**Abstract**

Regulated cell death predominantly involves apoptosis, autophagy, and regulated necrosis. It is vital that we understand how key regulatory signals can control the process of cell death. Pin1 is a cis-trans isomerase that catalyzes the isomerization of phosphorylated serine or threonine-proline motifs of a protein, thereby acting as a crucial molecular switch and regulating the protein functionality and their signaling pathways involved. However, we know very little about how Pin1-associated pathways might play a role in regulated cell death. In this paper, we review the role of Pin1 in regulated cell death and related research progress and summarize Pin1-related pathways in regulated cell death. Aside from the involvement of Pin1 in the apoptosis that accompanies neurodegenerative diseases, accumulating evidence suggests that Pin1 also plays a role in regulated necrosis and autophagy, thereby exhibiting distinct effects, including both neurotoxic and neuroprotective effects. Gaining an enhanced understanding of Pin1 in neuronal death may provide us with new options for the development of therapeutic target for neurodegenerative disorders.

**Key Words:** apoptosis; autophagy; calpain; central nervous system; necroptosis; necrosis; neurodegenerative diseases; neuron; Pin1; regulated neuronal death

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**Introduc**

Cell death is a fundamental process that is essential for the normal development and homeostasis of organisms (Bai et al., 2020; Moujalled et al., 2021). In general, there are three types of cell death: apoptosis, autophagy, and necrosis (Carloni et al., 2017; Bai et al., 2020). Apoptosis refers to regulated cell death (RCD) that occurs in developing tissues and plays an important role in homeostasis. RCD is characterized by chromatin condensation, nuclear fragmentation, and the formation of apoptotic bodies. Previous studies have reported that a large number of apoptotic proteins play a role in apoptotic signaling pathways, including caspases and B-cell lymphoma 2 (Bcl-2) family members (Bai et al., 2020; Özel et al., 2021). Autophagy is another form of RCD during which cellular contents, such as organelles, are engulfed by a double-membrane to form autophagosomes that are subsequently degraded by lysosomes (Napoletano et al., 2019; Bourdoux et al., 2021). Autophagy plays an important role in maintaining homeostasis and protecting cells against stressful stimuli. Traditionally, necrosis is considered to represent a form of accidental cell death that is characterized by membrane destruction, the release of internal materials, and inflammation (Chen et al., 2021; Hu et al., 2021b). However, recent research has provided evidence that some types of necrosis also can be regulated at the molecular level (Theobald et al., 2021; Tonnus et al., 2021). Other researchers have reported that this form of regulated necrosis (RN) includes necroptosis (Evans and Coyne, 2019; Yuan et al., 2019), pyroptosis (Lammert et al., 2020), and neutrophil cell death (Sung and Hsieh, 2021; Yan et al., 2021). RCD, featuring apoptosis, autophagy and RN, is recognized to be beneficial to the host by eliminating certain intracellular pathogens or stimuli (Guo et al., 2020; Wang et al., 2020b; Yan et al., 2021). It is vital that we know how RCD responds to pathogens or injuries.

Prolyl cis-trans isomerase NIMA-interacting 1 (Pin1) belongs to the parvulin subfamily and is an 18-kDa protein with a C-terminal PPIase domain and a N-terminal WW domain (Kumari et al., 2021; Zheng et al., 2021). Pin1 is able to bind and then isomerize phosphorylated serine-proline or phosphorylated threonine-proline (pSer/Thr-Pro) motifs, thus regulating a series of biological processes (Koikawa et al., 2021; Kumari et al., 2021). The WW domain responds to and binds to pSer/Thr-Pro sequences, while the N-terminal WW domain (Kumari et al., 2021). In addition to binding to the prolyl bond in the pSer/Thr-Pro motif, Pin1 can also specifically regulate the activity of mitotic and nuclear proteins in a phosphorylation-dependent manner (Kumari et al., 2021).

Pin1 is predominantly expressed in cell nuclei and functions as a mitotic regulator, thus playing a vital role in DNA replication and mitosis (Zhang and Zhang, 2019; Kumari et al., 2021). The targets of Pin1 include not only proteins that exert function in transcription and the cell cycle, but also those involved in many physiological and pathological processes, including apoptosis, proliferation, and maintenance of the cytoskeleton (Thorpe et al., 2004; Lepore et al., 2021). Pin1 acts as a context-specific signal transducer based on specific environmental signals (Oster et al., 2021). Researchers have found that Pin1 plays a dual role in cellular apoptosis (Baik et al., 2015; Dubiella et al., 2021; Fagiani et al., 2021). For example, Pin1 was shown to enhance the anti-cell death ability of Bcl-2 and inhibit apoptosis by directly inactivating Bcl-2 associated X (Bax) (Bianchi et al., 2019; Makinwa et al., 2020). However, Pin1 has also been shown to act as a promoter of cell apoptosis by enhancing the expression of pro-apoptotic genes, such as p53 (Balaganapathy et al., 2018; BlehIEL et al., 2021). Pin1 has been reported to be distributed in the central nervous system (CNS) and participate in a variety of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD) (Ghosh et al., 2013; Carnemolla et al., 2017; Iridoy et al., 2018; Napoletano et al., 2021; Sammini et al., 2021). An increasing body of evidence now supports the fact that Pin1 could exert a neuroprotective role or act as a promoter for neuronal death by upregulating survival-promoting factors or by downregulating death-suppression factors. However, the comprehensive regulatory pathways underlying the specific role of Pin1 in RCD has yet to be elucidated.

In this review, we set out to summarize our current knowledge of Pin1 in neuronal RCD and discuss the critical regulatory mechanisms associated with Pin1 in the CNS (Additional Table 1). In addition, Pin1 is an intriguing target for cancer therapy at present and could represent a desirable pharmaceutical target for neurological therapy. As such, we also summarize research relating to Pin1-specific inhibitors.

**Search Strategy**

We searched all literatures published from June 1998 to May 2021 that relates to the role of Pin1 in neuronal death (Figure 1) in this narrative review. We performed a PubMed search using the term “Pin1” AND “neuron” to identify potential neuronal death in neurodegenerative diseases that are mediated by Pin1 dysfunction. We next screened the results by the title, keywords, abstract and excluded non-neuronal death-related articles, and retrieved further papers by citation tracking.
Apoptosis

Apoptosis is controlled by several apoptotic genes and characterized by RCD (Buck and Yuan, 2012a, 2012b; Wang et al., 2022). Apoptosis can be divided into two pathways, the extrinsic and intrinsic pathways (Carneiro and El-Deiry, 2020; Nascimento et al., 2022). In the extrinsic pathway, apoptosis is induced by extracellular signals which then trigger the activation of caspases and caspase-mediated pathways (Carneiro and El-Deiry, 2020; Nascimento et al., 2022). The role of Pin1 in neuronal apoptosis has been investigated in many studies (Figure 2) (Becker and Bonni, 2007; Moujalled et al., 2021). For example, Pin1 has been reported to mediate neuronal apoptosis by promoting the expression of pro-apoptotic genes, such as p53 (Grison et al., 2011; Balagapanpathy et al., 2018). Literature indicates that Pin1 may participate in neuronal survival or apoptosis, depending on the specific development stages of neurons as well as the different tissues and diseases involved. In this regard, we focus on the different roles of Pin1 in apoptosis in different neurodegenerative diseases.

Pin1 mediates neuronal apoptosis in AD

AD is a leading dementia disease and affects the global population. AD is characterized by the accumulation of β-amyloid peptide (Aβ) with hyper-phosphorylated tau (p-Tau), a microtubule associated protein (Azimi et al., 2017; Gu and Liu, 2020; Li et al., 2021b; Blanchard et al., 2022). Lu et al. (2018) first reported that Pin1 was involved in the process of AD. In the normal human brain, Pin1 is mainly distributed in the neuronal nuclei. However, in AD patients, Pin1 is localized in both the neuronal cytoplasm and perikarya neurofilbrillary tangles (NTs); furthermore, the levels of Pin1 are significantly reduced in AD patients when compared to normal brains (Pastorino et al., 2006; Samimi et al., 2021). Analysis of Pin1 knockout mice showed that the accumulation of p-Tau, neuronal loss, and behavioral deficits appeared together (Thorpe et al., 2004; Arlotta et al., 2017). Qiu et al. (2013) have also reported that Pin1 could be a protective factor for TBI, which is beneficial to the recovery of brain function in TBI. In TBI, Pin1 could inhibit the processing of Aβ (Nowotny et al., 2015). Recent studies have shown that the in brains of TBI patients, Pin1 is widely distributed in the neurons and correlates with neurodegenerative pathologies (Kim et al., 2021; Qiu et al., 2021). Other research has shown that cis pT231-Tau, but not the trans form, contributes to neuronal pathology and functional impairment in a model of AD (P304Lamy et al., 2018; Qin et al., 2021). Recent studies showed that death-associated protein kinase 1 (DAPK1) plays a critical role in regulating cis pT231-Tau after TBI (Kim et al., 2021; Qiu et al., 2021). DAPK1 is involved in the ubiquitin-proteasome system (DAPK1-Pin1-iASPP), finally promoting neuronal death (Kim et al., 2021; Qiu et al., 2021). Furthermore, the pharmacological inhibition of DAPK1 activity significantly increases the levels of Pin1 and significantly decreases the expression of cis pT231-Tau and the extent of neuronal injury (Kim et al., 2021; Qiu et al., 2021). Thus, DAPK1-Pin1-cis pT231-Tau is a novel regulatory pathway in TBI, and exerts an important effect on the progression of TBI. Thus, the targeting of this pathway might be a potential therapeutic strategy for TBI (Tonnin et al., 2023).

Pin1 mediates neuronal apoptosis in PD

PD is a disease that is characterized by the loss of dopaminergic neurons and the formation of α-synuclein aggregates in Lewy bodies. Pin1 also has been reported to be implicated in the pathogenesis of PD (Matena et al., 2013; Ibarra et al., 2014). Previously, research has shown that Pin1 is located in the Lewy bodies of PD patients. In particular, the overexpression of Pin1 may facilitate the formation and stability of α-synuclein aggregation in experimental models of PD (Ryo et al., 2006). Other research has shown that Pin1 has a pro-apoptotic role and causes α-synuclein aggregation (Ghosh et al., 2013). However, until now, the precise regulatory mechanism underlying the upregulation of Pin1 in PD has yet to be fully elucidated. Ghosh et al. (2013) reported that the upregulation of Pin1 may be associated with the extracellular stress and may then contribute to the death of dopaminergic neurons. Therefore, the overexpression of Pin may mediate apoptosis and may represent a critical neurotoxic event in the pathogenesis of PD.

Pin1 mediates neuronal apoptosis in HD

HD is an autosomal dominant neurodegenerative disease caused by an expansion of a CAG repeat in the encoding hypertrophic kinase protein (Htt). This condition is characterized by the death of medium spiny neurons in the striatum (Tabrizi et al., 2020). It has been reported that mutated Htt binds to p53, increases the levels of p53 protein, enhances the phosphorylation of p53 at Ser15 and eventually results in the inactivation of p53 in the index of patients with HD (Grison et al., 2011). It is important to note that the functionality of Pin1 plays a key role in stimulating the pro-apoptotic role of p53 (Agostoni et al., 2016). First, mutated Htt promotes the activation of Pin1 by promoting the formation of a trans isoform of Pin1 from its inhibitor (inhibitor of apoptosis-stimulating protein of p53; IASPP), finally promoting the expression of a series of apoptotic genes (Grison et al., 2011). However, in contrast, another study found that Pin1 might act as a negative regulator for Htt accumulation in a genetic mouse model of HD (Carmella et al., 2017). These authors found that the overexpression of Pin1 led to a reduction of Htt accumulation and that this might occur via degradation by the ubiquitin-proteasome system (Carmella et al., 2017). Therefore, the role of Pin1 in neuronal apoptosis might have a different effect in that it may stimulate Htt clearance-mediated neuronal protection and promote p53 mediated-apoptosis (Grison et al., 2011). Furthermore, by using a genetic mouse model of HD, Agostoni et al. (2016) have shown that the role of Pin1 in neuronal death might be time-dependent (Agostoni et al., 2016). In the early stages, Pin1 activation reduces the DNA damage response. However, in the middle stages, the activation of Pin1 might be triggered by Htt, thus initiating the role of Pin1 in p53-mediated neuronal apoptosis. Interestingly, Pin1 significantly increases the amount of Htt accumulation (Agostoni et al., 2016). In summary, the role and mechanisms of Pin1 in neuronal apoptosis provides some support for the pathogenesis of HD. However, the role of Pin1 in HD still requires further research.

Pin1 mediates neuronal apoptosis in stroke

Strokes are a disease involving massive ischemic impairment of consciousness and motor; this condition is caused by the obstruction or rupture of blood vessels in the brain (Magnusson et al., 2014). Baik et al. (2015) reported that Pin1 contributes to the process of stroke through Notch signaling. The Notch signaling pathway plays an essential role in cerebral vascular development, neuronal differentiation, determination, and certain neural pathological diseases (Magnusson et al., 2014). Notch signaling has also been implicated in...
Figure 1 | Timetable of the milestones of Pin1-mediated neuronal death in neurodegenerative diseases

- AD: Alzheimer’s disease; HD: Huntington’s disease; PD: Parkinson’s disease; Pin1-1: Prolyl cis-trans isomerase NIMA-interacting 1; SCI: spinal cord injury; TBI: traumatic brain injury.

Figure 2 | The molecular mechanisms underlying Pin1-regulated apoptosis signaling pathways.

- In AD, reduced levels of Pin1 inhibits GSK-3β enzymatic activity; this could inhibit HIF-1 protein degradation and contribute to the expression of the cis isofrom of pT231-Tau. The increased production of Aβ accelerates the formation of the cis isofrom of pT231-Tau, finally promoting the progression of AD. Furthermore, caspase-3 can be activated by the accumulation of Aβ and promotes the formation of the cis isofrom of pT231-Tau. In TBI, increased levels of DAPK1 inhibits Pin1 and then promotes the transformation of cis pT231-Tau as well as TBI. In PD, the overexpression of Pin1 facilitates the formation and stability of α-synuclein aggregation and promotes caspase-3 activation, finally leading to PD.

Pin1 mediates neuronal apoptosis in SCI

SCI is a severe trauma that causes severe injury to the function of the motor and sensory neurons of the spinal cord and generally is associated with a poor prognosis (Yuan et al., 2021). Myeloid cell leukemia sequence-1 (Mcl-1), an anti-apoptotic factor of the Bcl-2 family, remains phosphorylated in the basal state (Carlet et al., 2021). In normal neurons, Pin1 binds to pT163-Mcl-1 and inhibits Mcl-1 ubiquitination and degradation (Li et al., 2017). However, after SCI injury, Mcl-1 undergoes degradation following the removal of Pin1, thus resulting in Bcl-2 inhibition and the release of cytochrome C into the cytosol (Li et al., 2017). Furthermore, the activation of c-Jun N-terminal kinase (JNK) pathway can perturb the interaction between Pin1 and phosphorylated Mcl-1, thereby promoting the release of cytochrome C (Li et al., 2007). The JNK pathway plays a complicated role in many physiological and pathological processes, such as cell apoptosis and differentiation, and may modulate apoptosis by various stress signals and inflammation (Zhang et al., 2021). JNK also promotes the mitochondrial apoptotic pathway by regulating the release of BAX under the control of Pin1 (Shen et al., 2009). Other reports have also indicated that Pin1 binds to the Ser178-Pro motif in phosphorylated death domain associated protein and promotes the degradation of death domain associated protein via ubiquitination (Ryo et al., 2007). Degraded death domain associated protein can interact with apoptosis signal-regulating kinase 1 and activate the apoptosis signal-regulating kinase 1/permanent receptor activator of nuclear factor κB (NF-κB) pathway (Ryo et al., 2007; Oh and Mouradian, 2018). Most importantly, Pin1 also binds with phosphorylated Bcl-2-interacting mediator of cell death, extra-long (BIM) at Ser65 and JNK-interacting protein 3 to form a complex (Becker and Bonni, 2006). Pin1 also mediates the isomerization of BIM and leads to a conformational change in pSer65-BIM, thereby promoting the degradation of BIM, finally promoting neuronal apoptosis and stroke (Balaganapathy et al., 2019).

Pin1 mediates neuronal apoptosis in epilepsy

Epilepsy is a neurodegenerative disorder that is characterized by repeated seizures caused by the uncontrolled and abnormal firing of neurons (Lu et al., 2019b). Early studies indicated that the expression of Pin1 was remarkably reduced in epileptic patients (Becker and Bonni, 2007; Tang et al., 2017). Studies of an epileptic mouse model suggested the interaction of Pin1 with N-methyl-D-aspartate (NMDA) receptors and that this might be associated with the excitotoxicity of pyramidal neurons (Tang et al., 2017). Excitotoxicity is a toxic event induced by an excess of excitatory amino acids receptors which leads to excitotoxic neuronal death (Li et al., 2019b). This report was further confirmed by other researchers who found that Pin1 deletion led to a significant increase in seizure susceptibility in chemical-induced epileptic mouse models (Becker and Bonni, 2007). Pin1 deletion was also shown to enhance the phosphorylation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors by phosphorylating calcium/calmodulin-dependent protein kinase II (CaMKII) (Becker and Bonni, 2007). In a clinical study, the levels of Pin1 were found to be reduced, while the levels of p-CaMKII and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors were increased in the cortex of epileptic patients (Tang et al., 2017). Thus, Pin1 in a mouse model of epilepsy, the re-expression of Pin1 in Pin1-deletion mice led to a significant down-regulation of p-CaMKII and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; this was accompanied by the effective suppression of seizure susceptibility (Tang et al., 2017). Thus, Pin1 is an important controlling effector in epilepsy; this indicates that Pin1 is an attractive therapeutic strategy for epilepsy (Hou et al., 2021).
Regulated Necrosis

Under chronic neurodegenerative diseases and accident conditions, such as ischemic injury, cells may undergo morphological changes involving necrosis (Charidimou et al., 2020). Traditional views consider that necrosis is a type of passive and uncontrolled cell death that occurs around the damaged tissues. However, in recent years, some reports have indicated that, in addition to the classic form of necrosis, there is a type of procedural necrosis that can be regulated but undergoes classical necrotic morphological changes (Degterev et al., 2005; Yuan et al., 2019). In 2019, Yuan’s team (Degterev et al., 2005; Yuan et al., 2019) first proposed a new term to define this form of RN, and referred to this as necroptosis, also known as programmed necrosis. RN is known to play vital roles in various physiological and pathophysiology processes, such as aging and neurodegenerative disorders. Thus far, a series of different types of RN have been identified, including receptor interacting protein 3-mediated necroptosis that can be induced by tumor necrosis factor, pyroptosis that relies on the activation of caspase-1 and is triggered by microbial infection, aerinastin-mediated ferroptosis that requires excess iron, and mitochondrial permeability transition dependent RN (Yuan et al., 2019). Although these types of RN are named distinctly, their regulatory signaling pathways exhibit some degree of crosstalk (Alu et al., 2020). For example, in some stimuli, such as excitatory amino acid injury and ischemia, calcium overloading could result in different types of RN (Ros et al., 2017). However, the precise control mechanisms underlying RN are still unclear and should be further investigated. Over recent years, the relationship between Pin1 and RN has been described in certain neurodegenerative disorders; for example, Pin1 knockout mice showed significantly increased levels of retinal nuclear necrosis (Figure 3) (Kuboki et al., 2009; Wang et al., 2017, 2019a). In this section, we discuss the role of Pin1 in RN and certain neurodegenerative disorders.

Figure 3 | The molecular mechanisms responsible for how Pin1 regulates RN and autophagy signaling pathways. In RN in brain ischemia and traumatic injury, Pin1 acts as an important down-regulator of DAPK1-induced excitotoxic necrosis. The overexpression of DAPK1 resulted in a strong and significant enhancement of necrotic neurodegeneration in postsynaptic neurons. A previous study has shown that CaMK activation and associated CaMK-dependent processes play a key role in the process of AD, DAPK1 acts up-stream of Pin1 (Bialik and Kimchi, 2011). Future studies now need to determine why the relationship between upstream and downstream of DAPK1 and Pin1 differ in a manner that is dependent on the cellular context (Ibarra et al., 2017).
Recent studies have revealed the underlying connections between Pin1-mediated autophagy and neuronal toxicity in AD (Del Rosario et al., 2015; Chao et al., 2021). It has been shown that increased levels of APP expression could cause AD. Reduced levels of Pin1 and increased levels GSK-3β, a 47-kDa isoform of the GSK3 family, were detected in the brains of AD patients and shown to be involved in the processing of APP processing (Del Rosario et al., 2015). It has also been reported that APP can be phosphorylated by GSK-3β, and that the activation of GSK-3β increases the production of APP and toxicity (Zhou et al., 2021). Further research showed that Pin1 could bind to the phosphorylated Thr330 motif of GSK-3β and inhibits its kinase activity in human neuronal and glioma cells (So and Oh, 2015). Pin1 deficiency or deletion of the binding site in GSK-3β led to an increase in GSK-3β activity, the increased stability of APP, and the production of toxic APP, thus suggesting the important role of Pin1 in neuronal death (Del Rosario et al., 2015). In addition, the over-expression of Pin1 can promote the inhibition of GSK-3β, thus inhibiting GSK-3β kinase activity, thus providing a novel mechanism for Pin1 in protection against AD (Min et al., 2005; Ma et al., 2012). Akt has also been identified as an intermediary between Pin1 and GSK-3β (Kim et al., 2009). GSK-3β is a target of Akt and can be inhibited by Akt activation (Kim et al., 2009). Eventually, Pin1 could affect the levels of GSK-3β protein by regulating Akt (So et al., 2015). In addition, Pin1 has been considered as a regulator of the protease (So and Oh, 2015). The inhibition of Pin1 restored GSK-3β expression by inhibiting proteasome degradation, and stimulated cell death via autophagy, as demonstrated by increased levels of light chain 3-II (So and Oh, 2015). It should be noted that the inhibition of GSK-3β induces the activation of Pin1. Therefore, these data suggest that GSK-3β may also be a mediator for the regulation of Pin1 activity in Alzheimer’s disease (So et al., 2021). Collectively, these data suggest that Pin1- GSK-3β pathway-mediated neuronal toxicity acts via autophagy in AD.

Inhibitors of Pin1 and Potential Clinical Applications

Pin1 is a potential therapeutic target for neurological diseases (Zabłocka et al., 2021). By screening a series of compound libraries, a number of Pin1 inhibitors have been identified that could provide protective effects by inhibiting nuclear factor kappa B (NF-κB) pathway (Chao et al., 2021). Their specificity to Pin1 PPIase domain activity, Pin1 inhibitors can be classified as either covalent or non-covalent types (Pinch et al., 2020). After binding to the Pin1 PPIase domain, covalent Pin1 inhibitors, such as juglone and KPT-6566, can induce a covalent modification of the Pin1 protein with the Pin1 catastrophic domain (Pinch et al., 2020). Most of the Pin1 inhibitors are non-covalent types, such as 2,3-(N,N,N,N-tetrafluorophenyl)isothiazol-3(4H)-one (TME-001), diethyl-1,3,6,8-tetrahydro-1,3,6,8-tetraoxobenzol-phenanthrene-2,7-dicarate (PiB), all-trans retinoic acid (ATRA), and arsenic trioxide (ATO) (Mori et al., 2011; Kozono et al., 2018; Bedouhene et al., 2021). Non-covalent Pin1 inhibitors can also bind to the Pin1 PPIase domain, but inhibit Pin1 activity in a competitive manner (Kozono et al., 2018). However, the Pin1 inhibitors identified thus far are associated with limitations that restrict their use in clinical applications (Additional Table 2). Highly specific and potent Pin1 inhibitors are urgently needed.

Juglone was the first identified inhibitor that can activate the activity of Pin1. Juglone has been shown to inhibit neuronal damage in some experimental models of disease, such as PD and AD. Juglone irreversibly inhibits Pin1 catalytic domain PPIase activity at high concentrations. Although the inhibition of juglone against Pin1 protects against both in vivo and in vitro, the lack of Pin1 specificity and toxicity at high concentrations create significant limitations with regards to potential application in clinical treatments. Therefore, further research now needs to evaluate or design potential Pin1-specific inhibitors for the treatment of various neurodegenerative diseases. KPT-6566 is known to degrade Pin1 with higher levels of specificity and can reduce the expression of cyclin D1. Furthermore, KPT-6566 can induce cell apoptosis by generating reactive oxygen species (ROS) and inhibiting cell proliferation in both breast and prostate cancer. More importantly, KPT-6566 inhibits the growth of tumor cells in vitro, which could easily reveal the underlying interactions of the active domain of Pin1 with specific inhibitors. Furthermore, efforts should be made to promote the efficacy of combined targeted therapies and to prevent drug resistance. However, these effects need to be further investigated in vitro and in vivo.

The inhibition of Pin1 restored GSK-3β expression by inhibiting proteasome degradation, and stimulated cell death via autophagy, as demonstrated by increased levels of light chain 3-II (So and Oh, 2015). It should be noted that the inhibition of GSK-3β induces the activation of Pin1. Therefore, these data suggest that GSK-3β may also be a mediator for the regulation of Pin1 activity in AD (So et al., 2021). Collectively, these data suggest that Pin1- GSK-3β pathway-mediated neuronal toxicity acts via autophagy in AD.

Conclusion

KCD, including apoptosis, autophagy, and RN, is a type of controlled cellular death that contributes to the physiological balance in cell survival and organ homeostasis. Over the past few years, several studies have indicated that the aberration of Pin1 expression is a pathological characteristic and plays a crucial regulatory role in neuronal KCD, especially in apoptosis. Pin1 dysfunction also occurs in patients with various neurodegenerative diseases and is correlated with poor therapeutic efficiency. The inhibition of Pin1 plays a vital role in neuronal survival. Therefore, Pin1 may represent a potential key target for the development of specific and potent Pin1 inhibitors. Intriguingly, Pin1 acts in both protective and harmful roles to regulate the neuronal death; the precise effects are dependent on different cellular contexts. This is because Pin1 mediates multiple mechanisms by binding with different targets at the same time. Future studies are needed to investigate such interactive networks and gain a better understanding of Pin1-mediated diseases. Remarkably, although many research studies have reported that Pin1 is an important target in apoptosis for the treatment of neurodegenerative diseases, such as AD, there are still many challenges. For example, we still need to investigate the specific role of Pin1 in RN and autophagy.

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Availability of data and materials: All data generated or analyzed during this study are included in this published article and its supplementary information files.

Open access statement: This is an open access journal, and therefore all content is freely available online. References cited in the Additional Table 2 are listed in the manuscript.

Additional files: Additional Table 1: Summary of Pin1 changes in neurodegenerative diseases. Additional Table 2: Summary of Pin1 inhibitors.
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### Additional Table 1 Summary of Pin1 changes in neurodegenerative diseases

| Cell death type | Disease | Pin1 changes in disease | Main molecule in disease | Role of Pin in disease | Reference |
|-----------------|---------|-------------------------|--------------------------|------------------------|-----------|
| Apoptosis       | AD      | Decreased in AD patients| Pin1, GSK-3β, APP, HIF-1α, Aβ, p-Tau | Inhibits apoptosis | Lu et al., 1999; Thorpe et al., 2004; Hashemzadeh-Bonehi et al., 2006; Pastorino et al., 2006; Kesavapany et al., 2007; Nowotny et al., 2007; Dakson et al., 2011; O’Brien and Wong, 2011; Lonati et al., 2014; Azimi et al., 2017; Xu et al., 2017; Rong et al., 2017; Samimi et al., 2021; Nakhiiri et al., 2020; Li et al., 2021a; Wang et al., 2020a; Zheng et al., 2021 |
| TBI             | Decreased in TBI models | DAPK1, Pin1, p-Tau | | | Kim et al., 2021; Qiu et al., 2021; Tonnis et al., 2021 |
| PD              | Increased in PD patients | Pin1, α-synuclein, caspase-3 | | | Ghosh et al., 2013; Matena et al., 2013; Ibáñez et al., 2014; Ryo et al., 2006 |
| HD              | Increased in HD patients; Decreased in HD models | Htt, Pin1, iASPP, p53 | Both inhibits apoptosis and promotes apoptosis | | Grison et al., 2011; Agostoni et al., 2016; Carnemolla et al., 2017 |
| Stroke          | Increased in Stroke models | Pin1, FBX7, NICD1, p53 | Promotes apoptosis | | Zacchini et al., 2002; Baik et al., 2015; Arumugam et al., 2018; Balaganapathy et al., 2018; Li et al., 2019 |
| SCI             | Increased in SCI models | Pin1, Daxx, ASK1, BIMα, JNK, Mcl-2, BAX, Bcl-2 | | | Becker and Bonni, 2006, 2007; Ryo et al., 2007; Barone et al., 2008; Shen et al., 2009; Li et al., 2017; Oh and Mouradian, 2018; Zhang et al., 2021 |
| Epilepsy        | Decreased in epileptic models | CaMKII, AMPA and NMDA receptors | | | Becker and Bonni, 2007; Tang et al., 2017; Hou et al., 2021 |
| Other neurodegenerative diseases | Decreased in age-related neurodegeneration patients | Lipofuscin | | | Hashemzadeh-Bonehi et al., 2006 |
| RN              | Increased in brain ischemia and traumatic injury models | Calcium, DAPK, Pin1 | | | Bialik and Kimchi, 2011; Del Rosario et al., 2015; Chen et al., 2017; Ibarra et al., 2017; Wang et al., 2017 |
| Retinal disease | Increased in retinal disease | Calcium, CaM, CaMKII, Pin1, CAST, Calpain2, AIF | Promotes RN | | Wang et al., 2017, 2019a, b; Cheng et al., 2018; Hou et al., 2021 |
| Autophagy       | Decreased in AD patients | Pin1, Akt, Ubiquitin, GSK-3β, Aβ, LC3-II | Promotes autophagy | | Min et al., 2005; Ma et al., 2012; Del Rosario et al., 2015; So and Oh, 2015; Kim et al., 2009; Chao et al., 2021 |

AD: Alzheimer’s disease; AIF: apoptosis-induced factor; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APP: amyloid precursor protein; ASK1: apoptosis signal-regulating kinase 1; Aβ: β-amyloid peptide; BAX: Bcl2-associated X; Bcl-2: B-cell lymphoma 2; BIMα: Bcl-2-interacting mediator of cell death, extra long; CaM: calmodulin; CaMKII: calmodulin-dependent protein kinase II; CAST: calpastatin; DAPK1: dual-specificity protein kinase A/C domain family, member K1; Daxx: death domain-associated protein with death domain; DAPK1: death-associated protein kinase 1; DAXX: death-associated protein with death domain; Daxx: death domain-associated protein with death domain; EL: endoplasmic reticulum; GSK-3β: glycogen synthase kinase 3β; HIF-1α: hypoxia-inducible factor 1α; Htt: huntingtin; LC3-II: microtubule-associated protein 1 light chain 3B; NMDA: N-methyl-D-aspartate; Pin1: proline-rich interacting protein 1; Rho: Rho family GTPase; RN: retinal neurodegeneration,
death-associated protein kinase 1; Daxx: death domain associated protein; FBW7: F-box and WD repeat domain containing domain protein 7; GSK-3β: glycogen synthase kinase-3β; HD: Huntington’s disease; HIF-1: Hypoxia-inducible transcription factor-1; Htt: Huntington; iASPP: inhibitor of apoptosis-stimulating protein of p53; JNK: C-Jun N-terminal kinase; LC3: long chain 3; Mcl-1: myeloid cell leukemia sequence-1; NICD1: Notch intracellular domain 1; NMDA: N-methyl-D-aspartic acid receptor; PD: Parkinson’s disease; Pin1: prolyl cis-trans isomerase NIMA-interacting 1; RN: regulated necrosis; SCI: spinal cord injury; TBI: traumatic brain injury.
### Additional Table 2 Summary of Pin1 inhibitors

| Drug            | Details                                                                 | Mechanisms of action                                                                 | Tested models      | Limitations                                           | Reference                                      |
|-----------------|-------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------|------------------------------------------------------|-----------------------------------------------|
| Juglone         | First Pin1 inhibitor; Has effect on CNS                                  | Irreversible inhibition of Pin1 PPIase catalytic domain; Degradation of Pin1 protein | Cell line; Mouse   | Non-specific inhibition                              | Ghosh et al., 2013; Liu et al., 2019a; Bedouhene et al., 2021 |
| KPT-6566        | Exerts both Pin1 inhibitory and cytotoxic effects; Inhibits cancer cells growth | Specific inhibition of Pin1 PPIase catalytic domain                                   | No testing in neurological diseases and clinical trial | Campaner et al., 2017                           |
| TME-001         | Inhibits cancer cells growth                                              | Competitive inhibition of Pin1 PPIase catalytic domain                                 | Cell line          | No testing in clinical trial; Poor solubility        | Mori et al., 2011                             |
| PiB             | Inhibits cancer cells growth; Has effect on CNS                          | Specific inhibition of Pin1 PPIase catalytic domain                                   | Cell line          | No testing in neurological diseases and clinical trial | Antonelli et al., 2016; Liu et al., 2019a      |
| DTM             | Inhibits cancer cells growth                                              | Competitive inhibition of Pin1 PPIase catalytic domain                                 | Cell line          | No testing in neurological diseases and clinical trial | Tatara et al., 2009; Fan et al., 2019          |
| 6,7,4'-THIF      | Inhibits cancer cells growth                                              | Competitive inhibition of Pin1 PPIase catalytic domain                                 | No testing in neurological diseases and clinical trial | Lim et al., 2017                                |
| EGCG            | Cell line; mouse                                                        | Degradation of Pin1 protein                                                           | No testing in neurological diseases and clinical trial | No-specific inhibition                          | Della Via et al., 2021                        |
| API-1           | Inhibits cancer cells growth; Causes G1 phase arrest                     | Degradation of Pin1 protein                                                           | Cell line          | Low efficacy                                         | Sun et al., 2019                              |
| 5'-NIO          | Inhibits cancer cells growth; Causes G1 phase arrest                     | Degradation of Pin1 protein                                                           | Cell line          | No testing in neurological diseases and clinical trial | Yoon et al., 2012                             |
| ATRA            | FDA approved for treatment of APL                                       | Specific inhibition of Pin1 PPIase catalytic domain; Degradation of Pin1 protein      | Cell line; mouse; human | No testing in neurological diseases and clinical trial; Non-specific inhibition | Kozono et al., 2018; Bedouhene et al., 2021 |
| ATO             | Inhibits cancer cells growth                                              | Degradation of Pin1 protein                                                           | No testing in neurological diseases and clinical trial | ATO: arsenic trioxide; ATRA: all-trans retinoic acid; CNS: central nervous system; DTMBipentamethylene thiuram monosulfide; EGCG: epigallocatechin-3-gallate; FDA: U.S. Food and Drug Administration; PiB: diethyl-1,3,6,8-tetrahydro-1,3,6,8-tetraoxobenzol-phenanthroline-2,7-diacetate; Pin1: prolyl cistrans isomerase NIMA-interacting 1; TMB29: 4,6-bis(benzyloxy)-3-phenylbenzofuran; TME-001: 2-(3-chloro-4-fluoro-phenyl)-isothiazol-3-one. | Kozono et al., 2018; Bedouhene et al., 2021 |
