**Peripheral CD8$^+$ T-cell Monitoring for the Prediction of Patient Response to Checkpoint Blockade Therapy**

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Immune checkpoints (IC) are mechanisms used to establish self-tolerance but are often hijacked by tumors for immune evasion. Immune checkpoint inhibitors (ICI) have seen recent success in the clinic, producing durable responses in a subset of patients with melanoma. However clinicians and researchers have yet to fully characterize mechanisms of de novo and acquired responsiveness to therapy. We have noted a correlation between higher expression of lineage-specific proteins and immunotherapy response, suggesting a breakdown of tolerance to melanocyte lineage specific self-antigens (5). This parallels the clinical observation that vitiligo, a pigmentation disorder resulting from autoimmune destruction of melanocytes, is more prevalent in patients that respond well to immunotherapy (3). Vitiligo has been shown to appear after anti-PD1 therapy in one out of four patients with melanoma and correlates with a better response to therapy (4). This effect is absent from most other types of cancers, implying that there may be epitope spread or some elements of lineage-specific tissue recognition. Based on these findings, we hypothesize that melanocyte lineage-specific antigens are recognized by the immune system during treatment with checkpoint inhibitor blockade in melanoma. We have established an approach to monitor T cell lineage-specific antigen recognition via analysis of peripheral blood-derived T cells during ICI therapy. Several melanocyte-specific antigens are upregulated and highly expressed in melanocytes and melanoma cells (gp100, tyrosinase, MAGEA1, MAGEA3, MART1, etc.) (1,2). Using an MHC dextramer panel with nine melanocyte-specific antigens, we have identified a subpopulation of CD8+ T-cells that are reactive to Tyrosinase and MART1. This subpopulation of CD8+ T-cells increased in frequency following anti-PD1 therapy, suggesting that checkpoint blockade promotes the breakdown of tolerance toward melanocyte-lineage self-antigens. We also noted that in several patients, an increase in lineage-specific antigen positive CD8+ T-cells correlated inversely with RECIST response and was more pronounced in patients with vitiligo. We hypothesize that monitoring of peripheral blood-derived CD8+ T-cell subsets may provide a tool for monitoring lineage-specific cellular recognition during ICI therapy. Moving forward we aim to characterize circulating antigen-specific T cell responses during ICI and undertake comparative analysis with paired tumor infiltrating lymphocytes (TIL) prior to and during ICI therapy.

References:

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