University of Basel

DBM Basel
Department of Biomedicine

OPEN MASTER THESIS PROJECT IN HUMAN GENETICS – VERIFICATION OF THE DISEASE-CAUSING VARIANT IN A FAMILY WITH HEREDITARY ANGIOEDEMA

Project background

Hereditary angioedema (HAE) is a rare and potentially fatal genetic disease manifested clinically by recurrent episodes of swelling of the subcutaneous and/or submucosal tissues in the hands, feet, limbs, face, intestinal tract, or airway. This is not only a cosmetic problem but is often extremely painful and can, in individual cases, lead to death by asphyxiation. HAE is usually inherited in an autosomal dominant manner. The majority of cases is caused by variants of the SERPING1 gene encoding C1 Inhibitor (C1-INH). C1-INH is a major regulator of critical enzymes that are implicated in the cascades of bradykinin generation which increases the vascular permeability and allow the flow of fluids into the extracellular space. Apart from HAE caused by variants in C1-INH (i.e. HAE-C1-INH), there are patients that do not have any variant in SERPING1. This form has been classified as HAE-nC1-INH (HAE with normal C1-INH). Currently, variants in seven different genes have been identified as causing HAE-nC1-INH: F12, PLG, ANGPT1, KNG1, MYOF, HS3ST6, and most recently CPN. In a substantial number of patients with HAE-nC1-INH, no disease-causing variant could be identified, suggesting that variants in so far unknown genes may be responsible for their phenotype. These patients are classified as HAE of unknown origin (HAE-UNK).

Short project description

In a Dutch family affected by HAE-UNK we have recently performed diagnostic DNA sequencing in the known genes causing HAE-nC1-INH. No disease-causative variant was identified in any of these genes. To extend our search to so far unknown genes, we then performed whole genome sequencing and identified a rare coding variant in a gene not previously known to be associated with HAE. The variant is present in affected members of the family and the molecular function of the gene would fit with a role in HAE. However, in order to provide functional evidence for the hypothesis that this gene variant is indeed causing HAE in this family, molecular studies in cellular models are required. This work will be the subject of the Master's thesis project. The Master student will investigate the impact of the variant on the function of the encoded protein, using techniques such as cell culture, transfection of cells, and Western Blot to verify a possible influence on the development of HAE.

Your role

Leveraging cutting-edge tools such as CRISPR and retroviruses, you will investigate the impact of type 1 interferon signaling on the CD8 T cell response to cancer immunotherapy using relevant mouse models. By analyzing scRNAseq datasets, you will identify specific targets downstream of type 1 interferon signaling responsible for the arrested response of exhausted CD8 T cells to PD-1 based therapy. Using gain-and-loss of function experiments in vivo, you will reveal the precise mechanism by which the identified target impairs CD8 T cell responses to immunotherapy. To achieve these goals, you will use and be trained for high dimensional flow cytometry, molecular engineering (CRISPR, Retroviruses design and production) and next generation sequencing approaches (scRNAseq and scATACseq).

We offer

- Work in a highly moRvated team and a supporRve research environment
- Overview of the principles of human geneRcs and in parRcular disease gene idenRficaRon
- Hands-on experience with cell culture and other research techniques
- ParRcipaRon in projects using cuVng-edge geneRc high throughput techniques

Your profile and how to apply

- Would you be excited to find the cause for a geneRc disease?
- Do you enjoy working in an inspiring research environment?
- Do you like to tackle sophisRcated research quesRons?

Contact

Then you should send your application including motivation letter and CV to
PD. Dr. Bettina Burger, bettina.burger@usb.ch