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MicroRNAs based regulation of cytokine regulating immune expressed genes and their transcription factors in COVID-19

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ABSTRACT

Background: Coronavirus disease 2019 is characterized by the elevation of a broad spectrum of inflammatory mediators associated with poor disease outcomes. We aimed at an in-silico analysis of regulatory microRNA and their transcription factors (TF) for these inflammatory genes that may help to devise potential therapeutic strategies in the future.

Methods: The cytokine regulating immune-expressed genes (CRIEG) were sorted from literature and the GEO microarray dataset. Their co-differentially expressed miRNA and transcription factors were predicted from publicly available databases. Enrichment analysis was done through minturnet, MiEAA, Gene Ontology, and pathways predicted by KEGG and Reactome pathways. Finally, the functional and regulatory features were analyzed and visualized through Cytoscape.

Results: Sixteen CRIEG were observed to have a significant protein-protein interaction network. The ontological analysis revealed significantly enriched pathways for biological processes, molecular functions, and cellular components. The search performed in the miRNA database yielded ten miRNAs that are significantly involved in regulating these genes and their transcription factors.

Conclusion: An in-silico representation of a network involving miRNAs, CRIEGs, and TF, which take part in the inflammatory response in COVID-19, has been elucidated. Thus, these regulatory factors may have potentially critical roles in the inflammatory response in COVID-19 and may be explored further to develop targeted therapeutic strategies and mechanistic validation.

Abbreviation: AHR, Aryl hydrocarbon receptor; ARDS, acute respiratory distress syndrome; BAL, Bronchoalveolar Lavage; CC, Cellular components; CCL2, C-C motif chemokine 2; CCL3, C-C motif chemokine 3; CCL4, C-C motif chemokine 4; CCR, CC chemokine receptor; CEBPA, CCAAT/enhancer-binding protein alpha; COVID-19, Coronavirus Disease 2019; CREM, cAMP responsive element modulator; CRIEGs, Cytokine regulating immune expressed genes; CSF2, Granulocyte-macrophage colony-stimulating factor; CSF3, Granulocyte colony-stimulating factor; CXCL2, Chemokine (C-X-C motif) ligand 2; CXCL8, Interleukin-8; CXCL10, C-X-C motif chemokine 10; CXCR, C-X-C chemokine receptor; DDIT3, DNA damage-inducible transcript 3 protein; DEGs, Differentially expressed genes; E2F1, Transcription factor E2F1; EGR1, Early growth response protein 1; EP300, Histone acetyltransferase p300; ESR1, Estrogen receptor, Nuclear hormone receptor; ETS2, Protein C-ets-2; FOXF3, Forkhead box protein F3; GO, Gene Ontology; GSEs, Gene Series Expressions; HDAC1, Histone deacetylase 1; HDAC2, Histone deacetylase 2; IL1B, Interleukin-1; IL2, Interleukin-2; IL6, Interleukin-6; IL7, Interleukin-7; IL9, Interleukin-9; IL10, Interleukin-10; IL17A, Interleukin-17A; IL-6, interleukin-6; IP-10, Interferon-Inducible Protein 10; IRF1, Interferon regulatory factor 1; JAK2, Tyrosine-protein kinase JAK2; JAK-STAT, Janus kinase (JAK)-signal transducer and activator; JUN, Transcription factor AP-1; KEGG, Kyoto Encyclopedia of Genes and Genomes; KLF4, Krueppel-like factor 4; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NFAT5, Nuclear factor of activated T-cells 5; NFKB1, Nuclear factor NF-kappa-B p105 subunit; NFKBIA, NF-kappa-B inhibitor alpha; NR1I2, Nuclear receptor subfamily 1 group I member 2; PDM, peripheral blood mononuclear cell; REL, Proto-oncogene c-Rel; RELA, Transcription factor p65; RUNX1, Runt-related transcription factor 1; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SIRT1, NAD-dependent protein deacetylase sirtuin-1; SP1, Transcription factor Sp1; STAT1, Signal transducer and activator of transcription 1-alpha/beta; STAT3, Signal transducer and activator of transcription 3; TLR3, Toll-like receptor 3 (TLR3); TNF, Tumor necrosis factor; TNF-a, Tumor Necrosis Factor-Alpha; VDR, Vitamin D3 receptor; XBP1, X-box-binding protein 1; ZFP36, mRNA decay activator protein ZFP36; ZNF300, Zinc finger protein 300, heme oxygenase-1 (HO-1); miEAA, miRNA Enrichment Analysis and Annotation t.

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1. Introduction

Cytokine storm in severe or critically ill coronavirus disease 2019 (COVID-19) patients is characterized by the elevation of a wide spectrum of inflammatory mediators. These include cytokines and chemokines originating from airway epithelial cells and various immune cells and act as independent risk factors for disease severity and mortality (Liu et al., 2020, p. 19).

Various cytokines and chemokines have been observed to play dominant roles in different stages of the COVID-19 disease. Association of COVID-19 severity and mortality with higher levels of interleukin-6 (IL-6) have been corroborated in various studies (Cummings et al., 2020; Hajifathalian et al., 2020; Ruan et al., 2020). However, depending upon the stage in the natural history of COVID-19 disease, SARS-CoV-2 has the menacing feature of longer persistence in the environment and various inanimate surfaces (Khokhar et al., 2020b) and different in.

2. Methodology

2.1. Identification of cytokines responsible for inflammation and cytokine storm in SARS-CoV-2

Several keywords including “Inflammation”, “Immunity”, “Immunogenetics”, “Cytokine storm”, “Acute respiratory distress syndrome”, “ARDS”, “COVID-19”, “cytokines”, “Coronavirus disease”, “SARS-CoV-2” and “Severe Acute Respiratory Syndrome” and “1999/01/01 to 2020/07/06” were searched in PubMed to identify cytokines responsible for inflammation and cytokine storm in SARS-CoV-2. (Supplementary Table 1) Fig. 1 summarizes in a flow chart the steps of data processing and analysis performed in the study. (Fig. 1).

2.2. Microarray data collection

We have searched in the GEO database several keywords including “SARS”, “Corona Virus”, “Blood”, “Homo sapiens”, “Expression profiling by array”, “bronchial epithelial cells” from 01/01/2012 to 17/12/2020. We found the GSE17400 contains bronchial epithelial cells of 9 (nine) samples.

2.3. Identification of cytokine regulating immune expressed genes (CRIEGs) responsible for inflammation and cytokine storm from SARS-CoV

GEO2R is an online interactive web tool used to compare two groups of samples in a GEO Series to identify differentially expressed genes across experimental conditions. We obtained differentially expressed genes (DEGs) from GSE17400 dataset for innate immune responses of human bronchial epithelial cells against SARS-CoV with the help of GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r/) with the cut-off criteria of \( p < 0.05 \). (Fig. 2)

2.4. Identification of common transcription factors (TFs) related to cytokine regulating immune expressed genes (CRIEGs)

Cytokines are mostly regulated at the transcriptional level by specific transcription factors (TFs) that recruit transcriptional machinery including cofactors (Carrasco Pro et al., 2018). We identified those TFs regulating CRIEGs that commonly appeared in all five different databases of transcription factor viz., - TRRUST, RegNetwork, ENCODE, JASPAR, and CHEA. The identification of TF-target regulatory relationships is a key step for revealing functions of TFs and their regulations on CRIEG expression. We Identified more than 32 common TFs of 16 CRIEGs from well-established microRNAs and TFs target prediction database mirNet Version 2 (Chang et al., 2020). We have created an interaction network between CRIEGs and its transcription factors through the Cytoscape software [24,25]. (Fig. 3, Supplementary Table 2).

2.5. Identification and assortment of common regulated miRNAs of CRIEGs and transcription factors of CRIEGs

Evolutionary conserved small non-coding RNA or MicroRNA affect the gene expression by binding to specific miRNAs and regulate cell growth, differentiation, and death. miRNAs regulate multiple functions of T-cell subsets through immune homeostasis and immune tolerance that control the development, survival, and activation (Caravelli et al., 2018). The miRNA that targeted cytokine and its transcription factor genes were predicted by different well-established miRNA target prediction databases miRDB, miRBase, mirNet Version 2, and TargetScan (Chang et al., 2020). We have created an interactomics network of CRIEGs and their transcription factors with target microRNAs through the Cytoscape software [24,25] (Fig. 3, Supplementary Table 2).
3. Results

3.1. Identification of cytokine regulating immune expressed genes (CRIEGs) responsible for inflammation and cytokine storm in SARS-CoV

We compared the genes and their transcription factors obtained from the literature search with that of SARS-CoV dataset (GSE17400) and found that majority of the identified genes and transcription factors were expressed in the SARS-CoV dataset. (Table 1). We found 16 CRIEGs (IL-1β, IL-2, IL-7, IL-8, IL-9, IL-10, IL-17, G-CSF, GM-CSF, IFN-γ, TNF-α, CXCL10, MCP1, MIP1A, MIP1B, and IL-6) from literature which is responsible for acute respiratory distress syndrome (ARDS) in COVID-19. Further, our analysis of CRIEGs from the SARS-CoV infected human bronchial epithelial cells dataset demonstrated that the over-expression of these genes in a short time (interval of 12 h, 24 h, and 36 h) increases the severity of the disease (Yoshikawa et al., 2010).

3.2. Identification of cytokine regulating immune expressed genes and construction of PPI network

All 16 CRIEGs show interactions among themselves, based on the STRING database. The average node degree is calculated based on a number of how many interactions (at the score threshold) that a protein have on the average in the network. The local clustering coefficient is use for connection of nodes in the network. Highly connected networks have high values. A minimum significant PPI enrichment p-value indicate that the nodes are not random and that the observed number of edges is significant. In this study, PPI network consisted of 16 nodes and 117 edges, the average local clustering coefficient was 0.977, and PPI enrichment p-value was highly significant (p < 0.001) (Fig. 4).
3.3. Identification of common transcription factors regulating CRIEGs

We identified the common transcription factors of CRIEGs through TRRUST, RegNetwork, ENCODE, JASPAR and CHEA databases. During this identification process, we found a total of 32 transcription regulators. All transcription regulators viz., AHR, CEBPA, CREM, DDIT3, E2F1, EGR1, EP300, ESR1, ETS2, FOXP3, HDAC1, HDAC2, HSF1, IRF1, JUN, KLF4, NFKB1, NFAT5, NR1I2, RELA, RUNX1, SP1, SPI1, STAT1, STAT3, VDR, XBP1, ZFP36, ZNF300 commonly regulated the transcription of 16 CRIEGs (Table 2).

3.4. Identification of common MicroRNAs targeting CRIEGs and TFs of CRIEGs

We identified the MicroRNAs targeting CRIEGs and its TFs from various microRNA databases like miRNet, TargetScan, miRDB, miRanda, miRWalk. In our analysis, we identified 10 multi-targeting miRNAs viz., hsa-miR-106a-5p, hsa-miR-155-5p, hsa-miR-98-5p, hsa-miR-24-3p, hsa-miR-204-5p, hsa-miR-124-3p, hsa-miR-335-5p, hsa-let-7c-5p, and hsa-miR-1-3p. Almost all of the above identified microRNAs targeted both CRIEGs and their transcription factors simultaneously. Interestingly, microRNA targeting CCL4 was an exception. All the ten (10) microRNAs were observed to target more than one CRIEGs and its TFs (Fig. 3).

3.5. Common Pathway enrichment analysis of CRIEGs, transcription factors of CRIEGs and common targeting MicroRNAs

STRING and DAVID were assessed to acquire KEGG pathways enriched by CRIEGs and their TFs, common Pathways of MicroRNAs by enrichment of two databases MIENTURNET and MiEAA. (Supplementary Fig. 1 & Supplementary Table 3). All databases were selected for preferred and significant ($p < 0.05$) common pathways. The total 17 common pathways are involved in cytokine storm regulatory mechanism like Adipocytokine signaling pathway, Chemokine signaling pathway, C-type lectin receptor signaling pathway, Cytosolic DNA-sensing pathway, Fluid shear stress and atherosclerosis, IL-17 signaling pathway, Insulin resistance, JAK-STAT signaling pathway, NF-kappa B signaling pathway, NOD-like receptor signaling pathway, Osteoclast differentiation, RIG-I-like receptor signaling pathway, T cell receptor signaling pathway, Th1 and Th2 cell differentiation, Th17 cell differentiation, TNF signaling pathway, Toll-like receptor signaling pathway (Fig. 5(A-C) & Supplementary Table 4).

3.6. Ontological analysis of CRIEGs

To get insights into the biomolecular significance of the identified CRIEGs, we performed gene ontology analysis by various databases and obtained enriched GO terms. STRING and DAVID were used to conduct the gene ontology analysis for CRIEGs within three categories: biological process, molecular function, and cellular component. Common statistically significant ($p < 0.05$) ontological processes have been identified.
Fig. 3. Each CRIEG and their Transcription factor and common targeting MicroRNAs interaction network (A)CCL4; (B)CCL2; (C)CCL3; (D)IL17A; (E)CXCL8; (F)IL2; (G)CXCL10; (H)IL10; (I) IL1B; (J)TNF; (K)JAK2; (L) IL6. (Cyan colored Ellipse shaped Node: CRIEGs; Brick colored diamond shaped node: Transcription factor of CRIEGs; Pink colored rectangle shaped Node: MicroRNAs; Each node inter-connected with another node by the edges).
Molecular functions cytokine activity, cytokine receptor binding, signaling receptor binding, growth factor receptor binding, growth factor activity, chemokine activity, G protein-coupled receptor binding, CCR/CCR1/CCR5/CXCR5 chemokine receptor binding. Some crucial biological processes such as cytokine-mediated signaling pathways, immune responses, cellular responses to lipopolysaccharide, positive regulation of cytokine production, leukocyte migration, leukocyte chemotaxis, positive regulation of response to stimuli, granulocyte migration, cell activation, regulation of cell population proliferation are regulated by CRIEGs. Cellular components (CC) found only extracellular space [Fig. 5(G (1–3)) & Supplementary Tables 5-7].

3.7. Ontological analysis of common transcription factors

To get deep insights into the biomolecular significance of the identified common TFs, we performed gene ontology analysis by various databases and obtained enriched GO terms. STRING and DAVID have been used to conduct the GO analysis of common TFs within three categories: BP, MF, and CC. Common statistically significant (p < 0.05) ontological processes have been identified through DAVID.

Important biological processes like positive regulation of transcription by RNA polymerase II, positive regulation of RNA metabolic process, regulation of immune system process, cellular response to interleukin-6, T cell differentiation, leukocyte activation, regulation of T cell differentiation, interleukin-21-mediated signaling pathway, regulation of innate immune response, interleukin-9-mediated signaling pathway, regulation of interleukin-12 production, immune response-regulating cell surface receptor signaling pathway are involved in the metabolic regulatory process of TFs.

Most of the TFs play significant roles in different MF like transcription factor binding, sequence-specific DNA binding, transcription regulatory region sequence-specific DNA binding, RNA polymerase II transcription regulatory region sequence-specific DNA binding, cis-regulatory region sequence-specific DNA binding, DNA-binding transcription factor activity, RNA polymerase II-specific, transcription regulator activity, RNA polymerase II cis-regulatory region sequence-specific DNA binding, DNA-binding transcription factor binding. Various transcription factors localization in multiple CC like nuclear chromatin, chromosome, transcription regulator complex, nucleoplasm, nuclear lumen, intracellular non-membrane-bounded organelle, protein-containing complex, host cell nucleus, RNA polymerase II transcription regulator complex. [Fig. 5(H (1–3)) & Supplementary

Table 1

| Cytokine Strom Gene | Transcription Factors of Cytokine Gene | P Value | F |
|---------------------|-------------------------------------|---------|---|
| CCL2                | AHR                                 | 0.01    | 6.07 |
| CCL4                | CREM                                | 0.03    | 4.59 |
| CXCL10              | DDIT3                               | 0.00    | 98.60 |
| CXCL8               | E2F1                                | 0.00    | 56.40 |
| IL6                 | EGR1                                | 0.00    | 139.00 |
| IL7                 | EP300                               | 0.00    | 24.60 |
| JAK2                | ESR1                                | 0.00    | 16.40 |
| TNF                 | ETS2                                | 0.02    | 5.26  |

| Cytokine Gene | Transcription Factors of Cytokine Gene | P Value | F |
|---------------|-------------------------------------|---------|---|
| HDAC1         |                                    | 0.03    | 4.49 |
| HDAC2         |                                    | 0.00    | 9.29 |
| JUN           |                                    | 0.00    | 132.00 |
| KLF4          |                                    | 0.00    | 58.10 |
| NFAT5         |                                    | 0.03    | 4.46 |
| NFkB1         |                                    | 0.00    | 12.70 |
| NFkBIA        |                                    | 0.00    | 81.60 |
| REL           |                                    | 0.00    | 14.20 |
| RUNX1         |                                    | 0.04    | 4.10 |
| SIRT1         |                                    | 0.00    | 26.40 |
| SP100         |                                    | 0.00    | 111.00 |
| SP140L        |                                    | 0.00    | 53.80 |
| STAT1         |                                    | 0.00    | 80.60 |
| XBP1          |                                    | 0.02    | 4.81 |
| ZFP36         |                                    | 0.00    | 14.40 |

Table 2

| Cytokine Gene | Transcription Factor | MicroRNAs |
|---------------|---------------------|-----------|
| IL1B          | AHR                 | hsa-miR-106a-5p |
| IL2           | CEBPA               | hsa-miR-155-5p |
| IL7           | CREM                | hsa-miR-98-5p |
| CXCL8         | DDIT3               | hsa-miR-24-3p |
| IL9           | E2F1                | hsa-miR-204-5p |
| IL10          | EGR1                | hsa-miR-124-3p |
| IL17A         | EP300               | hsa-miR-203a-3p |
| CSF3          | ESR1                | hsa-miR-335-5p |
| CSF2          | ETS2                | hsa-let-7c-5p |
| JAK2          | FOXP3               | hsa-miR-1-3p |
| TNF           | HDAC1               | hsa-miR-2 |
| CXCL10        | HDAC2               | hsa-miR |
| CCL2          | HSF1                | hsa-miR |
| CCL3          | JUN                 | hsa-miR |
| CCL4          | JUN                 | hsa-miR |
| IL6           | KLF4                | hsa-miR |
| NFAT5         | hsa-miR |
| NFkB1         | hsa-miR |
| NFkBIA        | hsa-miR |
| REL           | hsa-miR |
| RUNX1         | hsa-miR |
| SIRT1         | hsa-miR |
| SP100         | hsa-miR |
| SP140L        | hsa-miR |
| STAT1         | hsa-miR |
| XBP1          | hsa-miR |
| ZFP36         | hsa-miR |
| ZNF300        | hsa-miR |

a F: Moderated F-statistic combines the t-statistics for all the pair-wise comparisons into an overall test of significance for that gene (only available when more than two groups of samples are defined).
Fig. 5. (A). Venn diagram of common KEGG pathways involved in CRIEGs, TF of CRIEGs and MicoRNAs; (B) Common 17 KEGG pathways; (C) KEGG Pathways regulating CRIEGs, TF of CRIEGs and MicoRNAs; (D) Disease Category (DC) for MicroRNAs enrichments; (E) Gene Ontology (GO) for MicroRNAs enrichments; (F) RNA localization in cellular components; (G) Gene Ontology (GO) for CRIEGs (1) Cellular Component; (2) Biological Process (3) Molecular function; (H) Gene Ontology (GO) for TFs of CRIEGs (1) Cellular Component; (2) Biological Process (3) Molecular function.
3.8. Disease category, RNA localization and Ontological analysis of frequent targeting MicroRNAs

We identified the microRNA enrichment analysis from two different databases MIENTURNET and miEA. We found out the localization of cellular components, miRNA-disease relationship and ontological functions of these important microRNAs. These ten MicroRNAs are found in different parts of the cell, such as microvesicle, nucleus, exosome, cytoplasm, and mitochondrion. These miRNAs also correlate in many diseases such as SARS, lymphoma, inflammatory bowel disease, hepatitis B, hepatitis C, asthma, Acute Lung Injury, sepsis, HIV, Adenoviridae infections, aortic valve disease, Acute Kidney Failure, prion disease, chronic obstructive pulmonary disease, and human influenza.

Involvement of miRNA in various GO terms such as macrophage chemotaxis, positive regulation of B-cell activation, regulation of inflammatory response cytokine binding, IL-6 receptor binding, IL-6 Mediated Signaling Pathway, T-cell differentiation in thymus, IL-1 binding, response To IL-1, cellular response to IL-4, regulation of T-cell proliferation, viral entry into host cell via membrane fusion with the plasma membrane, positive regulation of IL-6 biosynthetic process, T-cell chemotaxis, IL-10 production, mast cell chemotaxis, viral reproduction, positive regulation of viral genome replication, viral entry into host cell. [Fig. 5(D-F) & Supplementary Tables 11-13].

3.9. Interactomical network of CRIEGs, TFs of CRIEGs and common targeting MicroRNAs

With the help of Cytoscape, we created a network of common targeting miRNAs of all the 16 CRIEGs and their 32 TFs. These interactions influence the host response to virus and contributes to the severity of the disease. The interactomical network has been depicted in Supplementary Figs. 2, 3, Figs. 3, and 6. Supplementary Fig. 2 depicts the interaction network of CRIEGs and the TFs that regulate the expression of CRIEGs. Supplementary Fig. 3 depicts the network of interaction among CRIEGs and TFs with their targeting microRNAs. Fig. 6. The CRIEGs and Transcription factors of CRIEG and MicroRNAs interaction network. (Brick colour node: CRIEGs; Dark blue colour node: Transcription factor of CRIEGs; Pink colour node: CRIEGs and their transcription factor targeting microRNAs). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
between CRIEGs MicroRNAs that regulate the expression of CRIEGs. Fig. 3 demonstrate the network of interaction between CRIEG, their TFs and the corresponding MicroRNAs for each of the individual CRIEGs. Lastly Fig. 6 depicts a wholesome interactome picture of various CRIEGs, their TFs and regulating MicroRNAs. (Supplementary Figs. 2, 3, Figs. 3, and 6.)

4. Discussion

MicroRNAs post-transcriptionally regulate the expression of target mRNA. RNA viruses are known to utilize the host miRNA machinery for their benefit. Hence, various studies have identified miRNAs as key players in the pathogenesis and therapeutics of viral diseases. Also, miRNA scan target viral genes as well as the host inflammatory machinery, as part of the host-pathogen interactions, to counter-act the impairing effects of infection (Ghosh et al., 2008). Demirci et al. have identified 67 different human miRNA that targets the spike protein of the SARS-CoV-2 virus (‘Sacar Demirci and Adan, 2020). The inflammatory cascades involved in the pathophysiological pathways of COVID-19 are crucial in the development of complications in COVID-19. These pathogenetic pathways constitute but are not limited to, receptor tyrosine kinases, the JAK/STAT pathway, TNF-α receptor and toll-like receptors, IL-6 and IFN-γ, cytokine storm, and macrophage activation (Yarmohammadi et al., 2020). Hence, exploring the regulatory networks of these inflammatory markers have the two-fold advantages of discovering the interconnected nature of these dysregulated pathways and unlocking the potential of novel mechanistic-based treatment strategies. However, a clear understanding of the miRNA response in SARS-CoV-2 is still elusive. Here, we have identified the miRNAs and transcription factors of the target miRNAs which provide the necessary insight into the genetic regulation of the inflammatory response in COVID-19.

Our in-silico analysis revealed ten miRNAs involved in the regulation of the common inflammatory genes and their transcription factors. The miR-155-5p has been widely studied in viral inflammatory pathways. It is a regulator of the HCV-induced TLR3/NF-κB pathway mediated inflammatory response. Further, elevated circulating levels of miR-155 were also observed in HBV infection (Bala et al., 2012; Wang et al., 2015). The role of miR-155-5p in the cytokine response through the TLR4/NF-κB/miR-155-5p/SCOS1 axis in monocyte-derived macrophages has been demonstrated in dengue (Arboleda et al., 2019). It has further been observed to be upregulated in B cells in EBV infection and in PBMC of HIV-1 infected patients (Dey et al., 2016; Gao et al., 2015). In JHMV-infected (a coronavirus) mice models, miR-155 enhanced the T-cell trafficking, cytokine secretion, and cellular effector functions (Dickey et al., 2016). Woods et al. studied 1908 mature murine miRNA expressions in influenza A virus (IAV)-infected type II alveolar cells and miR-155-5p was showed to have the highest expression (Woods et al., 2020). In Fe/C-electric circuits, miR-155-5p expression induced IL-6 and IP-10 production, responsible for the recruitment of leucocytes (McAdams et al., 2015). It also regulates the NF-κB and MAPK signaling pathways (Shi et al., 2020). Our analysis found miR-155-5p to be one of the ten identified miRNAs that possibly regulate cytokine expression and triggers an inflammatory response in COVID-19. Further, miR-155-5p was found to affect the expression of multiple transcription factors, including CEBPA, JUN, NFAT5, NFKB1, SP1, SP1, SAT1, STAT3, CEBPB, ZP36, ZNF300, ZFP36.

Another targeting miRNA identified in this study, miR-124-3p, was observed to be downregulated in JEV-infected human neural stem/progenitor cells (Mukhopadhyee et al., 2019). A mice model showed downregulation in miR-124-3p expression in ARDS. Treatment with miR-124-3p agonist attenuated the pulmonary injury and the levels of pro-inflammatory cytokines IL-6 and TNF-α by directly targeting p65, thus showing promise in in-vitro management of pulmonary injury (Liang et al., 2020, p. 65).

Yet another miR-203a has been demonstrated to have an antagonistic role in foot-and-mouth disease virus (FMDV) infection (Gutkoska et al., 2017). This miRNA was further studied in IAV infection where an upregulated miR-203a modulated the antiviral response by targeting DR1 gene (Zhang et al., 2018, p. 1). However, further studies are needed to consolidate its role in corona-virus infections. Our in-silico analysis showed miR-203a targets transcription factors NFKB1, RELA, CREBPPB, ATF4, ETS1 and 2.

miR-335-5p had the most predicted targets in the response against the Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) of alveolar macrophages. Contrarily, Dhorne-Pollet et al. observed no effects on cytokine expression in their study (Dhorne-Pollet et al., 2019). This may be attributed to the low level of expression of miR-335-5p in most tissues, which renders its effect to be negligible despite the abundant number of predicted targets (The Fantom Consortium et al., 2017). However, miR-24-3p facilitated PRRSV replication via suppression of heme oxygenase-1 (HO-1) (Xiao et al., 2015), and HO-1 has been reported to play role in anti-viral activity in several viral infections including HIV, hepatitis C virus, hepatitis B virus, enterovirus 71, influenza virus, respiratory syncytial virus, dengue virus, and Ebola virus (Espinoza et al., 2017, p. 1). Thus a high expression of miR-24-3p may be pathognomonic for the worsening of viral infection.

Another targeting miRNA identified in this study, hsa-let-7c-5p, directly affects ACE2 and TMPRSS2; two key players in the SARS-CoV-2 infection (Chauhan et al., 2020). In rhadondomyosarcoma cells, hsa-let-7c-5p promoted the replication of enterovirus 71 (EV71) by inhibiting the MAPK4K expression (Zhou et al., 2017). Overexpression of miR-let-7c attenuated the replication of HCV through HO-1 induction (Chen et al., 2019). A differential expression of hsa-let-7 in silico as a CRIEG indicates it has a role in immunomodulation in COVID-19.

Collectively, these studies demonstrate that mainly ten microRNAs (hsa-miR-106a-5p, hsa-miR-155-5p, hsa-miR-98-5p, hsa-miR-24-3p, hsa-miR-204-5p, hsa-miR-124-3p, hsa-miR-335-3p, hsa-let-7c-5p, hsa-miR-1-3p) regulate the role of inflammatory mechanism in viral infection. Our in-silico analysis points towards a similar potential regulatory role of miRNA in SARS-CoV-2 mediated inflammatory cascades. Many of the target miRNA found in this study, namely miR-106a-5p, miR-1-3p, miR-98-5p, miR-24-3p, and miR-204-5p have been observed to orchestrate the gene expression of IL-1β, IL-6, IL-10, IFNγ, IL-2, and IL-17 through TFs such as ERK, STAT1, and STAT3 (Shen et al., 2019; Srivastava et al., 2021; Zhi et al., 2020, Ye et al., 2014).

Although most of these data are derived from cancer and transplantation studies, a similar regulation mechanism may be functional in the case of COVID-19. The disease severity in COVID-19 had been associated with an influx of innate immune cells and inflammatory cytokines (Hadjadaj et al., 2020; Yale IMPACT Team et al., 2020, p. 19). The cytokine storm in COVID-19 leads to lung injury, multiple organ failure, and poor prognosis (Jose and Manuel, 2020; Mehta et al., 2020). TNF-α and IFN-γ together had shown to incite the cells to PANNOSis, inflammatory cell death involving the components of pyroptosis, apoptosis, and necroptosis. Further, JAK/STAT1/IRF1 axis was also involved in the regulation of inflammatory cell death due to PANNOSis (Karki et al., 2020). Further, IL-6 has also been shown to activate the Janus kinase-Signal Transducer and Activator of Transcription (JAK-STAT) pathway leading to immune activation (Luo et al., 2020, p. 19).

Apart from the above-mentioned transcription factors, NF-κB also plays a crucial role in the poor prognosis of severe COVID-19 disease. NF-κB leads to an accelerated inflammatory response with increased secretion of TNF-α and IL-6. This auto-amplified pro-inflammatory loop with impaired type I IFN response culminates in viral replication within the lungs and tissue damage (Hadjadaj et al., 2020). Recent studies have demonstrated the up-regulation of various miRNAs in COVID-19 patients, thus confirming our prediction. In comparison to healthy controls, miRNAs, including miR-21, miR-155, miR-208a and miR-499, had been demonstrated to be up-regulated in the COVID-19 patients (Garg et al., 2021; Mahesh and Biswas, 2019). The varying functional significance and organ specificity of these upregulated miRNAs, i.e. miR-155
5. Conclusion

The present study identifies an in-silico representation of a network involving miRNAs (hsa-miR-21a-3p, hsa-miR-15b-5p, hsa-miR-124-3p, hsa-miR-203a-3p, hsa-miR-203-5p, hsa-miR-135a-3p, hsa-miR-135b-5p, hsa-miR-143-3p), CRIEGs (CCL2, CCL4, CXCL10, CXCL8, IL6, IL7, JAK2, TNF), and TF (AHR, CREM, DDIT3, E2F1, EGR1, EP300, ER, ETS2, HDAC1, HDAC2, IRF1, JUN, KLF4, NFKB1, NFKBIA, REL, RUNX1, SIRT1, SP100, SP140L, STAT1, XBP1, ZFP36) which take part in the inflammatory response in COVID-19. This study has identified the CRIEGs and miRNA, the interactions between them, which are potentially critical and can be studied further to develop targeted therapeutic strategies. The data can also be used in exploring novel pathways, which occur following SARS-CoV-2 infection. However, the data needs to be experimentally validated in vitro and in vivo.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mgene.2021.100990.

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