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Review

Using chemo-drugs or irradiation to break immune tolerance and facilitate immunotherapy in solid cancer

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ABSTRACT

The immunity is dual host-protective and tumor-promoting in cancer development and progression. Many immune suppressive cells and cytokines in microenvironment can prevent cytotoxic T lymphocytes (CTL) and natural killer cells (NK) from killing tumor cells. Chemotherapy drugs and irradiation have been reported helpful in breaking immune tolerance and creating microenvironment for adoptive cell therapy. Low-dose cyclophosphamide or gemcitabine therapy can selectively deplete T regulatory cells (Treg). Paclitaxel can alter cytokine network at the tumor site, and 5-fluorouracil shows a pronounced effect on myeloid-derived suppressor cells (MDSC) depletion. Local tumor irradiation and total body irradiation (TBI) can also affect tumor microenvironment and facilitate immunotherapy. In this review, we summarize the particular effects of these agents and methods on immunomodulation, as well as their potential values in immunotherapy. The combination with immunotherapy represents a novel therapeutic strategy.

1. Introduction

It is known that immunity can not only protect against cancer development but also promote tumor growth, which is referred to as cancer immunoediting [1]. On one side, the immune system acts to counteract tumor progression in its early subclinical stage. On the other side, some specific innate and adaptive immune cells, effector molecules, and signal pathways function in synergism to stimulate tumor growth. These agents hamper cytotoxic T lymphocytes (CTL) and natural killer cells (NK) from recognizing and eliminating tumor cells, which makes tumor growth out of control, leading to death of the host.

Cancer immunotherapy has a rapid development in the past several decades. It is hoped by immunologists and oncologists to achieve robust antitumor immune response activation, and even an increase in survival in cancer patients [2]. Generally, immunotherapy includes antibodies, cytokines, vaccines, and adoptive cell therapies [3]. Ipilimumab and nivolumab are monoclonal antibodies of cytotoxic T-lymphocyte antigen 4 (CTLA-4) [4] and programmed death 1 (PD-1) [5] expressed on T cells, respectively. Blocking those two inhibitory receptors (CTLA-4 and PD-1) keeps T cells active. Cytokines, such as interleukin-2 (IL-2) and interferon-α (IFN-α), have been used in kidney cancer and melanoma, but their applications are limited because of the serious side effects. Vaccines and cellular therapies are under investigation in clinical trials, and face the challenge of survival benefit simultaneously. More recently, in MAGRIT study, a phase III trial about a kind of lung cancer vaccine, no improvement in progression-free survival was observed [6]. Clinical results of cellular therapy are mainly from small sample trials and retrospective studies. Therefore, large prospective randomized clinical trials with proper design are needed to further define their role.

The difficulty in cancer vaccine and cellular therapy development makes some researchers think about reasons and solutions. Immunotherapy initially focused on immune response activation. Various adoptive immune cells, such as cytokine-induced killer cells (CIK), tumor-infiltrating lymphocytes (TIL), γδT cells, and genetically engineered T cells, are under development [7]. As the deep understanding of the interactions in tumor microenvironments, immunosuppressive cells and inhibitory signal transduction gain much attention in anti-cancer therapy. Breaking immune tolerance is a theoretically feasible method for improving the efficiency of anti-cancer immunity, and a growing interest has been attracted to the ways of breaking immune tolerance in immunotherapy, especially after the success of ipilimumab and nivolumab [8]. Other inhibitory molecule targets, such as T-cell immunoglobulin and mucin domain 3 (TIM3) and killer cell immunoglobulin-like receptors (KIR), are under subclinical study.

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Chemotherapy drugs and irradiation are reported to be functional in modulating immune microenvironment [9], and the application is different from conventional therapy. We provide insights into the particular effects of these agents and methods on immune microenvironment, as well as their potential values in immunotherapy. The combination represents a new therapeutic strategy.

2. Immune tolerance factors

Several trials have suggested the cytotoxic effects of CIK and other adoptive immune cells on cancer cell lines in vitro [10]. Nevertheless, the immune system is extremely complex, and there is doubt whether the transferred cells keep cytotoxic when they meet with cancer cells in vivo. Many cells, cytokines and molecules are involved in immune tolerance in cancer patients, and they work together to dampen the efficacy of immunotherapy [11].

A myriad of studies have demonstrated the immunosuppressive capabilities of cancer-induced inhibitory cells. Regulatory T cells (Treg), myeloid-derived suppressor cells (MDSC), and tumor-associated macrophages (TAM) are closely related to immune tolerance. Other suppressor lymphocyte subsets have also been researched, including IL-10 producing B cells, B regulatory cells, type II NKT cells and type 17 T helper cells (Th17) [2]. Endogenous $CD4^+$ Tregs have a negative impact on adoptive immune cells transferred to cancer patients [12,13], furthermore, peripheral $CD4^+$ Treg levels are negatively associated with the clinical responses. $CD4^+CD25^+$ T cells also exist in the infused immune cells; however, it is Treg cells from the patients themselves that suppress anti-tumor responses [14]. MDSC are a group of heterogeneous myeloid cells with suppressive activity, containing precursors of granulocytes, macrophages, and dendritic cells. They play an important role in abrogating tumor cell immune clearance by antigen-specific T cells and promoting tumor progression in multiple murine models [15]. In vivo, MDSCs have been reported to suppress naïve T-cell responses in some models, but it is unclear how effector/memory T cells are affected, which is more relevant for tumor-infiltrating T cells [16]. TAMs represent another predominant population of inflammatory cells that present in solid cancer. TAMs are characterized as M2-like macrophages and are known to promote disease progression of different cancer types [17,18], especially associated with poor prognosis for advanced ovarian cancer. It has been proved that reduction of M2-macrophages and MDSC improves the efficacy of adoptive cell immunotherapy [19]. Overall, approaches to deplete endogenous suppressor cell populations can improve the efficiency of anti-cancer immunity.

Cytokines, such as IL-10, transforming growth factor-β (TGF-β) and colony stimulating factor 1 (CSF-1), are also reported outstanding in the development of immune tolerance [20]. In addition, PD-1, CTLA-4, T cell Ig and ITIM domain (TIGIT) and KIR are inhibitory receptors expressed on T cells or NK cells, and interactions with their ligands lead to inhibitory signal transduction.

3. Function of low-dose chemo-drugs on immunotherapy

Antitumor immunity can be activated during chemotherapy and contributes significantly to the overall survival [21]. Mccoy et al. found that in 40 cancer patients receiving platinum-based scheme, chemotherapy potentially provided a favorable environment for the development of anti-tumor immunity accompanied by transient Treg depletion and regeneration of the T-cell pool [22]. Nevertheless, conventional chemotherapy based on maximum tolerated doses (MTD) is usually used to eliminate quickly proliferating tumor cells, and the subsequent profound immunosuppression in tumor-bearing hosts facilitates rapid proliferation of chemoresistant tumor cells. This kind of therapy often induces clinical toxicity or serious complications, and cannot be tolerated by all patients, such as those with serious basic diseases.

Chemo-drugs in noncytotoxic concentrations are able to change immune system and facilitate immune activation with little toxicity (Fig. 1). The low-dose chemo-drugs, even without alterations of the bone marrow hematopoiesis, can be tolerated by most cancer patients. Chemotherapy in noncytotoxic concentrations breaks immune tolerance and enhances anti-cancer immunity by different mechanisms: modulate dendritic cells (DC) maturation [23], regulate the expression of auxiliary receptors in T cells [24], change the cytokine network in immune microenvironment, and deplete immunosuppressive cells. These chemo agents are active in depleting the high proliferative immunosuppressive cells, while spare low proliferative lymphocytes with protective function. Furthermore, the subsequent occupation of the microenvironment by $CD8^+$ T cells hampers the replenishment of suppressive cells following chemotherapy. Several chemotherapy drugs below are predominant in immunomodulation, and the application is different from conventional chemotherapy.

4. Cyclophosphamide

Cyclophosphamide (CTX) has emerged as a clinically feasible agent that induces effective antitumor immune responses in both vaccine and adoptive cell therapy models [25,26]. The underlying mechanisms of immune responses augmentation are complex, including the facilitation of T cells homing and CTL proliferation by the creation of space, the alteration of Th2/Th1 responses due to the cytokine network change, and the removal of Treg [27]. Doses and timing are two crucial points in its application. Research showed that CTX with low dose selectively depleted Treg, while with high dose lost its specificity in Treg cell depletion in cancer patients [28]. The similar conclusion was also gotten in mice with hepatoma that low-dose CTX (20 mg/kg) suppressed Treg while effector T cells appeared to be spared [29]. Wada et al. [26] demonstrated that in mice the optimal dose of CTX was 50 mg/kg, considering specific T-cell expansion, circulating B cells reduction and Treg depletion.

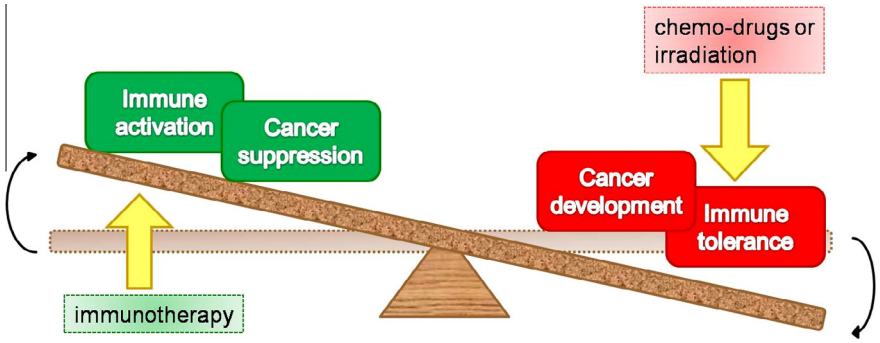

Fig. 1. Using chemo-drugs or irradiation to break immune tolerance and the change immune balance facilitating immunotherapy in solid cancer.