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A LIGHTning Strike to the Metastatic Niche

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Tumor-induced vascular alterations in distant organs have been linked to the spreading of cancer. In this issue of *Cell Reports*, He et al. (2019) show that targeting the cytokine LIGHT to the pulmonary vasculature prevents the establishment of lung metastasis in mice.

Tumor blood vessels often present with discontinuous basement membranes, loose endothelial-cell junctions, elevated permeability, and incoherent blood flow. These abnormalities limit drug delivery and trafficking of T lymphocytes in tumors (Munn and Jain, 2019). Tumors may also alter the properties of normal blood vessels in pre-metastatic niches—sites where cancer cells that disseminate from a primary tumor begin the colonization of a distant organ (Peinado et al., 2017). Writing in *Cell Reports*, He et al. (2019) show that reversing tumor-induced vascular abnormalities in pre-metastatic sites or early-established metastases limits lung colonization by the tumor and enhances the efficacy of immune checkpoint blockade, a clinically approved immunotherapy (Figure 1).

LIGHT (also known as TNFS14) is a secreted protein with immunostimulatory and pro-apoptotic functions. It binds both lymphotoxin-beta receptor (LTBR), which is expressed on various tumor-associated stromal cells, and Herpesvirus-entry mediator (HVEM), which is expressed on lymphoid cells (Tamada et al., 2000). Previous work has shown that a LIGHT variant engineered to target the angiogenic vasculature through an angiotropic peptide (LIGHT-VTP) could reprogram the blood vessels in experimental brain tumors (He et al., 2018). Notably, LIGHT-VTP converted a fraction of the tumor blood vessels into high endothelial venules (HEVs), which are specialized vessels present in most lymphoid tissues. HEVs are endowed with cuboidal—rather than flat—endothelial cells that facilitate extravasation of circulating lymphocytes, in part by secreting the T cell chemoattractant CCL21. Accordingly, LIGHT-mediated induction of intra-tumoral HEVs was associated with higher T cell numbers and a better tumor response to immune checkpoint blockade (He et al., 2018).

In the new study, He et al. (2019) examined the pulmonary blood vessels of mice carrying subcutaneously growing tumors. They found that the tumors had remotely altered the lung blood vessels, which became leakier and displayed abundant deposition of extracellular matrix. This may have created a favorable soil for the establishment of metastases by cancer cells that had left the primary tumor through systemic circulation. Remarkably, repeated injections of LIGHT-VTP reversed the pathological vascular phenotypes and inhibited colonization of the lung by circulating cancer cells. These results indicate that LIGHT-VTP can "normalize" the lung vasculature in tumor-induced pre-metastatic niches to suppress extravasation—or seeding—of metastatic cancer cells.

The VTP peptide efficiently recognized the pulmonary vasculature of tumor-bearing mice but had little affinity for that of naive mice (He et al., 2019). VTP, also known as "CGKRK" owing to its amino acid sequence, was shown previously to bind heparan sulfates on angiogenic blood vessels in mouse tumor models (Hoffman et al., 2003). Now, He et al. (2019) demonstrate that VTP also recognizes the vasculature of lungs that have been exposed to tumor-derived signals. Although the mode whereby VTP targets lung blood vessels of tumor-bearing mice remains unknown, it is possible that tumor-induced vascular hyperpermeability facilitated diffusion of LIGHT, while perivascular accumulation of extracellular matrix contributed to an increase in its binding and retention. It remains to be seen whether vascular changes that can be reversed by LIGHT-VTP also occur in other organs, such as the liver, which is a frequent site of cancer metastasis.

To further explore the potential of LIGHT-VTP for preventing or inhibiting metastasis, He at al. (2019) designed preclinical trials in mice carrying subcutaneous tumors. They administered LIGHT-VTP according to both neoadjuvant and adjuvant schedules. In the neoadjuvant setting, the targeted cytokine is deployed to tumor-bearing mice; the primary tumor is then surgically excised, and the development of lung metastasis is examined two weeks later. In the adjuvant setting, LIGHT-VTP is deployed only after excision of the primary tumor. Both settings recapitulate clinical treatments routinely implemented in patients with operable cancers. In either case, LIGHT-VTP abated lung colonization by cancer cells. These data imply that the targeted cytokine effectively inhibits at least two distinct steps in the metastatic cascade. First, it impairs the escape of cancer cells from the primary tumor, a process that is partly dependent on their ability to invade tumor blood vessels (intravasation). LIGHT-VTP may limit cancer-cell intravasation by increasing endothelial barrier integrity in the primary tumor (He et al., 2018), as seen with other vascular-normalizing agents, such as angiopoietin-2 blocking antibodies (Holopainen et al., 2012; Schmittnaegel et al., 2017). Second, LIGHT-VTP limits the arrival of cancer cells to the lung, likely by making the pulmonary vasculature less permissive to their extravasation.

Can LIGHT-VTP also impair the growth of pre-established metastases? To address this question, He et al. (2019) employed a model in which lung tumors

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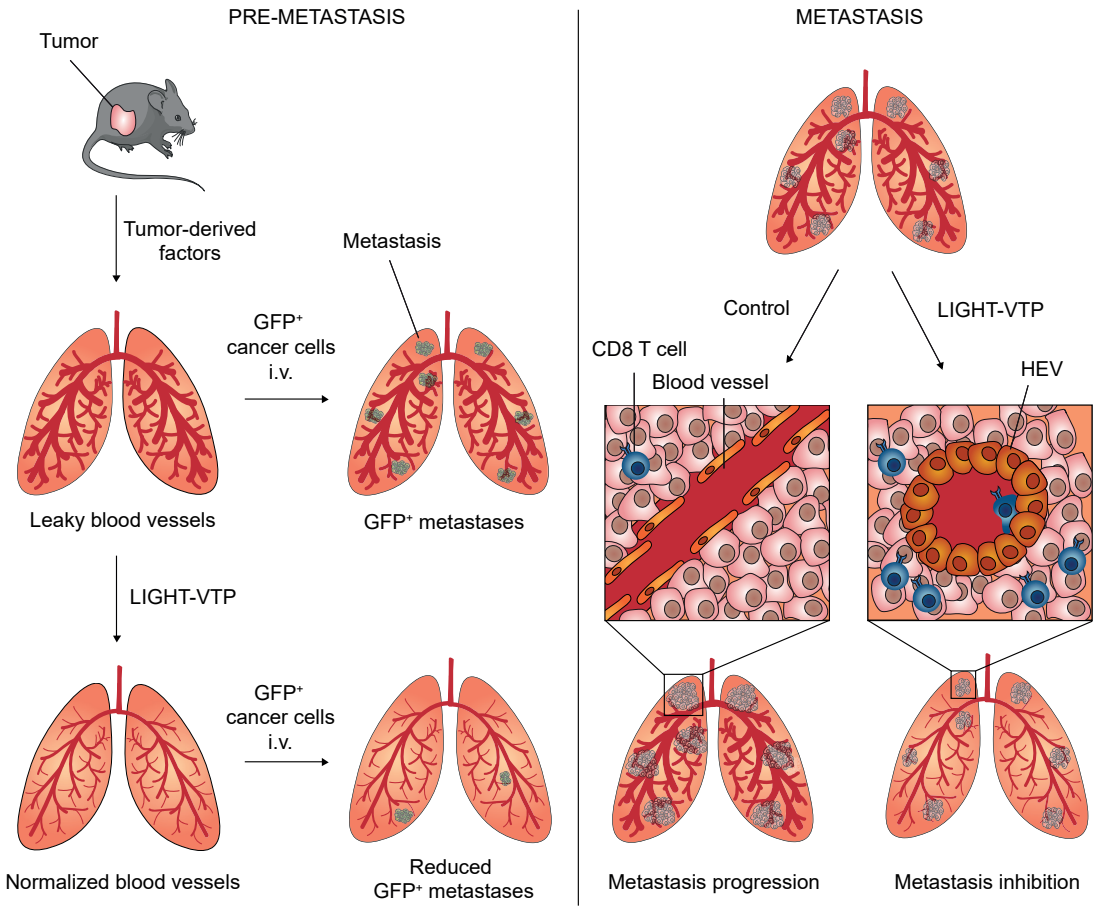

Figure 1. Vascular-Targeted LIGHT Both Prevents and Inhibits Metastasis in Mice

Left: In tumor-bearing mice, tumor-derived factors induce vascular leakiness and other abnormalities in the pre-metastatic lung that facilitate colonization by GFP$^+$ cancer cells inoculated intravenously (i.v.). LIGHT-VTP limits tumor-induced vascular permeability in the lung and impairs metastatic colonization. Right: In mice with early-established pulmonary metastases, LIGHT-VTP induces intra-lesional high endothelial venules (HEVs) that facilitate CD8$^+$ T cell infiltration, thereby limiting metastatic progression.

are established in mice through the intravenous injection of cancer cells. Although this model does not fully recapitulate the natural history of *bona fide* metastases, it can approximate metastatic lung disease in preclinical trials. The authors administered several doses of LIGHT-VTP to mice with pre-formed lung nodules. Similar to observations in primary tumors, LIGHT-VTP induced HEVs in the lung nodules. Moreover, it increased tumor infiltration by CD8$^+$ T cells with an activated (effector) phenotype, decreased the number of lung nodules, and extended the survival of the mice. These results support the notion that LIGHT-VTP has direct inhibitory activity on pre-established metastases. Notably, the anti-metastatic effects of LIGHT-VTP could be potentiated through the co-administration of an anti-PD1 antibody, strongly suggesting that they were, at least partly, T cell-dependent (He et al., 2019).

One of the most intriguing findings of He et al. (2019) is the ability of LIGHT-VTP to induce HEVs and to promote T cell infiltration in small lung nodules with the size of human cancer micrometastases (0.2 to 2 mm). In this regard, increasing studies indicate that human pulmonary metastases largely grow by co-opting pre-existing blood vessels (Kuczynski et al., 2019). Thus, it would be interesting to investigate whether LIGHT-induced HEVs originate from pre-existing (co-opted) or angiogenic (*de novo*) blood vessels. Regardless of the mechanisms involved, early and occult metastatic lesions are key targets of adjuvant (post-surgical) therapy, for example, in patients with triple-negative breast cancer, who frequently develop full-blown metastatic disease months or years after removal of the primary tumors. By generating HEVs and enhancing T cell infiltration, LIGHT-VTP may potentially sensitize micrometastases, which often lack meaningful T cell infiltrates, to immune checkpoint blockade.

Interestingly, He et al. (2019) found that anti-PD1 antibodies not only improved tumor response to LIGHT-VTP, but also increased metastasis-associated HEVs, suggesting a direct role for activated T cells in inducing HEVs. These findings attest to the intertwined regulation of vascular programming and adaptive immunity in tumors, which can be harnessed for therapeutic purposes.

A number of preclinical studies have shown that reversing vascular dysfunction by means of anti-angiogenic drugs may alleviate immunosuppression, facilitate T cell trafficking, and sensitize tumors to immune checkpoint blockade; however, these studies largely focused on primary tumors and did not examine metastatic disease or adjuvant therapy modalities (Allen et al., 2017; Munn and Jain, 2019; Schmittnaegel et al., 2017). By employing an array of metastasis models and treatment schedules, He et al. (2019) make a compelling case for LIGHT-VTP being a promising biological for sensitizing occult or overt metastases to immune therapy and, possibly, other anti-cancer agents.

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