Overall burden of tumor genome changes can predict patient outcomes

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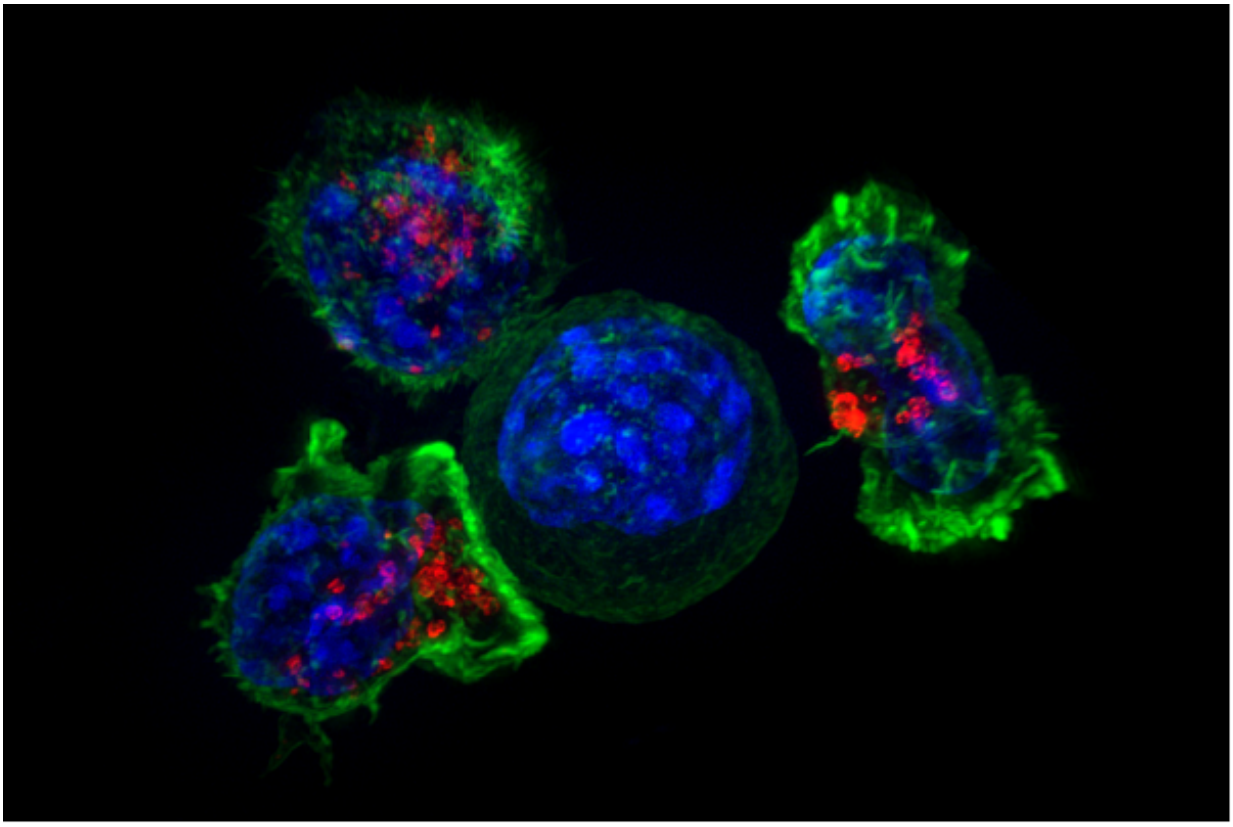

Killer T cells surround a cancer cell. Credit: NIH

Researchers have discovered a link between certain changes in the genome of a tumor and increased chances of death across multiple types of cancer.

Their findings, published in *eLife*, suggest the percentage of a tumor's genome with alterations in copy number (or 'copy number alteration'; CNA) is associated with mortality in a range of cancers. CNA refers to the fact that a genome can contain different numbers of copies of the same gene (the copy number), which can be altered in cancer, leading to the tumor having more or less copies of that same gene.

The research also shows that the percentage of these alterations in a tumor genome, known as the CNA burden, can be measured using a clinically approved sequencing technique, highlighting its potential to predict outcomes for cancer patients in a clinical setting.

"As clinical genomic analysis of tumors and tumor biopsies becomes more widespread, there is a growing need to understand the prognostic factors captured by genomic features including CNA," says lead author Haley Hieronymus, Senior Research Scientist in Charles Sawyers' lab at Memorial Sloan Kettering Cancer Center, US. "Many specific genes altered by CNA have been associated with cancer outcomes; however, the relationship between the outcome and the overall level of CNA harbored by a tumor is less well studied.

"We and others have previously found that, in primary prostate cancer, CNA burden and genome-wide CNA patterns are associated with both recurrence and the development of secondary malignant growths in other areas of the body, known as metastasis. But it is still unknown whether CNA burden is prognostic for prostate cancer survival, rather than recurrence and metastasis only, and whether the prognostic significance of tumor CNA burden extends to other cancer types. Our aim with the current study was to start addressing these questions."

To do this, Hieronymus and her team began by examining the genomic CNA landscape of prostate cancer in more than a hundred diagnostic biopsy specimens from a prostate cancer research group. This group

consisted of patients with localised prostate cancer who were not treated with surgery or radiation within six months of diagnosis. "Our initial analysis revealed that tumor CNA burden is associated with cancer-specific death, independent of standard clinical predictors," Hieronymus explains.

The team next studied patient groups with primary breast, endometrial, kidney, thyroid and colorectal cancer, in addition to prostate cancer. In what they called an "unanticipated outcome" of their work, they discovered that tumor CNA burden is also significantly associated with disease-free and overall survival in these cancer types, with varying degrees of association.

Finally, they studied the clinical feasibility of measuring tumor CNA burden using the US Food and Drug Administration-cleared MSK-IMPACT next-generation sequencing assay. This technique confirmed that tumor CNA burden is associated with overall and disease-specific survival in both primary and metastatic tumors, and across different cancer types.

"Our results suggest that ongoing and future studies into the biology underlying the association of tumor CNA burden with multiple cancer outcomes will be a fruitful area for future investigation," concludes senior author and Howard Hughes Medical Institute Investigator Charles Sawyers, Chair of the Human Oncology and Pathogenesis Program at Memorial Sloan Kettering Cancer Center. "For now, we've shown how this burden can be measured using an approved sequencing assay, demonstrating the potential for incorporating tumor CNA burden assessment into patient prognoses."

More information: Haley Hieronymus et al, Tumor copy number alteration burden is a pan-cancer prognostic factor associated with recurrence and death, *eLife* (2018). DOI: 10.7554/eLife.37294

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