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U of L researchers working to unravel the mystery behind one of the deadliest forms of cancer

A team of researchers at the University of Lethbridge is conducting research in a quest to uncover the mechanisms that make glioblastoma such an aggressive cancer, with hope the results could lead to new therapeutic interventions in the future.

Glioblastoma (GBM), the brain cancer that killed Gord Downie of The Tragically Hip and former American senator John McCain, has a dismal prognosis and survival rate.

“The median survival rate is about 15 months, even after chemotherapy, surgical removal of the tumour and radiation therapy,” says Dr. Nehal Thakor, a professor in the Department of Chemistry & Biochemistry and Campus Alberta Innovation Program Chair of Synthetic Biology and RNA-based Systems. “We are trying to understand how these cancer cells bypass cell-death pathways.”

Cell death, or apoptosis, occurs as a normal and controlled part of growth and development. In glioblastoma, cancer cells evade death, even after treatment, and continue to multiply in an uncontrolled fashion.

“What we’re really trying to understand is how these cancer cells are so good at surviving when they’re not supposed to,” says Dr. Joe Ross, a postdoctoral fellow in Thakor’s lab. “Why are they so good at surviving chemotherapy and radiation? It turns out that one of the things they’re really good at doing is translating proteins and the wrong types of proteins when they’re not supposed to.”

The team is focusing on mRNA (messenger RNA) and the factors that regulate translation of mRNAS that are involved in cell survival mechanisms. Messenger RNA carries genetic information from DNA to the ribosome, the part of the cell in charge of protein synthesis that allows important bodily functions to be carried out. In particular, Thakor and his team are looking into eukaryotic initiation factor 5B (eIF5B), a protein involved in the accurate initiation of translation from mRNA to protein.

“The eIF5B protein has been shown to play a role in normal translation but when cancer cells hijack normal processes and make them do abnormal things or make too much of certain

proteins, that can cause the cells to evade apoptosis, or programmed cell death," says Kamiko Bressler, a master's student who is part of the team. "Glioblastoma is especially good at that, which is why it's so hard to treat."

The study has shown that eIF5B is important for the translation of several proteins that all play anti-death roles, says Ross. That creates a double whammy because not only do the cells not die when they're supposed to, they also grow faster than they should.

Thakor and his team, which also includes Mikayla Fredriksen, Divya Sharma, Keiran Vanden Dungen and Nirujah Balasingam, recently learned their study, titled *Eukaryotic initiation factor 5B (eIF5B) provides a critical cell survival switch to glioblastoma cells via regulation of apoptosis,* has been accepted for publication in the *Cell Death & Disease* journal (SpringerNature/CDD press).

The team is now working with brain-tumour stem cells (BTSCs) to see if the cancer cells will grow in the absence of eIF5B or if they become more sensitized to therapeutic interventions. BTSCs are the main cause of relapse.

"If we can target eIF5B using a small molecular compound, then we can treat not only glioblastoma but other types of cancer that have similar mechanisms in place," says Thakor. "This proof-of-concept project has the potential to decode information related to the clinical management of GBM and will have an important beneficial impact on the health of Canadians."

This news release can be found online at glioblastoma research.

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