Cellular 'racetrack' accurately clocks brain cancer cell movement

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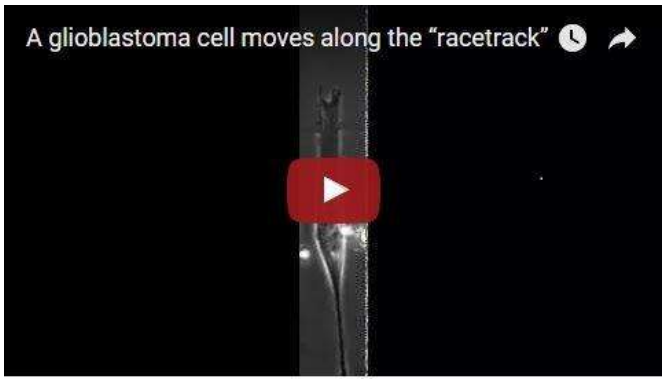

Timelapse photography shows a single glioblastoma cell migrating along a special slide. Credit: *Cell Reports*

Johns Hopkins Medicine researchers report they have developed an experimental laboratory test that accurately clocks the "speed" of human brain tumor cell movement along a small glass "track." The assay, so far tested on the cells of 14 glioblastoma patients, has the potential, they say, to predict how quickly and aggressively a given cancer might lethally spread.

"After I remove a brain tumor from a patient, the patient always asks me, 'Doc, how long do I have?' I don't have a reliable way to answer them," says Alfredo Quinones-Hinojosa, M.D., director of the Brain Tumor Surgery Program and professor of neurosurgery at the Johns Hopkins University School of Medicine. "But we have taken a step to creating a possible way to provide useful updates, inform treatment choices and perhaps develop new treatments faster."

According to the National Institutes of Health's Cancer Genome Atlas, glioblastoma—an aggressive cancer of the glial cells of the brain—accounts for about 15 percent of all adult brain tumors in the U.S., and even with surgery and other treatment, only 3 to 5 percent of people with the tumor survive five years.

In a report on the newly developed assay, published online June 9 in *Cell Reports*, the Johns Hopkins researchers say their "racetrack" test using chemically primed glioblastoma cells from different tumors removed surgically lets them visualize which cancers most quickly move, mimicking the initial migration that leads to brain cancer invasion.

Quinones-Hinojosa says results of several experiments with the assay suggest that tumors with the fastest cells paralleled the quicker recurrence and other clinical outcomes of 14 glioblastoma patients at The Johns Hopkins Hospital. Further and larger studies are need to confirm the assay's ability to determine the behavior of these cells, he cautions, but the research is a significant step because cell migration rates—and survival time—cannot be predicted using available genetic- or protein-based tests designed to predict treatment response.

The researchers designed the cell racetracks, which they described earlier in a 2012 *PLOS Biology* study, by engineering a glass slide with tiny plastic, parallel ridges going down its length. The ridges were designed to simulate the ridged surface of the brain, where migrating cancer cells move along the grooves of the white matter and blood vessels, following them like roadways, Quinones-Hinojosa says.

For the new experiments, the researchers first identified a chemical way to start the cell's engines and get them moving along the slide using platelet-derived growth factor (PDGF), which it's known to stimulate rapid growth in gliomas.

They tested PDGF to see if it would prime the glioblastoma cells for movement rather than growth by growing the glioblastoma cells from two different tumors on the racetracks with 20 nanograms per

milliliter of PDGF. When they placed these tumor cells on the slides for 24 hours, they took videos of the cells and measured their speed. Some cells from one of the tumors—belonging to the fastest 25 percent of cells from that tumor—responded to the PDGF treatment by moving about two times faster than controls made up of untreated glioblastoma cells. Conversely, the slowest 25 percent of the cells in the tumors moved at the same slower pace as the control tumor cells, meaning that PDGF strongly affected the faster cells.

"We learned from this experiment that we couldn't take the average of the fast and slow cells from each tumor because that would mask differences in the speedy outliers," says Quinones-Hinojosa. "We had to pay attention to the cells moving very fast because these are the really bad cells that we believe are going to cause the tumor to spread."

To see if their speed test had the potential to predict which brain tumors were the most aggressive, the scientists grew cells from 14 patient glioblastomas in PDGF, then placed them on the racetracks. Separately, they assessed 35 clinical factors in each of the patients, including measures of general health, tumor size, tumor shape, patient age, drug treatment and recurrence time after surgery.

When they compared the clinical data to the to the racetrack results, the researchers found that five patients with the fastest tumor cells had recurrence of their cancers within six months. The six patients with slower tumor cells had no recurrence between six and 22 months.

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