Natural selection and inflammation may hold key to age-associated cancer risk

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Curtis J. Henry, Ph.D., and CU Cancer Center colleagues show age-associated inflammation changes the tissue ecosystem in a way that lets cancer cells out-compete their healthy rivals. Credit: University of Colorado Cancer Center

The incidence of cancer increases with age. Conventional wisdom blames this on age-dependent accumulation of cancer-causing mutations. A University of Colorado Cancer Center study published in the *Journal of Clinical Investigation* tells another story: healthy cells are optimized for the ecosystem of healthy tissue; changes in this tissue ecosystem leave room for another, fitter "species" to emerge; inflammation frequently (but not necessarily!) associated with aging is a common mechanism of tissue disturbance that allows cells with cancer-causing mutations to out-compete their healthy rivals; this leads to a shift in the dominant population from healthy to cancerous cells.

"Our previous studies have computationally modeled the development of cancer driven by natural selection and now we can see it in mouse models," says Curtis Henry, PhD, research instructor at the CU Cancer Center and co-corresponding author of the paper, with James DeGregori, PhD, associate director for basic research at CU Cancer Center.

The paper focuses primarily on the "ecosystem" of B-cell progenitor pools, the cells that create one type of white blood cells - the cells that, when altered, can give rise to leukemia. The paper's central question is what allows a population of healthy B-cell progenitors to be replaced over time with a population of cancerous B-cell progenitors?

"We chose to focus on the role of inflammation in the bone marrow - one of the hallmarks of age-associated tissue changes - where these B-cell progenitor pools live," says Henry.

Importantly, the group showed that inflammation hurts the growth and maintenance of B progenitor cells.

"If that were the end of the story, we might only see a slower replenishing of white blood cells in older people," Henry says. But that's not the end of the story. In fact, cancerous mutations tend to alter cells in

ways that help them survive conditions of inflammation in bone marrow.

"Suddenly, the healthy cells that were the fittest are no longer the most fit. Because the tissue changed, cancer cells have a selective advantage," Henry says.

They show this inflammation-driven natural selection in mouse models. Specifically, the group worked with mice engineered to prevent inflammation. How would healthy and leukemia-initiated cells fare in these conditions that limit the effects of inflammation?

"Basically, without the effects of inflammation, B-cell progenitor pools stayed fit," Henry says.

Stopping inflammation reduced the ability of cells expressing the oncogene NRAS from taking over the bone marrow niche.

Cancer has been seen as an inevitable risk in the elderly - more time equals more chances for genetic mutations to kick-start diseases. But this line of study shows that increasing cancer risk may not be inevitable. Instead of simply being a matter of the passage of time, cancer development in aged populations may be partially dependent on inflammation-associated tissue changes.

"Despite the fact that cancer is largely a disease of old age, almost all cancer modeling in mice employs only young mice. This is based on the view that finding the genetic mutation that causes cancer should be enough to understand the disease," DeGregori says.

In these studies, the group instead tested both young and old mice. And in these studies, the older mice were more likely to develop leukemia, but only in the presence of age-associated inflammation. If age-associated inflammation was blocked, older mice were no more likely

than young mice to develop leukemia.

The work also implies that stopping the effects of inflammation on tissue could stop cancers from forming. Many drugs exist to reduce inflammation. For example, the entire class of non-steroidal, anti-inflammatory drugs (NSAIDs) has recently been demonstrated to reduce cancer incidence in humans. Still, inflammation is a critical program for our bodies, used, for example, to fight infections, and more work will need to be done to understand how to "tune" inflammation in the elderly to maximize beneficial effects while minimizing negative effects such as on cancer development.

"We believe that these studies have major implications for both aging (why do our tissues undergo functional decline in old age?) and cancer (why is cancer largely restricted to old age?). While it's premature to suggest that people should take medicines to fight inflammation as they age, we believe our results warrant further study into this potential strategy to combat the age-associated increase in cancer risk," Henry says.

More information: *Journal of Clinical Investigation*, www.jci.org/articles/view/83024

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