

Role of mono-ADP-ribosylation histone modification (Review)

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Abstract. The current knowledge regarding ADP-ribosylation modifications of histones, particularly mono-ADP-ribosylation modifications, is limited. However, recent studies have identified an increasing number of mono-ADP-ribosyltransferases and the role of mono-ADP-ribosylation has become a hot research topic. In particular, histones that are substrates of several mono-ADP-ribosyltransferases and mono-ADP-ribosylated histones were indicated to be involved in numerous physiological or pathological processes. Compared to poly-ADP-ribosylation histone modification, the use of mono-ADP-ribosylation histone modification is restricted by the limited methods for research into its function in physiological or pathological processes. The aim of the present review was to discuss the details regarding mono-ADP-ribosylation modification of histones and the currently known functions thereof, such as cell physiological and pathological processes, including tumorigenesis.

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1. Introduction

The occurrence and development of cancer may involve genetic as well as epigenetic changes (1). The complex processes of carcinogenesis cannot be fully explained by genetic mutations alone, as they also involve epigenetic alterations. Epigenetics, including DNA methylation, RNA editing, genomic imprinting and post-translational histone modifications, is a branch of genetics that investigates changes in gene expression without alterations in the primary DNA sequence. Abnormal epigenetic processes regulate gene expression, alter gene function and promote tumorigenesis. Epigenetics is also widely reported to have an important role in the early stages of neoplastic development and cancer progression (2). While the early focus was on the DNA sequence as a critical epigenetic marker in the progression of cancer, an increasing number of subsequent studies have been focusing on the function of histone modifications in tumorigenesis (3,4). Histone modifications include acetylation, phosphorylation, methylation, ADP-ribosylation, ubiquitylation and sumoylation, among which acetylation of histones has already been confirmed to be involved in the regulation of various types of cancer. As more mono-ADP-ribosyltransferases have been identified in recent years, the functions of mono-ADP-ribosylation of histones in human disease development, including cancer, have been further elucidated.

Mono-ADP-ribosyltransferase has been indicated to transfer one ADP-ribose from the co-factor NAD⁺ to target proteins (Fig. 1), and it has been hypothesized that there are ~1,000 mono-ADP-ribosylated proteins in cells (5). Several mono-ADP-ribosylated proteins, such as NF- κ B essential modulator (6), inositol-requiring enzyme 1 α , proline extensin-like receptor kinase1 (7), histones, RhoA and human α -defensin 1 (8) have been identified to be involved in regulating immunity, inflammation and the stress response. However, there is still a lack of understanding of the functions of most of these mono-ADP-ribosylated proteins due to limitations in the methods or the tools used.

Histones, a type of basic proteins that combine with DNA in the chromosome, include five types in eukaryotes, namely

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histone (H)1, H2A, H2B, H3 and H4 (4 types of core histones). A number of studies have indicated that poly-ADP-ribosylation of histones have important roles in DNA repair, replication, transcription (9,10), cell proliferation (11) and cancer, and may be associated with histone acetylation (12), methylation (13) and phosphorylation (14). However, there is a lack of research into the function of mono-ADP-ribosylation in physiological or pathological processes. The number of mono-ADP-ribosyltransferase types that have been detected in mammals has increased and these enzymes have been indicated to catalyze mono-ADP-ribosylation of histones. Mono-ADP-ribosylation of histones has also been associated with other modifications. The functions of mono-ADP-ribosylation of histones may comprise roles in important physiological pathways, which may include the development of malignant tumors (15).

2. Enzymes of mono-ADP-ribosylation in mammals

Approximately 22 members of the ADP-ribosyltransferase (ART) superfamily have been identified and have been indicated to have diverse roles. Certain ARTs modify proteins with chains of poly ADP-ribose or with mono ADP-ribose (mADPr) (Table I). According to the different structures of the catalytic domains, ARTs are divided into bacterial diphtheria toxin-like ARTs (ARTDs) (16) and clostridial C2 and C3 toxin-like ARTs (ARTCs) (17). ARTDs, which were previously termed the poly(ADP-ribose) polymerase (PARP) family and include 17 members (18,19), are widely distributed in cells and are mostly concentrated in the nucleus. Compared with ARTD1-6 possessing, ARTD7-17 (except ARTD13, which is catalytically inactive) only catalyzes mono-ADP-ribosylation (16,20), due to the absence of conserved glutamate. In addition, ARTD3 has been detected as a mono-ADP-ribosyltransferase in previous studies (21). ARTCs, as ectocellular ARTs, transfer mADPr from NAD⁺ to target proteins in the cytoplasm, cytomembrane and extracellular regions (22,23). Therefore, ARTCs are not able to mediate mono-ADP-ribosylation of histones, which are distributed in the nucleus. Apart from the aforementioned, members of the sirtuin (SIRT) family (SIRT1-7 always act as histone deacetylases) possess mono-ADP-ribosylation properties. SIRT4, as well as SIRT6 and -7, were indicated to have endogenous mono-ADP-ribosyltransferase activity in the mitochondria and the nucleus, respectively (24-27). However, only a small number of these mono-ADP-ribosyltransferases, such as ARTD3, -10, and -14 and SIRT4 and -6, have been reported to mono-ADP-ribosylate histones in vertebrates to date (28-32).

3. Histones are substrates of mono-ADP-ribosylation

All core histones and the linker histone H1 have been reported to undergo mono-ADP-ribosylated modification (Table II) (33). Histone H1 was indicated to be mono-ADP-ribosylated on glutamic acid E2, E14 and E116 (34), the arginine residue R34 (35) and at the COOH-terminal lysine residue K213 (36). In the rat liver, histone H2B was indicated to be mono-ADP-ribosylated on glutamate residue 2 of the γ -COOH group (37). Both in the chromatin and in the reconstituted recombinant nucleosomes of chicken, histone H2B E2 was a

specific target of PARP3 modification with mADPr (30). In histone H2B, the residues E18 and E19 were also indicated to be the principal sites modified by the ARTs in response to DNA double-strand breaks (38). After hepatoma cells are alkylated, H1 and H2B may be mono-ADP-ribosylated at the N-terminal fragment. Mono-ADP-ribosylation also modified the Arg residues of H2A, H3 and H4 and the glutamic residues of H2A and H2B (39). Previous studies identified K13 of H2A, K30 of H2B, K27 and K37 of H3 and K16 of H4 as ADP-ribose acceptor sites in poly-ADP-ribosylation (40); however, whether these are also ADP-ribose acceptor sites in mono-ADP-ribosylation requires further research. Therefore, the specific amino acid sites of mono-ADP-ribosylated modifications on H2A and H4 have remained elusive. It has remained to be determined which enzymes mediate mono-ADP-ribosylation of histones. With ongoing research, an increasing number of studies have identified specific enzymes involved in regulating the mono-ADP-ribosylation of histones. Human H2B was reported to be modified on E2 *in vitro* by using recombinant ARTD10 (41) and DNA damage was able to induce mono-ADP-ribosylation of H2B E18 and E19 *in vivo* by specific ARTs: Protein (ADP-ribosyl) transferase (ADPRT)1a and ADPRT2 (38). In addition, a silent information regulator 2 of yeast (SIR2)-related protein from the protozoan parasite *Trypanosoma brucei* (TBSIR2RP1), was indicated to catalyze mono-ADP-ribosylation of H2A, H2B and H4 in *Trypanosoma brucei* (42).

4. Methods for detecting mono-ADP-ribosylated histones

The detection of the enzymes and specific substrates of ADP ribosylation is an important step for identifying mono-ADP-ribosylated histones. Radiolabeled or chemically modified NAD⁺ has been widely used for detecting mono-ADP-ribosylated proteins *in vitro*. In the process of ADP ribosylation, radioactive-labeled ADP ribose of NAD⁺ combines with the target proteins and SDS-PAGE autoradiography may detect these radiolabeled molecules (43). Certain studies have used self-made ADP-ribosylated antibodies, as commercially available specific antibodies are limited; however, the sensitivity of the antibodies has not been satisfactory and they are not generally applicable for wider use (44,45). Osago *et al* (46) have already investigated more efficient antibodies, which were able to even detect specific arginine mono-ADP-ribosylated peptides. Apart from the methods mentioned above, certain other chemical tools may be used to detect ADP-ribosylated proteins, even mono-ADP-ribosylated histones, such as the use of ADPr (ADP-ribose)-peptides, analogues (ADPr-synthon) and ADPr-chains (47). There are several chemical synthesis peptides carrying mADPr, which may be used to detect the affinity between ADP-ribose and substrates (48). In addition, the incorporation of benzophenone photo-cross-linkers into synthetic peptides has been demonstrated to provide a way to probe for and enrich ADP-ribose binding proteins (49,50). As the methods for ADP-ribose peptide synthesis have improved, the development of corresponding antibodies may be possible (51). Thus, the specific antibody for histone mono-ADP-ribosylation may be improved to further investigate the function of histones in different fields.

Mass spectrometry (MS) and selective reader domains have also been used for detecting mono-ADP-ribosylated

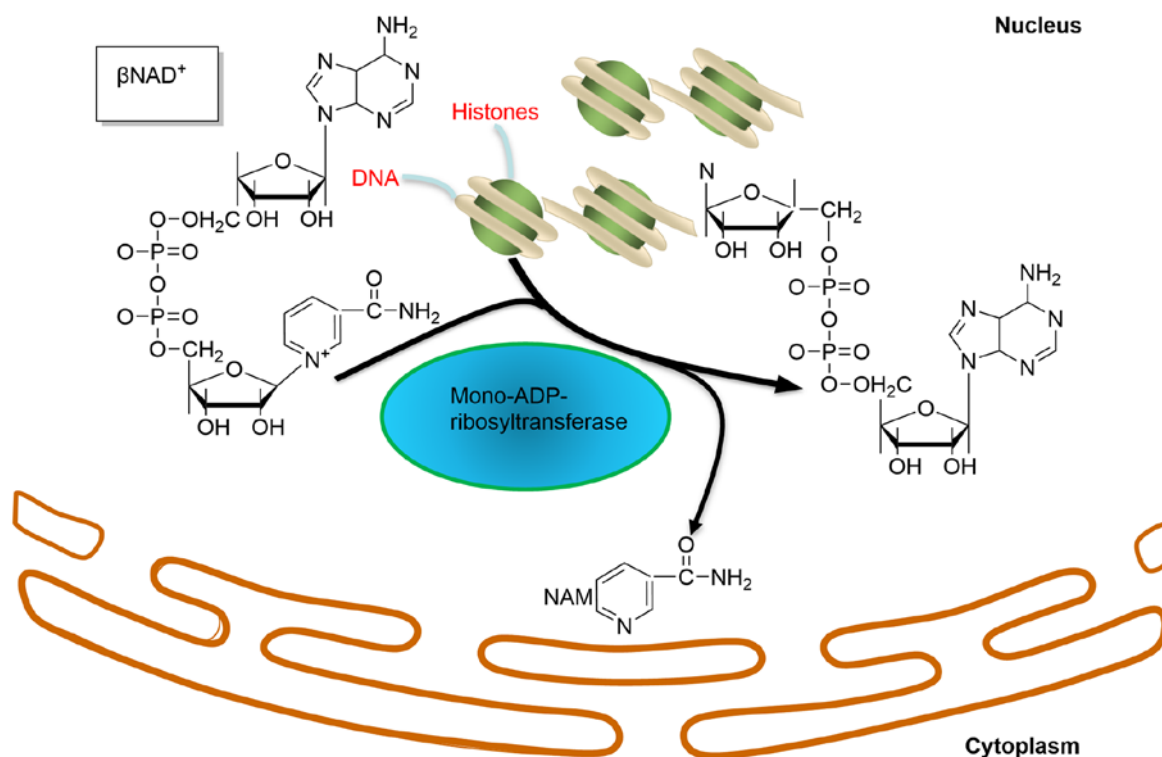


Figure 1. Schematic representation of the histone mono-ADP-ribosylation reaction.

proteins by identifying macrodomains, which may selectively bind ADP-ribose. H2A, one of a number of types of macrodomain-containing proteins, contains macro H2A, which is subdivided into macro H2A1.1, macro H2A1.2 and macro H2A2 (52,53). Only H2A1.1 has been indicated not to bind mono-ADP-ribose (54), while it has remained to be determined whether mono-ADP-ribose has connections with macro H2A1.2 and macro H2A2 (52). Therefore, MS may be an important method for identifying mono-ADP-ribosylated histones. For detecting the specific ADP-ribosylated residues, quadruple tandem MS was indicated to detect ADP-ribosyl-Arg and Arg-ADP-ribosylated peptides to identify the specific arginine site of mono-ADP-ribosylation in the target protein (55,56). In recent years, numerous MS-based proteomics have been developed, such as macrodomain-linked immunosorbent assay to identify mono-ARTs (57) and liquid chromatography-high-resolution tandem MS to identify mono-ADP-ribose acceptor sites (58,59). Furthermore, there are other methods allowing for the identification of mono-ADP-ribosylation, such as a phosphoproteomics approach via the enzymatic product of phosphodiesterase-treated ADP-ribose (60) or an aminooxy alkyne probe for detecting mono-ADP-ribosylated proteins (61). A mutagenesis approach has also been employed to detect the ADP-ribose acceptor site (5), which may be a novel way to study mono-ADP-ribosylation of histones.

5. Function of mono-ADP-ribosylated histones in DNA damage and repair

Mono-ADP-ribosylation of histones may be involved in DNA damage and repair (62) and the nucleosomal surface is the

main target (63). In the 1980s, Adamietz and Rudolph (64) reported that, when AH7974 hepatoma cells were damaged by the alkylating agent dimethyl sulfate, mono-ADP-ribosylation of histones increased by a factor of 12. Under the same conditions, the mono-ADP-ribosylated C-terminal extension of histone H1 and the N-terminal fragment of histone H2B was increased compared with that in untreated cells (65,66), which may modify DNA-histone association by adding two negative charges. TbSIR2RP1, catalyze the mono-ADP-modification of H2A and H2B, which may occur in response to DNA damage and be involved in DNA repair. Rulten *et al* (67) suggested that mono-ADP-ribosylated H1, catalyzed by PARP3, may accelerate DNA double-strand break repair by binding to aprataxin and polynucleotide kinase-like factor. Changes in the types of ADP-ribosylated histones may occur in DNA strand breaks, as in the P815 mouse mastocytoma and K562 human chronic myelogenous leukemia cell lines, mono-ADP-ribosylated histones appeared in the absence of DNA strand breaks due to the decrease of poly-ADP-ribose synthetase activity, whereas poly-ADP-ribosylated histones increased following DNA stand breaks (68).

6. Mono-ADP-ribosylation of histones in replication and transcription

ADP ribosylation of histone is also involved in DNA repair and replication. It has been indicated that histones are predominantly mono-ADP-ribosylated in lysates of non-dividing cells, while being poly-ADP-ribosylated in rapidly proliferating cells (62,69). However, evidence for the connection between mono-ADP-ribosylation of histones and replication is limited. Mono-ADP-ribosylated histones present in the nuclei under

Table I. Enzymes of ADP-ribosylation.

A, ARTDs			
Enzymes	Subcellular localization	Enzymatic activities	(Refs.)
ARTD1	Nucleus	Poly-ADP-ribosyltransferase	(16-19)
ARTD2	Nucleus	Poly-ADP-ribosyltransferase	(16-19)
ARTD3	Nucleus	Mono/Poly-ADP-ribosyltransferase	(22,31)
ARTD4	Nucleus/cytoplasm	Poly-ADP-ribosyltransferase	(16-19)
ARTD5	Nucleus/cytoplasm	Poly-ADP-ribosyltransferase	(16-19)
ARTD6	Nucleus/cytoplasm	Poly-ADP-ribosyltransferase	(16-19)
ARTD7	Nucleus	Mono/Poly-ADP-ribosyltransferase	(20,21)
ARTD8	Nucleus/cytoplasm	Mono/Poly-ADP-ribosyltransferase	(20,21)
ARTD9	Nucleus/cytoplasm	Mono/Poly-ADP-ribosyltransferase	(19)
ARTD10	Nucleus/cytoplasm	Mono/Poly-ADP-ribosyltransferase	(20,21,30,42)
ARTD11	-	Mono/Poly-ADP-ribosyltransferase	(20,21)
ARTD12	Nucleus	Mono/Poly-ADP-ribosyltransferase	(19-21)
ARTD13	Nucleus	Catalytically inactive	(20)
ARTD14	Nucleus	Mono/Poly-ADP-ribosyltransferase	(19,29)
ARTD15	Nucleus/cytoplasm	Mono/Poly-ADP-ribosyltransferase	(20,21)
ARTD16	-	Mono/Poly-ADP-ribosyltransferase	(20,21)
ARTD17	-	Mono/Poly-ADP-ribosyltransferase	(20,21)
B, ARTCs			
Enzymes	Subcellular localization	Enzymatic activities	(Refs.)
ARTC1-5	Ecto-cellular	-	(23,24)
C, special ARTs			
Enzymes	Subcellular localization	Enzymatic activities	(Refs.)
ADPRT1a	-	Mono-ADP-ribosyltransferase	(38)
ADPRT2	-	Mono-ADP-ribosyltransferase	(38)
D, Sirtuins			
Enzymes	Subcellular localization	Enzymatic activities	(Refs.)
SIRT1	Nucleus	-	(27,28)
SIRT2	Nucleus/Cytoplasm	-	(27,28)
SIRT3	Mitochondria	-	(27,28)
SIRT4	Mitochondria	Mono-ADP-ribosyltransferase	(25,32)
SIRT5	Mitochondria	-	(27)
SIRT6	Nucleus	Mono-ADP-ribosyltransferase	(26,33)
SIRT7	Nucleus (nucleoli)	Mono-ADP-ribosyltransferase	(25)
ARTDs, bacterial diphtheria toxin-like ADP-ribosyltransferases; ARTCs, clostridial C2 and C3 toxin-like ARTs.			

physiological conditions are considered to function in supporting the conversion of the chromatin loop into its transcriptional active structure (70). ARTD14, as a mono-ADP-ribosyltransferase of histones, was indicated to interact with aryl hydrocarbon receptor (AHR) leading to decreased AHR transcriptional activity (28).

7. Mono-ADP-ribosylation of histones in cell proliferation and differentiation

Mono-ADP-ribosylation of histones may promote or inhibit cell proliferation. It has been indicated that the

Table II. Mono-ADP- ribosylation of histones.

A, H1 substrate			
Modified amino acid	Enzymes	Effect of the reaction	(Refs.)
E2, E14E116 and K213	-	Regulation of H1-H1 interactions	(35,37)
R34	-	Blocks the cAMP-dependent phosphorylation of histone H1	(36)
Q/N	ARTD3	DNA repair	(22,63)
B, H2A substrate			
Modified amino acid	Enzymes	Effect of the reaction	(Refs.)
Unknown	Sir2	Response to oxidative stress/DNA damage	(43)
Unknown	Sir2	Inhibition of histone acetylation/silencing chromatin domains	(43,68)
R/E	-	Unknown	(40)
C, H2B substrate			
Modified amino acid	Enzymes	Effect of the reaction	(Refs.)
E2	ARTD3/ARTD10	Unknown	(31,38,42)
E18/E19	ARTs, Adprt1a/Adprt2	Response to oxidative stress/DNA damage	(38,39)
Unknown	Sir2	Inhibition of histone acetylation/silencing of chromatin domains	(43,68)
D, H3 substrate			
Modified amino acid	Enzymes	Effect of the reaction	(Refs.)
Unknown	SIRT6, Sir2	Inhibition histone acetylation/silencing chromatin domains	(33,43)
R	-	Cell proliferation	(11,40)
E, H4 substrate			
Modified amino acid	Enzymes	Effect of the reaction	(Refs.)
R	Sir2	Post-synthetic modification with acetylation of core histones	(27,28,40)
Unknown	Sir2	Response to oxidative stress/DNA damage	(43)
Unknown	ARTD10	Unknown	(42,66)
Unknown	Sir2-relatedprotein	Inhibition histone acetylation	(43)

mono-ADP-ribosylation of histone 3 at R117 may accelerate the proliferation of colon carcinoma cells by regulating P300 to increase the expression level of cyclin D1 and c-myc (11). By contrast, other studies have indicated that after P815 mouse mastocytoma and K562 human chronic myelogenous leukemia cell lines were treated with 5 mM butyrate or with serum-free media for blocking cell proliferation, the level of mono-ADP-ribosylated histones was higher compared with that in rapidly dividing cells. Of note, there were also no poly-ADP-ribosylated histones in the treated cells, while

an increase in poly-ADP-ribosylated histones was observed in the rapidly dividing cells (69). The cycle of the conversion of poly-ADP-ribosylated histones to mono-ADP-ribosylated histones may be an important regulatory factor in cell proliferation. In addition, a study by our group indicated that arginine 117 of histone H3 in LoVo colon carcinoma cells with low differentiation were modified by mono-ADP-ribosylation, while SW480 cells with high differentiation were not (71), which suggested that mono-ADP-ribosylated histones may vary across different colorectal cancer cell lines with different degrees of malignancy,

confirming the hypothesis that histone mono-ADP-ribosylation may have an important role in the development of tumors.

8. Association between mono-ADP-ribosylation of histones and other histone modifications

A wide range of histone modifications has been identified, which regulate signaling pathways in cell physiology and pathology. These modifications do not exist independently and there are connections among them. H4 is more likely to be mono-ADP-ribosylated while it is hyper-acetylated (40,72). Mono-ADP-ribosylation of H4 by ARTD10 may occur when K5, K8 and/or K16 are modified by acetylation; however, these interrelations were indicated to be relatively weak. In addition, mono-ADP-ribosylation of H3 R117 affected the transcription and expression level of demethylase ten-eleven translocation 1, thus regulating the methylation of tissue factor pathway inhibitor 2 in colorectal cancer (73). Furthermore, the decrease of mono-ADP-ribosylation of histones in colorectal carcinoma cells resulted in an increase of histone H3 trimethylated at lysine 4 and phosphatase and tensin homolog, thus reducing the phosphorylation of the PI3K/Akt signaling pathway. Mono-ADP-ribosylation of JHDM1A/KDM2A by SIRT6 led to an increase of histone H3 lysine 36 dimethylation levels to promote DNA repair (32). Methylation or acetylation of K20 in H4 may inhibit mono-ADP-ribosylation (29). When Arg34 of histone H1 is modified by mono-ADP-ribosylation, cyclic (c)AMP-dependent phosphorylation of histone H1 on Ser 38 may be inhibited (35). Arginine, which is located in the NH₂-terminal of the phosphate-accepting serine residue, was indicated to be important for phosphorylation by cAMP-dependent protein kinase. Hence, the change in the function of the arginine residue by mono-ADP-ribosylation may affect the phosphorylation of histones. In yeast, histone acetylation may be inhibited by mono-ADP-ribosylation of histones, which is catalyzed by SIR2 and may be responsible for inhibiting growth or silencing genes (74). It was also reported that reducing the ability of the mono-ADP-ribosyltransferase of SIR2 with a G270A mutation may not control gene silencing and it was hypothesized that histone acetylation may serve a bigger role rather than just in histone mono-ADP-ribosylation (75). Therefore, the efficiency of mono-ADP-ribosylation of histones by SIR2 requires further investigation.

9. Hydrolytic enzymes of histone mono-ADP-ribosylation

Mono-ADP-ribosylation is a reversible reaction, which may be hydrolyzed by Arg-specific mono-ADP-hydrolase, macroD1, macroD2, C6ORF130/TARG1 (76-78) and by serine mono ADP-ribosylhydrolase-3 (79). The content of macrodomain proteins primarily originates from viruses, such as α -virus, hepatitis E virus, severe acute respiratory syndrome coronavirus (SARS-CoV), feline infectious peritonitis virus and hCoV-229E macrodomains (80-82).

In a recent study, SARS-CoV-2 was reported to be able to remove mono-ADP-ribose (MAR) from a protein substrate (83). Whether the functions of histone modification were regulated by these hydrolytic enzymes requires further investigation. As the specific amino acid residues hydrolyzed by these hydrolases are different, the acceptor sites of histone

mono-ADP-ribosylation may be confirmed by the type of hydrolases able to hydrolyze the mono-ADP-ribosylation.

10. Conclusion

Mono-ADP-ribosylation has become a focus in the fields of immunity, inflammation, stress response, DNA damage response and cancer (5,84,85). Different target proteins and even different amino acid residues may determine the functions of mono-ADP-ribosylation. However, the number of identified target proteins of mono-ADP-ribosylation remains low at present, owing to the limited and simplistic methods, not to mention the exact number and location of the acceptor sites.

Histones are major target proteins; however, knowledge regarding their function in pathophysiological processes is currently limited. Histone modifications, similar to acetylation, methylation and phosphorylation, have already been reported to participate in multiple processes, particularly in tumorigenesis. Studies have indicated that mono-ADP-ribosylation of histones is able to regulate the DNA damage response, transcription and cell proliferation, which are also important factors in tumorigenesis. The connections between histone mono-ADP-ribosylation and other well-known histone modifications indicate that the combined effects of these modifications may regulate pathophysiological processes.

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Availability of data and materials

The datasets used/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JJZ and YT performed the literature search for relevant publications on the topic. YLW participated in drafting the manuscript and provided critical insight. JJZ and YT confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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