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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-ribosyl-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 Coronavirus 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 Coronavirus 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 over-expression of innate system cytokines IL-1B and IL-6 contributes to the...
development of Acute Respiratory Distress Syndrome (ARDS) [18]. Similarly, in COVID-19, cytokines associated with the Th1 response (IL-1β, 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 interferon response [19,20].

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

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