Researchers uncover potential biomarkers of positive response to immunotherapy

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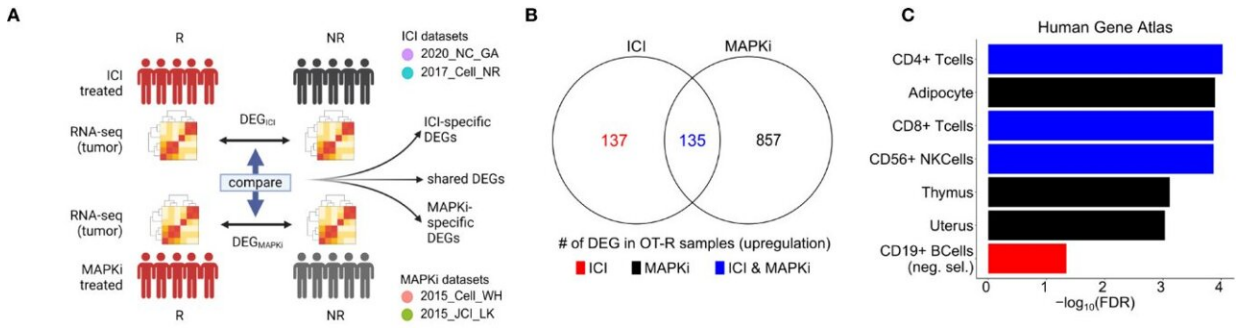

Response to ICI or MAPKi therapy is associated with increased T cell infiltration and enhanced interferon gamma (IFNγ) pathway activity in the tumor. (A) Schematic of comparative analysis between transcriptomic response to ICI or MAPKi therapy. (B) The number of differentially upregulated genes in ICI OT-R (on treatment-responding) tumors (red), MAPKi OT-R (black) or both (blue). The differentially expressed genes (DEGs) are computed with respect to the OT-NR (on treatment-non responding) tumors of each group. (C) Enriched cell marker genes (based on Human Gene Atlas using Enrichr tool) in ICI-specific, MAPKi-specific, and ICI and MAPKi-shared upregulated DEGs in (B). Credit: *Frontiers in Immunology* (2023). DOI: 10.3389/fimmu.2023.1176994

Scientists at the UCLA Jonsson Comprehensive Cancer Center have identified potential new biomarkers that could indicate how someone diagnosed with metastatic melanoma will respond to immunotherapy treatment.

The researchers found when T cells are activated, they release a protein called CXCL13, which helps attract more B cells and T cells to the tumor site. The B cells then show the T cells specific parts of the tumor, which leads to increased activation of the T cells and their ability to fight the cancer. This cooperation between T cells and B cells was associated with improved survival in patients diagnosed with metastatic melanoma who were treated with immunotherapy, but not for those who received targeted therapy (e.g., MEK inhibitors).

These findings could help guide new strategies to improve the effectiveness of melanoma cancer treatments. The research is published in the journal *Frontiers in Immunology*.

"Based upon our data, increased presence of B cells and CXCL13 protein in the tumor after immunotherapy treatment may be predictive biomarkers for durable immunotherapy response in melanoma patients and may be avenues to enhance the response rate to immunotherapy in patients diagnosed with melanoma," said co-senior author of the paper Willy Hugo, Ph.D., assistant professor of Medicine in the division of Dermatology at the David Geffen School of Medicine at UCLA and member of the UCLA Jonsson Comprehensive Cancer Center. "For example, combination of anti-PD1 treatments with CXCL13 or B cell-directed therapies may be strategies for patients who fail to respond to checkpoint immunotherapy alone."

Immune checkpoint inhibitors, which harness the body's immune system to better attack cancer cells, have revolutionized the way people with melanoma are treated. People with aggressive forms of the cancer are now living longer, healthier lives. Despite the remarkable success of using immune checkpoint inhibitors to treat people with advanced melanoma, it is still difficult to predict who will benefit from the therapy.

Identifying mechanisms that determine how tumors can become resistant to these therapies and understanding how to identify patients who will and will not respond to them is critical to developing new and improved treatments to help improve the response rate of these therapies.

To understand what may drive durable antitumor immune responses seen with checkpoint immunotherapy in some melanoma patients, and why such responses are less often seen in patients treated with other FDA-approved targeted therapies, such as mutant BRAF and MEK inhibitors, the UCLA team compared the immune responses induced by existing standard care targeted and immunotherapies for people with metastatic melanoma.

The team completed a comparative genomics analysis using published RNA-seq profiles of melanoma samples collected before and after either therapy. They found that response to immunotherapy, but not targeted therapy, is accompanied with significant infiltration of clonally diverse B cells. The increase of B cell infiltration in response to immunotherapy is accompanied by a significant upregulation of B-cell chemotactic factor, CXCL13, by T cells.

"This study suggests that CXCL13 may play an important role in bringing together T and B cells in the tumor microenvironment in patients who respond to checkpoint immunotherapy, and that this cooperation may be key to effective anti-tumor responses. Further studies are need to determine if these pathways can be boosted in non-responders to improve outcomes," said co-senior author of the paper Melissa Lechner, MD, Ph.D., assistant professor of Medicine in the division of Endocrinology at the David Geffen School of Medicine at UCLA and member of the UCLA Jonsson Comprehensive Cancer Center.

These data also support a role for antigen presentation by B cells to T

cells in the tumor microenvironment, and highlight the potential of using B cell-based cancer vaccines to enhance the effectiveness of immune checkpoint immunotherapies.

The team now plans to further explore these mechanisms in preclinical cancer models and test whether antigen presenting B cell and CXCL13 manipulation can improve anti-tumor immune responses in non-responders.

More information: Lizhong Ding et al, Antigen presentation by clonally diverse CXCR5+ B cells to CD4 and CD8 T cells is associated with durable response to immune checkpoint inhibitors, *Frontiers in Immunology* (2023). DOI: 10.3389/fimmu.2023.1176994

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