UC SANTA BARBARA

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Light-triggered stress response suppresses glioblastoma spread in 3D models

UC Santa Barbara researchers have found that triggering a stress response in glioblastoma cells, a type of aggressive brain cancer, can suppress their growth and invasion. Their findings suggest new therapeutics in the treatment of the hard-to-access tumors.

“There might be some interesting way to sensitize cancer stress responses to make chemotherapy drugs more useful or efficacious,” said synthetic biologist Max Wilson, a senior author on a paper published in the journal Cell Biochemistry & Function.

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Shining a light on glioblastoma

When our cells are subjected to stress, our cellular responses allow us to adapt, from wound healing to immune reactions to programmed cell death and other complex processes. Largely unchanged by evolution over millennia, this integrated stress response (ISR) is one of the body’s ways of adapting to stress, and preventing damaged cells from causing further damage to our bodies. Scientists have long

recognized the powerful role of the ISR in battling illness and injury, and enabling healing and recovery, but the task of connecting stress responses to individual illnesses, injuries and conditions has been a challenge.

Cancer presents a particularly sticky and intriguing puzzle for the research team. Tumors develop in and create highly stressful environments. They also seem to have found a way around the stress responses that would hinder or prevent a normal cell from growing in such environments.

“Cancers and tumors, by virtue of the fact that they’ve undergone rapid evolution in their genomes to maximize their growth rate, not only create what would feel to a normal cell as a stressful environment, it’s also increasingly clear that they rewire the stress response,” explained Wilson, an associate professor of molecular, cellular and developmental biology. While our stress responses make our normal cells more robust to stress, he added, “those cancer cells may have a tendency to try to hijack those stress responses to make themselves more robust.”

Of the cancers that can develop in the human body, glioblastomas are among the most difficult to treat. They’re located in the brain, which makes them very hard and highly risky to access, and their ability to spread makes any surgical intervention a huge challenge.

“One thing that’s very striking about a glioblastoma tumor is that it has all these tendrils that reach out and invade the neighboring tissue,” Wilson said. “So you can’t just cut a big hole around it to make sure you’ve got everything; you need to preserve as much brain as possible.”

Meanwhile, cancer treatments such as chemotherapies and radiation are typically the first line of treatment for the tumors, but such measures also cause stress and damage to the body.

What if there was another route to the tumor? Enter the Wilson Lab’s optogenetic ISR platform. Developed to tease out cellular stress responses, the platform uses light to create “virtual stress,” which triggers the ISR response without the actual physical stress or damage that could confound efforts to trace this signaling pathway.

“What that allows us to do is to look at the pure response to stress for the first time in these cells and understand what can be attributed to the response to stress in these cancers versus what can be attributed to the damage that is inducing the stress,” Wilson said. In previous work, the Wilson Lab showed that engineering control over the appropriate ISR pathway could allow for the screening of compounds and small molecules that could underlie new therapies for viral infections, with proof-of-concept results against Zika, herpes and respiratory syncytial virus.

By engineering glioblastoma and related brain tumor cells with photo-responsive proteins from plants, the researchers were able to activate the ISR in those cells with light alone — a so-called “virtual stress.” They found that the virtual stress dialed down the cells’ migration genes and cut the collagen they laid down into the extracellular matrix — the protein scaffold that tumor cells build and remodel as they push into surrounding tissue.

Led by graduate student researcher Lisa Månsson, the study’s lead author, the team then engineered the cells into mini 3D tumors by placing them into collagen-based cultures to see how they interacted with their neighborhood, similar to what would be happening in the brain.

“And we noticed that when we virtually activated the stress responses, we totally inhibited the invasion,” Wilson said. Switching the light off after a day let the cells resume their invasion within two days, and surprisingly, he added, only the side of the mini tumor that was subjected to light would stop growing. Meanwhile the unstressed side continued its invasion business as usual, when the expectation was that the entire tumor would respond. “I think it alludes to the fact that cancer also has to become more selfish than the rest of our body,” he said. The idea is that the stress might be inhibiting the tumor’s ability to make new proteins, but how that is coupled to migration at the molecular level remains to be studied.

This development, though still at very early stages, points to new possibilities in cancer therapeutics. In identifying the precise stress pathway for the cancer, it may become possible to formulate drugs that can trigger the ISR pathway to more precisely target the tumor and halt its progress without the kind of damage and side effects that often come with conventional chemotherapy. The experiments were done in cells grown in collagen rather than in animals, and the light-based tool is a

laboratory instrument for dissecting the pathway, rather than a proposed treatment, Wilson said.

“Right now, all cancer therapeutics are focused on killing the cancer, and rightly so,” he said. “But what if we just modified their behavior in a way that made it easier to cut out, or would allow you to live with it?” Such a strategy could be a new direction for hard-to-access cancers like glioblastoma.

Research in this paper was also conducted by Ethan Dickson, Lun Hao and senior author Angela A. Pitenis, all at UCSB.

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