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New biomarker identifies uveal melanoma patients at high risk for metastasis

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A study by J. William Harbour, M.D., associate director for Basic Research and leader of the Eye Cancer Site Disease Group at Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine, and colleagues published today in *Clinical Cancer Research* details the discovery of a biomarker that puts patients at a higher risk for metastasis of uveal melanoma. Among uveal melanomas categorized as class 1, those with high levels of the biomarker PRAME mRNA were more likely to metastasize than those with low levels of PRAME mRNA, indicating that patients with this biomarker be monitored more closely for metastatic disease.

The estimated five-year rate of metastasis was 0 percent for PRAME mRNA-low class 1 uveal melanomas and 38 percent for PRAME mRNA-high class 1 uveal melanomas. This research builds upon Harbour's identification of class 1 and 2 uveal melanomas in 2004.

There are about 2,000 to 3,000 cases of uveal melanoma diagnosed each year in the United States, according to Harbour, who is also a professor and vice chairman for Translational Research, the Mark J. Daily Endowed Chair, and director of the Ocular Oncology Service at Bascom Palmer Eye Institute, part of UHealth - the University of Miami Health System. He explained that uveal melanomas are categorized into class 1 and class 2 tumors by gene expression profiling and that class 1 tumors have a much lower chance of metastasizing than class 2 tumors.

"However, about 10 percent of patients with class 1 uveal melanoma do

develop metastasis," said Harbour. "The main purpose of this study was to identify a clinically useful biomarker for this subgroup of class 1 uveal melanomas, which in turn might help in the development of precision medicines for melanoma patients.

"We were surprised to find that one biomarker alone—PRAME—was sufficient to identify the subgroup of class 1 tumors with increased metastatic risk," continued Harbour. "These findings could have immediate clinical impact. The data imply that patients with class 1 uveal melanomas with increased PRAME expression should be managed differently than patients with class 1 uveal melanomas without PRAME expression. They should be monitored more closely for metastatic disease and they should be considered for clinical trials of adjuvant therapy."

Harbour and colleagues performed genome-wide analysis of mRNA isolated from five class 1 uveal melanomas that metastasized and eight class 1 tumors that did not metastasize. The most highly overexpressed mRNA in the tumors that metastasized was PRAME. Further analysis of PRAME mRNA levels showed that seven of seven class 1 tumors that metastasized had high levels of PRAME mRNA and that 16 of 19 class 1 tumors that did not metastasize had minimal levels of PRAME mRNA.

Among 64 class 1 uveal melanoma samples, 39 (61 percent) had low levels of PRAME mRNA (PRAME negative) and 25 (39 percent) had high levels of PRAME mRNA (PRAME positive). None of the patients with PRAME-negative tumors developed metastasis while seven of the patients with PRAME-positive tumors did.

To validate the association between high levels of PRAME mRNA and metastasis for class 1 uveal melanomas, the researchers analyzed two additional datasets. The first was a combination of two independently published datasets and the second was a dataset from Leiden University

in the Netherlands. In both these datasets, PRAME-positive tumors had a significantly increased risk for metastasis compared with PRAME-negative tumors.

Harbour noted that because this is a retrospective study, meaning that the researchers identified PRAME by looking back at patients who had been treated in the past, they are planning a prospective, multicenter study to validate the findings. He explained that the class 1/class 2 gene expression profile test remains the only prognostic assay for uveal melanoma that has ever been prospectively validated in a multicenter study and that they will hold PRAME to this same high standard of prospective validation.

Provided by University of Miami Miller School of Medicine