Selective Activation of Oxygen-Deprived Tumor-Infiltrating Lymphocytes through Local Intratumoral Delivery of CD137 Monoclonal Antibodies

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Summary: Hypoxia-inducing transcription factor-1α (HIF-1α) in hypoxic tumors induces the TNF receptor family member CD137 on tumor-infiltrating lymphocytes. This can be exploited for intratumoral low-dose injection of effective systemic immunotherapy with agonist CD137-specific monoclonal antibodies that induce circulation of systemic tumor-specific effector T cells capable of eradicating distant metastases. Cancer Discov; 2(7): 586-7. ©2012 AACR.

The provocative article by Palazón and colleagues (1) in this issue of Cancer Discovery for the first time reveals a surprising association between oxygen deprivation common in tumors and a CD137+ phenotype of tumor-infiltrating lymphocytes (TIL), allowing selective activation of TILs by local (intratumoral) therapy with CD137-directed monoclonal antibody. Hypoxia-inducible transcription factor-1α (HIF-1α) expression was found to be required for induction of expression of CD137 on the TILs. CD137 is a member of the TNF receptor family of molecules. These molecules together regulate life and death as well as activation of many different cell types, including dendritic cells and T lymphocytes (2). CD137 antibodies are interesting candidates for cancer immunotherapy because they exert considerable stimulatory activity on T cells. However, the systemic use of these antibodies, particularly upon repeated injection, has severe side effects such as liver toxicity by infiltration with T cells and splenomegaly (3, 4). Hypoxia is common in tumors and induces profound changes in the tumor microenvironment which are brought about, in part, by activation of a number of so-called hypoxia-inducible factors, HIF-1α, HIF-1β, HIF-2α, HIF-2β, HIF-3α, and HIF-3β. The complete mode of action of these different HIF factors has not been elucidated (5).

Palazón and colleagues (1) showed that HIF-1α was involved in the induction of CD137 on TIL infiltrating transplantable CT26 murine tumors because HIF-1α+ mice did not display CD137 on TIL-infiltrating CT26 tumors. The authors showed that one-twentieth the dose of anti-CD137 monoclonal antibody exerted similar effects as high-dose i.v. injection of this antibody. Also, low-dose intratumoral antibody delivery was able to clear distant tumors through circulation of tumor-specific T cells activated by the local injection.

The local delivery of agonist antibody therefore exerts these remarkable systemic effects through induction of circulation of effector T lymphocytes. These results confirm and extend observations made with local low-dose subcutaneous delivery of an agonistic monoclonal antibody against CD40, another TNF receptor family member. Anti-CD40 antibody does not directly activate T cells but acts through activation of dendritic cells that have ingested tumor antigens in tumor-draining lymph nodes (6). Also, in this case, liver toxicity was completely avoided, although distant tumors were eliminated by the induction of systemic circulation of tumor-specific CD8+ cytotoxic T lymphocytes expanding and migrating from the tumor-draining lymph nodes (6).

Clinical application of the principle of local intratumor immune activation has now also been pioneered, not with agonistic antibodies, but with a combination of low-dose local irradiation to promote antigen release from B or T lymphoma cells and local intra-lymphoma TLR9 ligand CpG injection. This has led to systemic B-cell lymphoma regressions (7), as well as T-cell lymphoma (mycosis fungoides) regressions (8). Interestingly, CD137 stimulation by monoclonal antibodies can also act synergistically in a human lymphoma xenograft model to promote the therapeutic action of antibody-dependent cellular cytotoxicity capacity of natural killer cells that, like T cells, express surface CD137 (9). Systematic treatment with a CTLA-4 checkpoint control blocking monoclonal antibody can cause substantial systemic toxicity, including severe diarrhea and other inflammatory diseases. Conceivably, these can also be avoided by local delivery of antibodies in the vicinity of tumor-draining lymph nodes.

The prospect of delivering powerful immunostimulants in combination with other therapeutic modalities only where it matters most, namely, at sites of tumor antigen release (promoted by irradiation or chemotherapy) and antigen loading of dendritic cells and associated tumor-specific TILs within tumors or within tumor-draining lymph nodes, is extremely attractive. Local delivery of these types of cancer immunotherapy thus offers the perspective of avoiding systemic toxicity by causing local expansion followed by systemic migration and circulation of high numbers of tumor-specific effector

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T cells. If one knows the specificity of these tumor-specific T cells, their activity can be further promoted by specific synthetic vaccines, again delivered locally, and by low-dose administration of interleukin (IL)-2 or IL-15 (10). Some degree of systemic immunomodulation may still be necessary to create a favorable microenvironment for T-cell entry into tumors that do not naturally allow optimal T-cell access. The resulting combination treatment of cancer is likely to be substantially less toxic and more specific than many of the current cancer treatments.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interests were disclosed.

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