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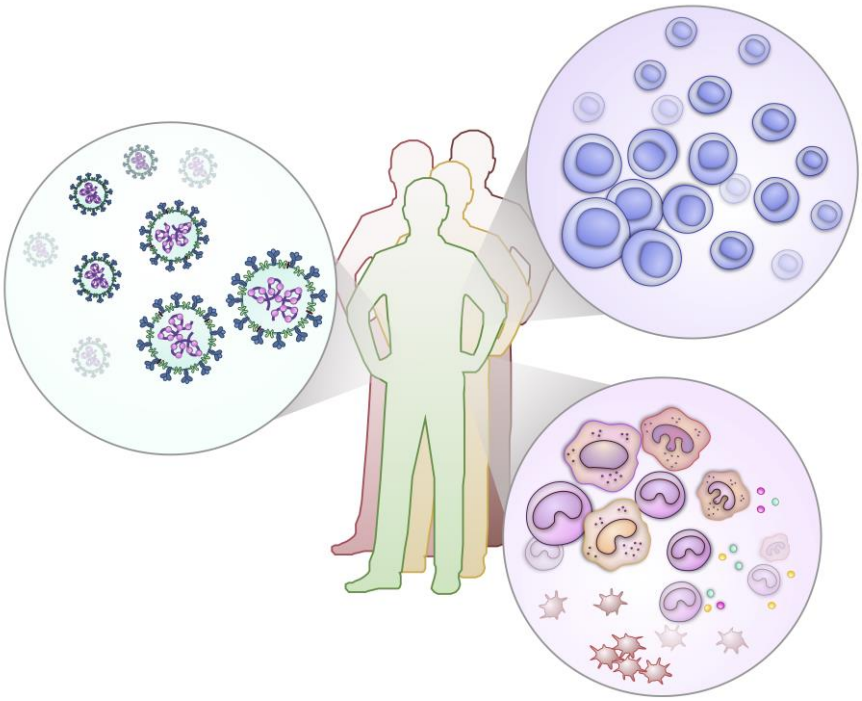

Mechanisms of Immune Dysregulation in COVID-19 and Chronic Lymphocytic Leukemia

Assessing functional innate immune profiles in two different disease modalities using standardized, clinically implemented methods

PhD Thesis

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SUMMARY IN ENGLISH

The immune system comprises a sophisticated network of tissues, cells, and signaling molecules working together to protect the host from threats that cause disease like pathogens and cancer.

Chronic lymphocytic leukemia (CLL) is a B cell malignancy associated with an increased risk of severe infections. Although different aspects of CLL-related immune dysfunction have been studied, clinical tools for identifying patients at risk are lacking. The emergence of targeted therapy has changed the paradigm for how we treat CLL. While efficacious in treating CLL, targeted therapy has also been shown to disrupt the cross talk between CLL and immune cells comprising the tumor-supportive microenvironment, which may lead to improved immune function. However, targeted therapy also entails complications. One such complication related to treatment with Bruton's tyrosine kinase inhibitors (BTKi) is bleeding, indicating dysregulation of the hemostatic branch of the immune system. Thus, mechanisms of immune dysregulation in CLL warrant further study and may enable development of clinical tools for identifying patients with risk of immune related complications such as infections or bleeding both prior to and during treatment.

In early 2020 the World Health Organization announced a global health crisis due to the coronavirus disease 2019 (COVID-19) pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). At the beginning of the pandemic, the immunopathology underlying the diverse clinical presentation of COVID-19 was largely unknown. In particular, the early immune mechanisms driving progression to severe and critical disease warranted further study. Patient related risk factors such as high age and comorbidities were inadequate to identify patients at risk of severe disease upon hospitalization, highlighting a need for improved risk stratification tools in clinical practice.

Paper I of this thesis investigated mechanisms of dysregulated immune hemostasis and potential contributions to bleeding risk in CLL patients receiving targeted treatment with the BTKi ibrutinib (IBR) combined with venetoclax (VEN), an inhibitor of the anti-apoptotic protein B cell Lymphoma 2 (BCL2i). The findings showed that CLL patients needing treatment exhibited impairments in primary hemostasis that improved significantly upon VEN+IBR combination therapy. The improvements were paralleled by a decline in bleeding-related adverse events. This study supports a CLL-induced platelet dysfunction that may predispose for risk of bleeding upon BTKi treatment, and that adding VEN to IBR may reduce this bleeding risk by rapidly eliminating CLL cells.

Paper II investigated mechanisms of innate immune dysfunction and the potential impact on disease severity trajectories in patients hospitalized with COVID-19. The findings showed that impairments in innate immune responses at time of COVID-19 hospitalization were associated subsequently developed disease severity. Based on functional immune assessment data, a functional immune response signature was identified for predicting risk of severe or critical disease upon hospitalization which was validated in a separate cohort.

These findings support a role of functional immunology in risk prediction and clinical assessment of COVID-19 with potential to be translated to other infectious diseases.

Paper III investigated **mechanisms of innate immune dysfunction** and the potential influence on infectious susceptibility in patients with CLL prior to and during targeted treatment. The findings showed that CLL patients needing treatment exhibited functional innate immune impairments along with a dysregulated myeloid compartment characterized by monocyte exhaustion and aberrant granulocyte activation. Targeted therapy with BTKi rapidly improved innate immune function which was paralleled by a decline in duration of infections. Long-term BTKi treatment or combined BTKi+BCL2i therapy sustained immune function while also restoring the myeloid compartment phenotypes, which was paralleled by a decline in infection frequency and severity. These findings propose a role of innate immune dysregulation in contributing to risk of infections in CLL and proposes short-term targeted therapy as potential strategy to reduce infectious risk.

The findings of this thesis highlights mechanisms of innate immune dysregulation that likely contributes to adverse disease trajectories and complications related to COVID-19 infection and CLL disease. This thesis proposes an impactful role of functional whole blood immunological methods as clinical risk assessment- and monitoring tools to be applied in the context of acute infection as well as chronic malignancy.