The Immunomodulatory Role of Glucokinase 1 (GCK1) lncRNA in Patients With COVID-19

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Abstract- Individuals infected with Coronavirus Disease 2019 (COVID-19) may exhibit a wide range of clinical symptoms, from asymptomatic cases to severe complications. This variation is likely associated with differences in immune response intensity, where specific long noncoding RNAs (lncRNAs) are known to regulate the interferon (IFN) signaling pathway. The present study aimed to comparatively investigate the relationship between Glucokinase 1 (GCK1) lncRNA expression and immune system activity in individuals with COVID-19. A total of 100 participants were included in the study. The expression of the GCK1 lncRNA gene was quantified using quantitative real-time polymerase chain reaction (qPCR), and the concentrations of IL-12, IFN-α, IFN-γ, and tumor necrosis factor-alpha (TNF-α) in cell culture supernatants were measured via Enzyme-Linked Immunosorbent Assay (ELISA). The findings revealed a significant upregulation of lncRNA-GCK1 expression in COVID-19 patients compared with the control group. Additionally, the levels of IL-12, IFN-α, TNF-α, and IFN-γ were considerably higher in patients, suggesting a potential association between increased lncRNA-GCK1 expression and an intensified inflammatory response. Collectively, the findings highlight lncRNA-GCK1 as a potential key regulator of immune activation in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and a promising biomarker candidate for monitoring disease dynamics and treatment outcomes.

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Introduction

The global pandemic caused by SARS-CoV-2, a member of the beta coronavirus family, is distinguished by its high transmission rate and diverse clinical outcomes, ranging from asymptomatic to severe respiratory distress, multi-organ failure, and death (1,2). The spherical, single-stranded positive-sense RNA virus has a diameter of roughly 100 nanometers, and its rapid spread has underscored the critical need for a deeper understanding of its characteristics and the host immune response (1,3). Investigating the immune response is essential for identifying important prognostic and diagnostic markers, which are vital for the effective management of severe cases and for developing targeted therapeutic strategies (4,5).

Recent studies have increasingly turned their attention to non-coding RNAs (ncRNAs), which are classified by their length. Transcripts longer than 200 nucleotides are designated as lncRNAs and have been shown to play a crucial role in regulating gene expression through various mechanisms (6). A significant function of certain lncRNAs is their ability to act as molecular decoys, disrupting signaling pathways and preventing the production of vital immune components like type I IFNs (7). Furthermore, research suggests that many lncRNAs, whose expression levels are altered during viral infections, act as either enhancers or suppressors in innate

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immune responses, particularly in IFN-associated pathways. This is highly relevant in critically ill COVID-19 patients, where IFN-α is a key target for antiviral therapies, highlighting the importance of lncRNAs in modulating the IFN pathway during viral respiratory infections (8).

Hexokinases are essential enzymes that facilitate the initial step in glucose catabolism by phosphorylating glucose into glucose-6-phosphate. The human genome contains four distinct hexokinase isoenzymes (HK1-HK4), with GCK, or HK4, playing a pivotal role in glucose sensing (9,10). GCK is primarily found in pancreatic β-cells and liver cells, where its activity significantly escalates in response to higher glucose concentrations. This property is crucial for maintaining glucose homeostasis and ensuring appropriate insulin secretion and metabolic regulation (11).

A more profound understanding of the mechanisms underlying SARS-CoV-2 pathogenesis could enhance the formulation of more effective treatment approaches. Given the emerging role of lncRNAs in immune regulation and the known metabolic alterations in COVID-19, this study focused on assessing the expression levels of GCK1 lncRNA in peripheral blood mononuclear cells (PBMC) from individuals diagnosed with COVID-19, in comparison to a healthy control group. Additionally, we explored the potential of GCK1 lncRNA to serve as a diagnostic biomarker for distinguishing COVID-19 from other conditions. This investigation aims to contribute valuable insights into the diagnostic landscape of the disease, potentially leading to improved clinical outcomes.

Materials and Methods

Sampling

This was an observational case-control study conducted from May to December 2020 at Shahinfar Hospital in Mashhad, Iran. A total of 100 individuals were included in the study: a case group of 50 inpatients with confirmed COVID-19 and a control group of 50 healthy individuals. The sample size was determined based on the availability of clinical samples and considered adequate based on a feasibility assessment and a review of similar studies, which was deemed sufficient to detect significant differences in the measured variables between the two groups. All participants provided written informed consent before sample collection, and the study received ethical approval from the Research Ethics Committee of Islamic Azad University of Mashhad Medical Science Branch (IR.IAU.MSHD.REC.1401.188). The case group consisted consecutively enrolled in patients who were diagnosed with COVID-19 based on a positive SARS-CoV-2 RT-PCR test from nasopharyngeal swabs, along with supporting clinical evaluations and characteristic findings on chest CT scans. Inclusion criteria for this group were defined as being over 18 years of age with a confirmed diagnosis, while patients with a history of autoimmune diseases, chronic inflammatory conditions, or known immunodeficiency were excluded. The control group consisted of 50 healthy, age- and sex-matched volunteers who were recruited from the general population attending the same hospital for non-COVID-19 related reasons. All controls were confirmed to be asymptomatic and negative for SARS-CoV-2 via RT-PCR testing. Exclusion criteria for the control group included a history of any chronic disease or long-term medication use. Demographic and clinical data, including age, sex, and symptomatology, were collected from all participants using a standardized questionnaire, with matching by age and sex performed to minimize potential confounding factors and ensure a reliable comparison between the two groups.

PBMC isolation

Approximately 8 mL of blood was collected under sterile conditions from both the COVID-19 and healthy control groups. Of this, 3 mL was used for serum preparation and stored at -70° C for subsequent analysis. PBMCs were isolated from heparinized blood samples via standard Ficoll-Paque (lymphosep) gradient centrifugation at a density of 1.077 g/mL (Biosera, UK). The isolated PBMCs were washed twice with RPMI 1640 medium (Sigma-Aldrich, Germany), and 5×10^6 cells were cultured in 5 mL of complete medium supplemented with 10% Fetal Bovine Serum (FBS). After a 48-hour incubation, the cultured cells and supernatant were collected for gene expression and cytokine level studies, respectively (12).

RNA extraction and cDNA synthesis

Total RNA was extracted using the Total RNA extraction kit from Yekta Tajhiz Azma (Tehran, Iran) according to the manufacturer's protocol. The purity and concentration of the extracted RNA were measured with a Nano Drop 1000 spectrophotometer (Nano Drop Technologies, USA), with an A260/A280 ratio between 1.8 and 2.1 considered acceptable. RNA integrity was verified by electrophoresis on a 1.5% denaturing agarose gel. To remove any genomic DNA contamination, RNA samples were treated with DNase. cDNA was synthesized

from the RNA samples using a cDNA synthesis kit from TaKaRa (Otsu, Shiga, Japan) and stored at -20° C until use (13).

qPCR analysis

QPCR was performed to quantify the mRNA expression levels of GCK1 lncRNA using the standard SYBR Green Premix Ex Taq2 (TAKARA) on an ABI 7300 Real-Time PCR system (Applied Biosystems, USA). Each qPCR reaction was carried out in a total volume of 20 µL and consisted of 40 cycles, with a thermal profile of 94° C for 30 seconds, followed by 60° C for 30 seconds, and 72° C for 30 seconds. All reactions were performed in triplicate to ensure the reliability and reproducibility of the gene expression data by minimizing technical errors. The specificity of the PCR products was confirmed via melt curve analysis. GCK1 lncRNA expression levels were normalized to the endogenous control gene, GAPDH, and the relative expression was calculated using the $2^{-\Delta\Delta Ct}$ method. Detailed primer characteristics are provided in Table 1 (14).

Cytokine quantification by ELISA

The concentrations of IFN-α, IFN-γ, IL-12, and TNF-α were measured in the supernatant of cultured PBMCs using specific ELISA kits (My BioSource, USA) according to the manufacturer's instructions. Each sample was analyzed in duplicate to reduce the impact of technical variation and enhance the robustness of the results. The cytokine concentrations were normalized to the initial cell count of 5×10^6 cells, as total protein content was not a variable in this study. Absorbance was read at 450 nm using a microplate ELISA reader (BP-800, Biohit, Finland), and cytokine concentrations were calculated from a standard calibration curve (15).

Statistical analysis

Data analysis was performed using SPSS version 22 (SPSS, USA) and GraphPad Prism version 8.0.1 (GraphPad Software Inc., USA). The normality of the data distribution was formally assessed using the Shapiro-Wilk test. For normally distributed data, unpaired t-tests and one-way ANOVA were used to compare groups, while the Chi-square ($\chi2$) test was applied for qualitative variables. The correlation between GCK lncRNA expression and cytokine levels was assessed using Pearson's correlation coefficient, with no adjustment for multiple comparisons. The diagnostic potential of GCK lncRNA as a biomarker was evaluated using receiver operating characteristic (ROC) curves and the area under the curve (AUC). A *P* of less than 0.05 ($P<0.05$) was considered statistically significant.

Results

Patient's demographic profile and laboratory findings

A total of 100 participants were included in this study: 50 individuals with a COVID-19 diagnosis and 50 healthy controls. The COVID-19 group had a mean age of 47.5±13.15 years, while the healthy control group had a mean age of 46.8±14.74 years. The two groups showed significant differences in several key laboratory parameters, as detailed in Table 2. Specifically, there were statistically significant variations in systolic blood pressure ($P=0.0021$), fasting blood sugar ($P=0.0045$), triglyceride levels ($P=0.0018$), LDL cholesterol ($P=0.0039$), and albumin concentrations ($P=0.045$).

Melt curve analysis of GCK 1 LncRNA

The melting temperature curve was analyzed to confirm the specificity of the primers used for quantitative real-time PCR. The analysis showed a single, distinct peak, with no additional peaks or signs of primer dimers (Figure 1). This finding indicates the specificity and reliability of the amplification process.

Expression levels of GCK 1 LncRNA

The mRNA expression levels of GCK 1 LncRNA were measured in serum samples from both healthy controls and COVID-19 patients. The quantitative real-time PCR results demonstrated a statistically significant increase in the expression levels of GCK 1 LncRNA in the COVID-19 group compared to the healthy control group ($P=0.0003$). The relative expression levels are shown in Figure 2.

Diagnostic value of GCK 1 LncRNA

To evaluate the potential of GCK 1 LncRNA as a diagnostic marker for COVID-19, we performed a ROCcurve analysis. The analysis produced an AUC of 0.8293, with a 95% confidence interval ranging from 0.7496 to 0.9090 (Figure 3).

Cytokine levels

The concentrations of various cytokines, including IL-12, IFN-α, IFN-γ, and TNF-α, were measured in the cell supernatant using ELISA. Compared to the healthy control group, individuals with COVID-19 showed a significant increase in the concentrations of IFN-γ ($P=0.0028$), IL-12 ($P=0.0041$), and TNF-α ($P=0.0036$). Conversely, a significant decrease in the levels of IFN-α was observed in the COVID-19 patient group ($P=0.0024$)

(Figure 4).

Correlational analysis of GCK 1 LncRNA and cytokine levels

A correlational analysis was performed to investigate the relationship between the expression of GCK 1 LncRNA and the levels of various cytokines. The analysis revealed a significant positive correlation between GCK 1 LncRNA levels and the concentrations of TNF-α (R=0.420, *P*=0.0028), IL-12 (R=0.430, *P*=0.0021), and IFN-γ (R=0.465, *P*=0.0008). In contrast, a significant negative correlation was found between High GCK 1 LncRNA levels and IFN-α levels (R=−0.350, *P*=0.0150).

Table 1. Quantitative Real-time PCR primers

Gene name	Sequence	Length	Annealing temperature
GAPDH	Forward Primer: 5′-TGAAGCAGGCATCTGAGGG-3′	19	67°C
	Reverse Primer: -5′ CGAAGGTGGAAGAGTGGGA-3′	19	67°C
lncGCK1	Forward Primer: 5′-CTCCTCGGGCTAGTAGAGCA-3′	20	68°C
	Reverse Primer: 5′ -CTGCATCGGTCTCATCACCT-3′	20	68°C

Table 2. A comparative analysis of the clinical and biological characteristics between individuals infected with COVID-19 and healthy

Parameters	Healthy control (mean±SD)	COVID-19 patients (mean±SD)
Age	47.5 ±13.15	46.8 ±14.74
Number of patients	50	50
Sex (Male/Female)	25/25	27/23
Clinical positive tests	0	50
Systolic blood pressure (mm Hg)	111.5 ± 11.9	127.8 ± 19.5*
Diastolic blood pressure (mm Hg)	73.35 ± 8.56	72.82 ± 11.25
BMI (kg/m2)	25.85 ±4.58	28.46 ± 5.22
Triglyceride (mg/dL)	130.2 ± 38.96	180.3 ± 64.38*
Cholesterol (mg/dL)	168.3 ± 42.30	192.5 ± 38.24
HDL-cholesterol (mg/dL)	46.42 ± 5.32	48.44 ± 5.32
LDL-cholesterol (mg/dL)	115.8 ± 23.48	141.9 ± 26.52*
Fasting blood sugar (mg/dL)	102.5 ± 25.62	130.8 ± 33.62*
Albumin (g/dL)	3.854 ± 0.3268	3.117 ± 0.1187*
Creatinine (mg/dL)	1.325 ± 0.868	1.258 ± 0.756
GFR	74.15± 23.32	76.16 ± 18.35

A significant difference is indicated at the 5% error level

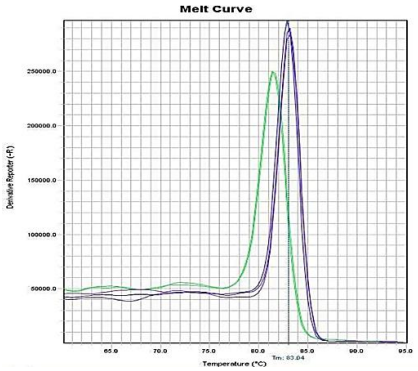

Figure 1. Melting curve of lncRNA GCK1

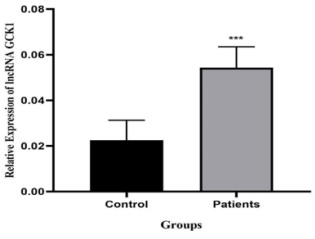

Figure 2. Analysis of the differences in GCK1 lncRNA expression levels in COVID-19 patients compared to healthy controls

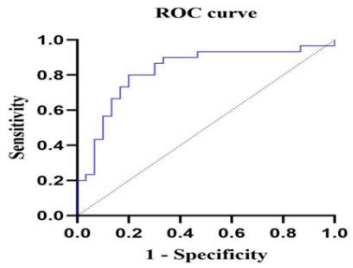

Figure 3. ROC curve of lncRNA GCK1 expression

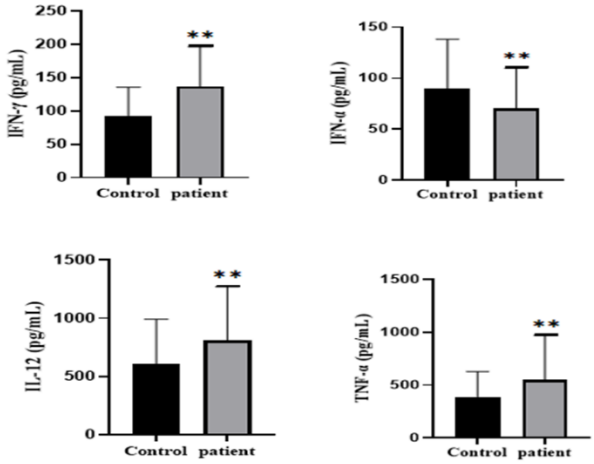

Figure 4. The evaluation of IL-12, IFN-α, TNF-α, and IFN-γ was performed using the ELISA technique, which indicated a significant difference of 0.01%

Discussion

This study evaluated the serum levels of GCK1 LncRNA and inflammatory cytokines in patients diagnosed with COVID-19. The results indicated that the expression of lncRNA-GCK1 was significantly elevated in individuals with COVID-19 when compared to the control group. A notable correlation was found between elevated levels of lncRNA-GCK1 and the occurrence of COVID-19. Additionally, our findings showed that the concentrations of IL-12, TNF-α, and IFN-γ were significantly higher, whereas IFN-α levels were decreased in patients suffering from COVID-19. This suggests a potential link between the increased expression of lncRNA-GCK1 and the heightened inflammatory response observed in these patients. The data implies that lncRNA-GCK1 may play a role in modulating the immune response during COVID-19 infection. The elevated levels of lncRNA-GCK1 in COVID-19 patients appear to be associated with an increase in proinflammatory cytokine production. This relationship highlights the potential importance of lncRNA-GCK1 in the pathophysiology of COVID-19 and suggests that it may serve as a biomarker for disease severity or progression. Further research is warranted to explore the underlying mechanisms and potential therapeutic implications of these findings.

COVID-19 is a multifaceted respiratory disease that presents a wide range of clinical symptoms, from asymptomatic cases to those that necessitate intensive medical intervention. Various studies have highlighted that several factors, including age, immune system functionality, underlying health issues, and genetic factors (such as differences in ACE2 and TMPRSS2 genes) significantly influence a person's susceptibility to the virus and the severity of their illness (16). Furthermore, the imbalance of cytokine levels, particularly those involving IL-6, TNF-α, and IFNs, plays a crucial role in the wide array of clinical manifestations seen in COVID-19 patients. This dysregulation can lead to an exaggerated immune response, which may exacerbate the severity of the disease in certain individuals. Understanding these underlying mechanisms is essential for developing targeted therapies and improving patient outcomes (17,18).

Type I IFNs, specifically IFN-α and IFN-β, are a category of cytokines that play a crucial role in the defense against SARS-CoV-2 and have been associated

with the severity of COVID-19 in various research studies (19). Research indicates that SARS-CoV-2 employs immunosuppressive mechanisms that hinder the immune response, as demonstrated by the findings of Shah et al., who revealed a delay in the expression of IFN-β during the early phases of infection. This suggests that the virus may manipulate the host's immune system to its advantage, contributing to the progression of the disease and the variability in patient outcomes (20).

The presence of asymptomatic individuals can be linked to the immune evasion tactics utilized by the virus, which may lead to a spectrum of clinical manifestations. The exact influence of type I IFNs on the outcomes related to SARS-CoV-2 infection is still not fully understood. Research has underscored the important regulatory functions of ncRNAs in the immune response driven by IFNs (21). lncRNAs, as a subset of regulatory ncRNAs, are crucial in shaping the innate immune response to SARS-CoV-2. Their role is particularly evident in the context of the IFN signaling pathway, where they interact with IFN-stimulating genes (ISGs). The variability in host immune responses among patients at different stages of symptom development may result in distinct patterns of lncRNA and ISG expression (22,23). The analysis of lncRNA profiles in patients infected with SARS-CoV-2 revealed a significant decrease in the IFN type I response. This observation points to a potential link between the immune evasion strategies employed by the virus and the levels of IFN present in the host (24). Given their involvement in the regulation of IFN, lncRNAs could emerge as important biomarkers and therapeutic targets in the management of SARS-CoV-2 infections. Their ability to influence immune responses suggests that they may play a critical role in the pathophysiology of the disease, offering new avenues for intervention and treatment strategies (25). Furthermore, research conducted by Ginn *et al.*, highlights the variability in lncRNA expression levels, which may serve as promising prognostic and diagnostic indicators for monitoring the course of viral infections (26).

The findings of this study on GCK1 lncRNA expression in COVID-19 patients are strengthened by a broader understanding of lncRNAs' roles in both metabolic and inflammatory processes. GCK, the enzyme associated with GCK1, is a key player in glucose metabolism, and research on related lncRNAs like lncLGR has shown their ability to regulate GCK expression in metabolic contexts like the liver (27). Given the metabolic dysregulation frequently observed in COVID-19, it is plausible that GCK1 lncRNA may similarly influence these pathways, linking metabolic dysfunction to the observed inflammatory response. Furthermore, other lncRNAs, such as NEAT1 and MALAT1, have been found to be differentially expressed in patients with severe COVID-19, highlighting the broader importance of lncRNAs in immune modulation and disease progression (28). The ability of lncRNAs to influence these complex pathways suggests they hold significant therapeutic potential. Modulating their expression could offer a novel strategy for regulating the immune response in viral infections and could serve as valuable biomarkers for monitoring disease severity and progression (29). Further investigation into the specific mechanisms by which GCK1 lncRNA influences cytokine production is warranted to fully explore its potential as a diagnostic and therapeutic target.

Limitations

This study has several important limitations that warrant consideration. As an observational case-control study, its findings are subject to selection bias, particularly as the COVID-19 group consisted solely of inpatients, which does not represent the full spectrum of disease severity. Consequently, the observed findings may not be specific to COVID-19 and could instead reflect general inflammatory processes or tissue damage associated with severe illness. A key methodological limitation is the separate measurement of GCK1 LncRNA from the cultured PBMC cells and cytokine profiles from the corresponding supernatant. This approach precludes a direct assessment of the mechanistic influence of GCK1 LncRNA expression on cytokine production within a single cellular environment. Furthermore, while the lncRNA expression demonstrated an acceptable AUC for distinguishing COVID-19 patients from healthy controls, its clinical utility in differentiating COVID-19 from other respiratory diseases remains uncertain, as the control group consisted exclusively of healthy individuals. The absence of formal power analysis also suggests a potential risk of being underpowered to detect smaller effect sizes.

The findings related to lncRNA expression levels revealed that lncRNA-GCK 1 was markedly elevated in individuals infected with SARS-CoV-2 when compared to the control group. This suggests a significant role of lncRNA-GCK 1 in the context of viral infection. Additionally, a strong positive correlation was identified between the expression levels of GCK 1 LncRNA and the concentrations of pro-inflammatory cytokines such as TNF-α, IL-12, and IFN-γ. This indicates that higher levels of GCK 1 LncRNA may be associated with

increased inflammatory responses during the infection. Conversely, a significant negative correlation was found between the levels of GCK 1 LncRNA and IFN-α levels. This suggests a complex interplay between lncRNA-GCK 1 and various cytokines, highlighting its potential role in modulating immune responses in SARS-CoV-2 infected patients.

The research was performed in alignment with the ethical standards outlined in the Helsinki Declaration, ensuring that all procedures adhered to the relevant guidelines and regulations as approved by the Islamic Azad University of Mashhad Medical Sciences Branch. Ethical approval and the necessary license were secured from the Research Deputy Ethics Committee of the institution, identified by the number 14001156 and the code IR.IAU.MSHD.REC.1401.188.

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References

1. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents 2020;55:105924.
2. Sharma A, Tiwari S, Deb MK, Marty JL. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): a global pandemic and treatment strategies. Int J Antimicrob Agents 2020;56:106054.
3. Dumache R, Enache A, Macasoi I, Dehelean CA, Dumitrascu V, Mihailescu A, et al. SARS-CoV-2: An Overview of the Genetic Profile and Vaccine Effectiveness of the Five Variants of Concern. Pathogens 2022;11:516.
4. Yang Y, Shen C, Li J, Yuan J, Wei J, Huang F, et al. Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19. J Allergy Clin Immunol 2020;146:119-127.e4.
5. Schultze JL, Aschenbrenner AC. COVID-19 and the human innate immune system. Cell 2021;184:1671-92.
6. Amini A, Khadivar P, Ahmadnia A, Alipour M, Majeed M, Jamialahmadi T, et al. Role of Curcumin in Regulating Long Noncoding RNA Expression in Cancer. Adv Exp Med Biol 2021;1308:13-23.
7. Jiang M, Zhang S, Yang Z, Lin H, Zhu J, Liu L, et al. Self-Recognition of an Inducible Host lncRNA by RIG-I Feedback Restricts Innate Immune Response. Cell 2018;173:906-19.e13.
8. Min J, Liu W, Li J. Emerging Role of Interferon-Induced Noncoding RNA in Innate Antiviral Immunity. Viruses 2022;14:2607.
9. Guo C, Ludvik AE, Arlotto ME, Hayes MG, Armstrong LL, Scholtens DM, et al. Coordinated regulatory variation associated with gestational hyperglycaemia regulates expression of the novel hexokinase HKDC1. Nat Commun 2015;6:6069.
10. Claeyssen E, Rivoal J. Isozymes of plant hexokinase: occurrence, properties and functions. Phytochemistry 2007;68:709-31.
11. Abu Aqel Y, Alnesf A, Aigha II, Islam Z, Kolatkar PR, Teo A, et al. Glucokinase (GCK) in diabetes: from molecular mechanisms to disease pathogenesis. Cell Mol Biol Lett 2024;29:120.
12. Turgeon CT, Sanders KA, Granger D, Nett SL, Hilgart H, Matern D, et al. Detection of SARS-CoV-2 IgG antibodies in dried blood spots. Diagn Microbiol Infect Dis 2021;101:115425.
13. Doleshal M, Magotra AA, Choudhury B, Cannon BD, Labourier E, Szafranska AE. Evaluation and validation of total RNA extraction methods for microRNA expression analyses in formalin-fixed, paraffin-embedded tissues. J Mol Diagn 2008;10:203-11.
14. He R, Du Y, Gan L, Mohsin MA, He BX. Development of a SYBR Green-based real-time quantitative polymerase chain reaction assay to detect enzootic nasal tumor virus in goats. Can J Vet Res 2021;85:145-50.
15. Lee JS, Song CH, Kim CH, Kong SJ, Shon MH, et al. Profiles of IFN-gamma and its regulatory cytokines (IL-12, IL-18 and IL-10) in peripheral blood mononuclear cells from patients with multidrug-resistant tuberculosis. Clin Exp Immunol 2002;128:516-24.
16. Baj J, Karakuła-Juchnowicz H, Teresiński G, Buszewicz G, Ciesielka M, Sitarz R, et al. COVID-19: Specific and Non-Specific Clinical Manifestations and Symptoms: The Current State of Knowledge. J Clin Med 2020;9:1753.
17. Hirano T. IL-6 in inflammation, autoimmunity and cancer. Int Immunol 2021;33:127-48.
18. Sapna F, Deepa F, Sakshi F, Sonam F, Kiran F, Perkash RS, et al. Unveiling the Mysteries of Long COVID Syndrome: Exploring the Distinct Tissue and Organ Pathologies Linked to Prolonged COVID-19 Symptoms. Cureus 2023;15:e44588.
19. Kim YM, Shin EC. Type I and III interferon responses in

SARS-CoV-2 infection. Exp Mol Med 2021;53:750-760.
20. Shah VK, Firmal P, Alam A, Ganguly D, Chattopadhyay S. Overview of Immune Response During SARS-CoV-2 Infection: Lessons From the Past. Front Immunol 2020;11:1949.
21. Min YQ, Huang M, Sun X, Deng F, Wang H, Ning YJ. Immune evasion of SARS-CoV-2 from interferon antiviral system. Comput Struct Biotechnol J 2021;19:4217-25.
22. Yang Q, Lin F, Wang Y, Zeng M, Luo M. Long Noncoding RNAs as Emerging Regulators of COVID-19. Front Immunol 2021;12:700184.
23. Ouyang J, Hu J, Chen JL. lncRNAs regulate the innate immune response to viral infection. Wiley Interdiscip Rev RNA 2016;7:129-43.
24. Enguita FJ, Leitão AL, McDonald JT, Zaksas V, Das S, Galeano D, et al. The interplay between lncRNAs, RNA-binding proteins and viral genome during SARS-CoV-2 infection reveals strong connections with regulatory events involved in RNA metabolism and immune response. Theranostics 2022;12:3946-3962.
25. Lin Y, Sun Q, Zhang B, Zhao W, Shen C. The regulation of lncRNAs and miRNAs in SARS-CoV-2 infection. Front Cell Dev Biol 2023;11:1229393.
26. Ginn L, La Montagna M, Wu Q, Shi L. Diverse roles of long non-coding RNAs in viral diseases. Rev Med Virol 2021;31:e2198.
27. Heydari R, Tavassolifar MJ, Fayazzadeh S, Sadatpour O, Meyfour A. Long non-coding RNAs in biomarking COVID-19: a machine learning-based approach. Virol J 2024;21:134.
28. Huang K, Wang C, Vagts C, Raguveer V, Finn PW, Perkins DL. Long non-coding RNAs (lncRNAs) NEAT1 and MALAT1 are differentially expressed in severe COVID-19 patients: An integrated single cell analysis. PLoS One 2022;17:e0261242.
29. Martinez-Castillo M, M Elsayed A, López-Berestein G, Amero P, Rodríguez-Aguayo C. An Overview of the Immune Modulatory Properties of Long Non-Coding RNAs and Their Potential Use as Therapeutic Targets in Cancer. Noncoding RNA 2023;9:70.