Toward precision medicine for a rare blood cancer [1]

Discovery [2]

Mantle cell lymphoma, a cancer of immune system B-cells, accounts for approximately 6 percent of non-Hodgkin lymphomas (NHL) and is considered a rare disease. It's also a form of NHL with a poor overall prognosis. A new study reveals that MCL comes in two distinct varieties at a genetic level, potentially explaining why some cellular samples of human MCL responded to two targeted compounds while others didn't.

Working with lymphoma experts from Charité – Universitätsmedizin in Berlin and the BC Cancer Research Centre in Vancouver, Canada, Novartis scientists provide evidence of two related but mutually exclusive molecular signaling pathways at play in MCL cell lines. Their findings, published [3] online in Nature Medicine in December, could lead to the development of genetic biomarkers to predict which patients will respond to a particular targeted therapy. They might also help clinicians combat cancer in MCL patients with insufficient treatment options.

"The age of precision medicine has arrived for oncology," said last author Frank Stegmeier, a director in oncology research at Novartis Institutes for BioMedical Research (NIBR) in Cambridge, MA. "If we understand the molecular deregulation of each cancer, then we can tailor the treatment for patients to specifically target these deregulated pathways. This will minimize unnecessary toxicities and provide maximum benefit to patients. Our study provides significant insights into personalized treatment options for MCL patients."

Frank Stegmeier - Oncology at NIBR

The project began about two years ago with a large-scale pharmacological profiling experiment. Novartis scientists screened 16 compounds across 119 hematological cancer cell line models—including 10 MCL lines—from the Cancer Cell Line Encyclopedia, a publicly available collection of about 1,000 annotated cancer cell lines developed by the Broad Institute of MIT and Harvard as well as Novartis.

The results for the MCL lines were particularly interesting. When the NIBR researchers—working with Georg Lenz, a principal investigator at Charité – Universitätsmedizin—dosed the MCL cell lines with the compounds ibrutinib and sotrastaurin, they noticed that four of the lines were affected by the compounds while six were not. This observation spurred the team to investigate why the drugs worked well against some MCL cell lines and not others.

Both drugs hit targets in the NF-?B pathway, which is a pro-survival mechanism switched chronically to the “on” position in certain cancers. The researchers reasoned that chronic activation of the NF-?B pathway was driving cancer growth in the four lines affected by the drugs. But what was fueling cancer growth in the MCL cell lines without sensitivity to the compounds?

An investigational compound called AFN700 provided some clues. Like ibrutinib and sotrastaurin, AFN700 suppresses NF-?B signaling. Predictably, it blocked the growth of the MCL cell lines with sensitivity to ibrutinib and sotrastaurin. Unexpectedly, it also showed activity against the MCL cell lines resistant to the two drugs.

The collaborators examined protein expression levels to figure out what was going on. They discovered that a different branch of NF-?B, which is called the alternative pathway, is over-active in the ibrutinib resistant cells.

The team dove deeper, turning to sequencing data, and found that six lines have mutations that the team linked to this alternative pathway. AFN700 hits a protein that is common to both the classical and alternative pathways, which explains why it works in all 10 cell lines.

The team performed experiments in cells to confirm the role of the mutations they discovered, solidifying the link with the alternative pathway, which is initially activated by the protein kinase NIK. And they showed that inhibiting NIK in cellular and mouse models of MCL stymied the disease.

Then they confirmed the findings in MCL patient samples in collaboration with Randy

Gascoyne, a principal investigator and physician at the BC Cancer Research Centre in Vancouver. In sequencing 165 MCL patient samples, the team found mutations in TRAF2 and BIRC3—the genes linked to the alternate pathway—in 15% of cases.

“Ibrutinib is very active in mantle cell lymphoma, but until this Nature Medicine paper, we really didn’t understand why most patients would respond to the drug while a subset would not,” Lenz, who treats MCL patients, said.

The data can potentially explain why ibrutinib was active against about 70 percent of MCL cases in a clinical trial published [3] in t*he New England Journal of Medicine* in June 2013 without providing the same benefit to the rest of patients studied.

Targeted sequencing of TRAF2 and BIRC3 in MCL patients could be used to predict whether they will respond to inhibitors of the classical NF-?B pathway. Gascoyne aims to follow up on this research and perform such sequencing on MCL patients in a planned Phase II clinical trial. Unfortunately, there are no approved inhibitors to give MCL patients whose tumors show activation of the alternative NF-?B pathway. Yet he believes this research will spur efforts to discover inhibitors for this purpose.

Note: Ibrutinib is a product marketed by Pharmacyclics and Johnson & Johnson. Sotrastaurin is an experimental compound from Novartis.

Read the Nature article [3]

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