Vaccination initiates the transport of target antigens and danger signals from sites of inoculation to draining lymph nodes (dLN) where adaptive immune responses are activated. Lymphatic vessels provide the roads over which these immunological signals travel. While the pre-existing lymphatic vasculature is necessary and sufficient to mediate response to vaccination (1), recent studies suggest that immune responses to vaccination could be boosted by expanding lymphatic vessels, a process called lymphangiogenesis. In fact, in mouse cancer models, lymphangiogenic tumors exhibit enhanced antigen transport to dLNs, antigen presentation, and response to experimental immune-targeted therapies (2, 3). These observations raise the intriguing possibility that delivery of a key lymphangiogenic growth factor, VEGF-C, could improve tumor immune surveillance, i.e., detection and elimination of cancer cells. Tumor-associated lymphangiogenesis, however, also increases risk of regional metastasis, likely precluding application of VEGF-C therapy within the tumor microenvironment itself. Writing in Science Advances, Sasso et al. (4) test the hypothesis that induction of lymphangiogenesis away from the tumor site, but in concert with tumor vaccination, can provide a supportive infrastructure that improves LN communication and vaccine responses.

The authors evaluate this approach in the context of cancer vaccines, which have the potential to train the immune system to eradicate tumors and prevent disease recurrence. Though the clinical success of therapeutic vaccines has been underwhelming, our growing understanding of how tumors evade immune detection—and how to target these mechanisms—has rekindled enthusiasm (5). While a number of vaccine platforms are in clinical trials, vaccines that harness a patient’s own cancer cells eliminate the challenge of determining antigenic targets while also generating immunity against a wide swath of tumor-associated antigens, thus reducing the probability of sub-clone resistance. Sasso et al. (4) postulated that irradiated tumor cells genetically engineered to secrete VEGF-C would both provide an antigen depot and boost lymphatic transport, paving a way toward better vaccine efficacy (Fig. 1).

The authors found that intradermal implantation of irradiated VEGF-C-expressing B16F10 murine melanoma tumor cells drove a cutaneous lymphangiogenic response associated with direct T lymphocyte recruitment and enhanced dendritic cell (DC) trafficking from the injection site to the dLN (4). While the implications of enhanced DC transport to LN are clear, the recruitment of T lymphocytes to the injection site, in particular, naive T cells, suggested the additional possibility of in situ activation. In fact, newly activated, antigen-specific CD8+ T cells accumulated at the injection site without first being activated in LNs. Instead, these T cells were activated at the vaccination site. These data implicated two potential mechanisms of action, 1) enhanced communication with LNs and 2) local, in situ activation (Fig. 1).

The authors also asked a critical translational question: Does lymphangiogenesis enhance immune responses to tumor-derived antigens? To evaluate this, they vaccinated mice with irradiated melanoma cells either expressing or lacking VEGF-C in conjunction with locally-administered adjuvants, which help augment vaccine responses. They found that the VEGF-C-expressing vaccine not only boosted T cell priming but generated responses to a broader repertoire of tumor-derived antigens, thereby improving overall immune protection. In addition, the authors compared their approach to GVAX—tumor cells expressing the cytokine GM-CSF. GVAX has been evaluated in multiple clinical trials but with limited success (6). VEGF-C expression triggered a stronger antitumor T cell response that conferred superior and more durable protection from tumor challenge than GVAX. Importantly, the new vaccine improved therapeutic responses to anti-PD-1 immune checkpoint blockade, an FDA-approved immunotherapy whose efficacy depends, in part, on a sufficient tumor antigen-specific T cell response. Several clinical trials are exploring the synergy of immune checkpoint blockade and cancer vaccines.

The superior potency of this vaccine technology relative to GVAX provides strong support for rapid clinical evaluation. Key to further development of this and other cancer vaccines is understanding the functionally relevant mechanisms of action. While the expansion of regional lymphatic vessels enhances transport to LNs and thereby reinforces T cell activation, CCL21-dependent recruitment of naive T cells and their in situ expansion may be a critical vaccine feature. The authors previously demonstrated that melanomas expressing high levels of CCL21 activate high-endothelial venule-like vessels that allow naive T cell infiltration (7), and that overexpression of VEGF-C increases CCL21 expression (2). In the presence of immune-activating adjuvants, these mechanisms may enhance vaccine responses through local T cell activation and expansion. This raises the possibility that vaccine efficacy may rely at least as much on the engineering of the inoculation site as it does on lymphatic vessel-dependent effects on DC and antigen transport. Therefore, the extent to which lymphangiogenesis is specifically required for vaccine efficacy remains to be determined. Engineering the
local microenvironment may both enhance LN responses and create a hub for immune activation post-vaccination, merits further exploration.

Continued optimization may also require a deeper understanding of how local VEGF-C pharmacokinetics effect lymphangiogenesis and immune responses. Indeed, when a different VEGF-C expressing melanoma cell line was used, naïve T cell infiltration into the inoculation site was reduced compared to B16F10 cells, potentially reflecting differential VEGF-C expression levels, release kinetics, or other collaborating, cell-derived factors. Hence, it may be important to develop cell-engineering strategies for more precisely tuning VEGF-C expression and release profiles. Dissecting these relationships may also facilitate engineering of injectable or implantable biomaterials (8) for spatiotemporally controlled release of VEGF-C to optimize lymphangiogenic immunopotentiation. Such a strategy could yield an enabling technology for improving immune responses to other cancer vaccine modalities, including cell-free platforms such as peptide and mRNA vaccines.

Despite their immense therapeutic potential, immunologic and translational barricades have created an arduous road for cancer vaccines over the past few decades. The study by Sasso et al. (4) lays the foundation for next-generation cancer vaccines that engineer the immune infrastructure and offer a new route to robust antitumor immunity.

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