

Research Article

The Antiviral Role of PML-NBs Against SARS-COV-2 (Coronavirus) A Study Conducted on Patients in Basrah Governorate

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Abstract

Background: Viral infection, including Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) infection, induces an immune response to restrict viral replication, which causes a lesion to the targeted body's tissue cells. **Objective:** To measure the expression levels of the PML and Daxx genes, which are important constituents of the PML nuclear bodies, in patients who have been infected by the SARS-CoV-2 virus in comparison to that of the healthy subjects. **Methodology:** Blood samples from 104 subjects who had tested positive for SARS-CoV-2 infection and 68 uninfected controls were obtained from laboratories in Basra, Iraq. The diagnosis of infection was made using qPCR followed by RNA isolation to check the levels of PML and Daxx genes. **Results:** The gene expression of the PML protein was low in infected samples compared to the control by 9.5 times, while the gene expression of the Daxx protein showed the opposite result, as its expression was increased in infected samples compared to the control by 3.7 folds. The findings indicated a 9.5-fold reduction in PML, suggesting that the viral action is targeting the anti-proliferative function of PML. Daxx, on the other hand, showed an increase in its expression by 3.7-fold. **Conclusion:** This indicates that SARS-CoV-2 infection has a varying effect on the expression of genes involved in the immune response performed by PML-NBs in hematopoietic cells of infected individuals, an invitation for further studies to understand the mechanism in which the virus takes control of the host's intrinsic immunity.

1. Introduction

Causative agent of Covid-19 is the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), at the end of 2019, most of the world's population was infected with the novel coronavirus (SARS-COV-2), since the beginning of the pandemic, SARS-COV-2 has infected more than 500 million people, and at least 6 million have lost their lives worldwide [1, 2]. This constituted a global pandemic that put the entire world in emergency situation, prompting international health institutions and global medical organizations to study the conditions that led to this pandemic, especially the conditions surrounding human cells and the genes associated with and affected by this virus, and how to prevent it and treat it in a way that limits the worsening status of the infected patients.

It also highlighted in detail the role of the immune system and how to confront the virus and identify the target that limits the virus's ability to worsen the infection. (SARS-COV-2) a virus belongs to the order *Nidovirales*, family *Coronaviridae*, genus *Betacoronavirus* [3–6]. It is classified into four genera: Alpha (α), Beta (β), Gama (γ) and Delta (δ) [5]. Infection in mammals is typically associated with β -COVs,

and SARS-CoV-2 belonging to the β -COVs [7, 8]. It is a spherical virus with a membrane containing spike proteins [2, 9, 10]. Its genome is represented by the virus, which is single-stranded positive RNA (SSRNA+), was sequenced with a nucleotide unit (30 kb). The body mounts an effective immune response that works to limit the replication of invading viral and their pathogenicity upon viral infection, through the combined activities of innate, and acquired immunity [11]. As is scientifically known, intrinsic immunity has distinctive features, namely that there are cellular restriction factors mediated by cellular proteins that are constantly expressed to limit the aggravation and spread of many viral pathogens as a first line of immune defence against infection [11–14]. The Promyelocytic Leukaemia (PML) protein, or TRIM (The Tripartite Motif), is a protein belong to a large family of over 70 human members. This family, known as Promyelocytic Leukaemia-Nuclear Bodies (PML-NBs), includes several small, modified ubiquitin (SUMOylate) cellular proteins, including PML, Speckled Protein of 100 Kilo Dalton (SP100, Alpha-Thalassemia Mental Retardation X- Linked syndrome (ATRX) and Dead-Domain associated Death (Daxx). SUMO plays a crucial role in modifying these proteins, which are found in varying structures within the cell nucleus [15].

PML-NBs perform a wide range of cellular activities, such as stress response, protein degradation, cell aging, viral infection, DNA damage, and interferon response [16–18]. SUMO-lyated proteins are also present [19], these dynamic structures move with permanent chromatin (SP100, Daxx) and the surrounding chromatin within the nucleus, as well as with several transient proteins such as p53, cAMP Response Element Binding (CREB) binding protein (CBP), and Homeodomain-Interacting Protein kinase 2 (HIPK2), depending on different cellular conditions such as cell transformation, stress, viral infection, and interferon treatment [15]. Post-translational modification by SUMO family proteins is of great importance in regulating many cellular pathways and proteins. The proteins that make up PML-NBs mediate aspects of innate immunity to limit viruses, as these proteins suppress this replication through mechanisms dependent on SUMO signalling [11]. The internal activation of cellular genes that defend against viruses, such as cytokines and PML-NBs, which are regulated by interferon treatment, is mediated by nuclear PMLs. Some viruses can produce anti-virus proteins, which have an individual effect on PML-NBs or those that affect the overall cellular structure [17–20]. Although PML-NBs have many functions in diverse cellular pathways, there are numerous indications of their association with the interferon system and their contribution to defence against viruses, as well as being preferred targets for viral infection [17]. This study aimed to measure the expression levels of the PML and Daxx genes, which are important constituents of the PML nuclear bodies, in patients who have been infected by the SARS-CoV-2 virus in comparison to that of the healthy subjects.

2. Materials and Methods

2.1. Samples collection

Total of (104) blood samples gathered from patients and all of them confirmed for infection with SARS-COV-2, in parallel (68) samples for a healthy persons treated as a control, all aged between 15-70 years, and all of them were diagnosed via qPCR technique, a random collection of the total (172) samples have been followed from a different area from Basra Governorate in Iraq Country through a two month period in November and December months of 2021. at -20°C , the collected blood samples were kept in EDTA plain, even molecular use for the purpose of genetic evaluation analysis. Those samples have been collected for the purpose of the evaluation of gene expressions for the related genes (*PML*, *Daxx* and *GAPDH*) as per sequences mentioned in Table 1. The laboratory works have been carried out in central lab for Medicine college in Basra University.

Table 1: Primers were used to evaluate gene expression

Primers	Sequences	References
PML	Forward	ACTGCCGAGGATGTTCCAAG
	Reverse	TCCTGTCGCTGCTGGATCTC
Daxx	Forward	TCTACAACCTTTGGCTGTCACCTC
	Reverse	GTCTCTTCTGTCTCTCGCCCT
GAPDH	Forward	GGTCGGAGTCAACGGATT
	Reverse	CCAGCATCGCCCCACTTG

2.2. Molecular Examination

2.2.1. RNA extraction

The extracted RNA from blood samples has been taken to analyze the *PML* and *Daxx* gene expression in the total (172) samples using Solarbio Cat# R1200 Kit from BEIJING SOLARBIO SCIENCE & TECHNOLOGY CO., LTD.

2.2.2. Reverse transcription to synthesize complementary DNA

By using Solarbio Universal RT-PCR Kit (M-MLV, free Taq Polymerase) Cat # RP1105 from BEIJING SOLARBIO SCIENCE & TECHNOLOGY CO., LTD., the cDNA obtained from the extracted RNA samples, under the mentioned conditions in the enclosed leaflet the reaction was carried out, and the RNA was mixed with the reaction components.

2.2.3. Gene expression assay (Relative quantification)

Reaction of qPCR was prepared using (Intron) Kit (CA: K-6210) and according to the enclosed instruction. The reaction mix was prepared by mixing 10 μl of SYBR Green and adding 3 μl of cDNA template, 100 Pmol of each forward and reverse primers of *PML*, *Daxx* and Glyceraldehyde 3- Phosphate Dehydrogenase (*GAPDH*), and 5 μl of Free (DEPEC-D. W) to make a final volume of 20 μl [21]. The q PCR conditions were set as follow: the reaction was submitted to a first step of denaturation at 94°C for 5 min followed by 45 cycles of

15 seconds of denaturation at 95°C, annealing step was set at 58°C for 30 sec, an extension step at 72°C for 45 sec with a final extension conducted at 72°C for 5 min [22].

2.3. Statistical analysis

For all samples the standard deviation analysis has been applied using Microsoft excel software for both *PML* and *Daxx* charts with three replicates, the results were normalized to the level detected in control samples. *GAPDH* considered as an internal control. Relative expression assay was achieved using SYBR green as intercalating dye. Obtained data were analyzed by $\Delta\Delta$ CTs, and the analysis considered for assessment and the average value of *GAPDH* for each sample used as a reference for calculation, the calculation considered and applied as per Livak and Schmittgen [23].

3. Results

3.1. qPCR examination

To evaluate the relative expression of *PML* and *Daxx* genes associated with SARS-COV-2 infection. The (172) blood samples underwent to qPCR examination. The synthesized cDNA from the extracted RNAs was used as a template and mixed with *PML* and *Daxx* specific primers, and to measure its gene expression the qPCR relative expression assay (SYBR green) were used.

3.1.1. PML relative expression and response in SARS-COV-2 infected samples

The finding shows that more than 9.5-folds detected for *PML* as a relative expression for negative patients with SARS-COV-2 compared with the positive infected samples Figure 1. The expression of *PML* gene was assessed in both positive and negative samples.

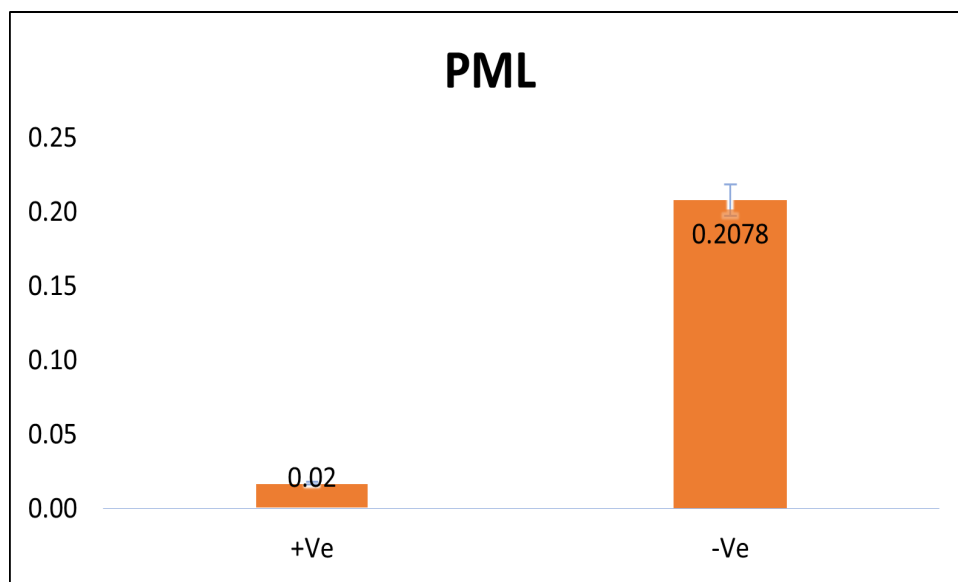


Figure 1: PML gene expression. PML- mRNA was detected by q PCR

3.1.2. Role of *Daxx* in an intrinsic immune response

During infection the evaluation of *Daxx* gene expression showed 3.7 folds more in the positive infected samples with SARS-COV-2 compared with the negative infected samples Figure 2.

4. Discussion

Studies are still ongoing to find out the precise mechanisms that regulate the immune aspects of the body, as we need more clarification to understand how the immune genes deal with viruses and pathogens in general, with the most precise details of the cellular protein-genetic mechanisms, and the relationship between the viral genome and PML-NBs is usually evident during infection, and research findings show that this relationship either improves or deteriorates, by assessing the increase or decrease in gene expression of PML-NBs. Our study showed that gene expression of the PML protein decreased in infected individuals compared to the control group by 9.5-folds less in positive infected samples, that may be supporting the idea that the virus counteracts the expression of this interferon regulatory analog to establish successful and organized replication foci.

Our study demonstrated that the gene expression level of the PML protein was low in infected samples compared to the control group, this can be attributed, in agreement with the study by Scherer and Stammger, to the fact that some viruses possess the ability to produce antiviral proteins that have a specific effect on PML -NBs, or those that affect the overall cellular structure [20], which may impair the antiviral efficacy of PML-NBs, this aligns with Everett and Chelbi-Alix's study, in which they reported that some viral proteins accumulate in PML nuclear bodies, causing their inactivation through various mechanisms [17]. The inconsistent gene expression of PML and PML-II proteins

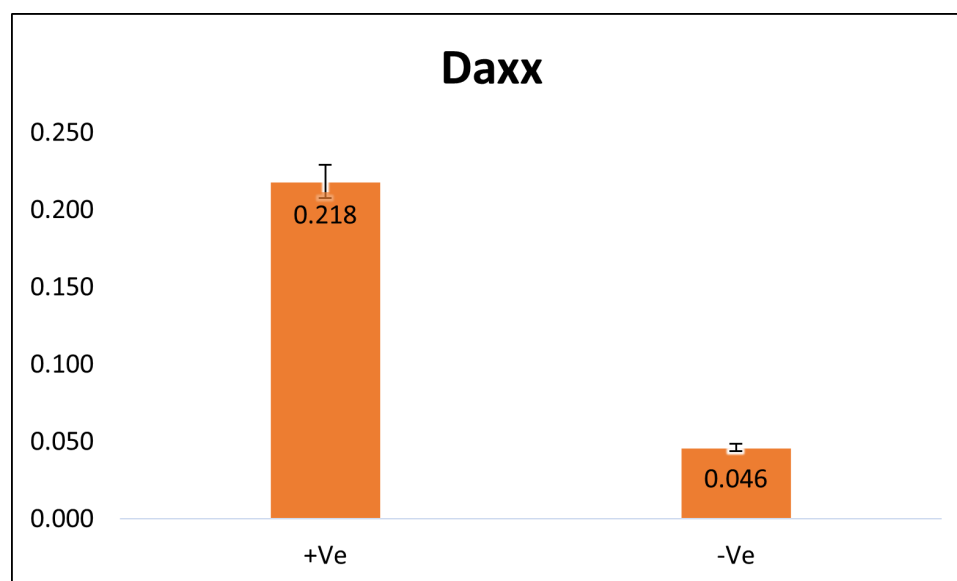


Figure 2: *Daxx* gene expression technical replicates

can be explained by the virus altering the splicing pattern of PML pre-mRNA, as seen in herpes simplex virus type- 1 (HSV-1) infection, which removes certain PML exons, such as exons 5 and 6. This leads to the inhibition of the antiviral function of the latter cytoplasmic transcript [24], this may provide a plausible explanation for the inconsistent gene expression of immune proteins across different types of viral infections. Our results are consistent with those of Singh et al., who reported a 68% reduction in PML expression in HPV-infected women with cervical cancer and precancerous changes [25]. Despite the numerous activities that PML-NBs perform in a wide range of cellular pathways—for example, the role of the PML protein in the mechanism of action of antiviral interferon—there is accumulating evidence that these nuclear bodies are preferred targets for viral infection, this may explain the low expression of the PML protein in this study, as it is likely a target for SARS-CoV-2, indicating that this virus has developed mechanisms to counteract host defenses.

Daxx protein is a support protein found in PML-NBs and is a restrictor of viral DNA, in addition to retroviruses Tang et al., Dutrieux et al., Porter et al., and Maillet et al., in this study, we found evidence of increased gene expression of the Daxx protein, in individuals infected with SARS-CoV-2 [26–29]. Its expression increased by 3.7-folds more in positive infected samples, which is consistent with what Kain et al., reported which was performed using CRISPR/Cas9 technology on human lung epithelial cells from patients infected with SARS-CoV-2 [2], that the Daxx protein is a potent inhibitor of viral replication, this virus, as the study indicated, appears to have developed a mechanism to at least partially evade the restriction imposed by this nuclear bodies. As previously mentioned, Daxx is a dynamic protein found in PML nuclear bodies, constantly binding to and dissociating, this rapid movement is essential for combating viruses such as Human Cytomegalovirus (HCMV), as it can sense the viral genome in conjunction with SP100 [30].

Both Daxx and PML induce an antiviral response in an interferon-stimulated environment, both HCMV and adenovirus employ the same strategy of disabling PML -NBs to evade the Daxx and PML-mediated interferon response [31]. Daxx plays a crucial role in the absence of an interferon response by protecting cells from viral invasion or limiting viral replication [32]. Regarding Daxx protein expression, our results are consistent with a AL-Asadi study, we conducted in HPV-infected women with cervical cancer and advanced degrees of cervical dysplasia, where the expression of this protein increased 9 -folds in virus-infected samples compared to virus-negative samples [33]. We need more studies to determine the precise targets that the virus selects to restrict the cellular defenses that limit the proliferation of those pathogens or disrupt their immune signals, thereby hindering the defensive gene expression of the host cells.

In the current study, expression of PML in SARS-CoV-2 positive blood samples was 9.5-fold lower compared to control samples from healthy donors. The reduced expression may point to downregulation of some of the intrinsic antiviral factors. PML/TRIM19 serves as organizing factor for PML nuclear bodies and is able to take part in antiviral response through recruiting proteins, which are responsible for interferon signaling and transcriptional processes. There is experimental evidence, which suggests that PML isoforms have restrictive effect on viral replication and increase IFN- β production via stabilization of IRF3. Thus, PML takes part in intrinsic and innate immunity [34]. However, this result should be interpreted carefully because whole blood RNA reflects heterogeneous population of leukocytes, and the quantitative PCR method used in the current study was able to measure transcripts levels and not proteins' level or isoforms profile. Thus, it could reflect virus immune evasion, changes in the population of leukocytes, or post-transcriptional regulation. Nevertheless, the obtained result is biologically feasible as there are reports demonstrating that RNA viruses are able to reorganize or antagonize components of PML-NB, thus reducing overall restriction .

On the contrary, DAXX expression increased 3.7-fold in SARS-CoV-2 infected blood samples. This result is important since DAXX has been characterized as potent SARS-CoV-2 restriction factor: low levels of DAXX reduce virus replication efficiency, while high levels significantly increase virus inhibition, particularly at the early post-entry step [35]. This increase might reflect host defense strategy to inhibit SARS-CoV-2 infection. However, increased mRNA expression level does not imply increased functional protein level. SARS-CoV-2 has been reported to relocate DAXX to replication sites in the cytoplasm and induce proteasome-mediated degradation of DAXX through papain-like protease of the virus [2]. Thus, the opposite expression levels of PML and DAXX suggest that SARS-CoV-2 is able to differentially regulate expression of PML-NB components: PML transcription is suppressed, and DAXX transcription is induced, yet neutralized post-translationally.

The size and direction of the changes do not indicate that both PML and DAXX play an identical role in antiviral protection. The decrease in the number of PML transcripts by 9.5 times can be more effective than the increase in the number of DAXX transcripts by 3.7

times since PML provides the organization of nuclear-body platform responsible for recruitment of many antiviral molecules. Importantly, PML protein is encoded by several alternatively spliced isoforms that contain unique C-terminal region and exhibit partly different antiviral activity. Therefore, measurement of the total level of PML mRNA is unable to reveal an isoform-specific redistribution where antiviral isoforms are decreased and other isoforms persist [36]. Such a case is important in the current study since only one primer pair was used and there was no determination of which PML isoforms are changed. Thus, the lower total level of PML is consistent with the association between SARS-CoV-2 infection and decreased ability of the host cell to defend itself via PML nuclear body. Nevertheless, the change in the total level of PML transcripts cannot prove that all functions of the body are disturbed.

An increase in DAXX transcripts can reflect a compensatory response rather than successful antiviral control. It is well-known that DAXX is a scaffolding protein whose ability to defend against viruses depends on the location of the protein in the cell, its interaction with other proteins, and the integrity of the structure. Therefore, induction of transcription cannot be enough in case when the virus removes the protein from its normal nuclear location. In human cells, SARS-CoV-2 infection was demonstrated to cause relocalization of DAXX to the cytoplasm and proteasomal degradation of the protein via PLpro, while DAXX protein restrains an early step of the viral life cycle [37]. In this context, the present 3.7-fold increase in the number of DAXX mRNA transcripts can co-exist with a decrease in the functionally active DAXX protein and represent a biologically meaningful explanation for both antiviral activity and virus replication. The opposite trends observed for PML and DAXX can reflect different regulatory steps since PML protein can be transcriptionally downregulated, while DAXX can be transcriptionally upregulated but then destroyed post-translationally. However, since peripheral blood rather than a defined respiratory cell population was studied, such results should be considered systemic molecular associations and not the measurements of events occurring within infected airway cells.

5. Conclusion

The results of our study enrich our knowledge with the conclusion that SARS-COV-2 infection exhibited an increase in the gene expression of the Daxx protein, while the PML protein showed a decrease in its gene expression in those infected with the virus compared to the control, indicating that this virus stimulates different signaling pathways within infected cells. This, in turn, stimulates an understanding of the virus's behavior and its mechanisms for dealing with the host's cellular defenses. Therefore, this approach helps in choosing the optimal treatment to combat viral infections, if we can accurately explain the behavior of these viruses through the gene expression of host cells towards these viruses.

Article Information

Ethical approval: Ethical approval was obtained from Basrah University/ Medical college/ Central Lab, and Basra education Directorate (Number 30619 on July 6th, 2021) before starting the study.

Informed Consent: Written informed consent was obtained from all participants before their inclusion in the study.

Data Availability: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest: The author declare that they have no conflict of interest.

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AI Use Disclosure: No generative artificial intelligence tools were used in the preparation of this manuscript.

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