FARMACIA, 2026, Vol. 74, 3

https://doi.org/10.31925/farmacia.2026.3.4 **REVIEW**

THE REGULATORY ROLE OF TAURINE IN AUTOPHAGY

ANTHONY M. KYRIAKOPOULOS [1,2]*, MIRUNA-MARIA APETROAEI-LEUCĂ [3], ANTONIS TSINTARAKIS [4], ARISTIDIS TSATSAKIS [5,6], PANAGIOTIS ZOUMPOURLIS [4], GABRIELA PURA [7], DEMETRIOS A. SPANDIDOS [8], VASSILIS ZOUMPOURLIS [4], STEPHANIE SENEFF [9]

[1]*Laboratory of Molecular Biology and Immunology. Department of Pharmacy, University of Patras, Rio-Patras, Greece*
[2]*Department of Research and Development, Nasco AD Biotechnology Laboratory, 18536 Piraeus, Greece*
[3]*"Carol Davila" University of Medicine and Pharmacy, 6 Traian Vuia Street, 020956, Bucharest, Romania*
[4]*Biomedical Applications Unit, Institute of Chemical Biology, National Hellenic Research Foundation, 11635 Athens, Greece.*
[5]*Laboratory of Toxicology, School of Medicine, University of Crete, 71003 Heraklion, Greece*
[6]*Health Sciences Department, Universidad Ecotec, Km. 13.5 Samborondón, Samborondón EC092302, Ecuador*
[7]*Faculty of Pharmacy, "Iuliu Haţieganu" University of Medicine and Pharmacy, 8 Victor Babeş Street, 400012, Cluj-Napoca, Romania*
[8]*Laboratory of Virology, Medical School, University of Crete, 71003 Heraklion, Greece*
[9]*Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology, Cambridge, MA, USA 02139*

**corresponding author: antkyriak@gmail.com*

Manuscript received: February 2026

Abstract

Taurine (2-aminoethanesulfonic acid) is an abundant amino acid with complex roles in cellular homeostasis and redox regulation. Beyond its cytoprotective and metabolic activities, emerging evidence indicates that taurine regulates autophagy, a major defense and recycling mechanism governing cell fate, survival, aging, and death. Deviations from this balance contribute to diseases including cancer and neurodegeneration. Taurine can promote autophagy to inhibit oxidative stress and rescue cells, or attenuate it under toxic conditions to prevent apoptosis. In non-malignant cells, it induces autophagy to maintain normal function, whereas in cancer it exerts anti-tumor activity via a ROS-dependent autophagy–mitochondrial apoptosis pathway. Recent studies also show that taurine and its transporter help fuel cancer. To clarify these differential effects, this review examines the relationships among taurine's physicochemical properties, signaling pathways, and key proteins regulating autophagy and apoptosis, and interprets the links among taurine, cell death, and the Warburg effect.

Rezumat

Taurina (acidul 2-aminoetansulfonic) este un aminoacid abundent, cu roluri complexe în menținerea homeostaziei celulare și în reglarea echilibrului redox. Dincolo de efectele sale citoprotectoare și metabolice, dovezile emergente indică faptul că taurina modulează autofagia, un mecanism esențial de apărare și reciclare celulară, implicat în controlul destinului celular, al supraviețuirii, îmbătrânirii și morții celulare. Dezechilibrele acestui sistem sunt asociate cu numeroase patologii. Taurina poate stimula autofagia pentru a reduce stresul oxidativ și a susține supraviețuirea celulară, dar poate și diminua acest proces în condiții toxice, prevenind, astfel, declanșarea apoptozei. În celulele non-canceroase, induce autofagia ca mecanism de menținere a funcției fiziologice normale. De asemenea, poate exercita efecte antitumorale prin activarea unei căi dependente de speciile reactive de oxigen (ROS), care conectează autofagia la apoptoza mitocondrială. Totodată, studii recente sugerează că taurina și transportorul său pot contribui la susținerea metabolică a celulelor canceroase. Pentru a clarifica aceste efecte aparent contradictorii, acest articol analizează relațiile dintre proprietățile fizico-chimice ale taurinei, căile de semnalizare implicate și proteinele implicate în reglarea autofagiei și apoptozei, precum și interconexiunile dintre taurina, moartea celulară și efectul Warburg.

Keywords: taurine, autophagy, signaling pathways, cell death, Warburg effect

Introduction

Taurine is not an essential amino acid in the strictest nutritional sense, since it is not utilized in protein synthesis. However, taurine has pluripotent properties on the preservation of cellular homeostasis and prevention of diseases such as neurodegeneration, inflammatory and toxicity-related conditions, as well as cancer (1, 2). Taurine contributes to the preservation of mitochondrial health and function by acting as an antioxidant and reducing reactive oxygen species (ROS) and reactive nitrogen species (RNS). Taurine exerts its protective effects against oxidative stress in mitochondria and other cellular compartments (*e.g.*, endoplasmic reticulum) that would otherwise lead to multiple pathological conditions (3). The inhibition of advanced glycation end products (AGEs)-related conditions by taurine, which enhances glucose utilization and metabolism, is a

sound example of disease prevention (4). Related studies on diabetic nephropathy reveal that taurine (similar to other antioxidants) prevents AGE-related hypertrophy, which has been associated with inflammation, fibrosis, and oxidative stress. Taurine exerts its protective effects by blocking potentially harmful signaling pathways such as the extracellular signal-regulated kinase (ERK), the c-Jun N-terminal kinase (JNK), and the p38 mitogen-activated protein kinase (MAPK) pathways (5).

The mitochondrial generation of ROS and their secondary species regulate cellular signaling pocesses and their disease outcomes, coordinating the survival or death, as well as the malignant transformation of normal cells (6). Moreover, ROS and their secondary products (which are potent signaling molecules) influence immune self-defense pathways, again by interfering with critical cellular signaling pathways (7). In this view, taurine, by acting as a potential regulator of ROS and RNS, could, to some extent, exert protective effects against deleterious cellular signaling pathways that lead to disease.

The propagation of cell signaling pathways is closely related to the regulation of autophagy, the cell's primary self-defense machinery (8). Autophagy is a complex recycling process and, although it generally protects cells from damage and death, it also determines cell fate by either preventing or triggering various apoptotic pathways, especially under severe stress. This dual role is particularly important in cancer. Cancer cells exploit autophagy and metabolic reprogramming to resist chemotherapy, survive, or undergo apoptosis (9). Therefore, taurine, by modulating ROS and RNS levels and thereby regulating the cell's redox potential, may influence autophagy. This regulation may provide survival mechanisms for normal cells (10, 11) while promoting lethality in cancer cells (12) through the modulation of various signaling pathways, including the JNK and p38 MAPK phosphorylations.

Of foremost importance in the potential regulation of autophagy by taurine, especially in cancer, is the involvement of the taurine transporter SLC6A6 (TauT). A crucial factor to address is the effect TauT exerts on the tumor microenvironment. Cancer cells often upregulate this transporter, thus allowing them to deplete the tumor microenvironment of taurine and therefore making it unavailable to the resident immune cells. Taurine deficiency in CD8+ T cells increases ER stress, which in turn induces T cell exhaustion. This promotes immune evasion and increases the potential for metastasis (13). While taurine supplementation helps cancer cells resist oxidative stress, it also, importantly, reinvigorates CD8+ T cells so they can effectively fight cancer in its niche. The dilemma is in some ways similar to but opposite from the dilemma faced with chemotherapy, which can directly promote tumor cell death but also harms immune cells, preventing them from attacking the tumor cells (14).

Therefore, it is of great importance to further analyze the role of taurine in regulating various signaling pathways, particularly those related to autophagy. The balancing of cellular redox potential and oxidative stress directly triggers and regulates autophagy. Moderate stress signals autophagy initiation, while severe stress activates autophagy for the removal of damaged proteins and mitochondria (15). This has severe implications for whether a normal cell will overcome stressful conditions, or whether a cancer cell finally dies or survives, through taurine's interactions. Taurine can either suppress or induce autophagy, depending upon the cell type and the environmental conditions (10, 11). The complex relationships between taurine and cell signaling and the autophagy behaviors of normal and cancer cells are thus investigated in depth.

In this paper, we investigate the ways in which taurine finely regulates autophagy in order to a) maintain cellular health in non-cancerous conditions, and b) become a strong anti-cancer activity modulator. Regarding cellular oxidative status, by modulating sensitive molecular switches, taurine influences autophagic mechanisms to promote cellular health under normal conditions. By contrast, in tumors, it drives cancer cells to follow apoptotic pathways and succumb to death. But this is not always the case, as taurine and its transporter Slc6a6 can also promote cancer (16). Therefore, we investigate the important distinctions that can cause cells to follow an autophagy-mediated death pathway to find clues and enlighten about the dual effects of taurine on cell survival and death. We discuss that taurine's pro-cancer effects may be due to intrinsic cancer cell autophagic defects or to its transporter-mediated antioxidant activities, rather than to taurine itself. Finally, we highlight that taurine could interfere with the Warburg effect, which increases lactate production in non-malignant conditions, and explain how this can further impact anti-cancer therapy.

Autophagy and the converging signaling pathways

Autophagy is initiated under conditions of cellular stress. These conditions encompass the depletion of nutrient availability, increased oxidative stress (ROS production), and subsequent activation of phosphorylating signaling cascades. The activation of autophagy may not only be lifesaving for the cell but can also, under certain conditions, lead to its death.

The level of cellular stress acts as a primary rheostat for cell fate. Low-to-moderate stress triggers pro-survival autophagy. This allows the cell to recycle nutrients and clear damaged organelles, restoring homeostasis. When the damage exceeds a threshold, autophagy shifts towards a pro-death mechanism, as

mitochondria release cytochrome c and caspases to launch an apoptotic response (17).

Pro-survival Bcl-2 family proteins bind to Beclin-1 to inhibit autophagy. Under stress, Beclin-1 is released to initiate survival-oriented autophagy. However, if Beclin-1 is cleaved by caspases, its C-terminal fragment translocates to the mitochondria to promote apoptosis (18). Atg5 and Atg12 are essential for autophagosome formation, but they can also be diverted to death pathways through cleavage by calpains (calcium-activated proteinases). Atg12 can bind to and inhibit pro-survival Bcl-2 members, directly triggering mitochondrial apoptosis (19).

The following section provides an overview of how kinase-mediated phosphorylation regulates the induction and progression of autophagy toward autophagy-dependent cell death.

The interplay between autophagy and the cell's phosphorylating-signaling network

The cell is evolutionarily endowed with sophisticated sensing mechanisms for external and internal stimuli, such as growth hormones (insulin), amino acids, and glucose, which initiate its signaling cascades that ultimately regulate metabolic status (growth), leading to either survival or death (20). Central to these energy-sensing signaling cascades are the phosphorylating kinases, which comprise several pathways that deliver the final key messages governing cellular metabolic fate (21). Mainly, the phosphokinase cascades regulate the transcriptional and translational control of metabolism, which, in turn, modulates its autophagic behavior (22). The phosphokinase interconnection with autophagy behavior probably plays the most important role in determining whether malignant or non-malignant cells follow survival or death pathways.

Amongst the most important regulatory kinase cascades for autophagy signaling are the serine/threonine mammalian target of rapamycin (mTOR) complex, the AMP-activated protein kinase (AMPK), and the mitogen-activated protein kinases, which mainly comprise the ERK, MAPK, and JNK pathways (23).

The initial sensing of the cell by either the growth factors (such as insulin), amino acids, and/or glucose initiates the AMPK, the ERK *via* the phosphatidylinositol (3,4,5)-trisphosphate (PIP3), and the Wnt/β-catenin (important for embryogenesis and growth of stem cells) signaling pathways, to ultimately control the activity of the mTORC1 complex. The Wnt/β-catenin pathway involves a kinase phosphorylation-induced degradation step of the β-catenin co-transcription activator (24).

The molecular events that initiate or inhibit autophagy.

There are many short- and long-term molecular pathways that govern the initiation of autophagy, but central to its initiation or inhibition are the activated forms of AMPK or mTORC1. They both influence the activation or the deactivation of the mammalian autophagy-initiating kinase (Ulk1) (25). In general, the activated AMPK initiates autophagy, whereas the activated mTORC1 inhibits autophagy. Both AMPK and mTORC1 exert their autophagy-initiating or inhibiting activities by directly phosphorylating different serine residues of ULK1.

However, more complex molecular events can intervene; for instance, the ERK1/2 signaling pathway has been shown to initiate autophagy independently of, or in crosstalk with, the mTOR axis. In certain contexts, ERK1/2 can overcome mTOR-mediated inhibition to promote the initiation of autophagy (26). Moreover, experiments with neuronal cells showed that direct AMPK-mediated phosphorylation of ULK1 could overcome mTORC1-mediated inhibition of autophagy (27). In other cell models, AMPK is concurrently activated with mTORC1 and antagonizes its activity, helping maintain cellular amino acid sufficiency through sustained autophagy (28). Overall, energy stress activates AMPK, which in turn promotes autophagy initiation through two mechanisms: direct phosphorylation of the ULK1 complex and indirect suppression of mTORC1 activity *via* TSC1/2-mediated Rheb inactivation (29). Furthermore, another major trigger for autophagy initiation, independent of mTOR-ULK1/2 interactions, is the intracellular accumulation of lactate (30), which is formed from pyruvate *via* lactate dehydrogenase (LDH) during glucose catabolism (31). Both lactate and the ULK1/2 stimulate the assembly of the Beclin-1 complex (8). The Beclin-1 is a potent autophagy kinase stimulator, a member of the PI3 kinase (PI3K) complex that aids in the formation of phosphatidylinositol 3-phosphate (PI(3)P), which is an important lipid for the autophagosome membrane formation (32). Upon the generation of PI(3)P, autophagosomes are formed and become nucleated, and autophagy is initiated (33). A negative feedback loop for autophagy to get initiated is the liberation of Beclin-1 from forming a strong complex with the BCL-2 proteins in the cytoplasm (34). A molecular event that causes the dissociation of Beclin-1 from Bcl-2 is the activation of the JNK pathway, which phosphorylates the Bcl-2 under oxidative stress conditions (35). Furthermore, the phosphorylation of Bcl-2 *via* activation of p38 MAPK under oxidative stress is a causative factor for apoptosis to occur (36). However, in both cases of either JNK or p38 MAPK activations, the phosphorylations of the Bcl-2 molecules (Bcl-2 or Bcl-XL) are responsible for the liberation of Beclin-1 from the Bcl-2 complex, to induce autophagy.

The induction of apoptosis through the initiation and elongation of autophagosomes is the focus of the following section, which describes how cells can also

die despite the life-rescuing self-defense mechanism of autophagy.

Autophagy and cell death.

Autophagy is normally a life-rescuing mechanism, initiated under conditions of low nutrient and energy availability to maintain cell survival. However, autophagy also encompasses molecular mechanisms that can promote cellular death *via* various apoptotic pathways. Evidently, this dysfunction in autophagy promotes diseases such as neurodegeneration (37). The basis of this disease category is primarily mitochondrial impairment. However, the autophagy-dependent cell death can be defined as circumstantial and dependent on cell signaling (38). In this section, we focus on cell death occurring concurrently with autophagy rather than on cell death induced by autophagy (apoptosis) (39).

Experimental evidence shows that central to autophagy-mediated cell death is the activation of the RAS oncogene by several growth factor signaling pathways and its downstream effects on cessation of mTOR complex activity via, *e.g.*, the activation of the ERK pathway (8, 40, 41). In simple terms, when oncogenic RAS is activated, as in most cancer cells, upon induction of autophagy, they do not adequately express the necessary autophagy proteins to sustain the recycling of materials essential for their survival. Moreover, the upregulation of Beclin-1 during RAS-induced autophagy, or of another BH3-containing Bcl-2 family protein, NOXA, induces the autophagy-dependent cell death.

Upon excessive stress conditions (as during oxidative stress), NOXA competes with MCL-1 (a pro-survival Bcl-2 protein that restricts apoptosis) and promotes the cell's death (42). The p53 upregulates NOXA expression, and it is tightly associated with increased death during autophagy (43). In conclusion, although the cell death during apoptosis is a complex phenomenon (44), rather, the aberrant release of Beclin-1 from the Bcl-2 complex initiates and propagates autophagy, and other molecular factors, such as Bcl-2 family proteins, interplay. In contrast, the lack of the autophagy machinery could promote autophagy-mediated apoptosis, especially in cancer cells (Figure 1).

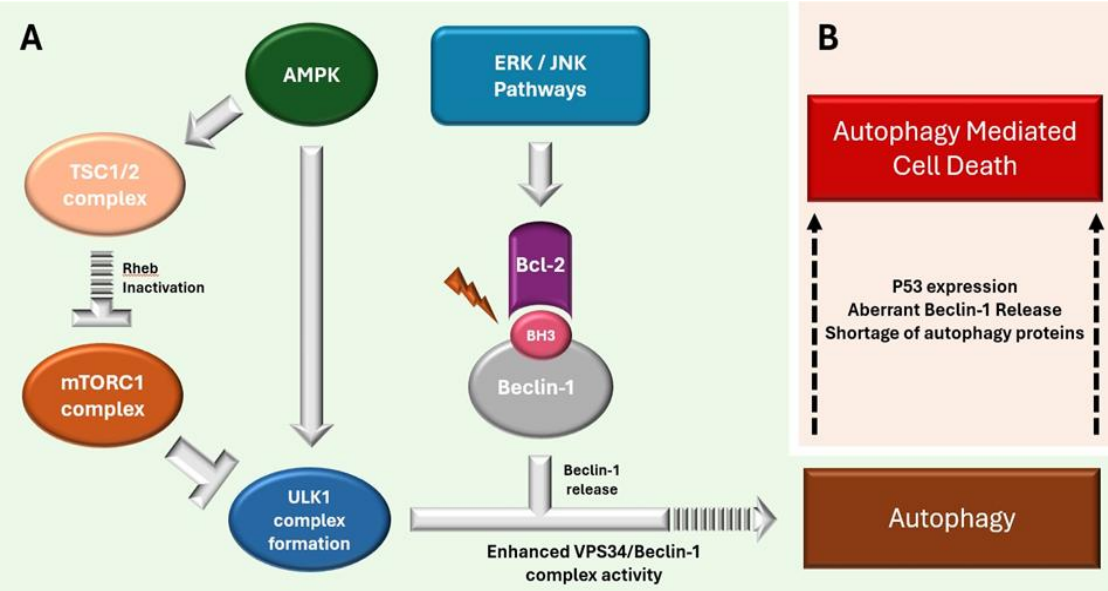

Figure 1.

Phosphorylating signaling and autophagy. A) The activation of AMPK in response to energy stress leads to direct activation of the ULK1 complex and indirect activation *via* TSC1/2-mediated inhibition of mTORC1 (*via* Rheb inactivation), thereby enabling autophagy initiation. In parallel, ERK/JNK signaling induces phosphorylation of Bcl-2, disrupting Bcl-2/Beclin-1 binding and releasing Beclin-1. Under stress conditions, the AMPK and ERK/JNK pathways can converge on the VPS34/Beclin-1 complex, thereby enhancing its activity and promoting autophagosome nucleation and autophagy progression. B) Several factors, including aberrant autophagy initiation signaling, p53 expression, and autophagy protein shortage, can shift the balance toward autophagy-mediated cell death

Beyond regulation of autophagy via the signaling pathways, taurine potentially exerts anti-cancer effects by enhancing mitochondrial health

Taurine has the molecular capacity and structural potential to alleviate, or even balance, cellular oxidative stress, thereby serving as a fine regulator of autophagic processes that may involve the apoptosis-autophagy pathway, leading to either cellular death or survival.

The autophagy-signaling pathways and taurine.

Autophagy, the housekeeping cell defense mechanism, is initiated by the activation of p38 mitogen-

activated protein kinase (MAPK) signaling as a result of ROS (45). Similarly, in another MAPK subfamily, namely JNK1/2/3, extracellular signal-regulated kinase (ERK)1/2 phosphorylations (activations) occur during MAPK activation, resulting in phosphorylation and nuclear translocation of the transcription factors c-Jun and c-Fos. These transcription factors are important for the induction of autophagy as they dimerize and form the activating protein-1 (AP-1) complex and concurrently induce the expression of several autophagy-related (atg) genes that further regulate the autophagy process (46). However, the induction and propagation of autophagy that lead to cell survival or apoptosis are more complex processes, as they also involve activation of Beclin-1 expression, which is induced by transcriptional activation by the c-Fos and C-Jun transcription factors. The Beclin-1 protein holds a key message response, as, when it becomes readily bound to the Bcl-2 proto-oncogene (anti-apoptotic protein), it blocks the initial steps of autophagy (47). When the Bcl-2-Beclin 1 complex becomes unbound, the Beclin-1 forms a complex with hVps34-protein X, and, when this complex (Beclin-1 hVps34-protein X) gets nucleated, it readily regulates autophagy (48).

Nevertheless, the activity of Beclin-1 is also regulated by caspase-mediated proteolytic cleavage. Caspase-mediated cleavage disrupts the autophagy-promoting function of Beclin-1, thereby reducing autophagy. Moreover, when the cleaved C'-terminal fragment of Beclin-1 translocates to mitochondria, it can induce the release of pro-apoptotic proteins such as cytochrome *c* and HtrA2/Omi, potentially enhancing apoptosis (49). These mechanisms show how cellular programs can shift from autophagy to apoptosis, with Beclin-1 redirected to enhance apoptotic signaling.

The regulation of autophagy is further complicated by the Nuclear factor erythroid 2–related factor 2 (Nrf-2) and its nuclear translocation activation. Indeed, the Nrf-2/Kelch-like ECH-associated protein 1 (Keap-1)/p62/antioxidant resistance element (ARE) (KEAP-1/p62/ARE) pathway axis is a crucial cellular system linking autophagy (cellular cleanup) with the Nrf2 antioxidant response, highly important for regulation of autophagy and apoptosis (50). Research is increasingly focused on this antioxidant signaling axis, particularly its involvement in the initiation or maintenance of autophagy, which is needed for cancer cell apoptosis, survival, and progression, as well as response to therapy.

Taurine and the Nrf-2-Keap-1 autophagy regulatory pathway

Multiple studies have established that the Nrf-2, apart from the regulation of oxidative stress, is a potent transcription factor that, once it translocates to the nucleus, regulates the initiation of autophagy and survival of cells (including cancer cells) (51). The mechanism of Nrf-2-dependent regulation of autophagy primarily originates from the protein structures of the Keap-1 protein and Nrf-2. When in the cytoplasm, the Nrf-2, through its NH_2 N-terminal domain, binds to and forms a complex with the Keap-1, thereby disabling the Nrf-2 from translocating to the nucleus and exerting its antioxidant activity. When the complex is maintained in the cytoplasm, Nrf-2 is kept at low levels and is regularly degraded *via* ubiquitination and proteasomal degradation. Keap-1 is a catalyser-adaptor protein of the Cullin-3 (Cul3)-RING ubiquitin E3 ligase complex (CRL3) in autophagosomes (52).

The Keap-1 protein is highly sensitive to electrophilic/oxidant stress, primarily due to its 27 cysteine residues (in humans), dispersed in catalytic domains of its structure (53, 54). The Keap-1 Kelch/DGR domain, which is responsible for binding Nrf-2, is further regulated in its interaction with the NH2 domain of Nrf-2 *via* the neighboring IVR (intervening region) domain. The IVR contains several cysteine residues that catalyze the tight Nrf-2-Keap-1 complex-forming interactions (55). Moreover, the BTB domain of Keap-1, which is close to the IVR, is important for the Keap-1 association within the CRL3 complex. It also contains the redox potential-sensitive cysteine residue Cys151 (56). The modification of the Cys151 residue within Keap1 is a critical event that disrupts its interaction with Cul3, leading to the dismantling of the CRL3 complex. The loss of CRL3 complex interactions will increase the Nrf-2 levels in the cell. This upregulates the Nrf-2 transcriptional activity and the induction of the cellular antioxidant defense (55, 56).

Taurine's structure sustains significant oxidations upon its encounter with ROS (scavenging reactions). Taurine's reaction with hydrogen peroxide (H_2O_2) is slow and depends on its high concentration in an oxidated cellular environment, where it induces the activity of Nrf-2, reduces oxidative stress, raises the cell's antioxidant defences and lowers the inflammatory responses, including those of Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB), and of inflammatory cytokines (such as IL-6, IL-1β and IL-8) (57). In this context, taurine serves a modulatory role in regulating autophagy and apoptosis, influencing cellular stress responses and survival pathways.

Myeloperoxidase (MPO) is an enzyme expressed by neutrophils that produces hypochlorite (HOCl), a powerful anti-microbial agent that can also be toxic to host cells. Taurine can easily react with hypochlorite, producing N-chlorotaurine as a product, thereby preventing cellular damage, reducing inflammation, and boosting antioxidant defenses (58). Hypochlorite is overexpressed in diseases like type II diabetes associated nephropathy (59). Probably,

the most robust reaction of taurine with ROS occurs with HOCl (60). In the MPO system, during inflammation, the HOCl, primarily produced by neutrophils, is captured by taurine in a highly efficient manner to produce its chlorinated derivative, N-Chlorotaurine (NCT or TauCl) (60). Similarly, in an oxidative environment like that of neutrophils during inflammation, taurine reacts readily with hypobromous acid (HOBr) to produce its brominated derivative N-bromotaurine (NBrT or Tau-Br) (61).

Apart from taurine's direct scavenging of potent ROS that will lower the overall oxidative stress in cells, both of the oxidized taurine derivatives, NCT and NBrT, cause the dissociation of Nrf-2 from the Keap-1/Nrf-2 complex, allowing its nucleation and the downstream activation of the antioxidant response elements (ARE) and heme oxygenase-1 (HO-1) transcription for the reduction of inflammation (60, 62). The anti-inflammatory function of NCT and NBrT relies on the activation of HO-1 expression (62). Although the raised oxidative stress causes the liberation of Nrf-2 from the Keap-1/Nrf-2 complex (63), taurine and its derivatives have the potential to produce an alternative system of antioxidant defense, which is essential for the endoplasmic reticulum (ER) and inner mitochondrial membranes, when there is raised oxidative stress. This will further define the cell's autophagy status and the direction towards a pathogenic or non-pathogenic outcome. The modulation of Nrf-2 and thus autophagy is also necessary for preventing disease outcomes, including cancer and neurodegeneration (64).

The potential regulation of Nrf-2 signaling by taurine to balance the redox potential

As already described, the Keap-1 protein contains key cysteine residues in its structural domains that govern its association with or dissociation from Nrf-2 in the cytoplasm. The Cys273 and Cys288 residues in the IVR domain of Keap-1 are essential for holding the Keap-1/Nrf-2 complex in a firm state and thus reducing Nrf-2 activity (55). Moreover, the BTB domain contains the critical Cys151 residue, which facilitates Keap-1 binding to Cul3, forming the CRL3 complex that targets Nrf-2 for proteasomal degradation. Adduction of Cys151 can inhibit Cul3 association with Keap-1, dismantling the CRL3 complex and ultimately inhibiting Nrf-2 proteasomal degradation (56). Nrf-2 is active under oxidative conditions but remains quiescent under normal conditions.

The cysteine residues contain an active thiol group that is subject to nucleophilic/oxidant attack. It has been remarkably demonstrated that the chlorinated derivative of taurine, NCT, markedly elevates the activity of Nrf-2 and HO-1 by also inducing their expression (60). This happens because NCT lowers the level of thiol group reduction through oxidative attack, thereby enabling the dissociation of Nrf-2 from Keap-1. High oxidative stress, as in chronic inflammation, will dismantle the Nrf-2 activity (65). Taurine stands in the middle of the regulation of oxidative stress through the Keap-1/Nrf-2 pathway by providing a balance on thiol-disulfide interchange reactions, which have multiple biological roles in preserving the redox homeostasis (66).

The activity of NCT, and therefore of taurine's physiology on the lowering of thiol group (cysteine) reduction, becomes of great importance for the thiol oxidation-based regulation of biological systems. The thiol groups of the Keap-1 cysteine residues in their oxidized state tend to form disulfide bridges. In contrast, in their reduced state, these disulfide bridges are converted to the previous thiol-SH free state.

Moreover, the thiol-disulfide exchanges affect the intracellular redox homeostasis and the overall cellular signaling (66). Therefore, taurine and its derivatives (NCT and NBrT) can provide a delicate mechanism of redox balancing between cysteine thiol oxidation and reduction states that permits regulation of the Nrf-2 liberation from the Keap-1/Nrf-2 complex and the CRL3 complex (avoiding further autophagosome degradation of Nrf-2).

In a study conducted by Seol *et al*. (60), the taurine-NCT system enhanced both the nuclear translocation of Nrf-2 and its expression and concentration in astrocyte cultures. Furthermore, the expression of ARE-Nrf2-responsive genes was enhanced. Clearly, the researchers found that the antioxidant cytoprotective effect of the taurine-NCT system used (200 μM NCT and 200 μM taurine) was due to the formation of disulfide bonds between the thiol groups of the Keap-1 protein. In other words, the increase of Keap-1 structural rigidity by taurine and NCT caused the liberation of Nrf-2 from the Keap-1 protein, and probably the liberation of Cul3 from the Keap-1 protein to form the CRL3 complex. This was confirmed by the subsequent addition of NCT (500 μM) to the cell cultures, which increased intracellular Nrf-2 concentrations, suggesting a halt in Nrf-2 autophagic degradation. Thus, the redox balancing of thiol-disulfide formation is essential for further explanations of the autophagic regulation by taurine and its derivatives, as will be discussed in the following section on therapeutic effects. This thiol-disulfide regulation may represent one step beyond the standard p38 MAPK, ERK, and JNK signaling pathways. Although the scientific evidence is currently scarce, taurine can plausibly regulate thiol-disulfide exchange *via* its antioxidant activities, which influence glutathione oxidation, and by reducing lactic acid production (67).

Several studies presented in Table I, including human studies on the direct measurement of thiol and disulfide in patients' serum and taurine, indicate that

taurine is possibly either an indirect or a direct regulator of thiol-disulfide exchange.

Several studies indicate that taurine can play a potent role in regulating thiol-disulfide exchange, particularly in mitochondria, through its interplay with glutathione and its induction of lactate production. A plausible autophagy regulation by Keap-1 and BCL-2 protein folding *via* taurine and its derivatives, NCT and NBrT, is illustrated in Figure 2. Moreover, in Figure 2, the possible mechanisms by which taurine and its derivatives can exert a strong influence on autophagy propagation through thiol-disulfide exchange regulation are illustrated.

Table I

Taurine intermediates as a thiol-disulfide exchange regulator

Study type	Relationship with thiol – disulfide exchange regulation	Reference
Cross-sectional study, 132 obese individuals aged ≥65 years	Taurine attenuates skeletal muscle senescence and protects against skeletal muscle disorders, indicating regulation of the thiol-disulfide redox balance	(68)
Rabbits	Taurine supplementation prevents oxidative stress induced by GSH depletion. Taurine reverses GSH oxidation (*i.e.*, increases GSH/GSSG ratio) and increases mitochondrial GSH levels.	(69)
An *in vitro* redox state-electron transfer study reconstituting the inner mitochondrial membrane disulfide relay	A reduced GSH state promotes efficient disulfide bond formation and the folding of oxidized mitochondrial proteins.	(70)
Human clinical study	During taurine depletion, the level of serum thiol increases in patients suffering from type II diabetes, cardiovascular disease, hypercholesterolemia, and hypertension. During taurine depletion, the same patients show high levels of lipid peroxidation (malondialdehyde) in blood.	(71)
Systematic review	A small dose of taurine (0.05 g) before strength-enhancing workouts may reduce muscle exhaustion and elevate antioxidant enzymes; taurine supplementation (1 g) before or after exercise reduces blood lactate levels.	(72)
Wistar albino rats	During acute mesenteric ischemia, the increase in serum lactate levels coincides with an overall decrease in serum and native thiol levels, indicating a disturbance of thiol–disulfide hemostasis (TDH).	(73)

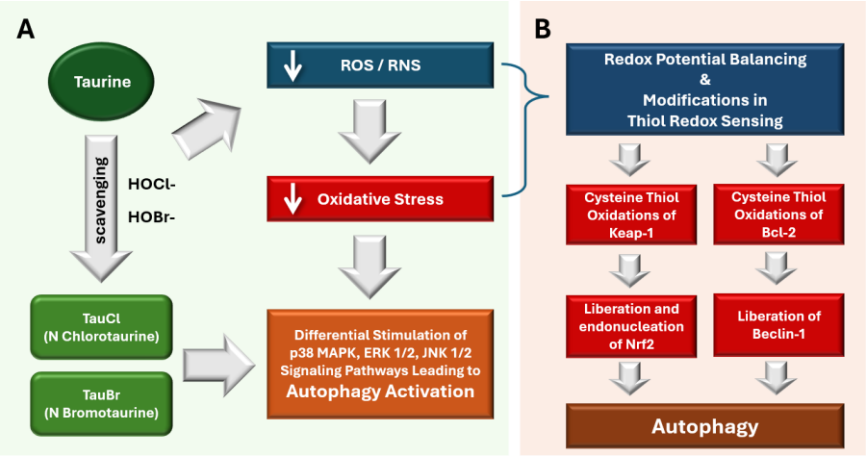

Figure 2.

Taurine and its derivatives, NCT and NBrT, can serve as a delicate redox-balancing mechanism during oxidative stress, modulating autophagy. A. Taurine and its derivatives, through ROS and RNS scavenging, reduce oxidative stress. This has the potential to modulate the stimulation of the p38 MAPK, ERK 1/2, and JNK 1/2 signaling pathways by ROS, thereby inducing autophagy. B. Furthermore, the oxidation of cysteine thiol groups in the key Keap-1 and Bcl-2 proteins by taurine and its derivatives can lead to the liberation of Nrf-2 from Keap-1 and Beclin1 from Bcl-2. These events ultimately initiate and propagate autophagy

The autophagic mechanisms regulated by taurine and their protective roles

Apart from Keap-1, a cysteine-thiol-rich sensor plausibly involved in taurine-mediated autophagy signaling, the anti-apoptotic mitochondrial protein Bcl-2 is another important molecular regulator of the balance between autophagy and apoptosis, which can be influenced by taurine. The cellular redox state determines whether key cysteine residues of Bcl-2 that affect binding to partner proteins such as Beclin-1 and ERK1/2 become oxidized and form disulfide bridges, or remain reduced and thus remain in their

free-thiol configuration (74, 75). This process is particularly important in the context of cancer progression, as described by Zając *et al*. in their glioma-related study (75). The oxidation of Bcl-2 cysteine residues could regulate cancer cells' survival through autophagy or death through apoptosis.

The following sections unravel the existing scientific evidence for the influence of taurine on autophagic or apoptotic propagation in human physiology and cancer. This evidence also identifies the therapeutic potential of taurine's antioxidant activities through autophagy. Additionally, this evidence plausibly identifies a thiol-disulfide exchange and thus altered protein folding due to taurine regulation of key cysteine residues (oxidized or reduced states).

Additionally, taurine can trigger programmed cell death (apoptosis) in various cancer cells by enhancing pro-apoptotic proteins, such as Bax and the p53 upregulated modulator of apoptosis (PUMA), and by decreasing anti-apoptotic ones (Bcl-2), activating mitochondrial pathways, while simultaneously protecting normal cells from damage by reducing oxidative stress and supporting immune function. The Bcl-2 Homology Domain 3 (BH3) is a critical protein-protein interaction motif in the Bcl-2 family of proteins, acting as a central mediator of programmed cell death (apoptosis) by binding to anti-apoptotic members like Bcl-2, and either activating or releasing pro-apoptotic partners (like BAX/BAK) to trigger cell death, functioning as a key "death domain" that senses stress and promotes apoptosis in response to cellular damage.

Under normal redox potential conditions, the Bcl-2, by binding to the Beclin-1 (at its BH3 domain), inhibits autophagy and its associated apoptosis (34). Moreover, under normal redox conditions in mitochondria, the Bcl-2 associates closely with pro-apoptotic proteins such as Bax (76), whilst the PUMA remains inactive, and cells are prevented from pursuing apoptosis (77). However, under elevated oxidation conditions, the PUMA becomes activated and associates with Bcl-2, whilst letting the Bax free to induce pores in mitochondrial membranes and induce autophagy that leads to apoptosis (74). This is a redox-sensitive mechanism in cells that prevents further pathogenic effects, such as tumorigenesis.

How taurine intervenes in the autophagy propagation that leads to disease through Bcl-2.

One of the best examples for analyzing the role of taurine in the propagation of autophagy under various conditions of oxidative stress in cells is its interference with the anti-apoptotic Bcl-2 proteins (Bcl-2, Bcl-2 XL) and the pro-apoptotic proteins BAX, BAK, and BAD. These proteins constitute a sensitive cellular signaling mechanism which ultimately regulates the intracellular Ca^{2+} concentration and cell fate, favoring either survival or death (78). These proteins regulate one another (*via* affinity bindings) through their Bcl-2 BH3 domains (79). These are redox-sensitive interactions (80) modulated by the oxidative states of the cysteine residues located in their interacting BH3 domains (81).

A study by Tu *et al*. showed that taurine has the potential to inhibit the proliferation of lung cancer cell lines in a concentration-dependent manner (82). In these experiments, taurine upregulated PUMA and Bax expression and downregulated Bcl-2 expression. Similarly, the same team showed that inhibition of xenograft tumors in nude mice treated with taurine was also due to the downregulation of Bcl-2 and upregulation of PUMA and Bax. In this context, the Bcl-2, PUMA, and Bax pattern could induce apoptosis in cancer cells by initiating autophagy, highlighting that a high Bax/Bcl-2 ratio could be a therapeutically important milestone in cancer therapy (83).

However, beyond the transcriptional anti-cancer control that taurine may have exerted (*e.g.*, by increasing the levels of p53 in cancer (84) and reducing the levels of NF-κB (85), the observed downregulation of Bcl-2 and upregulation of Bax could have occurred through translational and post-translational control of the BH3 binding domains of the BH3-only PUMA, or the Bid or the Bad proteins with Bcl-2 (86). The proteins PUMA, Bim, and Bad are competitors of Bax for binding to Bcl-2 but have distinct regulatory properties. The binding of Bcl-2 with Bim, for example, initiates the proteasomal degradation of Bcl-2 (87). However, these are all redox-sensitive proteins because of their cysteine residues in the BH3 domain, as mentioned before, and similar studies have shown that alterations in the cellular oxidative status can render PUMA and Bax as p53-independent apoptosis-signaling molecules (88). Therefore, taurine and its derivatives, NCT and NBrT, as redox potential modifiers, may have contributed to oxidative or reductive modifications of cysteine residues within the aforementioned BH3 domains (88), and, through potential structural rearrangements involving disulfide bond formation (by oxidations) or release to free thiols (by reductions), may have influenced conformational states that regulate interactions between Bcl-2 and Bax.

Furthermore, the potential anti-cancer pro-apoptotic effects of taurine on lung cancer cells are consistent with observations in breast cancer. In breast cancer, taurine can exert its apoptotic (breast cancer cell death) stimulus by downregulating the Bcl-2 and upregulating the PUMA and Bax (89). However, in both cases of taurine's potential anti-cancer effect on lung and breast cancer, taurine's influence on metabolic reprogramming must be emphasized. Taurine modulates glucose metabolism and decreases lactate accumulation in breast cancer cells. This may point to interference by taurine with the Warburg effect, which is associated with cancer cell invasion and metastasis (90). The ongoing Warburg effect, *i.e.*,

ongoing aerobic glycolysis in the tumor microenvironment, supports cancer cell proliferation and progression and can interact with autophagy-related processes that contribute to tumor survival, partly by limiting apoptotic responses (91).

The effects of taurine on apoptosis regulation, however, are reversed in non-malignant, but injured nerve cells. During injury, either by 2,5-hexanedione (a derivative of hexane) (92) or by H2O2 treatment (93), the elevated oxidative stress in the PC12 cell line used in both studies was reversed by taurine treatment. Moreover, apoptosis was prevented in both studies by stabilizing and normalizing Bcl-2 levels through a mitochondria-dependent pathway.

Finally, it should be noted that redox parameters differ between normal (even immortalized) cells and cancer cells. Cancer cells suffer inherently from oxidative stress (94). Thus, it may be that taurine and its derivatives act differently and exert a distinct modulation of the redox balance of cancer cells, leading to autophagy or apoptosis. During non-malignant oxidative stress conditions, taurine, by restoring anti-apoptotic conditions (through stabilization of Bcl-2 levels), attenuates further cellular damage.

Taurine's modulation of autophagy via the JNK and ERK signaling pathways

Autophagy and apoptosis are two distinct molecular mechanisms: autophagy promotes cell survival, whereas apoptosis leads to cell death. However, they both share common molecular switches that highlight their tight intercommunication (for review see (95)). One of the main orchestrators deciding between the cellular autophagic response and apoptosis is the Bcl-2 (Bcl-xL, Mcl-1) anti-apoptotic protein family and their partner-interacting proteins (Beclin-1, Bax, PUMA, Bid, Bad). During oxidative stress in lung epithelial cells, the oxidation of Bcl-2 cysteine residues (Cys158 and Cys229) downregulates the Bcl-2 functions and induces apoptosis (96).

Importantly, the interaction between Bcl-2 and the MAPK/ERK 1/2 pathway that suppresses apoptosis is disrupted during oxidative stress. Cysteine oxidations of Bcl-2 lead to conformational changes (*e.g.*, through the formation of disulfide bridges) in the anti-apoptotic protein and help determine whether cells undergo apoptosis (74, 75). However, this is evidence of how oxidative stress influences, through signaling pathways, the apoptotic or autophagic behavior of the cell. Therefore, taurine has the potential to act, by being a potential redox modifier, as an adjuster of the cell's fate *via* the signaling pathways. During cancer, ROS have the ability to activate both the ERK1/2 and JNK1/2 pathways and induce autophagy and apoptosis (97). Regarding taurine, however, it is important to include that the formation of the taurine derivative NCT may influence ERK1/2 activation, potentially *via* oxidative mechanisms involving the Epidermal Growth Factor Receptor (EGFR) (97).

In general, an activated JNK1/2 cascade, *via* complex molecular switches, would lead to ERK1/2 deactivation (98). However, according to Fey *et al*. (99), there is potentially a sustained positive interaction between the ERK and JNK cascades *via* the dual specificity phosphatases (DUSPs) 4/16, which dephosphorylate JNK, thereby modulating its activity. Such enhanced JNK activation may contribute to increased apoptotic signaling in cells (99). Nevertheless, enhanced activation of p38 MAPK can reverse ERK/JNK-induced apoptosis by deactivating ERK signaling.

During previous experiments (12), taurine showed a strong dose-dependent inhibition of proliferation on multiple human cancer (breast, colon, cervical, and skin) cell lines. The *in vitro* growth-inhibitory/cytotoxic effect of taurine was consistent with the *in vivo* tumor inhibition in colon cancer xenografts. It was concluded that taurine's anticancer activity was associated with the hyperactivation of the JNK1/2 pathways. In contrast, the ERK1/2 MAPK pathway remained consistently activated compared with the negative control cells (*i.e.*, was not affected in its activation). This signaling hyperactivation likely induced mitochondrial-related autophagy and apoptosis in cancer cells, influenced by the elevated oxidative stress status of these cells.

The concentrations of taurine derivatives formed during cancer cell cultures or in xenograft tumors *in vivo* were not measured in these experiments. It would be worthwhile and revealing to do so in similar future experiments. However, taurine itself was observed to exert a strong signaling influence on the JNK pathway, during which the p38 MAPK remained inactive, and the activation of the ERK pathway remained relatively constant. Similar findings of signaling pathway activations, which induce cancer cell death *via* autophagy-related apoptosis, are described in a study conducted by Wong *et al*. (97).

Figure 3 illustrates the influence of taurine in normal cells, promoting cell survival, and in malignant cells, promoting autophagy-mediated cell death *via* apoptosis. Taurine's influence on cell survival (normal cells) and cell death (malignant cells) is mediated by regulating key autophagy proteins, including Bcl-2 and p53.

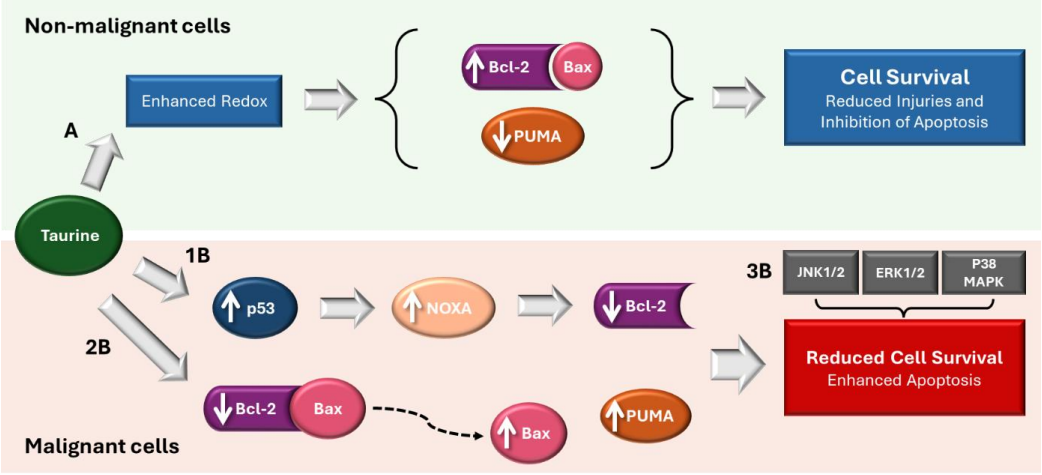

Figure 3.

The effects of taurine on apoptosis in the cases of non-malignant and malignant cells. **A**. Taurine, during non-malignancy, can stabilize the Bcl-2 anti-apoptotic proteins, maintaining the Bcl-2-Bax complex and downregulating PUMA. This enhances cellular survival and prevents injuries caused by apoptosis. **1B.** During malignancy, cancer cells are in a constant state of stress. Taurine upregulates p53 expression, which enhances the expression of NOXA proteins that downregulate Bcl-2 to induce apoptosis. **2B.** During malignancy, taurine downregulates the Bcl-2 and upregulates Bax and PUMA. This enhances apoptosis of cancer cells. **3B.** Moreover, the hyper-activation of the JNK1/2 signaling pathway, the upregulation of ERK1/2 through modulating oxidations of EGFR *via* taurine's derivative NCT, and the loss of p38 MAPK activation can contribute to apoptosis of cancer cells.

The expression of SlC6A6 and AZGP1 genes impacts taurine's pro-cancer effects

The gene SlC6A6 encodes the taurine transporter, Na^+/Cl^--dependent transporter (TauT), that is responsible for taurine as well as β-alanine, γ-aminobutyric acid (GABA), and hypotaurine transport across plasma membranes. The SlC6A6 expression is finely tuned by positive and negative feedback loops, as described in our previous review authored by members of this study (100). Some cancers, such as acute myeloid leukemia (AML), present increased expression of SlC6A6 due to hyperactive proto-oncogenes (101). As a result, taurine accumulates at a 1.7-fold higher level in leukemic bone marrow than in control bone marrow, a finding associated with the progression of leukemia. Interestingly, although AML cells initially require autophagic processes for survival, at later stages, leukemic stem cells (LSCs), which support leukemia progression, no longer require autophagy for survival (102). Therefore, taurine's previous influence on autophagy-mediated apoptosis (103) described in previous sections, seems unrelated to LCS cell progression. Thus, it is possible that, initially, AML cells benefit from taurine's over-accumulation due to TauT over-expression, but later stage LSCs, that do not use autophagy to survive, avoid the pro-apoptotic effects of taurine. The AZGP1 gene expresses the alpha-2-glycoprotein 1, zinc-binding protein (known as ZAG), which is an adipokine related to heart disease (104) (coronary disease, atherosclerosis, and stroke), to acute kidney disease (105), and to cancer progression (106). The ZAG-mediated metabolism in cancer enhances the mechanistic target of rapamycin (mTOR) P13/Akt signaling pathway, thereby increasing cell survival through autophagy (107). However, when overexpressed, it can downregulate the mTOR signaling pathway and repress tumor formation (108). Taurine, as well as proline, has been found for certain types of lung cancer to correlate with low ZAG expression rates and poor prognosis outcomes (108). To the best of our knowledge, the finding that taurine metabolism is associated with low ZAG expression requires further studies in this field, as low ZAG expression is frequently observed in other cancer cell types (109,110). This is due to an inherent genetic dysregulation in the cancer genome, independent of any taurine or proline treatment in these cells.

The dual effects of taurine in cancer inhibition or promotion

Taurine-mediated activation of autophagy has an anti-tumor effect in nasopharyngeal carcinoma (NPC). Both in vitro and in vivo studies described an upregulation of p53, LC3, and Beclin-1 by taurine, resulting in the shrinkage of NPC solid tumors (111,112).

Nevertheless, it cannot be ignored that taurine can also fuel cancer. The studies on AML and lung cancer promotion by taurine are, without doubt, serious clinical evidence. However, the central issue is: what key differentiator determines whether taurine promotes or inhibits cancer? Beyond the specific type of cancer cell or its level of differentiation, which controls whether it can utilize taurine beneficially to

proliferate (as is the case for leukemia cells), is the tumor microenvironment (TME) and the influence that taurine can have on it.

In the context of leukemogenesis, the recent study by Sharma *et al*. (113) showed that taurine and its transporter play a crucial role in the proliferation of aggressive myeloid cancers. This is due to mTOR upregulation and the subsequent increase in glycolytic rate induced by taurine uptake in the TME. This seems paradoxical because in other contexts, such as autoimmunity, taurine corrects CD4+ abnormalities by reducing mTORC1 signaling. Furthermore, although taurine has evident inhibitory activity against breast cancer, a recent study showed that taurine also plays a pro-proliferative role in this type of cancer (16). As the researchers of this study concluded, it is the cancer-promoting role of the taurine transporter, Slc6a6, that leads to uncontrolled proliferation in the TME by potentially exerting antioxidant capacity that enables cancer cells to survive and proliferate.

In summary, taurine is the identical molecule that may eradicate cancer and alleviate tumor-induced side effects, such as muscle atrophy, by functioning as an anti-inflammatory agent in the tumour microenvironment; yet, due to its concurrent transporter functions, taurine can also enhance cancer progression (114). Therefore, more studies on taurine dose and availability dependence in cancer are needed to elucidate these phenomena.

Taurine, the Warburg effect, and Autophagy.

In previous sections, it has been described how taurine, potentially by balancing redox potential during oxidative stress, can modulate autophagy, through which cancer cells die by apoptosis, mainly through Bcl-2 and scavenging of ROS (115). Relating taurine's physiological activities to the Warburg effect, Otto Warburg described that cancer cells survive even in the presence of oxygen by maximizing aerobic glycolysis, to produce ATP and metabolic intermediates (116). This describes the Warburg effect. However, during the Warburg effect, cancer cells vastly and rapidly metabolize glucose to produce lactate (an anaerobic glycolysis, lactic acid fermentation process), which is a low-energy-producing process, producing only two ATP molecules as compared to aerobic respiration in mitochondria that produces up to 32 ATP molecules (117). Nevertheless, due to the accelerated metabolism of glucose to lactate, cancer cells rapidly gain the energy they require to survive. In contrast, normal (non-malignant) cells utilize ATP more efficiently through oxidative phosphorylation, which is typically carried out by mitochondria.

Subsequently, cancer cells produce excess lactate and pyruvate via their glycolytic pathways (118). However, as established, non-malignant cells influenced by cancer cells follow a similar glycolytic pathway, producing lactate and pyruvate. The induction of the Warburg effect in non-malignant cells by cancer cells has been termed the reverse Warburg effect (119,120). In both malignant and non-malignant cells, the Warburg effect and the reverse Warburg effect, respectively, involve oxidative stress and an underlying mitochondrial dysfunction. Autophagy can be induced under various conditions associated with the Warburg effect, and it is particularly important for cancer cell survival and for protection against worse outcomes in other non-malignant disease conditions (120).

In the recent study performed by Kurtz *et al*. (121), that has reviewed several studies on taurine supplementation and exercise, one of the most striking findings is that taurine results in reduced lactate levels in muscles and blood.

Furthermore, iron overload is one of the major complications of β-thalassemia, resulting in ROS-dependent apoptosis (ferroptosis) due to increased oxidative stress (122). Concurrently increased lactate levels (lactic acidosis) can modulate ferroptosis, a process particularly important for cancer progression and survival (31). Therefore, therapeutic agents that can modulate lactic acidosis are valuable for disease prevention and for avoiding further deterioration in iron overload.

Moreover, in a recent study, a case of a patient with a β-thalassaemia trait was described who suffered from an iron homeostasis imbalance after mRNA COVID-19 vaccination (123). The patient had no recorded malignancy during the time of investigation. Regular and chronic taurine supplementation in this patient ameliorated iron overload, as evidenced by a reduction in blood ferritin levels (hyperferritinemia), and helped prevent lactic acidosis, which would further worsen the patient's hematological condition. The patient's low α-ketoglutarate and other TCA cycle metabolite levels relate to increased production of ROS in mitochondria, which leads to ferroptosis (31). Furthermore, in our previous experimentations on cancer cells, as already mentioned, it was found that taurine propagated autophagy by upregulating the JNK 1/2 pathway (12). The upregulation of JNK signaling under oxidative stress (ROS production) induces the autophagy-related proteins (Atg) and Beclin-1 (124). These proteins were also found to be upregulated by taurine during our cancer experimentations (12). Moreover, the upregulation of the Atg7 autophagic inducer protein is known to inhibit the Warburg effect and control cancer growth by maintaining autophagy (125).

Potentially, although further experimentation is needed to demonstrate the effect of taurine in controlling lactic acidosis, it is plausible that inhibition of the Warburg or reverse Warburg effect may have occurred in our patient's case (123). The induction

of the p53 tumor suppressor protein, as shown in our cancer study with taurine (12), has recently been found to suppress the Warburg effect (126). Interestingly, the patient described in the case study (123) also had elevated and long-lasting anti-p53 antibodies in the blood. Finally, taurine is known to reduce the expression of hypoxia-inducible factor 1α (HIF-1α) and other glycolytic enzymes, thereby reducing lactate production, which may contribute to the inhibition of the Warburg effect (127).

Conclusions

Taurine and its derivatives, NCT and NBrT, can modulate autophagy by influencing the redox potential of the cellular environment during oxidative stress. Several studies on thiol-disulfide exchange regulation point to taurine being either an indirect or a direct regulator. The increased oxidation of key cysteine residues in proteins such as Keap-1 and Bcl-2 may trigger the release of Nrf-2 and Beclin-1 from their respective complexes, promoting the initiation and propagation of autophagy. Moreover, taurine's influence on thiol-disulfide bridge balancing can also regulate apoptosis. The known stabilization of Bcl-2 and downregulation of PUMA by taurine in non-malignant cells exert a potential protective effect on injured cells against further injury induced by apoptosis. In contrast, taurine can downregulate Bcl-2 and upregulate Bax and PUMA in malignant cells, thereby driving cancer cells toward apoptosis via autophagy. In malignant cells, taurine synergistically contributes to the hyperactivation of the JNK1/2 pathway but does not appear to upregulate the p38 MAPK pathway. Meanwhile, the taurine derivative NCT can upregulate the ERK 1/2 pathway, inducing a potent apoptotic response across various cancer cell types. Moreover, the hyper-activation of the JNK 1/2 pathway in cancer cells by taurine can also activate the ERK 1/2 pathway to induce apoptosis, a process better characterized as autophagy-mediated cell death (apoptosis).

Inherent genetic dysregulation in cancer cells, such as SlC6A6 and AZGP1 gene expression, along with autophagy defects found in LSCs, may explain taurine's anticancer effects. In some cases, taurine appears to fuel certain cancers, such as AML, primarily through the SLC6A6 transporter and upregulation of glycolysis in the TME. Nevertheless, in other types of cancer, such as nasopharyngeal carcinoma and breast cancer, taurine inhibits tumor proliferation and kills tumor cells by apoptosis and via autophagy-mediated cell death. Finally, as the evidence presented suggests that taurine prevents lactic acidosis in non-malignant conditions, and several other studies report systemic reductions in lactate, further studies could explore whether taurine's anti-cancer efficacy is also attributable to inhibition of the Warburg effect through regulation of autophagy-mediated cell death.

Acknowledgement

Not applicable.

Funding

Not applicable.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

AI use disclosure

Not applicable.

Conflict of interest

Stephanie Seneff received funding from Quanta Computer, Inc., Taoyuan, Taiwan, under contract number 6950759. The other authors declare no conflict of interest.

References

1. Baliou S, Adamaki M, Ioannou P, Pappa A, Panayiotidis MI, Spandidos DA, et al. Protective role of taurine against oxidative stress (review). Mol Med Rep. 2021;24(4):605.
2. Seneff S, Kyriakopoulos AM. Taurine prevents mitochondrial dysfunction and protects mitochondria from reactive oxygen species and deuterium toxicity. Amino Acids. 2025;57(1):6.
3. Reddy VP. Oxidative stress in health and disease. Biomedicines. 2023;11(11):2925.
4. Huang JS, Chuang LY, Guh JY, Yang YL, Hsu MS. Effect of taurine on advanced glycation end products-induced hypertrophy in renal tubular epithelial cells. Toxicol Appl Pharmacol. 2008;233(2):220-226.
5. Huang JS, Chuang LY, Guh JY, Huang YJ. Effects of nitric oxide and antioxidants on advanced glycation end products-induced hypertrophic growth in human renal tubular cells. Toxicol Sci. 2009;111(1):109-119.
6. Hamanaka RB, Chandel NS. Mitochondrial reactive oxygen species regulate cellular signaling and dictate biological outcomes. Trends Biochem Sci. 2010;35(9):505-513.
7. Huang G, Shi LZ, Chi H. Regulation of JNK and p38 MAPK in the immune system: signal integration, propagation and termination. Cytokine. 2009;48(3):161-169.
8. Rusten TE. Autophagy regulation by signaling. Curr Opin Cell Biol. 2025;97:102595.
9. Liu S, Yao S, Yang H, Liu S, Wang Y. Autophagy: regulator of cell death. Cell Death Dis. 2023;14(10):648.
10. Yahyavy S, Valizadeh A, Saki G, Khorsandi L. Taurine induces autophagy and inhibits oxidative stress in mice

Leydig cells. JBRA Assist Reprod. 2020;24(3):250-256.
11. Sun Y, Dai S, Tao J, Li Y, He Z, Liu Q, et al. Taurine suppresses ROS-dependent autophagy via activating Akt/mTOR signaling pathway in calcium oxalate crystals-induced renal tubular epithelial cell injury. Aging. 2020;12(17):17353-17366.
12. Baliou S, Goulielmaki M, Ioannou P, Cheimonidi C, Trougakos IP, Nagl M, et al. Bromamine T (BAT) exerts stronger anti-cancer properties than taurine (Tau). Cancers (Basel). 2021;13(2):182.
13. Cao T, Zhang W, Wang Q, Wang C, Ma W, Zhang C, et al. Cancer SLC6A6-mediated taurine uptake transactivates immune checkpoint genes and induces exhaustion in CD8+ T cells. Cell. 2024;187(9):2288-2304.e27.
14. Sharma A, Jasrotia S, Kumar A. Effects of chemotherapy on the immune system: implications for cancer treatment and patient outcomes. Naunyn Schmiedebergs Arch Pharmacol. 2024;397(5):2551-2566.
15. Park H, Kim J, Shin C, Lee S. Intersection between redox homeostasis and autophagy: valuable insights into neurodegeneration. Antioxidants (Basel). 2021;10(5):694.
16. Cai P, Liu X, Lin M, Xie S, Yuan L, Lin Z, et al. The taurine-Slc6a6 axis promotes breast cancer progression by alleviating oxidative stress and accelerating cell cycle progression. Cells. 2026;15(2):207.
17. Mariño G, Niso-Santano M, Baehrecke EH, Kroemer G. Self-consumption: the interplay of autophagy and apoptosis. Nat Rev Mol Cell Biol. 2014;15(2):81-94.
18. Wirawan E, Vande Walle L, Kersse K, Cornelis S, Claerhout S, Vanoverberghe I, et al. Caspase-mediated cleavage of Beclin-1 inactivates Beclin-1-induced autophagy and enhances apoptosis by promoting the release of proapoptotic factors from mitochondria. Cell Death Dis. 2010;1(1):e18.
19. Rubinstein AD, Eisenstein M, Ber Y, Bialik S, Kimchi A. The autophagy protein Atg12 associates with antiapoptotic Bcl-2 family members to promote mitochondrial apoptosis. Mol Cell. 2011;44(5):698-709.
20. Yuan HX, Xiong Y, Guan KL. Nutrient sensing, metabolism, and cell growth control. Mol Cell. 2013;49(3):379-387.
21. Proud CG. Phosphorylation and signal transduction pathways in translational control. Cold Spring Harb Perspect Biol. 2019;11(7):a033050.
22. Sridharan S, Jain K, Basu A. Regulation of autophagy by kinases. Cancers (Basel). 2011;3(2):2630-2654.
23. Hazzalin CA, Mahadevan LC. MAPK-regulated transcription: a continuously variable gene switch? Nat Rev Mol Cell Biol. 2002;3(1):30-40.
24. MacDonald BT, Tamai K, He X. Wnt/beta-catenin signaling: components, mechanisms, and diseases. Dev Cell. 2009;17(1):9-26.
25. Kim J, Kundu M, Viollet B, Guan KL. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nat Cell Biol. 2011;13(2):132-141.
26. Han JH, Park HS, Lee DH, Jo JH, Heo KS, Myung CS. Regulation of autophagy by controlling Erk1/2 and mTOR for platelet-derived growth factor-BB-mediated vascular smooth muscle cell phenotype shift. Life Sci. 2021;267:118978.
27. Di Nardo A, Wertz MH, Kwiatkowski E, Tsai PT, Leech JD, Greene-Colozzi E, et al. Neuronal Tsc1/2 complex controls autophagy through AMPK-dependent regulation of ULK1. Hum Mol Genet. 2014;23(14):3865-3874.
28. Dalle Pezze P, Ruf S, Sonntag AG, Langelaar-Makkinje M, Hall P, Heberle AM, et al. A systems study reveals concurrent activation of AMPK and mTOR by amino acids. Nat Commun. 2016;7:13254.
29. Alers S, Löffler AS, Wesselborg S, Stork B. Role of AMPK-mTOR-Ulk1/2 in the regulation of autophagy: cross talk, shortcuts, and feedbacks. Mol Cell Biol. 2012;32(1):2-11.
30. Sun W, Jia M, Feng Y, Cheng X. Lactate is a bridge linking glycolysis and autophagy through lactylation. Autophagy. 2023;19(12):3240-3241.
31. Wu N, Wei X, Yu S, Yang L, Zhang X. Lactate in ferroptosis regulation: a new perspective on tumor progression and therapy. Pharmacol Res. 2025;218:107841.
32. Vergne I, Deretic V. The role of PI3P phosphatases in the regulation of autophagy. FEBS Lett. 2010;584(7):1313-1318.
33. Vega-Rubín-de-Celis S, Kinch L, Peña-Llopis S. Regulation of beclin 1-mediated autophagy by oncogenic tyrosine kinases. Int J Mol Sci. 2020;21(23):9210.
34. Marquez RT, Xu L. Bcl-2:Beclin 1 complex: multiple mechanisms regulating autophagy/apoptosis toggle switch. Am J Cancer Res. 2012;2(2):214-221.
35. He C, Zhu H, Li H, Zou MH, Xie Z. Dissociation of Bcl-2-Beclin1 complex by activated AMPK enhances cardiac autophagy and protects against cardiomyocyte apoptosis in diabetes. Diabetes. 2013;62(4):1270-1281.
36. De Chiara G, Marcocci ME, Torcia M, Lucibello M, Rosini P, Bonini P, et al. Bcl-2 phosphorylation by p38 MAPK: identification of target sites and biologic consequences. J Biol Chem. 2006;281(30):21353-21361.
37. Gómez-Virgilio L, Silva-Lucero MD, Flores-Morelos DS, Gallardo-Nieto J, Lopez-Toledo G, Abarca-Fernandez AM, et al. Autophagy: a key regulator of homeostasis and disease: an overview of molecular mechanisms and modulators. Cells. 2022;11(15):2262.
38. Denton D, Kumar S. Autophagy-dependent cell death. Cell Death Differ. 2019;26(4):605-616.
39. Kroemer G, Levine B. Autophagic cell death: the story of a misnomer. Nat Rev Mol Cell Biol. 2008;9(12):1004-1010.
40. Guo JY, Chen HY, Mathew R, Fan J, Strohecker AM, Karsli-Uzunbas G, et al. Activated Ras requires autophagy to maintain oxidative metabolism and tumorigenesis. Genes Dev. 2011;25(5):460-470.
41. Elgendy M, Sheridan C, Brumatti G, Martin SJ. Oncogenic Ras-induced expression of Noxa and Beclin-1 promotes autophagic cell death and limits clonogenic survival. Mol Cell. 2011;42(1):23-35.
42. Dumont A, Lohard S, Maillet L, Juin PP, Barillé-Nion S. NOXA the BCL-2 family member behind the scenes in cancer treatment. J Cell Signal. 2020;1(4):127-143.
43. Liang L, Weng J, You Y, He Q, Fan Y, Liao G. Role of Noxa in proliferation, apoptosis, and autophagy in human adenoid cystic carcinoma. J Oral Pathol Med. 2019;48(1):52-59.

44. Liu Y, Levine B. Autosis and autophagic cell death: the dark side of autophagy. Cell Death Differ. 2015;22(3):367-376.
45. Shen T, Miao Y, Ding C, Fan W, Liu S, Lv Y, et al. Activation of the p38/MAPK pathway regulates autophagy in response to the CYPOR-dependent oxidative stress induced by zearalenone in porcine intestinal epithelial cells. Food Chem Toxicol. 2019;131:110527.
46. Zhou YY, Li Y, Jiang WQ, Zhou LF. MAPK/JNK signalling: a potential autophagy regulation pathway. Biosci Rep. 2015;35(3):e00199.
47. Kang R, Zeh HJ, Lotze MT, Tang D. The Beclin 1 network regulates autophagy and apoptosis. Cell Death Differ. 2011;18(4):571-580.
48. Zalckvar E, Berissi H, Mizrachy L, Idelchuk Y, Koren I, Eisenstein M, et al. DAP-kinase-mediated phosphorylation on the BH3 domain of beclin 1 promotes dissociation of beclin 1 from Bcl-XL and induction of autophagy. EMBO Rep. 2009;10(3):285-292.
49. Tran S, Fairlie WD, Lee EF. BECLIN1: protein structure, function and regulation. Cells. 2021;10(6):1522.
50. Yu C, Xiao JH. The Keap1-Nrf2 system: a mediator between oxidative stress and aging. Oxid Med Cell Longev. 2021;2021:6635460.
51. Shan C, Wang Y, Wang Y. The crosstalk between autophagy and Nrf2 signaling in cancer: from biology to clinical applications. Int J Biol Sci. 2024;20(15):6181-6206.
52. Rojo de la Vega M, Chapman E, Zhang DD. NRF2 and the hallmarks of cancer. Cancer Cell. 2018;34(1):21-43.
53. Kansanen E, Kivelä AM, Levonen AL. Regulation of Nrf2-dependent gene expression by 15-deoxy-Delta12,14-prostaglandin J2. Free Radic Biol Med. 2009;47(9):1310-1317.
54. Saha S, Buttari B, Panieri E, Profumo E, Saso L. An overview of Nrf2 signaling pathway and its role in inflammation. Molecules. 2020;25(22):5474.
55. Yamamoto T, Suzuki T, Kobayashi A, Wakabayashi J, Maher J, Motohashi H, et al. Physiological significance of reactive cysteine residues of Keap1 in determining Nrf2 activity. Mol Cell Biol. 2008;28(8):2758-2770.
56. Cleasby A, Yon J, Day PJ, Richardson C, Tickle IJ, Williams PA, et al. Structure of the BTB domain of Keap1 and its interaction with the triterpenoid antagonist CDDO. PLoS One. 2014;9(6):e98896.
57. Shi Y, Zhong L, Fan Y, Zhang J, Dai J, Zhong H, et al. Taurine inhibits hydrogen peroxide-induced oxidative stress, inflammatory response and apoptosis in liver of Monopterus albus. Fish Shellfish Immunol. 2022;128:536-546.
58. Li JX, Pang YZ, Tang CS, Li ZQ. Protective effect of taurine on hypochlorous acid toxicity to nuclear nucleoside triphosphatase in isolated nuclei from rat liver. World J Gastroenterol. 2004;10(5):694-698.
59. Rovira-Llopis S, Rocha M, Falcon R, de Pablo C, Alvarez A, Jover A, et al. Is myeloperoxidase a key component in the ROS-induced vascular damage related to nephropathy in type 2 diabetes? Antioxid Redox Signal. 2013;19(13):1452-1458.
60. Seol SI, Kang IS, Lee JS, Lee JK, Kim C. Taurine chloramine-mediated Nrf2 activation and HO-1 induction confer protective effects in astrocytes. Antioxidants (Basel). 2024;13(2):169.
61. De Carvalho Bertozo L, Morgon NH, De Souza AR, Ximenes VF. Taurine bromamine: reactivity of an endogenous and exogenous anti-inflammatory and antimicrobial amino acid derivative. Biomolecules. 2016;6(2):23.
62. Olszanecki R, Kurnyta M, Biedroń R, Chorobik P, Bereta M, Marcinkiewicz J. The role of heme oxygenase-1 in down regulation of PGE2 production by taurine chloramine and taurine bromamine in J774.2 macrophages. Amino Acids. 2008;35(2):359-364.
63. Dodson M, de la Vega MR, Cholanians AB, Schmidlin CJ, Chapman E, Zhang DD. Modulating NRF2 in disease: timing is everything. Annu Rev Pharmacol Toxicol. 2019;59:555-575.
64. Hammad M, Raftari M, Cesário R, Salma R, Godoy P, Emami SN, et al. Roles of oxidative stress and Nrf2 signaling in pathogenic and non-pathogenic cells: a possible general mechanism of resistance to therapy. Antioxidants (Basel). 2023;12(7):1371.
65. Li R, Yan X, Zhao Y, Liu H, Wang J, Yuan Y, et al. Oxidative stress induced by nuclear factor erythroid 2-related factor 2 (NRF2) dysfunction aggravates chronic inflammation through the NAD+/SIRT3 axis and promotes renal injury in diabetes. Antioxidants (Basel). 2025;14(3):267.
66. Nagy P. Kinetics and mechanisms of thiol-disulfide exchange covering direct substitution and thiol oxidation-mediated pathways. Antioxid Redox Signal. 2013;18(13):1623-1641.
67. Seidel U, Huebbe P, Rimbach G. Taurine: a regulator of cellular redox homeostasis and skeletal muscle function. Mol Nutr Food Res. 2019;63(16):e1800569.
68. Dikmeer A, Eren F, Neselioglu S, Sahiner Z, Hafizoglu M, Karaduman D, et al. The Predictive Role of Thiol/Disulfide Homeostasis as an Oxidative Stress Parameter in Sarcopenic Obesity. Medicina. 2025;61(9):1708.
69. Sevin G, Kerry Z, Sozer N, Ozsarlak-Sozer G. Taurine supplementation protects lens against glutathione depletion. Eur Rev Med Pharmacol Sci. 2021;25(13):4520-4526.
70. Bien M, Longen S, Wagener N, Chwalla I, Herrmann JM, Riemer J. Mitochondrial disulfide bond formation is driven by intersubunit electron transfer in Erv1 and proofread by glutathione. Mol Cell. 2010;37(4):516-528.
71. Gashlan HM, Hana M, Mariam A. Blood lipid peroxidation (malondialdehyde), thiol, taurine levels and oxidative stress in Saudi diabetic patients. Biosci Biotech Res Asia. 2010;7:623-633.
72. Chen Q, Li Z, Pinho RA, Gupta RC, Ugbolue UC, Thirupathi A, et al. The dose response of taurine on aerobic and strength exercises: a systematic review. Front Physiol. 2021;12:700352.
73. Yıldırım MA, Kocabaş R, Kılınç İ, Şimşek G, Şentürk M, Çakır M, et al. Role of thiol-disulfide hemostasis in early diagnosis of acute mesentery ischemia: an experimental study. Ulus Travma Acil Cerrahi Derg. 2022;28(4):403-410.
74. Kowaltowski AJ, Fiskum G. Redox mechanisms of cytoprotection by Bcl-2. Antioxid Redox Signal. 2005;7(3-4):508-514.
75. Zając A, Maciejczyk A, Sumorek-Wiadro J, Filipek K, Deryło K, Langner E, et al. The role of Bcl-2 and

Beclin-1 complex in "switching" between apoptosis and autophagy in human glioma cells upon LY294002 and sorafenib treatment. Cells. 2023;12(23):2670.
76. Mahajan NP, Linder K, Berry G, Gordon GW, Heim R, Herman B. Bcl-2 and Bax interactions in mitochondria probed with green fluorescent protein and fluorescence resonance energy transfer. Nat Biotechnol. 1998;16(6):547-552.
77. Mansour MA, El-Salamoni MA, Mostafa HN. Harnessing PUMA's lethal potential: BCL-2 family dynamics and novel strategies to combat cancer recurrence. Cancer Treat Res Commun. 2025;44:100975.
78. Vervliet T, Parys JB, Bultynck G. Bcl-2 proteins and calcium signaling: complexity beneath the surface. Oncogene. 2016;35(39):5079-5092.
79. Cosulich SC, Worrall V, Hedge PJ, Green S, Clarke PR. Regulation of apoptosis by BH3 domains in a cell-free system. Curr Biol. 1997;7(12):913-920.
80. Dewson G, Kratina T, Sim HW, Puthalakath H, Adams JM, Colman PM, et al. To trigger apoptosis, Bak exposes its BH3 domain and homodimerizes via BH3:groove interactions. Mol Cell. 2008;30(3):369-380.
81. Dewson G, Ma S, Frederick P, Hockings C, Tan I, Kratina T, et al. Bax dimerizes via a symmetric BH3:groove interface during apoptosis. Cell Death Differ. 2012;19(4):661-670.
82. Tu S, Zhang XL, Wan HF, Xia YQ, Liu ZQ, Yang XH, et al. Effect of taurine on cell proliferation and apoptosis human lung cancer A549 cells. Oncol Lett. 2018;15(4):5473-5480.
83. Helaly NA, Esheba NE, Ammo DEA, Elwan NM, Elkholy RA. High Bax/Bcl-2 ratio is associated with good prognosis and better survival in patients with B cell chronic lymphocytic leukemia. Leuk Res. 2021;107:106604.
84. Xu M, Yu Y, Cao C. The dual role of taurine in cancer and immune metabolism. Trends Endocrinol Metab. 2025;36(10):878-881.
85. Barbiera A, Sorrentino S, Lepore E, Carfì A, Sica G, Dobrowolny G, et al. Taurine attenuates catabolic processes related to the onset of sarcopenia. Int J Mol Sci. 2020;21(22):8865.
86. Vela L, Gonzalo O, Naval J, Marzo I. Direct interaction of Bax and Bak proteins with Bcl-2 homology domain 3 (BH3)-only proteins in living cells revealed by fluorescence complementation. J Biol Chem. 2013;288(7):4935-4946.
87. Hantusch A, Rehm M, Brunner T. Counting on death - quantitative aspects of Bcl-2 family regulation. FEBS J. 2018;285(22):4124-4138.
88. Ghosh AP, Walls KC, Klocke BJ, Toms R, Strasser A, Roth KA. The proapoptotic BH3-only, Bcl-2 family member, Puma is critical for acute ethanol-induced neuronal apoptosis. J Neuropathol Exp Neurol. 2009;68(7):747-756.
89. Chen SH, Chen L. Clinical implications of taurine in breast cancer. Biochem Biophys Rep. 2025;44:102315.
90. Chen W, Li Q, Hou R, Liang H, Zhang Y, Yang Y. An integrated metabonomics study to reveal the inhibitory effect and metabolism regulation of taurine on breast cancer. J Pharm Biomed Anal. 2022;214:114711.
91. Pavlides S, Vera I, Gandara R, Sneddon S, Pestell RG, Mercier I, et al. Warburg meets autophagy: cancer-associated fibroblasts accelerate tumor growth and metastasis via oxidative stress, mitophagy, and aerobic glycolysis. Antioxid Redox Signal. 2012;16(11):1264-1284.
92. Li S, Guan H, Qian Z, Sun Y, Gao C, Li G, et al. Taurine inhibits 2,5-hexanedione-induced oxidative stress and mitochondria-dependent apoptosis in PC12 cells. Ind Health. 2017;55(2):108-118.
93. Pan C, Giraldo GS, Prentice H, Wu JY. Taurine protection of PC12 cells against endoplasmic reticulum stress induced by oxidative stress. J Biomed Sci. 2010;17(Suppl 1):S17.
94. Grek CL, Tew KD. Redox metabolism and malignancy. Curr Opin Pharmacol. 2010;10(4):362-368.
95. Wu HJ, Pu JL, Krafft PR, Zhang JM, Chen S. The molecular mechanisms between autophagy and apoptosis: potential role in central nervous system disorders. Cell Mol Neurobiol. 2015;35(1):85-99.
96. Luanpitpong S, Chanvorachote P, Stehlik C, Tse W, Callery PS, Wang L, et al. Regulation of apoptosis by Bcl-2 cysteine oxidation in human lung epithelial cells. Mol Biol Cell. 2013;24(6):858-869.
97. Wong CH, Iskandar KB, Yadav SK, Hirpara JL, Loh T, Pervaiz S. Simultaneous induction of non-canonical autophagy and apoptosis in cancer cells by ROS-dependent ERK and JNK activation. PLoS One. 2010;5(4):e9996.
98. Shen YH, Godlewski J, Zhu J, Sathyanarayana P, Leaner V, Birrer MJ, et al. Cross-talk between JNK/SAPK and ERK/MAPK pathways: sustained activation of JNK blocks ERK activation by mitogenic factors. J Biol Chem. 2003;278(29):26715-26721.
99. Fey D, Croucher DR, Kolch W, Kholodenko BN. Crosstalk and signaling switches in mitogen-activated protein kinase cascades. Front Physiol. 2012;3:355.
100. Baliou S, Kyriakopoulos AM, Goulielmaki M, Panayiotidis MI, Spandidos DA, Zoumpourlis V. Significance of taurine transporter (TauT) in homeostasis and its layers of regulation (review). Mol Med Rep. 2020;22(3):2163-2173.
101. Santoro N, Salutari P, Di Ianni M, Marra A. Precision Medicine Approaches in Acute Myeloid Leukemia with Adverse Genetics. Int J Mol Sci. 2024; 25(8):4259.
102. Porter AH, Leveque-El Mouttie L, Vu T, Bruedigam C, Sutton J, Jacquelin S, et al. Acute myeloid leukemia stem cell function is preserved in the absence of autophagy. Haematologica. 2017;102(9):e344-e347.
103. Chen Q, Kang J, Fu C. The independence of and associations among apoptosis, autophagy, and necrosis. Signal Transduct Target Ther. 2018;3:18.
104. Huang D, Mao X, Peng J, Cheng M, Bai T, Du M, et al. Role of adipokine zinc-α2-glycoprotein in coronary heart disease. Am J Physiol Endocrinol Metab. 2019;317(6):E1055-E1062.
105. Sörensen-Zender I, Beneke J, Schmidt BM, Menne J, Haller H, Schmitt R. Zinc-alpha2-glycoprotein in patients with acute and chronic kidney disease. BMC Nephrol. 2013;14:145.
106. Bing C, Bao Y, Jenkins J, Sanders P, Manieri M, Cinti S, et al. Zinc-alpha2-glycoprotein, a lipid mobilizing factor, is expressed in adipocytes and is up-regulated in mice with cancer cachexia. Proc Natl Acad Sci USA. 2004;101(8):2500-2505.

107. Verma S, Giagnocavo SD, Curtin MC, Arumugam M, Osburn-Staker SM, Wang G, et al. Zinc-alpha-2-glycoprotein secreted by triple-negative breast cancer promotes peritumoral fibrosis. Cancer Res Commun. 2024;4(6):1655-1666.
108. Liang TL, Chen Y, Zhou NJ, Shu X, Mi JN, Ma GY, et al. Taurine and proline promote lung tumour growth by co-regulating Azgp1/mTOR signalling pathway. NPJ Precis Oncol. 2025;9(1):90.
109. Liu J, Han H, Fan Z, El Beaino M, Fang Z, Li S, et al. AZGP1 inhibits soft tissue sarcoma cells invasion and migration. BMC Cancer. 2018;18(1):89.
110. Huang CY, Zhao JJ, Lv L, Chen YB, Li YF, Jiang SS, et al. Decreased expression of AZGP1 is associated with poor prognosis in primary gastric cancer. PLoS One. 2013;8(7):e69155.
111. Lai L, Wang Y, Peng S, Guo W, Li F, Xu S. P53 and taurine upregulated gene 1 promotes the repair of the deoxyribonucleic acid damage induced by bupivacaine in murine primary sensory neurons. Bioengineered. 2022;13(3):7439-7456.
112. Okano M, He F, Ma N, Kobayashi H, Oikawa S, Nishimura K, et al. Taurine induces upregulation of p53 and Beclin1 and has antitumor effect in human nasopharyngeal carcinoma cells in vitro and in vivo. Acta Histochem. 2023;125(1):151978.
113. Sharma S, Rodems BJ, Baker CD, Kaszuba CM, Franco EI, Smith BR, et al. Taurine from tumour niche drives glycolysis to promote leukaemogenesis. Nature. 2025;644(8075):263-272.
114. Chen CH, Chen YC, Chang YC, Hung CH, Huang CY, Tsai CL, et al. Taurine rescues cancer-induced atrophy in human skeletal muscle cells via ameliorating the inflammatory tumor microenvironment. Anticancer Res. 2024;44(5):1963-1971.
115. Levine B, Sinha S, Kroemer G. Bcl-2 family members: dual regulators of apoptosis and autophagy. Autophagy. 2008;4(5):600-606.
116. Botti J, Djavaheri-Mergny M, Pilatte Y, Codogno P. Autophagy signaling and the cogwheels of cancer. Autophagy. 2006;2(2):67-73.
117. Liberti MV, Locasale JW. The Warburg effect: how does it benefit cancer cells? Trends Biochem Sci. 2016;41(3):211-218.
118. El Sayed SM. Biochemical origin of the Warburg effect in light of 15 years of research experience: a novel evidence-based view (an expert opinion article). Onco Targets Ther. 2023;16:143-155.
119. Vincent AS, Phan TT, Mukhopadhyay A, Lim HY, Halliwell B, Wong KP. Human skin keloid fibroblasts display bioenergetics of cancer cells. J Invest Dermatol. 2008;128(3):702-709.
120. Gonzalez CD, Alvarez S, Ropolo A, Rosenzvit C, Bagnes MF, Vaccaro MI. Autophagy, Warburg, and Warburg reverse effects in human cancer. Biomed Res Int. 2014;2014:926729.
121. Kurtz JA, VanDusseldorp TA, Doyle JA, Otis JS. Taurine in sports and exercise. J Int Soc Sports Nutr. 2021;18(1):39.
122. Lin S, Zheng Y, Chen M, Xu L, Huang H. The interactions between ineffective erythropoiesis and ferroptosis in β-thalassemia. Front Physiol. 2024;15:1346173.
123. Kyriakopoulos AM, McCullough PA, Seneff S. Taurine intake ameliorates lactic acidosis and hyperferritinemia occurring after mRNA SARS-CoV-2 vaccination in a patient with β-thalassemia trait: a case report and review of literature. J Med Case Rep. 2026;20(1):108.
124. Cao Y, Klionsky DJ. Physiological functions of Atg6/Beclin 1: a unique autophagy-related protein. Cell Res. 2007;17(10):839-849.
125. Feng Y, Liu J, Guo W, Guan Y, Xu H, Guo Q, et al. Atg7 inhibits Warburg effect by suppressing PKM2 phosphorylation resulting reduced epithelial-mesenchymal transition. Int J Biol Sci. 2018;14(7):775-783.
126. Centeno D, Farsinejad S, Kochetkova E, Volpari T, Gladych-Macioszek A, Klupczynska-Gabryszak A, et al. Modeling of intracellular taurine levels associated with ovarian cancer reveals activation of p53, ERK, mTOR and DNA-damage-sensing-dependent cell protection. Nutrients. 2024;16(12):1816.
127. Chen X, Wenting A, Zhiqing H, Jia G, Zhao H. Taurine reduces glycolysis of pig skeletal muscle by inhibiting HIF-1α signaling. J Cell Physiol. 2025;240(2):e31461.