Acta Pharm. **75** (2025) 299–307
https://doi.org/10.2478/acph-2025-0024

Short communication

SARS-CoV-2 structural proteins affect the expression of *IL-8* and *TNF-α* cytokines and *APOBEC* genes in human lung A549 and liver Huh-7 cells

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Accepted June 12, 2025
Published online June 13, 2025

ABSTRACT

The apolipoprotein B mRNA editing catalytic polypeptide-like (APOBEC) proteins belong to a family of cytidine deaminases responsible for DNA and RNA sequence editing, playing pivotal roles in a wide range of biological processes, including immune responses, antiviral properties, and genetic mutations. In this work, we investigated the effect of SARS-CoV-2 structural proteins – Envelope (E), Spike (S), Nucleocapsid (N), Membrane (M) and protein ORF6 – on the expression of cytokines Interleukin 8 (IL-8) and Tumor Necrosis Factor-alpha (TNF-α), and APOBEC3s proteins (APOBEC3B and APOBEC3F) genes in Huh-7 and A549 human cell lines. While there is plenty of scientific evidence about the effects of SARS-CoV-2 on the inflammatory cascade, the current literature regarding the impact of SARS-CoV-2 on APOBEC expression is scarce. Our findings reveal a complex relationship between SARS-CoV-2 structural proteins and the host immune response, as certain viral structural proteins (S, M, E) modulate cytokine expression, potentially contributing to the dysregulated immune responses seen in COVID-19 patients. Additionally, our research uncovered interactions between viral proteins and *APOBEC* genes. This study contributes to a better understanding of the host-virus interactions in the context of SARS-CoV-2 infection and provides some insights into potential therapeutic targets for mitigating the immunopathological consequences of the disease.

Keywords: APOBEC, SARS-CoV-2, nucleocapsid, spike protein, envelope protein, A3B, A3F, IL-8, TNF-α

INTRODUCTION

APOBEC proteins are cytidine deaminases capable of DNA and RNA editing. They form the apolipoprotein B mRNA editing complex polypeptide 1–lik (APOBEC) family of enzymes. APOBEC proteins were discovered in all vertebrates, where they represent an innate immune response against endogenous and exogenous retroelements (1). APOBEC3 (A3) proteins belong to the APOBEC family of enzymes. APOBEC3 proteins are antiviral

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proteins that inhibit replication of retroviruses (1), herpesviruses, small DNA viruses (2) and RNA viruses including coronaviruses (CoVs) (3, 4). Initially, A3s were discovered as antiviral factors in HIV-1 infection, but later they were identified as general antiviral factors that block replication of a variety of viruses and retrotransposons (5–7). The most studied antiviral A3 action is inhibition of HIV-1 replication (6). Several groups have shown that A3F and A3G restrict HIV-1 viral replication by incorporation into the virions *via* interactions with viral nucleocapsid (NC) and viral RNA (5, 8). After viral infection of the target cells and uncoating, A3s localise to viral RNA and cause excessive C to U mutations during reverse transcription (9). Intriguingly, the APOBEC mutation pattern (G to A mutations) was discovered in numerous DNA and RNA viruses and retrotransposons (10). Notably, we were the first to identify G to A editing in retroelements of non-mammalian vertebrates, which suggested that APOBEC proteins predate mammals (11). Several APOBEC proteins were shown to edit C to U in RNA molecules *in vitro* (10, 12). Traces of C to U editing in SARS-CoV-2 virus indicate that APOBECs cause mutations also in SARS-CoV-2 (3, 10, 13). Although most of the knowledge surrounding the APOBEC family of cytidine deaminases and viral restriction comes from the study of retroviruses, herpesvirus and small DNA viruses, recent evidence showed that APOBEC3 enzymes can also deaminate RNA viral genomes, such as the positive-sense RNA genome of the beta-coronavirus SARS-CoV-2 (10, 14, 15). Analyses of SARS-CoV-2 genomic sequence data report a prevalence of C-to-U directional transitions in the genome of variants emerging during the COVID-19 pandemic (16). Consequently, the locations of C-to-U transitions were loosely associated with the base and structure context of RNA deamination favoured by APOBEC3 proteins (16), which suggests that APOBEC-mediated RNA editing could be a potential antiviral mechanism against RNA viruses (3). Although APOBEC-mediated anti-coronaviral activity may be plausible in virological terms, additional studies are essential to clarify APOBEC editing of SARS coronaviruses as well as how CoVs may antagonise these deaminases (3, 17).

SARS-CoV-2 has a roughly spherical or ellipsoidal capsid whose outer surface is covered with surface spike proteins (S). The outer membrane of the virus also contains the membrane protein (M) and the envelope protein (E), whereas the lumen of the virion contains the ribonucleoprotein complexes (RNP) consisting of the nucleocapsid protein (N) and the viral RNA genome (18). The spike protein (S) of SARS-CoV-2 is important for viral internalisation, but it can also induce proinflammatory cytokines in human and mouse macrophages, including IL-6, IL-1β, TNFα, CXCL1, CXCL2, and CCL2, indicating its important role in promoting inflammation (19). The S1 subunit of the spike protein promotes the production of pro-inflammatory cytokines by activation of Toll-like receptor 4 (TLR4) signalling in macrophages (19), as well as activation of MAPK and NF-κB signaling pathways in human lung and intestinal epithelial cells, with the latter resulting in increased production of IL-1β, IL-6, and IL-8, which are central to the cytokine storm observed in severe COVID-19 cases (20). Structural proteins of SARS-CoV-2 can cross the blood-brain barrier and act as pathogen-associated molecular patterns (PAMPs), triggering neuroinflammatory responses *via* Toll-like receptors (TLRs). This mechanism may contribute to the neurological and neuropsychiatric symptoms observed in COVID-19 patients (21).

Here, we investigated the impact of the SARS-CoV-2 structural proteins Envelope (E), Spike (S), Nucleocapsid (N), Membrane (M) and the protein ORF6 on the expression of inflammatory cytokines and APOBEC proteins in two different cell models that are per-

missive for SARS-CoV-2, human lung epithelial cells A549 and hepatocyte-derived Huh-7 cell line. A549 cells were chosen because infection with SARS-CoV-2 is associated with lower respiratory tract inflammation, while Huh-7 is particularly interesting due to its liver origin. The incidence of liver damage in COVID-19 patients is up to 53 %, and the liver has been identified as one of the main target organs for SARS-CoV-2 (22). In our study, we observed that overexpression of spike and envelope proteins, in particular, resulted in elevated levels of *IL-8*, *TNF-α* as well as *A3F* and *A3B* in the Huh-7 liver cell line, while the A549 lung epithelial cell line was much less affected.

EXPERIMENTAL

Cell culturing

Human lung cancer A549 and hepatocyte-derived cellular carcinoma cell line Huh-7 were cultured as described previously (23). Briefly, cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10 % FBS, 1 % glutamine, 1 % antimycotic/antibiotic (Gibco, Thermo Fisher Scientific, USA) at 37 °C, 5 % CO_2 and subcultured at 80 % confluency.

Cell transfections

One day before transfection, cells were seeded at a density of 1×10^5 *per* well in 12-well plates without antibiotics. The next day, 500 ng of respective plasmid (pLVX-EF1alpha-SARS--CoV-2-M-2xStrep-IRES-Puro, pLVX-EF1alpha-eGFP-2xStrep-IRES-Puro, pLVX-EF1alpha--SARS-CoV-2-S-2xStrep-IRES-Puro, pLVX-EF1alpha-SARS-CoV-2-E-2xStrep-IRES-Puro, pLVX--EF1alpha-SARS-CoV-2-N-2xStrep-IRES-Puro, pLVX-EF1alpha- SARS-CoV-2-orf6-2xStrep--IRES-Puro (Addgene™) was transfected using 1.5 μL PolyJet™ In Vitro DNA Transfection Reagent (SignaGen Laboratories, USA).

RNA isolation and quantitative PCR

Expression of target genes was analysed in RNA samples obtained from A549 or Huh-7 cells transfected with a respective plasmid. RNA isolation was performed 48 h after transfection using the PeqGold TOTAL RNA isolation kit (PeqLab, Germany) and reverse transcribed using High-Capacity cDNA Reverse Transcription kits (Thermo Fisher Scientific). The expression of target genes and housekeeping gene actin beta was measured by quantitative PCR (qPCR) using primers from Table I. For qPCR, 5× Hot FirePol EvaGreen qPCR Mix Plus (Solis, BioDyne, Estonia) was used, following the manufacturer's recommendations, on a LightCycler 480 (Roche Diagnostics, Switzerland). Cycling conditions were set at 95 °C for 10 min, followed by 45 cycles at 95 °C for 10 s and 62 °C for 35 s, followed by a melting curve analysis. All the samples were diluted to a final concentration of 2.5 ng μL^{-1}. All of the samples were quantified in triplicate. Gene expression was calculated using the standard curve method. Target gene expression was normalised with an actin beta (ACTB) housekeeping gene. The gene expression data are represented as normalised values to gene expression level in a control sample that was transfected with a plasmid backbone containing only the GFP coding region. This normalisation allowed minimisation of variations between different biological repeats.

Statistical analysis

Statistical analyses were performed using Prism 7.0 (GraphPad Software, USA). All qPCR experiments were performed in triplicate. Expression of genes of interest was corrected with the housekeeping gene actin-ß using the standard curve method. Data are presented as means ± SEM. Statistical significance was determined using one-way ANOVA, followed by Tukey's post-hoc tests. *P* values lower than 0.05 were considered statistically significant.

Table I. List of primers

Gene (human)	Forward (F) (5′-3′)	Reverse (R) (5′-3′)
ACTB	CTTCGCGGGCGACGAT	AATCCTTCTGACCCATGCCC
IL-8	GAGAGTGATTGAGAGTGGACCAC	CACAACCCTCTGCACCCAGTTT
TNF-α	TGGCCCAGGCAGTCAGATCA	GGCGGTTCAGCCACTGGAGC
A3B	GACCCTTTGGTCCTTCGAC	GCACAGCCCCAGGAGAAG
A3F	CCGTTTGGACGCAAAGAT	CCAGGTGATCTGGAAACACTT

RESULTS AND DISCUSSION

SARS-CoV-2 ORF6, M, S and E differentially modulate cytokine expression in A549 and Huh-7 cells

Clinical features of COVID-19 patients include elevated cytokine levels, and one of the possible explanations is the activation of the NF-κB signalling pathway triggered by SARS--CoV-2 infection. To investigate the effect of SARS-Cov-2 structural proteins on the level of two inflammatory cytokines, *IL-8* and *TNF-α*, A549 lung or Huh-7 liver cells were transfected with the respective structural protein (S, M, N, E and ORF6) or a GFP control plasmid and 48 hours after transfection the level of the cytokines was measured by Q-PCR. To exclude inter-experimental deviations, gene expression was always normalised to a control GFP plasmid. In Huh-7 cells, *IL-8* was generally upregulated in the presence of all tested structural proteins. Protein M led to a 1.38-fold ($p = 0.003$), protein S to a 2.81-fold ($p = 2.88 \times 10^{-8}$) and protein E to a 2.0-fold ($p = 0.004$) increase in the expression level of *IL-8* compared to a control GFP plasmid. In Huh-7 cells, ORF6 had no significant effect on the expression of *IL-8*, whereas in A549 cells, overexpression of the structural proteins did not modulate the expression of *IL-8*, with the exception of ORF6. The expression of ORF6 caused a 0.44-fold change ($p = 0.0008$) compared to a control GFP protein, indicating that ORF6 decreases the proinflammatory cytokine IL-8 in A549 cells. Indeed, ORF6 was previously shown to be the strongest antagonist of interferon expression and could suppress interferon signalling (24). Protein N did not affect the expression of IL-8 in any of the tested cell lines.

In Huh-7 cells, overexpression of structural proteins also led to increased expression of *TNF-α*. Protein M caused a 1.45-fold, protein S a 5.35-fold ($p = 0.049$) and protein E a 2.61-fold increase in *TNF-α* expression compared to cells transfected with a GFP protein.

Notably, only protein S caused significant upregulation of *TNF-α i*n Huh-7 cells (Fig. 1d). Similar to *IL-8*, the A549 cell line showed no significant changes in the expression of *TNF-α* after transfection with SARS-Cov-2 structural proteins. In contrast, ORF6 had no inhibitory effect on the expression of *TNF-α* in any of the cell lines tested.

According to a previous study by Chaolin Huang and colleagues (25), the clinical and laboratory features of COVID-19 patients showed that IL-8 is more elevated in severe cases than in non-severe cases of the viral infection. Clinical and immunological characterisation of the virus, using cytokine and chemokine measurement, showed that TNF-α levels were also markedly elevated in severe cases (25, 26). One possible mechanism is the activation of the NF-κB signalling pathway by the SARS-CoV-2 S protein, which was observed in mouse and human macrophages (19). Here we show that the structural protein S, but also E and M, can lead to increased cytokine levels in liver cells, which are also a host for viral replication, confirming and extending previous studies.

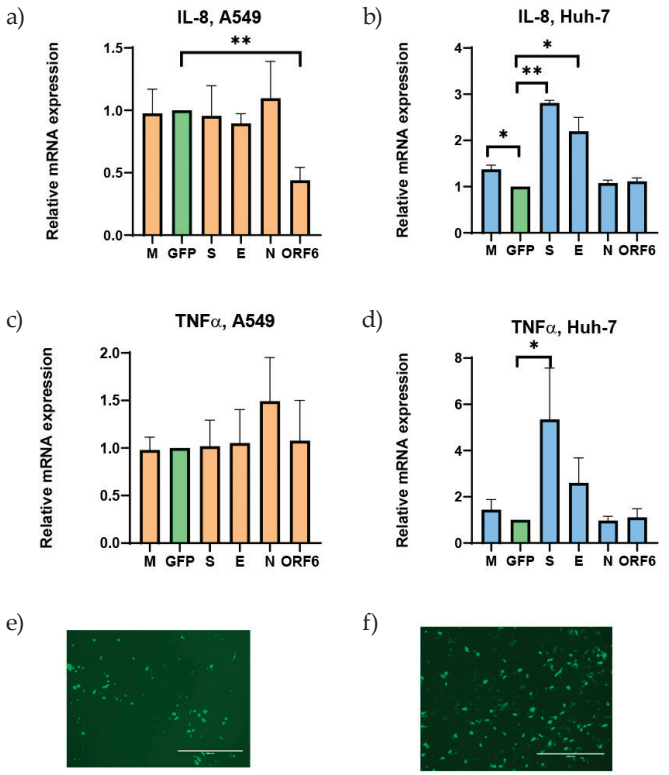

Fig. 1. Overexpression of SARS-CoV-2 S, E, and M proteins upregulates IL-8 and TNF-α expression. Huh-7 and A459 cells were transfected with the respective structural protein, and the level of mRNA was measured 48 h after transfection. *IL-8* expression: a) in A549 cells and b) in Huh-7 cells. *TNF-α* expression: c) in A549 and d) in Huh-7 cells. Representative images of the control GFP transfection (plasmid pLVX-EF1alpha-SARS-CoV-2-GFP-2xStrep-IRES-Puro) of: e) A549 cells and f) Huh-7 cells. All data are presented as mean relative gene expressions after normalisation with *β-actin* expression. The results are expressed as the mean ± SEM. * $p < 0.05$, ** $p < 0.01$. Scale bar 400 μm.

Structural proteins and their effect on APOBEC expression

Analyses of SARS-CoV-2 genomic sequence data revealed a prevalence of C-to-U directional transitions in the genome of variants emerging during the COVID-19 pandemic. Consequently, C-to-U transitions were associated with the base and structure context of RNA deamination favoured by APOBEC3 proteins (10, 15), which suggests that APOBEC-mediated RNA editing could be a potential antiviral mechanism against SARS--CoV-2 virus (3).

Here, we examined how the expression level of APOBECs changes upon expression of SARS-CoV-2 structural proteins. The overexpression of APOBECs is a prerequisite for their mutational activity. To examine the effect of structural proteins on the expression level of APOBECs, Huh-7 and A549 cells were transfected with structural proteins and 48 h after transfection, the level of APOBEC expression was evaluated by Q-PCR. In Huh-7 cells, overexpression of SARS-CoV-2 structural proteins M, S and E caused upregulation of *A3B*, 1.35-fold (p = 0.0005), 2.18-fold (p = 0.0001), 2.11-fold (p = 0.003), respectively. Similarly, the overexpression of structural proteins caused an increase in the *A3F* levels. Relative to cells transfected with GFP, *A3F* levels were 1.53-fold higher in cells transfected with protein M, 1.57-fold higher (p = 0,018) in cells transfected with protein S, and 1.52-, 1.55- (p = 0.0001) and 1.5-fold (p = 0.0008) higher in cells transfected with proteins E, N and ORF6, respectively (Fig. 2). In A549 cells, envelope protein (E) expression caused lower

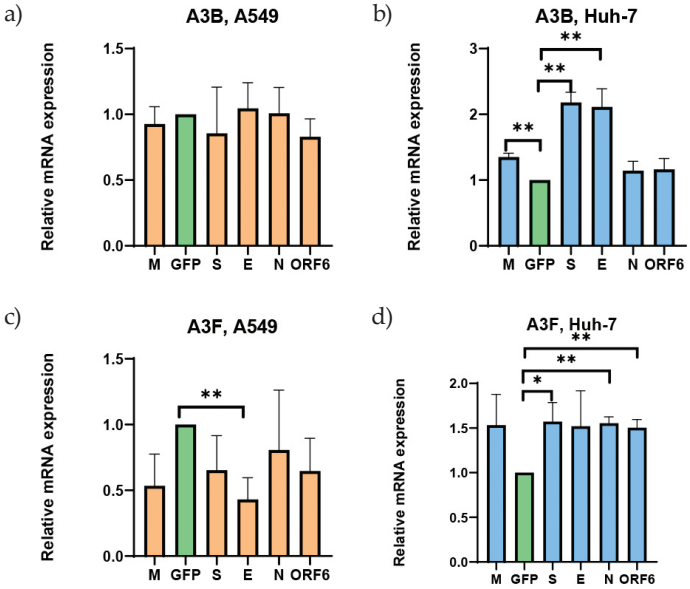

Fig. 2. Overexpression of SARS-CoV-2 S, E, and M proteins upregulates A3B expression in Huh-7 cells. Huh-7 and A459 cells were transfected with the respective structural protein, and the level of mRNA was measured 48 h after transfection. *A3B* expression: a) in A549 cells and b) in Huh-7 cells. *A3F* expression: c) in A549 cells and d) in Huh-7 cells. All data are presented as mean relative gene expressions after normalisation with β-actin expression. The results are expressed as the mean ± SEM. * $p < 0.05$, ** $p < 0.01$.

expression of *A3F* (0.43-fold (p = 0.007)), however no significant differences in *A3B* level were observed (Fig. 2).

Altogether, our results suggest that SARS-CoV-2 structural proteins, in particular S, M and E, cause an upregulation of *A3F* and *A3B* expression in liver Huh-7 cells. Similar to cytokine expression, *A3* proteins were much less affected in A459 cells, suggesting that different host cells respond differently to the presence of SARS-CoV-2 structural proteins.

The increase in APOBEC expression correlates with the increase in cytokine level, suggesting that the infection with SARS-CoV-2 could trigger the elevated levels of APOBECs, as APOBECs are interferon- and cytokine-inducible proteins.

In addition, recent studies suggest that expression of APOBEC family genes is often increased during viral infection. Based on that, we expected that expression of SARS--CoV-2 structural proteins would increase the expression level of APOBEC genes also in lung and liver cell lines (1, 27). Human APOBEC3's cytidine deaminases might play a critical role in the induction of mutations in the SARS-CoV-2 genome. The A3 family members, especially A3A and A3B, are intrinsic mutators of chromosomal DNA, and A3G represents a potent inhibitor of retrovirus replication (12, 28–31). However, Yoshihiro Nakata and colleagues (28) reported recently that A3B did not have a relevant effect on the mutation rate in the SARS-CoV-2 genome, which means that the cytidine deaminase expression doesn't necessarily correlate with its mutational activity.

CONCLUSIONS

Our study shows an increased expression of cytokines and APOBEC3s after exposure to the SARS-CoV-2 structural proteins. This effect was predominantly observed in hepatic Huh-7 host cells, whereas A549 lung epithelial cells exhibited a comparatively weaker response. Our results show that although SARS-CoV-2 can infect multiple organs and exhibits broad cell tropism (32), the consequences of infection are highly cell-dependent.

Acknowledgements. – The authors acknowledge the financial support from the Slovenian Research Agency (project No. J3-2518 and programs No. P1-0034 and P4-0127).

Conflicts of interest. – The authors declare no conflict of interest.

Authors contributions. – Conceptualization, N.L.; methodology, N.L., Š.T., and M.C.; analysis, Š.T. and N.L.; investigation, Š.T, M.C., M.B.M., and N.L.; writing, original draft preparation, M.C., M.B.M., and N.L.; writing, review and editing, N.L. and M.B.M. All authors have read and agreed to the published version of the manuscript.

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