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Review Article

Functional roles of receptor interacting protein kinase 1 in Alzheimer's disease

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Neurodegenerative diseases are a growing global issue. They tend to occur in the later stages of life and are primarily characterized by dementia, irritability, aggressiveness and poor cognitive function, among other manifestations. Pathologically, neurodegenerative diseases such as Alzheimer's and Parkinson's disease feature the progressive damage of neurons in the brain. Alzheimer's disease in particular is the sixth leading cause of death in the US. Its aetiology involves impaired cell signaling pathways that are crucial for cell survival through the modulation of tumor necrosis factor-α activity via the actions of receptor interacting protein kinase (RIPK) 1. The study of RIPK1 involvement in Alzheimer's disease had been ongoing for decades, and it was found to mediate two of the most common pathways implicated in the neuronal deaths seen in Alzheimer's disease: apoptosis and necroptosis. To a certain extent, the involvement of autophagy was also observed in the progression of neuronal death. In this review, the general structure of RIPK1 and the various cell death pathways it regulates, as well as its significance in Alzheimer's disease, are discussed.

Keywords: Alzheimer's disease, receptor interacting protein kinase

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Introduction

Over the last few decades, the world has seen the aging population succumb to Alzheimer's disease (AD). Clinical manifestations of this debilitating and

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disabling disease include dementia [1], progressive loss of cognitive function and memory as well as decreased mental capacity [2]. The common pathological findings in AD include neuronal damage, formation of senile plaques, neurofibrillary tangles and microglial activation [1]. In particular, senile plaques have been making a regular appearance in AD brains. They mainly occur due to the accumulation of beta-amyloid (Aβ) peptide derived from the improper folding of the amyloid precursor protein (APP).

With lengths ranging from 40 to 42 amino residues, Aβ is generated by the cleaving of APP by beta and gamma secretase – a protein complex comprised of presenilin, nicastrin and more – found within the neuronal membrane [3,4]. The Aβ peptide formed is released from the membrane into the extracellular space. In normal circumstances, these aggregates are cleared by a degradation mechanism called autophagy [5]. However, defective autophagy, coupled with mutations in the APP and presenilin genes, lead to overproduction and aggregation of toxic fibrillar Aβ [6]. Presenilin gene mutations are correlated with the increased production of Aβ1-42 [7,8]. This may be due to the enzymatic action of presenilin during the process of Aβ generation [9,10]. In addition, presenilin mutations were found to promote neuronal cell apoptosis [11].

In AD, the most abundant form of Aβ found is Aβ1-40, followed by Aβ1-42 [12]. The presence of Aβ plaques in turn activate microglia and astrocytes to release tumor necrosis factor (TNF)-α, a pro-inflammatory cytokine, which is toxic to neurons. These activated microglial cells tend to cluster around the periphery of the plaque, suggesting the involvement of microglia in the further development of the plaque [13,14]. Furthermore, several studies have reported a substantial increase in TNF-α level in both human and mice AD brains. Upon the deletion of the TNF-receptor 1 (TNFR1) gene in a mouse model, the formation of Aβ plaques was significantly reduced, which restored cognitive function and re-established protection against dopaminergic neurotoxicity [15]. On the other hand, Aβ induces oxidative stress and elevated intracellular Ca2+ concentration in neuronal cells [16,17]. Furthermore, it triggers apoptosis [18] by interacting with neuronal receptors, such as the receptor for advanced glycation endproducts (RAGE) [19] and the p75 neurotrophin receptor [20]. Aβ also activates the caspase cascade; and selective inhibition of the caspases particularly caspase-2 and caspase-12 inhibited Aβ-induced toxicity [21,22]. Apolipoprotein E (ApoE) was found to contribute to AD risk by regulating Aβ clearance [23]. It bound to Aβ differentially and modulated its fibrillogenesis [24-26]. It also affected the processing of tau in neurons [27,28]. Hence, humans expressing the ApoE protein are prone to develop plaque and vascular Aβ deposits [29]. Similar observations were noted in genetically engineered mice that expressed ApoE4 [30].

TNF-induced neuronal deaths have been largely associated with AD [15], and its signaling pathway have been associated with

receptor interacting protein kinase (RIPK) 1. RIPK1 determines the fate of the cell by modulating TNF-α and other receptors for cell survival or induction of apoptosis and necroptosis [31]. It also plays an important role in mediating autophagy (Fig. 1). Hence, RIPK1 has been the main interest for researchers to establish a direct relationship with AD. Over the years, the pathways mediated by RIPK1 and its role in neurodegeneration in AD have been investigated. In this review, the functional roles of RIPK1 in AD and the pathways it mediates are discussed.

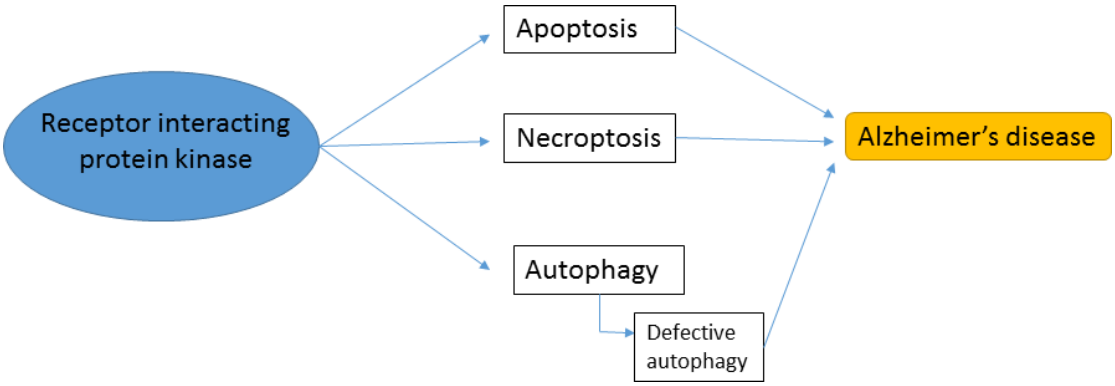

Figure 1. Apoptosis, necroptosis and autophagy are involved in the pathogenesis of Alzheimer's disease, mediated by the receptor interacting protein kinase.

General structure and functions of RIPK1

RIPKs are a group of serine/threonine kinases responsible for regulating cell death and survival. Kinase proteins usually play various roles in different pathways [32]. Seven types of RIPKs have been discovered presently, each denoted with a number in the order they were found. The general structure of RIPK consists of a kinase domain and protein-protein interaction motifs unique to each member [33]. RIPK1 is generally made up of an N-terminal kinase domain, a C-terminal death domain and an intermediate domain located in between [34-36]. The N-terminal kinase domain is crucial for inducing cell death [37] and activating the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB) pathway for cell survival [35]. Meanwhile, the C-terminal death domain binds to death domain receptors like TNFR1 and death-domain containing adaptor proteins such as TNF receptor type 1-associated death domain (TRADD) [33,35,36]. Lastly, the intermediate domain is responsible for activating the NF-KB pathway through the formation of complex 1 by

poly-ubiquitination of Lys-377. The intermediate domain also contains receptor interacting protein (RIP) homotypic interaction motifs (RHIM) that facilitates the interaction between RHIM-containing proteins and RIP3 for the formation of necrosome complex [33].

RIPK1 mediates pathological pathways associated with AD

Autophagy

Autophagy is a cellular degradation pathway important for promoting cell survival in stressful conditions and clearing out abnormally aggregated proteins [38,39]. This process is initiated in response to a stimulus like cellular starvation which stimulates the entrapment of cytoplasmic constituents within a cup-like membrane known as the phagophore, to form an autophagosome [40]. This autophagosome then fuses with lysosomes for the degradation of its contents by lysosomal hydrolases [40,41].

Currently, there is little evidence on how RIPK1 directly mediates autophagy in AD. However, defective autophagy has been implicated in the progression of neurodegeneration in AD [6]. For instance, the presence of autophagosomes in neurons has been reported, with a subsequent accumulation within dystrophic neurites of the two most affected regions of the brain: the hippocampus and cortex. Autophagosomes are rarely found in a healthy brain, hence elevated amounts suggests the failure of autophagy in mediating protein degradation [3]. Furthermore, because of this scarcity, earlier studies suggested that autophagy is inactivated in neurons. Nonetheless, more current research revealed that autophagy in neurons is actually very active, but the process requires a fully functional lysosomal degradation mechanism. In the pathogenesis of AD, lysosomal degradation is often impaired, which leads to the accumulation of autophagosomes in dendrites and axons. Even though there is a successful fusion between autophagosomes and lysosomes, the degradation of the substrates in the autolysosomes is disabled [42].

In states of injury, autophagy removes impaired organelles that would otherwise trigger cell death. This provides evidence that autophagy harbours cytoprotective qualities that are compromised in AD due to severe impairment of the cellular degradation pathway [43].

Apoptosis

A defective autophagy mechanism often redirects cells to another pathway called apoptosis. Apoptosis is a programmed cell death mechanism that has been extensively linked to neuronal death in AD. Its morphological characteristics include a shrunken cytoplasm, fragmented nucleus and cellular components, condensed chromatin and apoptotic body formation [43].

Overexpression of TNFR1 has been linked to apoptosis in AD brains [6].

Apoptosis is initiated by the activation of TNFRI during cell survival dysfunction. A deubiquitinating enzyme called cylindromatosis (CYLD) acts on RIP1 to disrupt complex I (consisting of TRADD, cellular inhibitors of apoptosis (cIAP) 1 and 2 and TNF receptor-associated factors (TRAF) 2 and 5) formed in the NF-KB pathway and releases RIP1 from the plasma membrane [44]. The RIP1 ubiquitination by the E3 ligases cIAP1 and 2 activates the cell survival pathway, but removal of these E3 ligases due to genetic deletion or presence of IAP antagonists leads to the formation of riptosome, a secondary complex consisting of RIP1, Fas-associated death domain (FADD) and caspase 8. Caspase 8 within the riptosome inactivates RIP1 by cleaving to induce apoptosis [31].

Several studies have shown that autophagy has the ability to inhibit apoptosis-induced cell death [31,43]. Apoptosis is delayed or prevented in nutrient-deprived cells by the turnover of redundant cellular components into substrates for energy.

Necroptosis

Necroptosis is a unique example of non-apoptotic cell deaths [36]. It is the regulated form of necrosis, with morphological characteristics that include decreased plasma membrane integrity, dysfunctional mitochondria, swollen organelles and lack of apoptotic bodies [44]. Factors such as TNF-α, toll-like receptors (TLR) and viral infections are known to trigger necroptosis [6,45].

Necroptosis is often activated in apoptosis-deficient conditions. In apoptosis, TNF signaling activation occurs when TNF-α binds with its receptor, followed by the formation of complex IIa consisting of RIP1, FADD and caspase 8 [36]. However, the absence of caspase 8 activity, which inactivates RIP1 to prevent the release of necroptotic signals [46], leads to the recruitment and phosphorylation of RIP3 by RIP1 to form complex IIb, otherwise known as the necrosome [45,47]. The activation of RIP3 subsequently triggers the phosphorylation of the pseudo-kinase mixed lineage kinase domain-like (MLKL) and induces its oligomerisation and translocation to the plasma membrane. As a result, integrity of the membrane is compromised and intracellular components escape to induce necroptosis [45,47,48].

There is increasing evidence suggesting the involvement of necroptosis in AD-associated neuronal damage. One study highlighted that neuronal cells, particularly the hippocampal neurons, are more prone to undergo TNF-α-induced necroptosis as compared to apoptosis. It was demonstrated that neuronal death was initiated by the CYLD-RIP1-RIP3-MLKL signaling pathway. Moreover, an over-expression of RIP1 and RIP3 was observed, along with an increase in

neuronal death upon intracerebroventricular administration of TNF-α [30]. This underlines the vital role of TNF-α in neuronal cell death. To further support this claim, the study demonstrated that by inhibiting the actions of RIP1, RIP3, MLKL and CYLD, which are necessary for inducing necroptosis, there was a significant reduction in neuronal cell death [30].

Crosstalk between apoptosis and necroptosis

Cellular response to TNF is complex. It may induce apoptosis or necroptosis depending on the cell type and cell death sensitizers. These regulated forms of cell death are thought to be complementary to each other. Hence, therapeutic approaches that target a single cell death mechanism may not be effective. Recent studies show that targeting multiple cell death paradigms are more effective in cytoprotection [49]. For example, lung damage, a common complication of kidney transplantation, was inhibited by the dual targeting of parthanatos and necroptosis [50]. Moreover, in renal ischaemia-reperfusion injury, the combined targeting of necroptosis, ferroptosis and cyclophilin D-dependent necrosis resulted in a better outcome compared to the non-treated or single inhibitor-treated groups in an animal study [51].

There is emerging evidence linking apoptosis and necroptosis pathways. A previous study showed that lipopolysaccharide stimulated the formation of RIPK1-RIPK3-FADD-caspase 8 complex in dentritic cells, and the complex was found to contribute to interleukin-1β processing [52]. When caspase 8 was depleted, the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome was assembled and this process was dependent on RIPK1, RIPK3, MLKL and phosphoglycerate mutase family member 5 (PGAM5) [53]. These findings suggest the involvement of necroptosis-associated factors, including RIPK in the inflammasome activation. In addition, RIPK1 was involved in the development of inflammation and necroptosis in motor neuron degeneration [54]. On the other hand, signaling via the TLR adaptor protein TIR-domain-containing adaptor-inducing interferon-β (TRIF) that leads to cIAP1- or cIAP2-mediated ubiquitylation of RIPK3 and cell survival has been shown to be involved in the necrosome-inflammasome interaction. Absence of the cIAPs caused RIPK3-mediated activation of caspase 8, which in turn led to the activation of the inflammasome and apoptosis. When both the cIAPs and caspase 8 were absent, RIPK3 and MLKL-dependent activation of inflammasome was enhanced [55]. Newton et al. found that kinase activity of RIPK3 was essential for necroptosis and may also play an important role in caspase 8 activation and apoptosis [56]. Taken together, necroptosis and apoptosis pathways were shown to share a few mediators such as RIPK3, caspase 8 and inflammasome (Fig. 2). It is worth noting that the different domain structures, such as death and caspase activation and recruitment domain (CARD) domains, which were found in the different

RIP family members determine the specific function of each RIP kinase [57].

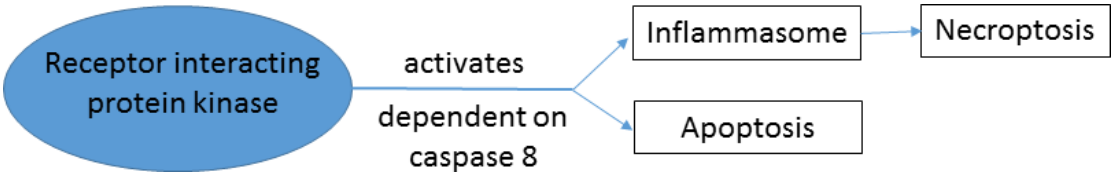

Figure 2. Receptor interacting protein kinase and caspase 8 are involved in necroptosis and apoptosis pathways.

Relevance of RIPK1-targeting drugs for AD

The development of novel therapies for AD has recently emerged; albeit none that specifically target RIPK1 activity. Considering the important role of RIPK1 in AD, RIPK1 inhibitors might act as potential drug for AD treatment. Recently, there is an increasing discovery of RIPK1 inhibitors with promising results. The discovery of necrostatins as a RIPK1 inhibitor was one of the earliest made. Necrostatin (Nec-1) had been identified as a small-molecule inhibitor that specifically inhibits the RIPK1 activity in necroptosis without interfering with other RIPK1-mediated pathways such as the NF-KB pathway [58]. Because of this, Nec-1 has become an important tool for establishing the role of RIPK1 in necroptosis through in vitro and in vivo assays. Despite the promising effects reported, the inhibitor has shown several limitations. It has a short half-life, moderate potency, and tends to generate unnecessary off-target effects. Thus, several analogues have been identified. Of these, 7-Cl-O-Nec-1, known as Nec-1s, reportedly improved pharmacokinetic features and does not interfere with indoleamine-2,3-dioxygenase (IDO) activity crucial for immune system function. However, it shares a similar structure to Nec-1, thus retaining similar characteristics such as moderate potency and off-target effects [59,60].

Another small-molecule RIPK1 inhibitor known as GSK'963 was discovered by Berger et al. This highly selective RIPK1 inhibitor is structurally different and 200 times more potent than necrostatins. Furthermore, it affects neither IDO activity, nor NF-KB activity, nor apoptosis [59]. On the other hand, the RIPK3 kinase inhibitor GSK'872 was able to reverse TNF-induced necroptosis [61].

Unfortunately, despite their ability to prevent necroptotic damage, these RIPK1 inhibitors are unavailable for clinical use. Thus, a study was conducted to ascertain possible RIPK1 inhibitory activities in clinically-approved drugs. Ponatinib and

pazopanib were identified as kinase inhibitors that directly inhibit RIPK1 in necroptosis in humans. Both drugs are highly potent and do not interfere with apoptosis. Moreover, ponatinib is capable of targeting other important components of necroptosis, including RIP3, MLKL and more, whereas pazopanib provides protection from necroptosis at very low concentrations, suggesting its potential use for future clinical applications. In the study, ponatinib and pazopanib were found to rescue TNF-α/Smac mimetic/z-VAD-FMK (TSZ)-induced necroptotic cell death. The two drugs inhibited necroptotic cell death driven by TNF, TRAIL and Fas ligand (FasL) in HT-29 cells. In contrast, the drugs did not inhibit apoptotic cell death triggered by FasL. Ponatinib targeted at two pathways in its cytoprotective effect: the necroptosis machinery and TNF signaling. Components of these mechanisms include RIPK1, RIPK3, MLKL, TGF-β-activated kinase 1 (TAK1), MAP3K7-binding protein 1 (TAB1) and TAB2. Ponatinib blocked the phosphorylation of RIPK1, RIPK3 and MLKL. The study found that MLKL S358D was not the drug target of ponatinib. On the other hand, pazopanib was found to directly bind and inhibit RIPK1 kinase activity. However, it did not block MLKL S358D-driven necroptosis and only moderately affected RIPK3 activity. Pazopanib blocked TSZ-induced phosphorylation of MLKL but did not interfere with the binding of RIPK3 to MLKL [62].

Structure-based virtual screening methods are useful in developing new drugs that target a specific protein. Usually, integration of different ensemble methods provide better virtual screening results. Hence, Fayaz and Rajanikant have developed dual ensemble screening method, a novel computational strategy that can be used in identifying diverse and potent inhibitors against RIPK1. Pharmacophoric information and appropriate protein structures for docking are crucial in the search for potential drug candidates that demonstrate correct ranks and scores after docking. Thus, in this new screening method, all the pharmacophore features present in the binding site were carefully considered. Ensemble pharmacophore was used in the pharmacophore-based screening of ZINC database to obtain compound hits [63]. Ponatinib is one of the drugs that has been identified as an inhibitor of RIPK based on the structure-based virtual screening method [64]. As Glu-in/DLG-out conformation of RIPK1 was found similar with Abl [65], the Bcr-Abl inhibitor, ponatinib was thought to be able to inhibit RIPK1. Using structure-guided design strategy that utilized the ponatinib scaffold, several novel inhibitors with greatly improved selectivity for RIPK1 were developed. In particular, a highly potent and selective 'hybrid' RIPK1 inhibitor termed PN10 which possessed the properties of ponatinib and Nec-1 have been developed. PN10 showed improved inhibition of necrosome formation and TNF-α synthesis compared to ponatinib [64].

Conclusion

Based on current evidence, it may be surmised that RIPK1 is the main mediator of the TNFR1 signaling pathway for the induction of apoptosis and necroptosis that contribute significantly to the progression of neuronal death in AD. Thus, blocking RIPK1 activity in both necroptosis and apoptosis without disrupting other important cellular pathways is likely to considerably alleviate the clinical effects of AD. Studies conducted on RIPK1 inhibitors have successfully demonstrated their potential in suppressing RIPK1 activity, but these inhibitors may not be available for clinical use in the near future. Increasingly potent RIPK1 inhibitors may be derived from the current RIPK1 inhibitors through the use of molecular modelling and drug design tools. Contradicting to the roles of RIPK1 in apoptosis and necroptosis which found contributing to the pathogenesis of AD, RIPK1 which also mediating autophagy may have protective effect against AD. Hence, more evidence should be gathered to support the use of RIPK1 inhibitors as a therapeutic regime for AD.

Competing interests

The authors declare that they have no competing interests.

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