Targeting two angiogenesis pathways could improve results of glioblastoma treatment

4 April 2016

Two companion papers from Massachusetts General Hospital (MGH) research teams suggest that targeting multiple angiogenesis pathways simultaneously could help overcome the resistance to anti-angiogenic treatment inevitably developed by the devastating brain tumor glioblastoma. Appearing in *PNAS* Early Edition, the reports describe how two different methods of inhibiting both vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2) in animal models not only normalized tumor blood vessels to a greater extent than anti-VEGF therapy alone but also shifted the action of tumor-infiltrating immune cells from a pro-tumor to an anti-tumor state.

"These papers offer a potential solution for glioblastoma's escape from anti-VEGF therapy, which is mediated by activating alternative growth factor pathways," says Rakesh K. Jain, PhD, director of the Steele Laboratory of Tumor Biology in the MGH Radiation Oncology Department and co-corresponding author of both papers. "In our back-to-back papers we not only provide proof-of-principle data that dual treatment strategies can slow glioblastoma growth and improve survival but also reveal the underlying mechanisms for these benefits."

The most common malignant tumor arising in the brain, glioblastoma is characterized by a highly abnormal, leaky and inefficient blood supply, caused by the overexpression of angiogenic factors like VEGF. These vascular abnormalities lead to swelling around the tumor and poor blood perfusion within the tumor, causing it to become more aggressive and resistant to chemotherapy and radiation treatment. While anti-VEGF treatment has become part of standard postsurgical treatment for glioblastoma, its beneficial effects are temporary and do not extend patient survival.

Previous studies from members of these MGH teams revealed that glioblastoma patients receiving anti-VEGF treatment also had a transient drop in blood levels of Ang-2. Levels of that factor rebounded as tumor progression resumed, suggesting that Ang-2 activity may contribute to resistance to anti-VEGF treatment. The researchers also found that, similar to VEGF, Ang-2 is expressed by all types of glioblastomas. To capture the diversity of different glioblastoma types, the investigators designed two methods of testing whether inhibiting both pathways could overcome treatment resistance.

One approach combined the use of the experimental oral anti-VEGF drug cediranib with an Ang-2-neutralizing antibody in two mouse models of glioblastoma and found that dual therapy improved blood vessel normalization and extended survival compared with cediranib treatment alone. Dual therapy also attracted tumor-associated macrophages (TAMs) to the tumors and increased the proportion of the anti-tumor form of those immune cells. Importantly, blocking the migration of TAMs to tumors reduced the benefits of dual therapy.

The second study used an antibody that targets both VEGF and Ang-2 and showed that dual treatment improved the architecture of tumor vessels in a mouse model with abnormal vessels. TAMs were reprogrammed to an anti-tumor state in both this tumor model and in another model not characterized by abnormal vasculature, indicating that vascular normalization was not the only mechanism of benefit. In fact, dual therapy promoted anti-tumor immunity by shifting the population of TAMs towards an anti-tumor form, consistent with the first study but regardless of whether or not surrounding blood vessels were abnormal.

"Our studies indicate that dual targeting of VEGF and Ang-2 could overcome some of the shortcomings of currently available glioblastoma therapies," says Jain, who is the Andrew Werk

Cook Professor of Tumor Biology at Harvard Medical School. "Clinically accessible agents are currently available for this dual targeting strategy, and our finding that dual therapy can also improve anti-tumor immune responses, irrespective of its effect on blood vessels, is particularly timely given the rapid development of new immunotherapies. These results open new avenues of research on novel combinations to obtain more durable results against this devastating disease."

More information: Dual inhibition of Ang-2 and VEGF receptors normalizes tumor vasculature and prolongs survival in glioblastoma by altering macrophages, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1525349113

Ang-2/VEGF bispecific antibody reprograms macrophages and resident microglia to anti-tumor phenotype and prolongs glioblastoma survival, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1525360113

Provided by Massachusetts General Hospital