In this issue of *Clinical Cancer Research*, Ueda and colleagues (1) and Terabe and colleagues (2) demonstrate, in two different tumor models, a combination therapy approach simultaneously vaccinating against specific tumor antigens while actively modulating the tumor microenvironment to enhance cancer vaccine efficacy and immunologic memory.

Cancer vaccines have long been pursued as a potential treatment for human malignancy because of the unique features of adaptive immunity including immunologic memory. A T-cell response specific for cancer-related proteins would have the capability to allow a tumor to be eradicated at any site in the body owing to homing of the T cell to antigen. Furthermore, cytotoxic T cells (CTL) would continue to proliferate and attack malignant cells as long as antigen was present in the environment. Finally, if a strong memory response was generated, antigen-specific T cells would persist ready to respond to and eradicate the cancer should it recur.

Unlike vaccines for infectious disease, in which immunizations are given prior to pathogen exposure, most cancer vaccines are administered to patients after they have acquired the disease. For this reason, most likely, despite the demonstration that tumor-specific immune responses can be elicited with vaccination in cancer patients, cancer vaccines are not associated with significant clinical response rates (3). Many potential mechanisms of treatment failure have been identified and most of those mechanisms are due to the negative impact the immunosuppressive tumor microenvironment has on the trafficking of cancer-specific T cells (4). A major modulator of immune suppression is transforming growth factor β (TGFβ), which is found in abundance in the tumor bed (Fig. 1A). Both studies presented in this issue, demonstrate depletion of TGFβ via systemic administration of a TGFβ-specific antibody, which significantly impacts the clinical effect of active immunization.

The majority of immunogenic proteins that have been described as tumor antigens are “self” proteins. Thus, tolerance to self is an important factor in tumor immune evasion. The study presented by Ueda evaluates the generation of immunity to nonmutated self antigens in glioma via vaccination. Immunizing against self to elicit tissue destructive T cells, i.e., CTL, is difficult as mechanisms of peripheral tolerance limit T-cell expansion (Fig. 1A). TGFβ mediates tolerance as the cytokine stimulates the proliferation of induced T regulatory (Treg) cells that may have been elicited by exposure to self tumor antigens (5). Treg secrete both interleukin (IL)-10 and TGFβ which inhibit CTL activation and function (6, 7). Generation of active CTL is an important feature of a therapeutic immune response. In the glioma model reported, systemic depletion of TGFβ resulted in a decrease in numbers of Treg with a resultant increase in circulating levels of type I cytokines, the growth factors needed to support and sustain CTL. Moreover, animals treated with combination anti-TGFβ and vaccine therapy demonstrated a significant increase in plasma levels of IL-15, a cytokine that promotes T-cell survival, and markedly increased persistence of tumor-specific T cells in vivo. Recent data in an infectious disease model suggest that TGFβ opposes the function of IL-15 by inducing apoptosis of rapidly proliferating antigen-specific T cells during clonal expansion, thus limiting immune-mediated pathology (8). Work presented here suggests TGFβ depletion potentially “rescues” cancer specific T cells from apoptosis resulting in higher levels of long-lived antitumor effector cells.

Terabe and associates evaluated vaccination along with TGFβ depletion in a nonself tumor model of human papilloma virus (HPV). Investigators immunized animals against HPV while administering anti-TGFβ and demonstrated that depletion of TGFβ resulted in the generation of CTL with high functional avidity. High avidity T cells are assumed to be a requirement for efficient tumor cell killing. Studies have suggested that cytokines may impact the quality of the interaction of CTL with peptide-MHC complexes thereby effecting avidity. Recent studies in ova transgenic mice suggested that IL-12 enhanced the function of ova-specific CTL, whereas TGFβ weakened the interaction with target (9). Data presented here, in the glioma model, demonstrate
TGFβ depletion results in elevated systemic levels of IL-12. Thus, increased HPV CTL avidity may not only be the result of TGFβ depletion but also IL-12 secretion (Fig. 1B). Of note, Terabe did not notice any changes in Treg levels with TGFβ depletion, nor were there any differences in levels of Th17 cells between experimental groups. This latter observation may be of concern as it is not clear, in either of the articles presented, that any animals were cured of their disease after combination treatment.

Stimulating a robust, high avidity, and persistent tumor-specific T-cell response is one of the few therapeutic modalities that has the potential to completely eradicate all tumor cells and result in cure of disease. Experiments done by Ueda and colleagues did not result in cure of glioma, and Terabe’s studies evaluated mice for protection against HPV-expressing tumors only up to 30 days, calling into question the ability to completely eradicate disease. Although it is clear that depletion of TGFβ enhanced vaccine efficacy, it is possible the same depletion prevented total tumor destruction. TGFβ is involved in the regulation of not only Treg but also inflammatory Th17 cells and actively works to maintain homeostasis of these opposing phenotypes (10). Th17 are a unique subset of CD4+ T cells that secrete IL-17 and are presumed to be operative in initiating destructive autoimmune pathology (10). Recent studies in murine tumor models have suggested that Th17 are an important effector phenotype for the eradication of established disease (11). Similarly CD8+ T cells that secrete IL-17 also display superior antitumor activity (12). In humans, the presence of high levels of Th17 cells has been associated with a better prognosis in ovarian cancer patients (13). A recent study suggests that elevated levels of TGFβ, although impairing the function of antigen-specific Th1 cells, have little effect on Th17, resulting in an immune response skewed to favor IL-17 secreting effectors (14). Theoretically, depleting TGFβ may predispose to a phenotype of T cell that is less capable of mediating tissue destruction (Fig. 1B). Although the articles presented in this issue focused on the immune modulatory aspects of TGFβ, it is important to note that the cytokine also has important effects in regulating tumor cell apoptosis, proliferation, and invasion. The tumor growth suppressive effects of TGFβ are well documented (15). How the depletion of TGFβ modified the biology of disease in the currently reported models was not completely explored.

With the understanding of the mechanisms of immune escape, more targeted approaches to stimulating immunity concurrent with modalities that attempt to disarm those mechanisms can be developed. Such approaches increase the chance of success of cancer vaccines, but may also unmask new issues that need to be addressed. Well-designed studies

**Fig. 1.** Immune modulation of the tumor microenvironment by TGFβ. A, Immune suppression induced by elevated levels of TGFβ. In the presence of IL-10 and TGFβ, and in an environment lacking IL-12, antigen-presenting cells (APC) inefficiently stimulate T cells. Induced by self tumor antigens, Treg are abundant. However, IL-17 producing T cells, Th helper (Th17), and IL-17 producing CD8+ T cells (Tc17) cells, which are resistant to the effects of TGFβ may predominate over other Th phenotypes and partially impede tumor progression. B, Immune stimulation induced by TGFβ depletion. In the presence of IL-12, APC efficiently stimulate high avidity T cells. Moreover, IL-15 enhances T cell survival in vivo. Th1 cells are predominant over Treg and Th17 and impede tumor progression via elaboration and maintenance of CTL.
that simultaneously evaluate the cause of tumor inhibition or destruction as well as define those mechanisms that may limit treatment efficacy are needed to translate novel vaccine strategies from mouse to man.

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Enhancing Cancer Vaccine Efficacy via Modulation of the Tumor Microenvironment

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