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Short Communication

Is haem the real target of COVID-19?

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ABSTRACT

Although a vaccination campaign has been launched in many countries, the COVID-19 pandemic is not under control. The main concern is the emergence of new variants of SARS-CoV-2; therefore, it is important to find approaches to prevent or reduce the virulence and pathogenicity of the virus. Currently, the mechanism of action of SARS-CoV-2 is not fully understood. Considering the clinical effects that occur during the disease, attacking the human respiratory and hematopoietic systems, and the changes in biochemical parameters (including decreases in haemoglobin [Hb] levels and increases in serum ferritin), it is clear that iron metabolism is involved. SARS-CoV-2 induces haemolysis and interacts with Hb molecules via ACE2, CD147, CD26, and other receptors located on erythrocytes and/or blood cell precursors that produce dysfunctional Hb. A molecular docking study has reported a potential link between the virus and the beta chain of haemoglobin and attack on haem. Considering that haem is involved in miRNA processing by binding to the DGCR8-DROSHA complex, we hypothesised that the virus may check this mechanism and thwart the antiviral response.

Background

To date, the COVID-19 pandemic has infected 165 million people worldwide, with 3,43 million deaths. Although a vaccination campaign has been launched, the situation is not under control. Some vaccines have been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) based on different mechanisms of action. Considering that these vaccines are currently the only way to control symptomatic infection from the virus, the induced immunity needs to be with prolonged activity. Moreover, the emergence of new variants, such as English, Brazilian, and Indian, which are much more contagious and aggressive, must be considered.

Therefore, it is important to find other strategies to prevent or reduce the virulence and pathogenicity of SARS-CoV-2.

Currently, the mechanism of action of SARS-CoV-2 remains unclear. In the early stages of the pandemic, clinical studies have shown systemic infection of patients, mainly attacking the respiratory and hematopoietic systems and homoeostasis [1]. The biochemical parameters of the patients showed a decrease in haemoglobin (Hb) level [2] and an increase in serum ferritin, erythrocyte sedimentation rate, C-reactive protein, and lactate dehydrogenase [3,4]. During the progression from mild to severe disease, an increase in bilirubin levels [5], and in some cases, porphyria [6] were observed. These data support a link between SARS-CoV-2 and iron metabolism, similar with other RNA viruses, such as hepatitis C and B, Ebola, human immunodeficiency virus (HIV), dengue, and Zika [7, 8–12].

Viral interactions with receptors located on erythrocytes and blood cell precursors and the haemoglobin molecule via ACE2, CD147, and CD26 have been highlighted [13–17]. Furthermore, a molecular docking study found that the viral ORF8 protein and surface glycoprotein bind to porphyrin and target haem on the 1-beta chain of Hb [18,19]. SARS-CoV-2 induces haemolysis [20,21], forms a complex with the released haem [22] and generates a quote of dysfunctional Hb with reduced oxygen and CO_2 transport [23]. Recent studies confirmed the increase in the production of haem and free haemoglobin [24] and demonstrated the link between SARS-CoV-2 and haem through a computational-experimental approach [25,26].

In this study, several lines of evidence suggest a potential link between virus and Hb: i) women who have lower Hb levels than men are less susceptible to infection COVID; ii) new-borns of infected mothers do not get sick; the beta chain of Hb appears a few weeks after birth; and iii) at the beginning of the pandemic, there was a very low percentage of

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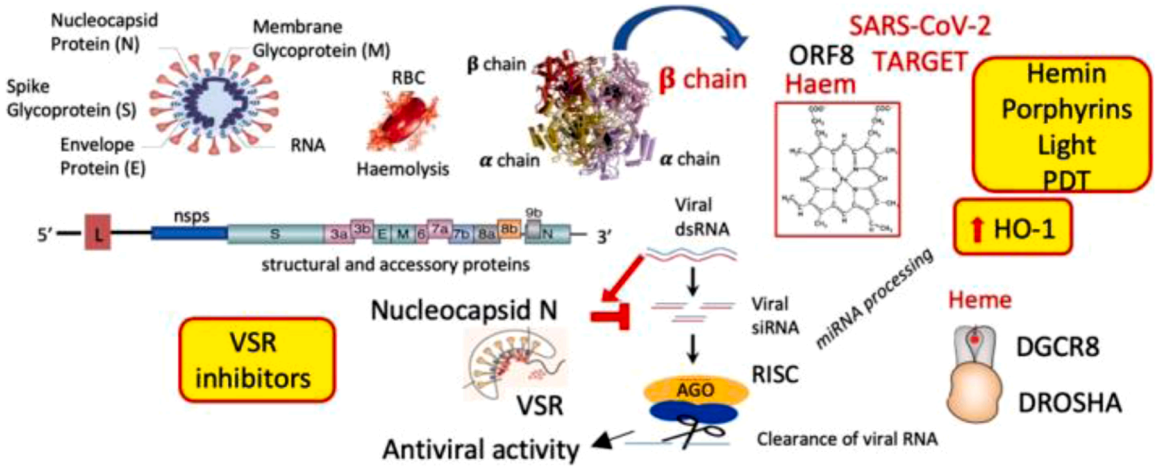

Fig. 1. Possible mechanism by which SARS-CoV-2 can regulate its replication by overcoming the antiviral system. SARS-Cov-2 targets B-chain haemoglobin after infection and haemolysis of red blood cells (RBCs) and binds haem through Orf8 releasing iron. The haem-DGCR8-DROSHA complex initiates RNA processing, resulting in virus-encoded miRNA. Some of these are cleaved by RISC, while others, such as nucleocapsid N, are viral suppressors of RNA silencing (VSRs). VSRs antagonize the RNAi pathway and thus the antiviral response. The possible therapeutic strategies are shown in the yellow square.

clinical cases in many Mediterranean regions, such as Tunisia, Libya, Sardinia, and Sicily. This is possibly due to many patients with beta-thalassaemia in these areas, a blood disease caused by abnormalities in the beta-chains of Hb [27–29].

During the quarantine period in March 2020, a case report of Slovenian skiers with COVID brought our interest in studying this disease. They found benefit from irradiation of the thoracic region with red to near-infrared radiation (R/NIR) combined with 660 and 920 nm, at a total fluence of 10 J/cm^2 (i.e. two 5 J/cm^2 sessions per day) (data not published). The efficacy of this treatment was confirmed a few months later by a Brazilian study in humans [30], based on an earlier study reporting the effect of light irradiation in mice with pneumonia [31].

It is known that light irradiation can induce the production of reactive oxygen species (ROS) with an increase in haem oxygenases 1 (HO-1) [32,33], leading to the destruction of haem. This may be the reason why individuals with high HO-1 levels, such as smokers, have a lower risk of infection [34]. It has been reported that the administration of hemin and metalloporphyrin, which upregulate HO-1 gene expression, inhibits the replication of viruses involved in iron metabolism, such as SARS-CoV-2 [35], and leads to a decrease in neutrophil infiltration and pneumonia with an increase in the interferon response [36].

Aim

All this evidence supports a strong relationship between COVID-19 and haem [19,37], although without any possible explanation.

Therefore, the important question is: why would the virus target haem? What would be beneficial to this?

Comments and suggestions

Haem is the functional group of various proteins, including cytochromes, Hb, and myoglobin, and is crucial for many different biological processes [38]. Haem also enters the cells freely and modifies proteins, DNA, and lipids [39,40]. Moreover, it can be transported out of the cell by the breast cancer resistance protein (BCRP) [41]. Haem also acts as a danger element in the signal damage-associated molecular pattern (DAMP) [37, 42–45] and activates Toll-like receptor 4 signalling (TRL-4) [46], which plays a crucial role in the innate immune system [47].

In addition, haem has been reported to be involved in miRNA processing [48]. The RNA-binding protein DiGeorge critical region-8 (DGCR8), essential for the first processing step, is a haem-binding protein [49]. The association (DGCR8-haem) promotes the expression of DGCR8 and the formation of the microprocessor, a complex containing RNase Drosha and DGCR8 for processing pri-miRNAs [50,51]. Thus, pri-miRNA processing is enhanced by haem both in vitro and in vivo, and variations in haem status can modulate DGCR8 activity.

Therefore, haem can serve as a signalling molecule that regulates various functions, such as transcription [52,53], cell signalling [54], and ion flux [55]. In addition, it is important to highlight that RNA interference (RNAi) functions in antiviral immunity [56-60].

This could explain why the virus attacks haem. Considering that the virus must live and replicate by exploiting the host, it is possible that miRNA processing must be maintained under strict control [61,62] to ensure its own gene expression and prevent host defence mechanisms that could destroy it [63] Fig. 1.

Therefore, it is important to consider the crucial role of the coronavirus N protein [64,65]. During the viral life cycle, the N protein encapsulates viral genomic RNAs to protect and introduce them into the host cell, suggesting that N is essential for viral RNA replication, particularly at the initiation step [66]. Moreover, N protein has been identified as a viral suppressor of RNA silencing (VSR) [65,67], which inhibits the production of viral siRNAs (vsiRNA) and the antiviral RNAi response during viral infection [68,69]. RNA-binding of SARS-CoV N is critical for its antagonism to interferon induction [70], as seen in ORF6 and ORF8 [71,72].

Furthermore, nonstructural protein 1 (nsp1) has been reported to bind to the 40S ribosomal subunit, resulting in the silencing of mRNA translation and blockage of retinoic acid-inducible gene I (RIG-I) and interferon-stimulated genes (ISGs), which are the key mediators of the innate immune responses against viral infection [73]. All data suggest that SARS-CoV-2 can antagonise RNAi in the initiation (i.e. siRNA biogenesis) and effector (i.e. RISC assembly and target cleavage) steps [66].

Our hypothesis revealed a new vision for the mechanism of action of SARS-CoV-2 that can effectively act through haem functions. This study aims to encourage molecular biologists and virologists to identify new potential targets to improve therapeutic strategies against SARS-CoV-2.

It has been reported that photobiomodulation can reduce the virulence of the virus by reducing ARDS and accelerating the regeneration of damaged tissue [74–76]. The efficacy of photobiomodulation may be because the virus is trapped in porphyrins. Exogenous administration of 5-aminolaevulinic acid has been reported to inhibit SARS-CoV-2 infection in vitro [77].

Our study will focus on the link between SARS-CoV-2, haem, and

exogenous porphyrins capable of binding viral RNA, using the classical plaque reduction neutralisation test (PRNT). This study mainly aims to understand whether PDT could be a good therapeutic strategy [78–81].

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