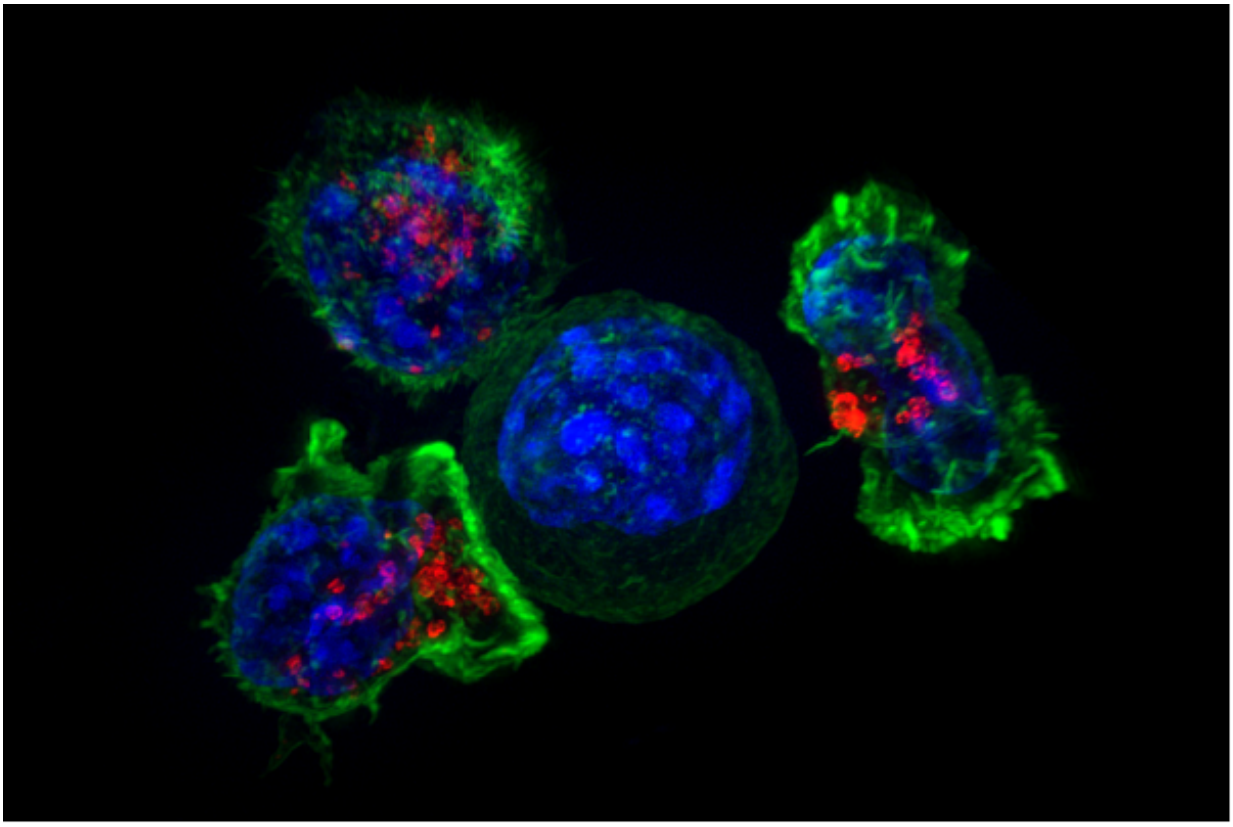
Patient-partnered research finds clues about a rare cancer's genetic roots

February 10 2020



Killer T cells surround a cancer cell. Credit: NIH

Working in close partnership with patients, scientists at the Broad Institute of MIT and Harvard, Dana-Farber Cancer Institute, and Count Me In have identified new causes of a rare cancer of blood vessel walls

called angiosarcoma. The research also points to possible therapeutic options for patients with this aggressive disease, who often have a poor prognosis.

The study is a result of the Angiosarcoma Project, a unique partnership between patients and scientists that empowers patients to contribute their medical records, biological samples, and voices to accelerate research. The work also shows how a crowd-sourced effort that unites a small and scattered group of patients can yield unexpected findings about a disease that has been difficult to study because it is so rare.

In the study, published in *Nature Medicine*, the researchers analyzed the genomes of nearly 50 tumor samples donated by angiosarcoma patients from across the United States and Canada. The team found dozens of mutated genes in various forms of the cancer, as well as clues suggesting that drugs approved for other types of cancer might be useful in treating some kinds of angiosarcoma.

"This work was only possible with our patient partners," said senior author Nikhil Wagle, an institute member at the Broad, a medical oncologist at Dana-Farber, an assistant professor at Harvard Medical School, and director of Count Me In. "The scientific insights they've helped generate have shed new light on the poorly understood roots of angiosarcoma, which urgently needs new treatment options for patients."

"When we saw the data for the first time, we were excited to see these discoveries were evident from the genomic data from the very beginning," said co-first author Corrie Painter, associate director of operations and scientific outreach for the Broad Cancer Program and associate director of Count Me In. "Working with patients to design and build the project from the start has been a phenomenal experience." Painter, a scientist, became a patient advocate after her own angiosarcoma diagnosis in 2010.

Patient partnership

The Angiosarcoma Project launched in 2017 and is part of Count Me In, which aims to catalyze research on several cancer types by directly engaging cancer patients online to enroll in biomedical studies, no matter where they live in the United States or Canada. Count Me In was built off the success of the initial effort, the Metastatic Breast Cancer (MBC) Project, which has also resulted in numerous discoveries. The Angiosarcoma Project aimed to assess this model of patient partnership in the context of a rare disease, where research is greatly needed to improve patient outcomes.

Angiosarcoma arises in endothelial cells, which form the inner linings of blood vessels and can occur anywhere in the body, but it is most commonly found in the skin, breast, liver, and spleen. It is an extremely rare cancer, with only 300 new cases each year in the United States, and prognosis is generally poor. Patients are scattered across the country, so large studies to find the illness's molecular underpinnings have not been feasible until now.

The ASCproject team established a social media working group to connect patients with angiosarcoma and loved ones online and invite them to help shape the project's outreach strategy. With feedback from patient partners, the team built an online portal at ascproject.org that allows patients in the U.S. and Canada to join the study and contribute their medical history and tumor or blood samples for DNA testing. Within 18 months of launching the ASCproject, 338 patients had registered, a large proportion of all patients in the U.S. with angiosarcoma.

With patient consent, the project staff obtained medical records and tumor samples from a subset of the registered patients. The Broad's Genomics Platform sequenced the exome, or protein-coding regions, of

47 of these tumor samples along with germline (inherited) DNA from the same patients. Co-first author Esha Jain, a computational biologist in the Wagle lab, led the analysis of the data, which revealed 30 genes that were frequently mutated in several tumors. Some of these genes had never been associated with angiosarcoma, such as PIK3CA, GRIN2A, and NOTCH2.

Potential treatment options

Most of the samples with mutations in PIK3CA were in cases of angiosarcoma of the breast. The researchers looked at where the mutations fell in the gene itself and deduced that they were likely to be "activating" mutations, meaning they give the protein a new or enhanced function. This suggests that blocking the PIK3CA pathway with an FDA-approved drug known as a PI3 kinase inhibitor could be helpful for patients with breast angiosarcomas that carry one of these mutations.

The PIK3CA gene is also mutated in breast adenocarcinoma, a different type of cancer that happens to occur in the same tissue, suggesting that something about the cellular environment of the breast encourages these tumors to develop.

"Findings like this can really open up the doors in terms of how we think about genes in tissue-specific contexts for cancer tumorigenesis," said Painter. "We never would have had that insight without this data."

The team measured the tumors' overall rate of mutation and learned that angiosarcomas of the head, neck, face, and scalp (HNFS) have a higher burden of mutations than the others. The pattern of those mutations has previously been linked to damage from ultraviolet radiation, suggesting that sun damage may have led to disease in these patients.

Because other tumors with excessive mutations have responded to

treatment with drugs known as immune checkpoint inhibitors (ICIs), the researchers hypothesized that these medicines might help patients with HNFS. In fact, they found two patients in the study with HNFS angiosarcoma who, after failing to respond to standard treatments, were given off-label ICIs and responded exceptionally well to the therapy. Despite needing to discontinue the treatment because of side effects, those patients remain disease-free today without any further treatment for their cancer. This suggests that ICIs could potentially help some patients with this subtype.

Growing impact

More work is needed to prove whether these non-standard treatments are effective for patients, but the findings have invigorated angiosarcoma research. At least three clinical trials are underway that now include angiosarcoma patients because of the data in this study, which was shared with the scientific and medical community before publication.

The ASCproject continues to enroll patients and analyze data, and it has now reached nearly 500 registered patients. "It was an aspirational goal that I honestly didn't know if we would ever reach, let alone achieve in two and a half years," said Painter.

Jim Chapdelaine, a guitarist and Emmy Award-winning recording musician in Hartford, Connecticut, was first diagnosed with angiosarcoma in 1976. He enrolled in the study in the hopes that his experience as an exceptionally long-lived survivor might help benefit other patients. "It feels amazing to know that I and others in the patient community helped fuel these new discoveries," he said. "I hope for a cure one day, but this study helps open scientific doors and we hope that people will now walk through them."

Painter explained that the new findings are hopeful, but also bittersweet,

as she remembers friends in the angiosarcoma community who did not survive the illness. "The participants in the ASCproject have signed up in the hopes that this will help people down the road," she said. "We are grateful that in the midst of their own diagnosis, they wanted to do their part to help prevent the suffering of other patients."

More information: The Angiosarcoma Project: enabling genomic and clinical discoveries in a rare cancer through patient-partnered research, *Nature Medicine* (2020). DOI: 10.1038/s41591-019-0749-z , nature.com/articles/s41591-019-0749-z

Provided by Broad Institute of MIT and Harvard