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Poly(ADP-Ribosyl)ation

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This book is dedicated
to the memory of Professor Paul Mandel,
Strasbourg, France, the founder of the field
of poly(ADP-ribose) research.

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PREFACE

The research field of poly(ADP-ribosyl)ation, which originated in the mid-1960s as an extremely narrow focus of interest for polynucleotide biochemists, has remained a rather stable field for a long time in terms of scientific orientation and researchers involved. Starting from the late 1980s, however, the scene has witnessed a tremendous influx of new people, fresh ideas and novel techniques, which led—especially over the last five years—to a breathtaking expansion of the field with regards to breadth and depth of scientific information available. What began as a peculiar posttranslational modification somehow associated with DNA repair has now invaded almost all sub-disciplines of biology and has also gained substantial interest by medical researchers and pharmaceutical companies, as there is a wide range of pathophysiological conditions linked with poly(ADP-ribosyl)ation.

The last comprehensive monograph on this topic was edited by Gilbert de Murcia and Sidney Shall in 2000, and therefore the demand for a fresh summary of the state-of-the-art is obvious, despite the recent creation of very helpful web resources, such as the "PARP Link" (http://parplink.u-strasbg.fr/index.html).

I should like to thank Landes Bioscience for the invitation to edit a monograph on this topic and all the contributors for their enthusiasm and compliance during the writing phase. May the 19 chapters collated in this book, covering many, but by no means all, aspects of poly(ADP-ribosyl)ation, be an useful update for the expert and may they provide, to the non-expert, enlightenment about this complex, highly dynamic and fascinating field!

Alexander Bürkle, M.D.

CHAPTER 1

Enzymes in Poly(ADP-Ribose) Metabolism

Ralph G. Meyer, Mirella L. Meyer-Ficca, Elaine L. Jacobson and Myron K. Jacobson

Abstract

Studies over many years have revealed the central importance of poly(ADP-ribose) metabolism in the maintenance of genomic integrity. While the involvement of poly(ADP-ribose) polymerase-1 (PARP-1) in this metabolism has been long known, more recent studies have demonstrated the contribution of many different genes coding for PARPs to promoting cellular recovery from genotoxic stress, eliminating badly damaged cells from the organism, and ensuring accurate transmission of genetic information during cell division. Additionally, emerging information suggests the involvement of ADP-ribose polymer metabolism in the regulation of intracellular trafficking, memory formation and other cellular functions. This chapter reviews the chemistry of ADP-ribose polymer metabolism and the enzymes that catalyze the synthesis and turnover of poly(ADP-ribose).

Overview of the Enzymes of Poly(ADP-Ribose) Metabolism

The metabolism of ADP-ribose (ADPR) polymers represents a reversible protein modification whose basic enzymology is depicted in Figure 1. The oxidized form of nicotinamide adenine dinucleotide (NAD+) is the substrate for polymer synthesis in reactions in which the glycosylic linkage between nicotinamide and ribose is cleaved, nicotinamide and a proton are released, and the ADPR moiety is used for polymer formation. Poly(ADP-ribose) polymerases (PARPs) catalyze three reactions involved in polymer synthesis.[1] Polymer initiation in most cases involves addition of ADPR to a protein carboxylate group, usually a glutamate residue. Polymer elongation involves formation of novel ribosyl-ribosyl linkages that result in both linear and branched polymer residues. The size of polymers in vivo is known primarily for polymers synthesized in response to genotoxic stress where polymer length varies from a few residues in linear structures to more than 100 residues in multibranched polymers.[1] The large variation in polymer size can be attributed to the rapid turnover of polymers and to the nature of the protein acceptors. Generally, automodified PARP-1 contains the largest polymers.[1] The functional roles of ADPR polymers can be attributed to modulation of the function of the protein to which the polymers are covalently attached and/or to noncovalent interactions with other cellular components. The ADPR polymers possess structural features found in both polynucleotides and polysaccharides. Polymers have a high density of negative charge that allows the formation of stable ionic interactions and multiple adenine rings capable of both hydrogen bonding and base stacking interactions.

The turnover of ADPR polymer residues is effected by poly(ADP-ribose) glycohydrolase (PARG) which catalyses hydrolysis of both linear and branched polymer residues yielding free ADPR.[1]

A third enzyme, ADP-ribosyl protein lyase, catalyzes the nonhydrolytic cleavage of protein proximal ADPR residues yielding the unique nucleotide ADP-3"-deoxy-pentos-2"-ulose (ADP-DP).[2] In addition to the basic enzymology shown in Figure 1, related enzyme activities

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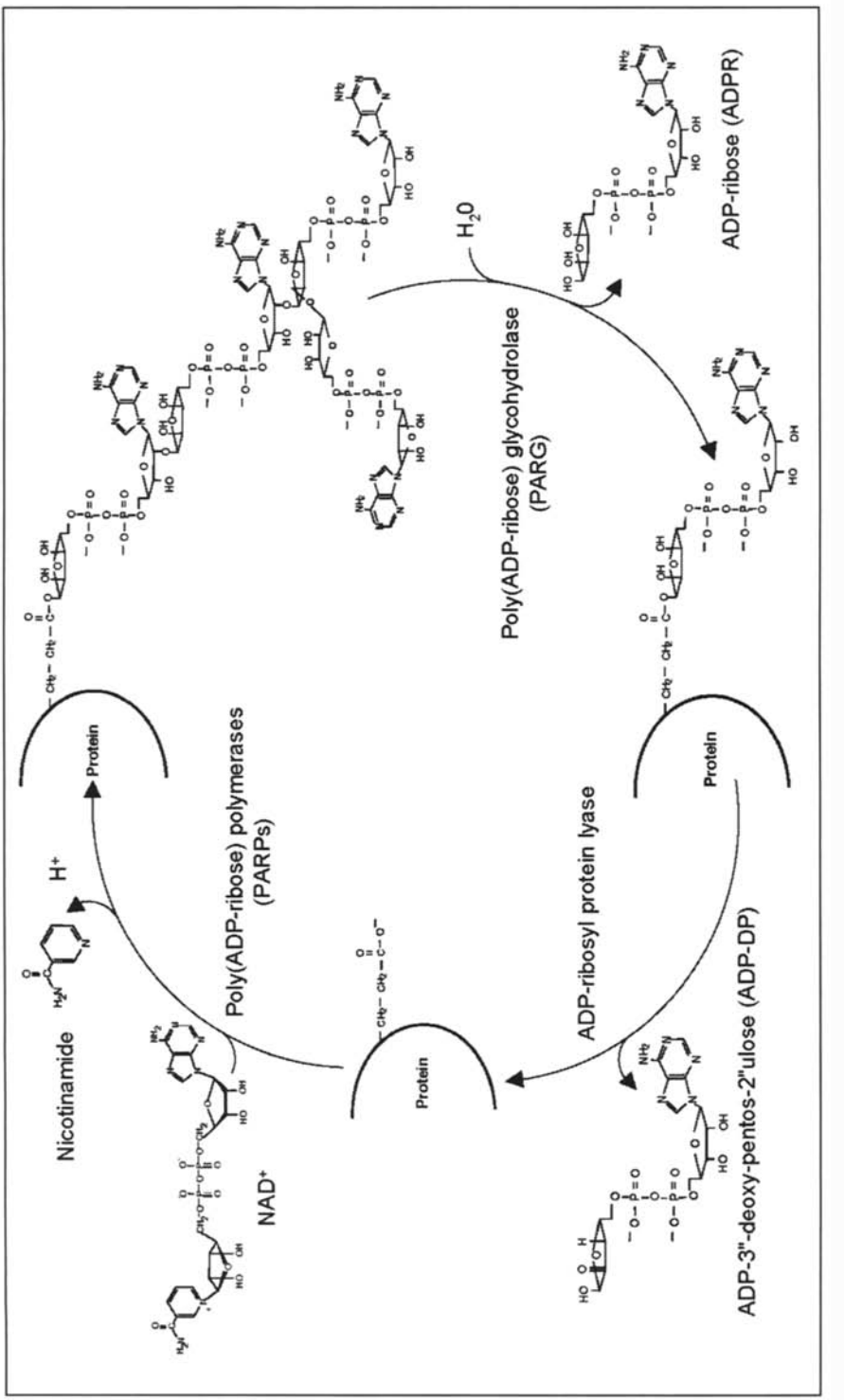

Figure 1. Reactions catalyzed by enzymes involved in the metabolism of ADPribose polymers.

are noteworthy. Besides their polymerase activity, PARPs contain NAD glycohydrolase (NADase) activity that directly convert NAD to nicotinamide and free ADPR.[1] The NADase activity is likely related to the ability of PARPs to synthesize ADPR polymers linked to proteins by a second class of linkages distinct from linkage to carboxylate groups.[3] Free ADPR readily reacts with protein lysine residues to form Schiff base derivatives that undergo rearrangement to stable ketoamine derivatives.[4]

The protein bound ketoamine derivatives can be elongated by PARPs to generate polymers linked to proteins via lysine residues.[5] Finally, free ADPR generated by the polymer turnover is a potent protein glycating sugar that can cause protein damage.[4] Thus, a highly active ADPR pyrophosphatase that converts ADPR to AMP and ribose 5-phosphate is an important enzyme related to this metabolism as ribose 5-phosphate is a much less potent glycating sugar.[6]

The PARP Family of Proteins

The role of ADPR polymer metabolism in the maintenance of genomic integrity has been appreciated for many years, despite the fact that only a single member of the PARP family was known for most of this time. However, many exciting advances during the past several years now demonstrate that many different genes code for proteins with PARP activity and thus a family of PARPs plays numerous roles in the maintenance of genomic integrity. Additionally, emerging evidence described below points to involvement in intracellular transport, memory formation, and other possible functions.

An example of the importance of ADPR polymer metabolism to the maintenance of genomic integrity is shown in Figure 2, where 5 of the 7 known PARPs are associated with the mitotic apparatus whose function is crucial to the accurate distribution of genetic material in cell division. Figure 3 provides an overview of the reported locations of PARPs in interphase cells. While the cell nucleus is still a major site of ADPR polymer metabolism, it is now clear that this metabolism is not restricted to the nuclear compartment. In this chapter, proteins that have been demonstrated to have PARP enzymatic activity are discussed, although it seems likely that other PARPs may yet be identified. Table 1 summarizes and compares some of the known properties of the various PARPs. All PARPs appear to share the property of catalyzing automodification, although the significance of this property is not yet apparent. Additionally, all PARPs are inhibited by 3-aminobenzamide and related compounds. This inhibition is not surprising as these inhibitors bind to the nicotinamide region of a NAD binding site similar in

Table 1. Comparison of properties of PARPs

Name	Chromosome Localization*	Size* # of aa	Size* kDa	Dependence	DNA Modification	Auto-Inhibition	3-AB Branching
PARP-1	1q41-42	1014	113	Yes	yes	yes	yes
PARP-2	14q11.2	583	66	Yes	yes	yes	yes
PARP-3	3p22.2-p21.1	540 533	61	?	yes	yes	yes
VPARP	13q11	1724	193	No	yes	yes	?
Tankyrase-1	8q23.1	1327	142	No	yes	yes	Not detected
Tankyrase-2	10q23.2	1166	127	No	yes	yes	?
TiPARP	3q25.31	657	76	?	?	?	?

* Information shown refers to human PARPs

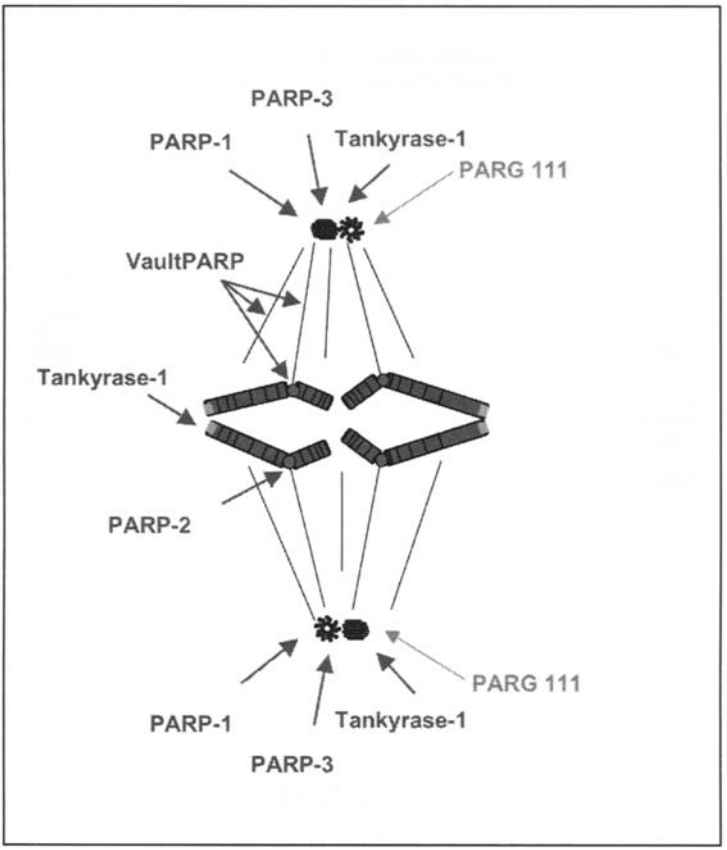

Figure 2. Schematic representation of the localization of different PARPs and the PARG 111 isoform in the mitotic spindle during cell division.

all PARPs. However, this shared property of inhibition should be kept in mind when evaluating the biological effects of these inhibitors.

PARP-1

PARP-1 (EC 2.4.2.30) was discovered more than 30 years ago and until a few years ago was thought to be the sole enzyme responsible for the synthesis of ADPR polymers. The human *PARP-1* gene has been mapped to chromosome 1 (1q42).[7,8] The PARP-1 protein contains 1,014 amino acids and consists of several domains with distinct functions. The polymerase activity is located in the C-terminal region while the N-terminal region contains a DNA binding domain (DBD) with two zinc fingers. The DBD is necessary for recognition and binding of DNA single and double strand breaks.

Moreover, the DBD contains a bipartite nuclear localization signal (NLS) and a caspase-3 cleavage motif. The region between the DBD and the catalytic center contains a BRCT domain (BRCA1 C-terminal domain) and an automodification domain. A hallmark of PARP-1 is that binding to DNA strand breaks results in a conformational change in the protein that leads to a 500 to 1,000 fold increase in catalytic activity.[1] After activation by DNA strand breaks, PARP-1 covalently modifies nuclear target proteins such as histones and catalyzes automodification of other PARP-1 molecules. Because of its very high abundance in the cell

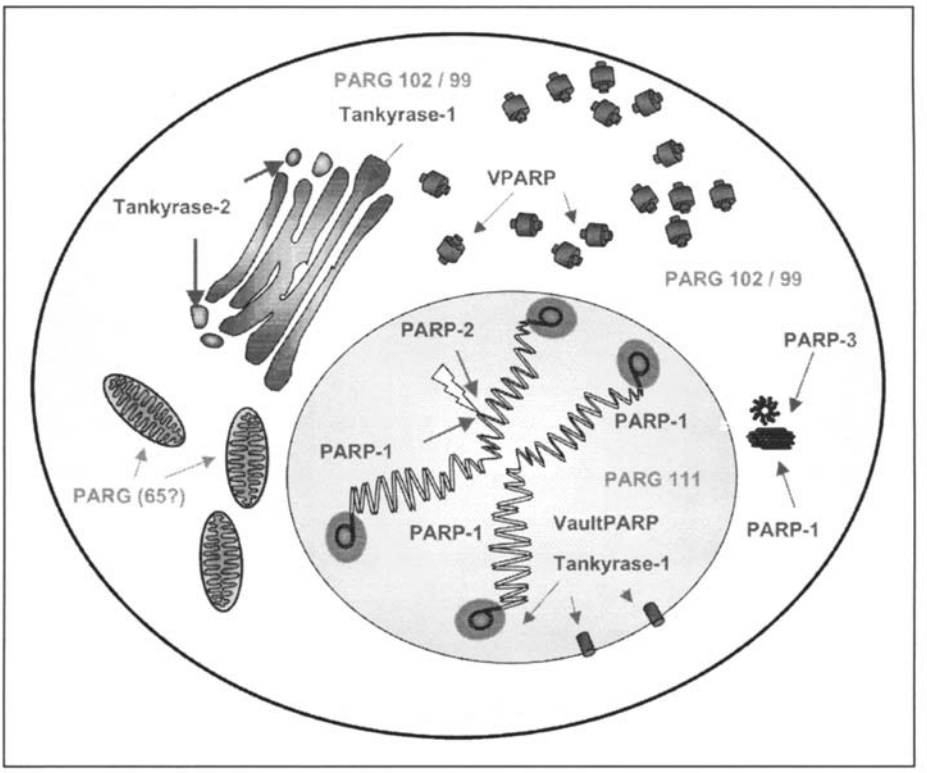

Figure 3. Schematic representation of the subcellular localization of different PARPs and different PARG isoforms in interphase cells.

nucleus and its potent catalytic activity following activation, PARP- 1 accounts for synthesis of the majority of ADPR polymer molecules produced following genotoxic stress. PARP-1 is located throughout the nucleus and in the centrosome. There is compelling evidence that PARP-1 initiated ADPR polymer cycles play many roles in the maintenance of genomic integrity including mediating cellular recovery following genotoxic stress, elimination of overly damaged cells, and ensuring proper segregation of genetic material at cell division. Many studies of PARP-1 are described in following chapters.

PARP-2

PARP-2 is the only other PARP known to be strongly activated by DNA strand breaks, but it accounts for only ~10% of activated cellular PARP activity following genotoxic stress.[9,10] PARP-2 is a protein of approximately 66 kDa, and the human *PARP-2* gene has been mapped to chromosome 14q11.2.[9,11] The protein domain structure resembles a "shorter" version of PARP-1 with a small N-terminal region of 64 amino acid residues featuring a DNA binding domain and NLS, and a larger C-terminal catalytic domain. Although initially PARP-2 was thought to be a PARP-1 "backup" with overlapping properties in base excision repair[10] the emerging picture indicates that PARP-2 has additional unique functions. PARP-2 knock-out in mice leads to an increased sensitivity towards ionizing radiation and decreased genomic stability.[12] The finding that PARP-2 locates to centromeres and telomeres[13,14] suggests an additional role in maintenance of genomic integrity by ensuring a proper distribution of the genetic material during cell division. Much additional information concerning PARP-2 can be found in the following chapter.

PARP-3

The *PARP-3* gene was reported simultaneously with the *PARP-2* gene and was mapped to chromosome 3p22.2-p21.1.[11] The presence of two different splice acceptor sites in exon 2 of the *PARP-3* gene allows generation of two different mRNAs. The shorter mRNA[11] lacks exon 1 and codes for a 533 amino acid protein and a longer mRNA containing exon 1 leads to the synthesis of a 540 amino acid protein.[15] It is possible therefore, that both differently spliced mRNA forms and different PARP-3 proteins exist in cells, either simultaneously or under different physiological conditions. Only recently, PARP-3 was shown to have poly(ADP-ribose) polymerase activity.[15] In this report, a possible function of PARP-3 in linking the DNA damage network to the mitotic fidelity checkpoint was proposed as PARP-3 colocalizes with the daughter centriole and is present at the centrosomes as has been shown also for PARP-1.[15] Overexpression of PARP-3 leads to accumulation of cells in G1/S. This effect is exerted by the 54 amino acids constituting the N-terminal portion of the protein. The N-terminal region of the shorter 533 amino acid PARP-3 form was reported not to have centrosomal retention.[15] Although PARP-3 colocalizes with the centrosome, it has no direct effect on centrosome duplication or amplification,[15] as has been shown for PARP-1.[16]

Tankyrase-1

Tankyrase-1 was the second PARP described, breaking the single PARP paradigm. Tankyrase-1 (also referred to as TANK1) was identified as an interaction partner of the telomeric repeat binding factor-1 (TRF-1).[17] Similar to TRF-1, it is located at the chromosome telomere region and it is important for the TRF-1 mediated regulation of telomere length. The *tankyrase-1* gene was mapped to chromosome 8q23.1.[18] It encodes an open reading frame of 1327 amino acids, which corresponds to a protein of 142 kDa.[17] The central domain of this protein contains 24 ankyrin (ANK) repeats, protein motifs of 33 amino acids that mediate protein-protein interactions. The Cterminal portion of Tankyrase-1 is homologous to the PARP-1 catalytic region. In addition to TRF-1, tankyrase also interacts with insulin-responsive amino peptidase (IRAP) and the telomerase binding protein Tab182.[19,20] Unlike PARP-1 and PARP-2, tankyrase-1 activity is not dependent on the presence of DNA strand breaks, but seems to be activated by phosphorylation state.[19] A detailed study of the ADPR polymers synthesized by tankyrase-1 did not detect branching of the polymer.[21] DNA synthesis is unidirectional in the 5' to 3' direction and thus requires the annealing of the Okazaki fragments on the lagging DNA strand for replication to proceed. This results in an "end of replication" problem at telomeres as the end of the linear. chromosomes are shortened during every cell division. Telomeres can be extended by the action of a ribonucleoprotein enzyme complex called telomerase. Telomerase is a cellular reverse transcriptase that elongates telomeres with the help of a RNA subunit with homology to the telomeric sequence. This enzyme is present in germ cells and some highly proliferative tissues like the intestine. Normal somatic cells do not contain significant telomerase activity and therefore telomeres are shortened with each round of DNA replication and cell division, leading to progressive telomere erosion and ultimately to an irreversible cell cycle arrest called "cellular senescence", or the "Hayflick Limit" in cell cultures. The elimination of certain cell cycle check point markers (e.g., mutation of p53 or pRb) leads to continued cell division and continued telomere shortening. After extensive telomere erosion, cells reach a phase characterized by severe genomic instability (chromosome fusions, building of anaphase bridges, etc.). While most of the cells die during this phase termed "crisis", a small fraction can escape cell death. Most of these cells display telomerase activity and they exhibit unlimited proliferation potential. The protruding GC-rich 3'overhangs of telomeres are protected from detection by the cellular DNA damage machinery by forming a unique loop structure.[22,23] TRF1, the main tankyrase-1 interaction partner, stabilizes the interaction of the double stranded telomere region and facilitates the formation of a structure called t-loop. The t-loop enables the GC-rich DNA overhang to invade the double stranded DNA region and form a displacement loop (D-loop), which then is stabilized by TRF2. Tankyrase-1 is thought to function in the maintenance or elongation of the telomere structure. In analogy to the histone shuttling model postulated for PARP-1,[24] it has

been proposed that poly-(ADP-ribosyl)ation of TRF1 by tankyrase-1 may provide a shuttle mechanism required to disassemble the telomeric loop structure during telomere elongation in telomerase positive cells. Taken together, tankyrase-1 might therefore act as a telomere length regulator by controlling the formation of "open" telomere structures and access of telomerase to the telomeric DNA substrate. Evidence for this mechanism is provided by the finding that tankyrase-1 overexpression leads to an increase in telomere length in human cells.[25]

During interphase, tankyrase-1 colocalizes with TRF1 to the telomeres and in addition resides in the nuclear pore complex. After breakdown of the nuclear envelope and nuclear pore complex during mitosis, it relocates to the pericentriolar matrix of the mitotic chromosomes. The subcellular localization of overexpressed tankyrase-1 is strictly dependent on the presence of available TRF1. Only when TRF1 also was overexpressed did overexpressed tankyrase-1 localize to the telomeres.[26] These interesting findings taken together with the fact, that tankyrase-1 itself does not contain a nuclear localization signal, suggest that subcellular distribution and activity of tankyrase-1 is strictly regulated by the cell cycle and TRF1.

A very interesting function of tankyrase-1 in meiosis has been proposed by Smith and de Lange because of the dual association of tankyrase with both telomeres and centrosomes.[26] During mitosis there is a close association between the chromosomal centromeres and the centrosomes. In contrast, an association between telomeres and centrosomes has been observed in the first meiotic division. During this phase, telomeres attach to the nuclear envelope and form a bouquet structure which facilitates pairing of the homologous chromosomes and meiotic recombination processes.[27,28] The base of this bouquet is always juxtaposed to the centrosome, and it displays a massive clustering of nuclear pore complexes to the site of chromosomal attachement.[29] Here, tankyrase could play a structural role comparable to ankyrins and mediate attachment of the telomeres to nuclear envelope. Consistent with this proposed role in meiosis, tankyrase transcripts are abundant in testis tissue.[17] In addition to its involvement in maintenance of genomic integrity, the association between tankyrase and insulin responsive amino peptidase (IRAP) in GLUT4 vesicles involved in glucose uptake also has implicated tankyrase-1 in the regulation of endosome vesicle trafficking.[19]

Tankyrase-2

In a yeast two-hybrid screen, Lyons et al. found a novel human tankyrase with high (~80% overall) amino acid identity to tankyrase-1.[30] Tankyrase-2 (also referred to as TANK2 or TNKL) is a 1166 amino acid protein of ~137 kDa, which lacks the histidine / proline / serine rich N-terminal region of tankyrase-1, but shares 85% homology with the corresponding ankyrin repeats, a sterile alpha motif module (SAM) and a PARP homology domain.[30,31] The *tankyrase-2* gene *(TNKS)* was mapped to chromosome 10q23.2, and is expressed in most tissues. Ankyrin repeats 10 to 19 mediate an interaction with Grb14, a protein of the SH2 domain family involved in signal transduction and membrane trafficking. Tankyrase-2 is found predominantly in the cytoplasm and associates with the low density microsome fraction. The subcellular distribution and the interaction with Grb14 indicates a role for tankyrase-2 in intracellular vesicle transport[30] as was also proposed in a similar context for tankyrase-1.[19] Like tankyrase-1, tankyrase-2 was found to localize preferentially to the perinuclear region and to interact with TRF1. Surprisingly, unlike tankyrase-1, overexpression of tankyrase-2 induced rapid cell death characterized by a loss of mitochondrial membrane potential, but not PARP-1 cleavage. This cell death was prevented in the presence of the PARP inhibitor 3-aminobenzamide, indicating that PARP activity was involved.[31]

Vault PARP (VPARP)

Vaults are large ribonucleoprotein complexes found in eukaryotic cells.[32] Isolated vault particles have a characteristic hollow barrel-like shape. They are predominantly localized in the cytoplasm and copurify with microtubules and ribosomes.[33-35] An association with nuclear components such as the nucleoli, the nuclear membrane and the nuclear pore complex also has been reported.[36] Based on the subcellular localization and the vault particle structure, a function in

intracellular transport has been proposed. In this context it also has been assumed that vault particles are important for intracellular detoxification by transporting drugs away from their subcellular target, as vaults, and especially the major vault protein (MVP), were found to be overexpressed in many drug resistant human tumor cell lines.[37-39]

With a mass of 13 MDa, vaults are the largest ribonucleoprotein complexes described to date. They are composed of a ribonucleic acid with species-specific length, and three proteins of 100, 193 and 240 kDa in size. The 100 kDa protein constitutes over 70% of the vault complex mass and therefore was designated "major vault protein" (MVP). The 240 kDa protein was identified as the telomerase associated protein 1 (TEP1), that also participates in the formation of the telomerase complex which is also a ribonucleoprotein complex. The 193 kDa vault subunit was found to have PARP activity and designated vault PARP (VPARP).[40] Although VPARP is an integral part of vaults, immunofluorescence studies and biochemical fractionations showed that its subcellular distribution overlaps only partly with that of the major vault protein.[40,41] Some of the cellular VPARP is present in the cytoplasm and the nucleus. In mitotic cells, an association of VPARP with the mitotic spindle has been observed.[40] The human *VPARP* gene has been mapped to chromosome 13q11.[42] The VPARP protein contains a ~300 amino acid domain that shows 28% sequence identity to the catalytic domain of PARP-1.

VPARP was shown to catalyze modification of MVP and automodification.[40] The VPARP N-terminal region has a BRCT domain similar to that of PARP-1 and VPARP possesses a glutamic acid rich stretch that resembles the PARP-1 automodification domain, thereby indicating putatively similar functions. In addition, VPARP seems to have additional functions that are independent from vaults. This is suggested by the presence of VPARP outside of typical vault locations such as cytoplasmic clusters ("VPARP-rods") as well as its association with the nuclear matrix[43] and the mitotic spindle.[40]

TiPARP

The most recent addition to the growing PARP family is 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) inducible PARP (TiPARP). It was discovered in mouse cells by using mRNA differential display in the analysis of the effects of halogenated aromatic hydrocarbons (HAHs). HAHs are important environmental and industrial contaminants that induce a wide range of adaptive and toxic responses in animals and humans.[44,45]

These responses are mediated by an alteration of signal transduction pathways via the aromatic hydrocarbon receptor (AhR) and a subsequent change in gene expression pattern. The *TiPARP* gene was found to be specifically upregulated in mouse cells after exposure to TCDD.[46] This upregulation is dependent on the presence of AhR and Arnt (the aromatic hydrocarbon receptor nuclear translocator).[47] The isolated *TiPARP* mRNA encodes a protein of 657 amino acids. Homology studies on the amino acid sequence revealed similarity with the catalytic domains of PARP-1 and Tankyrase-1.[46] In vitro expressed murine TiPARP has been shown to have PARP-1 activity. Recently, the human *TiPARP* gene was characterized and was found to consist of 6 exons, and to be located on human chromosome 3q25.31.[48]

The function of the TCDD inducible PARP is not clear at present. A connection between TiPARP and memory formation has been implied, as the *TiPARP* gene has over 90% sequence homology to the rat RM1 gene proposed to play a role in memory formation.[49]

It also has been shown that exposure to polychlorinated biphenyl's (PCB), which like TCDD are ligands of AhR, lead to decrements in learning and memory.[50] The general link between poly(ADP-ribosyl)ation and memory formation is also strengthened by the observation that poly(ADP-ribose) formation is a rapid response of neuronal cells to membrane depolarization.[51] The signal transduction involved in this response was independent of DNA strand breaks and was evoked by inositol 1,4,5,-triphosphate mediated Ca^{2+} mobilization.[51] Although this poly(ADP-ribose) synthesis has been proposed to be due to PARP-1, other PARPs such TiPARP may play a role in this context.

Poly(ADP-Ribose) Glycohydrolase (PARG)

While many different genes now are known to code for PARPs found in many different cellular locations (Figs. 2, 3), higher organisms appear to have only a single gene coding for PARG.[52] This raises challenging questions concerning how PARG is targeted to different locations within the cell and regulated to function as the opposing arm of ADPR polymer cycles initiated by different PARPs. While many questions remain, studies of the PARG protein and transcription of the *PARG* gene are beginning to provide answers to these questions. Figure 4 shows the human *PARG* gene exon structure[52] and the structure of three PARG isoforms that result from alternative splicing of *PARG* gene transcripts.[53] The PARG protein contains 4 putative domains[54] and the PARG isoforms differ only in domain A. All of the PARG isoforms contain a very protease labile site located at the junction of domains A and B. This provides an explanation as to why PARG isolated from cell extracts is typically 60 to 65 kDa in size[1] since the catalytic activity is present in the C-terminal fragment generated by protease cleavage. This region of PARG also contains a putative bipartite NLS with sequence homology to the NLS of PARP-1,[55] but this sequence does not appear to function as an NLS in PARG.[53] Protein domains B and D represent mostly alpha helical domains while domain C contains a series of beta sheets that are similar to the fold found in ADP-ribosyl transferases.[54] The catalytic active site is located in domain C which contains highly conserved amino acid residues involved in substrate binding and catalysis.[56]

Studies of the enzymatic properties of PARG have demonstrated that PARG catalyzes the hydrolysis of both linear and branched polymer residues (Fig. 1) by a predominately exoglycosidic mechanism although the enzyme has a low level of endoglycosidic activity.[57,58] The significance of the endoglycosidase activity of PARG is not clear but the enzyme has the potential to generate different products depending upon its state of saturation. For example, under conditions where the enzyme is not saturated with substrate, free ADPR and protein bound ADPR polymers would be the expected products, but when saturated with substrate the enzyme would be expected to generate free ADPR polymers. It has generally been assumed that PARG is unable to catalyze removal of the protein proximal ADPR residue, but a recent reexamination of this issue indicates that PARG can catalyze removal of protein proximal ADPR residues linked to protein carboxylate groups of histone H1.[5]

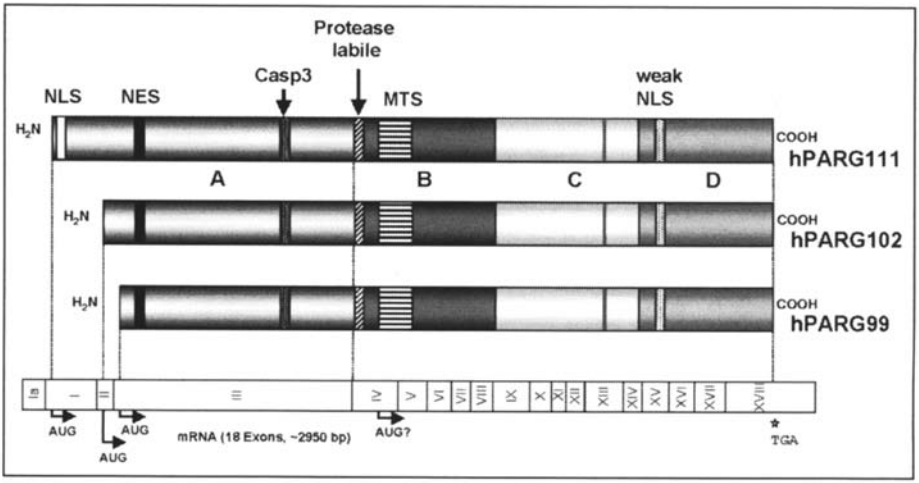

Figure 4. Schematic representation of the human PARG gene exon structure and of three PARG isoforms that result from translation of PARG mRNA splice variants. Abbreviations used are: NLS, nuclear localization signal, NES, nuclear export signal, MTS, mitochondrial targeting sequence.

The human *PARG* gene was mapped to chromosome 10q11.23 by in situ hybridization and by analysis using the NCBI "Genome Blast" program.[52,59] The *PARG* open reading frame consists of 18 exons and 17 introns. The catalytic center of the protein (domain C) is encoded by exons 9 to 14. The flanking B and D domains are encoded by exons 5 to 7 and 15 to 18, respectively. Exons 1 to 3 encode the putative regulatory region.[52] The *PARG* gene is oriented head to head with the gene coding for the translocase of the inner mitochondrial membrane 23 (*TIM23*). The two genes share a common bidirectional promoter that achieves different expression levels in both directions.[52] It is of interest that the PARG protein contains a putative mitochondrial targeting sequence and subcellular fractionation studies indicate that PARG is located in the mitochondrion.[60] The presence of PARG in mitochondria is intriguing, as no definitive demonstration of PARP activity in mitochondria has been reported.

Translation of alternatively spliced mRNAs leads to three PARG isoforms that differ in the A domain of the protein. Translation of all 18 exons results in a PARG of 111 kDa while splice variants omitting exon 1 or both exon 1 and 2 result in PARG isoforms of 102 kDa and 99 kDa, respectively.[53] Transient overexpression of the respective PARG variants and subsequent immunofluorescence analysis revealed that the PARG111 is targeted to the nucleus while PARG102 and PARG99 are targeted to the cytoplasm.[53]

This led to the identification of a strong NLS in the region of the protein coded for by exon 1.[53] A recent report using a fusion protein of enhanced green fluorescent protein (EGFP) and human PARG protein provided a new interesting addition to the already complex picture of subcellular PARG distribution as PARG was shown to colocalize and cofractionate with the centrosome.[61] The A domain of the PARG isoforms also contain other features that may be involved in regulation of the protein. A caspase cleavage (Casp3) site that is cleaved during apoptosis is present[62] and a putative nuclear export signal (NES) has been described.[63,64] While much remains to be learned about PARG, a picture is emerging in which a single PARG gene gives rise to multiple PARG proteins that are targeted to multiple locations within the cells to effect ADPR polymer turnover.

ADP-Ribosyl Protein Lyase

Early studies of ADP-ribose polymer metabolism concluded that PARG was unable to remove the protein proximal ADPR residue from acceptor proteins. This led to the isolation of an ADP-ribosyl protein lyase that catalyzes removal of the protein proximal ADPR residue linked to the acceptor protein.[2] Although this enzyme was discovered many years ago, it has received very little attention and consequently its structure function relationships and role in ADPR polymer metabolism are still poorly understood. Additional questions have been raised by recent studies that indicate that PARG can catalyze removal of protein proximal ADPR residues linked to carboxylate groups of histone H1.[5] It is possible that the property of both enzymes to catalyze removal of these residues represents redundancy in function or that specific polymer acceptor proteins require different enzymes to catalyze removal.

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