Bioorganic & Medicinal Chemistry Letters 26 (2016) 3395–3403

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Digest paper

Poly(ADP-ribose): From chemical synthesis to drug design

Mikhail S. Drenichev, Sergey N. Mikhailov *

Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Vavilov Str. 32, Moscow 119991, Russian Federation

ARTICLE INFO

Article history:
Received 30 March 2016
Revised 2 June 2016
Accepted 4 June 2016
Available online 6 June 2016

Keywords:
Poly(ADP-ribose)
Structure and properties
Biosynthesis
Cell functions
Chemical synthesis

ABSTRACT

Poly(ADP-ribose) (PAR) is an important biopolymer, which is involved in various life processes such as DNA repair and replication, modulation of chromatin structure, transcription, cell differentiation, and in pathogenesis of various diseases such as cancer, diabetes, ischemia and inflammations. PAR is the most electronegative biopolymer and this property is essential for its binding with a wide range of proteins. Understanding of PAR functions in cell on molecular level requires chemical synthesis of regular PAR oligomers. Recently developed methodologies for chemical synthesis of PAR oligomers, will facilitate the study of various cellular processes, involving PAR.

There are three main classes of biopolymers: polynucleotides (RNA and DNA), polypeptides, and polysaccharides, which range in their structure from linear to highly branched molecules. Poly (ADP-ribose) (PAR) can be considered as a fourth important biopolymer, which is involved in various life processes. PAR participates in numerous cellular processes such as DNA repair and replication, modulation of chromatin structure, transcription, cell differentiation, and also in pathogenesis of various diseases such as cancer, diabetes, ischemia and inflammations.[1–3] PAR is a homopolymer and consists of 2′-*O*-α-D-ribofuranosyladenosine units linked with pyrophosphate bonds. This disaccharide nucleoside is a member of a big class of natural compounds, widely found in nature. Compounds of this type have an additional monosaccharide residue attached to one of the nucleoside hydroxyl groups via an *O*-glycosidic bond. The presence of a disaccharide residue and a heterocyclic base makes their properties similar to those of carbohydrates and nucleosides. With its branched structure PAR mimics the structure of polysaccharides: amylopectin and glycogen.

In the recent reviews biochemical, biological and some medicinal aspects of PAR functions have been described in details.[4–7] The present review summarizes structural features, physicochemical properties, and chemical synthesis of PAR fragments and perspectives in drug design.

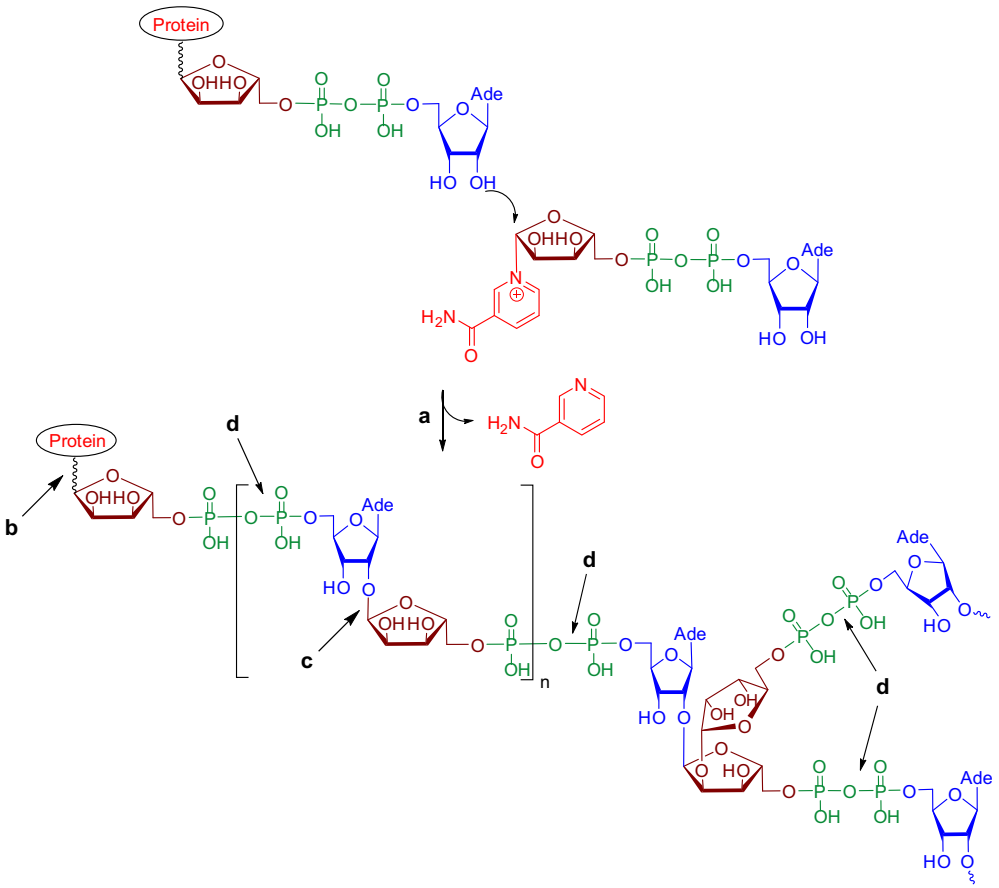
The structure of PAR and other charged biopolymers: PAR is a complex branched biopolymer, which consists of 2′-*O*-α-D-ribofuranosyladenosine units connected by pyrophosphate linkages (Scheme 1). Native PAR molecules consist of more than 200–300 monomeric units, in which linear segments of 20–50 units alternate with branched motifs.[1,2,8]

The chemical structure of PAR was determined by regiospecific enzymatic hydrolysis of the pyrophosphate bonds by snake venom phosphodiesterase with formation of disaccharide nucleotide **1** and trisaccharide nucleotide **2**. Their structures were determined by NMR spectroscopy.[9,10] Subsequent enzymatic dephosphorylation of compound **1** by alkaline phosphatase led to corresponding disaccharide nucleoside **3**.[8,9,11] Compounds **2** and **4** represent the core motif of PAR branching. The common feature of compounds **1**–**4** is the presence of α(1 → 2) glycosidic bonds (Fig. 1). The closest natural analogs of disaccharide monomeric unit of PAR are minor tRNA components—2′-*O*-β-D-ribofuranosyladenosine 5″-phosphate, Arp (**5**) and its guanosine derivative—Grp (**6**).[11–13]

The structure of PAR has some similarity to the structure of nucleic acids, since antibodies against PAR can recognize RNA and DNA.[1] Therefore, proteins participating in key cellular processes, such as DNA synthesis and repair, transcription, modulation of chromatin structure can directly or indirectly interact with PAR.[1,14] Ionic interactions with target proteins and some other binding modes (binding with disaccharide nucleoside or ADP-ribose–ADP-ribose junction or terminal ADP-ribose fragment) underlie the modulation of protein functions by PAR.[7] Upon binding to the target proteins, PAR modulates their functions. Covalent modification of proteins proceeds via formation of *O*-glycosidic bond (Glu/Asp, Ser/Thr residues) or via formation of *N*-glycosidic bond (Lys/Arg, Asn/Gln residues) and modulates the structure of histones and poly(ADP-ribose)polymerase (PARP-1) itself.[15,16] Covalent modifications of other amino acid residues, for example,

* Corresponding author.
E-mail address: smikh@eimb.ru (S.N. Mikhailov).

http://dx.doi.org/10.1016/j.bmcl.2016.06.008
0960-894X/



Scheme 1. Biosynthesis and cleavage of poly(ADP-ribose). *Enzymes*: (a) poly(ADP-ribose)polymerase; (b) (ADP-ribosyl)proteinlyase; (c) poly(ADP-ribose)glycohydrolase (PARG), (d) human Nudix hydrolase (hNUDT16).

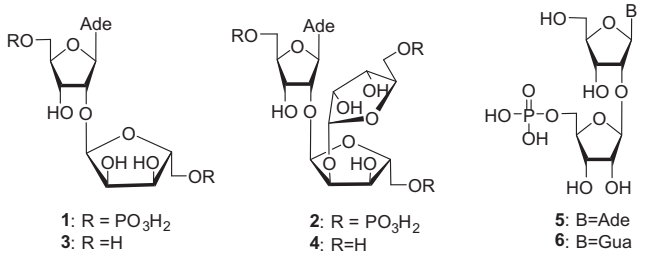


Figure 1. Structural fragments of PAR (**1**–**4**) and their closest natural analogs (**5**–**6**).

serine, *N*-acetyllysine, phosphoserine as well as covalent modification of DNA and RNA at the guanine bases also were detected.[15]

Numerous cellular proteins contain lysine and arginine-rich motifs, which are essential for ionic interactions with PAR. It has been also shown, that the formation of protein complexes with PAR depends on PAR molecular weight.[17] Thus, the key cellular protein p53 manifests the ability to form the complexes both with short PAR chains (14–16 units) and long PAR chains (>50 units). XPA protein, participating in DNA repair and recombination, does not form specific complexes with short PAR fragments, but manifests high binding affinity with long PAR chains (>50 units). Noteworthy, that binding affinity of proteins increases with the increase of PAR molecular weight.[17]

PAR is the most electronegative natural polymer (in pyrophosphate $pK_1 < 2.0$, $pK_2 = 2.64$)[18] with two negative charges per monomeric unit. Other biopolymers, such as DNA and RNA, contain only one phosphate group per monomeric unit and have only one negative charge at neutral pH. PAR structure has much in common with natural polysaccharides heparin and heparan sulfate as the presence of sulfate and carboxyl groups defines the substantial negative charge of these biopolymers under neutral conditions.[19] Due to its branched structure PAR mimics amylopectin and glycogen. Heparin is the most charged polysaccharide with the charge of −2.7 on the disaccharide unit (−1.35 on monosaccharide unit).

In general, PAR is a long branched biopolymer involved in many cellular processes and can interact with >500 proteins bearing specific binding sites.[4,14,20] Biological role of this important biopolymer is well understood but precise mechanism of action and molecular interactions with target proteins are unclear. Therefore, enzymatic or chemical synthesis of well-defined linear PAR oligomers is urgently needed to shed a light on these problems.

Biosynthesis and cleavage of PAR: Several enzymes are involved in biosynthesis and cleavage of PAR (Scheme 1). In cellular nuclei PAR is synthesized by poly(ADP-ribose)polymerases (PARPs) from NAD+ as a substrate (Scheme 1, pathway a). At present, PARP family consists of about 17 enzymes. PARP-1 (EC 2.4.2.30) appears to be the major poly(ADP-ribosyl)ating enzyme in higher eukaryotes.[1,21]

Biosynthesis of PAR includes at least three enzymatic reactions: (a) initiation (the attachment of the first ADP-ribose moiety to an acceptor amino acid); (b) elongation of PAR chain by joining of additional ADP-ribose monomers; (c) generation of branching points.[1,19] In vivo PAR is cleaved by several enzymes (Scheme 1, routes b–d).[22–25] ADP-ribosyl protein lyase catalyzes the cleavage of *O*-glycosidic bond between adenosinediphosphoribosyl residue and proteins (Scheme 1, pathway b).[22] *O*-Glycosidic bond between adenosine and ribofuranose moiety in PAR-polymer is split by