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Review

Poly(ADP-ribose): PARadigms and PARadoxes

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ABSTRACT

Poly(ADP-ribosyl)ation (PARylation) is a posttranslational protein modification (PTM) catalyzed by members of the poly(ADP-ribose) polymerase (PARP) enzyme family. PARPs use NAD^+ as substrate and upon cleaving off nicotinamide they transfer the ADP-ribosyl moiety covalently to suitable acceptor proteins and elongate the chain by adding further ADP-ribose units to create a branched polymer, termed poly(ADP-ribose) (PAR), which is rapidly degraded by poly(ADP-ribose) glycohydrolase (PARG) and ADP-ribosylhydrolase 3 (ARH3). In recent years several key discoveries changed the way we look at the biological roles and mode of operation of PARylation. These paradigm shifts include but are not limited to (1) a single PARP enzyme expanding to a PARP family; (2) DNA-break dependent activation extended to several other DNA dependent and independent PARP-activation mechanisms; (3) one molecular mechanism (covalent PARylation of target proteins) underlying the biological effect of PARPs is now complemented by several other mechanisms such as protein–protein interactions, PAR signaling, modulation of NAD^+ pools and (4) one principal biological role in DNA damage sensing expanded to numerous, diverse biological functions identifying PARP-1 as a real moonlighting protein. Here we review the most important paradigm shifts in PARylation research and also highlight some of the many controversial issues (or paradoxes) of the field such as (1) the mostly synergistic and not antagonistic biological effects of PARP-1 and PARG; (2) mitochondrial PARylation and PAR decomposition, (3) the cross-talk between PARylation and signaling pathways (protein kinases, phosphatases, calcium) and the (4) divergent roles of PARP/PARylation in longevity and in age-related diseases.

Contents

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1. Introduction to PARylation, historical overview

In the 1960s, three research groups pioneered the discovery of a novel nucleic acid-like macromolecule, poly(ADP-ribose) [PAR], whose formation turned out to depend on NAD^+ (Chambon et al., 1963; Nishizuka et al., 1967; Sugimura et al., 1967). The first group, headed by Paul Mandel, initially had assumed the homopolymeric reaction product to be poly-A but soon there was agreement in the newly founded field that the product is indeed PAR. Over the last 50 years this fascinating molecule has aroused the interest of a large number of scientists world-wide, coming from a very broad range of fields of scientific research.

The first phase of PAR research featured mostly biochemical work leading to the purification of the proteins responsible for its synthesis, *i.e.* poly(ADP-ribose) polymerase [PARP; later termed PARP-1 or ARTD1], and poly(ADP-ribose) glycohydrolase [PARG] (Bürkle, 2006; de Murcia and Shall, 2000). Another important biochemical topic was the identification of the target amino acids for covalent modification of proteins with PAR, *i.e.* glutamate, aspartate and lysine and the establishment of a quantitative assay to determine PAR levels in living cells (Juarez-Salinas et al., 1979).

In a second phase, cell biologist and pharmaco-toxicologists started to become interested in the subject matter, based on the availability of cell-permeable, first-generation PARP inhibitors like nicotinamide, benzamide or 3-aminobenzamide. Using such compounds, sensitization of cultured cells to the cytotoxic effects of low doses of alkylating agents was observed (Durkacz et al., 1980). This led, early on, to the idea of combining DNA-damaging cytotoxic agents used in cancer chemotherapy with PARP inhibitors in order to enhance the cytotoxic effect especially in poorly responsive cancer types.

A third phase of PAR research was triggered by the advent of molecular biology. Three groups pioneered the molecular cloning of PARP-1 cDNA (Cherney et al., 1987; Kurosaki et al., 1987; Suzuki et al., 1987), which brought an enormous stimulus to the field in a variety of ways.

A fourth phase may be viewed in the use of methodology of structural biology to tackle PARylation. This included the crystal structure of PARP-1 (Langelier et al., 2012; Ruf et al., 1996, 1998) followed by a more comprehensive coverage of the additional members of the PARP family (Karlberg et al., 2010) and the discovery of a histone macrodomain as a PAR-binding motif (Timinszky et al., 2009), see Section 2.2).

Our review is built around important paradigm shifts/milestones of the field and also highlights controversial issues (“paradoxes”).

2. Paradigm shifts in PARP research

2.1. Old paradigm #1: there is one PARP enzyme.
New paradigm: PARP-1 is one of the many members of the PARP family. But are all these newcomers bona fide PARP enzymes?

Purification of the major enzymatic activity that produced PAR yielded a ~116 kD protein, which was termed ADP-ribosyltransferase (ADPRT) or poly(ADP-ribose) synthetase (PARS) or poly(ADP-ribose) polymerase (PARP) [EC 2.4.2.30]. This nuclear protein is highly conserved and constitutively expressed. It is catalytically active as a dimer and is the major acceptor protein in intact cells, via automodification. It displays a characteristic three-domain structure, which can be further broken