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Review

Neuron Cell Death

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Abstract: Neuronal cell death in the central nervous system has always been a challenging process to decipher. In physiological condition, neuronal cell death is restricted in the adult brain even as people ages. However, in pathological conditions of various neurodegenerative diseases, the cell death and shrinkage of a specific brain region represent a fundamental pathological feature across different neurodegenerative diseases. In this review, we will briefly go through the general pathways of cell death and describe the evidence of the cell deaths in the context of common neurodegenerative diseases individually, discussing our current understandings of cell death in connecting with the renowned pathogenic proteins, including tau, amyloid-beta, alpha-synuclein, huntingtin, and TDP-43.

Keywords: apoptosis; necroptosis; neurodegeneration

1. Introduction

Neuronal cell death is the outcome after a neuron decides to activate well-orchestrated programs to terminate its existing, a process which could be triggered by internal and external signals throughout the lifetime. During the development of the human central neural system (CNS), the neurogenesis is often accompanied by the massive neuronal loss, a necessary part of constructing a functionally adequate commending center [1]. In despite there might be some occasional or arranged death events, extensive neuronal loss rarely occurs in the matured CNS [2]. During the ageing process, the neuronal loss is still limited, albeit in certain brain regions that observable difference of neuron numbers between young and old individuals may exist [3-6]. However, in many neurodegeneration diseases, there is a significant increase in the neuronal loss compared with age-matched controls, which also correlated with the disease progression with longitudinal examination [4, 7-11]. Based on these clinical observations, it is of enormous interest to find out what triggers the pathological changes and eventually results in cell death and regional brain shrinkage, which could ideally facilitate the development of the treatment to counteract the progression of diseases. In general, mature CNS neurons are very resistance to cell death when compared with immature neurons [12]. Neurons that are lasted for an individual's lifetime thus equipped to maintain cellular homeostasis by handling different stresses and cell death would be the final solution for a neuron only when multiple stresses piled up to a level beyond recovery capacity, which is the case commonly found neurodegenerative diseases. Nonetheless, neuronal dying is often a gradual process and believed to be in a regulated manner [4,7,11,13]. Uncontrolled and acute cell death are still limited and only found after sudden traumatic brain injury [14].

The characteristic of a neurodegenerative disease often links to pathological protein formation and in many cases, high-ordered aggregates formation [15-17]. These factors could stress the neurons and render subsequent cytotoxic events, which include increased reactive oxygen species, excitotoxicity, synaptic dysfunction, impaired protein degradation systems, endoplasmic reticulum

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(ER) stress, DNA damage, mitochondrial dysfunction, inflammation, cell cycle re-entry [18]. These are all substantial challenges and their mishandling eventually cause the neurons to die. However, the underlying signaling mechanisms of how these factors act toward the initiation of cell death remains elusive.

2. Types of cell death

In neurodegenerative diseases, apoptosis and necrosis are believed to be the two major death pathways for neurons [19,20]. The fundamental differences between apoptosis and necrosis lie in the disparity of cell morphology and if the cellular contents would leak out during the process [20,21].

2.1. apoptosis

Apoptosis is a type of programmed cell death (PCD). Some cytomorphological features of an apoptotic cell are recognized as size shrinkage, chromosome condensation, and DNA fragmentation [22-24]. During which process the apoptotic bodies would form eventually in many cases, and cellular contents generally would not leak out, which is believed to minimize the eliciting of immunological response [25]. The fragmented DNA could indicate the possible existence of apoptosis, which can occur at late-phase and be detected by Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay either *in vivo* or *in situ* [26,27].

The execution of apoptosis can be incited by signals either intrinsically or extrinsically. For the extrinsic pathway, death receptors are activated through binding the extracellular ligands [28], whereas for the intrinsic pathway, internal stimuli, such as DNA damage, could activate p53 and the up-regulation of pro-apoptotic factors of Bcl-2 family [29]. Both pathways alter the inner mitochondrial membrane permeability and by which to activate Bcl-2 homology region 3 (BH3)-only proteins that eventually cause the release of pro-apoptotic factors from mitochondria into the cytosol, including cytochrome C, Smac/DIABLO, HtrA2/Omi, and apoptosis-inducing factor (AIF) [30,31]. These factors subsequently promote the execution of apoptosis in a caspase-dependent or independent manner [31]. For example, the releasing of cytochrome C could activate the so-called initiator caspases, like caspase 9, which could ultimately lead to the formation of apoptosome and by which to ignite executor caspases, such as caspase 3, to cleave some essential protein substrates including Poly (ADP-ribose) polymerase (PARP) [32]. On the other hand, the releasing of Smac/DIABLO and HtrA2/Omi from mitochondria inhibit IAP (inhibitors of apoptosis proteins) activity to foster apoptotic execution. Therefore, the proceeding of apoptosis could be detected by measuring the expression of pro-apoptotic genes, the cleaved PARP [33,34], or the cytosolic cytochrome C levels [35].

2.2. Necrosis

Necrosis is an alternative mechanism of cell death that signified by cell swelling during this process; thus the integrity of cell membrane is lost, and the intracellular contents leak out. DNA breakage could also be involved in the degradation process, but it does not involve chromosome condensation [21,36]. Therefore, the pathologic features of necrosis could be differentiated from apoptosis [37]. This death pathway could be programmed. Among these pathways, the best-characterized one is termed "Necroptosis" [38,39].

In the past, necrotic cell death has been considered as an event without genetic determinants such that it is not programmed. However, the discovery of tumor necrosis factor (TNF) can induce necrosis suggests otherwise. Indeed, the activation of specific death receptors or Toll-like receptors could lead to the initiation of necroptosis [39]. The activation of death receptors, like TNF alpha receptor 1 (TNFR1), could leads to the recruitment a series of proteins including cellular inhibitors of apoptosis 1 and 2 (c-IAP1/2) and RIP1, namely RIPK1, forming protein complex I. Subsequently RIP1 could be translocated into the cytosol and interact with RIP3 in the necrosome, which indicate the initiation of necroptosis [7,40]. RIP3 could phosphorylate mixed lineage kinase-like protein (MLKL), the executor of the pathway which could translocate to the cell membrane and cause membrane rupture [41,42].

Therefore, detecting the protein interactions or protein levels of RIP1-RIP3-MLKL axis could be used to identify the existence of necroptosis [7].

3 Neuronal cell death in the adult human brain

Unlike many somatic cells, mature neurons in the adult human brain are resilient to various stresses and pro-apoptotic stimuli, such as deprivation of neurotrophic factors. Therefore, the majority of mature neurons in the CNS are capable of enduring and functioning throughout an individual's lifespan [12]. Intriguingly, a study has shown that mouse cerebellar progenitor cells transplanted to rat brain could survive through the rat lifespan, which is much longer than mouse [43]. It seems to suggest that there is no internal clock to define how long a neuron will live on. Nonetheless, this notion should not be viewed as matured neuron somehow evade cell death pathways because a limited loss of neurons still proceed during aging, and some canonical apoptotic molecules do involve in the pathogenesis of some neurodegenerative diseases. It should be noticed that it is not easy to observe the neuron death directly from clinical samples as died neurons may be eliminated within a couple of days. The caveat of linking program cell death with physiological and neurodegenerative conditions will remain until scientist could find specific markers for observation [19,44].

3.1. Neuronal cell death in the physiological condition

Neurogenesis in adult CNS is often accompanied by neuronal cell death, as an extension of development [45]. The lifelong neurogenesis process has been observed in many brain regions. Recently, it was found that hippocampal neurogenesis is continuous without significant concession even during the aging process [3,46]. In the amygdala, the neuron numbers continue to increase in adult, which is possibly contributed by both the local maturing of immature neurons and the migration of immature neurons to this region [47]. During this process immature neurons would follow the environmental cues and migrate to the target site, forming connections with the pre-existing mature neurons. The failed ones may undergo apoptosis and be eliminated by microglia [45,48].

During the aging process, neurons of specific brain region may become more susceptible to death as data from different studies have indicated [3,4,49-51]. What signal triggers the death of those vulnerable neurons? One would guess there might be a causal relationship between cell death and aging itself, which often marks by decreased activities in motion and cognition, a reminiscent of the pathological symptoms in neurodegenerative diseases. If so, then the susceptibility may be a result of differences in intrinsic metabolic efficiency, protein expression, associated morphological dynamics, as well as microenvironment where they reside in the brain [52-55]. By using single-cell expression profiling in combination with qRT-PCR, it was found that cholinergic neurons from different brain regions once were very similar, but become very different in the aged *Aplysia californica*. In the study, two neurons both showed up-regulation of mitochondrial respiratory chain proteins as they were aging, but one showed an up-regulation of pro-inflammatory proteins as well as neurodegenerative related protein homologs compared to the other, indicating the same type of neurons may perform differently [55]. Meanwhile, both neurons showed down-regulation of kinesin and dynein, suggesting that long projections of neurons may add up their susceptibility to cell death [55,56]. In another study, it was found that up-regulation of A-type K^+ channels in aged CA3 pyramidal neurons is associated with its hyperactivity, such that alteration of neuronal signaling pathways may contribute to the accumulation of excitotoxicity and thereby promoting cell death, which is more pronounced in pathological conditions like Alzheimer's disease (AD) and epilepsy [54,57]. For dopaminergic neurons in substantia nigra (SN), it was found in normal aged people the region could also suffer significant neuronal loss [51]. Part of the reason may be attributed to the intrinsic metabolic character of dopaminergic neurons, as the intracellular metabolism of cytosolic dopamine in cytosol or on mitochondria could generate reactive oxygen species (ROS) directly and reduce the pool of antioxidants, posting consistent stress to neurons and its mitochondria, which naturally prone to accumulate damage [58]. Also, in situ DNA damage detection by TUNEL assay or

PARP staining also support that specific neuron suffers from DNA damage stress in normal aged people [59-61]. Therefore, the neuronal cell death in the normal aging process has a link with the neuronal loss in neurodegenerative conditions, although the pathological hallmarks including protein aggregations are not commonly found in the healthy brain.

3.2. Neuronal cell death in neurodegenerative diseases

Neuronal cell death is one of the major pathological hallmarks of neurodegenerative diseases. There are some primary regions suffered neuronal loss while as diseases progress the regions could be expanded in some conditions. It should be noticed that local volume change may not associate with a change in neuron number as other factors such as reduced innervations of neurons could also contribute to this change without exacerbating cell death. Therefore, to definitively describe whether the brain region shrinkage is associated with cell death is by adopting a standard way to measure neuron number such as to count neuN-stained soma in brain sections [62]. A common hallmark that transpires in many neurodegenerative pathologies is the aberrant protein aggregations. While the composition and localization of the aggregates vary in different neurodegenerative diseases, it is generally accepted that the generation and accumulation of these proteinaceous materials could serve as a readout to quantitatively compare the severity. The irony is that despite protein aggregates may be responsible for the series of pathological development observed in the diseases, including neuronal cell death, one shall be cautioned to make a direct link to pathogenesis because we are still unclear whether some aggregates might be by-products or even have a protective effect to against cell death.

3.2.1 Alzheimer's disease

Memory loss is the most prominent clinical symptom of Alzheimer's patients, and it is correlated with the neuronal loss in the hippocampal region. The enduring of neuronal loss is correlated with the progression of the disease [63-66]. Of note, detectable neuronal loss in multiple regions precedes even before the clinical symptoms start to show, they include entorhinal cortex layer II, nucleus basalis of Meynert, and locus coeruleus [63]. As the disease advance, frontal cortex and other cortical/subcortical regions would also encounter neuronal loss and sometimes that could be very severe [65,66]. The death pathways involved could be apoptosis and necroptosis. Regarding apoptosis, it was suggested initiator or executor caspases were activated in the disease [67-71]. Besides, it has been reported that the levels of extrinsic apoptotic pathway protein Fas and its ligand were elevated in AD brain [72]. However, some reports claimed that apoptotic morphology was not observed in the brain sections [60,73]; instead, the cells showed swollen morphology and were positive for DNA fragmentation, implicating apoptosis may not be involved in AD pathogenesis [60]. Others also argue that the apoptosis theory and the clinical manifestations are incompatible because cells dictated to apoptosis program will die within days, and with such high levels of caspase-3 activity should have incited acute and massive neuronal loss. If that is the case, the clinical symptom of AD patients should be diagnosed at the early-phase of the disease rather than following a progressive disease course that could last for decades [74]. The authors also suggested other pathways of cell death might be involved, including necroptosis [74]. A recent study shows that necroptosis signaling was elevated dramatically in AD patients, as the protein levels of the RIP1-RIP3-MLKL axis increased, and so does the interaction between them [7].

Both tau and amyloid-beta are the pathogenic proteins for the disease. Moreover, the correlation of them with neuronal loss has been studied extensively. Therefore, we will discuss them separately here.

3.2.1.1 Tau and neuronal cell death

The microtubule-associated protein Tau is the pathogenic protein in AD, parkinsonism, and other types of dementia and neurological disorders. Tau protein is intrinsically-unstructured and thus could form high-ordered oligomers in different disease conditions, including neurofibrillary tangles (NFT), which represents the major pathological hallmark of AD. The development of NFT burden has been well-characterized regarding its accumulation in different brain regions [75,76]. Clinical

studies showed there is a strong correlation between NFT accumulation and the symptoms of disease progression, which includes neuronal loss [65,69,70]. Furthermore, the formation of Tau aggregates is correlated with DNA fragmentation, implicating a link to the apoptotic cell death [60].

On the molecular level, pathogenic tau could stress the neuron in multiple ways. Normally, Tau is associated with microtubule by which to support its structure. Pathogenic tau would detach from the microtubule, thereby the cytoskeleton system of the neuron is likely to be compromised. The detached Tau proteins in the cytosol are prone to form aggregations and further develop into NFT, which could not be degraded by the proteasome system nor the autophagic system, resulting in systemic defect [77,78]. Moreover, tau could interact with pre-synaptic protein synaptogyrin-3; thus Tau proteinopathy could cause defects on synaptic release [79]. Tau could also interact with PSD-95 and fyn to stabilize the NMDA receptor at post-synaptic, and pathogenic Tau might elicit excitotoxicity [80,81]. Tau has been suggested to cause cell cycle re-entry or arrest at later cell cycle stage, as a part of the cell cycle re-entry theory of AD, contesting the re-entry of cell cycle could steer mature neurons to death or be more susceptible to cell death [82]. Indeed, accumulation of Cdc2/cyclin B1 in NFT-positive neurons has been found in clinical samples [83]. Although whether Tau could induce neuronal apoptosis directly remains unsolved, an *in vitro* study showed that mutant tau could down-regulate IAP and activate caspase-3, which is accompanied by a significant increase of neurons arrested at G_2/M phase [84]. Another study found phosphorylation of several specific residues in Tau could induce an up-regulation of Cyclin D1 and BrdU incorporation [85]. Other studies also provided evidence to support the phosphorylation state of Tau could affect the induction of apoptotic cell death [86-88]. Interestingly, opposing the general conception that Tau phosphorylation could promote aggregates formation and potentiate its cytotoxicity, some of these studies suggested that de-phosphorylation of Tau would aggravate apoptosis, and conversely, the phosphorylated Tau could protect the neurons from acute death [86-88]. With all these unsettled arguments, one should recognize that the real scenario could be more sophisticated as the phosphorylation of Tau at different residues could have diversified impact to the downstream signaling that likely modifies cell death pathways. Regarding necroptosis, a study has found that phosphorylated Tau proteins were co-localized with RIP1 and phosphorylated MLKL extensively, indicating pathogenic Tau might associate with necroptosis activation [7].

3.2.1.2 Amyloid-beta and neuronal cell death

Amyloid-beta (Aβ) and its extracellular aggregation amyloid plaques is another pathological hallmark of AD. In contrast to NFT, the correlation of amyloid plaque with clinical symptoms or neuronal loss was inconsistent in that most studies suggested the correlation is weak [76,89,90]. Examination of postmortem brains revealed significant Aβ deposition in certain brain regions for both AD patients and healthy elderly [91]. Furthermore, by using PET imaging, it was found that hippocampal burden of Aβ in patients is similar to age-matched individuals [92]. However, immunoblotting results showed that the types of amyloid-beta in normal and in patients could be different [93]. Thus, it remains elusive to tight Aβ deposition with neuron death by pathological evidence.

Despite the shortfall of Aβ-linked cell death pathology, at the molecular level, several studies have suggested Aβ could stress the neuron in multiple ways. Aβ has been extensively associated with synaptic defects [94]. However, it is still indistinguishable of whether such effect is due to APP expression, Aβ monomers, selected Aβ plaques, or in combination. Moreover, the precise mechanism involved in Aβ-mediated synaptic malfunction remains to be elucidated [95-97]. On the other hand, *in vitro* study showed that, by short-term co-culture of Aβ40 or Aβ42 with hippocampal neurons, the neuronal cell membrane elasticity could drop by 30% and showed signs of old neurons [98]. Aβ42 is also proposed to have a role in cell cycle re-entry. Co-culture of Aβ42 with cortical neurons induced the up-regulation of cyclin D1 and E2F1, and such process was suggested to be mediated through the down-regulation of Wnt5a because its overexpression could rescue Aβ42-induced cell apoptosis [99]. Regarding necroptosis, there is no correlation between Aβ burden with necroptosis markers by far [7].

246 3.2.2. Parkinson's disease

247 The most prominent pathological feature of Parkinson's disease (PD) is the diminished substantia
248 nigra (SN), part of the output component of basal ganglia. The severe loss of dopamine (DA)-
249 producing nigral neurons and the associated decreased striatal DA level. Clinical study found on
250 average at least 50% nigral neurons were lost before the neurologist could make a positive diagnosis
251 of a patient with PD [100]. It is also noteworthy that at this point the measured DA level in the caudate
252 nucleus, the input nuclei receiving signals from SN, would be decreased by 70%-80% [101]. The
253 insufficient input of DA results in a down-regulation of excitatory signals and up-regulation of
254 inhibitory signals in the circuitry of the motor loops controlling body movement, which cause
255 symptoms of body movement such as rigidity and resting tremor in patients. Besides SN, a profound
256 neuronal loss was also observed in the ventral tegmental area, locus coeruleus, and raphe nucleus
257 [102-104]. Nevertheless, the correlation between SN neuronal loss and the disease progression still
258 stand out [104]. Regarding the death pathways in PD, it has long been suggested that apoptosis is the
259 chosen pathway to eliminate DA neurons in SN. It was found that almost every Lewy body-positive
260 neurons were also positive for pro-apoptotic Bax staining, suggesting neurons with the heavy protein
261 burden of protein aggregation were undergoing apoptosis [105]. The protein level of tumor
262 suppressor p53, a pro-apoptotic mediator, was increased in the caudate nucleus but not in SN in PD
263 brains [106]. In addition, the distribution of mitogen-activated protein (MAP) kinase (p38), another
264 pro-apoptotic regulator, was also changed in SN neurons [107]. The death of DA neurons has not
265 been directly linyked with necroptosis, but a recent *in vivo* study showed that necrostatin-1, a potent
266 inhibitor of RIP1, could ameliorate neuronal loss in MPTP treated mice, the classic toxin treated PD
267 model [108]. Therefore, it is possible that necroptosis is also involved in the death pathway of PD
268 [109].

269 3.2.2.1 α-Synuclein and neuronal cell death

270 α-Synuclein is thought to be the major pathogenic protein of PD because its aggregation forms
271 the core of Lewy-body [110], whereas the correlation of α-Synuclein burden with neuronal loss and
272 clinical symptoms progression is still under debate [111-115]. A study found among 179 healthy
273 elderly people, 33 of them had significant deposition of Lewy-bodies [114]. Specifically, 8 of the 33
274 people showed significant Lewy-bodies deposition in SN and matched Grade 3 of pathology
275 development by Braak's sporadic PD staging [116]. Another study recruited more individuals (1720
276 in total) and reached a similar conclusion [111]. While some reports found the positive-association
277 between Lewy-bodies deposition and SN neuronal loss is strong [113,116], the percentage of those
278 survived nigral neurons that bearing Lewy-bodies is stable throughout the disease progression, and
279 this correlation does not exist for cortical Lewy-bodies density and nigral neuronal loss [116].
280 Therefore, there is a possibility that nigral neurons are more sensitive to the Lewy-body, and this may
281 be related to the intrinsic ROS/RNS production, a character of the DA neurons.

282 On the molecular level, α-Synuclein expression in DA neurons has been linked to mitochondrial
283 dysfunction and oxidative stress. It should be noted that α-Synuclein overexpression *in vivo* often
284 requires a long time and a high expression level to induce significant pathological changes including
285 the neuronal loss in SN [117]. Thus, most of the study findings come from *in vitro* manipulations. By
286 co-culturing α-Synuclein with DA neurons, it was found that the cells were prone to apoptosis in the
287 presence of a minimal level of proteasome toxins, as more cells showed nuclear fragmentation and
288 caspases activation, which coincide with the observation that mitochondrial membrane potential was
289 also depolarized [118]. A recent study in neurons derived from the embryonic stem cells showed that
290 overexpression of α-Synuclein could result in mitochondrial membrane fragmentation, and wild-
291 type, but not disease-linked α-Synuclein, is required for the control of mitochondrial homeostasis
292 [119]. In another study, authors found α-Synuclein aggregates could cause lysosome membrane
293 rupture upon entering cells through endocytosis and by which to augment ROS level [120], which
294 could lead to cell death.
295

296 3.2.3 Huntington's disease

297 Huntington's disease (HD) is characterized by the loss of corpus striatum GABAergic medium
298 spiny neurons and cholinergic neurons. Opposing to the neuronal loss of substantia nigra in PD, the
299 loss of striatum neurons in HD caused an up-regulation of excitatory signals output through the
300 motor circuitry, and the patients show symptoms of ataxia. It is noteworthy that the neuronal loss is
301 not restricted at corpus striatum in HD brains, because a significant neuronal loss has been found
302 across the whole cerebral cortex [121]. In contrast to the complex genetic background of AD and PD,
303 HD is an uncomplicated autosomal dominant disease that sole caused by pathogenic gene huntingtin
304 that bearing an aberrant stretch of glutamine residues (encoded by >39 CAG/CTG repeats) at its N-
305 terminus [122].

306 3.2.3.1 Huntingtin and neuronal cell death

307 The mutant huntingtin protein (mHTT) could aggregate intracellularly, and proteins that
308 involved in the cell cycle or cell structure could co-aggregate to form inclusions [123]. Aggregates
309 could be found both in nucleus and cytosol [124]. However, the correlation of mHTT aggregation and
310 regional neuronal loss or disease progression is weak [124,125]. Therefore, whether the inclusions are
311 genuinely harmful is debated.

312 Regarding the molecular mechanism of cell death in HD, it has been suggested that mHTT could
313 cause proteasome impairment, interfere in cellular trafficking, decrease neurotrophic transcription,
314 and impair mitochondria [126-128]. Specifically, it was purposed that mHTT monomer could
315 hyperpolarize mitochondrial membrane by which to promote apoptotic cell death. On the other
316 hand, neuron bearing inclusions precedes a senescence process, which possibly finishes up with
317 necrosis [129]. By using a mHTT-derivative sensor, researchers were able to distinguish if
318 aggregations are formed in the neurons, and they discovered that neurons with the mHTT monomers
319 were positive for caspase-3 and died quickly, but for those with mHTT aggregates, cells experienced
320 a delayed cell death [129], arguing the high-ordered aggregates or inclusions might be protective.
321 Recently, a report showed that mHTT is not the only transcriptional product of the gene; HD-RAN
322 (repeat-associated non-ATG translation) proteins, including polyAla, polySer, polyLeu, and polyCys,
323 were also accumulated in HD human brains. Moreover, widespread caspase-3 activation, as well as
324 regional neuronal loss, was found in the cerebrum which showed a good correlation with HD-RAN
325 distribution, indicating HD-RAN could initiate apoptosis [125]. Regarding the mechanism, a recent
326 study indicated that HD-RAN could disrupt nucleocytoplasmic transport [130], a plausible functional
327 defect that could induce cell death.

328 3.2.4 Amyotrophic lateral sclerosis

329 Amyotrophic lateral sclerosis (ALS) mainly affects upper and lower motor neurons which
330 responsible for controlling voluntary muscles. The patients showed complex extremity symptoms as
331 well as cranial nerve symptoms. Postmortem brain showed that the corticospinal fibers and partial
332 upper motor neuron were lost, and the neurons of the anterior horn of the spinal cord were too
333 depleted [11,131]. The pathological hallmark of ALS is the cytoplasmic inclusion which is mainly
334 composed of TAR DNA-binding protein 43 (TDP-43), other proteins include the ones involved in
335 nucleocytoplasmic transport can also be found [132]. The correlation between TDP-43 inclusion and
336 the neuronal loss is relatively well [11,133]. In addition, TDP-43 inclusion is also a major pathological
337 hallmark of frontal-temporal dementia [133]. In some cases, the inclusions could also be TDP-43
338 negative, in which case FUS (fused in sarcoma)-containing inclusions were often found [131,134].

339 3.2.4.1 TDP-43 and neuronal cell death

340 In physiological condition, TDP-43 is mainly localized to the nucleus, where the protein can
341 directly bind to DNA and regulate gene expression. Also, TDP-43 plays a role in regulating RNA
342 metabolism [135]. In pathological condition, mutated TDP-43 proteins re-locate to the cytosol and
343 form aggregates. The toxicity of TDP-43 has been associated with mitochondria dysfunction, ROS
344 production, and nucleocytoplasmic transport impairment [136-138]. It was reported that TDP-43
345 preferentially locates to the mitochondria and could interact with respiratory complex I protein ND3

and ND6 to induce the complex disassembly, and blocking such interaction could suppress TDP-43-induced neuronal loss [139]. However, whether apoptosis mediates the neuronal loss induced by TDP-43 is still debated [140-143]. In one study, it was found that TDP-43 could induce the expression of pro-apoptotic proteins in a p53-dependent manner, and inhibiting p53 could rescue the neuronal cell death [143]. However, others have suggested the neuronal loss in ALS, either derived from patients or engineered animal models, is independent of caspase-3 activation [141,142]. By co-culturing astrocytes isolated from sporadic ALS patient with human embryonic stem cell-derived motor neurons, a profound neuronal loss was induced [141]. In this system, applying a pan-caspase inhibitor could lower caspase-3 level but do not rescue the neuronal loss [141]. Instead, applying necrostatin-1, an inhibitor of necroptosis could successfully abolish the induced neuronal loss [141], suggesting the necroptosis-mediated pathway may be responsible for the cell death in ALS.

4 Future directions

Traditionally, it is assumed that neuronal cell death in neurodegeneration diseases is a result of cellular stress induced by apoptosis. Part of the reason is that the mechanism of apoptosis was investigated much earlier than necrosis, and there are useful markers for testing. It is also because that apoptosis was believed to be the only form of programmed cell death, and necrosis was considered as a subsequent event of apoptosis, or an acute phenomenon not controlled by specific molecules. Nowadays, it becomes clear that other forms of cell death, including autophagic cell death and necrosis, could also be programmed. While the published reports have presented conflict results concerning whether apoptosis may be the sole pathogenic solution to eliminate neurons in various neurodegenerative conditions, which inevitably require further investigations. However, one shall also consider the emerging data that have suggested necrosis, especially the programmed forms, may also play a death role in the diseases. Importantly, it will be of significant impact to understand that, in the different disease context, how a neuron incites which death pathway to commit self-termination? What is the molecular mechanism drive such a decision? Does different cell death program dictate by specific disease context or physiological circumstance? So far, the progression on these issues is still limited. Also, addressing these questions are critical for the development of potential therapeutic strategies for treating these devastating diseases.

Abbreviations

ROS	Reactive oxygen species
RNS	Reactive nitrogen species
HD-RAN	Huntingtin disease-repeat-associated non-ATG translation
HD	Huntington disease
RAN	repeat-associated non-ATG translation
AD	Alzheimer's disease
PD	Parkinson's disease
DA	Dopamine
Aβ	Amyloid-beta
SN	Substantia nigra
NFT	Neurofibrillary tangles
RIP1	Receptor-interacting protein 1
RIP3	Receptor-interacting protein 3
PARP	Poly (ADP-ribose) polymerase
IAP	Inhibitors of apoptosis proteins
MLKL	mixed lineage kinase-like
TUNEL	Terminal deoxynucleotidyl transferase dUTP nick end labeling
PSD-95	Postsynaptic density protein 95
TDP-43	TAR binding protein-43
mHTT	The mutant huntingtin protein
ALS	Amyotrophic lateral sclerosis

PCD	programmed cell death
CNS	Central nervous system

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