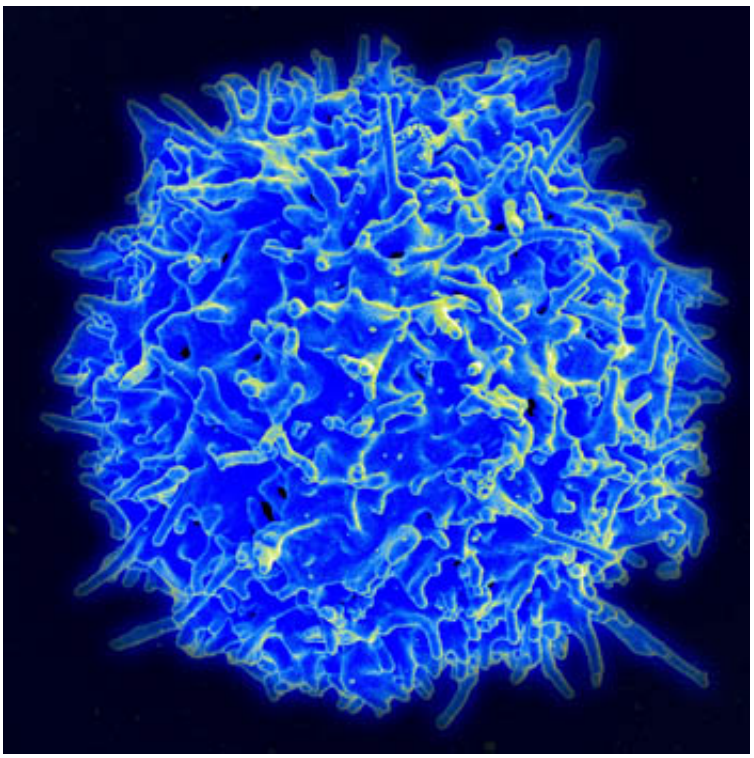
New technique predicts which melanoma patients are at risk for cancer recurrence, spread

January 20 2020



Scanning electron micrograph of human T lymphocyte or T cell. Credit: NIAID/NIH

For most patients, melanoma begins with a small, pigmented spot on their skin that they notice starts to change. Many primary melanomas can be cured by having this lesion removed, but melanoma can also recur

and spread; an analysis of the removed lesion can offer some information on the likelihood that the cancer will come back. Today, lesions are analyzed in much the same way that they were 100 years ago. Despite advances in molecular diagnostics for other forms of cancer, analysis of a skin cancer lesion is surprisingly simplistic. The lesion's thickness—patients with thinner melanomas tend to do better—and microscopic features, such as ulcerations, are considered, and a T stage of 1 through 4 is assigned. In a paper published in *Nature Cancer*, investigators from Brigham and Women's Hospital, in collaboration with international colleagues, present a new, quantitative technique that leverages DNA sequencing to make more sophisticated and accurate predictions about which primary melanomas are likely to recur and spread.

"As recently as 10 years ago the outlook for metastatic melanoma was dismal, but we now have treatments to offer patients with metastatic disease and may also be able to apply these treatments when primary disease hasn't metastasized," said corresponding author Thomas Kupper, MD, chair of the Department of Dermatology at the Brigham. "Because of the advent of these new immunotherapy treatments, it's important to have a clear idea of which patients are likely to progress so that we can tailor treatment accordingly."

Immune checkpoint inhibitors, which can reawaken T cells to mount an immune response against cancer cells, have radically changed outcomes and options available to patients whose skin cancer has spread. In some patients, they can elicit dramatic responses, including long-term remission, essentially curing a patient. But identifying patients at greatest risk for disease progression has remained an unmet need.

To address this, Kupper and colleagues sought to determine if certain measurable features of T cells could predict recurrence in patients whose primary melanoma had been removed and were free of disease. T1

melanomas (4mm) primary melanomas. The research team faced a unique hurdle in acquiring enough samples to conduct a robust study. Unlike most tumors, which are removed by a surgeon at a hospital, skin lesions can be removed in private practices and ambulatory clinics, which means that specimens are not concentrated in hospital settings. In addition, specimens must be kept for several years after removal, delaying their availability for research studies. To collect enough samples, investigators from the Brigham collaborated with colleagues at the Melanoma Institute of Australia and the Zealand University Hospital in Denmark to share resources. The current analysis includes more than 300 samples from patients across these sites.

The team compared samples from patients whose primary melanoma progressed to metastatic disease to patients whose primary melanoma did not. They used high-throughput DNA sequencing, performed by Adaptive Biotechnologies, to analyze the T cell repertoire of the tumors. The investigators found that of all variables identified, the T-cell fraction (TCFr; or proportion of cells in the lesion that were T cells) was a powerful, independent predictor of which patients would progress. Even for patients whose lesion thickness (T) was the same, TCFr was able to predict which patients were more likely to have metastatic disease. Patients with a TCFr of lower than 20 percent were more at risk of disease progression than patients with a TCFr of higher than 20 percent. For example, for patients with T3 melanoma (2-4mm thickness), five years after having their primary lesion removed, 51 percent of those with lower TCFr experienced recurrence, compared to 24 percent with higher TCFr.

The test used in this work is commercially available for research use only and is not currently yet available in the clinic. The authors also note that the current study is retrospective, looking at samples from patients whose outcomes are already known. Prospective studies of patients whose outcomes are not yet known will be needed to further validate the

test. If brought to the clinic, Kupper and colleagues envision that the test could strengthen current prediction models and improve patient care.

"This is a simple, elegant test. It's quantitative rather than subjective, and it may be able to add value to predictions about disease progression," said Kupper. "In the future, such a test could help us tailor treatment; patients with high TCFr may further benefit from checkpoint inhibitor therapy, while low TCFr patients may need additional intervention."

More information: Molecular analysis of primary melanoma T cells identifies patients at risk for metastatic recurrence, *Nature Cancer* (2020). DOI: 10.1038/s43018-019-0019-5 , nature.com/articles/s43018-019-0019-5

Provided by Brigham and Women's Hospital