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Some Cells in a Tumor Protect Against Metastasis

Study shows pericytes can play a paradoxical role in angiogenesis

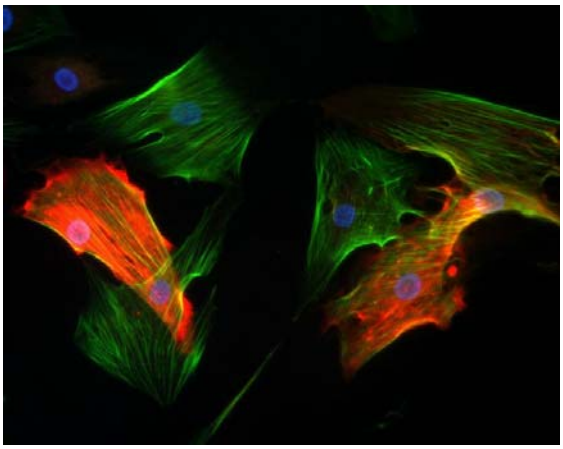
By cutting off a tumor's blood supply, angiogenesis inhibitors may shrink a tumor. But they inadvertently may make the tumor more aggressive and increase its odds of metastasizing, according to an article published earlier this month in *Cancer Cell.*

Raghu Kalluri, MD, PhD, chief of the division of Matrix Biology at Boston's Beth Israel Deaconess Medical Center and Harvard Medical School, along with his team, studied pericytes—cells that cover blood vessels and support their growth. The researchers wanted to find out whether targeting pericytes could have the same tumor-inhibiting effect as that found with angiogenesis inhibitors.

Using genetically engineered mice, Kalluri and his colleagues reduced the number of pericytes in implanted breast cancer tumors by 60%. The volume of the tumors in these mice dropped by 30%, compared with mice in the control group, in just 25 days. But startlingly, the pericyte-depleted mice had 3 times as many metastatic lung tumors as did those in the control group.

"This surprised us," says Kalluri. "If you were looking at tumor growth as the primary endpoint, the results would be good. But if you just look at that one factor, you have not made a full assessment of the cancer."

To figure out why tumors lacking pericytes were more likely to metastasize, the researchers examined the tumor microenvironment. They found 5 times as many hypoxic areas, suggesting that the tumor vasculature was weakening and growing leaky due to a lack of oxygen. In addition, they found evidence of tumor cells making the epithelial-to-mesenchymal transition, which promotes their mobility and is thought to be a first step in metastasis. In this way, the tumor cells survive and travel to distant sites.



Cultured pericytes (red) and myofibroblasts (green) are 2 prominent noncancerous cells found in tumors. (Their nuclei are blue.) These cells were isolated from a breast tumor. *Vesselina Cooke/Beth Israel Deaconess Medical Center*

The team also found a 5-fold increase in activation of MET, a receptor protein that promotes cell migration and growth. Additionally, they observed that small tumors deficient in pericytes were more likely to metastasize than were large tumors with a good number of pericytes.

Because commonly prescribed cancer therapies such as imatinib (Gleevec; Novartis) and sunitinib (Sutent; Pfizer) decrease pericytes in tumors, the researchers examined the impact of these agents on mouse tumors. As was the case in the genetically engineered mice, the drugs caused a significant drop in pericytes—this time 70%—and a 3-fold increase in secondary tumors. Experiments with implanted renal cell carcinoma and melanoma tumors yielded similar results.

Finally, to determine if the findings were relevant to patients, Kalluri's team examined 130 breast

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cancer tumors samples, comparing pericyte coverage with prognosis. Among the samples they assessed, they found that low numbers of pericytes in the tumor vasculature and high MET expression were correlated with the most invasive tumors, distant metastasis, and lower 5- and 10-year survival rates.

The upshot, says Kalluri, is that patients who take a pericyte-targeting drug may also need to take a MET inhibitor to help prevent the epithelial-to-mesenchymal transition and rein in cellular mobility.

The work also points to future avenues of tumor microenvironment research. "Not all cells in a tumor are cancer cells," explains Kalluri. "There are noncancerous cells like pericytes, fibroblasts, and immune and endothelial cells. Are these components helping cancer cells or are they protective? We can't always treat everything as though it's bad. We might be interfering with a protective mechanism." – *Suzanne Rose*

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