Background T cells play a central role in tumor immunity. In principle, T cell requires antigen recognition by T-cell receptor (TCR) to gain effector function. Antigen-driven activation leads to clonal T-cell expansion with generation of progeny cells that all express the same chromotypic TCR. This makes TCR analysis a useful tool to comprehensively and individually understand antigen-specific T-cell responses. Indeed, we previously showed that the TCR repertoires of CD8+ T cells but not CD4+ T cells are restricted with many clones in the blood of psoriasis patients. Together with the strong genetic association to HLA-C*06:02 causing an autoimmune CD8+ T-cell response against melanocytes in psoriasis, our results from TCR analyses clearly indicate an autoimmune pathogenesis of psoriasis.

**Patients and Methods**

Here, we utilize our expertise to understand how anti-tumor T-cell responses affect clinical responses and immune-related adverse events (irAEs) in therapeutic checkpoint inhibitions. We analyzed melanoma patients upon the therapeutic blockade of cytotoxic T-lymphocyte-associated protein 4 (CTLA4) or programmed cell death 1 (PD-1) using TCR Vβ-gene spectratyping.

**Results**

Surprisingly, we observed variable levels of restriction in CD4+ and extensive restrictions in CD8+ T-cell repertoires in the blood of melanoma patients compared to healthy controls. This indicates the presence of a substantial numbers of CD4+ and CD8+ T-cell clones in the blood prior to the initiation of immunotherapy. The clones detected in the blood were enriched in tumor-infiltrating lymphocytes (TILs). This suggests that melanoma-reactive T-cell clones circulate more frequently in melanoma patients, although it is generally assumed that tumor-specific T-cell clones are only detectable in TILs. Greater diversification particularly in CD4+ blood T-cell clones before immunotherapy correlated with long-term survival after CTLA4 or PD-1 inhibition. In patients who developed severe immune-related adverse events (irAEs) during CTLA4 blockade, we detected newly expanded blood T-cell clones, suggesting that newly emerged T-cell responses contributed to these irAEs.

**Conclusions**

Our data demonstrate that the diversity of T-cell clones in the circulation may reflect the anti-melanoma responses. This study provides a rationale for predicting clinical responses to checkpoint inhibitors using patient’s blood, and also emphasizes importance of CD4+ T cell-mediated anti-tumor immunity in melanoma.

**Disclosure Information**

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**DIVERSITY OF CD4+ BLOOD T-CELL CLONALITY PREDICTS LONGER SURVIVAL WITH CTLA4 OR PD-1 CHECKPOINT INHIBITION IN ADVANCED MELANOMA**

1A Arakawa*, 1S Vollmer, 1J Tietze, 1A Galinski, 1MV Hepp, 2C Berking, 1JC Prinz. 1Department of Dermatology and Allergy, LMU, München, Germany; 2University Hospital Rostock, Rostock, Germany, 3Universitätsklinikum Erlangen, Erlangen, Germany

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