Housing upgrade shrinks tumors in mice with cancer

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When mice with cancer get a boost in their social life and an upgrade in living conditions, their tumors shrink, and their cancers more often go into spontaneous remission Reported in the July 9th issue of the journal *Cell*, these findings offer powerful new evidence of the critical role that social connection and an individual's mental state, may play in cancer.

Living in an environment rich with physical, mental and social stimulation - a setting that causes mild stress - might by itself curb cancer growth, according to a new study led by researchers at The Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute.

The animal study, published in the July 9 issue of the journal *Cell*, also shows how this effect happens and that it might have therapeutic use.

The researchers discovered that an enriched environment activates a nervous-system pathway by which the brain talks to fat tissue. That pathway, called the hypothalamic-sympathoneural-adipocyte (HSA) axis tells fat cells to stop releasing a hormone called leptin into the bloodstream. Leptin normally helps restrain appetite, but this study discovered that it also accelerates cancer growth.

The enriched environment had the same cancer-curbing influence in models of melanoma and colon cancer.

"People tend to think that cancer survivors should avoid stress, but our

data suggests that this is not completely true," says research leader Dr. Matthew J. During, professor of neuroscience, of neurological surgery and of molecular virology, immunology and medical genetics.

"The anti-cancer effect we observed in this study was not due simply to increased activity by the animals, but rather it was induced by social and physical challenges that are associated with the release of stress hormones from the adrenal gland.

"But the most dramatic hormonal change we observed was the drop in leptin from fat after richer housing conditions activated the HSA pathway. That pathway is also present in humans, where it is likely to be activated by a more complex and challenging life," he adds.

The enriched environment created for this study housed 20 mice in large containers equipped with toys, hiding places and running wheels, along with unlimited food and water. Control mice were housed in groups of five in smaller, standard laboratory containers with no toys but with unlimited food and water.

The researchers injected human melanoma cells under the skin in both sets of animals. After three weeks of enriched housing, mice had tumors that were about half the size of those in control mice. With six weeks of enrichment, those tumors were 80 percent smaller than those in control animals, and almost 20 percent of the animals in the enriched group had no visible tumors at all. Control animals, on the other hand, all had visible tumors.

Investigating this effect further, During and his colleagues looked for changes in several metabolic hormones in the blood. Of those, leptin showed a dramatic drop in the enriched group.

A series of experiments demonstrated that leptin and the nervous system

pathway really did influence tumor growth. Blocking the hormone altogether, for example, mimicked the enriched-environment effect, and the animals developed smaller tumors.

Looking closely at the region of the brain called the hypothalamus, the researchers found that a gene called BDNF, which plays an important role in controlling food intake and energy balance, was much more active in the enriched group.

Transplanting extra copies of this gene into the hypothalamus of mice in standard housing mimicked the effects of the enriched environment and reduced the size of the tumors in these animals by 75 percent. Blocking the gene, on the other hand, cancelled this effect and caused even enriched animals to develop large tumors.

"This is the first time anyone has shown that putting a single gene into the brain could have an impact on peripheral cancer," During says.

Next, the researchers studied a strain of mice that was unable to make leptin and so lacked the hormone altogether. Infusing these animals with leptin, however, caused them to develop melanoma tumors that were 40 percent larger than those in similar animals infused with a saline solution.

Finally, an enriched environment had a similar cancer-controlling effect in both of two colon-cancer models. In one of these, tumors develop spontaneously in the intestine; in the other, visible tumors develop after cancer cells are injected under the skin.

Using the second model, researchers discovered that the anti-cancer effect occurred when animals were placed in the enriched environment after visible tumors were well established.

"This finding suggests that such an enriched environment might have therapeutic importance," During says.

During notes that increased physical activity - running in a wheel - alone did not produce the anti-cancer effect or activate the HSA axis. In contrast, increased activity reduced levels of the stress hormone corticosterone in control animals, whereas levels of this stress hormone rose in animals in enriched housing, an outcome likely due to the challenges and social conflicts associated with larger and more complex group housing.

"Overall, our study suggests that an environmental or genetic activation of this nervous system pathway leads to a marked drop in serum leptin levels, and that this inhibits tumor growth."

More information: During, Cao et al.: “Environmental and Genetic Activation of a Brain-Adipocyte BDNF/Leptin Axis Causes Cancer Remission and Inhibition.” Publishing in Cell 142, 52-64, July 9, 2010. DOI 10.1016/j.cell.2010.05.029

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