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Study tracks leukemia's genetic evolution, may help predict disease course, tailor care

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Tumors are not factories for the mass production of identical cancer cells, but are, in reality, patchworks of cells with different patterns of gene mutations. In a new study, researchers at Dana-Farber Cancer Institute and the Broad Institute show, more fully than ever before, how these mutations shift and evolve over time in chronic lymphocytic leukemia (CLL) – providing a strobe-like look at the genetic past, present, and future of CLL tumors.

Their report, which will be published online today by the journal Cell, suggests that evolution holds the key to understanding why CLL often recurs after treatment, and to the development of better therapies. The study helps explain why patients with a seemingly similar disease often don't derive the same benefit from therapy, why CLL recurs faster in some patients than others, and why therapy itself may speed the recurrence of the disease.

"One of the biggest challenges that patients with CLL and their physicians face is how to deal with relapse," said study co-senior author, Catherine Wu, MD, of Dana-Farber. "It's been clear for some time that tumors are collections of different subgroups of cells, each with a particular set of gene mutations, and that, over time, some of these subgroups become more prevalent and some less. So the tumor that you initially treat can be quite different, from a genetic standpoint, from the tumor that recurs later on."

For this study, Wu and her colleagues used next-generation gene-

sequencing technology to chart changes in close to 100 samples of CLL tissue. "From there," Wu explained, "we began exploring how these different subgroups of cells influence the effectiveness of therapy. What can these subgroups tell us about how the cancer originated and developed, and how – and how long – it will respond to treatment before relapsing?"

Co-senior author Gad Getz, PhD, of the Broad Institute and Massachusetts General Hospital, and colleagues analyzed the genetic material in CLL tissue samples from 149 patients. Getz noted that the analysis was made possible due to the marriage of two tools his team recently developed. The first, a highly sensitive mutation calling method known as MuTect (concurrently published in Nature Biotechnology) can detect mutations present in a small fraction of cells. The second, ABSOLUTE (developed by a co-first author of this work, Scott L. Carter, PhD), uses the detected mutations as well as copy-number alterations to identify sub-populations within the cancer cells, and associates each mutation with the fraction of cancer cells that carried it.

"These tools opened a new window into the complexity of cancer and its evolution," said Getz. "This allowed us to ask which sub-populations of cancer cells increase or decrease with therapy and what happens when treating a patient that has a subset of cancer cells with additional cancer-driving mutations."

Rather than probing the entirety of the cancer cells' DNA, they focused just on the sections of DNA that hold code for making cell proteins. With technology capable of reading the genetic code letter by letter, they scoured the cells' DNA for mutations – or spelling errors – in specific genes. For 18 patients, they sampled CLL cells several years apart, enabling them to track changes in the cells' genetic makeup over time.

Their findings:

- By taking genetic "snapshots" of CLL in many patients – some newly diagnosed with the disease, some who had undergone lengthy treatment, some whose disease had recurred – researchers were able to trace changes in the mix of subgroups of cells over time. This enabled them to reconstruct, in effect, a genetic biography of a patient's disease, identifying mutations that cropped up early in the disease, as well as those that came later.
- Certain "driver" mutations – named for their ability to spur cancer formation and growth – tend to appear early in the disease's development, while others emerge over time. The researchers discovered that the initial driver mutations tend to be unique to malignancies that originate in immune system B cells (such as CLL), while those that arose later are often found in other malignancies.
- In some cases, subgroups of cancer cells that had a fairly minimal presence before treatment came to predominate after treatment. "One way to think of this is that therapy 'leveled the field,' reducing the size of all the subgroups to the same basic level," Wu remarked. "The subgroups were then on an equal footing in competing with one another for survival. The ones that originally were somewhat rare may have gained a competitive advantage."
- The instances where patients donated CLL samples several years apart proved particularly interesting. Cells from patients who received chemotherapy during those years underwent a great deal of genetic evolution, showing marked increases in some cell subgroups and decreases in others, whereas samples from patients who didn't undergo such therapy were remarkably stable. "This suggests that, in some patients, treatment can actually hasten the evolution of the disease and speed its recurrence," Wu observed.
- Researchers were able to identify the cell subgroups that became more prominent in the later stages of the disease. In patients

where these subgroups were particularly predominant, the disease was likely to worsen rapidly, requiring prompt therapy. "In other words, the faster the disease is evolving, the more likely it is to take an aggressive form," Wu explained.

- From a practical point of view, advanced "sequencing" technology – which analyzes genes into their most basic components – combined with new analytical tools offers a feasible way to scan a large number of tissue samples, which is critical for finding links between gene mutations and the features of the disease itself and its response to treatment. The researchers' decision to concentrate on the protein-coding portions of DNA enabled them to scan more than 150 samples at a reasonable cost and in a reasonable amount of time, Wu related.

"Our findings have important implications for the future of diagnostic programs for patients with CLL," said the study's co-first author, Dan Landau, MD, of Dana-Farber, the Broad Institute, and Yale Cancer Center. "They can help us better understand how to not only predict which patients are likely to relapse, but also predict the genetic makeup of the relapse and tailor our therapy to those specific future mutations. Perhaps more importantly, these data challenge us to understand cancer evolution better in order to develop novel therapeutic paradigms that address the cancer evolutionary landscape."

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