MedicalXpress

Open chromatin profiling key to identifying leukemia cells of origin

July 11 2016

Every cancer starts with a single cell, and Jackson Laboratory (JAX) researchers have found a precise and reliable way—whole-genome profiling of open chromatin—to identify the kind of cell that leads to a given case of leukemia, a valuable key to cancer prognosis and outcome.

"Knowing the cell of origin of cancer cells can provide insight into tumor subtypes and possibly diagnostic and therapeutic benefit," says JAX Assistant Professor Jennifer Trowbridge, Ph.D., the lead author of the study published on July 11 in *Nature Communications*. "But existing methods to identify cell of origin from bulk tumor cell samples have been unsuccessful."

Chromatin is the material in the nucleus of the cell that condenses to form chromosomes during cell division, and consists of DNA, proteins called histones and RNA. Every type of cell has a characteristic chromatin structure that includes closed chromatin, which is tightly wound around nucleosomes and is relatively inactive, and open chromatin, looser stretches of the material that interact with regulatory elements encoded in DNA.

Trowbridge hypothesized that analyzing open chromatin in bulk tumor cells could provide a possible improved method to identify cancer cell of origin because of the cell-type specificity of chromatin structure.

Her lab worked with a mouse model of acute myeloid leukemia (AML) driven by expression of MLL-AF9, a fusion oncogene formed by a

chromosome translocation between human chromosomes 9 and 11. They began with five distinct, normal cell types found in the bone marrow in both mice and humans: long-term hematopoietic stem cells (HSCs), short-term HSCs, multipotent progenitors, common myeloid progenitors and granulocyte macrophage progenitors. The AML that developed from these different cells of origin had different penetrance and aggressiveness when engrafted in mice, with the stem cell-derived lines being the most aggressive and the committed progenitor lines the least. These patterns were also reflected in the frequency of leukemia-initiating cells in each cell line, with HSCs having the highest frequency and committed progenitors having the lowest.

To profile the open chromatin in these distinct AML samples, and compare them to open chromatin patterns in normal cells, Trowbridge collaborated with Duygu Ucar, Ph.D., an assistant professor at JAX who develops computational models to study gene regulation including chromatin structure. Together they identified open chromatin signatures and gene expression patterns in AML samples that may allow stem cell-derived AML to be distinguished from progenitor cell of origin AML.

These results bear out indications in human data that the stage of a progenitor cell when it becomes transformed to leukemia has an impact on its clinical progression, with earlier-stage cell of origin cancers being more aggressive.

The researchers note that, with further study of open chromatin in normal human stem and progenitor cell types as well as AML patient cohorts, this profiling approach will identify precise regions with prognostic significance based on cell of origin; in other words, a valuable human cancer biomarker.

Moreover, Trowbridge says, the collaboration between her lab and Ucar's—between wet-bench and computational scientists with

complementary strengths in mouse modeling and human genomics—is a highly promising model for future discovery.

"This study would not have been feasible without close collaboration with our computational colleagues that have great expertise in human genomics. This study took advantage of cutting-edge genomic and genome sequencing technologies that were new to us, and allowed us to rapidly extract the maximum value from these technologies, integrate and compare our findings to human genomic data, and reveal novel underlying biological mechanisms with the most promising translational relevance that we will continue to study."

More information: *Nature Communications*, DOI: 10.1038/NCOMMS12166

Provided by Jackson Laboratory