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Reply to 'COVID-19 severity, miR-21 targets, and common human genetic variation'

Recently, a letter from Dingsdag *et al.* discussed the importance of microRNAs (miRs) in severely ill COVID-19 patients as recently published by us.[1] The authors highlighted the importance of pro-fibrotic microRNA miR-21 in this context.[2] In general, patients suffering from the same pathological condition can manifest differences in the severity of symptoms depending upon the variability in their genetic and transcriptomic composition. In this regard, single nucleotide polymorphism variants (SNPs) are substantially important because it has already been shown that certain SNPs contribute to symptom expression in the context of COVID-19 infection.[3] The letter emphasized that 3′ UTRs of certain mRNAs of the transcriptome contain binding sites for miR-21, which could serve a therapeutic target in this regard. A gene locus associated with the severity of COVID-19, including an intronic segment of the *LZTFL1* gene, is associated with the above SNPs.[3,4] One particular SNP (rs35624553) in transcribed RNA is in proximity to the miR-21 target site. Due to the proximity of this binding site, the authors assume that alterations in the levels of miR-21 could regulate *LZTFL1* gene products, eventually leading to organ fibrosis and inflammatory processes.

Therefore, the authors of the letter hypothesize that a targeted study with manipulation of miR-21 could lead to substantial insight into the development of severe COVID-19 symptoms. By precisely modulating the post-transcriptional changes at the cellular level in COVID-19 patients, Dingsdag *et al.* were able to corelate cellular processes with extracellular findings.

The importance of SNPs and their association with the patient outcome has already been discussed in cancer.[5] In the context of colorectal carcinoma, SNPs located near the targets of miRs have been shown to influence disease risk.[6] Moreover, an association between the miR-related polymorphism and clinical outcome of patients was also demonstrated in non-small-cell lung carcinoma.[7] In future studies, the importance of SNPs and their interactions with miRs on gene regulation must also be considered.

Various *in vitro* models are suitable for further mechanistic studies. Of particular interest are cardiovascular or pulmonary cells infected with SARS-CoV-2 to evaluate cell-type specific interactions. Cells differentiated from human induced pluripotent stem cells are particularly suitable for meaningful validation of transcriptional and post-transcriptional regulations. In connection with COVID-19, our group has already demonstrated that the angiotensin-converting enzyme 2 receptor is regulated by miRs and is increased in differentiated cardiomyocytes where it serves as an entry receptor for SARS-CoV-2.[8]

In summary, the genetic and transcriptomic component plays an essential role concerning symptom expression in SARS-CoV-2 infection. Thus, by modulating miRs and their targets, it may be possible to influence COVID-19 symptom expression in the future.

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