Researchers leverage cell self-destruction to treat brain tumors

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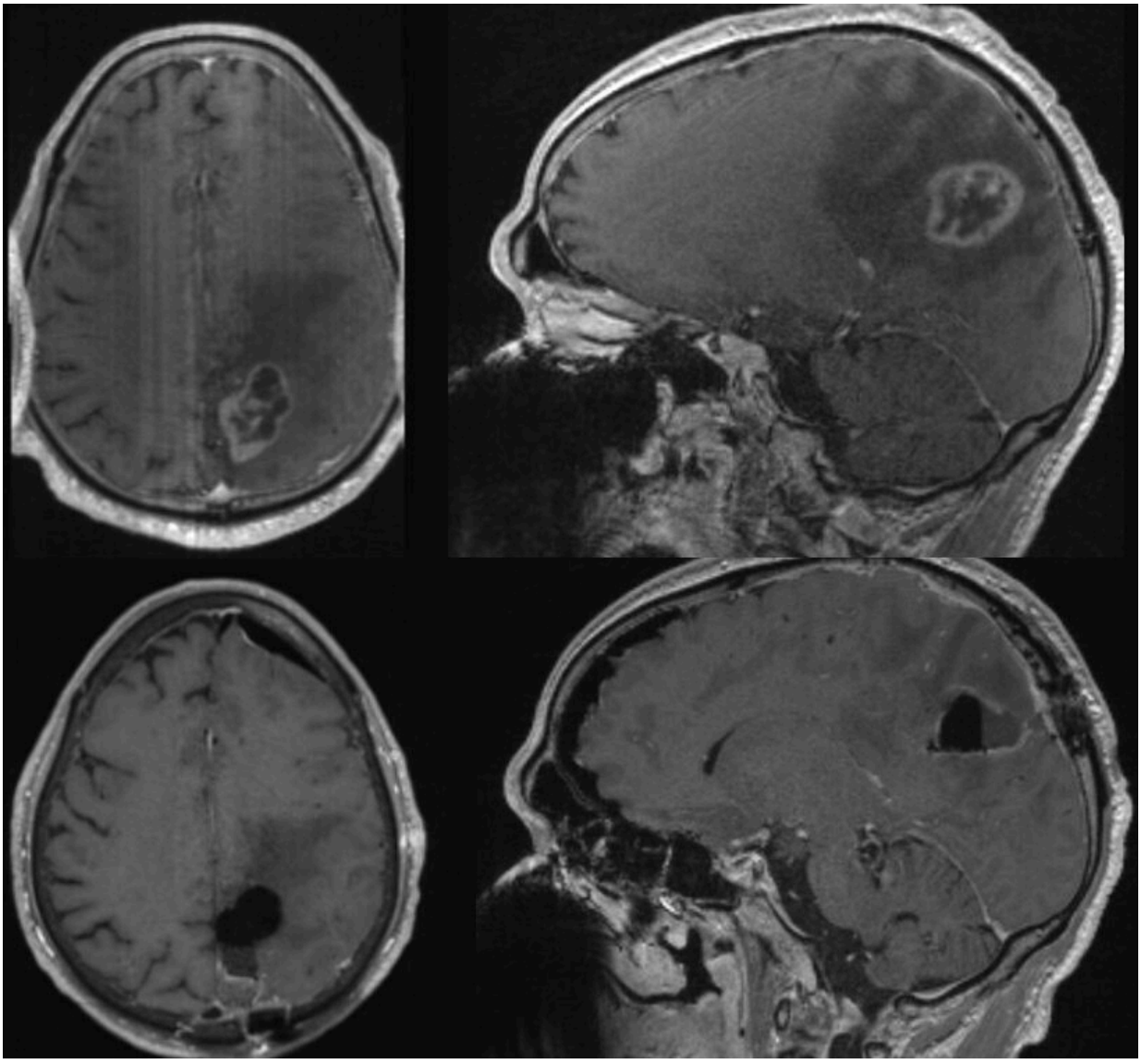


An MRI showing glioblastoma pre- and post-operation. Credit: Dominique

Higgins, MD, PhD

Glioblastoma is the most common type of brain tumor in adults. The disease is 100% fatal and there are no cures, making it the most aggressive type of cancer. Such a poor prognosis has motivated researchers and neurosurgeons to understand the biology of tumors with the goal of creating better therapies.

Dominique Higgins, MD, Ph.D., an assistant professor in the Department of Neurosurgery, has heeded the call. Higgins and a team of researchers at Columbia University have found that glioblastoma tumor cells are particularly sensitive to ferroptosis—a type of cell death that can be triggered by removing certain amino acids from the diet.

"First, we found that when we take away certain amino acids in animal models that the glioblastoma cells are more likely to die by ferroptosis," said Dr. Higgins. "Secondly, we found that removing these amino acids makes our drugs a lot more effective at inducing ferroptosis in cancer cells."

Their findings were published in *Nature Communications*.

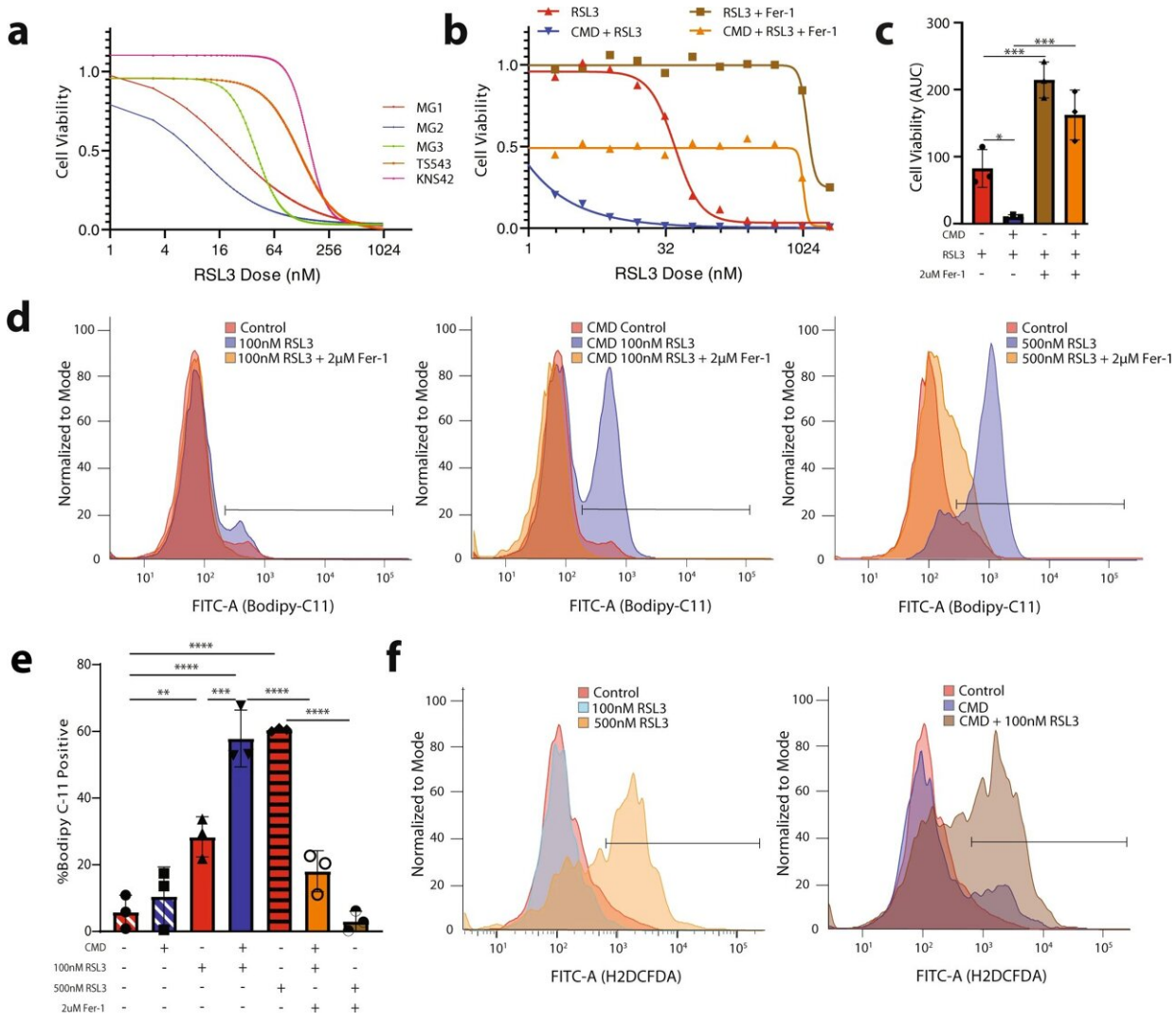
Ferroptosis is an iron-dependent type of "programmed cell death" or a biological process that causes cells to "self-destruct" on command. Our bodies don't need to kill cells unless absolutely necessary, so the process is tightly controlled by certain biological mechanisms. However, researchers are only now beginning to comprehend the process because ferroptosis was recognized only a decade ago.

"The recent discovery of ferroptosis adds to the excitement of it all," said Higgins, who is a member at the UNC Lineberger Comprehensive

Cancer Center. "It is really a rapidly growing body of research, and we are finding that it's a very important for a lot of biological processes, and not just in cancers."

Every cell has certain safety features to keep it from going through ferroptosis in an unpredictable way. Two amino acids, cysteine and methionine, are critical for preventing the process from starting in cells. We typically pick up these amino acids through our diet.

Therefore, Higgins' research team decided to focus their efforts on these components.



Cysteine and methionine deprivation (CMD) sensitizes glioma to RSL3-induced ferroptosis. **a** 384-well dose-response curves showing response to RSL3 from 5 glioma cell lines: MG1, MG2, MG3, TS543, and KNS42. **b** Representative 384-well dose-response showing MG3 cells treated with RSL3 (red), RSL3 plus 2 uM Ferrostatin-1 (brown), CMD plus RSL3 (blue), CMD plus RSL3 and 2 uM Ferrostatin-1 (orange). **c** AUC quantification for dose response curves from 3-independent 96-well dose response curves of MG3 murine glioma cell lines treated with RSL3 ± CMD ± 2 uM Ferrostatin-1. **d** Representative Bodipy-C11 flow data from MG1 cells: left panel shows DMSO control (red), 100 nM RSL3 (blue), and 100 nM RSL3 plus 2 uM Ferrostatin-1 (orange) treatment for 30 min. Middle panel shows the same conditions but with 6 h of cysteine methionine deprivation pretreatment. Right panel shows a higher dose of RSL3 treatment (500 nM). **e** Quantification of 3 independent experiments demonstrated in **d**. **f** Flow cytometry, using H2DCFDA of ex vivo organotypic slice cultures from a human primary glioblastoma (CUMC TumorBank 6193) cultured in control or CMD media and treated with RSL3. Data for **c** and **e** are presented as mean ± SD. Significance denoted by: *p