Mapping the Genetic Landscape of Brain Tumors

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Dr. Murat Günel

Meningiomas are the most common brain tumor, striking 170,000 Americans every year. Until recently they have largely been mysteries to medicine. Part of that mystery was solved earlier this year by a team of researchers led by Dr. Murat Günel, Professor of Neurosurgery, Neurobiology, and Genetics. Their discoveries promise to alter clinical treatment of patients afflicted with these tumors. The research was funded by a generous grant from the Gregory M. Kiez and Mehmet Kutman Foundation, which allowed the formation of the Brain Tumor research program at Yale.

Unlike more familiar brain tumors such as glioblastomas and medulloblastomas, which are ferociously malignant, fast growing, and usually fatal, meningiomas grow slowly and are benign 80 percent of the time. Nevertheless they can invade or pressure critical parts of the brain, causing neurological damage or stroke. They are typically treated through the invasive options of surgery or radiation. "There have been no chemotherapy options," Dr. Günel said, "because the genetic make-up of meningiomas has not been understood. Before our work, we largely did not know how these tumors happened."

Previous research had linked about half of meningiomas to a mutation of the gene NF2, though the mechanism remained unclear, as did the cause of all other meningiomas. To remedy this, Dr. Günel and his team took advantage of what he calls "the revolution of genomic technologies," carrying the cutting-edge research methods to the care of his patients after surgery. For a brain surgeon, he said, the most frustrating aspect is not to be able to cure a patient of their disease after a successful surgery. To gain a better insight into the genetic make-up of brain tumors in an attempt to achieve cure, his team, starting with Victoria Clark, a Yale MD/PhD student, genotyped and exome sequenced 300 meningioma tumors.

"We found that mutations of five genes explain around 85 percent of all benign meningiomas," Dr. Günel said. The roles played by four of the genes—AKT1, SMO, KLF4, and TRAF7 (the fifth is NF2)—were previously unknown. Further, the researchers learned that the tumors generated by these mutated genes grow in different parts of the brain. Tumors associated with NF2, for instance, tend to form in the cerebral hemispheres, whereas tumors associated with the other four genes group in areas along the front skull base.

"Thus, for the first time," wrote the team in *Science* (January 24), where the findings were announced, "it seems that the simple evaluation of a patient's MRI can offer insight into the molecular profile of the meningioma."

This genetic mapping and the resultant diagnostic insights will open the way for individualized treatments that target each type of meningioma. For instance, SMO mutations have been found in basal cell skin carcinoma and brain medulloblastomas. "There is already an FDA-approved drug for basal cell carcinoma," Dr. Günel said, "so we are testing it in the lab using cell cultures to see if the same drug has an effect on SMO mutant meningiomas." If so, he expects to begin clinical trials on patients with these tumors early in 2014.

That's good news, but SMO mutations account for less than five percent of meningiomas. NF2 mutations, on the other hand, are implicated in half of meningiomas but are not yet targeted by an FDA-approved drug. That's especially troubling since NF2 meningiomas are also the most likely to become malignant.

"But there are certain clear targets downstream of NF2 that are activated when NF2 is lost," Dr. Günel explained. "In our lab we are now testing experimental medications aimed at those." They hope to finish the testing on cell cultures within a year and then move to clinical trials. Meanwhile researchers at other institutions are in the midst of phase-II trials for a drug aimed at NF2 tumors in other types of cancer. Dr. Günel's team will incorporate those results into their studies. "There's a tidal wave of cancer research that is raising all of us," he said. "We're all learning from each other in the different cancer disciplines."

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The Yale researchers found a TRAF7 mutation in about a quarter of the meningiomas. Almost nothing is known about this gene, but wherever the team found its mutated form, they also found a better-known partner—either KLF4, a transcription factor, or AKT1, which activates the PI3K pathway. The PI3K pathway is well-known and has been implicated in cancer; several medications against it are now in clinical trials. Since TRAF7 is unstudied, Dr. Günel and his team are hoping to track its mutation through its co-existence with AKT1 and the PI3K pathway.

"It's interesting that they co-mutate," he said. "So what we are testing is, can a PI3K inhibitor affect that TRAF7 tumor? If the inhibitor breaks one leg of the cancer, can the cancer still run or does it stop?" If the PI3K inhibitor brakes the TRAF7 meningioma, the next step will be to figure out the downstream signaling mechanism of TRAF7. Because all this is unknown territory, Dr. Günel expects that exploring this gene will require more time than the other mutations associated with meningiomas.

Still, Dr. Günel's team has described the genetic landscape for 85 percent of these tumors. Drugs that target each specific mutation are on the way and will soon give people with meningiomas the option of personalized chemotherapy, which will be more effective and also less invasive than the current options of surgery and radiation. In fact, Dr. Günel and his colleagues at Yale Cancer Center now have a weekly Precision Medicine Tumor Board, in which they discuss the use of targeted therapies based on the individual genomic make-up of various cancers.

The genetic mapping of benign meningiomas was relatively easy to solve, noted Dr. Günel, because they have far fewer genetic abnormalities than cancerous tumors. "But the good thing," he adds, "is that it turns out there are not infinite ways that nature creates cancer. There are only a limited number of genes involved." The new genomic technologies are tracking these down, followed quickly by new drugs that target them.

For a brain surgeon, the biggest target is the most deadly brain cancer, glioblastoma multiforme (GBM). Dr. Günel is optimistic. "We have some really exciting findings," he said. "Next time, I hope we can talk about curing some of the GBMs."