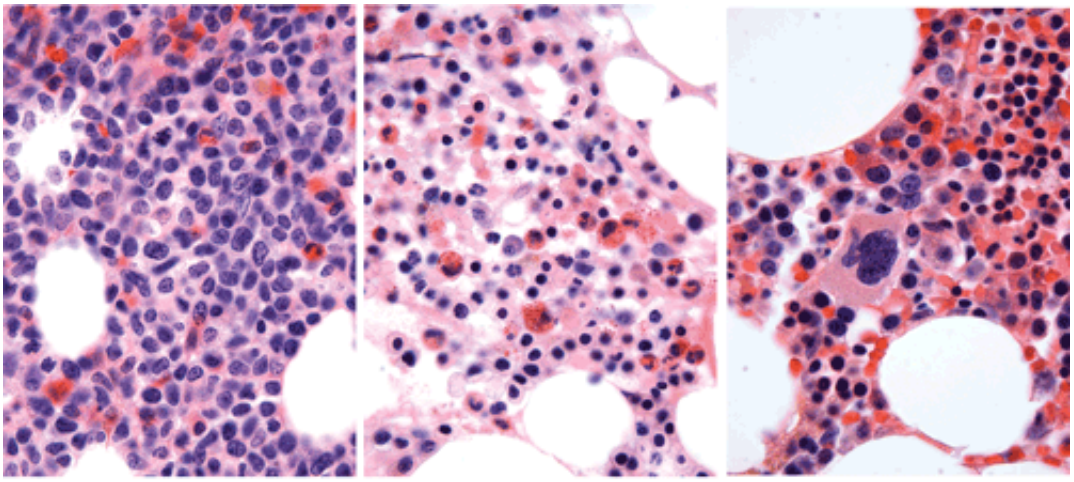
From molecular case studies: Genomics of exceptional responder to NOTCH inhibitor

October 6 2015



A histology staining of patient's bone marrow before (left), and after 4 weeks (middle) and 7 weeks (right) of treatment. The marrow contains mainly leukemic blasts prior to treatment that are subsequently cleared. Credit: Knoechel et al.

Normal T-cell development requires Notch signaling but hyperactivity can lead to cancer. Drugs that inhibit Notch, such as gamma-secretase inhibitors (GSIs), are currently being tested in different cancer types but clinical remission has yet to be reported. In a paper published in *Cold Spring Harbor Molecular Case Studies*, researchers describe an acute lymphoblastic leukemia (ALL) patient in which GSI treatment resulted in complete remission, suggesting that GSIs may hold therapeutic promise in ALL and other cancers.

The patient, a 53-yr-old male diagnosed with early T-cell precursor leukemia (ETP-ALL), was not responding to previous rounds of chemotherapy. At relapse, he was seen by physicians at Dana-Farber Cancer Institute and was enrolled in a clinical trial for the Notch inhibitor BMS-906024. He began to show immediate improvement and after three cycles of treatment received a blood stem cell transplant, and since has been cancer free for 19 months.

To determine the genetic basis for his exceptional response, researchers at the Dana-Farber Cancer Institute, Stanford University, Brigham and Women's Hospital and elsewhere performed targeted and whole-exome sequencing on his leukemic cells. They identified four potential mutations driving the cancer progression, including a novel mutation in the NOTCH1 gene resulting in hyperactive signaling. This mutated gene copy was also duplicated in the cancer genome, resulting in elevated expression. After treatment with GSI, the NOTCH1 mutation, along with two of the other mutations, were absent in the remission bone marrow.

Furthermore, the authors cultured the patient's leukemic cells to determine the molecular response to GSI treatment. Cells treated with GSI had greatly reduced levels of mutated NOTCH1 protein. RNA-seq analysis demonstrated that Notch target genes were sensitive to the treatment. Interestingly, however, a common oncogenic gene, MYC, was not sensitive to GSI. Epigenetic analysis determined that the enhancer driving MYC expression in the leukemic cells was not Notch-dependent, but rather BRD4-dependent, suggesting another possible therapeutic option for MYC-expressing tumors.

More information: *Cold Spring Harbor Molecular Case Studies*, molecularcasestudies.cshlp.org … ent/1/1/a000539.full

Provided by Cold Spring Harbor Laboratory