Editorial

Molecular insight: SERPINB3 and AR sensitivity might reduce the risk of COVID-19 infection and complications in prostate cancer patients receiving androgen-deprivation therapy

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INTRODUCTION

SARS-CoV-2 (COVID-19) entry into host cells is facilitated by the transmembrane protease TMPRSS2[1], which is expressed in both the lungs and prostate tissue[2]. Pre-clinical data suggest that TMPRSS2 expression can be modulated by the androgen receptor (AR)[3] and that androgen deprivation therapy (ADT) might protect patients from SARS-CoV-2 infection and reduces disease severity[4]. In a longitudinal study, Montopoli *et al*.[5], demonstrated that prostate cancer patients receiving ADT were likely to have four times less SARS-CoV-2 infection rates and disease severity compared with non-ADT patients. This study was supported by Patel *et al*.[4], where 58 prostate cancer patients infected with SARS-CoV-2 exhibited low disease severity, and concluded that ADT might limit severity of COVID-19 infection. However a study from Kwon *et al.*[6], was in disagreement with above findings and revealed no association between ADT treatment and its protection against COVID-19 infection. Subsequently, Klein *et al.*[7] studying a cohort of prostate cancer patients who received ADT, the percentage rate of positive and negative COVID-19 cases were almost same, 5.6 and 5.8% (OR 0.93; P = 0.8), highlighting that ADT treatment does not appear to be protective against COVID-19 infection.

MOLECULAR INSIGHT

Studies referenced above are solely based on clinical observations on prostate cancer patients with or without COVID-19 infection and their association with ADT, however the molecular insight(s) are unknown. To address the above, we performed a meta-analysis utilizing a database comprising of human prostate cancer patients who received ADT (GSE150368)[8], and compared with patients who did not receive ADT (GSE69223)[9]. Our rationale was based on AR sensitivity and the non-genomic function of AR. It is known that AR regulates the transcription of the transmembrane protease, serine 2 (TMPRSS2) required for SARS-CoV-2 infectivity [10]. Overlaying of the prostate cancer ADT database with COVID-19 disease showed significant interaction (p= 1.29E-26), while patients with no ADT did not exhibit any interaction.

Interestingly, the analysis identified genes associated with COVID-19 *viz*. Serpin Peptidase Inhibitor, Clade B (Ovalbumin), and Member 3 (SERPINB3) showing increase expression (5.8 fold, p value 7.50E-11) after ADT treatment and a high degree of interaction with COVID-19.

In humans, SERPINB3 is expressed in high level in the nasopharynx, bronchus membrane along with other cellular subsets and across tissues[11]. Functionally, SERPINB3 activates NF-κB and the expression of other pro-inflammatory cytokines[12], predominantly IL-6[13], which leads to an epithelial-mesenchymal transition (EMT)-like phenotypic changes that might respond as a first line of defense against COVID-19 infection. The SERPIN gene encodes plasminogen activator inhibitor (PAI), and reports suggest that PAI-2 expression markedly reduces the surface expression of the virus receptor molecules *viz*. CD55 (DAF), constitutive androstane receptor (CAR), and intercellular adhesion molecule 1 (ICAM-1) and thus inhibits the binding of virus to the cellular membrane. Lastly, we predict that SERPINB3 has ability to bind with TMPRSS2 at serine and threonine sites that may intervene or block the COVID-19 entry into the cell and inhibits its infectivity.

CONCLUSION

Elevated expression of SERPINB3 favors a role for initiation of the acute inflammatory response. SERPINEB3 might serve as promising prophylactic to inhibit the progression and severity of COVID-19, by hindering the entry of SARS-CoV-2, in part, *via* TMPRSS2 and inhibiting consequent inflammation, coagulopathies, and multiple organ failure.

STATISTICAL ANALYSIS

The GSE database was analyzed using GEO2R and IPA and the absolute value of log2 fold change greater than 1 was used, and an adjust p-value less than 0.05 were considered as differentially expressed. Differentially expressed genes (DEGs) were overlaid with the global molecular network in the Ingenuity pathway knowledge base

(IPKB). IPA was performed to identify diseases and functions, and gene networks that are significant to RNA-Sequencing outcomes and to categorize DEGs in specific diseases and functions such as COVID-19.

DECLARATIONS

Authors' contributions

Conceptualization: Verma S, Gupta S

Methodology: Verma S, Gupta S

Software: Verma S

Validation: Verma S, Gupta S

Formal analysis: Verma S

Investigation: Verma S

Resources: Gupta S

Data curation: Verma S;

Writing - original draft preparation: Verma S, Gupta S

Writing - review and editing: Verma S, Gupta S

Visualization: Verma S, Gupta S

Supervision: Gupta S

Project administration: Gupta S

Funding acquisition: Gupta S

All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

GSE150368 and GSE69223 and open data sources used to build the hypothesis. These data sources are available on the website at https://www.ncbi.nlm.nih.gov/gds/

Financial support and sponsorship

None.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Figure legend

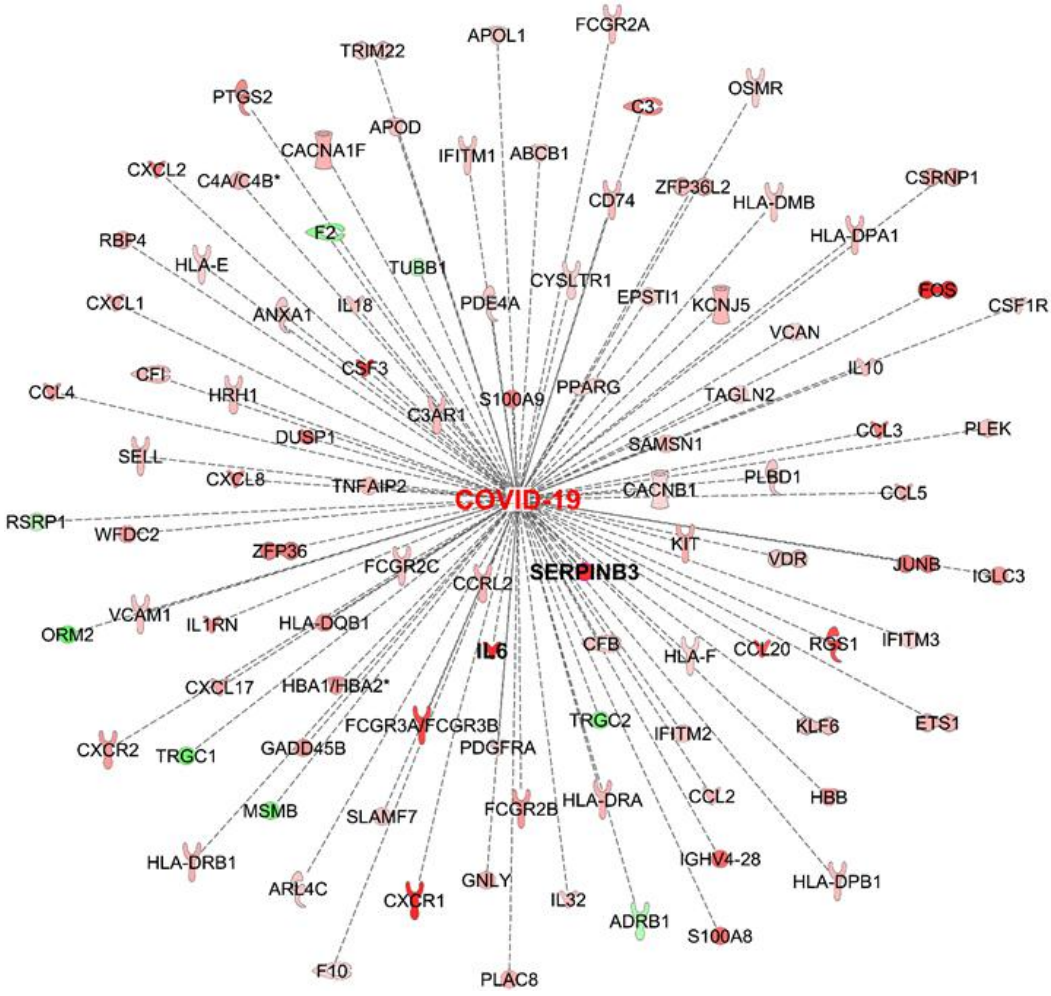

Figure 1. Differentially expressed genes (DEGs) of RNA-Seq. data of prostate cancer patients who received ADT was overlaid with COVID19, demonstrating significant interaction (*P value* 1.29E-26) between them with 98 molecules overlapped. Among them the expression of SERPINB3, IL6, FOS, FCGR3A/B, CXCR1 were significantly upregulated and highlighted in red color.