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The why behind mild COVID-19

Findings from all-Luxembourg study help to anticipate a personal COVID-19 health trajectory

From the start of the COVID-19 pandemic, the majority of published studies have focused on severe COVID-19 patients in order to understand the causes of critical illness. However, it is equally, if not more important to understand the protective immune factors in our body. Using state-of-the-art deep immune profiling and systems immunology-driven data analysis, the translational biomedical research team, which was led by the Department of Infection and Immunity of the Luxembourg Institute of Health, revealed that it is the unique combination of various early-stage immune responses that can differentiate between mild patients, hospitalized COVID-19 patients and their non-infected household controls.

The insurgence of COVID-19 has had dramatic effects worldwide, leading to an unprecedented diversification and intensification in research efforts to counteract its spread. However, while immunopathology has been widely studied in severe COVID-19 patients, immune responses in non-hospitalized patients have remained largely elusive. Furthermore, research to date has lacked a comprehensive multi-faceted approach to the full immune response following infection. It was therefore unknown, up to now, whether the immune alterations present in hospitalized individuals were also present in mild COVID-19 PCR-positive patients. To this end, Feng Hefeng and Markus Ollert from the Department of Infection and Immunity of the Luxembourg Institute of Health (LIH) led a study to reveal the early-stage immune features of patients who had recently contracted the virus but displayed mild COVID-19 symptoms only.

The all-Luxembourg study took full advantage of the translational medicine research structure established across the nation. The translational study was based on the cohort *Predicting the severity of COVID-19 infection*[1] ([Predi-COVID](#)), which was initiated in April 2020 to identify important risk factors and biomarkers associated with COVID-19 severity in Luxembourg. "*Our work was only possible thanks to the unique opportunity to conduct a population-wide PCR screening in Luxembourg from May 2020 on that allowed us to recruit many SARS-CoV-2-infected people with only mild or no symptoms,*" acknowledged Guy Fagherazzi, Director of the LIH Department of Precision Health and one of the two Principle Investigators (PI) of the Predi-COVID project. Indeed, since its launch in April 2020, the study has collected data from COVID-19 positive adults in Luxembourg, and followed their health evolution during the first three weeks after their diagnosis and beyond.

To obtain a comprehensive picture of the early-stage immune responses in COVID-19 infection, patients were categorised according to their symptoms' severity (asymptomatic, mild, and hospitalized). By comparing immune responses between the different groups in more than 100 patients and household controls, the team found that, within three days following the positive PCR

test, there was an early-stage increase in coordinated immune responses only in patients with mild symptoms. Key immune mediators like interferon beta and interferon gamma-induced protein 10 (IP-10) temporarily increased early-on according to the amount of virus present in the body of mild patients. After three weeks, these immune markers remained high in hospitalized patients, but decreased to normal values in mild patients. The early increase of crucial biomarkers in mild patients was accompanied by a rise in immune cells reacting specifically to the SARS-CoV-2 virus like CD4 T cells, which are part of the adaptive arm of the immune system, and of early-reacting innate immune cells, such as antigen-presenting cells and monocytes. Very importantly, these early immune reactions anticipated the presence of specific antiviral antibodies three weeks later in mild patients, a feature that was absent in hospitalized patients. While hospitalized COVID-19 patients mounted an equally strong T cell response as mild patients, the frequency of innate immune cells and the expression of key functional molecules on these cells were strikingly impaired already very early on during infection in hospitalized patients. According to Christophe M. Capelle, a Luxembourgish LIH Ph.D. graduate and first author of the study, turning on multiple immune functions in parallel and very early in a highly coordinated fashion appears to be a major contributor to the beneficial clinical outcome of patients with mild symptoms.

 "*These pioneering findings are the perfect example of the tremendous translational potential of our research infrastructure in Luxembourg,*" commented Dr Hefeng. "*The longitudinal Predi-COVID study gave us unique access to PCR-positive mild non-hospitalized COVID-19 patients, which empowered us to gain a comprehensive picture of distinct early-stage protective immune signatures in mild COVID-19 patients versus hospitalized patients, asymptomatic individuals and household controls during the first waves of the pandemic.*"

"*Our work provides a rich data and clinical sample resource based on the unique opportunity to fully explore and understand all essential facets of the early-stage and dynamic immunological changes following recent SARS-CoV-2 infection in mild COVID-19 patients, using an unbiased, combinatorial and prospective approach,*" added Markus Ollert, Director of the Department of Infection and Immunity of the LIH, who is the other PI of the Predi-COVID project. "*Our current study does not only provide information on the number and frequency of a wide spectrum of immune cells helping to defend against viruses like SARS-CoV-2 in our blood, but also on the functional status and characteristics of individual immune cell types.*"

These first research results of the Predi-COVID study were recently published in the leading biomedical journal *Cell Reports Medicine* by Cell Press under the full title: '[Combinatorial analysis reveals highly coordinated early-stage immune reactions that predict later antiviral immunity in mild COVID-19 patients](#)'. Predi-COVID will continue from 2022 onwards under the umbrella of CoVaLux (COVID-19, Vaccination & long-term health consequences of COVID-19 in Luxembourg), a national research effort coordinated by Research Luxembourg to address key unanswered questions related to COVID-19, with a particular focus on vaccination efficacy and the longer-term health impact of COVID-19.

[1]Fagherazzi G, Fischer A, Betsou F, et al. Protocol for a prospective, longitudinal cohort of people with COVID-19 and their household members to study factors associated with disease severity: the Predi-COVID study. BMJ Open 2020;10:e041834. doi:10.1136/bmjopen-2020-041834.

Funding and collaborations

About the Luxembourg Institute of Health (LIH)

The Luxembourg Institute of Health (LIH) is a public biomedical research organization focused on precision health and invested in becoming a leading reference in Europe for the translation of scientific excellence into meaningful benefits for patients.

LIH places the patient at the heart of all its activities, driven by a collective obligation towards society to use knowledge and technology arising from research on patient derived data to have a direct impact on people's health. Its dedicated teams of multidisciplinary researchers strive for excellence, generating relevant knowledge linked to immune related diseases and cancer.

The institute embraces collaborations, disruptive technology and process innovation as unique opportunities to improve the application of diagnostics and therapeutics with the long-term goal of preventing disease.

About Research Luxembourg

Research Luxembourg is a unified agile team of thought leaders working to learn, explore and make an impact to shape a better future. By connecting all players in Luxembourg and abroad, Research Luxembourg aims to become a leader in research and innovation focusing on four research priority areas: (1) Industrial and Service Transformation; (2) Personalised Healthcare; (3) Sustainable and Responsible Development; (4) 21st Century Education

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Scientific contact

Prof Dr med Markus Ollert, MD (markus.ollert@lih.lu);

Dr Feng Hefeng (Feng.He@lih.lu)

Department of Infection and Immunity
Luxembourg Institute of Health
Allergy and Clinical Immunology Research Group

Press contact

Arnaud D'Agostini
Head of Marketing and Communication
Luxembourg Institute of Health
Tel: +352 26970-524
E-mail: arnaud.dagostini@lih.lu