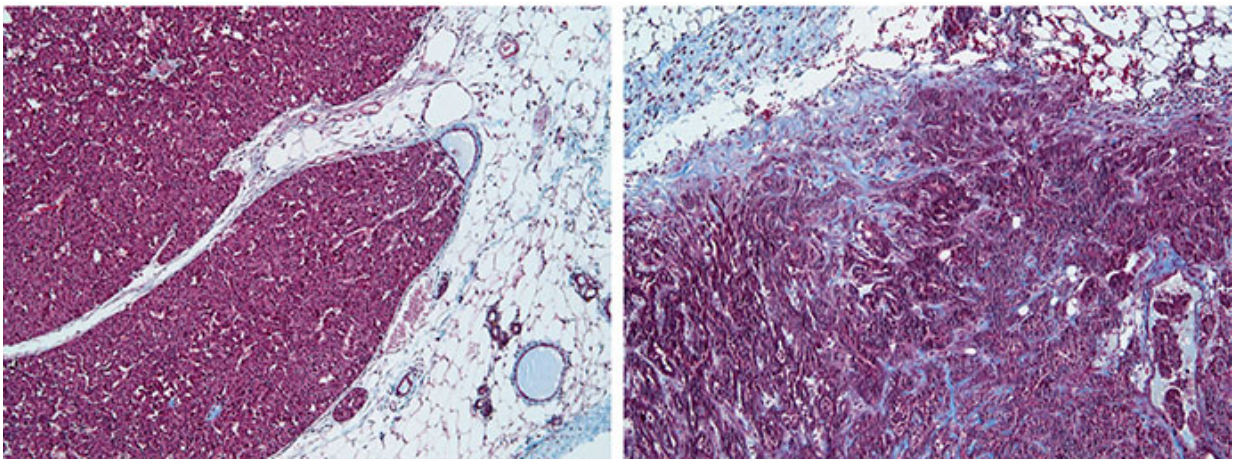


Tumor surroundings are shown to affect progression of different cancer subtypes

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Mikala Egeblad's team showed in mice that the progression of different types of breast cancer was influenced differently by the tissue -- the so-called tumor microenvironment -- in which the tumor is embedded. The tumor microenvironment contains many factors, including immune cells and blood vessels, that communicate with cancer cells and can promote tumor growth. On the left, a breast cancer type called luminal; on the right, a type called triple-negative/basal. The luminal microenvironment has less fibrosis (scar tissue, colored purple) and contains few inflammatory cells embedded within these fibrotic areas or in the surrounding fatty tissue (white). The triple-negative microenvironment contains more inflammatory cells and more fibrosis. Targeting a protein called MMP9, which promotes cancer and is linked with poor prognosis, slowed the course of the triple-negative/basal breast cancer, the one with the more profoundly altered microenvironment, but had no impact on the luminal cancer. Credit: Egeblad Lab, CSHL

Our environment can have a major impact on how we develop, and it turns out it's no different for cancer cells. In work published today in *Neoplasia*, a team of researchers led by Associate Professor Mikala Egeblad at Cold Spring Harbor Laboratory (CSHL) found that two different mouse models of breast cancer progressed differently based on characteristics of the tumor microenvironment - the area of tissue in which the tumor is embedded.

The [tumor microenvironment](#) includes cells and extracellular molecules that support the [tumor](#)'s growth. Egeblad and her team looked at two types of [breast cancer](#) driven by different mutations, and found very different microenvironments. One common factor was the presence of an extracellular protein called matrix metalloproteinase 9 (MMP9). It was expressed at similar levels in tumors from both breast cancer mouse models.

MMP9 previously has been linked to the progression of many types of cancers. When the researchers deleted the *Mmp9* gene, they found that the absence of the MMP9 protein delayed tumor onset only in one [mouse model](#), and had no effect in the other model.

Egeblad and her team found that whether MMP9 promoted cancer or not depended on the tumor microenvironment. Specifically, on the presence of another molecule that MMP9 is known to act on, called insulin-like growth factor binding protein 1 (IGFBP-1). "If IGFBP-1 is not there, MMP9 didn't really have an effect, but if it's there, then MMP9 has a role," says Egeblad. This suggests that IGFBP-1 interacts with MMP9 to promote tumor formation.

IGFBP-1 binds insulin-like [growth factors](#) (IGFs), which play a role in promoting cancer proliferation. "IGFBP-1 keeps the growth factors sequestered so they can't act on the [cancer cells](#) and can't make them proliferate," Egeblad says. "But if MMP9 is present, it degrades these

IGFBPs and releases the growth factors." The release of the IGFs then accelerates cancer progression.

Egeblad and her team looked in human cancer databases to see if the interaction between MMP9 and IGFBPs predicted [breast cancer prognosis](#) in humans. "We found that IGF-binding proteins are associated with a good prognosis, but if MMP9 is also present, there's no longer good association with survival," Egeblad says.

The study's results have implications for anti-cancer drugs that target MMPs, and may explain why previous clinical trials using MMP inhibitors have failed, Egeblad says. "Maybe you can actually think about using these inhibitors if you better understand their biology," she says. The new study suggests that trials of MMP inhibitors could focus on patients whose tumor microenvironment contains IGFBPs, she says.

More broadly, the research suggests that it may not be enough to see if a particular drug target is present in a certain type of cancer; researchers may also need to look for the presence of the molecules that the drug target acts upon. "It complicates things, but I think biologically it makes a lot of sense. You really need to dig deep and understand mechanistically what the target does," Egeblad says.

The lab's next goal is to look more generally at the differences in microenvironments in different types of cancer. "What we're starting to learn now is that the microenvironments are different in different tumors, and that there is really a very intricate interplay between what's driving the mutations in [cancer](#) cells and the type of microenvironment they build around themselves," Egeblad says.

More information: "Presence of insulin-like growth factor binding proteins correlates with tumor-promoting effects of matrix metalloproteinase 9 in breast cancer " appears online in *Neoplasia* on

May 27, 2105, 2015. The authors are: Jae-Hyun Park, Ph.D.; Morten G Rasch, Ph.D.; Jing Qiu; Ida K Lund, Ph.D.; Mikala Egeblad. The paper can be obtained online at: [\(15\)00047-0/fulltext](https://neoplasia.org/article/S1476-55...)

Provided by Cold Spring Harbor Laboratory

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