Josh Baxt
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Epigenetic Changes May Explain How Aging Increases Blood Cancer Risks

It is widely known that aging is the single biggest non-modifiable risk factor for cancer. Now, a new study conducted by researchers at Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine sheds new light on the factors associated with cellular aging and cancer risk.

From left, Hsuan-Ting (Emily) Huang, Ph.D., Maria Figueroa, M.D., first author Emmalee Adelman, Ph.D., and Alejandro Roisman, Ph.D., in front of the whiteboard on which they

brainstormed the research project.

The study was led by Sylvester's Maria Figueroa, M.D., associate professor of human genetics, and funded by the Leukemia & Lymphoma Society. It found that epigenetic changes in hematopoietic (blood forming) stem cells, as people age, may contribute to acute myeloid leukemia (AML) and possibly other blood cancers. The researchers' findings were published on May 13 in the journal *Cancer Discovery*.

While acute myeloid leukemia (AML) has long been linked to aging, scientists still don't fully understand the mechanisms that go awry. The researchers wanted to test whether changes in the epigenome – molecular markers that help cells determine which genes get turned on and off – could play a key role in age-related blood cancers. They were particularly interested in understanding how different levels of epigenetic control change with aging.

"If you think of all the genetic material as hardware, the epigenome is the software of the cell, responsible for determining the cell's behavior," Dr. Figueroa said. "We hypothesized that, with age, this epigenetic program is getting corrupted, which turned out to indeed be the case. As we age, there are significant changes, resulting in the epigenetic reprogramming of important regulatory components of the genome. Once this happens, they can't do their jobs as well as they could when they were young."

In the study, the investigators collected hemopoietic stem cells

(HSCs) from 41 people between 18 and 30, and 55 people between 65 and 75, none of whom had cancer. From there, they looked at epigenetic markers and gene expression levels in 59 donors (27 young and 32 old). The results showed thousands of epigenetic changes as HSCs age, profoundly impacting gene expression. In particular, these variations altered several genes that are essential for the normal functioning and differentiation of HSCs.

“Most notably, there’s a core set of changes that were reproducibly found among all individuals,” Dr. Figueroa said. “When those epigenetic changes affect certain genes, they put us at risk for malignant transformation.”

Many of these epigenetic changes affected regulatory regions of several transcription factors – proteins that control the expression of other genes. One of these, called KLF6, is important for blood formation and can be altered in AML.

The researchers also found that many of the epigenetic and expression changes seen as HSCs aged were similar to those seen in cancer cells. Though ominous, that does not mean they will become cancerous. Dr. Figueroa notes that cells don’t exist in isolation. They live in a microenvironment – in this case, bone marrow. The health of that environment, as well as external factors such as environmental exposures or co-existence of other stressors, may contribute to their ultimate fate.

“Not everyone who ages gets cancer,” Dr. Figueroa said, “and not everyone who has these epigenetic changes, or even gene

mutations, gets cancer, either. We hope this study will lead to further research into age-related changes to identify which of these changes and which co-existing factors are really critical to put us at risk for cancer, and if there is anything we can do to intervene and stop those changes."

Additional Sylvester authors were Emmalee R. Adelman, Ph.D., Hsuan-Ting Huang, Ph.D., Alejandro Roisman, Ph.D., and Antonio Colaprico, Ph.D. Authors from other centers were André Olsson, Ph.D., H. Leighton Grimes, Ph.D., and Nathan Salomonis, Ph.D., at Cincinnati Children's Hospital Medical Center, Tingting Qin, Ph.D., at the University of Michigan Medical School, R. Coleman Lindsley, M.D., Ph.D., at Dana-Farber Cancer Institute, and Rafael Bejar, M.D., Ph.D., at the University of California San Diego, Moores Cancer Center.