

Zooming in on selectins in cancer

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Selectins are involved in leukocyte and cancer cell trafficking, which can be targeted with drugs and nanoparticles (Shamay *et al.*, this issue).

Leukocytes are constantly circulating the body as the “royal guards,” ready to exit from blood vessels at any sites of injury or infection. The major regulators of leukocyte traffic are selectins, three types of adhesion molecules that are expressed by leukocytes (L-selectin), platelets (P-selectin), and vascular endothelium (E-selectin and P-selectin). As part of the inflammatory process, selectin cell surface expression is induced by cytokines and facilitates the initial interaction of leukocytes with the endothelium. This essential interaction slows down leukocyte circulation as part of the leukocyte rolling mechanism and enables further adhesion and extravasation to inflamed sites (Fig. 1A) (1).

CANCER TAKES OVER LEUKOCYTE TRAFFIC REGULATION

Cancer takes advantage of leukocyte traffic regulation for its own benefit in diverse ways. Tumors control endothelial expression of selectins by secreting specific cytokines. By orchestrating selectin expression and density on vascular endothelium, a tumor can recruit selected immune cells, such as monocytes, helping it establish the premetastatic niche. It can also obtain nutrients for its high metabolic requirements by promoting angiogenesis. Cancer also takes advantage of P-selectin elevation on activated platelets to form immune complexes, which allow it to escape recognition by macrophages. Thus, by controlling selectin expression, tumors can recruit cells and nutrients to design their microenvironment. The best-documented (2) use of selectins by cancer cells is that they use them for their own trafficking (Fig. 1B). By expressing selectin ligands such as sialyl Lewis A (SLe^a), sialyl Lewis X (SLe^x), or P-selectin glycoprotein ligand-1

(PSGL-1), the cancer cells acquire a leukocyte-like ability to spread to distant organs. Hence, cancer cells can control vascular traffic by governing both the “roads” (selectin expression on vascular endothelium) and the “passengers” (rolling cancer cells and leukocytes).

In a recent issue of *Science Translational Medicine* (3), Price *et al.* explored whether breast cancer cells can also take over hematopoietic stem cells’ (HSCs’) “parking lot” in the bone marrow (BM) to support cancer dormancy. Using intravital BM real-time microscopy in a breast cancer xenograft model, the authors showed that E-selectin that is constitutively expressed in sinusoidal vasculature and the perisinusoidal venule niche mediates breast cancer stem cell (CSC) homing. Moreover, the authors suggested that the interaction of CSCs with E-selectin induces dormancy, noting that CSC proliferation in separate nonsinusoidal regions of the BM occurs after E-selectin detachment. This work emphasized the essential role of selectins in cancer relapse.

CAN WE REGAIN CONTROL OVER SELECTINS?

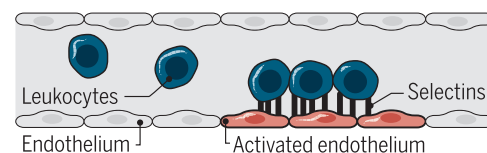
Tumor cells’ takeover of leukocytes’ traffic regulation mechanism enables them to not only promote their own transport and gather immune cells working on their behalf but also hide CSCs, which can enable future relapse. The main question is whether and how we can regain control of selectins and use them as potential therapeutic targets.

One possible strategy with promising results involves blocking the “roads” using small-molecule inhibitors, blocking antibodies, or other components that interfere with selectin-ligand interactions (Fig. 1C). This approach was shown to reduce metastases *in vivo* in several types of cancer. Price *et al.* (3) demonstrated substantial blockade of breast CSCs homing to BM using an E-selectin inhibitor, GMI-1271. This emphasized the therapeutic promise of selectin inhibitors for interfering with cancer dormancy and reducing the poten-

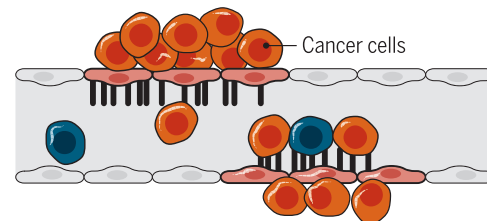
tial for cancer relapse. Indeed, clinical trials (ClinicalTrials.gov identifier: NCT02306291) testing the effects of GMI-1271 and other selectin inhibitors are currently being conducted in AML patients.

Another strategy uses selectins directly as moieties for active drug targeting (Fig. 1C). Major efforts have been directed toward developing drug carriers that would enable passive drug accumulation at tumor sites as a result of leaky tumor vasculature, known as the enhanced permeability and retention (EPR) effect. However, the EPR phenomenon appears to have a limited presence in human tumors and metastases. Because selectin overexpression is a marker for tumor vascular endothelium, targeting selectins may present an attractive approach for delivering drugs to tumors and metastasis sites. To devise targeted carriers, suitable targeting moieties (antibodies, peptide, or natural ligands) can be surface conjugated to nanoparticles that entrap chemotherapeutic agents or nucleic acids for manipulating gene expression (4, 5). In this issue of *Science Translational Medicine* (6), Shamay *et al.* present an elegant approach that combines the two strategies in a single platform. By devising drug carriers composed of the sulfated polysaccharide

A Leukocyte homing



B Cancer takes over



C Selectin-based therapy

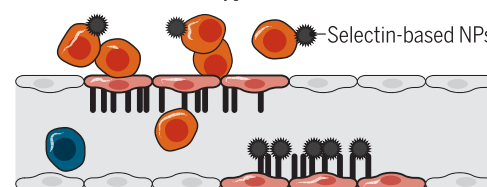


Fig. 1. Selectins as therapeutic targets in cancer. (A and B) Schematic illustration of selectins’ role in inflammation (A) and cancer progression (B). (C) This mechanism can be used for selectin-based targeted therapy.

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fucoidan, an inhibitor of P- and L-selectins, Shamay *et al.* were able to demonstrate efficient and robust encapsulation of chemotherapy drugs along with active targeting in several types of tumors in vivo. Fucoidan's dual function as both a drug carrier and a P-selectin ligand inhibitor may enable blocking of the "roads" and promote drug accumulation in the interior of tumors to eliminate cancer cells. The authors demonstrated that fucoidan-based nanoparticles (F-NPs) encapsulating chemotherapy drugs promoted tumor targeting in both primary and metastatic mouse models and resulted in shrinkage of the tumors and prolonged survival of tumor-bearing mice. F-NPs markedly improved the therapeutic outcome relative to dextran-based nanoparticles (D-NPs), controlling for baseline drug accumulation and efficacy mediated by the EPR effect.

To elucidate the mechanism by which F-NPs act in vivo, the authors conducted a set of experiments. By inducing P-selectin expression on tumor vascular endothelium, they demonstrated P-selectin's crucial role for F-NPs' active targeting. The authors measured in vitro drug penetration through a monolayer of endothelial cells and accumulation in tumor spheroids. Enhanced drug accumulation in tumors was observed as a result of F-NP treatment compared to the untargeted D-NPs, implying that active binding to endothelial cells promotes particle penetration. Overall, the authors suggested that F-NPs accumulate at vascular endothelial sites within tumors and penetrate tumor cells through activated endothelium. In addition to active targeting, F-NP penetration can also be supported by endothelial cell death and the EPR effect. As the authors pointed out, further studies in tumor models that lack EPR will be needed to elucidate the penetration mechanism.

Interestingly, Shamay *et al.* also showed that P-selectin is overexpressed not only at the tumor vascular endothelium but also on many types of tumors, such as lung, ovarian, lymphoma, and breast cancers, emphasizing its possible role as a targeting molecule at the tumor cellular level. Shamay *et al.* further demonstrated in vitro cellular drug targeting by F-NPs resulting in increased cell death over the untargeted, D-NPs control. The F-NP design exploits selectin expression on tumor vascular endothelium and perhaps on tumor cells.

Therefore, F-NPs are thought to deliver drugs through active targeting in addition to EPR drug accumulation. Besides, F-NPs can potentially block P-selectin from interacting with its ligands. Surprisingly, in melanoma and in breast metastatic mouse models, Shamay *et al.* demonstrated no therapeutic benefit from administration of free fucoidan. Because selectin-ligand interactions are multivalent and might be influenced by ligand density and conformation, a free fucoidan may not interact with P-selectin as F-NPs do. Nevertheless, testing F-NPs' inhibitory effects over the time course of metastatic progression may still uncover additional benefits from its possible role as an inhibitor of selectin-ligand interactions.

TARGETING SELECTINS: A POTENTIAL TWO-EDGED SWORD

Not all tumors exhibit homogeneous overexpression of vascular endothelium P-selectin. Because irradiation induces selectin expression, Shamay *et al.* explored whether the combination of irradiation with selectin-based therapy can be effective against tumors that lack endothelial expression of P-selectin. The use of irradiation might also allow control over the extent and duration of selectin expression. Indeed, the combination therapy showed promising therapeutic results, enhancing drug accumulation in tumors and dramatically decreasing tumor volume in the Lewis lung carcinoma mouse model. Yet, it is essential to note that P- and E-selectin induction by irradiation might also promote cancer aggression and encourage metastatic spread (7, 8).

Interfering with selectin function through selectin-based therapy may act as a two-edged sword, which could result in either cancer eradication or cancer progression. Selectins' role in leukocyte trafficking is a fundamental process. The presence of tumor-infiltrating lymphocytes negatively correlates with cancer severity (9). In fact, an immune scoring system (Immunoscore) based mainly on the presence of CD3⁺ and CD8⁺ T lymphocytes helps predict the clinical outcome for cancer patients. Moreover, clinical results of immune checkpoint blockade further emphasize the important role of adaptive immunity in fighting cancer (10). Damaging or blocking leukocytes' trafficking could also impact lymphocyte circulation in general, and for T lymphocytes,

in particular, this may hamper the antitumor immune response. This suggests a potential approach to personalized therapy, in which selectin-based therapy could be offered to patients with a low Immunoscore.

Further research that finds possible differences in selectin ligand types and density variations between cancer cells and leukocyte subsets may enable fine-tuning and optimization of selectin-based therapy. These strategies may allow the development of treatments that inhibit selectin interactions with cancer cells and prometastatic leukocyte subsets but still keep T lymphocyte circulation intact.

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