New biomarker identifies patients with aggressive lymphoma who don't respond to precision therapy
7 December 2020, by Steve Graff

A new biomarker discovered by a team that includes researchers from Penn Medicine identifies patients with an aggressive form of lymphoma unlikely to respond to the targeted treatment ibrutinib. It's a clinically actionable finding that will help guide physicians toward the right treatment for patients with activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL) who harbor these newly exposed mutations in the BCL10 gene.

The findings were presented during the plenary scientific session at the 62nd American Society of Hematology Annual Meeting & Exposition on Dec. 6 (abstract #3), Kojo S. J. Elenitoba-Johnson, MD, the Peter C. Nowell, MD, Professor in the Perelman School of Medicine at the University of Pennsylvania and Director of the Center for Personalized Diagnostics, serves as a co-author.

"This is a mechanism of resistance that was previously underappreciated," Elenitoba-Johnson said. "Ibrutinib would have been a candidate for such patients, but if they have these BCL10 mutations, another route for treatment should be prioritized."

Ibrutinib is a targeted therapy that blocks a protein called "Bruton's tyrosine kinase," which is part of a pathway that helps B cells thrive. Blocking BTK can make B cells, including cancerous B cells, die or prevent them from dividing. The drug has been shown to be useful in the treatment of relapsed and refractory forms of lymphomas and leukemias, but not all.

Mutations in BCL10, the researchers found, promote abnormal signaling pathways that allow cells to circumvent the drug's blockade.

The normal BCL10 binds to two other proteins known as CARD11 and MALT1 to trigger NF-kB signaling, which is important in normal B cell function. However, mutations in BCL10 subvert this pathway, and the mechanisms by which this is achieved are not well understood. The researchers discovered using a number of sophisticated techniques, including cyroelectron microscopy, that mutated BCL10 could be joining forces with other cellular culprits to drive lymphoma growth and resistance to treatment, but it wasn't clear what those were.

That's where Penn Medicine researchers came in, with their deep expertise in a technology known as mass spectrometry-based proteomic analyses, which drills down even further into the nuances of protein complexes. They identified new interactors—including NF-κB2 and TAB1—that showed how cells are capable of evading the drug through auxiliary signaling. If the process were a relay race, in a "normal" patient, the drug would knock the baton out of the first runner's hand to thwart cancer. But with these mutations, a runner from another team swoops in with a new baton to help finish.
"Cutting off the signaling up top would be immaterial because this protein has now acquired a new capability that subverts the mechanism by which the drug could effectively act as an inhibitor in lymphomas harboring these mutations," Elenitoba-Johnson said.

The findings add to the growing list of genetic drivers of cancers that continue to help inform treatment plans for lymphoma patients. DLBCL is the most common subtype of adult lymphomas, with more than 25,000 new cases a year in the United States. ABC-DLBCL is one of its most aggressive forms.

"Precision medicine is the goal, where individualized therapy, based on genetics and other factors, lets us treat patients with the right drug for the right disease at the right dose and at the right time," Elenitoba-Johnson said. "Identifying these new mechanisms strengthens that approach for patients with this type of lymphoma."

More information: 3 BCL10 Gain-of-Function Mutations Aberrantly Induce Canonical and Non-Canonical NF-Kb Activation and Resistance to Ibrutinib in ABC-DLBCL. ash.confex.com/ash/2020/webpro ... ram/Paper141363.html

Provided by Perelman School of Medicine at the University of Pennsylvania


This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.