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# Mechanisms and therapeutic potentials of cancer immunotherapy in combination with radiotherapy and/or chemotherapy

Wei-Di Yu[a,1], Guan Sun[b,1], Jun Li[c,1], Jiang Xu[d,*], Xiaochen Wang[a,*]

[a] Liver Transplantation Center of the First Affiliated Hospital and Collaborative Innovation Center for Cancer Personalized Medicine, Nanjing Medical University, Nanjing, Jiangsu Province, PR China
[b] Department of Neurosurgery, Yancheng City No.1 People's Hospital, The Fourth Affiliated Hospital of Nantong University, Yancheng, Jiangsu Province, PR China
[c] Department of General Surgery, The Affiliated Jiangning Hospital of Nanjing Medical University, 168 Gushan Road, Nanjing, Jiangsu Province, PR China
[d] Department of Rehabilitation, Huai'an Second People's Hospital, The Affiliated Huai'an Hospital of Xuzhou Medical University, Huai'an, China

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ABSTRACT

Immunotherapies based on T cells have gained significant success in the treatment of diverse cancers, however, several limitations also exist, including low response, acquired resistance and severe side effects, which lead to unfavorable outcomes. Recent studies found that traditional therapies, radiotherapy and/or chemotherapy may affect the immune condition in situ and cause abscopal effect, which may improve the response of immunotherapies, enhance the efficiency, and reduce the untoward effect. Here, we review the mechanisms uncovering the cancer immunotherapy and immunogenic effects of radiotherapy and chemotherapy, aiming to highlight the principles underlying the therapeutic potentials of cancer immunotherapy in combination with radiotherapy and/or chemotherapy and ultimately guide better designs for future synergistic cancer therapies.

## 1. Introduction

Strategies to harness antitumor immunity mediated by T cells have evolved as the most promising approach for the treatment of malignant tumors [1,2]. Compromised antitumor immunity mediated by T cells generally involves the following steps: (1) weak or unresponsive neoantigens released by dying tumor cells; (2) loss of MHC I molecules on tumor cells; (3) lacking of T cell infiltration in tumor; (4) dysfunction of antitumor T cells in tumor (Fig. 1). During the development and progression of cancer, one or several of the above steps could occur optimally [3,4]. Cancer immunotherapies targeting these compromised and rate-limiting steps are therefore designed to enhance or normalize the impaired antitumor immunity.

Despite that recent cancer immunotherapies like immune-checkpoint blockers (ICBs) and chimeric antigen receptor-T (CAR-T) cells have gained inspiring success, limited number of patients can obtain benefits attributed to low response and acquired resistance during the treatment, and severe side effects also lead to unfavorable outcomes [5–7]. Single targeting therapy generally results in extreme effect, unresponsiveness or overreaction, while combinational therapies show synergistic outcome with higher curative efficacy and less side effects [8–10].

Recent studies found that cancer patients receiving radiotherapy and/or chemotherapy showed distinct immunogenic patterns, which may improve the response of immunotherapies, enhance the efficiency and reduce the untoward effect [11,12]. Strategies that combine immunotherapy and traditional therapies like radiotherapy and/chemotherapy have shown strikingly exciting outcomes in clinical and basic researches [13–16], however the underlying mechanisms are still unclear.

Here, we reviewed the recent progresses on the mechanisms uncovering the cancer immunotherapy and immunogenic effects of radiotherapy and chemotherapy, discussed the advantages and disadvantages of current T cell based immunotherapies, and tried to explore the potentials and challenges of the synergistic strategies for the treatment of cancer. Additionally, we designed to highlight the principles underlying the therapeutic potentials of cancer immunotherapy in combination with radiotherapy and/or chemotherapy and ultimately guide better designs for future synergistic cancer therapies.

* Corresponding author. Liver Transplantation Center of the First Affiliated Hospital and Collaborative Innovation Center for Cancer Personalized Medicine, Nanjing Medical University, Nanjing, Jiangsu Province, 210029, PR China.
*E-mail addresses:* haeyxj@126.com (J. Xu), wangxc@njmu.edu.cn (X. Wang).
[1] These authors contributed equally to this study.

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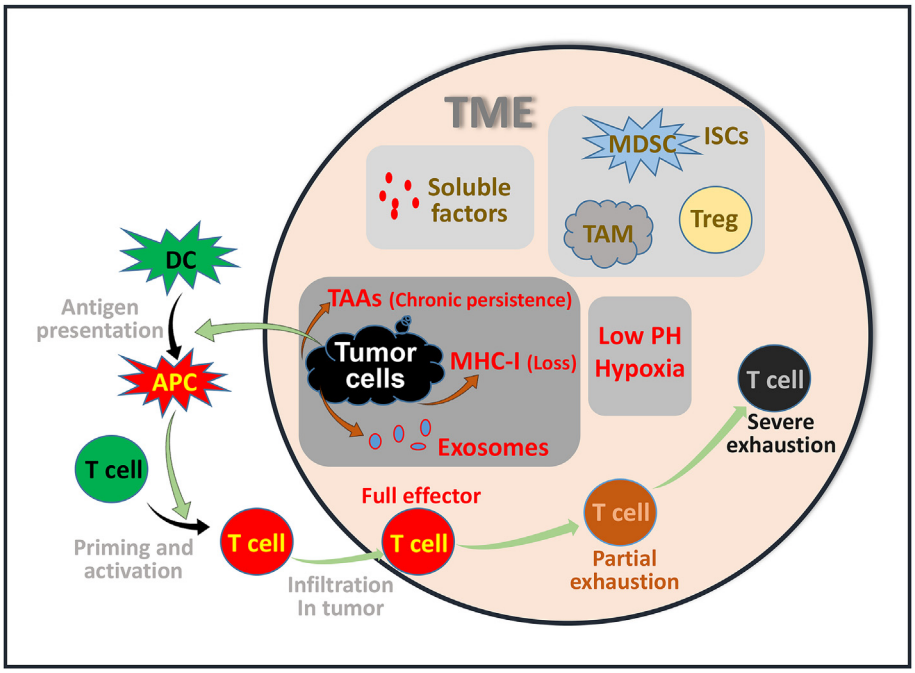


**Fig. 1.** Compromised antitumor immunity mediated by T cells generally involves the following steps: (1) weak or unresponsive neoantigens released by dying tumor cells; (2) Loss of MHC I molecules on tumor cells; (3) lacking of T cell infiltration in tumor; (4) dysfunction of antitumor T cells in tumor (T cell exhaustion). The development of $CD8^+$ T cell exhaustion may be attributed to complicated components in cancer microenvironment, such as persistent stimulation of tumor antigen, inhibition of immunosuppressive cells, such as Tregs, TAM and MDSCs, the imbalance of physical and chemical state (e.g. hypoxia and high level of lactate). TAA, tumor-associated antigens; APC, antigen presenting cells; DC, dendritic cells; TME, tumor microenvironment; ISC, immunosuppressive cells; Treg, regulatory T cells; MDSC, myeloid-derived suppressor cells; TAM, tumor-associated macrophages.

## 2. Cancer immunotherapy

Cancer immunity is characterized by the dysfunctional antitumor T cells and the immunosuppressive tumor microenvironment (TME) [17]. TME is composed of tumor cells, stroma, vascular elements, tumor-draining lymph nodes and the biomolecules around them. Abundant cellular and molecule events in TME shape the anti-tumor immune responses and determine the eventual efficacy of immunotherapy [18,19]. Common T-cell mediated antitumor immunity generally involves the following steps: (1) neoantigens from dying tumor cells are released and captured by antigen-presenting cells (APCs, eg. dendritic cells); (2) APCs present the captured antigens on MHC I and MHC II molecules to T cells; (3) the priming and activation of effector T cell responses against the cancer-specific antigens; (4) the activated effector T cells traffic to tumor site; (5) T cells infiltrate in tumor; (6) the activated effector T cells specifically recognize and bind to cancer cells (7) antigen-specific T cells kill the target cancer cells [3,18]. However, due to the complexity of tumor immune escape and the uncertainty of TME, one or several of the above steps could not perform optimally. Cancer immunotherapies are generally designed targeting these steps to normalize and ameliorate the antitumor immunity.

The achievements of immune checkpoint blockers in the treatment of unresectable or metastatic melanoma and non-small-cell lung cancer (NSCLC) make them the most dazzling cancer therapeutics at present [20]. These are designed for the neutralization of immunosuppressive factors and the activation of stimulating factors [21]. Adoptive cell therapy (ACT), which directly delivers modified immune cells to patients, has produced durable responses in the treatment of acute lymphoblastic leukemia (ALL) [22]. Additional therapeutics includes vaccines that promote DCs maturation and MHC I recognition [23], and small-molecule drugs to modulate TME (Fig. 2).

Although immunotherapies above have demonstrated effective in preclinical and clinical studies, benefit in most cases was limited. Durable responses may closely rely on the status of host immunity. 50%–60% patients show low or no responses to immune checkpoint blockers [24]. Over-stimulation of immunity leads to immune-related adverse effects (irAEs), which also confuse the prognosis [25]. In view of conventional therapies can impact immune system differently [26], oncologists are now exploring synergy of immunotherapy and conventional cancer therapies, as monotherapy fails to meet the actual treatment needs.

## 3. Immunological effects of chemotherapy

Conventional chemotherapeutics induce cell death by interfering directly with DNA or targeting key proteins required for cell division [27]. Decades of researches have shown that chemotherapy can play different roles in anti-tumor immunity [28]. The positive effects of standard chemotherapy on tumor immunity are mainly reflected in inducing immunogenic cell death as well as disrupting tumor escape strategies. Immunogenic dead tumor cells can release tumor-associated antigens (TAAs) and danger-associated molecular patterns (DAMPs), both of which recruit immune cells in TME positively [29]. Anthracyclines promote the transfer of intracellular calreticulin to the surface, providing phagocytic signals to DCs [30]. Standard-dose gemcitabine reverses defective cross-presentation of TAAs by DCs and enhances the cross-priming of $CD8^+$ T cells. Taxane and cyclophosphamide respectively deplete MDSCs and Treg cells, reducing the activity inhibition of T cells infiltrated in tumor [31]. Additional mechanisms include strengthen the effector T cell activity by co-stimulatory factors (B7-1) up-regulation or co-inhibitory factors (B7-H1) down-regulation, or the utilization of fas, perforin and granulozyme B, under which tumor cells are more sensitive to T-cell-mediated lysis [32].

Chemotherapy can interfere with tumor immunobiology through drug, dose and schedule [32]. When faced with the genetic heterogeneity of tumor and the complexity of TME, conventional chemotherapy in standard dose seems inflexible, resistance of chemotherapy is also very common in clinical. When cyclophosphamide is given in maximum tolerated doses (MTD), it will lead to apoptosis of newly formed tumor microvascular endothelial cells. However, this anti-angiogenic effect cannot transform into therapeutic benefits, for the damaged cells can repair themselves during schedule [33]. Moreover, bone marrow–derived circulating endothelial progenitor cells (CEPs) are thought to take part in the process of tumor vascularization. Bertolini et al. designed an experiment, they injected immune-deficient mice with human lymphoma xenografts. When the mice were treated with cyclophosphamide in MTD, CEPs was strongly mobilized within a few days after the end of the drug delivery cycle, and the tumors rapidly developed agent resistance [34]. Therefore, it is necessary to adjust the dose and schedule of chemotherapy, namely, metronomic

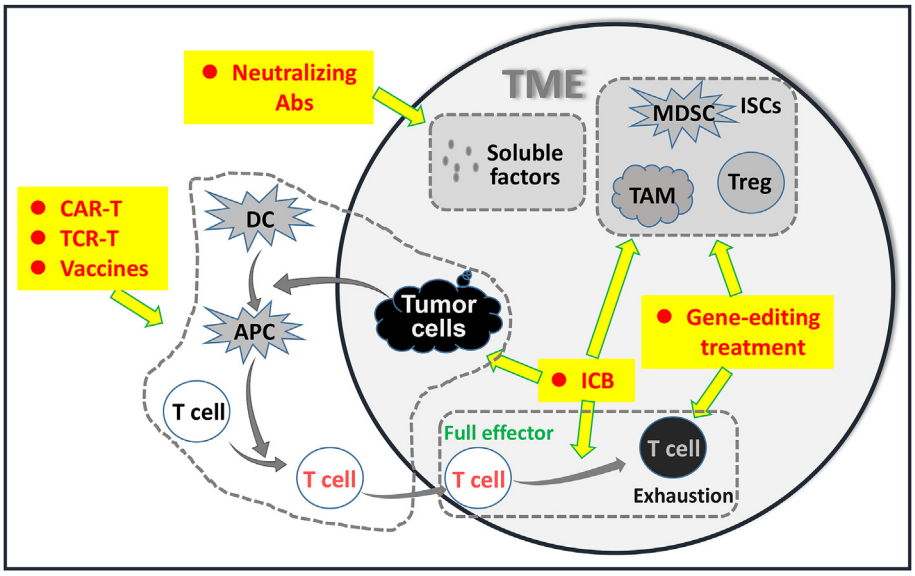


**Fig. 2.** Common T-cell mediated antitumor immunity generally involves the following steps: ACT (CAR-T, TCR-T), which directly delivers modified immune cells to patients; vaccines that promote DCs maturation and MHC I recognition; neutralizing antibodies to modify the immunosuppressive moleculars in TME; ICB to blocked immune check-point on T cells, tumor cells and immunosuppressive cells; gene-editing to enhance or restore the anti-tumor function of T cells. APC, antigen presenting cells; DC, dendritic cells; TME, tumor microenvironment; ISC, immunosuppressive cells; Treg, regulatory T cells; MDSC, myeloid-derived suppressor cells; TAM, tumor-associated macrophages; ACT, adoptive cell therapy; CAR-T, chimeric antigen receptor T-Cell immunotherapy; TCR-T, T cell receptor T-Cell immunotherapy; ICB, immune check-point blocker.

chemotherapy [35]. Combined with standard chemotherapy, metronomic chemotherapy acts on tumor endothelial cells, which show better genetic stability than tumor cells themselves [36]. Inhibition of tumor growth and development also starts from vascular inhibition or cell dormancy, with higher flexibility and less possibility of drug resistance. Metronomic chemotherapy suppresses tumor growth by inhibiting angiogenesis and cell dormancy [37].

Metronome chemotherapy can overcome the host's immunosuppression state through at least three aspects of immune regulation: (1) enhance the antigen presentation functions; (2) induce a protective T cell response; (3) inhibit immunosuppression in TME [38].

Synergy of chemotherapy and other tumor therapies has been widely used in clinical practice. Chemotherapy has a positive effect on tumor immunity, which makes the synergy of chemotherapy and immunotherapy a promising choice. In addition, giving chemotherapy after surgery can improve the immunogenicity of residual cells, providing a new idea for clinical combination therapy. However, activation of anti-tumor responses require the existence of a certain number of functional immune cells in vivo. In view of the non-targeted effect of MTD, immune cells will be exhausted or dysfunction during the drug use, which is also a problem need to be solved. Notably, the drug resistance of tumor is very complex. Rhythm dosing of low-dose cyclophosphamide makes the accumulation of MDSCs, eventually leading to tumor growth rebound [39,40]. While in another series of experiments, compared with the intermittent dosing, continuous dosing taxane to ovarian cancer cells show stronger anti-tumor responses both in vivo and in vitro, the resistance is also acceptable [41]. In addition to the drug, dose, and schedule, the final outcome also largely depends on the immune function of the body and the biological characteristics of the tumor itself.

## 4. Combination of cancer immunotherapy and chemotherapy

Chemotherapeutics such as taxanes can enhance toll-like receptor activity and promote DCs activation. Single-agent taxanes has been used as the fist-line therapy for triple-negative breast cancer [42,43]. While in patients with triple-negative breast cancer, programmed cell death ligand 1 (PD - L1) was found to be expressed mainly in immune cells, rather than on tumor cells. Thus atezolizumab, an immune checkpoint inhibitor that selectively targets PD - L1, has been used to suppress tumor immune responses [44]. The safety and activity of atzolizumab combined with nab-paclitaxel have been demonstrated in a phase 1b study of triple-negative breast cancer [45]. In another phase 3 trial, Schmid et al. found that compared with the fist-line therapy, nab-paclitaxel + atzolizumab can significantly prolong the progression-free survival (PFS). Notably, the PFS is significantly extended by 2.5 months in patients with PD-L1 positive tumors. (7.5 months with nab-paclitaxel + atezolizumab, 5.0 months with nab-paclitaxel + placebo) (Table 1). Moreover, side effects in this trial are predictable and controllable [46].

In addition to the triple-negative breast cancer, monotherapy of atezolizumab is also used in patients with recurrent or refractory small cell lung cancer (SCLC). While combination of atezolizumab and first-line chemotherapy (carboplatin/cisplatin + etoposide) may significantly improve both PFS and overall survival (OS) of patients with extensive SCLC. This suggests that synergy of cytotoxic therapy and immune checkpoint inhibition may be beneficial and feasible in clinical [47].

**Table 1**
Results of Clinical Trials Evaluating the Combination of immunotherapy and Chemotherapy.

| Disease | Protocol | number of patients | median PFS(mo) | median OS(mo) |
|---|---|---|---|---|
| SCLC{Horn, 2018 #20} | carboplatin and etoposide plus atezolizumab | 201 | 5.2 | 12.3 |
| | carboplatin and etoposide plus placebo | 202 | 4.3 | 10.3 |
| advanced triple-negative breast cancer{Adams, 2018 #113} | atezolizumab plus nab-paclitaxel | 451 | 7.2 | 21.3 |
| | atezolizumab plus placebo | 451 | 5.5 | 17.6 |
| melanoma{Di Giacomo, 2012 #115} | fotemustine plus IPI | 86 | 5.3 | 13.3 |
| NSCLC{Lynch, 2012 #114} | Carboplatin and paclitaxel | 204 | 4.2 | 8.3 |
| | Carboplatin and paclitaxel plus IPI | | 4.1 | 9.7 |
| | Phased IPI | | 5.1 | 12.2 |

Abbreviations: PFS, progression-free survival; OS, overall survival; SCLC, small cell lung cancer; IPI, ipilimumab; NSCLC, non-.small cell lung cancer.

## 5. Immunological effects of radiotherapy

Mechanisms of ionizing radiations leading to cell death are classically summarized as 5R's of radiobiology: repair of radiation damage, accelerated reproliferation after radiation, redistribution of the cell cycle, reoxygenation and radiosensitivity [49]. While the most representative mechanism of radiation therapy (RT) killing tumor cells is the irreparable DNA damage caused by double strand break (DSB) [50]. One of the characteristics of RT that distinguishes it from other conventional therapies is its ability to trigger anti-tumor responses far from irradiated site, known as abscopal effect [51]. It has been reported in many types of tumors since 1953, such as melanoma [52], hepatocellular carcinoma [53], NSCLC [54], and renal cell carcinoma [55]. Abscopal effect can also be reproduced in murine models, but not in mice with T cell deficient or $CD8^+$ T cell depletion. It can be speculated that the remote effects induced by radiation may be mediated by immune system [56]. During radiotherapy, DCs phagocyte dying irradiated tumor cells, leading to activation of the Stimulator of Interferon Genes (STING) pathway by tumor derived DNA fragments. Finally, the transcription of type I IFN genes is up-regulated. Type I IFN can enhance TAAs presentation by DCs to immune cells both in irradiated site and lymph nodes. Meanwhile, the activated immune cells can secrete type II IFNs, which stimulate the expression of MHC-1 at tumor cells surface [57]. This STING-mediated DNA-sensing pathway provides a reasonable explanation for abscopal effect [58]. Plenty of studies demonstrate that RT mediates its anti-tumor effects at least in part by synergizing with auto-immune system [59]. Lee et al. found that $CD8^+$ T cells can mediate efficacy during high-dose ablation radiotherapy [60]. Sublethal irradiation of tumors cells may increase the expression of MHC I-related antigens or tumor-related antigens in gastric adenocarcinoma and melanoma [61].

Similar to chemotherapy, RT induces immunogenic cell death by direct cytotoxic effects, resulting in the release of TAAs and DAMPs [62]. TAAs can be recognized and captured by DCs, and eventually presented to T cells for activation. DAMPs from dying irradiated tumor cells include heat shock proteins (HSPs), nucleotide and high mobility group box 1 molecules (HMGB1) [63]. DAMPs can be recognized by toll-like receptors and thus facilitate the presentation of TAAs to $CD8^+$ T cells by MHC I [64]. Perez et al. find that in vitro irradiation of melanoma, $CD8^+$ T cells infiltration in tumor site and DC-mediated phagocytosis are increased, which are responsible for the reduction of metastatic disease in radioma mice [65]. Other approaches that promote tumor immunity include up secretion of cytokines that induce recruitment of $CD8^+$ T cells towards tumor sites [66].

In contrast, the modification of radiotherapy in TME is very contradictory. On the one hand, RT enhanced the recruitment of anti-tumor T lymphocytes to TME by up regulating adhesion molecules [68]. On the other hand, RT can directly inactivate immune cells [69]. RT leads to the recruitment of MDSCs and Treg cells in TME, promoting immune tolerance towards tumor cells [70]. Also, the reactive oxygen species (ROS) produced by RT intensify the activation of TGF-β, a key barrier that inhibits RT-induced T cells responses to various endogenous tumor antigens [71]. Notably, tumor associated macrophages (TAMs) induced by irradiation often result in tumor recurrence and treatment failure [72].

The ideal scenario is to create an in situ vaccine by RT, thus produce a stable anti-tumor response to tumor epitopes that shared between primary and metastatic tumor sites [73]. While the immunosuppressive effect of RT has to be worrying. Abscopal effect is rare in monotherapy, especially in low-immunogenicity tumors. However, when RT is combined with tumor immunotherapy, it occurs more frequently in clinical [74]. Therefore, it is a reasonable solution to explore synergy of RT and immunotherapy. So far, many preclinical and clinical studies have achieved some results in the combination on tumor control [75].

## 6. Combination of cancer immunotherapy and radiotherapy

Anti-tumor immunity can be regulated by various cytokines. IL-2 promotes T cells priming and activation in cancer immunity cycle [3]. It is also proved to mediate abscopal responses positively in combination [80]. Another cytokine under study is GM-CSF, a catalyst which promotes DCs maturation [76]. In preclinical trials, irradiation of GM-CSF-secreting melanoma cells resulted in a sustained and stable anti-tumor response in mice. Objective abscopal responses can also be observed in patients with metastatic solid tumors [77].

Another method to improve radioactive immune response is transferring immune cells directly into the tumor. Irradiation before DCs injection may change the immunogenicity of tumor, the number of labeled DCs recruited at the tumor site was increased significantly [78]. When treating patients with high-risk soft tissue sarcoma in a phase I study, the combination shows no unexpected toxic reactions or serious adverse events, and 11 of the 18 patients (61%) survived without systemic recurrence during 2–8 years [79].

## 7. Conclusions

Despite that recent cancer immunotherapy has gained significant success, several side effects are unneglectable, such as extreme effect, unresponsiveness and overreaction. As traditional treatment, radiotherapy and/or chemotherapy may improve the response of immunotherapies, enhance the efficiency of reduce the untoward effect, through modifying immune condition in situ and cause abscopal effect. Strategies that combine immunotherapy and radiotherapy and/chemotherapy can synergistically improve the outcome for the treatment of cancer.

## Conflicts of interest

The authors declare no conflict of interest.

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