Understanding Melanoma Subtypes Provides Insights on Treatment Option

Scientists assembled the largest molecular dataset and used it to uncover new details that may help in diagnosis and treatment.

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Melanoma—the most serious form of skin cancer—is caused by damage from ultraviolet light which wreaks havoc on the DNA in melanocytes, skin cells involved in pigment production. To understand all the genetic alterations driving melanoma, Damon Runyon Clinical Investigator Eliezer Van Allen, MD, and his colleagues at Dana-Farber Cancer Institute have assembled the largest molecular dataset on this disease and used it to uncover new details that may help in diagnosis and treatment.

“Discoveries about the genomic landscape of melanoma have led to the development of effective targeted drugs for the disease and to strategies for determining which patients are most likely to benefit from some forms of immunotherapy,” said Van Allen. “Still, only a subset of patients benefits from these treatments. To identify new targets for therapies, we need a more comprehensive picture of the genomic alterations that underlie the disease.”

Building a comprehensive picture

For the new study, the researchers analyzed 1,048 melanoma patient samples—the largest number yet to be examined in a single study. They had to develop new analytical techniques and statistical framework to overcome the challenge posed by melanoma’s massively mutated genome. Previous molecular studies have identified four genomic subtypes of cutaneous melanoma, named for the genes that are mutated, or not mutated, within them. Three — BRAF, (N)RAS, and NF1 — are named for mutated genes in the MAP kinase signaling pathway, which carries signals from outside the cell to DNA in the nucleus. The fourth, triple wild-type (or TWT), is named for the absence of those mutations and has a pattern of mutations unrelated to damage from ultraviolet light. The subtypes have different clinical features and tend to respond better to some therapies than others.

Deciphering patterns of mutations

In this study, the researchers discovered that each subtype has a “preference” for certain mutated genes and pathways, and that some of these alterations may make the tumors more susceptible to immunotherapy. The BRAF and (N)RAS subtypes, for instance, often harbor sets of mutated

genes that make the tumors more vulnerable to immunotherapies known as checkpoint inhibitors, which unleash a potent immune system attack on cancer. Mutations in the genes for the SWI/SNF protein complex were a frequent feature of the (N)RAS subtype and are a sign that the tumor will respond well to immunotherapy. In addition to identifying potential new targets for therapy, these results shed light on the complex biology underlying specific cancer types.

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