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From toxins to mammalian enzymes: the diverse facets of mono-ADP-ribosylation

Giovanna Grimaldi[1], Daniela Corda[1], Giuliana Catara[1]

[1]Institute of Protein Biochemistry, National Research Council, Via Pietro Castellino 111, 80131 Naples, Italy

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1. ABSTRACT

The ADP-ribosylation of proteins is a phylogenetically ancient mechanism that involves the transfer of ADP-ribose from nicotinamide adenine dinucleotide (NAD^+) to specific amino acids of target proteins post-translationally. In the first part of this review, we briefly describe ADP-ribosylation as the mechanism of action of toxins, while giving particular emphasis to a non-conventional ADP-ribosylation reaction that is mediated by the fungal toxin brefeldin A (BFA). This modification results in the loss of the membrane fission activity of the C-terminal binding protein (CtBP)1/ BFA-ADP-ribosylated substrate (BARS), thus blocking progression of cells into mitosis, with important implications for the design of new anticancer drugs. In addition, we summarize the most recent findings on mammalian, intracellular mono-ADP-ribosyl transferase enzymes, underlining the emerging functional roles in which they are involved, including immune responses, transcriptional regulation, stress responses, cell survival. The observation that several mono-ADP-ribosyl transferases, such as PARP-10, PARP-12, PARP-13, are involved in a range of physiological processes points at the multifunctional feature of these proteins.

2. INTRODUCTION

The complex physiology of eukaryotic cells is regulated by a number of multilayered and interconnected mechanisms. Transcription of new mRNA, alternative RNA splicing, mRNA translation into proteins, and the following post-translational modifications to proteins create a continuously fine-tuned regulatory network. Of the various regulatory mechanisms available to the cell, the

Table 1. Bacterial toxins with mono-ADP-ribosyl transferase activity

Enzyme	Source	Substrate/amino acid	Effect
Toxins			
Diphtheria	*Corynebacterium diphtheriae*	EF-2/diphtamide715	Inhibition of protein synthesis
Exotoxin A	*Pseudomonas aeruginosa*	EF-2/diphtamide715	Inhibition of protein synthesis
Exotoxin S	*Pseudomonas aeruginosa*	Ras family/Arg41	Disruption of actin microfilaments
Cholera	*Vibrio cholerae*	$G_{alpha\ s}$, $G_{alpha\ t}$/Arg187	Inhibition of GTPase activity
LT1, LT2	*Escherichia coli*	$G_{alpha\ s}$, $G_{alpha\ t}$/Arg187	Inhibition of GTPase activity
Pertussis	*Bordetella pertussis*	$G_{alpha\ i}$, $G_{alpha\ o}$, $G_{alpha\ t}$/Cys351	Uncoupling of receptor and G protein
C2, iota t	*Clostridium botulinum*	Actin	Prevention of actin polymerization
C3	*Clostridium botulinum*	Rho, Rac/Asn41	Disruption of actin cytoskeleton
C3-like	*Clostridium limosum*	Rho, Rac/Asn41	Disruption of actin cytoskeleton
EDIN	*Staphylococcus aureus*	Rho/Asn41	Disruption of Golgi apparatus
VIP2	*Bacillus cereus*	Rho/Asn41	Disruption of actin cytoskeleton
SpvB	*Salmonella enterica*	Actin	Prevention of actin polymerization
Intracellular			
DRAT	*Rhodospirillum rubrum*	Dinitrogenase reductase/Arg101	Inhibition of dinitrogenase reductase

LT, lethal toxin; EDIN, epidermal cell differentiation inhibitor; VIP, vegetative insecticidal protein; SpvB, Salmonella plasmid virulence genes; DRAT, dinitrogenase reductase arginine-specific mono-ADP-ribosyl transferase

post-translational modifications serve particular purposes, as they are both highly dynamic and largely reversible. As a result of improved detection technologies, the list of protein modifications in the literature has risen to well over 200 (1). This extensive array includes many reversible post-translational modifications, and it creates a signaling diversity that is particularly suitable for relaying rapid messages within the cell.

The modification of proteins by ADP-ribosylation is a phylogenetically ancient mechanism that involves the transfer of ADP-ribose (ADPR) from NAD^+ to specific amino acids of target proteins, accompanied by the release of nicotinamide (2, 3). As with phosphorylation, this reaction is reversible, and thus the extent of protein modification by ADP-ribosylation also depends on the activity of the cellular ADP-ribosyl hydrolases that reverse the reaction, by hydrolysing the protein ADP-ribose linkage (2, 4).

Here, we briefly report on the ADP-ribosylation catalyzed by bacterial pathogenic toxins, with particular emphasis on a new and nonconventional ADP-ribosylation mechanism. We also provide a more comprehensive description of the intracellular mono-ADP-ribosylation catalyzed by members of the PARP family.

3. ADP-RIBOSYLATION BY TOXINS

The first reported example of ADP-ribosylation dates back to 1968, when diphtheria toxin was shown to mediate the transfer of the ADPR moiety from NAD^+ to the R-group of a post-translationally modified histidine of elongation factor-2 (5, 6). Since then, several toxins have been identified as catalyzing ADP-ribosylation of host target proteins. Examples of these toxins can be found in a diverse range of bacterial pathogens, and they are the main active agents in many diseases, including cholera, whooping cough, and diphtheria (7, 8). Table 1 provides a representative list of the members of the best-known ADP-ribosylating toxins, each of which has unique properties, including substrate specificity, target amino acid, and outcome of their ADP-ribosylation of the target protein [(2) and references therein]. In virtually all cases, the ADP-ribosylated targets are key regulators of cellular functions, and as this modification interferes with their activity, this leads to deregulation of key cellular processes, and eventually to cell death (7, 8).

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Recently, the mechanism of ADP-ribosylation mediated by the toxin brefeldin A (BFA) was uncovered, demonstrating the innovative and nonconventional way through which the functions of C-terminal binding protein (CtBP)1/ BFA-ADP-ribosylated substrate (BARS) can be selectively modulated (9).

3.1. The BFA-mediated ADP-ribosylation-like reaction

BFA is a well-known fungal toxin that causes dramatic morphological reorganization of the Golgi complex. This involves the redistribution of both resident and cargo proteins from the Golgi complex to the endoplasmic reticulum, which thus induces a rapid and reversible block of secretion (10-13). These effects are mainly achieved by inhibition of the ADP-ribosylation factor-1 (ARF1) exchange factor (14). In addition, part of the mechanism of action of BFA is mediated by its induction of ADP-ribosylation of the eukaryotic protein CtBP1/BARS (15, 16). After its cloning, CtBP1/BARS was discovered to be a short form of a member of the transcriptional co-repressor family of CtBPs, and was hence named CtBP1-short/BARS (hereafter referred to as BARS) (17).

BARS is a dual-function protein that is involved in two diverse biological processes: intracellular membrane trafficking and gene transcription (18, 19). BARS controls these two cellular functions by translocating to the appropriate cell compartment (cytoplasm or nucleus) as a result of specific post-translational modifications (phosphorylation or sumoylation, respectively). By binding cofactors that determine its specific conformation, BARS interacts with different sets of (cytoplasmatic or nuclear) interactors, to form protein complexes that control membrane fission in the cytoplasm or provide corepression of transcription in the nucleus (19). ADP-ribosylation of BARS by BFA occurs via a nonconventional mechanism that comprises two steps: (i) synthesis of a BFA-ADP-ribose conjugate (BAC) by ADP-ribosyl cyclases, such as CD38; and (ii) covalent binding of BAC into the BARS NAD^+-binding pocket (20). Similar to the synthesis of cyclic-ADPR and ADPR, ADP-ribosyl cyclases catalyze the formation of an ADP-ribosyl oxocarbenium ion intermediate that can react with the two hydroxyl groups of BFA (at positions 4 and 7), which results in BAC formation (Figure 1), which then binds covalently to BARS (9, 21).

Considering the different localization of the two proteins involved in the ADP-ribosylation of BARS by BFA (CD38 is a type II transmembrane protein; BARS is an intracellular protein), it follows that BAC is produced extracellularly and then translocates to the cytoplasmic space (through a CD38-dependent mechanism), where it binds BARS (9). The consequent BAC-mediated modification of BARS induces a conformational change that precludes BARS interactions with key partners involved in fission, such as 14-3-3 gamma and PAK1, thus leading to a loss of BARS fission activity. This acquires particular relevance considering the role of BARS in mitosis. It has been reported that the fission activity of BARS is required to induce the fragmentation of the Golgi complex that occurs during mitosis, and that this allows cells to proceed from G2 to M phase (the 'Golgi checkpoint') (22, 23). If this step is impaired in human HeLa cells in culture, cells cannot enter mitosis (Figure 1). Thus, as BFA-mediated ADP-ribosylation of BARS inhibits BARS fission activity, this blocks the entrance of cells into mitosis (9). This mechanism can be exploited in the design of anticancer drugs, and particularly for tumors characterized by high levels of CD38 (24).

Thus, as with other toxins, the BFA-dependent ADP-ribosylation reaction impairs the function of a protein crucial for cell survival.

4. THE POLY (ADP-RIBOSE) POLYMERASE FAMILY

The human genome contains 22 genes that encode proteins with ADP-ribosyl transferase (ART) activities, and these can be divided in two families: the ectoenzymes (ecto-ARTs), and the intracellular enzymes, which are known as the poly(ADP-ribose) polymerases (PARPs). A unified nomenclature that refers to these enzyme families has been proposed that sub-divides them into the diphtheria-toxin-like ARTs (ARTD), and the cholera-toxin-like ARTs (ARTC), according to the structural criteria of their catalytic domains (25). These PARP enzymes represent one of the major families of NAD^+-consuming enzymes, and they were originally identified through their ability to transfer multiple ADP-ribose moieties, and thus to form long and branched chains of poly-ADPR (26). It is now clear that this enzymatic activity characterizes only some of the members of the PARP family, as specified below.

The PARPs constitute an ancient family of enzymes that are encoded in humans by a set

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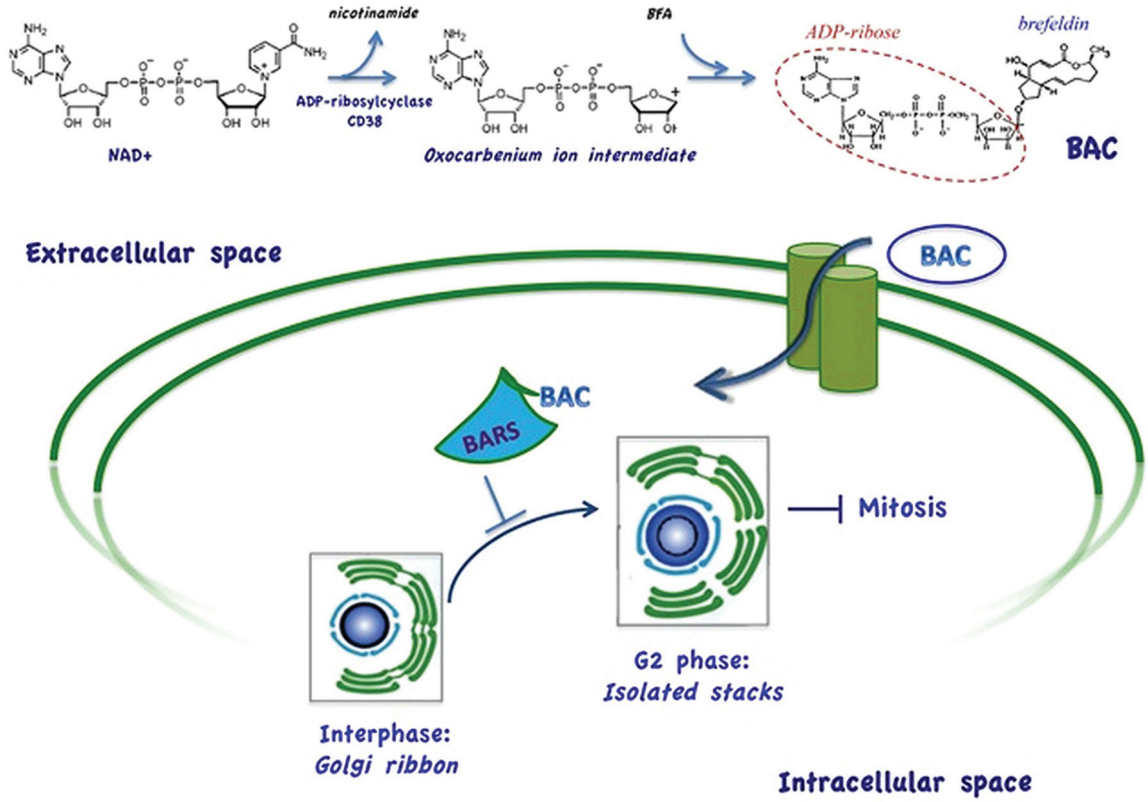

Figure 1. BAC-mediated ADP-ribosylation of BARS. ADP-ribosylation of BARS by BFA occurs via a nonconventional mechanism that comprises two steps: (i) synthesis of a BFA-ADP-ribose conjugate (BAC) by the ADP-ribosyl cyclases, such as CD38; and (ii) covalent binding of BAC to BARS. The synthesis step occurs extracellularly and then, once formed, BAC enters the cell through a CD38 dependent mechanism. BAC binding to BARS inhibits the BARS fission activity, thus blocking fragmentation of the Golgi ribbon during G2 phase. This results in an impairment of the entrance into mitosis.

of 18 different genes. To date, 17 different proteins have been identified that share the PARP catalytic domain, and that thus potentially have poly(ADP-ribose) polymerase activity towards protein substrates (25, 27). The polymerase activity depends on the presence of a well-conserved glutamate residue within the histidine–tyrosine–glutamate (H-Y-E) catalytic triad motif (27). However, the glutamate residue (*e.g.*, E988 in PARP-1) and other important features for poly(ADP-ribose) polymerase activity are not conserved or are absent in 11 PARP family members (see Table 2), which instead show different residues in the catalytic triad (e.g., I-L-Y) (25, 27). Moreover, two members of the family (*i.e.*, PARP-9, PARP-13) also show substitutions in the first histidine residue of the triad that is involved in NAD^+ binding, and for this reason they have been classified and demonstrated to be inactive as enzymes (25, 27, 28). The PARP family thus appears not to be homogenous regarding its catalytic activity, and can be divided into three major sub-groups: (i) the classical PARPs (PARP-1 to PARP-5); (ii) the inactive PARPs (PARP-9, PARP-13); and (iii) enzymes that function as mARTs, with clear experimental evidence for PARP-7, PARP-10, PARP-12 (Grimaldi, G. *et al.*, our unpublished data), PARP-14, PARP-15 and PARP-16 (28-34). Table 2 gives the new and old nomenclatures for the latter ARTs, along with the postulated or demonstrated enzymatic activity for members 6 to 16 of the PARP family.

The PARP family members have a multi-domain organization, a feature that is an integral part of their different and multiple cellular functions. PARP-1 is the most extensively studied member of the family, and it contributes to the control of nuclear processes, with key roles in DNA damage signaling pathways, chromatin modification, and transcriptional regulation (35). Similarly, regulatory functions have been established for PARP-5a/b,

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Table 2. Organization and enzymatic activity of the PARP family members with mono-ADP-ribosyl transferase activity

Family member	Transferase name	Subclass	Tryad motif	Enzymatic activity	Key functional motifs and domains	Functional role category
PARP-6	ARTD17		H-Y-Y	ND		Cell survival
PARP-7	ARTD14	CCCH-PARP	H-Y-I	Active	Zn-fingers, WWE	Transcriptional regulation
PARP-8	ARTD16		H-Y-I	ND		ND
PARP-9	ARTD9	Macro-Parp	Q-Y-T	Inactive	Macrodomain	Immune responses
PARP-10	ARTD10		H-Y-I	Active		Immune responses; Cell survival
PARP-11	ARTD11		H-Y-I	ND	WWE	ND
PARP-12	ARTD12	CCCH-PARP	H-Y-I	Active	Zn-fingers, WWE	Immune responses; stress
PARP-13	ARTD13	CCCH-PARP	H-Y- V	Inactive	Zn-fingers, WWE	Immune responses; stress
PARP-14	ARTD8	Macro-Parp	H-Y-L	Active	Macrodomain, WWE	Immune responses; Cell survival
PARP-15	ARTD7	Macro-Parp	H-Y-L	Active	Macrodomain	Stress
PARP-16	ARTD15		H-Y-I	Active		Stress
ND, Not determined						

which are also known as tankyrases 1/2, and which are involved in the control of telomere elongation, mitotic progression, proteasome regulation, and the Wnt signaling pathway (36-47).

While knowledge of the role of poly-ADP-ribosylation has grown over the past years, the cellular functions that are regulated by the members of the family that show mART activity have emerged only more recently [reviewed in (48)]. In addition, a screening analysis of the PARP family members identified further physiological roles for these enzymes, which include regulation of cell viability (PARP-5, PARP-8, PARP-13, PARP-14), membrane structure (PARP-8, PARP-16) and the actin cytoskeleton (PARP-9, PARP-14), even though the molecular basis of these processes are still not known (49). Nevertheless, new information on these mARTs is continuously emerging as a consequence of the growing interest in this field. This review describes the most recent findings on these mARTs.

5. FUNCTIONS REGULATED BY THE PARPs WITH mART ACTIVITY

5.1. PARPs and the immune response

5.1.1. Transcriptional regulation

To date, the roles of the PARPs in immune responses have been mainly related to their effects at the transcriptional level, as reported for PARP-9, PARP-10, and PARP-14 (31, 50-52). Here we will focus on the new functions of PARP-6 to PARP-16, while for the role of PARP-1 in immune responses, we refer the reader to a previous review (53).

The present knowledge of PARP-9 essentially refers to the induction of its expression by IFN gamma. Transfection of PARP-9 into lymphoma cells leads to increased expression of interferon-stimulated genes, which suggests a role for PARP-9 in modulation of immune responses (50). More details are instead available for PARP-10 and PARP-14.

PARP-10 has been demonstrated to take part in the mechanism that modulates the NF-κB signaling pathway, through interference in the interaction of NEMO with the upstream signaling components (51). In particular, the PARP-10–mediated ADP-ribosylation of NEMO results in a block of the modification of NEMO by K63-dependent polyubiquitination. As a consequence, the activation and translocation of the NF-κB transcription factor are prevented, leading to inhibition of NF-κB downstream target genes in response to interleukin (IL)-1b and tumor necrosis factor-αlpha stimulation (51).

PARP-14 was identified in a yeast two-hybrid screen as an interactor of STAT6, and consequently it was named collaborator of STAT6 (CoaSt6) (54). PARP-14 has been demonstrated to have a potentiating effect on IL-4–induced

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transcriptional activation by STAT6. This stimulatory effect on STAT6-driven gene expression is due to PARP-14–catalyzed ADP-ribosylation of p100, a STAT6 co-activator, which enhances the interactions of STAT6 with the basal transcription machinery (31). Later on, the same authors described the molecular mechanism responsible for this effect, defining PARP-14 as a transcriptional switch for STAT6-dependent gene activation (55). In particular, they demonstrated that under non-stimulating conditions (i.e., in the absence of IL-4), PARP-14 is bound to Stat6 promoter, where it recruits the histone deacetylases HDAC2 and HDAC3, thus blocking transcription. Upon IL-4 stimulation, STAT6 is activated by Janus kinase and binds to its promoter element. This event induces PARP-14 enzymatic activity, so that PARP-14 can modify itself as well as HDAC2 and HDAC3 in the complex. This results in the dissociation of PARP-14 and the HDACs from the promoter, while allowing access to coactivators, such as histone acetyltransferases like CBP/p300, to activate transcription (55).

Therefore, one of the ways through which the PARPs have a role in immune responses is through the regulation of transcription. Distinct roles in immune responses have been reported for other PARPs, which can mediate the shut-off of viral infection by RNA degradation or protein translation [see below; (56)].

5.1.2. PARPs in viral RNA degradation

Among the members of the PARP family with mART activity, the CCCH-type PARPs (PARP-7, PARP-12, PARP-13) constitute a distinct subfamily, as they share a similar organization, which comprises the PARP catalytic domain, WWE domains, and multiple CX8CX5CX3-like zinc fingers. The WWE domains are believed to be required for protein–protein interactions and for binding to *iso*-ADP-ribose, while the zinc finger domains are believed to be involved in the recognition of RNA, making them different from the PARP-1 zinc finger domains, which are instead involved in DNA recognition (57-59).

CCCH zinc fingers were originally discovered in tristetraprolin (TTP), which has two tandem zinc finger Cys-X8-Cys-X5-Cys-X3-His motifs through which TTP binds AU-rich elements present in the target mRNA (60). Through this binding with AU-rich elements and the recruitment of the exosome complex, TTP promotes rapid degradation of the bound mRNA, thus regulating the expression of a number of critical genes that are frequently overexpressed in inflammation and cancer (61, 62).

The first evidence that links PARPs that can bind RNA to viral replication refers to PARP-13. PARP-13 was best known as zinc-finger antiviral protein (ZAP), and it was discovered during a screening that was designed to identify cellular host factors that can interfere with infection by Moloney murine leukemia virus, a member of the *Retroviridae* family (63). The rat (r)ZAP and human (h)ZAP have been shown to have antiviral activities against sub-families of RNA viruses and DNA viruses *in vitro* (63-71). However, ZAP does not induce a universal antiviral condition, as other RNA viruses replicate normally in ZAP-expressing cells, which suggests that ZAP activity is highly reliant on virus-specific features (64). The mechanism by which ZAP targets viral expression relies on four CCCH-type zinc finger motifs in its N-terminal domain, through which it can bind viral RNAs (63, 67, 72). However, a conserved consensus sequence in RNA viral elements has not yet been identified (69, 71, 73). ZAP binding to viral RNAs correlates with their subsequent degradation *via* an exosome-dependent pathway and the inability of the virus to replicate efficiently (74-76). There are two isoforms of both human and murine PARP-13, which arise due to alternative splicing: a long isoform, ZAP-L, that has the C-terminus PARP-like domain, and a shorter isoform that lacks this domain, ZAP-S (66). The short form of rZAP, which was the first to be reported to have antiviral activity, was shown to impair viral infection by specifically preventing accumulation of viral mRNA transcripts in the cytoplasm of infected cells (63). As this antiviral activity was first detected for ZAP-S, the following studies focused on this short ZAP isoform without any consideration of the PARP domain. Later on, hZAP-L was found to significantly inhibit the replication of murine leukemia virus and of Semliki forest virus, with activities that were greater than that of hZAP-S, which raised the question of the role of the PARP domain in this function (66). As ZAP-L/PARP-13 belongs to the subfamily of enzymatically inactive PARPs (see above), the role of the catalytic triad motif of hZAP-L in terms of its antiviral activity was investigated (77). Importantly, single amino-acid substitutions in the catalytic triad motif of hZAP-L reduced its antiviral activity, while mutations of all three residues to alanine or to the canonical amino acids of active PARPs (H-Y-E) virtually abrogated these antiviral effects (77). Thus, this indicates an essential function of the inactive PARP-like domain in hZAP-L antiviral activity,

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which leads to the proposal that the effects of the substitutions in the catalytic triad might be linked to structural rearrangements that alter the accessibility of the RNA binding domain. Further investigations will contribute to the clarification of this aspect.

Although ZAP-S and ZAP-L are both expressed at basal levels and have a common antiviral restriction activity, several differences are emerging that lead to the hypothesis that these two isoforms of ZAP might have different functions in immune responses (56). ZAP-L might act as a basal antiviral effector, while ZAP-S might be an antiviral effector that can either suppress viral replication or potentiate innate immune signaling; *e.g.*, by activating the RNA helicase RIG-1 signaling cascade (78).

5.1.3. PARPs and translational control

RNA degradation does not appear to be the only mechanism adopted by PARPs to counteract viral replication. A study aimed at understanding the molecular basis of the antiviral activity induced by type I and II interferons (IFNs) showed that genes encoding several members of the PARP family (*i.e.*, PARP-7, PARP-9, PARP-11, PARP-12 and PARP-14) are up-regulated after stimulation by IFNs (79).

Along the same line of evidence, a further study showed that the gene coding for the long isoform of PARP-12 (PARP-12L) was one of the major genes stimulated after viral infection (80). In particular, PARP-12 has been validated as an IFN-stimulated gene that is specifically activated during Venezuelan equine encephalitis virus and other alphavirus replication clearance (81). By applying microarray-based technology and bioinformatic analysis, it was shown that several new genes have functions in the development of the type I IFN-induced antiviral state. Interestingly, the most potent inhibitory effect on the replication of Venezuelan equine encephalitis virus, as well as other alpha viruses and other RNA viruses, was mediated by the expression of PARP-12L (81). Moreover, two other PARPs that have similar PARP catalytic domains and putative RNA binding domains (i.e., PARP-7, PARP-10) also showed strong anti-alpha virus effects (81). Accordingly, it has been demonstrated that PARP-10 overexpression can reduce avian influenza virus replication, even though the mechanism has not been clarified (82). PARP-7, PARP-10 and PARP-12 inhibit Venezuelan equine encephalitis virus replication by regulation of host protein translation (81). To induce translational shut-off, PARP-12L directly interacts with ribosomes. Overexpression of full-length PARP-12 or of the different PARP-12 regions (*e.g.*, zinc fingers, catalytic domain) demonstrated that the interaction with ribosomes occurs through its zinc finger domains, although they are not sufficient to inhibit cellular translation, for which the catalytic domain is necessary. Importantly, the ADP-ribosylation activity of the PARP domain has a critical role in PARP-12L anti-viral effects. Point mutations in both the PARP-12 catalytic site or its main acceptor-modified site strongly affect PARP-12L translation inhibition, while retaining the ability to inhibit Venezuelan equine encephalitis virus replication (81). Thus, only the full-length protein has good antiviral effects, which demonstrates that both of the domains are essential for effective responses. Based on these data, it was proposed that there is more than one mechanism in the development of the anti-viral response: one more directly associated with RNA binding, and the other strictly correlated to inhibition of host protein translation, an effect that requires the PARP catalytic domain (81).

The molecular mechanisms underlying these effects are still unknown. However, the characterization of ribosomal subunits among PARP-12L interactors suggest, in our opinion, that some of these might be ADP-ribosylated by PARP12, and thus the functions of the transcriptional machinery are affected (81). Whether PARP-12 has similar roles in the regulation of mRNA translation in cells is not clear. To date, the only known link between PARP-12 and the regulation of translation is its role in cellular stress responses (30). Although these data are not yet defined at the molecular level, they lead to the conclusion that PARP-12 is an active enzyme that is involved in the regulation of diverse cell processes.

5.2. Transcriptional regulation

5.2.1. PARP-7

PARP-7 was identified as being among the genes that are up-regulated by the treatment of mouse hepatoma cells with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a prototype compound that belongs to the class of dioxins, and that causes pleiotropic harmful effects in mammalian species through modulation of gene expression. PARP-7 is broadly expressed in murine tissue, and it has been demonstrated to be a mART, with both auto-ADP-ribosylation and hetero-ADP-ribosylation activities (83). PARP-7 up-regulation is achieved *via* activation of the aryl hydrocarbon receptor (AHR), a protein that mediates the toxic effects derived from environmental contaminants, such as TCDD.

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PARP-7 co-localizes with ARH at the nuclear level, where it functions as a transcriptional repressor of AHR (29). The interaction between PARP-7 and AHR depends on the zinc finger and catalytic domains of PARP-7, and results in increased proteasome-dependent AHR degradation (29). The molecular mechanism underlying this effect is not clear, but it is possible that either PARP-7 ADP-ribosylates AHR, targeting it for degradation, or that it activates components of the proteasome to enhance TCDD-mediated AHR degradation.

5.3. PARP roles during the stress response

5.3.1. PARP-16

Human PARP-16 is a tail-anchored trans-membrane protein that is localized at the endoplasmic reticulum, where it is involved in the activation of the stress sensors PERK (protein kinase RNA-like endoplasmic reticulum kinase) and IRE1 alpha (serine/threonine-protein kinase/endoribonuclease IRE1) during the unfolded protein response (33-34). Under stress conditions, the mART activity of PARP-16 increases, leading to mono-ADP-ribosylation of PERK and IRE1 alpha, as well as of itself, PARP-16. The presence of the ADP-ribose moiety on PERK and IRE1 alpha should facilitate the dissociation of the member of the heat shock protein 70 family, binding immunoglobulin protein (BiP), from their luminal domains, thus resulting in an increase in PERK kinase activity and IRE1 alpha endonuclease activity, events that allow the unfolded protein response to proceed (34).

In addition, PARP-16 can ADP-ribosylate karyopherin beta 1 (also known as importin beta 1), a protein that is involved in the shuttling of proteins with nuclear localization signals between the cytosol and the nucleus, through the nuclear pore complex, which thus suggests a new role for mono-ADP-ribosylation in this process (33, 84).

5.3.2. PARPs and stress granules

Along with PARP-5 and PARP-15, PARP-12 and PARP-13 are key components of stress granules, which are cytoplasmic structures that can be induced by a variety of stimuli, including heat shock, hypoxia, and osmotic and oxidative stress (30). Stress granules include translationally arrested mRNAs, and they are now considered to be dynamic triage centers that sort mRNA for storage, decay, or re-initiation under stress conditions (85). Here, the stress-granule-localized proteins are ADP-ribosylated, including the microRNA-binding argonaute family members, thus contributing to the post-translational control of mRNA in the regulation of cellular responses to stress (30).

5.4. PARPs in cell survival

5.4.1. PARP-6

PARP-6 has been shown to be a negative regulator of cell proliferation. Indeed, overexpression of PARP-6 in HeLa cells results in growth suppression, which induces accumulation of cells in S-phase (86). This effect is related to the catalytic domain of PARP-6, as a PARP-6 mutant lacking the C-terminal catalytic domain had no effects. In agreement with a role for PARP-6 in cell-cycle control, immunohistochemical analysis has revealed that PARP-6 positivity is a feature of colorectal cancer tissue with well-differentiated histology, compared to the poorly differentiated tissue (86). PARP-6 acts as a tumor suppressor through its role in the control of cell-cycle progression.

5.4.2. PARP-10

As well as its involvement in immune responses, PARP-10, the founding member of the PARPs with mART activity, has an important role in cell-cycle progression. Indeed, overexpression of wild-type PARP-10, but not of a catalytically inactive mutant, interferes with cell proliferation, primarily by inducing apoptosis (87). Both its RNA recognition motif and its catalytic domain contribute to this effect, which suggests that PARP-10 targets specific substrates involved in the control of cell death through its RNA recognition motif (87). Along the same line, PARP-10 knock-down reduced apoptosis in response to DNA-damaging agents, thus further reinforcing the role of this mART in cell-cycle progression (88).

As for the other PARPs, the molecular basis that underlies the role of PARP-10 in mediating cell-cycle control is still under investigation. The recent *in vitro* identification of a number of PARP-10 substrates might help to clarify how PARP-10–mediated ADP-ribosylation regulates this process, as well other cell functions outside of the control of cell death (89). Indeed, PARP-10 has been demonstrated to shuttle between the nucleus and the cytoplasm, where it co-localizes with ubiquitin receptor p62, which thus suggests a link between the formation of PARP-10 bodies and autophagy (90).

5.4.3. PARP-14

As mentioned above, several members of the PARP family have been indicated as important factors in cell survival, as their knock-down results

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in cell death (49). Accordingly, PARP-14 transduces survival signals in murine primary B cells by regulation of the expression of B-cell survival factors, as well as by repressing an apoptotic program that involves the caspases (52, 54). In murine models, PARP-14 has been shown to facilitate B-lymphoid oncogenesis that is driven by oncogenic c-Myc (91).

More recently, PARP-14 was shown to be highly expressed in myeloma plasma cells, where it is associated with disease progression and survival of myeloma cells, through binding to and inhibition of c-Jun N-terminal kinase 1 (92). Importantly, this effect appears to be mediated by the PARP-14 catalytic activity, as the use of the general PARP inhibitor PJ34 or the depletion of PARP-14 enhances the sensitization of multiple myeloma cells to anti-myeloma agents. However, the mechanisms underlying these survival functions of PARP-14 have not been investigated.

6. CONCLUSIONS

ADP-ribosylation is an ubiquitous protein modification that is catalyzed by the PARPs, and it controls many cellular processes, including transcription, DNA repair, and cell-cycle progression (26, 48). This review has emphasized the mono-ADP-ribosylation reaction as an important mechanism in the regulation of protein activity, which has been adopted by both cellular enzymes and bacterial toxins. Intriguingly, the finding of the new mechanism for the ADP-ribosylation reaction that is driven by BFA contributes to the expansion of the significance of this post-translational modification in mammals. Of note, by inhibiting BARS-induced fission, this BFA-mediated ADP-ribosylation impairs cell-cycle progression, with potential applications as an anticancer therapy and for drug development (see above).

Within the wide spectrum of biological activities, the involvement of several PARPs that have mART activity in innate immune responses has attracted interest in the field of virology. For some of these, a clear role in inhibition of viral infection has been proposed (*i.e.*, PARP-7, PARP-10, PARP-12, PARP-13), which mainly relies on two mechanisms: the shut-off of the viral replication achieved by viral mRNA degradation (PARP-13); and the block of host protein translation (PARP-7, PARP-10, PARP-12). This latter aspect is of dual importance: while it can help towards a better understanding of viral infection mechanisms and viral clearance, at the same time, this uncovers a new cellular function of these mARTs; *i.e.*, the control of protein translation under physiological and pathological conditions.

Numerous disease states result from aberrant regulation of protein synthesis, and so understanding the molecular basis and mechanisms of translational control is of crucial relevance (93). The concept that mono-ADP-ribosylation can have a role in this process adds to the central physiological role of this post-translational modification. To date, the lack of tools (*e.g.*, antibodies, specific inhibitors, chromogenic substrates) for the study of mono-ADP-ribosylation *versus* poly-ADP-ribosylation has limited investigations in this field. However, with our increasing knowledge of mono-ADP-ribosylated substrates, as well as the identification of the pathways regulated by the PARPs, we would anticipate that soon many questions related to this post-translational modification will have an answer.

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Send correspondence to: Giovanna Grimaldi, Via Pietro Castellino 111, Naples, 80131, Tel: 39-0816132495, Fax: 39-081-6132277, E-mail: g.grimaldi@ibp.cnr.it

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