Genetic sequencing reveals drug resistance growth

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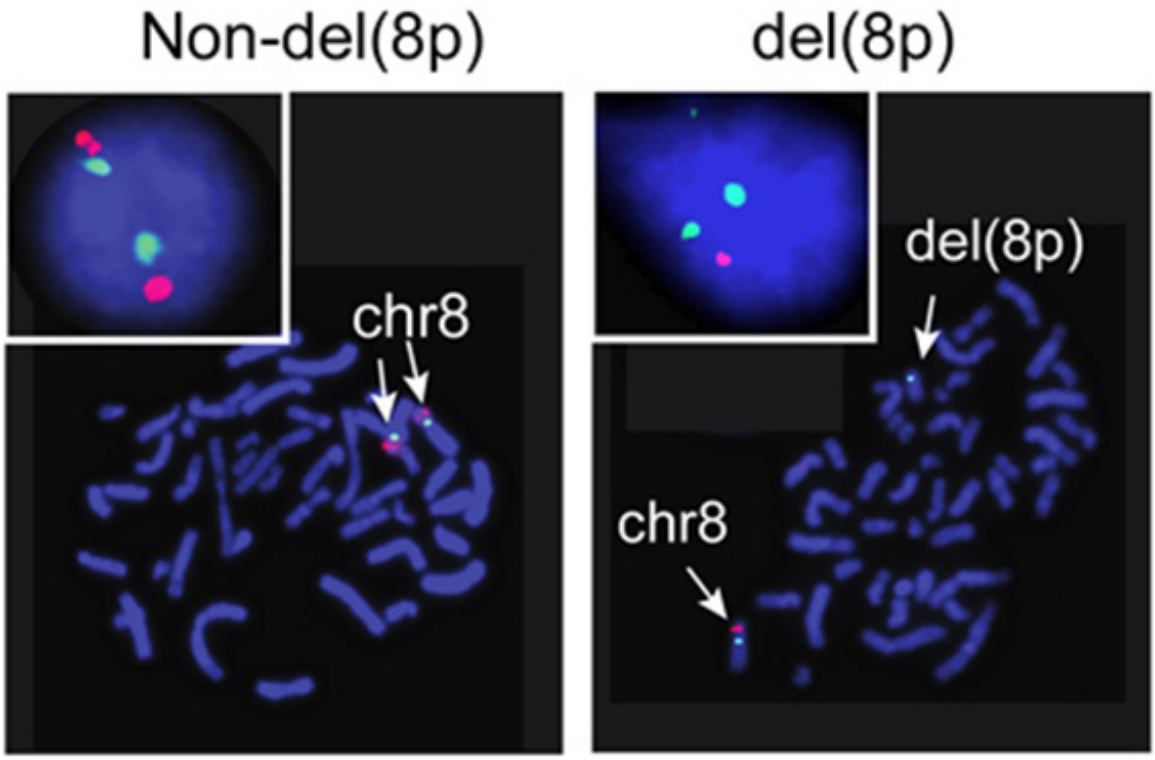

Microscopic image of the DNA of a leukemia cells - captured as chromosomes - illuminating the missing part of chromosome 8 (right insert), found in CLL patients with resistance to the targeted therapy ibrutinib. Credit: Weill Cornell Medicine

The rate at which genetically mutated cancer cells grow may help explain

why patients with a common form of leukemia develop treatment resistance, according to new research led by a Weill Cornell Medicine investigator. The findings demonstrate how mutations that arise before treatment begins can influence how the disease responds to therapies, and underscores the need to design regimens that can preempt resistance.

For their study, published May 20 in *Nature Communications*, the scientists investigated how some patients with chronic lymphocytic leukemia (CLL) – a type of cancer in which the lymph nodes make too many white blood cells – become resistant to the drug ibrutinib, which is used to treat the disease once other chemotherapy drugs have failed. They performed mathematical modeling of the growth rates of the sensitive and resistant cells, and discovered a small cluster of cancer cells survived ibrutinib therapy due to a genetic mutation present prior to treatment, allowing these ibrutinib-resistant cells to multiply and the disease to progress unabated. The findings could offer scientists a framework to guide the development of combination therapies that overcome drug resistance in CLL and in other cancers.

"In the future, this information will allow clinicians to devise a treatment plan adapted to the genetic differences seen among cancer cell populations," said Dr. Dan Avi Landau, assistant professor of medicine and of physiology and biophysics at Weill Cornell Medicine and a core member of the New York Genome Center. "Once we are able to characterize the spectrum of genetic changes that occur in cancer patients, we will be able to determine what combination of drugs could be used to eradicate the arising resistant cell populations."

The team of researchers, including members from M.D. Anderson Cancer Center, the Broad Institute and Harvard University, used blood samples from five patients with CLL – a form of leukemia the American Cancer Society predicts will account for nearly 19,000 new cases in 2016 – and performed genetic sequencing of their cancer cell DNA. To

assess the presence of genetic abnormalities, researchers took samples before and after treatment with ibrutinib.

In the study – supported by the National Institute of Environmental Health Sciences, the Burroughs Wellcome Fund 2015 Career Award for Medical Scientists, and the American Cancer Society – Landau developed a technique, for which a patent is pending, to calculate how fast the ibrutinib-resistant cancer cells multiplied, also known as their growth kinetics. With the growth kinetics data from each patient's cancer, the team predicted exactly when CLL would reoccur and which resistant cell populations would take over.

With support from the 2016 Sidney Kimmel Foundation Scholar Award and a grant from Stand Up to Cancer, Landau and his colleagues will continue to study the growth rates of these different cell populations in response to drug combinations.

"Being able to calculate cancer growth rates among resistant cells could be essential for cancer treatments in the future," said Landau, who is also a member of the Sandra and Edward Meyer Cancer Center and of the HRH Prince Alwaleed Bin Talal Bin Abdulaziz Alsaud Institute for Computational Biomedicine at Weill Cornell Medicine. "Since many patients eventually develop resistance to a drug, understanding the rate at which resistant cells grow in each individual case could provide insight for better treatments, leading to better patient prognoses."

Provided by Cornell University