

Review Article

14-3-3 proteins: an important regulator of autophagy in diseases

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Abstract: Autophagy is a cell digestion process that determines cell fate by promoting cell survival or inducing cell death in a cell context-dependent manner. Several classical signaling pathways, such as phosphoinositide-3-kinase and mammalian target of rapamycin, tightly regulate autophagy. 14-3-3 proteins regulate various signaling pathways by phosphorylation-dependent binding with partner proteins. 14-3-3 proteins also regulate autophagy by binding with autophagy-related proteins such as Beclin-1 and hVPS34. This review summarizes the role of 14-3-3 proteins in the control of autophagy in cancer, neurodegenerative diseases and other pathological conditions.

Keywords: 14-3-3 proteins, autophagy, cancer, neurodegenerative diseases

Introduction

Autophagy is a conserved process that plays a crucial role in many biological processes and pathological conditions, including adaptation to stress, metabolism, inflammation, neurodegenerative disorders and cancer [1]. Autophagy is classified into three subtypes: macroautophagy, microautophagy and chaperone-mediated autophagy [2]. Microautophagy is a process in which cytoplasmic content is directly engulfed into the lysosome [3]. Chaperone-mediated autophagy has been reported only in mammalian cells. In chaperone-mediated autophagy, the chaperone complex HSC70 recognizes the cytoplasmic content that contains the Lys-Phe-Glu-Arg-Gln (KFERQ) pentapeptide recognition sequence and subsequently binds to lysosome-associated membrane protein type 2A (LAMP-2A) for degrading the recognized cytoplasmic content [4]. Macroautophagy is referred to as autophagy that is a highly conserved process from yeast to mammals, and it has critical effect on various pathological conditions such as kidney diseases [5], cancers [6], immune responses [7], and infections [8] though the regulation of cell survival and cell death.

Overview of autophagy

Autophagy, also known as “self-eating” is a process in which damaged cell organelles and mis-

folded proteins are sequestered into autophagosomes, which then fuse with lysosomes to form autolysosomes. In autolysosomes, cytoplasmic constituents are degraded by lysosomal hydrolases for cyclic utilization. The formation of double-membrane autophagosomes involves the following steps: induction, nucleation, elongation, and formation a complete isolation membrane [9]. The ULK1/2-Atg13-FIP200 complex is required for the formation of phagophore membranes. For nucleation, the phagophore membrane phosphoinositide-3-kinase (PI3K)/Vps34 complex containing Vps34, Vps15, Beclin-1 is recruited. The Atg12-Atg5-Atg16 complex and Atg8/light chain 3-II (LC3-II) are two ubiquitin-like conjugation systems involved in the elongation and expansion steps in autophagosome formation. Mitogen-activated protein kinase (MAPK) and PI3K inhibit autophagy by activating the mammalian target of rapamycin (mTOR) complex. However, P53 has the opposite effect. The protein 5' adenosine monophosphate-activated protein kinase (AMPK) activates autophagy by upregulating the ULK1 complex. The process of autolysosome formation is shown in **Figure 1**.

Role of autophagy in neurodegenerative diseases

A common features of neurodegenerative diseases is the accumulation of a large number of

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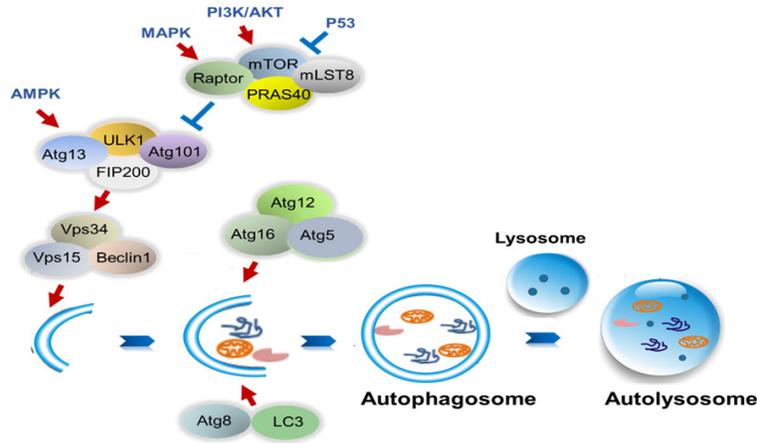


Figure 1. Model of regulation of autophagy process. The ULK1-Atg13-FIP200 complex promotes the recruitment of PI3K/Vps34 complex to phagophore membranes. The Atg12-Atg5-Atg16 complex and Atg8/LC3 are involved in the elongation and expansion steps of autophagosome formation. MAPK and PI3K inhibit autophagy by activating the mTOR complex; however, P53 has the opposite effect. AMPK activates autophagy by upregulating the ULK1 complex.

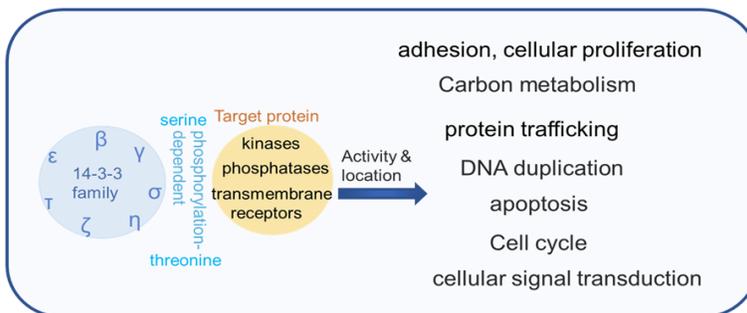


Figure 2. Model of the biological process of 14-3-3 proteins regulation. The 14-3-3 family contains seven isoforms (β , ϵ , η , γ , τ , σ , and ζ), all of which bind to target proteins and alter the modification, intercellular localization, and activity of target proteins by interacting with specific phosphothreonine and phosphoserine motifs, and then regulating the biological processes.

misfolded proteins in the cytoplasm. Autophagy is essential for the maintenance of local homeostasis in axon terminals, and impaired autophagy induces axon atrophy [10]. Mutated PTEN induced putative kinase 1 (PINK1) is one of the main genes that causes Parkinson's disease. The full-length PINK1 protein interacts with Beclin-1 to promote autophagy; however, the activity of Beclin-1 is decreased and autophagy is inhibited when the PINK1 protein is mutated [11]. Ravikumar *et al* found that in fly and mouse models of Huntington's disease, the inhibition of mTOR induces autophagy and eliminates the accumulation of polyglutamine [12]. Under normal conditions, the β -amyloid

proteins are degraded by autophagy. By contrast, in Alzheimer's disease, β -amyloid proteins are aggravated because the autophagic flux is impaired [13]. Thus, autophagy plays a key role in neurodegenerative diseases.

Role of autophagy in cancers

The cancer is one of the diseases of serious threat to human health and life nowadays. Many studies have reported that autophagy plays a dual role in cancer. Tang *et al* demonstrated that in a model of liver cancer induced by HBV infection, the expression of Beclin-1 mRNA and protein is higher in liver cancer tissue than in the healthy liver tissue [14]. Another study also showed that in many patients with colorectal or gastric cancers, the expression of Beclin-1 is detected in more than 80% of cancer tissue though immunohistochemistry. By contrast, the expression of Beclin-1 is low in normal mucosal cells of colon and stomach [15]. These results indicate that Beclin-1 may promote the development of cancer by inducing autophagy. Ren *et al* showed that autophagy is associated with tumor resistance. The ex-

pression of LC3-II is found to be higher in A549 cells resistant to cisplatin. When combined with 3-methyladenine (3MA; an inhibitor of autophagy), cisplatin induces more apoptosis in A549 cells [16]. Similar results were observed in another study, in which cisplatin treatment resulted in higher Beclin-1 expression and autophagosome formation in rat C6 glioma, human U251 glioma, and mouse L929 fibrosarcoma cell lines. Treatment with bafilomycin A1 (BafA1), wortmannin, or chloroquine enhanced DNA fragmentation and apoptotic cell death induced by cisplatin. Further research revealed that inhibition of AMPK enhanced cancer cell death induced by cisplatin, whereas mTOR

siRNA had the opposite effect [17]. The findings of the aforementioned studies suggest that autophagy reduces the sensitivity of cells to chemotherapy drugs in cancer. By contrast, Li *et al* found that GFP-LC3 punctate are increased in gastric cancer cells during treatment with harmine. LY294002, an inhibitor of PI3K, significantly increased the harmine cytotoxicity to the cells by enhancing the expression of Beclin-1 and LC3-II. In addition, 3-MA and BafA1 improved the viability of gastric cancer cells treated with harmine [18]. Lysine (K)-Specific Demethylase 2B (KDM2B) is a member of the JmjC-domain-containing histone demethylase (JHDM) family, which functions as a histone lysine demethylase. KDM2B knockdown inhibited gastric cancer cell proliferation by activating autophagy. In a mouse xenograft tumor model, tumor growth was also inhibited by the downregulation of KDM2B [19]. Hu *et al* demonstrated that endoplasmic reticulum stress enhanced cell apoptosis by inhibiting the PI3K/AKT/mTOR signaling pathway, thus triggering autophagy in chemical-resistant ovarian cancer cells treated with cisplatin [20]. In summary, the findings demonstrate that autophagy plays a pro-apoptotic role in cancer.

Under different experimental conditions, autophagy is regulated by mTOR, AMPK, MAPK, and PI3K signaling pathways to promote cell death or facilitate cell survival. 14-3-3 proteins are commonly expressed in eukaryotes and are involved in numerous cell biology processes such as autophagy.

Overview of 14-3-3 proteins

The 14-3-3 protein family contains highly conserved acid proteins that were initially separated from bovine brain tissue [21]. 14-3-3 proteins are mainly detected in the cytoplasm, nucleus, and cell membrane of eukaryotic cells, and are distributed in the Golgi apparatus, mitochondria and chloroplast [22]. These proteins have seven isoforms (β , ϵ , η , γ , τ , σ and ζ) encoded by different genes in mammalian cells. The expression of 14-3-3 isoforms varies in different tissue types [23, 24].

14-3-3 proteins function as homodimers and heterodimers. They bind to target proteins and alter the modification, intercellular localization, and activity of target proteins, mostly by interacting with specific phosphothreonine and phosphoserine motifs [25]. 14-3-3 proteins are

crucial regulators of many biological processes such as cell cycle progression, intracellular protein trafficking, apoptosis, DNA damage response, DNA replication, and transcriptional regulation. The regulatory roles of 14-3-3 proteins in biological processes are shown in **Figure 2**. 14-3-3 ϵ , γ , and ζ activate Raf, PI3K, and MSK1/2 to regulate the ERK signaling pathway in human fibroblasts, breast cells, prostate cells, and hematopoietic stem cells [26-28]. Overexpression of 14-3-3 ζ promotes cancer cell proliferation whereas the downregulation of 14-3-3 ζ inhibits cell proliferation by inducing the mitochondria-dependent apoptosis pathway [29-31]. Our previous study demonstrated that human umbilical cord mesenchymal stem cell-exosomal 14-3-3 ζ activates YAP by phosphorylation at the Ser127 site and promoted the formation of YAP and p-LATS complex, which restricts excessive cell expansion and collagen deposition during cutaneous regeneration [32]. In a mouse model, difopein, a general 14-3-3 antagonist, and 14-3-3 siRNA induced human glioma cell apoptosis and suppressed tumor growth [33]. These findings suggest that 14-3-3 proteins play a critical role in the regulation of diverse cellular responses.

Regulation of autophagy by 14-3-3 proteins in cancers

Although the role of 14-3-3 proteins in human osteosarcoma is somewhat unclear [34], 14-3-3 proteins are known to promote tumorigenesis by inhibiting autophagy in lung cancer [35], glioma [36], renal cell carcinoma [37], and cervical cancer [38]. However, these proteins also promote pro-survival autophagy activation in human glioblastoma [40] and pancreatic cancer under certain conditions [41].

Overexpression 14-3-3 τ in human osteosarcoma U2OS cells enhances the transcript levels of Beclin-1 and its protein expression. By contrast, 14-3-3 τ depletion inhibits the expression of Beclin-1, and 14-3-3 τ depletion significantly decreases GFP-LC3 punctate in U2OS cells induced by serum starvation or rapamycin. Further research showed that 14-3-3 τ induces autophagy by controlling of the E2F1-Beclin-1 signal axis [34]. However, the effects of autophagy are largely unclear.

In human lung cancer, AKT phosphorylates both Beclin-1 and vimentin, and 14-3-3 forms a complex with Beclin-1 and vimentin to promote

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Table 1. Role of autophagy in cancers regulated by 14-3-3 proteins

Experimental model	14-3-3 isoform	Target protein	Directly binding	Level of autophagy	Role of autophagy	Reference
U2OS cells	14-3-3 τ	Beclin 1	Unclear	Increased		[34]
Lung cancers	14-3-3	Beclin 1/vimentin	Yes	Decreased	Tumorigenesis	[35]
U251 cells	14-3-3 τ	Beclin 1	No	Increased	Apoptosis	[36]
		CLIC4	Yes			
RCCs cancer	14-3-3	AKT1S1	Yes	Decreased	Tumorigenesis	[37]
HeLa cells	14-3-3	Beclin1 S295/vimentin	Yes	Decreased	Tumorigenesis	[38]
LN18, U87-MG, U373 cells	14-3-3 ζ	TSC2 S1254	Yes	Increased	Pro-survival	[40]
PANC1, MIA PaCa-2	14-3-3	TFEB	Yes	Increased	Pro-survival	[41]
Cervical cancer cells	14-3-3 ζ	FOXO3a	Yes	Decreased	Apoptosis	[42]
HeLa cells	14-3-3	DENND3 serine 554 and 572 Rab12/LC3	Yes		Unclear	[43]
			No	Increased		
HeLa cells	14-3-3 ζ	hVPS34	Yes	Decreased	Apoptosis	[44]

Abbreviations: CLIC4, chloride intracellular channel 4; AKT1S1, AKT1 substrate 1; TSC2, Tuberous Sclerosis 2; TFEB, transcription factor EB; FOXO3a, fork head box O3; DENND3, DENN domain-containing protein 3.

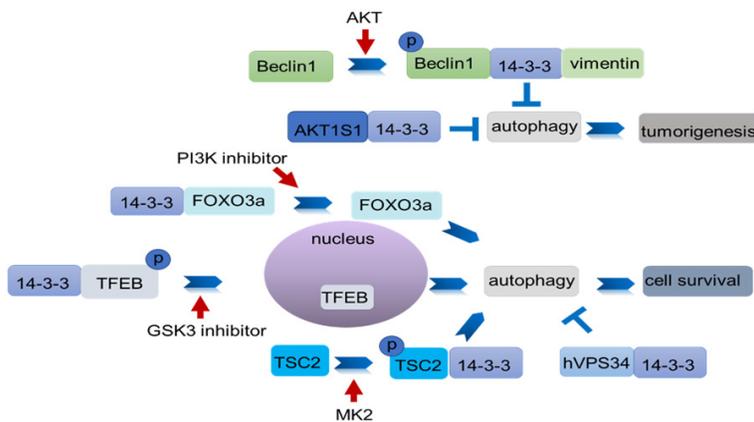


Figure 3. Model of 14-3-3 regulation of autophagy in cancers. 14-3-3 proteins inhibit or promote autophagy by binding with autophagy-related proteins to promote cancer cell survival or apoptosis. AKT inhibits autophagy by phosphorylating Beclin-1 at the S295 site and enhancing the formation of the Beclin-1/14-3-3/vimentin complex to promote tumorigenesis. AKT1S1 binds with 14-3-3 to promote cancer cell growth by inhibiting autophagy. PI3K inhibitors promote the dissociation of FOXO3a from 14-3-3 ζ to induce autophagy. The GSK3 inhibitor induces TFEB dephosphorylation and its dissociation from 14-3-3 and subsequently induces TFEB activation and nuclear translocation to activate autophagy. MK2 induces TSC2 phosphorylation and formation of TSC2/14-3-3 complex to promote autophagy. By contrast, 14-3-3 inhibits autophagy by binding with hVPS34 to induce cell apoptosis.

tumorigenesis by inhibiting autophagy [35]. In human glioma U251 cells, CLIC4 siRNA enhances autophagy and triggers endoplasmic reticulum (ER) stress-induced apoptosis under starvation conditions by interacting with 14-3-3 ϵ to indirectly activate Beclin-1 [36]. In renal cell carcinoma, the overexpression of pyruvate kinase M2 (PKM2) activates mTORC1 signaling by phosphorylating the mTORC1 inhibitor AKT1

substrate 1 (AKT1S1) on S202/203, and promotes the release of AKT1S1 from Raptor, thereby binding itself to 14-3-3 and promoting cell growth by inhibiting autophagy [37]. Wang *et al* also demonstrated that AKT inhibits autophagy by phosphorylating Beclin-1 at the S295 site and enhancing the formation of Beclin1/14-3-3/vimentin complex to promote tumorigenesis in human cervical HeLa cells [38]. This finding indicates that 14-3-3 proteins promote tumorigenesis by inhibiting autophagy.

Glioblastomas are the most life-threatening human brain tumors. Surgical resection combined with chemotherapy and radiotherapy has a certain therapeutic effect, but these treatment are associated

with a high degree of tumor recurrence [39]. Fettweis *et al* indicated that MAPKAPK2 (MK2) induces the phosphorylation of TSC2 at serine 1254 and an interaction with 14-3-3 ζ at 15 min after irradiation; both these events promote pro-survival autophagy activation in human glioblastoma LN18, U87-MG and U373 cell lines. By contrast, the MK2 inhibitor reverses this interaction. About 4h post-treatment, the

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Table 2. Role of autophagy in neurodegenerative diseases regulated by 14-3-3 proteins

Experimental model	14-3-3 isoform	Target protein	Directly binding	Level of autophagy	Neurotoxicity	References
PC12 cells	14-3-3ε	—	Unclear	Decreased	Attenuated	[45]
Cerebral I/R injury	14-3-3ε	—	Unclear	Decreased	Attenuated	[46]
PC12 cells	14-3-3	TFEB	Unclear	Decreased	Aggravated	[47]
AF5 cells	14-3-3ζ	—	Unclear	Decreased	Aggravated	[49]
ARPE-19 cells	14-3-3	TFE3	Yes	Decreased	Aggravated	[51]

recruitment of 14-3-3ζ by Receptor Interacting Protein 3 (RIP3) is in competition with that of TSC2; thus, TSC2 is inactivated through dephosphorylation, thereby inhibiting cell survival [40]. In human pancreatic cancer cells, GSK3 inhibitors CHIR99021 and SB216763 activate autophagy, and BafA1 and ATG5 siRNA increase cell apoptosis through GSK3 knockdown, indicating that autophagy has a protective effect against pancreatic cancer. Further investigation shows that GSK3 inhibitors promote the expression of dephosphorylation transcription factor EB (TFEB), which is a key regulator of autophagy and lysosomal biogenesis, leading to its dissociation from 14-3-3 and its transfer to the nucleus [41]. This finding demonstrates that 14-3-3 proteins promote cell survival by activating autophagy in some cancers under certain conditions.

14-3-3 proteins reduce the level of autophagy to induce cancer cell apoptosis. In cervical cancer, the PI3K pathway is frequently aberrantly activated. However, the antitumor effect of BKM120, a PI3K inhibitor is largely ineffective. Kim *et al* demonstrated that BKM120 causes the dissociation of fork head box O3 (FOXO3a) from 14-3-3ζ to induce autophagy in PIK3CA mutant cervical cancer cells [42]. Xu *et al* demonstrated that ULK mediates the binding of guanine nucleotide exchange factor DENND3 to 14-3-3 through phosphorylation at serine 554 and 572 and its GEF activity is subsequently upregulated to induce autophagy by promoting the interaction between Rab12 and LC3 in HeLa cells under starvation conditions [43]. The overexpression of 14-3-3ζ blocks C2-ceramide-dependent autophagy by interacting with hVps34 and decreasing its activity in HeLa cells, whereas rapamycin promotes the dissociation of hVps34 from 14-3-3 and induces autophagy. Knockdown of 14-3-3ζ by RNA interference has the same result [44]. Thus, 14-3-3 proteins play a key role in cancers by regulating autophagy through interaction with certain proteins shown in **Table 1** and **Figure 3**.

Regulation of autophagy by 14-3-3 proteins in neurodegenerative diseases

In neurodegenerative diseases, 14-3-3 proteins alleviate cell injury by indirectly inhibiting autophagy. Under some conditions, 14-3-3 proteins have the opposite effect.

14-3-3ε knockdown by siRNA increases autophagy and aggravates the injury of PC12 cell during rotenone treatment [45]. Another study suggested that 14-3-3ε has a neuroprotective effect on cerebral I/R injury. Delivery of 14-3-3ε into the brain by TAT reduces the formation of autophagosomes and attenuates I/R-induced neuronal apoptosis. Rapamycin inhibits the neuroprotective effect of TAT-14-3-3ε and aggravates I/R-induced brain infarct in SD rats, whereas 3-MA further increases this effect [46].

Gypenoside XVII (GP-17) promotes the elimination of Aβ40, AβPP, and Aβ42 in PC12 cells expressing the Swedish mutant of APP695 (APP695swe) and APP/PS1 mice by upregulating the expression of ATG5, LC3-II and LAMP-1. Furthermore, GP-17 induces autophagy and lysosome biogenesis by promoting the dissociation of transcription factor EB (TFEB) from TFEB/14-3-3 complexes, which leads to TFEB activation and its nuclear translocation [47]. Transthyretin (TTR) is a neuroprotective molecule that serves as a carrier protein of thyroxine (T4) and retinol through the binding protein (RBP) in plasma and cerebrospinal fluid (CSF) [48]. Vieira *et al* demonstrated that in TTR^{-/-} mice, the expression of 14-3-3ζ is decreased in the hippocampus in an age-dependent manner. The reduced expression of 14-3-3ζ is attributable to increase autophagy [49].

TFE3 is phosphorylated at Ser211 by mTORC1 and is retained in the cytosol through its interaction with active Rag GTPases and 14-3-3 in ARPE-19 cells under nutrient-rich conditions. Under starvation conditions, mTORC1 and Rags

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are inactivated which induces the dissociation of TFE3 from 14-3-3, and TFE3 is translocated to the nucleus, where it binds to the CLEAR elements to increase lysosomal degradation and autophagy induction in ARPE-19 cells [50]. Thus, in neurodegenerative diseases, 14-3-3 proteins regulate autophagy (Table 2), which promotes the degradation of accumulated protein.

Regulation of autophagy by 14-3-3 proteins in other diseases

Inflammation is a common pathological process. Gómez-Suárez et al suggested that the binding of 14-3-3 ζ with Raptor triggers autophagy to promote the degradation of 14-3-3 η , the inhibitor of phosphoinositide-dependent kinase 1 (PDK1) resulting in AKT phosphorylation at Thr308 in the mucosa of colitic mice and SW480 cells treated with IFN γ /TNF α . However, inhibition of 14-3-3 function promotes cell death during inflammation [51]. Another study showed similar results, the levels of p14-3-3 ζ (Ser58) is increased in the colonic mucosa of C57BL/6J mice treated with IFN γ /TNF α , and p14-3-3 ζ inhibits mTOR through its interaction with Raptor, which triggers autophagy and enhances AKT activation, which leads to chromogranin A production [52]. These findings suggest that autophagy plays a cytoprotective role in intestinal inflammation.

Under normal nutrient conditions, TFEB is phosphorylated at Ser211 by mTORC1 to promote the association of TFEB with 14-3-3 and the retention of TFEB in the cytosol. The inhibition of mTORC1 by LY294002, rapamycin, wortmannin, and PP242 leads to the dissociation of TFEB from 14-3-3 and its translocation to the nucleus, where TFEB interacts with the LAMTOR-RRAG-MTORC1 complex to activate autophagy in ARPE-19 cells [53].

Conclusions and prospects

Autophagy generally occurs during physiological and pathological processes; thus, it is critical for cellular responses to nutrient deprivation, stress, infection, and the development of diseases such as neurodegenerative diseases and cancer [9]. Depending on the conditions, autophagy may exert a beneficial or harmful effect. The inhibition of autophagy improves the chemosensitivity of glioma cells to cisplatin

[54]. Autophagy is elevated in hypoxic regions of tumors and protects tumor cells against various stressors [55]. There are many key regulatory proteins involved in autophagy; 14-3-3 proteins play an additional role in regulating autophagy by binding with other proteins. In cancer cells, 14-3-3 inhibits autophagy by interacting with Beclin-1 to promote tumorigenesis. In Alzheimer's disease, gypenoside XVII (GP-17) releases TFEB from TFEB/14-3-3 complexes, which leads to TFEB nuclear translocation and the induction of autophagy to reduce aggregated amyloid- β . Different isoforms of 14-3-3 proteins may have different effects on diseases. The specific isoform that mediates the autophagy-regulating role of 14-3-3 proteins in diseases warrants further investigation. Moreover, 14-3-3 proteins play an anti-apoptotic role by regulating Bcl-2, thus inhibiting autophagy [56]. Therefore, revealing the molecular processes of the 14-3-3 proteins involved in autophagy may help to increase the therapeutic effects on diseases such as cancer and neurodegenerative diseases.

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Disclosure of conflict of interest

None.

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