

Review

# Molecular Interactions of Autophagy with the Immune System and Cancer

**Running title:** Is autophagy in cancer protective or detrimental?

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**Abstract:** Autophagy is a highly conserved catabolic mechanism that mediates the degradation of damaged cellular components by inducing their fusion with lysosomes. This process provides cells with an alternative source of energy for the synthesis of new proteins and the maintenance of metabolic homeostasis in stressful environments. Numerous studies have demonstrated beneficial roles for the induction as well as the suppression of autophagy in cancer cells. Autophagy may induce either survival or death depending on the cell/tissue type. Radiation therapy is widely used therapeutic option to treat cancer, and it induces autophagy in human cancer cell line. Also, melatonin seems to affect cancer cell death via regulation of programmed cell death. In this review, we summarize the current understanding of autophagy and its regulation in cancer.

**Keywords:** Autophagy, Immune system, Cancer, Cell death, Metabolic homeostasis

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## Introduction

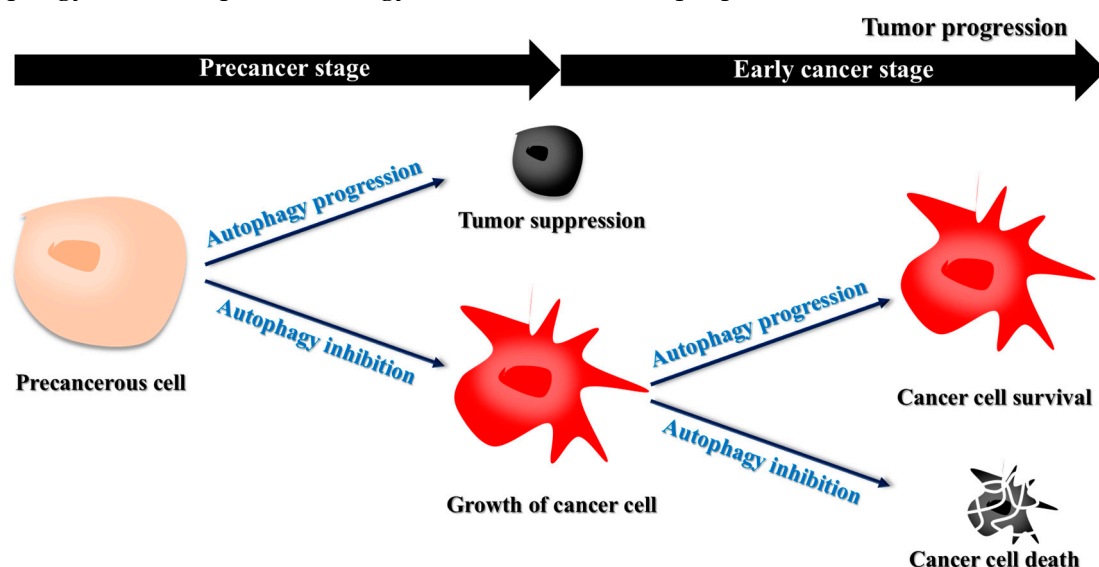
The term autophagy is derived from the Greek word meaning “self-eating” [1]. Autophagy is a catabolic process in which intracellular components are sequestered and degraded for recycling [2]. This process occurs under conditions of amino acid starvation, glucose deprivation, oxygen deficiency, growth factor withdrawal, and cellular damage [9]. The degradation of damaged or long-lived proteins and organelles provides the cell with a new energy source for recovery of homeostasis despite metabolic stress [9]. Three different types of autophagy have been identified: macroautophagy, microautophagy, and chaperone-mediated autophagy [3,4]. Macroautophagy results in the degradation of long-lived cytosolic proteins and organelles following their fusion with the lysosome and autophagosome, which engulf the substrate [3]. In microautophagy, however, the substrates are directly engulfed by the vacuole membrane and subsequently degraded [5]. In

chaperone-mediated autophagy, the target substrates are selected in a chaperone-dependent manner and then translocated to the lysosome for degradation [6]. Of these three mechanisms, macroautophagy is the most common [4] and has received the most attention [5]. Accordingly, this review focuses on macroautophagy (referred to hereafter as autophagy) and its roles in the immune system and in cancer. Because autophagy involves the transfer of cytoplasmic substrates to lysosomes, it has been implicated in both innate and adaptive immunities [7].

Defective autophagy and apoptosis may contribute to disease pathogenesis, including cancer [8,9], whereas the preservation of cellular homeostasis via autophagy is important for cancer prevention [10]. However, autophagy is a “double-edged sword”, because it not only suppresses but also promotes cancer cell survival [8,10]. These paradoxical functions of autophagy in cancer remain to be fully elucidated.

### The initiation of autophagy during cancer

In cancer cells, autophagy is regulated by phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) and activated protein kinase (AMPK) pathways [11]. Activation of PI3K results in production of phosphatidylinositol 3, 4, 5-triphosphate, which then binds to Akt [11], activating it and several downstream pathways, including mTOR [36]. AMPK is activated in response to energy depletion to induce autophagy [11]. Thus, autophagy inhibits cancer, whereas inhibition of autophagy enables the growth of precancerous cells [36,48]. At the early stage of cancer cell development, protein synthesis rather than degradation is needed for cancer cell growth [37, 51]. Therefore, autophagy inhibition in this step can cause cancer cell growth [51]. In advanced stages of cancer, autophagy is upregulated because cancer cells exploit autophagy for their survival under starvation conditions (Fig. 1) [36,49]. Based on these observations, inhibition of autophagy as a therapeutic strategy for cancer has been proposed [51].



**Figure 1.** Autophagy not only promotes but also prevents cancer.

### **Autophagy as an innate immune response against cancer**

Innate-immunity-mediated autophagy is regulated by the activation of innate immune receptors, including Toll-like receptors (TLRs) and nucleotide oligomerization domain (NOD)-like receptors (NLRs) [11]. TLRs induce inflammatory cytokine production by activating the NF- $\kappa$ B and MAPK pathways, mainly through myeloid differentiation primary response 88 (MYD88)-dependent pathways, either alone or in collaboration with TICAM1 (toll-like receptor adaptor molecule 1) -dependent pathways [12,14,15]. TLRs are usually expressed in cancer cells and are responsible for the regulation of autophagy as well as several immune responses [11]. Autophagy triggered by TLR3 and TLR4 was shown to contribute to the progression of lung cancer [12]. However, several studies have suggested that TLR activation enhances the survival, proliferation, and metastasis of cancer cells [12,16,17,18,19]. Furthermore, TLRs trigger the release of proinflammatory cytokines, chemokines, and immunosuppressive factors, leading to immune evasion and enhanced cancer cell resistance [12, 19].

While TLRs sense microbes on the cell surface, NLRs, which are important components of the innate immune system, recognize cytosolic bacteria. NOD1 and NOD2 detect intracellular microbes incorporating meso-diaminopimelic acid and muramyl dipeptide [20]. TLRs as well as NOD1 and NOD2 activate the NF- $\kappa$ B and MAPK pathways [20]. Moreover, they participate in regulating autophagy by interacting with ATG16L1, which mediates autophagosome formation, at the cell membrane [11,21]. NOD2 also recognizes invasive bacteria, thereby triggering autophagy and leading to NOD2-mediated host defenses [13]. Both NOD1 and NOD2 are thought to engage not only in innate and adaptive immune responses but also in the interaction between autophagy and cancer [11,22]. By altering the balance between pro- and anti-inflammatory cytokines, NOD1 and NOD2 modulate the risk of cancer [22]. However, much remains to be learned about the contributions of TLR and NLR to cancer immunity.

### **Autophagy as an adaptive immune response against cancer**

Autophagy also takes part in adaptive immunity by modulating T and B lymphocytes and plays a role in T cell survival, proliferation, homeostasis, and activation [11,23]. The autophagy protein Atg7 is required for T lymphocyte survival, and autophagy-deficient T cells exhibit increased reactive oxygen species generation, presumably due to the insufficient degradation of mitochondrial components [24]. Several studies have shown that defective autophagy induced by the ablation of pro-autophagic molecules, such as Vps34 and PI3K, is harmful to mitochondrial quality control, leading to disruption of T cell homeostasis and survival [11,25,26]. In cancer, autophagy may induce not only survival but also death of T cells. In addition, autophagy may promote the helper T lymphocyte response, thus enhancing tumor recognition [27]. Alternatively, autophagy may provide cancer cells with a survival advantage, protecting them against immunosurveillance by suppressing CD4<sup>+</sup> and CD8<sup>+</sup> T cells [28]. Based on these observations, autophagy is thought to play a dominant role in T cell function.

Autophagy is needed for the survival and differentiation of B cells as well [29]. ATG5, an autophagy-related gene, contributes to B cell survival during development [31]. B cell activation is induced by tumor-derived autophagosomes (Dribbles), which sequester various tumor antigens, in a TLR4/MYD88-dependent reaction [30]. However, autophagy has been

explored less in B cells than in T cells.

### **Autophagy and its regulatory function on cancer cell fate**

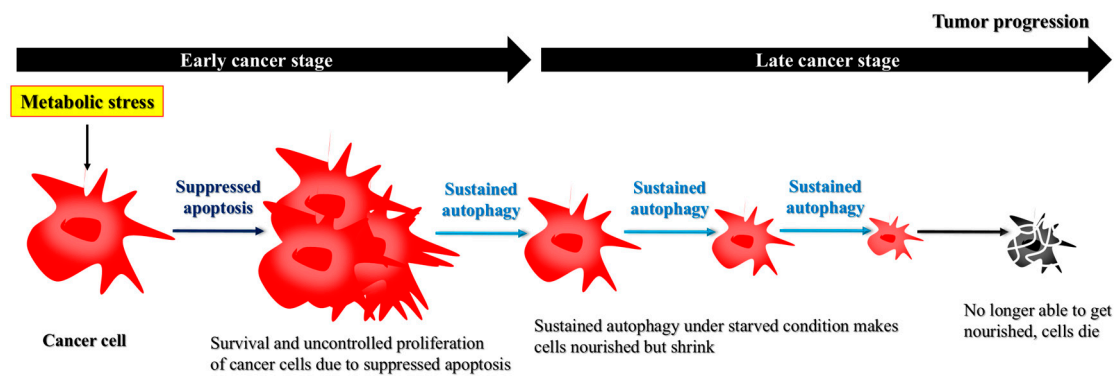
#### **Autophagy suppresses tumor development and induces cancer cell death**

A relationship between disrupted autophagy and cancer development has been demonstrated. For example, *BECN1*, an autophagy-related gene required for autophagosome formation, seems to act as a tumor suppressor, and certain brain tumors have been attributed to insufficient *BECN1* expression [33]. Lack of the Beclin-1 protein was suggested to be involved in the malignant transformation of cells [32], and levels of the autophagy marker LC3 level are reduced in cancer cells [34].

An interaction between autophagy and apoptosis to alleviate necrosis, leading to tumor suppression, has been proposed [35]. Autophagy may act as a tumor suppressor to limit tumor size [36]. These observations suggest that autophagy hinders tumor progression. Moreover, by sequestering damaged organelles, inducing cell differentiation, increasing protein catabolism, and promoting autophagic cell death, autophagy protects cells from becoming malignant [38]. Thus, while autophagy supports cell survival, it may also promote cell death in cases of imbalanced cell metabolism. Under the latter condition, autophagic cellular consumption surpasses the cellular capacity for protein synthesis [9]. However, autophagy may also protect cells from apoptotic cell death [51]. Furthermore, autophagy may induce cancer progression by increasing DNA damage and genomic instability [39].

#### **Autophagy drives cancer cell survival**

Although the primary role of autophagy seems to be to prevent cancer, once a tumor develops, autophagy is exploited by cancer cells and has a protective role [8]. Indeed, cancer cells exploit autophagy to adapt to a stressful environment and maintain homeostasis in the presence of cellular stress. Cancer cells, especially their poorly vascularized internal regions, have been shown to utilize autophagy for survival under starvation and low-oxygen conditions [36,37]. Interestingly, autophagy-induced cancer cell survival is enhanced in cancer cells with defective apoptosis. Apoptotic cell death is suppressed in response to metabolic stress, because of overexpression of the apoptotic inhibitor BCL2 [9]. Suppression of apoptosis prolongs cells survival and may cause the uncontrolled proliferation of malignantly transformed cells that otherwise would have undergone apoptotic cell death [9,50]. These apoptosis-defective cancer cells undergo autophagy to extend their lifespan, as sustained autophagy not only nourishes the cells but also reduces their size, allowing them to survive under nutrient-poor/starvation conditions [9]. However, over time the prolonged shrinkage and nutrient restoration can inhibit recovery and, ultimately, induce cell death (Fig. 2) [9]. Thus, while autophagy may induce cancer cell survival, as depicted in Fig. 1, the cells eventually die due to sustained autophagy. In other words, both the survival and death of apoptosis-defective cancer cells under metabolic stress are dependent on autophagy.



**Figure 2.** Apoptosis-defective cancer cells exploit autophagy to extend their survival, but these cells eventually die.

### Autophagy as a candidate for cancer immunotherapy

Radiation therapy is the most commonly used treatment option for cancer thanks to its tumor growth-delaying property [56, 57]. Radiation induce autophagy in human cancer cell lines [57]. The autophagy following radiation therapy can have both cytoprotective and cytotoxic effects [57]. Autophagy induction can enhance the effect of radiation therapy in human oral squamous cancer cell by causing sensitization to irradiation. Plus, PI3K/Akt pathway, which is a major regulator of autophagy, is thought to regulate cytotoxicity of post-radiation autophagy [57]. Conversely, other researchers reported that suppression of autophagy may augment radio-sensitization in human glioma cells [57, 58]. Therefore, the Janus-faced autophagy may induce either survival or death depending on the cell/tissue type [57].

Anti-cancer therapies can induce autophagy in apoptosis-defective cells, as the resultant cytotoxicity may evoke progressive autophagy, leading to autophagic cell death [9]. Therefore, therapeutic induction of autophagy may contribute to cancer cell removal. As described above, cells defective in apoptosis undergo autophagic death. This property has been exploited in the development of anti-cancer therapies, which cause cells to become resistant to apoptosis [40]. Thus, promoting autophagic death in cancer cells can be a therapeutic option for cancer treatment [40].

Generally, harmful stimuli induces apoptosis and autophagy at early stages [42]. Present authors recently proposed the therapeutic potential of melatonin against colon cancer [55]. According to the study, melatonin increased colon cancer cell death at early stage by activating apoptosis but also autophagy, which is evidenced by upregulation of bax, cleaved caspase 3, Beclin1 and LC3; lowered AKT/pAKT expression [55].

High-mobility group box 1 protein (HMGB1) is a nuclear protein that functions as a transcriptional enhancer and mediates inflammatory responses [44]. HMGB1 is secreted from inflammatory cells to evoke inflammation by binding to receptors such as the receptor for advanced glycation end products (RAGE) and TLR2/4 [42]. HMGB1 release is involved in the immune response against cancer cells [43]. This protein is not released from apoptotic cancer cell, indicating apoptotic cell death is non-inflammatory [54]. HMGB1 has also been shown to inhibit apoptosis while promoting autophagy [42]. Reduced HMGB1 expression may increase cancer cell sensitivity by limiting autophagy [42]. Based on the link between autophagy and apoptosis in cancer cells, HMGB1 may be an important therapeutic target in cancer treatment.

## Conclusion and perspectives

As previously mentioned, inhibition of autophagy encourages cancer cell growth; promotion of autophagy can be a cancer suppressor at early-stage cancer [37,51]. At the late stage of cancer, however, cancer cells utilize autophagy to protect themselves from anti-cancer therapy. Therefore, autophagy inhibitors (e.g. bafilomycin A1) can evoke cancer cell death through apoptosis and act as a cancer suppressor in this stage [37,40,51]. In other words, autophagy restrains cancer cell development, and promote survival of existing cancer cells [52]. Since cancer cells primarily undergo autophagy for self-protection [41], inhibition of autophagy has generally been proposed as a therapeutic strategy against cancer [45,46]. However, the promotion of autophagy may result in anti-cancer activity by inducing cytotoxic immune cells [11,47]. Indeed, within the same cancer, both inhibition and promotion of autophagy may be beneficial [49]. Therefore, an optimal combination of autophagy inhibition and promotion, according to the properties of the cancer, is needed. A better understanding of the roles of autophagy in cancer and immunity, and whether its induction or suppression will provide the desired effect, requires further study.

**Author contributions:** This review was conceptualized and designed by Yonggeun Hong and Chan Young Park; Yonggeun Hong and Yunho Jin wrote the manuscript; Yunho Jin and Yunkyung Hong collected the references and created the figures appearing in the manuscript under supervision by Yonggeun Hong. All authors commented on the manuscript and approved the final form of manuscript.

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