Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

The study on myeloid-derived suppressor cells (MDSCs) and T cells in melanoma patients with adverse events after immunotherapy immune checkpoint inhibitors

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Immune checkpoint inhibitors (ICI) represent a remarkable breakthrough in melanoma treatment. The therapy could considerably improve treatment outcomes, particularly for advanced melanoma patients. However, despite the great success of ICI therapy, approximately 30-60% of patients experience immunological side effects, known as immune-related adverse events (irAE). IrAE can be triggered by an overactivation of the immune system following ICI treatment. These adverse events can sometimes be fatal, leading to lasting organ damage, the requirement for systemic immunomodulatory treatment, and even treatment discontinuation. Therefore, biomarkers capable of predicting irAE onset or identifying patients at risk of experiencing irAE are crucial for effective diagnosis and management.
IrAE development might be attributed to an imbalanced immune system, which can be mediated by increased T cell activity or a loss of function of immunosuppressive cell subsets like regulator T cell (Tregs).
In the present study, I aimed to establish an immune profile in the peripheral blood of melanoma patients associated with irAE onset. For this purpose, I conducted routine laboratory tests and flow cytometry analysis of peripheral blood samples from 31 melanoma patients treated with anti-PD-1 monotherapy or anti-PD-1-/anti-CTLA-4 combination therapy. I investigated the activation status of T cells and the role of immunosuppressive subsets like Tregs and monocytic myeloid-derived suppressor cells (M-MDSCs) in patients with and without irAE. My analysis included different time points: before ICI start, during ICI treatment, at the onset of irAE, and during immunosuppressive treatment to manage irAE.
Overall, I observed a significantly improved progression-free survival (PFS) among patients with irAE. Additionally, I demonstrated an activation of $CD8^+$ T cells indicated by an upregulation of the early activation marker CD69, and an increased frequency of activated $CD4^+$ T cells ($CD4^+CD25^+FOXP3^-$) during irAE. Furthermore, I revealed a decrease in Tregs during irAE occurrence. Moreover, lower frequencies of Tregs correlated with more severe adverse events.
Another aim of this study was to evaluate the impact of immunomodulatory drugs following irAE on circulating immune cell subsets. Here, I observed that the number of M-MDSCs and Tregs tended to be elevated during immunosuppressive treatment.
Analysis of routine blood laboratory tests found increased LDH and CRP serum levels during adverse events.
Taken together, the present study identified that certain activated T cell subsets and the decrease of Tregs may lead to an imbalanced immune homeostasis, which could potentially promote the occurrence of irAE.