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## Stress may hasten growth of melanoma tumors

For patients with a particularly aggressive form of skin cancer — malignant melanoma — stress, including that which comes from simply hearing that diagnosis, might amplify the progression of their disease.

But the same new research that implies this also suggests that the use of commonly prescribed blood pressure medicines might slow the development of those tumors and therefore improve these patients' quality of life.

The study, the third by Ohio State scientists in the last two years that looked for links between stress hormones and diseases like cancer, is published in the journal *Brain, Behavior and Immunity*.

Eric Yang, a research scientist at the Institute for Behavioral Medicine Research (IBMR), exposed samples of three melanoma cell lines to the compound norepinephrine, a naturally occurring catecholamine that functions as a stress hormone. In times of increased stress, levels of norepinephrine increase in the bloodstream.

Yang and colleague Ronald Glaser were looking for changes in the levels of three proteins released by the cells. Glaser is a professor of molecular virology, immunology and medical genetics, member of the university's Comprehensive Cancer Center and director of the IBMR.

One of the proteins — vascular endothelial growth factor, or VEGF — plays a key role in stimulating the growth of new blood vessels needed to feed a growing tumor, a process called angiogenesis. The other two proteins, Interleukin-6 and Interleukin-8, are both involved in fostering tumor growth.

All three of the cell lines were grown from tissues taken from secondary tumors that had spread from a primary site and they signify aggressive forms of cancer. But one of them — C8161 — represented the most aggressive and advanced form of melanoma.

"We noticed that all three of these proteins increased in response to the norepinephrine," Yang explained, adding that in the C8161 cells "we got a 2,000 percent increase in IL-6. In untreated samples from this cell line, you normally can't detect any IL-6 at all.

"What this tells us is that stress might have a worse effect on melanoma that is in a very aggressive or advanced stage, and that one marker for that might be increased levels of IL-6," he said.

The researchers ruled out cell proliferation — an increase in the number of cells present — as a reason for the increase in all three proteins. That meant the only other answer was the cells were increasing their expression of the genes responsible for producing these compounds.

The researchers showed that the norepinephrine molecule binds to receptors on the surface of cancer cells, and once this linkage occurs, it stimulates the release of the proteins that support angiogenesis and tumor growth.

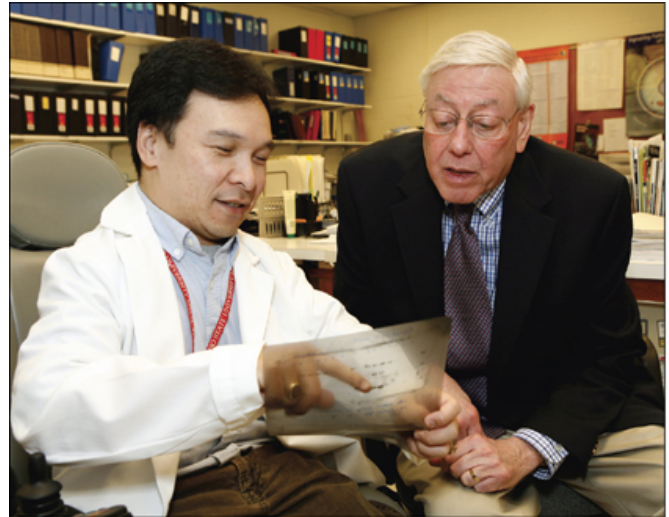
Yang and Glaser first confirmed that the receptors were present on cells in all three cell lines and then tested what would happen when the receptors were blocked by common blood pressure medicine — the so-called "beta-blockers."

When the beta-blockers did bind to the receptors, the production of the three proteins reduced significantly, suggesting that in patients with melanoma, using these types of medications might slow the progression of the disease in patients.

While the study was restricted to tumor cell lines, rather than using animal models or human patients, the findings are still exciting. The researchers found strong evidence that the same receptors are expressed on the surface of tumor cells from biopsies that were taken from melanoma patients. That supports the clinical importance of the results.

Two earlier studies on different tumor cell lines — one prepared from a multiple myeloma and the other from a nasopharyngeal carcinoma — also showed that exposure to norepinephrine increased the levels of proteins responsible for accelerating tumor growth.

The research is showing not only that different forms of cancer react differently to stress hormones but also



Eric Yang, left, a scientist at the Institute for Behavioral Medicine Research, and Ronald Glaser, professor of molecular virology, immunology and medical genetics, have worked on slowing down the progression of melanoma tumors.

Kevin Fitzsimons

The research is showing not only that different forms of cancer react differently to stress hormones but also that those reactions can vary within a specific form of the disease, with the possibility of a more aggressive form of the disease reacting more strongly to the stressors.

For melanoma patients, that can be very important since these tumors are able to metastasize, or spread, when they are much smaller than most other solid cancers. The American Cancer Society estimates that nearly 48,000 cases of melanoma are diagnosed each year and nearly 8,000 people are killed each year by the disease.

Other collaborators in the study included Sanford Barsky, professor and chair of pathology; and IBMR members Elise Donovan, Min Chen, Amy Gross, Jeanette Webster Marketon and Seung-jae Kim.

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