

Review Article

The Roles of CD4⁺ T Cells in Tumor Immunity

Yo-Ping Lai,¹ Chung-Jiuan Jeng,² and Shu-Ching Chen³

¹ Department of Internal Medicine, National Taiwan University Hospital, Taipei 100, Taiwan

² Institute of Anatomy and Cell Biology, School of Medicine, National Yang-Ming University, Taipei 122, Taiwan

³ Department of Medical Research, National Taiwan University Hospital, Taipei 100, Taiwan

Correspondence should be addressed to Shu-Ching Chen, mdchensc@ntu.edu.tw

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Activation of CD8⁺ cytotoxic T cells has long been regarded as a major antitumor mechanism of the immune system. Emerging evidence suggests that CD4⁺ T cells are required for the generation and maintenance of effective CD8⁺ cytotoxic and memory T cells, a phenomenon known as CD4⁺ T-cell help. CD4⁺ T-cell help facilitates the optimal expansion, trafficking, and effector function of CD8⁺ T cells, thereby enhancing tumor destruction. In addition, a specialized subset of CD4⁺ T cells, CD4⁺CD25⁺ regulatory T cells (T_{Regs}), effectively hampers anti-tumor immune responses, which has been proposed to be one of the major tumor immune evasion mechanisms. Here, we review recent advances in deciphering how anti-tumor immune responses are orchestrated by CD4⁺ T cells. We will also discuss the immunotherapeutic potential of CD4⁺ T-cell manipulation in anti-tumor immune response.

1. Introduction

Cell-mediated immunity plays an important role in immune responses against cancer. For example, CD8⁺ cytotoxic T lymphocytes (CTLs) are key effector cells in antitumor immunity [1]. In hosts with tumors, however, tumor-specific CD8⁺ T-cell responses are usually weak. The key to this paradoxical observation may lie in the fact that CD4⁺ T-cell help is insufficient for driving an effective antitumor immunity. CD4⁺ T cells play a cardinal role in orchestrating antibody production and the activation and expansion of CD8⁺ T cells, a phenomenon known as CD4⁺ T-cell help [2, 3]. CD4⁺ T-cell help is also required for the generation and maintenance of CD8⁺ T-cell memory [4–9]. Of note, such CD4⁺ T-cell help that programs the CD8⁺ T-cell responses is favored at the time of CD8⁺ T-cell priming [7, 9–12]. Importantly, increasing evidence has shown that CD4⁺ T cells significantly contribute to tumor protection *in vivo* [13–16].

Tumor cells, on the other hand, have also evolved different mechanisms to escape from host immunity, thereby defeating conventional cancer immunotherapy. Typical immunity-escaping strategies employed by tumor cells include the downregulation of target antigens and antigen-presenting machinery, as well as the recruitment of a special-

ized subset of CD4⁺ T cells, CD4⁺CD25⁺ regulatory T cells (T_{Regs}), into tumors [17–19]. In fact, the activation of T_{Regs} has been proposed to be one of the major tumor immune escape mechanisms [20–24]. This paper summarizes current understanding of the role of CD4⁺ T cells in shaping and augmenting antitumor immunity. We also discuss the adverse role of T_{Regs} in tumor immune surveillance.

2. The Conventional Concept of CD4⁺ T-Cell Help

Several *in vitro* and *in vivo* studies of allogeneic reactions support the idea that CD4⁺ T-cell help is required for the optimal induction and clonal expansion of cytotoxic CD8⁺ T-cell responses [3, 14, 25–29]. Several recent studies further suggest that CD4⁺ T cells can directly interact with CD8⁺ T cells via CD40–CD154 interactions [30], which directly contrasts with the early notion that CD4⁺ and CD8⁺ T cells are brought together on the same antigen-presenting cell for the effective delivery of interleukin-2 (IL-2) to neighboring CD8⁺ T cells [3, 31]. Alternatively, CD4⁺ T cells may condition dendritic cells to increase their ability to stimulate CD8⁺ T cells [32–35]. Moreover, a full CD8⁺ T-cell response is critically elicited by a temporal release of IL-2 from CD4⁺

T cells [36], which is consistent with the findings that neutralization of IL-2 significantly limits CD8⁺ T-cell growth [37–40]. Furthermore, IL-2 has previously been shown to be crucial for maintaining CD8⁺ T-cell function *in vivo* [41, 42].

CD4⁺ T cells also play a pivotal role in the generation and maintenance of functional and long-lived CD8⁺ memory T cells [4–9]. Of note, the presence of the CD4⁺ T-cell help during the priming phase of CD8⁺ T-cell activation is essential for the differentiation of CD8⁺ effector cells into memory cells [5, 7, 9, 11, 12]. By contrast, in the absence of CD4⁺ T-cell help during priming, less CD8⁺ T cells can develop into memory cells, and there is an increased likelihood of finding memory cells with phenotypic and functional defects [43]. These events are likewise required for eliciting an effective tumor-specific immunity.

3. CD4⁺ T Cells Orchestrate the Antitumor Immunity

3.1. Priming or Postpriming. During the priming phase CD8⁺ T cells, activated CD4⁺ T cells may help the activation of CD8⁺ CTL that occurs within tumor-draining lymph nodes. As discussed above, CD4⁺ T cells play important roles in facilitating the initial activation and expansion of CD8⁺ T cells. CD4⁺ T cells orchestrate the antitumor CD8⁺ CTL responses through direct cell-cell interaction and IL-2 stimulation. CD4⁺ T cells may directly help CD8⁺ T-cell activation via CD40–CD154 interaction [30, 44, 45]. Alternatively, activated CD4⁺ T cells may also produce IL-2 to support the activation and proliferation of CD8⁺ T cells [37–40]. Furthermore, CD4⁺ T cells also “license” dendritic cells (DCs) to activate CD8⁺ T cells either by cross-presenting tumor antigens to CD8⁺ T cells or by inducing the production and expression of cytokines and costimulatory molecules, respectively [32–35, 46]. The preceding events, altogether known as CD4⁺ T-cell help, significantly augment antitumor CD8⁺ T-cell responses during the priming phase.

CD4⁺ T cells may also provide help during the post-priming phase that occurs at the tumor site. An optimal CD4⁺ T-cell response can augment the accumulation of CD8⁺ T cells within tumor and promote the expansion, trafficking, and differentiation of the tumor-specific CD8⁺ T cells, both of which enhance antitumor immunity [13, 47–51]. Although nontumor-specific CD4⁺ T cells can instigate significant expansion of tumor-specific CD8⁺ T cells, they fail to promote the accumulation of the cells within tumor. In contrast, provision of tumor-specific CD4⁺ T-cell help increases the CD8⁺ T-cell expansion and augments the accumulation of both CD4⁺ and CD8⁺ T cells within tumor, leading to greater tumor destruction [52]. Moreover, cognate CD4⁺ memory T cells enhance the expansion of cognate CD8⁺ memory T cells as well as the infiltration and accumulation of these cells within tumor [53]. Taken together, the number of tumor-infiltrating CD4⁺ T cells correlates with the *antitumor* efficacy of CD8⁺ T-cell responses, suggesting that the tumor-specific CD4⁺ T cells render the tumor

environment receptive for CD8⁺ T-cell residence or facilitate the access of CD8⁺ T cells to tumor.

3.2. CD4⁺ T Cells Program the Tumor-Specific CD8⁺ T Cells. It becomes apparent that the great number of tumor-reactive CTL mounted by vaccination or provided by adoptive immunotherapy does not always attain effective tumor regression [54–57]. One of the most important factors that account for the poor antitumor responses is the lack of CD4⁺ T-cell help.

CD4⁺ T cells play an important role in the development of effective antitumor immunity [13–16, 58]. Both the number and function of tumor-specific CTL are significantly enhanced in the presence of tumor-specific CD4⁺ T-cell responses, whereas depletion of CD4⁺ T cells facilitates tumor progression and abrogates the survival of tumor-bearing hosts, indicating the importance of tumor-specific CD4⁺ T-cell help in maintaining the tumor-reactive CTL function *in vivo* [13, 14]. In addition, the efficacy of the antitumor responses induced by the combined administration of human CD4⁺ and CD8⁺ T cells is notably better than that by applying CD4⁺ or CD8⁺ T cells alone [59]. Interestingly, adaptively transferred CD4⁺ T cells can also activate endogenous CD8⁺ effector cells to induce CTL responses. Therefore, CD4⁺ T-cell help is critical for promoting effective antitumor CTL responses, which is achieved not only by maintaining the numbers of tumor-specific CD8⁺ T cells but also by the optimal CTL function.

The induction of an optimal primary T-cell immune response requires two signals [60, 61]. The first signal is elicited by the engagement of TCR by the peptide/MHC complex, which determines the specificity of T-cell activation [62]. The second signal, the costimulatory signal, is provided by ligation of accessory molecules, such as CD28 on T cells, to lower the activation threshold of TCRs, which further ensures the tumor-reactive cytolytic activity of CD8⁺ T cells [63, 64]. However, it has become clear that several other signals are also required to determine whether effective CD8⁺ memory T cells will be generated and maintained. For example, CD4⁺ T-cell help during the priming phase can program CD8⁺ T-cell response and shapes the long-term fate and function of CD8⁺ memory T cells [5–7, 12]. In contrast, in host deficient of CD4⁺ T cells, CD8⁺ memory T cells show few in numbers and the secondary CD8⁺ T-cell response is compromised. With CD4⁺ T-cell help during early priming, the CD4⁺ T-cell-derived IL-2 signals can drive the differentiation of CD8⁺ T cells to produce greater quantities of IFN- γ and Granzyme B on encountering tumor *in vivo* [36]. Accordingly, the tumor-specific CD8⁺ T cells may exert long-term antitumor activity when they are stimulated as well as helped by CD4⁺ T cells during priming. However, most tumor cells do not express the MHC class II molecules required for the successful generation of tumor-reactive CD4⁺ T cells. In addition, tumor cells may secrete some immunosuppressive mediators and induce a state of anergy [65, 66]. Altogether, the unhelped tumor-specific CD8⁺ T cells ultimately develop functional deficits. This

impairment leads to the suboptimal tumor-specific CD8⁺ memory T-cell response and tumor progression.

3.3. The Unconventional Effects of CD4⁺ T-Cell Help on Tumor Control. In addition to providing help for tumor-reactive CD8⁺ T-cell responses, CD4⁺ T cells may mediate tumor rejection through other mechanisms, including (1) cytotoxic effect on tumor cells, (2) upregulation of MHC molecules expression, (3) inhibition of angiogenesis, and (4) induction of tumor dormancy.

CD8⁺ T cells are specialized for lytic function and most of the solid tumors express MHC class I, but not class II molecules. Therefore, it is believed that CD8⁺ T cells are the main effector cells responsible for destroying tumors. However, tumor-reactive CD4⁺ T cells can develop cytotoxic activity and mediate tumor rejection via MHC-class-II-restricted antigen recognition in tumor cells [67, 68], suggesting that CD4⁺ T cells per se may be the effector cell of antitumor responses. Induction of tumor-reactive CD4⁺ T cells exhibiting cytolytic activities may therefore offer an advantage for cancer immunotherapy in cancer patients. The antitumor effects of CD4⁺ T cells are dependent on cytokine signaling, especially IFN- γ and TNF- α . These two cytokines, produced by CD4⁺ T cells, have cytotoxic effect on tumor cells [69–71]. IFN- γ can up-regulate MHC molecules to increase the number of pMHC complexes as well as to alter the antigen-processing machinery [72]. Consequently, the tumor recognition is enhanced, resulting in greater tumor cell lysis. In addition, CD4⁺ T cells induce tumor dormancy that prevents tumor escape [73]. This tumor-growth-inhibiting effect strictly requires both IFN- γ and TNF- α signaling. In this scenario, the absence of IFN- γ or TNF- α could lead to tumor progression and transformation. Furthermore, CD4⁺ T cells inhibit tumor angiogenesis through a combined action of IFN- γ and TNF- α , which induces DCs to produce potent antiangiogenic chemokines, CXCL10 and CXCL9 [70, 74]. Together, these studies highlight the antitumor mechanisms underlying how CD4⁺ T cells act in a tumor setting.

3.4. Regulatory T Cells. T_{Regs}, a specialized subset of CD4⁺ T cells, can suppress immune responses and maintain T-cell tolerance to self-antigens [75, 76]. It is known that T_{Regs} hamper the functions of CD8⁺ T cells and natural killer cells, the key effector cells of antitumor immunity [77, 78]. Accordingly, T_{Regs}-mediated immunosuppression has been proposed to be one of the important mechanisms involved in the tumor immune evasion.

An accumulation of T_{Regs} in tumors can dampen T-cell immunity to tumors and is thus the main obstacle to successful immunotherapy and active vaccination [79–81]. The frequency of T_{Regs} present in peripheral blood of patients with various cancers is higher than that of normal population [79–83]. Notably, T_{Regs} isolated from peripheral blood, ascites, or solid tumors remain suppressive to T-cell activation *in vitro* [79]. Likewise, T_{Regs} from tumor-bearing mice inhibited tumor rejection [21–23], indicating that T_{Regs} suppress tumor-specific immunity and

limit antitumor resistance. In contrast, depletion of T_{Regs} with anti-CD25 monoclonal antibody in animal models enhance antitumor immunity and tumor regression, further suggesting the involvement of T_{Regs} in tumor growth [19, 84–86]. Furthermore, when tumor-specific CD8⁺ T cells were adoptively transferred with either T_{Regs} or CD4⁺CD25⁻ T cells into host with melanoma, CD8⁺ T-cell-mediated immunity was abolished in those receiving T_{Reg} cells but not CD4⁺CD25⁻ T cells [79, 87, 88]. Collectively, these studies provide strong evidence that T_{Reg} cells can attenuate the antitumor immunity by downregulating the antitumor immune responses and ultimately facilitate the development of cancer.

Based on the fact that T_{Regs} can suppress tumor-specific immunity, well-planned manipulations of T_{Regs}, including depletion, blocking trafficking into tumors, and reducing their differentiation and suppressive mechanisms, may sensitize the established tumors to be destroyed by tumor-specific immune responses and thus provide additional therapeutic opportunities. It will be beneficial to tumor eradication by combining this strategy with various current therapeutic approaches.

4. Conclusion

Our present understanding of the importance of CD4⁺ T cells for antitumor immunity can be stressed in several facets. Firstly, an early notion is that CD4⁺ T cells provide help for inducing and sustaining the tumor-specific CD8⁺ T-cell responses. Secondly, the CD4⁺ T-cell help at priming is required for the generation and maintenance of CD8⁺ memory T cells. Thirdly, CD4⁺ T cells mediate the tumor rejection through cytotoxic effects on tumor cells, the upregulation of MHC molecules expression, antiangiogenesis, and the induction of tumor dormancy. Fourthly, the existence of the specialized subset of CD4⁺ T cells T_{Regs} indeed compromises antitumor immune responses. These insights pave the way for incorporating a holistic approach to improve cancer vaccination. Finally, future attempts to enhance an effective tumor-reactive immune response by immunotherapy or vaccination should be made by promoting tumor-specific CD4⁺ T-cell responses and targeting suppressive molecules on T_{Regs}.

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