

## Q&A: Mikala Egeblad on Tumor Microenvironment

*Targeting cells in the microenvironment as well as in the tumor could lead to better patient outcomes*

Over the past few decades, researchers have increasingly realized that cells in the tumor microenvironment—fibroblasts, macrophages, neutrophils, mast cells, and T cells—play a role in tumor growth. “Most of these cells have the capacity to slow down tumors, but they receive signals that push them in the other direction—promoting tumor growth,” explains Mikala Egeblad, PhD, who studies tumor microenvironment at New York’s Cold Spring Harbor Laboratory. She recently spoke with *Cancer Discovery*’s Suzanne Rose about how a tumor’s microenvironment may affect therapeutic responses and metastasis, as well as future research directions in the field.

### How does the tumor recruit these cells?

It can happen through complex signaling networks, with both direct and indirect signals from the cancer cells. For instance, fibroblasts will receive signals from the cancer cells and they in turn will send out additional signals to recruit immune cells. After they’ve been recruited, they send out signals to stimulate angiogenesis.

### How do cells in the tumor microenvironment impact cancer treatment?

When you give a patient anticancer drugs, cancer cells aren’t the only cells affected. There is evidence that fibroblasts, inflammatory cells such as macrophages, and endothelial cells respond to therapy by secreting survival factors—Wnt family members and interleukins—or by stimulating blood-vessel formation, which makes the tumor grow faster. It’s an adaptive response to the treatment.

That raises a lot of questions: Are the factors secreted from stromal cells going to have only transient effects? Could you reverse resistance mediated by these factors? Or does this generate an environment in which the cancer cells have the chance to adapt and accumulate more mutations so that they become more resistant? These are some of the big unknowns.

### Are some cancer cells innately resistant to chemotherapy? Or does something happen in the microenvironment to cause resistance?

There is certainly evidence that, e.g., acquired genetic changes can make cancer cells resistant to drugs from the get-go, but if subpopulations within the tumor undergo epithelial-mesenchymal transition, that can also make them more resistant. Stromal cells can send signals that can push these tumor cells to the epithelial-mesenchymal-transition-like phenotype, so that is another way that the microenvironment can cause resistance.

### Do these mechanisms drive metastasis as well?

We know that many of these same cells (fibroblasts and macrophages) and same factors (Wnt family members and transforming growth factor beta) are involved in driving metastasis.

Is that why metastatic disease is so hard to treat? Or is it because the microenvironment of metastatic disease is different from the microenvironment of the primary tumor? Those are big questions; I see a lot of us starting to tease out the answers.

### What are some potential approaches to targeting the microenvironment?

One approach is to try to prevent the immune cells from coming into the tumor in the first place—to prevent the adaptive response to chemotherapy. Clinical trials of drugs that target the signals that drive inflammatory cells into the tumors, such as macrophage colony stimulating factor 1, are under way. It’s been shown in mouse models that they have some effect on both primary and metastatic disease. It will be certainly interesting to see how well that approach works.

Another way is to try to target the signals that the immune cells and fibroblasts send out, such as interleukin 6 and some of the Wnt family members.

### Is there a difference between the microenvironment of a breast tumor versus, say, a pancreatic tumor?

Indeed, we have compared the effects of specific components of the microenvironment on metastasis and found completely different effects between breast and pancreatic cancer in our mouse models. We are also seeing differences between different models of breast cancer, and between metastatic and primary cancer. That means that understanding what the specific microenvironments are doing is going to be critical. We need a personalized approach against the tumor microenvironment, not just against genetic changes in the cancer cells.

### What do you see happening in your field in the next 5 years?

I think the tumor microenvironment field is going to embrace the tumor immunology field, where they have exciting results on checkpoint blockade in T cells. We’re starting to find out how the microenvironment plays a role in also regulating the T-cell response. How can we activate or deactivate the microenvironment to help with a checkpoint blockade therapy? I think that could be really exciting.

Researchers from Dana-Farber Cancer Institute [Boston, MA] just published a paper showing that VEGF levels may predict how well the checkpoint blockade therapy ipilimumab [Yervoy; Bristol-Myers Squibb] might work in melanoma patients [*Cancer Immunol Res* 2014;2:127–32]. That suggests that it’s possible to modulate the microenvironment to get better responses.

There is also a lot of literature showing that T cells can be inactivated by inflammatory cells in the microenvironment. Identifying and targeting those suppressive signals could really make a difference. ■



Connie Bruken

When it comes to treating cancer, “we need a personalized approach against the tumor microenvironment, not just the genetic changes in the cancer cells,” says Mikala Egeblad.