

'Cutting the cable' between CD8+ T and T regulatory cells enhances checkpoint immunotherapy

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The research showed that CD8+ T cells (yellow) activated by PD-1 blockade also interact with T regulatory cells (teal and red), which subsequently dampen the immune response against the melanoma tumor cells (blue). Credit: UC Irvine School of Medicine, Department of Physiology & Biophysics and Institute for Immunology



Checkpoint immunotherapy utilizing PD-1 blockade has become the standard of care for metastatic melanoma. While this treatment is effective in 40% of patients, the other 60% develop resistance, leading to tumor regrowth. A multidisciplinary research team led by the University of California, Irvine has identified a new strategy that could enhance the therapeutic effectiveness of this therapy by targeting the communication between immune cells within the tumor.

In a <u>study</u> published online today in the journal *Cancer Cell*, researchers demonstrate that while PD-1 blockade activates a potent antitumor response in CD8⁺ T cells, it also promotes the accumulation of T regulatory cells, decreasing the <u>immune response</u> against the tumor. The activation of these competing signals—one set combating the tumor and the other restraining the immune system—is likely a significant challenge in providing effective cancer treatment.

"Our latest research reveals that CD8⁺ T cells, activated by PD-1 blockade to target melanoma, also interact with T regulatory cells, which subsequently dampen the immune response against the tumor," said corresponding author Francesco Marangoni, UC Irvine assistant professor of physiology & biophysics.

"We analyzed the intricate dynamics of communication between $CD8^+ T$ and T regulatory cells, which are analogous to two telephone landlines connected by a cable. If we cut the cable, the $CD8^+ T$ cells won't be able to 'call' the T regulatory cells and instruct them to inhibit the immune response to the cancer."

Team members focused on the mechanism of communication between CD8⁺ T and T regulatory cells in tumors and identified a pivotal role for a molecule called ICOS, which is required for T cell activation. They found that by neutralizing ICOS and PD-1, CD8⁺ T cells increased their activity against the tumor but could no longer stimulate T <u>regulatory cells</u>



"Our work helped identify a reason why some patients treated with checkpoint blockade develop resistance to it," said first author Shannon Geels, a UC Irvine graduate student researcher in the Department of Physiology & Biophysics. "We found that communication between cells can lead to immunotherapy failure and that we can improve efficacy by interrupting specific messages exchanged by <u>immune cells</u>."

The next phase of this research involves understanding the complex communication network among various cell types in a tumor.

"We do not think there is only one 'phone cable' to cut," Marangoni said. "Our findings provide a promising pathway to increasing our understanding of communication among all cell types within a <u>tumor</u>. This will enable us to identify the messages that block the full potential of CD8⁺ T cells stimulated by PD-1 blockade so that we can maximize the benefit to patients."

Other UC Irvine team members included faculty and graduate students from the physiology & biophysics, biological chemistry, dermatology and developmental & cell biology departments; the Institute for Immunology; the Center for Complex Biological Systems; and the NSF-Simons Center for Multiscale Cell Fate Research; as well as faculty from Saint John's Cancer Institute in Santa Monica; the University of Alabama at Birmingham; and Massachusetts General Hospital and Harvard Medical School.

More information: Harvard Medical School, University of California, Interruption of the Intratumor CD8+ T cell:Treg Crosstalk Improves the Efficacy of PD-1 Immunotherapy, *Cancer Cell* (2024). DOI: <u>10.1016/j.ccell.2024.05.013</u>. <u>www.cell.com/cancer-cell/fullt ...</u> <u>1535-6108(24)00181-8</u>



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