Cell. Mol. Life Sci. (2012) 69:175–189
DOI 10.1007/s00018-011-0793-4

Cellular and Molecular Life Sciences

REVIEW

Functions of the poly(ADP-ribose) polymerase superfamily in plants

Rebecca S. Lamb · Matteo Citarelli · Sachin Teotia

Received: 14 April 2011 / Revised: 2 August 2011 / Accepted: 4 August 2011 / Published online: 23 August 2011

Abstract Poly(ADP-ribosyl)ation is the covalent attachment of ADP-ribose subunits from NAD^+ to target proteins and was first described in plants in the 1970s. This post-translational modification is mediated by poly(ADP-ribose) polymerases (PARPs) and removed by poly(ADP-ribose) glycohydrolases (PARGs). PARPs have important functions in many biological processes including DNA repair, epigenetic regulation and transcription. However, these roles are not always associated with enzymatic activity. The PARP superfamily has been well studied in animals, but remains under-investigated in plants. Although plants lack the variety of PARP superfamily members found in mammals, they do encode three different types of PARP superfamily proteins, including a group of PARP-like proteins, the SRO family, that are plant specific. In plants, members of the PARP family and/or poly(ADP-ribosyl)ation have been linked to DNA repair, mitosis, innate immunity and stress responses. In addition, members of the SRO family have been shown to be necessary for normal sporophytic development. In this review, we summarize the current state of plant research into poly(ADP-ribosyl)ation and the PARP superfamily in plants.

A recent review on this subject covering similar but not identical data was published during review of this manuscript [24].

R. S. Lamb (✉) · M. Citarelli
Department of Molecular Genetics, The Ohio State University, 500 Aronoff Laboratory, 318 W. 12th Ave, Columbus, OH 43210, USA
e-mail: lamb.129@osu.edu

S. Teotia
School of Biotechnology, Gautam Buddha University, Greater Noida, U.P. 201308, India

Keywords ADP-ribose · PARP · mART · Post-translational modification · Stress · Cell proliferation

Introduction

Post-translational modifications of proteins, such as phosphorylation, ubiquitination and acetylation, allow dynamic and reversible changes to function. The attachment of multiple ADP-ribose moieties to proteins, poly(ADP-ribosyl)ation, is a post-translational modification mediated by poly(ADP-ribose) polymerases (PARPs) and was first discovered in the 1960s [26, 27, 42, 50, 95, 114]. Although originally described in mammals, members of the PARP superfamily have now been identified through sequence similarity in all major groups of eukaryotes [32]. The PARP catalytic site, called the PARP signature, which consists of a ß-alpha-loop-B-alpha NAD^+ fold [101, 120], characterizes members of this superfamily. These proteins are best studied in humans, where 17 members are found, which combine diverse functional domains with the PARP catalytic domain [9, 60, 125]. True PARPs attach ADP-ribose subunits to target proteins; depending on the specific PARP involved, several to hundreds of ADP-ribose units can be attached to the target [78]. This process uses nicotinamide adenine dinucleotide (NAD^+), releasing nicotinamide as a reaction byproduct. However, not all proteins with PARP signatures actually function in poly (ADP-ribosyl)ation. For example, while both HstiPARP and HsPARP10 have non-conserved residues instead of an important catalytic glutamic acid [3, 88, 148], Hsti-PARP has PARP activity [88] while HsPARP10 acts as a mono(ADP-ribose) transferase (mART) [31, 79, 148]. In addition, two other human proteins that have replaced catalytic residues, HsPARP9 and HsPARP13, are

enzymatically inactive [79, 136]. This suggests that the functions of the PARP superfamily extends beyond poly(ADP-ribosyl)ation.

PARP superfamily members are involved in a broad range of functions, including DNA damage repair, cell death pathways, transcription and chromatin modification/remodeling (reviewed in [60, 78, 125]) and are targets for the development of anti-cancer drugs [61]. The first identified member of the PARP superfamily, human PARP1 (HsPARP1), remains the best studied. The PARP1 encoding gene is expressed nearly ubiquitously in mouse and other mammals [124]. The protein contains N-terminal DNA-binding zinc fingers, necessary to bind to double-strand breaks (Fig. 1a). In addition, the protein has a PADR1 domain, a domain of unknown function found in PARP1 and its orthologs [128] as well as a BRCA1 *C*-Terminus domain (BRCT), found predominantly in proteins involved in cell cycle checkpoints [21]. In addition, HsPARP1 contains a WGR domain of unknown function, although postulated to bind nucleic acids, and a PARP regulatory domain (PRD) [120, 127], before the C-terminal catalytic domain. HsPARP1 was originally found to function in association with DNA damage and repair pathways. In this context, it is activated upon binding to DNA strand breaks and autopoly(ADP-ribosyl)ates [58, 60]. The negatively charged ADP-ribose residues interfere with protein–protein and protein–DNA interactions, including the association of histones with DNA. In fact, histones bind poly(ADP-ribose) (PAR) with high affinity and this stimulates the removal of histones from DNA [7]. It is thought that this change in nucleosome occupancy frees DNA at the site of damage for efficient DNA repair. Histones themselves are also targets of mono- and poly(ADP-ribosyl)ation in mammals and in plants [145, 146], including on lysines [53, 91, 140]. The functional significance of this histone modification remains to be determined.

HsPARP1 and it orthologs in animal systems have been implicated in numerous other functions. Enzymatically silent PARP1 acts as a structural protein in chromatin and inhibits transcription by contributing to the condensation of chromatin [82, 97, 102, 139, 143]. However, when activated by developmental or environmental signals, PARP1 auto-modifies itself and other chromatin-associated proteins, opening chromatin to facilitate gene expression [59, 82, 138]. PARP1 has also been shown to have more direct roles in transcriptional regulation (reviewed in [83]). The broad range of roles for PARP1 suggests that other members of the PARP superfamily may also have many context-dependent roles.

In addition to HsPARP1, two other PARP superfamily members, HsPARP2 and HsPARP3, which are found in the same subgroup of the family as HsPARP1 [32], have been implicated in DNA repair in humans and other mammals. *PARP2* is expressed in a broad range of tissues and cell types [124]; however, *PARP3* expression shows tissue specificity in mouse [141]. It is thought that PARP2 and PARP3 function in conjunction with PARP1 during DNA repair and other processes such as gene regulation. Consistent with this hypothesis, while single mutant animals appear normal, *parp1/parp2* knockout mice die during embryogenesis [40], while *parp1/parp3* mice are very sensitive to DNA-damaging agents [19]. Both HsPARP2 and HsPARP3 have been shown to act in poly(ADP-ribosyl)ation with activity stimulated by DNA fragments [8, 19, 121]. However, HsPARP3 has also been reported to act as a mART toward histone H1 and to not be stimulated by DNA [87], suggesting that its enzymatic function maybe context dependent.

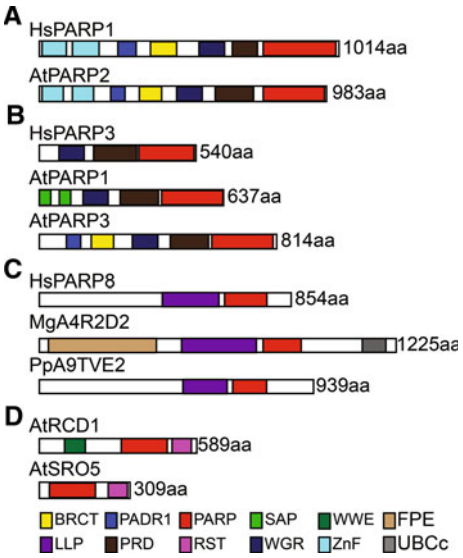

Fig. 1 Schematic representation of domains found in PARP superfamily proteins. Protein domains are illustrated by *colored boxes* and are defined according to Pfam 25.0 [34], unless otherwise noted. Proteins are shown to scale with their lengths in amino acids indicated. **a** Land plants contain proteins similar to HsPARP1. **b** Land plants contain proteins similar to HsPARP3. **c** Plants and other eukaryotes contain HsPARP8 orthologs. **d** The SRO family is land plant specific. *BRCT* BRCA-1 *C*-terminus domain (PF00533), *FPE* fungal PARP E2-associated domain [32], *LLP* domain of unknown function found in the PARP8 subfamily of the PARP superfamily (Citarelli, Lee and Lamb, unpublished data), *PADR1* domain of unknown function found in PARPs (PF08063), *PRD* PARP regulatory domain, *PARP* PARP catalytic domain (PF00644), *RST* RCD-SRO-TAF4 domain (PF12174), *SAP* presumed nucleic acid binding domain (PF02037), *UBCc* ubiquitin E2 catalytic domain (PF00179), *WGR* domain defined by conserved tryptophan, glycine and arginine residues (PF05406), *WWE* presumed protein-protein interaction domain characterized by tryptophan and glutamic acid residues (PF02825), *ZnF* DNA binding zinc finger domain (PF00645). *At Arabidopsis thaliana*, *Hs Homo sapiens*, *Mg Magnaporthe grisea*, *Pp Physcomitrella patens*

Removal of ADP-ribose from proteins

Poly(ADP-ribosyl)ation is a reversible modification, and poly(ADP-ribose) glycohydrolase (PARG) enzymes catalyze the hydrolysis of the glycosidic linkages of ADP-ribose polymers to produce free ADP-ribose. Thus, PARG reverses or counteracts the function of PARPs. In contrast to the PARP superfamily, only one or a handful of genes encode PARGs, although alternative splicing can produce multiple isoforms in mammals. PARG has been reported to be present in several subcellular compartments, including the nucleus and cytoplasm as well as mitochondria [20]. PARGs have not been extensively analyzed in plants. In the plant *Arabidopsis thaliana*, two genes encode putative PARGs, *AtPARG1/TEJ* (*At2g31870*) and *AtPARG2* (*At2g31865*), which resulted from gene duplication [23].

Free ADP-ribose is known to be toxic, and it has been speculated that the lethality of mutations in *PARG* genes in animals is at least partially due to buildup of this metabolite [57, 80]. Nudix (nucleoside diphosphates linked to moiety X) hydrolases catalyze the hydrolysis of a variety of nucleoside diphosphate derivatives [18]. Three members of this family in *Arabidopsis*, AtNUDT2, AtNUDT6 and AtNUDT7, have been shown to hydrolyze both ADP-ribose (to AMP and ribose-5-phosphate) and NADH in vitro [52, 99] and these seem to be physiological substrates [64, 98]. Overexpression of *AtNUDT2* has been shown to protect plants from depletion of NAD^+ and ATP under oxidative stress conditions, suggesting its involvement in recycling the ADP-ribose generated by ADP-ribosylation [98]. Similarly, inhibition of removal of ADP-ribose through loss of function in *AtNUDT7* has been shown to decrease the level of poly(ADP-ribose) in *Arabidopsis*, correlating with an increase in ADP-ribose [64], suggesting that PARP activity is inhibited in this background.

Distribution of PARP superfamily proteins in plants

Plants contain at least three types of PARP superfamily members

PARP activity in plants was first described in the 1970s, when it was demonstrated that a biochemical activity in the nuclei of wheat [145] and *Nicotiana tabacum* [146] was poly(ADP-ribosyl)ating histones. Since then, PARP superfamily members have been identified in plants, both by sequence similarity to animal proteins [13, 85] and through genetics [5]. Compared to humans, where this protein family contains 17 members and there are at least five different types of PARP subfamilies [32, 60], plants contain relatively few such proteins. All land plants contain orthologs of HsPARP1 and others that seem to be more related to HsPARP3 based on the sequence of their catalytic domains (Fig. 2 and Table 1; [32]). The HsPARP1 orthologs, typified by *Arabidopsis thaliana* PARP2 (AtPARP2), share a conserved domain structure with this protein (Fig. 1a). In common with other proteins that act in poly(ADP-ribosyl)ation, the plant HsPARP1 orthologs contain a so-called catalytic triad consisting of histidine-tyrosine-glutamic acid (HYE) residues within the PARP signature (Fig. 2a). The first two residues of this triad are necessary for NAD^+ binding [116] while the third is important for polymer formation [90]. Although none of the plant proteins in these groups have been demonstrated to have poly(ADP-ribosyl)ation activity to date, it is very likely that they do in fact have this activity, based on the high identity of the plant catalytic domains to those of HsPARP1 (Fig. 2a). *AtPARP2* is broadly expressed (Genevestigator; [151]), consistent with other *HsPARP1* orthologs.

The PARP superfamily members that are more similar to HsPARP3 within their catalytic domains are also found throughout land plants and are split into two distinct groups [32]. The first group, which contains the first plant PARP cloned, AtPARP1/APP [85], has an apparently plant-specific domain structure, containing two SAP domains in the *N*-terminus (Fig. 1b). SAP domains have been shown to bind to nucleic acids [100] and have also been demonstrated to function in localizing proteins to the kinetochore during mitosis [122]. In addition to the SAP domains, these proteins contain a WGR domain, a PRD domain and catalytic domain at the very *C*-terminus. These PARP superfamily members have the HYE catalytic triad within their PARP signature (Fig. 2b), and both AtPARP1 (Table 1; [13]) and *Zea mays* PARP1 (ZmPARP1; [89]) have been shown to have poly(ADP-ribosyl)ation activity, suggesting that all members of this group likely function in poly(ADP-ribosyl)ation. The second group of proteins similar to HsPARP3, typified by AtPARP3, do not contain SAP domains. They more closely resemble HsPARP2 in domain structure (Fig. 1b). Interestingly, these proteins have acquired changes in the catalytic domain such that they no longer contain an intact HYE catalytic triad (Fig. 2b). All members of this group contain a cysteine instead of the histidine at the first position and retain the glutamic acid at the third position. In angiosperms, the second position contains a valine instead of a tyrosine while seedless plants retain the tyrosine (Fig. 2b; [32]). The impact of these changes on catalytic activity of these proteins is unclear, although they would be predicted to eliminate NAD^+ binding and therefore enzymatic activity. In *Arabidopsis thaliana*, *AtPARP3* is expressed in developing seeds [16], suggesting a function during this part of the plant lifecycle.

Physcomitrella patens, a moss found in the basal land plant group the bryophytes, contains PARP superfamily

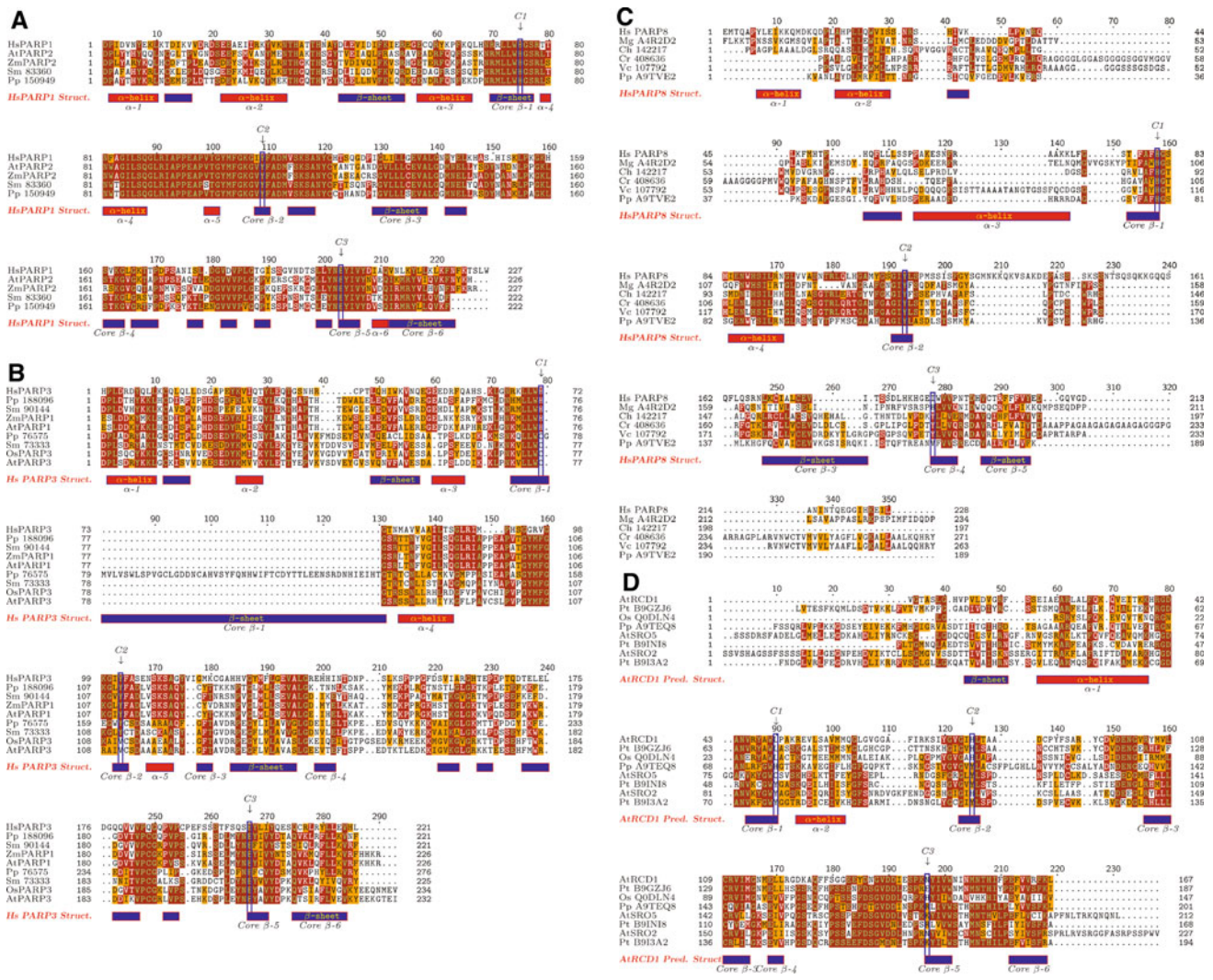

Fig. 2 Multiple alignments of the PARP catalytic domains of land plant PARP proteins. These alignments only show the conserved PARP catalytic domain and the numbers indicate amino acids within these domains. *Dots* indicated gaps introduced to optimize the alignment. Identical amino acids are indicated by *red shading* and similar amino acids by *orange shading*. The amino acids present in the catalytic triad are *boxed in blue* and labeled C1, C2 and C3. The alignments were generated using the MUSCLE3.8.31 multiple alignment tool, using default settings [45]. Structures were obtained from the RCSB Protein Data Bank [117], unless otherwise noted. **a** Multiple alignment of HsPARP1 and its land plant orthologs. The structural elements present in HsPARP1 are shown at the bottom of the alignment. **b** Multiple alignment of HsPARP3 and its land plant orthologs. The structural elements present in HsPARP3 are shown at the bottom of the alignment. **c** Multiple alignment of HsPARP8, MgA4R2D2 and their green algal and moss orthologs. The structural elements present in HsPARP8 are shown below the alignment. **d** Multiple alignment of members of the SRO family. The predicted structural elements present in AtRCD1 are shown below the alignment. The structural prediction was done using Phyre [76]. *Hs Homo sapiens*, *At Arabidopsis thaliana*, *Zm Zea mays*, *Sm Selaginella moellendorfii*, *Pp Physcomitrella patens*, *Os Oryza sativa*, *Mg Magnaporthe grisea*, *Ch Chlorella sp 142271*, *Cr Chlamydomonas reinhardtii*, *Vc Volvox carteri*, *Pt Populus trichocarpa*

members that are orthologous to HsPARP6, 8 and 16 (the PARP8 clade; [32]). Similar proteins are also found in some green algae, including *Chlamydomonas reinhardtii* and *Volvox carteri*, as well as many fungi and *Trichomonas vaginalis* within the Excavata [32]. However, this group of proteins appears to have been lost from vascular plants. No member of this clade, including those found in humans, have been functionally characterized. Interestingly, no green algae with sequenced genomes have any PARP superfamily members other than the PARP8-type. Other eukaryotic lineages have also lost most or all PARP-encoding genes from their genomes [32]. The moss protein in this group, A9TVE2, contains a long *N*-terminus with no known functional domains but containing an LLP domain, a domain of unknown function found only in the PARP8 clade of the PARP superfamily (Fig. 1c; Citarelli et al., in preparation). This protein contains a C-terminal extension with no apparent functional motifs. This domain structure is

similar to that seen in the human PARP8 protein (Fig. 1c); interestingly, the fungal members of this clade contain a C-terminal UBCc domain (Fig. 1c; [32]). UBCc domains are the catalytic domains found in E2 Ub-conjugating enzymes, which carry Ub and transfer it either directly to a substrate or to an E3 ligase [35]. The presence of this domain in some PARP8 clade proteins suggests a connection between ADP-ribosylation and ubiquitination. In common with its orthologs in other groups of eukaryotes, the catalytic domain of PpA9TVE2 contains changes suggesting that it functions in mono(ADP-ribosyl)ation rather than as a bona fide PARP, retaining the first two residues of the catalytic triad, but replacing the third residue (Fig. 2c). However, since no members of the PARP8 clade have been characterized either functionally or biochemically, it is not clear what function these proteins may be playing.

Finally, land plants have acquired a novel group of PARP-like proteins, the SRO family. These proteins are found throughout land plants and consist of two subgroups [32, 74]. The first is ubiquitous in land plants and contains a WWE protein-protein interaction domain [11] in the *N*-terminus and a C-terminal extension past the PARP catalytic domain (Fig. 1d). This extension contains an RST domain [73]. The second subgroup is found only in the eudicot group of flowering plants and contains proteins that have lost the N-terminal region and retain only the catalytic domain and the RST domain (Fig. 1d). These proteins contain variant PARP signatures and may not act enzymatically (Fig. 2d). In fact, AtRCD1, the first member of this group identified, appears to be inactive (Table 1; [74]). However, the catalytic triads within this group vary, with some members, such as PpA9TEQ8, retaining the NAD^+ binding residues (Fig. 2d; [32]). This suggests that activity must be assayed for multiple members before any conclusions on biochemical function can be formed for the family. Two members of this group from *Arabidopsis*, RCD1 and SRO1, have been shown to bind to transcription factors in yeast two-hybrid assays [17, 72]. The RST domain characteristic of the SRO family is also found in the transcription initiation complex component TAF4 [73]. These facts, along with the known roles of HsPARP1 in regulation of transcription and chromatin structure in absence of enzymatic activity, suggest that the SRO family may function in gene regulation at the transcriptional and/or chromatin level.

Functions of PARP superfamily members in plants

PARP proteins in DNA repair and the cell cycle

Bona fide PARPs were first discovered in association with DNA repair pathways and this is still the best-known and studied role of this class of enzymes (reviewed in [61]). HsPARP1 orthologs have been shown to be involved or implicated in DNA repair in animals [8, 118, 137], fungi [81, 126], *Trypanosoma cruzi* [46] and *Dictyostelium discoideum* [112]. It is likely that a role in DNA repair is shared by most orthologs of HsPARP1, HsPARP2 and HsPARP3. Although this has not been extensively studied in plants, there is some evidence supporting the involvement of PARPs in DNA repair in this group of organisms as well. In *Arabidopsis*, *AtPARP1* and *AtPARP2* expression is higher in genetic backgrounds that have increased DNA damage or replication stress [13, 113, 150] and in rapidly dividing tissues and stem cells in which the genome needs to be protected [93]. Their expression is induced by radiation [36, 43], genotoxic stress [30] and Gemini virus infection, presumably due to the presence of nicked viral replication intermediates [12]. AtPARP2 has been shown to bind DNA breaks [43]. PARP inhibitor studies suggest that PARP enzymes may participate in control of DNA recombination [110]. However, the studies done with PARP inhibitors need to be interpreted carefully. In plants, two inhibitors have been used: 3-aminobenzamide (3AB) and nicotinamide. 3AB is a competitive inhibitor of the poly(ADP-ribosyl)ation reaction [44] and is thought to act primarily on HsPARP1 and HsPARP2-like enzymes and to a lesser extent on HsPARP3-like enzymes, while nicotinamide, as one of the products of the ADP-ribosylation reaction, therefore inhibits it and would be expected to inhibit any enzyme with ADP-ribosylation activity or that produces nicotinamide (reviewed in [47]). However, both these compounds have suboptimal inhibitory potencies [44]. In addition, they are capable of inhibiting other enzymes in addition to PARPs. In particular, both 3AB (to a minimal extent) and nicotinamide inhibit sirtuins [55], histone deacetylases that couple lysine deacetylation to NAD^+ hydrolysis [54]. These enzymes are found throughout plants [54], and their activities are likely to be altered by application of nicotinamide and perhaps 3AB. *Arabidopsis* encodes two sirtuins, AtSRT1 and AtSRT2 [106]. Therefore, phenotypes seen upon 3AB and nicotinamide application should be examined closely, as it is unclear which PARP superfamily members are inhibited, to what extent and if sirtuins are also impacted. In addition, inhibitor studies offer no insights into any non-enzymatic functions PARP proteins might have. Despite the limitations of PARP inhibitor studies done to date and the lack of a direct demonstration of activity in DNA repair, it is very likely that plant PARPs similar to AtPARP1 and AtPARP3 are involved in this process.

In addition to roles in DNA damage response and repair, various members of the PARP superfamily have been shown to be involved in cell cycle control and mitosis. PAR accumulates along spindles in animals, suggesting a

role in spindle formation or regulation [29]. Tankyrase, a type of PARP confined to animals [32], is necessary for sister chromatid separation [63] and spindle function [28]. In plants, some studies also link poly(ADP-ribosyl)ation to cell cycle activity. PARP activity increases during exponential growth of *Arabidopsis* cell cultures and expression of *AtPARP1* and *AtPARP2* peaks during this time. This peak of PARP activity correlates with that of glutathione reductase and with an increase in the NAD^+/NADH pool size and ratio [48, 107]. A more direct link between plant PARPs and mitosis was found by examining the localization of AtPARP1 and AtPARP2 in mitotic cells. GFP-labeled proteins expressed in tobacco cells localized with chromosomes and the spindle during mitosis, while AtPARP1 also associated with these structures in *Arabidopsis* roots [14]. AtPARP1's association with chromosomes required the N-terminal SAP domains, while the localization of AtPARP2 required the two zinc fingers and associated regions. Based on these observations, it is likely that poly(ADP-ribosyl)ation and/or PARP proteins are likely to function during the cell cycle and mitosis in plant cells.

PARP superfamily proteins influence abiotic stress responses in plants

Poly(ADP-ribosyl)ation has been implicated in stress response in eukaryotes since at least the 1970s. In particular, HsPARP1 and other similar PARPs are known to be important in the balance between cell survival and death in response to a number of stresses. Overactivation of HsPARP1 can result in massive necrotic cell death and has been implicated in disease (reviewed in [37, 58–60, 68, 125, 130]). However, it is required for genomic integrity and to protect proliferating cells and some non-proliferating cell types against cell death induced by oxidative stress [39, 40, 66]. During apoptosis, HsPARP1 is proteolytically inactivated by cleavage into characteristic fragments by executioner caspases [25, 94, 96, 134, 149]; this inactivation is hypothesized to prevent energy depletion through NAD^+ consumption. The cleavage fragments have been shown to act in a dominant negative manner to prevent full-length HsPARP1 activity [149]. Therefore, HsPARP1's role as either a survival factor or a death signal is context dependent. In plants, the involvement of PARPs and poly(ADP-ribosyl)ation in abiotic stress response has been the best-studied function for the protein family.

The land plant PARPs similar to both HsPARP1 and HsPARP3 have been implicated in cell death. In soybean cells, upon induction of oxidative stress, PARPs are activated and cellular NAD^+ levels are reduced. This is followed by programmed cell death (PCD). This PCD could be inhibited by PARP inhibitors and/or by downregulation of PARP [10]. Consistent with this, overexpression of *AtPARP1* in soybean improved the resistance of soybean cells to mild oxidative stress [10]. The cleavage of PARP during cell death may also be shared with animals. Cultured tobacco cells undergo cell death upon heat shock. An antibody raised against HsPARP1 recognized a tobacco protein cleaved to approximately 89 KDa upon heat shock, a size consistent with the known cleavage product produced during apoptotic death in animal systems [135]. Application of 3AB and nicotinamide reduced the amount of death induced by heat shock, suggesting that PARP activity may be involved in the cell death.

Most of the work connecting PARP superfamily members with stress response in plants has been done in *Arabidopsis* (Fig. 3). Expression studies in this plant have implicated both *AtPARP1* and *AtPARP2* in response to abiotic stress. In particular, *AtPARP2* is upregulated by oxidative stress and salinity [30, 43, 98]. *AtPARP3*, although under normal conditions only expressed in seeds, can be upregulated by paraquat, salinity, high light intensity and drought [98]. Functionally, *AtPARP1* and *AtPARP2* have been implicated in abiotic stress response. Induction of PARP activity under oxidative stress conditions results in depletion of NAD^+ and ATP levels, and PARP inhibition can enhance the tolerance to this stress, suggesting that PARP activity is detrimental to plants under stress conditions (Fig. 3a; [98]). Consistent with this, downregulation of *AtPARP1* and *AtPARP2* by RNAi reduced stress-induced poly(ADP-ribosyl)ation and NAD^+ consumption, preventing ATP depletion. This prevented accumulation of reactive oxygen species and increased stress tolerance [38]. However, the consistent upregulation of these genes under abiotic stress conditions suggests that these genes must have a positive impact on survival at a certain level, similar to the situation seen in animals. As no true knockouts have been examined, this remains to be established. Another alternative hypothesis for the increased stress tolerance seen in *parp*-deficient plants, involves the potential increased levels of the cyclic nucleotide ADP-ribose (cADPR), which is synthesized from NAD^+ [142]. The plant hormone abscisic acid (ABA), important in abiotic stress response, signals through Ca^{2+}, and cADPR has been shown to act as a second messenger in this pathway before changes in gene expression [147]. Increased levels of cADPR levels in *Arabidopsis* can induce more than 100 ABA-responsive genes [123]. *parp*-deficient plants consume less NAD^+, increasing the availability of this metabolite and would be expected to facilitate increased production of cADPR. This increased cADPR could cause production of ABA-regulated stress response genes, conferring tolerance to the *parp*-deficient plants (Fig. 3a).

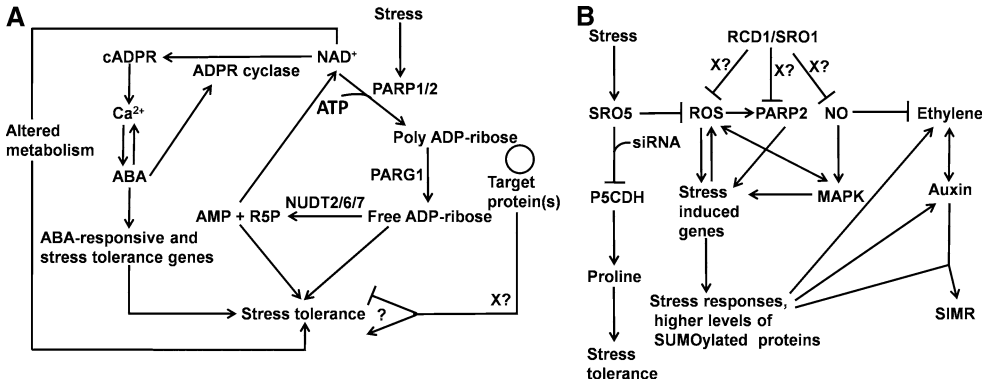

Fig. 3 PARP superfamily members are important for stress responses in *Arabidopsis thaliana*. **a** The activities of the bona fide PARPs, AtPARP1 and AtPARP2, must be balanced by PARGs and nudix hydrolases in order to maximize stress tolerance. The expression and/or activities of these proteins are induced under stress conditions, where they function to modify proteins that influence stress response. In order to avoid depletion of NAD^+, PARG and nudix activities release AMP and R5P, which can be recycled. In the absence of PARP activity, accumulated NAD^+ can be used to produce cADPR to activate ABA-responsive genes. **b** SRO family members modulate stress responses by repression of ROS and nitric acid. *ABA* absisic acid, *AMP* adenosine monophosphate, *ATP* adenosine triphosphate, *cADPR* cyclic nucleotide ADP-ribose, *MAPK* mitogen-activated protein kinase, NAD^+ nicotinamide adenine dinucleotide, *NO* nitric oxide, *P5CDH* Δ^1-pyrroline-5-carboxylate dehydrogenase, *R5P* ribose-5-phosphate, *ROS* reactive oxygen species, *SIMR* stress-induced morphogenetic response. References: [1, 4–6, 22, 33, 38, 49, 64, 65, 70, 71, 98, 104, 109, 115, 123, 131, 133, 142, 147]

In *Arabidopsis*, several plant-specific SRO family members of PARP-like proteins have been implicated in stress response. *RCD1*, the founding member of this group, was originally identified as a stress response gene [104] and encodes an SRO family member with a WWE domain in its *N*-terminus [5, 6, 104]. *rcd1* mutants are hypersensitive to ozone and other sources of apoplastic reactive oxygen species (ROS) [103, 131] as well as salt [131]. However, *rcd* mutants are resistant to UV-B and the herbicide paraquat, which generates reactive oxygen species in the plastid [5, 49]. *RCD1*'s paralog, *SRO1*, is also involved in stress response. Unlike *rcd1* plants, *sro1-1* plants are not resistant to chloroplastic ROS induced by paraquat and are resistant to apoplastic ROS. *sro1-1* plants also display opposite responses to *rcd1* mutants under salt stress, being resistant. Loss of either *RCD1* or *SRO1* confers resistance to osmotic stress [131]. Even under normal conditions *rcd1-3; sro1-1* plants show expression of stress response genes and accumulation of SUMOylated proteins (which have been shown to accumulate under multiple stresses [84, 92]), suggesting that RCD1 and SRO1 may function as inhibitors of stress responses [133]. Consistent with this interpretation is the fact that *rcd1* single mutants have been shown to accumulate reactive oxygen species (ROS; [104]) and nitric oxide [4] under non-stress conditions. In fact, many aspects of the developmental phenotype of *rcd1-3; sro1-1* plants (described below) resemble those of plants exposed to chronic low-level abiotic stress. The common stress-associated phenotypes seen under various abiotic stresses have been termed stress-induced morphogenetic response (SIMR; [109]). If RCD1 and SRO1 act as inhibitors of abiotic stress response, particularly accumulation of ROS (Fig. 3b), the growth phenotypes of their mutants may share pathways with SIMR. Interestingly, expression of *AtPARP2* increases in *rcd1-3; sro1-1* plants [133], implying that the SRO family of PARP-like proteins may regulate more traditional PARP-encoding genes, directly or indirectly.

Arabidopsis contains four members of the eudicot-specific group of short SRO family members, SRO2-5. Very little work has been done on these genes. *SRO2* is upregulated in response to high light in chloroplastic ascorbate peroxidase mutants [75]. SRO5 is the best-explored member of this group. *SRO5* expression is very low under normal conditions but its expression has been shown to be induced by salt treatment [22] and repressed by high light [77]. *sro5* plants were more sensitive to H_2O_2-mediated oxidative stress and to salt stress [22]. *SRO5* has also been implicated in regulation of proline metabolism at the small RNA level [22]. Δ^1-pyroline-5-carboxylate (P5C) is an intermediate in proline synthesis and catabolism. It has been shown to promote ROS production, reduce growth and induce the expression of stress genes [41, 62, 67]. *SRO5* and the gene-encoding Δ^1-pyrroline-5-carboxylate dehydrogenase (*P5CDH*), an enzyme that catabolizes P5C, overlap each other in the antisense orientation. This causes the formation of siRNAs from both loci. When *SRO5* is induced by salt stress, a 24-nt SRO5/P5CDH siRNA is produced, eventually leading to the downregulation of *P5CDH* and the accumulation of proline important for salt tolerance (Fig. 3b). Downregulation of *P5CDH* will also lead to ROS accumulation; SRO5 counteracts this ROS accumulation, implying it can act to inhibit some stress responses. It has not been shown that

this regulatory relationship between *SRO5* and *P5CDH* is found in any other plant species; however, the role of SRO5 in reducing ROS accumulation could be a core function of SRO family members.

Not surprisingly, since ADP-ribosylation has been implicated in response to environmental conditions, PARG genes are also implicated in stress response. *AtPARG1* is upregulated in response to gamma irradiation [36] and *AtPARG2* is upregulated by treatment with paraquat, salinity, high light and drought [98]. *parg1* mutants have lower tolerance to osmotic, drought and oxidative stress. Consistent with this, *parg1* plants had lower expression of two oxidative stress defense genes, *AtALTERNATIVE OXIDASE 1* and *AtASCORBATE PEROXIDASE 2* [86]. Clearly, there is a complicated relationship between poly(ADP-ribosylation) and abiotic stress tolerance.

The PARP superfamily and responses to biotic stress

Poly(ADP-ribosyl)ation and PARP superfamily proteins were first implicated in pathogen response indirectly. *AtNUDT7* was identified through gene expression studies to act downstream of *Arabidopsis thaliana* ENHANCED DISEASE SUSCEPTIBILITY1 (AtEDS1), an important regulator of both basal and receptor-triggered immunity [15]. *atnudt7* mutants had enhanced basal resistance, increased levels of salicylic acid (SA), a crucial signaling molecule required for expression of plant defense responses (reviewed in [56]), and spontaneous lesions on leaves, suggesting that defense responses were constitutive in these plants. The same year, this gene was identified by mutational analysis as having constitutive resistance against the biotrophic pathogenic bacteria *Pseudomonas syringae* [69]. Subsequent work has implicated AtNUDT7 in EDS-driven cell death and both SA-dependent and SA-independent defense pathways, perhaps by modulating redox balance or PARP activity [51, 52, 70, 129]

More direct evidence implicating PARPs and poly (ADP-ribosyl)ation in plant defense has been provided by examination of *Arabidopsis thaliana–Pseudomonas syringae* plant disease resistance gene (R)–bacterial avirulence (Avr) gene interactions. *AtNUDT7*, discussed above, and *AtPARG2* were induced in multiple such plant–pathogen interactions and also by the elicitor flg22 (flagellin epitope). PARP activity, as measured by amount of poly(ADP-ribose) accumulation, is increased after exposure of *Arabidopsis* to avirulent *Pseudomonas syringae* [2]. Consistent with an involvement of PARPs in the innate immune response in plants, the PARP inhibitor 3AB perturbs some responses to microbe-associated molecular patterns including callose deposition and other cell wall modifications [1, 2]. However, as mentioned above, 3AB can inhibit sirtuins. *AtSRT2* has been implicated in biotic defense and has been shown to negatively regulate plant basal defense against *Pseudomonas syringae* [144], again suggesting that results with inhibitors need be interpreted carefully. Plants mutant for both of the genes encoding PARGs in the *Arabidopsis* genome, *AtPARG1/TEJ* and *AtPARG2*, have accelerated necrotic disease symptoms when infected with *Botrytis* [1], supporting roles in defense against both biotropic and necrotrophic pathogens. Taken together, these results suggest that PARPs and poly(ADP-ribosyl)ation are involved in pathogen response in plants.

PARP superfamily members and plant development

Although PARPs have been extensively studied for their roles in genome integrity, stress response and apoptosis, relatively little work has been done on their role in development, although there is some evidence for their involvement. Mouse *parp1/parp2* mutants die embryonically, demonstrating that these genes are essential for development [40]. This is also true in *Drosophila melanogaster*, where loss of the single *PARP* gene found in this organism causes larval lethality [139]. Recently, *DrPARP3* was shown to act in ectodermal specification and neural crest development in zebrafish [119]. Taken together, this suggests that in animals at least PARP1, 2 and 3 are necessary for proper development. Downregulation of PARPs in the amoebae *Dictyostelium discoideum* has been shown to arrest development at the slug stage [111], suggesting that in Amoebozoa, sister group to the Opithokonts (animals, fungi and choanoflagalletes), development is also regulated by these enzymes.

In land plants, little is known about the roles in development of the PARPs orthologous to those found in other eukaryotes. Using in vitro induction of tracheary elements in both *Helianthus tuberosus* and *Pisum sativum*, 3AB treatment was shown to inhibit this process, suggesting that PARPs or sirtuins or both could be involved in this process [108]. Knockdown of *AtPARP1* and/or *AtPARP2* was not found to alter *Arabidopsis* development [38], although development was not closely examined. Silencing of the *AtPARP2* ortholog in oilseed rape (*Brassica napus*) did not alter its development either [142]. However, it is likely that the knockdown lines used in these studies retain some gene function; it is conceivable that total loss of these PARPs would be lethal in plants as has been seen in animals. As mentioned above, no functional work has been down on *AtPARP3* or its orthologs in other plants. Poly(ADP-ribosyl)ation has been implicated in establishment of circadian period in *Arabidopsis*. *AtPARG1/TEJ* was originally identified through a genetic screen for altered period length. *tej* mutants have a longer period and this can be rescued by 3AB treatment, suggesting that the phenotype is caused by

Table 1 Poly(ADP-ribose) polymerases in *Arabidopsis thaliana*

Arabidopsis thaliana gene	Locus ID	Human orthologs[a]	Selected plant orthologs[a]	Expression pattern[b]	Enzyme activity	References
AtPARP1	*At4g02390*	*HsPARP3*	*ZmPARP1* *OsPARP1* *VvA5AIW8* *Pp188096* *Sm90144*	Expressed in all organs	Yes [13]	[85]
AtPARP2	*At2g31320*	*HsPARP1*	*ZmPARP2* *OsPARP2* *VvD7U2A8* *Pp150949* *Sm83360* *Sm76668*	Expressed in all organs	ND	[13]
AtPARP3	*At5g22470*	*HsPARP3*	*OsPARP3* *PARP3* *VvA5AUF8* *VvD7TCW5* *MtPARP3* *Pp76575* *Sm73333*	Seeds	ND	[16]
AtRCD1	*At1g32230*	NA	*OsQ0DLN4* *OsQ336N3* *OsQ0J949* *OsQ654Q5* *VvA7PC35* *VvA5BDE5* *PtB9MU68* *PtB9GZJ6*	Expressed in all organs	No [74]	[17]
AtSRO1	*At2g35510*	NA	See *AtRCD1*[c]	Expressed in all organs	ND	[17]
AtSRO2	*At1g23550*	NA	*PtB9INI8* *PtB9HDP9* *PtB9HDP8* *PtB9HDP5*	Expressed in all organs	ND	[17]
AtSRO3	*At1g70440*	NA	See *AtSRO2*[c]	ND	ND	[17]
AtSRO4	*At3g47720*	NA	*VvA5BFU2* *PtB9I3A2* *PtB9IES0*	ND	ND	[17]
AtSRO5	*At5g62520*	NA	See *AtSRO4*[c]	Expressed in all organs	ND	[5]

NA not applicable, *ND* no data, *Mt Medicago truncatula*, *Os Oryza sativa*, *Pp Physcomitrella patens*, *Pt Populus trichocarpa*, *Sm Selaginella moellendorffi*, *Vv Vitis vinifera*, *Zm Zea mays*

[a] Orthologs as found in [32]

[b] Genevestigator [151]

[c] Represent paralogs in *Arabidopsis thaliana*

the buildup of poly(ADP-ribosyl)ated proteins, although it is unclear what these proteins are [105]. It is likely that AtPARP1 and/or AtPARP2 are the proteins responsible for the enzymatic activity regulating the circadian clock.

In contrast to the canonical PARP genes in plants, the SRO family members *RCD1* and *SRO1* appear essential for proper development in *Arabidopsis*. Loss of *RCD1* causes dramatic developmental defects including reduced stature, malformed leaves, early flowering, abnormal phyllotaxy, small and deformed floral organs, increased lateral root number and length, and shorter primary roots [5, 104, 131]. *sro1* plants display some subtle developmental defects

similar to the root and flower phenotypes of *rcd1-3*. However, plant height and leaf shape and size appear normal [131]. The majority of *rcd1-3; sro1-1* individuals die during embryogenesis [131], demonstrating that the SRO family may be necessary for land plant development. *rcd1-3; sro1-1* plants are very small; at least some of this decrease in height is caused by a decrease in cell elongation [131]. However, double mutant plants also make fewer cells [132]. Roots of these plants are shorter than wild-type and have a reduction in the size of the division zone. The division zone has fewer total cells and fewer mitotic cells. Morphology of the roots cells and planes of cell division are abnormal in addition to the defect in the number of cells. The shoot of *rcd1-3*; *sro1-1* plants also contains fewer cells. Although the division zone is small and disorganized in the root of *rcd1-3*; *sro1-1* plants, cell fate is generally correctly laid down as assayed by reporter gene expression. This suggests that cell fate decisions are not globally disrupted in this mutant background. Consistent with retention of proper cell fate decisions in the root, maxima of the plant hormone auxin are formed at the root pole and tips of forming cotyledons in the embryo and at the root tip postembryonically in double mutant plants and expression and polarization of components of the polar auxin transport system are largely normal. However, cell differentiation is disrupted in double mutant plants. Cells fail to elongate properly and specialized cell walls are not well formed [131, 132]. These results suggest that *RCD1* and *SRO1* are necessary for cell division and cell differentiation and, by extension, suggest that members of the SRO family in other plants are likely to be necessary for similar processes. As mentioned above, some of these growth phenotypes resemble those of SIMR, suggesting that accumulation or misregulation of ROS may be responsible for some of the phenotypes seen in *rcd1* and/or *sro1* plants, consistent with a role for SRO family members in redox regulation.

Conclusions

The PARP superfamily and poly(ADP-ribosyl)ation is clearly important for a variety of biological functions in plants, including DNA recombination and stress responses. In particular, the role of PARPs in abiotic stress responses is especially well established. In addition, a land plant-specific group of PARP-like proteins, the SRO family, is necessary for normal plant development. The PARP superfamily within plants contains several unique subfamilies, making plants an excellent system to examine interplays between different subfamilies of this large family. At least three subfamilies of PARPs appear to have arisen at the base of the land plants. These include the AtPARP1 group, which contains SAP domains, unique for PARP superfamily members, the AtPARP3 group, with unique substitutions within the catalytic domain and the SRO family. It is tempting, given the association of poly(ADP-ribosyl)ation and the SRO family with stress response and control of ROS, to speculate that these proteins evolved to help plant contend with the rigors of life on land, including increased exposure to UV-B light and desiccation stress. However, there is no information on gene content for the sister group to land plants, the streptophyte green algae. Until it is determined when these PARP subfamilies emerged, this question will remain open.

Fundamental questions remain in the field. First, only two proteins (AtPARP1 and ZmPARP1), which are similar to HsPARP3, have been demonstrated to have poly(ADP-ribosyl)ation activity while one member of the SRO family is enzymatically inactive. Given the variation within the catalytic domains of the plant PARP proteins, in particular the AtPARP3 subfamily and the SRO family, it is essential to determine which proteins have poly(ADP-ribosyl)ation or mono(ADP-ribose) transferase activity. Second, given the results that indicate overlap in function between HsPARP1 and HsPARP3, it is necessary to determine the extent to which the land plant PARPs similar to these proteins have redundant functions. This necessitates the isolation of null alleles in these genes and careful analysis of single, double and triple mutants. This will also reveal if PARPs are essential in plants as they are in animals. Third, no targets of ADP-ribosylation other than histones have been identified in plants. Even for histones, it is unclear which PARP(s) in plants is responsible for the activity that has been detected in the nucleus. It will be essential to identify targets of the various PARP enzymes and determine the effect of poly(ADP-ribosyl)ation on these proteins. Identification of these targets will provide insight into plant immunity and stress responses, as well as development. We are now in a position to develop a better understanding of the roles of PARPs and poly(ADP-ribosyl)ation in plants and the diversification of the proteins involved in this process in eukaryotes.

Acknowledgments We thank Dr. Patrice Hamel, Dr. David Mackey and Dr. Iris Meier (Ohio State University), members of the Lamb laboratory and an anonymous reviewer for helpful advice on the manuscript. We apologize to colleagues whose work we could not include due to space limitations.

References

1. Adams-Phillips L, Briggs AG, Bent AF (2010) Disruption of poly(ADP-ribosyl)ation mechanisms alters responses of *Arabidopsis* to biotic stress. Plant Physiol 152:267–280
2. Adams-Phillips L, Wan J, Tan X, Dunning FM, Meyers BC, Michelmore RW, Bent AF (2008) Discovery of ADP-ribosylation

and other plant defense pathway elements through expression profiling of four different *Arabidopsis-Pseudomonas* R-avr interactions. Mol Plant Microbe Interact 21:646–657
3. Aguiar RC, Yakushijin Y, Kharbanda S, Salgia R, Fletcher JA, Shipp MA (2000) BAL is a novel risk-related gene in diffuse large B-cell lymphomas that enhances cellular migration. Blood 96:4328–4334
4. Ahlfors R, Brosche M, Kollist H, Kangasjarvi J (2008) Nitric oxide modulates ozone-induced cell death, hormone biosynthesis and gene expression in *Arabidopsis thaliana*. Plant J 58:1–12
5. Ahlfors R, Lang S, Overmyer K, Jaspers P, Brosche M, Tauriainen A, Kollist H, Tuominen H, Belles-Boix E, Piippo M, Inze D, Palva ET, Kangasjarvi J (2004) *Arabidopsis* RADICAL-INDUCED CELL DEATH1 belongs to the WWE protein-protein interaction domain protein family and modulates abscisic acid, ethylene, and methyl jasmonate responses. Plant Cell 16:1925–1937
6. Ahlfors R, Macioszek V, Rudd J, Brosche M, Schlichting R, Scheel D, Kangasjarvi J (2004) Stress hormone-independent activation and nuclear translocation of mitogen-activated protein kinases in *Arabidopsis thaliana* during ozone exposure. Plant J 40:512–522
7. Althaus FR, Hofferer L, Kleczkowska HE, Malanga M, Naegeli H, Panzeter PL, Realini CA (1994) Histone shuttling by poly ADP-ribosylation. Mol Cell Biochem 138:53–59
8. Ame JC, Rolli V, Schreiber V, Niedergang C, Apiou F, Decker P, Muller S, Hoger T, Menissier-de Murcia J, de Murcia G (1999) PARP-2, A novel mammalian DNA damage-dependent poly(ADP-ribose) polymerase. J Biol Chem 274:17860–17868
9. Ame JC, Spenlehauer C, de Murcia G (2004) The PARP superfamily. Bioessays 26:882–893
10. Amor Y, Babiychuk E, Inze D, Levine A (1998) The involvement of poly(ADP-ribose) polymerase in the oxidative stress responses in plants. FEBS Lett 440:1–7
11. Aravind L (2001) The WWE domain: a common interaction module in protein ubiquitination and ADP ribosylation. Trends Biochem Sci 26:273–275
12. Ascencio-Ibanez JT, Sozzani R, Lee TJ, Chu TM, Wolfinger RD, Cella R, Hanley-Bowdoin L (2008) Global analysis of *Arabidopsis* gene expression uncovers a complex array of changes impacting pathogen response and cell cycle during geminivirus infection. Plant Physiol 148:436–454
13. Babiychuk E, Cottrill PB, Storozhenko S, Fuangthong M, Chen Y, O'Farrell MK, Van Montagu M, Inze D, Kushnir S (1998) Higher plants possess two structurally different poly(ADP-ribose) polymerases. Plant J 15:635–645
14. Babiychuk E, Van Montagu M, Kushnir S (2001) N-terminal domains of plant poly(ADP-ribose) polymerases define their association with mitotic chromosomes. Plant J 28:245–255
15. Bartsch M, Gobbato E, Bednarek P, Debey S, Schultze JL, Bautor J, Parker JE (2006) Salicylic acid-independent ENHANCED DISEASE SUSCEPTIBILITY1 signaling in *Arabidopsis* immunity and cell death is regulated by the monooxygenase FMO1 and the Nudix hydrolase NUDT7. Plant Cell 18:1038–1051
16. Becerra C, Puigdomenech P, Vicient CM (2006) Computational and experimental analysis identifies *Arabidopsis* genes specifically expressed during early seed development. BMC Genomics 7:38
17. Belles-Boix E, Babiychuk E, Van Montagu M, Inze D, Kushnir S (2000) CEO1, a new protein from *Arabidopsis thaliana*, protects yeast against oxidative damage. FEBS Lett 482:19–24
18. Bessman MJ, Frick DN, O'Handley SF (1996) The MutT proteins or "Nudix" hydrolases, a family of versatile, widely distributed, "housecleaning" enzymes. J Biol Chem 271:25059–25062
19. Boehler C, Gauthier LR, Mortusewicz O, Biard DS, Saliou JM, Bresson A, Sanglier-Cianferani S, Smith S, Schreiber V, Boussin F, Dantzer F (2011) Poly(ADP-ribose) polymerase 3 (PARP3), a newcomer in cellular response to DNA damage and mitotic progression. Proc Natl Acad Sci USA 108:2783–2788
20. Bonicalzi ME, Haince JF, Droit A, Poirier GG (2005) Regulation of poly(ADP-ribose) metabolism by poly(ADP-ribose) glycohydrolase: where and when? Cell Mol Life Sci 62:739–750
21. Bork P, Hofmann K, Bucher P, Neuwald AF, Altschul SF, Koonin EV (1997) A superfamily of conserved domains in DNA damage-responsive cell cycle checkpoint proteins. FASEB J 11:68–76
22. Borsani O, Zhu J, Verslues PE, Sunkar R, Zhu JK (2005) Endogenous siRNAs derived from a pair of natural cis-antisense transcripts regulate salt tolerance in *Arabidopsis*. Cell 123:1279–1291
23. Bowers JE, Chapman BA, Rong J, Paterson AH (2003) Unravelling angiosperm genome evolution by phylogenetic analysis of chromosomal duplication events. Nature 422:433–438
24. Briggs AG, Bent AF (2011) Poly(ADP-ribosyl)ation in plants. Trends Plant Sci 16:372–380
25. 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
26. Chambon P, Weil JD, Doly J, Strosser MT, Mandel P (1966) On the formation of a novel adenylic compound by enzymatic extracts of liver nuclei. Biochem Biophys Res Commun 25:638–643
27. Chambon P, Weill JD, Mandel P (1963) Nicotinamide mononucleotide activation of new DNA-dependent polyadenylic acid synthesizing nuclear enzyme. Biochem Biophys Res Commun 11:39–43
28. Chang P, Coughlin M, Mitchison TJ (2005) Tankyrase-1 polymerization of poly(ADP-ribose) is required for spindle structure and function. Nat Cell Biol 7:1133–1139
29. Chang P, Jacobson MK, Mitchison TJ (2004) Poly(ADP-ribose) is required for spindle assembly and structure. Nature 432:645–649
30. Chen IP, Haehnel U, Altschmied L, Schubert I, Puchta H (2003) The transcriptional response of Arabidopsis to genotoxic stress—a high-density colony array study (HDCA). Plant J 35:771–786
31. Chou HY, Chou HT, Lee SC (2006) CDK-dependent activation of poly(ADP-ribose) polymerase member 10 (PARP10). J Biol Chem 281:15201–15207
32. Citarelli M, Teotia S, Lamb RS (2010) Evolutionary history of the poly(ADP-ribose) polymerase gene family in eukaryotes. BMC Evol Biol 10:308
33. Clarke A, Desikan R, Hurst RD, Hancock JT, Neill SJ (2000) NO way back: nitric oxide and programmed cell death in *Arabidopsis thaliana* suspension cultures. Plant J 24:667–677
34. Coggill P, Finn RD, Bateman A (2008) Identifying protein domains with the Pfam database. Curr Protoc Bioinformatics Chapter 2: Unit 2 5
35. Cook WJ, Jeffrey LC, Sullivan ML, Vierstra RD (1992) Three-dimensional structure of a ubiquitin-conjugating enzyme (E2). J Biol Chem 267:15116–15121
36. Culligan KM, Robertson CE, Foreman J, Doerner P, Britt AB (2006) ATR and ATM play both distinct and additive roles in response to ionizing radiation. Plant J 48:947–961
37. D'Amours D, Desnoyers S, D'Silva I, Poirier GG (1999) Poly(ADP-ribosyl)ation reactions in the regulation of nuclear functions. Biochem J 342:249–268
38. De Block M, Verduyn C, De Brouwer D, Cornelissen M (2005) Poly(ADP-ribose) polymerase in plants affects energy homeostasis, cell death and stress tolerance. Plant J 41:95–106

39. de Murcia JM, Niedergang C, Trucco C, Ricoul M, Dutrillaux B, Mark M, Oliver FJ, Masson M, Dierich A, LeMeur M, Walztinger C, Chambon P, de Murcia G (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
40. de Murcia JM, Ricoul M, Tartier L, Niedergang C, Huber A, Dantzer F, Schreiber V, Ame J-C, Dierich A, LeMeur M, Sabatier L, Chambon P, de Murcia G (2003) Functional interaction between PARP-1 and PARP-2 in chromosome stability and embryonic development in mouse. EMBO J 22:2255–2263
41. Deuschle K, Funck D, Forlani G, Stransky H, Biehl A, Leister D, van der Graaff E, Kunze R, Frommer WB (2004) The role of [Delta]1-pyrroline-5-carboxylate dehydrogenase in proline degradation. Plant Cell 16:3413–3425
42. Doly J, Petek F (1966) Etude de la structure d'un compose "poly(ADP-ribose)" synthetise par des extraits nucleaires de foie de poulet. CR Hebd Scanc Acad Sci Ser D Sci Nat 263:1341–1344
43. Doucet-Chabeaud G, Godon C, Brutesco C, de Murcia G, Kazmaier M (2001) Ionising radiation induces the expression of PARP-1 and PARP-2 genes in *Arabidopsis*. Mol Genet Genomics 265:954–963
44. Durkacz BW, Omidiji O, Gray DA, Shall S (1980) (ADP-ribose)n participates in DNA excision repair. Nature 283:593–596
45. Edgar RC (2004) MUSCLE: multiple sequence alignment with high accuracy and high throughput. Nucleic Acids Res 32:1792–1797
46. Fernandez Villamil SH, Baltanas R, Alonso GD, Vilchez Larrea SC, Torres HN, Flawia MM (2008) TcPARP: a DNA damage-dependent poly(ADP-ribose) polymerase from *Trypanosoma cruzi*. Int J Parasitol 38:277–287
47. Ferraris DV (2010) Evolution of poly(ADP-ribose) polymerase-1 (PARP-1) inhibitors. From concept to clinic. J Med Chem 53:4561–4584
48. Foyer CH, Pellny TK, Locato V, De Gara L (2008) Analysis of redox relationships in the plant cell cycle: determinations of ascorbate, glutathione and poly (ADPribose)polymerase (PARP) in plant cell cultures. Methods Mol Biol 476:199–215
49. Fujibe T, Saji H, Arakawa K, Yabe N, Takeuchi Y, Yamamoto KT (2004) A methyl viologen-resistant mutant of *Arabidopsis*, which is allelic to ozone-sensitive rcd1, is tolerant to supplemental ultraviolet-B irradiation. Plant Physiol 134:275–285
50. Fujimura S, Hasegawa S, Shimizu Y, Sugimura T (1967) Polymerization of the adenosine 5'-diphosphate-ribose moiety of nicotinamide-adenine dinucleotide by nuclear enzyme. I. Enzymatic reactions. Biochim Biophys Acta 145:247–259
51. Ge X, Li GJ, Wang SB, Zhu H, Zhu T, Wang X, Xia Y (2007) AtNUDT7, a negative regulator of basal immunity in *Arabidopsis*, modulates two distinct defense response pathways and is involved in maintaining redox homeostasis. Plant Physiol 145:204–215
52. Ge X, Xia Y (2008) The role of AtNUDT7, a Nudix hydrolase, in the plant defense response. Plant Signal Behav 3:119–120
53. Golderer G, Grobner P (1991) ADP-ribosylation of core histones and their acetylated subspecies. Biochem J 277:607–610
54. Greiss S, Gartner A (2009) Sirtuin/Sir2 phylogeny, evolutionary considerations and structural conservation. Mol Cells 28:407–415
55. Grozinger CM, Chao ED, Blackwell HE, Moazed D, Schreiber SL (2001) Identification of a class of small molecule inhibitors of the sirtuin family of NAD-dependent deacetylases by phenotypic screening. J Biol Chem 276:38837–38843
56. Halim VA, Vess A, Scheel D, Rosahl S (2006) The role of salicylic acid and jasmonic acid in pathogen defence. Plant Biol (Stuttg) 8:307–313
57. Hanai S, Kanai M, Ohashi S, Okamoto K, Yamada M, Takahashi H, Miwa M (2004) Loss of poly(ADP-ribose) glycohydrolase causes progressive neurodegeneration in Drosophila melanogaster. Proc Natl Acad Sci USA 101:82–86
58. Hassa PO, Haenni SS, Elser M, Hottiger MO (2006) Nuclear ADP-ribosylation reactions in mammalian cells: where are we today and where are we going? Microbiol Mol Biol Rev 70:789–829
59. Hassa PO, Hottiger MO (2002) The functional role of poly (ADP-ribose)polymerase 1 as novel coactivator of NF-kappaB in inflammatory disorders. Cell Mol Life Sci 59:1534–1553
60. Hassa PO, Hottiger MO (2008) The diverse biological roles of mammalian PARPS, a small but powerful family of poly-ADP-ribose polymerases. Front Biosci 13:3046–3082
61. Heitz F, Harter P, Ewald-Riegler N, Papsdorf M, Kommoss S, du Bois A (2010) Poly(ADP-ribosyl)ation polymerases: mechanism and new target of anticancer therapy. Expert Rev Anticancer Ther 10:1125–1136
62. Hellmann H, Funck D, Rentsch D, Frommer WB (2000) Hypersensitivity of an *Arabidopsis* sugar signaling mutant toward exogenous proline application. Plant Physiol 123:779–789
63. Hsiao SJ, Smith S (2009) Sister telomeres rendered dysfunctional by persistent cohesion are fused by NHEJ. J Cell Biol 184:515–526
64. Ishikawa K, Yoshimura K, Harada K, Fukusaki E, Ogawa T, Tamoi M, Shigeoka S (2010) AtNUDX6, an ADP-ribose/NADH pyrophosphohydrolase in *Arabidopsis*, positively regulates NPR1-dependent salicylic acid signaling. Plant Physiol 152:2000–2012
65. Ishikawa K, Yoshimura K, Ogawa T, Shigeoka S (2010) Distinct regulation of *Arabidopsis* ADP-ribose/NADH pyrophosphohydrolases, AtNUDX6 and 7, in biotic and abiotic stress responses. Plant Signal Behav 5:839–841
66. Ishizuka S, Martin K, Booth C, Potten CS, de Murcia G, Burkle A, Kirkwood TB (2003) Poly(ADP-ribose) polymerase-1 is a survival factor for radiation-exposed intestinal epithelial stem cells in vivo. Nucleic Acids Res 31:6198–6205
67. Iyer S, Caplan A (1998) Products of proline catabolism can induce osmotically regulated genes in rice. Plant Physiol 116:203–211
68. Jagtap P, Szabo C (2005) Poly(ADP-ribose) polymerase and the therapeutic effects of its inhibitors. Nat Rev Drug Discov 4:421–440
69. Jambunathan N, Mahalingam R (2006) Analysis of *Arabidopsis* growth factor gene 1 (GFG1) encoding a nudix hydrolase during oxidative signaling. Planta 224:1–11
70. Jambunathan N, Penaganti A, Tang Y, Mahalingam R (2010) Modulation of redox homeostasis under suboptimal conditions by *Arabidopsis* nudix hydrolase 7. BMC Plant Biol 10:173
71. Jammes F, Song C, Shin D, Munemasa S, Takeda K, Gu D, Cho D, Lee S, Giordo R, Sritubtim S, Leonhardt N, Ellis BE, Murata Y, Kwak JM (2009) MAP kinases MPK9 and MPK12 are preferentially expressed in guard cells and positively regulate ROS-mediated ABA signaling. Proc Natl Acad Sci USA 106:20520–20525
72. Jaspers P, Blomster T, Brosche M, Salojarvi J, Ahlfors R, Vainonen JP, Reddy RA, Immink R, Angenent G, Turck F, Overmyer K, Kangasjarvi J (2009) Unequally redundant RCD1 and SRO1 mediate stress and developmental responses and interact with transcription factors. Plant J:268–279
73. Jaspers P, Brosche M, Overmyer K, Kangasjarvi J (2010) The transcription factor interacting protein RCD1 contains a novel conserved domain. Plant Signal Behav 5:78–80
74. Jaspers P, Overmyer K, Wrzaczek M, Vainonen JP, Blomster T, Salojarvi J, Reddy RA, Kangasjarvi J (2010) The RST and PARP-like domain containing SRO protein family: analysis of

protein structure, function and conservation in land plants. BMC Genomics 11:170
75. Kangasjarvi S, Lepisto A, Hannikainen K, Piippo M, Luomala EM, Aro EM, Rintamaki E (2008) Diverse roles for chloroplast stromal and thylakoid-bound ascorbate peroxidases in plant stress responses. Biochem J 412:275–285
76. Kelley LA, Sternberg MJ (2009) Protein structure prediction on the Web: a case study using the Phyre server. Nat Protoc 4:363–371
77. Khandelwal A, Elvitigala T, Ghosh B, Quatrano RS (2008) *Arabidopsis* transcriptome reveals control circuits regulating redox homeostasis and the role of an AP2 transcription factor. Plant Physiol 148:2050–2058
78. Kim MY, Zhang T, Kraus WL (2005) Poly(ADP-ribosyl)ation by PARP-1: 'PAR-laying' NAD^+ into a nuclear signal. Genes Dev 19:1951–1967
79. Kleine H, Poreba E, Lesniewicz K, Hassa PO, Hottiger MO, Litchfield DW, Shilton BH, Luscher B (2008) Substrate-assisted catalysis by PARP10 limits its activity to mono-ADP-ribosylation. Mol Cell 32:57–69
80. Koh DW, Lawler AM, Poitras MF, Sasaki M, Wattler S, Nehls MC, Stoger T, Poirier GG, Dawson VL, Dawson TM (2004) Failure to degrade poly(ADP-ribose) causes increased sensitivity to cytotoxicity and early embryonic lethality. Proc Natl Acad Sci USA 101:17699–17704
81. Kothe GO, Kitamura M, Masutani M, Selker EU, Inoue H (2010) PARP is involved in replicative aging in *Neurospora crassa*. Fungal Genet Biol 47:297–309
82. Kotova E, Jarnik M, Tulin AV (2010) Uncoupling of the transactivation and transrepression functions of PARP1 protein. Proc Natl Acad Sci USA 107:6406–6411
83. Kraus WL (2008) Transcriptional control by PARP-1: chromatin modulation, enhancer-binding, coregulation, and insulation. Curr Opin Cell Biol 20:294–302
84. Kurepa J, Walker JM, Smalle J, Gosink MM, Davis SJ, Durham TL, Sung DY, Vierstra RD (2003) The small ubiquitin-like modifier (SUMO) protein modification system in *Arabidopsis*. Accumulation of SUMO1 and -2 conjugates is increased by stress. J Biol Chem 278:6862–6872
85. Lepiniec L, Babiychuk E, Kushnir S, Van Montagu M, Inze D (1995) Characterization of an *Arabidopsis thaliana* cDNA homologue to animal poly(ADP-ribose) polymerase. FEBS Lett 364:103–108
86. Li G, Nasar V, Yang Y, Li W, Liu B, Sun L, Li D, Song F (2011) Arabidopsis poly(ADP-ribose) glycohydrolase 1 is required for drought, osmotic and oxidative stress responses. Plant Sci 180:283–291
87. Loseva O, Jemth AS, Bryant HE, Schuler H, Lehtio L, Karlberg T, Helleday T (2010) Poly(ADP-ribose) polymerase-3 (PARP-3) is a mono-ADP ribosylase that activates PARP-1 in absence of DNA. J Biol Chem 285:8054–8060
88. Ma Q, Baldwin KT, Renzelli AJ, McDaniel A, Dong L (2001) TCDD-inducible poly(ADP-ribose) polymerase: a novel response to 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin. Biochem Biophys Res Commun 289:499–506
89. Mahajan PB, Zuo Z (1998) Purification and cDNA cloning of maize Poly(ADP)-ribose polymerase. Plant Physiol 118:895–905
90. Marsischky GT, Wilson BA, Collier RJ (1995) Role of glutamic acid 988 of human poly-ADP-ribose polymerase in polymer formation. Evidence for active site similarities to the ADP-ribosylating toxins. J Biol Chem 270:3247–3254
91. Messner S, Altmeyer M, Zhao H, Pozivil A, Roschitzki B, Gehrig P, Rutishauser D, Huang D, Caflisch A, Hottiger MO (2010) PARP1 ADP-ribosylates lysine residues of the core histone tails. Nucleic Acids Res 38:6350–6362
92. Muthuswamy S, Meier I (2011) Genetic and environmental changes in SUMO homeostasis lead to nuclear mRNA retention in plants. Planta 233:201–208
93. Nawy T, Lee JY, Colinas J, Wang JY, Thongrod SC, Malamy JE, Birnbaum K, Benfey PN (2005) Transcriptional profile of the *Arabidopsis* root quiescent center. Plant Cell 17:1908–1925
94. Nicholson DW, Ali A, Thornberry NA, Vaillancourt JP, Ding CK, Gallant M, Gareau Y, Griffin PR, Labelle M, Lazebnik YA et al (1995) Identification and inhibition of the ICE/CED-3 protease necessary for mammalian apoptosis. Nature 376:37–43
95. Nishizuka Y, Ueda K, Nakazawa K, Hayaishi O (1967) Studies on the polymer of adenosine diphosphate ribose. I. Enzymic formation from nicotinamide adenine dinuclotide in mammalian nuclei. J Biol Chem 242:3164–3171
96. Nosseri C, Coppola S, Ghibelli L (1994) Possible involvement of poly(ADP-ribosyl) polymerase in triggering stress-induced apoptosis. Exp Cell Res 212:367–373
97. Nusinow DA, Hernandez-Munoz I, Fazzio TG, Shah GM, Kraus WL, Panning B (2007) Poly(ADP-ribose) polymerase 1 is inhibited by a histone H2A variant, MacroH2A, and contributes to silencing of the inactive X chromosome. J Biol Chem 282:12851–12859
98. Ogawa T, Ishikawa K, Harada K, Fukusaki E, Yoshimura K, Shigeoka S (2009) Overexpression of an ADP-ribose pyrophosphatase, AtNUDX2, confers enhanced tolerance to oxidative stress in *Arabidopsis* plants. Plant J 57:289–301
99. Ogawa T, Ueda Y, Yoshimura K, Shigeoka S (2005) Comprehensive analysis of cytosolic Nudix hydrolases in *Arabidopsis thaliana*. J Biol Chem 280:25277–25283
100. Okubo S, Hara F, Tsuchida Y, Shimotakahara S, Suzuki S, Hatanaka H, Yokoyama S, Tanaka H, Yasuda H, Shindo H (2004) NMR structure of the N-terminal domain of SUMO ligase PIAS1 and its interaction with tumor suppressor p53 and A/T-rich DNA oligomers. J Biol Chem 279:31455–31461
101. Oliver AW, Ame JC, Roe SM, Good V, de Murcia G, Pearl LH (2004) Crystal structure of the catalytic fragment of murine poly(ADP-ribose) polymerase-2. Nucleic Acids Res 32:456–464
102. Ouararhni K, Hadj-Slimane R, Ait-Si-Ali S, Robin P, Mietton F, Harel-Bellan A, Dimitrov S, Hamiche A (2006) The histone variant mH2A1.1 interferes with transcription by down-regulating PARP-1 enzymatic activity. Genes Dev 20:3324–3336
103. Overmyer K, Brosche M, Pellinen R, Kuittinen T, Tuominen H, Ahlfors R, Keinanen M, Saarma M, Scheel D, Kangasjarvi J (2005) Ozone-induced programmed cell death in the *Arabidopsis* radical-induced cell death1 mutant. Plant Physiol 137:1092–1104
104. Overmyer K, Tuominen H, Kettunen R, Betz C, Langebartels C, Sandermann H Jr, Kangasjarvi J (2000) Ozone-sensitive arabidopsis rcd1 mutant reveals opposite roles for ethylene and jasmonate signaling pathways in regulating superoxide-dependent cell death. Plant Cell 12:1849–1862
105. Panda S, Poirier GG, Kay SA (2002) tej defines a role for poly(ADP-ribosyl)ation in establishing period length of the *Arabidopsis* circadian oscillator. Dev Cell 3:51–61
106. Pandey R, Muller A, Napoli CA, Selinger DA, Pikaard CS, Richards EJ, Bender J, Mount DW, Jorgensen RA (2002) Analysis of histone acetyltransferase and histone deacetylase families of *Arabidopsis thaliana* suggests functional diversification of chromatin modification among multicellular eukaryotes. Nucleic Acids Res 30:5036–5055
107. Pellny TK, Locato V, Vivancos PD, Markovic J, De Gara L, Pallardo FV, Foyer CH (2009) Pyridine nucleotide cycling and control of intracellular redox state in relation to poly (ADP-ribose) polymerase activity and nuclear localization of glutathione during exponential growth of *Arabidopsis* cells in culture. Mol Plant 2:442–456

108. Phillips RHSW (1985) Characteristics of the inhibition of induced tracheary element differentiation by 3-aminobenzamide and related compounds. J Exp Bot 36:119–128
109. Potters G, Pasternak TP, Guisez Y, Palme KJ, Jansen MA (2007) Stress-induced morphogenic responses: growing out of trouble? Trends Plant Sci 12:98–105
110. Puchta H, Swoboda P, Gal S, Blot M, Hohn B (1995) Somatic intrachromosomal homologous recombination events in populations of plant siblings. Plant Mol Biol 28:281–292
111. Rajawat J, Mir H, Begum R (2011) Differential role of Poly (ADP-ribose) polymerase in *D. discoideum* growth and development. BMC Dev Biol 11:14
112. Rajawat J, Vohra I, Mir HA, Gohel D, Begum R (2007) Effect of oxidative stress and involvement of poly(ADP-ribose) polymerase (PARP) in *Dictyostelium discoideum* development. FEBS J 274:5611–5618
113. Ramirez-Parra E, Gutierrez C (2007) E2F regulates FASCIATA1, a chromatin assembly gene whose loss switches on the endocycle and activates gene expression by changing the epigenetic status. Plant Physiol 144:105–120
114. Reeder RH, Ueda K, Honjo T, Nishizuka Y, Hayaishi O (1967) Studies on the polymer of adenosine diphosphate ribose. II. Characterization of the polymer. J Biol Chem 242:3172–3179
115. Rodriguez MC, Petersen M, Mundy J (2010) Mitogen-activated protein kinase signaling in plants. Annu Rev Plant Biol 61:621–649
116. Rolli V, O'Farrell M, Menissier-de Murcia J, de Murcia G (1997) Random mutagenesis of the poly(ADP-ribose) polymerase catalytic domain reveals amino acids involved in polymer branching. Biochemistry 36:12147–12154
117. Rose PW, Beran B, Bi C, Bluhm WF, Dimitropoulos D, Goodsell DS, Prlic A, Quesada M, Quinn GB, Westbrook JD, Young J, Yukich B, Zardecki C, Berman HM, Bourne PE (2011) The RCSB Protein Data Bank: redesigned web site and web services. Nucleic Acids Res 39:D392–D401
118. Rouleau M, McDonald D, Gagne P, Ouellet ME, Droit A, Hunter JM, Dutertre S, Prigent C, Hendzel MJ, Poirier GG (2007) PARP-3 associates with polycomb group bodies and with components of the DNA damage repair machinery. J Cell Biochem 100:385–401
119. Rouleau M, Saxena V, Rodrigue A, Paquet ER, Gagnon A, Hendzel MJ, Masson JY, Ekker M, Poirier GG (2011) A key role for poly(ADP-ribose) polymerase 3 in ectodermal specification and neural crest development. PLoS One 6:e15834
120. Ruf A, Mennissier de Murcia J, de Murcia G, Schulz GE (1996) Structure of the catalytic fragment of poly(AD-ribose) polymerase from chicken. Proc Natl Acad Sci USA 93:7481–7485
121. Rulten SL, Fisher AE, Robert I, Zuma MC, Rouleau M, Ju L, Poirier G, Reina-San-Martin B, Caldecott KW (2011) PARP-3 and APLF function together to accelerate nonhomologous end-joining. Mol Cell 41:33–45
122. Ryu H, Azuma Y (2010) Rod/Zw10 complex is required for PIASy-dependent centromeric SUMOylation. J Biol Chem 285:32576–32585
123. Sanchez JP, Duque P, Chua NH (2004) ABA activates ADPR cyclase and cADPR induces a subset of ABA-responsive genes in *Arabidopsis*. Plant J 38:381–395
124. Schreiber V, Ame JC, Dolle P, Schultz I, Rinaldi B, Fraulob V, Menissier-de Murcia J, de Murcia G (2002) Poly(ADP-ribose) polymerase-2 (PARP-2) is required for efficient base excision DNA repair in association with PARP-1 and XRCC1. J Biol Chem 277:23028–23036
125. Schreiber V, Dantzer F, Ame JC, de Murcia G (2006) Poly(-ADP-ribose): novel functions for an old molecule. Nat Rev Mol Cell Biol 7:517–528
126. Semighini CP, Savoldi M, Goldman GH, Harris SD (2006) Functional characterization of the putative *Aspergillus nidulans* poly(ADP-ribose) polymerase homolog PrpA. Genetics 173:87–98
127. Simonin F, Hofferer L, Panzeter PL, Muller S, de Murcia G, Althaus FR (1993) The carboxyl-terminal domain of human poly(ADP-ribose) polymerase. Overproduction in *Escherichia coli*, large scale purification, and characterization. J Biol Chem 268:13454–13461
128. Staub E, Fiziev P, Rosenthal A, Hinzmann B (2004) Insights into the evolution of the nucleolus by an analysis of its protein domain repertoire. Bioessays 26:567–581
129. Straus MR, Rietz S, Loren Ver, van Themaat E, Bartsch M, Parker JE (2010) Salicylic acid antagonism of EDS1-driven cell death is important for immune and oxidative stress responses in *Arabidopsis*. Plant J 62:628–640
130. Szabo C, Dawson VL (1998) Role of poly(ADP-ribose) synthetase in inflammation and ischaemia-reperfusion. Trends Pharmacol Sci 19:287–298
131. Teotia S, Lamb RS (2009) The paralogous genes RADICAL-INDUCED CELL DEATH1 and SIMILAR TO RCD ONE1 have partially redundant functions during *Arabidopsis* development. Plant Physiol 151:180–198
132. Teotia S, Lamb RS (2011) RCD1 and SRO1 are necessary to maintain meristematic fate in *Arabidopsis thaliana*. J Exp Bot 62:1271–1284
133. Teotia S, Muthuswamy S, Lamb RS (2010) RADICAL-INDUCED CELL DEATH1 and SIMILAR TO RCD ONE1 and the Stress-Induced Morphogenetic Response. Plant Signal Behav 5:143–145
134. Tewari M, Quan LT, O'Rourke K, Desnoyers S, Zeng Z, Beidler DR, Poirier GG, Salvesen GS, Dixit VM (1995) Yama/CPP32 beta, a mammalian homolog of CED-3, is a CrmA-inhibitable protease that cleaves the death substrate poly(ADP-ribose) polymerase. Cell 81:801–809
135. Tian R, Zhang GY, Yan CH, Dai YR (2000) Involvement of poly(ADP-ribose) polymerase and activation of caspase-3-like protease in heat shock-induced apoptosis in tobacco suspension cells. FEBS Lett 474:11–15
136. Till S, Diamantara K, Ladurner AG (2008) PARP: a transferase by any other name. Nat Struct Mol Biol 15:1243–1244
137. 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
138. Tulin A, Spradling A (2003) Chromatin loosening by poly(-ADP)-ribose polymerase (PARP) at *Drosophila* puff loci. Science 299:560–562
139. Tulin A, Stewart D, Spradling AC (2002) The Drosophila heterochromatic gene encoding poly(ADP-ribose) polymerase (PARP) is required to modulate chromatin structure during development. Genes Dev 16:2108–2119
140. Ueda K, Omachi A, Kawaichi M, Hayaishi O (1975) Natural occurrence of poly(ADP-ribosyl) histones in rat liver. Proc Natl Acad Sci USA 72:205–209
141. Urbanek P, Paces J, Kralova J, Dvorak M, Paces V (2002) Cloning and expression of PARP-3 (Adprt3) and U3-55 k, two genes closely linked on mouse chromosome 9. Folia Biol (Praha) 48:182–191
142. Vanderauwera S, De Block M, Van de Steene N, van de Cotte B, Metzlaff M, Van Breusegem F (2007) Silencing of poly(ADP-ribose) polymerase in plants alters abiotic stress signal transduction. Proc Natl Acad Sci USA 104:15150–15155
143. Wacker DA, Ruhl DD, Balagamwala EH, Hope KM, Zhang T, Kraus WL (2007) The DNA binding and catalytic domains of poly(ADP-ribose) polymerase 1 cooperate in the regulation of chromatin structure and transcription. Mol Cell Biol 27:7475–7485

144. Wang C, Gao F, Wu J, Dai J, Wei C, Li Y (2010) *Arabidopsis* putative deacetylase AtSRT2 regulates basal defense by suppressing PAD4, EDS5 and SID2 expression. Plant Cell Physiol 51:1291–1299
145. Whitby AJ, Stone PR, Whish WJ (1979) Effect of polyamines and Mg^{++} on poly(ADP-ribose) synthesis and ADP-ribosylation of histones in wheat. Biochem Biophys Res Commun 90:1295–1304
146. Willmitzer L (1979) Demonstration of in vitro covalent modification of chromosomal proteins by poly(ADP) ribosylation in plant nuclei. FEBS Lett 108:13–16
147. Wu Y, Kuzma J, Marechal E, Graeff R, Lee HC, Foster R, Chua NH (1997) Abscisic acid signaling through cyclic ADP-ribose in plants. Science 278:2126–2130
148. Yu M, Schreek S, Cerni C, Schamberger C, Lesniewicz K, Poreba E, Vervoorts J, Walsemann G, Grotzinger J, Kremmer E, Mehraein Y, Mertsching J, Kraft R, Austen M, Luscher-Firzlaff J, Luscher B (2005) PARP-10, a novel Myc-interacting protein with poly(ADP-ribose) polymerase activity, inhibits transformation. Oncogene 24:1982–1993
149. Zhu P, Martinvalet D, Chowdhury D, Zhang D, Schlesinger A, Lieberman J (2009) The cytotoxic T lymphocyte protease granzyme A cleaves and inactivates poly(adenosine 5'-diphosphate-ribose) polymerase-1. Blood 114:1205–1216
150. Zhu Y, Weng M, Yang Y, Zhang C, Li Z, Shen WH, Dong A (2011) *Arabidopsis* homologues of the histone chaperone ASF1 are crucial for chromatin replication and cell proliferation in plant development. Plant J:443–455
151. Zimmermann P, Hennig L, Gruissem W (2005) Gene-expression analysis and network discovery using Genevestigator. Trends Plant Sci 10:407–409