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Targeting antitumor CD4 helper T cells with universal tumor-reactive helper peptides derived from telomerase for cancer vaccine

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Current cancer immunotherapies predominantly rely on CD8⁺ T cells to fight against tumors. However accumulative evidence showed that pro-inflammatory CD4⁺ helper T cells are critical determinants of effective anti-tumor immunity. The utilization of universal tumor-reactive helper peptides from telomerase represents a powerful approach to the fully use of CD4⁺ T cell-based immunotherapy.

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Critical Roles of CD4⁺ Helper T Cells in Antitumor Immunity

The cancer immunoediting hypothesis indicates that tumor cells could be immunogenic and that the adaptive immune system is involved in the active elimination and selection of tumor cells.[1] Among adaptive immune cells involved in antitumor responses, CD8⁺ T cells (CTL) have been considered as the main protagonists because they exhibit a direct cytotoxic activity toward cancer cells. However, recent advances on the fields indicate that different subpopulations of CD4⁺ T helper (T_H) lymphocytes regulate the antitumor response.[2] Among them, tumor-reactive CD4⁺ T helper 1 cells (T_H1), which produce IFN-γ, TNF-α and IL-2, play a critical role in the orchestration of cell-mediated immunity against tumors.[3] The concept of CD4⁺ T-cell help initially emerged from studies showing that successful generation of antitumor CTL depends on the presence of CD4⁺ T cells. Hence, adoptive cell transfer with CD4⁺ T_H cells induces tumor protection or regression, whereas depletion of CD4⁺ T cells inhibits vaccine-induced protective immunity.[4,5]

One generally accepted model implies that CD4⁺ T cells are necessary to license dendritic cells (DC) for efficient CD8⁺ T-cell priming through the interaction of costimulatory receptors such as CD40-CD40L.[6,7] T_H1 cells also promote NK cells and macrophages (M1) activation in vivo.[2,8] They have also been shown to contribute to the inhibition of tumor angiogenesis via an IFN-γ and TSP-1 dependent pathway.[9,10] Accordingly, in human, high density of tumor-infiltrating T_H1 cells has been shown as a good prognostic marker in several cancers.[11] The expression of the T_H1 specific transcription factor Tbet in tumor infiltrating lymphocytes predicts survival of breast cancer patients treated with traztuzumab and chemotherapy.[12] All above emphasize the growing interest to specifically target tumor-reactive CD4 T_H1 cells for cancer immunotherapy.

Use of Universal CD4 Helper Peptides from Telomerase as a Relevant Tool to Target CD4 T Cells in Vivo

Because CTLs have been shown as the most powerful effector cells, most previous cancer vaccines targeted MHC class I-restricted peptides derived from tumor antigens to stimulate anticancer CTL responses.[13] In the meanwhile; CD4⁺ T_H cells have gained interest in antitumor immunity and immunotherapy. As a result, increasing attention has focused on identifying MHC class II epitopes from tumor antigens to actively

target antitumor CD4+ T cells in vivo.[14,15] However, the use of tumor-reactive MHC class II helper peptide should require particular caution to prevent the induction of detrimental immune response as different subpopulations of CD4+ T cells are known to regulate host immune responses.[16] For instance, T_H2 and regulatory T cell are frequently associated with an inhibitory environment within the tumor[17] and the role of T_H17 cells in the antitumor response is still controversial and seems to depend on the type of cancer.[11,18]

In a recent study, we used an optimized reverse immunology approach to identify four novel MHC class II-restricted peptides derived from human telomerase reverse transcriptase (TERT).[19] TERT maintains telomere length in dividing cells and its expression is the predominant mechanism developed by malignant cells to escape telomere-dependent cell death.[20] Telomerase activity has been observed in the vast majority of cancers and emerges as a clinically relevant tumor antigen for immunotherapy.[21] These novel TERT-derived peptides referred as "Universal Cancer Peptides" (UCP), effectively bind to most commonly found HLA-DR molecules which increase their applicability in a large number of cancer patients.[19] This promiscuous binding capacity of UCP circumvents one major limit of the clinical use of tumor-derived helper peptides that only bind few MHC class II alleles.[14] UCP-specific CD4+ T-cell repertoire is present in human and naturally occurring CD4+ T-cells responses against UCP were detected in patients with various types of cancers and these cells mainly produce IFN-γ and TNF-α revealing their T_H1 polarization.

In a second study, UCP were use to actively target CD4+ T cells in a preclinical tumor model and the helper properties of UCP-specific CD4+ T cells were systematically analyzed.[22] Using the HLA-A2/HLA-DR1 transgenic mouse model, we showed that UCP vaccinations induce high avidity and tumor-specific CD4+ T_H1 polarized responses. The UCP-specific CD4+ T cells produced high amount of IFN-γ and IL-2 and but no IL-4, IL-5, IL-10 and IL-17. Co-immunization of MHC class I restricted tumor-derived peptides with or without UCP showed that UCP-specific CD4+ T cells fulfill helper features necessary to generate potent cellular antitumor responses. Indeed, the addition of UCP as helper peptide drastically increased tumor-specific CD8+ T cell responses. We showed that UCP-based vaccine was associated with high antitumor CTL avidity and memory, two critical functions for tumor eradication. Furthermore, the magnitude and quality of the CD8+ T cell responses were closely correlated with the number of IFN-γ and IL-2-secreting UCP-specific CD4+ T cells in vivo. The induction of DC activation represents one major helper mechanism used by CD4+ T_H1 cells to sustain antigen presentation and to provide costimulatory signals to CTL. This is referred as the "ménage à trois" model.[23] Fully DC activation was also found increased in vivo following UCP vaccination and in vitro after coculture of immature DC with UCP-specific CD4+ T cells. The upregulation of activation markers such as CD86 and MHC class II on DC depends on both IFN-γ and GM-CSF secretion and CD40L expression by UCP-specific CD4+ T cells (**Fig. 1**). Finally, by using a model of transplantable mouse melanoma (B16-HLA-A2),[24] we showed that the addition of UCP as helper peptide was required for effective protection against tumor growth in a therapeutic peptide vaccine using the HLA-A2+ self/TERT CTL peptides (pY988 or pY572).[25,26] Collectively our results provide a robust method to comprehensively analyze tumor-derived helper peptides and support that the stimulation of tumor-reactive CD4 T_H1 cells is a powerful method to improve the efficacy of cancer vaccines.

Tumor-Reactive Helper Peptides are More Effective for Intratumoral Recruitment of Effector CD8+ T Cells

A critical consideration for vaccination is the nature of the helper peptide used. One approach to induction of CD4+ T cell help is to use of xenogenic or non-tumor antigens that stimulate recall responses or nonspecific help. The synthetic helper peptide PADRE derived from keyhole limpet hemocyanin (KLH), and the tetanus toxoid-derived helper peptide are commonly used in anticancer vaccines.[27-30] Although, tumor-specific CTL responses appear to be increased by co-administration of non-tumor helper peptide, the clinical benefit of this strategy has not been clearly established, as exemplified in a recent study in melanoma. In this report, patients were vaccinated with MHC class I tumor-derived peptides in conjunction with either helper peptides derived from melanoma antigens or the tetanus-derived helper peptide. Although higher CD8+ T cell responses were induced in the arm with tetanus helper peptide than in melanoma helper peptides one, the clinical impact was quite similar in the two groups.[31] One explanation could be related to the inefficiency of non-tumor specific CD4+ T cells to guide effector CD8+ T cells within the tumor as recently demonstrated by Sherman L and colleagues.[32,33] Indeed, CD8+ effector T-cell recruitment within the tumor was enhanced by tumor-specific CD4+ T cells and this effect was promoted by IFN-γ-dependent production of chemokines such as CXCL9 and CXCL10. In addition, the production of IL-2 by tumor resident CD4+ T cells enhanced CD8+ T-cell proliferation and function.[34]

In our study, the use of UCP as helper peptide during therapeutic vaccine promoted tumor infiltration by tumor-specific CD8+ T cells which explain the best tumor control observed in mice (**Fig. 1**).[22] In a previous related study, Gross and colleagues reported that vaccination with the same self/TERT CTL peptides (pY572 and pY988) induced tumor protection only when coupled with a CD4+ helper peptide derived from the hepatitis B virus.[35] However around 25% of mice vaccinated prophylactically achieved tumor protection compared with 60% in our therapeutic vaccine study using TERT-derived UCP. Thus we speculate that the difference observed in the two studies could be related to the specificity of the helper signal delivered by CD4+ T cells. This new role of CD4+ helper T cells on CD8 T attraction to the site of attack emerges as a new general mechanism and has also been reported by Nakanishi et al. in the case of infected mucosa.[36] Thus only tumor-reactive CD4+ T cells are effectively able to induce a better homing of killer cells at the tumor site.

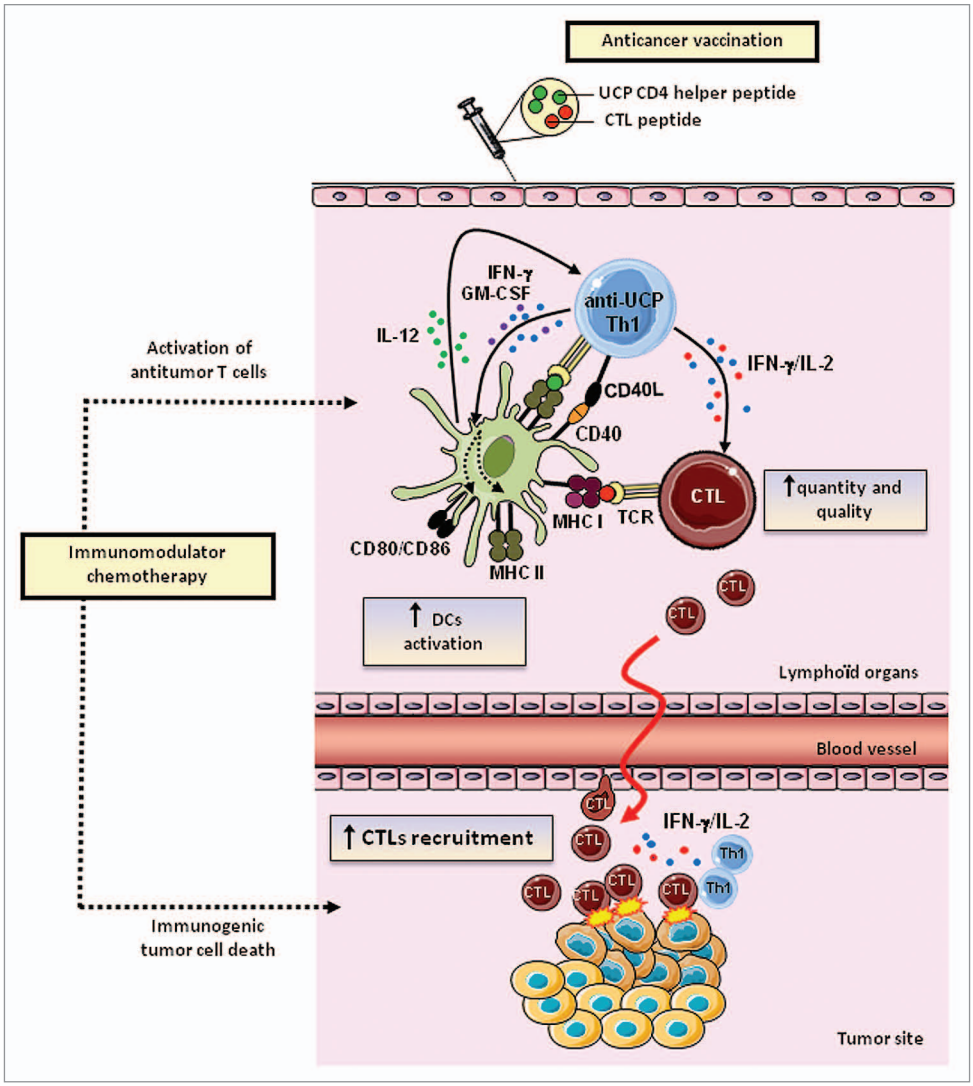

Figure 1. Antitumor immune effects of novel universal CD4 helper peptides derived from telomerase (UCP). UCP-based antitumor vaccines favor DC activation which provides costimulatory signals to antitumor CTL, enhancing their quantity, quality and recruitment at the tumor site. Concomittantly chemotherapy can act by promoting immunogenic cell death and antitumor T cell activation.

Interplay Between TERT-Specific CD4+ T Immune Responses and Cytotoxic Chemotherapy: An Emerging Synergistic Antitumor Effects

In a report by Godet and colleagues, we used the universal characteristic of UCP to monitor the UCP-specific CD4+ T-cell responses in metastatic non-small cell lung carcinoma (NSCLC) patients treated by platinum-based doublet chemotherapy. Naturally occurring UCP-specific T_H1 CD4 responses were found in 38% of these patients prior chemotherapy. We observed that the presence of this response prior treatment significantly increases the survival of chemotherapy responding patients (median overall survival: 13.2 vs 10 mo, p = 0.034).[19] 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. On other hand, patients with progressive disease after first line chemotherapy do not benefit from UCP-specific immune responses. These results strongly suggested the interplay between UCP-specific CD4 T_H1-cell immunity and chemotherapy efficacy.

Original work from Laurence Zitvogel and Guido Kroemer highlighted the capacity of several anticancer agents including classical chemotherapeutics, and targeted compounds stimulate tumor-specific immune responses either by inducing the immunogenic death of tumor cells or by engaging immune effector mechanisms.[37] Such an immunogenic cell death relies on the coordinated emission of specific signals from dying cancer cells and their perception by the host immune system. The molecular mechanisms imply the early exposition of calreticulin, ERP57 and the MRP on the cell surface together with the secretion of ATP.[38] In line with these observations, our data suggest that the tumor cell lysis induced by chemotherapy promotes an immunological milieu and the release of TERT, which is taken up by antigen presenting cells that subsequently

amplify preexisting tumor-specific CD4+ T cells.[39] An additional postchemotherapy monitoring of UCP-specific CD4+ T cell responses will be performed for a complete study of CD4+ T cell modulation.

In contrast to CD8 T cell responses, few data are available on the mechanisms by which anticancer drugs modulate antitumor CD4+ T cell immunity.[38] Although cyclophosphamide (CTX) has been thought as the most potent CD4-activating anticancer drug in several experimental models; the mechanisms underlying its effect are not well understood. In addition to its well-known effect of depleting suppressor T cells, recent data suggest a link between CD4+ T-cell responses and an immunogenic milieu such as proinflammatory cytokines induced by CTX.[40] We and others have shown that blocking VEGF/VEGFR pathway with antiangiogenic drugs modulates CD4+ Foxp3+ regulatory T cells number and functions in tumor-bearing mice and in metastatic cancer patients.[41,42] Thus, understanding how the efficiency of conventional chemotherapy influenced CD4+ helper T cell response is a challenging study for chemoimmunotherapy.

In conclusion, there is great interest for cancer vaccines to stimulate tumor-reactive T_H1 responses by using tumor-reactive CD4 helper peptides such as TERT-derived UCP that would extend the potential application to various types of cancers. These results also provide a new tool for comprehensive monitoring of antitumor CD4+ T cell responses and support the concept of the immunomodulation of chemotherapy efficacy in cancer patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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