Response to Panda et al.

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Key Words

COVID-19, SARS-CoV-2, Progranulin

Response

The clinical spectrum of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection ranges from the asymptomatic to life-threatening cases with acute respiratory distress syndrome or severe coagulopathies [1,2]. Understanding the molecular mechanisms underlying the different susceptibility to SARS-CoV-2 infection and the predisposition for the development of severe courses of coronavirus disease 2019 (COVID-19) may help to identify patients at risk and enable targeted therapies and timelines for treatment.

We reported that the immune-regulatory molecule progranulin (GRN) is specifically upregulated in SARS-CoV-2 positive patients with an association of GRN levels and disease severity [3]. With great interest, we read the letter by Panda and collaborators that further expands this view. They studied the association of a common genetic single nucleotide polymorphism (SNP) in the 3' untranslated region (3'UTR) of the progranulin gene (C>T, rs5848) which had earlier been shown to alter GRN mRNA and protein levels [4]. Interestingly, the authors found an association of C-allele frequency with both infection and mortality rate [5]. This finding supports the proposed link between GRN expression and the pathophysiology of COVID-19. The potential of GRN as a biomarker should be validated in an independent, prospective study.

In addition, several questions arise from this letter. First, the authors focused on a SNP that has previously been linked to GRN expression. However, it would be of interest to learn which additional associations between SNPs and COVID-19 outcomes would be uncovered by a more unbiased approach. Second, altered GRN levels in individuals carrying the T-allele have earlier been associated with an increased risk for neurodengerative disorders [6]. Confirming these associations in the now investigated collective would support the conclusions on COVID-19 drawn from the present study. Third, the current analysis is solely

based on determination of the genotype and does not take into account other factors that control GRN expression such as epigenetic modifiers [7]. Integrating data from genome-wide association studies with epigenetic information may reveal SNPs in non-coding regions linked to GRN expression. In addition, the role of microRNAs in the transcriptional regulation of GRN should be further investigated. Of note, miR-659-3p is downregulated by hypoxia, leading to a de-repression of GRN [8], which might contribute to GRN upregulation in patients with respiratory failure. Interference with this mechanism using antisense oligonucleotides could represent a novel approach for the treatment of COVID-19. However, binding of miR-659-3p to GRN is stronger in the T allele transcript than the C allele transcript, suggesting a larger inhibitory potential of miR-659-3p on GRN expression in individuals carrying the T allele [8].

In summary, the available evidence suggests that elevated GRN expression predisposes to SARS-CoV-2 infection susceptibility and mortality. Therefore, the potential of GRN as a biomarker to identify patients at risk and to predict outcome in COVID-19 should be furthr explored in a prospective study.

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Conflict of interest

None

Funding Source

None