Understanding the role of Poly(ADP-ribose) polymerase (PARP1) and PARP inhibitors in viral infection and pathogenesis

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Abstract

Poly (ADP-ribose) polymerase 1 (PARP1) is a post-translational modifying enzyme and is also known to act as transcription factor and co-activator. PARP1 has been shown to be involved with diseases resulting in increased inflammation and several viral diseases have also been associated with PARP1 activation. PARP1 facilitates influenza A virus entry in host cells by degrading interferon receptor type I. PARP1 regulates expression of NFkB and downstream cytokine production and its inhibition is known to attenuate the expression of inflammatory cytokines. Thus, PARP1 plays an important role in host-pathogen interactions and pathogenesis. Moreover, pre-clinical and in vitro studies have shown that PARP1 inhibition may affect viability of several viruses including affecting replication of the SARS-CoV virus, a distant relative of the SARS-CoV-2 virus, the one which caused the SARS epidemic of 2002. Covid-19 has been declared a global pandemic; with symptoms of the disease now not limited to respiratory distress alone. Severe inflammation is observed in the lungs leading to a surge of cytokine release systemically, affecting heart function, ischemia and stroke. Inflammatory cytokines which are associated with severe comorbidities and mortalities due to chronic diseases are being upregulated in an acute fashion. There is no immediate treatment, and only palliative care is being provided. The current review will discuss mechanisms of PARP1 activation during viral infection, inflammatory diseases, cytokine expression and possibility of PARP1 in regulating cytokine storm and hyper-inflammation seen with Covid-19.

Introduction

Covid-19 (*Co*rona*vi*rus *d*isease of 20*19*) is caused by severe acute respiratory syndrome Coronavirus (SARS-CoV-2) infection, which causes acute respiratory distress and lung fibrosis and has resulted in more than ~10 million reported cases and more than ~500,000 deaths worldwide as of 28th June 2020 (https://coronavirus.jhu.edu/map.html). The extent of the severity of disease is still to be assessed with reasons for mortality linked with Covid-19, being an evolving process with plethora of pathological conditions being reported in an acute period. Epidemiological and cross disciplinary aspect of the virus has been studied (Sun et al., 2020). A retrospective study reported from Wuhan reported that 100% of the patients suffered from acute respiratory distress syndrome and sepsis, more than 50% patients with type I respiratory failure, acute cardiac injury and heart failure, with some cases of kidney injury and hypoxic encephalopathy (Chen et al., 2020). The disease is fatal with seniors and people with comorbidities such as diabetes, obesity (Petrakis et al., 2020), asthma, cardiovascular risks (Cheng et al., 2020) etc. Moreover more recent reports suggest that the disease is not sparing people of younger age groups, with symptoms of acute inflammation and thrombosis leading to large vessel ischemic strokes becoming another reason for mortality in Covid-19 patients (Oxley et al., 2020). Vaccines and new drugs are being developed targeting various mechanisms through which SARS-CoV-2 may be affecting different biological pathways and organ failures, with an absolute cure still elusive.

To effectively target SARS-CoV-2, understanding the mechanisms of the CoV-family may be important.

Before the Covid-19, similar zoonotic outbreaks occurred with the SARS-CoV outbreak in 2002 (Drosten et al., 2003) and the MERS-CoV outbreak in 2012 . Prior to that human coronaviruses, HCoV-229E and HCoV-OC43, have existed and caused common cold (Malik, 2020). Interestingly SARS-CoV2 is not a direct descendent of SARS-CoV however both belong to order *Nidovirales* . This uniqueness in the SARS-CoV-2 or Covid-19 could explain why it may be so much more deadly than the viruses from the same genome order. Due to these similarities and uniqueness, often targeting the virus itself may become complicated. However, with more reports of pathological mode of action on cells and organs, various treatments are directed towards the pathogenesis of Covid-19.

Pathogenesis of Covid-19 mainly includes release of pro-inflammatory proteins also referred as a "cytokine storm", oxidative stress, cell death, activation of renin-angiotensin pathway and endothelial dysfunction which ultimately lead to lung injury. Identification of any drug or inhibitor beneficial in treating these pathogenesis, pulmonary symptoms or thrombosis would prove to be lifesaving at this time for Covid-19.

Poly (ADP-ribose) polymerase 1 (PARP1) is a polymerase enzyme with multifunctional role to play in a cell (Hassa, 2009; Rajawat et al., 2017a; Rajawat et al., 2017b), primarily maintaining genomic integrity and cell survival being the distinct feature. PARP1 regulates several genes either directly as transcription factors or as coactivator or inhibitor. Additionally, PARP1 has been reported to be involved in cytokine regulation, inflammation, pulmonary diseases and strokes. Therefore, PARP1 inhibition has emerged as a powerful tool to control inflammation in several organ injuries and diseases. PARP inhibitors are such compounds which are significantly beneficial in preventing or inhibiting inflammation, pulmonary disease symptoms, cardiovascular disease and stroke. Several PARP inhibitors are in clinical trial for cancer, neurodegenerative diseases and stroke. Some have been approved by FDA already; therefore, use of PARP inhibitors would be safe too. PARP1 has been shown to play a key role in the pathogenesis of several viral diseases (Grady et al., 2012; Hassumi-Fukasawa et al., 2012; Lupey-Green et al., 2018; Na et al., 2016; Xia et al., 2020). Moreover, PARP1 and other members of PARP family are known to exhibit either antiviral or pro-viral activities against various viruses.

In this review we have discussed the role PARP plays in regulating viral infection or virulence, pulmonary diseases, inflammatory diseases, cardiovascular diseases and in regulating cytokine storm. We also explore the role of PARP1 which may result in symptoms that has been observed in Covid-19 patients and hence the potential of PARP inhibitors to be used for reducing the SARS-CoV-2 mediated pathogenesis.

PARP1 and Viral infection

Several members of PARP family are reported to play varied roles in viral infections. PARP activity or PARylation can function as both enhancer and repressor of virus replication (Ko et al., 2013; Lupey-Green et al., 2017). PARP7, 10 and 12 reportedly inhibits replication of Venezuelan equine encephalitis virus (VEEV) (Atasheva et al., 2012; Atasheva et al., 2014). PARP1 is observed to be a facilitator of influenza A virus (IAV) infection through regulation of RNA dependent RNA polymerase (Rdrp polymerase) of influenza A virus. However, endogenous PARylation inhibited Rdrp assembly (Westera et al., 2019). Host protein PARP1 is reported to facilitate propagation of influenza A virus through degradation of interferon receptor type I (IFNAR) (Xia et al., 2020). This novel role of PARP1 could be utilized to design antivirals for influenza treatment and such study can also be expanded to other viruses which utilizes same receptor for entry in host. Furthermore, PARP1 is required for HIV-1 infection and integration in cells(Ha et al., 2001) and PARP1 activity is also required for transcriptional activation of HIV-1(Yu et al., 2018) . In addition to aforementioned studies, PARP1 inhibition has been found to be effective in management of HIV infection and replication *in vitro* (Rom et al., 2015). Although some contradictory reports are also there in context to HIV-1 infection but still PARP1 inhibition can be an effective strategy for viral disease management. Recent study has proposed the role of PARP1 in regulating the NK cell migration to the site of viral infection through production of CCL2 and further CCL2-CCR axis regulates the migration of NK cells (Shou et al., 2019). Another instance where interaction with PARP1 was found important for viral biology was Porcine reproductive and respiratory syndrome virus (PRRSV) (Liu et al., 2015), indicating that targeting PARP1 could be a viable option to inhibit virus proliferation.

Interestingly, few studies have recently been carried out to identify PARPs relationship with coronavirus infection and replication in mammalian cells. ADP-ribosylation of coronavirus nucleocapsid protein (N protein) was identified as a novel post translational modification (Grunewald et al., 2018). Several family of virus including Coronaviridae possess a macrodomain with poly(ADP-ribose) glycohydrolase activity. There are reports of a coronavirus macrodomain binding to ADP-ribose and further removal of mono ADP-ribose from proteins thus facilitates virus to replicate. These macrodomains are reported to counteract the antiviral ADP-ribosylation of PARP during infection. Although it has not been clear whether PARP1 is involved in inhibition of coronavirus replication but role of PARP-12 and -14 has been identified in enhancement of interferon production and coronavirus inhibition (Grunewald et al., 2019). Thus, PARP either promotes or inhibits the replication of viruses and their pathogenesis (Fehr et al., 2020). Further analysis of macrodomain of SARS-CoV-2 could highlight the use of PARP inhibitors for treatment of Covid-19.Interestingly, few studies have recently been carried out to identify PARPs relationship with coronavirus infection and replication in mammalian cells. ADP-ribosylation of coronavirus nucleocapsid protein (N protein) was identified as a novel post translational modification (Grunewald et al., 2018). Several family of virus including Coronaviridae possess a macrodomain with poly(ADP-ribose) glycohydrolase activity. There are reports of a coronavirus macrodomain binding to ADP-ribose and further removal of mono ADP-ribose from proteins thus facilitates virus to replicate. These macrodomains are reported to counteract the antiviral ADP-ribosylation of PARP during infection. Although it has not been clear whether PARP1 is involved in inhibition of coronavirus replication but role of PARP-12 and -14 has been identified in enhancement of interferon production and coronavirus inhibition (Grunewald et al., 2019). Thus, PARP either promotes or inhibits the replication of viruses and their pathogenesis (Fehr et al., 2020). Further analysis of macrodomain of SARS-CoV-2 could highlight the use of PARP inhibitors for treatment of Covid-19.

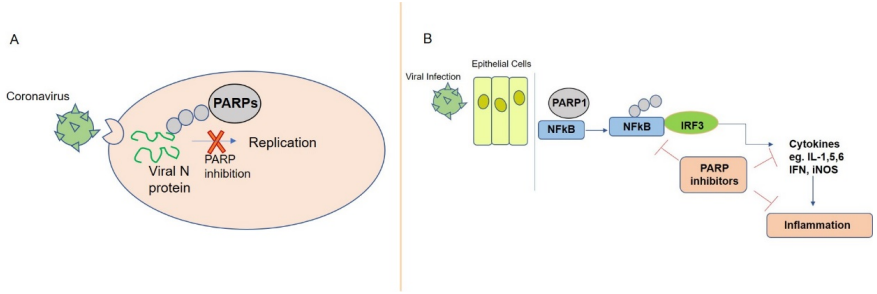


Figure 1. PARP role in viral infection. (A) ADP-ribosylation of macrodomain protein of Coronavirus. (B) PARP1 mediated inflammatory response to viral infection.

PARP1 and inflammatory disease

PARP1 activation is observed in both infectious and non-infectious diseases, simultaneous to inflammatory responses. Hyper-activation of PARP1 in response to DNA damage causes NAD and ATP depletion and consequently necrosis (Rajawat et al., 2007) , leading to inflammatory state in many diseases. PARP1 also plays an important role in regulating pro-inflammatory gene expression and subsequently cell death in the damaged tissues (Beneke & Burkle, 2007; Jagtap & Szabo, 2005). Several evidences reflect the role of PARP1 in activation of transcription factors like NFκB, AP-1, heat shock proteins, adhesion molecules in promoting inflammation. PARP1 is known to be a coactivator of AP-1 and NFκB and hence regulates their expression during chronic inflammation. PARP1- NFκB interaction then induces downstream signalling by inducing the expression of pro-inflammatory cytokines including IL-1, TNF-α, IFNγ and iNOS activation (Ba & Garg, 2011). Implication of PARP1 was also observed in renin-angiotensin system (RAS) that responds to inflammation (Reinemund et al., 2009). RAS signalling promotes viral entry and simultaneously inhibits or regulates severe lung injury and inflammation (Fung & Liu, 2019). PARP1 deletion or inhi-

bition was beneficial in lipopolysaccharides (LPS) induced pulmonary inflammation (Liaudet et al., 2002; Zerfaoui et al., 2009). Similarly, PARP1 inhibition delayed the gut inflammation during enterocolitis caused by Salmonella typhimurium (Altmeyer et al., 2010). Additionally, massive DNA damage induced PARP activation aggravates inflammatory response in ventilator induced lung injury (Kim et al., 2008; Vaschetto et al., 2008). Thus, PARP inhibition is anti-inflammatory and can control hyper-inflammation induced during several pathologies. Moreover, PARP1 also controls the immune function by destabilizing the Foxp3 in regulatory T cells (Treg) (Hori et al., 2017). PARP1 is known to destabilize Foxp3 by ADP-ribosylation, while, PARP inhibition stabilizes Foxp3 and subsequently downstream gene expression involved in Treg immune suppressive function (Luo et al., 2015).

Cytokine storm, which is represented by a dysregulated cytokine/chemokine response, has been shown to be one of the key biological manifestation during the SARS-CoV pandemic (Channappanavar & Perlman, 2017). While the cell types infected by the SARS-CoV-2 are still under investigation, the cytokine storm they may entail may be more varied and detrimental for the healthy cells, apart from the viral infection itself. Cytokine storm leads to hyper-inflammation that could be a major cause for mortality (Mehta et al., 2020). Hyper-inflammation can be curbed by inhibiting PARP with nicotinamide, as this might lead to inhibition of iNOS and downstream pro-inflammatory gene response. Furthermore, NAD and niacin supplementation could also prove to be beneficial in suppressing inflammation and oxidative stress induced cell death (Gharote, 2020). There are reports of the association of senescence with chronic obstructive pulmonary disorder (COPD). These senescent cells are also known to secrete pro-inflammatory cytokines such as IL-6, IL-8 and plasminogen activator inhibitor-I (PAI) (Kumar et al., 2014). Thus, senescence and senescence associated secretory phenotype (SASP) during viral infection cannot be neglected.

Table 1: PARP inhibitors in inflammatory diseases:

SNo.	Disease/ pathology	PARP inhibitors	Model	Ref
1.	Ischemia/ reperfusion	PJ-34	Mouse	(Black et al., 2006)
2.	Ischemic stroke	PJ-34	Rat	(Kauppinen et al., 2009)
3.	Cerebral ischemia	NU1025	Rat	(Kaundal et al., 2006)
4.	Heat stroke	PJ-34	Mouse	(Mota et al., 2008)
5.	Induced atherosclerosis	TIQ-A	Mouse	(Hans et al., 2009)
6.	Endothelial dysfunction	INO-1001	Mouse	(Benko et al., 2004)
7.	Airway inflammation	TIQ-A	Mouse	(Naura et al., 2008)

PARP1 and pulmonary disease

Fibrotic disease of the lungs idiopathic pulmonary interstitial fibrosis (IPF) is a result of enhanced fibroblasts proliferation and accumulation of collagen and extracellular matrix. This leads to alveolar injury, stiffening of airways, blood membrane thickening, chronic inflammation, damaged lungs and ultimately respiratory failure (Coultas et al., 1994; King et al., 2011). PARP1 enzyme is known to play critical role in many fibrotic disorders including heart (Gero et al., 2014), vessels (Abdallah et al., 2007), lungs (Genovese et al., 2005) and liver (Mukhopadhyay et al., 2014). Key observation of increased PARylation was reported in lung fibroblasts of IPF patients (Hu et al., 2013). PARP inhibitors are now reported to inhibit fibrosis and reduce collagen accumulation in liver. PARP1 inhibitor, HYDAMTIQ reduces the progression of bleomycin induced lung fibrosis by inhibiting the TGFβ/SMAD signalling pathway (Lucarini et al., 2017).

The characteristic feature of chronic obstructive pulmonary disorder (COPD) is airway inflammation, which could be due to reactive oxygen species (ROS) i.e. oxidative injury (MacNee, 2001). ROS induces PARP1 activation, although PARP role is to maintain genomic integrity, but excessive DNA damage could lead to PARP1 over-activation and finally cell death. One such study observed PARP1 activation in COPD via ROS and pharmacological inhibition of PARP1 or knockout has prevented epithelial cell injury and inflammation of airway (Boulares et al., 2003). It is interesting to note that oxidative stress, PARP1 and

NFκB axis is connected to the inflammation observed in COPD, asthma and acute lung injury. Another study examined the requirement of PARP1 for induction of iNOS under oxidative stress during allergen induced eosinophilia (Naura et al., 2008). Allergen exposure may activate PARP1 that subsequently induces iNOS expression through NFκB. Moreover, PARP1 also regulates IL-5 production which in addition with other cytokines promotes eosinophil recruitment and promotes inflammation in lungs. iNOS reciprocally regulates PARP1 activity and thereby try to inhibit inflammatory response (Naura et al., 2008). Inhibition of PARP1 prevented the airway infiltration of eosinophils through IL-5 suppression (Oumouna et al., 2006). PARP1 is also known to modulate the Th2 cytokine (Oumouna et al., 2006) and ICAM-1 (Zerfaoui et al., 2009) expression in airways and hence regulates the eosinophil recruitment in lung airways. It has also been identified that PARP1 activation is a prerequisite for STAT6 expression which regulates the expression of IL-5 and GATA3 (Datta et al., 2011).

Preclinical analysis of PARP inhibition in dust mite exposed mice resulted in blocking asthma like traits. Furthermore, clinical analysis of the lung specimens and PBMCs derived from asthmatic patients presented activation of PARP1 in such patients (Ghonim et al., 2015). Moreover, PARP1 also contributes in epithelial-mesenchymal transition in airway remodelling in chronic asthma by formation of ternary complex through TGFβ and NFkB (Stanisavljevic et al., 2011). Thus, PARP1 has multifaceted role in lung diseases and hence could be a probable target for targeting symptomatic treatment in Covid-19 patients.

PARP1 and cardiovascular disorders (stroke)

Accumulating evidences have reported PARP activation in oxidative stress related pathologies including cardiovascular disorders and stroke. Role of PARP1 in regulating the pathological stress in cardiovascular disease can be predicted by its interaction with Kruppel like factor 5 (KLF5) transcription factor (Suzuki et al., 2007). HYDAMTIQ, a PARP1 inhibitor has been illustrated to confer neuroprotection post stroke (Moroni et al., 2012). The reason for morbidity in multiple sclerosis, trauma and stroke is dysfunction of blood brain barrier and subsequently leukocyte infiltration and neuro-inflammation. Recent evidences have suggested PARP inhibition diminishes inflammation in leukocytes via attenuation of adhesion and migration (Rom et al., 2016).

The only approved treatment for thrombolysis in ischemic stroke is recombinant tissue plasminogen activator (rtPA), but at certain dose and in some conditions, it can aggravate the risk of haemorrhage. rtPA is reported to increase PARP1 activity and inhibition of PARP1 prevents the vascular toxicity of rtPA on brain (Teng et al., 2013). Thus, co-treatment of PARP inhibitor with rtPA seems to be a promising approach for handling thrombolysis effects. PARP1 inhibition has been shown to suppress inflammation-related plaque formation, another reason for ischemia (von Lukowicz et al., 2008).

Potential implication of PARP inhibitors in Covid-19

Several evidences have supported the involvement of PARP1 in oxidative stress mediated response, inflammation and various diseases. PARP-1 mediated inflammatory response caused by bacteria and other pathogenic agents like parasite and fungi has been elucidated. PARP1 is also known to regulate cytokine production and the string analysis also depict direct PARP1 interaction with some cytokines and indirect with few other cytokines known to be involved in Covid-19 (Fig 1). Although there are reports of PARP1 regulation of virus-host interaction and virus infection, but detailed mechanistic studies are required as PARP1 involvement in virus mediated inflammation is not elucidated fully. PARP1 mediated inflammation during fibrosis, ischaemia and stroke and its relationship with viruses, inspired us to think about probability of role of PARP1 in SARS-CoV-2 mediated inflammation. Further work is required to identify the link between SARS-CoV-2 virus infection and PARP1 mediated inflammation.

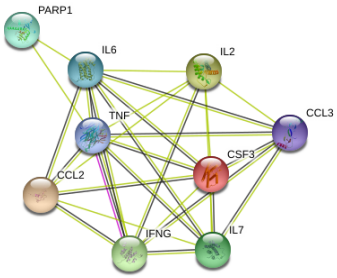
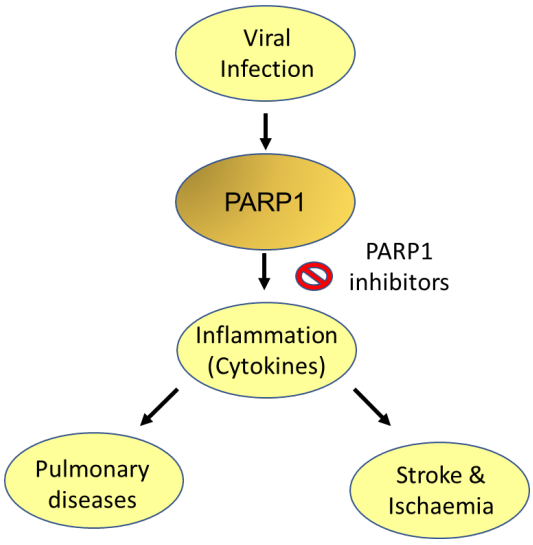


Figure 2. String analysis of PARP1 interaction with cytokines.

Multiple FDA approved PARP inhibitors are in clinical trials for cancer and other pathologies. Protective effects of PARP inhibitors have been demonstrated in *in vivo* models of non-oncological diseases. Recently *in silico* and *in vitro* analysis indicated that PARP inhibitor, a cancer drug Mefuparib (CVL218) exhibits antiviral activity against SAR-CoV-2. CVL218 was also shown to suppress the IL-6 production in PBMCs proposing its beneficial effect in SARS-CoV-2 induced immunopathology. The antiviral activity of CVL218 was more potent as compared to Remdesivir (Ge et al., 2020). Curtin and colleagues have also suggested the importance of repositioning of PARP inhibitors as a multi-pronged therapy for Covid-19 (Curtin et al., 2020). Based on these reports another PARP inhibitor, 2X-121 (former name E7449) has entered in preclinical study to assess its efficacy in Covid-19. 2X-121 is currently under Phase 2 for treatment of advanced ovarian cancer and metastatic breast cancer (https://clinicaltrials.gov/ct2/show/NCT03562832). These approaches have opened a new paradigm of inhibitors to be used against SARS-CoV-2 infection either directly or after repurposing. To explore a potential therapeutic for Covid-19, PARP inhibitors appear to be a promising approach.

Graphical Abstract



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Conflict of Interest

Authors declare No conflict of interest.

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