New study offers hope for hundreds of thousands impacted each year by aggressive brain cancer

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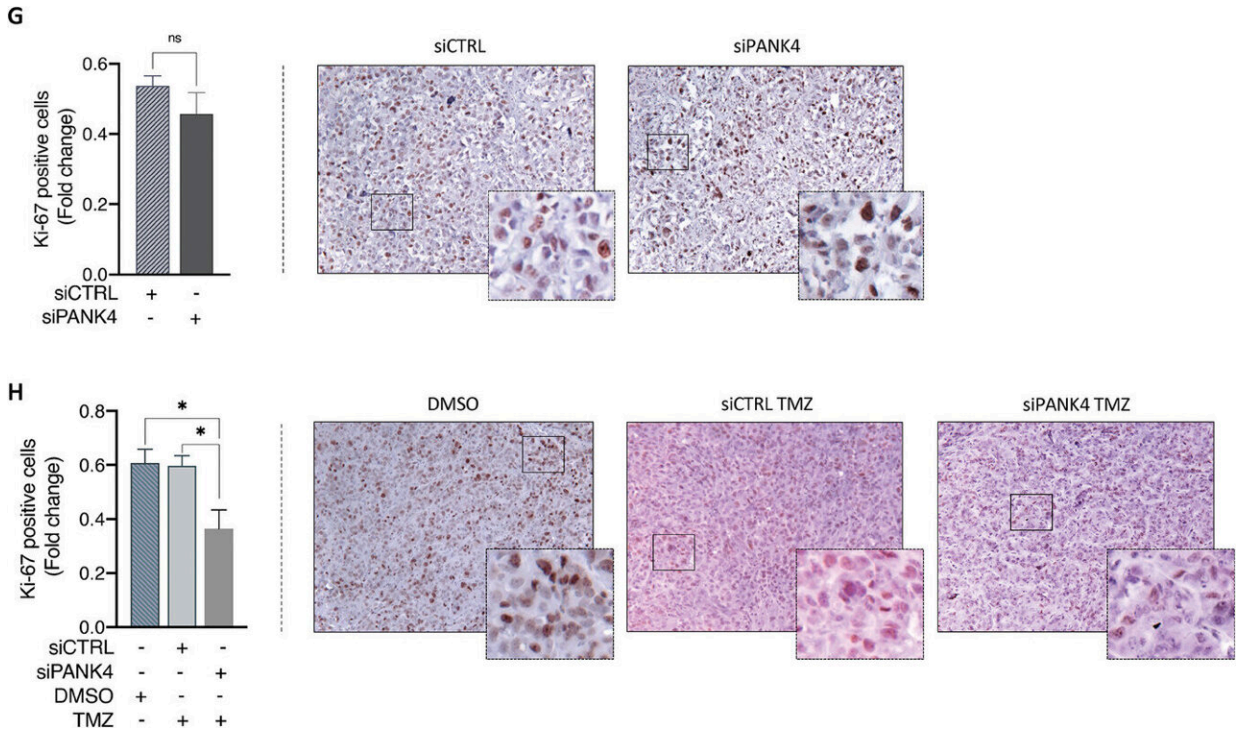

Abrogation of PANK4 sensitizes chemoresistant GBM tumors to TMZ treatment in vivo. A) Schematic representation of the experimental design of our in vivo study. Four mouse cohorts were established: siCTRL DMSO, siPANK4 DMSO, siCTRL TMZ, and siPANK4 TMZ (n = 6 mice per group). The figure was created with BioRender.com. B) Effect of PANK4 knockdown on tumor growth of mice carrying $T98G^{Res}$ xenografts (n = 6 mice per group). Western blot and densitometric analysis of PANK4 expression in tumor lysates from three distinct tumors is shown, confirming PANK4 knockdown efficiency. GAPDH was used

as a loading control. Error bars represent ± SEM. Significance was calculated using unpaired Student's *t*-test; asterisks (*) designate significant differences between conditions indicated with brackets (ns, not significant; *p ^{Res} xenograft mice were treated with either vehicle control or TMZ at the indicated concentrations (n = 6 mice per group), and D) the in vivo sublethal dose of TMZ was subsequently determined using the GraphPad Prism 9 software. (E and F) Effect of combined PANK4 knockdown and treatment with the sublethal dose of TMZ on tumor growth of T98G^{Res} xenograft mice. (G) Immunohistochemical (IHC) evaluation of Ki-67 expression in tumor sections from T98G^{Res} xenograft mice following PANK4 knockdown or H) treated with the sublethal dose of TMZ alone or following PANK4 depletion. The fold change of Ki-67-positive cells versus the total number of cells is shown. Data represent the average of four independent samples per cohort in duplicate. Representative images of Ki-67 immunohistochemical staining in harvested tumors from each cohort are presented. Original magnification, 20x. Scale bar, 50 µm. E–H) Results are expressed as mean ± SEM. Significance was calculated using unpaired Student's *t*-test; asterisks (*) designate significant differences between conditions indicated with brackets (ns, not significant; *p p Advanced Science (2024). DOI: 10.1002/advs.202306027

New research by the University of Sussex could help to increase life expectancy and improve treatment for an aggressive brain cancer, which impacts thousands of people every year in the UK, and hundreds of thousands worldwide.

In the study, published in the journal of *Advanced Science*, researchers have discovered that an understudied protein, called PANK4, is able to block cancer cells from responding to chemotherapeutic treatment for the highly intrusive brain cancer, glioblastoma.

Scientists at Sussex have demonstrated that if the protein is removed, cancer cells respond better to the main chemotherapy drug used globally for the treatment of glioblastoma.

Prof Georgios Giamas, Professor of Cancer Cell Signalling at the University of Sussex, explains, "Glioblastoma is a devastating brain cancer, and researchers are working hard to identify ways to delay the progression of the disease and tackle cell resistance to treatment."

"As this is the first time that PANK4 has been linked to glioblastoma, the next step is to develop a drug targeting this protein to try to reverse chemo-resistance and restore sensitivity, ensuring that patients receive the best treatment and have better outcomes."

Glioblastoma is one of the most aggressive forms of brain cancer. Approximately 3,200 adults are diagnosed with the disease each year in the UK, and around 250,000—300,000 globally, with a best-case survival rate of just one to 18 months after diagnosis.

Following surgery to remove the tumor, glioblastoma patients are typically treated with radiation and the chemotherapeutic drug, temozolomide. Although patients initially respond well to the drug, the cancer cells quickly develop resistance to this treatment.

The University of Sussex scientists led an international research team to understand the possible reasons for this resistance, helping to guide future therapies to improve quality of life and increase life expectancy for those with glioblastoma.

The team identified a protein called PANK4, which, when removed from the cancer cells, can lead to the cell's death and saw patients better responding to temozolomide.

Linked to this, the researchers found that patients expressing high levels of the PANK4 protein had lower survival rates.

Dr. Viviana Vella, research fellow at the University of Sussex, explains,

"There are a multitude of under-investigated proteins that may hold great potential for therapeutic intervention. Our study sheds light on this understudied protein, PANK4, unveiling a protective role in temozolomide-resistant cancer cells. Ultimately, PANK4 depletion represents a vulnerability that can now be exploited to restore sensitivity to the drug and improve treatment."

This study contributes to a body of research from the Sussex researchers, which focuses on the early diagnosis and treatment of glioblastoma.

The research group now hopes to develop a drug to reverse chemo-resistance and improve the outlook for patients.

More information: Viviana Vella et al, Kinome-Wide Synthetic Lethal Screen Identifies PANK4 as a Modulator of Temozolomide Resistance in Glioblastoma, *Advanced Science* (2024). DOI: 10.1002/advs.202306027

Provided by University of Sussex