LS16-060 - Systems precision medicine of inborn errors of the immune system (PrecisePID)

Abstract

Genetic diseases affecting the immune system, also called Inborn Errors of Immunity (IEI), are rare and severe conditions that prevent affected patients - mostly children - to fight infections. IEI are often associated with complex immune system dysregulation causing inflammation and to increased risk to develop tumors. While more than 400 IEI entities have already been discovered to date, numerous patients suffer from yet undiagnosed IEI entities. Such diversity and incomplete knowledge render the diagnosis of patients a very challenging task. In turn, early diagnosis is of crucial importance to implement adapted treatments for conditions that often worsen over time, with often fatal issues if efficient treatments fail to be implemented.

In this context, the PrecisePID project has consisted in applying a combination of innovative genetic, cellular biology and bioinformatics tools to accelerate the diagnosis of multiple patients suffering from this heterogenous group of rare diseases.

Finding the molecular origin of disease in a given patient consists in identifying mutations in a gene that cause a precise dysfunction of immune cells. Although sequencing approaches allow since a few years for a rapid sequencing of the entire genome of a patient, finding disease causing mutations is not straightforward because of the diversity of the genome among individuals (thousands of genetic variants are present in each individual). A key step towards the elucidation of the defective genes causing disease in individual patients has been the continuous improvement of our pipeline to sequence the exome (part of the genome encompassing the genes), to process the sequencing data and to filter the genetic variants.

In parallel, to expedite the analysis of functional defects in the immune cells from the patients, we have implemented innovative microscopy approaches allowing the parallel evaluation of primary cells from multiple patients and healthy donors used as controls. This approach has also been miniaturized to be compatible with the very limited amounts of cells recovered from small blood samples (obtained in most cases from sick children).

Both genetic data and immune cell function data have then been combined with bioinformatics tools, whereby information from undiagnosed patients has been compared to those of previously diagnosed patients. The comparison of multiple patients allowed inferring disease mechanisms in yet undiagnosed patients. Finally our experimental workflow provided support for a precise diagnosis of patients.

Through the project, we were able to identify and mechanistically dissect four novel IEI entities and to investigate the molecular etiology in more than 100 patients. It should be noted that our platform further holds promises for the implementation of drug screens that can be personalized to individual patients. We believe that the combination of innovations that we have combined to implement the PrecisePID project can be translated to other fields of rare diseases. Furthermore, the fundamental knowledge gained through the study of these rare immune defects are of unique value for the understanding of immune responses against infectious agents and tumors.

Scientific disciplines:
Immunology (40%) | Human genetics (30%) | Systems biology (30%)

Keywords:
primary immunodeficiency, high-throughput sequencing, high-content imaging, immune cell function, systems medicine

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Further links to the persons involved and to the project can be found under
https://www.gmbh.wwtf.at/funding/programmes/ls/LS16-060/