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THE ROLE OF POLY(ADP-RIBOSE) POLYMERASE-1 IN CNS DISEASE

T. M. KAUPPINEN AND R. A. SWANSON*

Department of Neurology, University of California at San Francisco, and Veterans Affairs Medical Center, 4150 Clement Street, San Francisco, CA 94121, USA

Abstract—Poly(ADP-ribose) polymerase-1 (PARP-1) is a nuclear enzyme that contributes to both neuronal death and survival under stress conditions. PARP-1 is the most abundant of several PARP family members, accounting for more than 85% of nuclear PARP activity, and is present in all nucleated cells of multicellular animals. When activated by DNA damage, PARP-1 consumes nicotinamide adenine dinucleotide (NAD^+) to form branched polymers of ADP-ribose on target proteins. This process can have at least three important consequences in the CNS, depending on the cell type and the extent of DNA damage: 1) Poly(ADP-ribose) formation on histones and on enzymes involved in DNA repair can prevent sister chromatid exchange and facilitate base-excision repair; 2) poly(ADP-ribose) formation can influence the action of transcription factors, notably nuclear factor κB, and thereby promote inflammation; and 3) extensive PARP-1 activation can promote neuronal death through mechanisms involving NAD^+ depletion and release of apoptosis inducing factor from the mitochondria. PARP-1 activation is thereby a key mediator of neuronal death during excitotoxicity, ischemia, and oxidative stress, and PARP-1 gene deletion or pharmacological inhibition can markedly improve neuronal survival in these settings. PARP-1 activation has also been identified in Alzheimer's disease and in experimental allergic encephalitis, but the role of PARP-1 in these disorders remains to be established.

Key words: DNA, transcription, inflammation, cell death, oxidative stress.

Poly(ADP-ribose) polymerase-1 (PARP-1) is an abundant nuclear protein that is present in all nucleated cells of multicellular eukaryote organisms. It consists of an N-terminal DNA-binding domain, an internal automodification domain, and a C-terminal catalytic domain (Fig. 1) (de Murcia et al., 1994; Kauppinen et al., 2006). PARP-1 becomes catalytically activated by DNA strand breaks or kinks. The activated enzyme consumes nicotinamide adenine dinucleotide (NAD^+) to form branched ADP-ribose polymers on nuclear acceptor proteins, which include DNA ligases, DNA polymerases, histones and PARP-1 itself (D'Amours et al., 1999). The poly(ADP-ribosyl)ation of histones causes chromatin loosening and is thought to thereby facilitate DNA repair and transcriptional regulation (Tulin and Spradling, 2003), and coordinate interactions among proteins involved in DNA repair. The poly(ADP-ribose) polymers are degraded by poly(ADP-ribose) glycohydrolase (Davidovic et al., 2001). PARP-1 accounts for at least 85% of maximal cellular PARP activity (Virag and Szabo, 2002). The remaining activity is due to other PARP species, the physiological functions of which are less well characterized.

Several highly potent PARP inhibitors have now been developed, and some of these are now entering clinical trials as chemotherapy sensitizing agent and for the treatment of acute cardiac ischemia (http://www.clinicaltrials.gov). The PARP inhibitors all share a carboxamide group attached to an aromatic ring, like the normal PARP substrate NAD^+, or a carbamoyl group built in a polyaromatic heterocyclic skeleton (Zhang and Li, 2002). Some of these agents have recognized off-target effects. For example, 3-aminobenzamide, 1,5-dihydroxyisoquinoline, and 1,11b-dihydro-[2H]benzopyrano[4,3,2-de]isoquinolin-3-one (GPI 6150) can be free radical scavengers, although this effect is demonstrable only at millimolar concentrations (Czapski et al., 2004). GPI 6150 also induces hypothermia, by an uncertain mechanism (Feng and LeBlanc, 2002). Newer, more potent inhibitors such as 3,4-dihydro-5-[4-(1-piperidinyl)butoxy]-1(2H)-isoquinolinone (DPQ) (Czapski et al., 2004), indeno-isoquinolinone, *N*-(6-oxo-5,6-dihydro-phenanthridin-2-yl)-*N*,*N*-dimethylacetamide (PJ34) (Besson et al., 2005), and 5-chloro-2-[3-(4-phenyl-3,6-dihydro-1(2*H*)-pyridinyl)propyl]-4(3*H*)-quinazolinone (Iwashita et al., 2004) inhibit PARP-1 activity at nanomolar or low micromolar concentrations. Antioxidant effects are unlikely at such low concentrations, but effects at other sites, especially at NAD^+-binding sites, cannot be excluded. It should also be noted that the currently available PARP inhibitors do not discriminate well between PARP-1 and the other PARP species.

Oxidative DNA damage is constant, normal occurrence in aerobic organisms (Halliwell and Gutteridge, 1989), and this necessitates continuous genomic surveillance and repair. Oxidative stress and DNA damage is markedly increased in several disease states, including ischemia–reperfusion, excitotoxicity, inflammation, and exposure to the toxins rotenone and 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP). PARP-1 activity is commensurably increased under these conditions and this increase can have at least three effects relevant to CNS disease; facilitated DNA repair, cell death, and inflammation (Fig. 2).

PARP-1 IN DNA REPAIR

A primary function of PARP-1 under basal conditions is the detection of DNA damage and prevention of chromatid

*Corresponding author. Tel: +1-415-750-2011; fax: +1-415-750-2273.
E-mail address: raymond.swanson@ucsf.edu (R. A. Swanson).

Abbreviations: AIF, apoptosis-inducing factor; DPQ 3, 4-dihydro-5-[4-(1-piperidinyl)butoxy]-1(2H)-isoquinolinone; EAE, experimental allergic encephalomyelitis; GPI 6150, 1,11b-dihydro-[2H]benzopyrano[4,3,2-de]isoquinolin-3-one; MMP-9, matrix metalloproteinase-9; MPTP, 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine; NAD^+, nicotinamide adenine dinucleotide; NF-κB, nuclear factor κB; PARP-1, poly(ADP-ribose) polymerase-1; TNFα, tumor necrosis factor alpha.

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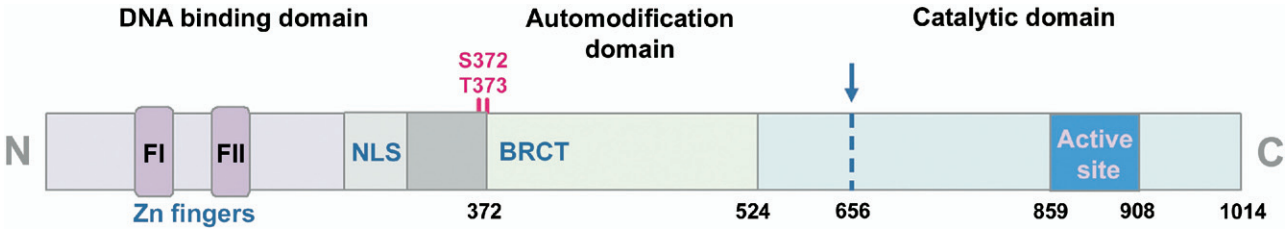

Fig. 1. Structure of PARP-1. PARP-1 contains an N-terminal DNA-binding domain, a nuclear localization sequence (NLS), an internal auto-modification domain, and a C-terminal catalytic domain. The DNA binding domain contains two zinc fingers. The auto-modification domain has a BRCT motif typical of many DNA repair and cell cycle proteins, and contains phosphorylation sites at S372 and T373 that regulate PARP-1 activity (Kauppinen et al., 2006). Proteolytic cleavage at the caspase cleavage site (arrow) inactivates the enzyme.

exchange. Evidence for this latter function comes in part from observations that PARP-1 gene deficiency leads to a variety of chromosomal aberrations, including ring chromosomes, Robertsonian configurations, dicentric chromosomes, and others (d'Adda di Fagagna et al., 2001; Samper et al., 2001). The mechanisms by which PARP-1 facilitates DNA are still being resolved, but it has been established that PARP-1 poly(ADP-ribosyl)ates many proteins involved in DNA repair, such as DNA ligases, DNA polymerases, histones, and PARP-1 itself (D'Amours et al., 1999; Huang et al., 2006). Poly(ADP-ribosyl)ation of histones induces local relaxation of the chromatin structure, which in turn facilitates access of repair proteins to damaged DNA (Rouleau et al., 2004). Other proteins have been identified as having binding domains for poly(ADP-ribose), including p53, p21, DNA-PK, XPA, XRCC1, DNA ligase III, and DNA polymerase epsilon (Masson et al., 1998; Pleschke et al., 2000). It has been suggested that these binding domains may facilitate recruitment of these proteins to sites of DNA damage, but this remains to be established.

THE PARP-1 CELL DEATH PROGRAM

Paradoxically, a second outcome that can result from PARP-1 activation is cell death. Cells with extensive DNA damage exhibit widespread PARP-1 activation, resulting in depletion of cytosolic NAD^+. This in turn leads to ATP depletion and energy failure (Ha and Snyder, 1999; Alano et al., 2004; Ying et al., 2005). A downstream and likely irreversible event in this cell death program is translocation of apoptosis-inducing factor (AIF) from mitochondria to the nucleus and subsequent DNA degradation (Yu et al., 2002). AIF is a flavoprotein with an important role in the normal function of the mitochondrial respiratory chain, but which mediates cell death when released from the mitochondria (Modjtahedi et al., 2006). The term "AIF" is somewhat misleading, because the cell death process induced by PARP-1 activation bears little resemblance to classical apoptosis; PARP-1-induced cell death does not generate apoptotic bodies, cytosolic annexin flipping, or DNA laddering, and it is not mediated by caspase activation (Yu et al., 2002). It is, however, a form of programmed cell death,

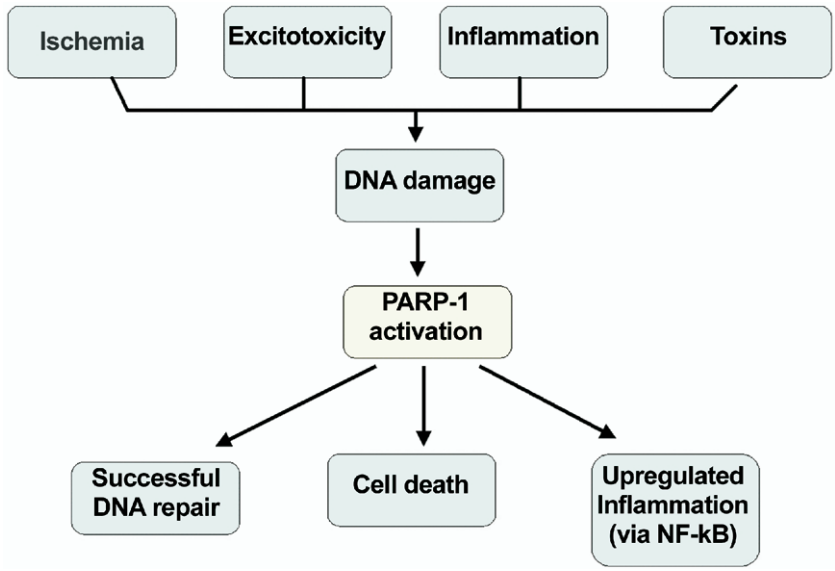

Fig. 2. Consequences of PARP-1 activation. Many CNS insults generate DNA damage, which in turn triggers PARP-1 activation. PARP-1 activation normally functions to facilitate DNA repair and prevent chromosomal rearrangements. With extensive DNA damage, PARP-1 activation triggers a cell death pathway. PARP-1 also functions as a co-activator of transcription factors such as nuclear factor κB (NF-κB), which regulates many aspects of the inflammatory response.