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RESEARCH HIGHLIGHT

Amplifying natural antitumor immunity for personalized immunotherapy

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T-cells engineered with T-cell receptors (TCR-T), chimeric antigen receptor (CAR) T-cells, and neoantigen vaccines have each demonstrated therapeutic success in clinical trials, but many of these therapies can only benefit a small group of patient types owing to the restriction of certain tumor-associated antigens; personalized immunotherapy customizes cancer treatments to each patient, achieving greater responses without damaging normal tissues. In a recent *Cell Research* paper, He et al. show that TCR-T cells engineered with TCRs from naturally occurring tumor antigen-specific (Tas) T-cells are an effective therapy against non-small cell lung carcinoma, and a promising agent for future immunotherapies.

Cellular immunotherapy has developed into a standard pillar for cancer treatment. White blood cells in the immune system known as T-cells facilitate a critical role in cancer immunity by directly killing tumor cells. Advances in TCR-Tcells engineered with T-cell receptor (TCR-T) and CAR T-cell therapies reveal that targeting tumor antigens with re-engineered T-cells is an effective cancer immunotherapy. However, immunotherapy failure is not rare, and is multifaceted, with barriers including: (1) the inter- and intra-tumoral heterogeneity of tumor-associated antigens (TAAs) limiting therapeutic effect, (2) the expression of key TAAs restricted to certain tumor types, and (3) the ability of tumors to exist in a dynamic and complex microenvironment of malignant cells, non-malignant cells, immune cell compartments and blood vessels that work individually or in combination to influence the sensitivity to immunotherapy. Furthermore, the expression of target antigens in normal developing cells may cause on-target off-tumor toxicity. Based on this background, cancer immunologists have begun to focus on personalized immunotherapy using polyclonal TCRs, providing improved tumor specificity.

Personalized immunotherapy is still in its infancy. The ability to predict neoantigens from tumor mutations remains challenging due to the influence of the tumor-immune microenvironment. Moreover, mapping targetable neoantigens from tumor mutations is complex and not translatable to a number of tumor types, specifically pediatric brain tumors which are driven by epigenetic modifications.[1,2] The presence of T-cells in human cancers is a sign of immune recognition. The host immune system selects tumor antigens and activates T-cells to specifically attack the tumor;[3] these naturally occurring tumor-infiltrating T-cells (TILs) typically have a high feedback rate and reduced risk of on-target off-tumor toxicity, making them an ideal immunotherapy for cancer treatment.[4,5] The use of TIL therapy for certain aggressive cancer types is a very effective treatment option.[6] Nonetheless, TILs are frequently present in limited numbers due to suppression by the tumor microenvironment,[7] therefore, attempts at extraction, expansion and investigation remain challenging.[8]

A reasonable approach to overcome this hurdle is to generate personalized TCR-T cells directly from tumor antigen-specific (Tas) T-cells (Fig. 1). In a recent paper of *Cell Research*, He and colleagues demonstrated the use of single-cell transcriptomic analysis, TCR sequencing and neoantigen stimulation to identify Tas cells and their biomarkers.[9] Tumor, peri-tumor, normal tissue and blood samples were collected from treatment-naïve patients diagnosed with non-small cell lung carcinoma. Using the 10× genomics platform, T-cell clones (isolated $CD45^+CD3^+$ T-cells) were traced from the tumor site to its adjacent tissues. Enrichment analysis demonstrated that blood and tissue-resident T-cells were grouped into distinct clusters; however, interestingly, markers of exhaustion (HAVCR2, CTLA4, TIGIT, LAG3 and TOX) were not restricted to exhaustion clusters, revealing an exhaustive feature of T-cells from tumor-enriched clusters, indicating repeated antigen stimulation. Distribution analysis of tumor-enriched T-cell clusters demonstrated that T-cells within these clusters were expanded by tumor antigens, and that TCR expansion is mediated by the stimulation of neoantigens derived from tumor mutations.

To identify biomarkers for T-cells containing TCRs which were exclusively expanded in the tumor, the authors analyzed differentially expressed genes between $CD4^+$ T-shared and T-specific cells, $CD8^+$ T-shared and T-specific cells, and $CD4^+$ T-shared and $CD4^+$ Treg cells. CXCL13, a known chemokine which regulates the movement of immune cells from the blood into the tumor (lymphocyte infiltration), was expressed in both $CD4^+$ and $CD8^+$ T-cells with tumor-specific TCRs. Furthermore, the percentage of $CXCL13^+$ cells in all tumor T-cells positively correlated with the tumor mutation burden, suggesting that CXCL13 is a distinct marker of T-cells specifically expanded in the tumor. By means of elegant in vitro tumor antigen stimulation, the authors demonstrated that TCRs exclusively expanded in tumors will respond to neoantigen stimulation, demonstrating that $CXCL13^+$ T-cells in tumors are in fact Tas T-cells. TCR-T cells engineered with the Tas TCRs effectively reduced the tumor burden in in vivo preclinical trials, using patient-derived xenograft models initiated from the original patient's tumor.[9] Finally, the clinical significance of CXCL13 expression levels in tumors was assessed in previous

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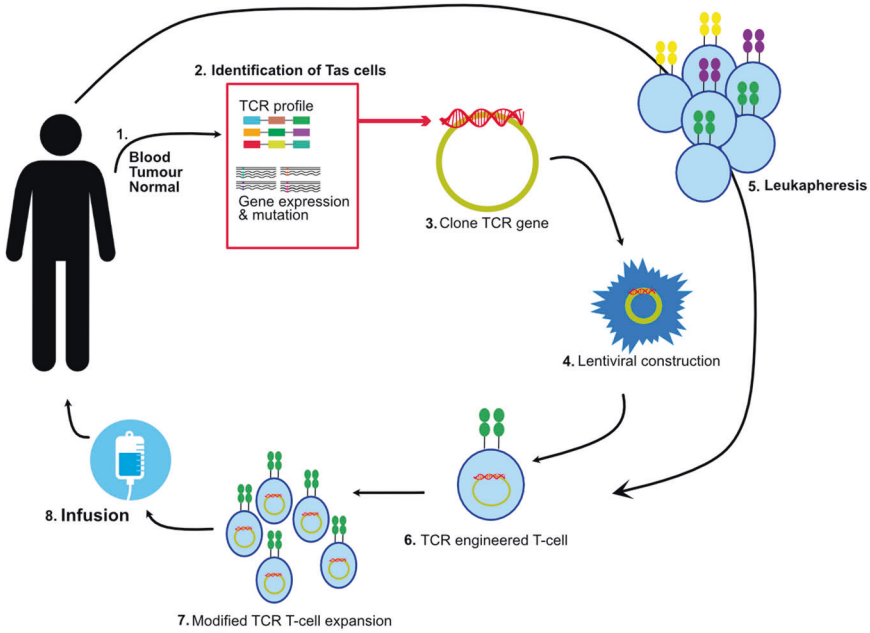

Fig. 1 The development of personalized Tas TCR-T cells. (1) Surgical tumor, peri-tumor, normal tissue and blood samples are collected from a patient. (2) Next-generation sequencing is performed on the tissues to identify potent neoantigen epitopes derived from tumor mutations; single-cell RNA-sequencing is performed on the T-cells from tissues and blood samples to identify Tas T-cells. (3) Personalized Tas TCRs are cloned, synthesized and (4) constructed into a lentiviral vector. (5) T-cells isolated from the peripheral blood of patients (leukapheresis) are (6) transduced with these TCRs. (7) Modified Tas TCR T-cells are expanded in vitro to generate sufficient numbers of cells for therapy and (8) re-infused back into the patient.

clinical trials;[10] high levels of CXCL13 were associated with progression-free survival, revealing that CXCL13 could predict the precise response to immune checkpoint blockade.

This exciting study demonstrates a significant clinical milestone for the use of Tas TCRs to treat autologous tumors. The current use of TILs for cancer treatment is a highly demanding option; however, Tas-engineered TCR-T cells are an encouraging personalized immunotherapy for cancer treatment. The ability to identify Tas cells and their markers could effectively and safely target patient-specific tumor antigens by boosting the patient's own natural immunity and predicting the response to immune checkpoint blockade, providing life-changing opportunities for patients unresponsive to current immunotherapies.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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