Immunomodulatory Antibody Therapy of Cancer: The Closer, the Better
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Immunomodulatory antibodies completely eradicate larger tumors in three murine tumor models. In the same issue, Mangsbo and colleagues (2) report that local injection of CD40 agonistic antibody to activate dendritic cells (DC) significantly suppresses tumor growth. Both preclinical observations suggest that a local route to deliver immunomodulatory antibodies with different mechanisms of action could be a better way to initiate, enhance, and maintain a strong local antitumor T-cell response. Both reports also demonstrate that intratumoral injection of immunomodulatory antibodies not only elicits rejection of local tumors but also results in systemic protective immunity against distant tumors or a rechallenge with the same tumors.

In this issue of Clinical Cancer Research, Dai and colleagues (1) report that locally delivering combinations of immunomodulatory antibodies completely eradicates larger tumors in three murine tumor models. In the same issue, Mangsbo and colleagues (2) report that local injection of CD40 agonistic antibody to activate dendritic cells (DC) significantly suppresses tumor growth. Both preclinical observations suggest that a local route to deliver immunomodulatory antibodies with different mechanisms of action could be a better way to initiate, enhance, and maintain a strong local antitumor T-cell response. Both reports also demonstrate that intratumoral injection of immunomodulatory antibodies not only elicits rejection of local tumors but also results in systemic protective immunity against distant tumors or a rechallenge with the same tumors.

The search for an optimal route of delivery of cancer immunotherapy agents has been a research focus since Coley's first clinical attempt of injecting mixed bacterial toxin into primary tumor tissues. At that time, intratumoral injection was considered by Coley to be crucial to a patient's survival (3). Since then, local delivery of immunotherapy agents, such as vaccines and adjuvants, has been the main route of immunotherapy administration for decades. However, in the 1980s, the use of IL2 in patients with melanoma and renal tumors changed the landscape of cancer therapy. As researchers realized that a strong systemic antitumor immune response could eventually not only reject local tumors but also prevent tumor metastasis, intravenous injection of immunomodulatory agents remained a major route of cancer immunotherapy until now. However, some limitations of systemic delivery have been identified. For example, it is unknown to what extent systemically delivered therapeutic agents eventually accumulate at the tumor sites. This is especially important for immunomodulatory antibodies, because they not only restore antitumor T-cell responses at tumor sites but may also release brakes for anti-self T-cell responses in nonmalignant tissues or organs when they are delivered systemically. To reach a therapeutic threshold, usually a high dose and/or repeat delivery is required for systemic therapies, thus increasing the risk of adverse effects. Although personalized formulation of antibody therapy could help reduce the side effects and maximize therapeutic effects, an alternative route of delivery of cancer immunotherapy agents should be considered and evaluated.

Recently, studies analyzing immune responses within tumors and related regulatory mechanisms have provided new evidence encouraging researchers to consider the local or intratumoral delivery routes for cancer immunotherapies. Thompson and colleagues (4) reported that naive CD8 T cells are primed within tumors by tumor cells or DCs and undergo differentiation to become effector CD8 T cells at tumor sites. Our group has observed an endogenous tumor-reactive CD8 T-cell response within tumors (5). We further showed that blocking the migration of lymphocytes from secondary lymphatic organs does not impair the accumulation of tumor-reactive CD8 T cells within tumor tissues, suggesting that resident naive CD8 T cells are primed and expand locally at tumor sites (5).

Although local resident CD8 T cells are primed or activated at tumor sites (4, 5), they cannot reject tumors as they are subjected to local regulatory mechanisms. To promote local antitumor immune response, Dai and colleagues (1) and Mangsbo and colleagues (2) report that local delivery of immunomodulatory antibodies with nonredundant functions is superior to systemic delivery in cancer treatment (Fig. 1). In their studies, an agonist antibody to CD40 is used to activate DCs for inducing effector CD8 T-cell differentiation. CD137 (4-1BB) agonist antibody is used to activate the costimulatory function of CD137 on CD8 T cells, as CD137 promotes T-cell proliferation, function, and survival (6). Because upregulation of PD-1 limits the antitumor activity of endogenous, tumor-reactive CD8 T cells within tumors (5), anti–PD-1-blocking antibody was used to block the coinhibitory signaling of PD-1 and its ligands (B7-H1/PD-L1 or B7-DC/PD-L2) expressed by tumor cells. Anti–CTLA-4-blocking (or to some degree depleting) antibody was used to remove another barrier within tumors, i.e., regulatory T cells (Treg) that preferentially express CTLA-4 (7). The combination of these three antibodies has demonstrated promising therapeutic effects in a previous report from the same group (8). However, following...
The potential mechanisms of local delivery of immunomodulatory antibodies in cancer treatment. At tumor sites, antigen-presenting cells (APC) activated by CD40 agonist antibody promote effector CD8 T-cell differentiation. The ligation of CD137 (4-1BB) with agonist antibody increases costimulatory signals, along with blocking of PD-1 with an antagonist antibody that decreases coinhibitory signals; the combined effects of these antibodies may increase the function and survival of effector CD8 T cells at tumor sites. In addition, an anti-CTLA-4 antibody, which blocks the signals of CTLA-4 or depletes CTLA-4+CD4 Tregs, may release effector CD8 T cells from the immunosuppression mediated by Tregs. Finally, anti-CD19 antibody depletes CD19+Bregs, thus promoting the shift from a protumor Th2 cell to an antitumor Th1 cell to generate antitumor effector CD4 T cells. Taken together, the combination of a set of immunomodulatory antibodies capable of targeting both stimulatory and regulatory mechanisms could lead to a long-term protective antitumor immunity.

Figure 1.
The potential mechanisms of local delivery of immunomodulatory antibodies in cancer treatment. At tumor sites, antigen-presenting cells (APC) activated by CD40 agonist antibody promote effector CD8 T-cell differentiation. The ligation of CD137 (4-1BB) with agonist antibody increases costimulatory signals, along with blocking of PD-1 with an antagonist antibody that decreases coinhibitory signals; the combined effects of these antibodies may increase the function and survival of effector CD8 T cells at tumor sites. In addition, an anti-CTLA-4 antibody, which blocks the signals of CTLA-4 or depletes CTLA-4+CD4 Tregs, may release effector CD8 T cells from the immunosuppression mediated by Tregs. Finally, anti-CD19 antibody depletes CD19+Bregs, thus promoting the shift from a protumor Th2 cell to an antitumor Th1 cell to generate antitumor effector CD4 T cells. Taken together, the combination of a set of immunomodulatory antibodies capable of targeting both stimulatory and regulatory mechanisms could lead to a long-term protective antitumor immunity.
References

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