Gene deletion allows cancer cells to thrive when migrating within the brain

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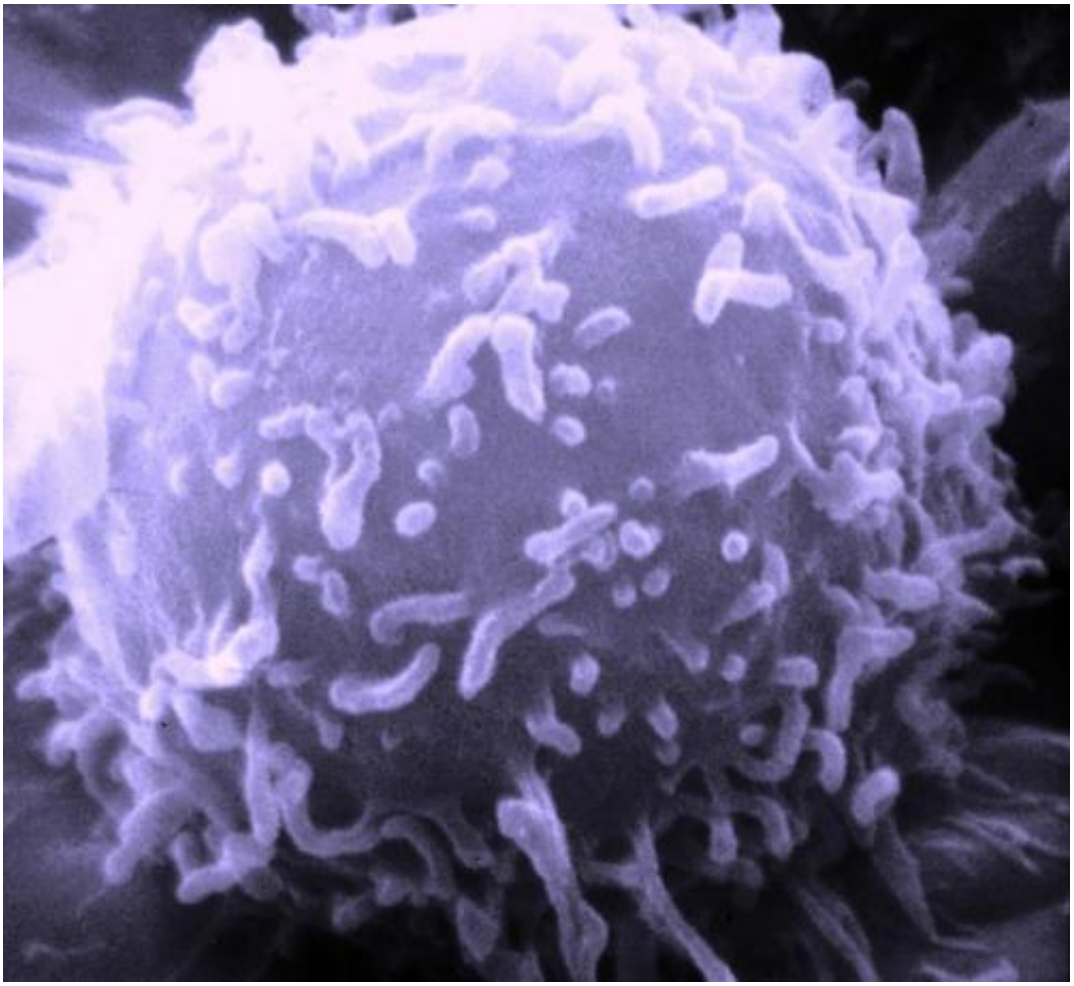

Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

Astronauts survive in space by wearing high-tech space suits. But how do brain cancer cells thrive when they migrate to inhospitable sites within the brain?

A study at The University of Texas MD Anderson Cancer Center believes their survival may be due to deficiency of a tumor suppressor gene called quaking (QKI), a potential new target for therapies. Findings from the study, led by Jian Hu, Ph.D., assistant professor of the Department of Cancer Biology, were published in the Nov. 14 online issue of *Nature Genetics*.

"Cancer stem cells require 'niches' to remain viable but it is unclear how they survive in an environment outside of these niches both within the same tissues or during invasion to other organs," said Hu. "We discovered that QKI is a major regulator of these cancer stem cells in glioblastoma, the deadliest type of brain tumor."

"Evidence is emerging that some brain cancer cells called glioma stem cells possess an inexhaustible ability to self-renew and produce tumors that resemble the features of original tumors," said Hu.

Self-renewal is a unique feature of all stem cells that creates identical "daughter" stem cells. To maintain this ability, they must be in a suitable environment providing them proper cellular cues. Hu's team knew that glioma stem cells thrived when they reside in niches, such as structures called subventricular zone, due to their ability to self-renew.

"However, left unanswered is how glioma stem cells still manage to maintain this 'stemness' when they invade and migrate from their niches to other areas where optimal niches are less likely to be available," said Hu.

The research team believed glioma stem cells must acquire the ability

for stemness maintenance independent of their niches during invasion and migration. Using a mouse model, they studied deletion of major suppressing genes including QKI to see what correlation might exist.

"Our previous studies showed that QKI is one of the tumor suppressor genes that can potentially regulate cancer stem cells and we confirmed this in our latest investigation," said Hu.

QKI impacted a vital cellular activity called endocytosis, responsible for degrading the cell receptors that are essential for maintaining stem cell self-renewal. Loss of QKI can greatly enrich the level of these receptors and consequently enhance the self-renewal capacity even when glioma stem cells are not in the niches. Just as a space suit protects the astronaut from the dangers of space, a deficiency of QKI makes the new environment safe for the transported cancer stem cell.

"This study may lead to cancer therapeutic opportunities by targeting the mechanisms involved in maintaining cancer stem cells," said Hu. "Although loss of QKI allows glioma stem cells to thrive, it also renders certain vulnerabilities to the cancer cells. We hope to design new therapies to target these."

More information: Qki deficiency maintains stemness of glioma stem cells in suboptimal environment by downregulating endolysosomal degradation, *Nature Genetics*, nature.com/articles/doi:10.1038/ng.3711

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