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Breakthrough in Melanoma Research

In a breakthrough that could lead to new treatments for patients with malignant melanoma, researchers from Mount Sinai School of Medicine have discovered that a particular protein suppresses the progression of melanoma through regulation of an oncogene, or gene responsible for cancer growth. The study is published in the December 23 issue of Nature.

Researchers studied the natural progression of melanoma using mouse and human cells, as well as patient samples and determined that the presence of a specific histone variant, which is a protein that helps package DNA, was directly related to the growth of melanoma. In all instances, researchers observed that as the melanoma became more aggressive, the presence of the histone variant macroH2A decreased. Researchers then manipulated macroH2A levels in melanoma and found that when they removed it in the early stages of the disease, the melanoma progressed more aggressively both in growth and metastasis. Adding macroH2A to late-stage aggressive melanoma cells created the opposite effect.

"We wanted to determine whether macroH2A is a passenger in this process or if it's crucial in the progression of melanoma," said Emily Bernstein, PhD, Assistant Professor of Oncological Sciences and Dermatology, Mount Sinai School of Medicine, and lead author of the study. When further investigating macroH2A function in melanoma, the researchers found that it regulates CDK8, a known oncogene for colorectal cancer. "CDK8 is highly expressed in aggressive melanoma, suggesting it also plays a major role in the process," Dr. Bernstein explained.

Through further functional studies, researchers found that eliminating macroH2A led to an increase in CDK8 expression, and the elimination of CDK8 in metastatic melanoma cells impaired their proliferation. These results suggest that macroH2A suppresses melanoma progression, at least in part, through the regulation of CDK8.

"Very little is known about melanoma epigenetics or the histone-mediated epigenetic changes in cancer in general, so these findings are a major step forward in our research. As we move ahead, we would like to determine how to inhibit CDK8 function, thereby inhibiting the growth of melanoma, as well as identify additional epigenetic changes in melanoma progression." said Dr. Bernstein. "What these discoveries really highlight is the need for further studies into the epigenetic code of cancer."

Melanoma is the most serious form of skin cancer and accounts for about 75 percent of all skin cancer deaths. Though the most preventable cause of melanoma is exposure to the sun's UV rays, other factors include genetics and immune system deficiencies. When detected early, melanoma is highly curable. According to American Academy of Dermatology, the average five-year survival rate for individuals whose melanoma is detected and treated before it spreads to the lymph nodes is 98 percent.

Avnish Kapoor, Matthew S. Goldberg, Lara K. Cumberland, Kajan Ratnakumar, Miguel F. Segura, Patrick O. Emanuel, Silvia Menendez, Chiara Vardabasso, Gary LeRoy, Claudia I. Vidal, David Polsky, Iman Osman, Benjamin A. Garcia, Eva Hernando, Emily Bernstein. The histone variant macroH2A suppresses melanoma progression through regulation of CDK8. Nature, 2010; 468 (7327): 1105 DOI: 10.1038/nature09590