

## DNA REPAIR '99

# Poly(ADP-Ribose) Polymerase in the Cellular Response to DNA Damage, Apoptosis, and Disease

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To ensure the accurate transmission of genetic information in dividing cells, specific biochemical pathways maintain integrity. Fundamental to these pathways is the recognition, by specific proteins, of genomic lesions, which signal the presence of DNA damage to other nuclear and cytoplasmic factors. DNA strand breaks, generated either directly by genotoxic agents (oxygen radicals, ionizing radiations, or monofunctional alkylating agents) or indirectly after enzymatic incision of a DNA-base lesion, trigger the synthesis of poly(ADP-ribose) by the enzyme poly(ADP-ribose) polymerase (PARP [E.C.2.4.2.30]). PARP is a nuclear zinc-finger DNA-binding protein that detects DNA strand breaks. At a breakage site, PARP catalyzes the transfer of the ADP-ribose moiety, from the respiratory coenzyme NAD<sup>+</sup> to a limited number of protein acceptors. These PARP substrates may influence chromatin architecture, as with histones H1, H2B, and lamin B, or they may act in DNA metabolism, as with DNA-replication factors and PARP itself (reviewed by de Murcia and Menissier-de Murcia 1994; Oei et al. 1997). Because of the high negative charge on ADP-ribose polymers (fig. 1A), poly(ADP-ribosylated) proteins lose their affinity for DNA and hence, in many cases, their biological activities. PARP and other modified proteins may be restored to their native state after poly(ADP-ribose) glycohydrolase. Therefore, poly(ADP-ribosylation) is an immediate posttranslational modification of nuclear DNA-binding proteins, induced by DNA damaging agents.

The physiological role of PARP has been much debated during this past decade, but molecular and genetic

approaches have been exploited only recently to study the role of the immediate poly(ADP-ribose) synthesis that occurs in response to DNA strand breaks. In this review, we summarize the most recent findings on PARP, which define unambiguously its role in cell response to DNA damage and repair, including cell death by apoptosis and some newly reported biological functions for PARP in different pathologies related to inflammatory injury to the cell.

### PARP and the DNA-Damage Surveillance Network

PARP activity is stimulated >500-fold on binding to DNA strand breaks. The human protein spans 1,014 amino acids and comprises three main sequence modules: an N-terminal DNA-binding domain (DBD) bearing two zinc fingers (FI and FII), which acts as a molecular nick sensor; a central automodification domain containing auto-poly(ADP-ribosylation) sites, which regulate PARP-DNA interactions; and a C-terminal catalytic domain, which performs nick-binding-dependent poly(ADP-ribose) synthesis (fig. 1; reviewed by de Murcia and Menissier-de Murcia 1994).

Independent experimental approaches have identified two surfaces on which PARP interacts with its partners (fig. 1A). Interestingly, in a two-hybrid screen we identified the base-excision repair (BER) factor XRCC1 (x-ray cross-complementing-1) as a partner of PARP (Masson et al. 1998). Both proteins interact by their BRCT (BRCA-1 C-terminus) motifs, and XRCC1 interacts with DNA ligase III by a second BRCT motif (Caldecott et al. 1996). This interaction provides strong evidence that PARP is a member of a BER multiprotein complex that comprises nick sensors (PARP and DNA ligase III), an adaptor factor (XRCC1), and the direct mediators of DNA repair (DNA polymerase  $\beta$  and DNA ligase III).

PARP knockout mice were developed to provide definitive answers about the physiological role of PARP in different cellular processes. We generated three PARP knockout mice independently, by disrupting exon 1 (Wang et al. 1997), exon 2 (Menissier-de Murcia et al. 1997), or exon 4 (Masutani et al. 1999) by homologous

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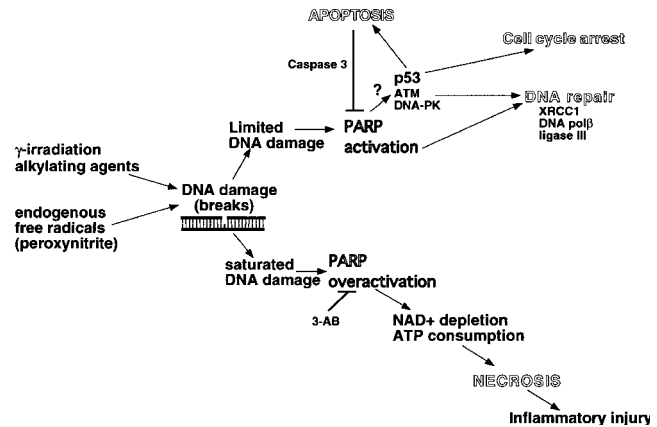
improves endonuclease access to chromatin. DNA fragmentation during apoptosis is produced by numerous single-strand nicks in the linker regions of chromatin, and PARP interacts preferentially with single-stranded DNA breaks (Le Cam et al. 1994). In this manner, PARP probably helps recruit BER proteins to repair damaged DNA. A recent study by Smulson et al. (1998) showed that the DNA-binding domain of PARP, which is isolated when it is cleaved by caspase-3, irreversibly binds internucleosomal DNA in apoptotic cells. This proteolytic fragment may contribute to the irreversibility of apoptosis, by preventing the access of DNA-repair enzymes to the lesion. The localization of PARP to the nuclear envelope (Dantzer et al. 1998) also suggests that its cleavage during apoptosis participates in nuclear disassembly and facilitates downstream events, all of which are delayed by the expression of the uncleavable PARP mutant.

The consequences of cleaving several caspase substrates have been probed in a similar manner, by the expression of uncleavable variants of these target proteins in cells that would otherwise undergo normal apoptosis. Sakahira et al. (1998) provided an elegant example of this approach in their study of caspase-activated deoxyribonuclease. Cells expressing an uncleavable variant of this protein failed to degrade DNA, but they displayed all the other characteristics of apoptosis. Cells that express a corresponding mutation in lamin, on the other hand, showed no signs of chromatin condensation or of nuclear shrinkage during apoptosis (Rao et al. 1996).

Inhibition of caspase activity causes a switch from apoptosis to necrosis (fig. 2; also see also Hirsch et al. 1997), a distinct form of cell death that often arises in cells deprived of ATP (Leist et al. 1997), as in ischemia. Induction of apoptosis therefore protects an organism from necrotic-tissue damage, and the inactivation of apoptosis may be important in many pathologies. Interestingly, PARP is also cleaved during necrosis, although the fragments differ from those found in apoptotic cells (Gillouf 1999) and retain biological activity for a longer time. Thus, as depicted in figure 2, the failure of cells to fully inactivate PARP could lead to massive NAD<sup>+</sup> consumption and energy depletion, which together contribute to cell death by necrosis (Szabo and Dawson 1998).

#### Apoptosis in PARP-Deficient Cells

DNA damage, such as is caused by treatment of cells with alkylating agents, activates PARP in normal cells (Menissier-de Murcia et al. 1997; Oliver et al. 1998) but also causes *PARP*<sup>-/-</sup> splenocytes to undergo apoptosis extremely rapidly (Wang et al. 1997; Oliver et al. 1998). The extreme sensitivity of *PARP*<sup>-/-</sup> cells to these agents could be explained by the accumulation of unrepaired



**Figure 2** PARP in the network of DNA damage surveillance and inflammatory cell injury. Under physiological conditions and after limited damage to DNA, PARP plays a role as a surviving factor allowing the activation of DNA-repair pathways, through recruitment of the BER complex. The decision for the cell to engage the apoptotic pathway after genotoxic damage takes place downstream of p53 activation. The molecular determinants that switch between DNA repair and cell cycle arrest, on one hand, and apoptosis, on the other hand, are not yet fully understood. Under pathological situations, in which free radicals can damage DNA, PARP activation by massive DNA damage might deplete NAD<sup>+</sup> cellular stores, altering glycolysis and mitochondrial respiration and leading to necrotic-cell death. The failure of the cell to cleave PARP may contribute to the depletion of cell energy during necrosis.

DNA damage. This view is supported by the observation that DNA rejoining, as measured by the comet assay, is prolonged in *PARP*<sup>-/-</sup> cells (Trucco et al. 1998). In contrast to our findings and to those of Wang et al. (1998), Simbulan-Rosenthal et al. (1998b) reported that PARP-deficient cells are resistant to cell death after CD95 treatment. This discordant finding would seem to indicate that PARP activates apoptosis only under some conditions. However, the use, in that study, of immortalized clones of stably transfected *PARP*<sup>-/-</sup> embryonic fibroblasts—rather than primary cells—may have altered the cells' responses to CD95. Overall, the current data suggest that PARP is a passive rather than an active player in the apoptotic process.

#### Sensing and Signaling of DNA Damage: PARP and p53

A number of studies have suggested a role for PARP and/or poly(ADP-ribose) in p53-mediated DNA damage, although the nature and the consequence of this interaction are controversial. Some groups have reported that inhibition or genetic disruption of PARP result in increased p53 accumulation due to the persistence of unrepaired DNA. In their pioneering study, Lu and Lane (1993) found that x-ray-induced p53 accumulation increased in cells treated with the PARP inhibitor, 3-ami-

nobenzamide. Our own results with splenocytes, bone-marrow cells, and primary embryonic fibroblasts from PARP-deficient mice show an increased accumulation of p53 after treatment with an alkylating agent (Menissier-de Murcia et al. 1997; F. J. Oliver, G. de la Rubia, J. Menissier-de Murcia, and G. de Murcia, unpublished data). A recent report by Simbulan-Rosenthal et al. (1998a) suggested that inactivation of PARP affects the duration but not the magnitude of p53 accumulation in  $\gamma$ -ray-irradiated Burkitt lymphoma cells. On the other hand, other groups have identified PARP as a necessary step for p53 expression and activation. Whitacre et al. (1995) suggested that cell lines that were defective in poly(ADP-ribosylation) had lower basal p53 levels than were seen in the parental cell line and that they failed to activate p53 in response to etoposide. Similar results were obtained with cells cultured in the absence of nicotinamide. A recent report by Wang et al. (1998) suggested that, in some cultured cells, poly(ADP-ribosylation) is required for rapid accumulation of p53, as well as for activation of sequence-specific DNA binding and trans-activation by p53 after DNA damage. Results obtained with PARP<sup>-/-</sup> fibroblasts from one group's knock-out mice suggest that the p53 accumulation is controlled by PARP-dependent and PARP-independent pathways but that p53 activation is largely independent of PARP (Agarwal et al. 1997).

It has been proposed that, at the molecular level, PARP induces p53 induction, either by direct protein-to-protein interaction or by poly(ADP-ribosylation) (Malanga et al. 1998). PARP also has been shown to stimulate DNA-PK activity in vitro by the enzyme's catalytic subunit, which, in turn, regulates p53 activity by phosphorylation (Ruscetti et al. 1998). Indeed, mice deficient in both PARP and the catalytic subunit of DNA-PK (the product of the *Scid* gene; Maizels 1999 [in this issue]) are highly prone to T-cell lymphomas. Neither genetic deficiency alone is sufficient to cause this phenotype, so it appears that PARP and DNA-PK cooperate to help maintain the integrity of the genome (Morrison et al. 1997). Thus, the role of PARP in p53 activation could be more complex than a direct activation. PARP might act via DNA-PK and/or other proteins to signal DNA damage to p53 (fig. 2). The phenotypes of mice with other combinations of genetic defects, such as *ATM* with *PARP* or *P53* with *PARP*, should clarify the complex interaction between the different pathways involved in signaling from DNA damage and transduction to p53.

### PARP in Different Pathologies

Studies from several laboratories indicate that PARP acts in the inflammatory response and in pathologies, such as brain ischemia, diabetes, and septic shock, that are associated with inflammatory cell damage. Several

mechanisms have been proposed to explain why inactivation of PARP (either pharmacologically or with genetically engineered animals that lack PARP) improves the clinical outcome of animals with those conditions.

Szabo and Dawson (1998) recently reviewed the evidence for the following model: either after inflammatory stress or during reperfusion after cerebral ischemia macrophages and endothelial cells activate a massive synthesis of nitric oxide (NO), which, in turn, is converted into a cytotoxic derivative, peroxytrite. This compound rapidly induces DNA single-strand breaks, leading to overactivation of PARP in neighboring cells. Depletion of cellular energy then causes mitochondria to generate free radicals and to kill the cells by a necrotic mechanism (fig. 2). Results from our group (F. J. Oliver, J. Menissier-de Murcia, and G. de Murcia, unpublished data) show a functional association between PARP and NF- $\kappa$ B, a key regulator of transcription during inflammation. Through this association, PARP—and, probably, poly(ADP-ribosylation)—regulate NF- $\kappa$ B-dependent transcription. Thus, PARP appears to promote inflammation, both by mediating the cytotoxicity of NO derivatives and by its affect on NF- $\kappa$ B. One or both of these mechanisms might explain the resistance of PARP<sup>-/-</sup> mice to brain ischemia, in which synthesis of NO and TNF- $\alpha$  up-regulation play a crucial role (Barone et al. 1997).

Two very recent reports, by Masutani et al. (1999) and Burkart (1999), indicate that PARP-mutant mice enjoy an increased resistance to streptozotocin-induced diabetes. Interestingly, this autoimmune condition results in part from inflammatory damage to pancreatic islet  $\beta$ -cells. Several studies have also implicated PARP in systemic lupus erythematosus (SLE), an autoimmune disorder characterized by production of autoantibodies against intracellular antigens, including DNA. In one study, individuals with SLE showed a 70% decrease in PARP activity (Lee et al. 1994). Moreover, a genetic susceptibility to SLE has been linked to 1q41-q42, which contains the *PARP* gene (Tsao et al. 1997; Moser et al. 1998). However, inheritance of this condition appears to be complex, and the chromosomal locus implicated also includes other plausible candidate genes, including the major-histocompatibility-complex gene.

### Future Lines of Investigation

#### *PARP in Transcription and Chromatin Remodeling*

Throughout the past several years, PARP has been shown to interact with a variety of transcription factors in addition to p53. The transcription factors YY1, AP2 (Oei et al. 1998), OCT1 (Nie et al. 1998), mCAT (Butler and Ordahl 1999), and DF4 (Plaza et al. 1999) all either

interact with PARP *in vitro* or are found to be poly(ADP-ribosylated). Interestingly, the automodification domain of PARP, which encompasses a BRCT domain (Leadon 1999 [in this issue]), is responsible for complex formation between PARP and Oct-1 or DF4 (fig. 1). The BRCT domain of *BRCA1* contains the minimal transcriptional activation domain of this protein and regulates p53-dependent gene expression (Ouchi et al. 1998). In spite of increasing evidence that PARP influences the transcriptional activation of a number of genes, further experimental approaches are needed to elucidate the molecular interaction between PARP and the transcription machinery. In this regard, the propensity of PARP to bind with DNA crossovers and to induce DNA loops in undamaged DNA deserves more attention (de Murcia and Menissier-de Murcia 1994). This property, which PARP shares with topoisomerases (Zechiedrich and Osheroff 1990), may have important implications for both the anchoring of chromatin loops to the nuclear matrix and the loading of transactivators at specific sites. Poly(ADP ribosylation) of histone H1 may represent a relative simple means by which the cell destabilizes higher-order chromatin structures (de Murcia et al. 1986) and improves the access of transcription factors to regulatory sequences. We postulate that PARP also ADP ribosylates DNA-bound transcription factors and modulates their biological activity, as has been shown for p53 (Malanga et al. 1998). Finally, ADP ribosylation may also regulate the level of DNA methylation (Zardo and Caiafa 1998), a well-known marker of promoter activity.

#### *PARP Homologues*

Although for many years it had been assumed that PARP activity is associated with a single protein, this assumption has been challenged by the recent discovery of two PARP homologues: (1) tankyrase, a protein with regions homologous to ankyrins and to the PARP catalytic domain (Smith et al. 1998), which binds to and negatively regulates TRF1, a factor involved in telomere maintenance; and (2) PARP-2, a novel mammalian DNA-damage-dependent poly(ADP-ribose) polymerase recently cloned in our laboratory (J. C. Amé, V. Rolli, V. Schreiber, Menissier-de Murcia, and G. de Murcia, unpublished data). The *PARP-2* gene maps to chromosomes 14C1 and 14q11.2 in mouse and human, respectively. Although it lacks a classic zinc-finger module, the recombinant mouse *PARP-2* binds to damaged DNA *in vitro* and catalyzes the formation of poly(ADP-ribose) polymers in a DNA-dependent manner. This novel PARP homologue localizes to the cell nucleus and may serve as a backup in cell lines that lack the 113-kD PARP protein. It is clear that more work will be necessary to unravel the properties of these enzymes and to develop

animal models in which PARP activity is totally abolished.

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