Using a genetic signature to overcome chemotherapy-resistant lung cancer

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Drs. Elisabeth D. Martinez, Dr. John Minna, and Dr. Maithili Dalvi. Credit: UT Southwestern

Patients with non-small cell lung cancer (NSCLC) often respond to standard chemotherapy, only to develop drug resistance later, and with fatal consequences. But what if doctors could identify those at greatest risk of relapse and provide a therapy to overcome or avoid it?

Researchers at UT Southwestern Medical Center believe they have an answer: a 35-gene signature that identifies tumor cells most likely to

develop resistance to treatment. The study, published today in *Cell Reports*, points to a new pharmacologic approach to target chemo-resistant lung cancer and even prevent development of such resistance in the first place.

"Cancer relapse after chemotherapy poses a major obstacle to treating lung cancer, and resistance to chemotherapy is a big cause of that treatment failure," said study co-author Dr. John Minna, a Professor and Director of in the Hamon Center for Therapeutic Oncology Research at UT Southwestern. "These findings provide new insights into why resistance develops and how to overcome it."

Dr. Minna, with additional appointments in Pharmacology and Internal Medicine, also holds the Sarah M. and Charles E. Seay Distinguished Chair in Cancer Research and the Max L. Thomas Distinguished Chair in Molecular Pulmonary Oncology.

Investigators studied mouse and cellular models of NSCLC, a type of lung cancer that the American Cancer Society estimates accounts for 85 percent of all lung cancer cases in the United States.

"Previous studies have shown that up to 70 percent of those cancers develop resistance to standard therapy, such as the platinum-taxane two-drug combo that is often given," said study senior author Dr. Elisabeth D. Martinez, Assistant Professor of Pharmacology and in the Hamon Center. Both she and Dr. Minna are also members of UTSW's Harold C. Simmons Comprehensive Cancer Center.

Using long-term on/off drug cycles, lead author and former postdoctoral researcher Dr. Maithili Dalvi developed a series of cellular models of progressive tumor resistance to standard chemotherapy that ranged from very sensitive to highly insensitive. Next, the researchers identified genes commonly altered during the development of resistance across

multiple cell line and mouse models and identified a 35-gene signature that indicated a higher genetic likelihood of chemotherapy resistance.

"It's like a fingerprint for resistance," Dr. Martinez said, adding that it was predictive in both cells and mouse models.

Next they compared this resistance biomarker using genetic profiles from human tumors in their National Cancer Institute (NCI) lung cancer Specialized Programs of Research Excellence (SPORE) database at UT MD Anderson Cancer Center in Houston. The database contained information on patient outcomes and those who had been treated with the two-drug chemotherapy. The genetic fingerprint for resistance correlated with cancer relapse in NSCLC patients in the database, she said.

Researchers discovered that as cancer cells developed greater resistance to chemotherapy, they progressively made higher amounts of enzymes called JumonjiC lysine demethylases. Dr. Martinez said these enzymes facilitate resistance by changing the expression of - or turning on and off - genes.

"Cancer cells use these enzymes to change, or reprogram, gene expression in order to survive the toxic stress of the chemotherapy. By changing the expression of genes, the tumor cells can adapt and survive the toxins," she said.

Investigators then tested two potential drugs, both JumonjiC inhibitors. One of them, JIB-04, was found by UT Southwestern researchers in the Martinez lab during a small-molecule screen conducted at the National Center for Advancing Translational Sciences' Chemical Genomics Center in Bethesda, Maryland.

"I believe this is the first report of NSCLC tumors taking advantage of

multiple JumonjiC enzymes to reprogram gene expression in order to survive chemotoxic stress. In addition, and this is the most fascinating part: Dr. Dalvi found that greater chemotherapy resistance defines a new susceptibility to the JumonjiC inhibitors," she said. "The cancer cells develop a new Achilles' heel that we can hit."

Because the chemo-resistant cancer cells are dependent on JumonjiC enzymes for survival, inhibiting those enzymes returns cancer cells to mortality and vulnerability to cell death, she explained.

"We think these JumonjiC inhibitors have the potential to be used either to treat tumors once they become resistant to standard therapies, or to prevent resistance altogether," she said. "In our experiments these inhibitors appear to be much more potent in killing cancer cells than normal cells."

Later, researchers tested whether the Jumonji inhibitors JIB-04 or GSK-J4 prevented chemotherapy resistance. This strategy succeeded in cell cultures and partially prevented resistance in animal models, Dr. Martinez said.

Provided by UT Southwestern Medical Center