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Tumor Treating Fields : Additional Mechanisms and Additional Applications

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To the Editor,

Glioblastoma (GBM) is the commonest malignant brain tumor with an almost uniformly lethal outcome. Despite aggressive surgical and adjuvant oncological intervention, median survival is around 12–15 months[10,14]. Although controversial, there is a trend favoring maximal safe resection in GBM surgery[2,4,5]. Conventional oncological treatments include radiotherapy and chemotherapy[10], although it is important to appreciate that there has been little improvement in the standard of care in patients with newly diagnosed GBM since the Stupp protocol was reported.

Tumor Treating Fields (TTFields) are low intensity, intermediate frequency, alternating electric fields which have been shown to significantly increase progression-free survival and overall survival in patients with primary and recurrent GBM[6,11-13]. An interesting recent article reviews TTFields in GBM, focusing on the anti-mitotic and anti-microtubule effects[22]. Briefly, TTFields arrest tumor cell mitosis in interphase, prolong tumor mitotic cycles, and cause cell fragmentation and inhibit tumor cell proliferation[22]. The authors are hereby congratulated on an excellent, well-balanced and authoritative paper. The opinions and observations provided here are merely additional novel mechanisms by which TTFields may contribute to an anti-glioma effect, beyond inhibiting mitosis. Accordingly, additional applications for TTFields are suggested herein.

Neuronal activity-dependent glutamatergic neurotransmission has been shown to play an essential role in the propagation of glioma[17,18,20]. The concept of the "neurogliomal synapse" has been put forth, whereby glutamate originating from neurons acts on postsynaptic glutamatergic receptors on glioma cells to promote glioma growth and invasiveness[16,19]. Blocking this glutamatergic signaling through anti-epileptic and anesthetic agents demonstrated anti-glioma effects[16]. An external electrical field may interfere with glutamatergic signaling – as has been demonstrated in patients with epilepsy[1] – and this may be another mechanism by which TTFields may exert its anti-glioma effect. Furthermore, glutamatergic signaling has been shown to promote metastasis of systemic tumors to the brain[21]. A role for TTFields in treatment of brain metastases has previously been proposed[3], and it will be interesting to see if a TTFields-mediated anti-glutamate role contributes here.

The cell of origin in GBM is thought to be endogenous neural stem cells residing in periventricular niches[7-9]. Electrical

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fields generated as a byproduct of deep brain stimulation have been shown to significantly influence the neural stem cell niche[15], potentially evoking a less gliomagenic niche. It is possible that TTFields exert a similar influence to prevent neural stem cells from promoting or contributing to glioma growth.

A potential drawback with TTFields as they stand is that anti-tumor efficacy and patient survival correlates with dose, which is the duration patients must be wearing their device[6,12]. Furthermore, GBM is typically a deep tumor, frequently extending to the margin of the lateral ventricles. The electrical field must penetrate soft tissue, calvarium, meninges, gray and white matter before tumor is reached. Each aforementioned anatomical structure confers electrical resistance and the electrical field would be dampened as a result. Two ideas emerge from this. Firstly, children have thinner skulls and extracranial soft tissue – TTFields may be more efficacious in this patient group owing to lesser impedance. However, supratentorial malignant gliomas are less frequent in children. Secondly, there is the possibility of retaining electrodes at the time of tumor surgery for the purposes of delivering a more focused electrical field at the site of the tumor. Therefore, there may be a role for surgical neuromodulation in GBM. Advances in electrical field therapy in GBM may be extrapolated to other tumors, including tumors outside of the central nervous system.

In conclusion, additional mechanisms to explain the anti-glioma effect of TTFields are presented here. Additional applications and indications are presented including a possible role for surgical neuromodulation. Further research is warranted.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

INFORMED CONSENT

This type of study does not require informed consent.

AUTHOR CONTRIBUTIONS

Conceptualization : AK
Data curation : AK
Formal analysis : AK
Funding acquisition : AK
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