New immunotherapy targets for MPN patients

(Vienna, May 8, 2019) **Myeloproliferative neoplasms (MPNs) are blood cancers characterized by excessive blood cell production, frequent thrombosis and transformation to acute leukemia. Oncogenic mutations in the *JAK2*, *CALR* and *MPL* genes have been identified as drivers of the disease along with many other MPN-associated mutations. While detailed knowledge of disease mechanisms is available, stem cell transplantation is still the only curative treatment but only for a small subset of eligible patients. Using cutting-edge technologies, scientists at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, together with researchers from the Medical University of Vienna and the University of Pavia were now able to identify possible targets for immunotherapy which could also serve as a blueprint for cancer vaccine production.**

Recent advances in T-cell based immunotherapy have raised hopes for curative treatments, capable of eliminating the cancer cell. A key requirement for targeted immunotherapy is the identification of antigens that are present in tumor cells but absent in healthy cells. These antigens are mutated parts of proteins present in the tumor cells of the patient. Traditionally, tumor antigen identification has been limited by either high costs or low sensitivity depending on the implemented methodology.

In this study, spearheaded by scientists at CeMM Research Center for Molecular Medicine in collaboration with researchers from the Medical University of Vienna and the University of Pavia, a novel RNA-based methodology has been developed for the systematic identification of cancer antigens for each patient. Fiorella Schischlik, first author of the study and PhD student at CeMM; reflects: “As a bioinformatician, with a particular interest in data analysis, I was excited to find how much useful information can be extracted from a single RNA sequencing data set.”

Using RNA sequencing performed on the tumor biopsy as a basis for target discovery is particularly efficient. First, only targets are identified that are expressed and therefore relevant and second, a variety of different mutation classes can be addressed. Fusions and splicing-related aberrations are examples of mutation classes, where RNA sequencing is the preferred method of their systematic discovery. In this study, the researchers were able to demonstrate that especially patients with mutations in the splicing factor *SF3B1* and *CALR* genes produce a variety of tumor specific peptides. These altered peptides could serve as a blueprint for cancer vaccine production.

Robert Kralovics, Principal Investigator at CeMM and corresponding author of the study is excited to start the next step in target validation: “We want to show that these tumor-specific antigens are capable of eliciting an immunogenic response in the patients and are, therefore, suitable to serve as *bona fide* targets for T-cell directed killing of the cancer cell. Finding immunotherapy targets in 62% of MPN patients – as a conservative estimation - is raising hope that many MPN patients might benefit from this approach.”

The study “Mutational Landscape of the Transcriptome Offers Putative Targets for Immunotherapy of Myeloproliferative Neoplasms” has been published in *Blood*.
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