Inhibition of Homodimerization of Poly(ADP-ribose) Polymerase by Its C-terminal Cleavage Products Produced during Apoptosis*

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The biochemical role of the C-terminal fragment of poly(ADP-ribose) polymerase (PARP) was investigated in HeLa cells undergoing UV-mediated apoptosis. During the course of apoptosis, the C-terminal cleavage product of PARP interacted with intact PARP and down-regulated PARP activity by blocking the homodimerization of PARP. The basic leucine zipper motif in the auto-modification domain of the C-terminal fragment of PARP represented the site of association, and Leu405 was critical to the ability of the basic leucine zipper motif to associate with intact PARP. The expression of the C-terminal fragment of PARP stimulated UV-mediated apoptosis. These results suggest that the C-terminal cleavage product of PARP produced during apoptosis blocks the homodimerization of PARP and inhibits the cellular PARP activity. The inhibition of the cellular PARP activity might prevent cellular NAD+ deple- tion and stimulate apoptosis by maintaining the basal cellular energy level required for the completion of apoptosis.

Many studies have described PARP as a positive regulator of apoptosis. The overexpression of PARP in the transfected cells was known to stimulate apoptosis (12). The pro-apoptotic role of PARP activation was further supported by the finding that a specific chemical inhibitor of PARP, 3-aminobenzamide, suppresses apoptosis (13). However, the controversial roles of PARP during apoptosis have been argued in the studies using PARP-deficient mice. Wang et al. (14) proposed a dispensable role of PARP in apoptosis by showing a normal level of apoptosis in PARP-deficient mouse cells treated with various apoptosis inducers. An indispensable role of PARP on apoptosis was presented by Simbulan-Rosenthal et al. (15), who reported an early burst of poly(ADP-ribose)lation of nuclear proteins during Fas-mediated apoptosis in PARP−/− cells, whereas no induction of apoptosis was shown in PARP+/− cells by Fas stimulation.

The importance of PARP cleavage in apoptosis has recently been recognized. For example, it has been suggested that the activity of PARP is stimulated by DNA breaks during the early course of apoptosis, but proteolytic cleavage decreases PARP activity in the late course of apoptosis (16). Oliver et al. (17) observed a delayed apoptosis in PARP−/− cells expressing an uncleavable mutant of PARP. They suggested that PARP cleavage might be a sign that cells should undergo apoptosis because cells were unable to repair the cellular injury triggered by the apoptosis inducers. More recently, the importance of PARP cleavage during apoptosis was emphasized by the finding that the extensive poly(ADP-ribose)lation of p53 early during apoptosis decreases, as activated caspase-3 cleaves PARP and the expression of p53-responsive pro-apoptotic genes, bax and Fas, is elevated during the late course of apoptosis (18). However, the biological relevance of PARP cleavage during apoptosis and the cellular function of the cleavage products have not been yet clarified.

Recent studies have proposed that an adequate level of intracellular ATP is required for the completion of apoptosis (19, 20). Because the intracellular ATP level is directly affected by the catalytic activity of PARP, apoptosis, an energy-requiring process, may well be influenced by PARP activity. The N-terminal fragment of PARP containing the DNA-binding domain preferentially binds to DNA breaks and prevents the activation of PARP, whose activity is stimulated by DNA binding (21). The pro-apoptotic role of the N-terminal fragment of PARP on apoptosis has been strongly supported by a recent finding that the N-terminal fragment of PARP irreversibly binds to DNA ends produced during apoptosis (22). However, the role of the C-terminal fragment of PARP on apoptosis has not been delineated. In the present study, we propose a putative role for the C-terminal cleavage product of PARP on apoptosis based on the following findings: (a) the C-terminal fragment of PARP interacts with intact PARP through an association between the auto-modification domains and (b) the C-terminal fragment suppresses its catalytic activity by block-
Fig. 1. Intermolecular association of PARP at the auto-modification domain. A, PARP deletion mutants were fused to GST. B, 35S-labeled PARP prepared by in vitro transcription/translation procedures was incubated with GST-fused PARP fragments. GST-fused PARP fragments were analyzed by 10% SDS-PAGE and Western blot analysis using monoclonal antibody against GST (bottom panel). Association of 35S-labeled PARP with GST-fused PARP fragments was examined by in vitro protein interaction assay (top panel). C, GST-fused PARP fragments with or without the bZip motif were resolved by 10% SDS-PAGE (middle panel). Interactions mediated by the bZip motif in the auto-modification domain of PARP were assessed by in vitro protein interaction assay (upper panel). IVT-PARP represents in vitro translated PARP before GST pull-down.

Experimental Procedures

Reagents and Antibodies—Radioactive chemicals, including [adenylated-32P]NAD (~1,000 Ci/mmol) and [35S]methionine (1,000 Ci/mmol) were obtained from Amersham Pharmacia Biotech. Anti-PARP monoclonal antibody against the C-terminal domain of PARP (MCA 1522) was purchased from Serotech. Monoclonal antibody against glutathione S-transferase (GST) was supplied by Sigma. Anti-green fluorescent protein (GFP) IgG was from CLONTECH. Monoclonal antibody against hemagglutinin (HA) was purchased from Roche Molecular Biochemicals. Annexin V-FITC was purchased from Pharmpingen.

Vectors—The cDNA encoding full-length human PARP and truncated PARP fragments were cloned in-frame to pEGFP-C1 (CLONTECH) or pEG vector to produce GFP or GST fusion products, respectively. For the active transport of GFP-N214 and GFP-M in the nuclei of HeLa cells, the PKKKRK sequence of the nuclear localization signal (NLS) in SV40 large T-antigen (23) was inserted between GFP and the N termini of PARP fragments by polymerase chain reaction using oligomers of 5'-GGAATTCGACCGCCGAAAGAAAAAGCGGAAGTGCGACGCGC-3' and 5'-GGCGGTGGACGTTCGCTTTTTCTTTGCGGAAATCAGTACC-3'. N214-NLS and M-NLS were then prepared by polymerase chain reaction to construct pEBG-N214 and pEBG-M, respectively. The vector constructs encoding PARP fragments were transfected into cells by employing LipofectAMINE reagent (Life Technologies, Inc.). The catalytic activity of PARP was assessed by examining auto-poly(ADP-ribosyl)ation of HA-PARP in 10% SDS-PAGE followed by autoradiography.

In Vitro Protein Interaction Assay—PARP derivatives were clonned in pGEX-5X-3, and GST-fused PARP fragments were produced in Escherichia coli BL21(DE3) cells. Purified GST fusion products (1 μg) were transferred to 200 μl of an assay buffer consisting of 20 mM Tris (pH 7.4), 100 mM NaCl, 2 mM EDTA, 0.1% Nonidet P-40, 2 mM dithiothreitol, 0.05% bovine serum albumin, and 5% glycerol (25). The 35S-labeled PARP was prepared by in vitro transcription/translation procedures using TNT linked kit (Promega). In vitro translated 35S-labeled PARP was treated with 1 unit of DNase I for 30 min prior to the incubation with GST fusion proteins at 4 °C for 1 h. The GST fusion products were recovered in glutathione-Sepharose 4B beads (Amerham Pharmacia Biotech) and washed three times with phosphate-buffered saline (pH 7.4). The 35S-labeled PARP bound to GST fusion products was analyzed by 10% SDS-PAGE and subsequent autoradiography.

Immunoprecipitation and Immunoblot Analysis—HeLa cells (107) were transfected with 2 μg of pEBG, pEBG-N214, pEBG-C215, pEBG-M, pEBG-PARP4M or pEBG-MAbZip and incubated for 36 h. Cells were lysed in a lysis buffer containing 100 mM Tris (pH 7.4), 150 mM NaCl and 1% Nonidet P-40 for 30 min on ice. After centrifugation, cell lysate at 10,000 × g for 5 min, the resulting supernatant was incubated with glutathione-Sepharose 4B resin for 1 h at 4 °C. The resin was washed three times with phosphate-buffered saline and the bound proteins were analyzed by Western blotting using monoclonal antibody against the C-terminus of PARP following by 10% SDS-PAGE.

Caspase Activity Assay—Cells were lysed in a lysis buffer containing 20 mM HEPES (pH 7.4), 100 mM NaCl, 0.5% Nonidet P-40, 10 mM dithiothreitol, 1 mM phenylmethylsulfonyl fluoride, and 1 μg/ml leupeptin. Caspase activity was measured using a fluorogenic peptide substrate, zVAD-AMC (Bachem). Cell lysate proteins (10 μg) were incubated with 20 μM of zVAD-AMC for 2 h at 30 °C, and caspase activity was monitored fluorometrically in a fluorescence spectrophotometer (excitation, 386 nm; emission, 465 nm).

Evaluation of Apoptosis—HeLa cells (105) expressing GFP fusion products were irradiated with 100J/m2 UV, resuspended in 100 μl of an incubation buffer containing 10 mM HEPES (pH 7.4), 140 mM NaCl, 2.5 mM CaCl2, and 5% Annexin-V-FITC solution (Pharmpingen) and incubated at room temperature for 15 min in the dark. Green fluorescent and annexin-V positive cells were analyzed by fluorescence activated cell sorter (FACScalibur System; Becton-Dickinson) (26). The apoptotic morphology of cells were evaluated by fluorescence microscopic observation (excitation, 490 nm; emission, 510 nm). After the induction of
apoptosis, cells were fixed with 4% para-formaldehyde for 30 min, and apoptotic cells expressing GFP with condensed nuclei were counted after staining the cells with Hoechst33342 (1 μg/ml) for 10 min.

RESULTS

Self-association of PARP at the bZip Motif in the Auto-modification Domain—PARP is a catalytic dimer, and the self-association of PARP is known to stimulate its catalytic activity (27, 28). PARP domains participating in the self-association were examined as shown in Fig. 1. GST-fused PARP fragments were incubated with [35S]PARP prepared by in vitro transcription/translation procedures, and [35S]PARP specifically bound to GST-fused PARP fragments was resolved by 10% SDS-PAGE after GST pull-down. To exclude the possibility of intermolecular linking of PARP mediated by the DNA duplex that contacts the DNA-binding domains of separate PARP molecules, DNA employed in in vitro transcription/translation procedures was digested with DNase I before GST pull-down. The interaction between intact PARP and the N-terminal fragment containing the DNA binding domain disappeared after DNase I treatment, suggesting that the association was mediated by DNA. In contrast, the C-terminal fragments of PARP maintained the association with [35S]PARP after DNase I treatment (Fig. 1B). Data shown in Fig. 1C indicate that the auto-modification domain of PARP is the site of intermolecular association. A bZip motif (amino acids 394–422) known to participate in protein-protein interaction (29, 30) has been identified in the auto-modification domain of PARP. Thus, we examined whether the bZip motif in the auto-modification domain provides a structural framework for the intermolecular association. Data in Fig. 1C strongly suggest that the bZip motif in the auto-modification domain of PARP represents the site of the association.

The intermolecular association of the cellular PARP was studied in Fig. 2. GST-fused PARP fragments were expressed in HeLa cells, and the association of GST fusion products with the cellular PARP was monitored by immunoblotting analysis using anti-PARP monoclonal antibody (Fig. 2A). Data demonstrate that the bZip motif in the auto-modification domain interacts with the cellular PARP. A putative role of the C-terminal fragment of PARP on the self-association was investigated in cells co-expressing HA-tagged PARP (HA-PARP) with GST-fused PARP fragments. The association of the endogenous cellular PARP with HA-PARP was almost completely inhibited by the PARP fragments containing the auto-modification domain (C215 and M). However, a PARP fragment that lacks the auto-modification domain (PARPAM) or an auto-modification domain that lacks the bZip (MΔbZip) failed to block the self-association of PARP in the transfected cells (Fig. 2B).

The bZip motif in the auto-modification domain of PARP contains invariable leucine residues (31). Thus, the function of the conserved leucine residues was evaluated in an experiment in which the leucine residues in the bZip motif were substituted, and the association of intact PARP with the mutated auto-modification domain was examined (Fig. 3). The leucine residues in the bZip motif were important for the association, and Leu(405) was of critical importance. The auto-modification domain in which Leu(405) was substituted to Arg(405) failed to interact with 35S-labeled PARP prepared by in vitro transcription/translation. However, the association between the auto-modification domain and intact PARP was not disturbed by the substitution of leucine residues to valine, implicating that hydrophobic interaction is involved in the association.

Suppression of PARP Activity by Expressing the C-terminal Fragment of PARP in HeLa Cells Irradiated with UV Light—The role of the C-terminal fragment of PARP on the cellular PARP activity was examined in co-transfected HeLa cells expressing HA-PARP and GST-fused PARP fragments. Cells were irradiated with 50 J/m² UV and incubated for 30 min in a
culture medium containing $^{32}$PNA$^-$. HA-PARP was then isolated by immunoprecipitation, and the cellular PARP was assessed by the transfer of $^{32}$P-labeled ADP-ribose moieties from NAD$^+$ to HA-PARP. The expression of the C-terminal fragments that contain the bZip motif (C-215 and M) suppressed the cellular PARP activity. The auto-modification domain that lacks the bZip motif (MΔbZip) failed to interfere with the cellular PARP activity. Data also showed that the cellular PARP activity was inhibited by the expression of PARP fragments containing N-terminal fragment (N-214 and PARP-D), a known trans-dominant inhibitor of PARP (32, 33). These results implicate that the C-terminal fragment of PARP as well as N-terminal fragment is the trans-dominant inhibitor of the resident PARP in HeLa cells (Fig. 4).

Stimulation of Apoptosis by PARP Cleavage Products—Apoptotic responses followed by UV irradiation (100 J/m$^2$) were evaluated by measuring the activation of $z$VAD-directed caspase and annexin-V binding to phosphatidyl serine at the surface of apoptotic HeLa cells. PARP cleavage products did not interfere with the caspase activation in cells undergoing apoptosis (Fig. 5A). The expression of the N-terminal or C-terminal fragment containing the bZip motif, induced elevated level of UV-mediated apoptosis, as assessed by the appearance of annexin-V binding at the cell surface (Fig. 5B). In addition, cells expressing the N-terminal or C-terminal fragment containing the bZip motif showed morphological changes characteristic to apoptosis, such as condensed nuclei (Fig. 5C).

**DISCUSSION**

Although PARP cleavage has been used as a prominent biochemical hallmark of apoptosis, the physiological relevance and functional consequence of PARP cleavage during apoptosis have not been clarified. A recent report by Oliver et al. (17) showed that Fas-induced apoptosis was delayed in cells expressing an uncleavable PARP mutant. Furthermore, Herceg and Wang (34) reported that the failure of PARP cleavage induced necrosis by the depletion of cellular energy in cells treated with various apoptotic inducers. These results suggested that the inactivation of PARP by the caspase-mediated proteolytic cleavage is a necessary requirement for the completion of apoptosis. In the present study, we attempted to interpret the biological meaning of the proteolytic cleavage of PARP during the course of apoptosis. We found that apoptosis requires the self-regulatory function of PARP, whose catalytic activity is regulated by its proteolytic cleavage products. The N-terminal fragment of PARP containing the DNA-binding domain preferentially binds to DNA breaks and thereby prevents the activation of PARP by PARP fragments in UV-treated HeLa cells. The effects of PARP fragments on the catalytic activity of the cellular PARP were evaluated by examining auto-poly(ADP-ribose)ylation of PARP in UV-treated HeLa cells. The $p$SR$^-$/HA-PARP (2 µg) was co-transfected with pEBG, pEBG-N214, pEBG-C215, pEBG-M, pEBG-PARP-D, or pEBG-MΔbZip (2 µg each) into HeLa cells (10$^5$). Co-transfected cells were irradiated with 50 J/m$^2$ UV and incubated for 6 h. Permeabilized cells were incubated with 10 µCi/ml of $[^{32}$P]NAD$^+$ for 30 min at 30 °C. HA-PARP was immunoprecipitated using monoclonal antibody against HA, and the transfer of $^{32}$P from $[^{32}$P]NAD to HA-PARP was analyzed by 10% SDS-PAGE and subsequent autoradiography.
Stimulation of Apoptosis by C-terminal Fragment of PARP

PARP (32, 33). It has been demonstrated that the N-terminal fragment of PARP irreversibly binds to DNA ends produced during apoptosis (22). The binding of the N-terminal fragment of PARP to DNA breaks has generally been known to contribute to apoptosis by blocking the access of repair enzymes to the DNA breaks generated during the course of apoptosis.

The roles of the C-terminal fragment of PARP on apoptosis have not yet been described. The present study proposes that the intermolecular association of the cellular PARP with the C-terminal fragment containing the auto-modification domain contributes to apoptosis by blocking the homodimerization of PARP in cells irradiated with UV. The C-terminal fragments of PARP containing the auto-modification domain interacted with intact PARP, whereas the N-terminal fragment containing the DNA-binding domain interacted with DNA. The association between the N-terminal fragment and intact PARP disappeared after DNase I treatment, suggesting that the association was mediated by DNA (Fig. 1). We further demonstrated that the bZip motif in the auto-modification domain is the site of self-association of the cellular PARP (Fig. 2A). The homodimerization of PARP was blocked by the expression of PARP cleavage products containing the bZip motif in HeLa cells (Fig. 2B). The hydrophobic amino acid Leu105 in the bZip motif was of critical importance in the structural framework required for the intermolecular association and an efficient dimerization of PARP (Fig. 3). The association of PARP with the basic components of the auto-modification domain in the C-terminal fragment seems to compete with the homodimerization of PARP.

There are number of studies suggesting that oligomerization serves as an important biochemical mechanism for the regulation of protein function. Dimerization was known to provide mechanisms for the modulation of catalytic activity of enzymes (35, 36) and receptor functions (37, 38). Several studies have also provided evidence for the inhibition of protein dimerization by the peptides derived from the same protein. For example, the catalytic activity of E. coli ribonucleotide reductase was shown to be inhibited by the C-terminal peptide, which inhibits the homodimerization of the enzyme (35). The truncated G protein-coupled receptors (GPCRs), which inhibit the formation of dimeric arrays of GPCRs, were also identified as negative regulators of GPCR function (37). It was known that the catalytic function of PARP is maximal when PARP tends to be inhibitory regulators of GPCR function (37). It was known that the protein-coupled receptors (GPCRs), which inhibit the formation of dimeric arrays of GPCRs, were also identified as negative regulators of GPCR function (37). It was known that the catalytic function of PARP is maximal when PARP tends to be inhibitory regulators of GPCR function (37).

REFERENCES

1. Cryns, V. G., and Yuan, J. (1998) Genes Dev. 12, 1551–1570
2. Lako, Y. A., Kuwana, M., Meyer, J., and Sato, M. S. (1994) J. Biol. Chem. 269, 28214–28220
3. Kaufmann, S. H., Desnoyers, S., Ottaviano, Y., Sather, D. B., andRosebud, D. A. (1998) J. Exp. Med. 187, 321–326
4. Yoshikawa, H., and Simbulan-Rosenthal, C. M. (1999) Cell. Death Differ. 6, 355–361
5. Ohashi, Y., Iwaya, A., Tanaka, Y., Yoshikawa, K., Kamiya, T., and Matsukage, A. (1998) Biochem. Biophys. Res. Commun. 250, 96–102
6. Russetti, T., Lehner, B. T., Halbrook, J. L., Le Trong, H., Hoekstra, M. F., Chen, D. J., and Peterson, S. R. (1998) J. Biol. Chem. 273, 14461–14467
7. Lindahl, T., Sato, M. S., Poirier, G. G., and Klungland, A. (1995) Trends Biol. Sci. 20, 405–411
8. Van Gool, L., Meyer, R., Tobisch, E., Cziepluch, C., Jauniaux, J. C., Mincheva, A., Lichter, P., Poirier, G. G., Burkle, A., and Kupper, J. H. (1997) Eur. J. Biochem. 244, 19–25
9. Rosenthal, C. M., Rosenthal, D. S., Iyer, S., Boulares, A. H., and Toyoshima, F., and Wang, Z.-Q. (1999) Mol. Cell. Biol. 19, 5124–5133
10. O'Shea, E. K., Rutkowski, R., Stafford, W. F., III, and Kim, P. S. (1989) Cell 59, 499–509
11. Landschulz, W. H., Johnson, P. F., and McKnight, S. L. (1989) Proc. Natl. Acad. Sci. U. S. A. 86, 3575–3580
12. Smulson, M. E. (1998) J. Biol. Chem. 273, 13705–13712
13. Rosenthal, D. S., Ding, S., Simbulan-Rosenthal, C. M., Vaillancourt, J. P., Nicholson, D. W., and Smulson, M. (1997) Exp. Cell. Res. 232, 313–321
14. Oliver, F. J., de la Rubia, G., Rolli, V., Ruiz-Ruiz, M. C., de Murcia, G., and Menissier-de Murcia, J. (1998) J. Biol. Chem. 273, 35335–35339
15. Simbulan-Rosenthal, C. M., Rosenthal, D. S., Lee, R., and Smulson, M. E. (1999) Cancer Res. 59, 2190–2194
16. Leist, M., Single, B., Castoldi, A. F. K., Kuhnhle, S., and Nicotera, P. (1997) J. Exp. Med. 185, 1481–1486
17. Eguchi, Y., Srivivasan, A., Tomasselli, K. J., Shimizu, S., and Toiyama, S. (1999) Cancer Res. 59, 2174–2181
18. Rhon, Y. L., Kirkland, J. B., and Shah, G. M. (1998) Biochem. Biophys. Res. Commun. 253, 1–10
19. Smulson, M. E., Pang, D., Jung, M., Dimtchev, A., Chasovskikh, S., Spoude, A. N., and Smulson, M. E. (1998) J. Biol. Chem. 273, 13705–13712
20. Smulson-Rosenthal, C. M., Rosenthal, D., Burkle, A., and Dritschilo, A. (1998) Cancer Res. 58, 4385–4388
21. Feldman, D. B., Roberts, B. L., Richardson, W. D., and Smith, A. E. (1984) Cell 34, 14461–14467
22. Grube, K., Kupper, J., and Burkle, A. (1991) Anal. Biochem. 193, 236–239
23. Takayama, S., Sato, T., Krajewski, S., Kochel, K., Irie, S., Millan, J. A., and Reed, J. C. (1995) Cell 80, 279–284
24. Kupper, J., Neufeld, T., Krajewski, S., Krajewska, M., and Reed, J. C. (1995) J. Biol. Chem. 270, 2190–2194
25. Krajewska-Mullen, M. C., Mullen, K. J., Shapovalov, I., Krajewski, S., and Reed, J. C. (1998) Blood 84, 1415–1420
26. Bauer, P. I., Buki, K. G., Akam, A., and Kun, E. (1996) Biochem. J. 324, 287–292
27. Miwa, M. (1993) J. Cell. Biochem. 51, 39–44
28. Herceg, Z., and Wang, Z.-Q. (1999) Mol. Cell. Biol. 19, 5164–5171
29. O'Shea, E. K., Rutkowski, R., Stafford, W. F., III, and Kim, P. S. (1989) Science 245, 646–648
30. O'Shea, E. K., Rutkowski, R., Stafford, W. F., III, and Kim, P. S. (1989) Science 245, 646–648
31. Uchida, K., Hanai, S., Ishikawa, K., Ozawa, Y., Uchida, M., Suginura, T., and Miwa, M. (1993) Proc. Natl. Acad. Sci. U. S. A. 90, 3481–3485
32. Molemaker, M., Veerman, A., Burkle, A., Mura, M., Kupper, J. H., Hoeijmakers, J. H. J., de Murcia, G. (1993) EMBO J. 12, 2109–2117
33. Schreiber, V., Hunting, D., Trueco, C., Gowans, E., Gruenwald, D., de Murcia, G., and de Murcia, J. M. (1995) Cancer Res. 59, 2190–2194
34. Herceg, Z., and Wang, Z.-Q. (1999) Mol. Cell. Biol. 19, 5124–5133
35. Clement, I., Sjoberg, B., M., and Huang, C. Y. (1991) Biochemistry 30, 5166–5171
36. Baek, K. J., Thiell, B. A., Lucas, S., and Stuehr, D. J. (1993) J. Biol. Chem. 268, 21120–21129
37. Zhu, X., and Wess, J. (1998) Biochemistry 37, 15773–15784
38. Toyoshima, F., Morishita, T., and Nishida, E. (1997) J. Cell. Biol. 135, 1005–1015
39. Tewari, M., Quan, L. T., O’Rourke, K., Desnoyers, S., Zeng, Z., Beidler, D. R., Poirier, G. G., Salvesen, G. S., and Dixit, V. M. (1995) Cell 81, 801–809
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