[Frontiers in Bioscience, Scholar, 8, 123-128, January 1, 2016]

Alternative mechanisms of inhibiting activity of poly (ADP-ribose) polymerase-1

Chandra Shaker Sriram[1], Ashok Jangra[1], Babul Kumar Bezbaruah[1,2], Athira K.V.[1], Shivaji Sykam[3]

[1]Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER), Narkachal Hilltop, Bhangagarh, Guwahati, Assam, India, PIN 78103, [2]Department of Pharmacology, Gauhati Medical College, Narkachal Hilltop, Bhangagarh, Guwahati, Assam, India, [3]IMS Health, Mumbai, Maharashtra, India

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1. ABSTRACT

Poly ADP-ribose polymerase (PARP-1), a DNA nick-sensor enzyme, is an abundant nuclear protein. Upon sensing DNA breaks, PARP-1 gets activated and cleaves NAD into nicotinamide and ADP-ribose and polymerizes the latter onto nuclear acceptor proteins including histones, transcription factors, and PARP-1 itself. Poly(ADP-ribosylation) mainly contributes to DNA repairing mechanism. However, oxidative stress-induced over-activation of PARP-1 consumes excess of NAD and consequently ATP, culminating into cell necrosis. This cellular suicide pathway has been implicated in several conditions such as stroke, myocardial ischemia, diabetes. Thus, it can be a rationale approach to inhibit the activity of PARP-1 for reducing detrimental effects associated with oxidative stress-induced over-activation of PARP-1. Several preclinical as well as clinical studies of PARP-1 inhibitors have been used in conditions such as cancer, stroke and traumatic brain injury. Conventionally, there are many studies which employed the concept of direct inhibition of PARP-1 by competing with NAD. Here, in the present review, we highlight several prospective alternative approaches for the inhibition of PARP-1 activity.

2. INTRODUCTION

Various intracellular and extracellular toxic stress factors cause DNA damage. The resultant DNA damage from the lesions of stress, if not repaired or incorrectly repaired, may cause mutations and chromosomal anomalies, cell death and pathological conditions such as inflammation, tissue damage etc (1). To defend their genome against the detrimental consequences of the stress lesions, each cell has sophisticated cellular networks to perceive the DNA damage, locate its presence and promulgate the proper mending pathway. Poly ADP-ribose (PAR) polymerisation is one of such important mechanisms, which percept the DNA damage. Additionally, PAR polymerisation acts as an overture in the inception of DNA repair mechanism (2).

Poly ADP-ribose polymerase (PARP-1), a DNA nick-sensor enzyme, is an abundant nuclear protein. Upon sensing DNA breaks, PARP-1 gets activated and cleaves NAD into nicotinamide and ADP-ribose and polymerizes ADP-ribose to form linear or branched polymers PAR. The resultant polymers of PAR can be transferred onto nuclear acceptor proteins including histones, transcription factors, and PARP-1 itself (2). PARylation (Poly(ADP-ribosylation)) contributes to DNA repair and to the maintenance of genomic stability. Owing to the high negative charge, PAR dramatically affects the function of target proteins, leading to electrostatic repulsion among histone proteins and DNA, a process implicated in chromatin remodeling, DNA repair and transcriptional regulation (2). The degree of the PARylation in response

to DNA damage largely depends on the nature and the amount of DNA breaks produced. During mild DNA damage, PARP-1 activity favors repair and survival by interacting with DNA repair enzyme cascade, such as such as X-ray repair cross-complementing protein1 (XRCC1) and DNA-dependent protein kinase. However, moderate DNA damage leads to apoptotic cell death, during which PARP-1 will be cleaved into two fragments by caspases. Cleavage of PARP-1 is assumed to foil the activation of PARP-1 by DNA damage and thereby it prevents cells from pathological consequences such as necrosis of cells (2).

On the other hand, in the cells with extensive DNA damage or damage that is not repaired, PARP-1 remains activated, leading to continued NAD+ depletion and further adenosine triphosphate (ATP) consumption in order to resynthesize NAD+ (2). Continued NAD+ depletion has been shown to induce a rapid mitochondrial dysfunction, which was followed by a collapse in mitochondrial potential, and the release of apoptosis-inducing factor (AIF) and cytochrome c (3). The mitochondrial energy failure also has been shown to be a direct consequence of PARP-1 hyper activation. A latest study has found that the PARP product PAR becomes catabolized to adenosine monophosphate (AMP) via the action of PARG and nucleoside diphosphate-X (NUDIX) hydrolases (3). The accumulated AMP then serves to compete with adenosine diphosphate (ADP) for binding to the adenine nucleotide transporter, thereby abrogating energy production by the mitochondria and further contributing to the ‘‘energy crisis’’. The resulting escalation of energy crisis would culminate to programmed necrosis (3, 4). This cellular suicide pathway has been implicated in several clinical indications such as stroke, myocardial ischemia, diabetes, diabetes-associated cardiovascular dysfunction, shock and traumatic central nervous system injury etc (2, 5). Thus for reducing or nullifying the detrimental effects associated with oxidative and nitrosative stress-induced over-activation of PARP-1, the concept of PARP-1 inhibition has been arrived. Several preclinical as well as clinical studies of PARP-1 inhibitors have corroborated their application in multiple indications such as cancer, stroke and traumatic brain injury etc. Hence, in the recent times the interest towards PARP-1 as a drug target has been peaked (2, 5). Generally for inhibiting the activity of PARP-1, there are two ways. One is to use the drugs or the agents which compete with PARP-1 for binding to the substrate NAD and the other one is inhibiting the activity of PARP by alternative methods (2).

3. CONVENTIONAL MECHANISM OF PARP-1 INHIBITION

Most of the existing PARP-1 inhibitors are competitive in nature and act by blocking the binding of NAD+ to the catalytic domain of the enzyme owing to their structural similarity with NAD. Conventionally several studies employed the concept of applying drugs or agents for competing with PARP-1 to bind with the substrate NAD, which resulted in a handful of drugs (2). In fact a few PARP-1 inhibitors (olaparib, veliparib, niraparib, rucaparib) are in different stages of clinical studies for ovarian cancer (6). In addition to cancer, several studies are underway for exploring the potential application of PARP-1 inhibitors in other indications such as stroke, myocardial ischemia, diabetes, diabetes-associated cardiovascular dysfunction, shock and traumatic central nervous system injury etc (2, 7). However, there is not much progress in the studies of PARP-1 inhibitors targeting indications other than cancer. Nevertheless, a Phase-1 clinical study of PARP inhibitor, JPI-289 has been completed for stroke (2, 7).

4. NON-CONVENTIONAL PROSPECTS OF PARP-1 INHIBITION

Besides to competing with PARP-1 for binding with the substrate NAD, there are ample of theoretical and practical ways to inhibit PARP-1 activity indirectly. For instance, it can be done either by preventing the generation of reactive oxygen or nitrogen species that lead to DNA strand breakage (and, thereby activation of PARP-1), or by utilizing ‘‘non-specific’’ or indirect inhibitors of PARP-1 such as xanthines, purines and vitamin D etc., (8,9).

4.1. Inhibiting the formation of reactive oxygen and nitrogen species

Many instances, in the recent research findings are strengthening the anti-oxidant approach. One such instance is alpha-lipoic acid, a multifunctional molecule, with a significant antioxidant component, has been demonstrated in preclinical studies to inhibit diabetes-associated PARP-1 overactivation (10). Similarly, supplementation of the endogenous antioxidant and reducing agent hydrogen sulfide (H2S) was also been demonstrated to be able to prevent the oxidant-mediated activation of PARP-1 in various *in vitro* and *in vivo* experimental settings (10-12). In addition to the above agents, direct inhibitors of nitric oxide synthase (13) agents that suppress the induction of iNOS, such as TNF-alpha antibodies, IL-1beta antibodies, glucocorticoids and several neutralizers of superoxide or peroxynitrite (14) all have the potential of indirectly preventing PARP-1 activation, which was corroborated in numerous preclinical studies (Figure 1). In addition, employing a peroxynitrite decomposition catalyst can also be potential modality for preventing the detrimental consequences associated with over activated PARP-1. Indeed, in a recent research report shown that utilization of FeTMPyP, a peroxynitrite decomposition catalyst along with a PARP-1 inhibitor reverses the neurobehavioral and neurochemical alterations in streptozotocin (STZ)-induced diabetic rats (15).

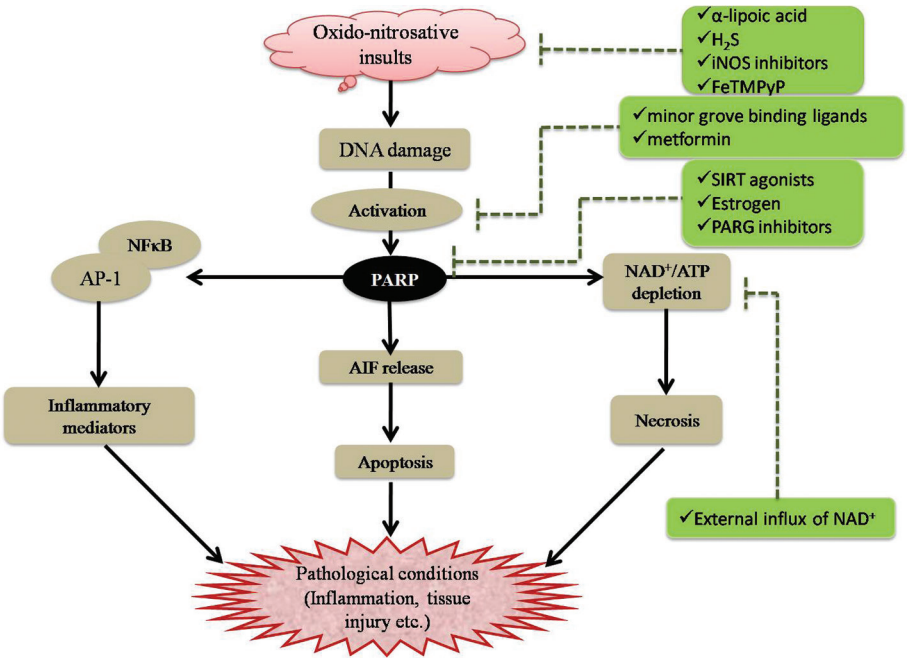

Figure 1. The central role of PARP-1 in oxidative and nitrosative stress-related pathology and prospective alternative drug targets. Oxidative and nitrosative-stress-induced DNA strand breakage triggers the activation of PARP-1, leading to apoptosis-inducing factor (AIF) release from the mitochondria and AIF-mediated, caspase-independent apoptotic cell death NAD/ATP consumption and consequent necrotic cell death. Oxidative and nitrosative stress also stimulate activation of redox-sensitive transcription factors such as Nuclear factor κ B (NFkB) and activator protein 1 (AP-1), key regulators of inflammatory cytokines and chemokines. Oxidative and nitrosative stress can be blocked by using agents such as α-lipoic acid, H2S and inducible Nitric acid synthase inhibitors etc., Successive step of DNA damage, PARP-1 activation could be hampered by minor grove binding lignads and lastly PARP-1 activity can be blocked by providing SIRT agonism, and employment of estrogen. In addition PARP-1 activity could be inhibited by employing poly(ADP-ribose)glycohydrolase (PARG) inhibitors. PARG inhibition increases cellular PAR levels thereby evokes self poly (ADP-ribosylation) of PARP-1, which can impede the activity of PARP-1. Similarly, over activation of PARP-1 can be prevented by providing external NAD+ influx.

The approach of preventing the formation of reactive oxygen and nitrogen species has its own set of advantage and disadvantage. In some cases, it could be an advantage because in addition to inhibiting PARP-1, the neutralization of ROS and RNS may have independent, additional advantages. It could be a limitation, because preventing the generation of reactive oxygen or nitrogen species, that when utilizing such compounds/modalities, it is very difficult to differentiate the relative contribution of PARP-1-dependent versus. PARP1-independent effects to observed biological response (2). Nitric oxide synthase inhibitors and various classes of catalytic antioxidants are at various stages of research or development, and such approaches, clearly, hold the opportunity for indirect prevention of PARP-1 activation in various disease conditions.

4.2. Alternative mechanisms for preventing PARP-1 activity

Targeting poly (ADP-ribose) glycohydrolase (PARG) can be a potential target for inhibiting the activity of PARP-1 alternatively (16). PARG is the main enzyme responsible for PAR degradation. By functional inhibition of PARG, PAR catabolism could be severely disturbed and causes extensive accumulation of PAR. PARG inhibition can indirectly inhibit the activity of PARP-1 by enhancing auto-phoshporylation of PARP-1 due to PAR accumulation. Further, recent experimental evidences are corroborating the beneficial effect of PARG inhibition in dealing with cancer. For instance, apoptosis and necrotic cell death pathways are found to be enhanced when PARG deficient cells are treated with DNA damaging agents (16), or ionizing radiation (17). Additionally, in a further study with PARG knockdowns of the T47D and MDA-MB-468 breast cancer cell lines have found to dramatically reduce the rates of cellular proliferation (18). Subsequent studies using the PARG inhibitor gallotannin successfully emulated the results obtained with the PARG knockdowns (18).

4.2.1. Trapping of PARP-1 at the DNA damage site

Alternatively, PARP-1 inhibitors can trap PARP-1 at the sites of DNA damage and form PARP1-protein DNA complexes. The trapped PARP-1-DNA complexes are highly toxic to the cells because they block DNA replication (19). Consequently, the cancer cells growth would be stopped by the attenuation of DNA replication process (19).

4.2.2. Minor grove binding ligands (MGBLs)

Similarly, preventing the activation of PARP-1 could also be used to stop the activity of PARP-1. A study strengthening this new avenue reports that, minor grove binding ligands (MGBLs) disrupt PARP-1 activation pathways (20). According to this modality, MGBLs prevent activation of PARP1 by blocking the binding of PARP-1 to preferential binding sites on the DNA molecule. This mechanism of PARP-1 inhibition of MGBLs could be useful in two ways, i.e as self-acting cytotoxic agent and as a component of combination chemotherapy to prevent DNA repair by PARP-1, thereby facilitating DNA damage in cancer cells caused by other anticancer drugs (20) (Figure 1).

4.3. Non-specific ways for inhibiting the activity of PARP-1

4.3.1. Targeting NAD and NAD dependent enzymes

Alternatively, external NAD+ influx could also be new avenue for indirectly inhibiting the detrimental effects of PARP-1; indeed experimental results from recent report are strengthening this avenue (21). The study reported that astrocyte death associated with over activation of PARP-1 can be prevented by providing external NAD+ influx. The study also proposes that intact NAD+ could get into astrocytes through connexinhemi channels and that process can play a key role in NAD+ -mediated prevention of PARP-1-triggered astrocyte death (21).

Besides to PARP-1, there is another protein called sirtuin (SIRT) which is an NAD+-dependent deacetylase enzyme involved in the same biological processes as PARP-1. Both SIRT and PARP-1 share a common co-factor nicotinamide adenine dinucleotide (NAD+) and several common substrates, including regulators of DNA damage response and circadian rhythms (22). Apparently, PARP-1 and SIRT under oxidative stress conditions regulate the activity of each other through various mechanisms. SIRT induction leads to protection against oxidative damage, while PARP activation is a detrimental consequence of oxidative stress (22). There is a large overlap between the oxidative stress mediated pathologies that are corrected by SIRT induction (23), or PARP inhibition due to joint regulation of key proteins involved in the pathologies (22). Considering all these evidences, it could be inferred that approaching SIRT activation can minimize the damaging effects of PARP and accordingly this hypothesis is being supported by some studies (23) (Figure 1).

4.3.2. Sequestration with estrogen

In addition, an *in vitro* study hypothesized that estrogen may also meddle with the functioning of PARP-1 indirectly (24). In this study, an interesting *in vitro* interaction can be noted between PARP-1, estrogen and the DNA, and these interactions are further reinforced by the presence of estrogen (24). Indeed, a model of interaction has been proposed between PARP-1, estrogen receptor α and DNA. The study suggests that PARP-1 and estrogen receptor α form a stable complex, which binds to DNA *in vitro* and the DNA binding of this complex is enhanced by estrogen. The stable complex of PARP-1 and estrogen sequesters PARP-1 to specific regions on the DNA, thereby making it difficult for PARP-1 zinc fingers to access and recognize DNA breakpoints (without which its activation would be inhibited) (24). Similarly, Metformin, a clinically used antidiabetic agent, has also been demonstrated to suppress PARP-1 activation *in vitro* (25). This study suggests that metformin is anticipated to have an indirect mechanism to inhibit the function of PARP-1 and the study also suggests the applicability of PARP-1 inhibitor in diabetic complications (25) (Figure 1).

5. CONCLUSION

Inhibition of poly (ADP-ribose) polymerases provides remarkable therapeutic benefits in various acute, often life-threatening diseases (e.g. reperfusion injury, septic and hemorrhagic shock, and stroke) as well as in chronic inflammations (e.g. arthritis, experimental allergic encephalomyelitis, asthma). Indeed, some of PARP-1 inhibitors are in clinical studies for cancer indications. These beneficial effects are likely to result from the improvement of cellular energy status, leading to cell survival. The development of PARP-1 inhibitors has come a long way since the discovery of prototype of PARP-1 inhibitors, aminobenzamides. As it is anticipated that selective PARP-1 inhibitors could produce more promising results and there are multiple studies are underway for the development of selective inhibitors. Consecutively, to drive the concept of PARP-1 inhibition to the new horizons, it is inevitable to incept the hunt for the nonconventional modalities of PARP-1 inhibition. So far, the of hunt for novel mechanisms of PARP-1 inhibition is only in its infancy, nevertheless some propitious events (MGBLs, PARG inhibitors etc.,) are also there in this expedition, which can give an impetus to the researchers to come up with flying colors in the near future.

6. ACKNOWLEDGEMENTS

All the authors significantly contributed for the manuscript.

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Abbreviations: PARP-1: poly (ADP-ribose) polymerase-1; NAD: nicotinamide adenine dinucleotide; PARG: poly(ADP-ribose) glycohydrolase; MGBLs: minor grove binding ligands; PARylation: Poly(ADP-ribosylation)

Key Words: PARP-1, DNA, Stress, Inflammation, Review

Send correspondence to: Chandra Shaker Sriram, Department of Pharmacology & Toxicology, NIPER, III Floor, Gauhati Medical College, Narkachal Hilltop, Bangagarh, Guwahati, Assam, India, PIN: 781032, Tel: 0361-2134538, Fax: 0361-2529457, E-mail: srshekhar@yahoo.com.