How cellular plasticity drives cancer metastasis

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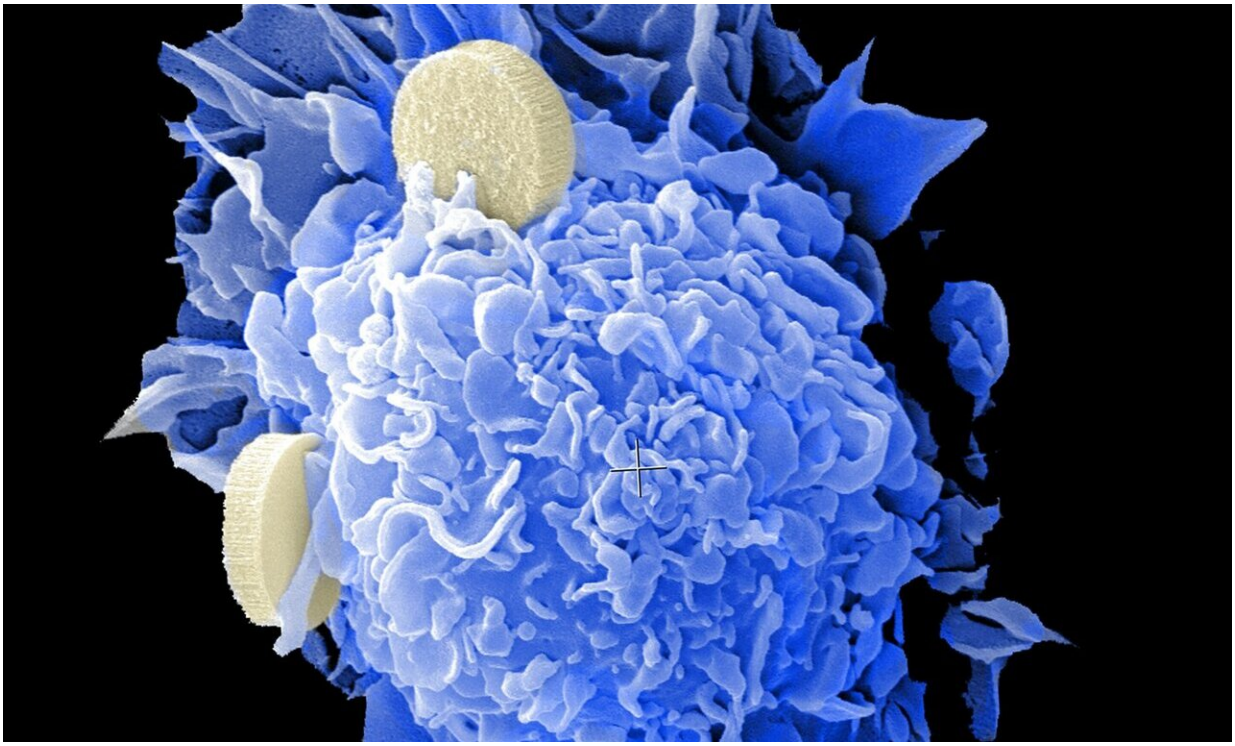

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About 90% of deaths from cancer are a result of metastasis—that is, from cancer's ability to spread from an initial primary tumor to seed new tumors throughout the body, often in the lungs, liver, and brain.

Metastasis relies on cancer cells' ability to adapt to different tissue

environments throughout the body by gaining improper access to a variety of playbooks stored in our genetic code—including gene programs that are generally available only during early stages of human development.

Today, researchers at Memorial Sloan Kettering Cancer Center (MSK) are using innovative approaches like single-cell sequencing technology and sophisticated computational tools to illuminate cancer cells' ability to take on new traits, and they're applying those findings toward treating or preventing metastasis.

In a plenary presentation at the 2024 American Association for Cancer Research (AACR) Annual Meeting, Dana Pe'er, Ph.D., Chair of the Computational and Systems Biology Program at MSK's Sloan Kettering Institute, highlighted three recent research collaborations between her lab and other labs at MSK that have shed new light on the ability of cancer cells to adapt and spread.

"It's not genetic mutations that are critical here, but the ability to access gene programs that normally are associated with other cell types—including early developmental and embryonic programs that should not be accessed by adult cells," Dr. Pe'er said in a recent interview. "We call this ability for cells to run new programs 'plasticity.' So cancer doesn't reinvent the wheel; it exploits gene programs that exist for other biological purposes."

In general, she notes, plasticity isn't a bad thing. It's important for early development and for regeneration after injury. The body also has built-in barriers to limit the scope of plasticity so that cells can't just run amok.

"But in cancer, these cells can wreak havoc because they've lost these natural barriers," says Dr. Pe'er, who is also a Howard Hughes Medical Institute Investigator.

Plasticity in colorectal cancer

In the first study Dr. Pe'er presented at AACR, she teamed up with MSK physician-scientist Karuna Ganesh, MD, Ph.D., to look at the differences in gene programs active in the primary tumors and metastatic tumors of patients with advanced colorectal cancer. Samples of both types of tumors were collected at the same time from 31 patients—the largest cohort of its kind—some of whom had undergone chemotherapy and some of whom had not.

They also created organoids from the patients' cells—three-dimensional clusters of cells that act more like human tissue than traditional laboratory cell cultures.

The study found that primary tumor cells largely run programs still associated with intestinal cells, while metastases often shed their heritage as intestinal cells and take on the characteristics of squamous cells or of neuroendocrine cells, which helps them invade and survive in new tissue contexts and makes them more resistant to treatment. The team also found that chemotherapy exacerbates these transformations. The findings were published as a preprint on *bioRxiv* in August 2023.

"The metastatic organoids were very different from the primary tumor organoids," Dr. Pe'er says. "And it matters what environment they're in, too. If you put the metastatic organoids into the liver of a mouse, they will adapt their identity in ways that primary tumor organoids are not able to—so they're a lot more plastic."

The team additionally found that a gene known as PROX1 restricted the ability of cells from the primary tumor to stray too far from their lineage as intestinal cells. But when this factor is removed, the cells gain access to many more types of cell lineages—which scientists call noncanonical. (For reasons that aren't fully understood, metastatic cells that lose the

restrictions imposed by Prox1 are already primed to go in these noncanonical directions.)

"I call it a mix-and-match buffet," Dr. Peer says. "Metastatic cells have this awesome power to combine gene programs across many different types of cells, endowing them with new abilities that allow them to adapt themselves to take advantage of different conditions and environments throughout the body."

Plasticity in pancreatic cancer

The second study Dr. Pe'er presented looked at about a dozen metastases collected from a single patient with pancreatic cancer, who donated their body for research under MSK's Last Wish Program. A collaboration with physician-scientist Christine Iacobuzio-Donahue, MD, Ph.D., Director of the David M. Rubenstein Center for Pancreatic Cancer Research at MSK, the research used advanced single-cell and computational approaches to look at the differences in active gene programs in genetically identical cancer cells—called clones—that had spread to different locations in the body. The findings of the study have not yet been published.

"What we see is that these clones are able to adapt to the pressures and metabolic demands of very different environments," Dr. Pe'er says. "And we see that they're able to access different gene programs that allow them to thrive in different places, different organs."

Moreover, even genetically different cancer cells tend to adapt to specific situations by accessing the same gene programs.

"The big question of a cancer cell is, 'Are you plastic or not?' And once you are, you can acquire all these different traits. The environment is what really determines what traits will be most advantageous," she says.

For example, the research showed that cells that metastasize to the peritoneum—the tissue that lines the abdominal cavity—are able to adapt their metabolism to take advantage of the lipid-rich environment and exploit it as an energy source, she notes.

Moving plasticity research from the lab to the clinic

Lastly, Dr. Pe'er highlighted a third collaboration—this time with neuro-oncologist Adrienne Boire, MD, Ph.D., a member of MSK's Human Oncology and Pathogenesis Program—that showed how plasticity can be turned against cancer cells.

The research led to a clinical trial for patients with leptomeningeal metastasis, which is when cancer has spread to the fluid and tissues of the spinal cord and brain. The team showed that cancer cells were able to survive in this challenging environment by reprogramming themselves to outcompete other cells for iron; this fuels their growth while also preventing immune defenders in the area from getting enough iron.

"It's an elegant solution on the part of the cancer cell," Dr. Boire says. "It's really unique biology that allows them to win the competition."

Based on that discovery, doctors at MSK are now determining whether a drug called deferoxamine could be an effective treatment for leptomeningeal metastases by helping to remove iron from the cerebrospinal fluid.

"The plasticity of these cells allowed several patients with several different cancers to overexpress the same two genes that are typically only expressed in myeloid cells," Dr. Pe'er says. "And the cells not only got aberrant access to these gene programs, but they also expressed the genes at 100 times the levels seen in their normal counterparts."

By injecting the study drug into the spinal fluid, the idea is to prevent the cancer cells from getting the iron they need to thrive. And so far, Dr. Pe'er told the audience, initial results from the trial have been extremely promising.

"The ultimate goal, though we're not there yet, would be to be able to target plasticity directly—to restore some of the biological barriers or inhibit plasticity with drugs," Dr. Pe'er says.

MSK is uniquely poised to pursue that aim, with strong collaborations between laboratory and clinical research; a high volume of patients that provides a wide variety of clinical samples from a wide variety of cancers, including rare ones; access to state-of-the art sequencing tools combined with some of the world's top computational expertise; and a significant number of physician-scientists who focus both on caring for patients and finding new ways to treat their disease.

"Not every cancer center would see enough patients with leptomeningeal metastasis to set up a clinical trial like this," Dr. Pe'er notes. "Or have someone like Dr. Boire, who not only cares for patients with metastasis to the central nervous system but who also runs a lab dedicated to studying the underlying molecular mechanisms."

Dr. Pe'er holds the Alan and Sandra Gerry Endowed Chair and is the Scientific Director of the Alan and Sandra Gerry Metastasis and Tumor Ecosystems Center.

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