Protein involved in early steps of melanoma development revealed

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Melanoma is one of the least common types of skin cancer, but it is also the most deadly. Melanocytes (pigment-producing skin cells) lose the genetic regulatory mechanisms that normally limit their number, allowing them to divide and proliferate out of control. One such regulator, called MITF, controls an array of genes that influence melanocyte development, function and survival.

Researchers at Sanford-Burnham Medical Research Institute (Sanford-Burnham) and their collaborators recently used a melanoma mouse model, cell cultures and human tissue samples to unravel the relationship between MITF and ATF2, a transcription factor (or protein that controls gene expression) that is more active in melanomas. The study, published December 23 in PLoS Genetics, demonstrates that the MITF is subject to negative regulation by ATF2, and such regulation is a key determinant in melanoma development. This work also reveals that the ratio of ATF2 to MITF in the nucleus of melanoma cells can predict survival in melanoma patients - relatively high amounts of ATF2 and correspondingly low MITF levels were associated with a poor prognosis.

"In the late 1990s, we began to observe that if you can inhibit ATF2, you can inhibit melanoma," explained Ze'ev Ronai, Ph.D., senior author of the study and associate director of Sanford-Burnham's National Cancer Institute-designated Cancer Center. "This latest study provides the first genetic evidence to support those initial observations. Here we show that mice lacking ATF2 in melanocytes do not develop melanoma even if they carry mutations seen in human melanoma. Moreover, ATF2 expression patterns can predict outcome in melanoma patients."

In this study, Dr. Ronai and collaborators from five medical centers in the U.S. and U.K. disrupted the ATF2 gene in the melanocytes of mice harboring mutations often seen in human melanoma. It turns out that ATF2 blocks MITF function in the early stages of melanocyte development. Without ATF2's foot on the brake in these mice, melanoma was inhibited thanks to its affect on MITF expression.

To determine exactly how ATF2 keeps the damper on MITF, the researchers then drilled down to melanocytes and melanoma cells in a dish. In about half the cell lines tested, they noted that ATF2's control over MITF is indirect - ATF2 actually controls a protein, called SOX10, which is in turn necessary for MITF expression. While this control was sustained in melanocytes and 50 percent of melanomas, the other half of melanoma cell lines circumvented this pathway altogether. With this knowledge, the researchers found they could induce or inhibit melanoma development by artificially manipulating ATF2 and MITF levels.

Dr. Ronai's research team also looked at an array of more than 500 human melanoma samples. Some of the samples were from primary melanomas, while others were taken from metastatic melanoma. Comparing the relative levels of these transcription factors to the ultimate outcome known for each patient, they determined that a high ratio of ATF2 to MITF was associated with metastatic disease and decreased 10-year survival in patients. This provides a potential prognostic tool for identifying those patients whose melanomas are more likely to metastasize to other organs.

"This study focused on MITF, but that's probably not the only story. I believe we will continue to find more factors modulated by ATF2 in melanoma," said Anindita Bhoumik, one of the study's first authors. "There are still many studies to be done, but this will help us better understand the different signaling pathways important to melanoma development, with the ultimate goal of discovering new therapies."

More information: Shah M, Bhoumik A, Goel V,

Dewing A, Breitwieser W, Kluger H, Krajewski S, Krajewska M, DeHart J, Lau E, Kallenberg DM, Jeong H, Eroshkin A, Bennett DC, Chin L, Bosenberg M, Jones N, Ronai ZA. A role for ATF2 in regulating MITF and melanoma development. *PLoS Genetics*. December 23, 2010.

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