Cell Transplantation
Volume 31: 1–3

DOI: 10.1177/09636897221138037
journals.sagepub.com/home/cll
SAGE

# The New T Cell Subset Opens a New Realm for Tumor Immunotherapy

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**Abstract**

Immunotherapy with immune checkpoint inhibitors had achieved great success. However, only a subset of patients responds positively to these therapies. The latest study published on *Nature* by Chou and colleagues found a new T cell subset from tumor-infiltrating T cells which lack PD-1 on the cell surface and potent cytotoxic activities against tumor cells. This finding provides a novel insight into the development of new therapies for tumors that do not respond to immune checkpoint blockade in the future.

**Keywords**

immunotherapy, tumor immune microenvironment, T cell subset

Over the decades, immunotherapy has proven to be effective in clinical cancer therapy. It can systemically boost the immune surveillance and/or locally regulate the tumor immune microenvironment (TIM), which is infiltrated with various types of innate and adaptive immune cells. These approaches include immune checkpoint inhibitors (ICIs), chimeric antigen receptor T cell therapies, cancer vaccines, and non-specific immunotherapies[1]. With the development of immunotherapy, ICIs are recognized as the most promising therapeutic option for various cancer types. For instance, cytotoxic T lymphocyte-associated protein 4, programmed death-1 (PD-1), and PD-L1 inhibitors or antibodies release the inhibitory brakes on cytotoxic T cells, contributing to activation of the immune system and exerting antitumor immune responses by recognizing new antigens. This achieved the clinical effect of restricting malignant progression and resulting in tumor elimination[2,3]. However, only a subset of patients responds positively to these therapies; therefore, new strategies should be developed or new cells should be identified to resolve this urgently problem.

We speculated whether lymphocytes that can eliminate cancer cells on a broad spectrum existed. Chou and collaborators[4] described a population of αβ T cell receptor (TCR)-positive FCER1G-expressing innate-like T cells with high cytotoxic potential (ILTCKs). This finding suggests a potential immune response approach for tumor elimination, which increased our interest.

In 2016, this study team reported for the first time, a new distinct group of non-circulating innate lymphocytes which displayed different from conventional cytotoxic T lymphocytes and natural killer (NK) cells. It was high expression of NK1.1, CD49a, CD103, and low or hardly expression of PD-1, CD28, and ICOS, which potent cytotoxic activitied against tumor cells[5]. However, where the cells came from, their immune characteristics, and how they function were still unknown. In this study, the authors further unveiled the ILTCKs in a systematic and comprehensive approach.

Single-cell RNA-sequencing was used to analyze the heterogeneity of tumor-infiltrating T cells from the breast tumor mice model, which revealed five distinct clusters (cluster 3 represented the αβILTCKs) with different markers and varied differentiation and proliferation states. To explore the differentiation process, the prostate cancer mice model and samples from breast tumors and human colorectal carcinoma with three-dimensional diffusion-map embedding were used. αβILTCKs were observed to be evolutionarily conserved tumor-induced immune cells. This differentiation process was significantly different from previously reported lymphocytes.

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Submitted: June 28, 2022. Revised: August 1, 2022. Accepted: October 24, 2022.

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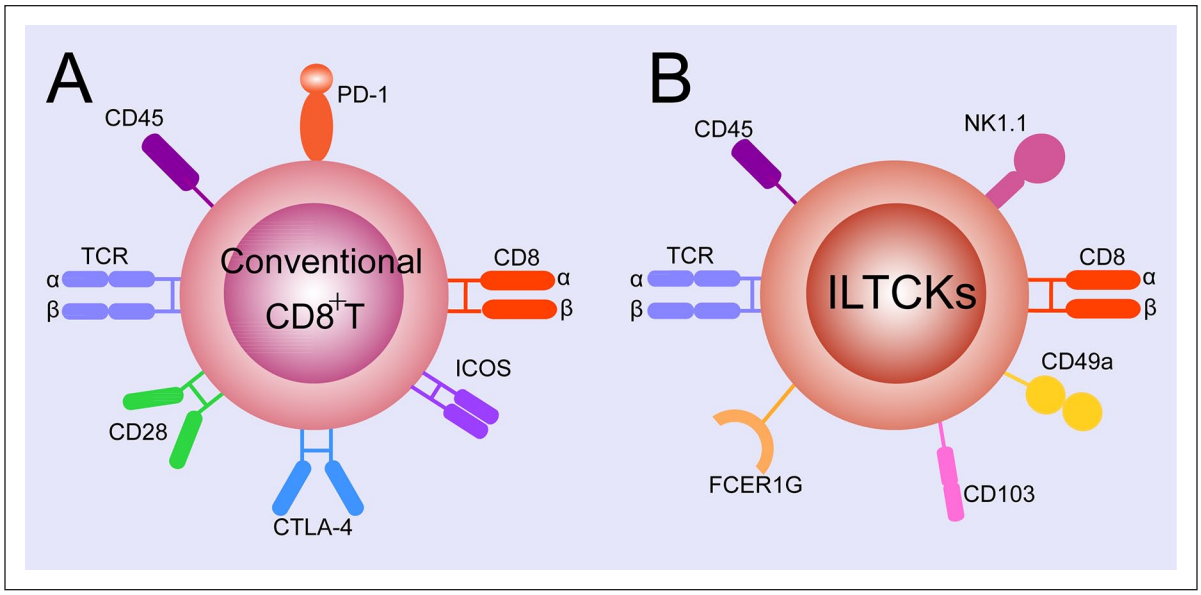


**Figure 1.** Schematic representation of the main cell surface makers difference between conventional $CD8^+$ T cells (A) and ILTCKs (B). ILCKs: innate-like T cells with high cytotoxic potential; PD-1: programmed death-1; TCR: T cell receptor.

The immunophenotype of αβILTCKs is identified as $CD45^+TCR\beta^+CD8\alpha^+PD\text{-}1^-NK1.1^+$ which is distinct from the conventional $CD45^+TCR\beta^+CD8\alpha^+PD\text{-}1^+NK1.1^-$ cells (Fig. 1). Because αβILTCKs lack PD-1 on the cell surface, these features contribute to the cell's continuous removal of tumor cells rather than exhaustion as observed in conventional cytotoxic T cells. In addition, αβILTCKs TCRs were mainly polyclonal with moderate clonal expansion and were able to recognize a broader range of unmutated tumor antigens without antigen-presenting cells; these were the innate lymphocyte characteristics. Moreover, the intratumoral αβILTCKs were not recirculated by the blood or lymph fluid; instead, they were continuously supplemented by thymic progenitors. Furthermore, the authors identified a new cell maker, FCER1G, as an αβILTCK lineage distinctive maker. The FCER1G expressing on NK cells can respond to the overactivation of $CD8^+$ T cells and suppress their function during viral infection[6]. Altogether, these new findings raised an interesting question: During T cell differentiation and development in the thymus, if self-reactive $CD4^+$ and $CD8^+$ conventional T cells undergo positive and negative selections, which results in robust elimination[7], how will αβILTCKs recognize autoantigens to avoid autoimmune diseases?

To avoid autoimmune diseases, the αβILTCKs TCRs recognize the self-antigen during early cell development, which inhibits downstream TCR signaling (self-antigen alone insufficiently activates αβILTCKs) and prevents cytotoxicity. In addition, the cytotoxicity of αβILTCKs induction depends on the pro-inflammatory cytokine interleukin (IL)-15 whose constitutive expression is low (insufficiently activates αβILTCKs) in normal tissue and high in tumor tissue[5]. This dual mechanism retains the αβILTCK in a normal development state and eliminates unmutated antigen without triggering an autoimmune response.

Previous studies have reported that the IL-15 promotes the growth and activation of cytotoxic $CD8^+$ T, NK, and dendritic cells[8,9]. Loss of IL-15 decreased T cell proliferation, increased tumor recurrence, and decreased survival in patients with colorectal tumors[10,11]. Similarly, IL-15 was required in the process of αβILTCKs development and activation. In this study, the author revealed that ablation of *il15* in the hematopoietic lineage of cells had no effect on the tumor-elicited αβILTCKs response and that both the IL-15 and the proportion of αβILTCKs were markedly increased in mammary tumor tissue. However, in *S100a8-cre-il15*$^{fl/fl}$ PyMT mice tumor model, they observed that tumor-infiltrating αβILTCKs were markedly reduced in tumor tissue, and the tumor growth was significantly promoted. Thus, these findings further confirmed that the cytokine IL-15 can promote αβILTCK development and is involved in activating the αβILTCKs cytotoxicity in the tumor model. Therefore, IL-15 expression can be a potential new tumor immune monitor for the clinical diagnosis of tumors.

New findings always generate a wealth of avenues for future investigation, and the work of Chou *et al.*[4] is no exception. First, this study used a massive mouse tumor model and frontier technology to investigate the role of αβILTCKs. Human colon tumor samples were used as well. It has not yet been investigated whether αβILTCKs exist in other types of human tumors and whether they are as effective as they were in colon tumors. Second, IL-15 is highly expressed in tumors and is critical for αβILTCKs activation. However, how IL-15 levels were regulated within the tumor microenvironment and the precise molecular mechanism of IL-15-induced αβILTCKs cytotoxicity remain unclear.

Third, this study opens a new direction for tumor immunotherapy; nevertheless, whether this inspiring basic research can be transformed into a clinical application will require more research in the future.

These new findings not only advance our understanding of tumor-infiltrating T cells in the microenvironment but also benefit patients with tumors for whom immune checkpoint blockade therapies were ineffective and may contribute significantly to developing therapeutic applications in immunotherapy. Taken together, these ground-breaking findings provide a novel insight into the fundamental cell biology of the T subset and contribute significantly to the development of new therapies for tumors that do not respond to immune checkpoint blockade.

## Author Contributions

CZ and WW designed and drafted the manuscript. HZ drew chart. CZ reviewed and revised the manuscript. All authors read and approved the final manuscript. All authors read and approved the final manuscript.

## Ethical Approval

This study was approved by our institutional review board.

## Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

## Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

## 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.

## Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by grant the key program of Shunde Hospital (grants SRSP2021003, SRSP2021016), high level medical talent training program of Foshan (grant 600016), Research Grant of Tianqing for Liver Disease (TQGB20150123), Clinical cultivation project of Shunde Hospital Southern Medical University (CRSP2019006).

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