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Preview

Illuminating the mechanism of IL-6-mediated immunotherapy resistance

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Huseni et al. report that IL-6-STAT3 signaling negatively impacts the anti-tumor function of cytotoxic T cells. Targeting IL-6 signaling may enhance tumor responses to immune checkpoint blockade therapy.

Immune checkpoint inhibitors (ICIs) can produce long-lasting responses in a subset of patients. However, many tumors are not responsive to ICI. Understanding the molecular mechanism underlying ICI resistance is critical for developing effective strategies to improve immunotherapy outcomes in cancer patients. In the article published in this issue, the Genentech team led by Nathaniel West and Mark Merchant connects ICI resistance with T cell-intrinsic IL-6 signaling.[1]

Interleukin 6 (IL-6) is an inflammatory cytokine produced in response to infections and tissue injuries. While transit induction of IL-6 is beneficial for host defense through the stimulation of acute phase responses and hematopoiesis, prolonged dysregulated IL-6 expression leads to chronic inflammation and autoimmunity.[2] Interestingly, a large body of work implicates IL-6 signaling in promoting tumor initiation, progression, and metastasis.[3] Furthermore, a downstream effector of IL-6, STAT-3, has been shown to stimulate tumor cell proliferation, survival, and invasion directly and by causing cancer-promoting inflammation, metabolic changes, and pre-metastatic niche establishment.[4]

Further enhancing our understanding of the role of IL-6 signaling in cancer, Huseni et al. show in this issue that IL-6 can protect tumors from immunotherapy.[1] This conclusion is based on the analysis of biospecimens from IMmotion150 clinical trial comparing anti-PD-L1 atezolizumab with or without bevacizumab with a tyrosine kinase inhibitor sunitinib in patients with renal cell carcinoma.[1] Huseni et al. observed that patients that developed progressive disease on atezolizumab tended to have high expression of IL-6 mRNA in their tumors. Furthermore, high tumor or plasma IL-6 expression was associated with poor overall survival in patients who received anti-PD-L1 treatment. These findings are in alignment with prior clinical studies showing an association between high serum IL-6 and ICB resistance.[5]

Importantly, Huseni et al. were able to illuminate the mechanism of IL-6-mediated immunotherapy resistance. By comparing pre-treatment PBMC samples from patients with low and high plasma IL-6 using scRNAseq technology, the investigators observed a loss of polyfunctional cytotoxic T lymphocytes (CTLs) in patients with low IL-6. Furthermore, a series of follow-up *in vitro* experiments demonstrated a negative impact of IL-6 on CTL effector differentiation and anti-tumor function. Mechanistically, the IL-6 impairment of CTL function was driven by STAT3-dependent induction of BATF.[1] In order to demonstrate the causative relationship between CTL-intrinsic IL-6 signaling and anti-PD-L1 resistance, Huseni et al. performed an elegant conditional knockout experiment removing IL-6R specifically in CD8 T cells. In alignment with their hypothesis, tumor-bearing mice with IL-6R-deficient CD8 T cells responded better to anti-PD-L1 blockade compared to mice with WT CD8 T cells.[1] These findings suggest that CTL-intrinsic IL-6 signaling negatively impacts anti-PD-L1 response.

The experimental findings described above suggest that tumor-derived and systemic IL-6 serves as an immune checkpoint that tumors highjack to evade killing by tumor-reactive CD8 T cells activated by ICI treatment. Therefore, there is a compelling rationale for co-targeting the IL-6 pathway in combination with ICI. Of note, inhibitors of IL-6 signaling are already available and widely used in clinical practice. These include antibodies targeting the IL-6 receptor, such as sarilumab and tocilizumab that are approved by the FDA for treatment of rheumatoid arthritis.[6] More recently, IL-6 receptor inhibitors have been employed to treat severe COVID-19.[7] Clearly, implementation of IL-6 and immune checkpoint co-targeting strategies in cancer treatment is feasible. Huseni et al. validated this strategy in a preclinical model by showing that combination of IL-6 receptor-targeting antibody (anti-IL-6R) with anti-PDL1 therapy was more likely to induce complete response compared to anti-PD-L1 alone. Anti-IL-6R alone did not induce complete response in any of the treated mice.[1] Interestingly, another group has recently demonstrated that co-targeting IL-6 can alleviate some of the ICI-associated adverse effects, such as colitis.[8]

Altogether these findings support further clinical investigations of IL-6 receptor blockade and ICI combinations. In fact, several clinical trials testing the ability of IL-6 targeting agents to enhance immune checkpoint blockade responses are already ongoing. These include NCT04691817 investigating anti-IL-6R tocilizumab and anti-PD-L1 atezolizumab in patients with non-small cell lung cancer and NCT05428007 evaluating another anti-IL-6R sarilumab in combination with anti-CTLA4 ipilimumab, anti-PD1 nivolumab, and LAG-3-blocking antibody relatlimab in patients with late-stage melanoma (ClinicalTrials.gov). It would be interesting

to see how these studies unfold to gauge the potential clinical benefit of co-targeting IL-6 signaling during immunotherapy.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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