'Reversible' tumor suppressor loss: Key to new brain cancer therapies?

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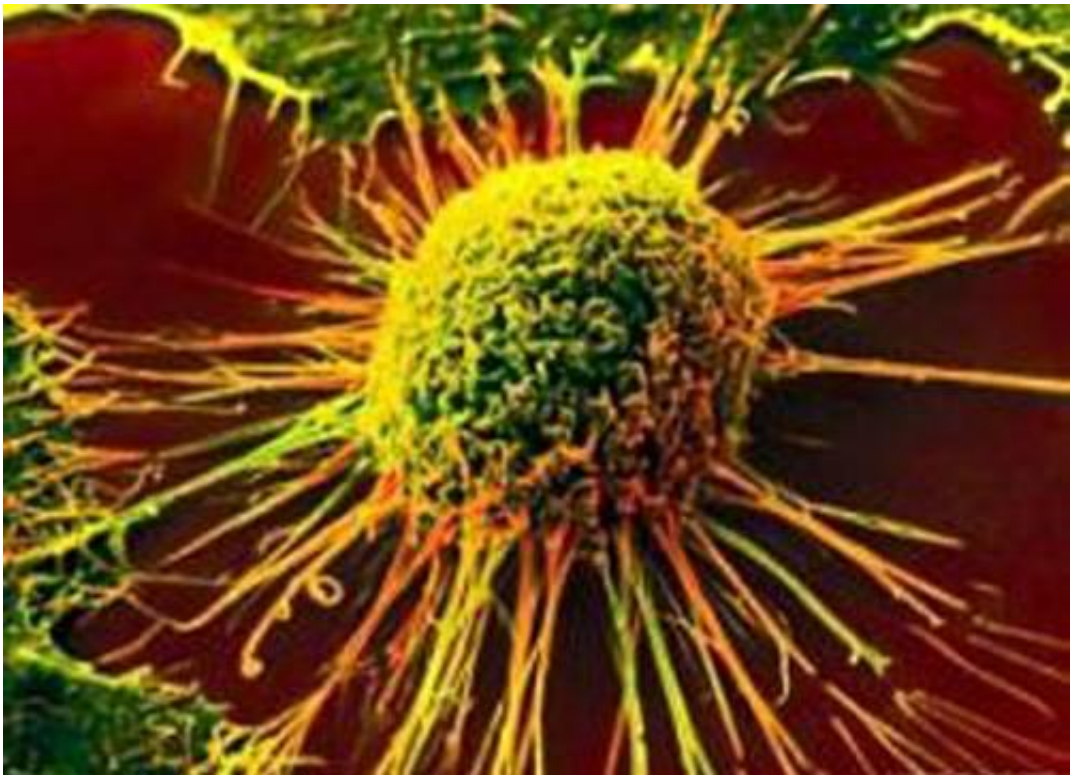

It's no surprise that people enjoy warm places like Hawaii but may suffer in hostile locales such as Antarctica. A tumor suppressor gene called PTEN is similar in that it is affected by the microenvironments of certain bodily organs to which it travels.

Scientists at The University of Texas MD Anderson Cancer Center have found that PTEN is regulated by different organs. For patients with brain metastases, this is not good, as PTEN in cells is shut off in the brain. Surprisingly, PTEN is restored once cells migrate to other organs.

It's a discovery that may be important for developing effective new anti-metastasis therapies of particular importance for advanced-stage brain cancer patients. The study findings were published in the Oct. 19 issue of *Nature*.

"Development of life-threatening cancer metastasis requires that tumor cells adapt to and evolve within drastically different microenvironments of metastatic sites," said Dihua Yu, M.D., Ph.D., deputy chair of the Department of Molecular and Cellular Oncology. "Yet it is unclear when and how tumor cells acquire the essential traits in a foreign organ's microenvironment that lead to successful metastasis. Our study showed that primary tumor cells with normal PTEN expression lose PTEN expression when they reach the brain, but not in other organs."

Yu's study found that metastatic brain tumor cells that have experienced PTEN loss have PTEN levels restored once they leave the brain. They determined that the "reversible" PTEN loss is induced by micro RNAs (miRNAs) from astrocytes located in the brain and spinal cord. Astrocytes, so called for their star shape, secrete exosomes that contain PTEN-targeting miRNAs and transfer PTEN-targeting miRNAs inter-cellularly to tumor cells via exosomes. Exosomes are tiny, virus-sized particles. MiRNAs are non-coding molecules known to play a role in regulation of gene expression.

The team also found that the PTEN loss in brain tumor cells led to an increased secretion of a cytokine known as CCL2, which recruits brain cells known as microglial cells to metastatic tumors. This enhances tumor cell growth and protects tumor cells from cell death, which leads

to life-threatening brain metastases.

"Our findings demonstrate a remarkable plasticity of PTEN expression in metastatic tumor cells in response to different organ environments, underpinning an essential role of co-evolution between the tumor cells and their microenvironment," said Yu. "This signifies the dynamic and reciprocal 'cross talk' between tumor cells and the metastatic environment. It may provide new opportunities for effective anti-metastasis therapies, particularly for advanced-stage brain cancer patients."

More information: Microenvironment-induced PTEN loss by exosomal microRNA primes brain metastasis outgrowth, DOI: 10.1038/nature15376

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