New Model of Leukemia Evolution Suggests Early Targetable Events

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Cancer arises through the acquisition of genetic mutations over time. During this process, mutated cancer cells diverge and make copies of themselves, giving rise to distinct lineages. By the time patients experience symptoms, their tumors contain a genetically diverse collection of cancer cells, each with an accumulation of mutations. If we could better understand the sequence of events that leads from a single mutation to a heterogeneous population of tumor cells, earlier detection and intervention might be possible. However, attempts to trace this evolution where it has already occurred (in model organisms, immortalized cell lines, or patient samples) face significant challenges.

Ideally, a cancer evolution model would start from the beginning—the first "driver mutation" that sets off the process of tumorigenesis. For the study of acute myeloid leukemia (AML), one of the most common blood cancers in adults, former Damon Runyon Innovator Eirini Papapetrou, MD, PhD, and her colleagues at Icahn Mount Sinai have created just such a model. They began with a group of induced pluripotent stem cells—ordinary cells that have been reprogrammed into stem cells. Then, using the gene editing tool CRISPR, the team introduced one, two, or three mutations into the stem cells to create lineages that capture the early stages of leukemogenesis: clonal hematopoiesis, myelodysplastic syndrome (MDS), and finally, AML.

By analyzing the genome of the cells in each stage, the researchers were able to identify what changes drive the progression of leukemia. They found that the earliest adverse changes involved genes related to inflammation and innate immunity, and further, that targeting these pathways was effective in all disease stages. These results suggest a promising avenue for early-stage intervention in MDS and AML, diseases that have thus far eluded effective treatment.

Understanding what causes disease progression is crucial for early diagnosis and intervention, but because cancers evolve rapidly, researchers have struggled to pinpoint the exact molecular changes occurring at each stage. Papapetrou's team has not only illuminated major events in leukemogenesis, but also demonstrated a means of pressing "pause" at key moments, potentially allowing researchers to watch other cancers unfold in slow motion as well.

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