



Sylvester Researchers Find Abundant Mutations in Metastatic Uveal Melanoma

New insights could inform diagnoses and treatment

In a study published in the *Nature* family journal *npj Genomic Medicine*, researchers with Sylvester Comprehensive Cancer and Bascom Palmer Eye Institute at the University of Miami's Miller School of Medicine, Columbia University, Memorial Sloan Kettering Cancer Center and other institutions have mapped mutations associated with uveal melanoma metastasis over time and anatomic location. These findings could lead to better cancer diagnostics and improved disease management.



J. William Harbour, M.D.

“We see a wide range of mutations in the metastatic tumors, many more than are usually found in uveal melanoma primary



tumors,” said co-senior author J. William Harbour, M.D., Dr. Mark Daily endowed professor of Ophthalmology, vice chair for translational research and director of Ocular Oncology at the Bascom Palmer Eye Institute, and associate director for basic science at Sylvester Cancer Center. “The disease gets very complex, very quickly once it metastasizes.”

In the study, researchers conducted rapid autopsies on two uveal melanoma patients, collecting biopsies from 11 tumors in each patient, including the primary tumor. Whole exome sequencing (which only analyzes gene sequences) was performed on the first patient and whole genome sequencing on the second.

Mapping Cancer's Progression

By analyzing the mutations in various tumors, the team mapped out the cancer’s progression over time and space. Secondary tumors emanated from both the primary tumor and other metastases. As this process continued, mutation levels increased.

As expected, the results showed relatively few mutations in the primary tumors. In fact, cells generally overcome a single dangerous mutation by becoming senescent, a form of cellular sleep. A secondary mutation subsequently eradicates this safeguard, allowing the cancer to grow and take hold. Dr. Harbour had previously identified two of the key genes (BAP1 and SF3B1) which the team believes undergo mutations during tumor evolution to cancel this senescence checkpoint. Despite this slow start, once the tumor metastasizes, mutations accelerate rapidly.

“The sheer number of mutations was really surprising,” Dr.



Harbour said. “Even though primary uveal melanoma tumors have quite few, when we get to the metastases, we start seeing many more, which suggests a loss of DNA damage repair and chromosome maintenance mechanisms.”

Diversity of Mutations

The study also identified some rare genetic variations. One patient had a mutated KRAS gene, a powerful and common oncogene in other cancer types that has never before been linked to uveal melanoma.

This diversity of mutations poses clinical challenges but also outlines a potential path forward. While it would be difficult, if not impossible, to surgically biopsy every metastatic tumor, liquid biopsies, which measure circulating tumor DNA in blood, could provide a more global read on a patient’s overall tumor burden. The Harbour lab is currently working to develop a liquid biopsy for uveal melanoma.

“A promising approach would be to monitor a uveal melanoma patient’s circulating tumor DNA, even if they seem to be responding to therapy,” Dr. Harbour said. “We could watch for new mutations that might herald treatment failure that could also suggest more effective therapies.”

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