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REVIEW / *Research and new development*

Thermal ablation and immunomodulation: From preclinical experiments to clinical trials

H. Takaki[a,*], **F. Cornelis**[b], **Y. Kako**[a], **K. Kobayashi**[a], **N. Kamikonya**[a], **K. Yamakado**[a]

[a] *Department of Radiology, Hyogo College of Medicine, 1-1 Mukogawa, Nishinomiya, Hyogo 663-8501, Japan*
[b] *Department of Radiology, Tenon Hospital, Paris VI University, AP—HP, 4, rue de la Chine, 75020 Paris, France*

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Abstract Accumulating evidence has shown that thermal ablation can induce spontaneous distant tumor regression, which is also known as *abscopal effect*. Abscopal effect might depend upon the activation of antitumor immune response. However, such responses induced by thermal ablation had been thought to be usually weak and that they rarely induce distant tumor regression. Recently, results of several preclinical and clinical studies have suggested that thermal ablation can induce therapeutically effective systemic antitumor immune response if appropriate immunomodulators are combined. To elucidate the mechanisms of these promising strategies, effects of thermal ablation on the immune system are overviewed. Furthermore, recent promising preclinical and clinical studies examining enhancement of systemic antitumor immune response by combining thermal ablation and immunomodulation are summarized.

Thermal ablation has been applied increasingly to treat both primary and metastatic cancers [1—5]. Traditionally, the efficacy of thermal ablation has rested mainly on its direct tumoricidal effect: how completely the target tumor can be ablated. Recently, indirect systemic effects have also gained attention, such as antitumor immune response caused by thermal ablation [6,7].

Accumulating evidence has suggested that thermal ablation can induce so-called *abscopal effects* in rare cases, which is the spontaneous regression of a remote no-target tumor [8—10]. Results of earlier studies suggest that abscopal effects might depend

* Corresponding author.
E-mail address: takakiharuyuki@gmail.com (H. Takaki).

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upon activation of the systemic antitumor immune response [11,12]. Although the abscopal effect is an extremely rare phenomenon, recent preclinical and clinical studies have suggested that thermal ablation can induce therapeutically effective systemic antitumor immune response if appropriate immunomodulatory approaches are combined.

To elucidate the mechanisms of these promising strategies, effects of thermal ablation on the human immune system are overviewed from the perspective of the cancer immunity cycle. Furthermore, results of promising preclinical and clinical studies that combine thermal ablation and immunomodulation are explained. Finally, current ongoing clinical trials are introduced.

Cancer immunity cycle

To elucidate the fundamental concept of interaction between the immune system and cancer, the cancer immunity cycle is a useful model (Fig. 1) [13]. In the first step of this model, tumor antigens are released by dead cancer cells and are captured by dendritic cells (DCs) for processing (step 1). Then, DCs present the captured antigens to naïve T cells (step 2), resulting in the priming and activation of cytotoxic T lymphocyte (CTLs) response against the tumor-specific antigens (step 3). Activated CTLs, which are the major effector cells for cancer elimination, traffic to (step 4) and infiltrate (step 5) the tumor microenvironment. Activated CTLs recognize the tumor antigen that is presented by major histocompatibility complex (MHC) class I molecules (step 6), and destroy their target cancer cells (step 7). Killing of the cancer cells releases additional tumor antigens (step 1 again), leading to the subsequent revolutions of the cancer immunity cycle. Therefore, theoretically, amplifying the cancer immunity cycle and enhancing anti-cancer activity.

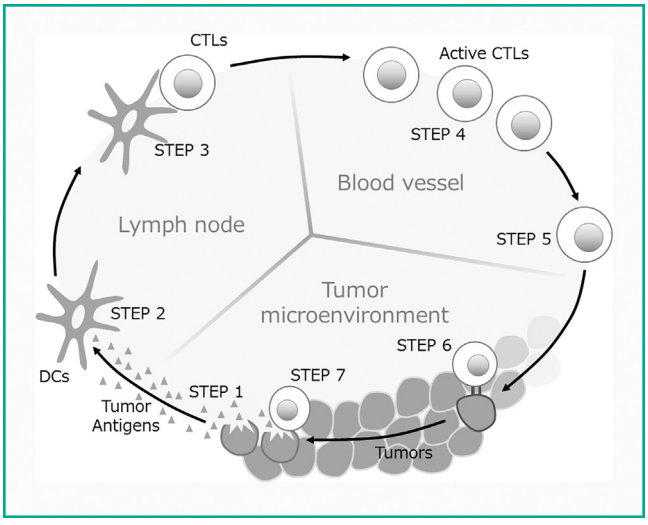

Figure 1. Cancer immunity cycle. The cancer immunity cycle is a model advocated by Chen and Mellman, which describes a series of multistep immune events triggered by cancer cell death [13]. In the first step of this model, tumor antigens are released by dead cancer cells and are captured by dendritic cells (DCs) (step 1). Then, DCs engulf and process the tumor-derived antigens and travel to the regional lymph node, where they become mature DCs (step 2). Mature DCs prime and activate cytotoxic T lymphocytes (CTLs), which respond against tumor antigens (step 3). Primed and activated tumor-specific CTLs traffic to the tumor bed via blood vessels (step 4). Tumor-specific CTLs infiltrate the tumor microenvironment (step 5). Tumor-specific CTLs recognize and bind to tumor cells via major histocompatibility complex (MHC) class I molecules on the tumor cells (step 6). Tumor-specific CTLs destroy cancer cells (step 7). Subsequently, more tumor antigens are released. The cancer immunity cycle starts all over again.

Cancer immunity cycle modulation by thermal ablation

After thermal ablation, various immune modulating factors such as tumor antigens, danger signals, and cytokines are released or expressed (Table 1). This section presents explanations of the mechanisms of how these substances modulate the cancer immunity cycle. It is most important to know that substances released after thermal ablation can modulate the cancer immunity cycle both positively and negatively.

Tumor antigen

Tumor destruction by thermal ablation induces the release of tumor antigen (cancer immunity cycle, step 1). Ghanamah et al. evaluated serial changes in carcinoembryonic antigen (CEA) values after RF ablation for liver metastasis from colorectal cancer [14]. In their study, 59% of patients (10/17) presented an increase in CEA at 1 day after RF ablation. Then, CEA levels decreased gradually, reaching a nadir at 3 months. Similarly, Leibovici et al. reported a transient increase of serum prostate specific antigen (PSA) after cryoablation for prostate cancer [15]. Increased release of tumor antigen after thermal ablation can amplify the cancer immunity cycle. den Brok et al. showed that antigen-positive DCs in draining lymph node increased significantly after thermal ablation using a mouse melanoma model [16]. They also showed that thermal ablation induces the maturation of antigen-positive DCs [16]. Nobuoka et al. reported that peripheral blood glypican-3 (GPC3, a carcinoembryonic antigen) specific CTLs after RF ablation increased in 5 of 9 HCC patients, although they were increased in only 1 of 9 patients after surgical resection [17].

Danger signals

For up-regulation of the cancer immunity cycle, the release of tumor antigens alone is insufficient: ''danger signals'' are also be necessary. Danger signals are endogenous molecules such as heat shock proteins (HSP) and high morbidity group box-1 (HMGB-1) [18–20]. Danger signals are released by or expressed in the injured or dying cell. They affect cancer immunity cycle in various respects. HSP 70 is a representative danger signal that is known to chaperon tumor antigens to DCs and then to cross-present the antigens to T cells (steps 2 and 3) [21]. HSP 70 also promotes the presentation of tumor antigens on the cell surface via enhancement of MHC class I expression, which might enhance cancer cell recognition by CTLs (step 6) [22]. Additionally, HSP 70 can enhance the killing of cancer cells (step 7) without

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