

Study identifies unique underlying molecular factors driving melanoma development

June 23 2022



Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

A new study reveals important molecular information that could help scientists develop more effective treatment and prevention strategies for a difficult-to-treat form of melanoma skin cancer.

In this new report, The Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC—James) researchers identify and describe key features of a gene mutation responsible for 15 to 20% of all melanomas.

Using a preclinical laboratory model, the team establishes that the frequency at which a specific *NRAS* gene mutation occurs in human [melanoma](#) is directly related to the ability of that gene mutation to initiate spontaneous melanoma formation.

"This means that properties of the mutant itself—rather than the ease at which that specific gene mutation occurs—is the cause of cancer formation," said corresponding author Christin Burd who serves an associate professor of molecular genetics in The Ohio State University College of Arts and Sciences, Department of Molecular Genetics and a member of the OSUCCC—James Molecular Carcinogenesis and Chemoprevention Program.

"*NRAS*-mutant cancers are challenging to treat because effective therapies beyond immunotherapy don't exist yet," said Burd. "Each [cancer type](#) seems to prefer a specific 'flavor' of mutant *NRAS*, and it has not been clear why this is."

The OSUCCC—James wanted to know what made the melanoma-promoting *NRAS* mutants different than those that promote other cancer types. Scientists say this knowledge could help investigators pinpoint the early events required for melanoma formation and develop treatments that prevent the disease.

Burd and colleagues report their findings in the June 7, 2022, issue of *Nature Communications*.

Study design and methods

To conduct this study, OSUCCC-James researchers developed genetically engineered models that would allow them to activate one of nine different *NRAS*-mutant variations in melanocytes, the pigment cells that form melanoma.

"Amazingly, when we activated these gene mutations only those found in the human disease caused melanoma to develop," said Burd. "Some mutants never led to melanoma, yet we know that they cause leukemia. This finding shows that selection of *NRAS* mutations is specific to each tumor type and occurs during cancer initiation, rather than in response to a specific mutagenic event like sun exposure."

Collaborating with Sharon Campbell, a structural biologist at the University of North Carolina (UNC) Chapel Hill, and Debbie Morrison at the National Institutes of Health, Burd's team identified that slight variances in the outward facing structure of *NRAS* mutants capable of initiating melanoma that made these proteins better able to interact with the signaling pathways that drive melanoma growth.

"Now we will work to target this unique structural feature of the melanoma-inducing *NRAS* mutants to prevent and/or treat the disease," said Burd. "Our work also demonstrates and confirms what was—until now—only speculation: that minor differences between the RAS mutants determine which 'flavors' can cause a particular cancer. Such a concept could be used to find vulnerabilities in other RAS-driven tumor types."

To facilitate similar discoveries, the team generated eight new and publicly available genetically engineered mouse models that will serve as an essential toolkit for the entire RAS community. Burd says these models can be used to activate and study the role of *NRAS* in other relevant cancer types such as [colon cancer](#), leukemia, myeloma, and

thyroid cancer. They can also be used to investigate new drugs for these diseases.

The preclinical research models developed in Burd's lab and used for this research are publicly available to scientists conducting research about other *RAS*-driven cancer types or working to develop new [cancer](#) therapies through the National Institute of Health's repository.

More information: Brandon M. Murphy et al, Enhanced BRAF engagement by NRAS mutants capable of promoting melanoma initiation, *Nature Communications* (2022). [DOI: 10.1038/s41467-022-30881-9](#)

Provided by Ohio State University Medical Center

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