Two new studies show how immunotherapies collaborate to boost T cell responses in melanoma

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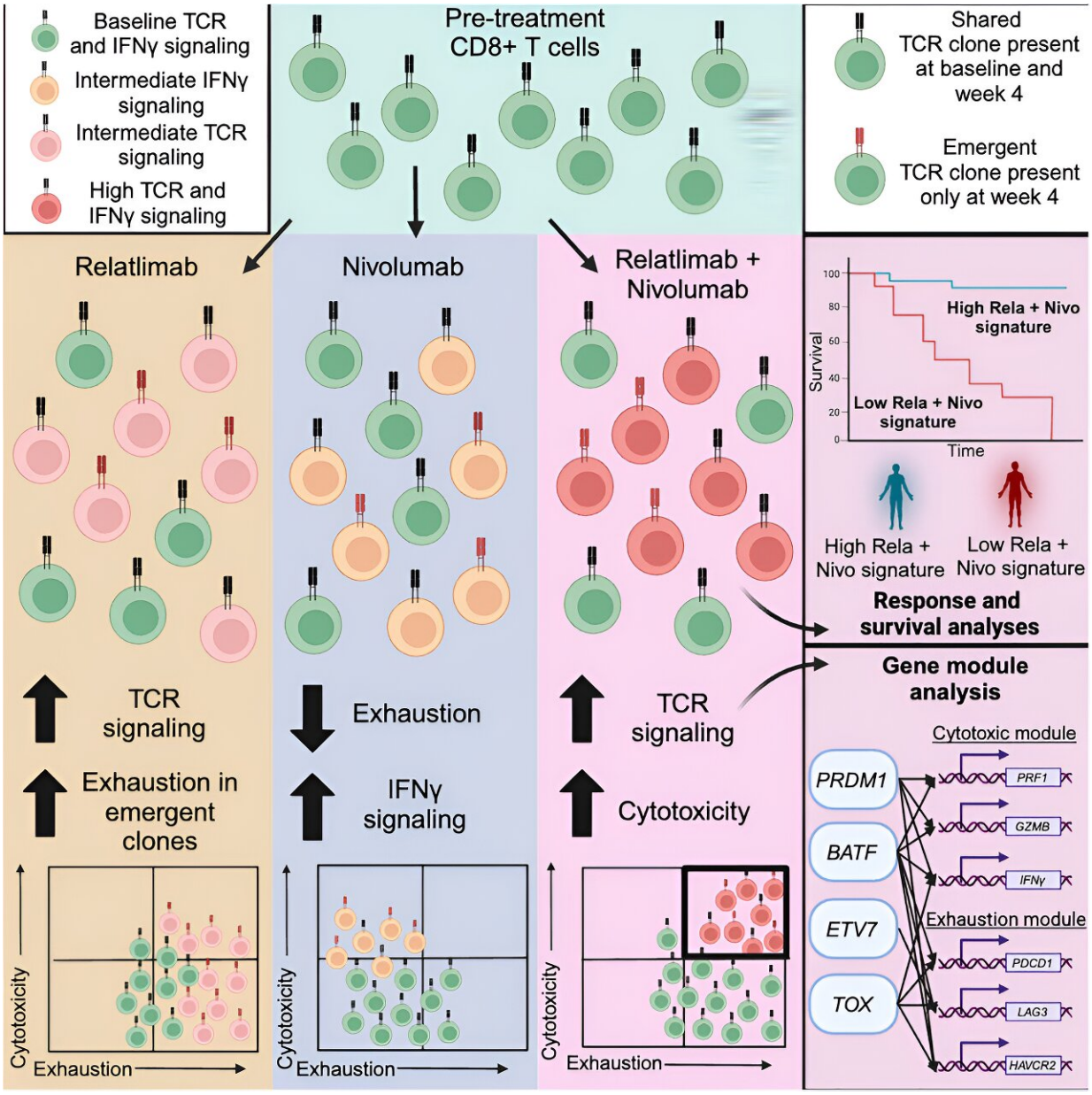

Credit: *Cell* (2024). DOI: 10.1016/j.cell.2024.06.036

Two studies published in the latest issue of the journal *Cell* by University of Pittsburgh researchers uncover how immunotherapies targeting the immune checkpoints PD1 and LAG3 work together to activate immune responses. The findings shed light on why combination therapies targeting both checkpoints can improve outcomes for melanoma patients compared to monotherapies targeting only PD1.

Using data from a human clinical trial and animal models, the researchers investigated responses of tumor-killing $CD8^+$ T cells. During extended battles with cancer, immune checkpoints accumulate on the surface of T cells, acting like brakes on their activity and driving exhaustion. Immune checkpoint inhibitors that help release these brakes and combat T cell exhaustion have revolutionized cancer treatment, but because many patients don't respond, more research is needed to understand how these drugs can be combined to improve their effectiveness.

"These studies are the first in-depth interrogation of the immune system's response to blocking PD1 and LAG3," said Dario A. A. Vignali, Ph.D., chair and distinguished professor of the Department of Immunology at Pitt, senior author on two of the papers. "We found that targeting PD1 versus both PD1 and LAG3 modulated the function of $CD8^+$ T cells in surprisingly different ways. Understanding these mechanisms is relevant for how we think about combination therapies and optimizing which drugs pair best."

In 2022, the LAG3-targeting drug relatlimab was approved by the U.S.

Food and Drug Administration as a combination treatment with nivolumab, which targets PD1, for patients with metastatic melanoma. This combination has been shown to greatly improve patient outcomes compared to nivolumab alone, but according to Vignali, the mechanisms underlying this enhanced anti-tumor immunity were unknown. These new studies help fill this gap.

For the first study, Vignali joined forces with co-senior authors John Kirkwood, M.D., distinguished service professor of medicine at Pitt and director of the Melanoma and Skin Cancer Program at UPMC Hillman Cancer Center and Tullia Bruno, Ph.D., assistant professor of immunology at Pitt, and lead author Anthony Cillo, Ph.D., assistant professor of immunology at Pitt. The researchers ran a clinical trial to investigate immune responses of melanoma patients who received relatlimab, nivolumab or both drugs.

Analyzing blood and tumor samples, they found that patients who received both drugs had enhanced $CD8^+$ T cell responses associated with improved cancer-killing prowess compared to those from patients treated with either drug alone, despite the cells retaining the hallmarks of exhaustion.

"We were surprised to see that blocking both PD1 and LAG3 at the same time led to much greater changes than you would expect from adding the effects of blocking PD1 or LAG3 by themselves," said Cillo. "These findings show that these immune checkpoints inhibit different aspects of $CD8^+$ T cell function, which allows them to synergize in an unexpected way."

According to the researchers, another key finding from analyzing patient samples is that relatlimab is not inert. This study was unique in that patients initially received four weeks of therapy with relatlimab alone, nivolumab alone or in combination, allowing the researchers to examine

the effect of each therapeutic regimen.

Several previous studies have found that relatlimab alone does not improve anti-tumor immunity but was only effective when combined with nivolumab. By showing how relatlimab impacts T cell responses, the new findings suggest that the therapy could be combined with other immunotherapies to improve responses.

"We are particularly excited about this research because the analyses were performed on samples from patients who had not received prior immunotherapy, which allowed us to assess the impact of LAG3 and PD1 alone and in combination on the immune response within these patient tumors," said Bruno. "This will give us further insight toward smart immunotherapy combinations for patients with the hope for improved efficacy."

The second study, led by Lawrence Andrews, Ph.D., senior scientist at Arcellx who did this work as a research scientist in Vignali's lab, and Samuel Butler, a current graduate student in Vignali's lab, used mice that had been genetically modified so that their $CD8^+$ T cells didn't produce PD1, LAG3 or both.

In a mouse model of melanoma, T cells deficient in both immune checkpoints enhanced tumor clearance and improved survival compared to those lacking either PD1 or LAG3, reinforcing the clinical trial results. Further, their experiments revealed mechanisms in which PD1 and LAG3 synergize to hinder anti-tumor immunity.

A third study, published in the same issue of *Cell*, led by University of Pennsylvania researchers and on which Vignali was a co-author, concurred with these observations and provided additional insights into how LAG3 and PD1 contribute to T cell exhaustion in different ways.

Collectively, these three papers provide mechanistic insight into how PD1 and LAG3 function alone and in combination and highlight opportunities for further clinical development.

More information: Anthony R. Cillo et al, Blockade of LAG-3 and PD-1 leads to co-expression of cytotoxic and exhaustion gene modules in CD8+ T cells to promote antitumor immunity, *Cell* (2024). DOI: 10.1016/j.cell.2024.06.036

Lawrence P. Andrews et al, LAG-3 and PD-1 synergize on CD8+ T cells to drive T cell exhaustion and hinder autocrine IFN-γ-dependent anti-tumor immunity, *Cell* (2024). DOI: 10.1016/j.cell.2024.07.016

Shin Foong Ngiow et al, LAG-3 sustains TOX expression and regulates the CD94/NKG2-Qa-1b axis to govern exhausted CD8 T cell NK receptor expression and cytotoxicity, *Cell* (2024). DOI: 10.1016/j.cell.2024.07.018

Provided by University of Pittsburgh

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