Scientists create mouse model of melanoma that generates hope for the use of targeted therapies

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Researchers have developed a new mouse model that allows them to replicate normal pigment cells at the earliest stages of conversion to malignant skin cancer in humans. After testing the mouse with a combination of two drug therapies, the team found the treatment caused a statistically significant regression in cancer cell development.

The study was led by scientists at the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center and the University of Vermont College of Medicine. The findings are published today (March 12, 2009) in the advance online edition of "*Nature Genetics*."

Melanoma is a type of skin cancer that develops from pigment cells called melanocytes. It is the most rapidly increasing cancer in the United States, according to the National Cancer Institute, with more than 62,000 people diagnosed with the disease in 2008. Of these, it is estimated that more than 8,000 will die within three to four years after a form of the recurrent disease spreads, or metastasizes, to other sites in the body.

"There has not been a major advance in the treatment of metastatic melanoma in the last 25 years," says Martin McMahon, PhD, senior co-author of the study and Efim Guzik Distinguished Professor in Cancer Biology at the UCSF. "While other cancers are more common, it is the rate of increase and the often aggressive course of the disease that

worries people who study melanoma."

By far the earliest and most common genetic alteration in melanoma is a mutation in an oncogene -- a gene that can cause normal cells to become cancer cells -- called BRAF. For this study, scientists generated a mouse that allowed them to switch on that oncogene in melanocytes. The research team found that the benign lesions observed in a mouse expressing the gene are very similar to the benign sun-induced moles that often develop in humans and which also contain BRAF mutations. Benign sun-induced moles generally never progress to malignancy, but such lesions are a potential precursor to cancer.

BRAF mutation is not the only genetic alteration observed in human melanoma. It is often found in combination with the silencing of PTEN, an important tumor-suppressor gene. By combining activation of the BRAF gene with deletion of the PTEN suppressor gene, the research team effectively modeled a combination of mutations seen in about 30 percent of all malignant melanomas. Under these circumstances the mice rapidly developed melanoma that displayed extensive metastasis.

Next, the researchers studied the impact of a combination of two different drugs on mouse melanoma. Each drug in its own unique way targeted the internal growth control circuits of cancer cells. One drug is an experimental therapy supplied by Pfizer Inc., that inhibits the action of a protein called MEK that acts "directly downstream of BRAF," McMahon explained. Consequently, oncogenic BRAF gene generates a series of signals that support a high level of MEK activity. The other drug, Rapamycin, is an immunosuppressant drug already in clinical trials for cancer. As single agents, these drugs could prevent the onset of melanoma but, more importantly, when administered in combination to mice with pre-existing melanoma, there was a modest but statistically important level of regression in cancerous cells, according to McMahon.

"The study indicates that the mouse model we have built, based on the cardinal genetic features of the human disease, can be used to test responses to targeted therapeutics," says McMahon. "The signal failure to improve the prognosis of metastatic melanoma patients is likely to be improved on in years to come by the use of agents that target specific genetic mutations in the disease. Nevertheless I believe it will up be three to five years before the types of pre-clinical experiments we are doing right now will result in improved prognosis for patients with metastatic melanoma."

The scientists emphasized that although they engineered mice with very specific genetic alterations, it is possible that human melanoma is genetically more complex than the model they have generated. To address this, McMahon and Boris Bastian, MD, professor of dermatology and clinical professor of pathology at UCSF, are discussing the possibility of making additional modifications to the mouse model to make it more relevant to the genetic complexity found in human melanoma.

"Although the combination of drugs we administered might not be used in the clinic, our work suggests further avenues of research in a pre-clinical setting and in clinical trials," says McMahon. "In fact it is fair to say also that there are a number of drugs already in clinical trials that target the same pathways we are interested in."

Source: University of California - San Francisco