Abstract #26 | Poster

Mechanisms of humoral immune dysfunction in the Eμ-TCL1 adoptive transfer mouse model of chronic lymphocytic leukemia

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Chronic lymphocytic leukemia (CLL) is the most common leukemia among adults. Despite advances in the control of the disease, CLL remains incurable. A hallmark of CLL is progressive immune deficiency, which significantly contributes to the premature death of patients. This deficiency is already observable in early stages of the disease, when the tumor burden is still low, suggesting that interactions between CLL cells and normal immune cells might impair their functionality. It is already known that CLL is accompanied by shifts in T cell subset distribution and impaired T cell functionality. However, despite its clinical significance, the effect of CLL cells on the humoral immune system remains critically understudied. This project therefore aims at elucidating the mechanisms of the CLL-associated humoral immune dysfunction.

The Eμ-TCL1 mouse model is the most commonly used model of CLL and reliably develops $CD5^+$ B cell leukemia that recapitulates key characteristics of human CLL. Here the adoptive transfer system is used, in which CLL cells from Eμ-TCL1 animals are transplanted into syngeneic, wild-type recipients, resulting in a rapid establishment and progression of the disease.

To gain insight into the effect of CLL on the T cell-dependent immune response, CLL-bearing animals were immunized with the T-dependent antigen NP-OVAL. Ten days later, the animals were sacrificed, and the normal residual B cells were analyzed via flow cytometry. CLL-bearing mice showed mostly a complete lack or sporadically a reduced number of splenic, germinal center B cells after immunization. This effect could be observed even at early stages of disease with minimally infiltrated spleens and therefore does not seem to be explained solely by a displacement of the healthy B cell compartment. Additionally, no reduction in the number of T follicular helper cells was observed in immunized CLL-bearing animals. Furthermore, resting B cells from CLL-bearing animals showed only a minor impairment in their activation capacity upon *ex vivo* stimulation with an anti-CD40 antibody.

As of now, the cause of the impaired response to immunization remains elusive. Potential explanations include an aberrant localization of immune cells or an impaired T cell-B cell interaction. To further explore these possibilities, we will employ scRNA sequencing and multiplex immunofluorescence to investigate the cause of this clinically relevant phenomenon at the single-cell level.