Immune suppression in the early stage of COVID-19 disease

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Introduction

COVID-19, the disease caused by infection with the virus SARS-CoV-2, has become a worldwide pandemic. As yet, we know very little about this new virus and its pathogenesis. At the beginning of the pandemic, research studies focused on the management and treatment of severe and critical patients. Statistics showed that the elderly, especially those with underlying conditions such as heart disease, lung disease, obesity and diabetes, have the most severe symptoms. As the virus has now spread globally, more information is available about younger infected people in their 30s to 50s. In a growing number of cases, symptoms were expected to improve, but suddenly got worse. Patients can develop acute respiratory distress syndrome (ARDS) or even die suddenly in a short period of time. This sudden change implies a "two-stage" pattern of disease progression, but the underlying mechanisms are unknown. In this work, we apply a mass spectrometry-based, data-independent acquisition (DIA) quantitative proteomic approach to analyze urine samples from COVID-19 infection cases, healthy donors and non-COVID-19 pneumonia cases. We expect our results to provide hints of how the two-stage pathogenesis occurs.

Methods

All 31 fraction samples were analyzed on a hybrid TIMS quadrupole time-of-flight mass spectrometer (timsTOF Pro, Bruker Daltonics) via a CaptiveSpray nano-electrospray ion source. The mass spectrometer was operated in data-dependent mode for the ion mobility enhanced spectral library generation. We set the accumulation and ramp time was 100 ms each and recorded mass spectra in the range from m/z 100–1700 in positive electrospray mode. The ion mobility was scanned from 0.6 to 1.6 Vs/cm2. The overall acquisition cycle of 1.16 s comprised one full TIMS-MS scan and 10 PASEF MS/MS scans Raw files were processed using a developmental version of Spectronaut (v14.0.200409.43655, Biognosys). The ion mobility enhanced library was generated from DDA-PASEF raw data using Spectronaut's Pulsar database search engine with 1% FDR control at PSM, peptide and protein level.

Results

➢ Comprehensive urine proteome analysis of COVID-19 disease

A total of 5991 proteins were identified in all thirty-seven samples. The levels of 1986 proteins were significantly changed in the COVID-19 group compared to the healthy donors and the non-COVID-19 pneumonia. Surprisingly, we identified nearly ten times more down-regulated proteins than up-regulated ones in the COVID-19 group. KEGG enrichment analysis revealed the molecular landscape associated with COVID-19 infections. More than ten pathways were significantly changed (Figure 1). In particular, COVID-19 had a strong impact on immune related pathways, tight junction (TJ) pathways and metabolic pathways.

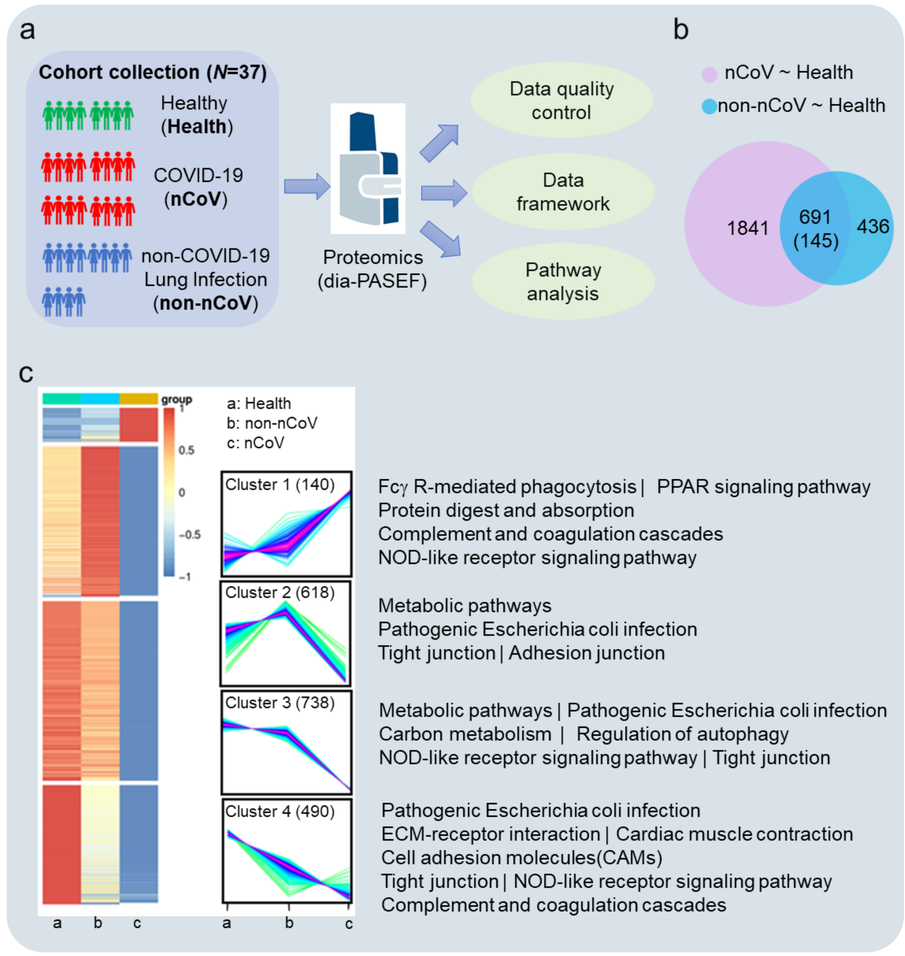

Figure 1: Quantitative urine proteomic studies.

➢ Immune system is suppressed in the early stage of COVID-19 disease, while activated in severe COVID-19 patients.

We further subdivided the COVID-19 patients into 9 moderate cases and 5 severe cases, and found, interestingly, that an activated immune response emerged to a certain extent in the late stage of the disease while the immunosuppression effect remained in the early stage (Figure 2) . This results indicate that in the late stage of the disease the immune response was activated which is in consistent with an excessive immune response and cytokine storm in patients in severe and critical stages of COVID-19 patients. Thus, we proposed a "two-stage" pathogenesis model for COVID-19 (Figure 3).

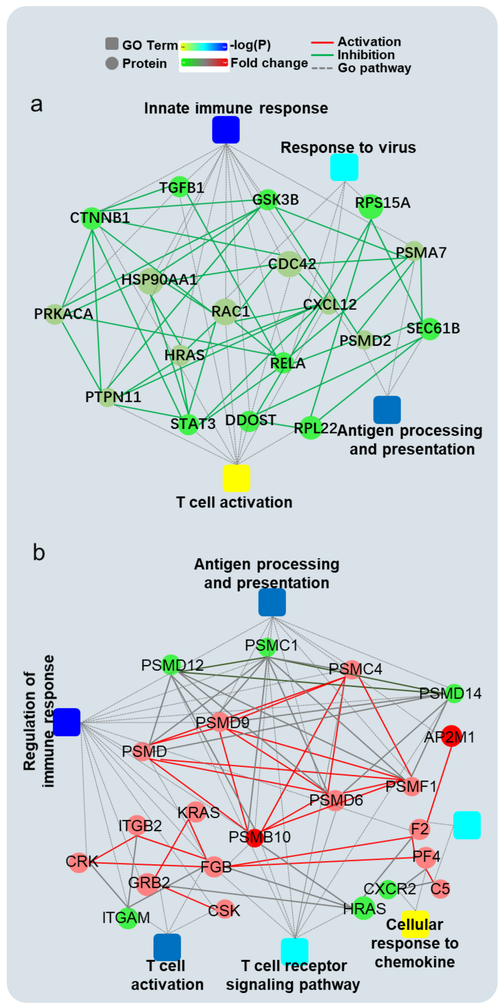

Figure 2: Immune system response in moderate and severe COVID-19 patients.

a. The interaction diagram of proteins involved in the innate immune response, response to virus, antigen processing and presentation and T cell activation.
b. The interaction diagram of proteins involving in antigen processing and presentation, complement activation, cellular response to chemokine, regulation of immune response, T cell activation, T cell receptor signaling pathway.

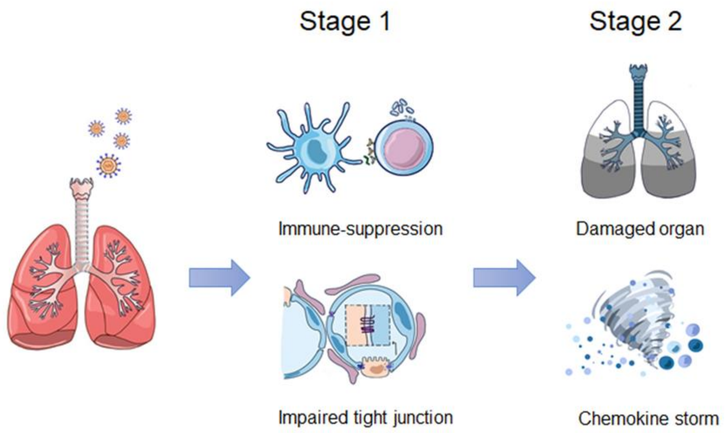

Figure 3: A "two-stage" pathogenesis model for COVID-19.

Conclusions

- The most advanced 4D-DIA technology was applied to discover the comprehensive map of the molecular changes associated with the COVID-19 disease
- Immunosuppression and tight junction impairment specifically occurred in COVID-19 patients. Interestingly, an activated immune response occurred in the late stage of the infections.
- These unusual features of COVID-19 will guide us to further understanding of COVID-19 pathogenesis, mechanistic study and clinical treatments.

References

(1) Immune suppression in the early stage of COVID-19 disease. Nat Commun 2020; 11(1):5859.