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Why do certain chemotherapies increase the likelihood of blood cancer?

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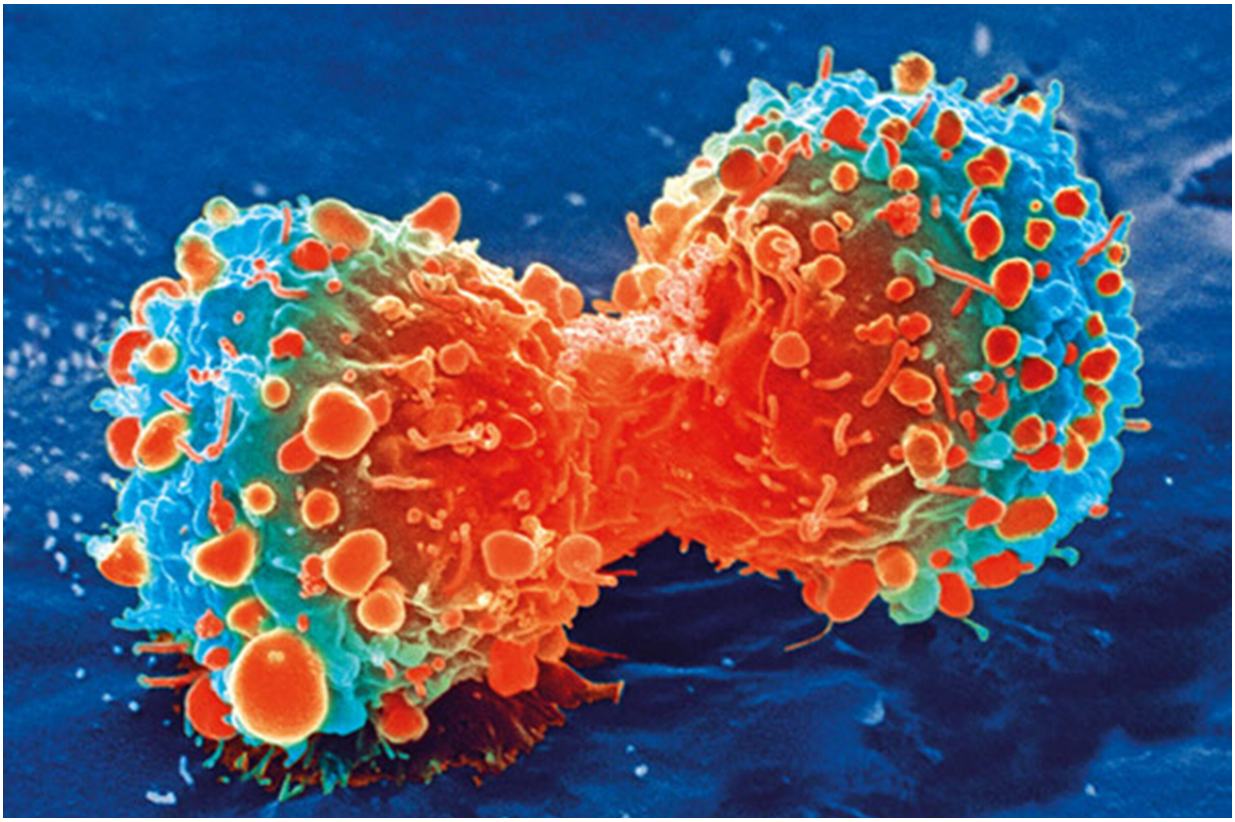

Cancer cell during cell division. Credit: National Institutes of Health

In recent years, improvements in cancer therapy have led to a significant increase in cancer survivorship. Experts estimate that by 2022, the United States will have 18 million cancer survivors, but a subset of those

survivors will have long-term health problems to be addressed.

One rare complication of cancer treatment is the development of a secondary blood cancer—therapy-related acute myeloid leukemia or myelodysplastic syndrome. These blood cancers are very aggressive and do not respond well to treatment. Historically, doctors thought that cancer treatments such as chemotherapy and radiation caused an accumulation of mutations in the blood that led to these therapy-related cancers.

In recent years, however, researchers have found that these mutations in the blood can also occur spontaneously with increasing age. This phenomenon is called clonal hematopoiesis (CH), and it's found in 10 to 20% of all people over age 70. The presence of CH increases the risk of developing a blood cancer. Using data from MSK-IMPACTTM, Memorial Sloan Kettering's clinical genomic sequencing test, researchers have shown that CH is also frequent in cancer patients.

In a study published in *Nature Genetics* on October 26, 2020, MSK investigators sought to understand the relationship between CH in cancer patients and the risk of later developing a treatment-related blood cancer. The study included data from 24,000 people treated at MSK. The researchers found CH in about one-third of them.

"Because many people treated at MSK have genetic testing done using MSK-IMPACT, we have this amazing resource that allows us to study CH in cancer patients at a scope that nobody else has been able to do," says physician-scientist Kelly Bolton, lead author of the study.

Decoding Genetic Changes Specific to Cancer Treatment

Focusing on a subset of patients on whom they had more detailed data, the investigators observed increased rates of CH in people who had already received treatment. They made specific connections between cancer therapies such as radiation therapy and particular chemotherapies—for example certain platinum drugs or agents called topoisomerase II inhibitors—and the presence of CH.

Unlike the CH changes found in the general population, the team found that CH mutations after cancer treatment occur most frequently in the genes whose protein products protect the genome from damage. One of these genes is TP53, which is frequently referred to as "the guardian of the genome."

The work was supported by the Precision Interception and Prevention (PIP) program at MSK, a multidisciplinary research program focused on identifying people who have the highest risk for developing cancer and improving methods for screening, early detection, and risk assessment.

The authors embarked on a three-year study to understand the relationship between CH and cancer therapy. For this part of the research, more than 500 people were screened for CH when they first came to MSK and then at a later point during their treatment. One finding from the study was that people with pre-existing CH whose blood carried mutations related to DNA damage repair such as TP53, were more likely to have those mutations grow after receiving cancer therapies, when compared to people who did not receive treatment.

"This finding provides a direct link between mutation type, specific therapies, and how these cells progress towards becoming a blood cancer," says Elli Papaemmanuil of MSK's Center for Computational Oncology, one of the two senior authors of the study. "Our hope is that this research will help us to understand the implications of having CH, and to begin to develop models that predict who with CH is at higher

risk for developing a blood cancer."

For a subset of patients with CH who developed therapy-related blood cancers, the researchers showed that blood cells acquired further mutations with time and progressed to leukemia. "We are now routinely screening our patients for the presence of CH mutations," adds computational biologist Ahmet Zehir, Director of Clinical Bioinformatics and the study's co-senior author. "The ability to introduce real-time CH screening for our patient population has allowed us to establish a clinic dedicated to caring for cancer patients with CH. As we continue to study more patients in the clinic, we expect to learn more about how to use these findings to find ways to detect treatment-related blood cancers early when they may be more treatable."

Applying Findings to Future Treatments

In the future, this research may help to guide therapy by indicating whether some chemotherapy drugs are more appropriate than others in people with CH. People who are at a high risk of developing a treatment-related leukemia also may benefit from a different treatment schedule. "We hope that this research will allow us to ultimately map which CH mutations a person has and use that information to tailor their primary care and also mitigate the long-term risk of developing blood cancer," Dr. Papaemmanuil says.

"We explored this in collaboration with investigators from the National Cancer Institute, Dana-Farber Cancer Institute, Moffit Cancer Center, and MD Anderson, and showed that such risk-adapted treatment decisions could achieve significant reduction of leukemia risk, without affecting outcomes for the primary cancer," Dr. Bolton adds.

The investigators also hope to use the data from this study to develop better methods for detecting CH-related blood cancers when they first

begin to form—and potentially to develop new interventions that could prevent CH from ever progressing to cancer. "We're excited about the idea of continuing to grow and expand the CH clinic as part of the integrated vision of PIP," says physician-scientist Ross Levine, who leads MSK's CH clinic and is a member of the Human Oncology and Pathogenesis Program.

"In addition to continuing to follow people who are at the highest risk of developing a secondary cancer, we want to continue to use the clinic as a vehicle for studies like this," he adds. "Our long-term goal is to move toward therapeutic interventions and preventing disease in a way that we've never been able to do before."

More information: Kelly L. Bolton et al. Cancer therapy shapes the fitness landscape of clonal hematopoiesis, *Nature Genetics* (2020). DOI: 10.1038/s41588-020-00710-0

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