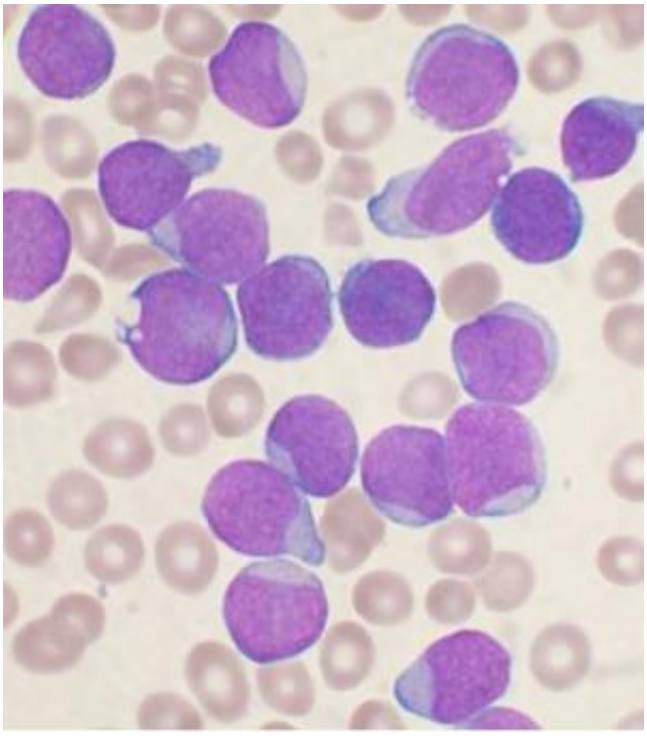
Childhood leukemias forged by different evolutionary forces than in older adults

January 11 2016



A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

For half a century, cancer researchers have struggled with a confusing paradox: If cancer is caused by the occurrence and accumulation of cancer-causing (oncogenic) mutations over time, young children should get less cancer as they have fewer mutations. Why then do young children have a higher incidence of leukemia than teenagers and young

adults?

A University of Colorado Cancer Center paper published today in the *Proceedings of the National Academy of Sciences* proposes a solution. Using a computational model describing the population dynamics of blood stem cells that give rise to leukemias, Drs. Andrii Rozhok, Jennifer Salstrom and James DeGregori provide evidence that the evolutionary force of genetic drift contributes to the ability of cancerous cells to overtake populations of healthy cells in young children. In contrast, genetic drift contributes almost not at all to leukemia formation in adults.

"Basically, leukemia risk early in life may be more dictated by chance than by the typical 'survival of the fittest' that characterizes leukemia formation in older adults," says James DeGregori, PhD, associate director for basic research at CU Cancer Center and the paper's senior author.

In previous work, the DeGregori lab has shown that the inevitable tissue declines associated with aging benefit blood stem cells (HSCs) with mutations that allow them to better adapt to the new ecosystem. (Very similar to how organisms have adapted to changes in earth's climate and landscape over time.) In contrast, the ecosystem of young tissue favors healthy cells - optimized by millions of years of co-evolution, most mutations make cells less fit for the ecosystem of young, healthy tissue and lead to purging of mutant cells from the tissue.

However, Rozhok and colleagues made a surprising discovery: Despite the ability of young tissue to select against cells with cancer-causing mutations, the computational model showed increased proportions of specific, mutation-bearing HSCs in the first few years after birth. Strikingly, they showed that these populations of mutated cells were not dependent on the effect of the mutation on cell fitness - these mutation-

bearing cells were not more fit than healthy cells without these mutations. Instead of the survival-of-the-fittest form of natural selection that drives the evolution of cancer in older adults, there was another force at work.

In fact, they discovered two factors that influence the development of early-life leukemia: the small HSC pool size at birth and the high rate of cell division necessary for body growth early in life.

It's easy to understand how more cell divisions early in life create greater risk; mutations largely happen during cell divisions, so more cell divisions will mean more mutations. This in turn increases the risk that some of these mutations could contribute to leukemia development.

But what about the small HSC pool size? Thus far, we've talked about two evolutionary forces: mutation and selection. But there is a third factor, often overlooked, that is critical in evolution. It is drift. Drift is the role of chance - the possibility that despite being less fit, an animal, organism or blood stem cell with cancer-causing mutation will survive to shift the genetic makeup of the population.

Importantly, the influence of drift is greater in small populations.

"Imagine if you flip a coin 10 times. You would not be surprised if 7 or more out of 10 flips gave you heads (in fact, the odds are about 1 in 6). But if you flipped the same coin 1,000 times, the odds of getting 700 or greater heads would be much smaller (less than 1 in a million)," DeGregori says. "Basically, the more trials we do, the less chance plays a role."

The same is true in stem cell pools. In small stem cell pools, such as for HSC pools very early in life, drift (chance) becomes much more important as a lucky genotype may end up with a larger share of the total

HSC pool than warranted by its fitness status. If this lucky cell clone happens to have a mutation that can start the HSC down the path towards being leukemic, then this drift-driven expansion should increase the risk of leukemia by increasing the number of HSCs with this mutation.

"Thus, early somatic evolution in HSC pools is significantly impacted by drift, with selection playing a lesser role," the paper writes.

Now consider the impact of drift as the HSC pool grows along with an infant's body to reach adult size. Just as more coin flips decrease the role of chance, so does the larger HSC pool size decrease the role of drift in the success of particular cells in the tissue. In addition, as the pool size reaches its maximum, the HSC division rate slows to a crawl (as these stem cells enter the maintenance rather than growth phase). With a landscape of healthy, youthful tissues and low rates of mutation due to low cell division rates, the odds of leukemia diminish.

"With a large population of healthy cells optimized to young, healthy tissue, the ability of mutations, including cancerous mutations, to drive uncontrolled cell proliferation is reduced," DeGregori says.

However, we did not evolve to live forever. The model shows that in old age, tissue decline promotes selection for adaptive mutations, leading to the expansion of potentially oncogenic HSC clones that will again increase the risk of leukemia. Thus this paper shows that in early life, leukemias are driven by mutation and drift whereas in later life, leukemias are driven by mutation and selection.

"We show that leukemias of children and older adults are different diseases, forged by different evolutionary forces, and propagated under different circumstances," DeGregori says.

Importantly, this understanding raises the possibility of a new approach

to cancer treatment: Could we manipulate the parameters of evolution for cells within our bodies? Could we manipulate the tissue ecosystem to decrease cancer risk? Considering our bodies as ecosystems that select against or allow the development of cancer offers a new avenue for combatting the disease.

More information: Stochastic modeling reveals an evolutionary mechanism underlying elevated rates of childhood leukemia, *Proceedings of the National Academy of Sciences*, www.pnas.org/cgi/doi/10.1073/pnas.1509333113

Provided by University of Colorado Denver