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Mitochondrial and Nuclear Cross Talk in Cell Death: Parthanatos

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Abstract

Poly(ADP-ribose) polymerase-1 (PARP-1) PARP-1 is an abundant nuclear protein first described to facilitate DNA base excision repair. Recent work has expanded the physiologic functions of PARP-1 and it is clear that the full range of biologic actions of this important protein are not yet fully understood. Regulation of the product of PARP-1, poly(ADP-ribose) (PAR), is a dynamic process with poly(ADP-ribose) glycohydrolase (PARG) playing a major role in the degradation of the polymer. Under pathophysiologic situations, over activation of poly(ADP-ribose) polymerase-1 (PARP-1) results in unregulated PAR synthesis and widespread neuronal cell death. Once thought to be necrotic cell death due to energy failure, we recently found that PARP-1 dependent cell death is dependent on the generation of PAR that triggers nuclear translocation of apoptosis-inducing factor (AIF) to result in caspase-independent cell death. This form of cell death is distinct from apoptosis, necrosis or autophagy and is termed Parthanatos. PARP-1 dependent cell death has been implicated in tissues throughout the body and in diseases afflicting hundreds of millions world wide including stroke, Parkinson's disease, heart attack, diabetes, and ischemia reperfusion injury in numerous tissues. The breadth of indications for PARP-1 injury make Parthanatos a clinically important form of cell death to understand and control.

Introduction

Cell death in the nervous system is an important cellular process for normal development. However, following cell stress, brain injury, trauma or ischemia, cell death becomes unregulated and leads to pathological outcomes in neurodegenerative disorders and stroke. In general, cell death is a complex phenomenon involving multiple pathways. Apoptosis is a pathway of cell death that involves sequential activation of biochemical events with caspases as major players. Necrosis on the other hand involves cell swelling and rupture of cellular membranes, which is biochemically or morphologically distinct from apoptosis. Autophagy is recently described as a critical pathway of cell death linked to neurodegenerative disorders. Originally autophagy was identified to play role in organelle and protein recycling. Apoptosis, necrosis or autophagy, though considered three distinct

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modes of cell death, may share common biochemical features for death execution. In traumatic brain injury, excitotoxicity, ischemia, and in many neurodegenerative disorders, poly (ADP-ribose) polymerase-1 (PARP-1) activation is an early biochemical cell death event. PARP-1 activation leads to a unique form of cell death that is in large part mediated via accumulation of poly (ADP-ribose) (PAR) and nuclear translocation of apoptosis inducing factor (AIF) from mitochondria. PARP-1 dependent cell death is caspase-independent and termed Parthanatos.

Poly (ADP-ribose) polymerase-1 (PARP-1) and cell death

Poly (ADP-ribose) polymerases include 18 putative isoforms based on protein sequence homology to a PARP catalytic domain. PARP's catalyze the process of poly (ADP-ribosyl)ation through transfer of ADP-ribose units on acceptor proteins. PARP-1 is the founding member of PARP family and accounts for more than 90% cellular PARP activity [1-5]. In response to DNA damage, PARP-1 uses NAD^+ as a substrate and attaches polymers of ADP-ribose (PAR) on different acceptor proteins (hetero-modification) or on PARP-1 itself (auto-modification) [3, 5]. PARP-1 takes part in genomic repair under physiological conditions thus is considered as a “genome guardian” [6, 7]. Mild genomic stress induces PARP-1 activation to repair damaged DNA, whereas excessive poly (ADP-ribosyl)ation due to massive DNA disruption in situations likes stroke, traumatic brain injury and ischemia/reperfusion injury in various organs, induces cell death [5] (Figure 1). Cytoprotection by either pharmacological inhibition or genetic knockdown of PARP-1 indicate that PARP-1 plays a significant role in cellular injury following stroke, trauma, ischemia-reperfusion of the heart, spleen, skeletal muscle and retina, as well as in arthritis and liver diseases [5]. Activation of PARP-1 has been implicated in Alzheimer's disease [8], the 1-methyl-4-phenyl-1, 2,3,6-tetrahydropyridine (MPTP) model of Parkinson's disease [9, 10], spinal cord injury [11], and experimental models of diabetes [12, 13]. Cell culture models of primary neurons, fibroblast or HeLa cells have been widely used to understand the cascade of PARP-1 pathology. Taken together, these data demonstrate a significant role of PARP-1 activation in broad and diverse disease conditions in different types of tissues or cell types, and demonstrate the need to understand and control PARP-1 pathophysiology.

PARP-1 dependent cell death, known as Parthanatos, is unique in terms of its biochemical and morphological features. The biochemical features of Parthanatos are distinct from classically defined pathways of cell death and include rapid PARP-1 activation, early PAR accumulation, mitochondrial depolarization, early nuclear AIF translocation, loss of cellular NAD and ATP, and late caspase activation [17-19]. Caspase activation, which is a hallmark of apoptotic cell death, does not appear to play any role in Parthanatos as broad spectrum caspase inhibitors are unable to protect cells [17]. Morphological features of Parthanatos include shrunken and condensed nuclei, membranes disintegration and cells become propidium iodide positive within a few hours after the onset [17-19] of Parthanatos.

PAR is death signaling molecule in PARP-1 activation

Previously, it was presumed that PARP-1-dependent cell death was due to intracellular energy depletion, resulting from excessive utilization of nicotine amide adenine dinucleotide

(NAD^+) [20] (Figure 1). NAD^+ is a cofactor for many energy generating processes including glycolysis, the Krebs cycle and the pentose phosphate pathway [21]. While over-activation of PARP-1 leads to depletion of cellular energy levels [20], clear evidence that direct utilization of NAD^+ by PARP-1 activation depletes cellular energy to the extent that can kill the cells is lacking. Studies have shown that increasing cellular energy substrates such as NAD^+ can provide protection against PARP-1 mediated cell death [22]. However, since NAD^+ can act on many independent cellular targets, it is difficult to draw direct conclusions. Consumption of NAD^+ as a substrate by PARP-1 not only generates PAR but also nicotinamide as a by product. Nicotinamide is an inhibitor of PARP-1 [23]. Protection offered by increasing cellular NAD^+ should be taken with caution as negative feedback on PARP-1 activity by excessive generation of nicotinamide cannot be ignored. Studies on primary cell cultures showed that PARP-1 activation leads to cell death, but energy depletion may not be a primary factor in cell death [24, 25]. Our data show that PARP-1 activation upon cell death stimuli forms toxic levels of PAR that kills cells [17]. PAR formed by PARP-1 activity translocates to cytosol to induce cell death via nuclear translocation AIF [17-19] (Figure 2). Although PAR is largely generated in the nucleus, it translocates to the cytosol. The contribution of cytosolic PAR has not been determined, but PARPs role in the cytosol cannot yet be ruled out. Although disruption of PARP-1, the major PARP isoform that predominantly resides in the nucleus completely prevents Parthanatos. In any case PAR in the cytosol induces a death signal cascade. Neutralization of cytosolic PAR by PAR specific antibodies or degradation via PARG protects against NMDA-induced cell death in mouse primary neurons [17]. Conversely, exogenous delivery of purified PAR kills cells [17]. The toxic potential of PAR increases with dose and polymer complexity. Highly complex and long chain polymers are more toxic than simple and shorter polymers [17]. Among the PARP family members, there are at least six different PARPs that are confirmed to synthesize the formation of PAR [26]. The heterogeneity in the complexity and structure of PAR may vary depending upon the PARP involved and hence the differential role of individual PARPs in cell death and survival.

Poly (ADP-ribose) Glycohydrolase (PARG) and Parthanatos

While there are many genes encoding different PARPs, only a single gene encoding PARG has been discovered so far. Human full length PARG appears to have two splice variants 102 kDa and 99 kDa [27]. The full length nuclear 111kDa form of PARG appears to be less abundant, whereas the splice variants are more abundant forms of cellular PARG and they tend to reside in the cytosol [27]. PARG catalyzes the hydrolysis of PAR to free poly (ADP-ribose) or ADP-ribose units by its endoglycosidic or exoglycosidic activity [28]. Data in the last decade suggest that PARG is an important cellular enzyme that plays a critical role in cell survival and death. Genetic deletion of PARG results in embryonic lethality in mice and drosophila due to accumulation and altered hydrolysis of PAR [29, 30]. Recently, we demonstrated that overexpression of cytosolic PARG results in cyto-protection against PARP-1 dependent cell death and Parthanatos [17]. Delivery of purified PAR induces cell death in HeLa cells and mouse primary neurons. Predigestion of PAR with recombinant PARG protects against PAR-mediated cell death [17]. Trophobalst cultures from E 3.5 PARG knock out mice survive only in presence of PARP inhibitor. Withdrawal of the PARP inhibitor induces PAR-dependent cell death in these cultures. PARP inhibitor withdrawal in

PARG knock out trophoblast cultures leads to increased PAR accumulation and cell death, which shows the cytotoxic potential of PAR and the importance of PARG in cell survival [29]. Transgenic mice over-expressing PARG are protected against excitotoxicity and stroke [17, 31]. All these data provide cumulative evidence that PAR hydrolysis by PARG is essential for cell survival and that accumulation of PAR is detrimental and cytotoxic.

Recently, a 39-kDa ADP-ribose-(arginine) protein hydrolase (ARH3) was identified and characterized to have PARG like activity [32]. Whether the PARG-like activity on ARH3 has any biological significance, is unknown. However, the role of PARG-like activity of ARH3 does not seem critical for cell death processes, since there is lack of compensation of PAR catabolism by ARH3 in drosophila and mouse genetic knock outs of PARG [29, 30]. Thus, ARH3 does not significantly contribute to the cell survival process or PAR hydrolysis during cell stress conditions.

Mechanisms of PAR-induced cell death: involvement of mitochondria

Mitochondria carry out oxidative phosphorylation and energy generation for cells. Besides being cellular powerhouses, mitochondria under cell-stress conditions also act as death centers by releasing death factors such as cytochrome c and AIF [33]. These proteins, once released from mitochondria can induce either caspase-independent (AIF) or caspase-dependent (cytochrome C) cell death pathways [33]. AIF is a mitochondrial flavoprotein important for the mitochondrial energy generating processes [34]. AIF was originally identified as a mitochondrial protein, involved in cell death [35]. Studies in the last decade have shown that AIF is indeed a cell death signaling molecule that translocates to nucleus to induce large scale DNA fragmentation [36, 37]. A link between PARP-1 toxicity and early AIF translocation is clearly established [19]. Genetic knockdown of AIF or studies using antibody neutralization have shown AIF as a cell death effector in PARP-1 toxicity and Parthanatos [18, 38]. It was not clear how PARP-1 activation induced AIF release from mitochondria. Recently, our data provided evidence that PAR is a signaling molecule to mediate mitochondrial AIF release [17, 18] (Figure 2). PAR is found in the cytosol minutes after NMDA-stimulation in mouse cortical neurons. PAR in the cytosol colocalizes with mitochondria, suggesting a direct interaction of PAR and mitochondria to induce AIF release [17, 18] (Figure 2). Harlequin (Hq) mice have an approximately 80% reduction in AIF expression [39] that makes them a useful tool to model AIF-mediated cell death. Our data shows that Hq mice are resistant to Parthanatos [18]. Cortical neurons from Hq mice displayed less toxicity against NMDA and purified PAR polymer [18]. Restoration of AIF levels by viral-mediated forced AIF expression rendered Hq neurons equally susceptible to NMDA-induced cell death as wild type neurons [18]. Hq mice also showed reduced lesions after excitotoxicity and stroke [18, 38, 40]. Taken together all these data indicates that AIF is a death effector in Parthanatos.

How PAR induces AIF release, is not clear. AIF can be released from mitochondria following mitochondrial permeability transition (mPT) or mitochondrial BAX translocation [41-43]. Nuclear AIF translocation was shown to be critical for BAX-dependent cell death [40]. A link between BAX and PARP-1 mediated cell death was recently reported by one study. It was demonstrated that BAX knock out fibroblasts are highly resistant to

PARP-1 dependent cell death [24]. Studies further suggest that BAX activation occurs downstream of PARP-1 activation [24]. However, a link between PARP-1 activation and BAX translocation is missing. Previous data from our laboratory indicate that Bcl2 overexpression does not protect cells against PARP-1 dependent cell death but only delays the onset of cell death [19]. It may be possible that cell death in BAX knock out cultures is also delayed because of prolonged mitochondrial integrity following PARP-1 activation. However, further studies are needed to explore the role of BAX and other Bcl2 proteins in PARP-1 dependent cell death. mPT is a well established mechanisms to induce AIF and cytochrome C in certain models of cell death [41-43]. mPt follows the formation of mitochondrial permeability transition pore opening (mtPTP). Although there are conflicting reports about the composition of the mtPTP, it is thought that the mtPTP is a proteinacious pore that is composed of ANT from inner mitochondrial membrane, voltage dependent anionic channel (VDAC) and cyclophilin D from mitochondrial matrix [44-46]. Recent data suggests that VDAC is not a critical component of mtPTP [47]. mtPTP can be inhibited by the immunophilin, cyclosporin A or bongkrekic acid [46, 48, 49]. mPT and loss of mitochondrial membrane potential is an early event in PARP-1 dependent cell death [19, 50]. Studies show that cyclosporin A can inhibit PARP-1 dependent cell death in astrocytes following N-methyl-N′-nitro-N-nitrosoguanidine treatment and blocking mtPTP by cyclosporin A can preserve mitochondrial NAD^+ pools [50, 22]. However, these studies should be taken with caution as cyclosporin A can act on many targets. Additional studies are required to identify any role of mtPTP in PARP-1 dependent cell death and Parthanatos.

Recent studies show that truncation of AIF by calpains can release AIF from mitochondria [51]. Along this line, it was shown that genetic knockdown of calpain can protect cells against cell death in which PARP-1 is activated [24]. Similarly, over expression of endogenous calpain inhibitor calpastatin can inhibit cell death after PARP-1 activation [24]. However, it remains to be identified whether calapin inhibition or genetic knockdown is indeed a factor for cell survival in PARP-1 dependent cell death or whether calpain inhibition simply delays the onset of cell death and AIF-translocation. Also, the lack of knowledge of mechanisms of calpain activation in PARP-1 dependent cell death makes it difficult to identify calpains as PAR dependent mediators of AIF release, moreover, there are likely to be calpain-dependent and calpain-independent mechanisms of AIF release. PAR binds to a wide array of proteins both covalently as well as non-covalently and alters their function and configuration. It is possible that there are many different proteins that are targeted by PAR to induce AIF release. The identification of such proteins is imperative to understand the complex pathway of nuclear-mitochondria cross talk in PARP-1 dependent cell death and Parthanatos.

Summary

The intriguing aspect emerging from Parthanatos is the nuclear/mitochondrial cross talk with PAR as an important player for cell death initiation. PAR is generated mainly in the nucleus and localizes to cytosol and interacts with mitochondria to induce cell death. Parthanatos is a unique form of cell death that occurs across organ systems, and is primarily mediated by toxic accumulation of PAR in the cytosol due to overactivation of PARP-1. Manipulation of PARG enzymatic activities may provide an important therapeutic approach to limit the toxic

effects of Parthanatos. Mitochondria are the main centers to release cell death factors. In the case of Parthanatos, cell death is executed by mitochondrial release and nuclear translocation of AIF (Figure 2). Nuclear AIF-translocation induces large scale DNA fragmentation, chromatin condensation and cell death. This form of cell death is caspase-independent as caspase inhibitors are ineffective in limiting Parthanatos. Although, the mechanism of Parthanatos include PAR as a signaling molecule to induce AIF release from mitochondria, however, the mechanistic aspects of the AIF-releasing capacity of PAR still remain unclear.

PAR is able to alter the protein structure and function of a number of proteins by either the process of poly(ADP-ribosy)ation or through non-covalent interactions. Identification of PAR-binding proteins and their characterization may provide a novel opportunity to understand the PAR-signaling mechanisms and to develop small molecule inhibitors to prevent toxic manifestations of Parthanatos.

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References

1. Smith S. The world according to PARP. Trends Biochem Sci. 2001; 26:174–9. [PubMed: 11246023]
2. Hong SJ, Dawson TM, Dawson VL. Nuclear and mitochondrial conversations in cell death: PARP-1 and AIF signaling. Trends Pharmacol Sci. 2004; 25:259–64. [PubMed: 15120492]
3. D'Amours D, et al. Poly(ADP-ribosyl)ation reactions in the regulation of nuclear functions. Biochem J. 1999; 342(Pt 2):249–68. [PubMed: 10455009]
4. Ame JC, Spenlehauer C, de Murcia G. The PARP superfamily. Bioessays. 2004; 26:882–93. [PubMed: 15273990]
5. Virag L, Szabo C. The therapeutic potential of poly(ADP-ribose) polymerase inhibitors. Pharmacol Rev. 2002; 54:375–429. [PubMed: 12223530]
6. Poirier GG, et al. Poly(ADP-ribosyl)ation of polynucleosomes causes relaxation of chromatin structure. Proc Natl Acad Sci U S A. 1982; 79:3423–7. [PubMed: 6808510]
7. Jeggo PA. DNA repair: PARP - another guardian angel? Curr Biol. 1998; 8:R49–51. [PubMed: 9427640]
8. Love S, Barber R, Wilcock GK. Increased poly(ADP-ribosyl)ation of nuclear proteins in Alzheimer's disease. Brain. 1999; 122(Pt 2):247–53. [PubMed: 10071053]
9. Outeiro TF, et al. Pharmacological inhibition of PARP-1 reduces alpha-synuclein- and MPP+-induced cytotoxicity in Parkinson's disease in vitro models. Biochem Biophys Res Commun. 2007; 357:596–602. [PubMed: 17449015]
10. Mandir AS, et al. Poly(ADP-ribose) polymerase activation mediates 1-methyl-4-phenyl-1, 2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism. Proc Natl Acad Sci U S A. 1999; 96:5774–9. [PubMed: 10318960]
11. Genovese T, et al. Inhibitors of poly(ADP-ribose) polymerase modulate signal transduction pathways and secondary damage in experimental spinal cord trauma. J Pharmacol Exp Ther. 2005; 312:449–57. [PubMed: 15452194]
12. de la Lastra CA, Villegas I, Sanchez-Fidalgo S. Poly(ADP-ribose) polymerase inhibitors: new pharmacological functions and potential clinical implications. Curr Pharm Des. 2007; 13:933–62. [PubMed: 17430191]

13. Szabo C. Roles of poly(ADP-ribose) polymerase activation in the pathogenesis of diabetes mellitus and its complications. Pharmacol Res. 2005; 52:60–71. [PubMed: 15911334]
14. Mandir AS, et al. NMDA but not non-NMDA excitotoxicity is mediated by Poly(ADP-ribose) polymerase. J Neurosci. 2000; 20:8005–11. [PubMed: 11050121]
15. Meli E, et al. Differential role of poly(ADP-ribose) polymerase-1in apoptotic and necrotic neuronal death induced by mild or intense NMDA exposure in vitro. Mol Cell Neurosci. 2004; 25:172–80. [PubMed: 14962750]
16. Cosi C, et al. The PARP inhibitor benzamide protects against kainate and NMDA but not AMPA lesioning of the mouse striatum in vivo. Brain Res. 2004; 996:1–8. [PubMed: 14670625]
17. Andrabi SA, et al. Poly(ADP-ribose) (PAR) polymer is a death signal. Proc Natl Acad Sci U S A. 2006; 103:18308–13. [PubMed: 17116882]
18. Yu SW, et al. Apoptosis-inducing factor mediates poly(ADP-ribose) (PAR) polymer-induced cell death. Proc Natl Acad Sci U S A. 2006; 103:18314–9. [PubMed: 17116881]
19. Yu SW, et al. Mediation of poly(ADP-ribose) polymerase-1-dependent cell death by apoptosis-inducing factor. Science. 2002; 297:259–63. [PubMed: 12114629]
20. Ha HC, Snyder SH. Poly(ADP-ribose) polymerase is a mediator of necrotic cell death by ATP depletion. Proc Natl Acad Sci U S A. 1999; 96:13978–82. [PubMed: 10570184]
21. Belenky P, Bogan KL, Brenner C. NAD+ metabolism in health and disease. Trends Biochem Sci. 2007; 32:12–9. [PubMed: 17161604]
22. Alano CC, et al. Differences among cell types in NAD(+) compartmentalization: A comparison of neurons, astrocytes, and cardiac myocytes. J Neurosci Res. 2007; 85:3378–85. [PubMed: 17853438]
23. Hageman GJ, Stierum RH. Niacin, poly(ADP-ribose) polymerase-1 and genomic stability. Mutat Res. 2001; 475:45–56. [PubMed: 11295153]
24. Moubarak RS, et al. Sequential activation of poly(ADP-ribose) polymerase 1, calpains, and Bax is essential in apoptosis-inducing factor-mediated programmed necrosis. Mol Cell Biol. 2007; 27:4844–62. [PubMed: 17470554]
25. Fossati S, et al. Neither energy collapse nor transcription underlie in vitro neurotoxicity of poly(ADP-ribose) polymerase hyper-activation. Neurochem Int. 2007; 50:203–10. [PubMed: 17052800]
26. Schreiber V, et al. Poly(ADP-ribose): novel functions for an old molecule. Nat Rev Mol Cell Biol. 2006; 7:517–28. [PubMed: 16829982]
27. Meyer-Ficca ML, et al. Human poly(ADP-ribose) glycohydrolase is expressed in alternative splice variants yielding isoforms that localize to different cell compartments. Exp Cell Res. 2004; 297:521–32. [PubMed: 15212953]
28. Davidovic L, et al. Importance of poly(ADP-ribose) glycohydrolase in the control of poly(ADP-ribose) metabolism. Exp Cell Res. 2001; 268:7–13. [PubMed: 11461113]
29. Koh DW, et al. Failure to degrade poly(ADP-ribose) causes increased sensitivity to cytotoxicity and early embryonic lethality. Proc Natl Acad Sci U S A. 2004; 101:17699–704. [PubMed: 15591342]
30. Hanai S, et al. Loss of poly(ADP-ribose) glycohydrolase causes progressive neurodegeneration in Drosophila melanogaster. Proc Natl Acad Sci U S A. 2004; 101:82–6. [PubMed: 14676324]
31. Cozzi A, et al. Poly(ADP-ribose) accumulation and enhancement of postischemic brain damage in 110-kDa poly(ADP-ribose) glycohydrolase null mice. J Cereb Blood Flow Metab. 2006; 26:684–95. [PubMed: 16177811]
32. Oka S, Kato J, Moss J. Identification and characterization of a mammalian 39-kDa poly(ADP-ribose) glycohydrolase. J Biol Chem. 2006; 281:705–13. [PubMed: 16278211]
33. Beal MF. Mitochondria take center stage in aging and neurodegeneration. Ann Neurol. 2005; 58:495–505. [PubMed: 16178023]
34. Pospisilik JA, et al. Targeted Deletion of AIF Decreases Mitochondrial Oxidative Phosphorylation and Protects from Obesity and Diabetes. Cell. 2007; 131:476–91. [PubMed: 17981116]
35. Susin SA, et al. Molecular characterization of mitochondrial apoptosis-inducing factor. Nature. 1999; 397:441–6. [PubMed: 9989411]

36. Krantic S, et al. Apoptosis-inducing factor: a matter of neuron life and death. Prog Neurobiol. 2007; 81:179–96. [PubMed: 17267093]
37. Modjtahedi N, et al. Apoptosis-inducing factor: vital and lethal. Trends Cell Biol. 2006; 16:264–72. [PubMed: 16621561]
38. Culmsee C, et al. Apoptosis-inducing factor triggered by poly(ADP-ribose) polymerase and Bid mediates neuronal cell death after oxygen-glucose deprivation and focal cerebral ischemia. J Neurosci. 2005; 25:10262–72. [PubMed: 16267234]
39. Klein JA, et al. The harlequin mouse mutation downregulates apoptosis-inducing factor. Nature. 2002; 419:367–74. [PubMed: 12353028]
40. Cheung EC, et al. Apoptosis-inducing factor is a key factor in neuronal cell death propagated by BAX-dependent and BAX-independent mechanisms. J Neurosci. 2005; 25:1324–34. [PubMed: 15703386]
41. Christophe M, Nicolas S. Mitochondria: a target for neuroprotective interventions in cerebral ischemia-reperfusion. Curr Pharm Des. 2006; 12:739–57. [PubMed: 16472163]
42. Vieira H, Kroemer G. Mitochondria as targets of apoptosis regulation by nitric oxide. IUBMB Life. 2003; 55:613–6. [PubMed: 14711007]
43. Er E, et al. Mitochondria as the target of the pro-apoptotic protein Bax. Biochim Biophys Acta. 2006; 1757:1301–11. [PubMed: 16836974]
44. Crompton M. The mitochondrial permeability transition pore and its role in cell death. Biochem J. 1999; 341(Pt 2):233–49. [PubMed: 10393078]
45. Crompton M, et al. Mitochondrial intermembrane junctional complexes and their involvement in cell death. Biochimie. 2002; 84:143–52. [PubMed: 12022945]
46. Halestrap AP, McStay GP, Clarke SJ. The permeability transition pore complex: another view. Biochimie. 2002; 84:153–66. [PubMed: 12022946]
47. Baines CP, et al. Voltage-dependent anion channels are dispensable for mitochondrial-dependent cell death. Nat Cell Biol. 2007; 9:550–5. [PubMed: 17417626]
48. Andrabi SA, et al. Direct inhibition of the mitochondrial permeability transition pore: a possible mechanism responsible for anti-apoptotic effects of melatonin. Faseb J. 2004; 18:869–71. [PubMed: 15033929]
49. Halestrap AP, Brennerb C. The adenine nucleotide translocase: a central component of the mitochondrial permeability transition pore and key player in cell death. Curr Med Chem. 2003; 10:1507–25. [PubMed: 12871123]
50. Alano CC, Ying W, Swanson RA. Poly(ADP-ribose) polymerase-1-mediated cell death in astrocytes requires NAD+ depletion and mitochondrial permeability transition. J Biol Chem. 2004; 279:18895–902. [PubMed: 14960594]
51. Cao G, et al. Critical role of calpain I in mitochondrial release of apoptosis-inducing factor in ischemic neuronal injury. J Neurosci. 2007; 27:9278–93. [PubMed: 17728442]

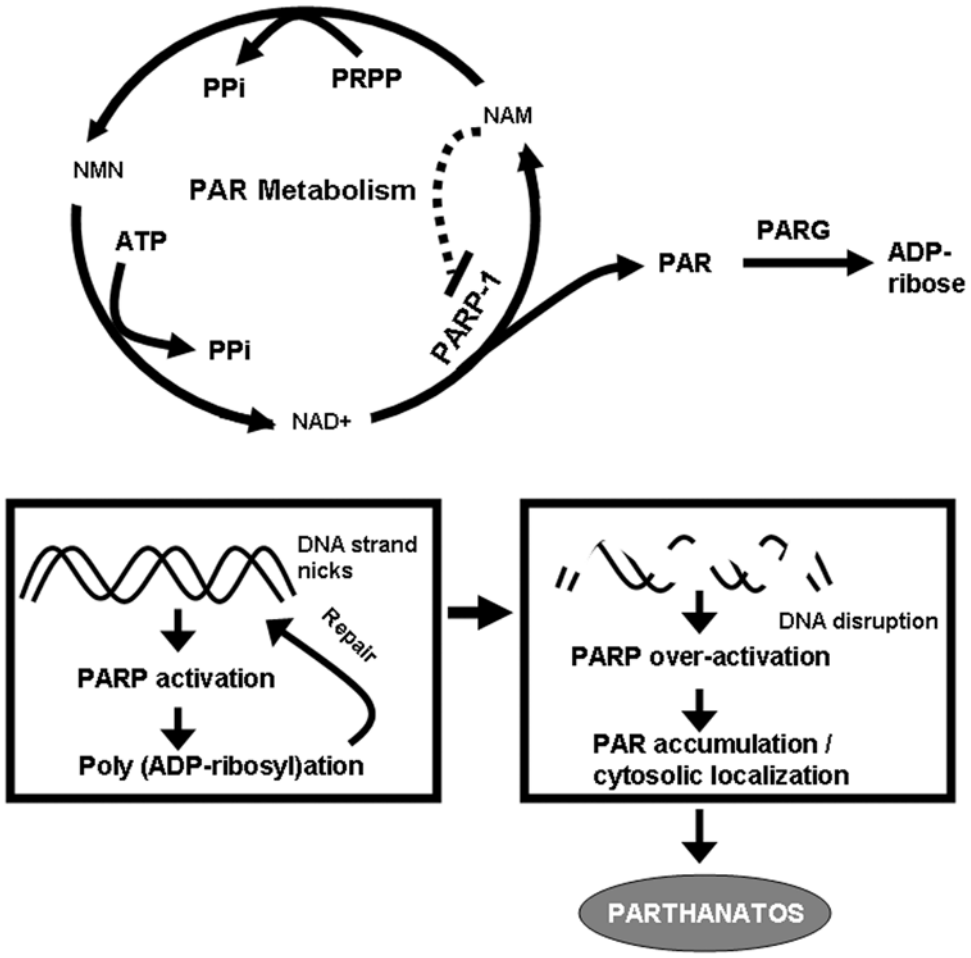

Figure 1.

PARP-1 utilizes NAD^+ as a substrate and builds-up PAR polymers on acceptor proteins. PAR generated by PARP-1 is hydrolysed by PARG into ADP-ribose or free PAR. In the process of PAR formation nicotinamine (NAM) is generated as a by product. NAM is a PARP inhibitor and may cause a negative feed back on PARP activity. NAM enters into NAD^+ synthetic cycle nicotine mono nucleotide and ATP as precursors. The reaction requires phosphor ribosyl-1-pyrophosphate (PRPP). NAM can inhibit PARP-1 by negative feed back effect. Mild DNA nicks or breaks activate PARP to induce DNA repair via poly(ADPribosyl)ation process. When the DNA damage is beyond the threshold of poly(ADPribosyl)ation-mediated repair, excessive PAR generated kills the cells via the process of Parthanatos.

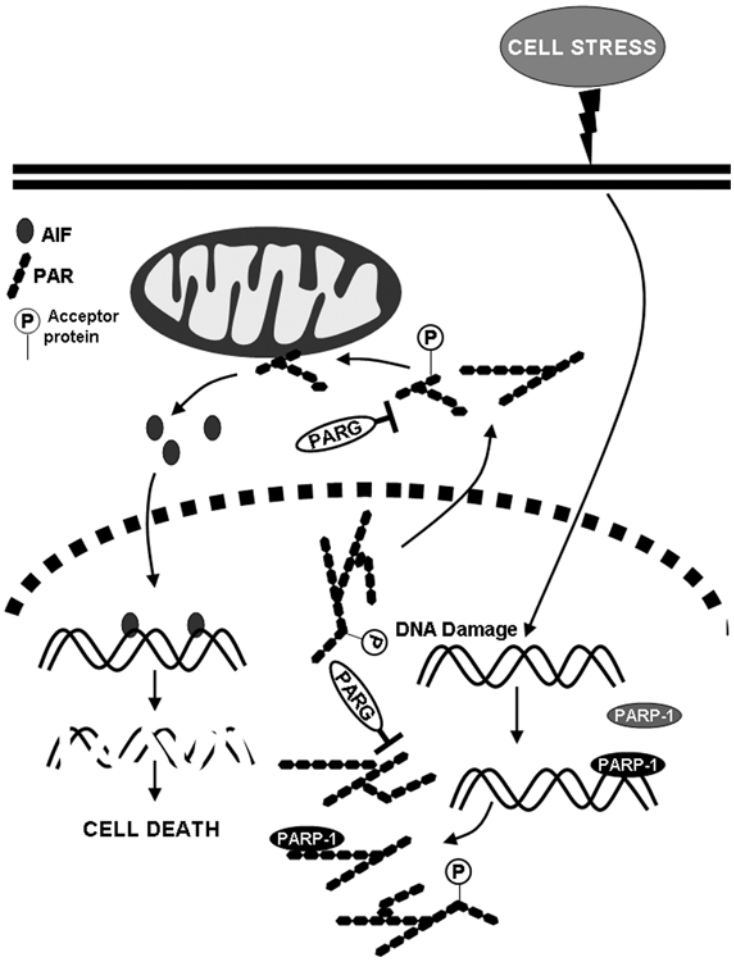

Figure 2.

PARP-1 activation and role of PAR in Parthanatos. DNA damage in cell stress conditions leads to PARP-1 activation. Active PARP-1 uses NAD^+ as a substrate and builds PAR on itself (auto-modification) and on various acceptor proteins (hetero-modification) in the nucleus. PARG can hydrolyze PAR in the nucleus to generate fee PAR or ADP-ribose. PAR accumulation induces cell death. PAR is mainly generated in the nucleus and translocates to cytosol either as attached polymer to poly(ADP-ribosyl)ated proteins or as a free polymer. Cytosolic isoforms of PARG can degrade PAR when present in optimal amounts in relation to PAR generated. In the cytosol PAR interacts with mitochondria to induce AIF release. On translocation to nucleus, AIF binds to DNA and mediates a large scale DNA fragmentation and cell death.