Chemical Toolkit Aids Study of Cancer Drug Resistance

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Cancer is extremely clever at finding ways to survive, so even the most successful new drugs tend to become less effective over time as the tumors develop resistance.

Often, cancer cells become resistant because of changes in the cells' genetic code, allowing them to counteract or sidestep the drugs' attack. But Jun Qi, PhD, of Dana-Farber Cancer Institute's Department of Cancer Biology, is focused on another source of resistance: so-called "epigenetic" changes that don't alter cancer cells' genetic makeup but activate gene activity — increased transcription — that spurts the cancer cells' growth.

"A major challenge in the field is that new drugs are working very well for three or four years, then drug resistance occurs," says Qi. "We realized the resistance can come from the epigenomic landscape. An increasing body of evidence suggests that non-mutational mechanisms contribute to the emergence of resistance… and this is often driven by epigenetic and transcriptional reprogramming."

"Our research focus is to combat this reprogramming using novel small molecules — targeting epigenetic proteins involved in these gene regulatory pathways," Qi explains.

Identifying strategies

Qi has developed a set of epigenetic tool compounds to identify the novel targets and potential therapeutic strategies for less-studied cancers and drug resistance mechanisms. The tool compounds include inhibitors (which block protein function), degraders (which remove proteins from cells), and probes used to explore the function of a targeted protein.

Qi and his colleagues are freely distributing the tool compounds with the aim of increasing the awareness of these tools and fostering collaborations within Dana-Farber and in the broader cancer field.

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Two recent publications should help raise that awareness. One study focused on rhabdomyosarcoma, a childhood cancer, the other on drug resistance in lymphoma.

For the study of rhabdomyosarcoma, reported in Nature Communications, the Qi team used a set of chemical probes to identify epigenetic molecules and circuits that increase the activity of genes involved in cancerous growth. The research also shed light on how drugs known as HDAC inhibitors might be used to treat cancers like rhabdoymyosarcoma.

The other paper, in Cancer Cell, described the use of Qi's tool compounds to unravel a mechanism of resistance to AB-199, or venetoclax, used to treat two types of B-cell lymphoma. Their experiments revealed that an important factor in resistance to venetoclax was increased activity of the protein MCL-1. Another factor was that some cancer cells that lost a portion of a chromosome containing the protein BCL2 — the target of venetoclax — rendering the cancer cells less vulnerable to venetoclax to become drug-tolerant "persisters." These leads suggest ways of using combinations of targeted drugs to treat persister lymphoma tumors to overcome drug resistance, say the researchers.

The "chemical toolbox" that Qi continues to develop has a number of advantages over other experimental methods, such as a faster readout of results. "The compounds can quickly identify where the drug resistance is taking place" in the interaction between cancer cells and drugs, he says.

Qi came to Dana-Farber in 2009, joining the laboratory of James Bradner, MD, who has since become president of Novartis Institutes for BioMedical Research. Qi was instrumental in developing a drug, named JQ1 after himself, to treat a variety of cancers. A derivative of JQ1 is now being tested in clinical trials.

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