancer for tumorigenic progression (40). According to these studies and our findings, we think that autophagy may play a protective role in cancer cells and its inhibition by either pharmacological agents or RNAi targeting essential autophagy regulators may a strategic approach for breast cancer treatment. However, for identifying potential strategic treatment, larger number of research is still needed to better understand the role of autophagy in tumors.

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