Text by Mitch Leslie
mitchleslie@comcast.net

Clearing the way for cancer cells

Endothelial focal adhesion kinase helps tumor cells enter the bloodstream.

Cancer cells have something that every prisoner longs for—a master key that allows them to escape. Jean et al. describe how a kinase that promotes tumor growth enables cancer cells to use this key (1).

Unless it can enter a blood or lymphatic vessel, a cancer cell is imprisoned in the tissue where it arises. Vascular endothelial growth factor (VEGF) is the tumor cell's master key. The growth factor loosens connections between endothelial cells in the wall of a blood vessel, enabling the cancer cell to squeeze through and plunge into the bloodstream. The protein vascular endothelial cadherin (VEC) helps fasten endothelial cells together (2). By binding to and activating the receptor VEGFR-2,VEGF triggers the phosphorylation of VEC (3). This alteration causes the complexes that contain VEC to fall apart, opening gaps between endothelial cells. Researchers haven't uncovered all of the steps between VEGFR-2 activation and VEC phosphorylation, however, and one protein that might be involved is focal adhesion kinase (FAK), which accumulates at cell–cell junctions in response to VEGF stimulation (4).

To pinpoint the protein's function, Jean et al. gave a FAK inhibitor to mice with fast-spreading breast cancer. Previous work had shown that the inhibitor thwarts tumor growth, and the researchers found that it prevented phosphorylation of tyrosine 658 in VEC from tumor-associated blood vessels. The team also dosed mice that had ovarian tumors with another FAK inhibitor. The treatment also curbed phosphorylation of tyrosine 658 in VEC, suggesting that FAK controls this event.

The researchers then injected VEGF into control mice and into mice with an enzymatically inactive variant of FAK in their endothelial cells. VEGF spurred phosphorylation of VEC's tyrosine 658 in the control rodents but not in the animals expressing kinase-dead FAK.

Another protein that promotes VEC phosphorylation is the tyrosine kinase Src. To gauge its interactions with FAK, the researchers tracked both proteins in lung endothelial cells. After a dose of VEGF, the two proteins moved to cell–cell junctions and settled near VEC. Adding a FAK inhibitor or a Src inhibitor prevented this migration, suggesting that the two proteins stimulate each other to relocate to these adhesions.

Jean et al. next tested whether FAK helps unlock endothelial layers. They determined the effect of VEGF-releasing tumor cells on endothelial cell cultures. Tumor cells first adhered to the endothelial layer and then slipped through. When the endothelial cells produced a kinase-dead form of FAK, the tumor cells were still able to stick to the layer but couldn't cross it. When the endothelial cell layers carried VEC mutants that could not be phosphorylated at tyrosine 658, tumor cells had a hard time slipping through. Mutations at other VEC phosphorylation sites had no impact, however.

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The researchers also measured FAK's effect on metastasis in mice that had been injected with invasive tumor cells. Compared with control animals, mice that expressed a kinase-dead version of FAK in their endothelial cells showed fewer tumor cells in their lungs. Blocking endothelial FAK curbed metastasis without altering tumor growth, the team found.

Jean et al.'s findings reveal a new role for endothelial FAK in the control of metastasis. "Our work places FAK in the pathway that controls vascular permeability," says senior author David Schlaepfer. Some details of the pathway remain unclear, however. The researchers' results suggest that FAK is downstream of Src, but how FAK gets activated after VEGF stimulation is still unknown. In addition, although Src and FAK simultaneously arrive at cell–cell adhesions, researchers don't know whether they journey there together. FAK inhibitors are being tested in clinical trials because they restrain tumor growth, and Jean et al.'s paper suggests that they may provide an additional benefit by curtailing metastasis.

Focal Point

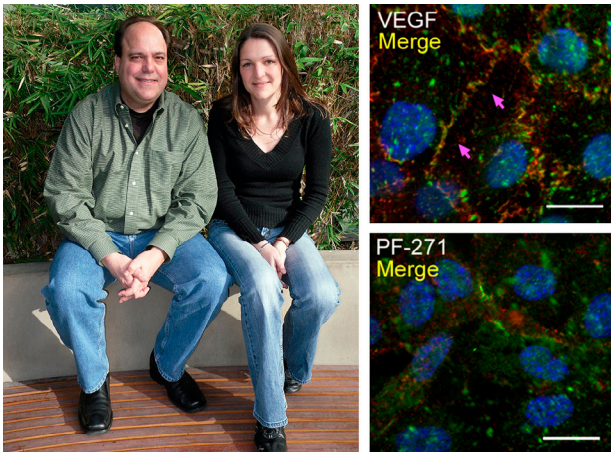

PHOTO COURTESY OF DAVID SCHLAEPFER

David Schlaepfer (left), Christine Jean (right), and colleagues (not pictured) discovered how FAK promotes cancer cell metastasis. They found that FAK works downstream of Src to help VEGF-expressing cancer cells open endothelial cell layers. FAK (green) and Src (red) gather near each other when cells are stimulated by VEGF (arrowheads, top), but the two proteins remain apart after addition of a FAK inhibitor (bottom).

1. Jean, C., et al. 2014. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201307067
2. Dejana, E., et al. 2009. *Dev. Cell*. 16:209–221.
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4. Chen, X.L., et al. 2012. *Dev. Cell*. 22:146–157.