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Multiscale modeling of glioblastoma

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As reviewed in the Editorial "*Targeting glioblastoma stem-cells: a recurrent challenge in neuro-oncology*" (1), we recently developed a 3D mathematical model of glioblastoma multiforme (GBM) progression and response to therapy (2). The development of the model necessarily required assumptions to be made about which key biological processes to incorporate and which to exclude. We aimed to develop a model that extensively defined the main features of GBM, which, as described in the Editorial, include invasiveness, intense proliferation, necrosis and neovascularization, as well as the crosstalk among GBM cells and cells in the microenvironment, and to use this model to test the effectiveness of different anti-GBM treatment strategies available in the clinical practice.

In our mathematical model, we assumed that GBM had a hierarchical structure containing glioblastoma stem cells (GSCs), more rapidly dividing glioblastoma committed progenitor cells (GCPs) and post-mitotic glioblastoma terminally differentiated cells (GTDs). This mimics the underlying structure of the normal brain and a recent clonal analysis of human GBM supports this assumption (3). We also accounted for nonlinear interactions between

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the GBM cellular populations and a tumor-induced neovascular network, which provides GBM cells with nutrients and oxygen as well as a perivascular niche for GSCs (4,5).

We were intrigued by the possibility that GSCs could transdifferentiate into vascular endothelial cells (GECs), as suggested by mouse xenograft models (6,7), thereby potentially providing an additional mechanism of neovascular development and of resistance to antiangiogenic therapy because it is thought that GECs are not VEGF-dependent (7). Further, GECs may also contribute to GBM resistance to anti-mitotic therapies such as radiation and chemotherapy (8) and GECs aid in maintaining GSCs, which are highly resistant to the currently used treatments. We thus incorporated a branch in the GBM lineage in our mathematical model to account for transdifferentiation of GSCs to GECs and tracked the spatiotemporal dynamics of all the cell types. We then tested the response of our simulated tumors to available monotherapies and combinatorial therapies. We found that monotherapies are ultimately limited in their effectiveness and that combinations of anti-mitotic, pro-differentiation (anti-GSC), and anti-angiogenesis and anti-GEC drugs already approved by the FDA could be used to target the major GBM and microenvironmental cell types, and could potentially lead to tumor eradication.

As the Editorial states, and as is discussed in our article, the presence of GECs in human tumors remains controversial as some studies have claimed that GEC are a rare population of cells in glioma in humans (9,10) making it questionable as to whether these GECs play a role in human GBMs. However, others claim that GECs may be found in clinical specimens (11) and it is our understanding that this is still an area of active research. For example, since the publication of our article, a new study revealed that 30 out of 64 clinical GBM patient samples showed evidence of GECs and in 21 of those 30 samples GECs were found to form vessels that constituted approximately 14–18% of the total number of vessels (12). The role of GEC vessels in resistance to anti-angiogenic treatment remains unknown.

Because the GSCs are relatively resistant to antimitotic therapies, but drive invasiveness of GBM, and may contribute to neovascular development, anti-GSC treatments should be tried. In our paper, we used pro-differentiation agents such as retinoic acid (RA) derivatives as an anti-GSC treatment. Such treatments have actually been tested in humans and clinical trials suggest that the best efficacy comes when RA derivatives are used in patients with recurrent GBM either as monotherapy using 13-cis-retinoic acid naphthalene triazole (13) or using 13-cis-retinoic acid in combination with temozolomide (14). More research in this direction is clearly merited.

The Editorial also discusses evidence for reprogramming of differentiated GBM cells to a tumor-propagating GSC-like state in *in vitro* models (15), and that this rate may be increased when GBM cells are subject to therapy (16). This could obviously confound our results. As mentioned in our article, we did explore therapy-induced reprogramming of GCP and GTDs although we did not explicitly present the results. The efficacy of the combination treatment we proposed depends on the dedifferentiation rates for which there is little experimental data, especially *in vivo* where the extent of reprogramming still needs to be investigated. When the reprogramming rates are sufficiently small, the combinatorial treatments we proposed are effective but when the rates are large, the therapies may fail due to a large

influx of GSCs, and in this case additional anti-reprogramming treatments (17) may be needed.

As stated in the Editorial, GBM (and microenvironmental) cells may acquire drug resistance and this may also confound our results. We acknowledge that we did not model specific cell-level genetic mutations that could give rise to resistant cell types. Instead, we modeled the cells as having different response rates to therapies. For example, the GSCs are the most resistant to anti-mitotic therapies. Thus, over time, anti-mitotic therapies will increase the fraction of GSCs in the GBM and will naturally lead to a decreased response of the tumor over time to anti-mitotic treatment. We did not model a variable response of cells to the other types of therapy we considered—anti-GSC, anti-angiogenic and anti-GEC—but our simulations show that the latter two treatments could enhance tumor invasiveness that ultimately makes the GBM refractory to these treatments. It would be interesting to decrease the response rates of the cells over time to the various therapies to mimic the development of drug resistance.

In summary, while the mathematical model we presented in (2) does not reproduce all the complexity of GBMs, we agree with the Editorial that the model does provide an elegant tool to test the nonlinear interactions between GBM cells, microenvironmental cells and their response to treatment in ways that are difficult to access experimentally. As new data becomes available the assumptions of the model can be updated to incorporate the new knowledge. Ultimately, the utility of the model is to develop hypotheses that can be experimentally tested, leading to new biological insight and more effective therapeutic strategies to be validated in future clinical trials.

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