Scientists discover a unique mechanism for a high-risk leukemia
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A research team led by St. Jude Children's Research Hospital scientists has discovered details of how the abnormal breakage and rearrangement of chromosomes in white blood cells triggers a particularly aggressive form of acute lymphoblastic leukemia (ALL). Such leukemias are cancers of white blood cells, in which genetic mutations trigger overproduction of immature cells, called lymphoblasts.

The discoveries of the malfunction underlying the type called "Ph-like ALL" will aid in designing treatments for the leukemia, researchers said, and also offer useful lessons for investigators studying similar leukemias and other types of cancer.

The researchers, led by corresponding author Charles Mullighan, M.B.B.S., M.D., a member of the St. Jude Department of Pathology, published their findings in the February 8 issue of the journal Cancer Cell. First authors on the paper were Ilaria Iacobucci, Ph.D., a postdoctoral fellow in Mullighan’s laboratory, and Yongjin Li, Ph.D., in the laboratory of author Jinghui Zhang, Ph.D., chair of the St. Jude Department of Computational Biology.

Although the investigators had previously identified an abnormal chromosome rearrangement in Ph-like ALL, little was known about the biological effects of that rearrangement. Iacobucci and colleagues set out to pinpoint those effects by studying human leukemic cells and mouse cells engineered to mimic the disorder.

Genomic analysis revealed the details of four distinctly different chromosomal rearrangements in the leukemia. All resulted in a truncated version of a gene called the erythropoietin receptor (EPOR) gene, and all produced the same outcome—driving the white blood cells to proliferate out of control. Li developed and applied the genomic analytical method used to define the truncations.

"To our knowledge, this is a previously unknown mechanism for leukemia," Mullighan said. "Our search of cancer genomic data has shown that there are many other examples of chromosomal rearrangements that alter genes' structure, but this type—where a truncating rearrangement leads to activation—is new."

In analysis of cells from patients with ALL, Iacobucci found the characteristic rearrangements in all the leukemic cells, suggesting these changes were fundamental to the development of cancer. And in experiments with mice, Iacobucci also showed that introducing the mutant receptor in blood cells gave rise to leukemia.

Importantly, Iacobucci and collaborators found the
chromosomal alterations arise early in the
development of the leukemia and persist as the
disease progresses.

"That finding was important because it suggests
that treatments for this leukemia targeting this
receptor won't just impact a subset of the leukemia
cells, allowing others to keep proliferating,"
Iacobucci said.

Mullighan said the group's findings will significantly
aid design and testing of treatments for Ph-like
ALL, including trials being developed by the
Children's Oncology Group (COG) and St. Jude.
The researchers expect that these trials will
commence in the near future, because drugs that
inhibit the over-activated biological pathway in the
leukemia already exist and are widely used to treat
other cancers. In fact, Iacobucci's experiments with
both engineered mouse cells and human leukemic
cells showed that using one of these drugs,
ruxolitinib, inhibited the out-of-control machinery.

The researchers also cited the case of an adult
patient at MD Anderson Cancer Research Center,
Houston, whose genetic analysis revealed EPOR-
rearranged ALL. That patient had not responded
significantly to other chemotherapy drugs, but when
given ruxolitinib, showed a major drop in leukemia
cells.

In experiments with leukemic cells, Iacobucci also
found that ruxolitinib worked synergistically to
enhance the effectiveness of three widely used
traditional chemotherapy drugs—dexamethasone,
vincristine and daunorubicin.

"We think these findings provide a useful road map
for planning more accurate testing of combination
chemotherapies," Mullighan said.

Of the potential for aiding clinical trials, co-author
Stephen Hunger, M.D., of Children's Hospital of
Philadelphia, said: "These findings expand the
number of ALL patients who should be amenable to
precision medicine therapies that add targeted
inhibitors to chemotherapy for ALL patients with
specific genetic changes in the leukemia cells."

Hunger said COG has developed a clinical trial
testing this strategy with ruxolitinib, which will begin
treating patients in mid-2016. Based on the results
of this St. Jude-led study, he said, the trial will
include children with ALL and EPOR
rearrangements. COG is a federally supported
clinical trials group focused exclusively on
childhood cancer.

More broadly, Mullighan said the findings highlight
the complexity of the chromosomal rearrangements
underlying the many types of ALL.

"These findings drive home the point that we are
dealing with a complex genomic landscape. Each
one of these rearrangements is potentially its own
entity, and each one merits its own detailed study.
You can't just map a rearrangement and assume
that it will produce the same mechanism in all
patients that will yield to the same treatment,"
Mullighan said, adding that "meticulous, detailed
genetic sequencing of the cancer cell genomes is
required to tease apart the subtle differences
among closely related cancers. Such sequencing is
also critical for definitive diagnosis of the cancers."

Mullighan emphasized the importance of such
detailed analysis in all cancers. "Often a lot of that
data generated by whole-genome sequencing may
not have been mined comprehensively, because
such rigorous analysis is very difficult. But to fully
understand these tumors, you have to look at large
numbers to make correlations; and to really
understand the driving mechanism, you have to find
the recurrent biological changes in the tumors."

Provided by St. Jude Children's Research Hospital