Glioblastoma multiforme is the most aggressive type of brain cancer with an average survival rate of 14.6 months1. Glioblastomas are difficult to treat due to the complexity and diversity of gain-and-loss function mutations affecting key signaling pathways in the different types of cells found in gliomas2. While some cancer cells may respond to treatment, other cells may not be affected at all2. The genetic complexity in gliomas has prevented the development of simple therapeutic targets making glioblastoma essentially untreatable. In this issue, (p.65) Kitambi et al. (2014) report a new vulnerability of glioblastoma cells to a vacuolation-induced cell death triggered by the small molecule vaquinol-1.

Genomic studies done on hundreds of glioblastoma patients have reported a multitude of loss-and-gain function mutations on tumor suppressors and proto-oncogenes leading to uncontrolled cell division, inactivation of cell-checkpoints, and cell survival characteristics of cancer cells3. Researchers at Karolinska Institute and colleagues at Uppsala University assumed that the complexity in mutations does not only promote tumor-genesis, but also affects other diverse cellular processes2. Under this assumption, the researchers hypothesized that they can exploit the loss-and-gain function mutations, which give glioblastoma cells unique cellular properties, to create selective therapeutic interventions.

Researchers conducted an unbiased search for a compound to target the unique properties of glioblastoma cells. Kitambi et al. (2014) screened and rescreened 1,364 molecules using three cell lines: mouse embryonic stem cells, human fibroblast, and glioma cells (GCs). Cell toxicity and cell viability were measured to narrow down the search for the most potent compound with selective cytotoxicity to glioma cells, a compound the researchers named vaquinol-1.

Vacquinol-1 triggered catastrophic and unconventional cell death in GCs. Live cell imaging showed that vaquinol-1 treated GCs showed rapid cell rounding, membrane ruffling to create macropinocytotic cups that engulfed extracellular liquid, and the formation and accumulation of vacuoles filled with extracellular fluid inside the cell. The vacuole number and size increased in as little as 10 minutes after treatment and led to the eventual rupture of the cell membrane. Further experiments revealed that vaquinol-1-induced cell death did not occur through apoptotic or autophagic dependent mechanisms. This finding prompted the researchers to look for pathways active during this type of unconventional cell death.

Once they had conducted an unbiased short hairpin RNA (shRNA) screen that targeted over 5,000 genes. The goal was to identify key genes that when knock-downed would render GCs resistant to vaquinol-1. GCs were treated with shRNAs and then underwent a 24-hour treatment with vaquinol-1. Results showed that GCs that survived treatment displayed different cell morphology and were resistant to vacuolation induced cell death. The researchers then sequenced the vaquinol-1 resistant cells, which revealed that activation of MKK4 is required for the pathway inducing vaquinol-1 cell death. When the gene MAP2K4 is knock-downed by shRNA, vaquinol-1 can no longer kill GCs.

In later experiments, researchers used a glioblastoma mouse model to test the efficacy of the drug. A group of 16 mice were injected with tumor cells derived from human glioblastoma patients. All mice developed large, highly vascularized tumors and showed areas of necrosis (dead tissue), as well as other key features of glioblastoma tumors. After 7 weeks of tumor growth, 8 mice were treated with an oral dose of vaquinol-1 and the other 8 mice were treated with a control. Results showed that despite the advanced stage of necrosis, vaquinol-1 treated mice showed significantly normal whole-brain morphology after 5 days of treatment. Vaquinol-1 treated mice also had significantly smaller tumors, or complete absence of tumor, and normal brain weight. In comparison, the mice treated with a control showed large tumors, hemorrhaging, high areas of necrosis, and increased brain weight. In addition, Vaquinol-1 treated mice showed significantly increased survival with a median of 80 days, whereas control treatment mice lived a median of 31.5 days.

The researchers concluded that oral administration of vaquinol-1 significantly impairs tumor progression and can prolong survival in mice.

Vaquinol-1 has the potential to be a treatment for glioblastoma as it showed favorable characteristics during preclinical trials. It showed adequate bioavailability, as the molecule can readily pass the cell membrane, high solubility with spinal cerebrospinal fluid, and a long half-life. Vaquinol-1 has the potential to treat the cells that lead to tumor reoccurrence. However, the most promising aspect of this treatment is its potential to target glioblastoma cells that do not respond to current treatments.

The current treatment for glioblastoma is tumor resection and aggressive chemotherapy/radiotherapy treatment1. However, even with aggressive treatment, only 3-5% of patients live longer than 3 years4. Some research has shown that the chemotherapy agent, Temozolomide (TMZ), causes mutations leading to TMZ resistant cells that promote tumor reoccurrence in patients5. Other studies have shown conflicting results for treatments that target the autophagic cell death pathways. Some show that treatments that inhibit autophagic processes lead to reduced tumor burden6, 7, but others also show that the autophagy process can promote cancer protection8. As such, we are in dire need for a more effective treatment.

Another aspect of glioblastoma reoccurrence is the small population of quiescent or dormant cells within gliomas3, 9. Conventional chemotherapy agents cannot target these quiescent cells with stem-cell-like qualities, as these treatments only target proliferating cells9. Vaquinol-1 has the potential as a therapeutic agent as it can target both quiescent GCs and proliferating GCs (refer to figure 1). Thus, this would promote tumor regression. The standard chemotherapy treatment, TMZ, only targets proliferating cells leaving quiescent GCs untreated and will later become active and drive tumor reoccurrence, malignancy, and tumor invasion in patients. Kitambi et al. (2014) are optimistic and hope to take this treatment to clinical trials as it has the potential to become the next standard care treatment for glioblastomas 10.

Figure 1. Comparison of standard care chemotherapy and vaquinol-1.

Standard care chemotherapy has limited selectivity towards cancer cells. Current treatment, such as TMZ, affects both proliferating cells and healthy brain cells, but has no effect on quiescent cells, cells with stem cell like properties. Despite aggressive chemotherapy treatments, these untreated quiescent cells can later become active and lead to tumor reoccurrence, drive malignancy, and tumor invasion in patients. Treatments with vaquinol-1 can kill both GC quiescent cells and GC proliferating cells, while leaving healthy cells alive. This promotes tumor regression.

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References


