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PARkinson's: From cellular mechanisms to potential therapeutics

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ABSTRACT

Our understanding of the progression and mechanisms underlying the onset of Parkinson's disease (PD) has grown enormously in the past few decades. There is growing evidence suggesting that poly (ADP-ribose) polymerase 1 (PARP-1) hyperactivation is involved in various neurodegenerative disorders, including PD, and that poly (ADP-ribose) (PAR)-dependent cell death is responsible for neuronal loss. In this review, we discuss the contribution of PARP-1 and PAR in the pathological process of PD. We describe the potential pathways regulated by the enzyme, review clinically relevant PARP-1 inhibitors as potential disease-modifying therapeutics for PD, and outline important factors that need to be considered for repurposing PARP-1 inhibitors for use in PD.

Contents

1. Introduction

Poly-ADP-ribose polymerase-1 (PARP-1), a 116 kDa nuclear protein, was the first member of the PARP family to be identified (Malapetsa et al., 1996). It consists of three functional domains, a DNA-binding domain, an auto-modification domain, and a catalytic domain; this enzyme plays a multitude of roles within the cell, including a central role in attracting DNA repair proteins to sites of DNA damage (Alemasova & Lavrik, 2019). PARP-1 utilizes NAD^+ as a substrate to catalyze the covalent addition of poly (ADP-ribose) (PAR) onto a wide array of acceptor proteins in a process known as PARylation (Hassa, Haenni, Elser, & Hottiger, 2006). During PARylation, adenosine diphosphate ribose (ADP-ribose) is covalently transferred onto glutamate, aspartate, or arginine residues on target proteins (Vyas, Chesarone-Cataldo, Todorova, Huang, & Chang, 2013). Recent findings have revealed that serine is also an important target residue for ADP-ribosylation under both DNA-damage and basal conditions (Larsen, Hendriks, Lyon, Jensen, & Nielsen, 2018; Leidecker et al., 2016). Notably, HPF1, a cofactor of PARP-1 and PARP-2, plays an essential role in promoting serine modification by providing an additional catalytic residue (Glu284 of HPF1), thus completing the PARP active site (Bonfiglio et al., 2017; Gibbs-Seymour, Fontana, Rack, & Ahel, 2016; Sun et al., 2021; Suskiewicz et al., 2020). PARylation is a reversable posttranslational

Abbreviations: ADP, adenosine diphosphate; HPF1, histone PARylation factor 1; PARG, poly(ADP-ribose) glycohydrolase; ARH3, ADP-ribose-acceptor hydrolase 3; NAD, nicotinamide adenine dinucleotide; TNF, tumor necrosis factor; IL, interleukin; LRRK2, Leucine-rich repeat kinase 2; PINK1, PTEN-induced kinase 1; SNpc, substantia nigra; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; 6-OHDA, 6-hydroxydopamine; AMPK, AMP-activated protein kinase; CREB, cyclic adenosine monophosphate response element-binding protein; RNF146, E3 ubiquitin ligase Really Interesting New Gene finger protein 146; BRCA, breast cancer gene.

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modification of proteins, where PAR degradation is mainly catalyzed by PARG (Feng & Koh, 2013; Pascal & Ellenberger, 2015), although recent discoveries indicate another PAR degradation pathway as well, catalyzed by ARH3 (Fontana et al., 2017; Mashimo, Kato, & Moss, 2013).

PARP-1 is involved in the base excision repair (BER) pathway, where it plays a role in the recognition of single-stranded breaks (SSBs) in DNA and mediates the recruitment of core factors to process the repair (Chaudhuri & Nussenzweig, 2017) (Fig. 1). PARP-1 has been implicated in other DNA damage repair pathways as well (Javle & Curtin, 2011), including nucleotide excision repair (NER), homologous recombination (HR), and non-homologous end joining (NHEJ).

Outside of its role in DNA repair, PARP-1 has been linked to chromatin modification and transcription regulation, whereby, the PARP-1/PAR complex interacts with histones and chromatin-associated factors; thereby, modulating chromatin structure and transcription regulation (Kraus & Hottiger, 2013). PARP-1 has been shown to function as a histone chaperone via PARylation of the H3A-H2B and H3-H4 histone complexes (Muthurajan et al., 2014); furthermore, PARP-1 binding to core histones has been reported to increase nucleosomal repeat length (Messner et al., 2010). While covalent interactions between PAR and PARP-1 targets have been heavily studied (Bowman & Poirier, 2015), it has also been shown that the polyanionic nature of PAR is sufficient to destabilize nucleosomes (Huletsky et al., 1989; Martinez-Zamudio & Ha, 2012; Realini & Althaus, 1992), indicating that covalent PARylation is not the only mode by which PARP-1 can regulate cellular processes.

In pathological settings, PARP-1 expression and activity are most commonly associated with human malignancies (Deshmukh & Qiu, 2015; Wang et al., 2016; Wei, Li, Lv, Zhang, & Tian, 2016); however, several lines of evidence point to an association of this enzyme in a variety of pathophysiological conditions involving inflammation (Ba & Garg, 2011; Rosado, Bennici, Novelli, & Pioli, 2013). Several studies have shown that PARP-1 plays a key role in up-regulating the expression of pro-inflammatory genes (Ba & Garg, 2011). For example, in a PARP-1 deficient mouse model of colitis-like inflammation, the mRNA and protein expression levels of TNFα and IL-17 were significantly reduced compared to WT mice; moreover, these mice presented with milder histopathologic changes, suggesting that absence of PARP-1 weakened their inflammatory immune response (Larmonier et al., 2016). A different study reported that PARP-1 expression was upregulated in a rat model of eccentric exercise-induced skeletal muscle damage, along with other pro-inflammatory markers, including cyclooxygenase-2, IL-1β, IL-6, TNF-α, and monocyte chemotactic protein-1 (Chiang et al., 2009). Furthermore, deletion of PARP-1 was shown to impair the immune response of ovalbumin-challenged mice, whereby, these mice presented with reduced production of IL-5, IL-10, IL-13, and granulocyte macrophage colony-stimulating factor (Ba & Garg, 2011). Altogether, these studies demonstrate that PARP-1 functions as a switch modulator that activates and represses transcription regulation and directly affects the cellular response to inflammation.

In addition to chronic and acute inflammation, PARP-1 hyperactivity has been linked with neurodegenerative disorders. Studies have shown that increased levels of PAR promote irreversible aggregation of intrinsically disordered proteins (IDP) (Altmeyer et al., 2015) and the association of PAR and protein aggregates may serve as a feed-forward mechanism that amplifies neurotoxicity and drives neurodegeneration (Kam et al., 2018). While the possible role of PARP-1 in diseases like Amyotrophic lateral sclerosis (ALS) (McGurk et al., 2018), Alzheimer's (AD) (Strosznajder, Czapski, Adamczyk, & Strosznajder, 2012) and Huntington diseases (HD) (Liu & Fang, 2019) have been already established,

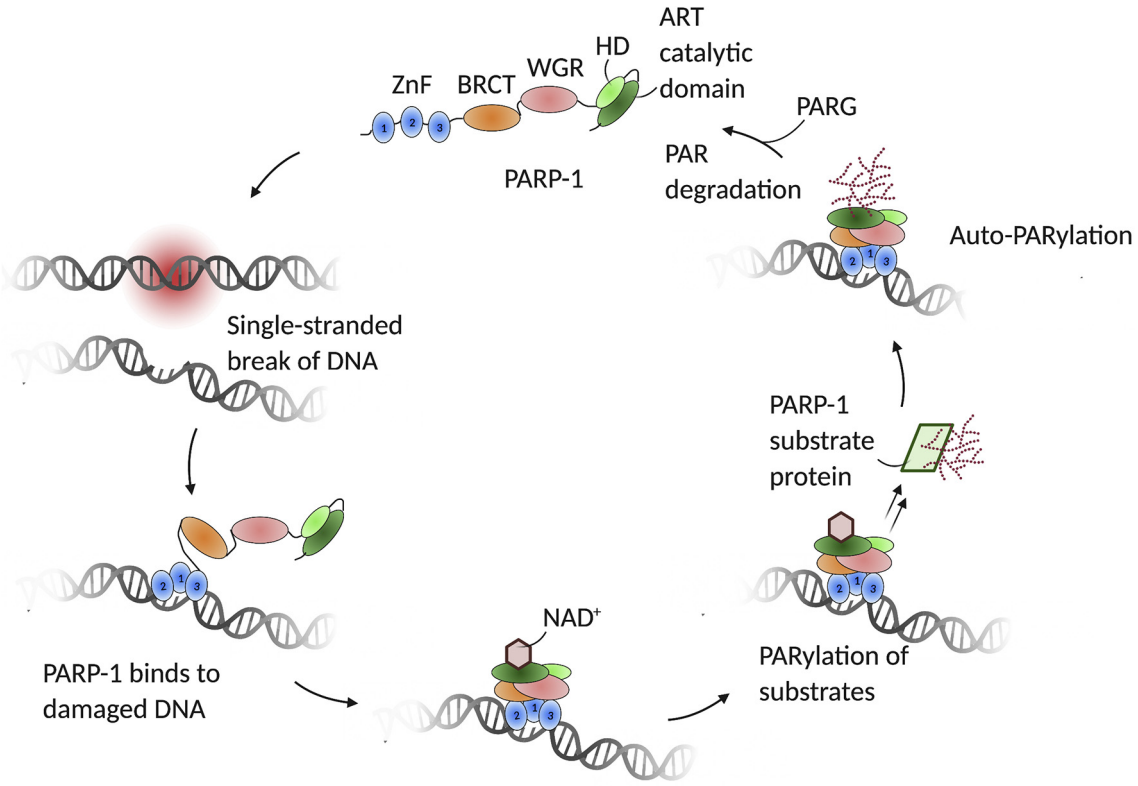

Fig. 1. Schematic model describing domain structure of PARP-1 and its catalytic cycle. PARP-1 consists of three zinc-finger related domains (ZnF 1, 2 and 3), the C-terminus domain (BRCT), the tryptophan-, glycine-, arginine-rich domain (WGR) and the catalytic domain with two subdomains, a helical domain (HD) and an ADP-ribosyltransferase (ART) catalytic domain. DNA damage results in PARP-1 binding to the damaged site and allosteric activation of the enzyme upon change in HD conformation (Altmeyer, Messner, Hassa, Fey, & Hottiger, 2009; Langelier, Planck, Roy, & Pascal, 2012). Next, PARP-1 substrate proteins are PARylated, mediating the recruitment of core factors to process the repair. Finally, PARP-1 auto-PARylation causes the release of the enzyme from DNA.

only recent advances have linked PARP-1 to the disease mechanism of Parkinson's disease (PD).

PD is the second most common neurodegenerative disorder, first described by James Parkinson nearly 200 years ago (Parkinson, 2002). Today millions of people worldwide are living with PD and it is estimated that the number of patients within the US will rise to approximately 1,238,000 by 2030 (Marras et al., 2018). The prevalence of PD increases with age such that it affects about 5% of individuals who are 85 years of age and older compared to 1% of people who are 65 years of age (Lee & Trojanowski, 2006). PD is characterized clinically by cognitive and motor impairments that include resting tremor, bradykinesia, and increased muscle tone. Characteristic neuropathology features of PD are the loss of pigmented dopaminergic neurons in the substantia nigra and the abnormal accumulation of α-synuclein (αSyn) in cytoplasmic and neurotic inclusions (known as Lewy bodies and Lewy neurites, respectively). αSyn is a 140 amino acid long, highly soluble, intrinsically disordered protein, that is predominantly localized to presynaptic terminals (Cookson, 2005). The exact function of this protein is still a mystery waiting to be solved, though there are several studies offering plausible explanations (Chandra, Gallardo, Fernandez-Chacon, Schluter, & Sudhof, 2005; Emamzadeh, 2016; Jin et al., 2011; Rodriguez-Araujo et al., 2013). Studies in songbirds, indicate that it may be involved in synaptic plasticity (George, Jin, Woods, & Clayton, 1995), while another report suggests that αSyn may mediate SNARE complex assembly and functions as a molecular chaperone for these complexes (Burre et al., 2010). Nevertheless, αSyn is a key player in PD as its fibrillated form is the major component of Lewy bodies and Lewy neurites. Furthermore, point mutations and multiplications of *SNCA* (the gene encoding αSyn) have been linked to familial forms of PD. Other genes that have been implicated in familial PD include *LRRK2*, *DJ-1*, *PINK*1 and *Parkin* (reviewed in reference (Klein & Westenberger, 2012)) and mutations in these genes can alter the onset and progression of the disease.

While our understanding of the mechanism and progression of PD have greatly increased in the last 20 years, many cellular mechanisms, including the driving force of assembly of pathologic αSyn and cell death mechanisms (Guiney, Adlard, Bush, Finkelstein, & Ayton, 2017; Venderova & Park, 2012), remain to be fully elucidated. Here, we review recent advances in understanding the role of PARP-1 in Parkinson's disease onset and progression, as well as, the implications for employing PARP-1 inhibitors (PARPi) as disease-modifying therapies for PD. We aim to highlight the possible role of PARP-1 in Parkinson's disease to further the understanding of disease mechanism and progression, which will be important for developing appropriate treatments.

2. The role of PARP-1 in disease mechanism and progression

Mounting evidence suggests that PARP-1 and PAR play crucial roles in various non-oncological diseases, including arthritis (Gonzalez-Rey et al., 2007), irritable bowel syndrome (Peralta-Leal et al., 2009), diabetes (Obrosova et al., 2004), and neurodegenerative disorders. For instance, increased PARP-1 expression and elevated levels of PAR were reported in the brains of ALS patients (Kim et al., 2004; McGurk, Mojsilovic-Petrovic, Van Deerlin, Shorter, et al., 2018). Furthermore, recent studies report that phase separation of ALS-associated proteins, TAR DNA binding protein of 43 kDa (TDP-43) and heterogeneous nuclear ribonucleoprotein A1 (hnRNP A1), are regulated by PAR-binding (Duan et al., 2019). These proteins accumulate in the cytoplasm of neurons and glia cells and are recruited into stress granules via liquid-liquid phase separation, a process promoted by PAR binding (McGurk, Gomes, Guo, Shorter, & Bonini, 2018). This abnormal aggregation and neurotoxicity of TDP-43 and hnRNP A1 can be mitigated by PARPi (McGurk, Mojsilovic-Petrovic, Van Deerlin, Shorter, et al., 2018).

Treatment with PARPi has shown promising results in other neurodegenerative diseases as well, such as HD and AD. In one study, HD R6/2 transgenic mice were treated with the PARPi INO-1001 and displayed increased longevity and decrease in signs of neurological dysfunction, compared to the control mice (Cardinale, Paldino, Giampà, Bernardi, & Fusco, 2015). Additionally, in patients with HD, elevated levels of PARP-1 expression were detected in neurons and glial cells (Vis et al., 2005). Similar results were reported for AD cases; whereby hyperactivation of PARP-1 led to the accumulation of PAR in the brain and highlighted the potential neuroprotective effects of PARPi (Abeti, Abramov, & Duchen, 2011; Kauppinen et al., 2011; Love, Barber, & Wilcock, 1999; Strosznajder, Jeśko, & Strosznajder, 2000).

Many neurodegenerative diseases share common features and molecular mechanisms. They are characterized by the abnormal accumulation of proteins, resulting in toxic inclusions and aggregates (Dugger & Dickson, 2017). Oxidative stress, mitochondrial dysfunction, and neuronal apoptosis are also common disease features, which led researchers to inquire on the role of PARP-1 not just in ALS, AD, and HD, but in PD as well.

2.1. PARP-1 inhibition or deletion confers neuroprotective effects

The first report related to PARP-1 activation in a PD mouse model was published more than two decades ago by Mandir et al., who studied the effect of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxicity in a PARP knockout ($PARP^{-/-}$) mouse model (Mandir et al., 1999). At the time of the study, MPTP-induced toxicity in mice represented a classic and well-established experimental PD model. Administration of MPTP replicates parkinsonian motor symptoms by producing loss of dopaminergic neurons within SNpc and increased oxidative stress. Interestingly, $PARP^{-/-}$ mice seemed to be resistant to the toxic effects of MPTP; conversely, WT mice showed 80–90% decrease in striatal DA, DOPAC and HVA one week after MPTP injections, while $PARP^{-/-}$ mice displayed significantly lower reductions in these levels. The absence of PARP also prevented neuronal death, as only a slight reduction in Nissl-stained SNpc neurons in knockout mice was observed, as opposed to 60% reduction in WT mice. Furthermore, the authors report that NO-induced DNA damage is necessary for PARP activation, as mice lacking the neuronal NO synthase gene did not show PAR formation either.

Since the role of PARP-1 in PD became apparent, many researchers wondered whether PARP-1 inhibitors (PARPi) have therapeutic potentials for PD. Treatment with various PARPi in MPTP injected mice prevented the loss of TH protein levels and the decrease of DA, DOPAC and HVA content of striatum, suggesting a possible neuroprotective property of these inhibitors (Cosi, Colpaert, Koek, Degryse, & Marien, 1996; Iwashita et al., 2004; Yokoyama et al., 2010). PARPi were also able to block αSyn induced cytotoxicity in H4 cells overexpressing αSyn, displayed weak neuroprotective effect in primary rat neurons treated with 1-methyl-4-phenylpyridinium (MPP^+) (Outeiro et al., 2007) and significantly inhibited PAR formation and NAD^+ depletion in PC12 and SH-SY5Y cells (Iwashita et al., 2004). Protection of the blood-brain barrier from functional damage was also reported in an LPS-induced PD rat model, treated with 3-aminobenzamide PARPi (Wu, Wang, Liu, & Xue, 2014). Furthermore, Mao et al. reported that PARP-1 plays an essential role in the regulation of autophagy, as inhibition of PARP-1 increased αSyn degradation via the up-regulation of autophagy ability and decreased the accumulation of αSyn in PD models (Mao et al., 2020). While the PARPi mentioned above displayed slight neuroprotective effects in PD mouse models, the use of these inhibitors as potential therapeutics for PD needs to be evaluated further – and will be discussed in detail later.

2.2. PARP-1 and the genetics of Parkinson's disease

Over the last two decades several genetic mutations, associated with PD, have been identified, accounting for 10–20% of PD cases (Thomas & Beal, 2007). *SNCA* was the first gene reported to cause autosomal-dominant PD, leading to early-onset symptoms of the disease

(Polymeropoulos et al., 1996; Polymeropoulos et al., 1997). Besides missense mutations, duplications and triplications of the entire gene have also been reported (Klein & Schlossmacher, 2006). There are many gene mutations that are associated with the disease, the most common ones include: *LRRK2*, *Parkin*, *PINK1* and *DJ-1*. While mutations in *LRRK2* genes are associated with late-onset and slow disease progression, mutations in *Parkin*, *PINK1*, and *DJ-1* are accountable for PD with autosomal recessive mode of inheritance (Klein & Westenberger, 2012). The role of PARP-1 gene in the progression of PD was also evaluated by two separate research groups. The first report, published by Infante et al., studied 146 PD patients and claimed that variations in the regulatory region of the gene seem to offer protection from PD and affect age onset (Infante et al., 2007). Another study however, involving 600 PD patients, failed to replicate this and reported that variations in the PARP-1 gene were not a susceptibility factor for PD (Brighina et al., 2011). As of today, the published results are inconclusive, and we do not have sufficient data to draw a firm conclusion; it is likely that studies involving larger groups of patients across multiple countries and regions will have to be conducted.

The role of PARP-1 in regulating expression of *SNCA* has also been studied. Association studies have shown that certain alleles of NACP-Rep1, a polymorphic complex repeat site upstream of *SNCA*, may increase the risk of sporadic PD and can modulate the expression levels of αSyn (Krüger et al., 1999; Tan et al., 2000); although results were not always replicated (Izumi et al., 2001; Khan et al., 2001). In order to understand the role of the complex in the control of *SNCA* expression, Robert L. Nussbaum and his group used a variety of in vivo and in vitro experiments and identified PARP-1 as a possible regulator for αSyn expression (Chiba-Falek, Kowalak, Smulson, & Nussbaum, 2005). The authors showed that PARP-1 interacts with the NACP-Rep1 site and through this interaction it acts as a transcription regulator of the *SNCA* gene. While the study introduces interesting new roles for PARP-1, the basis of the recognition of NACP-Rep1 and the mechanism of its involvement in transcriptional regulation is not clear.

2.3. Dopaminergic cell death: from DNA damage to αSyn fibrils and PAR

The death of substantia nigra dopamine neurons account for the motor symptoms of PD. While the mechanisms of neuronal cell death are not clearly understood, there is evidence showing that deterioration of DA neurons may arise from cellular disturbances of protein degradation systems, endoplasmic reticulum stress, oxidative stress, mitochondrial dysfunction, neuroinflammation, and disruption of the autophagy-lysosome system (reviewed in reference (Levy, Malagelada, & Greene, 2009)). Recent reports also highlight the involvement of PARP-1 enzyme and apoptosis inducing factor (AIF) in neuronal degradation (Kim et al., 2011). For instance, Kim et al. showed that hyperactivation of PARP-1 in a 6-OHDA PD mouse model leads to ATP depletion and AIF translocation, which in turn activates AMPK (Kim et al., 2013). However, blocking either PARP-1 or AMPK prevented 6-OHDA induced atrophic changes of DA neurons. Nuclear translocation of AIF and PARP-1 mediated neuronal degeneration was also noted in an LPS injected rat model (Burguillos et al., 2011).

While the involvement of PARP-1 in cellular death was clearly demonstrated in the earlier studies mentioned above, only recently, has it been proposed that pathologic αSyn-mediated neuronal cell death proceeds via a PARP-1-driven form of cell death known as parthanatos (Kam et al., 2018). Parthanatos is a cellular death mechanism that is distinct from other death processes, such as apoptosis or necrosis (David, Andrabi, Dawson, & Dawson, 2009). Parthanatos pathway is activated by extensive DNA damage, which leads to PARP-1 hyperactivation, and upregulation in PAR production. PARP-1 activation is also linked to overproduction of nitric oxide (NO). Excess NO and superoxide anion produce peroxynitrite, causing further DNA damage and leading to PARP-1 activation (Xia, Dawson, Dawson, Snyder, & Zweier, 1996; Zhang, Dawson, Dawson, & Snyder, 1994). Parthanatos does not depend on caspase activation, instead, it is mediated by PAR-induced AIF translocation from the mitochondria to the nucleus (Yu et al., 2002). The research team, led by Valina and Ted Dawson, found that treatment with αSyn pre-formed fibrils (αSyn PFF) in cultured primary neurons and in a mouse model of PD, increased intracellular nitric oxide synthase (NOS) levels, leading to DNA damage, PARP-1 activation, accumulation of PAR and neuronal cell death via parthanatos. These effects were blocked by pre-treatment with PARPi or deletion of the PARP-1 gene (Kam et al., 2018). Negatively charged PAR also modulated fibril formation by binding to positively-charged lysine residues on the N-terminal region of αSyn through electrostatic interactions, resulting in accelerated fibril formation (Kam et al., 2018; Puentes et al., 2021). Furthermore, in a feed-forward loop, PAR converts αSyn PFF into a more toxic fibril strain and increases its neurotoxicity in vivo and in vitro (Fig. 2). Additional studies, focusing on the molecular mechanism of PARP-1 mediated cell death, found that Ser/Thr protein kinase Akt1 suppresses parthanatos through a transcriptional mechanism mediated by CREB. Akt1-CREB pathway activation promoted the expression of RNF146 in neuronal cell culture, which in turn suppressed 6-OHDA-induced PARP-1 activation and cell death (Kim et al., 2020).

What drives the abnormal assembly of pathologic αSyn is not known, however studies have shown that PAR is involved in the early stages of αSyn aggregation. Schaser et al. reported that αSyn is recruited to sites of DNA damage and colocalizes with DNA damage markers, including PAR and γH2AX, suggesting that this could be the original source of PAR bound αSyn fibrils (Schaser et al., 2019). Puentes et al. have also shown that elevated levels of intracellular PAR promote the transition of αSyn into phosphorylated aggregate forms (Puentes, Lengyel-Zhand, Lee, et al., 2021). Proximity ligation assays revealed that the interactions between PAR and phosphorylated αSyn are predominant in a transgenic mouse model of PD pathology and in PD patients as well, further highlighting the association of PARP-1 and PAR in disease onset and progression. Finally, since PAR-αSyn fibrils are conformationally different from the wild-type fibrils (Kam et al., 2018), future studies should focus on elucidating the structural changes that result from these interactions, as this information will also aid in the development of therapeutics and imaging agents targeting aberrant αSyn.

3. PARP-1 inhibitors as potential disease-modifying therapeutics for PD

The availability and successful integration of PARPi in clinical settings has increased in recent years (Jiang, Li, Li, Bai, & Zhang, 2019). To date, the clinical applications of PARPi center around oncological applications, specifically in BRCA1/2 deficient cancers such as ovarian (O'Cearbhaill, 2018) and breast (Vinayak & Ford, 2010). However, preclinical studies have shown the therapeutic potential of PARPi in a wide variety of non-oncological chronic disease settings (Berger et al., 2018). Here, we provide an overview on the most clinically relevant PARPi to date, including a description of their mechanism of action and specifications on the physio-chemical properties of an ideal PARPi for the treatment of PD.

The rationale for the use of PARPi in clinical settings revolves around the concept of synthetic lethality (Lord & Ashworth, 2017), whereby, inhibition of PARP-1 activity in cells with a malfunctioning or deficient gene results in selective cell loss. A common feature among cancer cells involves faulty DNA repair machinery. In ovarian and breast cancers, for example, BRCA1/2 mutations result in defective HR (Elezaby et al., 2019). Since PARP-1 plays a key role in promoting genomic stability and modulating DNA repair, inhibition of this enzyme results in selective toxicity in cells that harbor germline loss-of-function BRCA1/2 mutations – this association of genetic deficiencies lead to cell death (Lord & Ashworth, 2017). Combination therapies with PARPi have also shown therapeutic promise in the areas of chemotherapy, antiangiogenics, and immunotherapy (Matulonis & Monk, 2017);

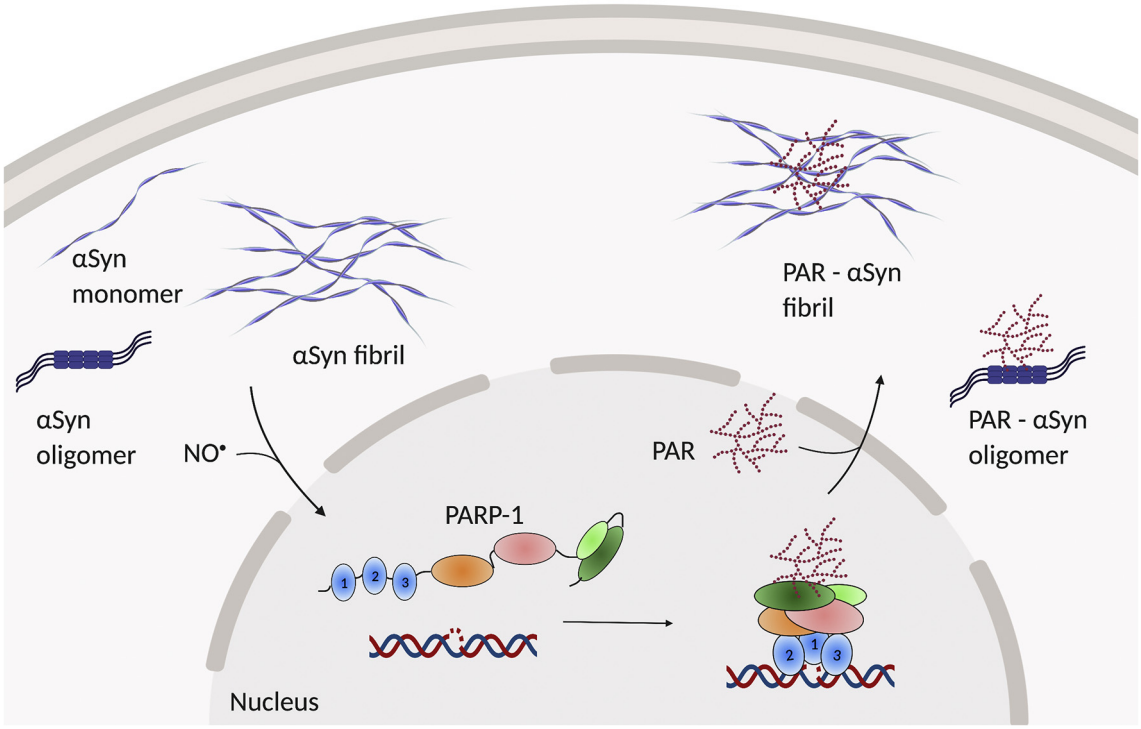

Fig. 2. Proposed molecular mechanism of PAR induced αSyn aggregation and formation of PAR + αSyn fibrils.

these combination studies may provide a scientific basis for the integration of adjunct PARPi treatment strategies in non-oncological settings.

3.1. Clinically relevant PARP-1 inhibitors

To date, the Food and Drug Administration (FDA) has approved 4 small-molecule PARPi for clinical applications in BRCA1/2 mutated cancers. These inhibitors include olaparib, rucaparib, niraparib, and talazoparib. In 2014, olaparib was the first PARPi approved by the FDA for germline BRCA mutated advanced ovarian cancer (Kim et al., 2015); in 2018, it was authorized for the treatment of germline BRCA mutated metastatic breast cancer (Armstrong & Clay, 2019). Current ongoing clinical trials with olaparib involve assessing its efficacy in a variety of cancers including endometrial, small cell lung, glioblastoma, and prostate. Similarly, other PARPi have also been utilized for treatment in BRCA mutated ovarian cancers, including rucaparib (Syed, 2017) and niraparib (Scott, 2017); both PARPi were approved as monotherapies for recurrent ovarian cancer responsive to platinum-based chemotherapy. The most recent PARPi to be approved for the treatment of BRCA mutated advanced breast cancer is talazoparib (McCann, 2019). Veliparib is another promising PARPi that is worth mentioning, as it is currently being studied in numerous phase III clinical trials (Coleman et al., 2019; Loibl et al., 2018).

The mechanism of action of clinical PARPi involve interactions with the binding site of the PARP cofactor NAD^+, along with modulation of PARP-1 allostery; whereby, PARP-1 is trapped onto cell chromatin (Hopkins et al., 2015; Murai et al., 2012; Zandarashvili et al., 2020). The differential modes of "PARP trapping" fall into three categories: Type I, allosteric pro-retention on DNA; type II, non-allosteric retention; and type III, allosteric pro-release. Studies have shown that the trapping potency of PARPi is directly linked to cytotoxicity. For instance, PARPi induced trapping appears to drive cytotoxicity in both cancer cells and healthy bone marrow (Hopkins et al., 2019). Talazoparib shows the highest trapping potency and a toxicity profile that is 100-fold higher compared to olaparib and rucaparib. After talazoparib, niraparib has the highest PARP-trapping capabilities, followed by olaparib, rucaparib, and veliparib (Fig. 3) (Zandarashvili et al., 2020). The PARP-1 trapping efficacy of veliparib is much lower compared to the other PARPi, however, veliparib is still able to inhibit PARP-1 activity in the nanomolar range. Furthermore, veliparib can cross the BBB (Donawho et al., 2007) and is currently being studied in the clinic for the treatment of glioblastoma in combination with temozolomide (Baxter et al., 2020). As such, veliparib and other PARPi with low trapping potencies may be more attractive drug candidates for some types of neurological disorders.

3.2. Repurposing PARP-1 inhibitors for non-oncological diseases

Some of the critical factors that need to be considered when investigating the use of PARPi in neurodegeneration, include addressing if implementation of these therapy strategies (I) significantly decreases disease severity and (II) whether they expand beyond current limitations in standard of care. Chronic progressive disorders like PD have serious limitations when it comes to disease therapy. Standard of care for PD includes treatment with Levodopa and other dopaminergic medications (Liao et al., 2020). These drugs primarily function by enhancing dopamine levels in the brain, this in turn improves motor symptoms and overall quality of life for PD patients. However, dopamine-based therapies loose efficacy over time, leading to the emergence of "dopa-resistant" motor symptoms (Thanvi & Lo, 2004). In this chronic and devastating setting, the current therapeutic options are not ideal; therefore, alternative disease strategies must be investigated as viable options.

Early in vitro and in vivo studies with PARPi in models of PD have shown promising results (Table 1), thus suggesting neuroprotective effects for these class of compounds. Notably, Kam et al. (2018), reported that αSyn PFF injected mice fed a diet containing veliparib, displayed diminished DA neuron loss and αSyn pathology compared to mice given a control diet. Similarly, a 2020 study reported that αSyn ^{A53T}-tg mice fed with veliparib for 3 mo (starting at 6 mo) showed reduced neurotoxicity and improved motor ability. Recently, Puentes et al. (Puentes, Lengyel-Zhand, Reilly, & Mach, 2021), reported that pre-treatment with a low toxicity olaparib analogue (**10e**) led to neuroprotective effects in SH-

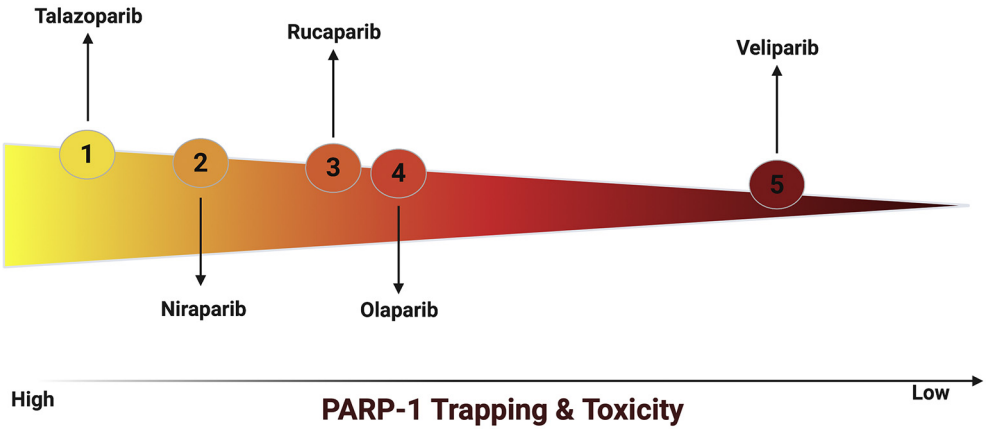

Fig. 3. PARP-1 trapping potencies and cytotoxicity profile of clinically relevant PARPi. The ability of PARPi to trap PARP-1 on DNA correlates with cytotoxic potency.

Table 1
Preclinical evaluation of PARPi in cell and rodent models of PD.

Experimental model	PARPi	Outcome
LPS injected rats	Benzamide	DA neurons protected from LPS-induced cell death (Burguillos et al., 2011)
LPS induced PD rat model	3-Aminobenzamide	Prevented structural and functional damage to BBB; protected DA neurons from degeneration and death (Wu et al., 2014)
H4 human cells overexpressing αSyn or primary rat neurons treated with MPP^+	4-ANI, PJ34 K245-14, EB47	Protection against αSyn toxicity in H4 cells; neuroprotective effect (Outeiro et al., 2007)
Primary cortical neurons; αSyn-PFF injected mice	veliparib, rucaparib, talazoparib	Protection against DA neuronal loss; reduction in αSyn pathology & prevention against behavioral deficits (Kam et al., 2018)
PC12 and SH-SY5Y cell culture; MPTP mouse model	FR255595	Attenuated PAR polymer formation and NAD+ depletion; neuroprotective effects (lower reduction of striatal DA, DOPAC and HVA content) (Iwashita et al., 2004)
MPTP mouse model	Benzamide and its derivatives	Reduced MPTP-induced catecholamine loss; prevented MPTP-induced striatal dopamine depletion and loss of noradrenaline (Cosi et al., 1996)
MPTP mouse model	Benzamide	Guarded against a decrease in DA, DOPAC, HVA and TH & increased GFAP protein levels in the striatum (Yokoyama et al., 2010)
SH-SY5Y and IMR-5 cell culture	10e	Protection of cells against αSyn fibrils mediated effects, DNA damage and oxidative stress (Puentes, Lengyel-Zhand, Reilly, & Mach, 2021)
αSyn^{A53T}-tg mice	Veliparib	Reduced neurotoxicity, improved motor ability (Mao et al., 2020)

SY5Y neuroblastoma cells following treatment with αSyn PFFs. Altogether, these data provide an encouraging outlook for the implementation of PARPi in non-oncological settings, however, it must be emphasized that extensive studies are still needed to thoroughly evaluate the therapeutic potential of low toxicity PARPi (*such as veliparib and **10e***) for applications as disease modifying therapies for PD.

Due to the nuclear localization of PARP-1, an ideal PARPi needs to passively diffuse across both the cell and nuclear membranes. For applications in non-oncological disease settings, such as neurodegeneration, an optimal PARPi candidate also needs to be able to penetrate the BBB. Moreover, the development of novel PARPi for neuro-based applications, should adhere to drug design guidelines that increase the likelihood of BBB penetration; some of these guidelines include: (I) molecular weight < 450 Da (van de Waterbeemd, Camenisch, Folkers, Chretien, & Raevsky, 1998), (II) polar surface area < 60–70 $Å^2$ (Kelder, Grootenhuis, Bayada, Delbressine, & Ploemen, 1999; van de Waterbeemd et al., 1998), (III) lipophilicity (Log P_{oct}) values between 1.5 and 2.7 (Pajouhesh & Lenz, 2005) and (IV) low binding affinity (K_d > 10 μM) to serum albumin (Pajouhesh & Lenz, 2005). Furthermore, efforts should be made to ensure that the PARPi compounds tested are not substrates for drug efflux pumps that line the BBB, including P-glycoprotein (PgP) and Breast Cancer Resistance Protein (PCRP), since both of these proteins play critical roles in transporting drugs out of the BBB (Patel & Patel, 2017). Consequently, future preclinical evaluation of PARPi compounds for neuro-based purposes must include the characterization of potential interactions between the PARPi being studied and these two main drug efflux proteins, since interactions with either of these transporters will significantly affect both the efficacy and dosage of the drug (Patel & Patel, 2017).

4. Conclusion and future direction

4.1. What is next in the field of PARP-1?

Over the years, a plethora of studies have been published on PARP-1 biology and the PARP family of proteins (Ba & Garg, 2011; Ke, Zhang, Lv, Zeng, & Ba, 2019; Martí et al., 2020). These studies have not only provided key insight on the role of PARP-1 in DNA repair mechanisms but have also highlighted the druggable properties of this enzyme. Currently, the level of interest in understanding PARP-1 biology is perhaps best rivaled by the numerous projects currently investigating this enzyme as a drug target (Jiao et al., 2017; Wang et al., 2017; Yokoyama et al., 2010). The elaborate ADP-ribose chains produced by PARP-1 (i.e., PARylation) along with the numerous processes regulated by PAR-bound proteins, suggest that PARP-1 activity is involved in a number of diverse cellular processes that extend beyond DNA repair mechanisms (Andrabi et al., 2006; Vyas et al., 2013). However, even with increased interest, there are still significant gaps in knowledge surrounding the function and downstream effects resulting from PARylation by PARP-1 and the role of PARP-1 activity beyond the nucleus i.e., the multifaceted roles of PAR in the cell.

PARP-1 activity accounts for the majority of PAR synthesis (>90%) (Alemasova & Lavrik, 2019; Andrabi et al., 2006; Koh, Dawson, & Dawson, 2005). Studies report that PAR is able to exit the nucleus and interact and modify a wide variety of proteins (Narne, Pandey, Simhadri, & Phanithi, 2017; Nossa et al., 2009; Rodríguez-Vargas, Oliver-Pozo, & Dantzer, 2019). These PAR-bound and PARylated proteins often contain low-complexity regions which promote the phase separation of biomolecular condensates (Altmeyer et al., 2015). PAR has been directly linked in promoting the phase separation of a number of macromolecules, including DNA repair factors at sites of DNA damage, stress granules (Duan et al., 2019), mitotic spindles (Leung, 2020), and nucleoli (Leung, 2014). The formation of these intracellular PAR-mediated condensates has been linked to both cancer and neurodegeneration (Leung, 2020). For instance, a number of in vitro studies have demonstrated that PAR promotes the phase separation of intrinsically disordered proteins implicated in neurodegenerative disease, including: FUS (Altmeyer et al., 2015), TDP-43 (McGurk et al., 2018), hnRNPA1 (Duan et al., 2019), and αSyn (Kam et al., 2018). Additional studies are merited in order to understand how PARP-1 hyperactivity and excess intracellular PAR polymer levels affect these complex cellular mechanisms – and how these effects relate to diseases. There are a number of outstanding questions regarding the fundamental role of PAR in promoting the phase separation and/or aggregation of these proteins. For example, we do not understand what lengths of PAR (i.e., short dimers/trimers or large complex chains) trigger phase separation, in addition we do not know what concentrations of PAR are needed to promote the transition of these intrinsically disordered proteins into aggregate states. Answering these basic questions will not only provide key insight on PARP/PAR biology but also help inform the development of pre-clinical models of PARP-1 hyperactivity.

Besides dynamic effects regarding phase separation, pathogenic PARP-mediated cellular processes have also been linked to negative effects on mitochondrial function (Ba & Garg, 2011). These effects include promoting mitochondrial-damage by disrupting mitochondrial energetics (due to excess NAD^+ consumption by PARP-1) (Orsucci, Mancuso, & Siciliano, 2008) and interfering with mitochondrial-mediated processes including mitophagy and the unfolded protein response (Orsucci et al., 2008; Yu et al., 2002). In addition, crosstalk between PAR and mitochondrial proteins promotes the translocation of AIF from the mitochondria to the nucleus, resulting in chromatin fragmentation and cell death (Orsucci et al., 2008; Zeng, Geng, Jia, Chen, & Zhang, 2018). From a therapy standpoint, it is important to continue advancing research efforts on developing PARPi for non-oncological diseases in order to assess if inhibition of this enzyme can mitigate disease-linked effects, such as the phase separation of biomolecular condensates as well as effects on mitochondrial function. Such studies may provide valuable insight to researchers interested in developing and evaluating new disease modifying therapies for neurogenerative disease. Altogether, these endeavors have the potential to not only expand our knowledge on PARP-1 function but also gain a better understanding on the role of PARP activity in disease settings beyond cancer.

With reference to PD, Kam et al. (2018), report that PAR levels are elevated in the cerebrospinal fluid of PD patients and that PARP-1 is active in the substantia nigra of these patients. They also report that PAR-bound fibrils of αSyn exert higher toxicity (25-fold) and resistance to degradation by proteases. Going forward, it may be of interest to evaluate if PAR interacts with pathogenic forms of αSyn outside of the brain. Recent studies (Challis et al., 2020; Kim et al., 2019) show that inoculation with αSyn PFF in the duodenum increase αSyn histopathology and promote the progression of pathogenic αSyn to the brain (gut-to-brain). It would be interesting to evaluate if αSyn PFF-mediated gut-to-brain transmission is affected in *PARP-1*/KO animal models and/or whether the transmission of pathogenic αSyn is enhanced if these animals are inoculated with PAR-bound αSyn PFF. In addition, a recent study by Arakhamia et al. (2020) demonstrated that neutralizing positively charged lysine residues in tau may play a role in increasing tau insolubility and promoting its aggregation. Therefore, it would be of scientific interest to evaluate if the electrostatic binding of PAR to lysine residues has an effect on the aggregation kinetics of other intrinsically disordered proteins implicated in neurodegenerative diseases.

4.2. PARPi as disease modifying therapies for Parkinson's disease

In the context of using PARPi as disease modifying therapies for PD, several factors must be taken into account; including, understanding the long-term effects of PARPi and assessing potential risks – if they occur – and whether these risks outweigh the deleterious effects of the disease; especially in patients who are not responding to standard of care therapies. Groups that aim to develop novel PARPi compounds for neuro-based purposes need to take into account not just BBB penetrance but also the cytotoxicity and specificity (i.e. off-target effects) of the compounds being studied. Ideally, these PARPi should be non-PgP substrates (Reilly et al., 2019) and exhibit weak PARP-1 trapping capabilities (Zandarashvili et al., 2020), since PARP-1 trapping is correlated with increased PARPi toxicity – including toxicity in healthy bone marrow (Hopkins et al., 2015). In addition, efforts should be made to ensure that PARPi intended for non-oncological applications have low toxicity profiles along with high affinity and specificity for their target. PARPi compounds that meet these criteria would be ideal candidates for further validation in preclinical models of PD and/or other neurological disorders that may be influenced by PARP-1 hyperactivity.

On that note, while PARP-1 activity has been reported in AD (Martire, Mosca, & d'Erme, 2015; Narne et al., 2017) and PD (Martire et al., 2015), and PARP-1-mediated cell death "parthanatos" has been linked to neuronal loss in PD (Kam et al., 2018) and HD (Cardinale et al., 2015), there is still a large gap in knowledge that prevents the implementation of PARPi therapies into the clinic. Therefore, in addition to developing PARPi for neurological applications, investigators also need to assess if current disease models have translational potential in order to realistically validate the neuroprotective effects of new PARPi compounds. This validation will be critical in ensuring the successful translation of new PARPi compounds from pre-clinical models of neurodegeneration to patients in the clinic. Furthermore, it may be of scientific interest to determine a viable therapeutic window (if any exists) with regards to PARPi therapy, along with its evaluation as a combination therapy with standard of care treatments.

Lastly, the goal of this review was not only to provide insight into the role of PARP-1 in PD but to also stimulate discussion on PARP-1 and PARPi therapy beyond cancer research. Understanding the role of PARP-1 in neurodegeneration and implementing PARPi therapies outside of cancer is an active area of research that is still in early development. However, as additional research in this field continues to move forward, the multifaceted roles of this DNA-repair enzyme in both acute and chronic disease settings will surely provide a nuanced perspective on the role of PARP-1 beyond the nucleus.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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