

A breakthrough for understanding glioblastoma—origin cells for deadly brain tumors identified

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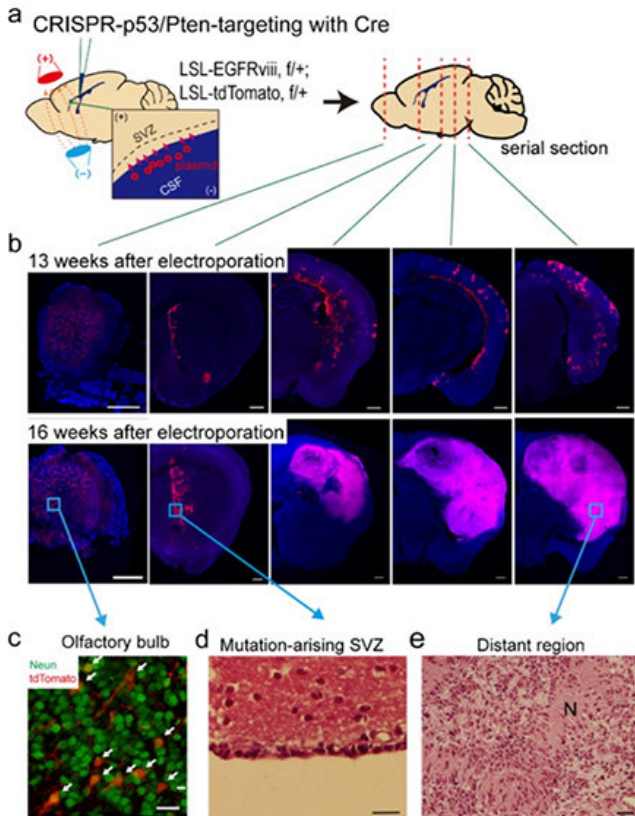


Figure 2. Glioma progression in genome edited mice carrying GBM mutations in the SVZ

A new study by KAIST researchers identified where the mutation causing glioblastoma starts. According to the study, neural stem cells away from the tumor mass are the cells of origin that contain mutation drivers for glioblastoma, one of the most aggressive brain tumor. This breakthrough research, reported in Nature on August 1, gives insights for understanding why glioblastomas almost always grow back, even after surgery, and suggests novel ways to treat glioblastoma, which was previously thought to be

incurable.

Like most cancers, glioblastoma is treated with surgery to remove as much of the tumor as possible, then radiation and chemotherapy. However, it almost always returns in less than a year and its median survival time is only 15 months. Precision therapeutic approaches targeting tumors themselves didn't lead to any breakthroughs.

Professor Jeong Ho Lee's team at the Graduate School of Medical Science and Engineering described direct genetic evidence through the deep sequencing of all triple-matched samples: normal SVZ tissue away from the tumor mass, tumor tissue, and normal cortical tissue. The research team studied 28 patients with glioblastomas and other types of brain tumors who underwent supra-total resection or other surgical resections of tumors, providing access to normal subventricular zone (SVZ) tissue (where neural stem cells are located) away from the tumor mass. The researchers used various deep and single cell sequencing technologies to conduct comparative DNA analysis on the samples from the patient's SVZ tissue and tumors.

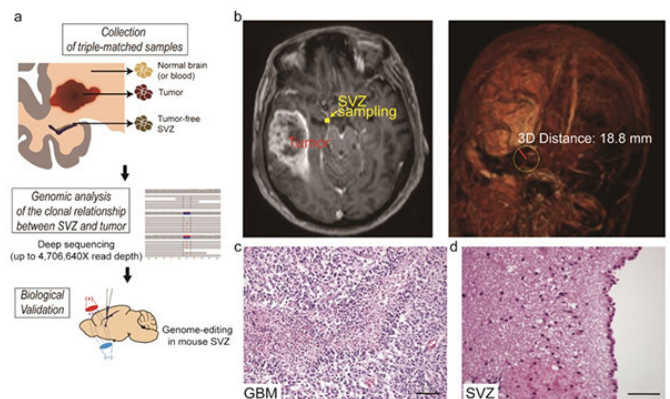


Figure 1. Genetic analysis of tumor-free SVZ tissue and matching tumor tissue from GBM patients. Credit: The Korea Advanced Institute of Science and Technology (KAIST)

They reported that normal SVZ tissue away from the [tumor](#) in 56.3% of patients with glioblastoma already contained low-level glioblastoma driver mutations that were observed at high levels in their matching tumors. Furthermore, the research team generated a genome edited mouse carrying glioblastoma mutations in the SVZ and showed that [neural stem cells](#) with mutations migrate from the SVZ lead to the development of glioblastomas in distant brain regions. (See the image below)

Professor Lee conducted this study in collaboration with Professor Seok-Gu Kang of the Brain Tumor Center at Severance Hospital of Yonsei University. He said, "It's easier to understand when we compare it to fireworks. Every flare flying around sky can be likened to cancer cells even though the fireworks are triggered on the ground. We found the trigger." The identification of this mutation pathway of glioblastomas will lead to a new paradigm for therapeutic strategies. He added, "Now, we can focus on interrupting the recurrence and evolution of glioblastomas."

Professor Lee has investigated [mutations](#) arising in the brain for a decade. He is developing innovative diagnostics and therapeutics for untreatable brain disorders including intractable epilepsy and [glioblastoma](#) at a tech-startup, SoVarGen. "All technologies we used during the research were transferred to the company. This research gave us very good momentum to reach the next phase of our startup," he remarked.

More information: Joo Ho Lee et al. Human glioblastoma arises from subventricular zone cells with low-level driver mutations, *Nature* (2018). [DOI: 10.1038/s41586-018-0389-3](https://doi.org/10.1038/s41586-018-0389-3)

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