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Is pre-existing antitumor CD4 T cell response indispensable for the chemotherapy induced immune regression of cancer?

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Insights into antitumor T-cell responses may help the development of more efficient treatments for lung cancer. The interplay between pre-existing antitumor CD4+ T-cell responses and platinum-based chemotherapy is crucial to improve patient survival. Accumulating evidence confirms that selecting cancer patients in whom chemotherapy can activate an anticancer immune response would largely improve the success of novel therapeutic approaches.

According to the cancer immunoediting hypothesis, tumor cells—at least initially—are immunogenic and the adaptive immune system is involved in their active elimination.[1] Among the immune cells that participate in this process, CD4+ helper T cells seem to play a major role in the generation and maintenance of effective antitumor immunity.[2] Thus, in humans, a high density of tumor-infiltrating Th1 cells has been shown to constitute a good prognostic marker in several cancers.[3] Pioneering work from Laurence Zitvogel and Guido Kroemer highlighted the capacity of some chemotherapy drugs to modulate antitumor immunity.[4] Understanding how the efficiency of chemotherapy is influenced by its effects on the immune system is one of the most challenging questions for tumor immunology. However, the impact of pre-existing tumor-specific Th1 responses on the therapeutic potential of anticancer drugs has been poorly studied, mostly due to technical reasons.

In a recent study, we used newly identified pan-HLA-DR-derived epitopes from the human telomerase reverse transcriptase (TERT), which we called universal cancer peptides (UCP), to monitor tumor-specific CD4+ Th1 cell responses. These UCPs could be recognized by CD4+ T cells isolated from different types of cancer.[5] The naturally occurring UCP-specific CD4+ T-cell response was studied in non-small cell lung carcinoma (NSCLC) patients using an interferon γ (IFNγ)-specific ELISPOT assay.

Among 84 metastatic NSCLC patients prospectively monitored prior to first line platinum-based chemotherapy, we detected spontaneous UCP-specific CD4+ Th1 responses in 38% of patients, while no response was found in healthy volunteers (n = 22). We then investigated the impact of the presence of UCP-specific CD4+ Th1 cells on the clinical outcome, in particular the response to chemotherapy. We demonstrated that the presence of anti-UCP immunity prior to treatment significantly increases the survival of chemotherapy-responding patients, as compared with patients that do not manifest UCP-specific T-cell immunity (median overall survival: 13.25 vs. 10 mo, p = 0.034).[5] On other hand, patients with progressive disease after first line chemotherapy do not benefit from UCP-specific immune responses. Of note, antiviral T-cell responses measured at the same time in the two groups of patients were similar and had no effect on survival, regardless of the response to chemotherapy. In our knowledge, these results demonstrate for the first time a synergistic effect between pre-existing tumor-specific Th1 CD4+ T cell responses and chemotherapy in cancer patients.

There are several distinct mechanisms through which some chemotherapeutic agents can modify the interactions between tumor cells and the host immune system.[6] Through their action on cancer cells, chemotherapeutics can restore or enhance the expression of tumor antigens, making them more easily recognizable by the immune system. Anthracyclines and oxaliplatin have been shown to induce immunogenic cell death, resulting in the priming of antitumor immune responses.[6] In line with these observations, our data suggest that the tumor cell lysis induced by platinum-based chemotherapy promotes the release of TERT, which is taken up by antigen presenting cells that subsequently amplify pre-existing tumor-specific T cells. By contrast, when chemotherapy was ineffective, tumor cell lysis and the consequent release of TERT were insufficient for the amplification of antitumor immune cells (**Fig. 1**). This would explain why pre-existing UCP-specific immune responses did not influence overall survival in patients with chemotherapy-refractory progressive disease. UCP-specific CD4+ Th1 responses after first line chemotherapy will be further monitored in NSCLC patients to confirm their persistence or

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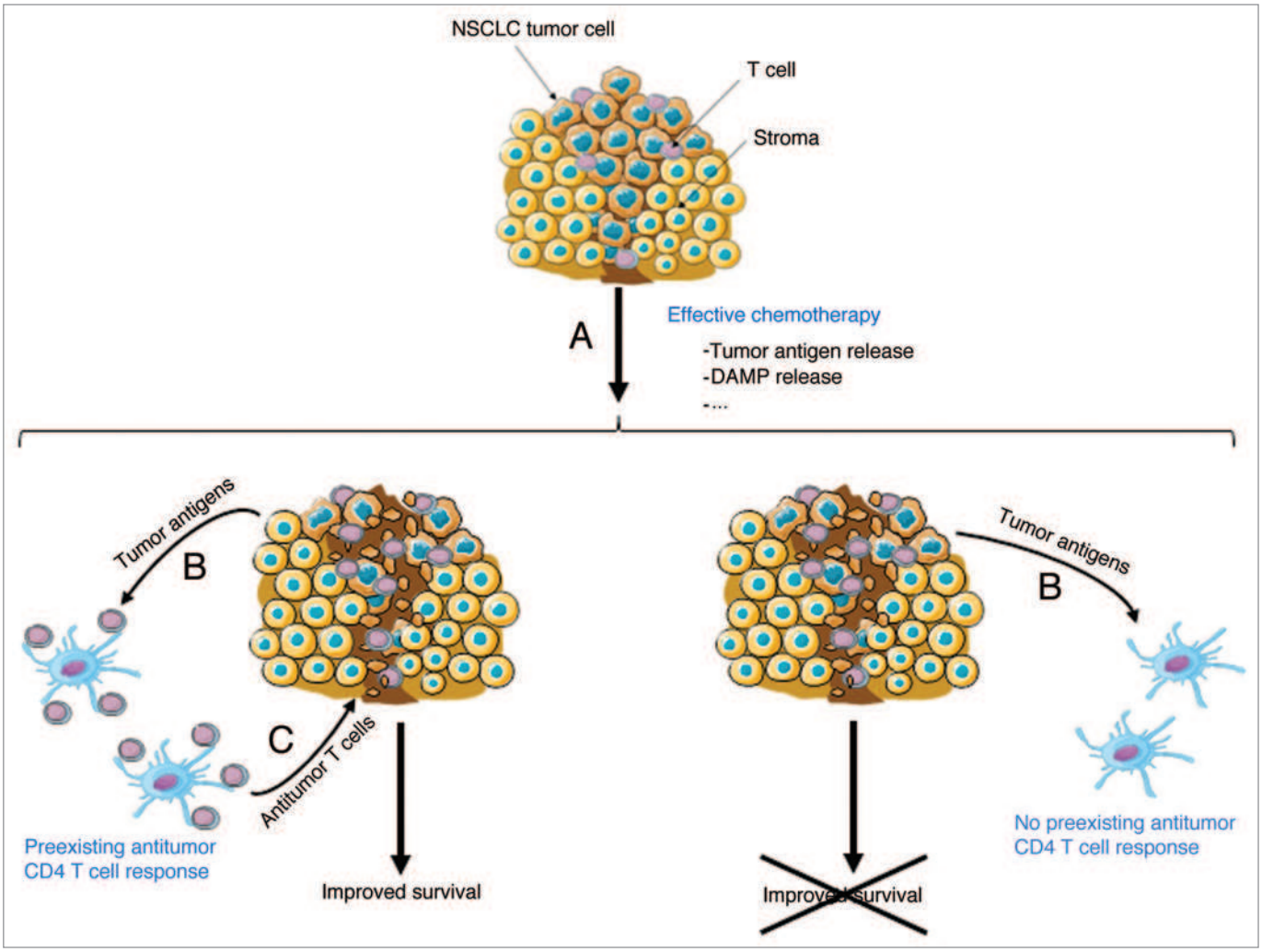


Figure 1. Role of pre-existing antitumor CD4+ T-cell responses in the chemotherapy-induced immune regression of cancer. (**A**) Effective chemotherapy induces immunological tumor cell death and tumor antigen release. (**B**) Tumor antigens are uptaked and processed by dendritic cells. (**C**) Activation of pre-existing tumor-specific CD4 Th1 cells promote an antitumor immunity that acts in synergy with chemotherapy effect.

amplification. In line with our results, Weide et al. have recently reported that the presence of circulating Th1 cells responding to Melan-A or NY-ESO-1 has a strong independent prognostic impact on survival among chemotherapy-treated advanced melanoma patients.[7] The importance of the interplay between antitumor T cells and conventional anticancer therapy is also supported by the improvement of tumor-specific immune responses observed in patients successfully treated by targeted agents such as imatinib mesylate or vemurafenib (which inhibits c-KIT and BRAF, respectively).[8,9]

In addition, the implication of antitumor T-cell responses on the clinical outcome of NSCLC patients is supported by the impressive results recently obtained with the blockade of the PD1 pathway.[10] The use of antibodies that alleviate the inhibition of antitumor T-cell responses clearly require the presence of spontaneous antitumor immunity prior to treatment. Thus, monitoring NSCLC patients for the presence of naturally occurring antitumor T-cell responses will allow for a better selection of patients for anti-PD1 therapy.

Collectively, our results provide a new tool for comprehensive monitoring of antitumor CD4+ Th1 responses and support the concept of the immunomodulation of chemotherapy efficacy in cancer patients. Our findings also point to the therapeutic relevance of TERT as a target for immunotherapy. Thus, UCPs may be used to provide compensatory measures to restore or improve anticancer immune responses.

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