TRANSLATIONAL REVIEW

Poly(ADP-Ribose) Polymerase Inhibition in Acute Lung Injury
A Reemerging Concept

Csaba Szabo[1], Vanessa Martins[1] and Lucas Liaudet[2]

[1]Chair of Pharmacology, Section of Medicine, University of Fribourg, Fribourg, Switzerland; and [2]Service of Adult Intensive Care Medicine, University Hospital Medical Center, Lausanne University, Lausanne, Switzerland

ORCID IDs: 0000-0003-3110-4235 (C.S.); 0000-0003-0062-0800 (V.M.); 0000-0003-2670-4930 (L.L.).

Abstract

PARP1, the major isoform of a family of ADP-ribosylating enzymes, has been implicated in the regulation of various biological processes including DNA repair, gene transcription, and cell death. The concept that PARP1 becomes activated in acute lung injury (ALI) and that pharmacological inhibition or genetic deletion of this enzyme can provide therapeutic benefits emerged over 20 years ago. The current article provides an overview of the cellular mechanisms involved in the pathogenetic roles of PARP1 in ALI and provides an overview of the preclinical data supporting the efficacy of PARP (poly[ADP-ribose] polymerase) inhibitors. In recent years, several ultrapotent PARP inhibitors have been approved for clinical use (for the therapy of various oncological diseases): these newly-approved PARP inhibitors were recently reported to show efficacy in animal models of ALI. These observations offer the possibility of therapeutic repurposing of these inhibitors for patients with ALI. The current article lays out a potential roadmap for such repurposing efforts. In addition, the article also overviews the scientific basis of potentially applying PARP inhibitors for the experimental therapy of viral ALI, such as coronavirus disease (COVID-19)–associated ALI.

Keywords: cell death; inflammation; cytokines; coronavirus; olaparib

Clinical Relevance

The current article lays out a potential roadmap for PARP (poly[ADP-ribose] polymerase) inhibitor repurposing efforts for acute lung injury (ALI). In addition, the article also overviews the scientific basis of potentially applying PARP inhibitors for the experimental therapy of viral ALI, such as coronavirus disease (COVID-19)–associated ALI.

PARP Activation, a Reemerging Pathophysiological Concept

PARP1, a Constitutive Mammalian Enzyme

PARP1 is a constitutive mammalian enzyme that is primarily expressed in the nucleus, where it is closely associated with the DNA (1–4). The biochemical reaction, catalyzed by PARP1, involves the transfer of ADP-ribose residues from nicotinamide adenine dinucleotide (NAD^+) onto various target substrates. The product of this reaction is a poly(ADP-ribose) (PAR) chain (Figure 1). The formation of PAR chains is a dynamic process: although PARP1 is involved in the generation of these chains, other enzymes, such as PARG (PAR glycohydrolase) and ARH3 (ADP-ribosylhydrolase 3), remove them and thereby create free PAR polymers or oligomers (1–4).

PARP1, which, in the early literature, is referred to simply as "PARP" (PAR polymerase; earlier designations include "ADP-RT" [ADP-ribosyltransferase] and "PARS" [PAR synthetase]) is the main member of a 17-member family of enzymes. The enzyme family is now officially termed the "ARTD (ADP-ribosyltransferase, diphtheria toxin–like) family" and refers to enzymes capable of catalyzing either

(Received in original form May 11, 2020; accepted in final form June 8, 2020)

Supported by the Swiss National Research Foundation.

Author Contributions: C.S., V.M., and L.L.: literature review and article writing.

Correspondence and requests for reprints should be addressed to Csaba Szabo, M.D., Ph.D., D.Sci., University of Fribourg, Chemin de Musee 18, Fribourg, 1700 Switzerland. E-mail: csaba.szabo@unifr.ch.

Am J Respir Cell Mol Biol Vol 63, Iss 5, pp 571–590, Nov 2020

Originally Published in Press as DOI: 10.1165/rcmb.2020-0188TR on June 8, 2020
Internet address: www.atsjournals.org

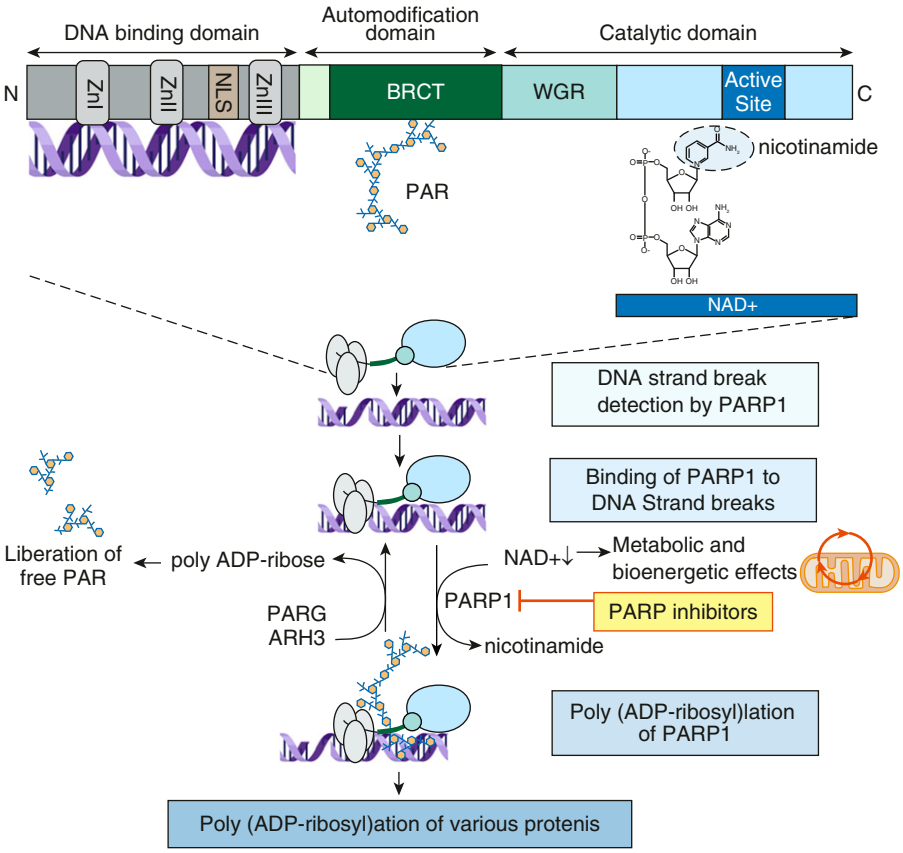

Figure 1. Overview of key biological functions of PARP1. The top part depicts the various domains of PARP (poly[ADP-ribose] [PAR] polymerase), including its DNA-binding domain, with its zinc fingers (ZnI, ZnII, ZnIII), which are essential for recognition of DNA-strand breaks. This domain also contains the NLS. The automodification domain contains the conserved BRCT fold that serves an important protein–protein interaction module in DNA repair and cell signaling. This domain accepts PAR polymers in the context of auto-PARylation of PARP1. The catalytic domain contains the active site of the enzyme, where binding and cleavage of nicotinamide adenine dinucleotide (NAD^+) takes place. It also contains the WGR domain, which is one of the domains involved in the RNA-dependent activation of PARP1. Below the domains, on the right side, the structure of NAD^+ is presented, with the nicotinamide part highlighted. The middle part of the figure shows the sequences of the PARylation process catalyzed by PARP, starting with recognition of the DNA-strand breaks by the DNA-binding domain (gray ovals depicting the zinc fingers binding to the DNA breaks), followed by the catalytic activation of the enzyme and the cleavage of NAD^+, the production of nicotinamide, and the generation of PAR polymers, which, in turn, PARylates various acceptor proteins as well as PARP itself. The consumption of NAD^+ has metabolic and bioenergetic effects. PARP inhibitors prevent the binding of NAD^+ to the active site of PARP and inhibit the catalytic activity of the enzyme. On the left side, the effect of PARG (PAR glycohydrolase) and ARH3 (ADP-ribosylhydrolase 3) is shown; these enzymes break down the PAR polymers, leading to the liberation of free PAR. Reprinted by permission from Reference 17. BRCT = BRCA1 C-terminal; NLS = nuclear localization signal; PARylation = poly–ADP-ribosylation; WGR = tryptophan-glycine–arginine-rich.

mono- or poly-ADP-ribosyl-transfer reactions (4). In the current article, we focus on PARP1 because this enzyme is responsible for the vast majority of cellular PAR formation, and this is the enzyme that has been implicated in the pathogenesis of acute lung injury (ALI).

One of the first recognized roles of PARP1 was the so-called "guardian-angel" function (i.e., its role in the regulation of DNA repair). Although PARP1 is not a DNA-repair enzyme *per se*, it plays a role in the maintenance of genome integrity, in significant part through the recruitment of DNA-repair enzymes to the sites of DNA damage (single- and double-strand breaks in the DNA, as a result, for instance, of oxidative/nitrative stress, ionizing radiation, or genotoxic drugs) (1–4). The nuclear concentration of PAR may also provide an "energetic role": it may be metabolized to ATP, which, in turn, is used by DNA-repair enzymes (5, 6). The translational consequence of these observations was the emergence of a novel therapeutic concept emerged in the field of oncology: via PARP inhibition, DNA repair may be suppressed and, thereby, cancer cell death may be therapeutically induced (4, 7, 8). Subsequent work has discovered that the cytotoxic anticancer effect of PARP inhibitors is most pronounced when the cancer cells have mutations in their HRR (homologous recombination DNA repair) system because, in such instances, the PARP1-dependent DNA-repair system becomes the "last man standing" in the process of DNA repair; elimination of this system, in turn, produces remarkable antitumor efficacy in such tumors (7, 8). Accordingly, ultrapotent (or third-generation) PARP inhibitors (such as olaparib, rucaparib, niraparib, and talazoparib) have recently been clinically approved in many countries); the approved therapeutic indications are typically HRR-deficient tumors (e.g., tumors with BRCA1 or BRCA2 mutations) (7, 8).

Although PARP1's role in DNA repair is not directly relevant in the pathophysiological context, as an active effector of ALI, this aspect of the enzyme is nevertheless very important because if therapeutic PARP inhibition suppresses or delays DNA repair, this must be considered as a potential risk factor or side effect of such therapy (*see* below).

PARP1, an Effector of Multiple Interacting Pathophysiological Cellular Events

Because the substrate of PARP1 is NAD^+, the suggestion was already raised in the 1980s by Nathan Berger's group that the activation of PARP may, in turn, have consequences for the cell's bioenergetic and metabolic status (9). Although the redistribution of PAR into the nuclear compartment is beneficial for DNA repair (*see* above), it can also result in a significant depletion of NAD^+ in the cytosolic compartment. This, in turn, has been shown to result in the depletion of cellular ATP concentrations. The "Berger Hypothesis" was originally developed on the basis of studies in cells subjected to ionizing radiation or genotoxic carcinogens such as *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine. However, follow-up studies have demonstrated that PARP

activation can also develop in response to *endogenous* production of hydroxyl radical or peroxynitrite (which can also create DNA single-strand breaks). PARP overactivation, and the subsequent bioenergetic "catastrophe" was subsequently demonstrated to induce a regulated form of cell necrosis (10–13). Moreover, the various components of the "Berger Pathway" (i.e., DNA damage, PARP activation, cellular energetic and mitochondrial deficits, and, most importantly, the beneficial effect of PARP inhibitors) have been demonstrated in various animal models of disease, ranging from reperfusion injury to various forms of local and systemic inflammation and various types of critical illness (14–17); many of these processes are also relevant for the pathogenesis of ALI (*see* below).

Although the "critical care condition" → "PARP overactivation" → "cell necrosis" scheme is attractive in its simplicity, studies over the last two decades revealed that, in fact, there are several different (often interacting, other times complementary) pathways involved in the pathophysiological aspect of PARP activation (Figure 2). According to the "classic pathway" (Figure 2A) (in reperfusion injury, circulatory shock, various forms of inflammation [as well as in a variety of other diseases]), reactive oxidants and free radicals are formed, for instance, as a consequence of a multitude of biochemical pathways, including reduced NAD^+ phosphate oxidase, and/or infiltration of the tissues with activated immune cells and the consequent release of various reactive species. These species, in turn, produce DNA damage (primarily in the form of single-strand breakage), which is, in turn, recognized by the zinc fingers of PARP1, which, in turn, activate this enzyme. When the DNA damage is widespread (because the oxidant burden is high), the extent of PARP1 activation can be so pronounced, that a subsequent cellular energetic deficiency (NAD^+ depletion, followed by mitochondrial inhibition and depletion of cellular ATP) can produces cell dysfunction (1, 14–17). For instance, in a rat model of endotoxic shock, peritoneal macrophages exhibit reduced NAD^+ and ATP concentrations and suppressed mitochondrial respiration; these effects are suppressed by inhibition of PARP by nicotinamide (18). Moreover, PARP activity (assessed by the rate of NAD^+ consumption in various tissues) were found to be significantly higher during shock in nonsurvivors compared with survivors in a porcine hemorrhagic-shock model (19). In addition, administration of the PARP inhibitor PJ-34 led to decreased serum HMGB1 concentrations (an indicator of cell necrosis) in mice subjected to cecal ligation and puncture (CLP) (20).

Figure 2B depicts an alternative mechanism, which is generally known as the "parthanatos concept." According to this mechanism (which has initially been demonstrated in neuronal models but has subsequently been also extended to a variety of other cells, tissues, and disease conditions), the poly–ADP-ribosylation (PARylation) of various acceptor proteins (as a result of PARP activation, as in

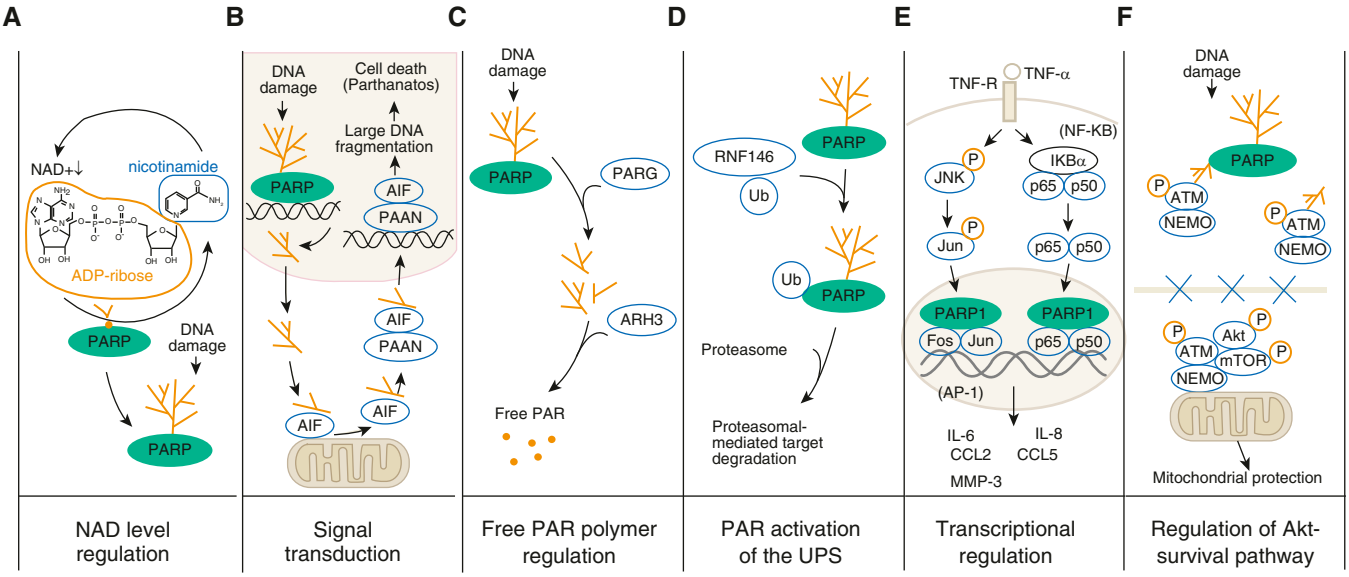

Figure 2. Mechanisms responsible for the cytoprotective and antiinflammatory effects of PARP inhibitors in nononcological diseases. (*A*) PARP activation and consequent NAD^+ depletion (the "Berger Hypothesis"). These processes can lead to a cellular energetic deficit and cell dysfunction; inhibition of PARP prevents these processes and exerts cytoprotective effects (inhibition of cell necrosis). (*B*) Role of PARP activation and free PAR polymers in inducing mitochondrial release of AIF (apoptosis-inducing factor), which, in turn induces cell death (parthanatos). Inhibition of PARP suppresses these processes and inhibits parthanatos. (*C*) The role of PARP in liberating free PAR polymers, which, on their own, exert cytotoxic effects; inhibition of PARP prevents free PAR polymer formation and suppresses cell death. (*D*) PARylation contributes to activation of the proteasome through an interaction with RNF146; PARP inhibitors suppress these processes. (*E*) Role of PARP in contributing to proinflammatory signal transduction via enhancing JNK-mediated (left sequence) and NF-κB–mediated (right sequence) activation of multiple genes and gene products. By inhibiting PARP, these processes are attenuated and inflammatory signaling can be attenuated. (*F*) PARP regulates the activation of the cytoprotective Akt pathway. Under normal conditions, PARylation anchors the ATM–NEMO complexes, which are retained in the nucleus. However, after PARP inhibition, the ATM–NEMO complex translocates to the cytoplasm, where Akt and mTOR are recruited to form the ATM–NEMO–Akt–mTOR cytoprotective signalosome, which, in turn, activates various mitochondrial protective and cell-survival pathways. Adapted by permission from Reference 17. ARH3 = ADP-ribosylhydrolase 3; ATM = ataxia telangiectasia mutated; NEMO = NF-κB essential modulator; P = phosphate group; PAAN = PARP-1–dependent AIF-associated nuclease; Ub = ubiquitin group; UPS = ubiquitin-proteasome system.

Figure 2A), is followed by the removal and degradation of PAR. Free PAR, in turn, leaves the nucleus and translocates into the cytosolic compartment of the cell. It also reaches the mitochondria, where it binds to specific mitochondrial receptors, resulting in the release of AIF (apoptosis-inducing factor). AIF, in turn, diffuses back to the nucleus, where it induces large-scale nuclear fragmentation and cell death (parthanatos). This process has been primarily indicated in central-nervous-system pathologies (21); its potential role in critical illness remains to be explored.

In addition, free PAR polymer can have independent roles as a pathogenetic factor (Figure 2C) because it can bind to various protein acceptors intracellularly (or even, in some cases, extracellularly). These PARylation reactions (a form of posttranslational modifications) have been shown to contribute to various pathophysiological processes ranging from neurodegeneration to vascular injury (21).

Another aspect of PARP relates to the fact that it can also regulate ubiquitylation-mediated protein-degradation reactions (Figure 2D). The process of ubiquitin-mediated protein degradation is involved in various cell-signaling and protein-quality-control processes. Iduna/RNF146, a constitutively expressed ubiquitin E3 ligase is activated by PARylation. In turn, proteosomally mediated degradation of various proteins can ensue, which may have various adverse effects on the cells affected by it (22, 23).

A significant further role of PARP1 relates to its regulatory role on gene transcription (Figure 2E). A general mechanism involved in this process relates to the modulation of chromatin structure (in principle, due to the fact that the PAR polymer is negatively charged), affecting the availability of the DNA to the enzymes involved in gene transcription. A secondary mechanism relates to transcriptional coregulation, and a third mechanism relates to the modulation of DNA methylation. In this context, PARP1 does not "need" to be activated by DNA-strand breaks; resting (constitutive) PARP can confer these actions, in some cases because of its scaffolding (protein–protein interaction) roles. Pharmacological PARP inhibitors in many (but not all) instances can significantly modulate the above processes, with the end result being the suppression of gene transcription in a semispecific manner. In many experimental models, the generation of proinflammatory cytokines and chemokines can be suppressed by PARP inhibitors, producing an antiinflammatory and/or immunomodulatory result (15, 23). However, in complex situations (e.g., *in vivo* models of disease), the antiinflammatory effects of PARP inhibitors may also be related to the interruption of various positive-feedback cycles of disease (1) (Figure 3). In the context of critical illness, PARP inhibitors have been demonstrated to suppress the activation of NF-κB and the subsequent production of various proinflammatory cytokines (e.g., TNF-α) (24) and various chemokines (e.g., MIP-1α and MIP-2) (25). The models used initially employed murine models of endotoxemia (24, 25) but were subsequently extended into in various rodent and large-animal models of sepsis, septic shock (16, 17), and ALI (*see* below).

Finally, PARP inhibition has been shown to activate the cytoprotective Akt pathway (Figure 2F). The first step in this process is that PARP inhibition increases the interaction between p-ATM and NEMO proteins, thereby facilitating the translocation of this complex from the nucleus into the cytoplasmic compartment. In turn, a cytoprotective signalosome (p-ATM–NEMO–Akt–mTOR) is formed, which induces the activation of Akt. Akt is a "master regulator" of various cell-survival pathways; its activation produces a cytoprotective phenotype (26).

The Therapeutic Efficacy of PARP Inhibitors in ALI

PARP Inhibitors Exert Beneficial Effects in Preclinical Animal Models of Lung Injury

Multiple lines of *in vivo* experiments have demonstrated that pharmacological PARP inhibitors or PARP1 deficiency can significantly improve the outcomes of various animal models of acute and chronic lung injury, including endotoxin- or sepsis-induced lung injury, pancreatitis-induced lung injury, lung inflammation elicited by various agents (e.g., zymosan, carrageenan or elastase), ventilator-induced lung injury, environmental agent– or drug-induced lung injury, or lung fibrosis and allergy/asthma–associated lung inflammation and dysfunction (26–84). Table 1 focuses on the findings related to the effect of PARP inhibitors in various forms of ALI and lung inflammation.

Generally, the effects of PARP inhibitors include the correction of the hyperinflammatory response (i.e., suppression of cytokine and chemokine production), reduction of the infiltration of the lung tissue and the alveolar space with inflammatory cells, reduced oxidative and nitrosative stress (most likely due to the interruption of the positive-feedback cycles outlined in Figure 3), improved pulmonary gas exchange, and improved histological status of the lung tissue. Importantly, the beneficial effects of PARP inhibition not only have been shown in rodent models but also hve been extended to several clinically more-relevant large-animal models of ALI (31, 40, 49, 50, 65).

However, it must be emphasized that the studies summarized in Table 1 have a number of limitations. For instance, many studies (especially the studies in the 90s) used first-generation PARP inhibitors, such as 3-aminobenzamide or nicotinamide; these agents have many additional pharmacological actions in addition to PARP inhibition, including antioxidant effects and inhibition of mono-ADP ribosylation (85–87). Although the use of such agents was acceptable when the available tools were limited, current and future work should use third-generation inhibitors, preferably in combination with PARP1-deficient animal models, as these animals are viable and commercially available. Another common limitation of many of the published studies is that they used only one sex of animals (typically male). Since the mid-2000s, it has become more and more obvious that the effect of PARP inhibitors in various rodent models of shock, inflammation, and reperfusion injury is sex-specific; in most (but not all) cases, male animals benefit more (as well as aged females and ovariectomized females), whereas the protective effect of PARP inhibitors in females is less pronounced (88, 89). However, it should also be mentioned that in some models (e.g., burn/smoke inhalation–associated lung injury), PARP inhibitors show significant therapeutic benefit in female large-animal models as well (e.g., References 40, 48). Moreover, in pancreatitis and pancreatitis-associated lung injury, both male and female mice were found to respond comparably well to PARP inhibition (56, 63, 90). We recommend that future studies, especially ones that focus on translationally relevant (i.e., clinically approved) PARP inhibitors,

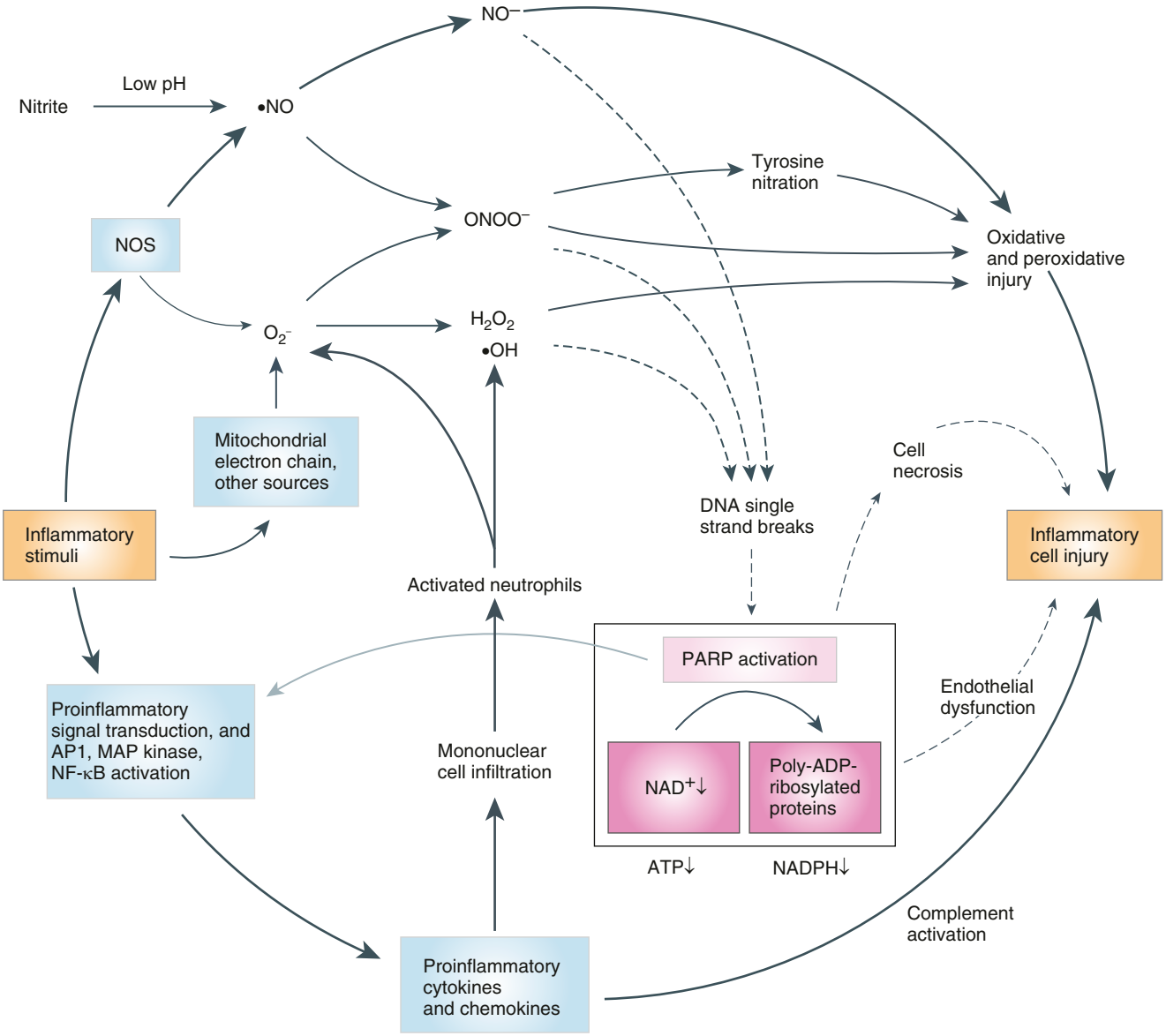

Figure 3. Pathophysiological triggers of PARP activation and interacting pathways of injury. Various pathophysiological conditions lead to the formation of various reactive oxygen species from various sources (such as the mitochondria, xanthine oxidase, or reduced NAD^+ phosphate [NADPH] oxidase). In inflammatory states, various proinflammatory pathways are stimulated in response to autoimmune responses and/or proinflammatory microbial components. The corresponding isoforms of NOS (nitric oxide [NO] synthase; brain NOS in the central nervous system, endothelial NOS in the cardiovascular system, and inducible NOS under inflammatory conditions) produce NO (but under conditions of L-arginine depletion, NOS can also produce superoxide). Under low-pH conditions (such as tissue hypoxia/acidosis), nitrite can also be converted to NO. Superoxide (which is produced from various cellular sources, including mitochondria) and NO react to yield peroxynitrite. Peroxynitrite and hydroxyl radical induce single-strand breaks in DNA, which, in turn, activate PARP. This can deplete the cellular NAD^+ and ATP pools. Cellular energy exhaustion triggers the further production of reactive oxidants. PARP activation leads to cellular dysfunction via the energetic mechanism as well as via several other pathways outlined in Figure 2. Oxidative and nitrative stress can cause endothelial-cell dysfunction, at least in part though the depletion of NADPH concentrations, which, in turn, leads to reduced endothelial NO formation. The cellular dysfunction is further enhanced by the promotion of proinflammatory gene expression by PARP, through the promotion of NF-κB, AP1 (activator protein-1), and MAP (mitogen-activated protein) kinase activation. PARP can also promote complement activation. The oxidant-induced proinflammatory-molecule and adhesion-molecule expression, along with the endothelial dysfunction, induce neutrophil recruitment and activation, which initiates positive-feedback cycles of oxidant generation, PARP activation, and cellular injury. For instance, tissue-infiltrating mononuclear cells produce additional oxidants and free radicals. PARP is also involved in triggering the release of mitochondrial cell-death factors, such as AIF. There are many oxidative and nitrosative injury pathways that are triggered by oxygen- and nitrogen-centered oxidants and free radicals, which act in parallel or in synergy with PARP-mediated pathways of cell injury. Although most of the pathways shown in the figure have been demonstrated in acute lung injury (ALI), the relative contribution of cell necrosis versus inflammatory cell injury, as well as the relative role of the various pathways shown in the figure, depends on the specific form of ALI and the stage of the disease. Reprinted by permission from Reference 1.

Table 1. Effects of PARP Inhibition in Preclinical Models of ALI and Lung Inflammation

Experimental Model	Animal Species	Effective Dose of the PARP Inhibitor	Effect of PARP Inhibition	Notes, Caveats, Limitations of the Study	Reference
Endotoxin-induced or sepsis-associated ALI					
LPS-induced ALI	Pig	3-AB (20 mg/kg i.v. pretreatment)	Protection against the LPS-induced, delayed suppression of lung compliance; prevention of the LPS-induced increase of nitrotyrosine immunoreactivity* in the lung	Many parameters were unaffected by 3-AB (e.g., the recruitment of inflammatory cells into the BAL fluid); no effect of 3-AB was noted on the LPS-induced changes in systemic hemodynamics. Limitations: [A], [B], [C], [D], and [J].	31
LPS-induced ALI	BALB/c mouse	PARP1 genetic deficiency or PJ34 (20 mg/kg i.p., applied as a 1 h after treatment)	Inhibition of cell infiltration into the BAL fluid; inhibition of protein extravasation into the alveoli; suppression of TNFα, IL-1β, and MIP-1α production; reduced NO metabolite concentrations in the BAL; inhibition of lipid peroxidation (MDA) in the lung tissue; reduced MPO† activity in the lung tissue; improved lung histopathology with less alveolar hemorrhaging and fewer inflammatory cells	Limitations: [C], [E], and [J].	35
LPS-induced ALI	Wistar rat	PJ-34 (10 mg/kg i.p. pretreatment)	Decreased MDA and MPO† activity in the lung tissue; reduced TNFα, IL-1β, and nitrite/nitrate serum concentrations, improved survival	Limitations: [B], [C], [E], and [J].	37
LPS-induced ALI	C57BL/6 $\times$ 129/Sv mouse	PARP1 genetic deficiency	Attenuated iNOS and ICAM-1 expression in the lung	Limitations: [D], [I], and [J].	39, 46
LPS-induced ALI	Rabbit	3-AB (10 mg/kg i.v. bolus + 5 mg/kg/h infusion, applied as a pretreatment)	Inhibition of iNOS expression in the lungs. Decreased pulmonary edema; reduced nitrotyrosine immunoreactivity* in the lung; inhibition of systemic NO overproduction. Reduced lipid peroxidation (TBARS) in the plasma (with a similar trend in the lung tissue). Inhibition of albumin extravasation into the alveoli. Improved lung histology. Reduction of ICAM-1 expression in the lungs and reduction of cell infiltration into the lung tissue. Inhibition of the enlargement of the alveolar septa. Reduced leukocyte adhesion to the pulmonary arterioles, capillaries, and venules. Normalization of the effect of LPS on the alveolar–arterial oxygen difference	3-AB did not affect NF-κB activation in the lung tissue. No effect of the inhibitor on systemic hemodynamics or on red-blood-cell velocity. No effect on granulocyte ROS production *ex vivo*. Limitations: [A], [B], [E], and [J].	39, 46
LPS-induced ALI	Rabbit	3-AB (10 mg/kg i.v. bolus + 2.5 mg/kg/h infusion, applied as a pretreatment)	Restoration of the pulmonary architecture; maintenance of the gas exchange barrier; attenuation of the pulmonary edema; inhibition of the enlargement of the alveolar septa. Decreased oxidative stress (TBARS) in plasma; inhibition of nitrotyrosine* immunoreactivity in the lungs. Normalization of the effect of LPS on the alveolar–arterial oxygen difference	Limitations: [A], [B], [E], and [J].	47

(Continued)

Table 1. (*Continued*)

Experimental Model	Animal Species	Effective Dose of the PARP Inhibitor	Effect of PARP Inhibition	Notes, Caveats, Limitations of the Study	Reference
LPS-induced ALI	BALB/c mouse	4-HQN (100 mg/kg i.p.) pretreatment and delayed-treatment protocols were both used	The PARP inhibitor improved survival in pretreatment and also when its administration was delayed to be given 1 h after the LPS challenge. It suppressed the hyperintensity of the MRI signal in the thoracic region (suggesting an inhibition of pulmonary inflammation and edema); decreased TNFα plasma concentrations; increased Akt phosphorylation and activation; attenuated ERK1/2, p90RSK activation; suppressed MAPK p38 activation; prevented NF-κB activation; inhibited c-Fos activation in the lung and in other tissues as well	When the administration of the PARP inhibitor was delayed to 6 h, the survival benefit was no longer seen. Limitations: [C], [D], [G], [I], and [J].	51
LPS-induced ALI	Sprague-Dawley rat	Nicotinamide (100 mg/kg i.v. pretreatment)	Systemic effects: protection against hypotension, erythropenia, and leukopenia. Protection against the increases in plasma markers of liver and kidney injury. Inhibition of NO, TNFα, and IL-1β production; prevention of pulmonary edema and pulmonary hemorrhage, protection against the infiltration of inflammatory cells into the lung; reduced protein extravasation into the alveoli; restoration of tissue ATP content	Limitations: [A], [B], [E], and [J].	58
LPS- or TNF-induced ALI	C57BL/6 mouse	PARP1-genetic deficiency	Reduced recruitment of inflammatory cells into the lung; suppressed lung inflammation; reduced expression of MCP-1, MIP-1α, KC, MIP-2; reduced CXCR2 expression; completely suppressed DARC expression	Limitations: [I] and [J].	64
LPS-induced ALI	Sprague-Dawley rat	3-AB (20 mg/kg i.v. pretreatment)	Systemic effect: protection against LPS-induced hypotension; prevention of acidosis and lactatemia; improved blood oxygenation. Improved pulmonary edema (evidenced by lung wet/dry weight ratio); decreased TNFα, IL-1β, and IL-6 expression in the lung; inhibition of NF-κB activation in the bronchial epithelial cells	3-AB inhibited the expression of PARP1 protein in pulmonary epithelial cells (as opposed or possibly in addition to its expected effect on PARP1 activity; perhaps this effect is related to the antioxidant effect of this inhibitor). Limitations: [A], [B], [C], [E], and [J].	66

(*Continued*)

Table 1. (*Continued*)

Experimental Model	Animal Species	Effective Dose of the PARP Inhibitor	Effect of PARP Inhibition	Notes, Caveats, Limitations of the Study	Reference
LPS-induced ALI	C57BL/6 mouse	DPQ (10 μg/kg i.p. pretreatment)	Inhibition of neutrophil infiltration into the lung (evidenced by histological analysis; also confirmed by measurement of lung MPO† activity); inhibition of lung vascular hyperpermeability; inhibition of the upregulation of TNFα, IL-1β, IL-6, MIP-2, iNOS, and CXCL-1 mRNA concentrations in the lung tissue and peritoneal macrophages); inhibition of cell death; maintenance of vascular permeability; inhibition of the activation of the NF-κB pathway; reduction in the number of apoptotic cells in the lung	The stated dose of the PARP inhibitor is much lower than generally used effective doses in the literature. A lower doses of the inhibitor (1 μg/kg) was reported as not effective. Limitations: [B], [C], [E], [G], and [J].	67
LPS-induced multiorgan-failure ALI	LACA mouse	Olaparib (5 or 20 mg/kg i.p. in 30-min post-treatment protocol relative to LPS)	PARP inhibition resulted in a suppression of macrophage and neutrophil infiltration into the BAL fluid; restoration of the pulmonary redox balance; decreased TNFα, IL-1β, and VCAM-1 mRNA expression. The LPS-induced oxidative stress in the lung (increase in MDA and decrease in GSH content) was also suppressed by the inhibitor. There were also various beneficial effects on renal function	A lower dose of olaparib (1 mg/kg) was not effective. The experimental group size is not stated in the article. Limitations: [C], [E], [G], and [J].	70
Hydrochloric acid + LPS ("two-hit model")-induced ALI and neuroinflammation	BALB/c mouse	Olaparib (5 mg/kg i.p.). Both a pretreatment protocol in which the inhibitor was given before each "hit" and a post-treatment protocol (start of olaparib administration 1 wk later and repeated three more times, 2 d apart each) were employed	Systemic effects: inhibition of cytokine concentrations (TNFα, IL-1β, IL-6) in the plasma. Inhibition of neutrophil infiltration into the lung; reduction in alveolar capillary damage; reduction in oxidative stress markers in the lungs; protection against the breakdown of blood–brain barrier; reduction of the extent of neuroinflammation; protection against cognitive impairment. Olaparib also inhibited HIF-1α protein expression in the lung and brain. The beneficial effects on cognitive impairment were maintained in the post-treatment protocol	Limitations: [C], [E], [G], and [J].	83
CLP-induced septic shock and ALI	129/Sv X C57BL/6 mouse	PARP1 genetic deficiency	Decreased TNFα, IL-6, and IL-10 concentrations in plasma; inhibition of MPO† in the lung tissue; improved survival; suppression of circulating markers of liver and kidney injury	Circulating NO concentrations and lipid peroxidation (MDA content) in the lungs was comparably elevated in wild-type and PARP1$^{-/-}$ animals after CLP. Limitations: [C], [E], [I], and [J].	36

(*Continued*)

Table 1. (*Continued*)

Experimental Model	Animal Species	Effective Dose of the PARP Inhibitor	Effect of PARP Inhibition	Notes, Caveats, Limitations of the Study	Reference
CLP-induced septic shock and ALI	C57BL/6 mouse	Olaparib (6–20 mg/kg total daily dose i.p., starting at 30 min after CLP and repeated 8 h and 24 h later)	Increased survival rate; attenuation of TNFα, IL-1α, IL-1β, IL-2, IL-4, IL-6, and IL-12p40 plasma concentrations reduced the Th17/Treg ratio in the blood. The PARP inhibitor also reduced bacterial CFUs, consistent with an enhancement of antibacterial immune defense	Although the CLP model was severe, no significant increases in lung MPO or MDA concentrations were observed after CLP, and olaparib did not affect these values. Histological analysis of the lung tissue revealed a slight emphysema in all groups. Limitations: [G] and [I].	81
Pneumonia					
P. aeruginosa instillation into the lungs	Sheep	INO-1001 (10 mg/kg i.v. bolus, followed by 0.3 mg/kg/h infusion. The start of the bolus inhibitor was delayed 1 h relative to the injury)	Decreased pulmonary edema and hemorrhage; inhibition of neutrophil infiltration into the lung tissue (histological analysis); improved gas exchange; protection against the obstruction of bronchi and bronchioles; decreased lipid peroxidation (MDA content in lung tissue); reduced nitrotyrosine* immunoreactivity; inhibition of iNOS mRNA expression. There was also a trend for improved survival	Limitations: [B], [C], [F], and [J].	48
Sepsis-induced pneumonia	Rabbit	PJ34 (10 mg/kg i.v. pretreatment)	Gut wet/dry ratios were improved in the sepsis/PJ34 group. There was a trend for reduced bacteremia	No hemodynamic effects of the PARP inhibitor were observed. Although a trend was noted, no statistically significant differences observed in lung wet/dry ratios between the sepsis and sepsis/PJ34 group. No significant differences were found in serum, peritoneal, and luminal gut lactate concentrations or in P_{CO_2} gap between experimental groups. Limitations: [B], [C], D], [I], and [J].	55
Lung inflammation					
Zymosan-induced systemic inflammation	Swiss Albino mouse; Wistar rat	3-AB (10–20 mg/kg i.v. pretreatment)	Attenuated MPO† in the lung tissue	Limitations: [A], [B], [C], [E], [I], and [J].	29
Zymosan-induced systemic inflammation	129/SV × C57BL6 mouse	PARP1 genetic deficiency	Improved pulmonary histology (reduction in interstitial hemorrhaging and mononuclear-cell accumulation)	Limitations: [C], [E], [I], and [J].	29
Zymosan-induced systemic inflammation	Long-Evans rat	GPI 6150 (40 mg/kg i.p., after treatment: two doses applied at 1 and 6 h after zymosan)	PARP inhibition decreased neutrophil migration and MPO† in the lung tissue; decreased pulmonary edema and improved histological picture of the lung. Hyperbilirubinemia and the increased alkaline-phosphatase concentrations were attenuated; survival rate was improved	Limitations: [C], [D], [I], and [J].	33

(*Continued*)

Table 1. (*Continued*)

Experimental Model	Animal Species	Effective Dose of the PARP Inhibitor	Effect of PARP Inhibition	Notes, Caveats, Limitations of the Study	Reference
Zymosan-induced systemic inflammation	BALB/c mouse	5-AIQ (3 mg/kg i.p, after treatment: two doses applied at 1 and 6 h after zymosan)	PARP inhibition attenuated pulmonary edema; reduced neutrophil infiltration into the lung; and lowered levels a lipid peroxidation marker (MDA) in the lung tissue; it also decreased pulmonary ICAM-1 and P-selectin expression; ameliorated the zymosan-induced increases in TNFα and IL-1β serum concentrations	Limitations: [E] and [J].	34
Carrageenan-induced lung inflammation	Long-Evans rat	3-AB (1–30 mg/kg i.p. pretreatment)	Inhibited plasma extravasation and PMN accumulation in the lungs; reduced plasma nitrite/nitrate concentrations; decreased nitrotyrosine* immunoreactivity in the lung tissue	Limitations: [A], [B], [C], [D], [I], and [J].	30
Carrageenan-induced lung inflammation	BALB/C mouse	5-AIQ (1.5 mg/kg i.p. pretreatment)	Reduced recruitment of inflammatory cells into the lung tissue; decreased IL-6, TNFα, and IL-1β plasma concentrations; increased IL-10 expression; reduced CD11a, CD62L, ICAM-1, and MCP-1 concentrations; decreased iNOS and COX-2 expression; suppressed the activation of the NF-κB system; reduced STAT3 expression; increased IL-4 expression; improved pulmonary histology	Treatment of carrageenan-injected animals with the inhibitor reduced $CD25^+$-, $GITR^+$-, and $CD25^+GITR^+$-expressing cell subsets in the pleural exudate; it also prevented the changes $Foxp3^+$ and $IL\text{-}17^+$ (the decrease or increase, respectively) in the peripheral blood and in the pleural exudate, suggesting an immunomodulatory effect of the PARP inhibitor. Limitations: [B], [C], [F], [G], and [J].	71
Elastase-induced lung inflammation and emphysema	BALB/c mice	Olaparib 5 or 10 mg/kg i.p., either daily or every 48 h, starting as a pretreatment	Decreased neutrophil and macrophage counts in the lung tissue; reduced concentrations of TNFα, IL-6, GCSF, KC, and MCP-1 in the BAL fluid; restored the pulmonary redox balance (increased ROS production, increased MDA concentrations, reduced GSH concentrations); inhibited NF-κB activation in the lung with consequent reduction of ICAM-1 and VCAM-1 expression. Protection against emphysema (air space enlargement)	Lower doses of olaparib (1 or 2.5 mg/kg) were not effective. Although this is principally a COPD model, there are several aspects of the study (effect of olaparib on inflammation and oxidative stress) that are relevant to the focus of the review (ALI). Limitations: [B], [C], [E], and [J].	80
Elastase-induced lung inflammation and emphysema	C57BL/6 mice	PARP1 genetic deficiency	Decreased neutrophil and counts in the lung tissue; reduced concentrations of TNFα, IL-6, KC, and GCSF in the BAL fluid; improved lung histology	Although this is principally a COPD model, there are several aspects of the study (role of PARP1 in pulmonary inflammation) that are relevant to the focus of the review (ALI). Limitations: [C], [D], [I], and [J].	80
Pancreatitis-associated ALI					

(*Continued*)

Table 1. (*Continued*)

Experimental Model	Animal Species	Effective Dose of the PARP Inhibitor	Effect of PARP Inhibition	Notes, Caveats, Limitations of the Study	Reference
Pancreatitis-associated ALI	Wistar rat	3-AB (10 mg/kg i.v.)	Prevention of the increase of P-selectin expression in the lungs; prevention of the increase in MPO† in the lung tissue; inhibition of PAF production; decrease of the infiltration of PMNs into the alveoli; prevention of alveolar wall thickening; improvement in lung histology	The PARP inhibitor also reduced the severity of pancreatitis. Limitations: [A], [B], [C], [E], and [J].	32
	129/Sv × C57BL/6 mouse	PARP1 or PARP2 genetic deficiency or PJ34 (10 mg/kg i.p.) or 3-AB (30 mg/kg i.p.)	The two PARP inhibitors and PARP1 deficiency suppressed lung inflammation; improved lung histological picture; lowered levels of MPO† in the lung tissue; decreased IL-6 and IL-1β plasma concentrations	The PARP inhibitors and PARP1 deficiency also markedly reduced the severity of pancreatitis. PARP2 deficiency reduced macrophage infiltration into the pancreas but did not affect any other pancreatic or pulmonary parameter investigated. Limitations: [B], [C], [E], and [J].	56
	Swiss-Webster mouse	PJ34 (15 mg/kg i.p. every 12 h) or KU0058684‡ (15 mg/kg i.p. every 12 h) PARP inhibitor administration started 36 h after the initiation of the insult to induce pancreatitis (CMDE diet)	The two PARP inhibitors were comparable in their effectiveness. They produced a reduction of alveolar capillary thickening, protected against inflammatory cell infiltration into the lung, protected against apoptosis, and decreased IL-6 and IL-1β plasma concentrations	Both PARP inhibitors also reduced the severity of pancreatitis and improved survival. Limitations: [C], [F], and [J].	63
I/R-associated ALI					
I/R-associated ALI	Long-Evans rat	INO-1001 (3 mg/kg i.v.)	Reduction in the I/R-induced vascular hyperpermeability; inhibition of the I/R-induced increase in MPO† in the lung; reduction of leukocyte infiltration into the BAL fluid; decrease of TNFα, MIP-1α, MIP-2, and CINC concentrations in the BAL fluid; inhibition of NF-κB activation in lung homogenates; inhibition of caspase-3 immunopositivity and protection against the increase in TUNEL immunoreactivity‡ in the lung	Limitations: [B], [C], [E], and [J].	52
I/R-associated ALI	Long-Evans rat	INO-1001 (3 mg/kg - i.t.)	The PARP inhibitor protected against the development of vascular hyperpermeability, attenuated MPO† in lung homogenates, suppressed neutrophil infiltration into the BAL fluid, and inhibited the activation of the AP-1 and NF-κB systems; reduced secretion of MCP-1 and CINC into the BAL fluid	The sex of the animals was not stated in the report. Limitations: [B], [C], [D], and [J].	41

(*Continued*)

Table 1. (*Continued*)

Experimental Model	Animal Species	Effective Dose of the PARP Inhibitor	Effect of PARP Inhibition	Notes, Caveats, Limitations of the Study	Reference
Hindlimb ischemia–reperfusion-associated remote ALI	Wistar rat	3-AB (10 mg/kg i.p. 30 min before the start of the lung reperfusion)	3-AB prevented the increase in MDA and concentrations in the lung tissue and plasma; it prevented the increase in lung MPO†; protected against the development of lung edema, prevented inflammatory cell infiltration into the lung; protected against the suppression of Na^+/K^+ ATPase activity in the lung tissue. Nitrotyrosine* immunoreactivity was also suppressed	Limitations: [A], [B], [C], [F], and [J].	54
I/R-associated ALI	Sprague-Dawley rat	Nicotinamide (100 mg/kg i.v. after treatment, starting 30 min after the beginning of lung reperfusion)	Nicotinamide suppressed pulmonary edema and vascular hyperpermeability. It reduced protein influx into the BAL fluid. It prevented the depletion of lung ATP, and it decreased NO, TNFα, and IL-1β production	PARP activation was demonstrated in the lung tissue after reperfusion; the study also confirmed the inhibitory effect of nicotinamide on lung PARP activation. Limitations: [A], [E], and [J].	60
I/R-associated ALI	Wistar rat	PJ34 (10 mg/kg i.v.)	Inhibition of pulmonary edema; suppression of lung inflammation; restoration of cellular ATP concentrations decreased TUNEL‡ staining in the lungs, together with suppression of TNFα and IL-6 production. Inhibition of oxidative stress markers in the lung tissue	Instead of PARP activation, the study focused on PARP1 cleavage; this process was apparent in the lung tissue after reperfusion; PJ34 inhibited this process. The PARP inhibitor also protected against hepatic and renal injury. A lower dose (5 mg/kg) of the inhibitor was less effective; a higher dose (20 mg/kg) produced lung edema on its own. Limitations: [B], [C], [E], and [J].	68
Organ allograft–associated ALI					
Tracheal allograft–induced obliterative bronchiolitis	Brown-Norway into Lewis rat	INO-1001 (5 mg/kg i.p. twice per day for 2 wk, starting immediately after transplantation)	Reduced luminal obstruction; decreased peritracheal inflammation; preservation of the integrity of the respiratory epithelium; attenuation of NF-κB activation; decreased TNFα expression; protection against caspase-3 activation and suppression of the development of TUNEL‡ immunoreactivity	Limitations: [C], [E], and [J].	42
Renal allograft–induced remote lung injury	Brown-Norway into Lewis rat	3-AB (10 mg/kg i.v.)	Decreased Rip1 expression; decreased hemorrhage and leukocyte infiltration into the lung; prevention of TUNEL‡ positivity in the lung tissue; suppression of TNFα production, improved lung histological pictures and injury scores	PARP1 expression and PARP activation (PAR immunostaining) over the course of the immune rejection was demonstrated. The efficacy of 3-AB was enhanced when it was combined with a necroptosis inhibitor. The interventions also protected against the primary (renal) injury. Limitations: [A], [C], [E], and [J].	73

(*Continued*)

Table 1. (*Continued*)

Experimental Model	Animal Species	Effective Dose of the PARP Inhibitor	Effect of PARP Inhibition	Notes, Caveats, Limitations of the Study	Reference
Lung transplantation: reconditioning of marginal donors via *ex vivo* lung perfusion	Sprague-Dawley rat	3-AB (perfusion for 3 h with 1 mg/ml of the inhibitor before transplantation)	Attenuated nitrosative and oxidative stress (protein carbonyls, nitrotyrosine*) in the transplanted lungs; reduced LDH release indicative of protection against cell necrosis; and IL-6 concentrations protect against the increase in lung compliance; improved lung histopathology and protection against perivascular edema in the transplanted lungs	PARP activation (PAR staining) and the inhibitory effect of 3-AB on this response was confirmed in the study. Limitations: [A], [E], and [J].	76
Lung transplantation: reconditioning of marginal donors via *ex vivo* lung perfusion	Sprague- Dawley rat	3-AB (perfusion for 3 h with 1 mg/ml of the inhibitor before transplantation)	The change in the IL-6/IL-10 ratio in the BAL fluid was attenuated by the PARP inhibitor. It also protected against the increase in lung compliance; reduced MPO†; reduced MDA and 3-nitrotyrosine* concentrations after transplantation; decreased cell infiltration after lung transplantation; improved lung histopathology after transplantation, together with a suppression of P-selectin and VCAM-1 expression	The inhibitory effect of 3-AB on PARP activation (PAR staining) was confirmed in the lungs. Limitations: [A], [C], [D], and [J].	82
Cardiopulmonary bypass–induced lung injury					
Cardiopulmonary bypass–induced ALI	Dog	PJ34 (5 mg/kg i.v.) or INO-1001 (1 mg/kg i.v.)	Improved pulmonary function and gas exchange	The PARP inhibitors also improved coronary vascular function and exerted beneficial systemic hemodynamic effects. Limitations: [A], [C], [D], and [J].	49, 50
Cardiopulmonary bypass–induced ALI	Piglet	INO-1001 (1 mg/kg/h i.v.)	Protection against the injury-associated increase of alveolar wall thickness; decreased TNFα and HSP70 concentrations in the lung	Intraalveolar erythrocyte or granulocyte counts were not significantly affected by the PARP inhibitor. Hemodynamic or oxygenation parameters were only slightly impaired or were unaffected by the bypass model, and the PARP inhibitor did not significantly affect them. Limitations: [A], [C], [D], and [J].	61
Burn- or thermal injury–associated ALI					
Burn and smoke inhalation–associated ALI	Sheep	INO-1001 (3 mg/kg i.v. bolus starting 1 h after injury, followed by 0.3-mg/kg/h infusion)	Improved respiratory mechanics; protection against the dysregulation of lymph flow; protection against the development of microvascular hyperpermeability; decreased pulmonary edema; decreased oxidative stress markers; improved histological picture of the lungs, prevention of the increase in pulmonary arterial pressure	Inhibition of PARP activation (PAR staining) in the lung by INO-1001 was confirmed by immunohistochemical analysis. The inhibitor also exerted beneficial hemodynamic effects (pulmonary vascular resistance, cardiac index, stroke volume index) in this model. Limitations: [F] and [J].	40
Thermally induced ALI	Wistar rat	3-AB (10 mg/kg i.p.)	Decreased MPO† and MDA in the lung tissue; decreased nitrotyrosine* immunoreactivity in the lungs	Beneficial effects were also noted in other organs (gut, kidney). Limitations: [A], [B], [C], [D], [I], and [J].	53

(*Continued*)

Table 1. (*Continued*)

Experimental Model	Animal Species	Effective Dose of the PARP Inhibitor	Effect of PARP Inhibition	Notes, Caveats, Limitations of the Study	Reference
Smoke inhalation–associated ALI	Sheep	PJ-34 (0.003 and 0.03 mg/kg/h i.v. infusion, starting 1 h after injury)	Improved respiratory mechanics; prevented the increased lung lymph flow and microvascular permeability; protected against the development of pulmonary edema	The beneficial effects were more pronounced in the group receiving the higher dose of the inhibitor. Systemic hemodynamic parameters were not significantly affected by the procedure, and PARP inhibition did not have any effect on them. Limitations: [F] and [J].	65
Scald-burn injury	BALB/c mouse	Olaparib (10 mg/kg/d i.p.)	Reduced pulmonary MPO† 7 d after injury; reduced pulmonary MDA concentrations 24 h after injury; suppressed the expression of TNFα and IL-1α, IL-1β, IL-12, and VEGF in the plasma	At the early time point (24 h after injury) olaparib did not protect against the elevation of pulmonary MPO†. Also, olaparib was not protecting the changes in MPO† in liver and kidney. No effect of olaparib was noted on MDA concentrations in lung 7 d after injury. Olaparib also attenuated the increases in plasma markers of pancreatic and renal injury. It affected one liver injury marker (ALT) but not ALP. Limitations: [B], [C], [E], [I], and [J].	84
VILI					
VILI	C57BL/6 mouse	PJ34 (20 mg/kg i.p.)	Decreased inflammation; protected against the development of lung edema; improved lung histological scores and histological pictures; protected against the loss of lung compliance; inhibited the increase in MPO† in the lung tissue; suppressed NF-κB activation; inhibited NO, TNFα and IL-6 production	The article does not specify the final tidal volume delivered to the mice. The ventilation time was only 2 h, suggesting that the injury was primarily mechanical because of overstretching ("barotrauma"), rather than being secondary to stretch-induced inflammation and cell death. Limitations: [B], [E], and [J].	59
	miR-223$^{-/+}$ mouse	PARP1 shRNA	Decreased inflammatory-mediator (TNFα, IL-1β, IL-6, CXCL-1) content in the lung; protected against protein extravasation into the BAL fluid; decreased epithelial injury marker (RAGE expression); reduced TUNEL‡ staining in the lung, inhibited lung edema	This study primarily focused on miR-223 and discovered that it regulated PARP1 expression. Thus, the functional role of PARP1 was evaluated in a VILI model. No pharmacological PARP inhibitors were used. The ventilation time was only 3 h, suggesting that the injury was primarily mechanical because of overstretching ("barotrauma"). Limitations: [E] and [J].	79
Environmental toxin–associated lung injury					
Paraquat-induced lung injury	Sprague-Dawley rat	3-AB (10 mg/kg i.p. twice a day for 4 d; first dose given in a 1 h after treatment)	3-AB decreased the paraquat-induced increases in LDH and neopterin concentrations; decreased TGF-β expression; reduced tissue oxidative stress markers; decreased pulmonary edema and hemorrhaging; inhibited leukocyte infiltration and mesothelial proliferation	Limitations: [A], [C], [F], and [J].	77

Definition of abbreviations: 3-AB = 3-aminobenzamide; 4-HQN = 4-hydroxyquinazoline; 5-AIQ = 5-aminoisoquinoline; ALI = acute lung injury; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AP-1 = activator protein-1; CFU = colony-forming unit; CINC = cytokine-induced neutrophil chemoattractant; CLP = cecal ligation and puncture; CMDE = choline/methionine-deficient/ethionine-supplemented; COPD = chronic obstructive pulmonary disease; COX-2 = inducible isoform of cyclooxygenase; DARC = duffy antigen receptor for chemokines; DPQ = 3,4-dihydro-5[4-(1-piperindinyl)butoxy]-1(2H)-isoquinoline; GCSF = granulocyte colony stimulating factor; GITR = glucocorticoid-induced TNFR-related; GPI 6150 = 1,11b-dihydro-[2H]benzopyrano[4,3,2-de]isoquinolin-3-one); GSH = glutathione (γ-l-glutamyl-l-cysteinyl-glycine tripeptide); HIF = hypoxia-inducible factor; HSP70 = heat shock protein 70; I/R = ischemia–reperfusion; ICAM = intercellular adhesion molecule; INO-1001 = *N*-(3-morpholin-4-ylpropyl)-5-oxo-6,11-dihydroindeno[1,2-c]isoquinoline-9-sulfonamide; iNOS = inducible NO synthase; KC = keratinocyte-derived chemokine; KU0058684 = research compound that is equivalent to the currently clinically approved anticancer drug niraparib or (S)-2-(4-(piperidin-3-yl) phenyl)-2H-indazole-7-carboxamide, marketed as Zejula; LACA = Laboratory Animal Centre A-strain; LDH = lactate dehydrogenase; MCP = monocyte chemoattractant protein; MDA = malon dialdehyde; MIP-1α = macrophage inflammatory protein 1 α, also known as CCL3; MIP-2 = macrophage inflammatory protein 2, also known as CXCL2; MPO = myeloperoxidase; MRI = magnetic resonance imaging; NO = nitric oxide; *P.* = *Pseudomonas;* PAF = platelet activating factor; PAR = poly(ADP-ribose), the enzymatic product of PARP; PARP = PAR polymerase; PJ34 = *N*-(5,6-dihydro-6-oxo-2-phenanthridinyl)-2-acetamide; PMN = polymorphonuclear neutrophil; ROS = reactive oxygen species; TBARS = thiobarbituric acid reactive substances; TGF = tumor growth factor; Th17 = T-helper cell type 17; Treg = T regulatory cell; VILI = ventilation-induced lung injury.

List of common limitations: [A]: First-generation PARP inhibitor used; these inhibitors have limited cell uptake and a poorly characterized pharmacokinetic profile *in vivo*; they also target several other enzymes in addition to PARP1; they can also exert nonspecific antioxidant effects. [B]: Pretreatment or cotreatment with the PARP inhibitor used only; no post-treatment (i.e., therapeutic window) was assessed. (This is not considered a weakness in the transplantation and bypass studies in which pretreatment or coadministration is clinically feasible.) [C]: No target engagement confirmed (i.e., no evidence that the pharmacological agent, indeed, inhibited the activity of its target, PARP1, or that the model produces suitable plasma concentrations of the inhibitor so that PARP1 inhibition can be expected). [D]: The study used animals of "either sex," or the sex of the animals was not stated. In either case, no separate analysis of sex effect was conducted. [E]: All-male study; no comparison of potential sex differences. [F]: All-female study; no comparison of potential sex differences. [G]: Although the study is a mouse study, the pharmacological approach was not combined with a genetic approach (PARP1-deficient mice). [H]: Group size is not explained. [I]: The number of the measured lung injury parameters was limited. [J]: Efficacy parameters were studied only; no investigation of the safety of the inhibitor (e.g., on DNA integrity or repair) was conducted.

*Inhibitory effect of pharmacological agents on tissue nitrotyrosine immunoreactivity was frequently equated with reduced production of the ROS peroxynitrite, which (similar to hydroxyl radical) is an endogenous trigger of DNA-strand breakage and subsequent PARP activation. However, subsequent studies demonstrated that other biochemical reactions (including reactions involving MPO) may also produce nitrotyrosine.

†Inhibitory effect of pharmacological agents on tissue MPO concentrations (in fact, the assay most commonly used measures MPO enzymatic activity and not MPO content) may also indicate effects on neutrophil degranulation, and/or neutrophil extracellular net formation and/or direct effects on the activity of the MPO enzyme. In the table, therefore, we distinguish "MPO content" from "neutrophil lung count" (evidenced by histological or flow cytometric analysis).

‡TUNEL positivity in tissue slides is often equated to apoptosis, but in fact it actually shows DNA-strand breakage, which can occur in conjunction of various forms of cell death or cell dysfunction.

should include separate animal groups of both sexes.

The Efficacy of Olaparib in ALI Offers a Potential Opportunity for Therapeutic Repurposing

The preclinical data demonstrating the efficacy of the clinically approved PARP inhibitor olaparib (or 4-(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl] carbonyl}-4-fluorobenzyl)phthalazin-1(2H)-one; marketed as Lynparza) in various experimental models of lung injury and/or various forms of critical illness (70, 72, 80, 81, 83, 84) are especially relevant from the translational standpoint. Olaparib (similar to the PARP inhibitors of other classes) improves pulmonary inflammation, counteracts pulmonary extravasation, reduces oxidative stress, and improves antioxidant status in the lung in various experimental models of ALI (70, 72, 80, 83) and, importantly, also exerts beneficial effects against the ALI-associated central-nervous-system dysfunction (e.g., cognitive defects) (83). Olaparib also exerts beneficial effects in other animal models that have a significant pulmonary-injury component and/or systemic hyperinflammatory component, including asthma models (72, 74), a pulmonary inflammation/emphysema model (80), and murine models of acute burn injury and pancreatitis (84, 90). In a murine model of sepsis (induced by CLP), olaparib improved survival and exerted beneficial effects on inflammatory-mediator production and immune-cell balance, but in this model, no significant pulmonary injury was noted, and olaparib had no effect on the various pulmonary parameters investigated (81).

As discussed previously (17, 81), the effective dose of the clinically approved PARP inhibitors in nononcological models is significantly lower than the doses of the same agents in oncology, most likely due to the fact that in nononcological models a partial inhibition of PARP is sufficient to exert therapeutic effects. Thus, it will be possible to find effective doses of olaparib for the therapy of nononcological conditions (in particular, in disease conditions in which the patients do not have any baseline defect in DNA-repair pathways, such as ALI) in which a partial inhibition of PARP exerts beneficial effects without interfering with DNA repair and DNA integrity. Indeed, in a CLP model, in which the efficacy and safety of olaparib were simultaneously assessed, olaparib (at the effective dose range of 6–30 mg/kg/d), olaparib beneficially modulated the cytokine and immune status of the animals and improved survival but did not exert any adverse effects on mitochondrial or nuclear DNA integrity in various tissues, including the lung (81). In a second study, in which the effect of PARP inhibition in a critical illness was assessed not only on efficacy parameters but also on DNA injury, the PARP inhibitor used (INO-1001, 4 mg/kg) provided hemodynamic stabilization in a porcine model of thoracic aortic cross-clamping–induced ischemia/reperfusion, without worsening the DNA damage in peripheral blood lymphocytes (91). It must be reiterated, however, that the above-mentioned models did not induce a significant degree of lung injury as a function of the sepsis or cross-clamping procedure (81, 91), and the safety of PARP inhibitors in models that are relevant for ALI remain to be evaluated in future studies.

The Potential Efficacy of PARP Inhibitors in Coronavirus-associated ALI

The current coronavirus disease (COVID-19) world epidemic is associated with a form of ALI, the clinical management of which remains challenging (92–94). Could PARP inhibitors possibly be effective against COVID-19–associated inflammatory responses and/or ALI? There are, unfortunately, no published studies evaluating the potential efficacy of PARP inhibitors in coronavirus-associated ALI, nor in other forms of viral pneumonia or ALI. Nevertheless, PARP inhibitors are effective in a variety of ALI models (Table 1), and, at the later stage of the disease, many of these models (especially the endotoxin- and sepsis-associated models) share many pathophysiological pathways and features with viral ALI. In fact, therapeutic modulation of IL-1β and IL-6 overproduction has been suggested as a potentially effective therapy in COVID-19–associated ALI (92–94), and PARP inhibitors have also been shown to be effective in downregulating the production of these mediators in various models of ALI (Table 1).

It must also be stressed that endothelial damage and dysfunction, as well as thrombosis and intravascular coagulation, are important components of COVID-19–associated diseases (95–97). Although PARP1 does not appear to play a major role in the regulation of thrombocyte function (nor does it directly regulate coagulation factors), PARP1 is known to play an active role in the pathogenesis of endothelial dysfunction, as shown in various disease models, including ALI, circulatory shock, diabetes, and heart failure (31, 34, 98, 99). Thus, we can hypothesize that a PARP inhibitor–associated protection against endothelial dysfunction may have a protective effect against COVID-19–associated thrombotic events.

A key question to be raised in this context is whether PARP is also involved in viral replication; what would be the expected effect of PARP inhibitors on viral replication and viral release in various forms of viral pneumonia or viral ALI (including COVID-19–associated lung diseases)? Some viruses express vPIP (PARP1-interacting protein), which has been implicated in facilitating viral replication (100). However, the mechanism of vPIP involves protein–protein interaction with PARP1 (and not catalytic PARP activation and subsequent PAR formation) (100). Protein–protein interactions would not be expected to be significantly affected by a pharmacological PARP inhibitor.

Importantly, PARylation responses in the host mammalian cells have been implicated in the replication of polyomavirus, and 3-aminobenzamide (3-AB; a first-generation PARP inhibitor) and 3,4-dihydropiperidine-isoquinoline (a second-generation PARP inhibitor) as well as genetic PARP1 deficiency have been shown to inhibit viral capsid protein expression and virion release in fibroblasts *in vitro* (101). 3-AB was also found to exert cytoprotective effects and inhibit herpes simplex virus 1 and John Cunningham virus replication and virion release (102–104), whereas *N*-(5,6-dihydro-6-oxo-2-phenanthridinyl)-2-acetamide (a second-generation PARP inhibitor) has suppressed the replication of human coronavirus OC43, although this effect is likely related to the action of the inhibitor on a molecular target other than PARP1 (105).

In contrast, the replication of the coronavirus JMHV (mouse hepatitis virus strain) was reported to be enhanced rather than inhibited by 3-AB (106); however, the mode of the regulation of this response was linked to another member of the PARP family (PARP14) rather than to PARP1

(106). Another coronavirus, the mouse hepatitis virus, was recently reported to induce the upregulation of another member of the PARP family, the TiPARP (TCDD-inducible PARP) family (107). The above-listed coronavirus effects are independent of PARP1 and are unlikely to be affected by the currently clinically approved PARP1 inhibitors, such as olaparib. Although one can speculate whether or not a PARP1 inhibitor may influence severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication or release, the fact remains that there are currently no direct studies evaluating the role of PARP1 and/or the effect of the clinically approved PARP inhibitors on SARS-CoV-2 *in vitro* or *in vivo*. Nevertheless, it should be emphasized that in several models of viral infection, PARP1 inhibitors are effective in counteracting the viral-associated cellular energetic disturbances, can exert cytoprotective effects *in vitro* (108).

Conclusions and Future Directions

Although the field of PARP and critical illness was born more than two decades ago, and it has steadily evolved and advanced over the years, the fact remained that these basic scientific advances could not be turned into translational efforts because no clinically approved PARP1 inhibitor was available to be used in patients. Major advances in the field of oncology have changed this situation, and now at least four clinically approved PARP inhibitors are available, with several additional PARP inhibitors in advanced clinical trials. As outlined in Reference 17, the possibility has, therefore, emerged that such inhibitors may be repurposed for various nononcological diseases. The evidence presented in the current article indicates that ALI may well be one of these indications, as there is a significant unmet clinical need, the available therapeutic options are limited, and there is a significant body of preclinical data (including translationally predictable large-animal models) showing preclinical efficacy of various PARP inhibitors in multiple models of ALI. Nevertheless, many of these models have significant limitations, as detailed in Table 1, necessitating further preclinical work in this area. The likely effective doses of PARP inhibitors in ALI are expected to be lower than the oncological doses, and they therefore are expected to be well tolerated. Moreover, the expected duration of a PARP inhibitor's administration in ALI is expected to be relatively short, which should improve the expected safety of such trials. Biomarkers (e.g., the measurement of PARylated proteins in the circulating blood cells or in cells obtained from the BAL fluid) may be suitable to confirm therapeutic-target engagement (i.e., confirm that the dose used is sufficient to inhibit PARP's enzymatic activity in the patients).

With respect to COVID-19–associated ALI (or viral lung diseases in general), the available preclinical data are very limited. We can reasonably assume that a PARP inhibitor may suppress the cytokine storm, may attenuate the cytotoxic effects of oxidants and free radicals produced in the late stage of viral ALI, and may improve endothelial function, but preclinical efficacy data in coronavirus-associated ALI models are currently not available. The current article should encourage direct studies to assess the effect of clinically approved PARP inhibitors in animal models of coronavirus-induced ALI, and if positive, may, in turn, encourage subsequent clinical testing of the concept. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1. Jagtap P, Szabó C. Poly(ADP-ribose) polymerase and the therapeutic effects of its inhibitors. *Nat Rev Drug Discov* 2005;4:421–440.
2. Luo X, Kraus WL. On PAR with PARP: cellular stress signaling through poly(ADP-ribose) and PARP-1. *Genes Dev* 2012;26:417–432.
3. Gupte R, Liu Z, Kraus WL. PARPs and ADP-ribosylation: recent advances linking molecular functions to biological outcomes. *Genes Dev* 2017;31:101–126.
4. Eisemann T, Pascal JM. Poly(ADP-ribose) polymerase enzymes and the maintenance of genome integrity. *Cell Mol Life Sci* 2020;77:19–33.
5. Oei SL, Ziegler M. ATP for the DNA ligation step in base excision repair is generated from poly(ADP-ribose). *J Biol Chem* 2000;275: 23234–23239.
6. Wright RH, Lioutas A, Le Dily F, Soronellas D, Pohl A, Bonet J, *et al*. ADP-ribose-derived nuclear ATP synthesis by NUDIX5 is required for chromatin remodeling. *Science* 2016;352:1221–1225.
7. Sachdev E, Tabatabai R, Roy V, Rimel BJ, Mita MM. PARP inhibition in cancer: an update on clinical development. *Target Oncol* 2019;14: 657–679.
8. Slade D. PARP and PARG inhibitors in cancer treatment. *Genes Dev* 2020;34:360–394.
9. Sims JL, Berger SJ, Berger NA. Poly(ADP-ribose) polymerase inhibitors preserve nicotinamide adenine dinucleotide and adenosine 5′-triphosphate pools in DNA-damaged cells: mechanism of stimulation of unscheduled DNA synthesis. *Biochemistry* 1983;22: 5188–5194.
10. Schraufstatter IU, Hinshaw DB, Hyslop PA, Spragg RG, Cochrane CG. Oxidant injury of cells: DNA strand-breaks activate polyadenosine diphosphate-ribose polymerase and lead to depletion of nicotinamide adenine dinucleotide. *J Clin Invest* 1986;77:1312–1320.
11. Szabó C, Zingarelli B, O'Connor M, Salzman AL. DNA strand breakage, activation of poly (ADP-ribose) synthetase, and cellular energy depletion are involved in the cytotoxicity of macrophages and smooth muscle cells exposed to peroxynitrite. *Proc Natl Acad Sci U S A* 1996;93:1753–1758.
12. Virág L, Salzman AL, Szabó C. Poly(ADP-ribose) synthetase activation mediates mitochondrial injury during oxidant-induced cell death. *J Immunol* 1998;161:3753–3759.
13. Ha HC, Snyder SH. Poly(ADP-ribose) polymerase is a mediator of necrotic cell death by ATP depletion. *Proc Natl Acad Sci U S A* 1999; 96:13978–13982.
14. Pacher P, Szabo C. Role of the peroxynitrite-poly(ADP-ribose) polymerase pathway in human disease. *Am J Pathol* 2008;173:2–13.
15. Laudisi F, Sambucci M, Pioli C. Poly (ADP-ribose) polymerase-1 (PARP-1) as immune regulator. *Endocr Metab Immune Disord Drug Targets* 2011;11:326–333.
16. Islam BU, Habib S, Ali SA, Moinuddin, Ali A. Moinuddin, Ali A. Role of Peroxynitrite-induced activation of poly(ADP-ribose) polymerase (PARP) in circulatory shock and related pathological conditions. *Cardiovasc Toxicol* 2017;17:373–383.
17. Berger NA, Besson VC, Boulares AH, Bürkle A, Chiarugi A, Clark RS, *et al*. Opportunities for the repurposing of PARP inhibitors for the therapy of non-oncological diseases. *Br J Pharmacol* 2018;175:192–222.

18. Szabó C, Zingarelli B, Salzman AL. Role of poly-ADP ribosyltransferase activation in the vascular contractile and energetic failure elicited by exogenous and endogenous nitric oxide and peroxynitrite. *Circ Res* 1996;78:1051–1063.
19. Skarda DE, Putt KS, Hergenrother PJ, Mulier KE, Beilman GJ. Increased poly(ADP-ribose) polymerase activity during porcine hemorrhagic shock is transient and predictive of mortality. *Resuscitation* 2007;75:135–144.
20. Walko TD III, Di Caro V, Piganelli J, Billiar TR, Clark RS, Aneja RK. Poly(ADP-ribose) polymerase 1-sirtuin 1 functional interplay regulates LPS-mediated high mobility group box 1 secretion. *Mol Med* 2015;20:612–624.
21. Dawson TM, Dawson VL. Nitric oxide signaling in neurodegeneration and cell death. *Adv Pharmacol* 2018;82:57–83.
22. DaRosa PA, Wang Z, Jiang X, Pruneda JN, Cong F, Klevit RE, *et al*. Allosteric activation of the RNF146 ubiquitin ligase by a poly(ADP-ribosyl)ation signal. *Nature* 2015;517:223–226.
23. Hassa PO, Hottiger MO. The functional role of poly(ADP-ribose) polymerase 1 as novel coactivator of NF-kappaB in inflammatory disorders. *Cell Mol Life Sci* 2002;59:1534–1553.
24. Oliver FJ, Ménissier-de Murcia J, Nacci C, Decker P, Andriantsitohaina R, Muller S, *et al*. Resistance to endotoxic shock as a consequence of defective NF-kappaB activation in poly (ADP-ribose) polymerase-1 deficient mice. *EMBO J* 1999;18:4446–4454.
25. Haskó G, Mabley JG, Németh ZH, Pacher P, Deitch EA, Szabó C. Poly(ADP-ribose) polymerase is a regulator of chemokine production: relevance for the pathogenesis of shock and inflammation. *Mol Med* 2002;8:283–289.
26. Gallyas F Jr, Sumegi B, Szabo C. Role of Akt activation in PARP inhibitor resistance in cancer. *Cancers (Basel)* 2020;12:E532.
27. Hoyt DG, Lazo JS. NAD depletion after *in vitro* exposure of murine lung slices to bleomycin. *Biochem Pharmacol* 1993;46:1819–1824.
28. Hoyt DG, Lazo JS. Acute pneumocyte injury, poly(ADP-ribose) polymerase activity, and pyridine nucleotide levels after *in vitro* exposure of murine lung slices to cyclophosphamide. *Biochem Pharmacol* 1994;48:1757–1765.
29. Szabó C, Lim LH, Cuzzocrea S, Getting SJ, Zingarelli B, Flower RJ, *et al*. Inhibition of poly (ADP-ribose) synthetase attenuates neutrophil recruitment and exerts antiinflammatory effects. *J Exp Med* 1997; 186:1041–1049.
30. Cuzzocrea S, Zingarelli B, Gilad E, Hake P, Salzman AL, Szabó C. Protective effects of 3-aminobenzamide, an inhibitor of poly (ADP-ribose) synthase in a carrageenan-induced model of local inflammation. *Eur J Pharmacol* 1998;342:67–76.
31. Albertini M, Clement MG, Lafortuna CL, Caniatti M, Magder S, Abdulmalek K, *et al*. Role of poly-(ADP-ribose) synthetase in lipopolysaccharide-induced vascular failure and acute lung injury in pigs. *J Crit Care* 2000;15:73–83.
32. Folch E, Salas A, Prats N, Panés J, Piqué JM, Gelpí E, *et al*. H(2)O(2) and PARS mediate lung P-selectin upregulation in acute pancreatitis. *Free Radic Biol Med* 2000;28:1286–1294.
33. Mazzon E, Serraino I, Li JH, Dugo L, Caputi AP, Zhang J, *et al*. GPI 6150, a poly (ADP-ribose) polymerase inhibitor, exhibits an anti-inflammatory effect in rat models of inflammation. *Eur J Pharmacol* 2001;415:85–94.
34. Cuzzocrea S, McDonald MC, Mazzon E, Dugo L, Serraino I, Threadgill M, *et al*. Effects of 5-aminoisoquinolinone, a water-soluble, potent inhibitor of the activity of poly (ADP-ribose) polymerase, in a rodent model of lung injury. *Biochem Pharmacol* 2002;63:293–304.
35. Liaudet L, Pacher P, Mabley JG, Virág L, Soriano FG, Haskó G, *et al*. Activation of poly(ADP-Ribose) polymerase-1 is a central mechanism of lipopolysaccharide-induced acute lung inflammation. *Am J Respir Crit Care Med* 2002;165:372–377.
36. Soriano FG, Liaudet L, Szabó E, Virág L, Mabley JG, Pacher P, *et al*. Resistance to acute septic peritonitis in poly(ADP-ribose) polymerase-1-deficient mice. *Shock* 2002;17:286–292.
37. Jagtap P, Soriano FG, Virág L, Liaudet L, Mabley J, Szabó E, *et al*. Novel phenanthridinone inhibitors of poly (adenosine 5′-diphosphate-ribose) synthetase: potent cytoprotective and antishock agents. *Crit Care Med* 2002;30:1071–1082.
38. Boulares AH, Zoltoski AJ, Sherif ZA, Jolly P, Massaro D, Smulson ME. Gene knockout or pharmacological inhibition of poly(ADP-ribose) polymerase-1 prevents lung inflammation in a murine model of asthma. *Am J Respir Cell Mol Biol* 2003;28:322–329.
39. Kiefmann R, Heckel K, Dörger M, Schenkat S, Stoeckelhuber M, Wesierska-Gadek J, *et al*. Role of poly(ADP-ribose) synthetase in pulmonary leukocyte recruitment. *Am J Physiol Lung Cell Mol Physiol* 2003;285:L996–L1005.
40. Shimoda K, Murakami K, Enkhbaatar P, Traber LD, Cox RA, Hawkins HK, *et al*. Effect of poly(ADP ribose) synthetase inhibition on burn and smoke inhalation injury in sheep. *Am J Physiol Lung Cell Mol Physiol* 2003;285:L240–L249.
41. Farivar AS, Woolley SM, Fraga CH, Thomas R, Salzman AL, Szabo C, *et al*. Intratracheal poly (ADP) ribose synthetase inhibition ameliorates lung ischemia reperfusion injury. *Ann Thorac Surg* 2004;77:1938–1943.
42. Farivar AS, Woolley SM, Naidu BV, Fraga CH, Byrne K, Thomas R, *et al*. Poly (ADP) ribose synthetase inhibition reduces obliterative airway disease in rat tracheal allografts. *J Heart Lung Transplant* 2004;23: 993–1002.
43. Genovese T, Mazzon E, Di Paola R, Muià C, Threadgill MD, Caputi AP, *et al*. Inhibitors of poly(ADP-ribose) polymerase modulate signal transduction pathways and the development of bleomycin-induced lung injury. *J Pharmacol Exp Ther* 2005;313:529–538.
44. Virág L, Bai P, Bak I, Pacher P, Mabley JG, Liaudet L, *et al*. Effects of poly(ADP-ribose) polymerase inhibition on inflammatory cell migration in a murine model of asthma. *Med Sci Monit* 2004;10: BR77–BR83.
45. Suzuki Y, Masini E, Mazzocca C, Cuzzocrea S, Ciampa A, Suzuki H, *et al*. Inhibition of poly(ADP-ribose) polymerase prevents allergen-induced asthma-like reaction in sensitized Guinea pigs. *J Pharmacol Exp Ther* 2004;311:1241–1248.
46. Kiefmann R, Heckel K, Doerger M, Schenkat S, Kupatt C, Stoeckelhuber M, *et al*. Role of PARP on iNOS pathway during endotoxin-induced acute lung injury. *Intensive Care Med* 2004;30:1421–1431.
47. Heckel K, Kiefmann R, Dörger M, Stoeckelhuber M, Goetz AE. Colloidal gold particles as a new *in vivo* marker of early acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 2004;287:L867–L878.
48. Murakami K, Enkhbaatar P, Shimoda K, Cox RA, Burke AS, Hawkins HK, *et al*. Inhibition of poly (ADP-ribose) polymerase attenuates acute lung injury in an ovine model of sepsis. *Shock* 2004;21: 126–133.
49. Szabó G, Soós P, Mandera S, Heger U, Flechtenmacher C, Bährle S, *et al*. INO-1001 a novel poly(ADP-ribose) polymerase (PARP) inhibitor improves cardiac and pulmonary function after crystalloid cardioplegia and extracorporal circulation. *Shock* 2004;21:426–432.
50. Szabó G, Soós P, Bährle S, Zsengellér Z, Flechtenmacher C, Hagl S, *et al*. Role of poly(ADP-ribose) polymerase activation in the pathogenesis of cardiopulmonary dysfunction in a canine model of cardiopulmonary bypass. *Eur J Cardiothorac Surg* 2004;25:825–832.
51. Veres B, Radnai B, Gallyas F Jr, Varbiro G, Berente Z, Osz E, *et al*. Regulation of kinase cascades and transcription factors by a poly(ADP-ribose) polymerase-1 inhibitor, 4-hydroxyquinazoline, in lipopolysaccharide-induced inflammation in mice. *J Pharmacol Exp Ther* 2004;310:247–255.
52. Woolley SM, Farivar AS, Naidu BV, Salzman A, Szabo C, Thomas R, *et al*. Role of poly (ADP) ribose synthetase in lung ischemia-reperfusion injury. *J Heart Lung Transplant* 2004;23:1290–1296.
53. Avlan D, Unlü A, Ayaz L, Camdeviren H, Nayci A, Aksöyek S. Poly (ADP-ribose) synthetase inhibition reduces oxidative and nitrosative organ damage after thermal injury. *Pediatr Surg Int* 2005;21: 449–455.
54. Koksel O, Yildirim C, Cinel L, Tamer L, Ozdulger A, Bastürk M, *et al*. Inhibition of poly(ADP-ribose) polymerase attenuates lung tissue damage after hind limb ischemia-reperfusion in rats. *Pharmacol Res* 2005;51:453–462.
55. Lobo SM, Orrico SR, Queiroz MM, Cunrath GS, Chibeni GS, Contrin LM, *et al*. Pneumonia-induced sepsis and gut injury: effects of a poly-(ADP-ribose) polymerase inhibitor. *J Surg Res* 2005;129: 292–297.

56. Mota RA, Sánchez-Bueno F, Saenz L, Hernández-Espinosa D, Jimeno J, Tornel PL, *et al*. Inhibition of poly(ADP-ribose) polymerase attenuates the severity of acute pancreatitis and associated lung injury. *Lab Invest* 2005;85:1250–1262.
57. Oumouna M, Datta R, Oumouna-Benachour K, Suzuki Y, Hans C, Matthews K, *et al*. Poly(ADP-ribose) polymerase-1 inhibition prevents eosinophil recruitment by modulating Th2 cytokines in a murine model of allergic airway inflammation: a potential specific effect on IL-5. *J Immunol* 2006;177:6489–6496. [Published erratum appears in *J Immunol* 179:5604.]
58. Kao SJ, Liu DD, Su CF, Chen HI. Niacinamide abrogates the organ dysfunction and acute lung injury caused by endotoxin. *J Cardiovasc Pharmacol* 2007;50:333–342.
59. Kim JH, Suk MH, Yoon DW, Kim HY, Jung KH, Kang EH, *et al*. Inflammatory and transcriptional roles of poly (ADP-ribose) polymerase in ventilator-induced lung injury. *Crit Care* 2008;12:R108.
60. Su CF, Liu DD, Kao SJ, Chen HI. Nicotinamide abrogates acute lung injury caused by ischaemia/reperfusion. *Eur Respir J* 2007;30:199–204.
61. Dhein S, Krause N, Ullmann C, Flister A, Lehmann S, Muth P, *et al*. Ischemic and inflammatory lung impairment by extracorporeal circulation: effect of PARP-inhibition by INO1001. *Pharmacol Res* 2008;58:332–339.
62. Naura AS, Hans CP, Zerfaoui M, You D, Cormier SA, Oumouna M, *et al*. Post-allergen challenge inhibition of poly(ADP-ribose) polymerase harbors therapeutic potential for treatment of allergic airway inflammation. *Clin Exp Allergy* 2008;38:839–846.
63. Mota R, Sánchez-Bueno F, Berenguer-Pina JJ, Hernández-Espinosa D, Parrilla P, Yélamos J. Therapeutic treatment with poly(ADP-ribose) polymerase inhibitors attenuates the severity of acute pancreatitis and associated liver and lung injury. *Br J Pharmacol* 2007;151: 998–1005.
64. Zerfaoui M, Naura AS, Errami Y, Hans CP, Rezk BM, Park J, *et al*. Effects of PARP-1 deficiency on airway inflammatory cell recruitment in response to LPS or TNF: differential effects on CXCR2 ligands and Duffy Antigen Receptor for Chemokines. *J Leukoc Biol* 2009;86: 1385–1392.
65. Hamahata A, Enkhbaatar P, Lange M, Yamaki T, Sakurai H, Shimoda K, *et al*. Administration of poly(ADP-ribose) polymerase inhibitor into bronchial artery attenuates pulmonary pathophysiology after smoke inhalation and burn in an ovine model. *Burns* 2012;38:1210–1215.
66. Si MK, Mitaka C, Tulafu M, Abe S, Kitagawa M, Ikeda S, *et al*. Inhibition of poly (adenosine diphosphate-ribose) polymerase attenuates lung-kidney crosstalk induced by intratracheal lipopolysaccharide instillation in rats. *Respir Res* 2013;14:126.
67. Wang G, Huang X, Li Y, Guo K, Ning P, Zhang Y. PARP-1 inhibitor, DPQ, attenuates LPS-induced acute lung injury through inhibiting NF-κB-mediated inflammatory response. *PLoS One* 2013;8: e79757.
68. Hatachi G, Tsuchiya T, Miyazaki T, Matsumoto K, Yamasaki N, Okita N, *et al*. The poly(adenosine diphosphate-ribose) polymerase inhibitor PJ34 reduces pulmonary ischemia-reperfusion injury in rats. *Transplantation* 2014;98:618–624.
69. Lucarini L, Pini A, Gerace E, Pellicciari R, Masini E, Moroni F. Poly(ADP-ribose) polymerase inhibition with HYDAMTIQ reduces allergen-induced asthma-like reaction, bronchial hyper-reactivity and airway remodelling. *J Cell Mol Med* 2014;18:468–479.
70. Kapoor K, Singla E, Sahu B, Naura AS. PARP inhibitor, olaparib ameliorates acute lung and kidney injury upon intratracheal administration of LPS in mice. *Mol Cell Biochem* 2015;400:153–162.
71. Ahmad SF, Zoheir KM, Ansari MA, Korashy HM, Bakheet SA, Ashour AE, *et al*. The role of poly(ADP-ribose) polymerase-1 inhibitor in carrageenan-induced lung inflammation in mice. *Mol Immunol* 2015; 63:394–405.
72. Ghonim MA, Pyakurel K, Ibba SV, Wang J, Rodriguez P, Al-Khami AA, *et al*. PARP is activated in human asthma and its inhibition by olaparib blocks house dust mite-induced disease in mice. *Clin Sci (Lond)* 2015;129:951–962.
73. Zhao H, Ning J, Lemaire A, Koumpa FS, Sun JJ, Fung A, *et al*. Necroptosis and parthanatos are involved in remote lung injury after receiving ischemic renal allografts in rats. *Kidney Int* 2015;87:738–748.
74. Ibba SV, Ghonim MA, Pyakurel K, Lammi MR, Mishra A, Boulares AH. Potential of inducible nitric oxide synthase as a therapeutic target for allergen-induced airway hyperresponsiveness: a critical connection to nitric oxide levels and PARP activity. *Mediators Inflamm* 2016;2016: 1984703.
75. Lucarini L, Durante M, Lanzi C, Pini A, Boccalini G, Calosi L, *et al*. HYDAMTIQ, a selective PARP-1 inhibitor, improves bleomycin-induced lung fibrosis by dampening the TGF-β/SMAD signalling pathway. *J Cell Mol Med* 2017;21:324–335.
76. Wang X, Wang Y, Parapanov R, Abdelnour E, Gronchi F, Perentes JY, *et al*. Pharmacological reconditioning of marginal donor rat lungs using inhibitors of peroxynitrite and poly (ADP-ribose) polymerase during *ex vivo* lung perfusion. *Transplantation* 2016;100:1465–1473.
77. Tuncer SK, Altinel S, Toygar M, Istanbulluoglu H, Ates K, Ogur R, *et al*. Poly-ADP-ribose polymerase inhibition provides protection against lung injury in a rat paraquat toxicity model. *Inflammopharmacology* 2016;24:155–161.
78. Zaffini R, Di Paola R, Cuzzocrea S, Menegazzi M. PARP inhibition treatment in a nonconventional experimental mouse model of chronic asthma. *Naunyn Schmiedebergs Arch Pharmacol* 2016;389: 1301–1313.
79. Neudecker V, Brodsky KS, Clambey ET, Schmidt EP, Packard TA, Davenport B, *et al*. Neutrophil transfer of *miR-223* to lung epithelial cells dampens acute lung injury in mice. *Sci Transl Med* 2017;9: eaah5360.
80. Dharwal V, Naura AS. PARP-1 inhibition ameliorates elastase induced lung inflammation and emphysema in mice. *Biochem Pharmacol* 2018;150:24–34.
81. Ahmad A, Vieira JC, de Mello AH, de Lima TM, Ariga SK, Barbeiro DF, *et al*. The PARP inhibitor olaparib exerts beneficial effects in mice subjected to cecal ligature and puncture and in cells subjected to oxidative stress without impairing DNA integrity: a potential opportunity for repurposing a clinically used oncological drug for the experimental therapy of sepsis. *Pharmacol Res* 2019;145: 104263.
82. Wang X, Parapanov R, Debonneville A, Wang Y, Abdelnour-Berchtold E, Gonzalez M, *et al*. Treatment with 3-aminobenzamide during *ex vivo* lung perfusion of damaged rat lungs reduces graft injury and dysfunction after transplantation. *Am J Transplant* 2020;20: 967–976.
83. Sahu B, Narota A, Naura AS. Pharmacological inhibition of poly (ADP-ribose) polymerase by olaparib, prevents acute lung injury associated cognitive deficits potentially through suppression of inflammatory response. *Eur J Pharmacol* 2020;877:173091.
84. Ahmad A, Olah G, Herndon DN, Szabo C. The clinically used PARP inhibitor olaparib improves organ function, suppresses inflammatory responses and accelerates wound healing in a murine model of third-degree burn injury. *Br J Pharmacol* 2018;175:232–245.
85. Mandel P. ADP ribosylation: knowledge and perspectives [in French]. *C R Seances Soc Biol Fil* 1987;181:105–115.
86. Virág L, Szabó C. The therapeutic potential of poly(ADP-ribose) polymerase inhibitors. *Pharmacol Rev* 2002;54:375–429.
87. Szabó C. Nicotinamide: a jack of all trades (but master of none?). *Intensive Care Med* 2003;29:863–866.
88. McCullough LD, Zeng Z, Blizzard KK, Debchoudhury I, Hurn PD. Ischemic nitric oxide and poly (ADP-ribose) polymerase-1 in cerebral ischemia: male toxicity, female protection. *J Cereb Blood Flow Metab* 2005;25:502–512.
89. Mabley JG, Horváth EM, Murthy KG, Zsengellér Z, Vaslin A, Benko R, *et al*. Gender differences in the endotoxin-induced inflammatory and vascular responses: potential role of poly(ADP-ribose) polymerase activation. *J Pharmacol Exp Ther* 2005;315:812–820.
90. Ahmad A, Haas De Mello A, Szczesny B, Törö G, Marcatti M, Druzhyna N, *et al*. Effects of the poly(ADP-ribose) polymerase inhibitor olaparib in cerulein-induced pancreatitis. *Shock* 2020;53:653–665.
91. Hauser B, Gröger M, Ehrmann U, Albicini M, Brückner UB, Schelzig H, *et al*. The parp-1 inhibitor ino-1001 facilitates hemodynamic stabilization without affecting DNA repair in porcine thoracic aortic cross-clamping-induced ischemia/reperfusion. *Shock* 2006;25: 633–640.

92. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun Rev* 2020;19:102537.
93. Wujtewicz M, Dylczyk-Sommer A, Aszkiełowicz A, Zdanowski S, Piwowarczyk S, Owczuk R. COVID-19: what should anaethesiologists and intensivists know about it? *Anaesthesiol Intensive Ther* 2020;52:34–41.
94. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. *Int J Antimicrob Agents* 2020;55:105924.
95. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, *et al*. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;395:1417–1418.
96. Noris M, Benigni A, Remuzzi G. The case of complement activation in COVID-19 multiorgan impact. *Kidney Int* [online ahead of print] 24 May 2020; DOI: 10.1016/j.kint.2020.05.013.
97. Wise J. COVID-19 and thrombosis: what do we know about the risks and treatment? *BMJ* 2020;369:m2058.
98. Szabó C, Cuzzocrea S, Zingarelli B, O'Connor M, Salzman AL. Endothelial dysfunction in a rat model of endotoxic shock: importance of the activation of poly (ADP-ribose) synthetase by peroxynitrite. *J Clin Invest* 1997;100:723–735.
99. Virág L, Jagtap P, Szabó E, Mabley JG, Liaudet L, Marton A, *et al*.; Garcia Soriano F. Diabetic endothelial dysfunction: the role of poly(ADP-ribose) polymerase activation. *Nat Med* 2001;7:108–113.
100. Chung WC, Kim J, Kim BC, Kang HR, Son J, Ki H, *et al*. Structure-based mechanism of action of a viral poly(ADP-ribose) polymerase 1-interacting protein facilitating virus replication. *IUCrJ* 2018;5:866–879.
101. Carbone M, Reale A, Di Sauro A, Sthandier O, Garcia MI, Maione R, *et al*. PARP-1 interaction with VP1 capsid protein regulates polyomavirus early gene expression. *J Mol Biol* 2006;363:773–785.
102. Grady SL, Hwang J, Vastag L, Rabinowitz JD, Shenk T. Herpes simplex virus 1 infection activates poly(ADP-ribose) polymerase and triggers the degradation of poly(ADP-ribose) glycohydrolase. *J Virol* 2012;86:8259–8268.
103. Nukuzuma S, Kameoka M, Sugiura S, Nakamichi K, Nukuzuma C, Takegami T. Suppressive effect of PARP-1 inhibitor on JC virus replication *in vitro*. *J Med Virol* 2013;85:132–137.
104. Rom S, Reichenbach NL, Dykstra H, Persidsky Y. The dual action of poly(ADP-ribose) polymerase -1 (PARP-1) inhibition in HIV-1 infection: HIV-1 LTR inhibition and diminution in Rho GTPase activity. *Front Microbiol* 2015;6:878.
105. Lin SY, Liu CL, Chang YM, Zhao J, Perlman S, Hou MH. Structural basis for the identification of the N-terminal domain of coronavirus nucleocapsid protein as an antiviral target. *J Med Chem* 2014;57:2247–2257.
106. Grunewald ME, Chen Y, Kuny C, Maejima T, Lease R, Ferraris D, *et al*. The coronavirus macrodomain is required to prevent PARP-mediated inhibition of virus replication and enhancement of IFN expression. *PLoS Pathog* 2019;15:e1007756.
107. Grunewald ME, Shaban MG, Mackin SR, Fehr AR, Perlman S. Murine coronavirus infection activates the aryl hydrocarbon receptor in an indoleamine 2,3-dioxygenase-independent manner, contributing to cytokine modulation and proviral TCDD-inducible-PARP expression. *J Virol* 2020;94:e01743-19.
108. Xu G, Li S, Liu X, Gao P, Chen X, Wang H, *et al*. PARP-1 mediated cell death is directly activated by ZIKV infection. *Virology* 2019;537:254–262.