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Cytotoxic T Cells Are Replaced by Novel Clones After Immune Checkpoint Blocker Therapy

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Immune checkpoint blockers are a major part of the modern therapeutic arsenal in many locally advanced and metastatic cancers. Two clinical response trends have emerged: in a minority of patients, they induce a long-lasting antitumoral response, but for most patients, they only provide short-lived benefits. Identifying responders prior to the treatment and modulating the tumor microenvironment in nonresponders are areas of active research. The immune tumoral microenvironment, especially T lymphocyte diversity and the abundance of their clonotypes, modifies the response to various immunotherapy agents, including immune checkpoint blockers.[1] In patients with basal cell carcinoma (BCC), initial studies have failed to show sustained clinical benefits with immune checkpoint blocker therapy.[2] In contrast, cemiplimab, a PD-1 inhibitor, was recently approved by FDA for metastatic cutaneous squamous cell carcinoma (SCC).[3]

A recent study by Yost et al performed single-cell RNA-sequencing and T cell receptor-sequencing of BCC tumors from 11 patients before and after pembrolizumab treatment to determine the change of T lymphocytes clonotypes among tumor infiltrating lymphocytes (TILs).[4] The authors have identified that pembrolizumab treatment primarily affected CD8+ T cells rather than CD4+ T cells. Compared with pretreatment BCC tumors, several subpopulations of CD8+ T lymphocytes were more abundant in posttreatment BCC tumors. Among these, chronically exhausted CD8+ T cells displayed the greatest clonal expansion following pembrolizumab therapy. Exhausted CD8+ T cells are a recently described subset of CD8+ T cells. They express markers of chronic activation, T cell dysfunction, and tumor reactivity.[5]

After pembrolizumab therapy, 84% of the exhausted CD8+ T cell clonotypes were novel. Namely, they were not detected in pretreatment BCC tumors. Moreover, 35.5% of novel exhausted CD8+ T clonotypes could be detected in peripheral blood posttreatment. Notably, 11.8% of novel exhausted CD8+ T cell clones could be detected in peripheral blood pretreatment, despite their complete absence in pretreatment BCC tumors, suggesting that peripheral T cells may contribute to the response to immune checkpoint blockers. In the end, the authors performed the same experiments in 4 patients with SCC before and after anti-PD-1 treatment. Similar results of posttreatment clonal replacement of CD8+ T cells, especially exhausted CD8+ T cells, were observed.

The study by Yost et al has several clinical implications for malignancies currently treated with anti-PD-1 agents, including cutaneous SCC. First, the pretreatment TILs undergo clonal replacement by a distinct set of novel tumor-specific T cell clonotypes. This is most striking in the tumor-specific exhausted CD8+ T cell subpopulation. Hence, characterizing the pretreatment TIL landscape may have limited clinical value. Second, a proportion of novel exhausted CD8+ T cell clonotypes forming the expanded posttreatment TIL repertoire are present circulating in the peripheral blood. Therefore, tumor-specific T cell response to immune checkpoint blockers may be monitored in peripheral blood. Finally, the reason for better response to immune checkpoint blockers in immune-infiltrated tumors compared to immune-desert tumors is probably due to their ability to constantly recruit new T cell clones. However, the source of the novel T cell clones and their influence on clinical response remain unknown.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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