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Mini-review

Immunotherapy and tumor microenvironment

Haidong Tang, Jian Qiao, Yang-Xin Fu *

Department of Pathology and Committee on Immunology, University of Chicago, Chicago, IL 60637, USA

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ABSTRACT

Recent exciting progress in cancer immunotherapy has ushered in a new era of cancer treatment. Immunotherapy can elicit unprecedented durable responses in advanced cancer patients that are much greater than conventional chemotherapy. However, such responses only occur in a relatively small fraction of patients. A positive response to immunotherapy usually relies on dynamic interactions between tumor cells and immunomodulators inside the tumor microenvironment (TME). Depending on the context of these interactions, the TME may play important roles to either dampen or enhance immune responses. Understanding the interactions between immunotherapy and the TME is not only critical to dissect the mechanisms of action but also important to provide new approaches in improving the efficiency of current immunotherapies. In this review, we will highlight recent work on how the TME can influence the efficacy of immunotherapy as well as how manipulating the TME can improve current immunotherapy regimens in some cases.

Introduction

Led by immune checkpoint inhibitor and chimeric antigen receptor (CAR) T cell therapies, cancer immunotherapy has shown remarkable long-term efficacy in patients with a variety of cancers [1–4]. Conventional therapies for cancers, such as radiation and chemotherapy, usually target the tumor cells themselves and can induce positive responses in the majority of patients. Despite initial responses to these conventional therapies, relapse and resistance often occur in patients with advanced cancer after prolonged treatment [5]. In significant contrast to conventional therapies, immunotherapy targets the immune system to provoke a systemic response against tumors. Clinical trials with immune checkpoint inhibitors have shown unprecedented durable responses [6], although these positive responses are limited to a small fraction of patients. The top priorities in the immunotherapy field therefore include understanding the mechanisms of action in detail and how we can extend the positive responses to a broader range of patients.

The immune system can recognize tumor antigens and kill tumor cells *in vitro* [7,8]. However, recognition of the tumor antigen alone is not sufficient for the host to eradicate established tumors *in vivo* [9–11]. An established tumor is a complex tissue composed not only of tumor cells but also of stromal cells, inflammatory cells, vasculature, and extracellular matrices (ECM), all of which are defined together as the tumor microenvironment (TME) [12,13]. Successful tumor control by immunotherapy requires the activation of the immune system, expansion of the effector cells, infiltration of activated effector cells to the tumor tissue, and destruction of the tumor cells (Fig. 1). However, the TME usually prevents effective lymphocyte priming, reduces its infiltration, and suppresses infiltrating effector cells, which leads to a failure of the host to reject tumors. The mechanisms accounting for the resistance to immunotherapy include the following: 1) an inhibitory microenvironment or lack of antigen stimulation/co-stimulation for immune cells, especially T cells, within the TME that may promote tumor growth and immune escape; 2) biological barriers around tumor tissues that can lead to inadequate numbers of immune cells migrating into tumor sites; 3) exhausted or short-lived activation of antigen-specific T cells with limited repertoires that fail to suppress tumor growth; and 4) poor direct or indirect antigen presentation in lymphoid tissues that lead to a lack of T-cell priming due to insufficient release of tumor antigens to the draining lymph node by the TME. Thus, a better understanding of the interactions between immunotherapy and the TME may provide new approaches to improve the response rates of current immunotherapies. As the contributions of the TME in conventional therapies have recently been reviewed [12], we will focus on the developments in understanding the interactions between immunotherapy and the TME.

Abbreviations: CAR, chimeric antigen receptor; TME, tumor microenvironment; PD-1, programmed cell death protein 1; PD-L1, PD-1 ligand; DC, dendritic cell; IFN, interferon; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; CD40L, CD40 ligand; ECM, extracellular matrix; CCL21, Chemokine (C-C motif) ligand 21; CXCL10, C-X-C motif chemokine 10; DPP4, dipeptidylpeptidase 4; TIL, tumor-infiltrating lymphocyte; HVEM, herpesvirus entry mediator; LTβR, lymphotoxin beta receptor; PRR, pattern recognition receptor; STING, stimulator of IFN genes.

* Corresponding author. Tel.: +1 773 307 5478; fax: +1 773 834 8940.
E-mail address: yfu@uchicago.edu (Y.-X. Fu).

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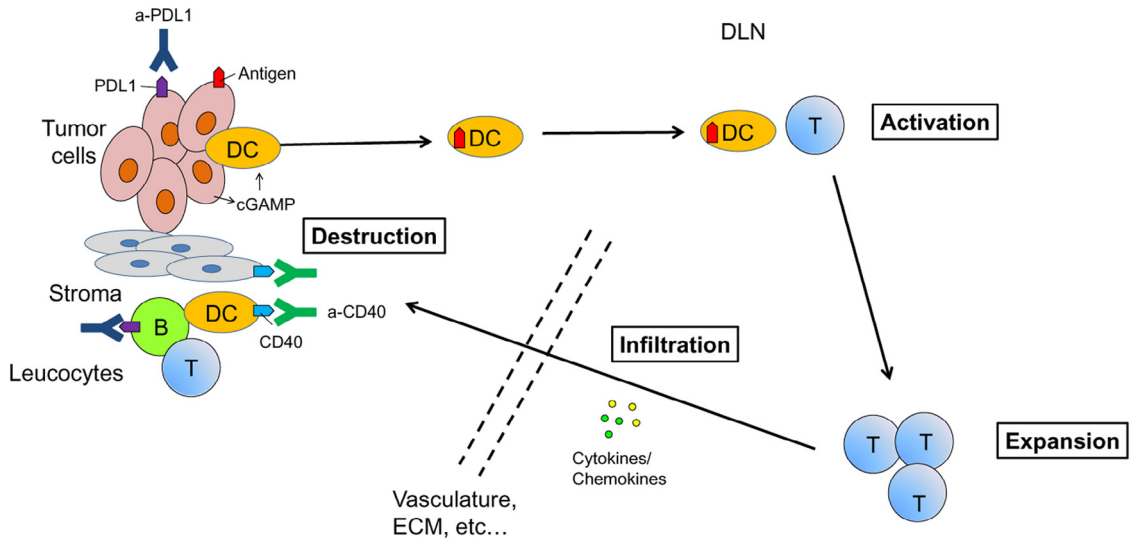

Fig. 1. Immunotherapy and the tumor microenvironment (TME). A successful tumor control induced by immunotherapy requires the activation of the immune system, expansion of the effector cells, infiltration of activated effector cells to the tumor tissue, and destruction of the tumor cells. Tumor barriers can greatly dampen those processes, while immunotherapy aims to enhance them. Effector T cells can be inhibited by checkpoint molecules, such as PDL1, expressed in the TME. The inhibition by PDL1 can be overcome by anti-PD1/PDL1. Stimulatory checkpoint antibodies are used to activate immune cells. But some antibody, eg anti-CD40, can also work on stroma cells for optimized tumor control. The ECM forms a barrier preventing T cells from reaching the TME for tumor destruction. On the other hand, lymphocyte infiltration can be enhanced by inducing/delivering cytokines/chemokines to the TME.

Interactions between immunotherapy and the TME

Immunomodulatory antibodies

Checkpoint blockade antibodies

Immune checkpoints refer to a series of pathways that can regulate T cell activity as either co-inhibitory or co-stimulatory signals [14], and they function to protect the host against autoimmunity under normal conditions [15,16]. Increasing evidence suggests that tumors use many of these pathways as important mechanisms to escape antitumor immune responses [6,17,18]. Among them, inhibitors targeting programmed cell death protein 1 (PD-1) and its ligand, PD-1 ligand (PD-L1 or B7H1), have shown the most impressive efficacy in clinical trials [3,4]. PD-1 is mainly expressed on activated T cells [19]. Although PD-L1 expression is limited in normal tissues, it is greatly increased on some tumor cells [20]. Interestingly, PD-L1 expression can be upregulated on many cells if they are stimulated by inflammatory cytokines, especially interferons (IFNs) [20]. PD-L1 engagement of PD-1 on T cells inhibits their activation and induces exhaustion [21]. A paradigm has been proposed suggesting that tumor-expressed PD-L1 inhibits T cells located within the tumor, which leads to a failure of the host rejecting the tumor. This idea is supported by the initial observation that patients with PD-L1-positive tumor cells are more likely to respond to anti-PD-1 therapy [3]. With the growing number of patient samples, however, some patients with PD-L1-negative tumor cells have also been observed to respond to PD-1/PD-L1-blockade therapies [22]. Additionally, recent retrospective clinical studies show a high correlation between responses to PD-L1 blockade and PD-L1 expression on tumor-infiltrating immune cells [23]. These studies raised the possibility that PD-L1 expression on cells in the TME besides the tumor cells may also play important roles for immune evasion.

In order to increase the response rate to checkpoint blockade therapy, several combination therapies have been developed [24]. Among them, the combination of anti-PD-1 with anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) has shown the best improvement in clinical trials [25–27]. CTLA-4 is another checkpoint molecule mainly expressed on regulatory T cells (Tregs) [28]. Blocking this pathway by anti-CTLA-4 depletes Tregs in tumor tissues, resulting in the expansion of antigen-specific cytotoxic T lymphocytes. The synergistic effects are mainly restricted to the local TME, as blocking lymphocyte trafficking after tumor is established has no effect on the synergy [29].

Immunostimulatory mAbs

In contrast to PD-1 and CTLA-4 that inhibit immune responses upon activation, the CD40/CD40 ligand (CD40L) pathway represents a different group of immune checkpoints that promote immune responses [30]. CD40 is expressed on B cells, monocytes, and dendritic cells (DCs). CD40L is primarily expressed on activated T cells and platelets [31]. Signaling through CD40 activates antigen-presenting cells and induces co-stimulatory and MHC molecule expression, resulting in increased antigen presentation and T-cell priming [32]. Agonist antibodies to CD40 have been developed to mimic CD40L engagement and can activate immune response both *in vitro* [33–35] and *in vivo* [36–38]; furthermore, several of these antibodies have entered clinical trials and show promising results [39,40]. Interestingly, although the original paradigm suggests that T-cell priming is increased downstream of CD40 activation, later studies indicate that T cells may be dispensable, at least in some tumor models [39]. Specifically, tumor regression induced by anti-CD40 depends on macrophages, but not T cells, in a mouse model of pancreatic ductal adenocarcinoma. Anti-CD40 activates macrophages, which then translocate to tumor tissues and induce the depletion of tumor stroma, leading to tumor regression [39]. The idea that stromal cells may play a more important role for the efficacy of CD40 agonist antibody treatment is supported not only in tumor models but also in other disease models. Indeed, Bouchlaka et al. has found in a recent study that systemic injection of CD40 agonist antibody together with IL-2 induces a cytokine storm and lethality in aged, but not young, mice [41]. A follow-up study shows that CD40 signaling induces macrophage activation within the visceral adipose tissues [42]. These activated macrophages produce very high TNF levels, leading to a cytokine storm. Interestingly, one possible reason to explain why lethality is found only in aged mice is that they tend to accumulate more fat in their organs than young mice. These possible adverse effects should be taken into account when applying the various CD40 therapies to cancer patients, as the