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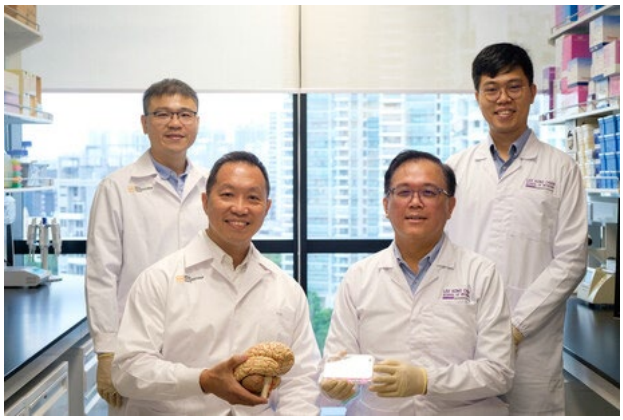
A new approach to treating drug-resistant glioblastoma



Glioblastoma is an often fatal form of brain cancer, with only 5% of patients surviving past five years as recurrence is almost inevitable. Now, Singaporean researchers have made a discovery that could pave the way for more effective and precise therapies for this deadly disease, preventing the cancer from recurring. Their work has been published in the journal *Neuro-Oncology*.

Currently, a chemotherapy drug called temozolomide (TMZ) is used to treat glioblastoma by damaging the DNA of cancer cells, preventing the cells from dividing. However, glioblastoma almost always grows back as the cancer eventually develops resistance to TMZ. This is because glioblastoma tumours consist of populations of cells with different properties — a characteristic known as genetic heterogeneity — making it more likely that some cells will adapt to and resist the treatment. There is also a dearth of treatment options for resistant glioblastoma, as not many drugs can cross the blood–brain barrier.

To understand the cellular mechanism behind drug resistance and find potential drug targets for resistant glioblastoma, researchers at Nanyang Technological University, Singapore (NTU Singapore) and the National Neuroscience Institute (NNI) compared the activity of protein kinases — enzymes involved in cellular signalling pathways associated with cancer growth and spread — in mesenchymal glioblastoma (ME) and proneural glioblastoma (PN) cells derived from patients. ME is the most aggressive type of glioblastoma that is resistant to treatment, while patients with PN have more favourable outcomes. During treatment, PN glioblastoma can transform into ME glioblastoma, leading to cancer relapses.

The scientists found that compared to PN, a type of protein kinase called mitogen-activated protein kinases (MAPK) were activated in ME. In particular, the activities of two MAPK, p38MAPK and MEK/ERK, were upregulated.

In ME, p38MAPK signalling increases the activity of transporter proteins that pump out drugs from cells. The p38MAPK signalling pathway also increases the ability of glioblastoma cells to repair DNA damage caused by TMZ. These processes enable the

cancer cells to survive treatment and contribute to the innate ability of ME to resist treatment.

On the other hand, MEK/ERK signalling pathways are activated when glioblastoma develops resistance following drug treatment — a phenomenon known as adaptive resistance. The researchers observed that when p38MAPK is inhibited, pH inside the cells decreases and calcium increases, which triggers MEK/ERK signalling and leads to an increase in the survival of glioblastoma cells. The drop in pH also affects the conversion of TMZ to its active compound, reducing its effectiveness.

The researchers implanted ME cells from patients into mice and found that mice treated with a combination of p38MAPK inhibitor ralimetinib, MEK inhibitor binimetinib and TMZ had the best survival at 72.5 days, compared to mice treated with TMZ alone (63 days). Binimetinib, also known as Mektovi, has been approved by the US FDA to treat melanoma, while ralimetinib has been tested in a Phase 1 trial in the treatment of glioblastoma.

Ralimetinib and binimetinib inhibited p38MAPK and MEK/ERK respectively, restoring the effectiveness of TMZ against ME. Inhibiting p38MAPK also decreased the expression of various drug transporter proteins and enhanced the retention of TMZ in cells.

“Our study has shown that glioblastoma acquires drug resistance through multiple pathways, highlighting the need for more precise treatments of the disease,” said study co-leader Associate Professor Andrew Tan, from NTU’s Lee Kong Chian School of Medicine (LKCMedicine).

“Instead of using a single drug, therapies that target the innate and adaptive mechanisms of drug resistance simultaneously could be feasible treatments for resistant glioblastoma tumours,” added first author Dr Hong Sheng Cheng, Dean’s Postdoctoral Fellow at LKCMedicine.

The researchers plan to conduct clinical trials to bring the treatment one step closer to the clinic. They also intend to employ cutting-edge molecular profiling techniques, alongside artificial intelligence technologies such as machine learning, to refine the strategic combination and delivery of drugs for the treatment of glioblastoma.

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