Molecular Therapy
Nucleic Acids
Commentary

Exploring pulmoprotection in COVID-19: Moving toward microRNA-based theranostics

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https://doi.org/10.1016/j.omtn.2024.102152

INTRODUCTION

The relentless struggle with the aftermath of COVID-19 has driven the medical community to seek innovative methods for predicting and managing the disease's complications. Complications such as an overactive immune response, manifesting as cytokine storms, and shifts toward a procoagulant state not only exacerbate symptoms but also elevate the risk of mortality and long-term health issues. Consequently, there is a pressing need for novel diagnostic tools and therapeutic strategies that not only track disease progression and complications but also serve as potential drug targets or can be influenced by pharmacological interventions. In the presented study by Perez-Pons et al.[1] titled "MicroRNA-centered theranostics for pulmoprotection in critical COVID-19," the authors shed light on the promising role of microRNAs (miRNAs) as dual-purpose theranostic agents. By focusing on a multicenter cohort of intensive care unit (ICU) survivors, the research elucidates the potential of miRNAs in mitigating diffusion impairment—a common but debilitating consequence of severe infection. This commentary aims to contextualize these findings within the broader spectrum of molecular and cellular therapies, underlining their significance and implications they pose for the field.

Since the outbreak of the COVID-19 pandemic, a significant number of survivors, particularly those who experienced severe illness, have continued to face post-acute pulmonary sequelae. COVID-19 survivors often experience a spectrum of long-term lung issues, with dyspnea being a common symptom reported by 42%–66% of individuals within 60–100 days post-infection.[2] Individuals who experienced severe forms of COVID-19, particularly those in need of intensive respiratory support, are more likely to suffer from long-lasting lung issues.[2] This includes diffusion impairment, which refers to a decreased ability of the lungs to transfer oxygen from the air into the bloodstream, as well as observable lung damage like pulmonary fibrosis on medical imaging.[2] The persistence of these health issues among survivors indicates a substantial impact on their quality of life and the healthcare system, stressing the urgency in identifying effective interventions and support mechanisms for those affected.

miRNAs IN PULMONARY PATHOLOGY

miRNAs are short, approximately 22 nt in length, and function as non-coding RNAs that play a crucial role in regulating cellular processes. They achieve this by targeting mRNAs to either inhibit their translation and/or promote their degradation. Over the past two decades, the involvement of miRNAs in a variety of conditions (including cancer, cardiovascular diseases, and responses to infections) was demonstrated. Specifically, miRNAs have been increasingly recognized for their roles in both the physiological and pathological states of lung health. These small RNAs affect various processes including lung development, homeostasis, inflammation, and responses to viral infections.[3] For instance, specific miRNAs like miR-155, miR-26a, and the let-7 family are instrumental in lung development and maintaining pulmonary homeostasis. miR-155, for example, plays role in T cell differentiation and immune responses within the lung.[3] In the context of pulmonary diseases, miRNAs have been implicated in the pathogenesis of idiopathic pulmonary fibrosis, where they regulate processes like epithelial-mesenchymal transition, crucial for the progression of fibrosis.[4] Furthermore, respiratory infections, which can exacerbate asthma and chronic obstructive pulmonary disease (COPD), have also been linked to miRNA function.[5]

miRNAs stability in blood and other bodily fluids makes them excellent candidates for non-invasive biomarkers, allowing for the early detection, diagnosis, and monitoring of disease progression. For example, the balance between serum miR-21 and miR-181a levels has been identified as a predictive marker for COPD among asymptomatic heavy smokers.[5] Additionally, variations in serum levels of certain miRNAs, such as a decrease in miR-20a, miR-28-3p, miR-34c-5p, and miR-100, alongside an increase in miR-7, have been observed in individuals with COPD, further supporting the potential of miRNAs as accessible biomarkers for pulmonary diseases.[5]

miRNA AS A THERANOSTIC TOOL FOR PULMOPROTECTION IN COVID-19

In their research, Perez Pons et al. investigated which miRNAs offer the best predictive value for pulmonary protection in the aftermath of severe COVID-19.[1] Their study aimed to identify miRNAs linked to diffusion impairment, explore the cellular and signaling pathways these miRNAs influence, and discover existing medications that could be repurposed to correct these altered pathways. The study involved 172 COVID-19 survivors from 22 Spanish ICUs. The researchers selected a panel of 16 miRNAs previously analyzed for their potential to predict COVID-19 severity in hospitalized patients.[6] Utilizing a machine learning approach (random forest feature selection), they identified miR-27a-3p, miR-93-5p, and miR-199a-5p as optimal predictors

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of diffusion impairment. Initially classified based on electronic health record data, patients were subsequently re-evaluated using a model that incorporated miR-93-5p and miR-199a-5p levels measured at ICU admission. This improved model significantly outperformed the original classification in terms of predictive accuracy, demonstrating the benefit of miRNAs as early biomarkers for patient outcomes. Subsequent bioinformatic analysis highlighted several pathways related to poor disease resolution, including fibrosis and cell senescence, areas previously identified as treatable traits. The study further validated these findings by measuring telomere length as an indicator of cell senescence in a separate cohort of post-discharge survivors, noting a trend toward shorter telomeres among those with impaired lung diffusion, although statistical significance was limited by the small sample size. Finally, the investigation extended to analyzing 1,133 miRNA target levels in an independent RNA sequencing dataset, identifying eight transcripts (CAV2, MAP1B, VLDLR, GSPT1, ATP1B2, ADAMTS1, CDCA7, and AKAP12) with differential expression related to lung-diffusion impairment in survivors. Additionally, the analysis pointed to four FDA-approved drugs (all from the digitalis group primarily used for the heart failure treatment) targeting ATP1B2, suggesting potential therapeutic repurposing opportunities. This study not only illuminates the role of specific miRNAs in the pathophysiology of COVID-19 but also underscores the potential of miRNA-based diagnostics and therapeutics in managing the disease's long-term pulmonary complications.

STEPS TOWARD NEW CONCEPTS

The presented study displays the effectiveness of an integrative methodology, where machine learning algorithms significantly enhance the search for viable diagnostic models. Despite the study's small scale, its approach underscores the value of synthesis, broadening the scope of comprehension and encouraging synergistic research efforts. However, further research is essential to fully unlock the clinical potential of this strategy and to elucidate the underlying pathophysiological mechanisms of the study's findings. Expanding this approach to larger cohorts and applying it to other complex chronic conditions, such as cardiometabolic diseases, could potentially lead to the repurposing of existing medications for improved treatments.

In the rapidly evolving field of RNA therapeutics, the identification of druggable RNA targets becomes increasingly crucial. This pursuit goes beyond just novel methods like antisense RNA or small inhibitory RNAs, which directly target and neutralize specific RNA molecules. It also includes the innovative repurposing of existing drugs, contingent upon their demonstrated effects on particular RNA targets. Such a dual approach not only facilitates the precise targeting of RNA molecules but also leverages RNA as a biomarker to evaluate the impact of treatment strategies. This embodies the innovative concept of theranostics, where therapy and diagnostic procedures are integrated, offering a holistic pathway to personalized medicine. Through such an approach, the potential for more effective and tailored therapeutic interventions is significantly enhanced, marking a pivotal advancement in the convergence of treatment and diagnostic precision. This broadened application promises to open new avenues in the quest for more effective and targeted therapies, reinforcing the pivotal role of integrated approaches in the future of medical research and patient care.

ACKNOWLEDGMENTS

M.S. is funded by the European Union (HORIZON-MSCA-2021-PF-MAACS 10106 4175) and the Ministry of Science, Technological Development and Innovation, Republic of Serbia through a grant agreement with University of Belgrade-Faculty of Pharmacy, no. 451-03-47/2023-01/200161.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Perez-Pons, M., Molinero, M., Benítez, I.D., García-Hidalgo, M.C., Chatterjee, S., Ba, C., González, J., Torres, A., Barbé, F., and de Gonzalo-Calvo, D. (2024). MicroRNA-centered theranostics for pulmoprotection in critical COVID-19. Mol. Ther. Nucleic Acids *35*, 102118.

2. Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M.V., McGroder, C., Stevens, J.S., Cook, J.R., Nordvig, A.S., Shalev, D., Sehrawat, T.S., et al. (2021). Post-acute COVID-19 syndrome. Nat. Med. *27*, 601–615.

3. Tomankova, T., Petrek, M., and Kriegova, E. (2010). Involvement of microRNAs in physiological and pathological processes in the lung. Respir. Res. *11*, 159.

4. Miao, C., Xiong, Y., Zhang, G., and Chang, J. (2018). MicroRNAs in idiopathic pulmonary fibrosis, new research progress and their pathophysiological implication. Exp. Lung Res. *44*, 178–190.

5. Maltby, S., Plank, M., Tay, H.L., Collison, A., and Foster, P.S. (2016). Targeting microRNA function in respiratory diseases: mini-review. Front. Physiol. *7*, 21.

6. De Gonzalo-Calvo, D., Benítez, I.D., Pinilla, L., Carratalá, A., Moncusí-Moix, A., Gort-Paniello, C., Molinero, M., González, J., Torres, G., Bernal, M., et al. (2021). Circulating microRNA profiles predict the severity of COVID-19 in hospitalized patients. Transl. Res. *236*, 147–159.