Abstract #65 | Poster

Deciphering the Pathomechanisms of HIV-Associated Lymphomas

V. Berg[1], N. Kahlert[1], K. Danielzik[3], A. Rosenwald[4], G. Ott[5], A. Ross[12], M. Dampmann[2], S. Dolff[6], S. Hartmann[9], P. Möller[8], M. Hummel[10], S. Esser[7], L. Thurner[11], D. Hoffmann[3], B. Budeus[1], R. Küppers[1]

[1] *University Hospital Essen, Institute of Cell Biology (Tumor Research), Essen, Germany*
[2] *University Hospital Essen, West German Tumour Centre, Essen, Germany*
[3] *University of Duisburg-Essen, Bioinformatics and Computational Biophysics, Essen, Germany*
[4] *University of Würzburg, Institute of Pathology, Würzburg, Germany*
[5] *Robert Bosch Hospital, Institute of Pathology, Stuttgart, Germany*
[6] *University Hospital Essen, Department of Infectiology, Essen, Germany*
[7] *University Hospital Essen, Department of Dermatology, Essen, Germany*
[8] *University Hospital Ulm, Department of Pathology, Essen, Germany*
[9] *University Hospital Essen, Department of Pathology, Essen, Germany*
[10] *Charité University Medicine, Institute of Pathology, Berlin, Germany*
[11] *University Hospital Saarland, José Carreras Center, Homburg, Germany*
[12] *University of Duisburg-Essen, Therapy Research in Neurogeriatrics, Essen, Germany*

HIV-associated lymphomas (HIVALs) affect about 1 in 10 people living with HIV (PLWH), contributing to high morbidity and mortality even in the era of effective antiretroviral therapy (ART). We investigated three different hypotheses on which mechanism(s) contribute to lymphomagenesis in PLWH.

First, we analysed the non-malignant lymphocytes of PLWH for evidence of alterations of B or T cell subsets, e.g. pre-malignant expansions. We found that most B and T cell subsets are substantially decreased in PLWH, but partially normalize under ART, confirming results of previous studies. Notable exceptions were the atypical/exhausted $CD21^{low}$ B cell subsets as well as the terminally differentiated T_{EMRA} T cell subsets, which were increased in PLWH. We found that the B cell receptor (BCR) repertoires of PLWH may be biased towards autoreactivity, as we identified elevated numbers of the intrinsically autoreactive *IGHV4-34* gene in several B cell subsets which decreased under ART.

Second, we performed whole exome sequencing (WES) or whole genome sequencing (WGS) on 26 HIVALs. We identified recurrent mutations in several genes associated with lymphomagenesis. HIVALs appear to be genetically similar to their HIV-negative counterparts, which corroborates the results of previous studies. Notable exceptions are the genes *FAT4* and *STAT3*, which are mutated in 31% and 19% of our HIVAL cohort, respectively. In HIV-negative DLBCL, mutation frequencies of these genes are much lower, raising the possibility that *FAT4* and *STAT3* are mechanistically important in HIVALs. As both genes can influence the activity of the Wnt pathway, there may be synergistic effects if they are concurrently mutated.

Third, we investigated the BCR specificities of HIVALs as chronic BCR stimulation can contribute to lymphomagenesis. We found that the majority of BCRs bind to one of two related autoantigens. Elevated titers against these two proteins were present in 3 of 4 sera of PLWH with lymphomas, but in only 1 of 5 sera of PLWH without a lymphoma. We anticipate that this finding may be used in clinical applications such as diagnostic testing and risk stratification.