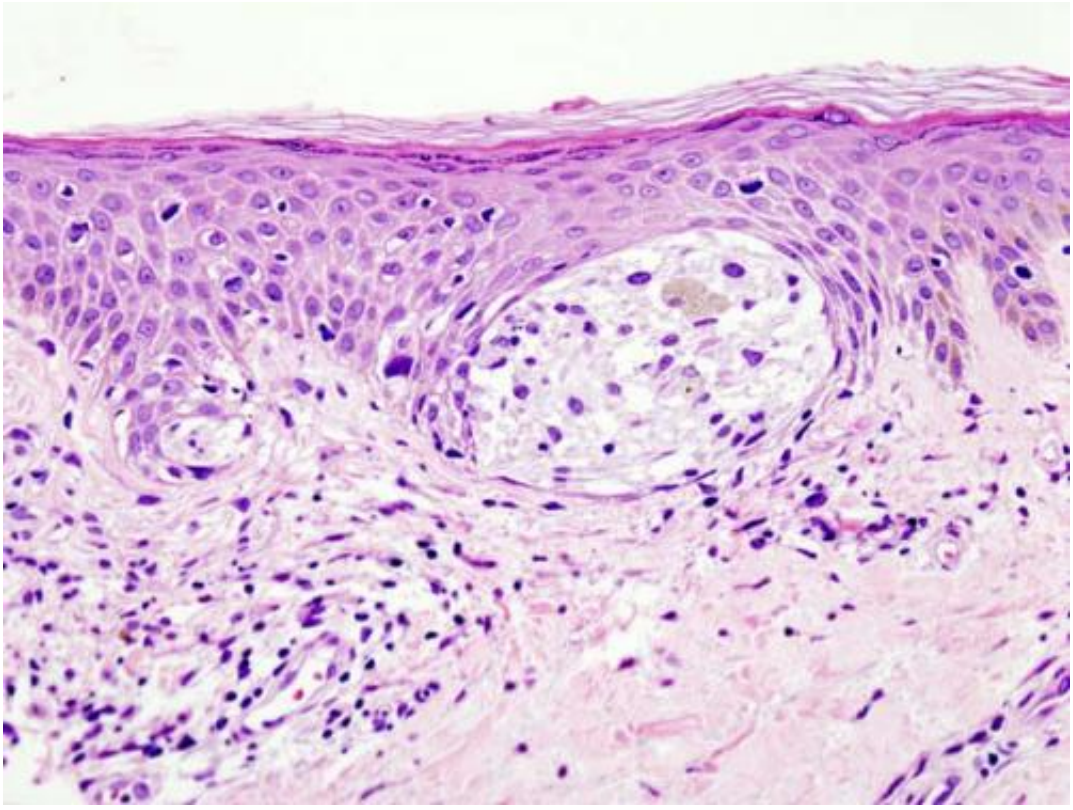
Rare melanoma carries unprecedented burden of mutations

September 8 2015, by Nicholas Weiler



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

A rare, deadly form of skin cancer known as desmoplasmic melanoma (DM) may possess the highest burden of gene mutations of any cancer, suggesting that immunotherapy may be a promising approach for treatment, according to an international team led by UC San Francisco

scientists. One of these mutations, never before observed in any cancer, may shield nascent DM tumors from destruction by the immune system and allow further mutations to develop.

"The focus of our lab has been to show that there's not just one 'melanoma' but many different types," said senior author Boris Bastian, MD, PhD, the Gerson and Barbara Bass Bakar Distinguished Professor in Cancer Research at UCSF. "We've already discovered genetic profiles that let us begin to separate them into groups and study them individually. But this is one type that has so far been left behind."

Unlike many melanomas which grow rapidly and appear as dark brown discolorations of the skin, DM is unusual in that it develops slowly and forms unpigmented scar-like bumps, occasionally accompanied by tingling sensations as the cancer grows into nerves. Its unusual appearance leads to delayed or incorrect diagnoses, which can be deadly, as the cancer tends to metastasize directly to the lung.

"Because these tumors are not pigmented, people often don't notice them until they're quite large," said lead author A. Hunter Shain, PhD, a postdoctoral fellow in Bastian's lab. "And then it might be too late."

DM accounts for four percent of melanomas, but until now its genetic basis was unknown, partly because it has been difficult for researchers to assemble a sufficient number of biopsy specimens to study. In previous research based on small numbers of specimens, scientists had looked for the mutations associated with more common forms of melanoma, but had found no leads, said Bastian, who is a member of the UCSF Helen Diller Family Comprehensive Cancer Center.

As a result, Shain said, "though DM is a very deadly form of melanoma, virtually nothing's known about it."

Sequencing tumors letter by letter

In the new study the researchers obtained 62 DM samples from UCSF, the Memorial Sloan Kettering Cancer Center in New York, and the Melanoma Institute Australia in Sydney, and performed next-generation, whole genome and exome sequencing, parsing the coding regions of the tumors' genetic code "letter by letter" to identify common mutations between the samples.

In line with its atypical clinical presentation, DM appears to be a genetic oddball among melanomas. The researchers detected few of the mutations commonly seen in other melanoma types, but instead identified mutations of pathways frequently implicated in other cancers for which some targeted therapies already exist.

Two other findings suggested an intriguing portrait of how DM develops, and how it might be treated.

First was the discovery that DM tumors carry a surprisingly high number of mutations. Most solid tumors carry about two mutations per million base pairs, the genetic "letters" that make up genomes. More common melanomas, which often are caused by exposure to the ultraviolet component of sunlight, have more mutations: about 15 per million base pairs. In the current study, however, DM tumors carried about 62 mutations per million base pairs.

"This is the highest number of mutations we've ever seen in an untreated tumor without any apparent defect in DNA repair," Bastian said.

A second key finding was that one of the most common DM mutations, never before seen in cancer cells, occurred in a promoter region that regulates expression of the NFKBIE gene, which plays an important role in turning down immune responses.

"This is the first time this gene has popped up in any cancer," Bastian said. "What's more, it's rare among known cancer mutations in that it resides in the regulatory 'dark matter' of the genome, and not within the part of a gene that codes for a protein. Regulatory mutations like this routinely escape all but the most comprehensive genomic analysis."

Potential for immune therapy

Many researchers believe that cancers with high numbers of mutations are quickly detected and destroyed by circulating immune cells before they spiral out of control. However, the mutated NFKBIE promoter may allow affected cells to fly under the radar of the body's immune surveillance long enough to accumulate the numerous other mutations that eventually drive the cells to a cancerous state, Bastian speculated.

"It may be like a cloak of invisibility for the cancer cells," he said.

Though this mechanism of cancer growth in DM is still unproven, it suggests that immune checkpoint blockade therapy, which has proven successful in treating more common forms of melanoma, could be a particularly effective first line of attack against DM, overcoming its putative hijacking of immune suppression.

"Other melanomas with high mutation burden tend to have increased sensitivity to immune checkpoint blockade," Bastian said. "We think successful tumors somehow quench the immune response, but through this technique, by adding an antibody that interferes with the quenching, you unleash the immune system and the tumors shrink away almost completely."

Provided by University of California, San Francisco