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Invited Mini Review

$CD4^+$ cytotoxic T cells: an emerging effector arm of anti-tumor immunity

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While $CD8^+$ cytotoxic T cells have long been considered the primary effector in controlling tumors, the involvement of $CD4^+$ "helper" T cells in anti-tumor immunity has been underappreciated. The investigations of intra-tumoral T cells, fueled by the recent advances in genomic technologies, have led to a rethinking of the indirect role of $CD4^+$ T cells that have traditionally been described as a "helper". Accumulating evidence from preclinical and clinical studies indicates that $CD4^+$ T cells can acquire intrinsic cytotoxic properties and directly kill various types of tumor cells in a major histocompatibility complex class II (MHC-II)-dependent manner, as opposed to the indirect "helper" function, thus underscoring a potentially critical contribution of $CD4^+$ cytotoxic T cells to immune responses against a wide range of tumor types. Here, we discuss the biological properties of anti-tumor $CD4^+$ T cells with cytotoxic capability and highlight the emerging observations suggesting their more significant role in anti-tumor immunity than previously appreciated. [BMB Reports 2023; 56(3): 140-144]

INTRODUCTION

In contrast to $CD8^+$ T cells with direct cytotoxic effector function, $CD4^+$ T cells have been shown to exhibit a diverse repertoire of indirect effector functions in response to numerous pathogenic challenges and environmental perturbations (1, 2). To perform these roles, naïve $CD4^+$ T cells can differentiate into several functionally distinct effector T helper (T_H) cell subsets, each of which in turn produces its signature cytokines that coordinate a particular T_H effector program (e.g., T_H1, T_H2, and T_H17); the differentiation is mainly directed by lineage-defining transcription factors, so-called master regulators. The best-defined T_H subsets include T_H1, T_H2, T_H17, follicular helper T cells (T_{FH}), and T regulatory (T_{reg}) cells, which need the expression of the master regulators T-bet, GATA-3, RORγt, BCL6, and FoxP3, respectively. Thus, $CD4^+$ T cells are known to offer "help" to appropriate immune effectors in their specific roles as the primary orchestrators of a broad range of immune responses.

The recent successes in cancer immunotherapy, including immune checkpoint inhibitors and gene-modified T-cell therapies, have revolutionized the field of cancer therapy (3-5). These successes have led to intense research efforts to define key immune cell subsets and their effector mechanisms that are responsible for anti-tumor immune responses. The efforts have predominantly focused on $CD8^+$ T cells because of their ability to directly engage and kill cancer cells expressing major histocompatibility complex class I (MHC-I) molecules. On the other hand, the role of $CD4^+$ T cells in anti-tumor immunity has been underestimated, presumably due to their traditional view as "helpers" and the lack of major histocompatibility complex class II (MHC-II) expression in most types of cancer cells. However, a growing body of evidence indicates that some of the $CD4^+$ T-cell populations can acquire cytotoxic effector programs and mediate direct tumor cell killing, a distinct from traditionally described "helper" function. Furthermore, although the MHC-II molecule is thought to be expressed primarily in specialized immune cells such as professional antigen-presenting cells (dendritic cells, B cells, and macrophages), it has become increasingly clear that a wide range of non-hematologic tumor cells can also express MHC-II molecules and present their endogenous tumor antigens to $CD4^+$ T cells (6-18). These recent works underline the significant contribution of $CD4^+$ cytotoxic T lymphocytes (CD4 CTLs) to potent tumor-specific immune responses and redirect attention toward their functional and therapeutic importance. Herein, we summarize the current understanding of the biology of CD4 CTLs, with particular emphasis on their important roles in anti-tumor immunity.

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THE DIRECT CONTRIBUTION OF CD4 CTLS TO ANTI-TUMOR IMMUNITY

In addition to a traditional indirect role in offering immunologic help, a growing body of evidence highlights the importance of a direct cytolytic role for CD4$^+$ T cells, especially in anti-tumor immunity. The first evidence came from preclinical studies in which the adaptive transfer of tumor-reactive CD4$^+$ T cells into lymphopenic mice followed by CTLA-4 blockade resulted in the regression of large established melanomas; the anti-tumor efficacy of the T cells depends on their expression of cytotoxic effector molecules (granzyme B and perforin) and direct recognition of MHC-II molecules expressed in the tumor cells (19, 20). Subsequent studies showed that administration of OX40 or 4-1BB agonist antibody promotes the generation of CD4 CTLs and leads to a potent anti-tumor immune response in the context of cyclophosphamide-induced lymphopenia or therapeutic vaccination (using Flt3-ligand-expressing melanoma cells), respectively (21, 22). Moreover, a clinical study found NY-ESO-1-specific CD4$^+$ T cells with cytotoxic phenotype after ipilimumab (CTLA-4 blockade) treatment in patients with advanced melanoma (23). These CD4$^+$ T cells demonstrate the ability to kill autologous melanoma cells that naturally express the cognate tumor antigen in an MHC-II-restricted fashion, suggesting a direct involvement of CD4 CTLs in the clinical efficacy of CTLA-4 blockade.

Recent advances in omics technologies further shed light on the clinical relevance of CD4 CTLs in cancer. Single-cell RNA sequencing analyses of intra-tumoral immune cells revealed CD4$^+$ T cells expressing cytotoxic molecules (granzymes, perforin, granulysin, and/or natural killer cell granule protein 7) in a broad range of cancer types, including solid tumors (head and neck cancer (24), breast cancer (25, 26), non-small-cell lung cancer (27), colorectal cancer (28), hepatocellular cancer (29, 30), bladder cancer (31), melanoma (7), neuroblastoma (32), and osteosarcoma (33)) as well as hematologic malignancies (B-cell chronic lymphocytic leukemia (34), Burkitt's lymphoma (35), and classical Hodgkin lymphoma (36)). Some of these studies further illustrated that the identified CD4$^+$ T-cell subsets displayed MHC-II-dependent direct cytotoxicity against patient tumor cells (37); more intriguingly, their presence was associated with a favorable prognosis (32) or clinical response to anti-PD-L1 therapy (7, 28, 31, 36) or therapeutic vaccination (38).

The therapeutic importance of CD4 CTLs also extends to chimeric antigen receptor (CAR) T-cell-based cancer immunotherapy. A recent study characterized long-term persisting CAR T cells in two patients with chronic lymphocytic leukemia who remained in complete remission more than ten years after infusion (39). Strikingly, the long-lasting CAR T cells were a functionally activated CD4$^+$ cell population that exhibits cytolytic characteristics, implying that cytotoxic CD4$^+$ CAR T cells are primarily responsible for long-term tumor control. This further underscores the crucial role of CD4 CTLs in the therapeutic efficacy of cancer immunotherapeutics widely used in the clinic.

GENERATION AND REGULATION OF CD4 CTLS

There are likely multiple layers of "differentiation pathways" that specify CD4 CTLs. Costimulatory signals (through OX40 (21), 4-1BB (22), and CD70 (40, 41)), cytokine (IL-2) (42), class I-restricted T-cell-associated molecule (CRTAM) (43), and lymphopenic condition (19, 20) appear to be involved in the generation of CD4 CTL. In addition, a previous work in which low antigen dose was associated with preferential CD4 CTL differentiation suggested that at the priming phase, T-cell receptor signal strength may contribute to the acquisition of cytotoxic activity by CD4$^+$ T cells (44). In parallel to these various extrinsic cues, CD4 CTLs are heterogeneous in their expression of transcription factors, such as Eomes, T-bet, Runx3, Blimp-1, and Hobit (alone or in combination thereof) (21, 42, 43, 45, 46), as opposed to other CD4$^+$ T-cell subsets (T_H1, T_H2, T_H17, T_{FH}, and T_{reg}), which are characterized by a single lineage-specifying transcription factor. It is conceivable that the basis for this transcriptional heterogeneity might rely upon distinct immunological microenvironments that the CD4 CTL populations were detected; they might be primed and/or regulated by different environmental cues (e.g., differences in secondary lymphoid tissues versus tumor tissues or those in the tumor microenvironment). However, this remains to be robustly investigated. Furthermore, it has been reported that certain well-defined T_H subsets (T_H2, T_H9, T_H17, and more frequently, T_H1) can acquire cytotoxic capacity, suggesting their functional plasticity (46-49). Although it has been proposed that the CD4 CTL populations are derived from the parental T_H subsets (50, 51), it still remains unclear whether they are intermediate subsets (in the transition to an ultimate fate) or mixed subsets with multi-functions (resulting from the conversion or undefined mechanisms). Taken together, these findings suggest that there are complex biologic features of CD4 CTLs across both cancer and other immune contexts, and this requires further study to better elucidate molecular mechanisms for their dynamic process with distinct microenvironmental cues in cancer-bearing hosts.

THE IMPLICATION OF CD4 CTLS IN CANCER IMMUNOTHERAPY

The recognition of the therapeutic potential of CD4 CTLs in cancer has spurred efforts to develop novel approaches that harness cytotoxic CD4$^+$ T-cell immunity to tumors. A recent study opens up a new approach for CD4 CTL-based cancer immunotherapy (40, 41). This work revealed that the Epstein-Barr virus signaling protein LMP1 enables B cells (including tumor B cells) to function as a "unique antigen-presenting cell" that directly primes CD4 CTLs. By exploiting the LMP1 signaling, an innovative approach was then developed to generate therapeutic CD4 CTLs against B-cell cancers. The produced CD4 CTLs exerted a potent anti-tumor activity against pre-established syngeneic B-cell lymphomas; the therapeutic efficacy was further enhanced upon the combination with PD-1 checkpoint block-

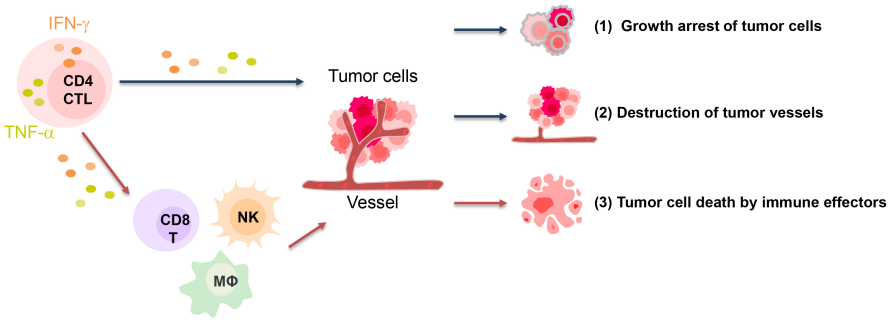

Fig. 1. MHC-Ⅱ-independent anti-tumor mechanisms of CD4$^+$ cytotoxic T lymphocytes (CD4 CTLs). CD4 CTLs can secret effector cytokines, IFN-γ and TNF-α, that (1) induce senescence-associated growth arrest in tumor cells, (2) destruct tumor blood vessels, and (3) stimulate immune effector cells, such as CD8$^+$ T cells ("CD8 T"), natural killer cells ("NK"), and macrophages ("Mø"), to kill tumor cells.

ade, resulting in complete regression of the tumor in the majority of mice. These results offer a solid foundation for the application of CD4 CTLs in cancer immunotherapy and a strong rationale for a combination therapy with CD4 CTLs and checkpoint blockade.

Apart from direct cytotoxicity, a major subset of CD4 CTLs appears to possess helper functions through the secretion of effector cytokines, such as IFN-γ and TNF-α. These cytokines have been shown to exert not only anti-tumor activity (via inducing growth arrest of cancer cells and destroying the tumor vasculature) (52, 53) but also stimulate other anti-tumor immune effectors such as CD8$^+$ T cells, natural killer cells, and macrophages in the tumor microenvironment (Fig. 1) (54-56). This MHC-II-independent mechanism may contribute to CD4 CTL-mediated anti-tumor immunity as another critical arm. Accordingly, CD4 CTLs have the therapeutic potential to control MHC-II-negative as well as MHC-II-positive cancers.

The MHC-II molecule is paramount for antigen presentation to CD4 CTLs, and their responses are thus dependent on the expression of MHC-II on target cells. Since this molecule is known to display a restricted tissue distribution, it has been believed that most tumor cells lack its expression and cannot be targeted by CD4 CTLs. However, MHC-II expression and antigen-presenting capabilities have been increasingly reported in diverse types of non-hematologic human tumors, including melanoma (6-8), breast cancer (9, 10), colorectal cancer (11, 12), ovarian cancer (13, 14), prostate cancer (15), glioma (17), bladder cancer (31), and non-small-cell lung cancer (18). Given that these solid tumors are derived from tissues that are normally incapable of presenting their endogenous antigens on MHC-II molecules, they could acquire the antigen-presenting capacity under specific contexts. Although MHC-II antigen presentation is known to be induced by IFN-γ in some tumor cells (57, 58), mechanisms for its induction and regulation in tumor cells largely remain unknown. Understanding these mechanisms will provide a basis for rational strategies to enhance MHC-II antigen presentation on otherwise negative tumor cells, converting them into targets of CD4 CTLs.

CONCLUDING REMARKS

CD4$^+$ T cells were initially viewed as mere "helpers" with indirect roles in the immune system. The discovery of CD4$^+$ T-cell subsets, which specialize to become cytolytic and exert direct cytotoxic effector functions, suggests their more significant role than previously thought. The recent preclinical and clinical data underline the critical roles of CD4 CTLs in anti-tumor immunity and therapeutic response to currently used cancer immunotherapeutics, such as checkpoint inhibitor therapy and CAR T-cell therapy. The emerging appreciation of the functional and therapeutic potential of CD4 CTLs should lead us to redefine our understanding of T-cell-mediated anti-tumor immunity and rethink the design of cancer immunotherapy. However, there remain knowledge gaps on the underlying mechanisms of how CD4 CTLs are generated and regulated in the distinct immunological microenvironments of cancer-bearing hosts and how MHC-II antigen presentation is induced in diverse cancer types. These novel biological insights will enable the development of novel immunotherapeutic strategies that exploit the unique capabilities of CD4 CTLs.

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CONFLICTS OF INTEREST

I.-K.C. has a patent about the use of EBV LMP1 cancer immunotherapy issued.

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