Glycosylphosphatidylinositol-anchored and Secretory Isoforms of Mono-ADP-ribozytransferases*

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Mono-ADP-ribosylation, a post-translational modification of proteins in which the ADP-ribose moiety of NAD is transferred to an acceptor amino acid, occurs in viruses, bacteria, and eukaryotic cells (1). The reaction is distinct from that catalyzed by poly(ADP-ribose) polymerase, a nuclear protein involved in DNA repair, cell differentiation, and the maintenance of chromatin structure (2). Among mono-ADP-ribosyltransferases, the bacterial toxins, cholera toxin, pertussis toxin, diphtheria toxin, and Pseudomonas aeruginosa exotoxin A are the best characterized in molecular structure, function, and substrate specificity (reviewed in Ref. 1). Mono-ADP-ribosyltransferases from mammalian and avian cells have been cloned and characterized, and specific target proteins have been identified (3, 4). In lymphocytes, a glycosylphosphatidyl-inositol (GPI)anchored transferase appears to be involved in immune modulation, whereas other isoforms in lymphocytes (5) and chicken heterophil granules (6) are membrane-associated but appear to be processed for secretion. Further, ADP-ribosyltransferases have been purified from brain, and data from several independent laboratories demonstrate that ADP-ribosylation is involved in neuronal function (7, 8). Deduced amino acid sequences of the vertebrate ADP-ribosyltransferases have similarities to those of viral and bacterial toxin transferases (9, 10) in regions that form, in part, an active site cleft, consistent with a common mechanism of NAD binding and ADP-ribose transfer (9).

The majority of the eukaryotic enzymes are arginine-specific transferases. ADP-ribosylation of arginine appears to be a reversible process; free arginine can be regenerated in ADP-ribosylated proteins by ADP-ribosylarginine hydrolases (1). ADP-ribosylarginine hydrolase activity was detected in the soluble fraction of turkey erythrocytes, cultured mouse cells, and rat skeletal muscle with deduced amino acid sequences known for rat, mouse, and human brain ADP-ribosylarginine hydrolases (11, 12).

ADP-ribosylation of cysteine was reported in bovine erythrocytes (13), and an NAD:cysteine ADP-ribosyltransferase that modified Goα was purified from human erythrocyte and platelet membranes (14). Consistent with this, ADP-ribosylcysteine linkages were detected in rat liver plasma membranes (15). ADP-ribosylation of cysteine can, however, occur nonenzymatically via the reaction of ADP-ribose, generated from NAD by NAD glycohydrolases, with cysteine (16). Nonenzymatic ADP-ribosylation of a cysteine in the heterotrimeric guanine nucleotide-binding (G) proteins (17). Based on these data, the ADP-ribose-cysteine produced by the human erythrocyte enzyme may have been generated nonenzymatically from free ADP-ribose. Because nitric oxide (NO) induced the noncovalent binding of the entire NAD molecule to a cysteine of glyceraldehyde-3-phosphate dehydrogenase (18), it is important to exclude NAD attachment to cysteine when assaying the radiolabeling of proteins with [32P]NAD.

This review summarizes information on the avian and mammalian ADP-ribosyltransferases and the recent advances in understanding their role in cellular metabolism.

Mammalian ADP-ribosyltransferases

The family of mammalian ADP-ribosyltransferases comprises five enzymes (ART1–5) based on similarities in their deduced amino acid sequences and conservation of gene structure (Fig. 1). ART1–ART5 were extensively purified from rabbit skeletal muscle as a 36-kDa protein (19) and subsequently cloned from rabbit (19) and human (20) skeletal muscle and mouse lymphoma (Yac-1) cells (21). The human ART1 gene is on chromosome 11p15 (22). The murine sequence is 75 and 77% identical to those of the rabbit and human muscle enzymes, respectively (21), consistent with considerable conservation of structure across species.

The deduced amino acid sequence of ART1 possesses hydrophobic amino- and carboxyl-terminal signal peptides that are characteristic of GPI-linked proteins (19, 20, 23). Rat mammary adenocarcinoma (NMu) cells, transformed with rabbit or mouse ART1 cDNAs, demonstrated membrane-associated transferase activity that was released into the medium by phosphatidylinositol-specific phospholipase C (PI-PLC), which cleaves the inositol phosphate moiety of glycosylinositol, with resulting reactivity with antibodies that recognize the inositol 1,2-cyclic phosphate moiety that remains after cleavage of the GPI anchor with PI-PLC (20), consistent with the presence of a GPI anchor on native transferases. In transformed NMu cells lacking the carboxy-terminal signal peptide, required for attachment of the GPI anchor, transferase activity was found in the medium (20).

In C2C12 mouse myoblasts, GPI-anchored ART1 activity, which appeared with differentiation of myoblasts to myotubes, catalyzed the ADP-ribosylation of integrin α7 (3). Modification of integrin α7 did not block α7β1 heterodimer formation or its association with the cytoskeleton or laminin. Incubation of embryonic chick myoblasts in vitro with [meta-iодобензилгуанидиний, an alternative substrate of NAD:arginine ADP-ribosyltransferases (24), however, inhibited proliferation and differentiation of the myoblasts (25). ADP-ribosylarginine hydrolase activity that was released into the medium by phosphatidylinositol-specific phospholipase C (PI-PLC), which cleaves the inositol phosphate moiety of glycosylphosphatidylinositol (GPI), with resulting partial loss of the inhibitory effect of NAD on CTL proliferation (27). Modification by the GPI-linked lymphocyte transferase of a 40-kDa membrane protein (p40) that complexes with the tyrosine kinase p56lck resulted in inhibition of p56lck action (4). It is noteworthy that T cell activation and lymphokine production can be mediated, in part, by signaling through GPI-anchored molecules (28, 29). Further, a GPI-linked transferase in CTL modified arginine in a manner consistent with a regulatory role for this modification in myogenesis.

ADP-ribosyltransferase activity with properties similar to those of the cloned ART1, was detected in mouse cytotoxic T lymphocytes (CTL) (27). Incubation of CTL with 10 mM NAD resulted in ADP-ribosylation of membrane proteins and inhibition of CTL proliferation. A 35-kDa protein with ADP-ribosyltransferase activity was released by incubation of intact CTL with PI-PLC, with resulting partial loss of the inhibitory effect of NAD on CTL proliferation (27). Modification by the GPI-linked lymphocyte transferase of a 40-kDa membrane protein (p40) that complexes with the tyrosine kinase p56lck resulted in inhibition of p56lck action (4). It is noteworthy that T cell activation and lymphokine production can be mediated, in part, by signaling through GPI-anchored molecules (28, 29).

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The abbreviations used are: GPI, glycosylphosphatidylinositol; PI-PLC, phosphatidylinositol-specific phospholipase C; CTL, cytotoxic T lymphocytes; LFA-1, lymphocyte function-associated molecule-1; PARP, poly(ADP-ribose) polymerase; CT, cholera toxin; LT, heat-labile enterotoxin of Escherichia coli; PT, pertussis toxin; DT, diphtheria toxin; ETA, P. aeruginosa exotoxin A; BFA, brefeldin A; kb, kilobase pair.
ADP-ribosyltransferases. In humans, the role of ART2 may be assumed by related proteins. The rat RT6 protein (33) and appears not to be expressed. In humans and chimpanzees, the sequences of mouse Rt6–1 and Rt6–2 are 79% identical, whereas the rat RT6 proteins, the mouse Rt6–1 was primarily an ADP-ribosyltransferase, with a relatively low level of NAD glycohydrolase activity (41). As in the rat, although reduced levels of mouse ART2 have been associated with immune-mediated disease, it has not been proven that pathogenesis of disease is related to enzymatic activity or lack thereof. Because mouse ART2 is capable of ADP-ribosylating exogenous proteins, however, this activity may result in effects similar to that observed in CTL.

ART3 and ART4—ART3 and ART4 were recently cloned from human testis (42) and spleen (43), respectively. The deduced amino acid sequences of ART3 and ART4 possess several regions of sequence similarity with ART1 and are 14 and 31% identical, respectively, to ART1. The hydropathy profiles of the amino- and carboxyl-terminal sequences of ART3 and ART4 demonstrate hydrophobic signal sequences consistent with the possibility that ART3 and ART4, like ART1, may be GPI-linked. The ART3 gene was localized to chromosome 4q13-q21 (42), and ART4 is on chromosome 12q13.2-q13.3 (43). On Northern analysis, a 1.8-kb band in human, 1.6-kb band in mouse, 1.6-kb band in poly(A)^+ RNA from heart hybridized with an ART3 cDNA probe (42). An ART4 probe hybridized with 1.4-, 2.4-, and 5.5-kb bands in poly(A)^+ RNA from spleen, ovary, and intestine (43).

ART5—An ART5 cDNA was cloned from Yac-1 murine lymphoma cells (5). Its deduced amino acid sequence has similarities to other ART proteins in regions believed to be involved in catalytic activity and is 32% identical to that of mouse ART1, approximately 30% identical to that of mouse ART2, and 29 and 25% identical to the human ART3 and ART4 proteins, respectively. Unlike ART1, ART5 had significantly more NAD glycohydrolase than ADP-ribosyltransferase activity, and although it catalyzed auto-ADP-ribosylation, ADP-ribosylation of other proteins was relatively poor. The membrane-associated ART5 enzyme activities were not solubilized by PI-PLC. Consistent with this, ART5 possesses a hydrophobic amino- but not carboxyl-terminal signal sequence and may be secreted instead of GPI-linked. On Northern analysis, an ART5 cDNA probe hybridized with 1.6- and 2.0-kb bands in poly(A)^+ RNA from testis, where it was most abundant, and a 1.6-kb band in poly(A)^+ RNA from cardiac and skeletal muscle (5). In muscle, the three other ART proteins (ART1, -3, and -5) are expressed whereas ART3 and ART5 are present in testis and ART1, ART2, and ART5 are expressed in lymphocytes.

The structures of the ART1, ART2, and ART5 genes are strikingly similar (Fig. 1). The amino-terminal signal peptide, a region containing the catalytic site, and the carboxyl-terminal signal sequence in the GPI-anchored transferases are encoded in separate exons. In ART1 and ART5, but not ART2, a short exon containing a basic amino acid-rich region is separated from the catalytic site, and the carboxyl-terminal signal sequence and other ART proteins in regions believed to be involved in catalytic activity and is 32% identical to that of mouse ART1, approximately 30% identical to that of mouse ART2, and 29 and 25% identical to the human ART3 and ART4 proteins, respectively. Unlike ART1, ART5 had significantly more NAD glycohydrolase than ADP-ribosyltransferase activity, and although it catalyzed auto-ADP-ribosylation, ADP-ribosylation of other proteins was relatively poor. The membrane-associated ART5 enzyme activities were not solubilized by PI-PLC. Consistent with this, ART5 possesses a hydrophobic amino- but not carboxyl-terminal signal sequence and may be secreted instead of GPI-linked. On Northern analysis, an ART5 cDNA probe hybridized with 1.6- and 2.0-kb bands in poly(A)^+ RNA from testis, where it was most abundant, and a 1.6-kb band in poly(A)^+ RNA from cardiac and skeletal muscle (5). In muscle, the three other ART proteins (ART1, -3, and -5) are expressed whereas ART3 and ART5 are present in testis and ART1, ART2, and ART5 are expressed in lymphocytes.

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The first vertebrate NAD:arginine mono-ADP-ribosyltransferases (transfersases A, B, C, and A') were identified and purified from turkey erythrocytes (55–58). Transfersases A and B were from the erythrocyte cytosol, and transfersases C and A' from the plasma membrane and nucleus, respectively. In addition to differences in localization, the transfersases had different kinetic and physical properties.

Two distinct chicken ADP-ribosyltransferases (AT1 and AT2) localized to heterophil granules were cloned from a bone marrow cDNA library (6). The deduced amino acid sequence contained an amino-terminal signal peptide but lacked a carboxyl-terminal GPI-attachment signal, compatible with AT1 and AT2 being in granules and secreted (Fig. 2). A third transfersase from a chicken erythroblast cDNA library had a deduced sequence 50–52% identical to those of the heterophil transfersases (59). Several in vitro substrates of the heterophil transfersase were identified (60) including nonmuscle actin and a 33-kDa heterophil granule protein, which is similar in amino acid sequence to the myb-induced myeloid protein-1, Mim-1. As with turkey transfersase A, it was not demonstrated that in vitro reactions catalyzed by the heterophil transfersase occur in cells.

Regions Conserved among ADP-ribosyltransferases

Despite lack of overall identity of deduced amino acid sequences, the bacterial toxin ADP-ribosyltransferases possess regions of sequence similarity that appear to form, in part, the catalytic site (9). Based on crystallography and computer modeling, the NAD-binding cleft of the bacterial toxins and that of eukaryotic transfersases appear to be composed of an α-helix bent over a β-strand (region II) (9), Arg-7 in region I of LT potentially binds the AMP-ribose or phosphate portions of NAD and also forms a hydrogen bond with the backbone carbonyl of Ser-61, which is located in region II (64). Ser-61 apparently maintains proper conformation of the active site of LT and does not play an essential role in catalysis (9). In region III, the carboxylate group of Glu-112 of LT and CT superimposes on that of Glu-148 of DT and Glu-553 of ETA and is in close proximity to the N-glycosidic bond of NAD (61).

The regions of amino acid sequence similarity among bacterial toxin transfersases are also apparent in alignments of the mammalian ADP-ribosyltransferases (10, 65). In computer modeling studies of the mouse ART2, Arg-126 on a β-strand (region I), Ser-147 on a β-strand followed by an α-helix (region II), and the active site Glu-184 on a β-strand (region III) are positioned in the catalytic cleft in a manner similar to that found in the crystal structure of the bacterial toxins, in particular, LT, CT, and PT (9, 65). In the alignment of deduced amino acid sequences of ART1, ART4, and ART5, a region I arginine and region II serine similar to those in LT and PT appear to be conserved. Although His-114 of rabbit ART1 aligns with His-21 of DT, its replacement with Asn did not abolish enzymatic activity (10). A recombinant mouse ART1 protein from which the first 121 amino acids were deleted possessed predominantly NAD glycohydrolase activity, but not ADP-ribosyltransferase activity (66). The truncated transfersase lacks His-110 (analogous to His-114 of rabbit ART1) but possesses Arg-174, which is consistent with the hypothesis that, the transfersase is similar to LT not DT and that as in LT, the conserved Arg may play a role in maintaining active site conformation and NAD binding.

Based on site-directed mutagenesis (10) and amino acid sequence alignment, the region containing Glu-X-Glu present in ART1 and ART5 is postulated to be analogous to Glu-110 and Glu-112 of CT and LT. In the mouse ART2 sequences (Rt6-1 and Rt6-2), Glu-207 in region III is replaced by Gln in the rat ART2 sequences (RT6.1 and RT6.2) (65). Replacement of Gln-207 of the rat ART2 (RT6.1) enzyme, which possesses predominantly NAD glycohydrolase activity, with Glu resulted in the generation of an arginine-specific ADP-ribosyltransferase and increased auto-ADP-ribosyltransferase activity, with little effect on NAD binding or NAD glycohydrolase activity (67, 68). After introduction of a Glu-X-Glu motif, the rat ART2 protein exhibited enzymatic activity like the mouse ART2 or ART1 transfersases. Thus, the first glutamate in the Glu-X-Glu motif appears to be responsible for arginine-specific ADP-ribosylation.
The deduced amino acid sequences of human poly(ADP-ribose) polymerase (PARP) (9, 69) and perhaps ART3 appear to have regions of similarity that align with DT and ETA. Moreover, crystal structure of the chicken PARP (70) and mutagenesis of human PARP (69, 71) demonstrated that Glu-888, which is essential for ADP-ribose chain elongation, is positioned in a cleft similar to that found in the bacterial toxins. These data are consistent with the hypothesis that several of the bacterial toxin and vertebrate transferases possess a common mechanism of NAD binding and ADP-ribose transfer and that differences observed in three-dimensional structures may reflect differences in substrate proteins.

Summary and Future Directions
Eukaryotic ADP-ribsosyltransferase activity has been detected in diverse sources, including turkey erythrocytes, rabbit skeletal muscle, and mouse testis. The mammalian ART proteins appear to be expressed in a tissue-specific manner. In muscle cells and lymphocytes, GPI-anchored ART enzymes modify integrins, consistent with a role in regulation of cell-cell or cell-matrix interactions (Fig. 2). In lymphocytes, the GPI-anchored ART1 and ART2 transferases are associated with modulation of immune function, which is intriguing and an area of active investigation. A subgroup of the ADP-ribsosyltransferases (including ART5 and the heterophil enzymes) lack a signal sequence and have been found in chicken heterophil granules, these proteins may be secreted (Fig. 2).

An intracellular ADP-ribosylation cycle in eukaryotic cells had been proposed (72) based on the presence of NAD:arginine ADP-ribosyltransferases and ADP-ribosylarginine hydrolases, which remove ADP-ribose, regenerating free arginine (protein) (Fig. 2). Proteins modified by GPI-anchored transferases are processed by extracellular phosphodiesterases and phosphatases (Fig. 2). Thus, three of the four families of transferases may exist, GPI-anchored, secreted, and intracellular.

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