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RESEARCH HIGHLIGHTS

Targeting IL-17A to manage immunotherapy-induced toxicity in melanoma

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The landscape of cancer treatment has been dramatically transformed by the advent of immune checkpoint inhibitors (ICIs), particularly in the management of advanced melanoma. However, despite their revolutionary success, the use of ICIs is often complicated by immune-related adverse events (irAEs), which can range from mild symptoms to severe, life-threatening conditions. Understanding the underlying mechanisms of these toxicities is crucial to enhancing the safety and effectiveness of immunotherapy [1].

In a recent study published in *Nature Cancer*, Dimitriou *et al.* [2] provide novel insights into the immunological processes driving irAEs in melanoma patients treated with ICIs. The researchers identified a significant increase in interleukin-17A (IL-17A) expressing $CD4^+$ T cells at the onset of irAEs, pointing to a type III immune response as a key factor in these adverse events. This discovery not only deepens our understanding of irAEs but also suggests a potential therapeutic target for mitigating these toxicities without compromising the antitumor efficacy of ICIs.

What sets these findings apart is their contribution to a broader understanding of the mechanisms behind ICIs' AEs compared to primary autoimmune diseases. While irAEs share certain immune mechanisms with autoimmune diseases, such as rheumatoid arthritis or psoriasis, the immunological context of ICIs is distinct because of the pharmacological disruption of immune checkpoints [3]. The study highlights the difference between irAEs and primary autoimmune disease by showing that IL-17A expressing $CD4^+$ T cells are particularly implicated in ICI-induced toxicity, which is not a prominent feature of many primary autoimmune conditions.

The study utilized a comprehensive approach, including proteomic analyses, multiplex cytokine and chemokine assays, and flow cytometry, to examine the immune profiles of melanoma patients undergoing ICI therapy. A critical finding was the consistent upregulation of IL-17A, along with other type I and III cytokines, at the onset of irAEs. These results were corroborated by the observation that IL-17A expressing $CD4^+$ T cells were significantly elevated in patients experiencing irAEs compared to those who did not.

Importantly, the authors provided proof-of-principle evidence for the therapeutic potential of targeting IL-17A in managing irAEs. In a small cohort of patients with severe, corticosteroid-refractory irAEs, treatment with the anti-IL-17A monoclonal antibody secukinumab led to a resolution of symptoms. Secukinumab, primarily used in the treatment of psoriasis, where IL-17A plays a well-established pathogenic role, offers a novel therapeutic option for

List of abbreviations: ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; IL-17A, interleukin-17A; AE, adverse event.

managing irAEs [4]. Its efficacy in these patients not only underscores the importance of IL-17A in both conditions but also suggests that treatment strategies from autoimmune diseases can be successfully repurposed for irAEs in cancer immunotherapy. This outcome suggests that IL-17A blockade could be a viable strategy for controlling irAEs, offering a new avenue for improving the safety profile of ICIs in melanoma treatment.

These findings are particularly relevant given the expanding use of ICIs across various cancers. The ability to identify patients at risk for severe irAEs through biomarkers like IL-17A could enable more personalized treatment approaches. Moreover, the successful use of secukinumab in this context opens the door to broader clinical trials aimed at validating IL-17A as a therapeutic target, potentially leading to the development of new protocols for managing irAEs.

The implications of this study extend beyond melanoma. The mechanisms of irAEs are likely to be similar across different cancers treated with ICIs, suggesting that these findings could have broader applicability. As such, researchers and clinicians should consider exploring the role of IL-17A and type III immune responses in other oncological contexts, with the goal of developing more effective and personalized immunotherapy strategies.

In conclusion, this study marks a significant advancement in the field of cancer immunotherapy. By identifying IL-17A expressing $CD4^+$ T cells as a central player in irAE development, the study not only enhances our understanding of these toxicities but also provides a promising new target for therapeutic intervention. As the use of ICIs continues to grow, these findings offer a path forward for improving patient outcomes by balancing the benefits of immunotherapy with the need to manage its associated risks effectively.

AUTHOR CONTRIBUTIONS

Kai Huang drafted and revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

The author declares no conflict of interest.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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