MOI Project 13

Functional fine-mapping of HLA- and KIR-mediate Hepatitis C immune control through long-read sequencing and single-cell transcriptomics

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Hepatitis C virus (HCV) is an important model for chronic viral infections and for characterizing the impact of chronic antigen stimulation and inflammation on the human immune system. The outcome of HCV infection is influenced by immunogenetic variability, in particular in the MHC/HLA and the LRC/KIR regions of the human genome, and associated with functional differences in NK and T cell populations, for example regarding the NKG2A receptor.

Due to the sequence complexity of the MHC/HLA and LRC/KIR regions, it has not been possible yet to determine the individual genetic variants driving the observed associations with HCV outcome in these genomic regions; in addition, it is not clear to which extent the observed associations between HCV outcomes and immune cell populations reflect preexisting and potentially genetically mediated differences (e.g. depending on the genotype in the KIR locus, which plays an important role in the regulation of KIR cells), or to which extent these differences relate to chronic immune stimulation and inflammation in e.g. chronically infected individuals.

The aim of this project is to better characterize the immune control of HCV and, conversely, the transcriptomic effect of chronic HCV infection on immune cell populations and on NK cells in particular. To achieve these aims, we will apply genetic and immune characterization approaches to a deeply characterized cohort of drug-injecting individuals (“people who inject drugs“ / PWIDs), comprising individuals with diverse outcomes after HCV as well as individuals who remain seronegative despite certain HCV exposure.

Specifically, we will

(i) carry out a comprehensive immunogenetic characterization of the PWID cohort based on long-read sequencing, focusing on the MHC/HLA and LRC/KIR regions of the human genome. This project component will leverage existing long-read-based immunogenetic genotyping approaches as well as contribute to the development of new methods through targeted sequencing and advanced bioinformatics;

(ii) use the generated immunogenetics data to fine-map the observed associations between immunogenetic variation and HCV outcomes, using e.g. multivariate logistic regression and linear mixed models (LMMs);

(iii) carry out a joint characterization of NK cell transcriptomes and phenotypes using single-cell transcriptomics with integrated phenotyping (CITE-seq):

(iv) analyze NK cell phenotypes and transcriptomes with respect to both genetic variability and with respect to differential HCV outcomes, using multivariate statistical modeling approaches.

In summary, this project, carried out in collaboration with the Timm lab, will contribute to an improved understanding of the interplay between genetic variation and immune cell function in the immune

control of HCV, using an exciting mix of state-of-the-art methods such as long-read sequencing, single-cell transcriptomics, and advanced algorithmics and bioinformatics.