New Insights into Drug Resistance in Small-Cell Lung Cancer

Scientists discover a single gene's role in drug resistance and look for ways to re-sensitize tumors to chemotherapy.

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Last week the National Cancer Institute released some good news for patients with lung cancer: improved treatments are driving down the death rate.

But there's a snag — the findings only apply to the most common lung cancer type, non-small cell lung cancer. People with small cell lung cancer, a less common but more aggressive type, have yet to see treatment advances improve their prognosis. After an initial response to chemotherapy, most patients see their tumors roar back, now with resistance to drugs.

Dr. David MacPherson, a scientist at Fred Hutchinson Cancer Research Center who specializes in studying small cell lung cancer, is working to give patients more options. New research from his team and their collaborators, published August 20 in the journal Genes & Development, improves our understanding of what causes drug resistance in small cell lung cancer, and how to reverse it.

"We were able to definitively show that activation of a single gene can cause a complete switch, from a tumor that melts away with chemotherapy to one that's essentially completely resistant [to chemotherapy]," MacPherson said.

His team was also able to reverse this drug resistance in mouse models of small cell lung cancer that use patient-derived tumor tissue. They discovered a vulnerability unique to these drug-resistant tumors, and using an experimental molecule that targets it, make the tumors melt away again.

A need for precision medicine

About 15 percent of lung cancer cases are small cell lung cancer. Chemotherapy has been the mainstay of this subtype's treatment for decades, but after an initial response, tumors quickly develop drug resistance and the disease progresses. When their tumors recur, patients find that their doctors have little to offer. Even the newly approved checkpoint inhibitors, the type of immunotherapy that's improving survival for patients with non-small cell lung cancer, only extends the overall survival of patients with small cell by a few months.

“We don’t have a good understanding of why [small-cell tumors] are sensitive [to chemotherapy] in the first place and how chemoresistance arises,” MacPherson said. “I consider that to be one of the central questions in small-cell research, and one that could be most impactful clinically. How does chemoresistance arise and how can we overcome it?”

He believes the answers lie in the small cell lung tumors’ genetics. Though most tumors share a couple of commonly mutated genes, the rest of their genetic changes vary widely between patients and is little understood. Those studying drug resistance have noticed a pattern, however: Cell lines made from chemotherapy-treated small-cell lung cancer patients are three or four times more likely to carry extra copies of genes in the Myc family. These genes are involved in many cellular processes, including growth. Though some of their functions overlap, each member influences cellular biology in a slightly different way.

“This [association] was indirectly implicating Myc-family amplifications in driving chemoresistance,” MacPherson said.

Because that association had been made by looking at cancer cells growing in lab dishes — which often don’t act the same way as cancer cells do in the body — MacPherson and his team decided to test the effects of two Myc-family genes on chemoresistance in models which better mimic tumors’ home environment.

Both Myc family members flip the switch to drug resistance

Two scientists in MacPherson’s lab teamed up to conduct the work. Dr. Eli Grunblatt, a former graduate student, and Dr. Nan Wu, a postdoctoral fellow, first looked at the role of Myc family member MYCN. They used genetic techniques to increase the amount of MYCN in a mouse model of small cell lung cancer. Excess MYCN made tumors develop more quickly and reduced the number of cancer-fighting immune cells inside them. Doses of chemotherapy that caused regression of tumors with normal MYCN levels had no effect on growth of MYCN-high tumors.

Grunblatt and MacPherson confirmed these results in patient-derived xenograft or PDX models, which use tumor tissue taken from patients and grown in mice. They genetically engineered samples from chemo-sensitive tumors to express high levels of one of two different Myc family members, MYCN and MYCL. Again, expression of either Myc family member flipped a biological switch. Unmodified tumors melted away in response to chemotherapy, but tumors with lots of either Myc family member did not.

It’s the one of the first times researchers have genetically manipulated tumor tissue used in PDX models to get a sense of how different genes contribute to chemotherapy response in a physiological environment, MacPherson said.

Finding MYCN’s vulnerability

Mutations that drive cancer often give tumor cells a growth and survival advantage over normal cells — but they can create new vulnerabilities, too. To see if MYCN creates this Achilles heel, Grunblatt and another student in the lab, Justin Norton, used CRISPR-based genetic tools to test

how hundreds of different genes may contribute to the drug resistance seen in small cell lung tumor cells with high amounts of MYCN.

The researchers found that a gene that helps MYCN sidestep the cells' usual protein-recycling system, called USP7, appeared to be key to its ability to promote drug resistance.

Grunblatt treated tumors with high levels of MYCN with an experimental small molecule that blocks USP7 activity.

"If we not only give chemotherapy [to the mice], but we also give the USP7 inhibitor, now that tumor melts away," MacPherson said. "So we could re-sensitize the chemoresistant tumor to chemotherapy by bringing down the level of Myc-N."

Further exploring small cell lung cancer biology

The findings suggest that blocking USP7, or other molecules that help MYCN promote drug resistance, has therapeutic potential, MacPherson said. RAPT Therapeutics, the company that provided the experimental drug that Grunblatt tested, is currently exploring the possibility of bringing it to the clinic.

In the meantime, MacPherson's lab is extending their PDX model-based strategy of testing the effects of genes on tumors in a more physiological context. It will help them better understand how different genes change the biology of small cell tumors, which could help point toward new therapeutic avenues, he said. They're also testing the potential roles that hundreds of different genes may play in drug resistance.

"The goal is to identify vulnerabilities associated with those [cancer] drivers and focus on the druggable vulnerabilities," MacPherson said. "And then develop a pipeline to reversing chemoresistance in a driver-specific manner."

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