Researchers Score Against Drug-resistant Cancers

Drug-resistant lung cancer research funded by the American Lung A...

Two laser-focused and resourceful researchers are on a quest to eradicate lung cancer, and with support from the American Lung Association are learning how and why the most serious tumors resist drug therapy.

Their work elevates the science to yet another level, and continues the progress begun more than a century ago. Meet the remarkable scientists behind important and potentially life-saving discoveries.

Johnathan Whetstine, Ph.D., is an associate professor at Harvard Medical School and Massachusetts General Hospital Cancer Center in Boston and a recipient of the American Lung Association's Lung Cancer Discovery Award. He and his team are in the second year of this award that allows them to continue to investigate the nuances of drug-resistant lung cancer.

Not new to the challenges of lung cancer research, he started the Whetstine Lab at Mass General in mid-2007. "Our lab has been pursuing how the structure of DNA can be altered and how that in turn alters the drug-resistant states of cells," he says.

Working alongside Dr. Whetsine is Sweta Mishra, Ph.D., a postdoctoral research fellow in Dr. Whetstine's lab for almost a year. She completed her doctorate at the University of Texas, Health Science Center at San Antonio. Funded through the American Lung Association's Senior Research Training Fellowship, Dr. Mishra is studying how tumors differ at the molecular level. She focuses on the role of chromatin-modifying proteins.

The role of DNA in cancer

First, to understand their work, it helps to be familiar with the terms "DNA" and "cancer research," often used together. DNA, short for deoxyribonucleic acid, is hereditary material found in humans and most all other organisms. Almost every cell in our bodies has the same DNA. Most of it is located in the cell nucleus and contains our unique genetic code or information.

Chromatin is a complex of DNA and proteins that's also located in the nucleus of each cell. Chromatin helps prevent DNA damage and controls gene expression—the process by which information encoded in a gene is actually used.

It's important to note that DNA damage and abnormal gene expression contribute to cancer growth. Scientists believe that understanding such mechanisms might shed light on why cancer develops in the first place.

They're also studying genomic instability. It's a characteristic of most cancers which result from mutations or changes in DNA repair genes, and it also drives cancer development. Their goal is to develop more effective chemotherapy for cancer treatment.

Understanding the keys to a cure

"One of the main challenges in the cancer field is that we as researchers don't really understand the fundamental mechanisms that cause tumor cells to become drug resistant," says Dr. Mishra. They do understand that all successful cancer therapies are limited by the development of drug resistance.

Through their work, both researchers know that DNA content becomes changed in drug-resistant disease. Now they want to know if that process can be regulated or controlled. Doing so might mean a future where patients don't have to worry about their chemotherapy or targeted therapy no longer working after several years. It might mean that lung cancer may be considered a chronic disease rather than a life-threatening condition.

The scientists have uncovered a new mechanism that allows cells to "select a piece of DNA which has self-protective genes in it," Dr. Whetstine says. The process isn't random, but is driven by other genes and proteins, and it happens across different species, he says.

"We unexpectedly discovered that cells naturally use a 'program' to make extra pieces of DNA and when that occurs, they make drug-resistant genes," he says. "We found that natural biology mimics what the cancer is doing. It hijacks a process that's built into the cells, enabling cells to 'select' those drug-resistant genes."

Genes exist within DNA to help promote cancer or help protect the cancer cells, he says. More DNA can be made within the genes to in turn produce a protein that can either protect or help tumors grow.

"Our discovery highlights that this process doesn't have to occur randomly but can be 'directed' by enzymes within the cell," says Dr. Whetstine. "This process can occur naturally, or can be 'helped' to occur within tumors."

Think of this simple analogy, he suggests. "It's like having an extra pair of socks and being able to use them when needed."

Additionally, the pair's findings lend insights beyond lung cancer. "This helps explain how cells fundamentally control their DNA content and in turn, their response to the environment," he says.

Both scientists have also learned that a tumor's "microenvironment," such as hypoxia or low oxygen content, can also influence critical processes. "Knowing more about this might actually alter conventional chemotherapy and the way we treat the tumors," says Dr. Mishra.

Excelling with extra help

The researchers say they probably wouldn't be where they are without the support of the American Lung Association.

"It gives us an opportunity 'to skate on the edge' with research that may be difficult to fund through traditional mechanisms," Dr. Whetstine says. "The American Lung Association allows us to ask that very important question centered on the lungs, even as we develop an understanding of a fundamental principle that will impact many cancers."

It takes a village, and researchers have built one. "Now, it's no longer a scientist working alone," he says. "It's no longer a physician working alone. It's no longer an agency working alone, or a foundation. It's a team that's involved as we all 'go make a discovery'."

The two researchers know that their work doesn't just apply to patients. "By extending time, by providing us resources to push the envelope, what it's possible to do inevitably affects not only the patient but also the families," Dr. Whetstine says.

Opening doors to opportunities

Besides the funding it provides for research investigations, the American Lung Association supports the future rising stars and building a community of research by funding outstanding fellows including Dr. Mishra.

"This award gives her the opportunity to not only pursue her question, but to also demonstrate to the world that she can become funded—essential for anyone who wants to pursue research at a high level," says Dr. Whetstine.

Dr. Mishra agrees wholeheartedly. "The American Lung Association fellowship has greatly helped move my projects forward. Fortunately, by the end of this year, we will submit our research as a manuscript to then be published."

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