Medical Xpress

Lung cancer driver ALK-fusion found in melanoma

October 23 2017

Melanoma. Credit: Wikimedia Commons/National Cancer Institute

Melanomas caused by sun exposure have been matched with targeted treatments and immunotherapies, in many cases dramatically extending patients' lives. However, there are other kinds of melanoma not related to sun exposure and because they are caused by different genetic changes, they are not susceptible to the same targeted treatments. This

often leaves patients with these non-sun melanoma subtypes without treatment options. A University of Colorado Cancer Center study published today in the journal *Molecular Cancer Therapeutics* may offer hope to some of these patients with melanomas caused by genetic changes not related to sun exposure. The study finds a genetic change called ALK-fusion in a patient sample of a melanoma subtype called mucosal melanoma. When researchers treated a tumor grown from this sample with the drugs crizotinib and ceritinib - both FDA approved to treat ALK-positive lung cancer - the tumor responded dramatically.

"Maybe these non-sun-exposed melanomas are molecularly more like a lung cancer or a colorectal cancer, and maybe we should be treating them like that," says Kasey Couts, PhD, assistant research professor at the CU School of Medicine, the paper's first author. Couts worked in the lab of CU Cancer Center investigator William Robinson, MD (a specialist in melanoma) and in collaboration with Robert C. Doebele, MD, PhD (a specialist in gene fusions).

The finding takes place in the context of growing awareness that the genetic changes that cause cancer may be shared across cancer types, and also that there are many ways these cancer-causing genes may be changed.

This study examined a specific kind of genetic change known as gene fusion in which partner genes that should sit in separate places on the genome are accidentally spliced next to each other in a way that creates a new "fusion protein". In this case, the gene ALK becomes fused with the gene EML4 to create the fusion gene EML4-ALK. This EML4-ALK fusion gene creates a protein that has been shown to cause a subset of non-small cell lung cancers, and has now been successfully targeted by a handful of FDA approved drugs.

The current study examined 45 melanoma patient samples, finding

EML4-ALK fusion in one, a sample of a melanoma subtype called mucosal melanoma, a form of the disease unrelated to sun exposure that often arises on mucosal surfaces such as the sinonasal tract, perinium, and vulvovaginal areas. Sure enough, when the group treated EML4-ALK tumor samples with ALK inhibitors developed to treat ALK-positive lung cancer, the tumors responded.

"It seems like these melanomas that don't come from sun exposure may have fusions not seen in the more common form of the disease, and thus may be more susceptible to targeted treatments that attack these fusions than they are to drugs developed to treat other kinds of melanoma," Couts says.

Interestingly, the group also explored a closely related genetic change in the ALK gene previously reported as a driver and possible target in 11 percent of melanomas. Rather than ALK fusion, this other kind of change results in the manufacture of a protein closely related to ALK, called an ALK alternate transcript isoform (ALKATi), which is basically a shortened form of ALK. The earlier work implied that melanomas with ALKATi may respond to ALK inhibitors, but the current study refutes this claim, finding that inhibiting EML4-ALK fusion but not ALKATi results in the death of cancer cells. A patient expressing ALKATi who was treated on a phase I clinical trial with an ALK inhibitor did not respond.

"We don't think the isoform will be the target. We think the fusion will be," Couts says.

She also suggests that oncologists treating melanoma may consider the use of broad genomic profiling to search for gene fusions that may be driving specific melanomas.

"In this study, we found ALK-fusion. In a previous study, we found

ROS1-fusion. It seems like especially in these non-sun-exposed melanomas that are most often driven by oncogenes not found in regular melanomas, multiplex screening could identify additional treatment options," Couts says, adding that any possible new treatments will have to be validated in the context of clinical trials.

Now the group continues to explore two major research directions, first continuing to show the rationale for the use of ALK-inhibitors to treat EML4-ALK fusion melanoma, and second exploring melanoma for additional genetic changes that may respond to targeted treatments.

More information: Kasey L. Couts et al, ALK inhibitor response in melanomas expressing EML4-ALK fusions and alternate ALK isoforms, *Molecular Cancer Therapeutics* (2017). DOI: 10.1158/1535-7163.MCT-17-0472

Provided by CU Anschutz Medical Campus