Cancer Biol Med 2025. doi: 10.20892/j.issn.2095-3941.2024.0453

EDITORIAL

Elucidating the synergistic roles of CD4$^+$ T and dendritic cells in antitumor immunity

Xiubao Ren[1,2,3]

[1]Department of Immunology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin 300060, China; [2]Department of Biotherapy, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin 300060, China; [3]Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Cancer Immunology and Biotherapy, Tianjin 300060, China

A recent publication by Espinosa-Carrasco et al.[1] has illuminated the critical roles of intratumoral immune triads—a unique cluster of CD4$^+$ T cells, CD8$^+$ T cells, and dendritic cells (DCs)—in mediating effective antitumor responses. These triads ensure that CD8$^+$ T cells receive the necessary help from CD4$^+$ T cells, mediated *via* the same DC, to effectively targeting and destroying cancer cells. The article's novel insight suggests a shift in focus from increasing the number of immune cells to optimizing their interactions within the tumor microenvironment. This groundbreaking study not only underscores the critical roles of CD4$^+$ T cells and DCs, but also highlights the intricate interplay among immune cell subsets within the tumor microenvironment.

Previous studies have revealed the importance of CD4$^+$ T cells in supporting CD8$^+$ T cell responses[2]. The essential roles of spatial positioning and interactions among immune cells within the tumor microenvironment have also been emphasized[3,4]. Studies on adoptive T cell therapy have demonstrated that co-transferring CD4$^+$ and CD8$^+$ T cells achieves better therapeutic outcomes than transferring CD8$^+$ T cells alone[2,5], because CD4$^+$ T cells help sustain CD8$^+$ T cells' effector functions and prevent their exhaustion. These studies collectively support the requirements for coordinated interaction among immune cell types, particularly CD4$^+$ and CD8$^+$ T cells, to achieve effective antitumor immunity. The concept of intratumoral immune triads adds a new layer of understanding for optimization of these interactions to enhance therapeutic outcomes.

Here, we discuss the scientific merits of this interesting study, emphasizing 3 key aspects: the importance of CD4$^+$ T cells and DCs; immune cell interaction networks; and a holistic approach to immunotherapy.

The crucial interplay between, and importance of, CD4$^+$ T and DCs in antitumor immunity

For decades, CD8$^+$ T cells have been the cornerstone of cancer immunotherapy, because of their direct cytotoxic effects against cancer cells. CD8$^+$ T cells have been extensively documented and widely researched[6]. However, recent advancements in immuno-oncology have indicated a major challenge: CD8$^+$ T cell dysfunction is an obstacle that substantially limits antitumor efficacy toward solid tumors. Consequently, interest has grown in exploring the potential of other immune cell subsets, particularly CD4$^+$ T cells and DCs, to enhance cancer immunotherapy. Espinosa-Carrasco et al.[1] have demonstrated that CD4$^+$ T cells engage with CD8$^+$ T cells on the same DC during the effector phase, thereby overcoming this dysfunction and licensing CD8$^+$ T cell cytotoxicity. This finding calls into question the adequacy of CD8$^+$ T cells alone in achieving effective antitumor immunity, while emphasizing the crucial and indispensable roles of CD4$^+$ T cells and DCs in this complex process.

CD4$^+$ T cells, often referred to as helper T cells, have multifaceted roles in the immune response. They are essential for activating and sustaining CD8$^+$ T cells, by providing necessary

Correspondence to: Xiubao Ren
E-mail: renxiubao@tjmuch.com
ORCID ID: https://orcid.org/0000-0003-4137-2049
Received October 10, 2024; accepted November 27, 2024;
published online December 11, 2024.
Available at www.cancerbiomed.org
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signals that enhance cytotoxic function[7]. Espinosa-Carrasco et al. have highlighted that, without the help of $CD4^+$ T cells, $CD8^+$ T cells can become exhausted or dysfunctional, and fail to effectively eliminate cancer cells. This interaction is mediated *via* antigen presentation by DCs, which bridge the innate and adaptive immune systems. DCs capture and process tumor antigens, and subsequently present them to both $CD4^+$ and $CD8^+$ T cells, thereby orchestrating a coordinated immune attack on tumors. Specifically, Espinosa-Carrasco et al. have revealed that within the tumor microenvironment, $CD4^+$ T cells play a critical role in reprogramming dysfunctional $CD8^+$ T cells, which are often characterized by the expression of inhibitory receptors, and an inability to produce effector cytokines and cytotoxic molecules essential for tumor clearance. This reprogramming occurs through the formation of intratumoral immune triads, wherein $CD4^+$ T cells interact with $CD8^+$ T cells on the same antigen-presenting cell, such as a DC. Within these triads, $CD4^+$ T cells mediate transcriptional and epigenetic reprogramming of $CD8^+$ T cells, thereby restoring their functionality and enabling their production of cytokines and cytotoxic molecules for effective elimination of cancer cells. Notably, the formation of these triads correlates with clinical responses to immune checkpoint blockade (ICB) therapy in patients with pleural mesothelioma; therefore, the presence of triads within tumor tissues might serve as a biomarker for predicting ICB efficacy and patient prognosis. Thus, this study not only advances understanding of the molecular mechanisms underlying antitumor immunity, but also opens new avenues for the development of immunotherapies targeting the formation and function of triads to enhance cancer treatment efficacy.

This study is unique in its innovative approach to understanding immune cell interactions within tumors. By highlighting the critical roles of $CD4^+$ T cells and DCs, in addition to $CD8^+$ T cells, the authors have provided a more comprehensive view of the immune landscape in cancer. Their findings underscore the importance of considering the synergistic mechanisms among immune cells rather than focusing on individual cell types in isolation (**Figure 1**).



Figure 1 God Erlang, Sun Wukong, and Nezha represent 3 types of immune cells: DCs, $CD8^+$ T cells, and $CD4^+$ T cells, respectively, which work together in effectively recognizing and killing tumor cells.

Importance of immune cell interaction networks

Immune triad formation within tumors indicates the complexity and interdependence of immune cell subsets. These three-cell clusters facilitate crucial interactions that cause $CD8^+$ T cell reprogramming and activation, and ultimately lead to tumor elimination. The study emphasizes the need to understand and harness these interaction networks, which constitute the mechanism underlying immunotherapy efficacy. Focusing on these networks might enable researchers to identify novel targets and develop more effective therapeutic strategies.

Immune cell interaction networks are not limited to $CD4^+$ T cells, $CD8^+$ T cells, and DCs. The tumor microenvironment is a dynamic and complex ecosystem in which various immune cells, including regulatory T cells (Tregs), natural killer (NK) cells, B cells, macrophages, neutrophils, and myeloid-derived suppressor cells interact and influence one another's functions. Beyond immune cells, various non-immune cells are involved in forming the immunosuppressive microenvironment, including cancer-associated fibroblasts, adipocytes, vascular endothelial cells, and pericytes. These cells also directly or indirectly affect immune cells in the tumor microenvironment.

Understanding these interactions is crucial for developing comprehensive immunotherapy strategies. For instance, Tregs suppress effector T cell activity, whereas NK cells directly kill cancer cells and modulate other immune cell activity. Mapping these networks might help researchers identify points of intervention to enhance the overall immune response against tumors.

The need for a holistic approach in immunotherapy

Traditionally, immunotherapy has used targeted approaches focusing on enhancing the activity of a single immune cell type or pathway. Espinosa-Carrasco et al.[1] argue for a more holistic strategy aimed at improving the overall immune response within the tumor microenvironment. This holistic approach would require a deeper understanding of the intricate interactions among immune cell subsets and the development of combination therapies that simultaneously target multiple pathways.

The clinical translation prospects of this discovery are promising. The insights gained from this study might facilitate the development of new immunotherapy strategies promoting immune triad formation, thus potentially enhancing the efficacy of existing treatments, such as adoptive T cell therapy and ICB therapies. A holistic approach to immunotherapy would integrate various treatment modalities to achieve synergistic effects. For example, ICB could be combined with cytokine therapies, vaccines designed to enhance DC function, or other immunotherapies[8,9]. Strategies aimed at modulating the tumor microenvironment to enhance its conduciveness to immune cell infiltration and activation might further enhance immunotherapy efficacy. For example, targeting tumor stromal components or using agents that normalize the tumor vasculature has been found to improve the delivery and effectiveness of immune cells within tumors[10]. Moreover, multiple immunotherapies could be combined with traditional treatments, such as chemotherapy or radiotherapy[11].

Immune profiling could also be used to determine the presence and functionality of immune triads within an individual patient's tumor. The information gained could guide the selection of the most appropriate immunotherapy strategies for each individual. Personalized treatment plans could then be developed according to specific immune cell interactions within a patient's tumor. Optimizing immune cell interactions decreases the likelihood of tumors developing resistance to immunotherapy. Personalized treatments focused on enhancing specific immune interactions might potentially minimize adverse effects by decreasing the need for high doses of broad-spectrum immunotherapies.

Enhancing the formation and stability of immune triads through such therapies might yield more durable and robust antitumor responses. This holistic approach to immunotherapy, which emphasizes overall improvement in the immune response, might potentially enable more effective and personalized cancer treatment.

Closing remarks and outlook

The presence and activity of immune triads might potentially serve as a novel biomarker. By analyzing the infiltration and interaction patterns of these immune cell subsets within tumor tissues, clinicians could gain insights into the immune competence of the tumor microenvironment. This information might aid in stratifying patients into prognostic groups to enable personalized treatment strategies according to patients' likelihood of responsiveness to immunotherapy.

Moreover, the functional integrity of immune triads holds promise in predicting therapeutic outcomes. Tumors with robust immune triads have elevated likelihood of responding favorably to immunotherapies, such as ICB or adoptive cell transfer, because of their ability to mount effective anti-tumor immune responses. In contrast, tumors lacking or exhibiting dysfunctional immune triads might require alternative therapeutic approaches or combination therapies to overcome immune suppression and induce tumor regression.

From a prognostic standpoint, dynamic changes in the composition and function of immune triads during treatment might provide valuable insights into disease progression and treatment resistance. Monitoring these changes through serial biopsies or non-invasive imaging techniques might enable early identification of patients likely to require adjustments in their treatment regimen, to maintain or enhance therapeutic efficacy.

In conclusion, the study by Espinosa-Carrasco et al.[1] represents a major advancement in the understanding of antitumor immunity. The study elucidates the critical roles of $CD4^+$ T cells and DCs, and the importance of immune cell interaction networks, thereby paving the way to the development of more effective and targeted immunotherapy strategies. As the field of cancer immunotherapy advances, a holistic approach focused on improving the overall immune response within tumors, rather than simply enhancing the activity of individual immune cell types, will be imperative to unlock the full potential of immunotherapy and bring new hope to patients with solid tumors. The insights gained from the study might also expand the strategies for more personalized cancer treatments. Focusing on the specific interactions among immune cells might enable the development of personalized immunotherapy tailored to each patient's unique tumor environment, thereby improving outcomes and decreasing adverse effects. These advances represent a major step forward in the quest to achieve more precise and individualized cancer care.

The implications of this study extend beyond the immediate findings, by calling for a paradigm shift in the approach to cancer treatment and emphasizing the need for comprehensive understanding of the tumor immune landscape.

Moreover, a key aspect of this study was the use of advanced detection technologies to identify and characterize these immune cell interactions. Advancements in detection technologies continue to drive progress in immunotherapy, by enabling a more detailed understanding of immune cell interactions and the tumor microenvironment. This enhanced understanding would facilitate the development of more targeted and effective treatment strategies, thereby improving the outcomes of patients with cancer.

Although the study provides robust evidence of the importance of immune triads, areas that warrant further investigation persist. Future research will be necessary to explore other cell interaction networks within the tumor microenvironment, including the roles of Tregs, NK cells, B cells, and macrophages, as well as non-immune cells, such as cancer-associated fibroblasts. Long-term studies are needed to assess the durability and safety of therapies designed to enhance immune triad formation. Fostering collaborations among researchers, clinicians, and patients would accelerate the translation of these findings into clinical practice, and ultimately improve outcomes for patients with cancer.

Conflict of interest statement

No potential conflicts of interest are disclosed.

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Cite this article as: Ren X. Elucidating the synergistic roles of $CD4^+$ T and dendritic cells in antitumor immunity. Cancer Biol Med. 2025; 22: 1-5. doi: 10.20892/j.issn.2095-3941.2024.0453