Modeling mayhem: predicting invasion and proliferation kinetics in IDH1 mutant glioblastoma with mathematical models

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The molecular genetics of glioblastoma (GBM) are complex, and efforts are underway to systematically investigate their association with tumor aggressiveness and patient outcome. Mutation in the isocitrate dehydrogenase 1 (IDH1) gene produces an alternative metabolite, 2-hydroxylutarate instead of alpha-ketoglutarate and is strongly associated with lower grade gliomas. The majority of GBMs containing the IDH1 mutation are secondary, and diagnostic approaches to distinguish IDH1 wild-type and mutant tumors as well as primary and secondary GBM are under development.

Magnetic resonance imaging (MRI) is a standard diagnostic approach used to provide glioma grading based on contrast enhancement, edema, as well as necrosis; however its diagnostic power is limited as MRI alone cannot provide an accurate measure of tumor aggressiveness based on just these parameters. Efforts have been made to increase the accuracy of MRI using additional parameters such as blood volume and metabolite measurements that enhance diagnostic sensitivity. Despite these advances, the ability to distinguish invasive tumor cells remains a challenge. Mathematical modeling and extrapolation of MRI data is being evaluated as an alternative approach to enhance the diagnostic power of MRI, including estimating the extent of invasion, that does not involve additional imaging or probes. Integrating computational modeling into predictions of GBM classification (primary versus secondary) as well as mutation status (such as wild-type or IDH1 mutant) represents the next steps for these approaches.

Using a previously described model based on serial MRI data that calculates aggressiveness based on rate constants that represent proliferation ($r$) and dispersion ($D$), Swanson and colleagues compare wild-type and IDH1 mutant gliomas. By combining these two parameters, an aggressiveness ratio can be computed, which may help in distinguishing between wild-type and IDH1 mutant tumors.
be generated (\(p/D\)) that predicts prognosis, extent of hypoxia, and possibly primary GBM characterized by increased proliferation and secondary GBM characterized by decreased proliferation and increased diffusion\(^1\). In a well-characterized patient cohort of 178 gliomas (158 of which were GBM) from the Cancer Genome Atlas (TCGA) and two academic medical centers, the authors found that while tumors may display identical rates of proliferation, the IDH1 mutant tumors often have increased rates of dispersion. Overall, the wild-type tumors had a significantly higher aggressiveness ratio as compared to the IDH1 mutant tumors. These differences were present both in primary and secondary GBM, with a more significant difference present in secondary GBM. Taken together, the model presented by the authors distinguished between wild-type and IDH1 mutant tumors based on differences in proliferation and dispersion (Fig. 1). The authors confirm that IDH1 mutant tumors are less aggressive and possess an elevated invasion profile based on MRI. These findings can be applied to pre-operative MRI data and allow for predictions based on IDH1 status that can be integrated into the clinical management plan.

The results of the computational modeling also support the go or grow hypothesis\(^1\) that predicts that rapidly proliferating cells have a lower invasion capacity while cells with a higher propensity to invade have lower proliferation. Invasion is a hallmark of GBM and remains a challenge to the treatment of the disease. While the signaling pathways responsible for invasion are being evaluated for the development of additional anti-GBM therapies, recent observations that anti-angiogenic therapies can increase the invasiveness of GBM\(^1\) suggest that invasion can also be a therapeutic resistance mechanism. How IDH1 mutation status relates to invasion remains largely unexplored. The authors’ model predicts that IDH1 mutant tumors would be more invasive, and this has been confirmed by an independent group based on serial imaging with a novel biomathematical model. The ability to accurately predict and detect IDH1 mutation status remains a priority for the neuro-oncology community. The authors’ computational modeling approach is a complementary method to antibody\(^1\) and metabolite\(^1\) based detection methods. Moving forward, accurately identifying key mutations linked to tumor grade and outcome will be essential to ensure that the most accurate diagnosis and treatment plan is provided for each patient.

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### References


