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Gene plays 'Jekyll and Hyde' in brain cancer

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Perhaps the only positive spin one can put on the brain cancer glioblastoma is that it's relatively uncommon. Other than that, the news is bad. It is nearly always fatal, it tends to strike people in the prime of their lives, and the limited treatment options have changed little over decades. It's no wonder then that many researchers are determined to find new ways treat this poorly understood type of cancer.

One approach focuses on a gene called STAT3. In several tumors, STAT3 takes the role of an oncogene, that is, a gene whose normal functions are derailed and, as a result, becomes a driving force in a tumor's development. Clearly then, blocking STAT3 would deal a major blow to such tumors.

But a new study led by a team at Harvard Medical School has found that STAT3 isn't always the villain. While it does behave as an oncogene in certain types of glioblastoma, in others it becomes what's called a "tumor suppressor gene," a type of gene often responsible for keeping the renegade cancer cells in check.

In other words, the same gene in the same cancer can play a completely different role from one person to the next, depending on genetic nuances between individuals. The results appear online February 6 in Genes and Development.

"This discovery lays the foundation for a more tailored therapeutic intervention," says Azad Bonni, an associate professor of pathology at Harvard Medical School, and senior author on this study. "And that's

really important. You can't just go blindly treating people by inhibiting STAT3."

When most people think of brain cells, they think of neurons, those cells whose electric signaling gives rise to our consciousness. But another class of brain cells called astrocytes (named after their uncanny resemblance to stars) actually outnumber neurons ten to one. Despite their name, astrocytes play a less glitzy role than neurons do. Typically, they're support cells, involved with functions such as providing nutrients to nerve tissue and repairing scars. However, nearly all brain cancers occur in astrocytes, or in the neural stem cells that generate astrocytes.

Bonni, a neurologist and neuroscientist by training, decided to investigate the genetic etiology of glioblastoma by studying whether certain regulatory genes that control the generation of astrocytes during normal development also play a role in these tumors. The logic here is simple: since disease is often the breakdown of a normal biological process, the more we understand how cells get it right, the more we understand what can go wrong. And since STAT3 is a key gene that turns neural stem cells into astrocytes during normal development, what is its role in glioblastoma"

Bonni and two lead authors, Núria de la Iglesia and Genevieve Konopka, in collaboration with investigators in the laboratory of Ronald DePinho at the Dana-Farber Cancer Institute, began by genetically manipulating mouse astrocytes, then placing them into a second group of mice whose immune systems had been compromised. The findings surprised them.

Taking advantage of previously published data, the researchers looked closely at how two genes, EGFR and PTEN—whose mutated forms are associated with glioblastoma—affect the function of STAT3 in astrocytes. Bonni's group found when EGFR is mutated, STAT3 is an oncogene; with a PTEN mutation, STAT3 is a tumor suppressor.

“EGFR, in its normal state, is a transmembrane receptor, usually performing its functions at the cell surface,” says Bonni. “However, when it’s mutated, we find it in the cell’s nucleus interacting with STAT3—and turning it into an oncogene. STAT3 itself is not mutated or damaged. It’s the process of regulating STAT3 that gets damaged.”

With PTEN, it’s a completely different story. PTEN is itself a tumor suppressor gene. When PTEN becomes disabled in astrocytes, these potential tumors still have STAT3 standing in their way. This is because STAT3 acts as a tumor suppressor normally in astrocytes. However, as more PTEN becomes disabled, a cascade of molecular events is set in motion with the express purpose of inhibiting STAT3 function and thus turning the tide in the cells toward tumor formation.

The researchers confirmed these findings in human glioblastoma tumors as well.

“The belief that STAT3 can only be an oncogene has been a pretty entrenched dogma in the field,” says Bonni, “so we performed many, many experiments to make sure this was correct. It took some very persistent investigators in my lab to get the job done. As a result, we’re convinced of our data.”

While glioblastoma tends to be uncommon, STAT3 has also been implicated in prostate and breast cancers, so these results may translate to other types of tumors as well.

In addition, the findings contribute to the growing body of evidence for “personalized medicine,” showing that many types of cancers contain subgroups that require different treatments.

Source: Harvard Medical School