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Review

PARP-1 involvement in neurodegeneration: A focus on Alzheimer's and Parkinson's diseases

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ABSTRACT

DNA damage is the prime activator of the enzyme poly(ADP-ribose)polymerase1 (PARP-1) whose overactivation has been proven to be associated with the pathogenesis of numerous central nervous system disorders, such as ischemia, neuroinflammation, and neurodegenerative diseases. Under oxidative stress conditions PARP-1 activity increases, leading to an accumulation of ADP-ribose polymers and NAD^+ depletion, that induces energy crisis and finally cell death. This review aims to explain the contribution of PARP-1 in neurodegenerative diseases, focusing on Alzheimer's and Parkinson's disease, to stimulate further studies on this issue and thereby engage a new perspective regarding the design of possible therapeutic agents or the identification of biomarkers.

Contents

1. Introduction

Neurodegenerative disorders, in particular Alzheimer's disease (AD) and Parkinson's disease (PD), are a growing public health concern because of the rapid increase in life expectancy in the developed world. Neurodegeneration affects a wide percentage of people and is increasing to epidemic proportions in all industrialized countries (Reitz et al., 2011), albeit the etiology remains elusive.

However, it is known that oxidative stress, which originates from an unbalanced production of reactive oxygen species (ROS), plays a crucial role in AD and PD pathophysiology (Huber et al., 2006; Yu et al., 2009; Zuo and Motherwell, 2013). ROS generation causes damage to major macromolecules in cells, including lipids, proteins and nucleic acids (Hayashi, 2009). DNA damage is the primary activator of the enzyme poly(ADP-ribose)polymerase-1 (PARP-1) that catalyzes the reaction of poly(ADP-ribosylation), a post-translational modification of proteins involved in many

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physiological processes, such as gene expression, maintenance of genomic stability, and cell death (Aredia and Scovassi, 2014a; Beneke, 2012; Burkle, 2006; Burkle and Virag, 2013; Krietsch et al., 2013). Increased PARP-1 activity leads to a drastic reduction of NAD^+ levels, with consequences on the ATP production and impairment of cell functions (Alano et al., 2010). Thus, extensive PARP-1 activation has been linked to the development and progression of various chronic diseases including diabetes, cancer, viral infections, and neurodegenerative diseases (Kauppinen and Swanson, 2007; Pacher and Szabó, 2005; Peralta-Leal et al., 2009; Strosznajder et al., 2005; Sykora et al., 2013; Tempera et al., 2010).

PARP-1 uses a spectrum of strategies to induce cell death, including its ability to modify proteins, acting as a modulator, both spatially and temporally, of a variety of cell signaling pathways regulating, cell death, gene expression and cellular bioenergetics (Aredia and Scovassi, 2014b; Krietsch et al., 2013). It is known that activation of PARP isoforms other than PARP-1 also contributes to NAD^+ depletion and concomitant metabolic changes, but the majority of evidences and studies on this issue are addressed to PARP-1, which is main characterized member of the family. In this review, we focus on the contribution of PARP in Alzheimer's and Parkinson's diseases to stimulate further studies on this issue and thereby engage a new perspective regarding the development of possible therapeutic agents or the identification of biomarkers.

2. PARP-1 structure and activity

Over the years, the enzymes responsible for the reaction of poly(ADP-ribosylation) have been given different acronyms (ADPRT, PARS, and PARP), but currently they are called pADPr polymerases (PARPs) or ADP-ribosyltransferases (ARTs) (Hottiger et al., 2010). The PARP family comprises 17 proteins, encoded by different genes (Ame et al., 2004; Uchida et al., 2001), and it could be divided into six classes based on phylogenetic analyses of PARP catalytic domains (Perina et al., 2014).

PARP-1, a 116-kD, a nuclear enzyme, consists of three main domains: the N-terminal DNA-binding domain (DBD), the automodification domain (AMD) and the C-terminal catalytic domain (Kameshita et al., 1984; Kurosaki et al., 1987).

The DBD is located at the N-terminus of the enzyme and contains 2 zinc fingers (Cherney et al., 1987; Mazen et al., 1989) that recognize altered DNA structures and dramatically stimulate PARP-1 activity, one zinc finger domain that mediates interdomain contacts (Langelier et al., 2008) and two helix-loop-helix motifs able to mediate strong interactions between DNA and proteins. It also presents a high proportion of basic residues, which are probably involved in the interaction of the enzyme with DNA and the nuclear localization signal (NLS).

The AMD is localized in the central region and contains the majority of the glutamic acid residues that are involved in PARP-1 automodification (Desmarais et al., 1991; Marsischky et al., 1995), and also lysine residues (Altmeyer et al., 2009). The enzyme is able to modify itself in an intermolecular reaction of autopoly(ADP-ribosylation), which leads to the inhibition of PARP-1 and acts as a signal for the degradation of the polymer by poly(ADP-ribose) glycohydrolase (PARG) (D'Amours et al., 1999; Simonin et al., 1993). Moreover, the automodification domain contains a leucine-zipper motif and a BRCT (BRCA1C-terminus: breast cancer susceptibility protein C-terminus) domain, which is found also in several proteins that regulate cell-cycle checkpoints and DNA repair (Bork et al., 1997). The C-terminal region is involved in the catalytic synthesis of poly(ADP-ribose) polymers (PARs) by using NAD^+ as a substrate.

By sequencing and comparison of the nucleotide sequence of the PARP-1 cDNA from various organisms, it has been demonstrated that the enzyme is well preserved (Ruf et al., 1996). In particular the "PARP signature" motif (Rolli et al., 1997), between the residues 859 ± 908 localized in the C-terminal, is a highly conserved sequence, suggesting a critical role for PARP enzymatic activity in cellular functions (de Murcia and Menissier de Murcia, 1994; Ogata et al., 1981; Ruf et al., 1996; Steffen et al., 2013). The loss of the last 45 amino acids of this domain, leads to a loss of PARP-1 activity. Crystallographic studies have shown that the active site of this domain has a structural motif, β-α-loop-β-α responsible for the binding to NAD^+ (Jung et al., 1994).

In the presence of DNA breaks, PARP-1 catalyzes the formation of PARs, which are synthesized by different enzymatic activities of PARP-1, including (i) initiation, (ii) elongation, and (iii) branching. The enzymatic reaction consists in the cleavage of NAD^+ into nicotinamide and ADP-ribose and the consequent addition of ADP-ribose units to glutamate or aspartate residues on target proteins, such as PARP-1 itself and histones, via ester linkages (D'Amours et al., 1999). The ADP-ribose units in the PAR polymer are linked via glycosidic ribose-ribose $1'' \rightarrow 2$ bonds to produce a long linear chain (Altmeyer et al., 2009), and through $2 \rightarrow 1$ glycosidic bond, for branching of PAR polymers every 20–50 residues (Burkle, 2005). The pyrophosphate, rather than a single phosphate group, is the linking group between ribose sugars creating some special bulk to a PAR bridge, which may have an additional role in cell signalling.

The degradation of poly(ADP-ribose) is carried out by PARG (Hatakeyama et al., 1986), which hydrolyses the adenosine terminus of a branch, releasing free ADP-ribose monomers. PARG has endoglycosidase activity (by recycling the PAR formed on PARP-1 that could be rapidly degraded) or exoglycosidase activity (free PAR and mono(ADP-ribose)) (Davidovic et al., 2001).

3. Involvement of PARP-1 in neurodegenerative diseases

3.1. In vivo PARP-1 activation

Love et al. (1999) were the first to report a correlation between PARP-1 and AD showing higher levels of PAR in AD human brains by immunostaining assay. So far other groups have demonstrated PARP-1 activation in AD using various transgenic mice models: a significative PARP-1 activation was demonstrated at 3 months of age when early amyloid deposit occurs in the hippocampus and enthorinal cortex of TgCRND8 mice bearing the double Swedish (KM670/671/NL) and Indiana (V717F) mutations (Martire et al., 2013). hAPPJ20 mice bearing the Swedish (K595N) and Indiana (M596L) mutations, which accumulate amyloid beta peptide (Aβ) by 6 months of age, crossed with PARP-$1^{-/-}$ mice attenuated the brain dysfunctions developed, such as microglial activation hippocampal synaptic integrity and cognitive function (Kauppinen et al., 2011). Moreover, direct Aβ injections into the hippocampus of PARP-$1^{-/-}$ mice or mice treated with the PARP-1 inhibitor PJ34 showed a lower microglial activation compared to controls, thus confirming the protective role of PARP-1 genetic or pharmacological inhibition. PARP-1 activity increases in Sprague–Dawley rats treated with Aβ (Turunc Bayrakdar et al., 2014), but interestingly, Aβ peptide injection had no effect on PARP-1 activity in the brain of aged rats, maybe because of the inhibitory effect of NO synthase on PARP-1 activity (Strosznajder et al., 2000).

PD shares a common feature with AD, the oxidative stress, that, as above mentioned, is able to activate PARP-1. Several papers have reported that mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a toxin known to induce PD-like symptoms (Dawson and Dawson, 1996), showed an enhanced PARP-1 activity (Cosi et al., 1996; Iwashita et al., 2004; Wang et al., 2003; Wu et al., 2014b). In particular, Mandir et al. (1999) examined the effects of MPTP in PARP-$1^{-/-}$ mice, demonstrating that they are resistant to the toxic effects of MPTP. Moreover,