CMLS, Cell. Mol. Life Sci. 62 (2005) 719–720
1420-682X/05/080719-02
DOI 10.1007/s00018-004-4502-4

CMLS Cellular and Molecular Life Sciences

The expanding universe of poly(ADP-ribosyl)ation

L. Virág

Department of Medical Chemistry, Research Center for Molecular Medicine, Medical and Health Science Center, University of Debrecen, 4026 Debrecen, Bem tér 18/B (Hungary), e-mail: lvirag@jaguar.unideb.hu

Poly(ADP-ribosyl)ation is a posttranslational protein modification the discovery of which dates back to 1963 when Chambon, Weill and Mandel described the basic features of this process [1]. Later the enzyme responsible for this activity was identified and named poly(ADP-ribose) transferase/synthetase/polymerase (PADPRT, PARS, PARP). Other fundamental observations including the biochemical and structural characterization of the enzymatic reaction and polymer architecture followed. The next period of poly(ADP-ribosyl)ation research was based on pharmacological investigations providing valuable data on the dual nature of PARP. The enzyme emerged as a DNA damage sensor protein assisting DNA repair and cell survival on the one hand and the mediator of cytotoxicity on the other hand. A new era of PARP research ensued when three independent laboratories concurrently generated mice deficient in PARP. Experiments using these animals and their cells confirmed both the 'guardian angle' as well as the 'perpetrator of cell death' functions of PARP. Moreover, the observation that PARP activity is not fully absent in PARP knockout cells initiated a search for new PARP enzymes. The discovery of PARP-2 and other PARP homologues laid down the foundation for the existence of a PARP enzyme family and the original PARP enzyme was renamed PARP-1. By searching the National Center for Biotechnology Information (NCBI) protein database for sequences identical to residues 796–1014 of the human PARP-1 catalytic domain, de Murcia's lab cloned 18 complementary DNAs (cDNAs) coding for putative PARP homologues [2]. The proliferation of the enzyme family represents an important aspect of the expansion of the PARP universe. As of yet, only seven PARP homologues characterized at the protein level have been shown to carry out poly(ADP-ribosyl)ation. Although as all putative PARPs contain the PARP signature sequence, it is likely that all these enzymes are capable of poly(ADP-ribosyl)ation.

Another level of expansion of the PARP universe relates to the increasing number of biological regulatory functions that have been assigned to poly(ADP-ribosyl)ation. In parallel, the footprint of poly(ADP-ribosyl)ation was found in new intracellular locations. Once poly(ADP-ribosyl)ation was thought to be confined to the nucleus and its function restricted to DNA nick sensing. Instead we now know that even the founding member of the enzyme family (PARP-1) can localize outside the nucleus and can occur, for example, in the centrosomes and in the mitochondria. Other PARP enzymes can also display extranuclear localization with PARP-3 localizing to centrosomes, PARP-4 localizing to cytoplasmic ribonucleoprotein assemblies named vaults, and tankyrases 1 and 2 (PARP-5 and -6) occurring in both the Golgi and the pericentriolar material. The functions of PARP-1 have also been extended to the regulation of fundamental cellular processes ranging from transcription, replication, protein degradation and memory formation. In recent years we have also gained a more detailed insight into the mechanisms of certain PARP-1 functions. For example, Berger's PARP-mediated suicide pathway was found by us and other groups to lead to necrotic type cell death [3] in severely DNA damaged cells, providing support for the challenging statement that necrotic cell death is regulated and is not, as was previously thought, a passive form of cell death. Moreover, Valina Dawson's group identified translocation of apoptosis inducing factor (AIF) from the mitochondria to the nucleus as a poly(ADP-ribosyl)ation-dependent crucial step of DNA-damage-induced neuronal cell death [4]. Along the lines of the PARP-DNA repair connection, probably the most exciting discovery in the field was that one of PARP-1's main contributions to DNA repair is to provide energy. Ziegler's group showed that the $(ADP\text{-}ribose)_n$ polymer can be converted to ATP utilized by DNA ligase III [5]. The discovery of new PARP homologues such as tankyrases 1 and 2 , along with vPARP (vault PARP), widened the circle of PARP-regulated processes which now include the regulation of telomere length and vault function.

The third level of expansion of the poly(ADP-ribosyl)-ation universe is represented by the increasing efforts to revitalize an old player in the field, poly(ADP-ribose)

glycohydrolase (PARG). As discussed in detail by Guy Poirier in this multi-author review series, PARG research is soon to become a hot topic in the field, with several exciting new observations and some highly debated issues. Recently it has become clear that unlike the high number of PARP genes, a single gene codes for PARG. However, the enzyme exists in three alternatively spliced/translated forms [6]. Surprisingly, the most abundant isoform is located outside the nucleus showing perinuclear localization, whereas the less abundant full-length form localizes to the nucleus [6]. Recently, knockout mice deficient in either the full length (110 kDa) or in all three (99 kDa, 103 kDa and 110 kDa) isoforms of PARG have been generated [7, 8] and will likely add new momentum to poly(ADP-ribosyl)ation research with special regard to the role of polymer catabolism. Whereas the partial knock out mice were viable, total knockouts were embryonic lethal. However, both types of knockout mice were hypersensitive to genotoxic stress. The embryonic lethality of total PARG knockout mice may be due to the role played by PARG in development with special regrard to neuronal development. Furthermore, *tej*, a PARG homologue, was found to regulate circadian rhythm in plants [8], adding a new function to the long list of processes regulated by poly(ADP-ribosyl)ation.

One of the factors that has made poly(ADP-ribosyl)ation a dynamic field and attracted many new scientists to the PARP arena is the diverse medical implications of poly(ADP-ribosyl)ation and the applicability of the results. Significant efforts have been made to exploit the involvement of PARP-1 in the protection of genomic integrity, transcriptional regulation of inflammatory mediators and the PARP-1-driven suicidal mechanism. Notably, various classes of potent pharmacological PARP inhibitors have been developed for the potentiation of anticancer therapy as well as for the treatment of various forms of inflammation and ischemia-reperfusion injuries [9]. Several clinical trials are under way to confirm the beneficial effects of PARP inhibition in clinical settings. By comparison, the development of PARG inhibitors is lagging behind PARP inhibitor development. Therefore, it is not yet known whether pharmacological interventions targeting poly(ADP-ribose) catabolism are as promising as those of the polymerases.

The reviews published in this multi-author review series discuss the state of the art of poly(ADP-ribosyl)ation, focusing on selected aspects such as the role of PARPs in DNA repair, cell death, carcinogenesis and new data on poly(ADP-ribose) catabolism.

1 Chambon P., Weill J. D. and Mandel P. (1963) Nicotinamide mononucleotide activation of new DNA-dependent polyadenylic acid synthesizing nuclear enzyme. Biochem. Biophys. Res. Commun. **11:** 39–43.
2 Ame J. C., Spenlehauer C. and de M. G. (2004) The PARP superfamily. Bioessays **26:** 882–893.
3 Virag L., Scott G. S., Cuzzocrea S., Marmer D., Salzman A. L. and Szabo C. (1998) Peroxynitrite-induced thymocyte apoptosis: the role of caspases and poly (ADP-ribose) synthetase (PARS) activation. Immunology **94:** 345–355.
4 Yu S. W., Wang H., Poitras M. F., Coombs C., Bowers W. J., Federoff H. J. et al. (2002) Mediation of poly(ADP-ribose) polymerase-1-dependent cell death by apoptosis-inducing factor. Science **297:** 259–263.
5 Oei S. L. and Ziegler M. (2000) ATP for the DNA ligation step in base excision repair is generated from poly(ADP-ribose). J. Biol. Chem. **275:** 23234–23239.
6 Meyer-Ficca M. L., Meyer R. G., Coyle D. L., Jacobson E. L., and Jacobson M.K. (2004) Human poly(ADP-ribose) glycohydrolase is expressed in alternative splice variants yielding isoforms that localize to different cell compartments. Exp. Cell Res. **297:** 521–532.
7 Cortes U., Tong W. M., Coyle D. L., Meyer-Ficca M. L., Meyer R.G., Petrilli V. et al. (2004) Depletion of the 110-kilodalton isoform of poly(ADP-ribose) glycohydrolase increases sensitivity to genotoxic and endotoxic stress in mice. Mol. Cell Biol. **24:** 7163–7178.
8 Koh D. W., Lawler A. M., Poitras M. F., Sasaki M., Wattler S., Nehls M. C. et al. (2004) Failure to degrade poly(ADP-ribose) causes increased sensitivity to cytotoxicity and early embryonic lethality. Proc. Natl. Acad. Sci. USA **101:** 17699–17704.
9 Panda S., Poirier G. G., and Kay S. A. (2002) tej defines a role for poly(ADP-ribosyl)ation in establishing period length of the arabidopsis circadian oscillator. Dev. Cell **3:** 51–61.
10 Virag L. and Szabo C. (2002) The therapeutic potential of poly(ADP-ribose) polymerase inhibitors. Pharmacol. Rev. **54:** 375–429.