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Targeting interleukin-6 could help relieve immunotherapy side effects

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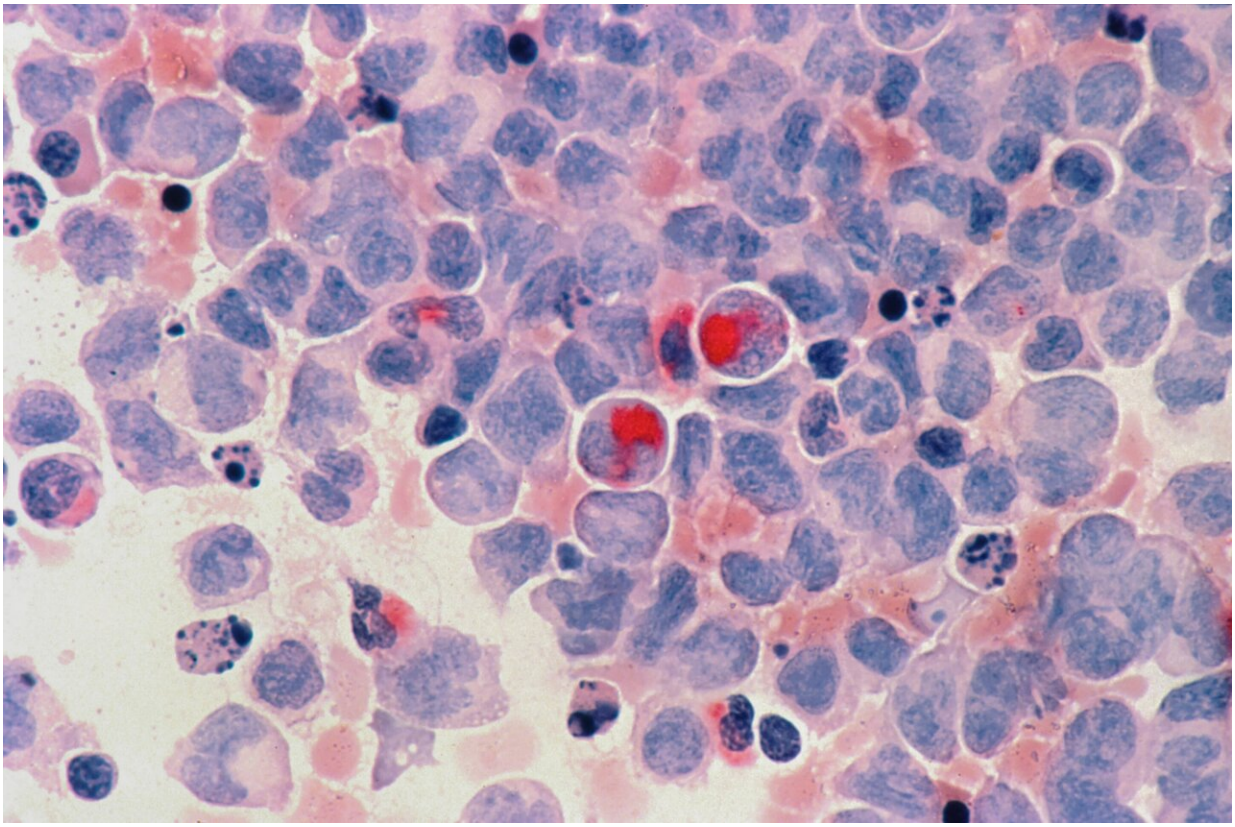

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Researchers at The University of Texas MD Anderson Cancer Center have identified a novel strategy to reduce immune-related adverse events from immunotherapy treatment by targeting the cytokine interleukin-6

(IL-6). The study, published today in *Cancer Cell*, establishes a proof of concept for combining immune checkpoint blockade with cytokine blockers to selectively inhibit inflammatory autoimmune responses.

While combination immunotherapy with anti-PD-1 and anti-CTLA-4 agents has revolutionized treatment for multiple cancer types, it also has high toxicity rates, which can affect quality of life and lead to treatment discontinuation. Often, patients whose cancers respond to combination immunotherapy also experience high-grade side effects. Immune-related enterocolitis (irEC), an inflammatory bowel condition, is the most common serious complication.

"We need to overcome immune toxicity, first and foremost, to support patients and reduce their symptom burden," said senior author Adi Diab, M.D., associate professor of Melanoma Medical Oncology. "Secondly, we know that there are multiple, non-overlapping mechanisms of resistance in the tumor microenvironment. In order to build an effective multi-agent immunotherapy regimen, we have to overcome the barrier of immune-related toxicity so that patients can continue receiving the optimum treatment."

The translational study analyzed patient tissue, preclinical models and retrospective data to determine how the IL-6 T-helper 17-cell (Th17) pathway contributes to toxicity and can be inhibited to separate the inflammatory autoimmune response from the antitumor immune response.

Preclinical studies reveal immunobiology of immune-related adverse events

IL-6 has been associated with immunotherapy resistance in preclinical models, but the mechanism was not well understood. IL-6 also is associated with several autoimmune diseases, and IL-6 blockers are

approved to treat rheumatologic disorders and other autoimmune conditions.

Comprehensive immune profiling of matched samples of irEC tissue and normal tissue from patients treated with immune checkpoint blockade (12 patients in the observation cohort and 11 in the validation cohort) revealed distinct immune signatures in the inflamed tissue (where IL-6 and Th17 were upregulated) compared to normal tissue. Furthermore, the IL-6 gene signature was upregulated in those whose tumors did not respond to immunotherapy, but the increased levels were not seen in responders.

Based on this observation, the researchers then used several preclinical models to evaluate the effect of an IL-6 blockade on autoimmunity and on response to anti-CTLA-4 therapy. The combination of an IL-6 blocker with immune checkpoint inhibitor decreased experimental autoimmune encephalomyelitis (EAE) symptoms and improved tumor control, indicating that the combination could suppress inflammatory response and potentially enhance antitumor immunity.

Observational cohort validates IL-6 strategy, prospective clinical trial in progress

To validate the findings, the researchers performed a retrospective analysis of 31 patients with melanoma who were treated with immune checkpoint blockade between January 2004 and March 2021 and also received an IL-6 blocker to treat inflammatory arthritis and other immune-related adverse events. Patients in the cohort received IL-6 blockade a median of 3.7 months after beginning to experience side effects, and the researchers noted a 74% improvement in symptoms after a median of two months on IL-6 blockade therapy.

Of the 26 patients with evaluable tumor response before (or early in)

IL-6 blockade therapy and at follow-up, the best overall response rate to immune checkpoint blockade was 57.7% before IL-6 blockade initiation and 65.4% after therapy. These clinical results supported the preclinical findings, which determined that targeting IL-6 can alleviate immune-related adverse events without compromising the efficacy of immunotherapy.

"Cytokine blockers have been well established to block autoimmunity. The novelty of this study is bringing cytokine targeting to tumor immunity and demonstrating that autoimmunity and antitumor immunity are not necessarily overlapping immune responses but can be decoupled at the cytokine level," Diab said. "IL-6 is only one cytokine, but this work offers proof of principle for taking the science to the next level by targeting multiple cytokines in a multi-layered approach."

Based on these results, Diab is leading an investigator-initiated Phase II prospective clinical trial (NCT04940299) to assess the safety and efficacy of IL-6 blockade in combination with anti-PD-1 and anti-CTLA-4 therapy in several different cancer types.

More information: Adi Diab, Interleukin-6 blockade abrogates immunotherapy toxicity and promotes tumor immunity, *Cancer Cell* (2022). DOI: 10.1016/j.ccell.2022.04.004. www.cell.com/cancer-cell/fullt … 1535-6108(22)00166-0

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