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Parthanatos: Mechanisms, Modulation, and Therapeutic Prospects in Neurodegenerative Disease and Stroke

Liu Yang[1,2,a], **Lauren Guttman**[1,6,a], **Valina L. Dawson**[1,2,3,4,5,*], **Ted M. Dawson**[1,2,3,4,6,*]

[1]Neuroregeneration and Stem Cell Programs, Institute for Cell Engineering, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.

[2]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA

[3]Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD 21218, USA

[4]Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA

[5]Department of Physiology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA

[6]Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA

Abstract

Parthanatos is a cell death signaling pathway that has emerged as a compelling target for pharmaceutical intervention. It plays a pivotal role in the neuron loss and neuroinflammation that occurs in Parkinson's Disease (PD), Alzheimer's Disease (AD), Huntington's Disease (HD), Amyotrophic Lateral Sclerosis (ALS), and stroke. There are currently no treatments available to humans to prevent cell death in any of these diseases. This review provides an in-depth examination of the current understanding of the Parthanatos mechanism, with a particular focus on its implications in neuroinflammation and various diseases discussed herein. Furthermore, we thoroughly review potential intervention targets within the Parthanatos pathway. We dissect recent progress in inhibitory strategies, complimented by a detailed structural analysis of key Parthanatos executioners, PARP-1, AIF, and MIF, along with an assessment of their established inhibitors. We hope to introduce a new perspective on the feasibility of targeting components within the Parthanatos pathway, emphasizing its potential to bring about transformative outcomes in therapeutic interventions. By delineating therapeutic opportunities and known targets, we seek to emphasize the imperative of blocking Parthanatos as a precursor to developing disease-

*Correspondence to: Ted M. Dawson, M.D Ph.D. (tdawson@jhmi.edu) or Valina L. Dawson, Ph.D. (vdawson1@jhmi.edu).
[a]These authors contributed equally to this work.

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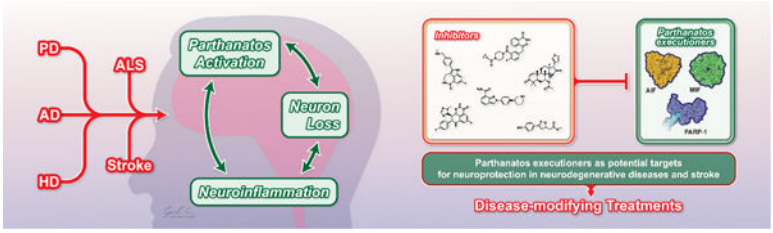
modifying treatments. This comprehensive exploration aims to catalyze a paradigm shift in our understanding of potential neurodegenerative disease therapeutics, advocating for the pursuit of effective interventions centered around Parthanatos inhibition.

Graphical Abstract



Keywords

Poly ADP-Ribose (PAR); Poly ADP-Ribose Polymerase (PARP); Macrophage migration inhibitory factor (MIF); Apoptosis inducing factor (AIF); PAANIB-1; Cell Death

1. Introduction

Neurodegenerative diseases and stroke pose a significant threat to the aging population of the United States, impacting millions. Characterized by the loss of neurons, these conditions not only result in devastating disabilities and eventual death, but also diminish the opportunity for a peaceful and fulfilling life. Despite the urgent need for neuroprotective treatments, there are currently no FDA approved drugs available for patient use to prevent cell death in neurodegenerative disease or stroke [1–3]. The primary route of cell death in these diseases is Parthanatos, a cell death signaling pathway that is triggered by pathological stressors. Parthanatos, or Poly(ADP-ribose) polymerase-1 (PARP-1) dependent cell death, is activated by extensive DNA damage. In turn, PARP-1 becomes hyperactivated and produces long and branched poly-ADP ribose (PAR) polymers. PAR production and translocation to the cytosol induces a cascade of events, including PAR binding to mitochondrial apoptosis-inducing factor (AIF), AIF translocation to the cytosol, AIF binding to macrophage migration inhibitory factor (MIF), co-translocation of AIF-MIF complex to the nucleus, and large-scale DNA fragmentation by MIF nuclease activity. These steps result in subsequent cell death [4].

In this comprehensive review, we provide an in-depth and updated description of the Parthanatos mechanism. We also discuss how this mechanism is involved in diverse neurodegenerative diseases and stroke, along with its complex role in neuroinflammation. Subsequently, we offer a comprehensive strategy for potential interventions at various stages within the Parthanatos pathway. Furthermore, we present a structural and functional aspect of each Parthanatos executor, their interactions, and existing inhibitors. This analysis aims to stimulate innovative concepts regarding the feasibility of targeting Parthanatos for therapeutic purposes. Overall, we aim to initiate a wave of future research focused on Parthanatos inhibition, fostering the development of disease-modifying treatments, along with emphasizing the importance of Parthanatos in numerous devastating diseases.

2. Molecular mechanism and modulation of Parthanatos

Parthanatos is a regulated form of cell death that is characterized by hyperactivation of the DNA damage sensing enzyme, PARP-1 [4–7]. Its unique portmanteaux name originates from the death signal, PAR polymer, synthesized by PARP-1 and *Thanatos*, the personification of death in Greek mythology, describes PAR mediated cell death. Distinct from other cell death pathways, like apoptosis or necroptosis, Parthanatos is caspase-independent and does require Bax or apoptotic activating factor-1 (Apaf-1) [7–9]. The Parthanatos signaling pathway is the primary cell death mechanism responsible for neuron loss in many diseases [10, 11].

Parthanatos can be initiated by various stressors, such as: ischemia, pathologic α-synuclein, pathologic β-amyloid (Aβ), and glutamate activation through N-methyl-D-aspartate (NMDA) glutamate receptors. These stressors can induce oxidative stress and extensive DNA damage, in turn hyperactivating PARP-1 [3, 10, 12]. There are also other modes of PARP-1 hyperactivation that are independent of DNA damage, such as signal-regulated kinase 2 (ERK2) [13] and aminoacyl-tRNA synthetase complex interacting multifunctional protein-2 (AIMP2) [14]. In response to these stressors, a cascade of events unfolds that is determined by the route of PARP-1 activation; DNA damage dependent or independent. The stressors that initiate the DNA damage dependent route commonly do so by causing oxidative stress or glutamate excitotoxicity. For instance, neuronal energy deprivation, disruption of cellular homeostasis, and neuronal depolarization that occurs in ischemia triggers neurons to release an excessive amount of glutamate [3, 15]. Pathological α-synuclein and Aβ, hallmarks of Parkinson's Disease (PD) and Alzheimer's Disease (AD), respectively, can trigger an increase in nitric oxide (NO) by several mechanisms, including enhancing glutamate excitotoxicity [3, 10, 16, 17].

Excessive glutamate release activates NMDA receptors (NMDAR), which increase the flux of intracellular calcium (Ca^{2+}), binding to calmodulin (CaM). Ca^{2+}-CaM complex formation results in the hyperactivation of neuronal nitric oxide synthase (nNOS), that is responsible for synthesizing NO [18]. To synthesize NO, nNOS first hydroxylates L-arginine into N^{ω}-hydroxy-L-arginine, followed by oxidation into L-citrulline and NO. NO becomes pathological as it relocates to the mitochondria and reacts with the superoxide anion ($O_2^{\cdot -}$), a byproduct of the mitochondrial electron transport chain [19]. This reaction yields peroxynitrite ($ONOO^-$), a powerful prooxidant, which diffuses from the mitochondria to the nucleus and induces DNA damage (Fig. 1) [20–24].

PARP-1 surveils DNA for double stranded breaks. DNA, upon being attacked by high-order reactive oxygen species (ROS), such as peroxynitrite, leads to PARP-1 hyperactivation [25–27]. The PARP-1 protein (116 kD) is divided into three functional domains. The N-terminus (42 kD) contains three zinc-finger motifs that bind to DNA, sense DNA breaks, and contains the nuclear localization sequence (NLS). Its center (16 kD), is a BRCA1 C-terminal motif for protein-protein interactions and sites for self-ADP-ribosylation. Additionally, its C-terminus (55 kD), is the catalytic domain that contains a binding site for NAD+ along with the PARP signature motif that synthesizes PAR [28, 29]. Facing mild DNA damage, PARP-1 facilitates the repair of DNA strand breaks by synthesizing PAR polymers and

acting as a scaffold for the DNA repair machinery. PARP-1 synthesizes PAR by utilizing oxidized NAD+ produced by ATP. However, in the condition of extensive DNA damage, hyperactive PARP-1 produces abnormally long and branched PAR polymers [10, 30].

These negatively charged and complex PAR polymers, products of aberrant PARP-1 activity, translocate from the nucleus into the cytoplasm. It was recently discovered that PARylation and the binding of PAR to histone H1.2 is responsible for PAR translocation. Once PAR binds to H1.2, H1.2 functions as a carrier for PAR. The amount of PAR able to translocate into the cytosol via H1.2 is dependent on Iduna (RNF146), a PAR dependent E3 ubiquitin ligase [31, 32]. Iduna ubiquitinates PARylated H1.2, disturbing PAR's route of exportation to the cytosol [33]. PAR accessing the cytosol is arguably a critical step that enables the rest of the toxic Parthanatos cascade (Fig. 1) [34].

Upon reaching the cytosol, PAR binds and inhibits hexokinase 1 (HK-1), a key enzyme for glucose metabolism [35]. This results in mitochondrial release of HK-1, causing depletion of NAD+, inhibition of glycolysis, and bioenergetic failure [36, 37]. PAR also binds to the mitochondrial oxidoreductase, AIF in the cytosol [12]. The binding of PAR and AIF is required for the induction of the remaining mechanistic steps that result in Parthanatic cell death. Once PAR binds to AIF, it induces AIF's release into the cytosol by disturbing its mitochondrial binding, likely through a conformational change (Fig. 1) [38]. AIF predominantly resides in the mitochondrion inner membrane and intermembrane space [39], but a portion of AIF is located on the cytosolic portion of the mitochondria, which accounts for 20–30% of the total AIF population [40]. This extramitochondrial AIF is the PAR releasable AIF [38, 40, 41]. Amino acid residues Arg588, Lys589 and Arg592 located on the D3 domain of AIF are critical for high-affinity PAR binding and mutating these residues block PAR-induced AIF translocation. The distinct binding sites that AIF has for PAR, separate from its binding sites for DNA, imply an evolutionary significance, reinforcing their interdependence [38].

Following the interaction between AIF and PAR, AIF is released from the mitochondria and forms a complex with Parthanatos-associated apoptosis-inducing factor (AIF) nuclease (PAAN), also known as MIF in the cytosol. MIF is a member of the PD-D/E(X)K family of nucleases and is the primary catalyst of DNA fragmentation in Parthanatos, operating independently of its tautomerase activity [42, 43]. AIF recruits MIF to the nucleus, orchestrating co-translocation; this mechanism is highly dependent on the E22 region of MIF [43]. The interaction between AIF and MIF is also dependent on the activity of histone deacetylase 6 (HDAC6). The inhibition of HDAC6 results in MIF acetylation, which disrupts AIF-MIF binding and impairs MIF translocation to the nucleus. This implies that HDAC6 plays a crucial role in ensuring that the final steps of Parthanatos are executed [44]. Once the AIF-MIF complex reaches the nucleus, MIF has primary responsibility in DNA fragmentation while AIF enhances MIF nuclease activity by increasing its binding affinity to DNA. MIF preferentially cleaves single-stranded DNA (ssDNA) and accomplishes this through the utilization of both its endonuclease and exonuclease activities. As a whole, MIF nuclease activity is powerful and causes large-scale DNA fragmentation, eventually leading to cell death (Fig. 1) [4, 42, 43].

3. Parthanatos in neuroinflammation

3.1 Neuroinflammation and neurodegenerative disorders

While classic neurodegenerative diseases such as AD, PD, Amyotrophic Lateral Sclerosis (ALS), and Huntington's Disease (HD) exhibit distinct pathogenic mechanisms, involving various protein aggregates and genetic variants, they share a common characteristic of chronic neuroinflammation. Immune system dysregulation is not solely a secondary response in neurodegenerative disease but plays a pivotal role in initiation and progression. The prevailing pathology, protein aggregation, induces neuroinflammation that accelerates protein aggregation and neurodegeneration. The immune response's significance is underscored by mutations in immune-related genes as neurodegeneration risk factors [45, 46]. Although our understanding remains incomplete, the pathogenesis of neurodegeneration involves numerous signaling pathways and various cell types of the central nervous system. The modulation of inflammatory signaling pathways, either through inhibition or augmentation, is acknowledged as a promising therapeutic approach for neurodegenerative diseases. Several interventions targeting these pathways have shown promising results in animal models and clinical trials [47].

Using PD as an illustrative example, this neurodegenerative condition, the second most common disorder of its kind, is characterized by Lewy bodies containing aggregated α-synuclein and the preferential loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc), and α-synuclein deposition and degeneration throughout the brain [48]. Neuroinflammation, orchestrated by microglia and astrocytes, is a significant hallmark. Evidence suggests that increased microglial activity correlates with the decline of nigrostriatal DA neurons and degeneration in other brain regions, highlighting the role of the innate immune system in PD pathogenesis [49]. Pathological α-synuclein activates microglia, which produce proinflammatory cytokines and transform astrocytes into toxic activated forms. Excessive microglial activation and elevated inflammatory factors, including TNF-α, are observed in PD patients. Activated microglia contribute to the production of IL-1α, TNF-α C1q, IL-6 and other cytokines, with the release of these mediators potentially contributing to disease progression. Inhibiting the release of these pro-inflammatory molecules may impede PD progression [48, 50–52]. Astrocyte activation also leads to the production of IL-1β, TNF-α and other cytokines, exacerbating damage. In astrocyte cell lines and primary mouse astrocytes, there is increased inducible nitric oxide synthase (iNOS), NO, ROS, and expression of the inflammatory cytokine, IL-6. Additionally, astrocytic nuclear factor kappa B (NF-κB) signaling is activated, releasing substantial amounts of TNF-α, IL-1β, amplifying the neuroinflammatory response and worsening neuronal damage. Elevated expression of glial fibrillary acidic protein (GFAP), cyclooxygenase-2 (COX-2), and iNOS, along with increases in TNF-α and IL-1β, can reciprocally lead to astrocyte activation, further triggering neuroinflammatory responses [51, 53, 54]. In a recent report by Guttenplan et al., toxic astrocytes also use saturated lipids as a mechanism to induce cell death. Astrocyte-specific knockout of elongation of very long chain fatty acids protein 1 (ELVOL1), a lipid synthesis enzyme, attenuated astrocyte toxicity, axonal injury, and neuronal death. Astrocytes induce toxicity via lipids by secreting very-long-chain fatty acid acyl chains (VLCPC) and long-chain saturated free fatty

acids (FFA) [55]. These findings underscore the integral role of microglial and astrocytic activation in inflammatory cytokine regulation, emphasizing their significant contribution to the neuroinflammatory pathogenesis of PD.

3.2 Parthanatos induces activation and recruitment of microglia and astrocytes

Microglia and astrocytes play crucial roles in the central nervous system's innate immune system. They contribute to the production of immune regulators and expressing receptors associated with innate immunity, such as complement receptors and Toll-like Receptors (TLRs) [52]. Parthanatos participates in recruiting microglia and astrocytes to sites of oxidative stress and protein aggregation. While both oxidative stress and protein aggregation can independently trigger Parthanatos, the subsequent PARP-1 hyperactivation also produces pro-inflammatory cytokines that further enhance microglia and astrocyte activation [56]. PARP-1 is a co-activator of NF-κB, which releases TNF-α and iNOS that promote increased ROS. In turn, ROS further damages DNA and creates a loop that results in a continuous cycle of increasing pro-inflammatory factors, Parthanatos activation, and microglia and astrocyte activation and recruitment [56]. PARP-1 induced microglia activation contributes to the loss of blood brain barrier (BBB) integrity and promotes astrogliosis in AD cell models. PARP-1 inhibition and ablation were found to reverse this phenotype [57]. PARP-1 also increases microglial cytokine expression. This may occur by PARP-1 regulation of Il1B and Tnf expression through nucleosomal histone ADP-ribosylation, increasing accessibility of DNA [58].

The role of Parthanatos in enhancing the response of microglia and astrocytes is exemplified by experiments involving PARP-1 inhibitors. In primary cortical neurons treated with Methyl-N'-Nitro-N-Nitrosoguanidine (MNNG), the PARP-1 inhibitor, PJ34, attenuated microglial activation, including microglial markers such as: NO, iNOS, TNF-α, NF-κB, and ROS [59]. It was also reported that in rats and pigs subject to controlled cortical impact (CCI), the PARP-1 inhibitor, veliparib, suppressed microglia activation, reactive astrocytosis, and cell death [60]. Collectively, these studies suggest that Parthanatos further induces and activates the toxic responses by microglia and astrocytes. Future investigations should focus on Parthanatos blockers and regulators that reduce inflammatory responses in neurodegenerative disease models.

3.3 Cytosolic DNA-sensor signaling pathway triggered by Parthanatos

TLRs, a subset of highly conserved pattern recognition receptors (PRRs), are essential for recognizing endogenous danger signals and pathogens [61]. The fragmented DNA resulting from Parthanatos, entering the cytoplasm, may function as a damage-associated molecular pattern (DAMP). In neuroinflammation, TLRs also perform important functions in combination with inflammasomes [62]. An inflammasome is a multimeric protein complex composed of the PRR (mainly NLR), the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD), and the effector protein caspase-1, which when induced, activates the IL-1β and IL-18 precursors into functional mature proteins via caspase-1-induced cleavage. The mature pro-inflammatory interleukins are then extracellularly secreted, initiating inflammatory responses [63]. While NLRP3 is an extensively studied inflammasome in neurodegenerative diseases, research suggests that

astrocytes and microglia also express the absent in melanoma 2 (AIM2) inflammasome, which is activated and upregulated in animal models of neurodegenerative diseases [62, 64, 65].

MIF, initially recognized for its significant role in inflammation and innate immunity, has recently emerged as a crucial mediator in Parthanatos [4, 43]. Its nuclease activity, responsible for the final step of genomic DNA fragmentation, highlights its newfound importance in this cell death pathway. Examination of postmortem brains and cerebrospinal fluid from individuals with PD, revealed markers indicative of Parthanatos activation linked to α-synuclein pathology [66]. Elevation in MIF levels make it a potential biomarker candidate for early-stage PD [67, 68]. Elevated MIF has also been reported in human AD brains and are correlated with biomarkers for tau hyperphosphorylation. MIF inhibition and deficiency in AD mouse models decreased proinflammatory cytokines and improved cognitive function [69]. Therefore, it is not hard to speculate that MIF, acting as a principal executor in Parthanatos, makes a substantial contribution to neuroinflammation.

Various cellular nucleic acid sensors, including cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS) and AIM2, are crucial for recognizing DNA as an immune-stimulatory molecule [70]. cGAS, mainly located in the cytoplasm, recognizes double stranded (ds) DNA, synthesizing the second messenger cyclic guanosine-adenosine diphosphate (cGAMP), that induces downstream signaling. The endoplasmic reticulum membrane protein stimulator of interferon genes (STING) is activated by cGAMP and is a key component of innate immunity. The cGAS-STING signaling pathway contributes to neurodegeneration in PD, in part, by detecting mitochondrial dsDNA during mitochondrial injury [71]. Mice lacking STING exhibit resistance to pathological α-synuclein [72]. Activated STING phosphorylates TANK-binding kinase 1 (TBK1), resulting in the activation of NF-κB, which upregulates inflammatory factors, initiating the NLRP3 inflammasome assembly involved in PD pathogenesis [73, 74]. In the MPTP mouse model, NLRP3 inflammasome-mediated neuroinflammation contributes to loss of DA neurons [75]. Evidence shows that loss of ubiquitin E3 ligase, parkin activity results in spontaneous NLRP3 inflammasome assembly and DA neuronal death through upregulation of PARIS (ZNF746) [76]. Additionally, AIM2, expressed in neurons and glia, is a part of the PYHIN family of proteins that directly recognize and bind cytoplasmic dsDNA through its HIN structural domain without sequence specificity [77]. The PYRIN structural domain recruits the downstream ASC to activate caspase-1, which is involved in the maturation and secretion of IL-1β and IL-18. PD patient samples show elevated IL-1β and caspase-1 levels [78]. AIM2 indirectly activates the NLRP3 inflammasome, intensifying neuroinflammation in PD and extending its influence beyond its conventional role by enhancing the STING pathway [79].

Neurodegeneration induced by pathological α-synuclein is mediated through PAAN/MIF nuclease activity [42]. Depletion of MIF or nuclease-deficient MIF were shown to prevent α-synuclein-induced neurodegeneration. In addition, a novel MIF nuclease inhibitor, PAANIB-1, prevented neurodegeneration in diverse PD models [4, 42]. Intriguingly, MIF was demonstrated to be essential for NLRP3-dependent IL-1β release, but not for AIM2-dependent IL-1β release, while playing a crucial role in NLRP3 inflammasome assembly

[80]. Therefore, investigating the intricate mechanisms by which PAAN/MIF contributes to and influences neuroinflammation could significantly contribute to the therapeutic advancement for neurodegenerative disorders.

4. The role of Parthanatos in neurodegenerative disease and stroke

The Parthanatos signaling cascade plays a pivotal role in the cell death that occurs across diverse neurodegenerative diseases and stroke. A few examples of these neurodegenerative diseases are PD, AD, ALS, and HD. While the specific pathology varies among these forms of neurodegeneration, an important commonality is toxic protein aggregation that induces cell death. This section will cover the role of Parthanatos in these diseases and examines the current progress in drug research aimed at disrupting this pathway.

4.1 Parkinson's Disease (PD)

PD is the most prevalent movement disorder and the second most prevalent neurodegenerative disease [48, 81, 82]. Roughly 90,000 Americans are diagnosed with PD annually, and 10 million are currently living with it globally [83]. However, the actual amount of people that are living with PD is likely much higher, considering the number of patients that are undiagnosed or misdiagnosed. PD pathology is characterized by the relatively selective progressive death of DA neurons in the SNpc, although other neurons degenerate throughout the nervous system [84]. The death of DA neurons results in motor symptoms such as: resting tremor, bradykinesia, rigidity, and degeneration of other neurons which contribute to the gastrointestinal abnormalities, depression, and non-motor features of PD [84, 85]. Current drug treatments for PD include various therapeutics that increase dopamine signaling, such as L-DOPA. However, these treatments lack efficacy in later stages of disease progression and there are no available disease-modifying treatments for patients [84].

Loss of neurons in PD is driven, in part, by pathological α-synuclein, which aggregates and misfolds, forming oligomers and fibrils that exhibit prion-like spreading and serve as initiators of the Parthanatos cell death cascade [66, 86]. Pathologic α-synuclein initiates Parthanatos through the generation of NO. Inhibition of NOS with Nω-Nitro-L-arginine methyl ester hydrochloride (L-NAME) prevents α-synuclein preformed fibril (PFF) induced NO generation, DNA damage, PARP-1 activation, and cell death in primary cortical neurons. Pathologic α-synuclein uses this mechanism to kill DA neurons. One intrastriatal injection of α-synuclein PFF in WT mice reduces 50% of DA neurons in 6 months and genetic deletion and drug inhibition of PARP-1 blocked this loss of DA neurons. This suggests that Parthanatos is the primary route of cell death in PD [66].

Interestingly, Parthanatos activation also increases the neurotoxicity of pathologic α-synuclein, functioning as a feed-forward loop. PAR, the product of PARP-1 hyperactivation, directly increases the fibrillization rate and creates a more toxic form of α-synuclein. This results in a feed-forward cycle of PARP-1 hyperactivation, elevated PAR that increases the toxicity of α-synuclein, and enhancement of the subsequent PARP-1 activation [66, 87]. Moreover, this loop continuously escalates the severity of Parthanatic cell death, which likely contributes to rapid PD progression. PARP-1 inhibition may also lower pathologic

α-synuclein levels in transgenic mice overexpressing mutant α-synuclein [88]. One study showed that PARP inhibition was not protective in a pathologic α-synuclein model, which may be due to the extent of PARP inhibition [87], since high levels of PARP inhibition are required to attenuate pathologic α-synuclein toxicity [89].

Since Parthanatos may be the primary route of cell death in PD, inhibiting components and interactions in this pathway have promising therapeutic potential. As mentioned, in mouse models of PD, both PARP-1 inhibitors [66, 88, 89] and PARP-1 genetic deletion [66] successfully block the toxicity of pathologic α-synuclein. While PARP-1 inhibitors are already available to humans for the treatment of cancer, it may be valuable to repurpose this drug for the treatment of PD [90]. However, because PARP-1 plays an essential role in non-pathological DNA repair processes, there is potential for several unintended side-effects [1, 91]. The inhibition of a later-stage Parthanatos player or interaction may provide a more promising approach for interfering with Parthanatic cell death. Our group recently identified the compound PAANIB-1, a specific and selective MIF nuclease inhibitor that is brain penetrant prevents neurodegeneration in PD cell and mouse models. This confirms that it is possible to prevent the execution of Parthanatos by inhibiting later-stage components [4, 42]. Future studies focused on additional MIF nuclease inhibitors holds particular promise.

4.2 Alzheimer's Disease (AD)

AD is the most prevalent neurodegenerative disease and form of dementia that currently effects over 6 million Americans [92]. The neuropathological hallmarks of AD include the accumulation of Aβ peptides in extracellular deposits and the formation of neurofibrillary tangles (NFT) composed of hyperphosphorylated tau protein [93]. These toxic components contribute to widespread neuronal loss, initially affecting areas like the entorhinal cortex, basal nucleus of Meynert, and the locus coeruleus. As AD progresses, neuron loss spreads to brain areas such as the hippocampus, amygdala, and temporal lobe [93]. The degeneration of these brain areas results in severe memory impairment, language deficits, and cognitive decline [93].

In AD, Parthanatos is initiated, in part, by oxidative stress. Pathological Aβ aggregates, hyperphosphorylated tau, and mitochondrial dysfunction induce oxidative stress, leading to DNA damage [94]. Pathological Aβ is predominantly generated through the cleavage of mutated amyloid precursor protein (APP) by β and γ secretases [95]. This cleavage yields $A\beta_{1–40/42}$, which forms β-sheet rich fibrils [94]. $A\beta_{1–40/42}$ is primarily located in the hippocampus and entorhinal cortex, where it leads to increased oxidative stress markers and glutamate excitotoxicity [94, 96–98]. Metal ions such as copper, zinc, and iron entrapped in Aβ plaques accelerate pathogenesis by generating ROS, activating nNOS, and promoting Aβ aggregation [94, 99, 100]. Tau is subject to this oxidative stress, partially induced by Aβ, which promotes NFT formation [101]. Tau, in its pathological NFT form contributes to ROS-induced DNA damage [102]. Additionally, the impairment of glycolysis and ATP production in AD inhibits normal mitochondrial function, increasing leakage and ROS production [103]. These multitude of oxidative stress sources in AD results in DNA strand breaks and subsequent PARP-1 hyperactivation, initiating the Parthanatos cascade [104, 105].

In human AD brains, there is evidence of elevated PARP-1 activity and PAR levels along with PARP-1/PAR colocalization with Aβ, tau, and microtubule-associated protein 2 (MAP2) [104]. An early-stage mouse model of AD also reported heightened PARP-1 activation in the hippocampus and cortex [106]. It is likely that PARP-1 and PAR create a feed-forward loop with Aβ and tau, increasing Aβ deposition and tau NFT formation, similar to the feed-forward loop in PD [104, 107]. Interestingly, elevated levels of AIF have been reported in association with cell death in the cortex of TgCRND8 AD mouse models [108]. Increased levels of MIF have also been detected in the CSF of AD patients [50]. A recent study suggests that MIF also is enriched in the vicinity of Aβ plaques and binds directly to oligomerized Aβ. Hence, it is possible that MIF plays a role in amyloidgenesis [109]. Furthermore, knockout of PARP-1 in AD mouse models reduces microglial activation, prevents cognitive dysfunction, protects synaptic integrity, and prevents PAR accumulation along with AIF translocation to the nucleus [110, 111]. PARP mutations were reported to protect neurons from mitochondrial toxicity and prevent neurodegeneration in flies expressing Aβ-Arc [112]. These data strongly suggest that the activation of Parthanatos in AD plays a substantial role in disease progression.

Inhibition of Parthanatos in AD holds particular promise similar to PD. PARP-1 inhibitors stand out as strong candidates, slowing AD progression and offering neuroprotection even in early stages of the disease in models of AD [110, 111]. Inhibition of PAR or PARylation is also a promising target by potentially blocking the execution of Parthanatos and disrupting the toxic feed-forward loop with Aβ and tau [113]. Like in PD, MIF nuclease inhibitors in AD mouse models should be evaluated to explore their role as potential AD disease modifiers.

4.3 Amyotrophic Lateral Sclerosis (ALS)

ALS, also known as motor neuron disease (MND), is a very rare and fatal neurodegenerative disorder. It is characterized by degeneration of neurons that project from the cortex to the brainstem (upper motor neurons) alongside neurons that project from the brainstem to the spinal cord (lower motor neurons). The loss of these neurons results in muscle weakness, paralysis, and eventual death [114]. Despite the pathogenesis of ALS remaining largely enigmatic, a distinctive hallmark of the disease is aggregation of phosphorylated TAR-DNA binding protein 43 (TDP43) inclusions [115]. There are also several genetic associations correlated to ALS pathology including superoxide dismutase 1 (SOD1) and translocated in liposarcoma/fused in sarcoma (TLS/FUS) variations and C9ORF72 repeat expansions among others [116–118]. Likely by oxidative stress, TDP43 protein aggregates cause Parthanatos activation [114].

In human ALS brains, augmented expression of PARP-1 is observed in critical regions such as the motor cortex, parietal cortex, and cerebellum [119]. Moreover, elevated levels of PAR have been identified in the nuclei of motor neurons in the spinal cord of ALS brains, further suggesting the association between PARP-1 dysregulation and ALS pathology [120]. In an ALS mouse model harboring the superoxide dismutase 1 (SOD1) G93A mutation, spinal cord AIF was reported to translocate from the mitochondria to the nucleus [121]. This offers a possible mechanistic explanation for motor neuron death in ALS[11]. PARP −1

activation promotes the cytosolic accumulation of TDP-43[122] and the TLS/FUS protein is dependent on PARP-1 for recruitment to sites of oxidative stress and binds directly to PAR [123]. C9ORF72 of arginine-rich dipeptide repeat proteins toxicity is enhanced by PAR. Neurodegeneration in C9ORF72 fly models and patient-derived induced pluripotent stem cell differentiated neurons is suppressed by reduction of PAR [124]. These findings emphasize the complexity and diversity of ALS pathology, with Parthanatos emerging as a potential central orchestrator of disease progression.

While investigations for potential Parthanatos blockers remain limited for ALS, progress has been achieved with PARP-1 inhibitors. Axonal degeneration in C. Elegans models of ALS is reduced by genetic deletion and pharmacological inhibition of PARP [125]. Notably, veliparib protects neurons from TDP43-induced cell death [120]. Additionally, olaparib was reported to reduce cytotoxicity caused by TDP43 overexpression[126]. Similar to other neurodegenerative disorders, there are many drug targets to explore for inhibiting Parthanatos players and interactions that could lead to disease-modifying treatments for ALS.

4.4 Huntington's Disease (HD)

HD is a fatal neurodegenerative disorder that currently affects 41,000 people in the United States and puts another 200,000 at risk [127]. It is characterized by symptoms such as chorea, dystonia, psychiatric conditions, memory loss, and speech dysfunction. Death typically occurs 15–20 years after the onset of the disease [128]. HD is caused by an autosomal dominant mutation in the Huntington (*HTT*) gene on the short arm of chromosome 4, which leads to a high number of repeats of the CAG trinucleotide (>36) [129, 130]. This mutation causes the production of an expanded string of polyglutamine (Q) on the N-terminus of the huntingtin protein (htt). This expanded string of Q breaks off into toxic fragments and accumulates, leading to the loss of medium spiny neurons in the striatum [131]. There is no cure for HD and current drug treatments do not prevent cell death.

There is compelling evidence for the occurrence of Parthanatos in HD and its pivotal role in neuronal loss. The htt protein is involved in DNA damage repair and serves as a scaffold for other DNA damage response proteins, facilitating their translocation to sites of oxidative stress. In HD, the deficit of oxidative stress-induced DNA damage repair is indicative of a relationship to Parthanatos [132]. In human HD brains, there is evidence of elevated PARP-1 expression in both neurons and glial cells within the caudate nucleus [133]. Additionally, the PARP-1 inhibitor INO-1001 was neuroprotective in HD mice harboring the R6/2 mutation [134, 135]. This intervention not only extended survival time, but also increased cAMP response element-binding protein (CREB) and brain derived neurotrophic factor (BDNF) levels while decreasing striatal atrophy, neuronal intranuclear inclusions, and microglial activation [134]. Paradoxically, recent findings reported significantly reduced PAR levels in the cerebral spinal fluid (CSF) of HD patients compared to healthy controls. Patient derived fibroblasts also showed reduced PARP-1/2 activity despite increased DNA damage. Notably, elevated PAR levels, consistent with other studies, were only observed upon inhibition of poly(ADP-ribose) glycohydrolase (PARG), a key PAR degrading enzyme. PAR and htt

protein binding was also reported, along with the identification of the PAR-binding motif in the htt protein. Importantly, this study highlights that PAR is dysregulated in HD and may account for the inability to repair DNA. CSF-PAR levels could also differ from intraneuronal PAR levels, suggesting the existence of complex dynamics in PAR processing [136].

Indeed, these studies strongly suggest that Parthanatos plays a role in the pathology of HD. Despite an incomplete mechanistic understanding, the dysregulation of PAR is evident, and neuroprotective effects are observed with PARP-1 inhibitors in HD mice [134, 135]. Future studies should further investigate the complex Parthanatic mechanism that occurs in HD and explore potential Parthanatos pathway inhibitors for developing disease-modifying treatments for this fatal disease.

4.5 Stroke

Stroke is a debilitating or lethal event that impacts over 750,000 people per year in the United StatesS and stands as the third leading cause of disability [137]. About a quarter of these incidences occur in patients that have experienced a stroke previously, highlighting the reoccurring nature of this condition [137]. 87% of strokes are ischemic, which can be characterized by an interruption of blood flow to different brain regions, resulting in neuronal cell death [138]. Brain areas subjected to these hypoxic conditions can permanently lose function, contributing to morbidity and mortality. Current treatments, such as intravenous administration of tissue-type plasminogen activator (tPA) to break up blood clots, primarily involve methods of restoring blood flow to the brain. However, given the limited therapeutic window for stroke patients, it is unusual that these treatments can be administered in time before serious brain injury occurs [139]. There are currently no treatments available to protect the brain from cell death during or after stroke, or for a reperfusion injury after tPA – leaving a critical gap in stroke management [3].

During cerebral ischemia, rapid depletion of ATP initiates neuronal depolarization, triggering a surge of glutamate signaling. This cascade of events, culminating in excitotoxicity, is a precursor to Parthanatos. NMDARs, upon overactivation, lead to a post-synaptic influx of intracellular Ca^{2+} that activates nNOS [140–142]. Calcium-dependent nNOS activation requires the postsynaptic density 95 (PSD95) scaffolding protein, which brings nNOS and NMDA receptors in close proximity [143, 144]. Additionally, NMDA receptor-induced superoxide production is dependent on its interaction with the NADPH oxidase 2 (NOX2) subunit; PSD95 is required for NMDA receptor-induced NOX2 activation [145]. The subsequent activation of nNOS results in the generation of NO, and peroxynitrite ($ONOO^{-}$) [19, 146]. Simultaneously, ischemic conditions cause mitochondrial impairment, inducing accumulation of free radicals [19, 146]. The collective effect of these superoxides inflict DNA damage, culminating in PARP-1 hyperactivation [3]. It is likely that PARP-1 hyperactivation occurs immediately following ischemia; in rodent models, both PAR formation and NO generation have been identified within minutes after middle cerebral artery occlusion (MCAO) [147, 148].

Glutamate excitotoxicity is prevented by PARP inhibitors [149] and genetic deletion of PARP-1[150]. Ischemic damage following stroke is also attenuated by genetic deletion of PARP-1 [150]. Numerous studies have confirmed that PARP inhibition and genetic

deletion of PARP-1 in ischemic rodent models substantially reduces tissue damage[3, 151]. In the context of both transient and permanent MCAO, interventions targeting PARP-1 provide neuroprotection – from mitigating cell death to alleviating neuroinflammation. PARP-1 inhibition downregulates NF-κB transcription in microglia, reduces matrix metalloproteinase-9 (MMP9), diminishes infarct volume, and preserves the integrity of the blood brain barrier [3, 151].. However, there is a gap in literature concerning sexual dimorphism in the context of PARP-1 inhibition in ischemia [3]. Interestingly, male mice exhibit a more prominent reduction of iNOS, MMP9, and behavioral deficits following PARP-1 inhibition, while both sexes experience a nearly equivalent reduction in microglia activation [152].

In addition to PARP-1 inhibitors, crocetin, a natural antioxidant, blocks Parthanatos in MCAO rat models by inhibiting NOX2. This inhibition was found to reduce ROS production, PARP-1 activation, PAR production, and AIF translocation in conditions of oxygen glucose deprivation (OGD) and excitotoxicity-induced Parthanatos [153]. Moreover, crocetin protects PARylated HK-1, a substrate vulnerable to degradation by the E3 ubiquitin ligase RNF146, by direct binding; this protection of HK-1 prevented mitochondrial dysfunction and DNA damage that would otherwise result in irreversible cell death signals [153].

Overexpressing PARG reduces infarct volume further supporting a role for PAR signaling in stroke damage [30]. Translocation of AIF from the mitochondria to the nucleus in stroke requires PARP-1 or PARP-2 activation [27]. MIF was also shown to be a major mediator of Parthanatic cell death in acute ischemic disorders via its nuclease activity [43]. Collectively, these studies suggest that Parthanatos is a substantial route of cell death that causes neuronal loss in ischemia and blocking its execution results in neuroprotection.

5. Targeting Parthanatos for stroke and neurodegenerative therapeutics

5.1 Overview of promising intervention points in Parthanatos

Acquiring a comprehensive understanding of the Parthanatos mechanism and the delineation of responsibilities among its effectors enables the proposal of comprehensive strategies to prevent cell death. This involves targeting potential nodes, such as preventing PARP-1 hyperactivation, inhibiting PAR polymer formation, blocking the release of mitochondrial AIF to the cytoplasm, hindering the recognition and nuclear translocation of MIF by AIF, and mitigating large-scale genomic DNA fragmentation orchestrated by the PAAN/MIF pathway (Fig. 2). Given that neurodegenerative diseases and ischemic neuronal injury activate PARP-1 and that Parthanatos is emerging as a contributor to these disorders, targeting any of the cascade steps within this cell death pathway presents a promising therapeutic strategy for Parthanatos-dependent disorders, including PD, AD, ALS, HD, and stroke.

PARP-1, acknowledged as a poly-ADP-ribosyltransferase responsible for catalyzing poly-ADP-ribosylation of proteins, plays a pivotal role in DNA repair [25, 26, 154]. Its involvement in repair begins with the recognition of DNA breaks within chromatin, followed by the recruitment of repair factors like HPF1, ultimately facilitating the mending of DNA

strand breaks [155–157]. Beyond its engagement in the base excision repair (BER) pathway, PARP-1 also contributes to double-strand break (DSB) repair by promoting homologous recombination repair through PARylation [158]. When encountering mild levels of DNA damage, appropriately activated as a “DNA damage receptor,” PARP-1 supports DNA damage repair and cell survival. In instances of severe DNA damage, hyperactivation of PARP-1 triggers the initiation of the Parthanatos cell death pathway [30, 159, 160]. Hence, regulating the degree of PARP-1 activation emerges as an effective strategy to impede the initiation of this pathway.

PAR plays a crucial role in the initial phase of Parthanatos. Hyperactivated PARP-1 produces PAR, which sets in motion the Parthanatic cell death cascade by acting as death signal depending on the dose and complexity of the polymer [30]. Thus, controlling intracellular PAR formation is an effective strategy to impede Parthanatos progression. PAR catabolism involves dynamic processes where PARG and ADP-ribosyl-acceptor hydrolase-3 (ARH3) enzymes degrade PAR polymers [161]. They hydrolyze ribose-ribose bonds, releasing PAR of varying lengths and ADP-ribose monomers. As we described [7, 24], “PARG and ARH3 protect cells from Parthanatos by degrading PAR and preventing the initiation of Parthanatos” [30, 162–164]. Iduna (RNF146) is neuroprotective by binding and ubiquitinating leading to the degradation of PARylated and PAR binding proteins [15, 31]. These regulatory elements in PAR dependent signaling present potential therapeutic targets for Parthanatos. Further studies aimed at elucidating the mechanisms and regulatory processes governing PAR-degradation would significantly bolster our understanding and reinforce the effectiveness of PAR-degradation enzyme systems as potential therapeutic avenues for targeting Parthanatos. Another research gap exists in the incomplete understanding of PAR polymer translocation from the nucleus to the cytoplasm. It is hypothesized that specific binding partners associate with PAR to facilitate translocation. Recent research indicates that PARP-1 PARylates histone H1.2, facilitating direct binding of PAR to histone H1.2 and, thus enabling its role as a molecular carrier. Recent research indicates that PAR directly binds to histone H1.2, allowing it to function as a molecular carrier [33]. Effective strategies to inhibit the cytoplasmic transfer of PAR require further investigation, but inhibition of H1.2 holds promise.

Another crucial aspect garnering attention as a potential target for inhibiting Parthanatos is the release of the extramitochondrial AIF from mitochondria and its subsequent translocation into the nucleus [38, 151]. Studies indicate that the binding of PAR to AIF is indispensable for AIF release and translocation. The mechanism behind AIF release is not fully elucidated but is hypothesized to unfold in two sequential steps: first, NAD+ depletion induces mitochondrial membrane depolarization and prompts conformational changes in AIF; second, the PAR molecule directly engages with the C-terminus of mitochondrial AIF. Both the PAR polymer and its protein-bound form can act on AIF, leading to AIF release and translocation to the nucleus [38, 41]. Developing small molecule drugs to block the interaction between AIF and PAR is deemed an effective strategy for preventing diseases caused by Parthanatos.

In comparison to extensive studies on PARP-1 and AIF in Parthanatos, MIF has received relatively less attention due to its late discovery in Parthanatos. MIF is a PARP-1-dependent

AIF-mediated nuclease that cleaves DNA into fragments approximately 50,000 bp in size [43]. In Parthanatos, MIF enters the nucleus with the assistance of AIF and exerts its nuclease activity, ultimately contributing to the degradation of large DNA segments [42, 43]. MIF, a versatile protein with various modes of activity, including functions as a proinflammatory cytokine, tautomerase, and oxidoreductase [165], was found to have nuclease activity in 2016, confirming its role as a downstream effector in the Parthanatos cascade [43]. The glutamate residue in the 1st α-helix of MIF is crucial for its nuclease activity, which is independent of its tautomerase or oxidoreductase function. The prospect of creating pharmaceutical agents tailored to selectively inhibit MIF's nuclease activity is promising. Moreover, the use of small molecules acting as allosteric inhibitors of MIF, employing acetylate modifications for MIF, also offer promise by inhibiting the MIF-AIF interaction. This inhibition, coupled with the suppression of MIF translocation, contributes to neuroprotective effects by mitigating Parthanatos [166, 167]. Therefore, inhibition of the MIF-AIF interaction and MIF nuclease activity are also key therapeutic objectives.

Despite numerous promising possibilities, it is important to acknowledge that clinical studies investigating the treatment of neurodegenerative diseases through the inhibition of Parthanatos have not been clearly documented. This approach may present a series of challenges, including concerns about tissue specificity, efficacy, potential side effects, and other factors. However, by thoroughly dissecting the mechanism of Parthanatos and comprehending the essential roles and characteristics of its executors, it offers a solid starting point for the development of structure-based drug design strategies targeting critical proteins within this pathway.

5.2. Structural and functional insights into Parthanatos executors as therapeutic targets

Structural insights into target proteins play a crucial role in the process of therapeutic development. Understanding the three-dimensional structure of a target protein, its complexed structure with the interactive chaperones, any conformational changes, and the binding modes with agonists or antagonists provides valuable information about its function, mechanism of action, and potential binding sites. This knowledge is essential for designing and optimizing drug candidates with high specificity and efficacy. In the Parthanatos pathway, the primary mediators PARP-1, AIF, and MIF have been a focal point of interest as potential protein targets for intervention.

5.2.1 PARP-1 structure and inhibitors—PARP-1 is a notably abundant enzymatic member within the PARP family, primarily localized within the cellular nucleus. It functions as an initial responder, identifying and aiding in the repair of DNA damage [154]. The pivotal role of PARP-1 has gained increased attention, particularly in the context of neurodegenerative diseases marked by progressive neuron loss caused by DNA damage [168]. As briefly mentioned, PARP-1 protein is of 116-kDa and its structure is composed of several distinct domains (Fig. 3A). First is a DNA Binding Domain that is positioned at the N-terminus. This domain encompasses the nuclear localization signal (NLS) and three zinc finger structures, aiding in DNA binding and fostering protein-protein interactions. Second is the automodification domain that contains sites for self-ADP-ribosylation and a BRCA1 C-terminal (BRCT) motif that facilitates protein-protein interactions. Third, a

tryptophan-glycine-arginine-rich (WGR) domain that links two nucleosomes, positioning broken DNA for ligation. The binding of DNA induces structural changes in PARP-1 that signals DNA breaks to its catalytic domain. Fourth, a C-terminal catalytic domain that consisting of the helical domain (HD) and the ADP-ribosyl transferase (ART) domains that as the binding region for the substrate NAD+ during PARP-1-mediated PARylation. In the context of these domains, Zn1, Zn3, WGR, and the catalytic domain are crucial for initiating PARP-1 activation in response to DNA double-strand breaks, whereas Zn2 and BRCT domains are not essential for this process [28, 169]. However, the Zn2 domain is essential for PARP-1 activation in the presence of DNA single-strand breaks, which are prevalent in routine cellular processes [170–172]. The multi-domain assembly of PARP-1 functions as an allosteric switch, releasing the auto-inhibition of the C-terminal catalytic domain through a conformational change. This transition allows PARP-1 to become catalytically active [173]. The dynamic nature of PARP-1 is also highlighted by the potency of some PARP-1 inhibitors in trapping the enzyme at DNA damage sites, which impedes PAR synthesis and DNA repair [174].

While the comprehensive three-dimensional structure of the human PARP-1 protein remains unsolved, detailed information on the structures of individual domains with their DNA-bound states and the binding modes of inhibitors are extensively documented [169, 173, 175, 176]. Pascal et al., reported crystal structures of DNA double-strand breaks in complex with the individual Zn1 and Zn2 domains. The structure demonstrated a novel bipartite mode of sequence-independent DNA interaction through the Zn1-DNA and Zn2-DNA [177–179].structures. Reconfiguration of a specialized region of the Zn1 domain through a hydrophobic interaction with exposed nucleotide bases initiates activation of PARP-1 [176]. The same group solved “the crystal structure of a DNA double-strand break in complex with human PARP-1, Zn1, Zn3, and WGR-CAT. The Zn1, Zn3, and WGR domains collectively bind to DNA, forming a network of interdomain contacts that link the DNA damage interface to the catalytic domain, inducing structural distortions that destabilize the CAT” [173]. Rudolph et al. reported how the BRCT domain of PARP-1, which was not previously recognized as a DNA-binding domain, is selectively involved in binding intact DNA. They also reported its cryo-EM structure in a complex with a nucleosome [180]. However, this domain did not result in the conformational change and activation of the catalytic domain. The interaction of DNA with Zn1, Zn3, and the WGR domain triggers conformational alterations in both the HD and ART domains through inter-domain interactions, orchestrating the regulatory signal. The DNA-bound complex crystal (4DQY) proved that the Zn1-Zn3 interface is vital for the allosteric modulation but not directly important for DNA binding (Fig. 3A) [178]. Mutations on the WGR, HD, and Zn3 domain, which damage the interaction surfaces between them, impair PARylation activity [177]. In the PARP-1 CAT domain, the enzymatic pockets that bind NAD+ and catalyze ADP-ribosylation include the key catalytic residues H862, Y896, Y907 and E988, according to the crystal structure 6BHV binding an NAD+ analog [179].

Effective inhibition of PARP-1 activity is an attractive target for the treatment of Parthanatos-associated diseases. PARP-1 represents an important upstream signal in Parthanatos cascade reactions, and PARP-1 inhibitors hold great potential for the neurological treatment of these disorders. Development of PARP-1 inhibitors has been

focused primarily on cancer treatment via PARP-1 trapping, impeding DNA damage repair, and inducing cell death [181, 182]. Co-crystal structures of PARP-1 bound with inhibitors indicates that these compounds imitate the nicotinamide structure found in NAD+ and attach to the nicotinamide and adenosine binding regions within the CAT structural domain of PARP-1 [174]. This leads to the competitive inhibition of PARP-1 activity. PARP-1 inhibitors not only bind to PARP-1, but they also trap DNA, thereby preventing base excision repair (BER) and converting single-strand breaks (SSBs) to double-strand breaks (DSBs). Additionally, they indirectly induce the phosphorylation of DNA-dependent protein kinase substrates necessary for non-homologous end joining (NHEJ) and obstruct replication, resulting in replication fork collapse and subsequent cell death [174]. Several PARP inhibitors are approved by the United States FDA for clinical cancer treatment, including olaparib, rucaparib, niraparib, and talazoparib, which are potent PARP-1 DNA trappers (Fig. 3B) [183, 184]. Inhibition of DNA repair is likely to be an undesirable side effect, as PARP-1 inhibition is intended to cause cell death in cancer cells with BRCA mutations. This dichotomy has stunted the use of PARP-1 inhibitors in clinical trials for neurodegenerative disease and stroke [185]. Hence, future development of PARP-1 inhibitors should be focused on interfering with PARP-1 catalytic activity and avoidance of DNA trapping [186]. Consistent with this notion, current PARP-1 inhibitors, in addition to being potent DNA trappers, reduce PAR polymer formation, maintain NAD+ and ATP levels, prevent mitochondrial dysfunction, and inhibit AIF release, culminating in suppressed neuronal death and alleviated neuroinflammation in neurodegenerative diseases [167, 168]. For instance, pathological α-synuclein stimulates PARP-1, hastening the creation of pathologic α-synuclein leading to cell death via Parthanatos. In primary cortical neurons, the PARP-1 inhibitors, veliparib, rucaparib, and talazoparib, were effective in averting α-synuclein PFF-induced PARP-1 hyperactivation and subsequent cell death [51]. Veliparib was observed to diminish cell death mediated by TDP43 in spinal cord cultures and olaparib mitigated cytotoxic effects induced by TDP43 in motor neuron cells within ALS models [11, 120]. However, the complete three-dimensional structure of PARP-1 remains elusive, posing limitations and knowledge gaps for advancing structure-based drug development targeting PARP-1 for Parthanatos inhibition. Further progress in cryo-electron microscopy and AI-assisted structural biotechnology may significantly contribute to resolving this issue.

5.2.2 AIF structure and inhibitors—AIF is a multifaceted protein that undergoes translocation from the mitochondria to the cytoplasm and subsequently to the nucleus, where it facilitates chromatin condensation and DNA degradation, ultimately culminating in cell death. It serves as a pivotal mediator in Parthanatos, particularly in response to exposure of DNA-damaging toxins like MNNG, NMDA, or oxidative stress [8, 9, 187]. Beyond its pro-cell death role, AIF holds significant physiological importance within the mitochondria. Under normal conditions, AIF functions as an oxidoreductase, relying on NADH and its binding to FAD, where it contributes to the maintenance of mitochondrial structural integrity [188]. AIF also plays a crucial role in sustaining mitochondrial oxidative respiratory chains and energy metabolism [189]. The precursor gains entry into the mitochondria exclusively when it is in a non-native configuration, indicating that its folding process in the cytoplasm is either inhibited or delayed [190, 191]. Only the non-native precursor forms of AIF can penetrate the mitochondria, and upon refolding, exhibit cell death related activity regardless

of its FAD binding status [188, 192]. The cellular functions related to AIF's induction of Parthanatos can be distinguished from its involvement in mitochondrial respiration and the maintenance of cell viability [6, 187]. AIF's multifaceted functionality is intricately tied to its distinctive structure.

The AIF gene encodes a 67-kDa polypeptide that is directed into the mitochondria, where it undergoes processing that results in protein anchoring to the inner mitochondrial membrane [192, 193]. More precisely, proteolytic cleavage occurring between Met53 and Ala54 generates a mature 62-kDa variant of AIF, predominantly situated within the mitochondrial intermembrane space [194]. AIF is released from the mitochondria via two distinct mechanisms. In the setting of Parthanatos, PAR generated by PARP-1 activation translocate from the nucleus to the mitochondria where it binds the extramitochondrial 62-kD AIF leading to a conformational change, and mitochondrial AIF release, and subsequent translocation to the nucleus [38]. The intramitochondrial AIF is released from the mitochondria in response to cell death stimuli that induce mitochondrial membrane depolarization and permeabilization. This occurs via cysteine protease cleavage of AIF at the Leu101/Gly102 site, resulting in the removal of a 50 amino acid segment at the N-terminus, generating a soluble mature AIF with a molecular weight of 57 kD. This 57-kD processed AIF is released from the mitochondria, exiting into the cytoplasm from the intermembrane space [194]. Both the 62-kD and 57-kD are transported into the nucleus through the presence of two NLS on AIF (Fig. 4A) [192, 194]. Human AIF is comprised of 613 aa, whereas mouse AIF consists of 612 aa, reflecting an impressive 92% sequence homology and a conserved three-dimensional structure, as confirmed by crystallographic structure analyses (Fig. 4B) [195, 196]. AIF seems to have evolved distinct binding characteristics for DNA and PAR. The interaction between AIF and PAR exhibited high affinity and saturable binding kinetics. The major PAR binding site within AIF was identified as residing within amino acids 567–592, localized within the D3 domain of the protein [38].

The nuclear translocation of the AIF-MIF complex constitutes a crucial stage in Parthanatos [43]. Although a definitive AIF inhibitor that can prevent AIF's migration from the mitochondria to the nucleus remains elusive, an increasing body of research is dedicated to elucidating this mechanism to enhance the development of targeted intervention approaches. In the context of hypoxic-ischemic conditions, neurons deficient in Cyclophilin A (CypA) were unable to demonstrate the nuclear translocation of AIF, underscoring the vital role played by CypA in facilitating this process [197, 198]. Gurbuxani et al. uncovered a specific direct interaction between cytoplasmic HSP70 and AIF, which hindered AIF's ability to migrate to the nucleus [199, 200]. Deletion mutations in AIF, such as AIF△150–268, AIF△122–262, and site mutations R192A and K194A, demonstrated a robust capacity for nuclear transport once their interaction with HSP70 was disrupted. These data support that AIF, released from mitochondria into the cytoplasm, relies not only on its intrinsic NLS but also on the assistance of CypA for effective nuclear translocation, while highlighting the inhibitory role of HSP70 in this process [199]. Additionally, the discovery that PAR binds to AIF's C-terminal region offers insights into a potential therapeutic approach: preventing PAR binding to AIF. The amino acids Arg588, Lys589, and Lys592 in AIF's structure play a pivotal role in PAR binding [38]. Mutating these residues to Ala or Leu significantly disrupt the interaction between PAR and AIF. While the interactive interface between MIF

and AIF has been postulated, complex structures have yet to be elucidated [43, 166]. Inhibiting the binding of MIF to AIF could potentially impede MIF's nuclear translocation and the subsequent cascade of reactions in Parthanatos. Furthermore, selectively obstructing the interaction between AIF and CypA holds the potential to impede AIF's translocation into the nucleus [198]. Peptides designed to inhibit AIF binding to human CypA have been developed, serving as promising neuroprotective agents by acting as CypA ligands to obstruct AIF binding [201].

5.2.3 MIF structure and inhibitors—MIF was first identified in 1966 when researchers discovered a protein in the culture supernatant of activated T lymphocytes that inhibited macrophage migration, leading to its name, "macrophage migration inhibitory factor" (MIF) [202]. It is a pivotal proinflammatory cytokine that exhibits ubiquitous expression in diverse cell types and tissues. Beyond its well-established role in mediating inflammation and innate immunity, extensive research has illuminated MIF's influence on an array of cellular processes. These include modulation of cell migration, chemotaxis, and growth, inhibition of p53-dependent cell death, and promotion of cell proliferation [165, 203]. Such multifaceted actions underscore MIF's pleiotropic impact on both physiological and pathological processes.

MIF demonstrates substantial interspecies homology, boasting a 90% sequence similarity between human and rodent-derived variants. In contrast, D-dopachrome tautomerase (MIF-2/D-DT) exhibits a comparatively lower homology, with approximately 30% sequence similarity to MIF [203, 204]. The MIF monomer is a ~12 kD protein comprising 115 amino acids, characterized by the presence of two antiparallel α-helices and a four-stranded β-folded sheet that forms a barrel-like structure featuring a prominent solvent-permeable channel at its core (Fig. 4C) [205]. Similar structural determinations have been reported for MIF in other species [206–208]. The distinctive 3D structure of MIF has been associated with its *in vitro* oxido-reductase activity and keto-enol tautomerase activity, with the enzyme's active site situated within the hydrophobic pocket between adjacent subunits. The crystallographic examination using X-ray resolved the structure of the MIF complex bound to the substrate 4-hydroxyphenylpyruvate (4-HPP) [209]. This substrate has been widely employed in small molecule inhibitor studies targeting MIF's tautomerase activity. Critical amino acid residues in the active pocket include proline at the N-terminal position 2, lysine at position 33, isoleucine at position 65, tyrosine at position 96, and asparagine at position 98, with most being conserved. Lys33 and Ile65 form electrostatic and hydrogen bonding interactions with 4-HPP, respectively. Aromatic residues like Tyr37, Tyr96, and Phe114 engage in π-π interactions with the ligand. Asn98, located on the binding site's opposite side, forms a hydrogen bond with 4-HPP. The substrates utilized, including D-dopachrome and 4-HPP, are non-physiological. Enzymatically active substrates under physiological conditions remain unidentified [210]. Efforts to develop small molecule inhibitors targeting its tautomerase activity have been extensively pursued as therapeutic strategies to block MIF's proinflammatory function.

Numerous small molecule inhibitors targeting MIF's tautomerase activity can be broadly categorized into five groups. (1) Tautomerase substrate analogs like ISO-1 [211]; (2) Small molecules discovered through computational methods, including coumarins,

benzoxazolones, and pyrazole-based compounds [212, 213]; (3) Inhibitors identified via high-throughput screening, such as ebselen and p425 [214]; (4) Clinically approved drugs, including ibudilast and iguratimod [215–218] ; and (5) Natural products, like flavonoids and epoxyazadiradione [217–219]. Despite the significant progress in developing small molecule MIF tautomerase inhibitors, clinical trials in this field are still in their early stages, primarily due to lower-than-anticipated potency or the emergence of undesirable side effects [210]. The development of additional MIF tautomerase inhibitors still remains necessary. To date, a diverse range of small molecule inhibitors targeting MIF's tautomerase activity has been documented. Insights from structural biology have elucidated multiple molecular mechanisms by which these inhibitors diminish or disrupt MIF's tautomerase activity. These mechanisms include competitive inhibition through binding to the MIF active site, allosteric inhibition, covalent modification of the catalytic center at Pro2, and the induction of MIF trimer disassembly by certain small molecules [210].

The recent discovery of MIF's nuclease activity offers new opportunities for innovative screening methods and expands the potential for identifying inhibitors related to Parthanatos and neuroinflammatory pathways. In 2016, it was discovered that MIF possesses nuclease activity during its involvement in Parthanatos, where it interacts with AIF [43]. MIF's nuclease functionality is attributed to its possession of three PD-D/E(X)K superfamily domains, which are prevalent in numerous nucleases. Additionally, MIF features a CxxCxxHx(n)C zinc finger domain, a common structural motif found in proteins involved in DNA damage responses. MIF preferentially binds to stem-loop single-stranded DNA and preferentially cleaves single-stranded DNA (ssDNA) with protruding 3' ends [43, 220]. The crux of MIF's nuclease activity resides in the E22 site within the PD-D/E(X)K domain, identified as the most crucial element for MIF's nuclease function through 3D modeling. Knockout of MIF, nuclease deficient MIF, or the MIF nuclease inhibitor, PAANIB-1 effectively prevents Parthanatic cell death in cellular and animals models [4, 42]. Thus, MIF's role as a nuclease upon translocation into the nucleus is pivotal in the progression of Parthanatos. PAANIB-1 exclusively affects MIF's nuclease function, avoiding interference with its other roles indicating that MIF's tautomerase and cytokine activities are separated from its nuclease activity [4, 42, 221]. This MIF nuclease selectivity minimizes potential side effects related to altering MIF's multifunctionality. The discovery that MIF's nuclease activity is druggable without interference with other MIF functions, highlights the potential of MIF nuclease activity as a viable important pharmacological target for addressing neurodegenerative diseases and ischemic damage associated with Parthanatos.

5.3. Strategies for novel neuroprotective drug development targeting PAAN/MIF

The identification of the first MIF nuclease inhibitor, PAANIB-1, originated from a high-throughput screening of a rapafucin library, inspired by rapamycin and containing 45,000 macrocyclic compounds [222] based on MIF's nuclease activity [42]. Rapamycin is a natural macrocyclic lactone antibiotic produced by bacteria *Streptomyces hygroscopicus*. It is an FDA-approved immunosuppressant drug with antifungal and antitumor effects, also indicated for organ rejection prophylaxis in transplant patients with a high safety provide [223]. Following MIF nuclease inhibitory assays and Parthanatos inhibition screening, PAANIB-1 emerged as a relatively potent and highly selective inhibitor of MIF nuclease

activity and Parthanatos. Additionally, it crossed the blood brain barrier and performed well in orthogonal animal models of PD by preventing the loss of DA neurons and neurobehavioral deficits in the intrastriatal α-syn PFF model, AAV human α-syn midbrain injection model, and the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxication model of PD [223].

In addition to advancement of PAANIB-1 along conventional investigational new drug (IND) enabling studies, PAANIB-1 can serve as a structural foundation, providing a crucial backbone for subsequent modification and optimization of MIF nuclease inhibition. Utilization of X-ray crystallography and cryo-electron microscopy (cryo-EM) of PAANIB-1 bond to MIF will enable thorough analysis of atomic-level interactions, providing a solid theoretical foundation for subsequent structure optimization and improvements in activity and selectivity. Admittedly, the incomplete characterization of the pharmacological properties of PAANIB-1, including its specificity, metabolism, and specific binding modes, suggests that there is still considerable groundwork required before it can advance to clinical development. Meanwhile, expanding the chemical library of MIF nuclease inhibitors is warranted as it will provide additional chemical scaffolds that selectively target MIF nuclease inhibition. Once three-dimensional complex structures are solved, computer- and AI-assisted virtual screening for ligands at PAANIB-1 binding sites and MIF-AIF interacting surfaces will be promising tools for developing additional MIF nuclease and Parthanatos cell death inhibitors.

6. Conclusion

Parthanatos is a regulated cell death pathway, in which overactivation of PARP-1 in response to DNA damage, results in the accumulation of PAR polymers. PAR exits the nucleus with the help of carrier, H1.2. Subsequently, extramitochondrial AIF binds to PAR and translocates from the mitochondria to the cytosol, where it forms a complex with MIF. HDAC6 prevents MIF acetylation, enabling the formation of the AIF-MIF complex formation. The AIF-MIF complex then enters the nucleus, leading to extensive genomic DNA fragmentation through the nuclease activity of MIF. Parthanatos triggers the activation and recruitment of microglia and astrocytes, playing a significant role in neuroinflammation through pathways such as cGAS/STING/NLRP3 and the activation of the AIM2-ASC inflammasome. Neuroinflammation is a crucial hallmark of neurodegenerative disease. Parthanatos is also implicated in stroke and various neurodegenerative disorders, including AD, PD, HD, ALS. Consequently, targeting Parthanatos has emerged as a promising approach for neurodegenerative and stroke therapeutics. In-depth understanding of the molecular structures and functions of Parthanatos executors, including PARP-1, AIF, and MIF, holds great potential for the development of novel neuroprotective drugs for neurodegenerative diseases. Exploring MIF's nuclease activity as a therapeutic target involves employing various methodologies, such as: structure-based analysis, computer and AI-assisted virtual screening, screening of additional compound libraries. These strategies hold the potential to provide valuable insights and lead compound candidates for the inhibition of Parthanatic cell death.

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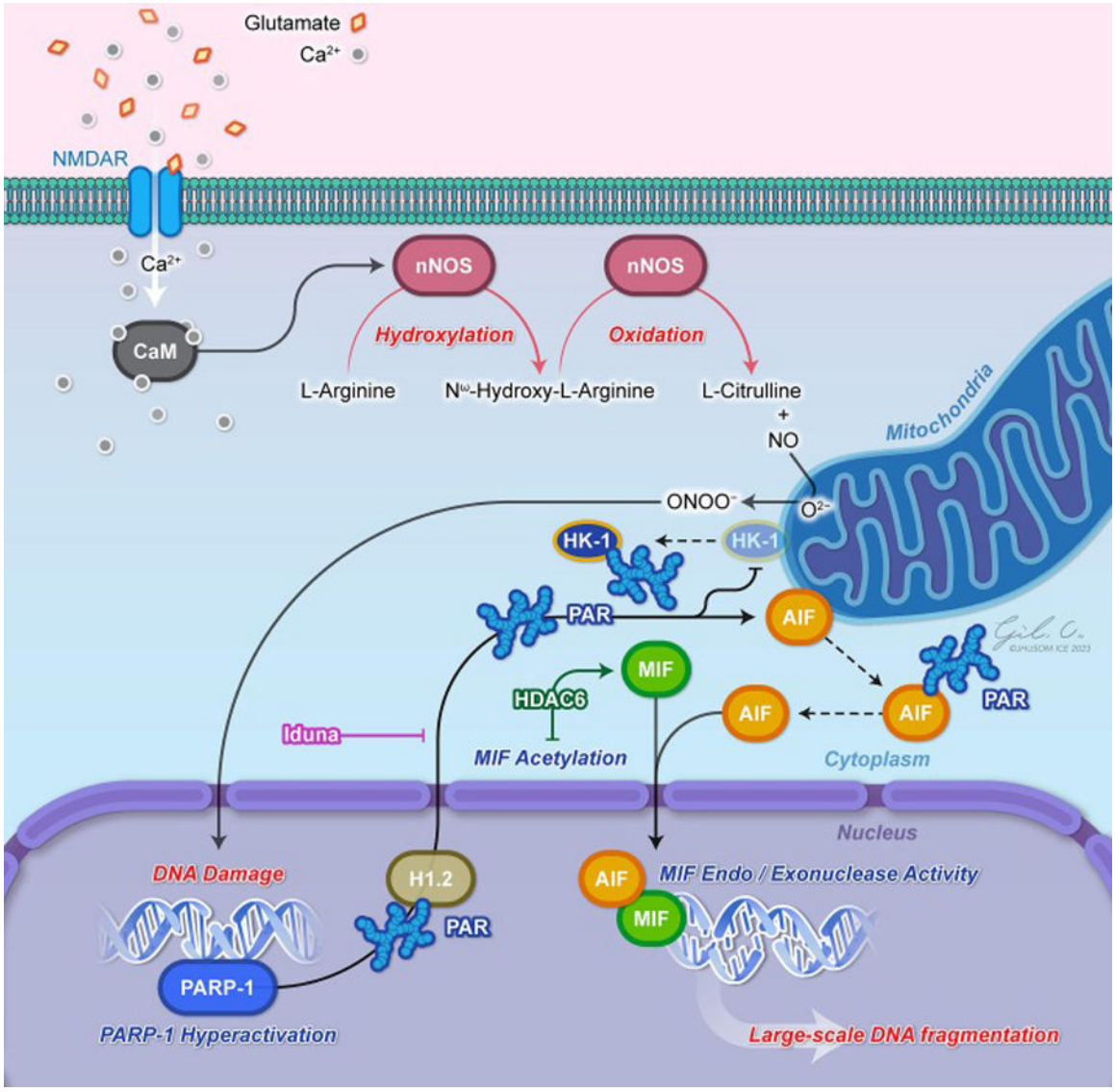

Fig 1. Parthanatos cell death mechanism.

Parthanatos can be initiated by glutamate excitotoxicity which permits excessive influx of Ca^{2+} through NMDARs. Once Ca^{2+} reaches the cytosol, it forms a complex with calmodulin (CaM), which activates nNOS. nNOS hydroxylates L-arginine into N^{ω}-hydroxy-L-arginine, then oxidizes N^{ω}-hydroxy-L-arginine into L-citrulline and NO. NO reacts with superoxide anion ($O_2^{\cdot -}$) in the mitochondria to produce peroxynitrite ($ONOO^-$). $ONOO^-$ moves from the cytosol into the nucleus and induces DNA damage, hyperactivating PARP-1. PARP-1 hyperactivation results in the production of large and branched PAR polymers. H1.2 acts as a carrier for PAR out of the nucleus and into the cytosol, while Iduna can inhibit its translocation. Once PAR reaches the cytosol, it binds to HK-1, causing the release of HK-1 from the mitochondria. PAR-HK-1 binding results in glycolytic impairment and the inability to generate NAD+, leading to energy failure. PAR also binds AIF located on the cytosolic portion of the mitochondria causing AIF's release from the mitochondria where it binds to MIF and recruits it to the nucleus as a unit. HDAC6 prevents MIF acetylation, which

allows for AIF/MIF binding and translocation to the nucleus. Once the AIF/MIF complex reaches the nucleus, MIF uses both its endonuclease and exonuclease activity to cleave DNA, resulting in large-scale DNA damage and subsequent cell death.

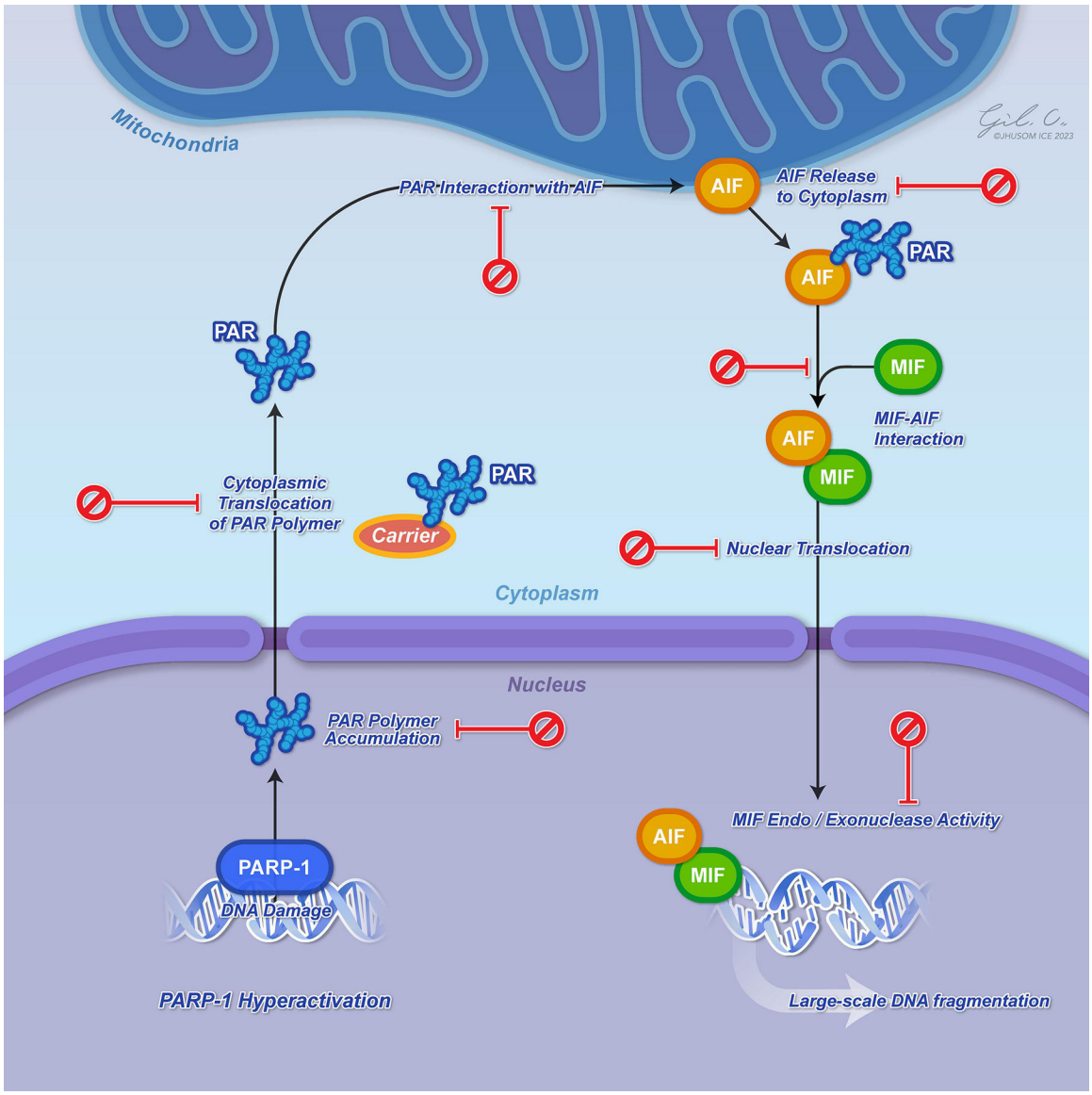

Fig 2. Overview of the intervention points in Parthanatos.

Potential inhibitory targets in Parthanatos include the attenuation of PARP-1 hyperactivation, the disruption of PAR polymer formation and its subsequent translocation into the cytoplasm, the containment of AIF release into the cytoplasm, the interference with the interaction between AIF and MIF, their subsequent nuclear translocation, and the inhibition of MIF's nuclease activity.

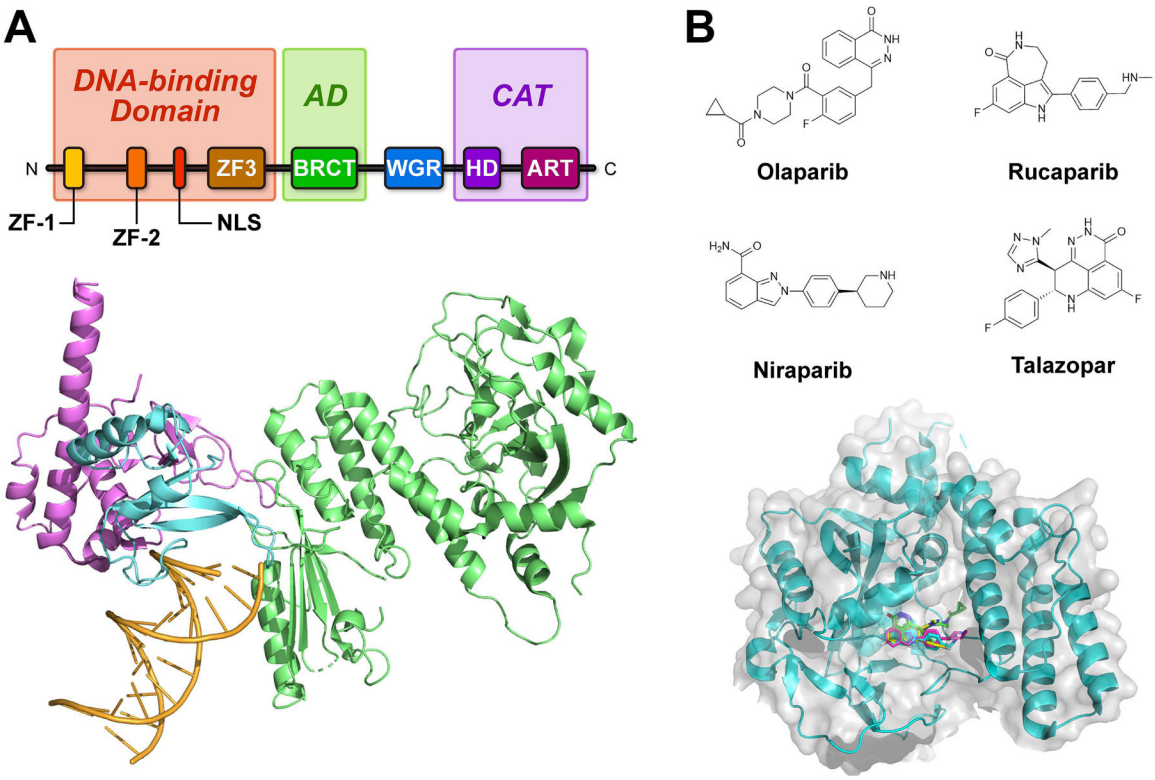

Fig 3. Human PARP-1 structure and inhibitors.

(A) PARP-1 protein domains contain an N-terminal DNA-binding domain with three zinc finger motifs and an NLS, a central automodification domain (AD) with a BRCT motif for protein-protein interaction and glutamate and lysine residues for self ADP-ribosylation, a WGR motif responsible for DNA binding, a C-terminal catalytic domain (CAT) that contains a helical (HD) and ART domain that encompasses the active NAD+-binding site during PARP-1-mediated PARylation. 3D protein structure of PARP-1 bound to DNA (below, PDB: 4DQY) was generated by PyMOL [224]. Zn1 (blue), Zn3 (meganta), WGR and CAT domains (green) are shown in bound with a dsDNA (orange). (B) Four FDA-approved PARP-1 inhibitors. The structural superposition of these four PARP-1-inhibitor complexes is illustrated. Protein structure is shown in light grey surface representation. Olaparib is represented as green sticks (PDB: 7KK4), rucaparib as blue sticks (PDB: 6VKK), niraparib as magenta sticks (PDB: 7KK5), and talazoparib as yellow sticks (PDB: 7KK3). All of these inhibitors bind to the CAT domain of PARP-1.

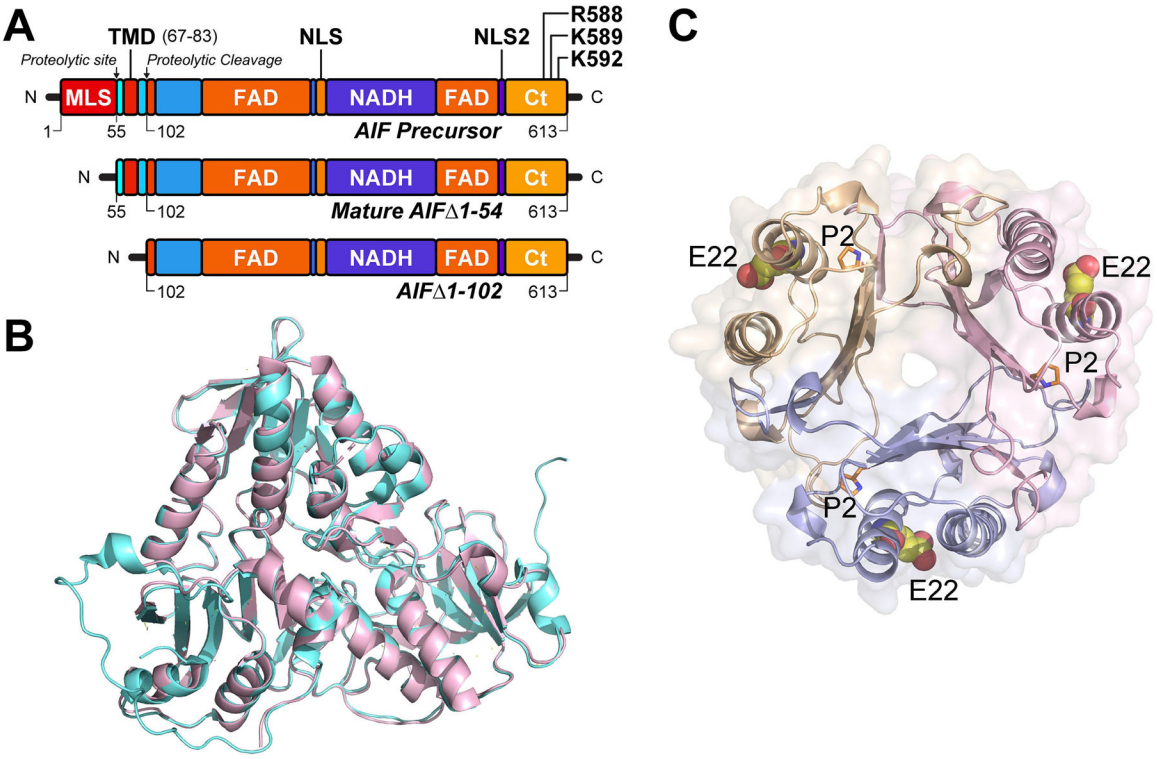

Fig 4. AIF and MIF structures.

(A) Overview of Human AIF structures, encompassing the precursor, mature, and truncated apoptogenic forms. (B) A three-dimensional structure superposition of human AIF (pink, PDB: 1M6I) and mouse AIF (blue, PDB: 1GV4). (C) The three-dimensional structure of human MIF (PDB: 1MIF) is presented in light grey surface representation. Tautomerase activity sites are visualized as orange sticks, and the critical residue E22, responsible for MIF nuclease activity, is represented as a yellow sphere. This figure was generated using PyMOL [224].