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Research on hemophagocytic syndrome uncovers new gene regulating the human immune system

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Researchers from the VIB-UGent Center for Inflammation Research and the Ghent University hospital, together with research teams from the Helmholtz Zentrum in München and the National University of Australia in Canberra, identified a new genetic cause of hemophagocytic syndrome, a rare immune disease characterized by a dangerous and uncontrolled overproduction of cytokines known as cytokine storm. This discovery provides new insights into the human immune system and could inspire new treatments for this deadly immune disease.

When brakes are not working

Uncontrolled activation of the immune system, which occurs in hemophagocytic syndrome, is rare but deadly. It is estimated to afflict one in 100,000 children. In a number of children, genetic mutations have been identified that cause this overactivation. These mutations prevent the natural brakes of the human immune system from working. This means that the immune system keeps on fighting, even when the infection has already been resolved.

Early recognition of the genetic mutations causing this fatal disease is crucial for any reasonable attempt to permanently restore a normal function of the immune system. In an international collaboration, research teams at the Ghent University hospital, VIB-UGent Center for Inflammation Research, Helmholtz Zentrum München and the National

University of Australia discovered the role of a new mutation in the gene Roquin-1 in a young patient suffering from recurring hyperinflammation, resembling hemophagocytic syndrome.

This research is part of the VIB Grand Challenges Program on primary immune deficiencies. Primary immune deficiencies are a group of diseases in which genetic defects cripple the immune system. Due to their rare and complex nature, primary immune deficiencies are often missed or diagnosed very late. By combining the clinical expertise amongst others present in the partner universities with the scientific knowledge and cutting-edge technology present within VIB teams, the consortium aims to improve diagnosis and treatment of the patients suffering of these rare immune disorders.

Finding genetic defects

The identification of this new gene variant in a young Flemish boy initiated an international collaboration to understand its role in the human immune system. Using state-of-the-art technology present in the VIB-UGent Center for Inflammation Research together with in-house developed algorithms, the researchers were able to characterize the immune system of the patient at the single cell level.

At the same time, researchers in the Helmholtz Zentrum in München and the National University of Australia were trying to understand the role of mutations in Roquin-1 in mice suffering from immune disease. Comparing the results of the patient with those found in mice revealed both stunning parallels and intriguing differences, which helped to understand the development of this immune disease. These mouse models also allowed the researchers to test and validate alternative treatment options for this rare immune disease.

"The identification of a genetic defect in Roquin-1 by the genetic

department of the Ghent university hospital was the start of a very challenging project. Only by teaming up with the research teams in VIB and experts on this particular gene in Germany and Australia, we were able to connect the dots, prove the role of this gene variant and provide insights how this resulted in disease" says Simon Tavernier, first author of this publication.

New insights in the origins of immune diseases

By identifying the role of Roquin-1 as a regulator of the human immune system, the researchers discovered a new mechanism how human immune disease can arise. Professor Heissmeyer (Helmholtz Zentrum, Germany) emphasizes the importance of these findings: "Our research will stimulate the scientific efforts to understand how Roquin-1 functions in the human immune system. It is likely that we will also find additional mutations in Roquin-1 in patients with other immune diseases such as autoimmunity."

How will these findings impact the life of the patient and other patients suffering from hyperinflammation? According to Dr. Patrick Verloo (University Hospital Gent), the clinician taking care of the patient, this will benefit the patients directly: "The identification of this new mutation might help us to diagnose the disease earlier and start a more suitable treatment."

Prof. Filomeen Haerynck (Primary Immunodeficiency Research Lab, University Hospital Gent) also stresses the significance of the collaborative approach of the VIB Grand Challenge Program, combining the expertise of both clinicians and scientists to reveal the genetic causes underpinning these rare immune diseases. "This kind of translational research is of utmost importance. It is clear that only a profound understanding of the origins of these rare immune diseases will improve the diagnosis and care of these patients."

More information: S. J. Tavernier et al. A human immune dysregulation syndrome characterized by severe hyperinflammation with a homozygous nonsense Roquin-1 mutation, *Nature Communications* (2019). DOI: 10.1038/s41467-019-12704-6

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