Abstract #3 | Poster

The Influence of HIV on the B Cell System and Lymphomagenesis

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Human immunodeficiency virus (HIV) infection can nowadays be effectively controlled by antiretroviral therapy (ART). However, the incidence of B cell non-Hodgkin lymphoma (B-NHL) is still ten times higher in people living with HIV (PLWHIV) than in the general population, meaning that roughly 10% of PLWHIV will be diagnosed with B-NHL at some point. This project aims to elucidate how HIV infection influences the B cell system and contributes to lymphomagenesis, potentially informing therapeutic or prophylactic targets.

We will examine both the normal B cells of PLWHIV and HIV-associated lymphomas. B cells of PLWHIV (n = 51) were investigated by flow cytometry. The B cell composition of PLWHIV differs from that of HIV-negative persons. For example, the number of IgM^+/IgD^+ memory B cells is diminished in PLWHIV, while the $CD21^{low}$ and transitional subsets are expanded. These changes are only partially reverted by effective ART. B cell subsets from 10 patients were sort-purified and the B-cell receptor (BCR) repertoires are sequenced to identify pre-lymphomagenesis alterations in the B cell system, e.g. expanded clones.

Recurrent mutations and mutational signatures of HIV-associated lymphomas are identified after whole genome sequencing (WGS) of lymphoma samples (n = 6). After appropriately filtering the WGS data, recurrent mutations and mutational signatures were identified. Mutations will be selectively validated using a PCR-based Sanger sequencing approach. Additional samples and pre-existing datasets will be added to the analysis, and the results will be compared to datasets of HIV-negative lymphomas to identify factors unique to HIV infection.

Finally, the BCRs of HIV-associated lymphomas may contribute to lymphomagenesis *via* persistent stimulation by their cognate antigens. BCRs of 28 HIV-associated lymphomas were sequenced, revealing that a large portion of BCRs is nonfunctional due to deleterious mutations in either the heavy- or light chain loci. 7 productive clones for which both heavy and light chain V(D)J regions could be sequenced in full were expressed as soluble IgG for use in autoantigen- and HIV-specific assays, e.g. protein arrays or lateral flow assays, determining the specificities of the BCRs.