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Role of Long Noncoding RNA *HSD17B3-AS1* in Trauma for COVID-19

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ABSTRACT

COVID-19, an acute respiratory syndrome caused by the SARS-CoV-2 virus, was first reported in late 2019 in Wuhan, China, and rapidly escalated into a global pandemic. The condition can lead to organ dysfunction and, ultimately, death through acute respiratory distress syndrome (ARDS). Disease severity has been linked to proinflammatory cytokines, which activate the NF-κB and STAT transcription factors in infected cells. It has been proven that lncRNAs play an essential role in reducing or increasing inflammatory factors. This makes them potentially valuable in recognizing pathogenesis pathways and therapeutic targets in COVID-19. Nanocurcumin is known as an antioxidant, tumor suppressor, and anti-inflammatory substance, and it can be effective in reducing inflammation caused by the disease of COVID-19.

This study analyzed Sequence Read Archive data from COVID-19 patients with acute versus milder symptoms, identifying dysregulated genes and noncoding RNAs. To verify this correlation, the expression of the candidate gene was evaluated with quantitative polymerase chain reaction (qPCR) in mouse models, while immunoglobulin (Ig) G titer was measured using enzyme-linked immunosorbent assay (ELISA) in mouse serum samples.

Here, we introduced a novel lncRNA called HSD17B3-AS1, suggested as a therapeutic target in COVID-19 patients with acute symptoms. Furthermore, we revealed that nanocurcumin reduces the expression of HSD17B3-AS1, which leads to reduced inflammation in mice.

These results suggest that HSD17B3-AS1 plays a significant regulatory role in managing COVID-19, and the downregulation of HSD17B3-AS1 by Nanocurcumin presents a promising treatment option for minimizing complications in COVID-19 patients.

Keywords: COVID-19; Long non-coding RNA; Trauma

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China, in late 2019. It rapidly grew into a global pandemic.[1-4,5] Acute respiratory distress syndrome (ARDS), in conjunction with other complications such as multiple organ failure and thrombotic events, leads to fatal outcomes in a small fraction of these patients. In contrast, the majority of the patients exhibit milder symptoms and recover within a short period.[6]

Evidence suggests that COVID-19 is associated with elevated levels of inflammatory cytokines and chemokines.[7] Many studies have shown that high levels of proinflammatory cytokines are produced in epithelial

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cells and immune cells of COVID-19 patients.[8] Among the most significant inflammatory mediators are interleukins (IL)-1, IL-2, IL-6, and tumor necrosis factor-α (TNF-α).[9,10] Recent studies have shown a strong correlation between plasma levels of IL-6 and mortality rates in COVID-19 patients. These conditions indicates a cytokine storm.. Cytokine storm is an intense immune response during which the body rapidly releases excessive cytokines into the bloodstream. Indications and manifestations encompass fever, inflammation characterized by redness and swelling, as well as severe fatigue and nausea. On occasion, trauma can escalate to a severe or potentially fatal extent, resulting in the failure of multiple organs. Therefore, fatal cytokine storm disease induced by cytokine storm is characterized by cytokine release syndrome (CRS).[11-13] Therefore, the timing of diagnosis and treatment of cytokine storms could be life-saving in SARS-CoV-2 patients.[14]

Noncoding RNAs are key regulators of innate immunity.[15] They are rapidly expressed upon the activation of the innate immune response through NF-κB proinflammatory transcription factors.[16] They also control various aspects of innate immunity, such as the maintenance of hematopoietic stem cells, the differentiation and apoptosis of myeloid cells, and the activation of monocytes, macrophages, and dendritic cells.[17]

Curcumin, a hydrophobic polyphenol obtained from the rhizome of the *Curcuma longa*, is a major pigment in turmeric. It has anticancer properties by modulating pathways involved in tumorigenesis. Curcumin induces cell death and inhibits cell growth and proliferation through various mechanisms.

In this study, we investigate the role of noncoding RNAs in the induction of trauma in patients with fatal SARS-CoV-2 infection. We analyzed the sequence read archive (SRA) data from COVID-19 patients and identified a molecular pathway involved in the disease. We then evaluated the effect of nanocurcumin on modulating the effects of the proinflammatory cytokines and genes involved in the pathway.

MATERIALS AND METHODS

Differential Expression of Long Noncoding RNA (lncRNAs), Messenger RNAs (mRNAs), and MicroRNAs

The public gene expression dataset (SRP 262885) from the University of Utah was retrieved using the keywords "COVID-19" and "ICU and non-ICU patient" in the SRA database (http://www.ncbi.nlm.nih.gov/sra) to explore the differential expression in mRNA, lncRNA, and miRNA in SARS-CoV-2 patients. RNA expression data in COVID-19 patients were analyzed using Galaxy, an online platform for bioinformatic analysis, using the Deseq2 package with the following cut-off criteria: |log2 fold change (FC)> 2 and p<0.01.

Enrichment Analysis

For functional and pathway enrichment analysis, Enrichr (https://maayanlab.cloud/Enrichr) was used to carry out gene ontology (GO) analysis, including cellular component (CC), molecular function (MF), biological process (BP), and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis.

lncRNA-miRNA-mRNA Related Network

StarBase,[18] miRcode[19,] and TargetScan,[20] are bioinformatics software used to investigate the relationship between lncRNAs, mRNAs, and miRNAs.

The Competing Endogenous RNA (ceRNA) Regulatory Network

lncRNA-miRNA-mRNA regulatory network related to COVID-19 was constructed based on the predicted lncRNA and miRNA targets to display the interaction among lncRNA, miRNA, and mRNA. The network was visualized using Cytoscape 3.6.1 software.[21]

Quantitative Real-time Polymerase Chain Reaction

Quantitative real-time polymerase chain reaction (qRT-PCR) was performed on Applied Biosystems Quant Studio 5 (Thermo Fisher Scientific, USA). Total RNA was extracted from a nasopharyngeal swab in viral transport medium (VTM) culture using Trizol (Roche, CA, USA) and reversely transcribed into cDNA using First Strand cDNA Synthesis Kit (Roche, CA, USA). The $2^{-\Delta\Delta CT}$ method was used to analyze the relative expression levels of lncRNAs. Primer sequences are available in the Supplementary Table.

In vivo Animal Model Study

Mice were used as the main animal model to evaluate the role of nanocurcumin in COVID-19. Twenty male BALB/c mice aged 5 weeks were purchased from Tarbiat Modares animal lab and maintained under

pathogen-free conditions. Animals were divided into 4 groups: Spike+pcDNA3.1(+)/ Mock pcDNA3.1(+) and Nanocurcumin (Gemini surfactant UGS 1450)[22] + Spike+pcDNA3.1(+)/PBS+ Mock pcDNA3.1(+). To induce viral infection, 2000 ng/kg of Spike+pcDNA3.1(+) and 0.5 mL/kg of nanocurcumin were injected intramuscularly. The mice were treated for 14 days. Then, the expression levels of target genes were evaluated. The mice used in this study were prepared following the approval of the Ethics and Scientific Committees of Baqiyatallah University of Medical Science.

RESULTS

Differential Expression Analysis of lncRNAs, mRNAs, and miRNAs from Public SRA Data

We identified 2600 differentially expressed mRNAs (DEGs), 490 differentially expressed lncRNAs (DELs), and 290 differential expressed miRNAs (DEMs). We used log Fc> 2 and *p* value<0.01 to evaluate the expression changes in DEGs, DELs, and DEMs. Based on these criteria, we found 250 upregulated and 250 downregulated mRNAs as well as 150 upregulated and 140 downregulated lncRNAs. The volcano plot and heat map analysis show the expression of the deregulated lncRNAs and mRNAs (Figures 1A and 1B).

Functional and Pathway Enrichment Analysis

Gene ontology (GO) analysis, including cell components (CC), biological function (BF), molecular pathway (MP), and KEGG analysis, revealed 10 MF, 7 Biological protein (BP), 5 CC, and 20 pathways related to DEGs (*p value*<0.05). The top 5 GO analyses and top 10 KEGG pathways are shown in Tables 1 and 2.

Prediction and Construction of the lncRNAs-miRNAs-mRNAs Network

The bioinformatics interaction between lncRNA, miRNA, and mRNA was investigated using the starBase online database. In the following, miRNA targets were analyzed using two online bioinformatics software, TargetScan and miRcode. The competing endogenous RNA (ceRNA) regulatory network was performed based on the lncRNA's ability to compete for MRE binding in miRNA target genes, as well as the ability of the lncRNAs to sponge miRNAs, and ultimately, a regulation expression network was designed (Figure 2).

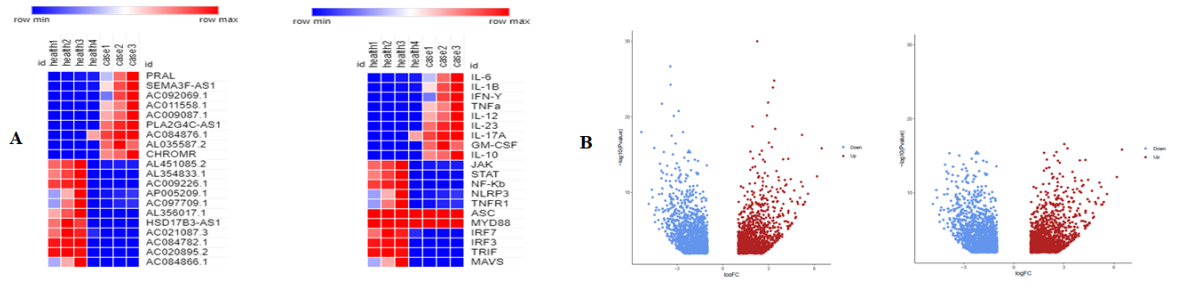
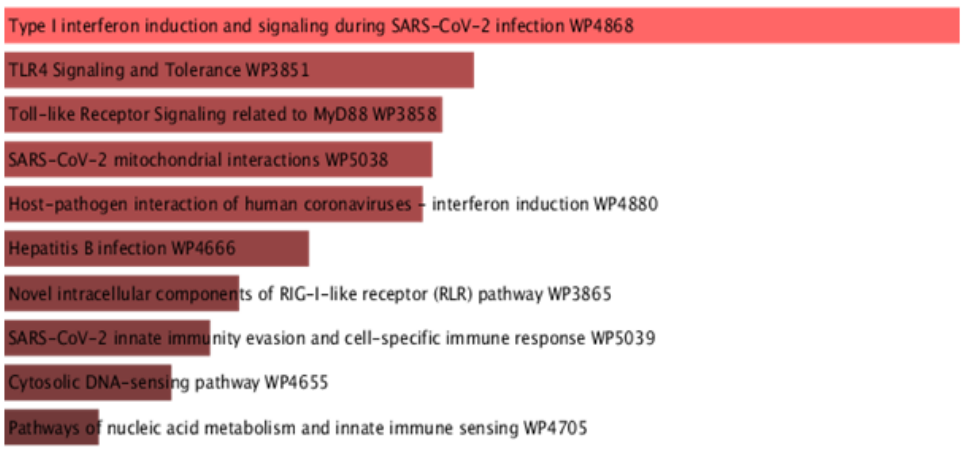


Figure 1. Volcano plots and heat map diagrams of dysregulated genes. A) The volcano plot shows the distribution of dysregulated lncRNAs and mRNAs COVID-19 patients. B) The heat map shows the detailed expression patterns of dysregulated lncRNAs and mRNAs in COVID-19 patients. lncRNA: long noncoding RNA; mRNA: messenger RNA.

Table 1. Gene ontology (GO) analysis of differentially expressed long noncoding RNAs (DELs) associated with COVID-19.

Category	ID	Description	*pe*
GO-BP (Biological protein)	GO:0032727	positive regulation of interferon-alpha production	9.642e-7
GO- BP	GO:0039528	cytoplasmic pattern recognition receptor signaling pathway in response to virus	0.00004255
GO- BP	GO:0032647	regulation of interferon-alpha production	0.000001939
GO- BP	GO:0008063	Toll signaling pathway	0.004990
GO- BP	GO:0032728	positive regulation of interferon-beta production	0.000005978
GO-MF (Molecular function)	GO:0035325	Toll-like receptor binding	0.01095
GO-MF	GO:0005123	death receptor binding	0.01490
GO-MF	GO:0042834	peptidoglycan binding	0.01490
GO-MF	GO:0050700	CARD domain binding	0.01589
GO-MF	GO:0032813	tumor necrosis factor receptor superfamily binding	0.02764
GO-CC	GO:0031903	microbody membrane	0.05076
GO-CC (cell components)	GO:0005778	peroxisomal membrane	0.05171
GO-CC	GO:0010008	endosome membrane	0.04126
GO-CC	GO:0030659	cytoplasmic vesicle membrane	0.05462
GO-CC	GO:0098588	bounding membrane of organelle	0.03939

Table 2. KEGG pathway analysis of the target genes corresponding to dysregulated genes in COVID-19 patients. GO: gene ontology, DEL: differentially expressed long noncoding RNA.



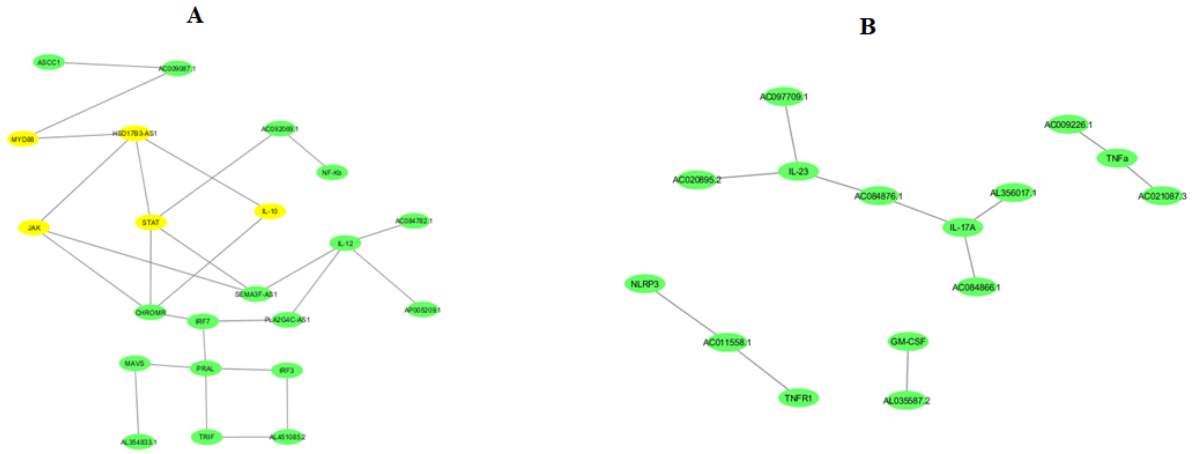


Figure 2. The long noncoding RNA (lncRNA)-microRNA(miRNA)-messenger RNA (mRNA) and competing endogenous RNA (ceRNA) network analysis in covid-19 patients. A) The protein-protein interaction (PPI) network based on differentially expressed genes (DEGs), differentially expressed long noncoding RNAs (DELs), and differentially expressed messenger RNAs (DEMs) was constructed by Cytoscape. B) Three main competing endogenous RNA (ceRNA) networks in COVID-19 patients.

In Vivo Characterization of COVID-19

Antibody titration against the SARS-CoV-2 spike protein was performed to confirm the infection of mice with SARS-CoV-2. Heightened levels of lncRNA HSD17B3-AS1 and transcription factors such as JACK, STAT, and NFK-B demonstrated disease advancement in mice that were exposed to Spike+pcDNA3.1(+) compared to mice subjected to Mock pcDNA3.1(+).

Furthermore, the presence of nanocurcumin alongside Spike+pcDNA3.1(+) in mice reduced the expression of lncRNA *HSD17B3-AS1* and proinflammatory cytokines (Figure 3).

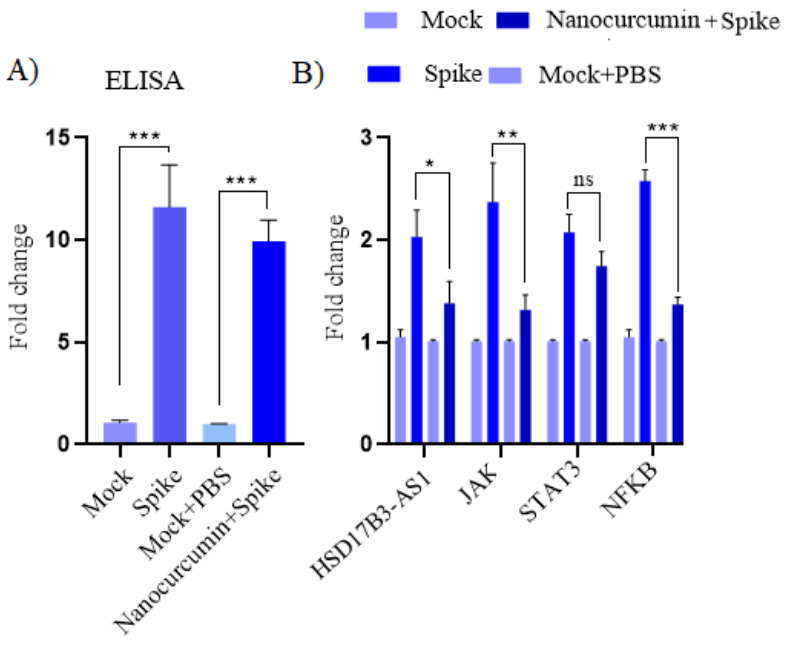


Figure3. Stimulation of the trauma model in vivo. A) Enzyme-linked immunosorbent assay for Immunoglobulin G mouse injection with Spike+pcDNA3.1(+)compressed pcDNA3.1(+). B) qPCR of gene expression in mouse models (ns: not significant, *p<0.05, **p<0.01, ***p<0.001).

DISCUSSION

Most patients infected with SARS-CoV-2 exhibit asymptomatic, mild, or moderate manifestations. However, approximately 15% to 20% of patients develop severe pneumonia, with about 5% experiencing ARDS. In addition, certain patients present with secondary dysfunction and deep vein thrombosis in the lower extremities. Remarkably, the leading causes of mortality in COVID-19 patients include cardiovascular, respiratory, and renal failures, septic shock, and hemorrhage.[23]

Recent studies have shown that in patients with severe SARS-CoV-2 infection, the expression of proinflammatory cytokines is significantly increased compared to patients with mild symptoms. This finding underscores the vital role of proinflammatory cytokines in instigating cytokine storms in these patients.[24] Cytokine storm causes acute respiratory disease and organ failure.[25]

The attachment of the SARS-CoV-2 virus to ACE2 receptors on epithelial and endothelial triggers their endocytosis. This process leads to a reduction in the ACE2 receptor, consequently elevating the levels of free angiotensin in plasma. Angiotensin, in turn, binds to angiotensin II type 1 receptors, initiating the expression of TNF-α, heparin-binding epidermal growth factor-like growth factor (HB-EGF), and IL-6Rα in the various cell types. The binding of TNF-α and HB-EGF to their respective receptors, as well as the interaction between the IL6-IL6R complex and gp130 on non-immune cells, activates the NF-κB and STAT3 pathways. Ultimately, this cascade upregulates IL-6 and trauma in COVID-19 patients.[26]

Evidence supports the role of noncoding RNAs as regulators of gene expression in many infectious diseases.[27] MicroRNAs, as a class of noncoding RNAs, are expressed in different tissues and cells and play a key role in various physiological and pathological processes.[28] Studies have revealed the potential of targeting the microRNA network as an effective therapeutic approach in managing COVID-19.

Because these noncoding RNAs are seriously influential in regulating the expression of cytokines chemokines. As a result of the increased expression of proinflammatory interleukins, patients will present with a more severe disease (Figure 4).

Recent studies indicate that nanocurcumin may serve as a complementary anti-inflammatory medication for patients with moderate involvement of COVID-19, potentially inhibiting inflammatory complications.[37] Furthermore, the Immunomodulatory effects of nanocurcumin have been evaluated in mild and severe COVID-19 patients.[38] Our study aligns with previous research, demonstrating that coinjection of nanocurcumin along with Spike DNA in mice reduces the expression of lncRNA *HSD17B3-AS1* and proinflammatory cytokines (Figure 4).

This finding provides insight into the interplay between various cytokines in COVID-19 and their possible role in regulating inflammatory cell death and the subsequent development of multiple organ failure.

The findings of this study also suggest that the detection and targeting of lncRNA *HDR17B3-AS1* expression in COVID-19 patients can be regarded as a novel diagnostic strategy.

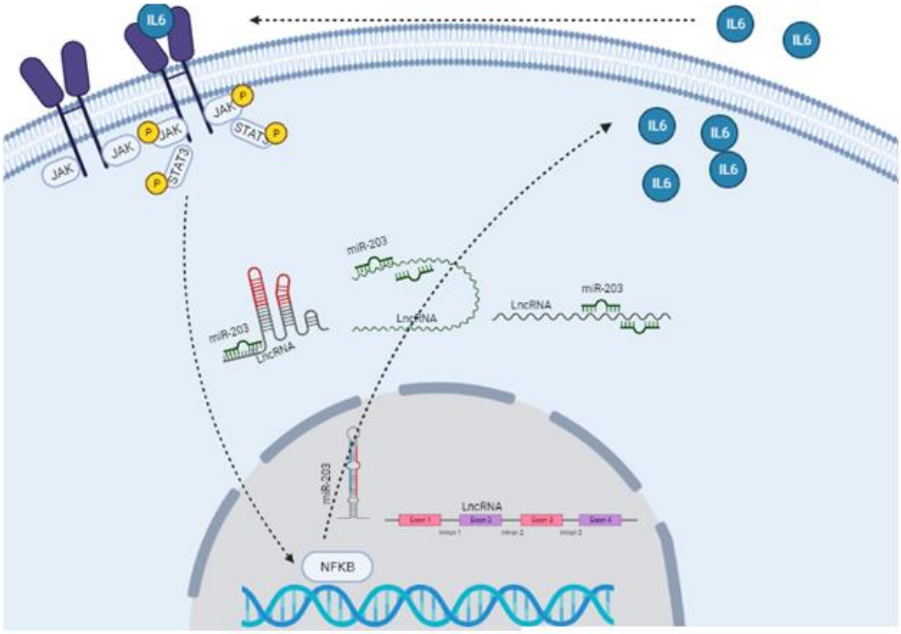


Figure 4. lncRNA HDR17B3-AS1 expression is elevated in cells with sponge miR-203, which results in increased expression of JAK and STAT proteins. Phosphorylation of these proteins in the vicinity of IL-6 receptors activates the JAK/STAT pathway and transcription from the NF-κB transcription factor. Increased expression of NF-κB by stimulating the transcription of the *IL6* gene. Increased *IL6* expression in cells is one of the causes of trauma and organ failure.

STATEMENT OF ETHICS

This study was approved by the Ethics and Scientific Committee of Baqiyatallah University (IR.BMSU.REC.1399.506).

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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