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SARS-CoV-2 and miRNA-like inhibition power

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ABSTRACT

(1) Background: RNA viruses and especially coronaviruses could act inside host cells not only by building their own proteins, but also by perturbing the cell metabolism. We show the possibility of miRNA-like inhibitions by the SARS-CoV-2 concerning for example the hemoglobin and type I interferons syntheses, hence highly perturbing oxygen distribution in vital organs and immune response as described by clinicians; (2) Hypothesis: We hypothesize that short RNA sequences (about 20 nucleotides in length) from the SARS-CoV-2 virus genome can inhibit the translation of human proteins involved in oxygen metabolism, olfactory perception and immune system. (3) Methods: We compare RNA subsequences of SARS-CoV-2 protein S and RNA-dependent RNA polymerase genes to mRNA sequences of beta-globin and type I interferons; (4) Results: RNA subsequences longer than eight nucleotides from SARS-CoV-2 genome could hybridize subsequences of the mRNA of beta-globin and of type I interferons; (5) Conclusions: Beyond viral protein production, COVID-19 might affect vital processes like host oxygen transport and immune response.

Introduction

Viruses act in host cells by reproducing their own proteins for reconstituting their capsid, duplicating their genome [1] and leaving non-coding RNA or DNA remnants in host genomes [2]. Moreover, RNA viruses can also form complexes with existing mRNAs and/or proteins of host cells. Thereby they might prevent protein function, behave like microRNAs [3–6] or ribosomal RNAs [6–8], inhibiting or favoring the translation of specific proteins of host cells [9–17]. If these proteins are vital for the host, viral pathogenicity is much greater than that caused by viral replication. With regard to SARS-CoV-2, binding to existing host proteins has already been described [18]. Here, we aim to describe a potential miRNA-like action by viral RNA, in particular at the level of i) oxygen transport by hemoglobin, whose beta-globin and gamma 2 subunits synthesis can be inhibited, and ii) immune response, where type I interferon synthesis can be inhibited. We are not intending to prove here experimentally these inhibitions by small RNAs issued from the SARS-CoV-2 genome, but to prepare this future empirical step by pointing out its potential hybridizing power. In Section 3, we describe a method for finding SARS-CoV-2 inhibitory RNA sub-sequences, and results are given in Section 4, discussed in Section 5. Some perspectives of this work concerning an extension to the inhibition of translation of olfactory and interferon receptors are proposed in Section 6.

Hypothesis

We assume in this paper that short RNA sub-sequences (about 20 nucleotides in length) coming from the SARS-CoV-2 virus genes hybridize the messenger RNA of key human proteins involved in important metabolism as oxygen metabolism (hemoglobin), olfactory perception (olfactory receptors) and immune system (type I interferon), and hence, can inhibit their ribosomal translation.

Methods

Focusing on the seed part of miRNA-like sequences having a putative 8 nucleotide hybridization seed inhibition effect [19–20] (minimum 7), we compare data from different databases
[21–26] using BLAST [27]. Fig. 1 shows microRNA 129-5p, a known inhibitor of a human foetal hemoglobin component, the gamma-globin 2, replaced in adult by the beta-globin regulated as the other component alpha-globin, by microRNAS [28–32]. Two sub-sequences from the SARS-CoV-2 genome, namely from genes of ORF10 and protein S, show the same hybridizing potential.

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***Homo sapiens* hemoglobin subunit gamma 2 (HBG2), mRNA NCBI Reference Sequence: NM_000184.3**

```
5′-ACACTCGCTTCTGGAACGTCTGAGGTTATCAATAAGCTCCTAGTCCAGACGCCATGGGTCATTTCACAGA
   GGAGGACAAGGCTACTATCACAAGCCTGTGGGGCAAGGTGAATGTGGAAGATGCTGGAGGAGAAACCCTG
   GGAAGGCTCCTGGTTGTCTACCCATGGACCCAGAGGTTCTTTGACAGCTTTGGCAACCTGTCCTCTGCCT
   CTGCCATCATGGGCAACCCCAAAGTCAAGGCACATGGCAAGAAGGTGCTGACTTCCTTGGGAGATGCCAT
                  hsa-miR-129-5p 3′-TGTCGTTCGGGTCTGGC-5′
   AAAGCACCTGGATGATCTCAAGGGCACCTTTGCCCAGCTGAGTGAACTGCACTGTGACAAGCTGCATGTG
   GATCCTGAGAACTTCAAGCTCCTGGGAAATGTGCTGGTGACCGTTTTGGCAATCCATTTCGGCAAAGAAT
   TCACCCCTGAGGTGCAGGCTTCCTGGCAGAAGATGGTGACTGGAGTGGCCAGTGCCCTGTCCTCCAGATA
              protein S gene SARS-CoV-2 3′-CTGAAGTAGTGGAGATTAATGT-5′
   CCACTGAGCTCACTGCCCATGATGCAGAGCTTTCAAGGATAGGCTTTATTCTGCAAGCAATCAAATAATA
                ORF10 gene SARS-CoV-2 3′-TTCTAAGTAAGACGTGTTCTCATCTG-5′
   AATCTATTCTGCTAAGAGATCACACA-3′
```

Fig. 1. Complete mRNA sequence of the subunit gamma 2 of the fetal human hemoglobin [22]. Sequences in green (resp. red) come from protein S and ORF10 genes of SARS-CoV-2 (resp. hsa miR 129-5p), which can inhibit its ribosomal translation. Probability of length 8 anti-match in red (resp. 9 and 11 in green) by chance in 577 nucleotides equals 0.035 (resp. 0.017 and 0.0003) (T-G and G-T matches counting for ½). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

***Homo sapiens* hemoglobin subunit beta (HBB), mRNA NCBI Reference Sequence: NM_000518.5**

```
5′-ACATTTGCTTCTGACACAACTGTGTTCACTAGCAACCTCAAACAGACACCATGGTGCATCTGACTCCTGAGGA
            RNA-dependent RNA polymerase SARS-CoV-2   3′-TCACGTAGAACTAGGAGTATT-5′
   GAAGTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGTGGATGAAGTTGGTGGTGAGGCCCTGGGCAGGCTG
   CTGGTGGTCTACCCTTGGACCCAGAGGTTCTTTGAGTCCTTTGGGGATCTGTCCACTCCTGATGCTGTTATGG
   GGCAACCCTAAGGTGAAGGCTCATGGCAAGAAAGTGCTCGGTGCCTTTAGTGATGGCCTGGCTCACCTGGACA
                     mir-451a   3′-TTGAGTCATTACCATTGCCAAA-5′
   CCTCAAGGGCACCTTTGCCACACTGAGTGAGCTGCACTGTGACAAGCTGCACGTGGATCCTGAGAACTTCAGG
                                                              3′-TGTCCGGC
   CTCCTGGGCAACGTGCTGGTCTGTGTGCTGGCCCATCACTTTGGCAAAGAATTCACCCCACCAGTGCAGGCTG
   CCTGTTCACGTTAT-5′ miR-92a-3p
   CCTATCAGAAAGTGGTGGCTGGTGTGGCTAATGCCCTGGCCCACAAGTATCACTAAGCTCGCTTTCTTGCTGT
      3′-ATTTTCACCTTTTACTACGCC-5′ Protein S SARS-CoV-2
   CCAATTTCTATTAAAGGTTCCTTTGTTCCCTAAGTCCAACTACTAAACTGGGGGATATTATGAAGGGCCTTGA
   GCATCTGGATTCTGCCTAATAAAAAACATTTATTTTCATTGCAA-3′
```

Fig. 2. Human beta-globin gene [24] potentially targeted by a subsequence of the gene of the SARS-CoV-2 RNA-dependent RNA polymerase (in blue) and by a subsequence of the gene of the SARS-CoV-2 protein S (in green) [23], by the human microRNAs hsa miR 92a-3p (in red) and hsa miR 451a (in red). Probability of red anti-matches of length 8 in a sequence of 624 nucleotides equals 0.04 and for the blue (resp. green) subsequence is 0.005 (resp. 0.017) (T-G and G-T matches counting for ½). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Results

We will apply the method from Section 2 for showing examples where RNA subsequences of the SARS-CoV-2 genome have an inhibitory potential on the ribosomal translation of human mRNAs of the same type as that shown in Section 2 for human micro-RNAs. For example, miRTarBase shows that microRNA hsa-mir-92a-3p targets the beta-globin HBB subunit of adult hemoglobin, inhibiting its translation [25]. This is also the case for microRNAs involved in the maturation of erythrocytes like miR-451a [26–31]. We exhibit on Fig. 2 sub-sequences of the SARS-CoV-2 protein S and polymerase genes [23] having the same length of anti-matching as these microRNAs on the mRNA of the hemoglobin beta-globin (HBB) subunit gene.

The second example concerns the gene of the spicule protein S of SARS-CoV-2, which shares a long subsequence of length 14 (664–678) with the gene of the Gag protein of the virus HERV-K102 (Fig. 3). Its potential targets are the mRNAs of human hemoglobin subunit beta-globin [22], human hemoglobin subunit gamma-globin 2 (HBG2) [23], human type 1 interferons and the human receptor ACE2.

The classical protein–protein interaction of the spicule protein S of SARS-CoV-2 is with the human protein receptor ACE2, but there exists a putative miRNA-like translation inhibition due to a subsequence (in green) of the protein S gene (Fig. 3) matching the ACE2 mRNA (Fig. 4). The human endogenous retrovirus HERV-K102 [32] has been described as having an antagonizing power on HIV-1 replication, by stimulating antibody production. It is indeed capable of high replication rate *in vivo* and *in vitro* and this high particle production can stimulate an early protective innate immune response against HIV-1 replication. It could play the same role in SARS-CoV-2. A possible mechanism of this immune stimulation could be due to the fact that both Gag protein of HERV-K107 and protein S of SARS-CoV-2 share common sub-sequences as the subsequence of length 15 nucleotides from the protein S of the SARS-CoV-2 given in green on Fig. 5.

Discussion

When we combine the antibody power originated by the endogenous human retrovirus HERV-K102 envelop protein (whose part of its mRNA is shared by the SARS-CoV-2 protein S [36]) with the putative inhibitory role of circRNAs capable to block the miRNA-like action of SARS-CoV-2, one could understand why certain carriers of SARS-CoV-2 are completely asymptomatic and therefore, by mimicking their defence mechanisms, consider a possible therapy against SARS-CoV-2. Indeed, if we look on the “sponge effect” of circRNAs against microRNAs [37–39], one can consider a therapeutic effect erasing pathogenic actions of microRNAs.

For example, in the case of the human let-7e microRNA, a sub-sequence of human circular RNA PVT1 [40] hybridizes hsa-let-7e (Fig. 6), thus preventing it from exerting a too important inhibition on the translation of proteins such as the gamma-globin 2. There exists a subsequence of the protein S of SARS-CoV-2 (Fig. 6), on which a similar action would be possible, hence reducing the miR-like pathogenicity of the protein S, but with less efficiency, with a hybridization free energy ΔG equal to -4.6 kcal/mol vs -11 for the hsa-let-7e.

SARS coronavirus 2 isolate USA/MN1-MDH1/2020, complete genome GenBank: MT188341.1: 21512-25333 protein S

5′-ATGTTTGTTTTTCTTGTTTTATTGCCACTAGTCTCTAGTCAGTGTGTTAATCTTACAACCAGAACTCAAT
TACCCCCTGCATACACTAATTCTTTCACACGTGGTGTTTATTACCCTGACAAAGTTTTCAGATCCTCAGT
TTTACATTCAACTCAGGACTTGTTCTTACCTTTCTTTTCCAATGTTACTTGGTTCCATGCTATACATGTC
TCTGGGACCAATGGTACTAAGAGGTTTGATAACCCTGTCCTACCATTTAATGATGGTGTTTATTTTGCTT
CCACTGAGAAGTCTAACATAATAAGAGGCTGGATTTTTGGTACTACTTTAGATTCGAAGACCCAGTCCCT
ACTTATTGTTAATAACGCTACTAATGTTGTTATTAAAGTCTGTGAATTTCAATTTTGTAATGATCCATTT
TTGGGTGTTTATTACCACAAAAACAACAAAAGTTGGATGGAAAGTGAGTTCAGAGTTTATTCTAGTGCGA
ATAATTGCACTTTTGAATATGTCTCTCAGCCTTTTCTTATGGACCTTGAAGGAAAACAGGGTAATTTCAA
AAATCTTAGGGAATTTGTGTTTAAGAATATTGATGGTTATTTTAAAATATATTCTAAGCACACGCCTATT
AATTTAGTGCGTGATCTCCCTCAGGGTTTTTCGGCTTTAGAACCATTGGTAGATTTGCCAATAGGTATTA
ACATCACTAGGTTTCAAACTTTACTTGCTTTACATAGAAGTTATTTGACTCCTGGTGATTCTTCTTCAGG
TTGGACAGCTGGTGCTGCAGCTTATTATGTGGGTTATCTTCAACCTAGGACTTTTCTATTAAAATATAAT
GAAAATGGAACCATTACAGATGCTGTAGACTGTGCACTTGACCCTCTCTCAGAAACAAAGTGTACGTTGA
AATCCTTCACTGTAGAAAAAGGAATCTATCAAACTTCTAACTTTAGAGTCCAACCAACAGAATCTATTGT
TAGATTTCCTAATATTACAAACTTGTGCCCTTTTGGTGAAGTTTTTAACGCCACCAGATTTGCATCTGTT
TATGCTTGGAACAGGAAGAGAATCAGCAACTGTGTTGCTGATTATTCTGTCCTATATAATTCCGCATCAT
TTTCCACTTTTAAGTGTTATGGAGTGTCTCCTACTAAATTAAATGATCTCTGCTTTACTAATGTCTATGC
AGATTCATTTGTAATTAGAGGTGATGAAGTCAGACAAATCGCTCCAGGGCAAACTGGAAAGATTGCTGAT
TATAATTATAAATTACCAGATGATTTTACAGGCTGCGTTATAGCTTGGAATTCTAACAATCTTGATTCTA
AGGTTGGTGGTAATTATAATTACCTGTATAGATTGTTTAGGAAGTCTAATCTCAAACCTTTTGAGAGAGA
TATTTCAACTGAAATCTATCAGGCCGGTAGCACACCTTGTAATGGTGTTGAAGGTTTTAATTGTTACTTT
CCTTTACAATCATATGGTTTCCAACCCACTAATGGTGTTGGTTACCAACCATACAGAGTAGTAGTACTTT
CTTTTGAACTTCTACATGCACCAGCAACTGTTTGTGGACCTAAAAAGTCTACTAATTTGGTTAAAAACAA
ATGTGTCAATTTTAACTTCAATGGTTTAACAGGCACAGGTGTTCTTACTGAGTCTAACAAAAAGTTTCTG
CCTTTCCAACAATTTGGCAGAGACATTGCTGACACTACTGATGCTGTCCGTGATCCACAGACACTTGAGA
TTCTTGACATTACACCATGTTCTTTTGGTGGTGTCAGTGTTATAACACCAGGAACAAATACTTCTAACCA
GGTTGCTGTTCTTTATCAGGATGTTAACTGCACAGAAGTCCCTGTTGCTATTCATGCAGATCAACTTACT
CCTACTTGGCGTGTTTATTCTACAGGTTCTAATGTTTTTCAAACACGTGCAGGCTGTTTAATAGGGGCTG
AACATGTCAACAACTCATATGAGTGTGACATACCCATTGGTGCAGGTATATGCGCTAGTTATCAGACTCA
GACTAATTCTCCTCGGCGGGCACGTAGTGTAGCTAGTCAATCCATCATTGCCTACACTATGTCACTTGGT
GCAGAAAATTCAGTTGCTTACTCTAATAACTCTATTGCCATACCCACAAATTTTACTATTAGTGTTACCA
CAGAAATTCTACCAGTGTCTATGACCAAGACATCAGTAGATTGTACAATGTACATTTGTGGTGATTCAAC
TGAATGCAGCAATCTTTTGTTGCAATATGGCAGTTTTTGTACACAATTAAACCGTGCTTTAACTGGAATA
GCTGTTGAACAAGACAAAAACACCCAAGAAGTTTTTGCACAAGTCAAACAAATTTACAAAACACCACCAA
TTAAAGATTTTGGTGGTTTTAATTTTTCACAAATATTACCAGATCCATCAAAACCAAGCAAGAGGTCATT
TATTGAAGATCTACTTTTCAACAAAGTGACACTTGCAGATGCTGGCTTCATCAAACAATATGGTGATTGC
CTTGGTGATATTGCTGCTAGAGACCTCATTTGTGCACAAAAGTTTAACGGCCTTACTGTTTTGCCACCTT
TGCTCACAGATGAAATGATTGCTCAATACACTTCTGCACTGTTAGCGGGTACAATCACTTCTGGTTGGAC
CTTTGGTGCAGGTGCTGCATTACAAATACCATTTGCTATGCAAATGGCTTATAGGTTTAATGGTATTGGA

GTTACACAGAATGTTCTCTATGAGAACCAAAAATTGATTGCCAACCAATTTAATAGTGCTATTGGCAAAA
TTCAAGACTCACTTTCTTCCACAGCAAGTGCACTTGGAAAACTTCAAGATGTGGTCAACCAAAATGCACA
AGCTTTAAACACGCTTGTTAAACAACTTAGCTCCAATTTTGGTGCAATTTCAAGTGTTTTAAATGATATC
CTTTCACGTCTTGACAAAGTTGAGGCTGAAGTGCAAATTGATAGGTTGATCACAGGCAGACTTCAAAGTT
TGCAGACATATGTGACTCAACAATTAATTAGAGCTGCAGAAATCAGAGCTTCTGCTAATCTTGCTGCTAC
TAAAATGTCAGAGTGTGTACTTGGACAATCAAAAAGAGTTGATTTTTGTGGAAAGGGCTATCATCTTATG
TCCTTCCCTCAGTCAGCACCTCATGGTGTAGTCTTCTTGCATGTGACTTATGTCCCTGCACAAGAAAAGA
ACTTCACAACTGCTCCTGCCATTTGTCATGATGGAAAAGCACACTTTCCTCGTGAAGGTGTCTTTGTTTC
AAATGGCACACACTGGTTTGTAACACAAAGGAATTTTTATGAACCACAAATCATTACTACAGACAACACA
TTTGTGTCTGGTAACTGTGATGTTGTAATAGGAATTGTCAACAACACAGTTTATGATCCTTTGCAACCTG
AATTAGACTCATTCAAGGAGGAGTTAGATAAATATTTTAAGAATCATACATCACCAGATGTTGATTTAGG
TGACATCTCTGGCATTAATGCTTCAGTTGTAAACATTCAAAAAGAAATTGACCGCCTCAATGAGGTTGCC
AAGAATTTAAATGAATCTCTCATCGATCTCCAAGAACTTGGAAAGTATGAGCAGTATATAAAATGGCCAT
GGTACATTTGGCTAGGTTTTATAGCTGGCTTGATTGCCATAGTAATGGTGACAATTATGCTTTGCTGTAT
GACCAGTTGCTGTAGTTGTCTCAAGGGCTGTTGTTCTTGTGGATCCTGCTGCAAATTTGATGAAGACGAC
TCTGAGCCAGTGCTCAAAGGAGTCAAATTACATTACACATAA-3′

Fig. 3. mRNA sequence of the protein S of the virus SARS-CoV-2 [23]. The first green subsequence of length 14 (664–678) occurs in mRNA of Gag protein of the virus HERV-K102 [27]. The second of length 23 (1112–1134) anti-matches a mRNA subsequence of hemoglobin subunit beta-globin [22]. The third of length 22 (1200–1221) anti-matches a mRNA subsequence of hemoglobin subunit gamma-globin 2 (HBG2) [23]. The fourth of length 24 (2032–2055) matches a subsequence of mRNA of many type 1 interferons. Highlighted in yellow are sub-sequences common with the SARS furin cleavage site [33–34]. The fifth of length 25 (3152–3176) matches a subsequence of mRNA of the receptor ACE2. Blue: mutations whose location of both codon and nucleotide involved [35] are, in order: 635 gCtagTt, 1133 aAgaaGg, 2045 cGgacAg and 3189 ttG > ttT. The probabilities of the above matches and anti-matches will be given in the following in Figures concerning each of them. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

***Homo sapiens* ACE2 mRNA, complete cds GenBank: AB046569.1**

5′-TTTTTAGTCTAGGGAAAGTCATTCAGTGGATGTGATCTTGGCTCACAGGGGACGATGTCAAGCTCTTCCT
GGCTCCTTCTCAGCCTTGTTGCTGTAACTGCTGCTCAGTCCACCATTGAGGAACAGGCCAAGACATTTTT
GGACAAGTTTAACCACGAAGCCGAAGACCTGTTCTATCAAAGTTCACTTGCTTCTTGGAATTATAACACC
protein S SARS-CoV-2 3′-CTGTTTACCGTCCTCGTCAACACTT-5′
AATATTACTGAAGAGAATGTCCAAAACATGAATAACGCTGGGGACAAATGGTCTGCCTTTTTAAAGGAAC
AGTCCACACTTGCCCAAATGTATCCACTACAAGAAATTCAGAATCTCACAGTCAAGCTTCAGCTGCAGGC
TCTTCAGCAAAATGGGTCTTCAGTGCTCTCAGAAGACAAGAGCAAACGGTTGAACACAATTCTAAATACA
ATGAGCACCATCTACAGTACTGGAAAAGTTTGTAACCCAGATAATCCACAAGAATGCTTATTACTTGAAC
CAGGTTTGAATGAAATAATGGCAAACAGTTTAGACTACAATGAGAGGCTCTGGGCTTGGGAAAGCTGGAG
ATCTGAGGTCGGCAAGCAGCTGAGGCCATTATATGAAGAGTATGTGGTCTTGAAAAATGAGATGGCAAGA
GCAAATCATTATGAGGACTATGGGGATTATTGGAGAGGAGACTATGAAGTAAATGGGGTAGATGGCTATG
ACTACAGCCGCGGCCAGTTGATTGAAGATGTGGAACATACCTTTGAAGAGATTAAACCATTATATGAACA
TCTTCATGCCTATGTGAGGGCAAAGTTGATGAATGCCTATCCTTCCTATATCAGTCCAATTGGATGCCTC
CCTGCTCATTTGCTTGGTGATATGTGGGGTAGATTTTGGACAAATCTGTACTCTTTGACAGTTCCCTTTG
GACAGAAACCAAACATAGATGTTACTGATGCAATGGTGGACCAGGCCTGGGATGCACAGAGAATATTCAA
GGAGGCCGAGAAGTTCTTTGTATCTGTTGGTCTTCCTAATATGACTCAAGGATTCTGGGAAAATTCCATG
CTAACGGACCCAGGAAATGTTCAGAAAGCAGTCTGCCATCCCACAGCTTGGGACCTGGGGAAAGGCGACT
TCAGGATCCTTATGTGCACAAAGGTGACAATGGACGACTTCCTGACAGCTCATCATGAGATGGGGCATAT
TCAGTATGATATGGCATATGCTGCACAACCTTTTCTGCTAAGAAATGGAGCTAATGAAGGATTCCATGAA
GCTGTTGGGGAAATCATGTCACTTTCTGCAGCCACACCTAAGCATTTAAAATCCATTGGTCTTCTGTCAC
CCGATTTTCAAGAAGACAATGAAACAGAAATAAACTTCCTGCTCAAACAAGCACTCACGATTGTTGGGAC
TCTGCCATTTACTTACATGTTAGAGAAGTGGAGGTGGATGGTCTTTAAAGGGGAAATTCCCAAAGACCAG
TGGATGAAAAAGTGGTGGGAGATGAAGCGAGAGATAGTTGGGGTGGTGGAACCTGTGCCCCATGATGAAA
CATACTGTGACCCCGCATCTCTGTTCCATGTTTCTAATGATTACTCATTCATTCGATATTACACAAGGAC
CCTTTACCAATTCCAGTTTCAAGAAGCACTTTGTCAAGCAGCTAAACATGAAGGCCCTCTGCACAAATGT
GACATCTCAAACTCTACAGAAGCTGGACAGAAACTGTTCAATATGCTGAGGCTTGGAAAATCAGAACCCT
GGACCCTAGCATTGGAAAATGTTGTAGGAGCAAAGAACATGAATGTAAGGCCACTGCTCAACTACTTTGA
GCCCTTATTTACCTGGCTGAAAGACCAGAACAAGAATTCTTTTGTGGGATGGAGTACCGACTGGAGTCCA
TATGCAGACCAAAGCATCAAAGTGAGGATAAGCCTAAAATCAGCTCTTGGAGATAGAGCATATGAATGGA
ACGACAATGAAATGTACCTGTTCCGATCATCTGTTGCATATGCTATGAGGCAGTACTTTTTAAAAGTAAA
AAATCAGATGATTCTTTTTGGGGAGGAGGATGTGCGAGTGGCTAATTTGAAACCAAGAATCTCCTTTAAT
TTCTTTGTCACTGCACCTAAAAATGTGTCTGATATCATTCCTAGAACTGAAGTTGAAAAGGCCATCAGGA
TGTCCCGGAGCCGTATCAATGATGCTTTCCGTCTGAATGACAACAGCCTAGAGTTTCTGGGGATACAGCC
AACACTTGGACCTCCTAACCAGCCCCCTGTTTCCATATGGCTGATTGTTTTTGGAGTTGTGATGGGAGTG
ATAGTGGTTGGCATTGTCATCCTGATCTTCACTGGGATCAGAGATCGGAAGAAGAAAAATAAAGCAAGAA
GTGGAGAAAATCCTTATGCCTCCATCGATATTAGCAAAGGAGAAAATAATCCAGGATTCCAAAACACTGA
TGATGTTCAGACCTCCTTTTAGAAAAATCTATGTTTTTCCTCTTGAGGTGATTTTGTTGTATGTAAATGT
TAATTTCATGGTATAGAAAATATAAGATGATAAAAATATCATTAAATGTCAAAACTATGACTCTGTTCAG-3′

Fig. 4. mRNA sequence of the human protein receptor ACE2. The green 5′-3′ seed subsequence of length 10 is the reverse of an RNA sequence of the protein S of SARS-CoV-2. The probability to observe such an anti-match of length 10 by chance in a sequence of 2581 nucleotides equals 0.003. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

We can also compare the putative miRNA-like inhibitory efficacy of the protein S in other coronaviruses than SARS-CoV-2. By taking for example the SARS CoV Rs672 virus observed in 2006, it is possible to exhibit in the RNA sequence of its protein S gene some sub-sequences similar to those from SARS-CoV-2 involved in a miRNA inhibitory effect (Fig. 7): they have less nucleotides anti-matching their protein targets, which could explain lesser virulence of the SARS epidemic than of the SARS-CoV-2 outbreak.

Among the symptoms of the COVID-19 disease, anosmia is frequently described. This defect could be due to a miRNA-like inhibition of mRNAs of genes from olfactory receptor family (Fig. 8).

Perspectives

The perspectives of the present work are in the more in-depth study of unconventional mechanisms of action of the SARS-CoV-2 virus, in particular those concerning the disturbances of oxygen transport observed in many patients [41,42]. We can also notice the resemblance of a SARS-CoV-2 sub-sequence with hsa-miR-let-7b, the microRNA the most upregulated in Kawasaki disease [43] described as potentially linked to SARS-CoV-2 infection [44]. The SARS-CoV-2 virus could have, more than a direct protein–protein interaction (proposed in [16] despite the criticisms of [45]), an effective inhibitory action *in vivo* of the same type as that predicted here *in silico* on the synthesis of subunits of human hemoglobin, and this action is more important for SARS-CoV-2 than for other coronaviruses (like the SARS CoV Rs672 on Fig. 8). This hypothesis is in agreement with numerous studies showing a decrease of adult human hemoglobin blood concentrations in severe COVID-19 cases [46,47], presenting an increase of the high-sensitivity C-reactive protein as one of the three major predictors of severity [48], like in ß-thalassemia [49] and viral infections [50]. Hence, one could envisage a therapy blocking pathologic inhibitor effects on ribosomal translation

***Homo sapiens* endogenous retrovirus HERV-K102, complete sequence GenBank: AF164610.1: 1112-2596 Gag protein**

5′-ATGGGGCAAACTAAAAGTAAAATTAAAAGTAAATATGCCTCTTATCTCAGCTTTATTAAAATTCTTTTAA
AAAGAGGGGGAGTTAAAGTATCTACAAAAAATCTAATCAAGCTATTTCAAATAATAGAACAATTTTGCCC
ATGGTTTCCAGAACAAGGAACTTTAGATCTAAAAGATTGGAAAAGAATTGGTAAGGAACTAAAACAAGCA
GGTAGGAAGGGTAATATCATTCCACTTACAGTATGGAATGATTGGGCCATTATTAAAGCA**GCTTTAGAAC**
CATTTCAAACAGAAGAAGATAGCGTTTCAGTTTCTGATGCCCTTGGAAGCTGTATAATAGATTGTAATGA
AAACACAAGGAAAAAATCCCAGAAAGAAACGGAAGGTTTACATTGCGAATATGTAGCAGAGCCGGTAATG
GCTCAGTCAACGCAAAATGTTGACTATAATCAATTACAGGAGGTGATATATCCTGAAACGTTAAAATTAG
AAGGAAAAGGTCCAGAATTAGTGGGGCCATCAGAGTCTAAACCACGAGGCACAAGTCATCTTCCAGCAGG
TCAGGTGCCCGTAACATTACAACCTCAAAAGCAGGTTAAAGAAAATAAGACCCAACCGCCAGTAGCCTAT
CAATACTGGCCTCCGGCTGAACTTCAGTATCGGCCACCCCCAGAAAGTCAGTATGGATATCCAGGAATGC
CCCCAGCACCACAGGGCAGGGCGCCATACCCTCAGCCGCCCACTAGGAGACTTAATCCTACGGCACCACC
TAGTAGACAGGGTAGTGAATTACATGAAATTATTGATAAATCAAGAAAGGAAGGAGATACTGAGGCATGG
CAATTCCCAGTAACGTTAGAACCGATGCCACCTGGAGAAGGAGCCCAAGAGGGAGAGCCTCCCACAGTTG
AGGCCAGATACAAGTCTTTTTCGATAAAAATGCTAAAAGATATGAAAGAGGGAGTAAAACAGTATGGACC
CAACTCCCCTTATATGAGGACATTATTAGATTCCATTGCTCATGGACATAGACTCATTCCTTATGATTGG
GAGATTCTGGCAAAATCGTCTCTCTCACCCTCTCAATTTTTACAATTTAAGACTTGGTGGATTGATGGGG
TACAAGAACAGGTCCGAAGAAATAGGGCTGCCAATCCTCCAGTTAACATAGATGCAGATCAACTATTAGG
AATAGGTCAAAATTGGAGTACTATTAGTCAACAAGCATTAATGCAAAATGAGGCCATTGAGCAAGTTAGA
GCTATCTGCCTTAGAGCCTGGGAAAAAATCCAAGACCCAGGAAGTACCTGCCCCTCATTTAATACAGTAA
GACAAGGTTCAAAAGAGCCCTATCCTGATTTTGTGGCAAGGCTCCAAGATGTTGCTCAAAAGTCAATTGC
CGATGAAAAAGCCCGTAAGGTCATAGTGGAGTTGATGGCATATGAAAACGCCAATCCTGATGTCAATCAG
CCATTAAGCCATTAA-3′

Fig. 5. Complete RNA sequence of the Gag protein of the virus HERV-K102 [36]. The green subsequence of length 14 (271–285) is present in the RNA sequence of the protein S of virus SARS-CoV-2 [22]. The probability to observe this match of length 14 by chance in a sequence of 1475 nucleotides equals 10^{-6}. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

***Homo sapiens* Pvt1 oncogene (PVT1), long non-coding RNA NCBI Reference Sequence: NR_003367.3**

5′-CTCCGGGCAGAGCGCGTGTGGCGGCCGAGCACATGGGCCCGCGGGCCGGGCGGGCTCGGGGCGGCCGGGA
CGAGGAGGGGCGACGACGAGCTGCGAGCAAAGATGTGCCCCGGGACCCCCGGCACCTTCCAGTGGATTTC
CTTGCGGAAAGGATGTTGGCGGTCCCTGTGACCTGTGGAGACACGGCCAGATCTGCCCTCCAGCCTGATC
TTTTGGCCAGAAGGAGATTAAAAAGATGCCCCTCAAGATGGCTGTGCCTGTCAGCTGCATGGAGCTTCGT
TCAAGTATTTTCTGAGCCTGATGGATTTACAGTGATCTTCAGTGGTCTGGGGAATAACGCTGGTGGAACC
hsa-let-7e 3′-**CCTTTCGAT**C**CT**CCG
ATGCACTGGAATGACACACGCCCGGCACATTTCAGGATACTAAAAGTGGTTTTAAGGGAGGCTGTGGCTG
GC**AT**-5′
AATGCCTCATGGATTCTTACAGCTTGGATGTCCATGGGGGACGAAGGACTGCAGCTGGCTGAGAGGGTTG
AGATCTCTGTTTACTTAGATCTCTGCCAACTTCCTTTGGGTCTCCCTATGGAATGTAAGACCCCGACTCT
TCCTGGTGAAGCATCTGATGCACGTTCCATCCGGCGCTCAGCTGGGCTTGAGCTGACCATACTCCCTGGA
GCCTTCTCCCGAGGTGCGCGGGTGACCTTGGCACATACAGCCATCATGATGGTACTTTAAGTGGAGGCTG
AATCATCTCCCCTTTGAGCTGCTTGGCACGTGGCTCCCTTGGTGTTCCCCTTTTACTGCCAGGACACTGA
GATTTGGAGAGAGTCTCACTCTGTGGTCCAGGCTGAAGTACAGTGGCATGATCCCAGGTCACTGCAACCC
3′-**GTGAGGTAT**GT**G**AA**TT**T**T**C**A**C**C**-5′ **Protein S SARS-CoV-2**
CCACCTCCCGGGTTCAAGTGATCCTCCTGCCTCAGCCTCCCGAGTAGCTGGTATTACAGGCGTGTGCCAC-3′

Fig. 6. RNA sub-sequence of the circPVT1 [22]. The RNA sequence in red is the microRNAs hsa miR let-7 inhibited by its “sponge” hsa-circ-PVT1. The RNA sequence in green is a sub-sequence of the protein S of SARS-CoV-2 on which hsa-circ-PVT1 could serve as inhibitor. Anti-match probability of a sub-sequence of length 9 in a sequence of length 1946 is 0.06 (resp. 0.03) for the red (resp. green) sub-sequence. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of hemoglobin subunits, using for example circular RNAs as blockers of possible viral miRNA-like mechanisms (Fig. 7) [51–54]. Another direction could be to search if furin cleavage site sub-sequence has the same type of interaction with key proteins like Rac small GTPase (a protein from the Rho GTPase family, which is a strong determinant of the virus-induced IFNbeta response [55–56]), implicated in replication of many important viral pathogens infecting humans or like interferons. A first example is given by the human small GTPase 1 (Fig. 9) in which the inhibition of the SARS-CoV-2 protein S gene is possibly obtained through the same miRNA-like subsequence as for all type 1 interferons. The host immune system is indeed reacting to viral intrusion first with synthesis of type I interferons IFNalphas and IFNbetas [57–58]. They are messengers allowing the activation of cellular defenses blocking viral replication. In humans, these type I interferons are bound to interferon receptors, and then, they induce proteins with antiviral actions: RNA-dependent protein kinase (PKR), 2′,5′-oligoadenylate synthetase (OAS), RNase L, and Mx protein GTPases [59].

In the same way, the miRNA-like subsequence of SARS-CoV-2 protein S gene from its furin cleavage site anti-matches the mRNA of the MCT1 gene involved in the lactate shuttle between astrocytes and neurons (Fig. 11) and this effect decreases the energy provided to the brain [61,62]. That could explain some neurological and

Bat SARS CoV Rs672/2006, complete genome GenBank: FJ588686.1: 20894-24619 protein S

5′-GATTGTGTTGCTGATTACACTGTTCTCTACAACTCAACTTCATTTTCAACTTTTAAATGTTATGGAGTTT
CTCCCTCTAAGTTGATTGACTTGTGCTTTACAAGTGTGTATGCTGATACATTCTTGATAAGATCTTCAGA
AGTAAGGCAAGTTGCACCAGGTGAAACTGGTGTTATTGCTGACTATAACTACAAACTGCCTGATGACTTT
ACAGGCTGTGTCATAGCTTGGAACACTGCTAAACAAGATCAGGGCCAGTATTATTATAGATCCTCCAGAA
AAACAAAACTTAAACCTTTTGAGAGGGATCTAACTTCTGACGAAAATGGTGTACGTACTCTTAGTACTTA
TGACTTCTATCCTAATGTGCCTATTGAATATCAGGCTACTAGGGTTGTTGTGCTTTCATTCGAGCTTCTA

AATGCACCTGCTACAGTTTGTGGACCTAAATTATCCACAGGACTTGTTAAGAACCAGTGTGTCAATTTCA
ATTTTAATGGACTCAAAGGTACTGGTGTTCTGACTGATTCTTCAAAGAGATTTCAGTCATTTCAACAATT
TGGAAGAGACACGTCGGATTTCACTGATTCCGTTCGTGACCCGCAAACATTGCAGATACTTGACATTACA
CCATGTTCTTTTGGTGGTGTGAGTGTAATAACACCTGGAACAAATGCTTCATCTGAAGTGGCTGTTCTTT
ACCAAGATGTAAACTGCACCGATGTCCCAACAGCCATACGTGCAGACCAATTAACACCAGCTTGGCGCGT
TTACTCAACCGGAGTAAATGTGTTTCAAACACAAGCTGGCTGTCTTATTGGAGCTGAACATGTTAACGCT
TCGTATGAGTGTGACATTCCTATTGGTGCTGGCATTTGTGCTAGCTACCATACAGCTTCTACTCTACGTA
GTGTAGGTCAGAAATCCATTGTGGCTTACACTATGTCTTTGGGTGCAGAAAATTCTATTGCTTATGCTAA-3′

Fig. 7. RNA sub-sequence of the SARS CoV Rs672 protein S gene. Nucleotides in green are homologous to those of SARS-CoV-2 protein S gene (in green on Fig. 3), which could explain the lesser virulence of SARS as compared to SARS-CoV-2 due to fewer anti-matches with their miRNA-like targets. The probability to observe by chance a sub-sequence of length 31 in a sequence of 3722 nucleotides with exactly 3 errors equals $3\ C_{31}^{3}\ 0.25^{31} = 3\ 10^{-15}$ and for a sub-sequence of length 11 equals $9\ 10^{-4}$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

***Homo sapiens* olfactory receptor family 4 subfamily E member 1 (OR4E1), mRNA NCBI Reference Sequence: NM_001317107.1**

5′-TTAAATGACCAAATGATTGATGCAGATACTGTGTTATATTAGACTTTTTTTCTAATTCTTTACAGGTTGT
CTAACAAAGAGAATGGAAGAGGCCATCCTACTCAATCAAACTTCTTTAGTGACATATTTTCGGCTTAGAG
GTTTATCTGTAAATCATAAGGCACGGATAGCTATGTTTTCCATGTTCCTCATTTTTTATGTCCTGACACT
GATTGGGAATGTTCTCATTGTCATAACTATTATCTATGACCACCGGCTCCATACTCCCATGTATTTCTTC
CTCAGCAACCTGTCCTTTATTGATGTCTGCCACTCCACTGTCACTGTCCCCAAGATGCTGAGAGACGTGT
GGTCAGAGGAAAAGCTCATCTCTTTTGATGCCTGTGTGACCCAGATGTTCTTCCTGCACCTCTTTGCCTG
CACAGAGATCTTCCTCCTCACCGTCATGGCCTATGATCGGTATGTGGCCATCTGTAAACCCCTGCAGTAC
ATGATAGTGATGAACTGGAAGGTATGTGTGCTGCTGGCTGTGGCCCTCTGGACAGGAGGGACCATCCACT
CCATAGCCCTCACCTCCCTTACCATCAAGCTGCCCTACTGTGGTCCTGATGAGATTGACAACTTCTTCTG
TGATGTACCTCAGGTGATCAAGCTGGCCTGCATTGACACCCACGTCATTGAGATCCTCATTGTCTCCAAC
AGTGGATTGATCTCCGTGGTCTGTTTTGTGGTCCTGGTGGTGTCCTACGCAGTCATCCTGGTGAGTCTGA
GGCAGCAGATCTCCAAGGGCAAGCGGAAGGCCCTGTCCACCTGTGCAGCCCATCTCACTGTAGTTACACT
3′-ATCGATGTGA
GTTCCTGGGACACTGCATCTTCATCTATTCCCGCCCATCCACCAGCCTCCCAGAGGACAAGGTAGTATCT
TGCACGGGCGG-5′
GTGTTTTTCACTGCAGTCACCCCCCTGCTGAACCCCATTATCTATACCCTTAGGAATGAAGAAATGAAGA
GTGCCTTAAACAAGTTAGTGGGGAGAAAAGAGAGAAAAGAAGAAAAATGAAAATGTCTACGTCCTTAGGA
TACGTGGTGCTCCAAATTAAAGAAGCGCCTTGCAAAGAATAAGTTACATACCATAT-3′

Fig. 8. Complete mRNA sequence of the human olfactory receptor family 4 subfamily E member 1 (OR4E1) [22]. The RNA sequence in green is a sub-sequence of the protein S of SARS-CoV-2, which can exert a miRNA-like inhibition of the translation of OR4E1. The probability to observe such an anti-match of length 12 by chance in a sequence of 577 nucleotides equals $5\ 10^{-4}$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

neuropsychiatric complications observed in SARS-COV-2 patients, since the earliest cohorts featured non-specific neurological symptoms, such as dizziness and headache.

In [63], it is described a release of massive amounts of calprotectin (S100A8/S100A9) in severe cases of COVID-19. Studies about human microRNAs like hsa miR-320a-5p, hsa miR-1-24-5p and hsa miR 26b-3p identify the calprotectin as possible targets [64–66]. These microRNAs are inhibitors of the calprotectin (Fig. 12), but they can be hybridized by small sequences from protein S of SARS-CoV-2, which could play the same role as microRNAs sponges than the cellular circular RNAs [67], i.e., they can suppress their inhibitory power on the messenger RNA of their target proteins (Fig. 12).

Eventually, the mutations observed on SARS-CoV-2 [35,68–69] can be neutral (without any effect), favorable (less pathogenic) or deleterious (more pathogenic). Among them, we have (mutations in red):

Neutral: *Homo sapiens* hemoglobin subunit gamma 2 (HBG2) 5′-**GCTTTATTCTGCAAGCAA**-3′
protein S SARS-CoV-2 3′-TGAGGTATTGTGGATTTT-5′
Homo sapiens Rac family small GTPase 1 (RAC1) 5′-**CTGTGTGCCTGGCAC** -3′
protein S SARS-CoV-2 3′-GATGCACGGGCGACT-5′
Favorable: *Homo sapiens* ACE2 mRNA 5′-**GACAAATGGTCTGCCTTTTTAAAGG**-3′
protein S SARS-CoV-2 3′-CTTTTTACCGTCCTCGTCAACACTT-5′
Homo sapiens interferon regulatory factor 1 (IRF1) 5′-**CCTGTGTGCCTGGCACCTGCTA** -3′
protein S SARS-CoV-2 3′-TGATGCACGGGCGACTCCTCTT -5′
Deleterious: *Homo sapiens* HERV-K102 Gag protein 5′-**GCTTTAGAACCATTT**-3′
protein S SARS-CoV-2 5′-GTTTTAGAACCATTT-3′
Homo sapiens hemoglobin betaglobin (HBB) 5′-**TCAGAAAGTGGTGGCTGGTGTGG**-3′
protein S SARS-CoV-2 3′-GGATTTTCACCTTTTACTACGCC-5′

We can notice also that the protein S gene is not the only SARS-CoV-2 gene anti-matching important human molecules. It is for example the case of the ORF10 protein with the human gamma-globin 2 (Fig. 13).

On Fig. 13, the free energy and enthalpy are given in kcal/mol for two hybridizations [70–71] between subsequences of SARS-CoV-2 genes and subsequences of genes of two important proteins of the human metabolism of oxygen, involved in the oxygen transportation in adult for the first (the human hemoglobin beta-globin (HBG) subunit) and the in embryo for the second (the human hemoglobin gamma-globin 2 (HGG 2) subunit).

We have summarized the probabilities of anti-matches of Figs. 2 to 11, allowing for the comparison between the classical miRNA action and the putative inhibitory influence the protein S gene of SARS-CoV-2 can have on the translation of important human proteins.

The Table 1 presents the probability P and free energy ΔG (kcal/mol) of the anti-matches between human genes and protein S gene subsequences (TG and GT counting for ½), which are precisely described from Figs. 2 to 11. All these probabilities are less than 5 10^{-2} showing the significance of the corresponding associations, which could be at the origin of the brakes observed on many metabolisms, thus explaining the ubiquitous and inconstant nature of the symptoms of COVID-19. They concern indeed many organs, in a sequence and with a duration difficult to anticipate, the cases observed ranging from asymptomatic or mildly affected patients to severe patients suffering from numerous chronic co-morbidities, the worsening of which due to COVID-19 leading sometimes to death.

Conclusion

To conclude, the natural history of the SARS-CoV-2 virus remains widely unknown and it is still too early to say whether the many mutations observed will cause it to evolve in a favorable direction from a human point of view. There are for example some mutations surely deleterious [71,72], but also others favoring the positive role of some human miRNAs against SARS-CoV-2 [73–75] suggesting a possible therapy. The present proposal of a miRNA-like mechanism would at least allow to see, for a predictive purpose, what mutations (depending for example on geoclimatic factors [76]) are keeping, losing or reinforcing its pathogenicity.

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CRediT authorship contribution statement

Jacques Demongeot: Writing - review & editing, Conceptualization, Methodology, Investigation, Resources, Data curation, Writing - original draft. **Hervé Seligmann:** Writing - review & editing.

***Homo sapiens* Rac family small GTPase 1 (RAC1), transcript variant Rac1, mRNA NCBI Reference Sequence: NM_006908.5**

5′-TAATGGAGTGAGCGTAGCAGCTCAGCTCTTTGGATCAGTCTTTGTGATTTCATAGCGAGTTTTCTGACCA
GCTTTTGCGGAGATTTTGAACAGAACTGCTATTTCCTCTAATGAAGAATTCTGTTTAGCTGTGGGTGTGC
TTTTTGTTACAGATTAATTTTTCCATAAAACCATTTTTTGAACCAATCAGTAATTTTAAGGTTTTGTTTG
TTCTAAATGTAAGAGTTCAGACTCACATTCTATTAAAATTTAGCCCTAAAATGACAAGCCTTCTTAAAGC
CTTATTTTTCAAAAGCGCCCCCCCCATTCTTGTTCAGATTAAGAGTTGCCAAAATACCTTCTGAACTACA
protein S SARS-CoV-2 3′-GATGT
CTGCATTGTTGTGCCGAGAACACCGAGCACTGAACTTTGCAAAGACCTTCGTCTTTGAGAAGACGGTAGC
GATGCACGGGCG-5′
TTCTGCAGTTAGGAGGTGCAGACACTTGCTCTCCTATGTAGTTCTCAGATGCGTAAAGCAGAACAGCCTC
CCGAATGAAGCGTTGCCATTGAACTCACCAGTGAGTTAGCAGCACGTGTTCCCGACATAACATTGTACTG
TAATGGAGTGAGCGTAGCAGCTCAGCTCTTTGGATCAGTCTTTGTGATTTCATAGCGAGTTTTCTGACCA
GCTTTTGCGGAGATTTTGAACAGAACTGCTATTTCCTCTAATGAAGAATTCTGTTTAGCTGTGGGTGTGC
CGGGTGGGGTGTGTGTGATCAAAGGACAAAGACAGTATTTTGACAAAATACGAAGTGGAGATTTACACTA
protein S SARS-CoV-2 3′-GATGTGAT
CATTGTACAAGGAATGAAAGTGTCACGGGTAAAAACTCTAAAAGGTTAATTTCTGTCAAATGCAGTAGAT
GATGCACG-5′
GATGAAAGAAAGGTTGGTATTATCAGGAAATGTTTTCTTAAGCTTTTCCTTTCTCTTACACCTGCCATGC
CTCCCCAAATTGGGCATTTAATTCATCTTTAAACTGGTTGTTCTGTTAGTCGCTAACTTAGTAAGTGCTT
TTCTTATAGAACCCCTTCTGACTGAGCAATATGCCTCCTTGTATTATAAAATCTTTCTGATAATGCATTA-3′

Fig. 9. MiRNA-like subsequence of SARS-CoV-2 protein S gene (from its furin cleavage site) anti-matching a subsequence of the human GTPase 1 gene. The probability to observe such anti-matches of length 9 by chance in the of the 2301-length sequence of the whole human GTPase 1 gene equals 0.017.

Homo sapiens interferon alpha 7 (IFNA7), mRNA NCBI Reference Sequence: NM_021057.2

```
5′-TACCCACCTCAGGTAGCCTAGTGATATTTGCAAAATCCCAATGGCCCGGTCCTTTTCTTTACTGATGGTC
   GTGCTGGTACTCAGCTACAAATCCATCTGCTCTCTGGGCTGTGATCTGCCTCAGACCCACAGCCTGCGTA
   ATAGGAGGGCCTTGATACTCCTGGCACAAATGGGAAGAATCTCTCCTTTCTCCTGCTTGAAGGACAGACA
   TGAATTCAGATTCCCAGAGGAGGAGTTTGATGGCCACCAGTTCCAGAAGACTCAAGCCATCTCTGTCCTC
   CATGAGATGATCCAGCAGACCTTCAATCTCTTCAGCACAGAGGACTCATCTGCTGCTTGGGAACAGAGCC
   TCCTAGAAAAATTTTCCACTGAACTTTACCAGCAACTGAATGACCTGGAAGCATGTGTGATACAGGAGGT
   TGGGGTGGAAGAGACTCCCCTGATGAATGAGGACTTCATCCTGGCTGTGAGGAAATACTTCCAAAGAATC
                                          hsa miR let-7b-5p 3′-CTTTGGTGTGTTG
ACTCTTTATCTAATGGAGAAGAAATACAGCCCTTGTGCCTGGGAGGTTGTCAGAGCAGAAATCATGAGAT
GATGATGGAG-5′                3′-TGCACGGGCGGCTCCTCTTAATC-5′ protein S Covid-19
   CCTTCTCTTTTTCAACAAACTTGAAAAAAGGATTAAGGAGGAAGGATTGAAAACTGGTTCATCATGGAAA
   TGATTCTCATTGACTAATGCATCATCTCACACTTTCATGAGTTCTTCCATTTCAAAGACTCACTTCTATA
ACCACCACAAGTTGAATCAAAATTTCCAAATGTTTTCCT-3′
```

Homo sapiens interferon regulatory factor 1 (IRF1), transcript variant 5, non-coding RNA NCBI RefSeq: NR_149069.2

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5′-AGAGCTCGCCACTCCTTAGTCGAGGCAAGACGTGCGCCCGAGCCCCGCCGAACCGAGGCCACCCGGAGCC
   GTGCCCAGTCCACGCCGGCCGTGCCCGGCGGCCTTAAGAACCCGGCAACCTCTGCCTTCTTCCCTCTTCC
                3′-TGCACGGGCGGCTCCTCTTAAT-5′ protein S Covid-19
   ACTCGGAGTCGCGCTCCGCGCGCCCTCACTGCAGCCCCTGCGTCGCCGGGACCCTCGCGCGCGACCGCCG
   AATCGCTCCTGCAGCAGAGCCAACATGCCCATCACTCGGATGCGCATGAGACCCTGGCTAGAGATGCAGA
   TTAATTCCAACCAAATCCCGGGGCTCATCTGGATTAATAAAGTGAGTGTAACTCTTTGGGTTTTCCTGCC
   ACTGTTTTAACCCATGTACTTCTGGAGGGACCAAAGCTTCAGATGCAGCTCAAAAAGGGAAGTGATAACG
   GGACAAGCAGGTGTTTCTCCCAGTGGGTCCTGCATGCAGGGAGTGTGCACGGCCCAGCCTGGGCCTCACT
      3′-GTCTACGAAACTGTTATGATA-5′miRNA 301a-3p
   TGCATGACTCCTGCCTTCTTCCCTTCTTGAGGTAGGGCACCCACCTGAAGGCACTTCCAGTTTCCAGCAG
   CAAGACTTTCCAGCATCTGCAGAGCTGGAGTTCTGCTCTCCTCTAAGCGAGACCCTTACAAACATACACA
   GCACTCTGCAGGGCTCCAATCGAACAAATAGAAGACTGAGAAGTGGATGCTGCTGGGCAGAAACGTGCCT
   GGCTTAGCAGAGGACAAACGAGTTAATCTTGCACCAGTCACTCTGGCCCAAGAAGCCTATAGCTGGTGCA
   CTTGGGGCAACATAGACCCTATAGACTTAGTAGCAATGATAGTATTCATAATAATAGCTAATGCTTACTG
   AACACTCCCTGTGTGCCTGGCACCTGCTAAGTATGTTATTTACATTGTGTCATTTAATCCTCGCAGTAGT
      3′-TGATGCACGGGCGGCTCCTCTT-5′ protein S Covid-19
   CCTGTGGGTTAGATCTTACTAATGTCATCATTTTCAGATAAGTAAACAGAGGCACTGAGAGGTAGATCAT
AAGATCACACAAAAAGTGATGAAGCCAAGATTTGAACTTGAACGGTCTGACTCAGAAATCTT-3′
```

Fig. 10. MiRNA-like subsequence of SARS-CoV-2 protein S gene (from its furin cleavage site) anti-matching sequences from the human type 1 interferon (IFNA7) or interferon regulatory factor (IRF1). In the first case, the sequence is the whole mRNA of IFNA7 and the probability to observe such an anti-match of length 8 by chance in a sequence of 730 nucleotides equals 0.04. In the second case, the sequence of the whole mRNA of IRF1 contains to targets and the probability to observe the last anti-match of length 11 by chance in a sequence of 1032 nucleotides equals $2\ 10^{-3}$. In red, miRNA inhibiting sequences [59–60]. The probability to observe by chance the micro-RNA hsa miR let-7b-5p anti-match of length 9 in the first 730-length sequence equals 0.02 and the micro-RNA hsa miR 301a-3p anti-match of length 9 in the second 1032-length sequence equals 0.016. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Homo sapiens **clone peg2135 MCT1 (MCT1) mRNA, complete cds GenBank: AY364258.1**

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5′-ATGTTCAAGAAATTTGATGAAAAAGAAAATGTGTCCAACTGCATCCAGTTGAAAACTTCAGTTATTAAGG
   GTATTAAGAATCAATTGATAGAGCAATTTCCAGGTATTGAACCATGGCTTAATCAAATCATGCCTAAGAA
                                hsa miR 342-5p 3′-GAGTTAGTGTCTATCGTGGG-5′
   AGATCCTGTCAAAATAGTCCGATGCCATGAACATATAGAAATCCTTACAGTAAATGGAGAATTACTCTTT
   TTTAGACAAAGAGAAGGGCCTTTTTATCCAACCCTAAGATTACTTCACAAATATCCTTTTATCCTGCCAC
   ACCAGCAGGTTGATAAAGGAGCCATCAAATTTGTACTCAGTGGAGCAAATATCATGTGTCCAGGCTTAAC
   TTCTCCTGGAGCTAAGCTTTACCCTGCTGCAGTAGATACCATTGTTGCTATCATGGCAGAAGGAAAACAG
   CATGCTCTATGTGTTGGAGTCATGAAGATGTCTGCAGAAGACATTGAGAAAGTCAACAAAGGAATTGGCA
   TTGAAAATATCCATTATTTAAATGATGGGCTGTGGCATATGAAGACATATAAATGAGCCTCAGAAGGAAT
   GCACTTGGGCTAAATATGGATATTGTGCTGTATCTGTGTTTGTGTCTGTGTGTGACAGCATGAAGATAAT
                protein S SARS-CoV-2 3′-TGCACGGGCGGCTCCTCTT-5′
   GCCTGTGGTTATGCT G-3′
```
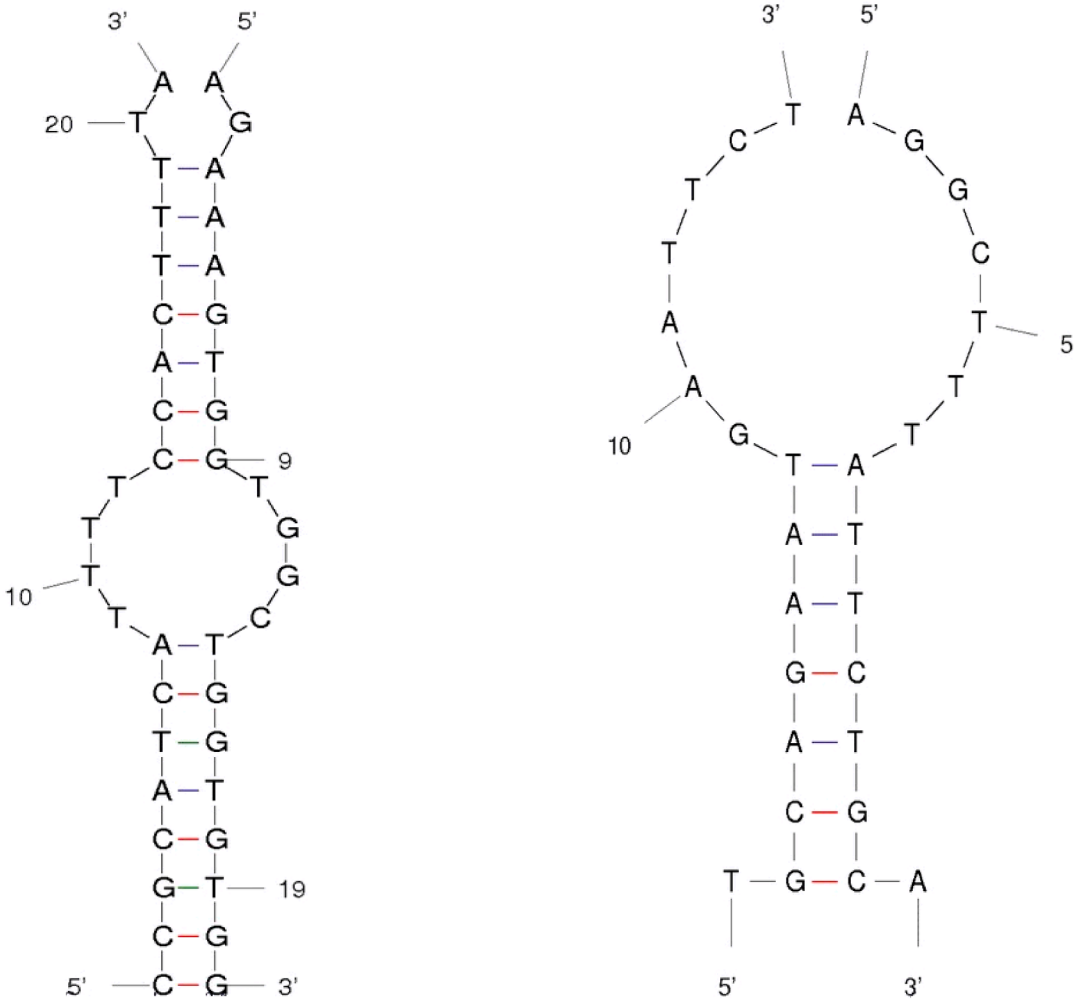

Fig. 11. MiRNA-like subsequence of SARS-CoV-2 protein S gene (from its furin cleavage site) anti-matching the mRNA of the human MCT1 gene. The probability to observe this anti-match of length 9 by chance in a sequence of 638 nucleotides equals $2.5\ 10^{-3}$. In red, the micro-RNA hsa miR 342-5p inhibiting the human MCT1 gene sequence with a subsequence of length 8 and this anti-match has the probability 0.02 to occur by chance in a sequence of 638 nucleotides. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

***Homo sapiens* S100 calcium binding protein A9 (S100A9) calprotectin, mRNA NCBI Reference Sequence: NM_002965.4**

AAACACTCTGTGTGGCTCCTCGGCTTTGACAGAGTGCAAGACGATGACTTGCAAAATGTCGCAGCTGGAA
CGCAACATAGAGACCATCATCAACACCTTCCACCAATACTCTGTGAAGCTGGGGCACCCAGACACCCTGA
GGAGGAGTTAGATAAATATTTT protein S SARS-CoV-2
CCTTCTTGGCCCTTCTCTTCCG hsa miR-320a-5p
ACCAGGGGGAATTCAAAGAGCTGGTGCGAAAAGATCTGCAAAATTTTCTCAAGAAGGAGAATAAGAATGA
TGACTATAGTCGAGTCATCCGT hsa miR-1-24-5p
ACTGATGCTGTCCGTGATCCAC protein S SARS-CoV-2
AAAGGTCATAGAACACATCATGGAGGACCTGGACACAAATGCAGACAAGCAGCTGAGCTTCGAGGAGTTC
ATCATGCTGATGGCGAGGCTAACCTGGGCCTCCCACGAGAAGATGCACGAGGGTGACGAGGGCCCTGGCC
AGTTGAGGCTGAAGTGCAAAT protein S SARS-CoV-2
TCGGTTCATTACCTCTTGTCC hsa miR 26b-3p
ACCACCATAAGCCAGGCCTCGGGGAGGGCACCCCCTAAGACCACAGTGGCCAAGATCACAGTGGCCACGG
CCACGGCCACAGTCATGGTGGCCACGGCCACAGCCACTAATCAGGAGGCCAGGCCACCCTGCCTCTACCC
AACCAGGGCCCCGGGGCCTGTTATGTCAAACTGTCTTGGCTGTGGGGCTAGGGGCTGGGGCCAAATAAAG
TCTCTTCCTCCAA

Fig. 12. MiRNA-like subsequences of SARS-CoV-2 protein S gene (in green) anti-matching human microRNAs (in red) having as target the calprotectin (S100A9). The probability to observe the first anti-match of length 9 by chance in a sequence of 569 nucleotides equals 3.5 10^{-2}. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



DNA at 37°C, C_T = 0.00001 M
$[Na^+]$ = 1 M, $[Mg^{++}]$ = 0 M
ΔG = -9.0 kcal/mol, ΔH = -85.9 kcal/mol

DNA at 37°C, C_T = 0.00001 M
$[Na^+]$ = 1 M, $[Mg^{++}]$ = 0 M
ΔG = -8.8 kcal/mol, ΔH = -66.3 kcal/mol

Fig. 13. Hybridization between subsequences from SARS-CoV-2 genome and human genome. Left: hybridization between a subsequence of the SARS-CoV-2 Protein S gene and a subsequence of the gene of the human hemoglobin beta-globin (HBG) subunit (Fig. 2). Right: hybridization between a subsequence of the SARS-CoV-2 ORF10 gene and a subsequence of the gene of the human hemoglobin gamma-globin 2 (HGG 2) subunit (Fig. 1).

Table 1
Probability P and free energy ΔG (kcal/mol) of anti-matching between human genes and protein S gene subsequence (TG and GT counting for ½).

Matching subsequence (protein S)	Human/viral gene	P	ΔG	Fig.
CTTCATTTTCAACTTTTAAATGTTATGGAGT	virus SARS CoV Rs672 Protein S	$3\ 10^{-15}$		7
protein S GCTTTAGAACCATT	HERV-K102 protein Gag	10^{-6}		5
Anti-matching subsequence				
hsa-miR-129-5p TGTCGTTC	human γ-globin 2	0.035	-6.7	1
protein S CTGAAGTAG	human γ-globin 2	0.017	-2.6	1
ORF10 AAGTAAGACGT	human γ-globin 2	$3\ 10^{-4}$	-8.8	1
RNA-dependent RNA polymerase ORF1ab TCACGTAGAACTAGGAGTATT	human beta-globin	$5\ 10^{-3}$	-11.2	2
miR 451a TGAGTCAT	human beta-globin	0.04	-3.2	2
protein S TTTTCACC	human beta-globin	0.017	-9	2
miR 92a-1-5p TGTCCGGC	human beta-globin	0.04	-8.2	2
protein S CTGTTTACCG	human ACE2	$3\ 10^{-3}$	-9.5	4
protein S GTGAGGTAT	human circPVT1	0.03	-4.6	6
let-7e CCTTTCGAT	human circPVT1	0.06	-11	6
protein S ATCGATGTGATG	human olfactory receptor OR4E1	$5\ 10^{-4}$	-7.7	8
protein S GATGTGATG	human GTPase 1	0.017	-6.8	9
let-7b-5p CTTTGGTGT	human type 1 interferon IFNA7	0.04	-3.2	10
protein S GCACGGGC	human type 1 interferon IFNA7	0.04	-10.7	10
miR 301a-3p GTCTACGAA	human type 1 interferon IRF1	0.016	-3.6	10
protein S GATGCACGGGC	human interferon regulatory factor IRF1	$2\ 10^{-3}$	-8	10
miR 342-5p GAGTTAGT	human MCT1	0.02	-3.9	11
protein S GCACGGGCG	human MCT1	$2.5\ 10^{-3}$	-4	11

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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