REVIEW

PARPs and ADP-ribosylation: recent advances linking molecular functions to biological outcomes

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The discovery of poly(ADP-ribose) >50 years ago opened a new field, leading the way for the discovery of the poly(ADP-ribose) polymerase (PARP) family of enzymes and the ADP-ribosylation reactions that they catalyze. Although the field was initially focused primarily on the biochemistry and molecular biology of PARP-1 in DNA damage detection and repair, the mechanistic and functional understanding of the role of PARPs in different biological processes has grown considerably of late. This has been accompanied by a shift of focus from enzymology to a search for substrates as well as the first attempts to determine the functional consequences of site-specific ADP-ribosylation on those substrates. Supporting these advances is a host of methodological approaches from chemical biology, proteomics, genomics, cell biology, and genetics that have propelled new discoveries in the field. New findings on the diverse roles of PARPs in chromatin regulation, transcription, RNA biology, and DNA repair have been complemented by recent advances that link ADP-ribosylation to stress responses, metabolism, viral infections, and cancer. These studies have begun to reveal the promising ways in which PARPs may be targeted therapeutically for the treatment of disease. In this review, we discuss these topics and relate them to the future directions of the field.

ADP-ribosylation is a reversible post-translational modification (PTM) of proteins resulting in the covalent attachment of a single ADP-ribose unit [i.e., mono(ADP-ribose) (MAR)] or polymers of ADP-ribose units [i.e., poly(ADP-ribose) (PAR)] on a variety of amino acid residues on target proteins (Gibson and Kraus 2012; Daniels et al. 2015a). This modification is mediated by a diverse group of ADP-ribosyl transferase (ADPRT) enzymes that use ADP-ribose units derived from β-NAD^+ to catalyze the ADP-ribosylation reaction. These enzymes include bacterial ADPRTs (e.g., cholera toxin and diphtheria toxin) as well as members of three different protein families in yeast and animals: (1) arginine-specific ecto-enzymes (ARTCs), (2) sirtuins, and (3) PAR polymerases (PARPs) (Hottiger et al. 2010). Surprisingly, a recent study showed that the bacterial toxin DarTG can ADP-ribosylate DNA (Jankevicius et al. 2016). How this fits into the broader picture of cellular ADP-ribosylation has yet to be determined.

In this review, we focus on the mono(ADP-ribosyl)ation (MARylation) and poly(ADP-ribosyl)ation (PARylation) of glutamate, aspartate, and lysine residues by PARP family members. While many reviews have been written on PARPs in the past decade, we highlight the current trends and ideas in the field, in particular those discoveries that have been published in the past 2–3 years.

PARPs and friends: writers, readers, erasers, and feeders

PARPs interact physically and functionally with a set of accessory proteins that play key roles in determining the overall outcomes in PARP-dependent pathways. By borrowing from and adding to descriptions used by the histone modification field (Hottiger 2015), PARPs can be thought of as "writers" of ADP-ribose, and the accessory proteins can be thought of as "readers" (ADP-ribose-binding domains [ARBDs]), "erasers" (ADP-ribose and PAR hydrolases), "feeders" (NAD^+ synthases), and "consumers" (NAD^+ hydrolases) (Fig. 1). These are elaborated on in more detail below.

The PARP family: ADP-ribose writers

The PARP family consists of 17 members that have distinct structural domains, activities, subcellular

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At the same time, a number of aspects of the biology of PARPs and related proteins remain to be explored. For example, we still know very little about the broad spectrum of biology dependent on the PARP family of proteins. In addition, our understanding of the different catalytic-dependent and catalytic-independent functions of PARPs is limited. Furthermore, while numerous examples of ADP-ribose "reader" domains exist in nature, a comprehensive understanding of the functions of the proteins that contain these domains has been elusive.

With respect to ADP-ribosylation, the factors that drive selectivity and specificity for different substrates by different PARPs have been incompletely elucidated. Additionally, determining the repertoire of targets of distinct PARPs and their sites of ADP-ribosylation in different tissues is in its infancy. Likewise, the broader spectrum of amino acids that function as acceptors of ADP-ribose is still being defined (e.g., serine and cysteine) (Leidecker et al. 2016; Westcott et al. 2017). Such information would provide new insights into the biological roles of PARP across tissues and in disease states. One of the greatest needs and most significant challenges in the field, however, is moving beyond the identification of sites of ADP-ribosylation toward the determination of the functional relevance of ADP-ribosylation at those sites, which will reveal the definitive biological consequences of ADP-ribosylation. Finally, the field has not fully explored the therapeutic potential of PARPis. In conclusion, even after five decades of research on PARPs and ADP-ribosylation, much work remains to be done.

Competing interest statement

W.L.K. is a founder and consultant for Ribon Therapeutics, Inc.

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