Researchers identify lethal molecular alterations after current therapies fail patients with metastatic melanoma

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In a new translational study from UCLA Jonsson Comprehensive Cancer Center, researchers analyzed genetic changes in the organs of recently deceased patients to understand how metastatic cutaneous melanoma spreads in those who had initially benefited from precision therapies. Results are published online ahead of print in *Nature Medicine*.

The researchers, including collaborators at the Lineberger Comprehensive Cancer Center in Chapel Hill, North Carolina, and the Vanderbilt-Ingram Cancer Center in Nashville, Tennessee, said unveiling the landscape of DNA and RNA alterations across multiple organs of metastasis may provide new direction in cancer therapeutics to address therapy failure.

"We hope to reconstruct, from the end of life, the lethal journey melanoma traverses across time and body sites," said Dr. Roger Lo, a UCLA Jonsson Comprehensive Cancer Center researcher and a professor of medicine and molecular and medical pharmacology at the David Geffen School of Medicine at UCLA. "We need to know how many ways, even within the same patient, the cancer evades these powerful therapies, what underlying processes create 'new species' capable of escaping therapies, whether the cancer co-opts different organs to help it spread and resist therapies."

Much of what scientists know about cancers and treatment comes from the first point of patient contact—when cancer is newly diagnosed, has not overtly spread in the body, and has not been treated, either surgically or with systemic therapy. Much less is known about cancer in patients with metastatic, terminal disease, possibly in hospice care, and for whom the medical establishment has little more to offer.

This research addresses these questions, using so-called "rapid" or "warm" autopsies shortly after death in previously consented patients to conduct "biopsies" that would not be ethically justified in living patients.

Lo said the research team retrieved, within hours of death, tumors that had spread to all possible organs of patients who had initially benefited from precision therapies that have been developed over the past 10 to 15 years.

"We are taking a much-needed approach to understand cancer-related death, which usually results after the cancer has spread to distant sites, even after treatment with multiple systemic therapies. These therapies can be highly active initially but lose efficacy over time in a process termed 'acquired therapy resistance.' Alternatively, they may not work right from the outset through 'innate resistance,'" said Lo, the article's senior author.

The research team deciphered common-denominator mechanisms by which cancers become therapy-resistant, thereby providing critical clues to new therapeutic strategies. The scientists also found potential ways the metastatic cancer cells took advantage of specific organ environments, which points to the need for distinct approaches in treating patients with metastatic disease disproportionally affecting one or a few organs.

"The ability of cancers to escape precision treatments results from outgrowth of variant subpopulations that harbor traits allowing them to be impervious to the therapies, sometimes by taking advantage of a particular organ's environment," Lo said.

Cutaneous melanoma is regarded as one of the most metastatic and mutated human malignancies. Precision therapies targeting melanoma either block a critical cancer growth-and-survival pathway activated by mutations, or they reawaken the body's cancer-killing T cells.

The researchers focused on two major subtypes of metastatic cutaneous melanoma classified by cancer-causing mutations in key genes called BRAF and NRAS. Patients whose melanoma harbors a BRAF gene

mutation—found in about half of patients—have treatment options using either BRAF-targeted therapy or therapies known as immune checkpoint blockade. These are usually initiated one after another, such as when the first therapy fails to shrink tumors or stops working after a period of time. Patients whose melanoma harbors a NRAS gene mutation—found in about 20% of patients—have immunotherapy as their only standard-of-care option.

"We analyzed the DNA and RNA landscape from this autopsy cohort and, cognizant of the caveats of cross-study comparisons, singled out salient traits of terminal melanoma that distinguished it from early-stage melanoma and melanoma that had never been treated with either form of therapy," said Sixue Liu, Ph.D., a post-doctoral fellow on the Lo team and the lead author.

Liu emphasized that this study found one of the two therapies—that which targets the BRAF mutation-activated MAPK pathway—can actually change the mutational profile of melanoma. Such a shifted mutational signature represents an imprint of DNA-mutagenic processes and/or defective DNA damage repair processes, which may have diagnostic or therapeutic implications.

"Warm autopsies represent a unique, precious, and humbling opportunity that allows for our deceased patients to 'talk' and guide next generations of treatments, such that future patients suffer less and live longer. It is clear that end-stage melanoma escapes both types of therapies by evading the immune system," said Dr. Stergios Moschos, associate professor of medicine who led the rapid autopsy program at the University of North Carolina at Chapel Hill. "This study puts a sharp focus on alternative strategies to make the cancer visible to our body's anti-tumor immune system."

More information: Multi-organ landscape of therapy-resistant

melanoma, *Nature Medicine* (2023). DOI: 10.1038/s41591-023-02304-9