

Review

# The ADP-Ribosyl-Transferases Diphtheria Toxin-Like (ARTDs) Family: An Overview

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**Abstract:** Poly-ADP-ribosylation is a post-translational modification that occurs in multicellular organisms, including plants and some lower unicellular eukaryotes. The founding member of the PARP family is PARP1. To date, 17 members of the PARP family have been identified, which differ from each other in terms of domain organization, transmodification targets, cellular localization, and biological functions. In recent years, considering structural and biochemical features of the different members of the PARP family, a new classification has been proposed. Thus, enzymes firstly classified as PARP are now named diphtheria-toxin-like ARTs, abbreviated to ARTDs, in accordance with the prototype bacterial toxin that their structural aspects resemble, with numbers indicating the different proteins of the family. The 17 human ARTD enzymes can be divided on the basis of their catalytic activity into polymerases (ARTD1–6), mono-ADP-ribosyl-transferases (ARTD7–17), and the inactive ARTD13. In recent years, ADP-ribosylation was intensively studied, and research was dominated by studies focusing on the role of this modification and its implication on various cellular processes. The aim of this review is to provide a general overview of the ARTD enzymes, with a special focus on mono-ARTDs.

**Keywords:** ADP-ribosyltransferase; post-translational modification; mono-ADP-ribosylation; poly-ADP-ribosylation; ARTD; ART; NAD

## 1. Introduction

The human ARTD enzyme family consists of 17 multidomain proteins that can be divided on the basis of their catalytic activity into polymerases (ARTD1–6), mono-ADP-ribosyl-transferases (ARTD7–17), and ARTD13, which is thought to be enzymatically inactive. Poly-ADP-ribosylation is a PTM that occurs in multicellular organisms, including plants and some lower unicellular eukaryotes, but it is not seen in prokaryotes and yeast [1]. The reaction consists of the addition of multiple ADP-ribose groups on proteins. The first description of poly-ADP-ribosylation dates back to 1963, when Chambon et al. reported the formation of a nucleic acid-like polymer from NAD<sup>+</sup> [2]. In the following years, poly-ADP-ribosylation was intensively studied, and research was dominated by studies focusing on the role of this modification and its implication on various cellular processes (recently reviewed in [3,4]).

Poly-ADP-ribose (PAR) is a homo-polymer of ADP-ribose units synthesized with  $\beta$ -NAD<sup>+</sup> as a substrate. The chain length of the polymer is heterogeneous, and in vitro it can reach 200 units. ADP-ribose chains that are shorter in length than 11 units are referred to as oligo-ADP-ribose [5,6]. PAR is irregularly branched with the number of branches increasing with the length of polymer. The average branching frequency is approximately one branch for every 20–50 units of ADP-ribose. Formation of the polymer is obtained through three different steps: initiation reaction (or mono-ADP-ribosylation of the substrate), elongation of the polymer, and branching [7].

PARP1 is the founding member of the PARP family and, for many years, it was the only PARP enzyme known. PARP1 is activated by DNA strand breaks, and its role in the cellular response to genotoxic and oxidative stress has been widely recognized and studied, with some PARP inhibitors being evaluated in several clinical trials as anticancer therapeutics [8–17]. Olaparib was the first PARP inhibitor to be used for the therapy of patients with ovarian tumors and, more recently, it has been approved by US Food and Drug Administration (FDA) for the treatments of this type of cancer [18]. Moreover, two other PARP inhibitors such as rucaparib and niraparib have recently been approved by FDA for the therapy of patients with ovarian tumors, and there are other PARP inhibitors such as talazoparib and veliparib that are currently under clinical trials [14,15,19–21].

The observation of PARP activity in PARP1<sup>-/-</sup> mice accelerated the discovery of other PARPs. Firstly, four similar enzymes (PARP2–5) were identified and characterized, and along with PARP1 they constitute the classical *bona fide* PARP family [22,23]. Then, an in-silico analysis of the human genome suggested the existence of other proteins that share similarities with PARP1 catalytic domains [24]. To date, 17 members of the PARP family have been identified, which differ from each other in terms of domain organization, transmodification targets, cellular localization, and biological functions [24–26].

However, recent enzymatic data support the view that the earlier proposed name “PARP” and the provided numbering are no longer accurate. Firstly, the term polymerase is commonly used for template-dependent DNA or RNA synthesizing enzymes, but not for enzymes that modify proteins at a defined amino acid [24]. Moreover, some of the recently identified PARP members were reported to catalyze mono-ADP-ribosylation, and thus do not comply with the name polymerase [24,27]. Furthermore, some PARP members (e.g., PARP5a and PARP5b) have been shown to be distinct proteins encoded by different genes, rather than splice variants, and therefore should be numbered individually [28].

Thus, for all these reasons, a new classification has been proposed, based on structural and biochemical features of all ARTs. In line with this new nomenclature, enzymes firstly classified as PARP are now named diphtheria-toxin-like ARTs, abbreviated ARTDs, in accordance with the prototype bacterial toxin that their structural aspects resemble, with numbers indicating the different proteins of the family, assigned on the base of the similarity of the catalytic domain and retaining the number previously assigned wherever possible [28]. Table A1 shows new and old nomenclature of these ARTs, their type of activity, cellular localizations and functions.

## 2. The ARTDs Domains

All ARTDs share a conserved ADP-ribosyl-transferase (ART) domain, which is usually located at the C-terminus of the protein (except in ARTD4). This ART domain represents the catalytic core required for ART activity [24,29].

Besides the ART domain, ARTDs contain many other motifs and domains that differ between all the enzymes and are involved in different functions, such as DNA or RNA binding, protein-protein interactions, cell signaling, or enzyme localization [30]. The key functional ARTDs motifs and domains are discussed below.

ARTD1–3 are characterized by PRD and WGR domains. The PRD is the PARP regulatory domain, and it is thought to be involved in the modulation of the PAR chain branching [31,32]. The WGR domain represents a motif characterized by the presence of the conserved amino acid residues tryptophan (W), glycine (G), and arginine (R). It has high affinity for PAR polymers, and it has been described as a nucleic acid binding domain [10,33]. It participates in DNA binding and mediates domain–domain contacts that are essential for DNA-dependent activity [32].

ARTD1 also contains three zinc finger (ZF) and one breast cancer type 1 susceptibility protein (BRCA1) carboxy-terminal (BRCT) domains. The ZF domain is a small structural motif usually involved in a wide range of functions, including DNA- or RNA-binding, protein-protein interactions, and membrane association [34]. Specifically, two of the three ZF domains of ARTD1, indicated as ZF-1 and ZF-2, are involved in DNA-binding, acting as DNA nick sensor [13,33,35]. The third ZF domain, referred to as ZF-3, is unrelated to ZF-1 and ZF-2, since it is not involved in DNA binding.

Instead, it has a role in protein-protein interactions and is crucial for ARTD1 activation and for its DNA-dependent stimulation [36–38]. In addition to ARTD1, also ARTD12 and ARTD13 contain typical ZF motifs in their N-terminal domains, and they have been implicated in RNA-binding [33,39].

The BRCT domain, also present in ARTD4, is a domain predominantly found in cell cycle checkpoint proteins and plays a role in the DNA damage response [40]. Studies on ARTD1 BRCT domain suggest it is important for protein-protein interaction in both DNA repair and cell signaling pathways [41–43].

The vault protein inter-alpha-trypsin (VIT) and the von Willebrand type A (vWA) domains are distinctive features of ARTD4, which probably function in mediating protein-protein interactions [33,44]. Also the major-vault particle interaction domain (MVP-ID) is a unique characteristic of ARTD4, and it is involved in the interaction with the major vault protein, as suggested by name [45].

ARTD5 and ARTD6, also known as tankyrases, are characterized by the presence of the sterile alpha motif (SAM) and the ankyrin repeat domains (ARD). SAM is a domain important for mediating multimerization of tankyrases, while ARD is involved in protein-protein interactions [46–49]. Both ARTD5 and ARTD6 contain five ARD in their N-terminal region [33,47,50,51]. Additionally, ARTD5 is characterized by the presence of the HPS domain, a N-terminal domain containing histidine, proline, and serine, with a hitherto unclear function [52].

The a1pp or macro domain (A1pp/macro) is specifically found in ARTD7, ARTD8, and ARTD9, which are also known as macro domain containing-mono-ARTDs. Multiple macro domains have been found in these ARTDs, with two in ARTD9 and ARTD7, and three in ARTD8 [33,53]. Macro domains have been described as binding modules that are able to recognize the ADP-ribosylated target, either the mono-ADP-ribosylated or the poly-ADP-ribosylated one, through the binding of the last residue of the poly-ADP-ribose chain [54–56]. Macro domains 2 and 3 of ARTD8 have been shown to recognize mono-ADP-ribosylated substrates [57]. Macro domain 2 of ARTD9 has been reported to bind ARTD1-generated poly-ADP-ribose chain at DNA damage sites [58,59]. The function of ARTD9 macro domain 1 of both ARTD8 and ARTD9 still remains to be defined, since ARTD8 and ARTD9 do not bind either poly- or mono-ADP-ribose.

Uniquely among the macro domain containing-mono-ARTDs, but together with ARTD11, ARTD12, ARTD13, and ARTD14, ARTD8 is characterized by the WWE domain [33]. It is a domain containing the conserved amino acid sequence tryptophan-tryptophan-glutamate (W-W-E) that has been described to be able to recognize iso-ADPR [60]. Structural information about the WWE domain was initially obtained studying ubiquitination-related proteins, another family of proteins characterized by this domain [61]. However, the determination of the solution structures of ARTD8 and ARTD11 WWE domains demonstrated that these domains have some features resembling those of the ubiquitination-related proteins, but also display several unique structural features [62,63].

The ubiquitin interaction motif (UIM) is characteristic of ARTD10. This enzyme contains two UIMs that have been reported to interact with K63-poly-ubiquitin chains, promoting mono-ADP-ribosylation of NF- $\kappa$ B (Nuclear Factor- $\kappa$ B) essential modulator (NEMO) and preventing its poly-ubiquitination [64]. As a consequence, NF- $\kappa$ B nuclear translocation is inhibited, and this results in impairing the expression of target genes [64]. In addition to this role in inflammation, ARTD10 is also involved in the S-phase repair [65]. Indeed, ARTD10's UIMs have been shown to interact with ubiquitinated PCNA (Proliferating Cell Nuclear Antigen) and to be important in maintaining PCNA ubiquitination levels [66].

Comparison of the ART domain of all the ARTDs shows that six diphtheria-toxin-like enzymes are characterized by the presence of a glutamate in the histidine-tyrosine-glutamate (H-Y-E) triad motif (ARTD1–6); the remaining 11 members are characterized by the lack of this glutamate residue, that is, they are replaced by isoleucine (I), leucine (L), threonine (T), valine (V), or tyrosine (Y; ARTD7–17). This glutamate has been demonstrated to be crucial for polymer elongation and, based on its presence, ARTDs have been classified as poly-ARTDs (ARTD1–6), mono-ARTDs (ARTD7–12; ARTD14–17) enzymes, or catalytically inactive ARTD13 [24,27–29,67].

### 3. The Poly-ARTDs: (ARTD1 to ARTD6)

ARTD1–6 are members of the ARTDs that are typical PARPs, as they all possess the conserved glutamate residue of the H-Y-E triad, which is crucial for polymer elongation [1,28,29,33,68].

ARTD1/PARP1 is the best studied member of this ARTDs group, with a well-defined and detailed structural basis for its DNA damage-dependent activity [10,69,70]. It is a nuclear protein, but there are studies suggesting that ARTD1 could also be present in the mitochondria [71–73].

This protein consists of three modular domains: a N-terminal DNA binding domain consisting of three ZF domains, an automodification domain, and a C-terminal ART domain containing the conserved H-Y-E motif [7,33,38,44]. The DNA binding domain plays a critical role in the recognition of DNA strand aberrations and concurrent activation of ARTD1 [13,38,74]. The automodification domain is comprised of a BRCA1-carboxy terminus-like module that mediates several protein-ARTD1 and DNA-ARTD1 interactions [38,75–78]. ARTD1 is responsible for the majority of PARP activity in the cell, and it accounts for approximately 85–90% of mammalian cell poly-ADP-ribosylation activity [38,79].

ARTD1 is best known for its function in the base excision repair pathway during DNA damage [7,63,80–82]. It acts as a DNA damage sensor and a signaling molecule binding to both single and double-stranded DNA breaks [35,44]. ARTD1-DNA binding leads to a conformational change of the enzyme, followed by extensive auto-ADP-ribosylation and hetero-ADP-ribosylation of different forms of histones, such as H1, H2B, H3, and H4, the main targets of ARTD1 [74,75,83–85]. This causes a complete decondensation of the chromatin structure, allowing access to DNA regions that are normally weakly accessible [84,86].

In this context, the histone PARylation factor 1 (HPF1; also known as C4orf27) has been recently identified as a regulator of the role of ARTD1 in the DNA damage response [87]. HPF1 interacts with ARTD1, forming a robust complex that promotes hetero-ADP-ribosylation of histones, in turn limiting the DNA damage-induced ARTD1 auto-modification. Indeed, in the absence of HPF1, ARTD1 is hyper-ADP-ribosylated and therefore unable to ADP-ribosylate histones [87]. Moreover, serine was identified as a new target residue for endogenous ADP-ribosylation on histones [88], and HPF1 has been revealed to be the factor conferring serine specificity to both ARTD1 and ARTD2 [89]. Specifically, three serines, targets of endogenous ADP-ribosylation, are located on the ARTD1 automodification domain ([89]; reviewed by [90,91]). Of note, Palazzo and colleagues have recently demonstrated that the ARTD1/HPF1-dependent ADP-ribosylation on serine represents the major fraction of ADP-ribosylation occurring after DNA damage. In the absence of HPF1, glutamate/aspartate becomes the main target residue for ADP-ribosylation, thus leading one to consider serine as the primary residue to be ADP-ribosylated in the DNA damage response [92].

This recent discovery leads to the question of what the key amino acid targets of the active ARTD enzymes are [93,94]. While the amino acidic specificity has been clarified for a different and smaller family of mono-ADP-ribosyl-transferase, the ARTC family, multiple amino acid targets have been reported for the ARTD enzymes, including lysine (ARTD1, ARTD3, ARTD10, ARTD11, and ARTD15), aspartate (ARTD1, ARTD2, ARTD3, ARTD10, ARTD11, ARTD12, ARTD15, and ARTD17), glutamate (ARTD1, ARTD2, ARTD3, ARTD8, ARTD10, ARTD11, and ARTD15), serine (ARTD1, ARTD2), and cysteine (ARTD11, ARTD12, ARTD16, and ARTD17). This topic has been recently reviewed by Choen [95].

Apart from its role in DNA repair, ARTD1 is also involved in other complex biological processes such as apoptosis, maintenance of genomic integrity, regulation of replication and differentiation, inflammation, and transcriptional regulation [26,44,70,86,96–98].

Because of its crucial role in mitosis and cancer, ARTD1 has been at the front line of drug discovery since the 1980s, and the first clinical trial for an ARTD1 inhibitor was initiated in 2003 with rucaparib [99]. Since then, other further inhibitors have entered clinical trials with the aim of blocking the mechanism of repair of damaged DNA through ARTD1 inhibition, and thus enhancing the DNA damage caused by chemotherapy and radiotherapy [11,15,16,19]. Currently, several PARP inhibitors such as olaparib, niraparib, talazoparib, veliparib, and the same rucaparib are under clinical trials [19]. Some of them are in the last steps of these trials, while olaparib, rucaparib, and

niraparib have been recently approved by FDA for the treatment of relapsed ovarian cancer [18,20,21]. PARP inhibitors have been specifically used for the treatment of advanced ovarian cancer associated with BRCA1 and BRCA2 mutations. BRCA1- and BRCA2-mutated cells, which are associated with abnormal homologous recombination (HR) repair of DNA, have been shown to be hypersensitive to PARPP inhibitors through the mechanism of synthetic lethality, that is, they are effective at inducing cell death in BRCA-mutant cells, but not in normal ones [100]. Importantly, PARP inhibitors represent one of the first therapeutic strategies aimed at exploiting synthetic lethality [101].

ARTD2/PARP2 is a DNA-dependent nuclear protein which, among all the ARTD members, is the closest relative of ARTD1, since it displays the highest sequence homology (69% similarity; [25]). Like ARTD1, ARTD2 contains a WGR domain, which is required for DNA-dependent activity, and has its catalytic domain located at the carboxy terminus [28]. However, its DNA binding domain is different from that of ARTD1 and, considering that the DNA binding domain of ARTD2 shows no homology to any other ARTDs reported, it may be responsible for the different substrate specificity [102,103].

The main role of ARTD2 is the same of ARTD1, as it acts as a sensor and signaling molecule in response to DNA damage [69]. Similarly to ARTD1, ARTD2 is activated by DNA nicks, and this leads to its auto-ADP-ribosylation and synthesis of long branched chains of PAR [32,69,104,105]. In addition to its role DNA repair, ARTD2 has other proposed functions in genome integrity, spermatogenesis, adipogenesis, and immune cell development [106–110].

ARTD3/PARP3 is a poly-ARTDs sharing high degree of structural similarity of ARTD catalytic domain and with a conserved glutamate residue as compared to ARTD1 and ARTD2 [28,33]. It has been firstly identified as a core component of the centrosome preferentially located at the daughter centriole throughout all stages of the cell cycle [111]. ARTD3 overexpression interfered with the G1/S phase cell cycle progression, and it was described to interact with ARTD1 at the centrosome [111]. Nevertheless, further studies disputed the centrosomal localization of ARTD3 and suggested that ARTD3 localized to the nucleus and associated with polycomb group proteins is involved in gene silencing and DNA repair networks including DNA protein kinases, DNA ligase III and IV, Ku70 and Ku80, and ARTD1 [112,113]. Boehler and colleagues demonstrated that ARTD3 cooperates with ARTD1 during the cellular response to DNA double-strand breaks, which is pertinent to association with Ku and Ligase IV [112].

Initially, auto-ADP-ribosylation and hetero-ADP-ribosylation activities of ARTD3 were described as mono-ADP-ribosyl-transferase activity [114]. However, a later report has suggested that ARTD3 possessed poly-ADP-ribosyl-transferase activity [112]. In particular, ARTD3 was described to poly-ADP-ribosylate the nuclear mitotic apparatus protein (NuMA) directly and indirectly through ARTD5, suggesting that ARTD3 was required for mitotic spindle integrity during mitosis [112]. Collectively, these reports implicate ARTD3 in the maintenance of genomic integrity, mitotic spindle integrity, and transcriptional repression.

ARTD4/PARP4/vPARP is the largest member of the ARTD family and has originally been identified as a component of mammalian cytoplasmic ribonucleoprotein complexes called vault particles that have been proposed to be involved in multidrug resistance of human tumors and to function in intracellular transport [45]. ARTD4 associates with two essential proteins of the vault particle, major vault protein (MVP) and telomerase-associated protein (TEP1; [45]). ARTD4 is also present in the nucleus, where it is not attached to the vault components, and at the mitotic spindle, suggesting that it may play multiple roles not yet identified [45].

The structure of ARTD4 is unusual, since it is the only ARTD member to have its catalytic domain located at the N-terminal portion of the protein [26,28,33]. It is comprised of five major domains, which are the BRCT motif, the catalytic ARTD domain, the breast cancer vault protein inter- $\alpha$ -trypsin (VIT) domain, the von Willebrand type A (vWA) domain, and, finally, the major vault protein particle interacting domain (MVP-ID; [28]). BRCT domain is thought to bind phosphorylated DNA damage-sensing proteins [115]. VIT and vWA domains are presumed to mediate protein-protein interactions [44]. MVP-ID is involved in the interaction with the major vault protein, as suggested by its name. MVP mRNA (messenger RNA) levels are shown to be an indicator of multidrug resistance

(MDR), which is a major cause of chemotherapy failure in cancer patients [116–118]. Despite this unique feature, ARTD4 is catalytically active, and poly-ADP-ribosylates MVP as well as itself [33,45,65,119].

ARTD5/PARP5a/Tankyrase-1 and ARTD6/PARP5b/Tankyrase-2 are two closely related ARTD family members sharing 83% sequence identity between each other and 89% sequence identity with the catalytic ARTD domain [50,52,120]. They differ from other ARTD members because of their unique domain organization, which is composed of a SAM domain, which is required for tankyrases oligomerization, and the characteristic catalytic ARTD domain [26,28,33,121]. Their N-terminal consists of a region comprising of 24 ankyrin repeats, which are segmented into five ARD (ARD I-V) and are used to interact with the target proteins [38,50,51,121]. ARTD5 has an additional region at the N-terminal that contains an HPS domain; this additional region most likely has a regulatory function, although it is not well studied and its main function is unknown so far [38,52,121].

Tankyrase-1 localizes to multiple subcellular sites, as it has been found in the cytoplasm, as well as in the nucleus [38,122–124]. Although tankyrase-1 does not contain an NLS, it is present in the nucleus through its interaction with the telomeric repeat binding factor 1 (TRF1), which contains an NLS [38,122,124,125]. The intracellular location of tankyrase-2 is less characterized, but it has been reported to have a localization similar to that of tankyrase-1 [38,121,126]. Tankyrases have been implicated in a diverse range of functions including telomere maintenance, WNT signaling, mitosis, and mediation of insulin stimulated glucose uptake [33,121].

ARTD5 has first been discovered as a factor that regulated telomere length by binding the negative regulator of telomere length TRF1, and was originally named tankyrase 1 due to its interaction with this factor [50]. ARTD5 catalyzes auto-poly-ADP-ribosylation and poly-ADP-ribosylation of TRF1, and a careful analysis of ARTD5 auto-ADP-ribosylation revealed that it synthesizes ADP-ribose polymers with an average length of 20 ADP-ribose units, but polymers lack branching [121,127].

ARTD6 has also been reported to associate with and poly-ADP-ribosylate TRF1, indicating a potential redundant role of ARTD5 and ARTD6 in telomere regulation [52,121,123]. ARTD6 also associates with ARTD5, and both enzymes share most of their protein partners including insulin-responsive aminopeptidase (IRAP), NuMA and 182 kDa tankyrase-binding protein (TAB182; [38,52,121,124,126,128].

Overall, the recent findings about poly-ARTs and their relative targets establish poly-ADP-ribosylation as a protein modification involved in an impressive array of regulatory pathways. A better understanding of the role of these enzymes in both these physiological and pathophysiological processes will be of clinical relevance.

#### 4. The Active Mono-ARTDs

As previously mentioned, the mono-ARTs of the ARTD family have amino acid substitutions in their catalytic centers that enables them to attach just mono ADP-ribose moieties to the target proteins [27,28]. This subfamily is comprised of ARTD7–ARTD17, excluding ARTD13, which is described as inactive or pseudo ARTD. Despite the fact that ARTD9 and ARTD13 lack both the catalytic glutamate, as well as the histidine of the H-Y-E triad, and were predicted to be catalytically inactive [24,74,129], recently, a mono-ADP-ribosyl-transferase activity has been described for ARTD9 [67].

The remaining mono-ARTDs do not contain the catalytic glutamate of the H-Y-E motif that is characteristic of polymer forming ARTDs, since it is required for elongation of the ADP-ribose chain [24]. For instance, the glutamate E988 in human ARTD1 (hARTD1) has been shown to be essential for the ARTD1 elongation reaction and, thus, for the formation of poly-ADP-ribose chains [130,131]. Despite this fundamental difference, mono-ARTDs also modify acidic residues, and they are proposed to utilize the glutamate of the substrate protein and thus follow the substrate-assisted catalysis mechanism [27].

Several studies indicate that mono-ARTDs play critical roles in intracellular signaling, such as transcription, immunity, inflammation, and stress response, and have been linked to many human diseases, including neurodegenerative and inflammatory diseases, and the onset and progression of cancers [132,133].

## 5. ARTD7, ARTD8, and ARTD9

ARTD7 (PARP15/BAL3) was originally identified, together with ARTD8 (PARP14/BAL2), as a gene closely related to ARTD9 (PARP9/BAL1; B-aggressive lymphoma 1 [53,65,134].

These three members of the ARTD family are characterized by the presence of N-terminal macro domains, with two in ARTD9 and ARTD7, and three in ARTD8 [53]. Thus, these are collectively known as macro domain containing-mono-ARTDs. Macro domains are protein domains known to bind mono- and poly-ADP-ribose [57,135,136]. Recently, macro domains 2 and 3 of ARTD8 were reported to recognize and read mono-ADP-ribosylated ARTD10 and substrates of ARTD10 [57]. It has been demonstrated that these two ARTD8 macro domains bind to mono-ADP-ribosylated targets, and this association is strictly dependent on the presence of mono-ADP-ribosylation, as the ARTD8 macro domains do not associate with poly-ADP-ribosylated proteins [57]. Thus, they have been indicated as mono-ADP-ribosylation reader modules.

Both ARTD7 and ARTD8 demonstrate auto-mono-ADP-ribosylation activity [53].

Little is known about ARTD7, besides that it is localized to stress-granules along with ARTD8; it has been reported to have a transcriptionally repressive function through its N-terminal macro domains, and its auto-ADP-ribosylation activity has been suggested to counteract the repressive effect of the macro domains [53].

Whereas ARTD7 remains poorly characterized, ARTD8 is better understood and has been implicated in STAT6 (Signal Transducer and Activator of Transcription 6)-dependent transcriptional control and cytokine-regulated control of cellular metabolism [137,138]. Thus, it is also known as CoaSt6 (Collaborator of Stat6) and as an activator of interleukin 4 (IL-4)- and Stat6-dependent transcription. ARTD8 potentiated IL4-induced STAT6 transactivation via its macro domains and catalytic activity [138,139]. ARTD8 also catalyses ADP-ribosylation of p100, a protein that interacts with RNA polymerase II and functions as a bridging factor between Stat6 and the transcription machinery [140]. However, the functional consequences of this modification remain to be characterized in detail.

Similarly, the role of ARTD8-mediated ADP-ribosylation of the HDAC2 and HDAC3 histones deacetylases remains unclear. However, in the presence of IL-4, the ART activity of ARTD8 is activated, and HDAC2 and HDAC3 are ADP-ribosylated and released from their promoters, allowing the binding of Stat6 and the consequent transcription [140]. In line with this, a catalytically inactive mutant of ARTD8 did not enhance Stat6-mediated transcription, and ART inhibitors blocked IL-4-dependent transcription [138].

Moreover, in response to IL-4, ARTD8 is also involved in proliferation and survival of B-lymphocytes, with a role in the regulation of the glycolytic activity of these cells [137,141]. This is in line with the requirement for a major supply of cellular biomass to sustain continuous cell growth and proliferation of cancer cells. ARTD8 also interacts with and stabilizes the phosphoglucose isomerase/autocrine motility factor (by inhibiting its ubiquitination), a cytosolic and secreted enzyme that is essential for glycolysis and gluconeogenesis that is involved in tumor progression and metastasis [142]. Recently, ARTD8 was also identified as a downstream effector of the Jun N-terminal kinase 2 (JNK2)-dependent pro-survival signal by binding to and inhibiting JNK1 pro-apoptotic activity, promoting the survival of myeloma cells [143].

Intriguingly, ARTD8 has been found to be localized not only in the nucleus but also at the cell periphery where, together with ARTD9, it associates with actin fibres [144]. Because human actin has been previously reported to be modified not only by bacterial toxins but also by a not-yet-identified endogenous enzyme [132,145], it could be hypothesized that the ART activity of ARTD8 can modify actin, affecting actin polymerization and cell proliferation. Finally, the ART activity of ARTD8 has been seen to be involved in the pathogenesis of asthma using a murine model of allergic airway disease, in line with the regulatory role of ARTD8 on IL-4- and STAT6-dependent transcription and with the roles that IL-4 and STAT6 have in asthma [146]. Allergic airway disease is attenuated in ARTD8-deficient mice or mice treated with the ARTD inhibitor PJ34 [146]. Interestingly, recent reports

demonstrated that ARTD8 could have similar effect in the development of different kinds of allergic inflammation [147–149].

Thus, considering the widely studied roles of ARTD8 in cancer and its emerging role in allergic airway diseases, the targeting of ARTD8 activity appears to be of particular therapeutic relevance for lymphoma, myeloma, and asthma.

ARTD9 was considered enzymatically inactive until recently, when its mono-ADP-ribosyl-transferase activity was described [67].

ARTD9 is a nucleo-cytoplasmic shuttling protein that has been identified as a risk-related gene product in aggressive diffuse large B-cell lymphoma (DLBCL), the most common non-Hodgkin lymphoma ([134,150–152]. ARTD9, as for the other members of the macro domain-containing mono-ARTDs family (ARTD7 and ARTD8), has two prototypical macro domains within the N-terminus, which can bind mono- and poly-ADP-ribose [33,55,58]. It has been described as possessing transcriptional repressive activity that is dependent on interaction through these macro domains but independent of its catalytic activity [53,55].

Over-expression of ARTD9 promoted lymphocyte migration, indicating a tumor-promoting role in high-risk DLBCL [134], which has been suggested to be through modulation of interferon gamma (IFN $\gamma$ ) signaling-related gene expression [151]. It is known that IFN $\gamma$  is secreted by host-activated tumor-infiltrating T lymphocytes, and it induces expression of ARTD9 and its interactor BBAP (B-lymphoma and BAL-associated protein) in DLBCL cell lines. ARTD9 induction, in turn, promotes the transcription of interferon-controlled genes [151]. Thus, by inhibiting the host immune response against the lymphoma, ARTD9 can function as a transcriptional activator of tumor genes in an inflammatory environment. Furthermore, ARTD9 has been identified as a novel co-repressor of transcription of interferon response factor 1 (IRF1), a tumor suppressor [150]. ARTD9 directly interacts with STAT1 $\beta$  (signal transducer and activator of transcription 1 isoform  $\beta$ ) to inhibit IRF1 expression, repressing the anti-proliferative and pro-apoptotic INF $\gamma$ -STAT1-IRF1-p53 complex [150].

ARTD9 has also been linked to the DNA damage response pathway [59]. In response to DNA strand breaks, ARTD9 and its partner BBAP are recruited to DNA damage sites and co-localized with ARTD1 and its product poly-ADP-ribose [59]. At the DNA damage sites, ARTD9 and BBAP mediate the specific recruitment of the adaptor protein RAP80 (receptor-associated protein 80) and checkpoint mediators 53BP1 (p53 binding protein 1) and BRCA1 through BBAP-mediated ubiquitination, which limits early and delayed DNA damage and enhances cellular viability [59]. More recently, it has been reported that an ADP-ribosyl-transferase activity associated with ARTD9 in complex with the histone E3 ligase Dtx3L is important for DNA damage repair. The ubiquitin molecule is modified at its carboxyl terminal on glycine 76, a residue involved in ubiquitin conjugation to target protein, thus inhibiting protein ubiquitylation [67].

## 6. ARTD10

ARTD10, also known as PARP10, was the first member of the ARTD family to be identified as a mono-ARTDs and was initially discovered through in silico screening of ARTD family members [25]. It is a 150-kDa enzyme that comprises several domains of potential functional relevance. With the exception of the ART catalytic domain, ARTD10 domain structure is unique from the other ARTDs. In addition to the C-terminal ART catalytic domain (amino acids 818–1025), the ARTD10 sequence is characterized by an RNA-recognition motif (RRM; amino acids 11–85), a glycine-rich domain (amino acids 281–399); a glutamic acid (Glu)-rich region (amino acids 588–697) containing two ubiquitin interaction motifs (UIM; amino acids 650–667, 673–690); and a leucine-rich nuclear export sequence (NES; amino acids 598–607). The RRM and the glycine-rich domain are both involved in the RNA binding [153,154].

ARTD10 is predominantly cytosolic under basal conditions, but it can shuttle between the cytoplasmic and the nuclear compartments [155]. The nuclear export of ARTD10 is mediated through its NES, while a region that acts as a nuclear localization signal (NLS), which has been mapped in the middle of ARTD10, defines its nuclear import [27].

Besides mono-ADP-ribosylation, ARTD10 undergoes auto-ADP-ribosylation, as well as modifying each of the four core histones. It has also been reported to interact with the proto-oncoprotein c-Myc, a key transcriptional regulator of cell proliferation [27,154]. When overexpressed in various cell lines, ARTD10 acts as an inhibitor of the c-Myc- and H-ras-mediated cell transformation, and this role is independent of its ADP-ribosylation activity; neither c-Myc nor its heterodimerization partner Max were ADP-ribosylated by ARTD10 [154]. However, the catalytic activity of ARTD10 is strictly required to inhibit cell proliferation, since its catalytically inactive mutant is not effective [156]. Specifically, the catalytically active ARTD10 inhibits cell proliferation, as revealed by measurements of living cells, and this is a consequence of apoptosis induction, as determined by Annexin V staining and by analysis of cleaved ARTD1 [156].

Although it remains unknown which protein(s) are mono-ADP-ribosylated by ARTD10 to mediate this growth inhibitory phenotype, a possible candidate is the glycogen synthase kinase 3 beta (GSK3 $\beta$ ), which is known to regulate cell proliferation and whose kinase activity is inhibited once it is modified by ARTD10 [153,157].

The ARTD10 target GSK3 $\beta$  appears to play a role in neurodegenerative disorders, as its overexpression causes neuronal cell death [158]. GSK3 $\beta$  has been implicated in the fatal neurodegenerative disease amyotrophic lateral sclerosis (ALS), which is characterized by degeneration of motor neurons, resulting in progressive motor paralysis. Mutations in the gene coding for superoxide dismutase (SOD1) are associated with approximately 20% of familial ALS. Different studies have shown that GSK3 $\beta$  inhibition can prevent motor neuron cell death in an in vitro ALS model that is characterized by expression of the G93A mutant of human SOD1 [159]. Thus, through mono-ADP-ribosylation of GSK3 $\beta$ , ARTD10 can act as an inhibitor of cell proliferation and also as a regulator of neuronal cell death.

We have recently provided evidence that ARTD10 interacts with and mono-ADP-ribosylates the glyceraldehyde 3-phosphate dehydrogenase (GAPDH), a glycolytic enzyme that links metabolic activity to various cellular processes, including cell survival and proliferation [160]. The co-localization of GAPDH and ARTD10 occurs in well-defined cytosolic cell bodies, which we have shown to be rounded membrane-free structures. Inhibition of ARTD10 activity resulted in the release of GAPDH from these cytosolic cell bodies, indicating that the catalytic activity of ARTD10 is required to recruit GAPDH, but it is not required to induce the formation of these cell bodies. Moreover, the dehydrogenase activity of GAPDH appears not to be regulated by its ADP-ribosylation, thus leading to hypothesis that ADP-ribosylation is important for the recruitment of GAPDH into cell bodies [160].

In line with an emerging role of ARTD10 as a tumor suppressor, recently it has been demonstrated that ARTD10 interacted with and mono-ADP-ribosylated Aurora A, thus inhibiting its kinase activity and regulating its downstream signaling [161].

Moreover, ARTD10 has been linked to metabolic processes, as it has been shown to influence mitochondrial oxidative metabolism. ARTD10 depletion using specific shRNAs increased the mitochondrial oxidative capacity and glycolysis of different cancer cellular models [162]. Moreover, lower ARTD10 expression was associated with increases in fatty acid oxidation [162]. However, further studies are necessary for better understanding ARTD10 role in metabolic regulation.

ARTD10 has also been reported to have a role in the NF- $\kappa$ B transcription factor signaling. The NF- $\kappa$ B family is involved in cell proliferation, innate and adaptive immune responses, and further crucial processes, like inflammation and tumorigenesis [163]. ARTD10 is a regulator of the NF- $\kappa$ B pathway by mono-ADP-ribosylating NEMO, reducing its poly-ubiquitination and activation of NF- $\kappa$ B [64]. However, unlike the regulation of c-Myc, the regulation of NF- $\kappa$ B is dependent on ARTD10 catalytic activity and on the UIMs [64]. Moreover, in addition to its role in cell signaling pathways that regulate proliferation and apoptosis, ARTD10 expression can also be induced by LPS and IFN $\alpha$ , which indicates its further involvement in immunological processes [164].

## 7. ARTD11, ARTD16, and ARTD17

ARTD11, ARTD16, and ARTD17 are three mono-ARTDs that, with the exception of the typical mono-ART catalytic domain, remain to be characterized for the presence of other motifs and domains. ARTD11, also denoted as PARP11, and ARTD16, also referred to as PARP8, are minimally investigated members of the mono-ARTDs. The limited studies available for them indicate they have no known domains outside of their catalytic one, with the exception of the single tryptophan-tryptophan-glutamate (WWE) domain of ARTD11, which has been reported to bind ADP-ribose [62]. Additionally, their functions have not been determined to date. ARTD11 has been shown to be expressed in adult testicular tissues, preferentially in differentiating spermatids undergoing nuclear reorganization, elongation, and condensation [165]. Specifically, the enzyme has been shown to localize at the nuclear envelope of transfected cells, and this localization is dependent on the presence of intact WWE domain and ADP-ribose transferase domain, whereas the catalytic activity was not required [165]. Deletion of *artd11* gene in mice causes nuclear envelope defects that can determine teratozoospermia resulting in male infertility [165].

ARTD17, also known as PARP6, is a mono-ARTD with possible involvement in cancer. It has been described as a negative regulator of cell-cycle progression in HeLa cells, as ARTD17 overexpression was reported to arrest cells in S-phase, and this was dependent on the presence of the catalytic domain [166]. Moreover, a role for ARTD17 as tumor suppressor involved in colorectal cancer development has been proposed. The immunohistochemical analysis of human colorectal cancer specimens has shown that ARTD17 expression is inversely correlated with Ki-67, which is a well-known proliferation marker, and is associated with a good prognosis. Thus, it has been hypothesized that ARTD17 expression levels might be used as a prognostic biomarker for improved survival of patients with colorectal cancer [166]. However, the catalytic activity of ARTD17 has not been evaluated, and its potential activity in other cellular functions has not yet been fully determined.

## 8. ARTD12

ARTD12, also known as PARP12, is a member of the mono-ARTDs whose function is still incompletely characterized. ARTD12 belongs to a subgroup of ARTD family members characterized by the presence of typical ZF motifs in its N-terminal domain, which are known to bind to viral, and also cytoplasmic, RNAs [39,167–169]. Thus, it is also referred to as ZC3HDC1, zinc finger CCCH type domain containing 1. ARTD12 exists in two isoforms denoted as long (L) and short (S) ARTD12 (ARTD12L and ARTD12S, respectively [170]). ARTD12L is a protein composed of 711 amino acids containing all the five ZF domains and the ART domain, which is crucial for the catalytic activity. ARTD12S is a protein of only 485 amino acids that contains the same five ZF domains, but lacks the ART domain [170]. ARTD12 is a mono-ADP-ribosyl-transferase with automodification activity, and it possesses at least two distinct subcellular locations and related functions. Unlike many other ARTD members, ARTD12 is largely excluded from the nucleus and appears to localize into distinct cytoplasmic structures in a protein domain-dependent manner [171].

Upon ectopic expression or exposure to oxidative stress, it is recruited to stress-granules (SGs), in which ARTD12 blocks mRNA translation through its association with the translational machinery. Both the N-terminal domain and the integrity of the catalytic domain are essential for this function [171,172]. Moreover, ARTD12 associates with both long and short isoforms of ARTD13 (short isoform is missing the catalytic domain), ARTD5, and ARTD7 within these stress granules [172]. Otherwise, under stimulation with lipopolysaccharide (LPS), ARTD12 localizes into structures unrelated to SGs. The association into these structures has been found to correlate with increased NF- $\kappa$ B signaling, suggesting a role for ARTD12 in inflammation [171]. ARTD12 has been recently identified as a putative anti-viral gene, belonging to a large family of interferon-stimulated genes (ISGs) whose expression is often induced during viral infections [173,174]. After infection by the alphavirus Venezuelan equine encephalitis virus (VEEV), ARTD12L is up-regulated and exhibits inhibitory effects on replication [170]. The same inhibitory effects on replication of VEEV have also been shown for other alphaviruses and RNA viruses [170]. Interferon stimulation up-regulates *Art12*

gene expression to counteract infections through inhibition of both cellular translation and virus replication. These inhibitions and antiviral activities depend on its binding to polyribosomes, via its RNA-binding domain, and require its catalytic activity [175]. This process has been suggested to be a cellular defense against invading viral pathogens, although this has not yet been mechanistically investigated [176]. More recently, expression of ARTD12 has also been found elevated in tissues from mice subjected to bacterial superantigen Staphylococcal enterotoxin B (SEB)-mediated toxic shock, suggesting a potential role of this protein during immune activation [177].

## 9. ARTD14

ARTD14 is a 75-kDa nuclear mono-ARTD that is also known as PARP7 or TiPARP (2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-inducible PARP). Its expression is induced by TCDD, which is a carcinogen and a potent activator of the ligand-activated transcription factor aryl hydrocarbon receptor (AHR; [178,179]). Once activated by ligand binding, AHR translocates into the nucleus, dimerizes with its binding partner AHR nuclear translocator (ARNT), and acts as a transcription factor [179].

Upon TCDD treatment, a decreased gluconeogenesis is observed, which is at least in part due to repression of AHR-mediated transcription of phosphoenolpyruvate carboxykinase (PEPCK). ARTD14 over-expression reproduces the TCDD effects on glucose metabolism, and it has been suggested that ARTD14 mediates these TCDD effects [178]. TCDD-dependent transcriptional induction of ARTD14 leads to ADP-ribosylation of cytosolic and mitochondrial PEPCKs [180]. However, as AHR suppression also enhances ADP-ribosylation, it is clear that the complex modulatory effects on ADP-ribosylation by AHR are far from being defined at present [180]. Further research has shown that ARTD14 is itself regulating AHR signaling in a negative feedback loop by acting as a transcriptional repressor [181]. However, it also acts with a different mechanism from that of AHR repressor (AHRR), as the silencing of ARTD14, but not that of AHRR, increases TCDD-induced AHR protein levels, whereas the silencing of both ARTD14 and AHRR enhances AHR transactivation [182].

Interestingly, over-expression of MACROD1, one of the members of the macro domain family, but not that of MACROD2, is able to reverse the repressive effect of ARTD14, as shown in a reporter gene assay, and interacts with AHR [183]. This evidence suggests that ARTD14-mediated mono-ADP-ribosylation functions as an important PTM in the pathway controlling the response to environmental toxins, and that MACROD1 might antagonize the repressive effect of ARTD14 by removing mono-ADP-ribosylation from ARTD14, AHR, and other so-far-unidentified substrates [65].

## 10. ARTD15

ARTD15, previously known as PARP16, is the smallest member of the ARTD family. It was the first ARTDs to be found to associate with the endoplasmic reticulum (ER; [184]). It is a single-pass transmembrane protein with the N-terminal region (amino acids 1–280) positioned towards the cytoplasm, and the very short C-terminal tail (amino acids 300–322) in the ER lumen. In line with this orientation towards the cytosolic compartment, ARTD15 interacts with and modifies the nuclear transport factor karyopherin- $\beta$ 1/importin- $\beta$ 1 (Kap $\beta$ 1; [184]). Kap $\beta$ 1 is selectively mono-ADP-ribosylated by ARTD15, and this modification has been hypothesized to control the nucleo-cytoplasmic shuttling of cellular proteins, as the pivotal role of Kap $\beta$ 1 is to be a carrier protein regulating the transport of various cargo proteins through the nuclear pore complex [184]. However, it remains open as to what the consequences of mono-ADP-ribosylation are for the function of Kap $\beta$ 1.

ARTD15 also demonstrates auto-mono-ADP-ribosylation, which could be inhibited with some well-characterized ARTD inhibitors, such as MIBG (meta-iodobenzylguanidine) and PJ34 (*N*-(6-oxo-5, 6-dihydrophenanthridin-2-yl)-*N*, Ndimethylacetamide HCl; [184,185]). Furthermore, mono-ADP-ribosylation has not been reported to occur at arginine, glutamate, or cysteine residues and could not be reverted by ADP-ribosyl-hydrolase 1 and 3 (ARH1, ARH3; [184]). Moreover, ARTD15 is required for activation of two proteins involved in the ER stress response during the unfolded protein response (UPR): the double-stranded RNA-dependent protein kinase (PKR)-like

ER kinase (PERK) and the inositol-requiring enzyme 1 $\alpha$  (IRE1 $\alpha$ ; [186]). During ER stress, ARTD15 has been found to auto-ADP-ribosylate itself and ADP-ribosylate PERK and IRE1 $\alpha$ , increasing their kinase activities and the endoribonuclease activity of IRE1 $\alpha$ , which are necessary for a proper execution of the UPR [186]. However, the role of ARTD15 in the UPR needs further investigations. Considering the ability of ARTD15 to modify Kap $\beta$ 1, PERK, and IRE1 $\alpha$ , it is emerging as a novel attractive therapeutic target, since it has a role in the regulation of nucleo-cytoplasmic trafficking and in the UPR, cellular processes that are both involved in different diseases, such as inflammation, neurodegeneration, and cancer [132].

A recent study has implicated ARTD15 activity in cystic fibrosis (CF). This study provided evidence that analogs of latonduine, through the modulation of ARTD15 activity, restored one of the most common mutations of the CF transmembrane conductance regulator gene (CFTR; [187]). This CFTR mutation generates a protein that is misfolded and retained in the endoplasmic reticulum. To date, a promising therapeutic approach was represented by the use of latonduine, a marine sponge metabolite identified as a corrector of this mutation. A series of latonduine analogs has further been developed, and it has been shown to function as a corrector of CFTR mutation through the inhibition of ARTD15 activity and the consequent blocking of IRE1 $\alpha$  ribosylation [187]. The ribosylation of IRE1 $\alpha$  has been reported to be essential for its activation during the UPR [186]. Preventing this activation through ARTD15 inhibition and IRE1 $\alpha$  activity modulation blocked the increased expression of chaperones, which should have helped to process the misfolded CFTR in the ER before transport for proteasomal degradation, thus allowing partially misfolded mutated CFTR to escape the ER quality control and traffic to the plasma membrane [187]. Indeed, when surface expression of mutated CFTR is restored, it retains some function; however, its stability in the plasma membrane and open probability are reduced compared with wild-type channels [188,189]. These findings, in addition to opening new areas of investigation about IRE1 $\alpha$  role in CFTR rescue, also strengthened the importance of ARTD15-mediated ADP-ribosylation and its emerging role as a therapeutic target for different diseases, including those with protein-trafficking defects.

## 11. The Inactive ARTD13

Until recently, ARTD9 and ARTD13 were considered to be enzymatically inactive, as their biological roles were reported to be independent from their ADP-ribosyl-transferase activity. However, recently a mono-ADP-ribosyl-transferase activity has been described for ARTD9 [67]; thus, we can presume that further investigation will clarify whether ARTD13 can also be considered a true active mono-ADP-ribosyl-transferase.

ARTD13, also known as Zinc-finger Antiviral Protein (ZAP/ZC3HAV1) or PARP13, according to previous classification, is a type 1 interferon-inducible host factor that regulates viral RNA transcripts. It was initially identified as zinc finger antiviral protein in a screen for host factors that confer resistance to retrovirus murine leukemia virus (MLV) infection [190–192]. However, ARTD13 antiviral activities have been later expanded to other retroviruses (HIV, human immunodeficiency virus), as well as different viral families [193–195].

ARTD13 binds directly to specific viral mRNAs through its N-terminal zinc finger domains, and it recruits cellular mRNA degradation factors to promote degradation of the target viral mRNA and the inability of the virus to replicate efficiently [39,167,194,195]. These antiviral properties are not due to ADP-ribosylation, since full-length ARTD13 is not catalytically active, nor is its short isoform [27,172].

In fact, in humans ARTD13 exists in two major isoforms resulting from alternative splicing: full-length ARTD13.1 and truncated ARTD13.2 [144,196]. Both isoforms lack ARTD activity and are unable to ADP-ribosylate target proteins: the catalytic domain of ARTD13.1 lacks amino acid residues required for ADP-ribosylation activity, whereas ARTD13.2 completely lacks the catalytic domain. Three additional isoforms have been predicted based on sequence analyses, but their expression in humans has not been experimentally verified [197]. The two isoforms have been recently reported to localize to cytoplasmic stress granules along with ARTD5, ARTD7, and ARTD12, and, interestingly

when over-expressed, both of them decrease miRNA-mediated silencing [172]. ARTD13 is unique among ARTDs, as it is the only catalytically inactive ARTD shown to be targeted for ADP-ribosylation by other ARTDs [129,144,172].

In addition to the antiviral functions of ARTD13, it acts as a pro-apoptotic and a pro-inflammatory factor, and is a component of the TNF (tumor necrosis factor)-related apoptosis-inducing ligand (TRAIL) mediated immune response to cancer [197]. For all these reasons, ARTD13 represents a promising therapeutic target for the treatment of multiple disease states, including viral infections, autoimmune diseases, and cancer.

## 12. Conclusions

ARTD is a large family of proteins that comprises both poly-ARTs and mono-ARTs, as well as inactive enzymes. The fact that some members of the ARTDs have been established as important players in the regulation of the activity of several target proteins with key functions in different cellular pathways makes these enzymes highly attractive as therapeutic targets for human disease. So far, a wide range of ARTD inhibitors has been developed in different research areas such as cancer therapy, ischemia, stress response, and neurodegenerative diseases [198–200]. Moreover, the availability of the crystal structure of the catalytic domain of some ARTDs further improved studies on ARTDs inhibitors [199,201].

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## Appendix A

Table A1. ARTD family.

New Classification	Old Classification	Enzymatic Status	Catalytic Motif	Ribosylation Activity	Cellular Localization	Funtion(s)
ARTD1	PARP1	Active	H-Y-E	Poly	Nucleus, mitochondria	DNA damage sensor, apoptosis, maintenance of genomic integrity, regulation of replication and differentiation, inflammation, transcriptional regulation, mitosis, cancer
ARTD2	PARP2	Active	H-Y-E	Poly	Nucleus	DNA damage, genome integrity, spermatogenesis, adipogenesis and immune cell development
ARTD3	PARP3	Active	H-Y-E	Poly	Nucleus	Maintenance of genomic integrity, mitotic spindle integrity and transcriptional repression
ARTD4	PARP4/vPARP	Active	H-Y-E	Poly	Cytoplasm, nucleus	Intracellular transport, multidrug resistance of human tumors
ARTD5	PARP5a/Tankyrase-1	Active	H-Y-E	Poly	Cytoplasm, nucleus	Telomere maintenance, WNT signaling, mitosis and mediation of insulin stimulated glucose uptake
ARTD6	PARP5b/Tankyrase-2	Active	H-Y-E	Poly	Cytoplasm, nucleus	
ARTD7	PARP15/BAL3	Active	H-Y-L	Mono	Stress granules	Transcriptional repressive function
ARTD8	PARP14/BAL2/CoaSt6	Active	H-Y-L	Mono	Nucleus, cell periphery, stress granules	Proliferation and survival of B-lymphocytes, regulation of glycolytic activity, cancer, allergic airway diseases
ARTD9	PARP9/BAL1	Active	Q-Y-T	Mono	Cytoplasm, nucleus	Promotion of lymphocyte migration when over-expressed, DNA damage response
ARTD10	PARP10	Active	H-Y-I	Mono	Cytoplasm, nucleus	Cell proliferation, apoptosis, immunological processes, tumor metastasis, mitochondrial oxidative metabolism
ARTD11	PARP11	Active	H-Y-I	Mono	Cytoplasm, nucleus	Spermatids differentiation
ARTD12	PARP12/ZC3HDC1	Active	H-Y-I	Mono	Stress granules	Inflammation, antiviral activities
ARTD13	PARP13/ZAP/ZC3HAV1	Inactive	Y-Y-V	-	Stress granules	Antiviral activities, pro-apoptotic and pro-inflammatory functions
ARTD14	PARP7/TiPARP	Active	H-Y-I	Mono	Nucleus	Glucose metabolism
ARTD15	PARP16	Active	H-Y-Y	Mono	Endoplasmic reticulum	Nucleo-cytoplasmic transport, Unfolded Protein Response (UPR), cystic fibrosis (CF)
ARTD16	PARP8	Active	H-Y-I	Mono	Nucleus, cytoplasm	Unknown
ARTD17	PARP6	Active	H-Y-I	Mono	Cell membrane	Cancer, cell-cycle progression

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