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Review

Reprogramming cellular events by poly(ADP-ribose)-binding proteins

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ABSTRACT

Poly(ADP-ribosyl)ation is a posttranslational modification catalyzed by the poly(ADP-ribose) polymerases (PARPs). These enzymes covalently modify glutamic, aspartic and lysine amino acid side chains of acceptor proteins by the sequential addition of ADP-ribose (ADPr) units. The poly(ADP-ribose) (pADPr) polymers formed alter the physico-chemical characteristics of the substrate with functional consequences on its biological activities. Recently, non-covalent binding to pADPr has emerged as a key mechanism to modulate and coordinate several intracellular pathways including the DNA damage response, protein stability and cell death. In this review, we describe the basis of non-covalent binding to pADPr that has led to the emerging concept of pADPr-responsive signaling pathways. This review emphasizes the structural elements and the modular strategies developed by pADPr-binding proteins to exert a fine-tuned control of a variety of pathways. Poly(ADP-ribosyl)ation reactions are highly regulated processes, both spatially and temporally, for which at least four specialized pADPr-binding modules accommodate different pADPr structures and reprogram protein functions. In this review, we highlight the role of well-characterized and newly discovered pADPr-binding modules in a diverse set of physiological functions.

Contents

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1. Introduction

It was almost 50 years ago that poly(ADP-ribose) (pADPr) was discovered as an adenine-containing RNA-like polymer (Chambon et al., 1963) and early on, there were indications that pADPr turnover is very tightly regulated in mammalian cells (Nishizuka et al., 1967; Reeder et al., 1967; Ueda et al., 1972). Cellular levels of pADPr are governed by the finely tuned balance of the synthetic poly(ADP-ribose) polymerases (PARPs) and degrading poly(ADP-ribose) glycohydrolase (PARG) enzyme activities. In the human genome, 17 proteins share a PARP signature sequence homologous to the catalytic domain of the founding and most described member PARP1. In the context of DNA damage, PARP1 generates within minutes approximately 90% of all pADPr, preferentially on itself (automodification). However, pADPr accumulation is transient, as it is rapidly degraded by PARG (Davidovic et al., 2001). Notably, the polymerase activity has been demonstrated for only six of the PARP family members (PARP1, PARP2, PARP3, PARP4/vPARP, Tankyrases 1 and 2). Based on experimental and structural examinations, it has been proposed that the other PARP family members are either inactive (PARP9/BAL and PARP13/ZAP) or carry a mono-ADP-ribosyl transferase activity (PARP6, TiPARP, PARP8, PARP10, PARP11, PARP12, PARP14/BAL2, PARP15/BAL3, PARP16) (Goenka et al., 2007; Hottiger et al., 2010; Kleine et al., 2008). Their functions are only starting to emerge, but suggest an important role for these poorly studied proteins.

1.1. Poly(ADP-ribosyl)ation

The seminal work by Benjamin and Gill (1980a,b) showed that PARP1 activity is highly stimulated by the presence of DNA containing single- and double-strand breaks, a discovery that has been followed up by a succession of studies that linked pADPr metabolism to maintenance of genome stability (Meyer-Ficca et al., 2005). Mono- and poly-(ADP-ribosyl)ation are reversible and phylogenetically ancient posttranslational protein modifications, for which the list of acceptor/target proteins is still expanding. Poly(ADP-ribosyl)ation can be achieved covalently or non-covalently (Fig. 1A). The covalent posttranslational modification (PTM) occurs on glutamic, aspartic or lysine residues, while non-covalent interactions between proteins and pADPr add another level for modulating proteins biological activity. This PTM has profound physico-chemical implications, as poly(ADP-ribose) bears two negatively charged phosphate groups per ADP-ribose (ADPr) residue, i.e. twice as many charges than DNA or RNA (Fig. 1A). The size and flexibility of pADPr polymers render them capable of mediating multiple contacts with protein surfaces, thus providing a significant enhancement in binding efficiency. Such physico-chemical attributes of the pADPr are capable of contributing to the creation of a scaffold for the assembly of multiprotein complexes. Accumulating evidence indicates that pADPr actually conveys a broad spectrum of cellular signals through direct binding of a variety of protein motifs to pADPr, such as the DNA damage response, replication, chromatin structure, transcription, telomere homeostasis and cell death (Krishnakumar and Kraus, 2010).

Given the structural complexity of the pADPr polymers, it is not surprising to observe that several evolutionary conserved protein domains have emerged to accomplish unique functions through interactions with pADPr. Indeed, the average chain length of pADPr synthesized by the PARP family members can range from very short and linear oligomers to extended molecules of up to 200 units and branched at every 20–50 residues (Fig. 1B) (Alvarez-Gonzalez and Jacobson, 1987; D'Amours et al., 1999; Kiehlbauch et al., 1993; Kleine et al., 2008; Tanaka et al., 1977). There are very limited investigations conducted on the physico-chemical properties of pADPr, such as flexibility and conformation, but the formation of helical pADPr structures was postulated upon protein binding (Minaga and Kun, 1983a,b; Schultheisz et al., 2009).

1.2. The emergence of non-covalent pADPr recognition motifs

The first experimental lines of evidence for proteins that bind pADPr in a non-covalent, yet specific, manner were given in the late 1960s and early 1970s when it was shown that histones possess high affinity for pADPr (Honjo et al., 1968; Nakaz-