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Review

PARP inhibitors: New tools to protect from inflammation

Vincenzo Giansanti [1], Francesca Donà [1], Micol Tillhon, A. Ivana Scovassi *

Istituto di Genetica Molecolare CNR, Via Abbiategrasso 207, I-27100 Pavia, Italy

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ABSTRACT

Poly(ADP-ribosylation) consists in the conversion of β-NAD^+ into ADP-ribose, which is then bound to acceptor proteins and further used to form polymers of variable length and structure. The correct turnover of poly(ADP-ribose) is ensured by the concerted action of poly(ADP-ribose) polymerase (PARP) and poly(ADP-ribose) glycohydrolase (PARG) enzymes, which are responsible for polymer synthesis and degradation, respectively. Despite the positive role of poly(ADP-ribosylation) in sensing and repairing DNA damage, generated also by ROS, PARP over-activation could allow NAD depletion and consequent necrosis, thus leading to an inflammatory condition in many diseases. In this respect, inhibition of PARP enzymes could exert a protective role towards a number of pathological conditions; i.e. the combined treatment of tumors with PARP inhibitors/anticancer agents proved to have a beneficial effect in cancer therapy. Thus, pharmacological inactivation of poly(ADP-ribosylation) could represent a novel therapeutic strategy to limit cellular injury and to attenuate the inflammatory processes that characterize many disorders.

Contents

1. Introduction

1.1. Poly(ADP-ribosylation): basic features

Poly(ADP-ribosylation) is a post-translational modification of nuclear proteins that consists of the production of poly(ADP-ribose) and its binding to several acceptor proteins. Poly(ADP-ribose) polymerase (PARP) enzymes initiate the reaction by converting the substrate β-NAD^+ to ADP-ribose, with the liberation of nicotinamide and protons (Fig. 1), and then elongate ADP-ribose to form polymers bound to nuclear acceptor proteins. For a longtime, glutamic acid in the acceptor proteins (including PARP itself) was considered the preferential target of poly(ADP-ribosylation); more recently, lysine residues were identified as acceptors of ADP-ribose in PARP-1 [1] and PARP-2 [2]. Poly(ADP-ribose) turnover is regulated by the enzyme poly(ADP-ribose) glycohydrolase (PARG), which degrades it to free ADP-ribose and AMP.

As deduced from genome sequence analysis [3,4], a family of PARPs was identified, consisting of 17 members showing a "PARP signature" in the catalytic domain at the C-terminus [5]. The properties of the best-known PARPs have been recently reviewed ([6–9] and references therein). The most abundant PARP, PARP-1 (EC 2.4.2.30), is a 113 kDa zinc-finger protein with a modular structure

* Corresponding author. Tel.: +39 0382 546334; fax: +39 0382 422286.
E-mail address: scovassi@igm.cnr.it (A.I. Scovassi).
[1] These authors contributed equally to the manuscript.

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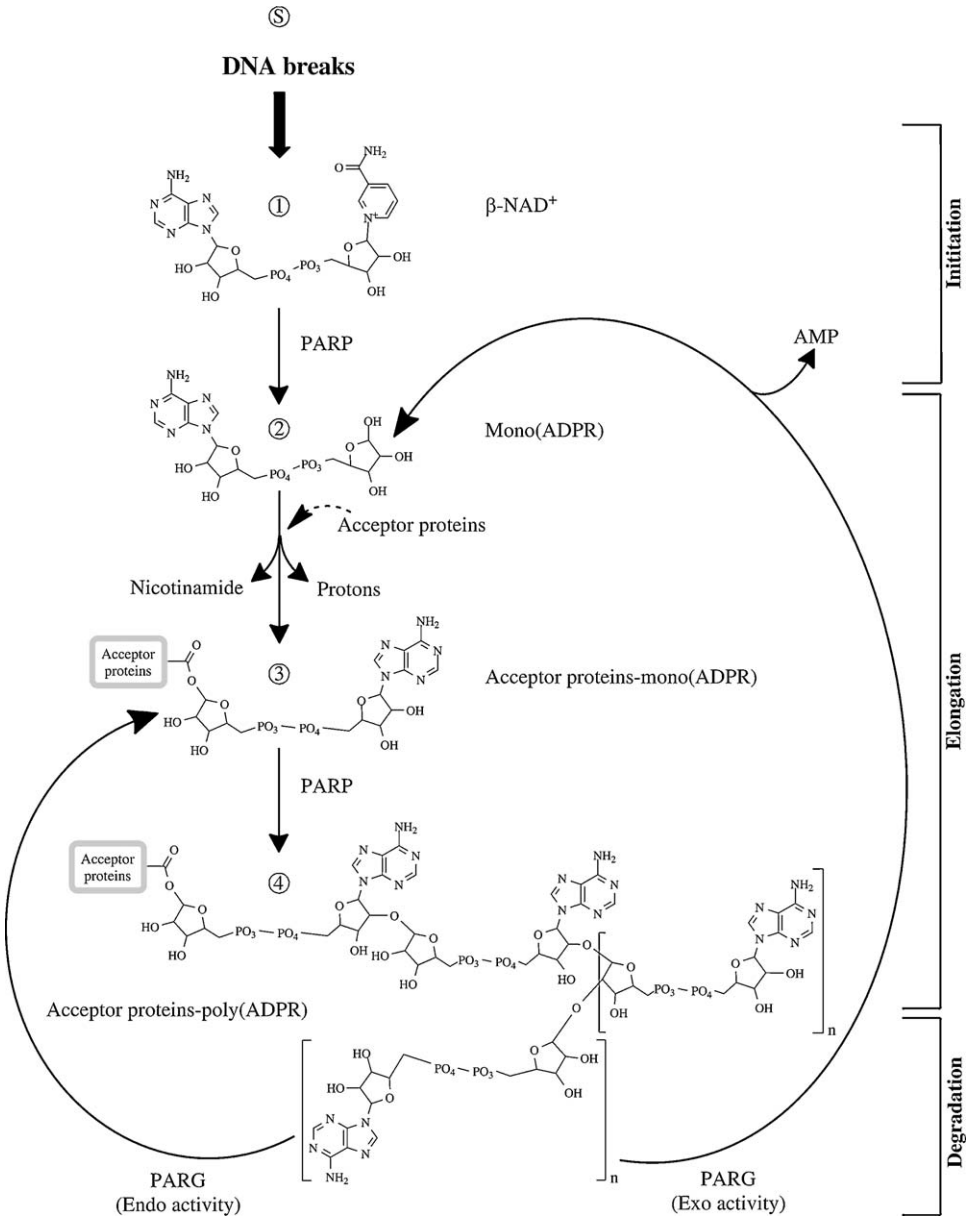

Fig. 1. Biochemical features of poly(ADP-ribosylation). The reaction starts (S) in the presence of DNA breaks and converts the substrate β-NAD+ (1) into mono(ADP-ribose) (2) bound to acceptor proteins (3); then, poly(ADP-ribose) is formed (4). PARP activity is responsible for both initiation and elongation steps, while PARG acts during the degradation phase. ADPR: ADP-ribose; NAD: nicotinamide adenine dinucleotide; PARP: poly(ADP-ribose) polymerase; PARG: poly(ADP-ribose) glycohydrolase.

composed of the N-terminal DNA binding domain (DBD) essential for the recognition of DNA breaks, a central automodification domain that mediates PARP-1 autoribosylation, and the C-terminal catalytic domain required for the conversion of NAD+ into ADP-ribose.

Since further studies revealed that some PARP family members are in fact mono(ADP-ribosyl) transferases, recently a new nomenclature for (ADP-ribosyl) transferases has been proposed [10]. The schematic structure of the so far described 18 ADP-ribose-synthesizing enzymes is illustrated in Fig. 2.

1.2. Multiple roles of poly(ADP-ribosylation)

Poly(ADP-ribosylation) is implicated in many basic processes such as DNA replication, repair, and transcription [6,7,11–13]. Its active involvement in gene expression and chromatin organization has also been demonstrated [14–17].

A number of laboratories addressed the functional role of poly(ADP-ribosylation) mainly focusing on PARP-1, which is responsible for about 90% of the total poly(ADP-ribosylation) activity [18]. The activity of PARP-1 is mainly dependent on DNA damage, and agents generating ss- and ds-DNA breaks activate the enzyme. Given that PARP-1 acts as a DNA damage-sensor molecule [19], it has also been considered as a "guardian of the genome" [20,21] and recently described as a "multi-talented molecule" [22].

In fact, PARP-1 plays a double role: as represented in the Yin–Yang paradigm (Fig. 3), PARP-1 is normally acting as a pro-survival factor, essentially because of its role in promoting DNA repair; under massive DNA damage/stress conditions, it turns on the dark side, thus driving cells to necrosis. The double role of PARP-1 justifies the requirement for a fine regulation of its activity. The best example of a signaling pathway controlling the unwanted effects of PARP-1 over-activation is represented by apoptosis in response to damage conditions. When controlled, "acute" PARP-1 activation promotes DNA repair; however, under excessive DNA breaks, a "chronic" synthesis of poly(ADP-ribose) results in energy deprivation [23–25]. For the correct apoptotic machinery to go on,

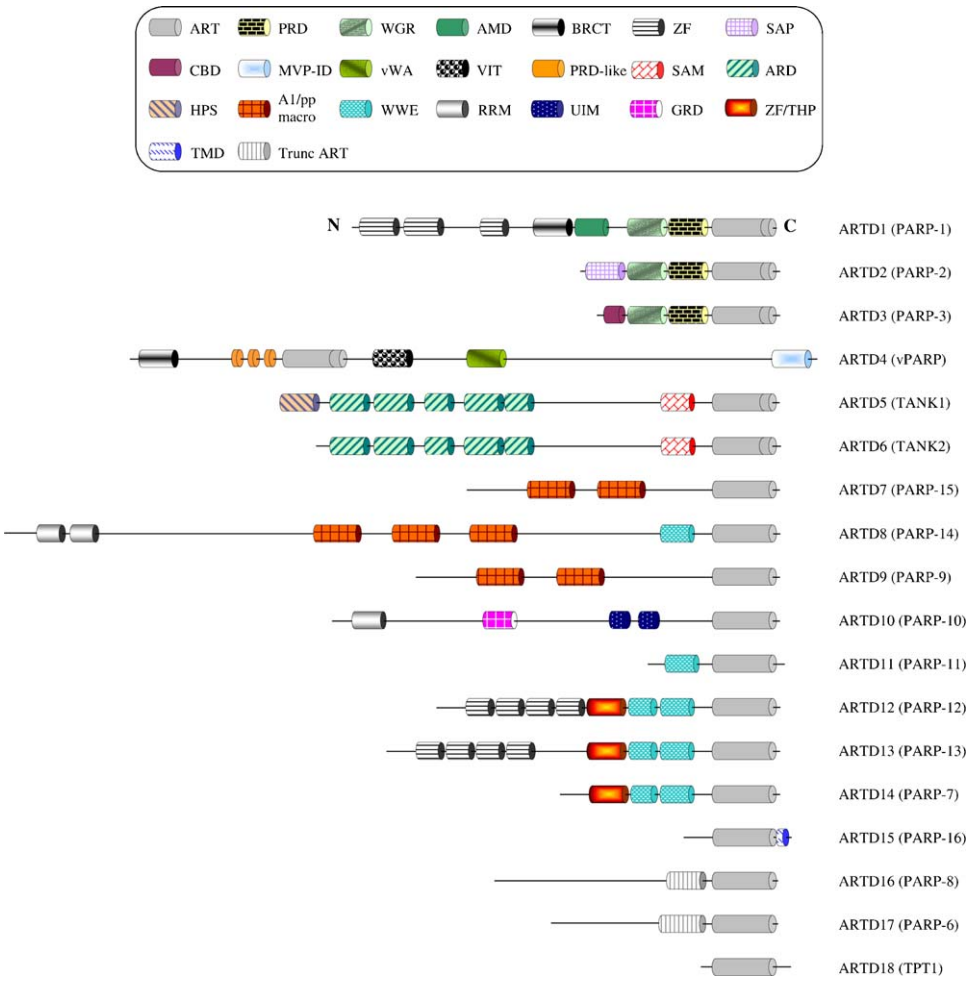

Fig. 2. Alignment of ADP-ribosylating enzymes. According to Hottiger et al. [10], a new nomenclature for PARPs has been adopted, based on the general ability to produce ADP-ribose, thus moving from poly(ADP-ribose) polymerase to ADP-ribosyl transferase. All ADPRTs (former PARPs) display the so-called "PARP signature" within the catalytic domain, corresponding to residues 859–908 of PARP-1 sequence. For abbreviations, see [10].

it is necessary to impede a massive NAD depletion by inactivating PARP-1. This job is mainly done by caspases, which cleave PARP-1 generating two inactive fragments, thus saving NAD for the energy required to carry on the apoptotic process [23–28]. Although caspase proteolysis of PARP-1 is generally considered an essential factor for driving cells to apoptosis, under some experimental conditions PARP-1 cleavage appears to be dispensable for apoptosis occurrence (reviewed in [27,28]). Notably, PARP-1 is also involved in a paradigm of caspase-independent death called "parthanatos", characterized by the accumulation of poly(ADP-ribose) and the release of apoptosis inducing factor (AIF) from mitochondria [29,30]. Recently, a link between PARP and autophagy has been described [31].

1.3. Poly(ADP-ribosylation) and inflammation

The relationship between PARP activity and inflammation has been widely investigated. The link with inflammation was firmly established by the pharmacological inhibition of PARP activity, which allowed the attenuation of the inflammation response [32,33]. The mechanisms underlying this effect are not solely ascribable to the above-described paradigm "PARP activation – NAD consumption – necrosis", but imply also a role of PARP-1 in regulating inflammatory factors (Fig. 4). Indeed, it has been reported that PARP-1 physically interacts with NF-κB, one of the main pro-inflammatory transcription factors [34,35]. The association with NF-κB/p50 requires PARP-1 acetylation by p300/CREB-binding protein [36,37]. In turn, PARP-1 acetylation could be abrogated by PARP-1 sumoylation, which competes with acetylation for regulating PARP-1 transactivation functions [2,38,39]. Once bound to PARP-1, NF-κB interacts with other proteins, binds DNA and activates the transcription of several genes implicated in different processes, including inflammation, cell proliferation, differentiation and death [40]. In addition, PARP-1/NF-κB interaction regulates the production of pro-inflammatory cytokines, such as TNFα, MIP1α, IL-1 and IFNγ, as well as the activity of enzymes like iNOS [41–46].

Of note, PARP-1 forms a functional complex with hypoxia inducible factor-1 (HIF-1), which promotes gene expression to adapt cells to hypoxic conditions, and whose activity requires the transcriptional co-activation by PARP-1 [47]. Analogously, a functional interaction of PARP-1 with the transcription factor Krüppel-like factor 5 (KLF5) has been described, thus supporting a role of PARP-1 in regulating the cardiovascular response to pathological stress [48]. A further function of transcriptional regulator is exerted by PARP-1 towards Forkhead box O (Foxo) transcription factors, which are regulated not only by phosphorylation but also by poly(ADP-ribosylation) [49]. PARP-1 is also implicated in the renin–angiotensin system (RAS) that counteracts inflammation, being an actor of nuclear signaling and possibly acting as a novel node within the RAS network [50]. Moreover, PARP-1 could act on inflammation by influencing the proteasome, which plays a major role in the degradation of oxidatively modified proteins also by its interaction with PARP-1: indeed, 20 S

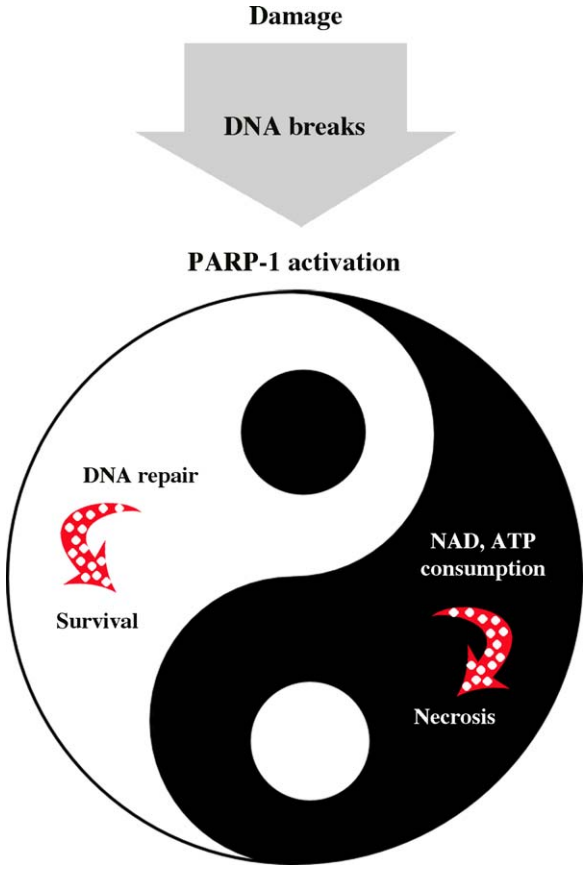

Fig. 3. The Yin–Yang paradigm of PARP-1 activation. DNA breaks stimulate the synthesis of poly(ADPR); when their amount is so limited that they could be repaired, PARP-1 acts as a pro-survival factor (white function). On the contrary, under more drastic damage conditions, its over-activation implies excessive NAD and ATP consumption and, in turn, drives cells to necrosis (black function).

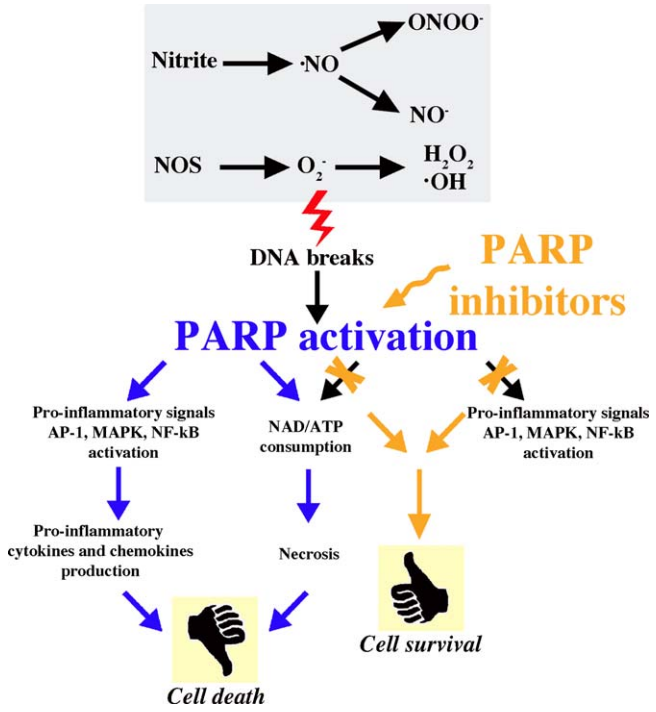

Fig. 4. Effect of pro-inflammatory signals on PARP-1 activity. Oxidative and nitrosative stress leading to the production of oxygen-derived free radicals (superoxide and hydroxyl radicals) and high-energy oxidants (peroxynitrite) activate PARP. Its over-activation promotes necrosis through energy consumption and also by modulating the expression of pro-inflammatory factors like AP-1, MAPK, NF-κB, and down stream cytokines and chemokines. The use of PARP inhibitors abolishes the inflammation cascade and saves cells.

proteasome is known to interact non-covalently both with poly(ADP-ribose) and automodified PARP-1. The evidence that in the presence of the PARP inhibitor 3-aminobenzamide, proteasome activation is inhibited, suggests that poly(ADP-ribosylation) could modulate the removal of oxidized proteins [51].

2. Poly(ADP-ribosylation) inhibitors

2.1. Search for inhibitors

Nicotinamide (NA) and 3-aminobenzamide (3-AB) (Fig. 5) were the first compounds used to inhibit poly(ADP-ribosylation). Nicotinamide (pyridin-3-carboxylic acid amide) inhibits the conversion of NAD into ADP-ribose [52,53] and, when administered in S phase, affects the rate of DNA replication [54], possibly interfering with nucleotide synthesis [55]. Benzamide (benzoic acid amide), which mimics the nicotinamide moiety of NAD, was recognized as a promising inhibitor [56] and further used as a lead compound to produce derivatives with new residues in the 3-position, including 3-aminobenzamide and M-methoxybenzamide.

Instrumental information for structure–activity studies was obtained through the crystal structure of the catalytic domain of chicken PARP-1 [57], and the consequent identification of the site of interaction between inhibitors and NAD-binding region [58]. Analogously, the definition of the crystal structure of PARP-2 [59] provided new tools to design selective inhibitors of this enzyme.

Other benzamide analogues have been designed, variously substituted at the level of the ring of the lead molecule or modified at the level of the amidic function or the benzene ring [60]. The cyclization of an open benzamide structure or the creation of a further ring system on the existing cyclic amide allowed the development of 2nd generation PARP inhibitors: tricyclic benzimidazole carboxamides were designed by locking the carboxamide in the favored conformation through intramolecular hydrogen bonds (e.g. NU1085) or by incorporation into a ring system (e.g. NU1025), and proved to potentiate the cytotoxicity of chemotherapeutic drugs [61]. Among tricyclic inhibitors, a series of diazepinoindolones optimized for space-filling and atomic interactions within the NAD-binding site of PARP-1, were able to inhibit poly(ADP-ribosylating) enzymes [62].

As a result of a large-scale survey, new inhibitors were discovered, including 4-amino-1,8-naphtalimide, 6(5H)- and 2-nitro-6(5H)-phenanthridinones and 1,5-dihydroxyisoquinoline,

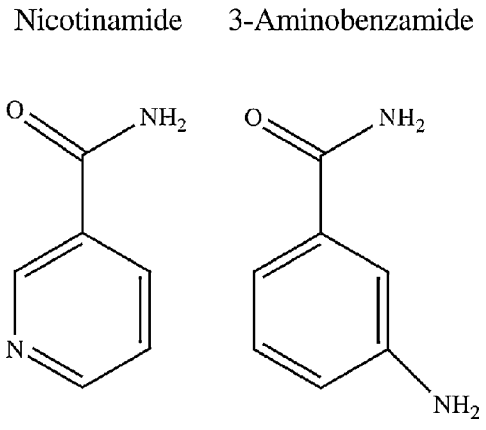

Fig. 5. Structure of nicotinamide and 3-aminobenzamide.

all characterized by the presence of a carbonyl/carbamoyl group in crucial positions [63,64]. Isoquinolones have been further studied, and some of them proved to protect from several diseases [65,66]. The active contribution of several Companies to the identification and development of new PARP inhibitors is described in [67–69].

Some compounds are currently used in preclinical studies and clinical trials, mainly against cancer [70–76], thus representing a promising strategy to beat this disease in combination with conventional chemotherapeutic drugs or as single agents (see http://www.clinical trials.gov).

2.2. Use of inhibitors to elucidate the physiological role of poly(ADP-ribosylation)

The first application of PARP inhibitors was the validation of the specificity of biochemical assays. *In vitro* reconstituted poly(ADP-ribosylation) systems based on NAD^+ incorporation were checked by adding PARP inhibitors to the reaction mixture. Analogously, *in vivo* assays under conditions of pharmacological inhibition of PARP allowed the setting of accurate procedures for measuring endogenous and/or activated poly(ADP-ribosylation).

The understanding of the physiological role of poly(ADP-ribosylation) has been greatly facilitated by the study of the effects of specific inhibitors on basic processes. After the elegant demonstration by Durkacz et al. [77], many reports indicated that 3-AB prevents intracellular NAD drop, hypersensitizes cells to DNA-damaging agents and slows down DNA repair. Of note, the use of inhibitors allowed the discovery that PARP-1 is mainly involved in the base excision repair (BER) pathway, interacts with a number of partners [22,78–81] and may function as a "BER sensor" [82].

After about 30 years of intense use and development of PARP inhibitors, molecular and genetic approaches have been exploited to study the dynamics of poly(ADP-ribose) synthesis that occurs in response to DNA-strand breaks, and to define unambiguously its role in the cell response to DNA damage and repair, in cell death, and during the inflammatory process.

In 2000 two leaders in the field of poly(ADP-ribosylation), namely Sydney Shall and Gilbert de Murcia, tried to answer the question "What have we learned from the deficient mouse model?" By comparing the accumulated body of data originated from pharmacological inhibition of PARP with the modern PARP-1 KO results, they concluded that "All three, independent, knockout animals show hypersensitivity both to alkylating agents and to ionising radiation, consistent with the earlier observations with the enzyme inhibitors. It is of some interest to note that the above data derived with the use of PARP-1 inhibitors was in fact confirmed by an entirely different procedure which did not involve inhibitors" ([83] and references therein). After these considerations, we watched a "renaissance" in the poly(ADP-ribosylation) field and an impressive effort to develop new, specific and potent inhibitors.

3. Beneficial effects of PARP inhibitors in inflammatory disorders

As summarized in Fig. 4, PARP-1 over-activation mediated by the generation of free radicals, reactive oxygen species and peroxynitrite can be detrimental because of energy depletion and consequent necrosis of neuronal cells, immune-stimulated macrophages, endothelial cells and fibroblasts [40,84,85]. PARP inhibitors exert a protective effect towards a number of inflammatory conditions, listed in Tables 1 and 2, which focus on recent results obtained by administering 3-AB or new generation compounds to animals (dogs, guinea pigs, mice, pigs, rats) suffering from experimentally-induced inflammatory diseases. As a general effect, these compounds allowed the attenuation of inflammation and rescued animals from many pathological signs. Table 1 refers to experimental conditions that imply heart or brain inflammatory processes, such as ischemia/reperfusion, stroke and neuronal death. The therapeutic effects of PARP inhibitors in various forms of heart failure, cardiomyopathies, circulatory shock, cardiovascular diseases and atherosclerosis have been widely described [86]. A recent review focused on PARP-1 as a promising target for developing drugs to be used for the pharmacological treatment of post-ischemic brain damage [87]. Table 2 reports representative results obtained on diabetes and other disorders characterized by acute or chronic inflammation. The beneficial effects of PARP inhibition in various models of diabetes and diabetic complications are strictly correlated with the evidence that PARP is a causative factor in the pathogenesis of this disease [88], as suggested by the finding that PARP-1 KO mice were

Table 1
Effect of PARP inhibitors on inflammatory diseases.

Pathological condition	Animal	PARP inhibitor	Effect	Reference
Ischemia/reperfusion	Pig	INO-1001	Hemodynamic stabilization	[116]
Ischemia/reperfusion	Mouse	PJ-34	Inhibition of inflammation	[117]
Heat stroke	Mouse	PJ-34	Stroke attenuation	[118]
Heart failure	Rat	INO-1001	Improved cardiac function	[119]
Chronic heart failure	Rat	L-2286	Prevention of heart failure	[120]
Hypertension	Rat	L-2286	Protection	[121]
Atherosclerosis	Mouse	PJ-34	Inhibition of atherosclerosis	[122]
Induced atherosclerosis	Mouse	TIQ-A	Atherosclerotic plaque regression	[123]
Endarterectomy	Rat	INO-1001	Prevention of hyperplasia	[124]
Heart storage	Rat	INO-1153	Cardioprotection	[125]
Extracorporal circulation	Dog	INO-1001	Improvement of functions	[126]
Endothelial dysfunction	Mouse	INO-1001	Restoration of function	[127]
Endothelial dysfunction	Rat	PJ-34; 3-AB	Prevention	[128]
Cerebral ischemia	Rat	NU1025	Neuroprotection	[129]
Cerebral ischemia	Rat	DR2313	Neuroprotection	[130]
Ischemic stroke	Rat	PJ-34	Improved post-stroke	[131]
Focal cerebral ischemia	Rat	5-AIQ	Attenuation of inflammation	[132]
Neuronal death	Mouse	PJ-34	Decreased damage	[133]
Neuronal death	Mouse	BA	Improved memory	[134]
Neuronal damage	Rat	ONO-1924H	Neuroprotection	[135]
Retinal death	Rat	PJ-34	Neuroprotection	[136]
Photoreceptor death	Rat	NA	Protection of retina	[137]
Hypoxia/reoxygenation	Mouse	DPQ	Protection	[138]
LPS-induced inflammation	Mouse	3-AB	Reduced brain death	[139]

Table 2
Effect of PARP inhibitors on diabetes and other diseases.

Pathological condition	Animal	PARP inhibitor	Effect	Reference
Experimental diabetes	Rat	ISO	Protection from neuropathy	[140]
Experimental diabetes	Rat	4-ANI	Good nerve conduction	[141]
Experimental diabetes	Rat, Mouse	GPI-15427	Protection from fiber loss	[142]
Experimental diabetes	Rat	4-ANI	Attenuation	[143]
Diabetic cardiomiopathy	Mouse	3-AB	Protection	[144]
Diabetic nephropathy	Rat	GPI-15	Protection	[145]
Chronic diabetes	Mouse	3-AB	Protection	[146]
Allergen-induced asthma	Guinea pig	3-AB	Rescue of respiratory abnormalities	[147]
Airway inflammation	Mouse	TIQ-A	Decrease in inflammation	[148]
Airway inflammation	Mouse	TIQ-A	Protection	[149]
Induced colitis	Rat	GPI 15427/16539; NIC; ISQ	Anti-inflammatory activity	[150]
Colon inflammation	Rat	NA; ISQ	Reduction	[151]
Hepatocarcinoma	Mouse	DPQ	Protection	[152]
Induced pancreatitis	Mouse	3-AB	Reduced inflammation	[153]
Necrotic pancreatitis	Mouse	3-AB	Protection	[154]
Renal injury	Rat	ISO	Protection	[155]
Induced nephrotoxicity	Rat	PJ-34	Attenuation	[156]
Induced cystitis	Mouse	3-AB	Protection	[157]
Erectyle dysfunction	Rat	INO-1001	Neuroprotection	[158]
Induced periodontitis	Rat	5-AIQ	Decrease in inflammation	[159]
Spinal cord trauma	Mouse	3-AB; 5-AIQ	Reduced tissue injury	[160]
Experimental arthritis	Mouse	AIQ	Downregulated inflammation	[161]

protected from streptozotocin-induced diabetes [89,90]. The reported protective effect of PARP inhibitors on asthma and airway inflammation is in line with that reported on lung diseases [91].

Few studies have been conducted in humans; an *in vivo* study that tested the anti-inflammatory effects of PARP inhibitors flavonoids revealed that they attenuate cytokine release in blood from patients with Chronic Obstructive Pulmonary Disease of type 2 diabetes, thus suggesting a potential use as nutraceutical agents [92]. Shrikhande et al. [93] described the positive effect of the angiotensin II receptor blocker valsartan on circulation of type 2 diabetes patients, possibly mediated by the inhibition of poly(ADP-ribose) synthesis.

4. Concluding remarks

Inflammatory processes generate oxidative/nitrosative stress as well as lipid peroxidation and, by consequence, excess reactive oxygen/nitrogen species (ROS/RNS) and DNA-reactive aldehydes, which may act as direct or indirect damaging agents through their reaction with other chemicals or structural cellular components. Oxidative stress and inflammation have been implicated in many diseases, including neurodegenerative disorders, hypertension, asthma, lung injury, heart failure and stroke. The use of PARP inhibitors in different inflammatory situations was found to be beneficial, given that in general they were able to attenuate inflammation and to release noxious symptoms. Of course, the encouraging data obtained in animal models require confirmation in humans, where a careful examination of side effects of PARP inhibitors is needed.

The specific inhibition of the other PARPs is still an open question. PARP-2, a DNA-damage dependent enzyme, shares with PARP-1 key functions in the cellular response to DNA damage. By consequence, inhibitors that target the conserved catalytic domain of PARP proteins, affect both activities [94]. Selective PARP-2 inhibitors have been searched [95–97]: UPF-1035 and -1069 compounds were developed, and found extremely useful to explore the biological functions of PARP-2 [98]. The crystal structure of the catalytic domain of human PARP-2 defined its interaction with the inhibitor ABT-888 and opened new perspectives in the development of selective PARP-2 inhibitors [99]. Analogously, the recent determination of the crystal structure of PARP-3 [100] revealed that it differs from PARP-1 in the loops surrounding the active site, thus providing the basis for developing specific inhibitors against this enzyme.

Also the inhibition of telomeric tankyrases has been considered as a tool against cancer, given that these PARPs regulate telomere metabolism [67]. Huang et al. discovered that a small molecule, XAV939, inhibits tankyrase 1 and tankyrase 2 [101]; McCabe et al. [102] silenced tankyrase 1 through shRNA thus obtaining a cancer cell line with stable reduction of tankyrase 1 expression. Remarkably, these strategies proved to help in treating BRCA-associated cancers [101,102], thus increasing the potential applications of PARP inhibitors [103,104]. In this respect, a novel yeast cell-based screening of tankyrase inhibitors has been recently developed [105].

As a cautionary note, it has to be reminded that the newest generation of PARP inhibitors may not only inhibit PARPs but also other NAD-consuming proteins, e.g. mono(ADP-ribosyl) transferases and sirtuins [106,107]. Furthermore, studies based on the pharmacological inhibition of PARPs could be more reliable if they would include PARP-deficient cell lines or siRNA experiments.

Finally, we have to mention the possible beneficial use of compounds that selectively inhibit PARG enzyme, thus altering the turnover of poly(ADP-ribose) and favoring its intracellular accumulation [67,108]. Although the pharmacological relevance of PARG inhibitors is still debated [109–111], they could be helpful in elucidating PARG functions and in attenuating diseases, as in the case of chemosensitization of cancer cells [112], and protection from inflammation [113] or brain injury [114]. To speed up the analysis of the effects of potential PARG inhibitors, a new procedure has been recently developed [115].

In conclusion, there is a tremendous interest in poly(ADP-ribosylation) as a target for modulating the impact of NAD consumption on cellular metabolism. Powerful strategies against cancer, based on the pharmacological inhibition of PARPs, are already adopted in clinical medicine; further work is required to develop adequate protocols for successful attenuation of inflammation in multifaceted disorders.

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