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Understanding the Origins of Infectious Diseases and Epidemics Using an Integrated Systems Biology Approach

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Abstract

The COVID-19 pandemic has been ravaging the globe for more than two years, and it has put the responses of all major international governments to pandemic situations to the test. The molecular mechanisms that result in heterogeneous patient outcomes and the reasons of post-COVID state are two important areas of research that are still not fully understood (AKA Long-COVID). In this study, we introduce the HYGIEIA initiative, which uses a multi-omic strategy assisted by network medicine to address the immense problems posed by the COVID-19 pandemic. It is envisaged that the logistics used in this study, in addition to investigating COVID-19, will be adaptable to additional infectious agents, pandemic-like scenarios, as well as other complicated, non-infectious disorders. We first review prior studies on COVID-19 in the context of the microbiome, host genome, viral genome, proteome, metabolome, and transcriptome. We next go over a suggested methodology for a large-scale multi-omic longitudinal study that would use mass spectrometry (MS) and high-throughput sequencing (HTS) to look at the aforementioned biological strata. Last but not least, we go over how a network medicine strategy may be utilised to evaluate the data and uncover important findings, with the ultimate goal being the implementation of these findings into clinics to enhance patient care.

Keywords: COVID-19 • Post COVID condition • Proteomics • Metabolomics • Genomics • Metagenomics • transcriptomics • Network medicine

Introduction

Most COVID-19 patients will typically recover in two to three weeks if their disease development is modest to moderate, while patients who arrive with severe disease will often require at least six weeks to recover. Afterward, COVID-19-related symptoms, which most frequently include fatigue and muscle weakness, dyspnea, joint and chest discomfort, and neurocognitive impairment, will continue to be present in about 54% and 34%, respectively, of hospitalised and non-hospitalized patients. It's interesting to note that a literature review from the Belgian Health Care Knowledge Center revealed an increasing trend of the incidence of displaying post-COVID symptoms depending on study follow-up, with a median incidence of 17% (non-hospitalized patients) and 50.9% (hospitalised patients) at 1-3 months, increasing to 25% (non-hospitalized patients) and 62% (hospitalised patients) at 6 months+ follow up. According to several studies, between 30% and 90% of people still have chronic post-COVID symptoms six months after the disease first appeared. Although the exact cause of the post-COVID syndrome is yet unknown, it has been noted to more frequently afflict people who had a severe COVID-19 or who needed to be admitted to the hospital. Additionally, patients who presented with more than five symptoms during the disease's acute phase, patients who are female, patients who are obese, and patients who had diabetes are more likely to develop the condition.

Su et alrecent's multi-omic study focused on single-cell-omics and examined post-COVID circumstances between two and three months after COVID-19 diagnosis. They stated that 61% of patients had at least one symptom, and they additionally Type 2 diabetes, reactivated EBV, autoantibodies, and SARS-CoV-2 blood virus load are the four key risk factors for developing post-COVID symptoms. If examined at diagnosis, these risk variables may be used to predict a patient's likelihood of acquiring a post-COVID disease. For instance, the majority of the patients did not have any recognised autoimmune disorders, although about half of the patients showed auto antibodies at follow-up and upon diagnosis, indicating the possibility of a pre-existing subclinical ailment in these patients. The study was able to classify patients into four different immunological endpoints: type 1, type 2, intermediate, and naive, in addition to these risk variables. These endpoints were distinguished by distinct immunological responses, severity of COVID-19 illness, and risk of a post-COVID syndrome is emerging. However, this study's lack of a genomic component made it impossible to draw any conclusions about the relationship between host genomes and the existence of autoantibodies or patient immunological endpoint subgroups.

Cohort population, inclusion standards, and sampling techniques

The main layout of the clinical trial and sample collection, with 225 total patients and 50 total controls intended to be recruited from Cliniques Universitaires Saint-Luc (CUSL), Brussels, Belgium, patient recruitment is now proceeding. The entire cohort size may go above this because patients are also being gathered from other institutions in Belgium's Brussels and Wallonie region in a multi-centric effort. The patient population will be divided into three categories-mild/moderate, severe, and critical—each consisting of 75 people. There will be two groups of the control population: 25 patients with respiratory failure and 25 healthy people. Patients will be over the age of 18 and will give their informed consent. Using nasopharyngeal (NP) swabs, a SARS-CoV-2 RT-PCR assay will be used to evaluate the COVID-19 status. The CDC's recommendations for disease severity will be used to categorise patients. Hypoxemic respiratory failure from an infectious cause, excluding SARS-CoV-2, should be the diagnosis for respiratory failure controls, and they shouldn't have tested positive for SARS-CoV-2 during the previous six months. Healthy controls should not have tested positive for SARS-CoV-2 within the previous six months and should appear without respiratory failure (i.e., SpO2 > 93%).

Whole EDTA blood, TempusTM Blood RNA Tube, heparinized plasma, and NP swabs will be used as the biological samples. They will be collected twice, once at the time of patient inclusion during the acute phase and once about three months later. Later Time points may be added for patients beyond

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three months, however this project's main objective is to look into patients who are showing signs of post-COVID disease at that point. Until the multi-omic analysis starts and patient recruitment is complete, all samples will be kept at 80 °C.

Top-down, traditional shotgun proteomic profiling

The TOP 14 Abundant Protein Depletion kit (Thermo Fisher Scientific, Waltham, MA, USA) will initially be used to protein deplete plasma samples in a ratio of 500 mL depletion resin to 18 mL plasma. Samples will be depleted, heated to 95°C for 5 minutes, cooled, and 300 L of the sample added to a different LoBind Eppendorf tube (Thermo Fisher Scientific, Waltham, MA, USA). After that, 5 mM of DTT will be added, and it will be stirred at 1000 RPM for 1 hour at 56°C (Thermomixer C). After that, 50 mM of chloroacetamide will be added, and the mixture will then be incubated at room temperature in the dark for 30 minutes. 100% TCA will be added to the sample following incubation. The sample will be aggressively vortexed (10 s) and spun down before being incubated on ice for 30 minutes at a final concentration of 15%.

The tube will then undergo three washes as follows after being centrifuged at 4000 g for 5 minutes and the supernatant being removed: 500 mL of 100% acetone was added, and the mixture was then centrifuged at 4000 g for 5 minutes while being refrigerated to 20°C and pulse-sonicated for 2 minutes at 37 kHz. The pellet will be reconstituted in 75 L TEAB 50 mM by two cycles of sonicating for 2 min and quickly vortexing after three repetitions to guarantee that all acetone has been removed from the tube (10 s). Finally, a 1:50 protease:protein ratio of trypsin will be applied and agitated at 750RPM while incubating at 37°C overnight. The Pierce high pH reversed-phase peptide fractionation kit will be used to divide the sample into fractions once it has been incubated (Thermo Fisher Scientific, Waltham, MA, USA). A total of 1.2 g of peptide in 8 l of buffer will next be analysed by reverse phase chromatography coupled to mass spectrometry using an Orbitrap Exploris 240 system paired with an Ultimate 3000 RSnano LC system. Fractions will then be freeze-dried and resuspended in 20 L 3.5% ACN/0.1% TFA.

Discussion

As data are produced, individual networks will be built for each of the -omic data mentioned above using network-based statistical approaches (such as the nearest neighbour algorithm). The edges connecting the nodes, which represent the patients, will be based on the pairwise similarity of the -omic data. Patients will group together as a result of -omic tests, signalling similar molecular markers. These clusters will subsequently be labelled with specific characteristics and results, such as individuals who developed severe illness or did not. Following a differential investigation of these clusters, chemicals, bacteria, proteins, and genes exhibiting various patterns would be found. The fusion of each network would be the last phase in the multi-omic integration process. The channels will be combined using similarity network fusion (SNF), and a feature ranking systemwill arrange the features according to the network contribution for a given patient outcome, producing a ranking list of the most significant features/pathways that can be studied. Such a method will be used to identify multi-omic differences between the acute and post-COVID phases of patients, shedding new light on potential causes or biomarkers of the post-COVID sequelae. This method will not only be used to identify differences between patient groups (i.e., mild/moderate vs. severe) [1-10].

Conclusion

In this article, we examine transcriptomics, proteomics, metabolomics, metagenomics, host and viral genetics, and highlight the developments in COIVD-19 research within a multi-omic overview of the disease. We point out current gaps in our understanding of the disease, including the pathogenesis of the condition that follows COVID-19, the relationship between COVID-19-induced changes in the respiratory microbiome and transcriptomic variations, and interactions between viral transcripts and host ncRNA, to name a few. We also point out the need for more thorough multi-omic research in the field of COVID-19 study.

The ultimate goal of such a project is to enhance patient treatment by thoroughly examining the multi-omic state of each patient both before and after SARS-CoV-2 infection in order to find previously unidentified traits, biomarkers, or effects of COVID-19 disease. In addition, we hope to accept the procedures, Improved novel-disease research efficiency and quick clinical translation are made possible by the bioinformatics and logistics created during this project, which may be quickly deployed when another pandemic-type event occurs.

Acknowledgement

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Conflict of Interest

None.

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