Chapter 16
Cell Death Mechanisms of Neurodegeneration

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Abstract There are common mechanisms shared by genetically or pathologically distinct neurodegenerative diseases, such as excitotoxicity, mitochondrial deficits and oxidative stress, protein misfolding and translational dysfunction, autophagy and microglia activation. This indicates that although the original cause may differ in individual diseases or even subtypes of certain disorders, these disrupted common cell functions and signaling, together with aging, may lead to final execution of cell death through similar pathways. The variable neurodegenerative disease symptoms are probably caused by the type, location, and connection of the cell

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populations that suffer from dysfunction and loss. Besides apoptosis, necroptosis, and autophagy, an important form of death termed parthanatos plays a prominent role in stroke and several neurodegenerative diseases, which is due to PARP-1 overactivation, PAR accumulation, nuclear translocation of the mitochondria protein AIF, and large-scale DNA cleavage. Understanding the mechanisms and interactions of cell death signaling will not only help to develop neuroprotective strategies to halt neurodegeneration, but also provide biomarkers for monitoring disease progression and recovery.

Keywords Neurodegenerative diseases • Cell death • Oxidative stress • Excitotoxicity • Parthanatos • Mitochondria • Nitric oxide • AIF

Abbreviations

3-MA	3-Methyladenine
6-OHDA	6-Hydroxydopamine
Aβ	β-Amyloid peptide
AD	Alzheimer's disease
AIF	Apoptosis-inducing factor
AIMP2	Aminoacyl-tRNA synthetase complex interacting multifunctional protein-2
ALS	Amyotrophic lateral sclerosis
AMPK	AMP-activated protein kinase
APP	Amyloid precursor protein
ARH3	ADP-ribosylhydrolase 3
BRCT	BRCA1 C-terminal
CNS	Central nervous system
DPQ	3,4-Dihydro-5-(4-(1-piperidinyl)butoxyl)-1(2H)-isoquinolinone
HD	Huntington's disease
IFNγ	Interferon gamma
KO	Knock out
LPS	Lipopolysaccharide
MCAO	Middle cerebral artery occlusion
MNNG	*N*-Methyl-*N*′-nitro-*N*-nitrosoguanidine
MPP+	1-Methyl-4-phenylpyridinium
MPT	Mitochondrial permeability transition
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MS	Multiple sclerosis
mTOR	Mechanistic target of rapamycin
NAD+	Oxidized nicotinamide adenine dinucleotide
Nec-1	Necrostatin-1
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NLS	Nuclear localization sequence

NMDA	*N*-Methyl-D-aspartate
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
OGD	Oxygen glucose deprivation
P53	Tumor protein 53
PAAN	Parthanatos-dependent AIF-associated nuclease
PAR	Poly(ADP-ribose)
PARP1	Poly(ADP-ribose) polymerase 1
PARG	Poly(ADP-ribose) glycohydrolase
PBM	PAR-binding motif
PBZF	PAR-binding zinc finger
PD	Parkinson's disease
PI3K	Phosphoinositide3-kinase
PSM	PARP signature motif
ROS	Reactive oxygen species
siRNA	Small interfering RNA
SOD1	Superoxide dismutase 1
TH	Tyrosine-hydroxylase
TNF	Tumor necrosis factor
TNFR1	TNFα receptor 1
RIPK1	Receptor-interacting protein kinase 1
RIPK3	Receptor-interacting protein kinase 3
Z-VAD-fmk	*N*-Benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone

16.1 Introduction

Neurodegenerative diseases are caused by interactions of genetic factors (mutation of disease-associated genes) and environmental factors (including aging and life style). These disorders share common features, like excitotoxicity, synaptic dysfunction, misfolded protein aggregation, reactive oxidative stress (ROS), mitochondrial deficits, dysregulation of intracellular calcium, trophic factor loss, axonal transport deficits, transcription and translation disruption, and finally cell loss. Early cognitive and mood symptoms seen with neurodegenerative disease patients are mostly due to the impaired synaptic and other cellular function, and networking of affected cells by either gain-of-function or loss-of-function of the mutated disease protein. Disrupted cell functions together with aging-induced accumulation of DNA damage and oxidative stress gradually overwhelm the self-defense system including protein quality control system (for example, ubiquitin and autophagy) and others, leading to a shift in life-death balance culminating in programmed cell death (PCD). It is likely that multiple cell death pathways are involved in the cell loss in neurodegenerative diseases and in experiment models of neurodegeneration. The fate (survival or

death) and major path to death (how to die) of cells depend on the source, duration, and dose of different stressors, as well as the type, previous challenges, and metabolic conditions of the cell. Several types of cell death including apoptosis, necrosis, autophagy, and parthanatos may be involved in neurodegeneration [1]. We will briefly discuss apoptosis, necroptosis, autophagy and focus on parthanatos and their involvement and therapeutic potential in neurodegenerative diseases.

16.2 Cell Death in Neurodegeneration

16.2.1 Apoptosis

Apoptosis is the most studied and well-known form of PCD, which is found in both development and diseases. The generally accepted definition of apoptosis is an active form of cell death with cell plasma membrane and organelle integrity and mediation by caspases activation [2], which includes extrinsic apoptosis and caspase-dependent intrinsic apoptosis defined by Nomenclature Committee on Cell Death (NCCD) [3]. There are markers of apoptosis in postmortem tissues of patients, as well as in cell and animal models of neurodegenerative disorders, including Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [2, 4]. It is worth noting that certain cell death-related phenomenon may accompany a cell death process while the final execution is carried out by a different cell death mechanism [3]. Reactive oxygen species, DNA damage, loss of mitochondria membrane potential, and aggregation of misfolded proteins are all common features associated with most neurodegenerative disorders and major forms of neuronal death. On the other hand, inhibiting cell death by Z-VAD-fmk, a pan caspases blocker, usually results in delayed death by autophagy or necrosis [1, 5]. Thus, extra caution needs to be taken when classifying a certain type of death as apoptosis.

16.2.2 Necroptosis

Necroptosis was first defined in 2005 as a regulated form of non-apoptotic cell death with necrotic cell morphology, triggered by TNFα receptor 1 (TNFR1) and can be inhibited by receptor-interacting protein kinase 1 (RIPK1) inhibitor necrostatin 1 (Nec-1) [3, 5, 6]. Besides death receptor activators, such as TNF and IFNγ, ROS have also been shown to promote necroptosis [5, 7]. Necroptosis has been shown to contribute to delayed mouse ischemic brain injury, which can be inhibited by necrostatin-1 [6]. Nec-1 reduced motor neuron death in coculture with astrocytes from ALS patients [8] and delayed motor deficits in the R6/2 transgenic mouse model of

Huntington's disease [9]. A group recently detected activation of RIPK1 and RIPK3 in multiple sclerosis (MS) patient cortical samples and also showed that RIPK1 inhibitor 7-Cl-O-Nec-1 reduced oligodendrocyte death in two MS animal models [10].

16.2.3 Autophagy

Autophagy ("self-eating") is a process by which cells form intracellular autophagosomes (double-membrane structures) to "eat up" intracellular organelles and aggregated proteins and deliver them to lysosomes for degradation and nutrient recycling [11]. Several pathological mutations of proteins in AD, PD, HD, and ALS are linked to deficits of autophagy, such as substrate recognition, lysosome acidification, trafficking, and membrane permeabilization [12], which will not be discussed in detail here. Autophagy plays important role in cleaning up damaged mitochondria and aggregated proteins and thus contributes to neurodegenerative pathology. Indeed, upregulated autophagy can promote the clearance of pro-aggregate proteins, such as mutant huntingtin, and protect against neurodegeneration in both cell and animal models [13]. Defects in autophagy primarily play a role in neurodegeneration, but autophagy itself can also be involved in several forms of cell death.

16.2.4 Parthanatos

Parthanatos, previously known as PARP-1-dependent cell death, is the second most studied form of cell death. When massive DNA damage is induced by ionizing radiation, prolonged toxic treatment of the DNA-alkylating agent *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG) or *N*-methyl-D-aspartate (NMDA), oxygen glucose deprivation (OGD), hydrogen peroxide and other ROS, as well as ischemia and reperfusion, poly(ADP-ribose) polymerase-1 (PARP-1) overactivates and produces branched, long-chained poly (ADP-ribose) (PAR) polymers [14–17]. Ischemia and reperfusion causes massive release of the excitatory neurotransmitter glutamate, which excessively activates glutamate receptors, especially the NMDA receptor, and causes a large calcium influx, resulting in the activation of neuronal nitric oxide synthase (nNOS) and cell death, called "excitotoxicity" [18–20]. nNOS plays an important role in excitotoxicity since nNOS deletion and NOS inhibitors protect primary brain cultures or mice against NMDA excitotoxicity, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and middle cerebral artery occlusion (MCAO)-induced neuronal injury [18, 19, 21–23]. Nitric oxide (NO) is able to diffuse freely through the plasma membrane and react with superoxide (O2.−) to form peroxynitrite (ONOO−), which induces DNA damage and PARP-1 activation [14, 24–26]. This "excitotoxicity" hypothesis is able to explain, at least in part, the cell death in acute ischemia and traumatic brain injury, as well as progressive neuron loss in neurodegenerative conditions such as HD, AD, PD, MS, and ALS [27–29].

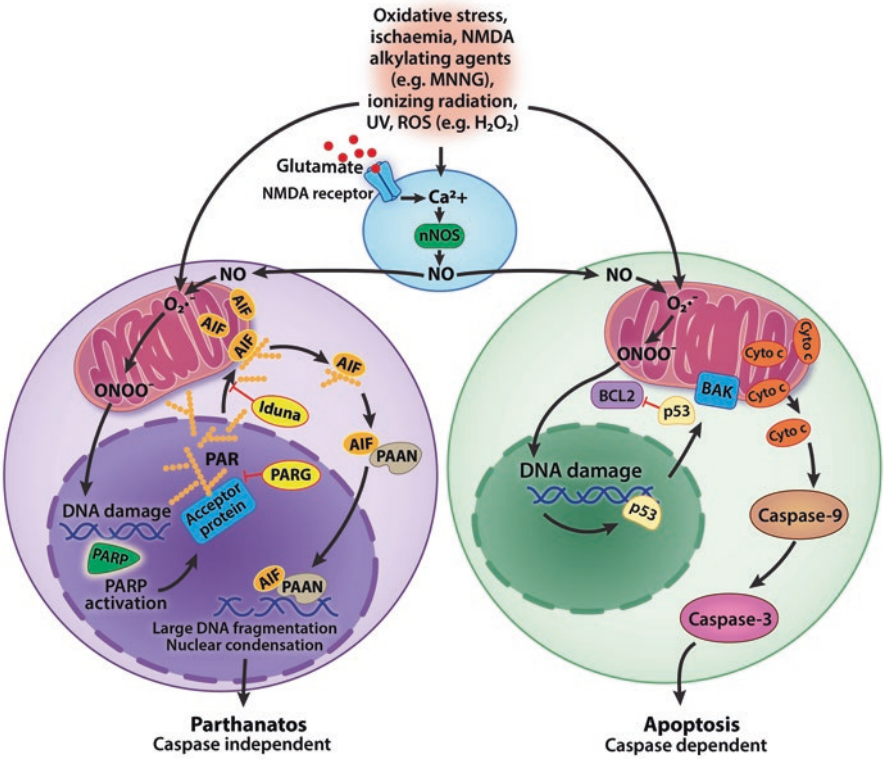

Fig. 16.1 Comparison of the major signaling mediators in caspase-independent parthanatos and caspase-dependent apoptosis. Stressors such as ROS, NMDA, ischemia, alkylating agents (MNNG), radiation, UV can activate PARP-1 directly or indirectly through activation of nNOS, which produces NO to induce ROS and the subsequent DNA damage. PARP-1 overactivation produces free PAR by PARG-mediated hydrolysation, which serves as a death signal from the nucleus to mitochondria, where it induces the release of AIF. AIF then translocates together with a presumed nuclease PAAN to the nucleus where it induces large fragmentation of DNA. This form of cell death is called "parthanatos," which can be completely blocked by PARP-1 inhibitors, but not pan-caspase inhibitors including Z-VAD-fmk. Under some stress conditions with limited amount of DNA damage, cell may undergo apoptosis through p53 activation, which results in disrupted balance of BCL2 (anti-apoptotic) and BAK (pro-apoptotic) and the release of cytochrome c (Cyto c). Cytochrome c then associates with Apaf1 (not shown) and activates procaspase-9, which cleaves and activates caspase-3, results in protein degradation, DNA fragmentation, and cell death. Thus, this caspase-dependent apoptosis is distinct from parthanatos, and can be blocked by caspase inhibitors

Under toxic stimuli and pathological conditions when PARP-1 is overactivated, the release of PAR polymers from the nucleus to cytosol and mitochondria induces translocation of apoptosis-inducing factor (AIF) from mitochondria to the nucleus, which leads to large-scale DNA fragmentation (approximately 50 kb) and chromatin condensation, followed by cell death, termed parthanatos (Fig. 16.1) [14–17]. This form of cell death named from "*par*" (for PAR polymer) and "*Thanatos*" (the

personification of death in Greek mythology) is now officially recognized by the NCCD [3, 14, 17]. It has been thought previously that when PARP-1 overactivates, cells die due to cellular NAD^+ and ATP depletion, in a way similar to necrosis. However, recent studies in primary cell cultures and mice stroke models indicate that energy depletion is not the primary cause of PARP-1 mediated cell death [30, 31]. In fact, mouse primary neurons are resistant to NMDA-induced cell death when cytosolic PAR was neutralized with PAR-specific antibodies [32]. On the other hand, introducing exogenous PAR polymer through lipid-based delivery results in neuron death, with higher dose and more complex PAR polymers inducing more death [32]. The other study [33] showing PAR polymer was able to induce AIF translocation from mitochondria to nucleus in cell-free in vitro assay further confirmed that PAR polymer is the mediator of death signal in parthanatos. The PAR-induced AIF translocation can be prevented by pretreatment of PAR degrading enzymes, but not the pan-caspase inhibitor z-VAD-fmk [33], indicating that the AIF release in parthanatos is distinct cellular event from that in apoptosis.

Unlike caspase-dependent apoptosis, parthanatos cannot be rescued by pan-caspase inhibitors (such as Z-VAD-fmk), does not form apoptotic bodies, and causes large-scale instead of small-scale DNA fragmentation [17, 34]. Although both parthanatos and necrosis involve loss of cell membrane integrity, parthanatic cell death is distinct from necrosis, as it is marked with PARP-1 activation and AIF translocation and is not accompanied by cell swelling [17, 34]. The common triggers and signaling differences of caspase-dependent apoptosis and caspase-independent parthanatos are illustrated in Fig. 16.1.

The major forms of cell death found in neurodegenerative diseases are summarized in Table 16.1 (adapted from [3, 14, 17]). It is worth noting that the cell may favor one form of death over others depending on the nature, length, and degree of the stress as well as the pre-stimuli status of the cell. Thus, only cell death that can be completely blocked by inhibitors or deletion of PARP-1 should be considered as parthanatos primarily [14]. A more detailed summary of conditions that trigger parthanatos and the cellular events involved in parthanatos can be found in some recent reviews [14–17].

16.3 Components of Parthanatos

16.3.1 PARP-1

PARP-1 is the most abundant and best characterized member of the 17 mammalian PARP family proteins. PARP-1 is responsible for production of more than 90% of cellular PAR polymers [35, 36]. It is a nuclear protein with three major functional domains: (1) an N-terminal DNA-binding domain with three zinc finger motifs to sense DNA strand breaks and a nuclear localization sequence (NLS); (2) a central automodification domain for self (ADP-ribosyl)ation and a BRCA1 C-terminal

Table 16.1 Major cell death forms found in neurodegenerative diseases

Forms of death		Apoptosis	Necroptosis	Autophagic cell death	Parthanatos
Triggers related to neurodegeneration	Excitotoxicity	Y			Y
	Oxidative stress	Y	Y		Y
	DNA damage				Y
	Cytosolic calcium overload	Y			Y
	Aggregation of misfolded proteins			Y	Y
	Trophic factor withdrawal	Y			
	Nutrient starvation		Y	Y	
Cell morphology		Chromatin condensation, small DNA fragmentation, apoptotic bodies, cell membrane blebbing	Cellular swelling, cell membrane rupture and release of intracellular content; usually accompanied by autophagy	Autophagic vacuoles	Loss of membrane integrity, chromatin condensation, large DNA fragmentation
Key mediators		Caspases, Bak, Bax, Cytochrome C	RIPK1, RIPK3	mTOR, PI3K, Beclin 1, ATG	PARP-1, AIF
Inhibitors		Caspases inhibitors, Bcl-2	Necrostatin 1	3-MA	PARP inhibitors, PARG, Iduna
Loss of membrane integrity		N	Y	Y	Y
Energy-required		Y	N	Y	N
Inflammation		N	Y	N	N
Example of neurologic and neurodegenerative diseases		AD, PD, HD, ALS, ataxias, ischemia	Ischemia, ALS, HD, MS	AD, HD, PD, ALS	Ischemia, PD, AD, HD, ALS
Landmark cellular events		Caspases activation	RIPK3 activation	Autophagosome formation, lysosome degradation	AIF translocation to nucleus

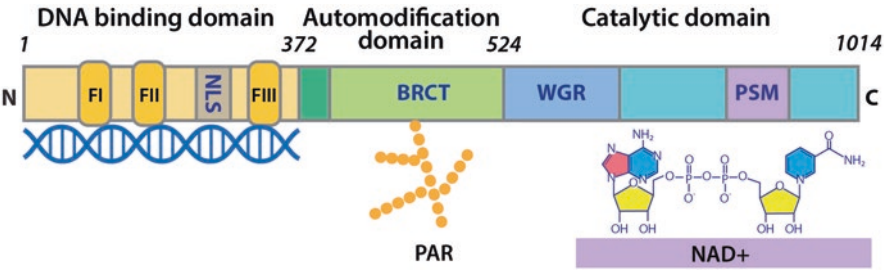

Fig. 16.2 PARP-1 function domains. PARP-1 has three major function domains: the N-terminal DNA-binding domain, the auto-modification domain, and a C-terminal catalytic domain. The DNA-binding domain contains three zinc fingers that are important for DNA binding and DNA damage detection (FIII is dispensable) and a nuclear localization signal (NLS). The auto-modification domain has a BRCT motif for protein–protein interaction and glutamate and lysine residues as acceptors of ADP-ribose to regulate PARP-1 activity. The catalytic domain is composed of enzyme active site responsible for adding ADP-ribose from NAD^+ to protein acceptors and a highly conserved sequence called the PARP signature motif (PSM) found in all members of PARP family proteins [15, 37]

(BRCT) motif for protein–protein interaction; (3) a C-terminal catalytic domain with NAD^+-binding domain and conserved PARP signature motif (PSM) for PAR synthesis (Fig. 16.2) [35, 37]. PARP-1 is known to regulate DNA repair, transcription, cell differentiation, mitochondrial function, and cell death [35, 36, 38–41].

Under physiological conditions, PARP-1 activity remains at a low level, but can increase up to 500-fold in a few seconds when sensing mild DNA damage [35]. Upon activation (Fig. 16.3), PARP-1 synthesizes negatively charged PAR by hydrolyzing oxidized nicotinamide adenine dinucleotide (NAD+) and linking them through glycosidic bonds (Fig. 16.3) with branching every 20–50 ADP-ribose units on average [42, 43]. PAR, averaging 50–200 units, are covalently attached to a variety of nuclear acceptor proteins by forming an ester bond with a glutamate, aspartate, or C-terminal lysine residues [41]. The nuclear acceptors of this post-translational modification, poly (ADP-ribosyl)ation, includes PARP-1 itself, histones, DNA ligase II, topoisomerases, DNA polymerases, transcription factors, and a host of other proteins [36]. Through this wide-ranged poly (ADP-ribosyl)ation and BRCT interaction, PARP-1 recruits DNA repair proteins to the DNA damage site to facilitate DNA repair [44]. Poly (ADP-ribosyl)ation of target proteins can alter its enzymatic activity, subcellular localization, and prevent protein–protein or protein–nucleic acid interactions. Possibly due to long branching and negative charge, PAR can modify the charge or mask the binding motif or functional domain of acceptor proteins [36, 41, 45].

Given that structure and levels of PAR depend on the cell energy level and other factors of poly (ADP-ribosyl)ation, PARP-1 can promote both cell survival and death depending on the stress stimuli and status of the cell [37]. Mild or moderate stresses usually lead to PARP-1 activation that result in DNA repair and transcription regulation to restore genome stability, degrade oxidized or damaged proteins, and maintain homeostasis [37, 45–47]. On the other hand, hyperactivation of PARP-1 by severe or sustained stresses causes cell death programs, such as parthanatos [15, 48].

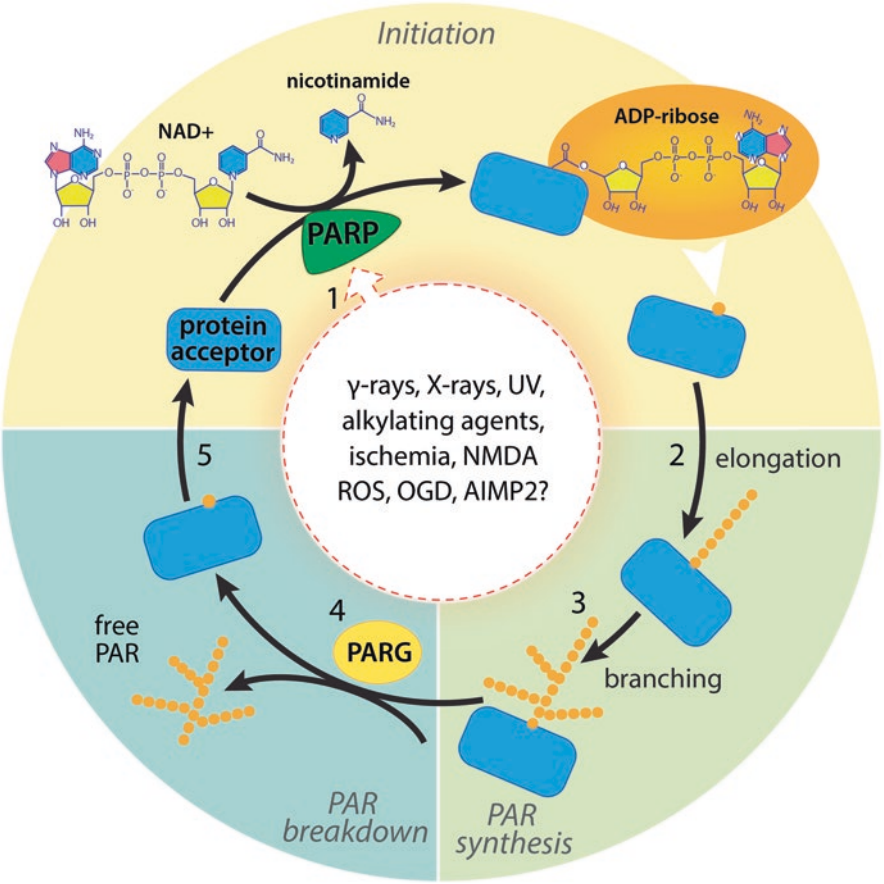

Fig. 16.3 Poly (ADP-ribosyl)ation metabolism. Several stressors activate PARP directly or indirectly through DNA damage, including the recently discovered PD-associated protein AIMP2. Activated PARP converts NAD^+ to ADP-ribose, attaches it to a protein acceptor, and discharges nicotinamide (*1*, Initiation stage). The poly (ADP-ribose) long chain elongates (*2*, Elongation) and branches (*3*, Branching) until being dehydrolyzed by PARG (*4*, Breakdown). Mono-ADP-ribosyl-protein lyase then removes the final ADP-ribose on the protein acceptor (*5*) [15]

16.3.2 PARG

After PARP activation, poly (ADP-ribose) glycohydrolase (PARG) or the recently identified ADP-ribosylhydrolase 3 (ARH3) rapidly hydrolyze the glycosidic bonds to break down PAR from its modified proteins [15]. Therefore, poly (ADP-ribosyl) ation is an immediate, but transient (degrades within minutes), and strictly regulated post-translational modification [35, 46]. Full-length PARG localizes to the nucleus, but other splice variants with enzyme activity have been found in the cytosol and mitochondria [14, 49, 50].

Overexpression of PARG was found to protect against excitotoxicity, focal ischemia, H2O2, and PAR-mediated cell death [32, 51, 52]. On the other hand, reducing PARG increased the sensitivity of cells to DNA damaging agents, excitotoxicity, and ischemia. The PARG knockout (KO) mouse is embryonically lethal at around embryonic day 3.5 [32, 53]. Hanai and others have reported that mutant Drosophila lacking the PARG catalytic domain are lethal at the larval stages. Some mutants reached the adult stage at higher developmental temperature of 29 °C, but showed progressive neurodegeneration with reduced locomotor activity, extensive accumulation of PAR in central nervous system (CNS), and a short lifespan [54]. These results suggest that poly(ADP-ribose) metabolism is required for maintenance of the normal function of neuronal cells. In addition, PARG overexpression prevented PARP-1-dependent mitochondrial AIF release and cell death [33]. All this evidence suggests that PARG plays a critical role in the normal function of neuronal cells and parthanatos by regulating PAR levels [55].

16.3.3 PAR

PAR is a large, negatively charged polymer that can be either attached as a post-translational modification to a protein or as a free polymer produced by PARG hydrolysis (Fig. 16.3) [56]. Free or protein-bound PAR polymers can bind to other proteins non-covalently through their conserved PAR-binding motifs, including PAR-binding motifs (PBMs), macrodomains, WWE domains, and PAR-binding zinc finger (PBZF) domains [37]. These motifs usually overlap with other functional domains and thus the PAR polymer can alter the structure, function, and localization of its binding proteins [41, 56]. Free PAR polymer accumulation has been implicated as the major death signal in parthanatos, ischemic stroke, and some neurodegenerative diseases [14, 32, 33]. How the highly negatively charged large PAR polymer escapes from nucleus to mitochondria and induces parthanatos is not clear. It is presumed that a protein partner may bind PAR and help transport the death signal out of nucleus to mitochondria. Further study revealing the mechanism of PAR translocation will provide novel insight on how to prevent the death signal from escaping the nucleus.

16.3.4 AIF

AIF is a dual function molecule: it is a mitochondrial flavoprotein with important NADH oxidase activity, yet it is able to translocate to nucleus to induce large-scale DNA fragmentation upon toxic stimuli [57–59]. Studies using antibody neutralization, small interfering RNA (siRNA), and Harlequin mutant mice (express ~20% AIF compared to wild-type), all indicate that AIF is a death effector of parthanatos [33, 34, 60, 61]. It was originally thought that AIF resides in the mitochondrial intermembrane space [62]. However, a recent study using biochemical and electron

microscopic analyses revealed that a small pool (30%) of AIF resides on the mouse outer mitochondrial membrane and is responsible for the rapid AIF release and neuron death following NMDA stimulation [63]. Unlike its name, AIF mediates caspase-independent cell death (parthanatos), while other death factors (such as cytochrome C) released from mitochondria participate in caspase-dependent cell death (Fig. 16.1). Some crosstalk between caspases and AIF have been proposed [64, 65].

AIF is a high-affinity PAR-binding protein [66], and the binding of PAR with AIF is required for the release of AIF from the mitochondria to induce cell death, but it is not required for its NAD^+ oxidase activity, or ability to induce DNA fragmentation [67]. PAR binding to AIF on the outer surface of mitochondria decreases its affinity to the mitochondria facilitating its release [67]. AIF translocation to the nucleus seems to be the no-return point for cell death in excitotoxicity, ischemia, and some neurodegenerative disorders [68, 69]. However, how PAR is released from the nucleus and what is the nuclease downstream of AIF are two missing links of parthanatos.

16.3.5 Iduna

Iduna, also known as ring finger protein (RNF) 146, is an E3 ubquitin ligase named after the Norwegian goddess of protection and eternal youth. It ubiquitinates poly (ADP-ribosyl)ated substrates and targets them for degradation [70, 71]. Iduna was recently demonstrated as a novel endogenous inhibitor of parthanatos and protects neurons from excitotoxicity both in vitro and in vivo, as well as MCAO-induced stroke in mice [72]. Furthermore, the neuroprotective function of Iduna relies on its binding ability with PAR, since mutations of Iduna's PBM motif result in attenuated protection [72]. Under mild toxic stimulations, Iduna can be induced and works as a guard in the cytosol to degrade PAR or PAR-binding proteins to prevent parthanatos, presumably by preventing PAR from reaching mitochondria and release AIF.

16.4 Parthanatos and Neurodegenerative Diseases

16.4.1 PARP-1 and Neurodegeneration

PARP-1 has emerged as a major death regulator in both acute neuronal injury and neurodegenerative disorders. Oxidative stress, one of the most important common features of neurodegenerative disorders and aging diseases, is able to activate PARP-1. Involvement of PARP-1 has been found in human patient brains, as well as cellular and rodent models of stroke [73], trauma [74], spinal cord injury [75], AD [76–79], PD [80–84], HD [85], MS [86], and ALS [87, 88] [14, 89]. Furthermore, PARP inhibitors and genetic deletion of PARP-1 are profoundly neuroprotective in

NO-mediated toxicity [24], NMDA excitotoxicity [34, 90, 91], as well as experiment models of ischemic injury [73, 92], traumatic brain injury [74], AD [77], HD [93], and PD [82–84, 94].

16.4.1.1 Parkinson's Disease

Parkinson's disease is a complicated neurodegenerative movement disorder that results from the selective loss of dopaminergic neurons in the substantia nigra [95]. MPTP, a toxin known to induce PD-like symptoms, has been reported to increase PARP-1 activity in mice [69, 83, 96]. PARP-1 KO mice are highly resistant to MPTP-induced neurotoxicity compared to WT mice [83]. In another study, PARP-1 inhibitors ameliorate α-synuclein cytotoxicity, as well as primary dopaminergic neurons treated with 1-methyl-4-phenylpyridinium (MPP(+)) [84]. Both pretreatment and posttreatment with the PARP-1 inhibitor benzamide attenuated MPTP-induced neuronal damage in mice [94]. Moreover, in a 6-hydroxydopamine (6-OHDA) in vitro PD mice model, PARP-1 KO mice show reduced dopaminergic neurodegeneration and related PD symptoms, due to the suppression of AMP protein kinase (AMPK) activation and AIF nuclear translocation [81]. Mutations of parkin and loss of its ubiquitin E3 ligase function are associated with familial PD [97]. The parkin substrate aminoacyl-tRNA synthetase complex interacting multifunctional protein-2 (AIMP2) is found in Lewy body inclusions of PD substantia nigra and its accumulation leads to dopamine neuron death [98, 99]. A recent study [82] found that AIMP2 accumulation directly leads to PARP-1 overactivation and results in selective, age-dependent progressive loss of dopaminergic neurons, while the PARP-1 inhibitor AG-014699 or PARP-1 gene deletion protects AIMP2 transgenic mice against dopamine neuron loss and behavioral deficits.

16.4.1.2 Alzheimer's Disease

Alzheimer's disease is a dementia characterized by the accumulation of the β-amyloid peptide (Aβ) and hyperphosphorylation of the microtubule-associated protein tau within the brain [100]. The correlation between PARP-1 and AD was first reported in 1999, indicating higher levels of PARP-1 and PAR in AD postmortem human brains by immunostaining [77]. Early PARP-1 activation was detected in the entorhinal cortex and hippocampus of AD Swedish and Indiana double mutation mice at 3 months of age when initial amyloid deposition takes place. The increase of PARP-1 activity in Aβ-treated human SH-SY5Y cells can be prevented by PARP-1 inhibitor, MC2050 [79]. Moreover, Aβ injection increases PARP-1 levels in rat brains and nicotinamide, an endogenous PARP-1 inhibitor, downregulates PARP-1 and oxidative stress induced by Aβ [78]. Moreover, mice treated with the PARP-1 inhibitor PJ34 and PARP-1 KO mice have lower microglial activation after Aβ injections compared to controls [76]. In the same study, PARP-1 deletion attenuated the microglial activation and cognitive deficits in AD mice with Swedish and

Indiana double mutations [76]. PARP-1 activation and accumulation of PAR have also been observed in astrocytes and microglia treated with different species of Aβ or transfected with human amyloid precursor protein (APP) [76, 79, 89, 101].

16.4.1.3 Huntington's Disease

Huntington's disease is an autosomal-dominant, progressive neurodegenerative disorder due to expanded CAG repeat mutations that results from polyglutamine expansion at the N-terminus of the huntingtin protein [102]. Huntington's disease manifests with ≥35 polyglutamine expansions. A strong neuronal and glial PARP expression and weak caspase-3 activation accompanied by massive cell death are detected in the caudate nucleus of severely affected HD brains, suggesting that caspase-mediated neuronal death has little contribution to HD pathology [85]. A recent study reported that R6/2 HD mice treated with the PARP-1 inhibitor INO-1001 survived longer and displayed ameliorated neurological dysfunction than the control mice, confirming the neuroprotective effect of PARP-1 inhibition in HD [93].

Involvement of PARP-1 in other neurodegenerative disorders will not be described in detail here. There are concerns about long-term use of PARP inhibitors for chronic neurodegenerative diseases due to the potential side effects including genome instability [103]. However, PARP-1 KO mice are viable and are resistant to numerous toxic stimuli as mentioned above, which suggests that PARP-2 or other PARP family members may also play a role in DNA repair and maintaining genome stability. Nevertheless, new potent selective PARP-1 inhibitors, which cross blood–brain barrier, such as AG-014699 and AG14361, could be beneficial in preventing or delaying neurodegenerative disease progression.

16.5 Involvement of Other Parthanatos Components in Neurodegeneration

In addition to PARP-1, AIF translocation has also been described in several neurodegenerative disorders and experiment models [57]. The first evidence for the involvement of AIF in neurodegenerative diseases is that cortical neurons of harlequin mice with reduced AIF expression were highly resistant to glutamate excitotoxicity [60]. AIF nuclear translocation from mitochondria has been reported in PC-12 cells [104], mouse dopaminergic cell lines [105, 106], and in vivo tyrosine-hydroxylase (TH)-positive neurons [69] treated with MPTP. Chu et al. has also found that MPP+ treatment results in nuclear translocation of AIF and cell death that cannot be prevented by caspase inhibitors but can be significantly reduced by short hairpin RNA against AIF [106]. Nuclear translocation of AIF has also been found in primary neurons of PD patients and in

lipopolysaccharide (LPS)-injected mouse nigral dopaminergic neurons [107]. Interestingly, both Aβ and non-Aβ component of amyloid plaques induced PARP-1 activation and AIF translocation from mitochondria to nucleus in rat brain slices, but had no effect on caspase-3 activity [108]. Moreover, AIF release from the mitochondria and translocation into the nucleus were also observed in both in vitro and in vivo retinal degeneration models [109, 110] and the motor neurons of symptomatic superoxide dismutase 1 (SOD1) G93A transgenic mice, a model of ALS [111]. Despite the fact that harlequin mice are resistant to numerous forms of acute brain injury, they suffer from slow, progressive neurodegeneration, accompanied by markers of oxidative stress [112, 113], probably due to the loss of pro-survival mitochondrial function of AIF. Nevertheless, as a critical mediator of caspase-independent programmed cell death, future studies to reveal AIF isoforms functions, its protein function regions and pro-parthanatos nuclear partners, will lead to the development of more selective drugs to treat degenerative diseases and other neurological disorders involving AIF [114]. In fact, a nuclear effector of AIF-induced DNA cleavage and cell death has been identified and named as PAAN (parthanatos-dependent AIF-associated nuclease) by our laboratory.

Iduna (RNF146/dactylidin) is upregulated early in highly vulnerable brain tissues of AD patients compared with aged controls [115], suggesting that Iduna may function as a molecular protector molecular early in the progression of neurodegenerative diseases. It will be interesting to investigate if Iduna function is impaired in neurodegenerative disorders, which could contribute to possible poly-(ADP-ribosyl)ated damaged or toxic protein accumulation.

16.6 Conclusions

In summary, parthanatos plays important roles in exitotoxicity, acute neurological diseases such as ischemic stroke and traumatic injury, and neurodegenerative disorders including PD, AD, HD, ALS, and MS. Although cell death itself is the endpoint event at the late stage of neurodegeneration, pharmacological inhibitors and genetic deletions of the mediators in cell death show beneficial effect in cellular and animal models of neurodegenerative diseases, indicating that preventing or reducing cell loss are still promising therapeutic interventions that could probably slow down the disease progress [1]. Further investigation of parthanatos-signaling mechanisms and roles of parthanatos mediators in different neurologic and neurodegenerative disorders are essential. We have highlighted some potential drug targets in the parthanatos-signaling pathways in Fig. 16.4.

It will also be important to understand the interactions between parthanatos and other major forms of cell death in neurodegenerative diseases (Fig. 16.5). For example, PARP-1 can be cleaved by activated caspases, which reserves the energy needed for cell execution by apoptotic machinery [116]. While on the other hand, cells with

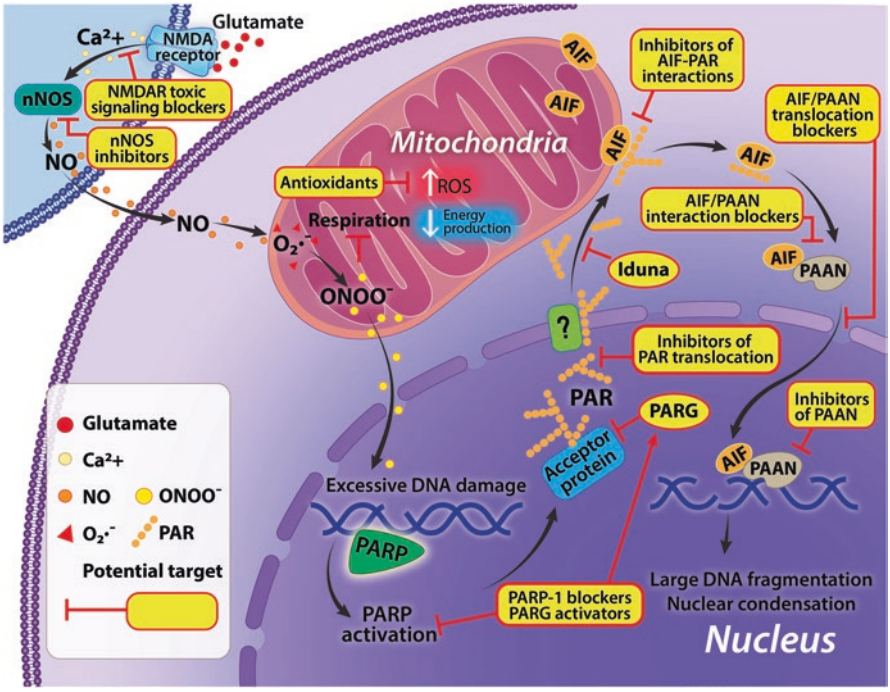

Fig. 16.4 Therapeutic targets of parthanatos. When excitotoxicity is involved, the beneficial effect of NMDAR toxic signaling blockers (such as Tat peptides interfering NR2B/PSD-95 and PSD-95/nNOS binding, [121–123]), NMDAR blocker (memantine, [124, 125]) and selective nNOS inhibitors [20] have been shown in experiment models and clinical trials in ischemia and some neurodegenerative disorders. Antioxidants can also reduce ROS and thus protect cells from parthanatos and other forms of death. The neuroprotective effect of PARP-1 inhibitors has been elaborated in the chapter. Other potential therapeutic targets downstream of PARP-1 activation includes but is not limited to: activation of endogenous PARP-1 blocker PARG and Iduna (such as preconditioning), prevention of death signal (PAR) translocation from nucleus to mitochondria, prevention of AIF release and translocation to nucleus with its partner PAAN, as well as disruption of critical mediator interactions and inhibition of PAAN nuclease function. *Highlighted boxes* with *red outlines* are therapeutic targets proposed for neurological and neurodegenerative disorders involving parthanatos

PARP-1 overactivation suffer from cellular NAD^+ and ATP depletion and undergo either necroptosis [117] or PAR polymer-mediated parthanatos [15], possibly accompanied by autophagy [118, 119]. It is worth mentioning that cell death factors such as PAR, AIF, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and tumor protein 53 (p53) are involved in various cell death programs and neurodegenerative diseases, and understanding their roles and interactions in these conditions will contribute to the development of therapies and biomarkers for neurodegenerative diseases [1, 14, 120].

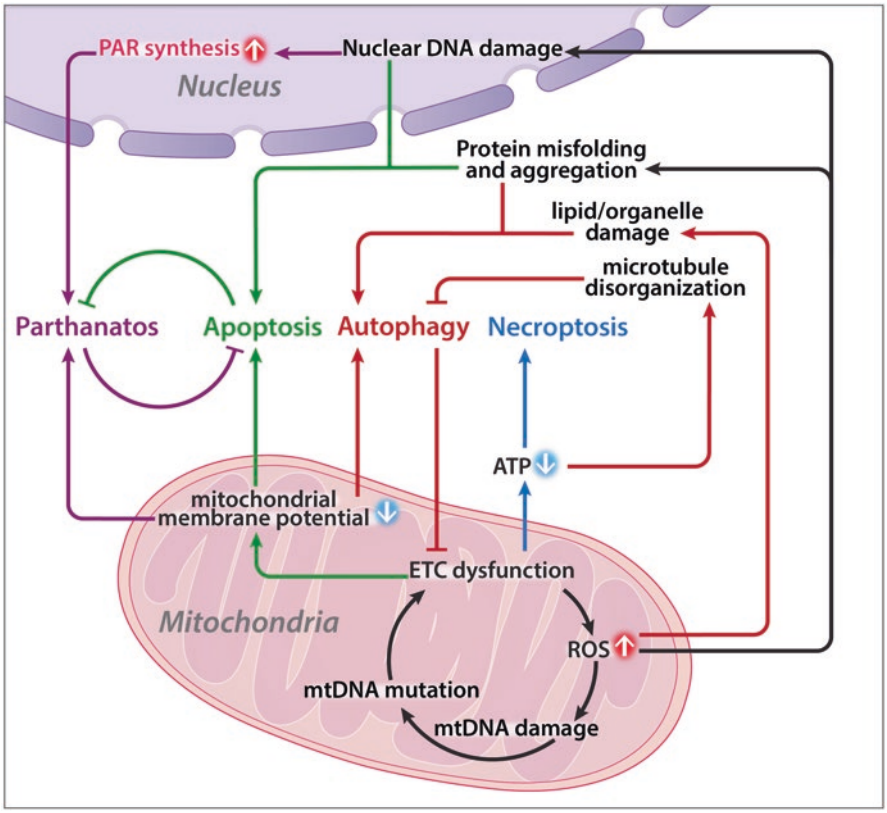

Fig. 16.5 Interactions of cell death programs in neurodegenerative disease context. The main interconnected cell death programs in neurodegenerative disorders (parthanatos: *purple*, apoptosis: *green*, necroptosis: *blue*, and autophagy: *red*). Mitochondrial dysfunction, ROS, and associated DNA damage are the most common source of trigger of all four types of death, which happen to be the most affected cell targets in neurodegenerative diseases and aging. Some secondary deficits including protein misfolding, organelle damage, microtubule disorganization can also promote several forms of cell death. Some of the interplays between different types of death are also shown here (adapted from [126])

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