Anti-malarial drug shows promise for brain cancer treatment
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Glioblastoma multiforme (GBM) is an aggressive form of cancer in the brain that is typically fatal. But new findings by VCU Massey Cancer Center and VCU Institute of Molecular Medicine (VIMM) researchers could help increase the effectiveness of the most common current treatments with the addition of lumefantrine, an FDA-approved drug used to treat malaria.

While the current standard of care involving radiation and temozolomide, an anti-cancer chemotherapy, can marginally extend the lives of patients with glioblastoma multiforme brain tumors, resistance of GBM to these therapies is a frequent occurrence. Additionally, the five-year survival rate of GBM patients treated with the standard of care is less than 6 percent, and no current therapies prevent recurrence.

The researchers have focused on discovering FDA-approved drugs and more uncommon agents that could potentially help counteract glioblastoma's resistance to and effectiveness of treatment. "Our studies uncovered a new potential application of the antimalarial drug as a possible therapy for glioblastoma multiforme resistant to the standard of care entailing radiation and temozolomide," said Paul B. Fisher, M.Ph., Ph.D., FNAI, the principal investigator of the study recently published in the journal Proceedings of the National Academy of Sciences.

Specifically, lumefantrine can inhibit a genetic element involved in cancer development and progression, Fli-1, which controls resistance of glioblastoma multiforme to radiation and temozolomide.

During in vitro studies (conducted with cells grown in culture) researchers found that incorporating lumefantrine while treating glioblastoma killed cancer cells and suppressed tumor cell growth. This occurred in both glioblastoma cells sensitive to and those that otherwise would be resistant to radiation and temozolomide. Furthermore, during in vivo studies (conducted using mice containing a transplanted human glioblastoma multiforme in their brains), lumefantrine inhibited tumor growth caused by both therapy-sensitive and therapy-resistant glioblastoma cells.

Discovering lumefantrine's ability to neutralize the body's resistance to radiation and chemotherapy came through genetic and molecular approaches that identified the new genetic element "Fli-1" as an important genetic element controlling resistance to therapy. This discovery became a focal point of the current research. Researchers found that "heat shock protein B1," also known as HSPB1, is prominent in glioblastoma tumors, and its expression is regulated by Fli-1. Innovative screening strategies for Fli-1 inhibitors identified lumefantrine as a prospective agent that could bind
to Fli-1, inactivate it and thereby suppress expression of important genes regulating growth, survival and oncogenicity (ability to cause tumors) of glioblastoma multiforme.

In addition, two key processes essential for cancer invasion and spread known as extracellular matrix (ECM) remodeling and epithelial mesenchymal transition (EMT) are important factors that regulate glioblastoma's ability to respond and resist radiation and chemotherapy. Those two processes are regulated by Fli-1 and are inhibited by lumefantrine.

To help treat glioblastoma, researchers will further explore other means to counteract therapy resistance induced by Fli-1.

"These preclinical studies provide a solid rationale for Fli-1/HSPB1 inhibition with lumefantrine as a potential novel approach for glioblastoma management," Fisher said. "Identification of drugs like lumefantrine from FDA-approved therapeutic agents and from uncommon sources provides opportunities to broaden the breadth and versatility of current therapeutic regimens for glioblastoma multiforme patients."

Beyond glioblastoma, an elevated expression of Fli-1 can be seen in cancers such as melanoma, ovarian cancer, breast cancer and others, researchers said, suggesting that blocking the cancer-promoting effects of Fli-1 might help other cancer patients as well.

"The present results may have broader implications than just treating glioblastoma," Fisher said.


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