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Regulation of Autophagy and It's Role in Cancer

R. J. Patel[1], R. M. Sherasiya[2], N. N. Parmar[1], A. A. Makwana[2]
[1] Veterinary Officer, District Panchayat Surendranagar, Department of Animal Husbandry, Government of Gujarat, 363001, India.
[2] Veterinary Officer, District Panchayat Kutch, Department of Animal Husbandry, Government of Gujarat,363621, India.
Corresponding author: ritupatel21799@gmail.com
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Abstract

Autophagy, a conserved lysosomal degradation pathway, plays a multifaceted and context-dependent role in cancer. Under physiological conditions, autophagy maintains cellular homeostasis by removing damaged organelles, misfolded proteins, and reactive oxygen species, thereby preventing genomic instability and tumor initiation. However, once a tumor is established, cancer cells often exploit autophagy to survive metabolic stress, hypoxia, and therapeutic insults. Elevated autophagy supports tumor progression by promoting nutrient recycling, sustaining mitochondrial function, and enabling resistance to chemotherapy, radiotherapy, and targeted agents. Conversely, in certain genetic backgrounds or tumor types, excessive or defective autophagy can induce cell death, senescence, or heightened immune recognition, indicating its potential as a therapeutic vulnerability. Current research focuses on modulating autophagy—either inhibiting it to sensitize tumors to treatment or activating it to restore tumor-suppressive functions—yet clinical outcomes remain variable due to the pathway's intricate regulation and heterogeneity across cancers. Understanding the molecular determinants governing autophagy's dualistic behavior is essential for designing effective autophagy-targeted therapies and integrating them with existing treatment regimens.

KEYWORDS: Autophagy, Cancer, Molecular regulation,

INTRODUCTION

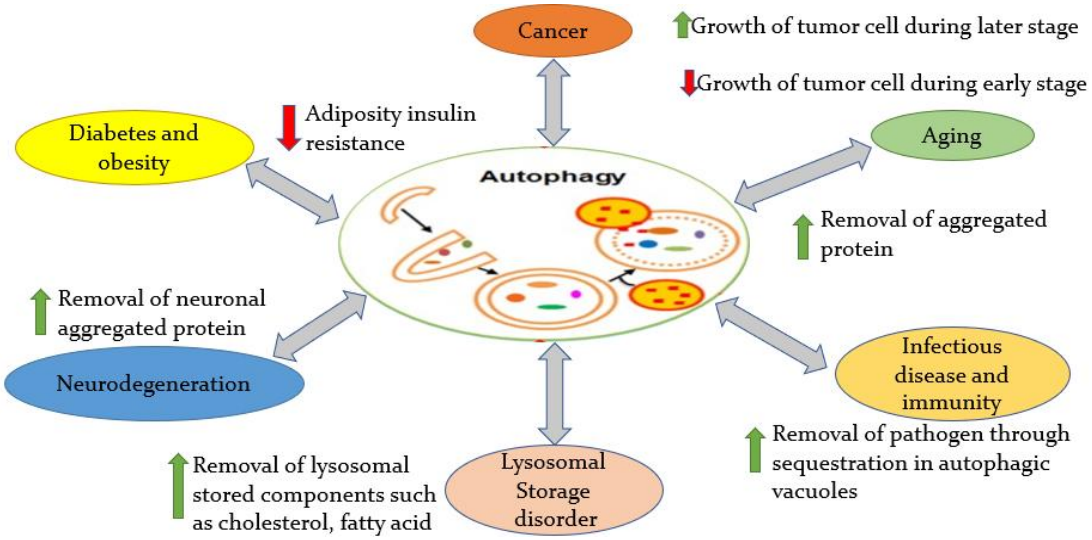
Autophagy is a multifaceted and highly conserved cellular process that involves the lysosomal breakdown and recycling of intracellular macromolecules, such as aggregated cellular proteins and damaged organelles. Christian de Duve was the first to describe autophagy, which is derived from the Greek terms auto for "self" and phagein for "eating"(Wen and Klionsky, 2019).

Autophagy is an intracellular degradation process that happens in response to a variety of stressful situations, including organelle injury, the presence of aberrant proteins, and

nutrition restriction. (Yun and Lee. 2018). Cell homeostasis is determined by a precise balance of cellular component creation and breakdown.

In **2016**, **Yoshinori Ohsumi** was awarded the Nobel Prize in Physiology or Medicine for his breakthroughs in understanding the mechanisms of **autophagy**.

❖ **Autophagy Plays Greater Variety of Pathophysiological Roles in many Diseases**



(Lei and Kilonsky. 2021)

The Two Main Routes for Degrading Intracellular Proteins

Ubiquitin-proteasome pathway	Autophagy-lysosome pathways
Short-lived proteins involved in cell-cycle control or stress response are selectively marked and consecutively degraded.	They involved in the more than 90% of cellular proteins with a long half-time. Autophagy may not only be involved in degradation of long-lived proteins, but may also compromise the ubiquitin-proteasome system.

(Apel *et al*., 2009; Korolchuk *et al*., 2009)

The Three Major Forms of Autophagy

1. **Macroautophagy:** It is the autophagy-related protein (ATG)-dependent pathway. Most autophagy-related genes (ATG) contribute to autophagosome formation (Cassidy and Narita, 2022).

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2. **Microautophagy:** In micro autophagy cellular material is directly transported to the lysosome without the need for autophagosome.
3. **Chaperone mediated autophagy:** Chaperone-mediated autophagy involves the selective degradation of proteins with a specific-signal sequence called the ‘‘KFERQ’’ motif and is dependent on molecular chaperone Hsc70 (Tandia, 2011).

Function of autophagy:

Autophagy breaks down damaged or defective cytosolic organelles and proteins, acting as a quality control and waste disposal process for the cell. Autophagy-mediated breakdown also allows the cell to recycle nutrients and other substrates for use in biosynthesis and energy production—especially during periods of stress or hunger (Rangel *et al*., 2021).

MOLECULAR BASIS OF AUTOPHAGY

Process of autophagy

The autophagosome, an endomembranous organelle, is the primary morphological hallmark of autophagy. The creation of the autophagic isolation membrane (also known as autophagophore) in the cytoplasm is directed by an assembly of ATG components.

- Key regulators for phagophore includes
- Beclin 1
- Serine/threonine-protein kinase ULK1
- autophagy-related LC3 proteins
- GABARPs (gamma- aminobutyric acid receptors-associated protein)
- Omegasomes, which are phosphatidylinositol-3-phosphate (ptdIns3P) positive endoplasmic reticulum domains, form isolated crescent-shaped phagophores in the cytoplasm.
- Other cellular components involved in phagophore production include the Golgi apparatus, mitochondria, and plasma membrane-derived endosomes.
- The phagophore elongates and closes, resulting in the formation of an autophagosome, which is recognized as a double-membrane structure within the corresponding endomembrane system.
- The maturation of autophagosomes is triggered by the movement of syntaxin 17, a SNARE protein, to the outer membrane of the autophagosome. (Mizushima *et al.,* 2011)

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Regulation of autophagy

Autophagy is triggered by environmental stresses like a lack of nutrients. The process is suppressed by mTOR, the cell's nutrient-sensing kinase, and activated by AMPK, a key controller of cellular energy balance.

- Positive regulation: It is regulated by AMPK/ULK pathway
- Negative regulation: It is regulated by PI3K/AKT/mTOR pathway

AUTOPHAGY AND CANCER

Autophagy is often viewed as a "double-edged sword" in cancer because it can both promote and suppress tumor formation. Its impact varies with the cancer type, stage, and genetic background. In the early phases of tumor development, autophagy helps restrain tumor growth by removing damaged organelles, lowering oxidative stress, and preventing DNA damage. However, in later stages, cancer cells commonly increase autophagy to support their survival, proliferation, and spread. (Li *et al*., 2020)

Autophagy exhibits two contrasting roles in cancer. In the early stages, it functions as a tumor-suppressive process by breaking down damaged proteins and organelles—particularly mitochondria—thereby maintaining cellular quality control, lowering ROS levels, and limiting genomic instability. It also prevents necrotic cell death in cells that cannot undergo apoptosis, which helps reduce inflammation and restrain tumor initiation. In some situations, autophagy can even contribute directly to cell death. In contrast, during later stages of tumor progression, autophagy becomes advantageous for cancer cells. It provides nutrients under metabolic stress and supports mitochondrial function by supplying key metabolic intermediates, ultimately fostering cell survival and tumor expansion. Additionally, autophagy enables cancer cells to develop resistance to various therapies. (Avalos *et al*., 2014)

MOLECULAR REGULATION OF AUTOPHAGY IN CANCER

Many complex regulatory networks that control autophagy have been linked to several tumor- suppressive and oncogenic pathways.

1. mTOR signalling pathway and cancer
2. DAP kinase and cancer
3. P53/TP53 and cancer
4. The Ras/Raf/ERK signalling pathways and cancer

(Swamy *et al*., 2021)

1. mTOR signaling pathway and cancer

The mechanistic/mammalian target of rapamycin complex 1 (mTORC1) is the most widely

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recognized inhibitor of autophagy. This serine–threonine kinase regulates core autophagy components in response to nutrient availability and growth factors. mTORC1 suppresses autophagy by phosphorylating the ULK complex to block autophagy initiation, or by inhibiting the activity of the PtdIns3K complex 1, thereby preventing autophagosome formation. Importantly, abnormal activation of mTORC1 is strongly linked to cancer development (Saxton and Sabatini, 2017).

2. DAP kinase and cancer

The death-associated protein kinase (DAPK), part of a family of five serine/threonine kinases, functions as a tumor suppressor and regulates several cellular processes, including apoptosis and autophagy. In many tumors, DAPK expression is reduced, and its cancer-preventive role is tied to its ability to trigger cell death through both apoptotic and autophagic pathways. DAPK1 can inhibit tumor growth through p53-dependent or p53-independent apoptosis.

3. p53/TP53 and cancer

Encoded by the TP53 gene, is one of the most important tumor-suppressor proteins in the human body. It is often called *"the guardian of the genome"* because it protects cells from becoming cancerous. Missense mutations (most common): result in defective p53 protein. Some mutant p53 proteins gain oncogenic "gain-of-function" properties—promoting invasion, metastasis, and therapy resistance.

4. The Ras/Raf/ERK signalling pathways and cancer

The Ras/Raf/extracellular signal-regulated kinase (ERK) signalling pathway is critical for practically all cell activities and governs various anti-proliferative processes such as apoptosis, autophagy, and senescence. ERK activity can increase apoptotic pathways by inducing mitochondrial cytochrome c release or caspase-8 activation, as well as persistent cell cycle arrest and autophagic vacuolization. The two ERK isoforms, ERK2 and ERK1, are members of the mitogen-activated protein kinase (MAPK) family. These enzymes are activated by a phosphorylation cascade, which amplifies and transfer signals from the cell membrane to the nucleus.

When the receptor is activated, the membrane-bound Guanosine-5'-triphosphate (GTP)-loaded Ras kinase forms a complex with Raf kinase and becomes active. Raf then phosphorylates MAPK 1 and 2, which activates ERK1/2 via phosphorylation. Eventually, active ERKs regulate the phosphorylation of several cytoplasmic and nuclear substrates involved in critical cellular functions. Mutations in Ras or Raf frequently cause deregulation

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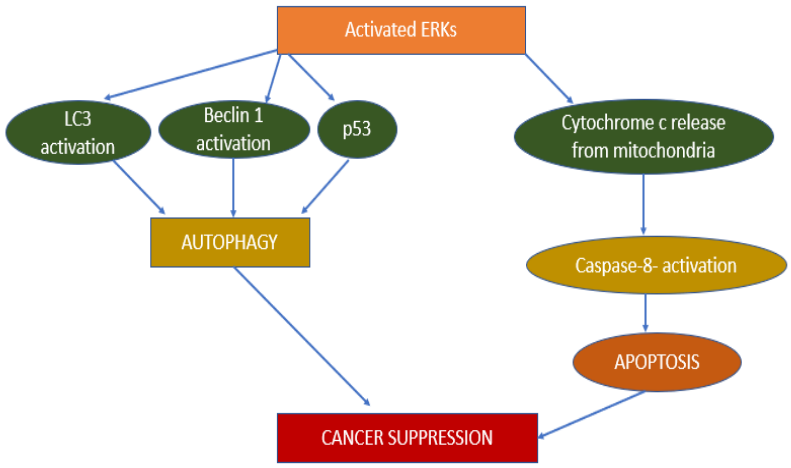
of the Ras/Raf/ERK pathway in cancers, which is especially seen in malignant melanoma, pancreatic, intestinal, and thyroid malignancies.

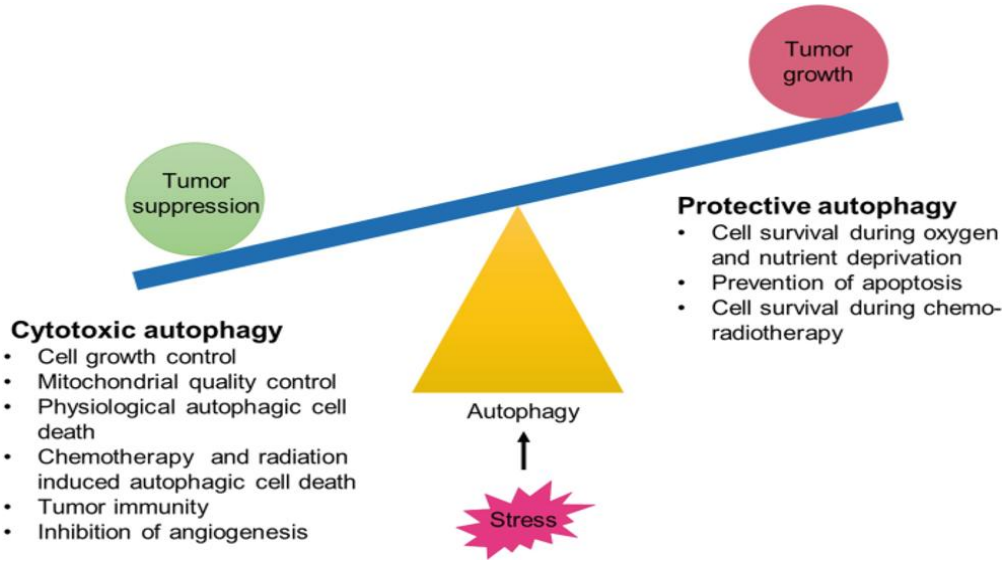
ERK activation is also linked to autophagic cell death in response to stressors such as amino acid deficiency. The ERK-dependent mechanism activates autophagy by inducing both LC3 and Beclin 1. p53 is also connected with ERK-regulated autophagy induction, as ERK facilitates p53 phosphorylation, which leads to p53-induced autophagy (Swamy *et al*., 2021)

5. ERK Signalling Pathways and Cancer



(Swamy *et al*., 2021)

➢ ROLE OF AUTOPHAGY IN TUMOR SUPPRESSION AND TUMOR GROWTH



(Mittal *et al.,* 2020)

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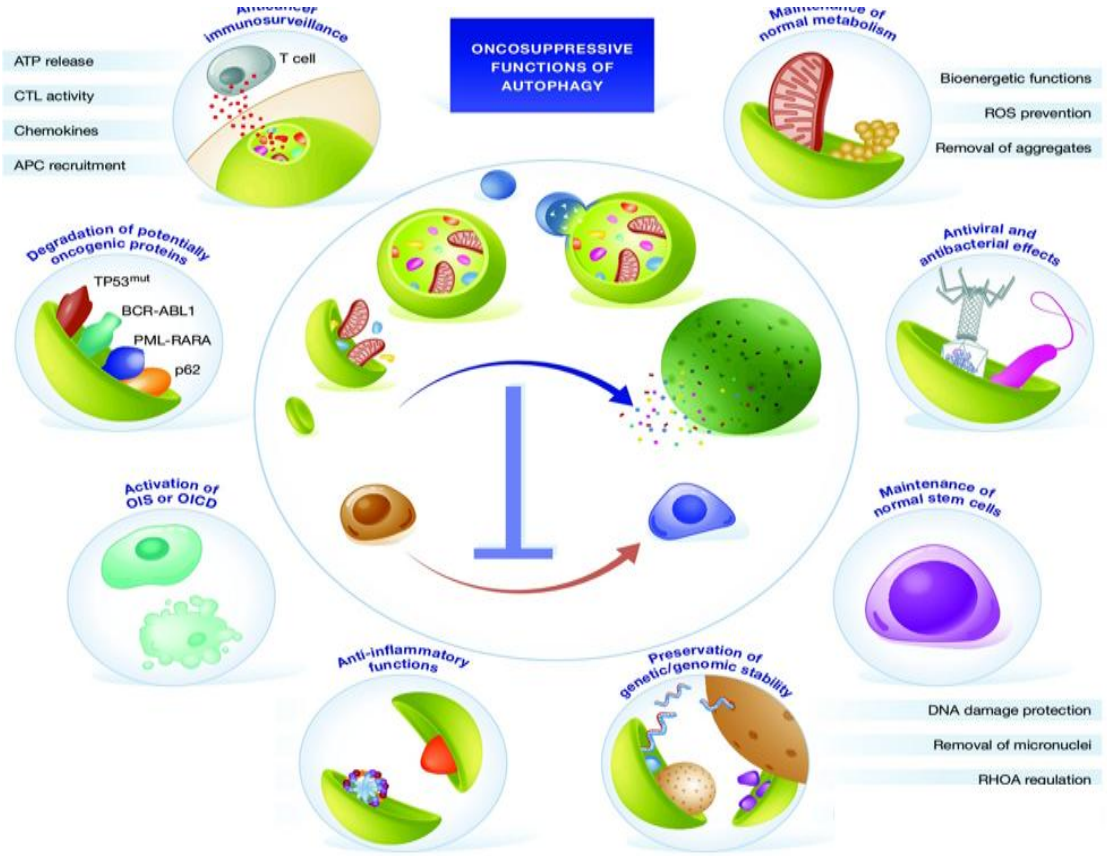
Autophagy and Tumor Suppression:

The **BECN1 gene**, a key regulator of autophagy, serves as an essential link between autophagic processes and tumor suppression. Loss of BECN1 function enhances tumorigenic potential, whereas reintroduction of BECN1 expression has been shown to inhibit tumor growth. Additionally, autophagy suppresses **Ras-driven epithelial tumorigenesis** by preventing the build-up of reactive oxygen species (ROS). Beyond this, autophagy limits the expansion of transformed cells by promoting **oncogene-induced senescence**, a state in which cells remain metabolically active but permanently withdraw from the cell cycle.

Autophagy also contributes to tumor suppression through its ability to trigger **autophagic cell death**. This form of death, classified as **type II programmed cell death**, is marked by extensive cytoplasmic vacuolization and elevated autophagic activity. Unlike apoptosis, autophagic cell death proceeds without caspase involvement and does not elicit the inflammatory responses typical of necrosis, which could otherwise support tumor development. Although frequently observed during embryonic development, autophagic cell death also occurs in post-developmental contexts. (Bishop and Bradshaw, 2018)



(Galluzzi *et al*., 2015)

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Autophagy and Tumor Initiation

Impaired autophagy can result in the buildup of **p62**, which contributes to tumor initiation. Elevated p62 levels can activate various oncogenic signaling pathways that drive cellular proliferation, enhance oxidative stress, and promote inflammation. These effects collectively foster genomic instability and persistent tissue damage, thereby facilitating spontaneous tumor development. (Bishop and Bradshaw, 2018)

p62, also known as **sequestosome 1**, is a selective autophagy substrate. Under normal autophagic conditions, p62 contains a short **LC3-interacting region (LIR)** that enables direct binding to LC3, leading to its targeted degradation through the autophagy pathway. When autophagy is impaired, p62 is no longer efficiently degraded, resulting in its accumulation—a phenomenon frequently observed in human cancers. Consequently, elevated p62 levels are widely used as a biomarker for autophagy inhibition or defects in autophagic flux. Aberrant p62 accumulation has been reported in gastrointestinal tumors, prostate cancer, hepatocellular carcinoma, breast cancer, and lung adenocarcinoma, supporting the view that p62 buildup contributes to tumor progression and that autophagy suppresses tumorigenesis in part by limiting p62 accumulation. (Komatsu *et al*., 2012)

Autophagy and Tumor Progression

The "autophagy switch" refers to the paradoxical transition from tumor suppressor to tumor promoter. When oxygen and nutrients are limited early in tumor growth, cancer cells resist metabolic stress by activating autophagy, allowing them to survive.

Autophagy is induced during hypoxia via the hypoxia-inducible factor (HIF-1) and AMPK signaling pathways. HIF-1 increases BH3, disrupting the connection between Beclin 1 and Bcl-2, allowing Beclin 1 to trigger autophagy. (Amaravadi *et al*., 2016)

Under stressful conditions, autophagy plays an important role in the onset of tumor dormancy. Tumor cell dormancy leads to tumor recurrence and development, as well as patient morbidity and mortality. (Gomis and Gawrzak, 2016)

Role of Autophagy in Anoikis

Autophagy and anoikis could play important roles during metastasis. Autophagy and anoikis can help normal epithelial cells adapt to external stimuli like ECM separation by preserving cellular homeostasis.

However, in initial cancers, autophagy may act as a pro-metastatic role, promoting metastasis by allowing tumor cells to resist anoikis and enter dormancy. (Taddei *et al*., 2011)

➢ Autophagy and Cancer Metastasis

As tumors proceed to higher stages of malignancy, tumor cells can evolve ways to commence local invasion and increase motility, culminating in migration to distant

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regions. This is known as cancer metastasis, which is a characteristic of carcinogenesis. The role of autophagy in cancer metastasis is complex, as it performs both pro- and anti-metastatic roles depending on the demands of the metastatic process.

Autophagy combats environmental and cellular stressors during metastasis. Autophagy reduces tumor cell necrosis. Tumor necrosis is related with macrophage infiltration. Macrophages and other cells in an inflammatory infiltrate create cytokines and chemokines, which affect cell proliferation and angiogenesis. (Degenhardt *et al*., 2006)

The AMP-activated protein kinase (AMPK) mediates TRAIL-induced autophagy by inhibiting mammalian target of rapamycin complex 1, a powerful autophagy inhibitor. Autophagy is enhanced in cancer cells that are resistant to the metastasis suppressor TRAIL, resulting in cancer metastases. (Martin *et al.,* 2008)

CONCLUSIONS

Autophagy is a self-digestive process that is essential for maintaining metabolic and genetic cellular equilibrium. There are three types of autophagic pathways: macroautophagy, microautophagy, and chaperone-mediated autophagy.

Autophagy flow begins with the creation of the phagophore and ends with the removal of autophagosomal cargo. Autophagy plays a dual role by encouraging and restraining tumors, depending on the stage and kind of the tumor, as well as cell types.

Autophagy acts as a tumor suppressor in the early stages of cancer progression; yet, in the later stages, autophagy promotes cancer growth and metastasis.Many cancer-related signaling pathways are linked to autophagy on numerous levels, demonstrating autophagy's dynamic role in cancer.

FUTURE PROSPECTS

The most serious clinical concern is frequent tumor development and cancer recurrence following treatment, which is primarily attributable to therapeutic resistance. s In the near future, standard cancer treatment combined with autophagy activity modulation, increasing or inhibiting via autophagy inducers or inhibitors based on tumorigenesis and cancer stage, could be regarded a promising anticancer therapy. More research is needed to understand and clarify how autophagy influences cancer development and treatment.

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