

Researchers prove that leukemias arise from changes that accumulate in blood stem cells

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(Medical Xpress)—Imagine that a police bomb squad comes upon a diabolically designed bomb controlled by a tangled mass of different wires, lights and switches, some of which have a real function while others are decoys. The police don't know how to begin defusing the bomb because they don't know which parts are important. Then imagine the police discover the bomb-making factory and are able to see hundreds of these bombs at various stages of construction. With this information, they can reconstruct how the bomb was put together, and therefore how to disarm it.

For a team of researchers at the Stanford University School of Medicine, the bombs they need to defuse are killer leukemias. The researchers report that they have used advanced techniques to survey what's in the "bomb factory:" the [stem cells](#) that produce all blood cells. In the process, they have proven a controversial theory that [blood cancers](#)—and perhaps all cancers—arise only when mutations accumulate over long periods of time in stem cells.

The research, published Aug. 29 in *Science Translational Medicine*, also sets the stage for the discovery of more effective therapies for defeating deadly cancers.

People with acute leukemias—cancers of the blood—are especially difficult to cure. Although doctors can drive leukemias into remission with chemotherapy, most of these cancers eventually come roaring back. About 60 percent of those who get [acute myelogenous leukemia](#) will

ultimately die from it, a statistic that has improved little in the past 30 years.

Cancer is caused in part by [genetic mutations](#), but [cancer cells](#) are often full of these mutations, some of which are important and some not.

"Each cancer-causing mutation is potentially a [therapeutic target](#) because we might be able to fix or block it, but we have to know which mutations to focus on," said Ravi Majeti, MD, PhD, assistant professor of hematology and a co-principal author of the paper. His fellow principal co-authors are bioengineering professor Stephen Quake, PhD, and professor of pathology Irving Weissman, MD, who directs Stanford's Institute for Stem Cell Biology and Regenerative Medicine and the Ludwig Center for Cancer Stem Cell Research and Medicine at Stanford.

The researchers decided to test a hypothesis Weissman made more than a decade ago: That the progression from a normal stem cell to a [leukemia](#) stem cell occurs mostly in blood stem cells.

Weissman hypothesized that rare mutations and gene translocations accumulate in a line of blood stem cells to the point that the cancer or leukemia can break free of growth constraints and spread, eventually leading the altered blood stem cell to produce a progenitor cell from which leukemia arises. This hypothesis was investigated by graduate students Max Jan and Ryan Corces-Zimmerman, and postdoctoral scholar Thomas Snyder, the three co-first authors who conducted genetic analyses of 80-500 individual blood stem cells from each of six leukemia patients.

In the leukemia patients, even normal-seeming blood stem cells had one or more mutations because the cells were part way through the process of accumulating the mutations and other heritable changes in gene expression to become highly malignant. When the researchers compared

mutations in these seemingly normal blood stem cells with the [leukemia cells](#), they could reconstruct exactly which mutations led to the leukemia, and the order in which the mutations arose. They did this by looking for blood-forming stem cells with a single mutation, which they knew must be the first, then finding other stem cells with that first mutation plus one other, which they could then identify as the second. They continued to do this until they found examples of stem cells at each stage of mutation accumulation, leading up to the full set of mutations found in the actual leukemia cell.

The research confirms a once controversial theory. The traditional view has been that any blood cell could turn cancerous if it picked up the "right" mutations. Stanford scientists like Weissman have suggested that, in reality, only blood stem cells could accumulate enough of the those mutations to become cancerous. That's because when blood stem cells divide into two, one cell retains its stem cell properties in order to self-renew, while the "daughter" cell continues to divide. The blood stem cells are therefore present throughout life, while the stem cells' progeny have life spans from days to weeks only.

"The natural mutation rate is slow enough that only the stem cells are around long enough to accumulate all of the necessary mutations and other inherited changes in gene expression to develop the cancer," said Weissman. "I guarantee that in any room there are people who have [blood cells](#) with a cancerous mutation, but it doesn't matter because in almost every case those cells die out naturally before they get the whole set of mutations that will give rise to an actual leukemia."

Majeti, who is also a member of the Stanford Cancer Institute and the Institute for Stem Cell Biology and Regenerative Medicine, pointed out that having the correct model of how leukemias arise is important because it helps determine what kind of therapy might be most effective. "Because relapse is a clinical problem, we need to know if chemotherapy

has somehow not killed all the leukemia cells, or perhaps it did kill all the leukemia cells, but new leukemias are arising from this pool of stem cells with preleukemic mutations," Majeti said. "In the first case, we would want to do a better job of killing the leukemia cells, but in the latter case, for some patients it wouldn't matter how well you do at killing leukemia cells if you don't eliminate the mutated blood stem cells." The next phase of the team's research will focus on answering such questions, he added.

And although the research deals with leukemia, the implications could be much broader, Weissman said. "This confirms the hypothesis that for leukemias, all of the early mutation events occur in blood-forming stem cells, but it opens the possibility that the same will be true for other cancers, and perhaps all cancers. The progression to the cancer might occur in the normal stem cells of any particular tissue, and the cancer would only emerge as the full set of [mutations](#) accumulate."

The leukemia findings are not only significant medically, but also showcase the benefits of conducting interdisciplinary research, said Quake, who located part of his advanced bioengineering research group to Stanford's Lokey Stem Cell Research Building so that studies like this could be done more often. "This research highlights how advances in high technology and advances in stem cell research can complement each other to address difficult problems, such as human leukemias, which could not be answered by technology or medicine alone," he said.

Provided by Stanford University Medical Center

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