BROAD T ANTIGEN-SPECIFIC CD8+ T CELL REPERTOIRE IS ASSOCIATED WITH RESPONSE TO PD-1 BLOCKADE IN VIRUS POSITIVE MERKEL CELL CARCINOMA

¹Ulla Hansen*, ²Candice Church, ¹Amalie Bentzen, ³Steven Fling, ³Nirasha Ramchurren, ⁴Suzanne Topalian, ²Paul Nghiem, ¹Sine Hadrup. ¹Technical University of Denmark, Kgs. Lyngby, Denmark; ²University of Washington, Seattle, USA; ³Fred Hutchinson Cancer Research Center, Seattle, WA, USA; ⁴Johns Hopkins University School of Med., Baltimore, MD, USA

Background Merkel cell carcinoma (MCC) is an aggressive human skin cancer primarily induced by Merkel Cell Polyomavirus (MCPyV) driven by expression of the oncogenic T antigens (T-Ags): Large T and Small T antigen. Checkpoint inhibition therapy blocking the programmed cell death protein-1 (PD-1) pathway has proven effective with a clinical response rate up to 58%,¹ highlighting the critical role of immune surveillance for tumor control. Yet, evidence for the impact of T-Ag-specific T cells following immunotherapy is still limited.

Methods Potential CD8+ T cell epitopes derived from the T-Ags and the Viral capsid protein 1 (VP1) were predicted with netMHCpan 4.0 as 9- and 10-mer peptides with a rank score <2 for binding to 33 different HLA class I types. Peripheral blood mononuclear cells (PBMC) were obtained from 24 MCPyV+ MCC patients prior and post anti-PD-1 therapy initiation (CITN-09/Keynote-017). T cell recognition of the MCPyV-derived peptides during therapy was evaluated using the high-throughput technology of DNA barcode labeled pMHC multimers. Phenotypic characteristics of multimer-binding T cells were evaluated for selected patients.

Results Across all patients, 40 T-Ag-specific CD8+ T-cell populations were detected recognizing 31 epitopes restriction to 14 different HLA class I types. T-Ag-specific CD8+ T cells were detected in responders (complete and partial response, n=17) during therapy with a trend of increased number of responses observed after therapy initiation. Whereas only a single T-Ag-specific population was detectable in non-responders (stable and progressive disease, n=7). Moreover, the T cell repertoire after therapy initiation was significantly increased in the responder group compared to non-responder with the T-Ag-specific T cells showing an activated effector memory phenotype.

Conclusions The current study indicates that the T-Ag-specific T cells are associated with clinical benefit to checkpoint inhibitor therapy. Furthermore, the broad identification of novel T-Ag-derived T cell epitopes could potentially facilitate the use of targeted T cell therapy to enhance T cell recognition and clearance of MCC in combination with checkpoint inhibition.

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REFERENCE

1. Nghiem P, Bhatia S, Lipson E. Three-year survival, correlates and salvage therapies in patients receiving first-line pembrolizumab for advanced Merkel cell carcinoma. *J Immunother cancer* 2021;9:e002478.

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