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# Molecular atlas of small cell lung cancer reveals unusual cell type that could explain why it's so aggressive

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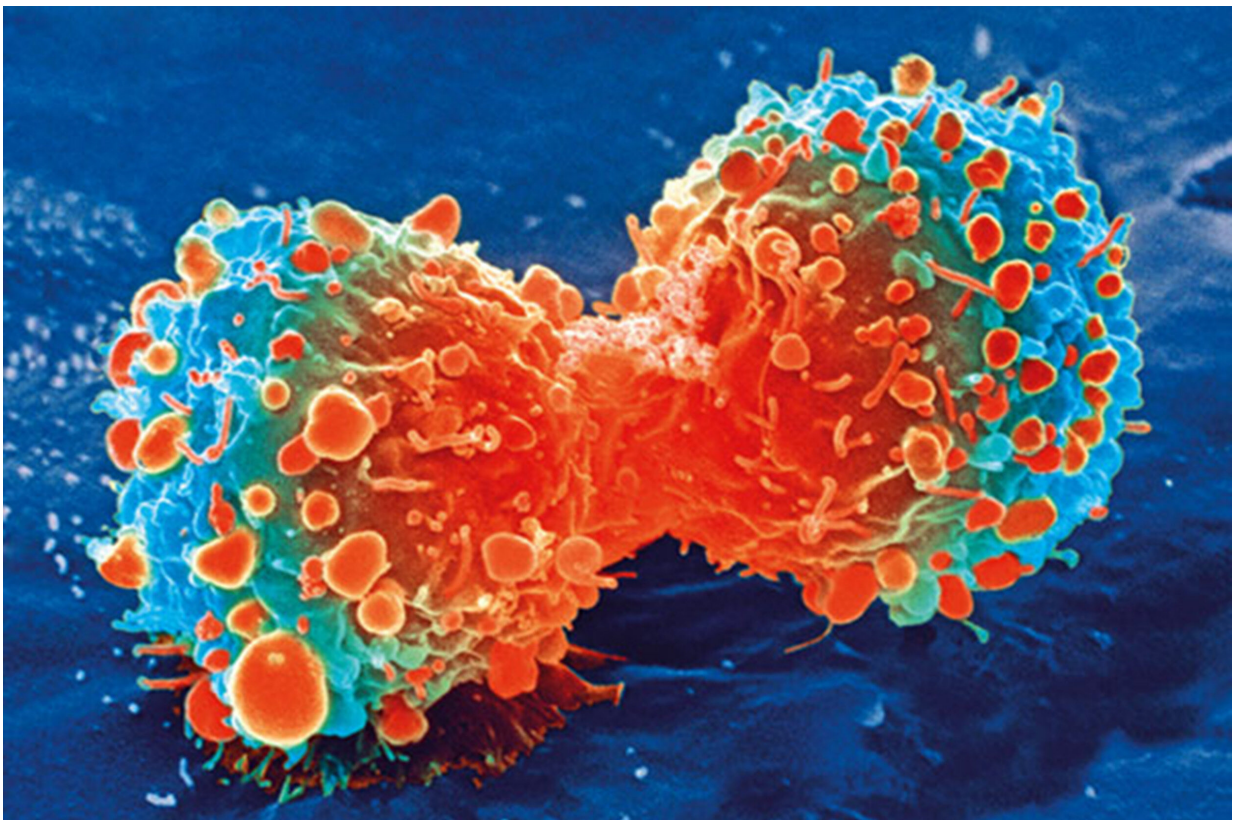

Cancer cell during cell division. Credit: National Institutes of Health

Imagine you're about to go on a cross-country trip, stopping at spots along the way to admire local attractions. You'd probably want to have

road atlas handy, containing maps at different scales, covering both the major highways and the roads of smaller cities and towns—or at least a GPS that can access a digital atlas with this information.

Until recently, cancer researchers have been like cross-country travelers with only a few maps of a few popular cities. And because of how fast some cancers grow, the maps quickly go out of date. This situation has hindered doctors' ability to understand what's really going on inside tumors and develop effective treatments.

The Human Tumor Atlas Network (HTAN) was created to change that. It aims to develop high-resolution maps of many kinds of cancer so that doctors could have a more-complete view of the textured terrain of tumors—including how they change over time to become more deadly. HTAN is funded by the National Cancer Institute and involves a consortium of cancer centers across the United States.

After several years of painstaking research, the first such atlas from investigators at Memorial Sloan Kettering Cancer Center—for small cell lung cancer—is now ready for viewing, and it's full of new insights.

"The most exciting thing we found is a rare population of stem-like cells within these tumors that is closely correlated with patient outcomes," explains Charles Rudin, a physician-scientist at MSK who co-led the lung cancer project. "The more enriched they are in the tumor, the worse the prognosis."

Not only that, but these stem-like cells have metastatic properties—meaning they're prone to spread—and researchers found them across many SCLC tumors that otherwise were very different.

"That was a massive surprise," says Dana Pe'er, a computational biologist at MSK who is a principal investigator of the HTAN and co-led

the lung cancer atlas project. "It raises the possibility that this tiny fraction of cells could be driving metastatic behavior across tumors."

Small cell lung cancer is one of the deadliest cancers. It tends to spread early and aggressively; two-thirds of cases are already metastatic at diagnosis. Chemotherapy is not very effective. The researchers hope their new atlas, which was published October 14, 2021, in the journal *Cancer Cell*, will lead to improvements in care for people with the disease.

## A Collaborative Effort Leads to a Novel Finding

Building the atlas required years of collaborative work from two groups with very different areas of expertise: clinicians like Dr. Rudin with disease-specific expertise in small cell lung cancer and computational biologists like Dr. Pe'er and her team.

Dr. Rudin points to the fact that there are four co-first authors on the paper—an unusual occurrence—as evidence of the diversity of skillsets needed to complete a study like this. The co-first authors are Joseph Chan, Álvaro Quintanal-Villalonga, Vianne Ran Gao, and Yubin Xie.

Dr. Pe'er, Chair of the Computational and Systems Biology Program at the Sloan Kettering Institute, took the lead on the computational side of things. She is an expert in single-cell RNA seq (scRNAseq), a technique that allows scientists to get a detailed picture of which genes are turned on in many hundreds of cells at the same time.

By applying scRNAseq to SCLC tumor specimens obtained from patients at MSK, Dr. Pe'er and her team were able to find this rare population of stem cell-like cells lurking amidst the cells of the surrounding tumor, like locating a needle in a haystack.

"We would never have been able spot these cells with bulk sequencing," she says. "We really needed single cell analysis to find them." (Bulk sequencing is what researchers would do before scRNAseq was available—essentially putting the tumor in a blender and sequencing all the RNA that fell out.)

## Homing in on Molecular Changes

The single cell technique also allowed the team to go further. Within the cells making up this tiny population, one gene stood out: *PLCG2*. This gene makes a protein that acts as a "second messenger"—it relays signals from one protein to another.

"*PLCG2* did not initially strike me as the sort of gene that would be involved in regulating stem cell populations," Dr. Rudin says. "It seems like more of a worker bee."

But indeed, *PLCG2* does seem to be playing an important role. The gene is most highly expressed in this stem cell-like population, the scientists found. And when they experimentally increased or lowered its activity in cancer cell lines, it altered the ability of the cancer cells to metastasize.

They researchers think that these *PLCG2*-high cells could be part of the explanation for SCLC's aggressiveness. If so, it could open up new possibilities for treatment.

"The thought is that if we can develop strategies to selectively target this cell population, we might be able to suppress metastasis and ultimately improve outcomes for patients with small cell lung cancer," Dr. Rudin says.

"What we really want to do is try to stop metastasis in its tracks," Dr. Pe'er adds. "But to do that, we need to better understand these rare cell

populations that seem to be driving it. That's the goal of this atlas."

**More information:** Signatures of plasticity, metastasis, and immunosuppression in an atlas of human small cell lung cancer, *Cancer Cell* (2021). DOI: 10.1016/j.ccell.2021.09.008 , www.cell.com/cancer-cell/fullt … 1535-6108(21)00497-9

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