[Frontiers in Bioscience, Landmark, 20, 431-439, January 1, 2015]

Past and current topics on ADP-ribosylation reactions

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1. ABSTRACT

The milestone of Adenosine Diphosphate-ribosylation studies was the paper by Paul Mandel's group in 1960s, first describing a "sort" of polyadenylic acid synthesized upon addition of nicotinamide mononucleotide in rat liver nuclear extracts. Nicotinic Acid or Niacin is the precursor of Nicotinamide Adenin Dinucleotide. In 1960s this compound was known mainly as coenzyme of most redox processes in metabolism. The discovery of enzymes that covalently transfer Adenosine Diphosphate-ribose moiety of Nicotinamide Adenin Dinucleotide to acceptor proteins, thereby altering their function, or are able to synthesize cyclic Adenosine Diphosphate-ribose, has given rise to the era of one of the most studied and still surprising reversible post – translational modification reactions. Over 50 years, developing the research on Adenosine Diphosphate-ribosylation has provided the basis to interconnect several processes thought to be very distant each other, opening new perspectives in their regulation and in therapeutic intervention. Here a synthesis of the history and the main and recent goals reached studying Adenosine Diphosphate-ribose in all its features are provided by a series of reviews including the most advanced research.

2. INTRODUCTION

The discovery of poly(ADP-ribose) by Paul Mandel group in 1960s, gave rise to the era of an important and widespread reversible post – translational modification reaction catalyzed by enzymes using Nicotinamide Adenine Dinucleotide (NAD^+) as a substrate (1). From 1960s this niacin - derived compound became the first and main character of this story and its prevalent role of coenzyme in most redox processes in metabolism was associated with an emerging function as donor of the Adenosine Diphosphate-ribose (ADP-ribose) moiety in fundamental enzymatic reactions (2-13).

Enzymes were discovered able to covalently transfer mono- or poly-ADP-ribose to acceptor proteins, thereby altering their function (2-8), or to synthesize cyclic ADP-ribose (10). They seemed to interest numerous and different biological fields and very often they were studied separately as multiple independent facets of the same reaction (13-17).

Between 1990s and the beginning of 2000s the number of collected information was enormous in all branches of ADP-ribosylation, but still the link between them was unknown or at least uncertain (16-21).

In the last 15 years the development of the research on ADP-ribosylation and its exponential amplification have provided the basis to interconnect several processes thought to be very distant each other (18-24). The most recent research has given sense to a wide and often unexplainable involvement of ADP-ribosylation reactions and has opened new

perspectives in their regulation and in therapeutic intervention (25-39).

3. HISTORY AND DEVELOPMENT OF ADP-RIBOSYLATION REACTIONS: FROM THE EARLIEST STUDIES TO THE RECENT RESEARCH TARGETS

The initial classification of two enzyme families (mono-ADP-ribose transferases, mARTs, and poly-ADP-ribose polymerases, PARPs (7, 8, 14)) is now considered extremely simple as compared to the numerous proteins synthesizing ADP-ribose from NAD^+ and differently involved in either one or the other group (26). The reviews in this Special Issue, discussed below, provide an accurate evidence of the progress in this research field.

ADP-ribosylation reactions are phylogenetically ancient (40-44). At present they can be classified into four major groups: mono-ADP-ribosylation, poly-ADP-ribosylation, synthesis of cyclic ADP-ribose, and of *O*-acetyl-ADP-ribose (8, 10, 18, 26, 38). In these groups structurally similar enzymes have been demonstrated to differ in their ability to synthesize mono- rather than poly(ADPribose) (26, 45).

3.1. Mono-ADP-ribosylation reactions

Mono-ADP-ribosylation is defined a post-translational modification that consists of the enzymatic transfer of ADP-ribose moiety from NAD^+ to acceptor proteins. In viruses and prokaryotes, mono-ADP-ribosylation is mainly, but not exclusively, a mechanism used to take control of the host cell (7, 8, 45, 47). A non-conventional mono-ADP-ribosylation reaction is described in the review by Grimaldi *et al.*, that is mediated by the fungal toxin brefeldin A (BFA) (45). This modification results in the loss of the membrane fission activity of the C-terminal binding protein (CtBP)1/BFA-ADP-ribosylated substrate (BARS), thus blocking progression of cells into mitosis, with important implications for the design of new anticancer drugs (45).

A wide survey of mono-ADPribosylation is in the review by Fabrizio *et al.* (47). They summarize all the results in the field up to the most advanced findings (7, 8, 23, 33, 35, 47). They underline that in mammals many protein functions are regulated by mono-ADP-ribosylation catalysed by two families of toxin-related cellular ADP-ribosyltransferases: ecto-enzymes that modify various cell-surface proteins, like integrins and receptors, and intracellular enzymes that act on a variety of nuclear and cytosolic proteins (47). These two families have been recently renamed the ARTCs (clostridia toxin like) and ARTDs (diphtheria toxin like), depending on their conserved structural features, and in terms of their relationships to the bacterial toxins (19, 46, 47). As widely discussed in this review it has been demonstrated that mono-ADP-ribosylation by the ARTC and ARTD enzymes is involved in many pathophysiological conditions, like inflammation, cancers and neurodegeneration, and so drug discovery has been approached by developing and characterising inhibitors that are specific for these individual ARTCs, ARTDs (47).

It is worth nothing that within the two groups of ARTs, enzymes structurally identified as PARPs but exhibiting mono-ADP-ribosylating activity are enclosed (45, 46). Grimaldi *et al.* in their review highlight that the PARP family thus appears not to be homogenous regarding its catalytic activity, and can be divided into three major sub-groups: (i) the classical PARPs (PARP-1 to PARP-5); (ii) the inactive PARPs (PARP-9, PARP-13); and (iii) enzymes that function as mARTs (45).

Mono-ADP-ribose in an acetylated form (*O*-acetyl-ADP-ribose) is produced by sirtuins (SIRTs) a rather recently discovered family of deacetylases (38, 47, 48, 49, 50). In the context of all NAD^+-dependent reactions leading to ADP-ribose synthesis, sirtuins play a central role as cellular NAD^+ consumers and cross-talkers in signaling pathways. SIRTs often function as beneficial mediators of calorie restriction in health- and life-span (48-50). In the review by Faraone Mennella the interplay between SIRTs and PARPs is summarized. It is described as an example of a link between two ADP-ribosylation reactions previously thought to be independent regulatory mechanisms (48).

Since ARTCs, ARTDs and sirtuins are involved in the same pathophysiological conditions, cited above, drug discovery represent the new approach leading to novel compounds that should provide new insights into the mechanisms of crucial cellular functions, which include nucleo-cytoplasmic trafficking, UPR signalling and the regulation of cell survival and cell death (47-50).

The cyclic form of ADP-ribose (cADPr) is generated by ADP-ribosyl cyclases from NAD^+ (10. 44, 51). cADPr regulates cytosolic (Ca^{2+}) increase (51). The mammalian ADP-ribosyl cyclases

(CD38 and CD157), are ecto-enzymes which exhibit their catalytic activity at the cell surface, but there is also evidence for the existence of alternative intracellular enzymatic activities (52). Well-characterized ARCs were identified in invertebrate and vertebrate animals, whose common gene structure allows to trace their origin to the ancestor of bilaterian animals (44). In this paper Ferrero *et al.* used a phylogenetic approach to review the current state of the ARCs, to better understand the evolution of function in this family (44). Similarly to ARTs, this family of structurally-related enzymes shows disparate functions in different animal models. The ARCs are versatile enzymes that can manipulate NAD^+, NAD^+ phosphate (NADP) and other substrates to generate various bioactive molecules including nicotinic acid adenine dinucleotide diphosphate (NAADP) and ADP-ribose (ADPR) (44).

3.2. Poly-ADP-ribosylation reactions

Compared to mono-ADP-ribosylation, the synthesis of Poly-ADP-ribose (PAR) is a rather elaborate protein modification and is catalysed by PARPs (26, 37). The turnover of PAR is tightly regulated. This modification can be removed by the hydrolytic action of poly(ADP-ribose) glycohydrolase (PARG) and ADP-ribosylhydrolase 3 (ARH3) (2, 9, 12, 16, 24).

PARP is the acronym of poly(ADP-ribose) polymerase, used in an old nomenclature, now replaced by ARTD, according to the mART activity of several PARPs (37, 45, 47).

The number and the diversity of the PARP superfamily members is very large and has been discovered from the first identification of PARP2 (53). Many different genes coding for PARPs contribute to promote cellular recovery from genotoxic stress, eliminating extensive damaged cells from the organism, and ensuring exact inheritance of genetic information during cell division (19, 26, 37). However, the majority of the 17 human PARP genes are poorly characterized.

PARP-1, is one and the most relevant of the nuclear members of the family involved in DNA repair and apoptotic pathways (54-61).

The most known role of poly(ADP-ribose) metabolism in the maintenance of genomic integrity is centered on PARP1 and PARP2 activities (26, 36). DNA damage-induced PARylation significantly changes local chromatin structure and triggers the accumulation of several DNA damage response (DDR) proteins at the DNA lesions (62). In their review, Golia *et al.* discuss the regulation of chromatin structure and DNA damage repair machineries by DNA damage-induced poly-ADP-ribosylation (62). They highlight the role of PARylation in both recruiting a number of chromatin remodeling enzymes, which relax chromatin at the sites of DNA damage, and silencing chromatin by recruiting the NuRD complex and PRC2 (62). They underline also some contradictory results about the role of PARP1 in DNA repair: PARylation appears to mostly stimulate both HR and NHEJ in normal cells; however, there are also observations of PARylation negatively regulating HR or NHEJ (62).

Poly(ADP-ribosylation) is activated as an emergency process in crucial situations such as DNA damage and cellular stress, as discussed in the review of Aredia and Scovassi (63). These authors detail the properties of poly(ADP-ribose) as a signalling molecule in different paradigms of cell death, *i.e.* apoptosis, parthanatos, necroptosis and autophagy (63). In some types of cell death that are characterized by an active synthesis of PAR, the accumulation of the polymer represents a death signal able to activate a cascade of events converging to caspase-independent cell death pathways, including parthanatos and necroptosis (63). They conclude that the detection of PAR within the cells could be a marker not only of persistent DNA damage but also of prolonged stress conditions and a prerequisite for cell death induction (63).

As animal PARPs, also plant enzymes are associated with DNA repair transcriptional regulation and cell death (64). In addition, plant PARPs are implicated in response to abiotic and biotic stresses, in stress tolerance and in developmental processes too, as summarized by Bianchi and De Maio (64). Moreover the well demonstrated involvement of PARPs, PARGs and SRO (Similar to RCD-One) family in abiotic and biotic stress responses induces to hypothesize that the modulation by poly-ADP-ribosylation might represent a useful way to allow survival of economically valuable plant species in harsh or unpredictable enviromental conditions.

Recent screening analyses of the PARP family members identified further physiological roles for these enzymes, which include regulation of cell viability (PARP-5, PARP-8, PARP-13, PARP-14),

membrane structure (PARP-8, PARP-16) and the actin cytoskeleton (PARP-9, PARP-14), even though the molecular basis of these processes are still not known. Nevertheless, new information on these mARTs is continuously emerging as a consequence of the growing interest in this field (45). Within the wide spectrum of biological activities, the involvement of several PARPs that have mART activity in innate immune responses has attracted interest in the field of virology (45). For some of these, a clear role in inhibition of viral infection has been proposed (i.e., PARP-7, PARP-10, PARP-12, PARP-13), which mainly relies on two mechanisms: the shut-off of the viral replication achieved by viral mRNA degradation (PARP-13); and the block of host protein translation (i.e., PARP-7, PARP-10, PARP-12) (45). The latter aspect is of dual importance: while it can help towards a better understanding of viral infection mechanisms and viral clearance, at the same time, this uncovers a new cellular function of these mARTs; i.e., the control of protein translation under physiological and pathological conditions (45).

However, limiting the studies to the enzymes of PARylation cannot fulfill the whole knowledge to understand this reaction. An interesting topic is discussed by Rosenthal and Hottiger (65). They highlight that in order to define the functional role of cellular ADP-ribosylation and the functional contribution of distinct ARTD family members, it is necessary to identify all ADP-ribosylated proteins, that they call “ADP-ribosylome”, as well as their modified residues in the context of different cellular conditions and stresses. They summarize the most recent progress in defining the cellular ADP-ribosylome and the efforts to detect ADP-ribose acceptor sites by enzymatic reactions and mass-spectrometry (65). The results from such studies help to predict the cellular contribution and function of all ARTD members, and therefore constitute the foundation for their detailed and comprehensive analysis *in vivo* (65).

Lastly, but not for importance, a fine regulatory role has to be attributed to the enzymes mainly responsible of reverting the reaction, PARG and ARH3 (65, 66, 67). In their review Rosenthal and Hottiger report also about a newly discovered enzyme family, pyrophosphohydrolases (nudix), able to hydrolyze ADP-ribose. In contrast to PARG and ARH3, the nudix enzymes do not remove protein bound ADP-ribose or PAR, but hydrolyze the pyrophosphate bond within ADP-ribose, generating AMP and ribose 5-phosphate. The nudix superfamily is conserved in all kingdoms of life and is defined by its characteristic 23 amino acid nudix box motif $Gx_5Ex_5(UA)xREx_2EExGU$, where U is a hydrophobic amino acid (65).

The discovery of PARG as a specific PAR-catabolizing enzyme dates back to more than 40 years ago (66, 68, 69). Since then, several aspects of PARG structure, substrate specificity, mode of action *in vitro* and subcellular localization have been clarified (70). However, historically, research has focused mainly on poly(ADP-ribose) synthesis pathways, with a scarce or less defined knowledge about PAR degradation. Recently, understanding of the latter has improved. A review by Timinsky’s group summarizes current knowledge about the protein modules recognizing poly(ADP-ribose) and discusses the newest developments on the complete reversibility of poly(ADP-ribosyl)ation (71).

Distribution of PARGs strictly follows the distribution of PARP proteins in eukaryotic species (72). At least one of the macrodomain proteins that hydrolyse terminal ADP-ribose is also always present (72). Therefore, it was presumed that the last common ancestor of all eukaryotes possessed a fully functional and reversible PAR metabolism and that PAR signalling provided the conditions essential for survival of the ancestral eukaryote in its ancient environment. PARP proteins are far less prevalent in bacteria and were probably gained through horizontal gene transfer (72). Only eleven bacterial species possess all proteins essential for a functional PAR metabolism, although it is not known whether PAR metabolism is truly functional in bacteria. Several dsDNA viruses also possess PARP homologues (73).

4. CONCLUSIONS

Nicotinamide Adenine Dinucleotide (NAD^+) is known mainly as coenzyme of redox reactions for energy transduction and is consumed as substrate in regulatory reactions removing nicotinamide and producing ADP-ribose (26, 46). Several families of ADP-ribose synthesizing enzymes use NAD^+ as substrate and control processes like DNA repair, replication and transcription, chromatin structure and others (44-48). Since NAD^+-dependent reactions involve degradation of the dinucleotide, a constant supply of the pyridinic substrate is required for its homeostasis (18, 48).

Here, the most recent findings on ADP-ribosylation reactions and their roles have been discussed in parallel with the pioneering research started on 1963 with the discovery of ADP-ribose by Paul Mandel and colleagues (1, 26, 44-48, 62-65).

It is clear that this field is going expanding towards new findings and trying to explain the different emerging functions in which the ADPribosylating enzymes play roles, including immune responses, transcriptional regulation, stress responses, cell survival (44-47, 62-65). Moreover due to the complexity of reactions, involving different kinds of products (MAR, linear and /or branched PAR, cADPR, O-acetyl ADPribose) and a lot of targets of modification, "more large-scale systematic studies and new approaches are needed to build a comprehensive database of all ADP-ribose modifications" (45, 47, 62, 65).

As stated by some authors of the reviews in this Special Issue, "increasing knowledge of mono-ADP-ribosylated substrates, as well as the identification of the pathways regulated by the PARPs, …" will help to solve "…. many questions related to this post-translational modification" (45, 47, 65).

5. ACKNOWLEDGEMENTS

I wish to thank the authors who contributed to this Special Issue providing high quality reviews.

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Key Words: ART, PARP, PARG, ARH3, ADP-ribosylation, Review

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