Preface

Our understanding of how Poly(ADP-ribose) polymerases (PARPs) function has reached a new level. It has become clear that these abundant and ubiquitous proteins regulate crucial processes of the cell cycle, DNA repair, genomic stability, and transcriptional regulation. Being involved in basic cell functions, PARPs mediate rapid responses to environmental stress, infection, nutrition changes, and hormonal signals. PARP research has gained tremendous importance for advancement of cancer treatments following a recent discovery that tumor growth can be suppressed by PARP inhibitors in people with a BRCA1 or BRCA2 mutations, which are typical in breast, ovarian, and prostate cancer.

The basic enzymatic reactions catalyzed by PARPs involve transferring ADP-ribose moiety from NAD either to a protein acceptor or to an existing Poly(ADP-ribose) (pADPr) chain. Most commonly, the target is a glutamic acid molecule, whereas modification of other amino acids may also occur. The average pADPr chain length varies from 2 to 200 ADP-ribose units. Poly(ADP-ribosylation) alters the physical and enzymatic properties of acceptor proteins which become highly negatively charged as a result. pADPr levels in vivo are determined based on a balance between the relative rates of PARP-dependent synthesis and the rates of Poly(ADP-ribose) glycohydrolase (PARG)-dependent degradation. The human genome has 17 or 18 PARP-related genes with a low functional redundancy. These include genes of PARP1/PARP2 proteins that were reported as nuclear enzymes responsible for DNA repair/apoptosis triggering, transcriptional regulation and chromatin remodeling, as well as genes of tankyrases, which are enzymes involved in telomere regulation, mitotic spindle assembly, and Golgi apparatus function. Because of likely functional redundancies, the presence of multiple paralogous PARPs in mammals greatly complicates their analysis. Fortunately, the genomes of model organisms, such as Drosophila and Caenorhabditis elegans encode a reduced number of PARPs, making these animals invaluable model systems to study the functions of poly(ADP-ribosylation).

This volume of the Methods of Molecular Biology series on Poly(ADP-Ribose) aims to achieve the following three goals to advance PARP research: (1) explain how PARP proteins act within the normal development of an organism as well as within pathogenic conditions, (2) expand the knowledge of developmental pathways regulation, and (3) facilitate the development of new therapeutic drugs and methods to experimentally target PARP-dependent processes. The chapters in Part I describe in vivo and in vitro biochemical approaches to detection and quantification of poly(ADP-ribose) and assaying its biological functions, as well as the techniques for the purification of recombinant PARP proteins. The chapters in Part II provide a compendium of genetic manipulation approaches using human tissues and cell cultures in addition to different model organisms, ranging from bacteria to mammals. Finally, chapters in Part III discuss the implementation of novel strategies aiming to discover and test small molecule inhibitors of PARP proteins.

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