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Melanoma transcriptome reveals novel genomic alterations not seen before

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Melanoma, the most deadly form of skin cancer, afflicts more than 50,000 people in the United States annually and the incidence rate continues to rise. In a study published online in *Genome Research*, scientists have delved deeper than ever before into the RNA world of the melanoma tumor and identified genomic alterations that could play a role in the disease.

The latest high-throughput DNA sequencing technologies are ushering in a new era of discovery in cancer genomics that promises to reveal molecular mechanisms of the disease. Beyond cataloging the genetic mutations present in tumors, application of high-throughput sequencing to the RNA "transcriptome" can uncover other genomic alterations missed by DNA sequencing and identify potential targets for therapy.

For example, two adjacent genes can be transcribed together in a single "chimeric" RNA transcript. This RNA message is then translated into a protein with an altered or new function. In addition, rearrangements of the genome can cut and paste genes together, creating "gene fusions." These events occur in normal cells, but they also have the potential to cause disease. Recently these alterations have been detected a few tumor types, and it is very likely that more will be found in other cancers such as melanoma.

To capture the full spectrum of genomic alterations present in the expressed genes of melanoma, a team of researchers in the United States and Switzerland performed an integrative analysis of melanoma tumors

using RNA sequencing and structural genomic data. The group identified 11 novel gene fusions involving several common cancer-related genes, and 12 cases of chimeric transcripts. "This is the first direct evidence for these types of genetic alterations in melanoma," said Michael Berger, a research scientist at the Broad Institute and first author of the report.

A particularly interesting finding was that a recurrent chimeric transcript was found involving the *CDK2* gene, known to be required for melanoma cell proliferation. The authors suggest that the functional role of the aberrant *CDK2* transcript is an attractive target of future investigation. In addition to novel gene fusions and chimeric transcripts, the research group also identified many other alterations in the melanoma tumors, including novel mutations, alternative splice variants, and expression changes.

Berger noted that this type of cancer transcriptome analysis is very appealing, as it complements common DNA-based genomic sequencing and characterization approaches to capture a more complete picture of the cancer genome. "Such studies should help reveal the cancer RNA world," added Levi Garraway, an Assistant Professor at Harvard Medical School/Dana-Farber Cancer Institute and the study's senior author, "thereby nominating many new genetic targets relevant to tumor biology and drug discovery."

More information: www.genome.org

Provided by Cold Spring Harbor Laboratory

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