Scientists find key driver for treatment of deadly brain cancer

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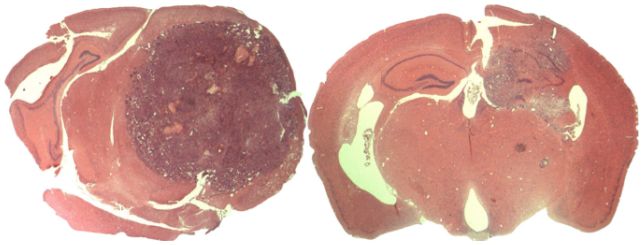

Scientists at the Salk Institute have discovered how a protein helps glioblastoma proliferates so quickly and how to turn off this engine of tumor growth using a peptide called NBD. A tumor in an untreated mouse brain (left) grew much more than a tumor treated with the NBD peptide (right). Credit: Salk Institute

Glioblastoma multiforme is a particularly deadly cancer. A person diagnosed with this type of brain tumor typically survives 15 months, if given the best care. The late Senator Ted Kennedy succumbed to this disease in just over a year.

But scientists at the Salk Institute have discovered a key to how these tumor cells proliferate so quickly —and ways to turn this engine of tumor growth into a target for cancer treatment.

"This is a disease for which there has been practically no improvement in treatment outcome for years," said Inder Verma, professor in the Salk Institute's Laboratory of Genetics and senior author of the paper published January 8, 2016 in the journal *Science Advances*. "It is clear that even if a surgeon removes 99.99 percent of a glioblastoma multiforme tumor, what is left behind will come back and grow into more tumor."

To study how glioblastoma multiforme spreads, Verma's team focused on a transcription factor called nuclear factor kB (or NF-kB). A transcription factor is a protein that binds to DNA and controls the fate of gene expression for a particular set of genes. Several known factors can trigger NF-kB activity in a cell, including ultraviolet and ionizing radiation, immune proteins (cytokines) and DNA damage.

In the case of glioblastoma multiforme, Verma and colleagues ran a battery of tests to show how overzealous NF-kB activity pushed the cancer cells to proliferate, and how stopping NF-kB slowed cancer growth and increased survival.

Scientists Dinorah Friedmann-Morvinski and Inder Verma find key driver for treatment of deadly brain cancer. Credit: Salk Institute

"Our experiments confirmed that NF-kB is required for the cancer cell to proliferate," says Dinorah Friedmann-Morvinski, first author of the paper and currently a researcher in the department of biochemistry and molecular biology at Tel Aviv University in Israel. "But now we have finally found a way to ameliorate the tumor to increase lifespan."

Verma's team started with a mouse model of glioblastoma multiforme and used genetic tools to manipulate cells into shutting down NF-kB activity

in two ways. The team ramped up the presence of a protein called IkBaM, which inhibits NF-kB activity. They also eliminated an enzyme that increases NF-kB activity. With less NF-kB activity, tumor growth slowed and mice lived significantly longer then mice whose NF-kB activity was left alone. But while these genetic experiments demonstrated the role of NF-kB in glioblastoma multiforme, they aren't a feasible treatment in humans.

"So we asked how could we manipulate the system using pharmacology rather than genetics," says Verma.

Scientists have long suspected that one reason why glioblastoma multiforme comes back so quickly after surgery is the so-called tumor microenvironment. In other words, a tumor changes the environment of its surroundings (nearby tissues) to make it easier for cancer cells to thrive, Verma explains.

Instead of using genetic tools, Verma and colleagues sought to treat the brain tumors in a way that also changed the tumor microenvironment. The scientists fed mice a peptide (called NBD) that is known to block NF-kB activity when NF-kB is triggered by cytokines (proteins produced by the immune system). The NBD peptide easily travels across the central nervous system, and can successfully penetrate glioblastoma tumor cells. Treating mice with the NBD peptide doubled their typical survival time compared to mice that didn't get the NBD peptide.

"We could increase survival time from one month without treatment to three months with treatment," says Verma. "That's a profound increase in life expectancy, especially considering a mouse only lives for two years." Yet, while the NBD peptide kept the tumors at bay, the peptide treatment eventually causes toxicity, most likely in the liver. So researchers explored another tactic to slow NF-kB activity.

Curbing NF-kB activity can be tricky because NF-kB has many important roles: it helps regulate cell survival, inflammation and immunity among many other functions in the cell.

"The ultimate goal is to block NF-kB, but because it turns on many genes—at least 100—our aim became finding the handful of genes that directly affect tumor growth," says Verma. "Then we can be more selective in treatment."

Salk scientists tracked which genes were influenced by NF-kB and found one, Timp1, which has been previously implicated in lung cancer. Targeting the Timp1 gene in treatment also slowed tumor growth and increased survival time in mice by a few months.

"In the future we want to focus on ways to reduce the toxicity of anti-NF-kB drugs," said Friedmann-Morvinski. "We may do this by specifically targeting these drugs to the tumor, or by identifying downstream targets of the NF-kB pathway, like Timp1, that also prolong survival." Further experiments may identify treatments that target NF-kB activity in a safe, but effective way.

More information: "Targeting NF-?B in glioblastoma: A therapeutic approach," by D. Friedmann-Morvinski; R. Narasimamurthy et al. *Science Advances*, advances.sciencemag.org/content/2/1/e1501292

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