Blocking protein leads to fewer, smaller skin cancer tumors

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(PhysOrg.com) -- New research suggests that blocking the activity of a protein in the blood could offer powerful protection against some skin cancers.

In the study, normal mice and mice that had a genetically engineered protein deficiency were exposed to almost a year of ultraviolet light that mimics chronic sun exposure. The mice that lacked the protein developed fewer, smaller, less aggressive and less vascular skin cancer tumors than did the normal mice.

Because a low-dose drug that blocks the protein's activity in the blood is currently under investigation by a Pennsylvania pharmaceutical company, the researchers hope that someday, a simple pill might help prevent or treat nonmelanoma skin cancer in people at highest risk for the disease.

More than 1 million cases of nonmelanoma skin cancer are diagnosed in the United States each year, according to the National Cancer Institute. The two most common types are basal cell carcinoma, which forms in small cells in the base of the outer layer of skin, and squamous cell carcinoma, which forms in cells that compose the surface of the skin.

The protein is called macrophage migration inhibitory factor, or MIF. It is a pro-inflammatory cytokine present in human blood that generates inflammation in response to infection, offering protection against some pathogens. But in this research, MIF emerged as a contributor to the

chronic inflammation that precedes the development of skin cancer after long-term sun exposure. Previous studies have implicated MIF in other cancers, as well.

"Our data show that MIF appears to be affecting multiple pathways that are important for tumor generation and progression. It also is clear here that there is a link between inflammation and cancer," said Abhay Satoskar, associate professor of microbiology at Ohio State University and a coauthor of the study.

"No one else has shown this in a skin cancer model."

The study is scheduled for publication in the March 2009 issue of the *Journal of the Federation of American Societies for Experimental Biology*.

The scientists exposed normal mice and mice deficient in MIF to ultraviolet B light, the type of radiation from the sun that damages the skin. The mice were exposed to the light three days per week for 46 weeks, with doses increased regularly after week 13 to account for skin adaption to UVB exposure. The exposure in the study was designed to accelerate tumor growth and far exceeded the UVB exposure that humans experience over the same time period.

By week 37, more than two-thirds of the mice exposed to UVB light had developed at least one tumor, and all mice had developed tumors by week 45. The MIF-deficient mice averaged 2.89 tumors per mouse at the end of the exposure, compared to an average of 5.27 tumors per normal mouse. Overall, the MIF-deficient mice on average had about half as many tumors and significantly smaller tumors than did the normal mice. The tumors on the MIF-deficient mice were also less likely to be malignant than were tumors on normal mice.

Satoskar and colleagues compared a number of tumor characteristics on

the two groups of UVB-exposed mice to confirm the MIF deficiency's role in lowering the incidence of skin cancer.

The MIF-deficient mice had almost twice as many tumor-suppressor cells of the p53 gene than did normal mice, suggesting that the presence of the MIF protein interferes with this tumor suppressor's ability to do its work. The MIF-deficient mice also had lower concentrations of the protein vascular endothelial growth factor (VEGF) than did normal mice. VEGF has previously been found to promote the development of blood vessels in certain types of cancer tumors, so the lower amount of the protein in MIF-deficient mice means the tumors they did develop had less vascular support to grow, Satoskar said.

Finally, MIF-deficient mice exposed to UVB rays had lower levels of three markers for inflammation, indicating an important link between MIF and the inflammatory response in skin that follows UVB exposure.

The scientists also observed that the MIF deficiency did not cause any significant side effects in the mice. Under normal circumstances, the amount of MIF in the blood remains constant.

"Some MIF is not bad, but we think that if it goes above a certain threshold, it starts doing crazy things," Satoskar said. "We're not aware of the natural existence of a MIF deficiency in humans, but in a mouse, we don't see any toxic effects."

MIF is also an important target for skin cancer research because previous studies have identified five polymorphisms in the MIF gene in humans. Polymorphisms are mutations in genes that, in the case of MIF, might make some individuals produce higher or lower levels of the protein, which could influence their susceptibility to skin cancers.

Satoskar and colleagues plan to examine biopsies of patients who have

been diagnosed with squamous cell or basal cell carcinoma to see if these patients have a polymorphism on the MIF gene that would suggest a genetic predisposition toward the cancer.

"If we find a correlation, a MIF-gene polymorphism could become a biomarker to predict skin cancer. That would mean people who have a polymorphism that makes them high MIF producers would be more likely to develop skin cancer if they are exposed to the sun," Satoskar said. "We don't know yet whether there is a correlation, however."

The researchers also plan to begin tests of the drug under development in their MIF-deficient mouse model. The drug is based on a small molecule that blocks the activity of MIF in the blood and has been effective in other animal models of inflammatory diseases at a very low dose.

"Our goal is to move forward to see whether this molecule is a new target for prevention and/or treatment of this disease," Satoskar said.

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