Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Immunology Letters 224 (2020) 38–39

Contents lists available at ScienceDirect

Immunology Letters

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

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Sequence homology between human PARP14 and the SARS-CoV-2 ADP ribose 1'-phosphatase

The 16-subunit SARS-CoV-2 replicase-transcriptase complex is currently under intense investigation as a putative drug target.

In addition to containing proteinases, RNA-processing enzymes, and exonucleases, this complex exhibits ADP-ribose-1′-phosphatase (ADRP) activity [1].

It is understood such activity may have emerged to counteract ADP-ribose-mediated signaling, which has been demonstrated to be vital in coordinating the mammalian immune response to viral infections [2].

Poly(ADP-ribose) polymerase family member 14 (PARP14) has numerous immunomodulatory roles including promotion of interferon expression in response to Coronaviridae infections [3], suppression of macrophage activation [4], and induction of the Th2 response [5].

We have found that the ADP-ribose-binding domains of both proteins share a significant degree of homology [2,6] (Fig. 1.). This supports a hypothesis that Coronaviridae ADRP enzymes may have co-evolved to counter the ADP-ribosylation activity of regulatory proteins such as PARP14 as they both bind ADP-ribose in the same context [6].

Within the class Mammalia, the ADP-ribose-binding domains of PARP isoforms from bat (*Myotis*) species are among the most similar to SARS-CoV-2 sequences (data not shown). This is consistent with the prevalent theory that the virus evolved from a strain found in bat species [7], with the inference being that co-evolution of the virus and the bat caused them to adopt the same ADP-ribose-binding strategy.

In mouse models, attenuation of the SARS-CoV ADRP increased the sensitivity of the virus to interferon α [8] and PARP14 inhibition caused a reduction in interferon β mRNA levels by an ADP-ribosylation-dependent mechanism [3]. Interferon γ can also increase the propensity for ADP-ribosylation of PARP14 [9]. The SARS-CoV ORF6 protein has been implicated in blockade of the transit of STAT1 into the nucleus, circumventing the interferon-α/β-mediated antiviral immune response [10]. It follows that the interferon axis and PARP14 activity appear conspicuously linked and recent literature has elucidated a role for interferon therapy in COVID-19 [11].

Macrophage Activation Syndrome (MAS) has been found to complicate severe COVID-19 [12]. ADP-ribosylation of STAT1 by PARP14 suppresses macrophage activation, in opposition to PARP9 [4]. It is possible that viral suppression of STAT1 transit and ADP-ribose cleavage both contribute to MAS (Fig. 2.).

PARP14 has been found to regulate STAT6-dependent transcription to promote the Th2 response and IL-4 release [5,13]. This is particularly pronounced in lung tissue [14]. This has important ramifications for the host response to SARS-CoV-2 infection.

The Th2 response, which involves IL-4, IL-5 and IL-9 (Fig. 2.), serves to promote IgE release and encourage T-cell migration to inflamed tissue in allergic disease [15]. Of interest, Th2 predominance is noted in patients with atopic asthma [15], who appear underrepresented in severe COVID-19 cases [16] and one recent study revealed patients on anti-IL-4 therapy were found to exhibit no increased risk of severe COVID-19 [17].

In Middle East Respiratory Syndrome (MERS), a condition caused by the coronavirus EMC/2012, downregulation of Th2 cells and overexpression of innate system cytokines IL-1B and IL-6 contributes to the

protein mono-ADP-ribosyltransferase PARP14 [Homo sapiens]

Sequence ID: NP_060024.2 **Length:** 1801 **Number of Matches:** 1

See 1 more title(s)

Range 1: 818 to 937 GenPept Graphics ▼ Next Match ▲ Previous Match

Score	Expect	Method	Identities	Positives	Gaps
56.6 bits(135)	2e-06	Compositional matrix adjust.	40/125(32%)	60/125(48%)	16/125(12%)

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            V+VNA+N  LKH GG+A AL+KA     +Q + D  +K  G L  G + +      L
Sbjct  818  VVVNASNEDLKHYGGLAAALSKAAGPELQADCDQIVKREGRLLPGNATISKAGKLPYHHV  877

Query  275  LHVVGPNLNAGE----------DIQLLKAAYENFNSQDILLAPLLSAGIFGAKPLQSLQV  324
            +H VGP  +  E           +QL     E +  + I + P +S+G+FG       L
Sbjct  878  IHAVGPRWSGYEAPRCVYLLRRAVQLSLCLAEKYKYRSIAI-PAISSGVFGF----PLGR  932

Query  325  CVQTV  329
            C+ T+
Sbjct  933  CVETI  937
```

Fig. 1. 32 % homology between the ADP-ribose-binding domain of SARS-CoV-2 and human PARP14*.

https://doi.org/10.1016/j.imlet.2020.05.008
Received 10 May 2020; Accepted 25 May 2020
Available online 11 June 2020

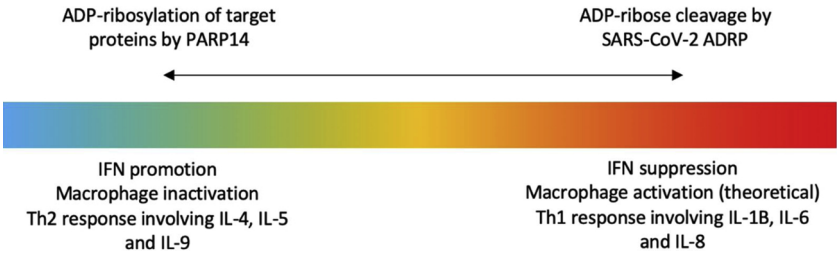

Fig. 2. Graphical summary of the immune sequelae of the antagonism between the activity of human PARP14 and coronaviral ADRP.

development of Acute Respiratory Distress Syndrome (ARDS) [18].

Similarly, in COVID-19, cytokines associated with the Th1 response (IL-1B, IL-6 and IL-8) correlate with morbidity and mortality [19]. Cytokine storm in COVID-19 is a pathogenic mechanism for morbidity and mortality, which again implicates dysregulation in the Th1 response [19,20].

The effect of this proposed antagonism between SARS-CoV-2 ADRP and PARP14 activity appears to have myriad effects. These include skewing of the Th1:Th2 cytokine ratios, the evasion of host interferons, and macrophage activation. Susceptibility to MAS and cytokine storm, understood as poor prognostic factors in COVID-19, may be consequences of this relationship, compounded by a faltering host interferon response.

This might provide a model by which SARS-CoV-2 can maintain high levels of viral RNA, whilst simultaneously contributing to the deleterious effects to the host. Further experimental studies are needed to establish whether therapies within the PARP axis could be beneficial in severe COVID-19.

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