Mutations need help from aging tissue to cause leukemia

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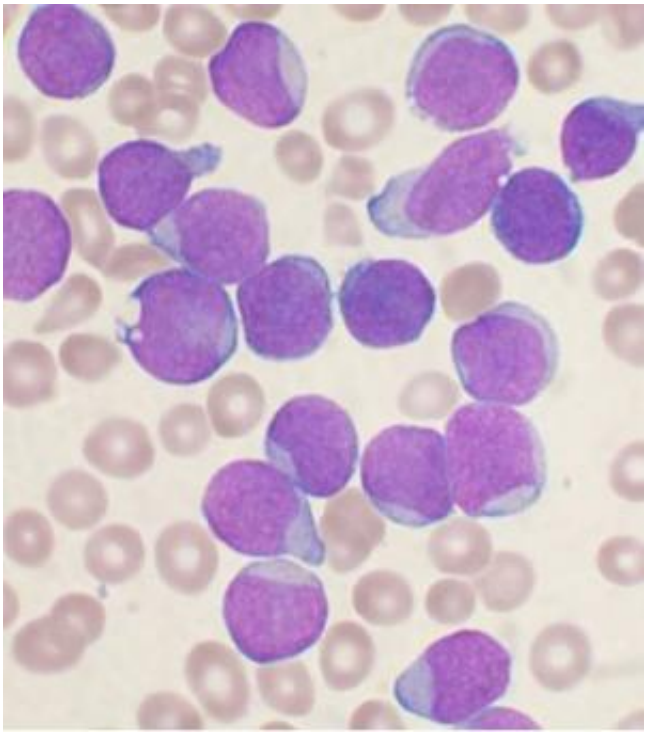

A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

Why are older people at higher risk for developing cancer? Prevailing opinion holds that, over time, your body's cells accumulate DNA damage and that eventually this damage catches up with the body in a way that causes cancer. A University of Colorado Cancer Center study published today in the journal *Aging* shows that this prevailing opinion is

incomplete. In addition to DNA damage, cancer depends on the slow degradation of tissue that surrounds cancer cells, something that naturally comes with aging.

"It's really all about natural selection and survival of the fittest," says James DeGregori, PhD, investigator at the CU Cancer Center, professor of Biochemistry and Molecular Genetics at the CU School of Medicine, and the paper's senior author.

"When you're young, healthy cells are optimized to the surrounding tissue - they're the 'fittest'," DeGregori says. "At that point, any mutation that affects function makes a cell less fit, so cells with mutations, even cancer-causing mutations, are out-competed by the young, fit, healthy cells. But when the tissue landscape changes with aging, healthy cells may no longer be optimized to their surroundings. In this aged landscape, mutations may actually make certain cells better, allowing them to out-compete the normal cells and form tumors. That's why older people get cancer."

Working in the DeGregori Lab, postdoc and first author Andrii Rozhok, PhD, created mathematical models of just this kind of natural selection in hematopoietic or blood cells. Like predicting the weather, Rozhok combined several variables into a model and then asked how well the model could predict what we see in the real world. For example, in the case of weather, accurately taking into account barometric pressure and the calendar day could predict a snowstorm. Similarly, if you were to believe prevailing opinion, you'd say that mutation accumulation would predict leukemia development. When Rozhok plugged only mutation variables into his model, however, there was poor fit. That is to say, the model could not accurately predict stem cell changes over time or leukemia development.

"We knew mutations would play a role, perhaps even a big role, but it

became clear there was something else going on. We had been looking inside cells for the causes of cancer, but that wasn't enough. There was something happening outside the cells that mattered, and that something is what allows cancer to form," DeGregori says.

Rozhok and colleagues then added more variables to the model to account for microenvironmental tissue decline. Suddenly, there was a much better fit. The new model, driven by age-related changes in stem cell fitness and behavior, accurately predicts the point at which a cancer cell might out-compete the normal cells and become a leukemia. Importantly, the model demonstrates that the systemic processes accompanying general tissue decline with age have a crucial power in governing cancer cell fates and the odds of developing cancer.

"We'd always thought the tissue landscape was important, but we didn't know how important," DeGregori says. He points out that natural selection only "cares" about the human body until it passes reproductive age. "We have programmed maintenance that takes care of our bodies and keeps us fit until around age 40. At that point, our maintenance program gets lazy. Our tissue landscape starts to change, and unfortunately it changes in ways that allow cancer cells to out-compete normal cells."

In all, "We show that mutations, although necessary, cannot promote blood cancer development without an age-altered tissue microenvironment," the researchers write.

"This implies that in addition to research and drug development aimed at the genetic mutations associated with cancer, we need to work on maintaining the fitness of our tissue landscape in order to prevent cancer cells from taking over. Natural selection has provided us with a very effective mechanism to accomplish this maintenance until middle age; what comes after may be up to us," DeGregori says.

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