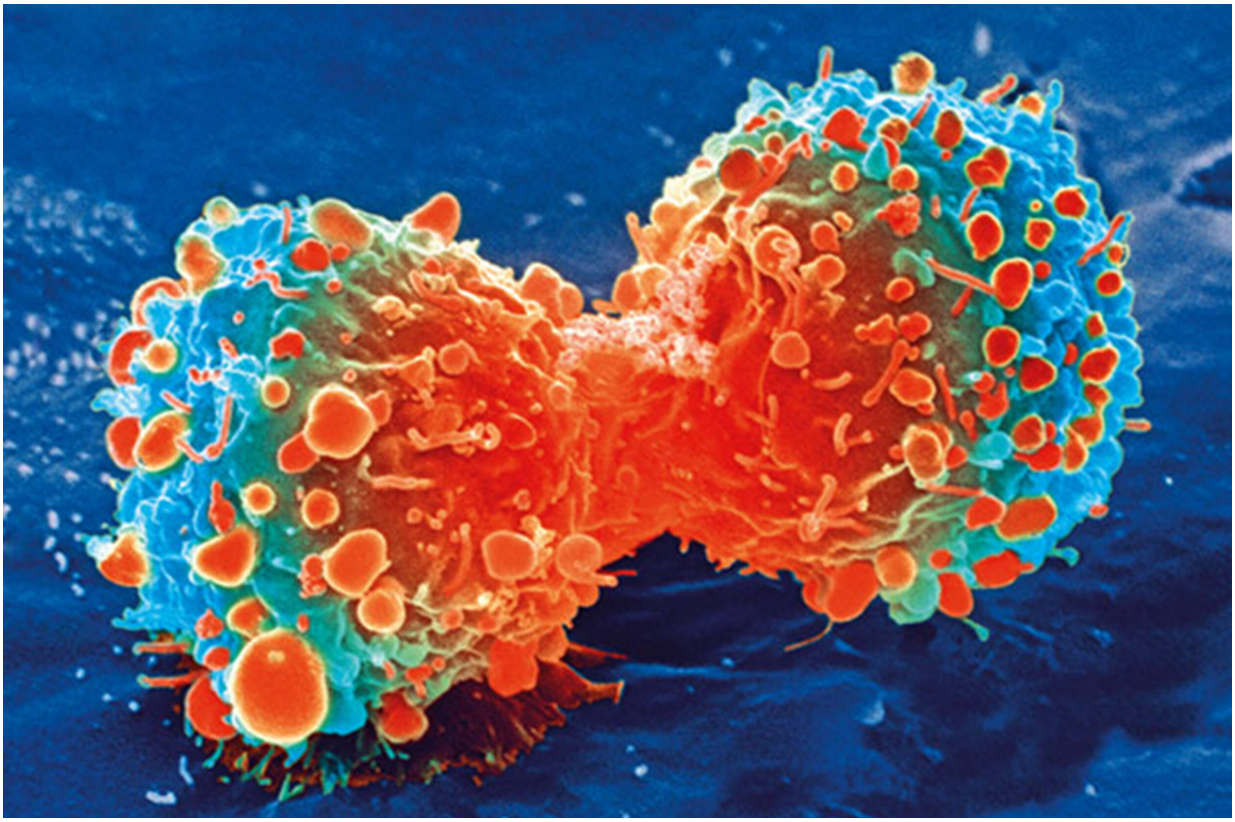
MedicalXpress

# Researchers create novel cell model of aging-related colon cancer risk

April 11 2019



Cancer cell during cell division. Credit: National Institutes of Health

Johns Hopkins Kimmel Cancer Center researchers say a new study of clusters of mouse cells known as "organoids" has significantly strengthened evidence that epigenetic changes, common to aging, play a

essential role in colon cancer initiation. The findings show that epigenetic changes are the spark that pushes colon-cancer driving gene mutations into action, the researchers say.

The model was designed to mimic alterations more likely to cause cancer in colon cells over time, potentially providing the framework for measuring such alterations in human lab-grown colon cells to assess cancer risk.

Most cancers contain epigenetic and genetic alterations, but how they work together to cause cancer was not well understood, says Stephen Baylin, M.D., the Virginia and D.K. Ludwig Professor for Cancer Research and professor of oncology and medicine. The researchers found that epigenetic alterations characterized by changes in DNA methylation—a process by which cells add tiny methyl chemical groups to a beginning region of a gene's DNA sequence, often silencing the gene's activation—are a key component of cancer initiation. In their laboratory model, known cancer-driving gene mutations did not cause colon cancers to form unless epigenetic methylation changes to the DNA were also present.

The findings were reported in the February issue of *Cancer Cell*.

Cancer is primarily a disease of aging, with the majority of cancers occurring in people over age 60. To study colon cancer in the setting of aging, Baylin and senior corresponding author Hari Easwaran, Ph.D., assistant professor of oncology, and team used a mouse colon organoids derived from six- to eight-week old mice. Organoids are lab- grown cells that clump together and resemble specific normal organs, such as the colon in this case, and can grow indefinitely. The researchers compared colon organoids with and without mutations in the BRAFV600E, a known cancer-driving gene mutation common particularly to human right sided colon cancer.

"As the organoids aged, they remained genetically stable but became epigenetically unstable, even without the BRAF mutation being introduced" says Easwaran. The scientists found that acquired DNA methylation during "aging" of the organoids, silenced cancer protective genes in a pattern similar to human aging that associates with risk for colon cancer by decade.

The team engineered the colon organoids to contain a transgenic BRAF mutation they could activate on demand. In all of the BRAF-activated organoids, DNA methylation was necessary for the mutation to initiate tumor development. Without this epigenetic change, the mutation did not initiate cancer in mice.

"Our study indicates that promoter DNA methylation-mediated silencing for important stem cell regulator genes play critical roles in allowing the BRAF mutant oncogene to initiate cancer," says Easwaran.

The introduced BRAF mutation took four to five months to cause tumors in the young organoids, which had only a few DNA methylation changes, but only took two to three weeks in the old organoids that accumulated more epigenetic changes. When the researchers artificially inactivated some of the key genes in the young organoids, it transformed young organoids into old organoids, and they became sensitive to rapid tumor formation by the BRAF mutation.

"Essentially, we 'aged' young cells to become old, methylation-wise. In general, the risk of cancer increases with age, but if we can shift the epigenetic landscape through lifestyle changes to limit the impact of methylation fluctuations, we might be able to prevent cancer from developing," says Easwaran. "Although these studies were done to examine BRAFV600E-mediated tumorigenesis, we believe our findings apply to the cancer driver roles of other oncogenic mutations."

Diet, high caloric intake and aging-related inflammation are among the factors believed to support the evolution of epigenetic instability as cancers form.

"What is exciting to me is the creation of a potential aging model and cancer risk in the lab in which the genes being manipulated have functional significance for the events taking place," says Baylin. "If what we are seeing in these mouse studies occurs in actual human aging, the model will provide much insight into means for preventing and/or intercepting cancer development."

Easwaran and Baylin say an assay could be created to monitor for epigenetic changes that predict for colon cancer risk. "If a 50- or 60-year old has genes that are methylated like an 80-year old, that might infer increased risk for cancer," says Easwaran.

The next step, they say, is to confirm these findings in larger cohort study, examining tissue samples from people over time.

**More information:** Yong Tao et al. Aging-like Spontaneous Epigenetic Silencing Facilitates Wnt Activation, Stemness, and BrafV600E-Induced Tumorigenesis, *Cancer Cell* (2019). DOI: 10.1016/j.ccell.2019.01.005

Provided by Johns Hopkins University School of Medicine