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Tackling the COVID-19 "cytokine storm" with microRNA mimics directly targeting the 3'UTR of pro-inflammatory mRNAs

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ABSTRACT

COVID-19 is characterized by two major clinical phases, the SARS-CoV-2 infection of target cells and tissues, and a deep inflammatory state, known as "cytokine storm", caused by activation of pro-inflammatory genes, such as NF-kB, STAT-3, IL-6, IL-8, IL-1ß. Among possible anti-inflammatory agents, the "microRNA targeting" should be carefully considered, since it is well known that microRNAs are deeply involved in the expression of cytokines, chemokines and growth factors. The working general hypothesis is that targeting the microRNA network might be important for the development of therapeutic approaches to counteract the COVID-19 induction of inflammatory response. This hypothesis is based on several publications demonstrating the use of miRNA mimics for inhibitory effects on the production of proteins characterizing the COVID-19 "cytokine storm".

Introduction

COVID-19 is characterized by two major clinical phases [1]. The first is the SARS-CoV-2 infection of target cells and tissues, leading to important clinical manifestations and complications, such as pulmonary failure [1]. The second phase is a deep inflammatory state, known as "cytokine storm", caused by activation of pro-inflammatory genes, such as NF-kB, STAT-3, IL-6, IL-8, G-CSF [2–9]. In COVID-19 cytokine storm, this perturbation is initiated via attachment of the SARS-CoV-2 spike protein to ACE2 receptor, followed by the ACE/Ang II/AT1R axis activation leading to hyperactivation of NF-κB by IL-6/STATs axis [3]. Although SARS-CoV-2 itself activates NF-κB through pattern recognition receptors, it is the simultaneous activation of NF-κB and STAT-3 that enhances NF-κB activation machinery (the IL-6 amplifier) [4]. This hyper-activation of NF-κB via the IL-6 in the lung tissues induces a cytokine storm with subsequent ARDS (Acute Respiratory Distress Syndrome) that has been observed in severe COVID-19 patients [6,7]. In fact, several studies found a clear relationship between the hyper-inflammatory state and the severity of the disease [6–9]. The pharmacological approach for treating ARDS needs novel anti-inflammatory reagents as different COVID-19 patients might respond differently to these treatments [10–17].

Table 1 shows a partial list of studies outlining the induction of cytokines, chemokines and growth factors in COVID-19 [8,18–25]. As clearly evident, IL-1β, IL-6 and IL-8 are found up-regulated in most studies. Interestingly, upregulation of these proteins following SARS-CoV-2 infection is associated with poor outcome of the COVID-19 patients [7,8]. Finally, the therapeutic importance of these molecules is supported by the ongoing clinical trials based on their targeting, such as NCT04381052 (based on the IL-6 inhibitor Clazakizumab), NCT04247226 (based on the IL-8 neutralizing agent BMS-986253) and NCT04603742 (based on Anakinra, a recombinant IL-1 receptor antagonist, inhibiting both IL-1α and IL-1β).

Among possible anti-inflammatory strategies, the "microRNA targeting" should be carefully considered [26], since it is well known that microRNAs are deeply involved in the expression of cytokines, chemokines and growth factors [27].

MicroRNAs are from 19 to 25 nucleotides noncoding RNAs that regulate gene expression by targeting mRNAs, leading to translational repression or mRNA degradation [28,29]. Since their discovery, the number of microRNA sequences deposited in the miRBase databases is significantly growing [30]. The complex networks constituted by miRNAs and RNAs lead to the control of highly regulated biological functions, such as differentiation, cell cycle and apoptosis [31].

Fig. 1 shows microRNAs potentially regulating the expression of IL-1β, IL-6 and IL-8. Some miRNA-binding sites (which are boxed) are in

Abbreviations: miRNAs, microRNA; 3′UTR, 3′ untranslated region; IL, interleukin; mRNA, messenger RNA; ARDS, acute respiratory distress syndrome.

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Table 1
Proteins involved in the COVID-19 "Cytokine Storm"

Cytokines, chemokines and growth factors	Biological sample	Reference	Notes/comments
IL-2, IL-7, IL-10,M-CSF, G-CSF, MCP-1, MIP1-α, TNF-α	Serum	Costela-Ruiz et al., 2020 [18]	Up-regulated in serum of patients admitted to ICUs (Intensive Care Units).
IL-6	Blood	Chen et al., 2020 [19]	Increased in 52% of admitted hospital patients with a diagnosis of COVID-19 pneumonia.
IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1-α, and TNFα	Plasma	Huang et al., 2020 [20]	Up-regulated in the acute phase of the illness, in plasma samples of patients affected by COVID-19 infection.
IL-6	Plasma	Wang et al., 2020 [21]	The level of IL-6 in peripheral blood is an early indicator of cytokine release syndrome in COVID-19–associated pneumonia.
IL-1β, IL-1Rα, IL-7, IL-8, IL-9, IL-10, FGF, GM-CSF, IFNγ, G-CSF, IP10, MCP1, MIP1-α, PDGF, TNF-α, VEGF	Serum	Zhang et al., 2020 [22]	The listed ILs are increased in SARS-CoV-2 infection, among which IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP-1α, TNF-α are higher in severe patients, while no major differences of serum IL-6 levels in ICU and non ICU patients were found.
IL-2R, IL-6, IL-10, TNF-α	Plasma	Chen et al., 2020 [23]	IL-2R, IL-6, IL-10, TNF-α were markedly higher in severe cases than in moderate cases. Of note, IL-6 levels were increased in both moderate and severe cases.
IL-1β, IL-6, IL-8, IL-10, sTNFR1	Plasma	McElvaney et al., 2020 [24]	The listed ILs levels were detected in healthy volunteers, hospitalized but stable patients with COVID-19 (COVID stable patients), patients with COVID-19 requiring ICU admission (COVIDICU patients). IL-1β, IL-6, IL-8, and sTNFR1 were all increased in patients with COVID-19. COVIDICU patients could be clearly differentiated from COVID stable patients, and demonstrated higher levels of IL-1β, IL-6, and sTNFR1 but lower IL-10.
TNF-α, IL-6, IL-10	Serum	Diao et al., 2020 [25]	Levels of TNF-α, IL-6, and IL-10 were significantly increased in infected patients, and their levels in ICU patients were significantly higher than in non-ICU patients.
IL-6, IL-8, TNF-α	Serum	Del Valle et al., 2020 [8]	High levels of IL-6, IL-8 and TNF-α at the time of hospitalization are strong predictors of patient survival.

common and might participate to a network responsible to a co-regulation of these genes in COVID-19. The list of the miRNA binding sites that are present in the 3′UTR of IL-1β, IL-6 and IL-8 mRNA is enlisted in Table 2. The data are derived from Chou et al. [32] and Huang et al. [33].

The hypothesis

The working general hypothesis is that targeting of the microRNA network might be important for the development of therapeutic approaches to counteract the COVID-19 induction of inflammatory response (Fig. 2). This hypothesis is based on several publications demonstrating the use of miRNA mimics for inhibitory effects on the production of proteins characterizing the COVID-19 "cytokine storm". For instance, Fabbri et al. have demonstrated that miR-93-5p targets and inhibits the expression of IL-8 gene. Accordingly, transfections of several cell lines with pre-miRNA sequences lead to (a) increase of intracellular miR-93-5p content and activity and (b) sharp decrease of IL-8 mRNA content and IL-8 release [34]. In addition, Oglesby et al. reported that miR-17 overexpression in airway epithelial cells decreases interleukin-8 production [35]. Concerning IL-6, Hong et al. reported that polyethylenimine (PEI) was successfully employed to deliver plasmid DNA containing miR-200c into target cells, and that this procedure caused an increased expression of miR-200c associated with effective inhibition of IL-6, IL-8, and CCL-5 [36]. They reported that miR-200c directly targets the 3'UTR of IL-6, IL-8 and CCL-5.

Experimental evaluation of the hypotheses

Choice of the anti-miRNA molecule

This is a key step in designing a meaningful approach to negatively control the COVID-19 associated "cytokine storm". In fact, several microRNA target sites are present in the 3'UTR of cytokine/chemokine mRNAs. An *in silico* analysis based on the analysis of molecular interactions between microRNAs and target sites present in the 3'UTR of pro-inflammatory mRNAs might be of great help for understanding the theoretical stability and possible importance of these interactions and for designing potential bioactive sequences. This is shown in Fig. 3 (boxed area). The sequence of the agomiR might be designed to display an even increased affinity to the target mRNA in respect to the original miRNA sequence. The miRNA mimicking approach (outlined in Fig. 2) might help in verifying which miRNA should be mimicked in order to decrease mRNA/protein expression.

Experimental strategy to verify potential anti-inflammatory activity of miRNAs targeting the 3′UTR regions of COVID-19 associated pro-inflammatory mRNAs

In order to validate the hypothesis cytokines/chemokines/growth factors should be analysed using well known biochemical approaches (for instance those based on ELISA and Bio-plex assays). One example has been reported in several studies and it is based on the use of a 27-plex analyzing, among others, most of the COVID-19 associated cyto/chemokines, such as IL-6, IL-8, IP-10, G-CSF and TNF-α. The experimental approach that might be employed is described in Fig. 3 and it is based on the induction of pro-inflammatory mRNAs following exposure of in vitro growing cell lines to the SARS-CoV-2 Spike protein. This treatment leads to a fast and reproducible increase of the expression of pro-inflammatory mRNA, as published by Wang et al. [37] who reported an upregulation of IL-6 and TNF-α induced by SARS-coronavirus spike protein in murine macrophages via NF-kB pathway.

The key steps of the experimental strategy are summarized in Fig. 3. Among the cell lines that have been demonstrated to respond to SARS-CoV-2 Spike exposure are human airway epithelial Calu-3 cells, CFBE41o- and the IB3-1 human cystic fibrosis (CF) bronchial epithelial

cells, and the mouse RAW 264.7 macrophage-like cells [37–40].

The experimental plan should verify (a) response to different concentrations of SARS-CoV-2 Spike protein for different length of time; (b) co-treatment with different concentrations of pre-miRNAs targeting pro-inflammatory mRNAs that have been found over-expressed on COVID-19; (c) isolation of RNA and quantitation of pro-inflammatory mRNAs by RT-qPCR; (d) analysis of the secretome profile.

Recombinant SARS spike glycoprotein is commercially available. In addition, several plasmids for recombinant SARS-CoV-2 Spike production might be obtained from different sources; for instance, a SARS-CoV-2 (2019-nCoV) Spike RBD Gene ORF cDNA clone expression plasmid, C-His tag (Codon Optimized) is available from Sino Biological.

Final experimental validation

The final experimental validation of the tested approaches should be based on infection of target cells with viable SARS-CoV-2 viral particles and testing the activity on pro-inflammatory mRNAs and secretome profile. In addition, suitable delivery systems should be considered and tested, in order to develop treating strategies for COVID-19 patients carrying other pathologies. This should be considered a primary goal for the development of treatments of COVID-19 patients affected by associated pulmonary diseases, such as cystic fibrosis, COPD and asthma. In this context, aerosolic delivery might be considered, as well as the use of novel delivery reagents, such argininocalix[4]arene macrocycles as reported by our research group for miRNA delivery [41].

Consequences of the hypothesis and discussion

The expected outcomes of the approach described in this paper are the following.

- Development of a protocol based on the exposure of target cells to the SARS-CoV-2 spike protein, in order to induce high expression levels of genes involved in the COVID-19 “cytokine storm”.
- Protocols for the alteration of the inflammasome using miRNA targeting and/or mimicking.

Table 2
miRNAs potentially targeting the 3′UTRs of IL-1β, IL-6 and IL-8 mRNAs.

mRNA	miRNA binding sites
IL-1ß	miR-21-5p, miR-204-5p, miR-376c-3p, miR-155-5p, miR-181c-3p, miR-587, miR-101-3p, miR-10b-5p, miR-126-3p, miR-128-3p, miR-129–2-3p, miR-203a-3p, miR-34a-5p, miR-34c-5p, miR-375, miR-429, miR-449a, miR-7-5p
IL-6	miR-155-5p, miR-125a-3p, miR-149-5p, miR-192-5p, miR-590-3p, miR-100-5p, miR-671-5p, miR-20a-5p, let-7b-5p, miR-16-5p, miR-376a-5p, miR-335-5p, miR-98-5p, miR-124-3p, miR-1-3p, miR-34a-5p, miR-98-5p, miR-99a-5p, miR-191-5p, miR-128-3p, miR-138-5p, miR-182-5p, miR-195-5p, miR-203a-3p, miR-205-5p, miR-21-3p, miR-21-5p, miR-221-3p, miR-27a-3p, miR-27a-5p, miR-330-3p, miR-34b-5p, miR-375, miR-429, miR-7-5p, miR-373-3p, miR-372-3p, miR-302a-3p, miR-148b-3p, miR-133a-3p, miR-122-5p
IL-8	miR-195-5p, miR-20a-5p, miR-106a-5p, miR-17-5p, miR-30c-1-3p, miR-93-5p, miR-373-3p, miR-520c-3p, miR-10a-3p, miR-1225-5p, miR-23a-3p, miR-23b-3p, miR-296-3p, miR-302c-5p, miR-302d-5p, miR-450a-5p, miR-493-5p, miR-499a-3p, miR-519d-3p, miR-520a-3p, miR-526b-3p, miR-5582-3p, miR-587, miR-664a-3p, miR-1-3p, miR-429, miR-34a-5p, miR-155-5p, let-7b-5p, miR-124-3p, miR-126-3p, miR-16-5p, miR-27a-3p, miR-335-5p, miR-1291, miR-138-5p, miR-101-3p, miR-107, miR-129–2-3p, miR-130a-3p, miR-146a-5p, miR-147a, miR-194-5p, miR-203a-3p, miR-21-3p, miR-21-5p, miR-210-3p, miR-212-3p, miR-214-3p, miR-221-3p, miR-29a-5p, miR-29a-3p, miR-30d-5p, miR-376a-5p, miR-671-5p, miR-7-5p, miR-941, miR-99b-5p, miR-520f-3p, miR-372-3p, miR-148b-3p, miR-133a-3p, miR-9-5p, miR-30a-5p

- Protocols for combined treatments using pre-miRNA molecules in combination with anti-inflammatory drugs already used in COVID-19 therapeutic protocols.

Conclusions

The proposed approaches might lead to the development of protocols for the reduction of the expression of key components of the COVID-19 “cytokine storm” [1–5]. This is a major issue in the management of COVID-19 patients [6–17]. As far other DNA- and RNA-based therapeutic interventions [42] suitable delivery systems should be considered for optimizing the proposed treatment.

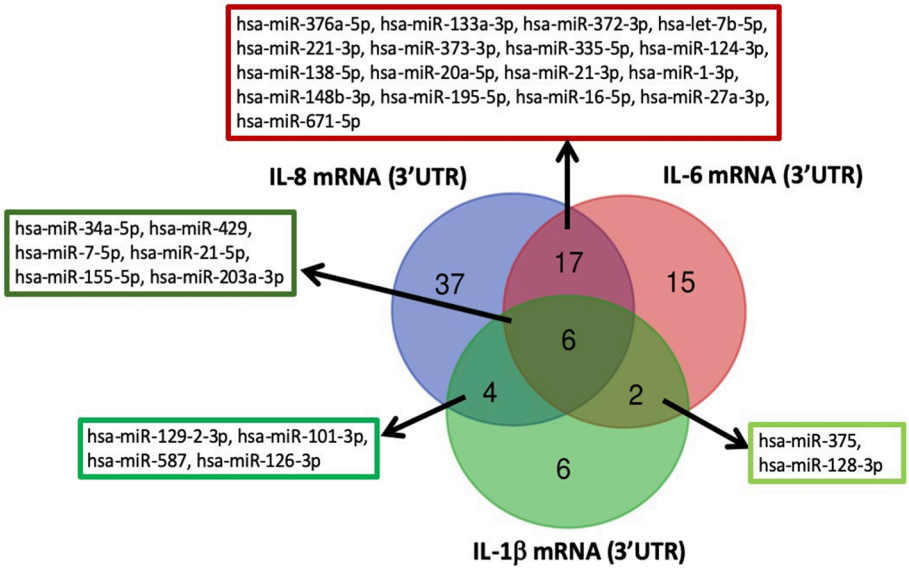

Fig. 1. Veen diagram showing (a) the number of miRNA binding sites present in the 3′UTR of IL-1β mRNA (18 miRNA binding sites), IL-6 (40 miRNA binding sites) and IL-8 mRNA (64 miRNA binding sites) and (b) the miRNA binding sites found in common (which are enlisted in the boxes).

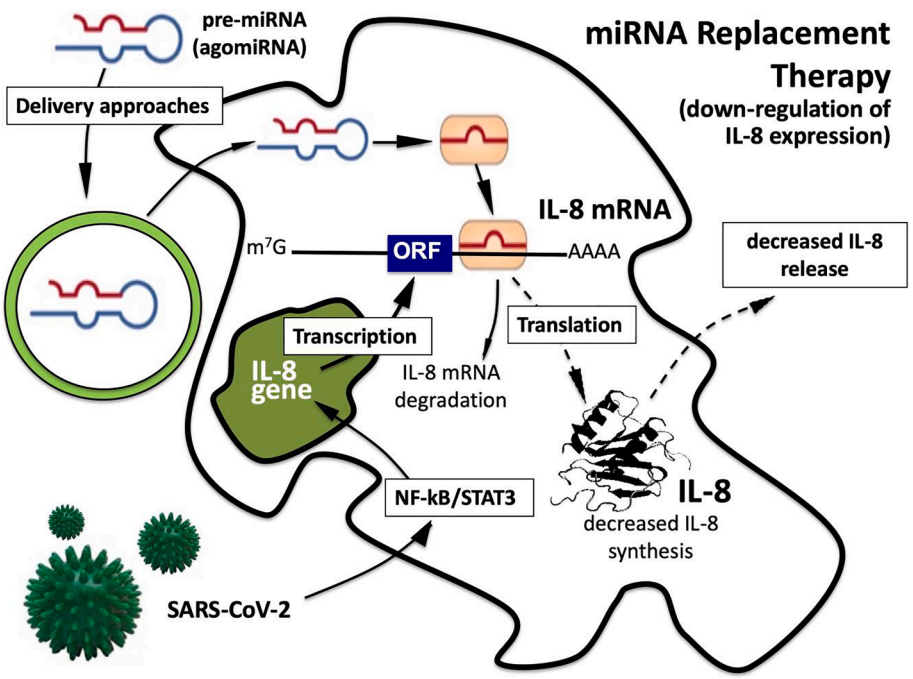

Fig. 2. Possible use of "miRNA therapeutics" for downregulation of SARS-CoV-2 induced IL-8 gene expression. The upregulation of the IL-8 gene, occurring through the NF-kB/STAT-3 axis [3] might be strongly inhibited by transfection of pre-miRNA (agomiRNA) targeting the 3'UTR of IL-8 mRNA. This might lead to IL-8 mRNA degradation or inhibition of IL-8 translation and consequent release. Evidences supporting (a) SARS-CoV-2 mediated IL-8 transcription and (b) post-transcriptional, miRNA dependent regulation of IL-8 production have been reported in several studies [3,4,34–36].

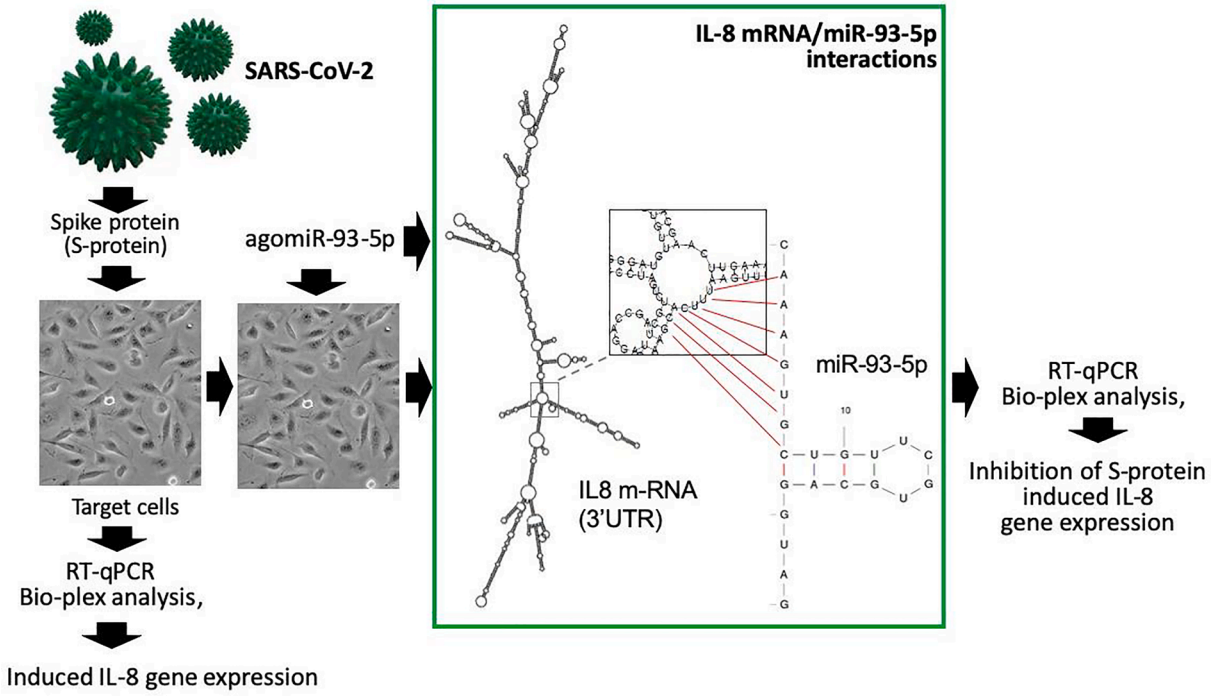

Fig. 3. Evaluation of the hypothesis. Induction of IL-8 upregulation can be obtained by exposing cultured in vitro cell lines to the SARS-CoV-2 Spike protein (S-protein). Possible inhibition of IL-8 gene expression can be obtained by transfection of the cells with agomiR molecules (in the example agomiR-93-5p) able to interact with the 3′UTR sequence of IL-8 mRNA (as depicted in the boxed area). Effects on mRNA content and translation (see also Fig. 2 for a scheme of the agomiR-mediated effects) can be analyzed by RT-qPCR and ELISA (or Bio-plex approaches).

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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