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Research progress of protein phosphatase 2A in cellular autophagy

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Abstract: Autophagy is an important metabolic process. It facilitates the recycling of intracellular substances by removing, degrading, and recycling damaged organelles, proteins, and lipids in lysosomal vacuoles and plays an important role in maintaining cellular homeostasis. Protein phosphatase 2A (PP2A) is a key serine/threonine phosphatase and one of the main cell cycle regulatory enzymes. As PP2A activity is essential for the cell, dysfunction or dysregulation of PP2A can affect various physiological processes, including autophagy. Here, we review the autophagy-related factors that target PP2A in different diseases, such as breast cancer, colorectal cancer, liver cancer, and Alzheimer's disease, to maintain cell homeostasis by modulating the level of autophagy through mTORC1/ULK1 pathway, MAPK pathway, or AMPK pathway.

Introduction

In eukaryotic cells, cellular growth processes, such as differentiation, proliferation, survival, and apoptosis, are controlled by the regulation of protein phosphorylation. According to the physiological state of the cell, proteins can interconvert between phosphorylated and dephosphorylated status, and the process is regulated by specific protein kinases and protein phosphatases (Mumby and Walter, 1993). Biological systems have many protein kinases, mainly two families—protein tyrosine kinase and protein serine/threonine kinase (Johnson and Hunter, 2005). Phosphatases can be categorized into three superfamilies: serine/threonine phosphatase (PSP), tyrosine phosphatase (PTP), and bispecific phosphatase (DSP) (Hunter, 1995; Shi, 2009; Virshup and Shenolikar, 2009). PP2A is a member of the PSP family. As a current research hotspot, many studies have proved that PP2A has an important regulatory effect on the cell cycle, apoptosis, and autophagy through the dephosphorylation of substrates. Here we comprehensively review the participation of PP2A in the autophagy process in recent years to guide the further role exploring of PP2A in cellular autophagy.

The biological role of protein phosphatase 2A in cells

PP2A is an important serine/threonine phosphatase that plays a multifaceted key role in cell cycle regulation. PP2A regulates cell cycle initiation pathways and cell cycle checkpoints and dephosphorylates more than 300 substrates involved in the cell cycle (Wlodarchak and Xing, 2016). PP2A is complex in structure and usually exists in two different forms: dimer or trimer (Mayer-Jaekel and Hemmings, 1994; Cohen, 1997). Each PP2A holoenzyme consists of a catalytic subunit C, a regulatory subunit B, and a scaffold subunit A, whose assembly, intracellular localization, enzyme activity, and substrate specificity are dynamically regulated (Xu *et al.*, 2006). PP2A catalytic subunit (PP2Ac) has a spherical structure encoded by two different genes, α and β, which have 97% sequence similarity. PP2Ac is commonly expressed in almost all tissues, with the greatest content in the heart and brain. The level of PP2Ac protein expression in cells is translationally regulated to maintain constant levels (Baharians and Schönthal, 1998). Similar to PP2Ac, the PP2A scaffold subunit can also generate two isoforms, Aα and Aβ encoded by *PPP2R1A* and *PPP2R1B*, which have 86% sequence homology (Hemmings *et al.*, 1990). The PP2A regulatory subunits encoded by 15 different genes in the human genome are structurally diverse, with at least 26 different transcripts and splice variants. It is considered the primary regulator of the PP2A whole enzyme and may act as a targeted regulator to provide temporal and spatial specificity (Zolnierowicz *et al.*, 1994). PP2A participates in cellular processes by forming structurally distinct whole enzyme families that are spatially and temporally regulated by specific regulators. Activated PP2A can regulate all cellular signaling pathways, including the mammalian target of rapamycin/Unc51-like kinase (mTORC1/ULK1) pathway and mitogen-activated protein kinase (MAPK) pathway (Wlodarchak and Xing, 2016).

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The biological function of autophagy in cells

Autophagy is a process in which components within eukaryotic cells self-degrade; in this process, the substance to be degraded is transported to the lysosome or vacuole to be degraded by hydrolases. Autophagy is a relatively conserved process in biological evolution; it is an important way to maintain homeostasis within cells and plays an integral role in cell proliferation, differentiation, and aging (Kroemer, 2015). The three main subtypes of autophagy are microautophagy (obtaining intracytoplasmic matter directly through the inversion of the endosomal chamber restriction membrane), chaperone-mediated autophagy (chaperone-mediated recruitment of unfolded proteins to lysosomes through KFERQ-like polypeptide sequences), and macroautophagy (characterized by autophagosomes of bimeal vesicles that completely engulf specific substances before fusing with lysosomes to enter the lysis chamber). Macroautophagy is the best-characterized form of mammalian autophagy and is often referred to as autophagy (Kocak *et al*., 2022). Autophagy includes the initial formation of a bi-membrane structure called a pre-autophagosomal structure, engulfing the autophagic target and continuing to form closed autophagosomes. More than 30 autophagy-related gene products control the formation of autophagosomes, which are the core of autophagy (Dikic and Elazar, 2018). Autophagosomes are double-membrane vesicle structures that transport damaged organelles, long-lived proteins, and even invading pathogens to lysosomes through the fusion of the outer membrane with the lysosomal membrane (He and Klionsky, 2009). After lysosomal fusion, the contents of the lysosome are degraded, and nutrients are recovered by cells (Mizushima, 2018). The main function of autophagy is to recover and re-uptake nutrients from the cytoplasm and degrade specific components to prevent cell damage under metabolic stress conditions, promote cell survival against a state of energy and nutrient deficiency, and respond to various cytotoxic injuries. For example, damaged mitochondria are treated by mitophagy (Pickles *et al*., 2018) or xenophagy (Sharma *et al*., 2018). Autophagy was initially thought to involve non-selective chelation and degradation of cytoplasmic contents. Of late, many types of selective autophagy have been found in various physiological processes, such as mitochondrial autophagy, reticular phagocytosis (Reggiori and Molinari, 2022), and sugar autophagy (Zhao *et al*., 2018).

Participations of protein phosphatase 2A in cellular autophagy

Protein phosphatase 2A changes autophagy levels through the mammalian target of the rapamycin signaling pathway

The mTOR is the target of rapamycin, or sirolimus, produced by the bacterium *Streptomyces hygroscopius*. It belongs to the phosphoinositide 3-kinase (PI3K)-related kinase family and is an atypical serine/threonine protein kinase, which can form mTOR complexes 1 (mTORC1) and 2 (mTORC2) with several proteins (Laplante and Sabatini, 2012). Many different cellular processes are associated with the mTOR pathway. The regulation of this pathway is also extremely complex, especially in relation to PP2A. Here we simply explain how PP2A regulates autophagy levels through a pathway involving mTOR.

Oncoprotein phosphatase 2A inhibitor (CIP2A), an endogenous PP2A inhibitor, has been identified as an oncoprotein that promotes the initiation and progression of various cancers. Many studies have pointed out that CIP2A is involved in the regulation of mTORC1 and autophagy (Puustinen and Jäättelä, 2014; Puustinen *et al*., 2014; Liu *et al*., 2017). While CIP2A has been shown to inhibit autophagy, its degradation can be enhanced by autophagy activation (Chen *et al*., 2010; Liu *et al*., 2017). By studying the role of CIP2A in doxorubicin-resistant breast cancer, (Zhu and Wei, 2021) found that CIP2A knockdown led to an increase in the activity of PP2A, and the expression of autophagy markers MAP1LC3B (LC3B) and Beclin1 was up-regulated (Zhu and Wei, 2021). It suggests that PP2A has a positive regulatory effect on autophagy, and the specific mechanism remains to be explored.

Hypoxia-inducible factors 1 (HIF1) and HIF2, negatively regulated by HIF prolyl hydroxylase (PHD) family members PHD1, PHD2, and PHD3, are major executors of cellular responses to hypoxia. The study by di Conza *et al*. (2017) shows that the mTOR downstream kinase P70S6K phosphorylates PHD2 at serine 125 (S125), resulting in enhanced HIF1α degradation. PP2A directly dephosphorylates PHD2 at S125 through its regulatory subunit B55α, leading to a further decrease in PHD2 activity and, ultimately, increased HIF1α accumulation (di Conza *et al*., 2017). Under hypoxic conditions, HIF1α stabilizes to promote cancer cell survival by initiating autophagy, which requires transcriptional induction of BNIP3 and BNIP3L (Mazure and Pouysségur, 2010). Silencing B55α prevents the upregulation of hypoxia-induced autophagy markers BNIP3 and BNIP3L and inhibits the degradation and induction of autophagy substrates p62 and LC3B (di Conza *et al*., 2017). These results suggest that the stabilization of HIF1α by PP2A/B55α promotes colorectal cancer cell survival through autophagy in a PHD2-dependent manner.

The cluster of differentiation (CD)24 is a glycoprotein expressed on the surface of most B lymphocytes and in some tumors. Recent studies have shown that CD24 expression is associated with the occurrence and development of many tumors, including prostate cancer (Zhang *et al*., 2016), cervical cancer (Sung *et al*., 2010), non-small cell lung cancer (Majores *et al*., 2015), gastric cancer (Sastry *et al*., 2014), and breast cancer (Suyama *et al*., 2016). However, in different tumors or tumor environments, CD24 has different roles and different ways of activating its downstream signaling (Baumann *et al*., 2005; Tang *et al*., 2014). When studying CD24 in hepatocellular carcinoma (HCC) with sorafenib resistance, Lu *et al*. (2018) found that CD24 overexpression induces the mTOR/protein kinase B (Akt) pathway inactivation, increases PP2A protein production, and increases autophagy levels. Sorafenib treatment in sorafenib-resistant cells induces morphological and biochemical features of autophagy. Compared to CD24-knockdown sorafenib-resistant cells, non-knockdown cells show abundant bimodal vacuolar structures, which are characteristic morphology of autophagosome, with increased LC3-II protein expression and decreased p62 (Lu *et al*., 2018). These phenomena suggest that CD24 regulates sorafenib resistance by activating autophagy in HCC.

Manganese (Mn) exposure leads to autophagy disruption and contributes to neurodegenerative diseases like Parkinson's syndrome (PD) and Alzheimer's disease, but the specific toxicity mechanism is unclear. One study revealed that PP2Ac methylation is involved in autophagy modulation by Mn. Through the activation of the mTORC1 signaling pathway, the down-regulation of PP2Ac methylation can ameliorate the abnormal autophagy induced by Mn in mouse neuroblastoma cells (N2a). In this way, the cytotoxicity and oxidative stress caused by Mn exposure can be effectively alleviated, suggesting that autophagy regulation plays a protective role in Mn-induced neurotoxicity (Xu *et al.*, 2021b).

PD is a neurodegenerative disease, more common in the elderly. Autophagy is considered a promising therapeutic approach due to its important regulatory role in PD. Piperine (PIP) is a kind of traditional Chinese medicine containing amide alkaloids, which has pharmacological effects such as protecting the cardiovascular system, anti-tumor, and anti-inflammatory. Liu *et al.* (2016) reported that PIP inhibits mTORC1 by activating PP2A, thereby inducing autophagy. However, these protective effects were attenuated after the inhibition of PP2A activity using okadaic acid, suggesting that PP2A is a target of PIP (Liu *et al.*, 2016). These findings indicate that PIP exerts neuroprotective effects by inducing autophagy in PD models and may become a drug with therapeutic effects on PD.

The autophagy pathway for glycogen degradation is known as glycogen autophagy, and it includes the sequestration and degradation of glycogen within autophagy vesicles with the release of free glucose (Kalamidas and Kondomerkos, 2010). Activation of mTOR is found to reduce glycogen autophagy by inhibiting PP2A, which acts as a common target of glucagon, insulin, and cAMP downstream of mTOR, and promotes α-1,4-glucosidase synthesis when active (Kalamidas *et al.*, 2004). A study of cardiotoxin (CTX) by Chiou *et al.* (2019) showed that the addition of CTX causes calcium-dependent degradation of PP2Ac and phosphorylation of AMP-activated protein kinase subunit α (AMPKα). In CTX3-treated cells, the phosphorylation of AMPKα increased, and the expression of autophagy-related protein LC3 increased, while the expression of p62 decreased. Overexpression of PP2Ac attenuates CTX-induced AMPKα phosphorylation. CTX-induced autophagy is achieved through AMPK-mediated inhibition of the Akt/mTOR pathway. CTX is suggested to cause autophagy and apoptosis through the Ca^{2+}/PP2A/AMPK axis (Chiou *et al.*, 2019).

Protein phosphatase 2A changes autophagy levels through the mitogen-activated protein kinase (MAPK) pathway

MAPKs are serine/threonine protein kinases activated by substances such as cytokines, growth factors, hormones, and neurotransmitters (Widmann *et al.*, 1999). MAPK signaling pathway plays an important role in regulating many physiological processes in eukaryotic cells, such as gene expression, metabolism, apoptosis, and survival (Cargnello and Roux, 2011). All MAPK signaling cascades consist of a three-layered module of protein kinases, with the MAPK kinase at the top (also known as MKKK or MAP3K), the MAPK kinase in the middle (also known as MKK, MEK, or MAP2K), and the bottom MAPK (Martínez-Limón *et al.*, 2020).

A morphological feature of autophagy is the formation of acidic vesicular organelles (AVOs) (Puglisi et al., 2019). Wu *et al.* (2019) showed that apoptosis induced by the drug penfluidol could be inhibited by activating PP2A, which can inhibit Akt and MAPK activities. Furthermore, penfluidol-treated cells induced ROS-mediated autophagy by triggering LC3 turnover (LC3B-I to LC3B-II transition), p62 degradation, and formation of AVOs. Inhibition of ROS-mediated autophagy significantly enhances penfluidol-induced apoptosis. At the same time, patients with acute myeloid leukemia (AML) with high expression of PP2A have also been observed clinically to have a good prognosis (Wu *et al.*, 2019). Taken together, these findings suggest that penfluidol-mediated autophagy is a pro-survival mechanism, and inhibiting its protective effect may improve the efficacy of AML treatment.

Protein phosphatase 2A changes autophagy levels through other pathways

Microcystin-leucine-arginine (MC-LR) has been identified as a harmful substance that causes liver toxicity. A study on a mice model with MC-LR-induced breakdown of apical ectoplasmic specialization (ES) revealed that down-regulation of the actin cross-linking protein palladin might be associated with the apical ES disassembly in mouse testis after MC-LR exposure (Xu *et al.*, 2021a). MC-LR interferes with the interconnection between palladin and other actin-related proteins, thereby hindering the organization of F-actin. After exposure to MC-LR, AMPK could be activated by reduced PP2A activity, to then up-regulate the expression of LKB1 and CAMKK2, increase LC3B-II expression, down-regulate the autophagy substrate SQSTM1/p62 expression, and increase the level of autophagy. MC-LR induces degradation of palladin through AMPK/ULK1-mediated autophagy, which may lead to apical ES disturbance and shedding of spermatocytes from the seminiferous epithelium. These experimental phenomena may provide new perspectives for understanding MC-LR-induced male infertility.

The effect of PP2A on substrate phosphorylation determines its important role in the regulation of the cell cycle. Zhong *et al.* (2020) found that fingolimod (FTY720), a novel immunosuppressant, could dephosphorylate AMPKα at Thr172 by activating PP2A to activate the PP2A/AMPKα pathway. Induction of autophagy resulted in increased expression of LC3B, decreased expression of p62, and decreased expression of phosphorylated eukaryotic elongation factor 2 (eEF2), ultimately leading to myeloma cell death (Zhong *et al.*, 2020).

Renal tubular epithelial cells require a large amount of fatty acid oxidation for energy, and energy production requires the regulation of AMPK. The function of AMPK in acute kidney disease and tubular epithelial cells has not been elucidated. Ma *et al.* (2022) found that AMPKα prevents tubular epithelial cell damage in ischemia/reperfusion-induced acute kidney injury. Ischemia/reperfusion activates PP2A and dephosphorylates AMPKα at the Thr172 site. Decreased AMPK activity suppresses autophagy levels and reduces the ability of cells to clear dysfunctional mitochondria. The allosteric AMPK activator C24 restores

fatty acid oxidation and reduces tubular apoptosis in renal tubules after ischemia/reperfusion-induced cell injury. It works by targeting the PP2A-AMPK axis to antagonize the dephosphorylation process of PP2A, significantly increase autolysosomes in renal tubules, and promote mitophagy (Ma *et al*., 2022).

Diabetes mellitus-related cardiomyopathy (DMCMP) is one of the important cardiovascular complications of diabetes mellitus. It is a type of primary and specific cardiomyopathy with changes in myocardial structure and function caused by hyperglycemia and insulin resistance. Researchers studied the role and mechanism of PP2A in DMCMP *in vivo* and *in vitro* and found that the enhanced activity or increased expression of PP2A in DMCMP can up-regulate the expression of nuclear factor NF-E2-related factor 2 (Nrf2) by increasing the LC3B2/LC3B1 ratio and decreasing P62 protein expression, to increase the level of autophagy, thereby initiating protective autophagy in cardiomyocytes (Guan *et al*., 2019). In the study of basal muscle-invasive bladder cancer, Xu *et al*. (2020) found that long non-coding RNA-small nuclear RNA host gene 1 (SNHG1) can competitively bind with PP2Ac to inhibit its interaction with c-Jun, thereby promoting the phosphorylation of c-Jun, and mediate the transcription of MMP2. SNHG1 is also found to significantly induce autophagy in cells by inducing an increase in the abundance of autophagy-related proteins. Overexpression of SNHG1 not only induces the formation of autophagosomes but also converts LC3-I into LC3-II; consequently, the expression of ATG3 and ATG7 is up-regulated, and the binding rate of ATG5 and ATG12 is also high, which indirectly suggests the relationship between PP2A and autophagy (Xu *et al*., 2020). In a comprehensive phosphoproteomic analysis, the researchers found that ULK1, a protein required for autophagy vacuolation, is not only a target of PP2A, but also directly phosphorylates the PP2A subunit striatin, activates PP2A, and exerts positive feedback to promote autophagy-dependent protein turnover (Hu *et al*., 2021).

Clinically, multiple myeloma (MM) is incurable due to drug resistance. The results of some studies on the pathogenesis of MM suggest that growth factor-independent-1 (GFI-1) can increase the level of sphingosine 1-phosphate (S1P) by regulating sphingolipid metabolism, independent of the p53 state (Petrusca *et al*., 2022). GFI1 inhibits the expression of S1P phosphatase (SGPP1), thereby maintaining high intracellular S1P levels and keeping PP2A inactive, resulting in high c-Myc protein levels. Reduced intracellular S1P levels induce cell death via autophagy and conversion of LC3-I to LC3-II and reveal that GFI1-mediated protection of MM cell viability through S1P and p53WT is an independent pathway.

Metformin is a commonly used drug in the clinical treatment of diabetes. Studies have demonstrated that in addition to increasing insulin sensitivity, it can also induce mitophagy (Zhao and Sun, 2020). To initiate mitophagy, PINK1 is phosphorylated to activate parkin, which then builds ubiquitin chains with proteins on the mitochondrial outer membrane to recruit autophagy receptors (Lazarou *et al*., 2015). However, the molecular mechanism of metformin-induced mitophagy has not been elucidated. (Zhao and Sun, 2020) found that the use of metformin can reduce the apoptosis of high glucose-induced human renal epithelial cells. Mechanistically, metformin restores parkin protein expression and mitophagy by activating PP2A and inhibiting NF-κB. The relative mRNA and protein expressions of the mitophagy genes *MFN2*, *PARKIN*, *PINK1*, *LC3-II*, and *LAMP2* are up-regulated in metformin-treated cells, indicating that metformin significantly affects the mitophagy process (Zhao and Sun, 2020). Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment to alleviate disability in patients with moderate to severe PD. Preclinical studies have shown that stimulation of the rat STN can reduce the loss of substantia nigra dopaminergic neurons (Musacchio *et al*., 2017), but the specific mechanism is unclear. Du *et al*. (2018) found that in a rat model of PD, STN-DBS could induce autophagy through PP2A inactivation and dissociation of the Bcl-2/Beclin1 complex, thereby inhibit 6-OHDA-induced PD cell damage, and exert a neuroprotective effect. In short, STN-DBS inactivates PP2A and initiates autophagy to protect neurons, thereby providing the molecular basis for the neuroprotective effect of STN-DBS on PD (Du *et al*., 2018).

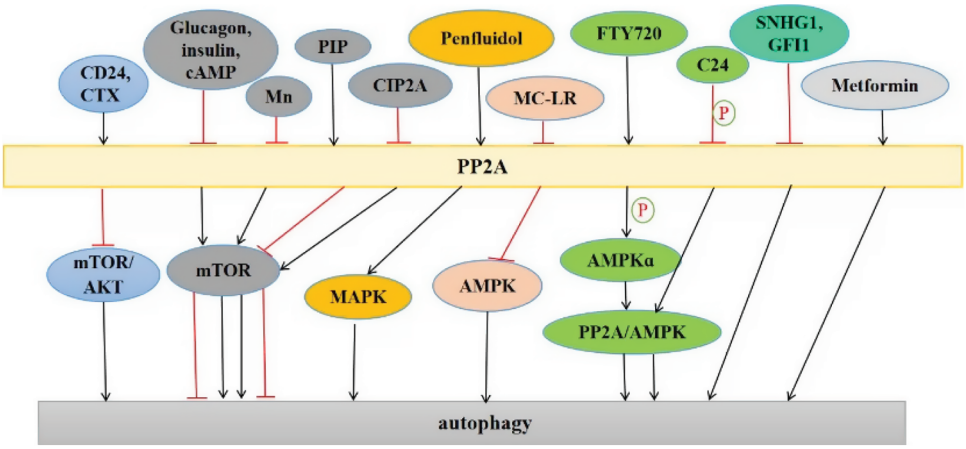

FIGURE 1. PP2A alters autophagy levels through different pathways. Note: PP2A, protein phosphatase 2A; mTOR, mammalian target of rapamycin; CTX, cardiotoxin; Mn, manganese; PIP, piperine; CIP2A, oncoprotein phosphatase 2A inhibitor; MC-LR, microcystin-leucine-arginine; FTY720, fingolimod; GFI1, growth factor independence-1. The black arrow indicates "promoting effect," the red line indicates "inhibiting effect," and P indicates "dephosphorylation."

TABLE 1

Various substances that target protein phosphatase 2A (PP2A) to alter autophagy levels

Substances	Target subunits	Biological functions	References
CD24	PP2A	Increases levels of autophagy	(Lu *et al.*, 2018)
Glucagon, insulin, cAMP	PP2A	Reduces autophagy	(Kalamidas *et al.*, 2004)
CTX	PP2Ac	Causes autophagy and apoptosis	(Chiou *et al.*, 2019)
PHD2	B55α	Increases autophagy levels and improves cell survival	(di Conza *et al.*, 2017)
Mn	PP2Ac	Improves autophagy disorders, alleviates cytotoxicity and oxidative stress	(Xu *et al.*, 2021b)
PIP	PP2A	Induces autophagy	(Liu *et al.*, 2016)
CIP2A	PP2A	Increases levels of autophagy	(Zhu and Wei, 2021)
Penfluidol	PP2A	Increases cytoprotective autophagy	(Wu *et al.*, 2019)
MC-LR	PP2A	Induction of Palladin degradation by autophagy	(Xu *et al.*, 2021a)
FTY720	PP2A	Induction of autophagic death in myeloma cells	(Zhong *et al.*, 2020)
Allosteric AMPK activator C24	PP2A	Promotes mitophagy, reducesapoptosis	(Ma *et al.*, 2022)
PP2A	–	Promotes cardiomyocyte autophagy and apoptosis	(Guan *et al.*, 2019)
Long non-coding RNA-SNHG1	PP2Ac	Promotes the phosphorylation of c-Jun and increases the level of autophagy	(Xu *et al.*, 2020)
ULK1	PP2A	Promotes autophagy -dependent protein turnover	(Hu *et al.*, 2021)
GFI1	PP2A	Induces autophagy, leads to cell death	(Petrusca *et al.*, 2022)
Metformin	PP2A	Restores mitophagy, reduces apoptosis	(Zhao and Sun, 2020)

Notes: PP2A, Protein phosphatase 2A; CTX, cardiotoxin; PHD2, prolyl hydroxylase2; Mn, manganese; PIP, piperine; CIP2A, oncoprotein phosphatase 2A inhibitor; MC-LR, microcystin-leucine-arginine; FTY720, fingolimod; ULK1, unc-51 like autophagy activating kinase 1; GFI1, growth factor independence-1.

Conclusion and Outlook

As shown in Fig. 1 and Table 1, different molecules can target PP2A through the mTORC1/ULK1 pathway and MAPK pathway or directly target the PP2A-AMPK axis, to increase or decrease the level of autophagy, improve physiological conditions, and maintain cell homeostasis. In short, a complex regulatory network between PP2A and autophagy, and the two are interconnected and inseparable, but the specific molecular mechanism for the interconnection between the two is still unclear. This study briefly explains the regulatory relationship between PP2A and autophagy. Only by continuing to study the relationship between the two can we provide new clues for the further study of PP2A and the application of clinical PP2A inhibitors.

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