Am. J. Hum. Genet. 64:1282–1288, 1999

DNA REPAIR '99
Poly(ADP-Ribose) Polymerase in the Cellular Response to DNA Damage, Apoptosis, and Disease

F. Javier Oliver, Josiane Menissier-de Murcia, and Gilbert de Murcia

UPR 9003 du Centre National de la Recherche Scientifique, Laboratoire Conventionné avec le Commissariat à l'Énergie Atomique, École Supérieure de Biotechnologie de Strasbourg, Strasbourg

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^+ 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. 1*A*), 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.

Received March 10, 1999; accepted for publication March 17, 1999; electronically published April 12, 1999.

Address for correspondence and reprints: Dr. F. Javier Oliver, Centre National de la Recherche Scientifique, Laboratoire Conventionné avec le Commissarait à l'Énergie Atomique, École Supérieure de Biotechnologie de Strasbourg, Boulevard Sébastien Brant, F-67400 Illkirch-Graffenstaden, Strasbourg, France. E-mail: Javier.Oliver@esbs.u-strasbg.fr

This article represents the opinion of the authors and has not been peer reviewed.

0002-9297/99/6405-0006$02.00

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. 1*A*). 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 β 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

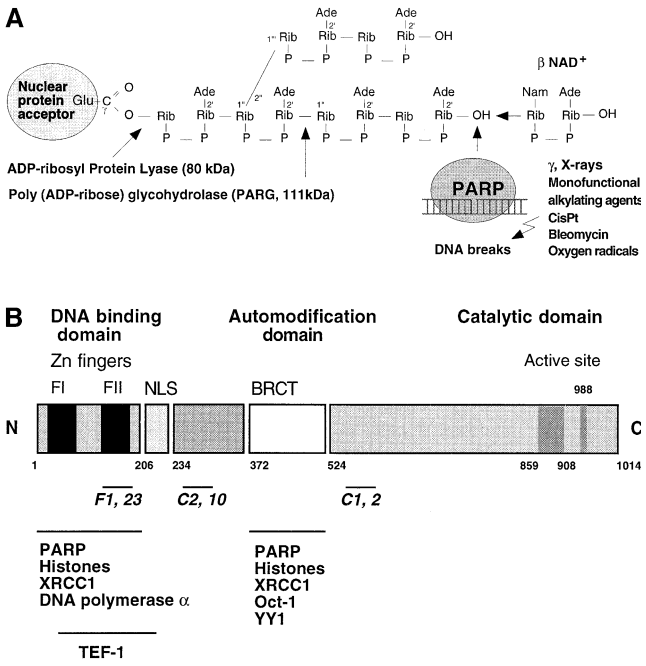

Figure 1 *A,* Metabolism of poly(ADP-ribose) during DNA damage and repair induced by various genotoxins. *B,* Domain structure of human PARP. PARG = poly(ADP-ribose) glycohydrolase; NLS = nuclear-localization signal. Indicated below the domain structure is the epitope map of several commonly used antibodies to human PARP. Shown below are the binding sites of various PARP partners, including PARP itself, histones, DNA polymerase-α, XRCC1, Oct-1, YY1, and TEF-1.

recombination. We reported that PARP-deficient mice are hypersensitive to monofunctional alkylating agents, such as N-methyl-N-nitrosourea (MNU) and γ-rays, which are potent PARP activators in wild-type (wt) littermates. These results were confirmed in two other constructs, at the animal level (Wang et al. 1997) and at the cellular level (Masutani et al. 1999). As expected, MNU and γ-ray irradiation of mutant mice led to an increase in reciprocal exchange of DNA segments in sister chromatids. These data demonstrate the crucial role of PARP in the processing of DNA lesions induced by monofunctional alkylating agents and γ-ray irradiation, both of which trigger the BER pathway.

We evaluated the DNA-repair capacity of PARP-deficient cells, by single-cell electrophoresis, using the "comet assay," which monitors the level of broken DNA in a given cell. After treatment with genotoxins, PARP-deficient cells display a considerably prolonged delay in DNA strand–break rejoining, compared with a wt cell line (Trucco et al. 1998). Whole-cell extracts from PARP-deficient cell lines are also defective in the BER pathway's polymerization step, which replaces long patches of basic sites (Dantzer et al., 1999), which is consistent with evidence that PARP interacts with XRCC1.

PARP and Apoptosis

Apoptosis, or programmed cell death, is a fundamental biological process that plays an important role in early development, cell homeostasis, and diseases such as neurodegenerative disorders and cancer (reviewed by Evan and Littlewood 1998; also see other reviews in the same issue of *Science*). Apoptosis can occur in response to a number of stimuli, such as genotoxic damage and withdrawal of growth factors, or after activation of specific receptors, such as CD95 and the TNF receptor. Morphologically, this form of cell death is characterized by membrane blebbing, cell shrinkage, chromatin condensation, and DNA cleavage, until finally the cell is fragmented into membrane-bound apoptotic bodies. There is increasing biochemical evidence that the caspase family of cysteine proteases mediates the highly ordered process leading to cell death. Caspases are responsible for the disabling of critical homeostatic and repair enzymes, as well as of key structural components during apoptosis. Caspases exist in the cytoplasm as inactive proenzymes, which are processed to a large and a small subunit to form the active enzyme (Thornberry and Lazebnik 1998).

Cleavage of PARP during Apoptosis

Kaufmann et al. (1993) showed that PARP is cleaved by caspases at a single site at an early stage of apoptosis, thus separating PARP DBD from its catalytic domain and inactivating the enzyme. PARP cleavage has been shown in almost all forms of apoptosis, but, whenever apoptosis is inhibited by such mechanisms as Bcl-2 overexpression or caspases inhibition, PARP cleavage is also blocked (Duriez and Shah 1997). These findings suggest that loss of PARP function is required for the efficient completion of apoptosis. To address this model, we expressed a noncleavable variant of the enzyme in PARP-deficient cells. Cells that express the PARP mutant D214A-PARP were exposed to anti-CD95 antibody, a treatment that induces apoptosis in wt cells, and we observed a significant delay in cell death (Oliver et al. 1998). Morphological analysis also showed significantly retarded cell shrinkage and nuclear condensation, indicating that the cleavage of PARP during apoptosis facilitates cellular disassembly, particularly of the nucleus, and ensures the completion and irreversibility of this process.

We propose that caspases cleavage of PARP promotes apoptosis in two respects: (1) the absence of PARP—and also of the DNA-dependent protein kinase, another early target of caspases (Casciola-Rosen et al. 1996)—disables key aspects of the cellular genomic surveillance mechanism and prevents unnecessary DNA repair that would delay chromatin degradation; and (2) PARP cleavage

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 a 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^+ consumption and energy depletion, which together contribute to cell death by necrosis (Szabo and Dawson 1998).

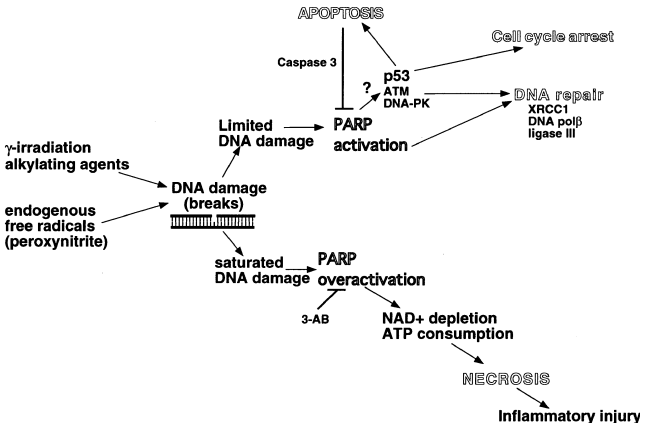

Figure 2 PARP in the network of DNA damage surveillance and inflammatory cell injury. Under physiological conditions and after limited damage to DNA, PARP plays a role as a surviving factor allowing the activation of DNA-repair pathways, through recruitment of the BER complex. The decision for the cell 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^+ 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.

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 $PARP^{-/-}$ splenocytes to undergo apoptosis extremely rapidly (Wang et al. 1997; Oliver et al. 1998). The extreme sensitivity of $PARP^{-/-}$ cells to these agents could be explained by the accumulation of unrepaired DNA damage. This view is supported by the observation that DNA rejoining, as measured by the comet assay, is prolonged in $PARP^{-/-}$ cells (Trucco et al. 1998). In contrast to our findings and to those of Wang et al. (1998), Simbulan-Rosenthal et al. (1998*b*) 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 $PARP^{-/-}$ 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. (1998*a*) suggested that inactivation of PARP affects the duration but not the magnitude of p53 accumulation in γ-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 $PARP^{-/-}$ fibroblasts from one group's knockout 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 reperfussion 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-κB, a key regulator of transcription during inflammation. Through this association, PARP—and, probably, poly(ADP-ribosylation)—regulate NF-κB–dependent transcription. Thus, PARP appears to promote inflammation, both by mediating the cytotoxicity of NO derivatives and by its affect on NF-κB. One or both of these mechanisms might explain the resistance of $PARP^{-/-}$ mice to brain ischemia, in which synthesis of NO and TNF-α 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 β-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.

Acknowledgments

We are indebted to our colleagues of the PARP group—A. Agustin, J. C. Amé, F. Dantzer, C. Niedergang, V. Rolli, B. Rinaldi, G. de la Rubia, and V. Schreiber—for their contribution to the work summarized in this review. We are grateful to Dr. S. Shall for critical reading of the manuscript. We apologize for the exclusion, because of the length limit of this review, of very important references. This work was supported by the Association pour la Recherche contre le Cancer, Electricité de France, le Commissariat à l'Énergie Atomique, and la Fondation pour la Recherche Médicale.

References

Agarwal ML, Agarwal A, Taylor WR, Wang ZQ, Wagner EF, Stark GR (1997) Defective induction but normal activation and function of p53 in mouse cells lacking poly-ADP-ribose polymerase. Oncogene 15:1035–1041

Barone FC, Arvin B, White RF, Miller A, Webb CL, Willette RN, Lysko PG, et al (1997) Tumor necrosis factor-alpha: a mediator of focal ischemic brain injury. Stroke 28: 1233–1244

Burkart V, Wang Z-Q, Radons JR, Heller B, Herceg Z, Stingl L, Wagner EF, et al (1999) Mice lacking the poly(ADP-ribose) polymerase gene are resistant to pancreatic beta-cell destruction and diabetes development induced by streptozocin. Nat Med 5:314–319

Butler AJ, Ordahl CP (1999) Poly(ADP-ribose) polymerase binds with transcription enhancer factor 1 to MCAT1 elements to regulate muscle-specific transcription. Mol Cell Biol 19:296–306

Caldecott K, Aoufouchi S, Johnson P, Shall S (1996) XRCC1 polypeptide interacts with DNA polymerase β and possibly poly(ADP-ribose) polymerase, and DNA ligase III is a novel molecular "nick sensor" in vitro. Nucleic Acids Res 24: 4387–4394

Casciola-Rosen L, Nicholson DW, Chong T, Rowan KR, Thornberry NA, Miller DK, Rosen A (1996) Apopain/CPP32 cleaves proteins that are essential for cellular repair: a fundamental principle of apoptotic death. J Exp Med 183: 1957–1964

Dantzer F, Nasheuer HP, Vonesch JL, de Murcia GA, Ménissier-de Murcia J (1998) Functional association of poly(ADP-ribose) polymerase with DNA polymerase alpha-primase complex: a link between DNA strand break detection and DNA replication. Nucleic Acids Res 26: 1891–1898

Dantzer FSV, Niedergang C, Trucco C, Flatter E, de la Rubia G, Oliver FJ, Rolli V, Menissier-de-Murcia J, et al (1991) Role of poly(ADP-ribose) polymerase in base excision repair. Biochimie 81:69–75

de Murcia G, Huletsky A, Lamarre D, Gaudreau A, Pouyet J, Daune M, Poirier GG (1986) Modulation of chromatin superstructure induced by poly(ADP-ribose) synthesis and degradation. J Biol Chem 261:7011–7017

de Murcia G, Menissier de Murcia J (1994) Poly(ADP-ribose) polymerase: a molecular nick-sensor. Trends Biochem Sci 19: 172–176

Duriez PJ, Shah GM (1997) Cleavage of poly(ADP-ribose) polymerase: a sensitive parameter to study cell death. Biochem Cell Biol 75:337–349

Evan G, Littlewood T (1998) A matter of life and cell death. Science 281:1317–1322

Guillouf C, Wang TS, Liu J, Walsh CE, Poirier GG, Moustacchi E, Rosselli F (1999) Fanconi anemia C protein acts as a switch between apoptosis and necrosis in mitomycin C-induced cell death. Exp Cell Res 246:384–394

Hirsch T, Marchetti P, Susin SA, Dallaporta B, Zamzami N, Marzo I, Geuskens M, et al (1997) The apoptosis-necrosis paradox: apoptogenic proteases activated after mitochondrial permeability transition determine the mode of cell death. Oncogene 15:1573–1581

Kaufmann SH, Desnoyers S, Ottaviano Y, Davidson NE, Poirier GG (1993) Specific proteolytic cleavage of poly(ADP-ribose) polymerase: an early marker of chemotherapy-induced apoptosis. Cancer Res 53:3976–3985

Leadon SA (1999) Transcription-coupled repair of DNA damage: unanticipated players, unexpected complexities. Am J Hum Genet 64:1259–1263 (in this issue)

Le Cam E, Fack F, Menissier-deMurcia MJ, Cognet JA, Barbin A, Sarantoglou V, Revet B, et al (1994) Conformational analysis of a 139 base-pair DNA fragment containing a single-stranded break and its interaction with human poly(ADP-ribose) polymerase. J Mol Biol 235:1062–1071

Lee JS, Haug BL, Sibley JT (1994) Decreased mRNA levels coding for poly(ADP-ribose) polymerase in lymphocytes of patients with SLE. Lupus 3:113–116

Leist M, Single B, Castoldi AF, Kuhnle S, Nicotera P (1997) Intracellular adenosine triphosphate (ATP) concentration: a switch in the decision between apoptosis and necrosis. J Exp Med 185:1481–1486

Lu X, Lane DP (1993) Differential induction of transcriptionally active p53 following UV or ionizing radiation: defects in chromosome instability syndromes? Cell 75:765–778

Maizels N (1999) Immunoglobulin class-switch recombination: will genetics provide new clues to mechanism? Am J Hum Genet 64:1270–1275 (in this issue)

Malanga M, Pleschke JM, Kleczkowska HE, Althaus FR (1998) Poly(ADP-ribose) binds to specific domains of p53 and alters its DNA binding functions. J Biol Chem 273: 11839–11843

Masson M, Niedergang C, Schreiber V, Muller S, Menissier-de Murcia J, de Murcia G (1998) XRCC1 is specifically associated with poly(ADP-ribose) polymerase and negatively regulates its activity following DNA damage. Mol Cell Biol 18:3563–3571

Masutani M, Suzuki H, Kamada N, Watanabe M, Ueda O, Nozaki T, Jishage K, et al (1999) Poly(ADP-ribose) polymerase gene disruption conferred mice resistant to streptozotocin-induced diabetes. Proc Natl Acad Sci USA 96: 2301–2304

Menissier-de Murcia J, Niedergang C, Trucco C, Ricoul M, Dutrillaux B, Mark M, Oliver FJ, et al (1997) Requirement of poly(ADP-ribose) polymerase in recovery from DNA damage in mice and in cells. Proc Natl Acad Sci USA 94: 7303–7307

Morrison C, Smith GC, Stingl L, Jackson SP, Wagner EF, Wang ZQ (1997) Genetic interaction between PARP and DNA-PK in V(D)J recombination and tumorigenesis. Nat Genet 17: 479–482

Moser KL, Neas BR, Salmon JE, Yu H, Gray-McGuire C, Asundi N, Bruner GR, et al (1998) Genome scan of human systemic lupus erythematosus: evidence for linkage on chromosome 1q in African-American pedigrees. Proc Natl Acad Sci USA 95:14869–14874

Nie J, Sakamoto S, Song D, Qu Z, Ota K, Taniguchi T (1998) Interaction of Oct-1 and automodification domain of poly(ADP-ribose) synthetase. FEBS Lett 424:27–32

Oei S, Griesenbeck J, Schweuger M (1997) The role of poly(ADP-ribosyl)ation. Rev Physiol Biochem Pharmacol 131:127–173

Oei SL, Griesenbeck J, Schweiger M, Ziegler M (1998) Regulation of RNA polymerase II-dependent transcription by poly(ADP- ribosyl)ation of transcription factors. J Biol Chem 273:31644–31647

Oliver FJ, de la Rubia G, Rolli V, Ruiz-Ruiz MC, de Murcia G, Menissier-de Murcia J (1998) Role of PARP and PARP cleavage in apoptosis: lesson from an uncleavable mutant. J Biol Chem 273:33533–33539

Ouchi T, Monteiro AN, August A, Aaronson SA, Hanafusa H (1998) BRCA1 regulates p53-dependent gene expression. Proc Natl Acad Sci USA 95:2302–2306

Plaza S, Aumercier M, Bailly M, Dozier C, Saule S (1999) Involvement of poly(ADP-ribose)-polymerase in the Pax-6 gene regulation in neuroretina. Oncogene 18:1041–1051

Rao L, Perez D, White E (1996) Lamin proteolysis facilitates nuclear events during apoptosis. J Cell Biol 135:1441–1455

Ruscetti T, Lehnert BE, Halbrook J, Le Trong H, Hoekstra MF, Chen DJ, Peterson SR (1998) Stimulation of the DNA-dependent protein kinase by poly(ADP-ribose) polymerase. J Biol Chem 273:14461–14467

Sakahira H, Enari M, Nagata S (1998) Cleavage of CAD inhibitor in CAD activation and DNA degradation during apoptosis. Nature 391:96–99

Simbulan-Rosenthal CM, Rosenthal DS, Ding R, Bhatia K, Smulson ME (1998*a*) Prolongation of the p53 response to DNA strand breaks in cells depleted of PARP by antisense RNA expression. Biochem Biophys Res Commun 253: 864–868

Simbulan-Rosenthal CM, Rosenthal DS, Iyer S, Boulares AH, Smulson ME (1998*b*) Transient poly(ADP-ribosyl)ation of nuclear proteins and role of poly(ADP-ribose) polymerase in the early stages of apoptosis. J Biol Chem 273: 13703–13712

Smith S, Giriat I, Schmitt A, de Lange T (1998) Tankyrase, a poly(ADP-ribose) polymerase at human telomeres. Science 282:1484–1487

Smulson ME, Pang D, Jung M, Dimtchev A, Chasovskikh S, Spoonde A, Simbulan-Rosenthal C, et al (1998) Irreversible binding of poly(ADP)ribose polymerase cleavage product to DNA ends revealed by atomic force microscopy: possible role in apoptosis. Cancer Res 58:3495–3498

Szabo C, Dawson VL (1998) Role of poly(ADP-ribose) syn-

thetase in inflammation and ischaemia-reperfusion. Trends Pharmacol Sci 19:287–298

Thornberry NA, Lazebnik Y (1998) Caspases: enemies within. Science 281:1312–1316

Trucco C, Oliver FJ, de Murcia G, Menissier-de Murcia J (1998) DNA repair defect in poly(ADP-ribose) polymerase-deficient cell lines. Nucleic Acids Res 26:2644–2649

Tsao BP, Cantor RM, Kalunian KC, Chen CJ, Badsha H, Singh R, Wallace DJ, et al (1997) Evidence for linkage of a candidate chromosome 1 region to human systemic lupus erythematosus. J Clin Invest 99:725–731

Wang X, Ohnishi K, Takahashi A, Ohnishi T (1998) Poly(ADP-ribosyl)ation is required for p53-dependent signal transduction induced by radiation. Oncogene 17: 2819–2825

Wang ZQ, Stingl L, Morrison C, Jantsch M, Los M, Schulze-Osthoff K, Wagner EF (1997) PARP is important for genomic stability but dispensable in apoptosis. Genes Dev 11: 2347–2358

Whitacre CM, Hashimoto H, Tsai ML, Chatterjee S, Berger SJ, Berger NA (1995) Involvement of NAD-poly(ADP-ribose) metabolism in p53 regulation and its consequences. Cancer Res 55:3697–3701

Zardo G, Caiafa P (1998) The unmethylated state of CpG islands in mouse fibroblasts depends on the poly(ADP-ribosyl)ation process. J Biol Chem 273:16517–16520

Zechiedrich EL, Osheroff N (1990) Eukaryotic topoisomerases recognize nucleic acid topology by preferentially interacting with DNA crossovers. EMBO J 9:4555–4562