Scientists leverage interference between signaling pathways for cancer treatment

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Markus Müschen, M.D., Ph.D., chair of City of Hope's Department of Systems Biology and The Norman and Sadie Lee Foundation Professor in Pediatrics Credit: City of Hope

In order for cancer to form in the human body, normal cells must acquire multiple mutations before they develop toward the disease. It was previously believed that these mutations acted in concert in the progression of cancer. But a new *Nature* study led by City of Hope's Markus Müschen, M.D., Ph.D., chair of the Department of Systems Biology and The Norman and Sadie Lee Foundation Professor in Pediatrics, uncovered a new aspect of this theory.

In a paper published today, Müschen and an international team of researchers outline their findings that individual mutations only promote progression toward leukemia if they converge on one single pathway. In addition, some mutations actually generate "noise" that drown out central elements of cancer development.

"Surprisingly, mutations that are not aligned with the central cancer pathway but instead promote growth and survival in divergent directions are counterproductive and even prevent overt transformation into cancer," said Müschen, who is the corresponding author of the new study. "The concept of multistep cancer progression suggested that acquisition of additional mutations would invariably promote cancer, but we found that many of these mutations, in fact, lead to a dead end and stop cancer progression rather than promoting it."

The team reached this conclusion after analyzing 1,148 patient-derived B cell leukemia samples to see how mutations either cooperated or antagonized each other. Current targeted therapies in cancer are based mainly on suppressing the principal driver of cancer, but the study's findings offer a previously unrecognized strategy to enhance treatment responses.

As a strategy for preventing drug resistance and relapse, Müschen and his colleagues explored an alternative approach based on reactivating suppressed pathways in order to interfere with the principal oncogenic driver and potentially amplify treatment responses.

"We have developed drug combinations that would mimic these effects," Müschen said. "Like a mutation that activates a divergent pathway, we found drugs to reactivate pathways that diverge from the central oncogenic driver to disrupt oncogenic signal transduction in these cells."

Müschen and his team are now testing various drug combinations.

"In these combinations, one drug directly inhibits the central oncogenic driver, while the second drug reactivates divergent pathways that were silenced during the transformation process," Müschen said. "If successful for leukemia, we may be able to test this approach for the treatment of other cancers."

More information: Lai N. Chan et al. Signalling input from divergent pathways subverts B cell transformation, *Nature* (2020). DOI: 10.1038/s41586-020-2513-4

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