

Autophagy, apoptosis, and cellular homeostasis: A physiological perspective

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ARTICLE INFO

Received: 01 July 2026

Accepted: 29 July 2026

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Keywords:

Autophagy, Apoptosis, Cellular homeostasis, Cell signaling, Physiology, Programmed cell death.

ABSTRACT

Cellular homeostasis is a basic mechanism that keeps biological processes stable by balancing cell death and survival. The two main, interrelated processes that control this dynamic are autophagy and apoptosis. While apoptosis serves as a planned removal strategy for cells suffering irreversible damage, autophagy promotes stress adaption by preserving the quality of intracellular components. This review aimed to analyze the functional relationship between autophagy, apoptosis, and cellular homeostasis from a physiological perspective, emphasizing the molecular mechanisms underlying the interaction of these two processes. Based on a synthesis of the most recent scientific literature from significant biomedical databases, this article is organized using a narrative review methodology. The findings demonstrate that autophagy and apoptosis are connected by a complex regulatory network that includes the mTOR, AMPK, p53, and Bcl-2 protein family pathways. Depending on the degree and duration of stress, this crosstalk enables cells to transition between executive and adaptive systems. Additionally, through controlling energy, ROS, and the release of pro-apoptotic substances, mitochondria serve as signal integration hubs that dictate the course of cellular reactions. One important factor in preserving cellular homeostasis is the ratio of autophagy to apoptosis. This system's dysregulation plays a major role in the pathophysiology of many illnesses, such as cancer and neurological conditions. The development of therapeutic approaches based on precise manipulation of cellular pathways is anticipated to be aided by a deeper comprehension of these integrative mechanisms.

Introduction

The processes that preserve fundamental cell functioning in the face of changes in both internal and external environments are the core focus of cellular physiology (Long *et al.*, 2025). Cellular homeostasis, or the capacity of cells to maintain constant internal conditions through the dynamic regulation of several biochemical and molecular processes, is a key idea in this discipline (Wang and Qin, 2022). Throughout the cell's life cycle, an adaptive balance between synthesis, degradation, and signaling responses results in homeostasis, which is not static (Alber and Suter, 2019).

The equilibrium between cell survival and death is essential for preserving homeostasis (Gudipaty *et al.*, 2018). In addition to being necessary for survival, cells must also be able to manage their own death when they sustain irreversible damage (Hajibabaie *et al.*, 2023). Maintaining tissue integrity, avoiding the buildup of defective cells, and guaranteeing coordinated regeneration all depend on this equilibrium (Kulkarni *et al.*, 2016). Tissue deterioration, cancer, and chronic inflammatory illnesses are just a few of the clinical ailments that can result from disruption of this system (Armstrong *et al.*, 2018).

Autophagy and apoptosis are two important biological mechanisms that control this equilibrium (Wu *et al.*, 2014). An internal disintegration process called autophagy serves as a recycling system for cellular constituents, such as damaged organelles and aggregated proteins (Gómez-Virgilio *et al.*, 2022). In situations where nutrients are scarce or the environment is stressful, cells can use this process to sustain their energy source and lessen metabolic stress (He, 2022). Contrarily, apoptosis is a

type of controlled cell death that doesn't cause an inflammatory reaction (Elmore, 2007). This process contributes to the removal of cells that are no longer required in a particular physiological environment, infected, or genetically damaged (Mustafa *et al.*, 2024).

Even while autophagy and apoptosis have been well investigated separately, little is known about how they interact and integrate into cellular homeostasis (Gump and Thorburn, 2011). Several studies show that these two processes are linked by a complex molecular regulatory network rather than functioning independently (Xi *et al.*, 2022; Shao *et al.*, 2025). The mechanistic target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) signaling pathways, together with regulatory proteins including the Bcl-2 family and p53, are known to function as convergence sites connecting survival and death signaling systems (Hindupur *et al.*, 2015). However, research on the kinetics of transitioning between autophagy and apoptosis as well as the variables influencing which pathway predominates are still underway (Kakkar *et al.*, 2026).

Furthermore, scientists still don't fully understand how cells combine different stress signals to decide between elimination and adaptation. Autophagy's reciprocal link with apoptosis and its contextual role as a protective mechanism that can turn pro-death under specific circumstances show a regulatory complexity that is yet not fully understood systematically (Ahsan *et al.*, 2024).

Against this background, this review aimed to provide a comprehensive overview of the mechanisms of autophagy and apoptosis from a cellular physiology perspective, focusing on their roles in maintaining homeostasis. The molecular underpinnings of each activity, their regulatory relationships, and the physiologic and pathological consequences of

imbalances in these systems are all included in the debate. It is therefore anticipated that this article will offer a comprehensive grasp of the dynamics of cell life and death in relation to physiology and illness.

Autophagy in cell physiology

Autophagy is an evolutionarily conserved intracellular degradation mechanism that plays an important role in maintaining cell homeostasis by controlling the quality of proteins and organelles under physiological and stressful conditions.

Definition and basic mechanisms of autophagy

Through the breakdown and recycling of intracellular components, autophagy, an evolutionarily conserved catabolic mechanism, preserves cellular homeostasis (You *et al.*, 2025). Autophagy functions physiologically as an adaptive system that enables cells to react to stressful situations such as organelle damage, especially mitochondria, hypoxia, the build-up of misfolded proteins, and food restriction (Khandia *et al.*, 2019). This mechanism is necessary to preserve the integrity of the cell's organelles and proteome in addition to being degradative (Murrow and Debnath, 2013).

Generally speaking, there are three primary forms of autophagy: macroautophagy, also known as autophagy, microautophagy, and chaperone-mediated autophagy (CMA) (Parzych and Klionsky, 2014). In the context of cell physiology, macroautophagy is the most prevalent and extensively researched kind of autophagy (Yasasilka and Lee, 2024). The development of double-membrane vesicles known as autophagosomes, which separate cytoplasmic material and subsequently merge with lysosomes to create autolysosomes, where enzymatic degradation takes place, is a hallmark of macroautophagy (Ke, 2024a).

A complicated signaling regulation network, mainly involving energy and nutrition sensing systems like mTOR and AMPK, controls the onset of autophagy (Meijer *et al.*, 2015). When there are sufficient nutrients, mTOR is active and inhibits the start of autophagy (Deleyto-Seldas and Efeyan, 2021). On the other hand, when there is a lack of energy, AMPK activity suppresses mTOR and causes the Unc-51 Like Autophagy Activating Kinase 1 (ULK1) complex to form, which is the first stage of autophagosome formation (Akers *et al.*, 2012).

The Beclin-1–Vps34 (class III PI3K complex) complex is involved in the autophagosome nucleation stage and contributes to the development of phagophore membranes (McKnight and Zhenyu, 2013). The ATG12–ATG5–ATG16L1 complex and the transformation of LC3-I to LC3-II, which binds to the autophagosomal membrane and is frequently employed as a measure of autophagy activity, are two ubiquitin-like conjugation systems that subsequently mediate membrane expansion and autophagosome elongation (Otomo *et al.*, 2013).

The autophagosome and lysosome fuse at the end of this process to form the autolysosome, where hydrolytic enzymes break down the trapped components into simple molecules like amino acids, fatty acids, and nucleotides that can be used again for cellular metabolism (Ke, 2024b). Therefore, autophagy is an essential recycling mechanism for preserving cell viability under both physiological and pathological stress, in addition to being a method for disposing of cellular waste (Shim and Liton, 2022).

Main molecular pathways of autophagy (mTOR, AMPK, and Beclin-1 Complex)

A molecular signaling network that incorporates cellular stress, food availability, and energy state controls autophagy (Singh, 2012). mTOR, AMPK, and the Beclin-1 complex—which binds to class III phosphoinositide 3-kinase (PI3K)—are three essential elements that are essential to this control (Wang *et al.*, 2019).

One important negative regulator of autophagy is mTOR (Jung *et al.*, 2010). By phosphorylating ULK1, mTOR Complex 1 (mTORC1) inhibits autophagy initiation under normal settings with sufficient food supply, hence preventing the production of autophagosomes (Park *et al.*, 2016). Through the PI3K/AKT pathway, which increases the anabolic state of the cell and inhibits intracellular breakdown processes, cell growth cues like insulin and growth hormones also affect mTOR activity (Omoekan *et al.*, 2024).

On the other hand, when the AMP/ATP ratio rises, indicating an energy shortfall, AMPK functions as a cellular energy sensor (Gowans and Hardie, 2014). Direct suppression of mTORC1 and direct phosphorylation of the ULK1 complex, which permits the start of the autophagic apparatus, are the two primary ways that AMPK activation triggers autophagy (Smiles *et al.*, 2024). As a result, AMPK functions as a metabolic switch that causes cells to transition from an anabolic to an adaptive catabolic state (Viollet *et al.*, 2009).

The activity of the Beclin-1–Vps34 complex (class III PI3K complex) is also crucial for the early phases of autophagosome formation (Morris *et al.*, 2015). Beclin-1 serves as a scaffolding platform that controls the recruitment of additional autophagy proteins and starts the nucleation of phagophore membranes (Tran *et al.*, 2021). This complex's activity can be influenced by interactions with regulatory proteins like Bcl-2, which can directly bind to Beclin-1 to block it and link autophagy regulation to the apoptosis pathway (Baek *et al.*, 2025).

A dynamic and contextual autophagy regulation mechanism is shown in the integration of mTOR, AMPK, and Beclin-1 (Tamargo-Gómez and Mariño, 2018). Beclin-1 functions as an execution control point during the initial phases of autophagic vesicle production, whilst mTOR and AMPK function as opposing energy state sensors (Cao *et al.*, 2024). These three pathways work together to maintain a balance between cell survival and the breakdown of superfluous intracellular components by ensuring that autophagy activation happens promptly and in accordance with the physiological needs of the cell (Kang *et al.*, 2011). The sequential activation of autophagy, from cellular stress sensing to autolysosomal degradation and metabolite recycling, is illustrated in Figure 1.

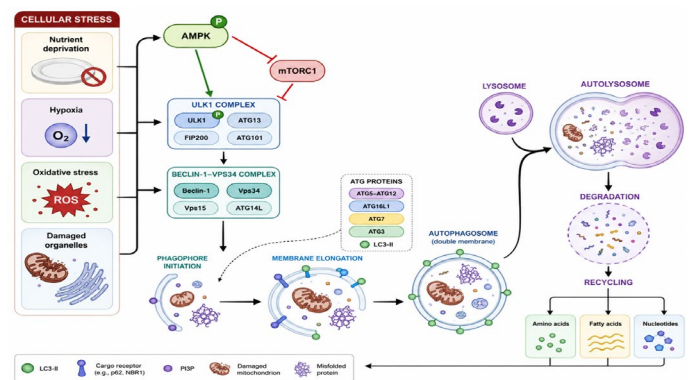


Figure 1. Core molecular mechanism of autophagy in cellular stress adaptation.

The role of autophagy in cellular stress adaptation

One important adaptive mechanism that helps cells survive under a variety of physiological and pathological stress circumstances is autophagy (Moloudizargari *et al.*, 2017). A coordinated reaction to disturbances in internal homeostasis, such as nutritional stress, hypoxia, oxidative stress, and the buildup of damaged cellular components, is reflected in the activation of this mechanism (Liu *et al.*, 2025).

By breaking down cytoplasmic components into fundamental metabolites like amino acids and fatty acids, autophagy offers a substitute energy source when nutrients are scarce (Singh and Cuervo, 2011). The mitochondrial oxidative pathway then uses these molecules to continue producing adenosine triphosphate (ATP) (Nolfi-Donagan *et al.*, 2020). Therefore, autophagy serves as a metabolic survival strategy that enables

cells to adjust to changes in the availability of energy (Anselme *et al.*, 2025).

By decreasing energy needs and removing malfunctioning organelles, especially mitochondria, autophagy contributes to lowering the metabolic load of cells under hypoxic conditions (Li *et al.*, 2022). Additionally, by lowering the overproduction of reactive oxygen species (ROS), this mechanism helps shield cellular macromolecules from additional oxidative damage (Manful *et al.*, 2025).

Moreover, autophagy is essential for the reaction to proteotoxic stress (Cheng *et al.*, 2023). Organelle failure and cellular disruption can result from the buildup of misfolded proteins or protein aggregates (Moreno-Gonzalez and Soto, 2011). Cells are able to identify and break down these protein clumps through the selective autophagy mechanism, which preserves the quality of the proteome and stops the activation of cell death pathways (Zaffagnini and Martens, 2016).

Mitophagy becomes an essential selective mechanism when organelles, especially mitochondria, are damaged (Ding and Yin, 2012). In order to preserve metabolic efficiency and stop unchecked apoptosis, mitophagy makes sure that mitochondria that undergo membrane depolarization or generate excess ROS are eliminated (Wang *et al.*, 2023).

Autophagy in physiological and pathological conditions

Autophagy serves as a basal cell quality management system to provide the best possible turnover of intracellular components under physiological settings (Sridhar *et al.*, 2012). Without interfering with regular cellular activity, this mechanism promotes organelle renewal, protein quality control, and metabolic balance regulation (Hampton and Garza, 2009). Basal autophagy activity is essential for preserving effective cell function and structural integrity in tissues with high metabolic activity, such as the liver, muscles, and nervous system (Czaja *et al.*, 2013).

By removing particular organelles and proteins that are no longer required, autophagy also aids in cellular remodeling during embryonic development and cell differentiation (Levine and Kroemer, 2008). This function implies that autophagy has a role in controlling the dynamics of tissue development in addition to providing protection (Xie *et al.*, 2025). Moreover, elevated autophagy activity under specific physiological circumstances, like fasting or exercise, indicates metabolic modifications that enable the effective reuse of intracellular resources (Zhou *et al.*, 2025).

Depending on the level and setting of activation, autophagy dysregulation in pathological settings can lead to a variety of illnesses (Hein *et al.*, 2025). Reduced autophagy activity is frequently linked to the buildup of harmful proteins and damage to organelles, which can lead to the onset of neurodegenerative illnesses including Parkinson's and Alzheimer's (Lior *et al.*, 2025). Proteostatic equilibrium is disrupted and persistent cellular stress is elevated when cells are unable to break down damaged components (Shukla and Narayan, 2025).

On the other hand, in some circumstances, excessive autophagy activation might promote the survival of cells that would normally be eliminated, especially in cancer (Patergnani *et al.*, 2021). Autophagy can serve as a pro-survival strategy in this situation, allowing tumor cells to endure adverse microenvironments including hypoxia and nutritional shortage (Zhang *et al.*, 2025a). This implies that autophagy can function as a tumor-supporting mechanism in later stages after initially acting as a tumor-suppressor process (Jalali *et al.*, 2025).

Additionally, autophagy contributes to host defense mechanisms in infectious disorders by degrading intracellular pathogens through the process of xenophagy (Paulus and Xavier, 2015). Nonetheless, some harmful microbes have developed strategies to avoid or even take advantage of the autophagy system in order to survive (Deretic and Levine, 2009). This demonstrates that autophagy is a very dynamic process with contextual roles that vary depending on the cellular circumstances and stress type experienced (Yuk *et al.*, 2012).

Apoptosis as a controlled cell death program

Apoptosis is a form of programmed cell death that occurs in a coordinated manner and is essential in maintaining tissue homeostasis by eliminating cells that are damaged or no longer physiologically needed.

Definition and characteristics of apoptosis

Apoptosis is a type of controlled, energy-demanding programmed cell death that aims to preserve tissue homeostasis without inducing an overwhelming inflammatory response (Zhang *et al.*, 2025b). This process is a basic mechanism in cell physiology that contributes to the establishment and maintenance of tissue structure during organism development, the regulation of cell quantity, and the elimination of cells with damaged deoxyribonucleic acid (DNA) (Elmore, 2007).

Apoptosis is distinguished morphologically by a number of unique and well-coordinated cellular alterations (Mustafa *et al.*, 2024). Cell shrinkage, increased cytoplasmic density, and chromatin condensation along the nuclear membrane (pyknosis) are among the initial steps (Kari *et al.*, 2022). As the process continues on, the cell separates into apoptotic entities that are still covered by an unbroken plasma membrane after the nucleus fragments (karyorrhexis) (Prokhorova *et al.*, 2015).

Until the very end, the plasma membrane's integrity is preserved, preventing the leakage of intracellular materials into the extracellular environment (Ammendolia *et al.*, 2021). This sets apoptosis apart from necrosis, which is typically defined by the rupture of membranes and the triggering of an inflammatory reaction (Hu and Zheng, 2008). A clean, non-inflammatory clearance procedure follows the recognition and phagocytosis of apoptotic materials by phagocytes or nearby cells via efferocytosis (Liu *et al.*, 2024).

In terms of biochemistry, apoptosis entails the successive activation of a family of particular protease enzymes known as caspases (Nadendla *et al.*, 2025). Important structural and regulatory proteins, such as nuclear proteins, cytoskeleton components, and DNA repair factors, are degraded as a result of this activation (Dos Santos and Toseland, 2021). The intrinsic pathway (mitochondria-mediated method) and the extrinsic pathway (death receptor-mediated pathway), which both converge on the activation of executor caspases, are the two primary processes that make up the apoptotic pathway (Gupta *et al.*, 2009).

The biological role of apoptosis as a cellular quality control process is reflected in its essential features, which go beyond morphological and biochemical alterations (Renehan *et al.*, 2001). At the organismal level, this mechanism guarantees the removal of potentially dangerous cells, preserves the equilibrium between cell division and death, and promotes the structural and functional stability of tissues (Mustafa *et al.*, 2024).

Intrinsic and extrinsic pathways of apoptosis

The intrinsic (mitochondrial-dependent) and extrinsic (death receptor-mediated) pathways are the two primary, interrelated mechanisms that regulate apoptosis (Khosravi-Far and Esposti, 2004). Although the initial triggers of these two pathways are different, they both result in the activation of executor caspases, which carry out cell death (Galluzzi *et al.*, 2008).

Different types of intracellular stress, including as DNA damage, oxidative stress, hypoxia, and disruption of calcium and protein homeostasis, trigger the intrinsic route (Lemanowicz *et al.*, 2026). The Bcl-2 family of proteins, which are important modulators of mitochondrial membrane permeability, mediates the reaction to these circumstances (Shamas-Din *et al.*, 2013). Increased mitochondrial outer membrane permeability (MOMP) results from an imbalance between pro-apoptotic proteins (like Bax and Bak) and anti-apoptotic proteins (like Bcl-2 and Bcl-xL) (Qian *et al.*, 2022). This causes cytochrome c to be released into the cytosol, where it combines with ATP and Apaf-1 to form the apoptosome (Suhaili *et al.*,

2017). The principal effectors of apoptosis, caspase-3 and caspase-7, are activated after caspase-9, the initiator caspase, is activated by this complex (Brentnall *et al.*, 2013).

On the other hand, extracellular ligands engage with cell surface death receptors to initiate the extrinsic route (Ashkenazi, 2015). TNF receptor 1 (TNFR1), TRAIL receptors, and Fas (CD95) are some of these receptors (Green, 2022). Adaptor proteins like Fas-associated death domain protein (FADD) are recruited when ligands like TNF- α or Fas ligand (FasL) bind to their receptors, causing receptor trimerization (Guicciardi and Gores, 2009). The death-inducing signaling complex (DISC), which is formed by this complex, activates either caspase-8 or caspase-10 as initiator caspases (Gnesutta and Minden, 2003). Following this caspase activation, executioner caspases are either directly activated or activated through mitochondrial signal amplification via the cleavage of the Bid protein to tBid (Shelton *et al.*, 2009).

There are important sites of contact between the two pathways despite their different activation processes, mainly because of the extrinsic pathway's use of mitochondria as signal amplifiers (Wang and Youle, 2009). Cells can react to different death stimuli more effectively and cooperatively thanks to this integration (Lu *et al.*, 2024). Therefore, in both normal and pathological settings, a cell's choice to survive or undergo apoptosis depends on the regulatory balance between the intrinsic and extrinsic pathways (Raducka-Jaszul *et al.*, 2020).

Protein regulation (Bcl-2 family and caspase cascade)

The Bcl-2 protein family and the proteolytic caspase system interact dynamically to regulate apoptosis at the molecular level (Hussar, 2022). These two elements combine pro-survival and pro-apoptotic signals to establish a core axis that defines a cell's commitment to programmed death (Burlacu, 2003).

A key modulator of the intrinsic apoptosis process, the Bcl-2 protein family regulates the permeability of the outer mitochondrial membrane (Qian *et al.*, 2022). This family includes pro-apoptotic proteins like Bax, Bak, and the BH3-only family (e.g., Bid, Bad, Bim, Puma, and Noxa) as well as anti-apoptotic proteins like Bcl-2, Bcl-xL, and Mcl-1 (Vogler *et al.*, 2025). The stability of the mitochondrial membrane is determined by the ratio of expression and activity between these two divisions (Uren *et al.*, 2005). Pro-apoptotic factors such as cytochrome c, Smac/DIABLO, and AIF are released into the cytosol when pro-apoptotic proteins are activated, causing Bax/Bak oligomerization on the mitochondrial membrane (Adrain *et al.*, 2001).

The main way that apoptosis is carried out is by the caspase cascade, which uses multistep proteolytic activation (Parrish *et al.*, 2013). Caspases are divided into two categories: executor caspases (like caspase-3, -6, and -7) and initiator caspases (like caspase-8, -9, and -10) (McIlwain *et al.*, 2013). Initiator caspases are activated by the development of particular multiprotein complexes, such as the DISC in the extrinsic pathway or the apoptosome in the intrinsic pathway (Park, 2012). When initiator caspases are active, they cleave and trigger executor caspases, which subsequently break down a range of cellular regulators and structural substrates (Boatright and Salvesen, 2003).

Nuclear lamins, cytoskeletal proteins, poly(ADP-ribose) polymerase-1 (PARP-1), and other nuclear and cytoplasmic proteins are all broken down by caspase-3, the main executor caspase (Frolova *et al.*, 2023). DNA fragmentation, chromatin condensation, and the creation of apoptotic bodies are among the morphological alterations typical of apoptosis brought on by this proteolytic activity (He *et al.*, 2009).

The relationship between the caspase cascade and the Bcl-2 family points to a crucial mitochondrial control point (Hussar, 2022). Cellular stress signals and Bax/Bak activation are linked by BH3-only proteins, although anti-apoptotic Bcl-2 proteins are important inhibitors of this process (Lomonosova and Chinnadurai, 2008). Therefore, this regulatory mechanism produces precise life-or-death decisions by integrating cel-

lular inputs from metabolic, genotoxic, and extracellular environmental factors in addition to determining the activation of apoptosis (MacFarlane and Williams, 2004).

The role of apoptosis in tissue development and homeostasis

By removing superfluous, redundant, or possibly dangerous cells, apoptosis plays a crucial part in controlling embryonic biology and preserving tissue homeostasis (Singh *et al.*, 2019). By assuring accurate tissue structure construction during morphogenesis and preserving cell population balance in mature tissues, this process functions as a programmed cellular selection mechanism (Gagliardi and Primo, 2019).

By removing temporary cells, apoptosis aids in the evolution of organ architecture during embryonic development (Brill *et al.*, 1999). The separation of digits in vertebrate limbs, when interdigital tissue is specifically removed to create distinct digit structures, is a well-known example (Kaltcheva *et al.*, 2016). Additionally, apoptosis contributes to the nervous system's patterning by removing extra neurons during neurogenesis in order to maximize synaptic connection and signal transmission efficiency (Hollville *et al.*, 2019).

Apoptosis serves to preserve a balance between cell division and death in the setting of adult tissue homeostasis (Gavrilescu and Denkers, 2003). Apoptosis guarantees the systematic removal of senescent, injured, or altered cells without jeopardizing the structural integrity of high-turnover tissues including the intestinal epithelium, epidermis, and hematopoietic system (Salminen *et al.*, 2011). In order to preserve long-term cell number stability, this mechanism cooperates with stem cell growth (Mustafa *et al.*, 2024).

By removing cells with irreversible DNA damage or compromised metabolic performance, apoptosis also contributes to cellular quality control (Zhang *et al.*, 2025c). In these cells, the apoptotic pathway is activated to stop the accumulation of mutations that can cause neoplastic transformation (Solano-Gálvez *et al.*, 2018). Therefore, apoptosis uses tumor suppressor mechanisms to prevent the development of cancer (Gielecińska *et al.*, 2023).

Additionally, controlling the immune response depends on the balance of apoptosis (Hildeman *et al.*, 2007). One important strategy for preventing autoimmunity is the thymus's negative selection process, which eliminates autoreactive cells (Shirafkan *et al.*, 2024). Additionally, if the pathogen is successfully eradicated, effector immune cells must undergo apoptosis in order to resolve the inflammatory response and prevent tissue damage from protracted inflammation (Chen *et al.*, 2017).

Cellular homeostasis: an integrative concept

Cellular homeostasis is a dynamic regulatory state that enables cells to maintain internal stability through coordinated control of metabolic, signaling, and structural processes in response to environmental fluctuations.

Definition of cellular homeostasis

A state of dynamic equilibrium known as cellular homeostasis enables cells to preserve their internal stability in the face of alterations in the extracellular environment (Müller *et al.*, 2025). The ability of the cell to continuously adapt to physiological fluctuations through the coordinated regulation of numerous biological processes, such as metabolism, biomolecule synthesis and degradation, ion transport, and responses to stress signals, is what this concept refers to rather than a static state (Choi *et al.*, 2025).

In order to maintain intracellular parameters including pH, ion concentration, redox status, energy availability, and protein integrity, cellular homeostasis is essentially accomplished through the integration of sensory, signal transduction, and effector systems (Hajjar and Zhou, 2023).

Important signaling pathways including mechanistic target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), and mitogen-activated protein kinase (MAPK) serve as a bridge between the cell's adaptive responses and the external environment in this intricate regulatory network (Soliman, 2013).

The equilibrium between anabolic and catabolic processes is also crucial for maintaining homeostasis (Wu *et al.*, 2024). The breakdown of damaged or unnecessary cellular components, which is facilitated by processes like autophagy and the proteasome, must be balanced with the activity of biomolecule creation (Wong and Cuervo, 2010). Cellular stress can build up as a result of imbalances in various areas, which can upset the internal integrity of the cell (Poljšak and Milisav, 2012).

Additionally, cellular homeostasis includes the strict regulation of proliferation, differentiation, and programmed cell death in order to govern the dynamics of cell survival (Rudin and Thompson, 1997). While autophagy functions as an adaptive system to preserve cell viability in challenging situations, apoptosis is a method for removing cells that are no longer functional (Bata and Cosford, 2021). The way these two processes interact illustrates how homeostasis is a flexible but regulated system (Shliapina *et al.*, 2021).

Balance between survival and death signaling

One important factor in preserving cellular homeostasis is the ratio of survival to death signaling (Valls and Esposito, 2022). The integration of several signaling pathways that react to intracellular damage, metabolic state, and microenvironmental factors determines whether a cell will survive or undergo programmed death (Kist and Vucic, 2021).

Pro-growth pathways including phosphoinositide 3-kinase / protein kinase B (PI3K/AKT), mitogen-activated protein kinase / extracellular signal-regulated kinase (MAPK/ERK), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) are typically activated to mediate survival signals (Hamouda and Essafi-Benkhadir, 2023). By phosphorylating downstream targets that block pro-apoptotic proteins like Bad and boosting mTOR activity to promote cell biosynthesis and growth, the PI3K/AKT pathway plays a critical role in boosting cell viability (Roy *et al.*, 2023). While NF- κ B promotes the production of anti-apoptotic genes including Bcl-2, c-IAPs, and survivin, increasing cell resistance to death stimuli, the MAPK/ERK pathway aids in cell proliferation and differentiation (Guo *et al.*, 2024).

On the other hand, a number of stresses, including growth factor deficiency, redox imbalance, DNA damage, and chronic inflammation, trigger death signals (Selvaraj *et al.*, 2025). Increased activity of pro-apoptotic Bcl-2 family proteins, caspase activation, and the production of stress mediators like p53 are all components of this pathway's activation (Singh *et al.*, 2019). Depending on the degree of damage, the p53 protein acts as a central regulator that can guide cells toward apoptosis, DNA repair, or cell cycle arrest (Ozaki and Nakagawara, 2011).

These two systems interact in a competitive and integrated manner (Ozaki and Nakagawara, 2011). The predominance of survival signals under normal physiological settings guarantees sustained cell function and regulated proliferation (Gupta *et al.*, 2010). However, the balance shifts in favor of the activation of death signaling pathways as a defensive strategy to stop aberrant cell propagation when the accumulation of damage surpasses a tolerance threshold (He *et al.*, 2024).

Additionally, connections between the mTOR pathway and autophagy, as well as cross-modulation between NF- κ B and caspases, are examples of cross-regulatory processes that support this dynamic balance (Xu *et al.*, 2026). For instance, autophagy may serve as a survival strategy during the initial phases of stress, but it may also trigger apoptosis in more severe circumstances (Mariño *et al.*, 2014). This finding implies that contextually integrated signal gradients, rather than binary decisions, are the cause of cell decisions (Ullman *et al.*, 2008).

Interaction of autophagy and apoptosis in homeostasis

Apoptosis and autophagy are two basic processes that work together to control cellular homeostasis (Fan and Zong, 2013). They have different but related roles in deciding the fate of cells (Thorburn, 2008). While apoptosis functions as a planned elimination strategy when cell damage is irreversible, autophagy often acts as an adaptive mechanism that preserves cell life through the breakdown of damaged intracellular components (Hsieh *et al.*, 2009).

These two processes have a link that is controlled by overlapping molecular regulatory networks rather than being independent (El-Khattouti *et al.*, 2013). A number of important proteins have two roles in connecting autophagy and apoptosis, allowing cellular responses to change according to the severity and duration of stress (Su *et al.*, 2013). Beclin-1, which interacts with the anti-apoptotic protein Bcl-2, is one significant example (Decuypere *et al.*, 2012). The Beclin-1–Bcl-2 complex can prevent the start of autophagy, but when it dissociates, the autophagic machinery can be activated and the apoptotic route may be unlocked by altering mitochondrial permeability (Marquez and Xu, 2012).

Additionally, mitochondria are essential for signal integration, which determines the predominance of apoptosis and autophagy (Bloemberg and Quadri, 2019). By removing malfunctioning organelles, activation of autophagy, especially mitophagy, aids in preserving mitochondrial function under mild to moderate stress (Mishra *et al.*, 2022). However, the release of pro-apoptotic substances such as cytochrome c causes the cellular response to change toward apoptosis when mitochondrial damage is severe and permanent (Gupta *et al.*, 2009).

Moreover, autophagy can be directly influenced by caspases, the main effectors of apoptosis (Tsapras and Nezis, 2017). Essential autophagy proteins including Beclin-1 and ATG family proteins can be cleaved by activating specific caspases, which suppresses autophagic flux and increases the cell's commitment to programmed death (Li *et al.*, 2011). On the other hand, by lowering cellular stress and maintaining organelle function, consistently high autophagy can prevent apoptosis (Chueh *et al.*, 2023).

The degree and duration of the stress input determine how these two mechanisms interact (Dong *et al.*, 2023). Autophagy typically takes center stage in the early phases as a defense mechanism to preserve cell viability (Rahman *et al.*, 2025). However, a regulatory shift toward apoptosis as a method of regulated elimination takes place when stress is sustained or surpasses the cell's ability for adaptation (You *et al.*, 2025).

Molecular crosstalk in the regulation of cellular homeostasis (p53, NF- κ B, and ROS signaling)

A central regulatory network connecting cellular stress responses to functional choices like repair, adaptation, or cell elimination is formed by the integration of the p53, NF- κ B, and ROS pathways (Ak and Levine, 2010). Through variations in redox status, enzymatic activity, and gene expression, crosstalk between these three elements enables cells to react contextually to a variety of internal and external stimuli (Liu *et al.*, 2025).

DNA damage, hypoxia, and metabolic imbalance are some of the genotoxic stressors that activate the p53 protein, a crucial genomic regulator (Wang *et al.*, 2026). By activating pro-apoptotic genes like Bax, Puma, and Noxa, p53 can drive cells toward apoptosis or cause cell cycle arrest through p21 expression, giving time for DNA repair mechanisms (Molnar *et al.*, 2026). Moreover, p53 functions as a mediator between cellular energy state and genomic stability via controlling metabolism and autophagy (Rahman *et al.*, 2022).

A transcription factor called NF- κ B is typically linked to inflammatory reactions and cell viability (Park and Hong, 2016). By boosting the expression of anti-apoptotic genes like Bcl-2, c-FLIP, and inhibitor of apoptosis proteins (IAPs), NF- κ B activation fortifies cell resistance to death signals (Ye *et al.*, 2025). However, NF- κ B activity is contextual because, depend-

ing on the stimuli and interactions with other pathways like p53, it can potentially induce apoptosis or senescence (Carrà *et al.*, 2020).

ROS modulate both pathways by acting as oxidative stress agents and signaling molecules (Hong *et al.*, 2024). ROS serve as second messengers in the physiological control of cell division and proliferation (de Almeida *et al.*, 2022). On the other hand, excessive ROS buildup damages proteins, lipids, and DNA, which triggers the stress response via p53 and NF- κ B (Schieber and Chandel, 2014). Additionally, ROS can alter protein activity by oxidizing cysteine residues in regulatory domains, which can impact downstream signaling and transcriptional activity (Iliadis and Panikolaou, 2024).

ROS, NF- κ B, and p53 interact in a mutually modulatory manner (Carrà *et al.*, 2020). While NF- κ B can prevent p53 activation by inducing anti-apoptotic proteins, p53 can decrease NF- κ B activity through a trans-repression mechanism (Culmsee *et al.*, 2003). However, p53 and NF- κ B target gene products that are involved in the antioxidant system, including glutathione peroxidase (GPx) and superoxide dismutase (SOD), can also reverse ROS, which can act as an initial trigger that activates both pathways (Jomova *et al.*, 2026).

Interaction of autophagy and apoptosis

The interplay between autophagy and apoptosis is an integrated regulatory mechanism that determines cell fate during stress responses, with a crucial role in maintaining cellular homeostasis. The stress-dependent switch from protective autophagy to apoptotic execution is summarized in Figure 2.

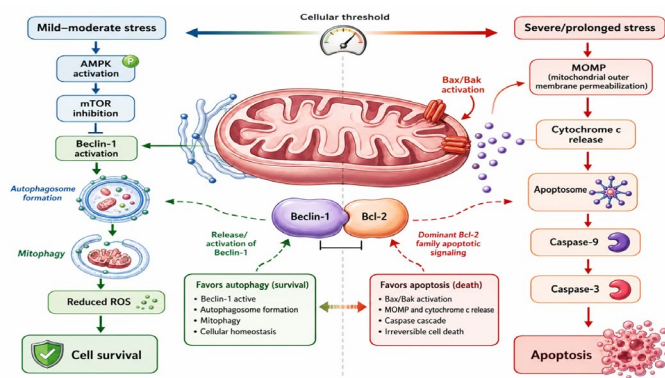


Figure 2. Molecular crosstalk and switching between autophagy and apoptosis.

Switching mechanism between autophagy and apoptosis

When stress beyond a compensation threshold, a cell's ability to continue survival through adaptive mechanisms or undergo programmed death is determined by the regulatory process that switches between autophagy and apoptosis (Kapuy, 2024). The integration of metabolic signals, cellular damage, and the modification of important regulatory proteins functioning at several levels of molecular control govern this system rather than a single pathway (Chandel, 2021).

Autophagy is typically triggered in the early phases of a stress reaction as a defense mechanism to maintain the intracellular environment by breaking down accumulated proteins and malfunctioning organelles (Khandia *et al.*, 2019). AMPK activation and mTOR inhibition, which encourage autophagosome production and elevated autophagic flux, are the main mediators of this activation (Arab *et al.*, 2024). By lowering oxidative stress levels and preserving cellular energy supply, autophagy serves as a buffering mechanism to postpone apoptosis during this stage (Siedlecka-Kroplewska *et al.*, 2025).

When autophagy's adaptive ability is insufficient to handle persistent cellular damage, apoptosis takes over (Levine and Kroemer, 2008). The connection between the anti-apoptotic protein Bcl-2 and Beclin-1 is a crucial regulatory point in this flip (Pattingre *et al.*, 2005). In addition to

initiating autophagy, dissociation of the Beclin-1-Bcl-2 complex raises Bax/Bak activity, which in turn causes mitochondrial membrane permeability and the release of apoptogenic factors (Young *et al.*, 2013).

In this transition process, mitochondria are essential for signal integration (Palabiyik, 2025). Effective autophagy, especially through mitophagy, allows cells to prevent the buildup of ROS and preserve the quality of their mitochondria (Li *et al.*, 2022). On the other hand, if mitochondrial damage is unchecked and progressive, cytochrome c is released, triggering the caspase cascade and changing the cell's reaction from survival to apoptosis (Khan *et al.*, 2022).

Additionally, caspase activation directly contributes to the deactivation of autophagy components (Tsapras and Nezis, 2017). Essential proteins including Beclin-1 and ATG family proteins are known to be cleaved by caspase-3 and caspase-8, which inhibits the autophagic machinery and increases the commitment to cell death (Li *et al.*, 2011). On the other hand, when autophagy continues, pro-apoptotic signals are diminished by lowering cellular stress and preventing p53 activation, which delays the start of apoptosis (Wu *et al.*, 2015).

Co-regulation of autophagy and apoptosis under stress conditions

Autophagy and apoptosis under cellular stress are controlled by coordinated systems that enable cells to progressively modify their responses based on the severity and duration of the insult (Ornatowski *et al.*, 2020). Molecular damage, metabolic signals, and the activity of regulatory proteins that act as connecting nodes between the two pathways are all involved in this co-regulation (Talukdar and Chatterji, 2023).

Autophagy activation takes over as the primary response to preserve cell viability in the early stages of stress (Shabkhizan *et al.*, 2023). Energy sensors like AMPK and the inhibition of mTOR activity, which encourages the breakdown of cytoplasmic components to preserve energy supply and lower the proteotoxic load, support this process (Zhang *et al.*, 2025d). By lowering ROS accumulation and enhancing organelle quality, especially mitochondria through mitophagy, autophagy serves as a buffer mechanism in this situation, delaying the activation of apoptosis (Zorov *et al.*, 2014).

Regulation switches in favor of apoptotic activation if stress persists or results in permanent damage (Singh *et al.*, 2019). Increased pro-apoptotic signals like p53 activation, protein imbalances in the Bcl-2 family, and the release of mitochondrial factors all have an impact on this shift (Qian *et al.*, 2022). This state indicates a turning point at which autophagy's ability to adapt is insufficient to preserve cellular equilibrium (Levine *et al.*, 2008).

Multifunctional proteins that function as molecular switches also mediate the coordination of these two processes (Levine and Klionsky, 2004). During apoptosis activation, caspases can proteolytically alter a number of autophagy components, such as Beclin-1 and ATG proteins, which inhibits autophagic flux and strengthens cell commitment to death (Messer, 2017). On the other hand, by boosting the production of anti-apoptotic proteins, elements of survival pathways like NF- κ B and AKT can inhibit apoptosis activation while preserving basal levels of autophagy activity (Kakkar *et al.*, 2026).

Moreover, the direction of regulation is largely dependent on the redox condition of the cell (Sies *et al.*, 2024). While severe ROS buildup triggers the apoptotic pathway through mitochondrial damage and caspase activation, moderate increases in ROS can trigger autophagy as an adaptive response (Chen *et al.*, 2025). As a result, ROS serve as threshold regulators that control the switch between death and survival signals (Di Meo *et al.*, 2016).

The role of mitochondria as a signal integration center

In particular, mitochondria play a crucial role in the coordination of autophagy, apoptosis, and metabolic stress responses, all of which influ-

ence cell fate decisions (Rambold and Lippincott-Schwartz, 2011). Apart from their function in producing ATP via oxidative phosphorylation, mitochondria also serve as sensory platforms that assess alterations in energy status, redox state, and cellular damage to produce suitable biological reactions (Kuznetsov *et al.*, 2022).

Through the dynamics of fusion and fission, mitochondria control energy balance within the framework of homeostasis, allowing for response to changing metabolic demands (Adebayo *et al.*, 2021). While fission permits the dispersion of damaged mitochondrial components for later removal through mitophagy, fusion promotes the homogeneity of mitochondrial components to preserve respiratory function (Twig *et al.*, 2008). This process keeps the population of mitochondria in good condition and stops malfunctioning organelles from building up (Ma *et al.*, 2020).

Additionally, mitochondria are a significant generator of intracellular ROS, which function as signaling molecules in adaptive control at physiological levels (Shadel and Horvath, 2015). However, unchecked ROS levels can cause protein degradation, mitochondrial DNA mutations, and membrane lipid oxidation, all of which can jeopardize the cell's bioenergetic integrity (Sendtner *et al.*, 2025). Depending on the degree of damage, this situation is a major trigger for the activation of either the autophagy or apoptosis pathways (Chen *et al.*, 2025).

Through the PINK1–Parkin pathway-mediated mitophagy process, mitochondria contribute to the regulation of autophagy (Vincow *et al.*, 2013). When PINK1 builds up on the outer membrane of depolarized mitochondria, Parkin is called upon to ubiquitinate membrane proteins, designating the organelle for lysosomal breakdown (Bayne and Trempe, 2019). This mechanism keeps the cell's metabolic stability and stops pro-apoptotic signals from being released (Gonçalves and Morais, 2021).

On the other hand, because of enhanced outer membrane permeability in cases of severe injury, mitochondria become the main source of apoptosis activation by the release of cytochrome c into the cytosol (Webster, 2012). The cell is headed toward programmed cell death as a result of this event, which also activates the caspase cascade and causes apoptosome formation (Waterhouse *et al.*, 2001). Other pro-apoptotic proteins including Smac/DIABLO, which increase caspase activation by blocking inhibitor of apoptosis proteins (IAPs), are also released by mitochondria in addition to cytochrome c (Edison *et al.*, 2012).

In order to determine the direction of the cell's reaction, mitochondria also closely interact with important signaling pathways like p53 and Bcl-2 family proteins (Mustafa *et al.*, 2024). While Bcl-2 family proteins govern mitochondrial membrane permeability as a crucial regulatory point between survival and death signals, p53 activation can boost the expression of pro-apoptotic proteins that target mitochondria (Silva *et al.*, 2026).

Biological implications of autophagy–apoptosis regulatory dysfunction

Cellular homeostasis is directly impacted by dysregulation of autophagy and apoptosis, which can lead to a number of clinical diseases (Ichimiya *et al.*, 2020). The buildup of molecular damage, organelle disarray, and compromised tissue integrity result from an imbalance between these two processes, which hinders the cell's capacity to react adaptively to stress (Qin *et al.*, 2026).

When autophagy fails, cells are unable to eliminate damaged intracellular elements including aggregated proteins and malfunctioning mitochondria (Glick *et al.*, 2010). The buildup of these substances raises oxidative and proteotoxic stress, which eventually speeds up the apoptotic pathway's activation (Kannan and Jain, 2000). This illness is frequently linked to the pathophysiology of neurodegenerative disorders, where a significant contributing element to the advancement of neuronal degeneration is poor protein elimination (Martínez *et al.*, 2010).

On the other hand, in some circumstances, hyperactivation of autophagy may have a detrimental consequence by preserving the survival of cells that ought to be destroyed (Ryter *et al.*, 2014). Tumor cells, which

use autophagy as an adaptation mechanism to hypoxia and nutritional deficits in the cancer microenvironment, frequently exhibit this behavior (Jalali *et al.*, 2025). In these circumstances, autophagy increases the survival of cancerous cells, which leads to therapeutic resistance (Carretero-Fernández *et al.*, 2025).

Tissue stability is also significantly impacted by dysregulation of apoptosis (Yusupova *et al.*, 2023). The buildup of aberrant cells with genetic alterations is made possible by a decreased sensitivity to apoptotic signals, which raises the possibility of neoplastic transformation (Lee *et al.*, 2023). On the other hand, excessive cell loss brought on by unchecked increases in apoptotic activity can result in tissue deterioration and organ failure (Chaudhry *et al.*, 2022).

Chronic inflammatory illnesses are also influenced by the improper interaction between autophagy and apoptosis (Netea-Maier *et al.*, 2016). Damage-associated molecular patterns (DAMPs), which intensify innate immune system activation and sustain an extended inflammatory state, can be released when injured cells cannot be effectively eliminated (Lin *et al.*, 2025a). This intensifies tissue damage by starting a pathogenic loop (Rani *et al.*, 2017).

Physiological and clinical implications

Physiologically and clinically, the regulation of autophagy and apoptosis plays a crucial role in determining cellular integrity and underlies various pathological processes when their balance is disturbed. Table 1 summarizes the physiological and clinical implications of autophagy and apoptosis regulation in various biological conditions, including aging, cancer, and neurodegenerative diseases. The major pathological outcomes and therapeutic intervention points related to the autophagy–apoptosis imbalance are presented in Figure 3.

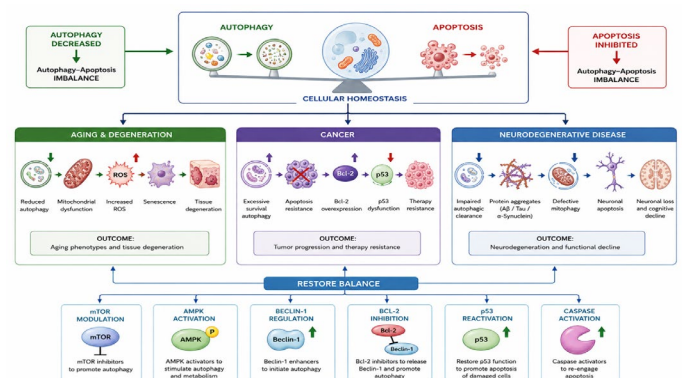


Figure 3. Pathological consequences and therapeutic modulation of autophagy–apoptosis imbalance.

Role in aging and cell degeneration

The gradual build-up of biomolecular damage and a reduction in the ability of intracellular maintenance and repair systems lead to cellular aging (Tenchov *et al.*, 2024). In this regard, autophagy and apoptosis are important modulators of tissue integrity and cell quality that together control the rate of biological aging (Cheon *et al.*, 2019).

Aging causes a decrease in basal autophagy activity, which lowers the efficiency with which accumulated proteins and malfunctioning organelles are broken down (Kaushik *et al.*, 2021). Proteostasis is compromised, oxidative stress is elevated, and bioenergetically incompetent mitochondria accumulate as a result of this situation (Jagtap *et al.*, 2023). Through a harmful positive feedback mechanism, this mitochondrial malfunction increases the generation of ROS, hastening the damage to cellular components (Trigo *et al.*, 2023).

Concurrently, contextual alterations occur in the regulation of apoptosis (Werry *et al.*, 2023). Certain tissues are more susceptible to apoptotic signals, which leads to a gradual loss of cells and a diminished ability to

regenerate tissue (Sundaram and Kanneganti, 2025). However, resistance to apoptosis arises in other organs, resulting in the build-up of senescent cells that maintain metabolic activity but lose their ability to proliferate and acquire a pro-inflammatory secretory phenotype known as senescence-associated secretory phenotype (SASP) (Liao *et al.*, 2021).

Tissue deterioration is accelerated by the interaction of dysregulated apoptosis and reduced autophagy (Ahsan *et al.*, 2024). Cellular function is hampered by the buildup of misfolded proteins, damaged DNA, and disrupted membrane lipids caused by ineffective cellular clearance processes (Reisz *et al.*, 2018). Additionally, elevated ROS brought on by mitochondrial malfunction intensifies the activation of stress pathways, ultimately tipping the scales in favor of senescence or permanent cell death (Sendtner *et al.*, 2025).

These alterations lead to diminished organ regeneration potential, diminished physiological function, and heightened vulnerability to degenerative illnesses in the setting of systemic tissues (Marchi *et al.*, 2012). This accumulation of disturbances has the greatest effect on tissues with rapid turnover rates, like muscle and the nervous system (Giorgi *et al.*, 2018).

Relationship with cancer

Depending on the stage of tumor formation and the microenvironmental context, autophagy and apoptosis can play either suppressive or promotive roles in the complicated process of carcinogenesis (Ariosa *et al.*, 2021). One of the main features of cellular transformation and the development of cancer is the imbalanced control of these two processes (Hama *et al.*, 2023).

Autophagy often serves as a defense mechanism during the initiation stage by preserving genomic stability and minimizing the build-up of cellular damage (Zhu *et al.*, 2026). Autophagy helps prevent mutagenesis, which can lead to neoplastic transformation, by removing damaged organelles and lowering oxidative stress (Roy and Debnath, 2010). Increased genomic instability and the build-up of carcinogenic aggregated proteins are linked to the malfunction of these systems, especially reduced autophagic flux (Zhang *et al.*, 2022).

On the other hand, autophagy may change to a pro-survival process during advanced tumor development (Patergnani *et al.*, 2021). Under adverse microenvironmental conditions, such as hypoxia, food deprivation,

Table 1. Physiological and clinical implications of autophagy–apoptosis regulation in aging, cancer, and neurodegenerative diseases and their therapeutic potential.

Biological/Clinical context	Role of autophagy and apoptosis	Key mechanisms involved	Pathological/Therapeutic implications	References
Aging and cellular degeneration	Reduced autophagy leads to accumulation of damaged proteins and organelles; apoptosis undergoes context-dependent alterations (enhanced sensitivity or apoptosis resistance)	Decreased autophagic flux, mitochondrial dysfunction, increased ROS generation, impaired proteostasis, activation of cellular senescence and SASP	Tissue degeneration, reduced regenerative capacity, functional decline, and increased susceptibility to degenerative diseases	Cheon <i>et al.</i> (2019); Kaushik <i>et al.</i> (2021); Liao <i>et al.</i> (2021); Jagtap <i>et al.</i> (2023); Tenchov <i>et al.</i> (2024); Sundaram and Kanneganti (2025)
Cancer – initiation stage	Autophagy acts as a tumor suppressor; apoptosis eliminates transformed or damaged cells	Clearance of dysfunctional organelles, ROS reduction, maintenance of genomic stability	Reduced autophagy promotes genomic instability, mutagenesis, and neoplastic transformation	Roy and Debnath (2010), Yang <i>et al.</i> (2011a); Ariosa <i>et al.</i> (2021); Zhang <i>et al.</i> (2022); Hama <i>et al.</i> (2023); Zhu <i>et al.</i> (2026)
Cancer – progression stage	Autophagy shifts toward a pro-survival mechanism; apoptosis becomes suppressed	Activation of PI3K/AKT/mTOR signaling, p53 mutation, Bcl-2 family overexpression, impaired caspase activation	Enhanced tumor survival, metabolic adaptation, and resistance to chemotherapy and radiotherapy	Plati <i>et al.</i> (2011); Fernald and Kurokawa (2013); Pandey <i>et al.</i> (2021); Patergnani <i>et al.</i> (2021); Simabuco <i>et al.</i> (2018)
Cancer – adaptive cellular plasticity	Dynamic switching between autophagy and apoptosis depending on stress conditions	Beclin-1–Bcl-2 interaction, NF-κB signaling, autophagic cell death (controversial)	Increased tumor adaptability and survival under therapeutic stress	Hsieh <i>et al.</i> (2009); Denton <i>et al.</i> (2012); Nouri <i>et al.</i> (2020); Xi <i>et al.</i> (2022); Sadati <i>et al.</i> (2025)
Neurodegenerative diseases (Alzheimer's and Parkinson's disease)	Impaired autophagy causes accumulation of neurotoxic proteins; excessive apoptosis contributes to neuronal loss	Accumulation of β-amyloid, tau, and α-synuclein; impaired mitophagy; elevated ROS; caspase-3 activation	Progressive neuronal degeneration, synaptic dysfunction, and proteotoxic stress	Ryter <i>et al.</i> (2019); Kim <i>et al.</i> (2022); Guo <i>et al.</i> (2024); Bhushan <i>et al.</i> (2026); Passi <i>et al.</i> (2026); You <i>et al.</i> (2026)
Neuronal mitochondrial dysfunction	Inefficient mitophagy enhances oxidative stress and apoptotic susceptibility	Electron transport chain disruption, ROS accumulation, Bax/Bcl-2 imbalance, intrinsic apoptosis activation	Accelerated neuronal injury and irreversible neuronal loss	Zündorf and Reiser, (2011); Anilkumar and Prehn (2014); Zhu <i>et al.</i> (2024); Huang <i>et al.</i> (2025)
Major signaling pathway dysregulation	Dysregulated signaling aggravates disease progression through disturbed autophagy–apoptosis balance	Hyperactivation of mTOR, PI3K/AKT signaling, p53 dysfunction, NF-κB-mediated inflammation and survival signaling	Progression of degenerative disorders and tumor development	Simabuco <i>et al.</i> (2018); Rahman <i>et al.</i> (2022); Lin <i>et al.</i> (2025b)
Autophagy-based therapeutic targets	Adaptive modulation of autophagy to restore cellular homeostasis	mTOR inhibition/activation, AMPK activation, Beclin-1 regulatory modulation	Improved proteostasis, enhanced neuronal protection, and regulation of tumor cell survival	Yang <i>et al.</i> (2011b); Decuypere <i>et al.</i> (2012); Wang <i>et al.</i> (2022); Gómez-Virgilio <i>et al.</i> (2022); Marafie <i>et al.</i> (2024); Yi <i>et al.</i> (2025)
Apoptosis-based therapeutic targets	Restoration of programmed cell death sensitivity	Inhibition of anti-apoptotic Bcl-2 family proteins, p53 reactivation, modulation of caspase cascade	Elimination of cancer cells and damaged cells resistant to apoptosis	Kang and Reynolds (2009); Pistritto <i>et al.</i> (2016); Herrero <i>et al.</i> (2016); Qian <i>et al.</i> (2022)
Combination therapeutic approaches	Simultaneous modulation of autophagy and apoptosis	Coordinated regulation of survival–death signaling pathways and cytotoxic therapy integration	Enhanced therapeutic efficacy and reduced drug resistance	Xie <i>et al.</i> , (2020); Al-Odat <i>et al.</i> (2022)
Advanced therapeutic technologies	Precision targeting of cellular pathways	Nanodelivery systems and pathway-specific drug targeting	Reduced systemic toxicity and improved precision medicine outcomes	Sun <i>et al.</i> (2025); Kouri <i>et al.</i> (2025)

and treatment stress, cancer cells use autophagy to sustain metabolism (Yang *et al.*, 2011a). This adaptation increases resistance to chemotherapy and radiation by enabling tumor cells to continue producing energy through the recycling of intracellular components (Pandey *et al.*, 2021).

In cancer, apoptosis is also markedly dysregulated, mostly due to the inactivation of pro-apoptotic pathways and the increased production of anti-apoptotic proteins (Plati *et al.*, 2011). Common ways that cancer cells avoid programmed cell death include p53 mutations, overexpression of the anti-apoptotic Bcl-2 family, and compromised caspase activation (Fernald and Kurokawa, 2013). This gives cancerous cells a selective advantage to endure and grow unchecked (Kelly and Strasser, 2011).

A high level of adaptive flexibility can be seen in the interaction between autophagy and apoptosis in cancer (Xi *et al.*, 2022). Increased autophagy as a backup survival strategy can counteract apoptotic suppression under some circumstances (Hsieh *et al.*, 2009). On the other hand, severe therapeutic stress can change autophagy's protective role to autophagic cell death, a type of programmed cell death, but this idea is still debatable in the literature (Denton *et al.*, 2012).

Additionally, the regulation of these two processes in cancer is strengthened by the involvement of signaling pathways like p53, NF- κ B, and PI3K/AKT/mTOR (Nouri *et al.*, 2020). While p53 mutations not only prevent apoptosis but also interfere with metabolic control and autophagy, activation of the PI3K/AKT/mTOR pathway is frequently linked to enhanced proliferation and suppression of autophagy (Simabuco *et al.*, 2018). By inducing anti-apoptotic genes and regulating inflammation in the tumor microenvironment, NF- κ B increases tumor survival (Sadati *et al.*, 2025).

Neurodegenerative disease

A progressive loss of neuronal function linked to the build-up of damaged proteins, organelle dysfunction, and compromised control of cell death are the hallmarks of neurodegenerative disorders (Kim *et al.*, 2022). Given that nerve cells have a very limited capacity for regeneration and significantly rely on effective intracellular maintenance systems, autophagy and apoptosis play critical roles in determining neuronal survival in this environment (You *et al.*, 2026).

One of the primary pathogenetic pathways causing the build-up of neurotoxic protein aggregates is impaired autophagy (Polajnar and Zervovnik, 2014). Through lysosomal degradation, autophagy contributes to the removal of misfolded proteins and malfunctioning organelles under normal settings (Ryter *et al.*, 2019). However, reduced autophagic flux efficiency causes the build-up of proteins like β -amyloid, tau, and α -synuclein in conditions like Parkinson's and Alzheimer's (Bhushan *et al.*, 2026). This buildup increases neuronal degeneration, causes proteotoxic stress, and impairs synaptic function (Passi *et al.*, 2026).

Through increased ROS production brought on by disruption of the electron transport chain, mitochondria also play a crucial role in the pathophysiology of neurodegenerative diseases (Guo *et al.*, 2024). Neuronal structural damage is accelerated and oxidative stress is made worse by mitochondrial malfunction that is not successfully removed by autophagy (Zhu *et al.*, 2024). This disorder increases vulnerability to apoptotic pathway activation and produces an unstable cellular environment (Huang *et al.*, 2025).

By activating the intrinsic route brought on by oxidative stress, DNA damage, and compromised calcium homeostasis, apoptosis contributes to the gradual death of neurons (Zündorf and Reiser, 2011). Degenerating neural tissue often exhibits downregulation of Bcl-2 and activation of pro-apoptotic proteins like Bax (Anilkumar and Prehn, 2014). Moreover, neuronal structural proteins are broken down by caspase activation, especially caspase-3, which results in cellular disintegration and programmed neuronal death (Unnisa *et al.*, 2023).

Changes in the microenvironment have a significant impact on how autophagy and apoptosis interact in the nervous system (Xi *et al.*, 2022).

In addition to increasing the buildup of neurotoxic substrates, decreased autophagy can hasten the activation of apoptosis because of unchecked increases in cellular stress (Kazmi *et al.*, 2025). On the other hand, in the absence of sufficient regenerative compensating mechanisms, excessive apoptotic activation may hasten neuronal loss (Chi *et al.*, 2018).

Moreover, neurodegenerative diseases are made worse by deregulation of signaling pathways like mTOR, p53, and PI3K/AKT (Lin *et al.*, 2025b). While p53 failure upsets the equilibrium between cell repair and death, excessive mTOR activation can impede autophagy (Shim *et al.*, 2021). This imbalance leads to a long-term state that promotes the advancement of illness (Rahman *et al.*, 2022).

Potential therapeutic targets based on modulation of autophagy and apoptosis

Since both autophagy and apoptosis are important regulators of cellular homeostasis and drivers of cell destiny, modifying them has become a critical therapeutic approach in a number of complicated disorders (Rahman *et al.*, 2024). In order to restore the equilibrium between survival and cell death mechanisms in certain disease situations, this strategy focuses on modifying important molecular pathways (Gómez-Virgilio *et al.*, 2022).

Central regulators including mTOR, AMPK, and the Beclin-1 complex are important therapeutic targets in autophagy modulation (Yang *et al.*, 2011b). In illnesses like cancer and protein buildup, when more cellular breakdown is advantageous, inhibition of mTOR has been extensively investigated as a means of inducing autophagy (Marafie *et al.*, 2024). On the other hand, excessive autophagy that causes pathological cell death can be suppressed by activating mTOR in particular situations (Yi *et al.*, 2025). Because AMPK functions as an energy sensor that guides cells toward adaptive responses by boosting autophagic flux, it is also a crucial target (Wang *et al.*, 2022).

One way to more precisely regulate autophagy start at the execution level is to modify how Beclin-1 interacts with regulatory proteins like Bcl-2 (Decuypere *et al.*, 2012). While stabilizing this connection may restrict autophagy in circumstances where excessive activation is harmful, dissociation of this complex may increase autophagy activity under proteotoxic conditions (Diab *et al.*, 2023).

Restoring cell sensitivity to programmed death is typically the goal of therapeutic approaches in the context of apoptosis, especially in cancer (Pistritto *et al.*, 2016). To eliminate obstacles to the activation of the apoptotic pathway, inhibitors of anti-apoptotic proteins such as the Bcl-2 family (e.g., Bcl-2, Bcl-xL, Mcl-1) have been produced (Kang and Reynolds, 2009). Moreover, p53 function reactivation via protein stabilization or mutation correction has emerged as a crucial strategy to reestablish cell cycle regulation and trigger death in aberrant cells (Herrero *et al.*, 2016).

The caspase cascade, which can be altered to improve the effectiveness of apoptosis execution in cells resistant to death signals, is another area of interest (Qian *et al.*, 2022). Therapeutic responses can be improved by selectively activating initiator or executioner caspases, particularly when combined with cytotoxic drugs (MacKenzie and Clark, 2008).

Given the close relationship between autophagy and apoptosis, contemporary therapeutic strategies also stress the significance of concurrent regulation of these two processes (Xie *et al.*, 2020). Combination techniques that promote apoptotic activation in irreversibly injured cells while inducing autophagy early in the stress phase may improve therapeutic selectivity and lower drug resistance (Al-Odat *et al.*, 2022).

Additionally, specialized modulation of autophagy and apoptosis pathways at the cellular level is made possible by developments in nanotechnology and tailored drug delivery systems, which increase treatment efficacy while reducing systemic side effects (Sun *et al.*, 2025). In order to develop precision therapeutics for a variety of degenerative, inflammatory, and neoplastic disorders, focused manipulation of these two pathways offers a viable multifaceted approach (Kouri *et al.*, 2025).

Therapeutic perspective

A mechanism-based approach to treating complex disorders involving faulty cellular homeostasis is reflected in the development of therapeutic methods that target autophagy and apoptosis (Gómez-Virgilio *et al.*, 2022). These two paths provide different but related points of action, allowing for the creation of more accurate treatments suited to certain disease situations (Kumar *et al.*, 2025).

Depending on the therapeutic requirement, either inductive or inhibitive pharmacological methods can be used to modify autophagy (Tonkin-Reeves *et al.*, 2023). The general goal of autophagy induction is to improve the removal of harmful intracellular components in conditions like neurodegenerative illnesses and protein accumulation disorders (Guo *et al.*, 2018). On the other hand, cancer cells that depend on autophagy to sustain metabolism in the face of microenvironmental stress may use autophagy inhibition as a tactic to decrease adaptive survival mechanisms (Zhang *et al.*, 2021). Regulators including mTOR, AMPK, and elements of the Beclin-1 complex, which are involved in the autophagy initiation stage, are important molecular targets in this strategy (Cao *et al.*, 2024).

Restoring or improving planned cell death pathways is the main goal of apoptosis-based therapeutics, especially in situations when aberrant cells show resistance to death signals (Wang *et al.*, 2024). To ensure effective apoptosis, this tactic entails triggering the caspase cascade, reactivating p53 function, and blocking anti-apoptotic proteins from the Bcl-2 family (Pistritto *et al.*, 2016). Since apoptosis evasion is a crucial indicator of cancer, this strategy is extremely pertinent to cancer treatment (Wani *et al.*, 2023).

In order to improve therapeutic efficacy in multifactorial disorders, combination methods that regulate autophagy and apoptosis are being developed more frequently (Takács-Vellai, 2023). After both routes are interfered with simultaneously, cellular responses can be regulated progressively, with autophagy being triggered first to reduce stress and apoptosis being activated after irreversible cell damage has occurred (Shao *et al.*, 2025). Additionally, this tactic may lessen the therapy resistance that frequently results from using just one method (Xi *et al.*, 2022).

Nevertheless, there are still several obstacles in the way of the therapeutic application of autophagy and apoptosis targeting (Ye *et al.*, 2023). Determining the ideal dosage and timing of therapies is made more difficult by the intricate control of both pathways, their highly contextual nature, and the possibility of biphasic effects (destructive versus protective) (Korn *et al.*, 2023). Additionally, the unpredictability of therapy outcomes is increased by the heterogeneity of responses among tissues and people (Sormani *et al.*, 2023). The scarcity of particular biomarkers to track autophagy and apoptosis activities in real-time in clinical settings presents another difficulty (Zafar *et al.*, 2025).

Therapeutic approaches based on modifying autophagy and apoptosis have a lot of promise for the advancement of precision medicine; however, in order to guarantee the efficacy and safety of interventions, a deeper comprehension of the molecular regulatory dynamics and thorough clinical validation are needed (Al-Odat *et al.*, 2022).

Conclusion

Apoptosis and autophagy are two basic processes that work together to maintain cellular homeostasis by striking a balance between cell death and metabolic adaption. While apoptosis functions as a planned execution mechanism when cell damage is irreversible, autophagy acts as a protective response to preserve cell viability under stressful circumstances. Their interplay creates a dynamic regulatory mechanism that integrates energy signals, molecular damage, and microenvironmental circumstances to decide cell fate.

Understanding these pathways in the context of physiology and illness is crucial since dysregulation of the autophagy-apoptosis balance contributes to a number of maladies, including cancer, neurodegener-

ative diseases, and inflammatory disorders. Thus, more investigation is required to fully understand the molecular switching mechanisms, pinpoint certain indicators of both processes' activity, and create treatment approaches that can contextually and selectively modify both pathways.

Acknowledgement

The author thanks to Badan Riset dan Inovasi Nasional for the funding support for this study.

Conflict of interest

The authors declare that there is no conflict of interest.

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